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Discovery of CNS Penetrant CXCR2 Antagonists for the Potential Treatment of CNS Demyelinating Disorders

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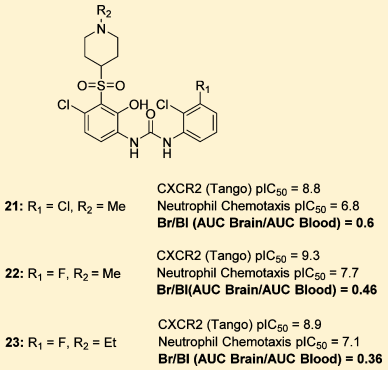
Supporting Information

ABSTRACT: Structure−activity relationship exploration of the historical biarylurea series led to the identification of novel CNS penetrant CXCR2 antagonists with nanomolar potency, favorable PK profile, and good developability potentials. More importantly, the key compound **22** showed efficacy in a cuprizone-induced demyelination model with twice daily oral administration, thereby supporting CXCR2 to be a potential therapeutic target for the treatment of demyelinating diseases such as multiple sclerosis.



KEYWORDS: *CXCR2 antagonists, CNS penetration, diarylureas, cuprizone model, demyelination and remyelination, demyelinating disorders, multiple sclerosis*

Chemokines, or chemotactic cytokines, comprise a family of inducible secreted molecules of small molecular weight (8−10 kDa).[1−3] On the basis of their disposition and number of invariant cysteines, chemokines have been grouped into four main classes, namely, the CXC, CC, C, and CX3C families.[4] Chemokines can be released from a number of inflammatory and structural cell types following stimulation and act through chemokine receptors that belong to the G-protein-coupled receptor (GPCR) superfamily.[5−7] Expressed on neutrophils, lymphocytes, dendritic cells, and many other cell types, chemokine receptors play a role in leukocyte homing, human immunodeficiency virus entry, angiogenesis, tumor growth and metastasis, development, and inflammation of the central nervous system (CNS) in addition to the mediation of migration of leukocytes to the inflammatory sites (chemotaxis).[8−10]

CXCR2, also known as IL-8RB, is an ELR+ CXC chemokine receptor and binds a number of CXC chemokines including CXCL1 (GRO-α), CXCL2, CXCL3, CXCL5, CXCL7, and CXCL8 (IL-8).[11] It is well documented that CXCR2 plays an important role in the activation and recruitment of neutrophils to sites of inflammation, providing a biological basis of positioning CXCR2 as an appealing drug target for several inflammatory diseases such as arthritis, chronic obstructive pulmonary disease (COPD), asthma, and psoriasis.[12−15] In addition to neutrophils, CXCR2 is also expressed on oligodendrocyte progenitor cells (OPCs) in the CNS.[16] Recently, CXCR2 was described to influence response in neutrophils that mediate demyelination as well as in OPCs that mediate myelin repair, exerting both a peripheral function to promote demyelination and a CNS mechanism to impair remyelination.[17−20] In light of its fundamental role in demyelination and remyelination, CXCR2 antagonists may be suitable for therapeutic development in clinical demyelinating disorders such as multiple sclerosis (MS), a devastating heterogeneous inflammatory demyelinating disorder of the CNS affecting young adults.[21,22]

To date, a number of small molecule CXCR2 antagonists with distinct chemical structures have been disclosed.[23−31] However, earlier reports mainly focused on their applications in peripheral diseases and none of those were described to be CNS penetrant. As illustrated above, the CNS penetrant CXCR2 antagonists should, in principle, have better pharmacological effect on MS for their robust contribution to the CNS mechanisms that control remyelination, relative to non-CNS penetrant compounds. To identify CNS penetrant CXCR2 antagonists for potential MS therapeutics, we focused our attention on a series of biarylureas that not only block the

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functional binding interaction between CXCR2 and its chemokine ligands but also display a high degree of selectivity for CXCR2 over CXCR1.[25,32,33] In addition to a urea moiety bridging two phenyl rings, the series features a phenolic group whose acidity appears to be an important factor to the activity. Its well-established SAR indicated placement of a bulky electron withdrawing sulfonamide moiety at an adjacent position to urea improved potency as well as pharmacokinetic properties (e.g., decrease the rate of glucuronidation).[32] While urea has been one of the most widely used structure components in the discovery of biologically active small molecules, the urea-containing compounds usually appear to bear less favorable physicochemical properties that usually result in low aqueous solubility and poor permeability,[34] raising concerns on their potential of CNS penetration as crossing brain−blood barrier (BBB) frequently requires compounds to have fewer hydrogen bond donors/acceptors (HBD/HBA), lower polar surface areas (PSA), higher calculated Log P (cLogP) values, and fewer rotatable bonds (Figure 1).[35,36] In

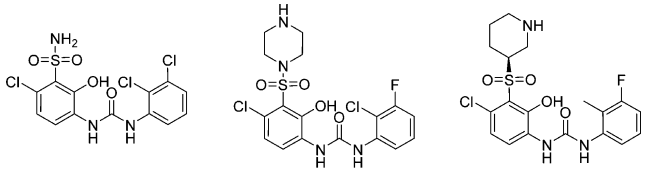

Figure 1. Representative urea compounds that have entered clinical trials.

this letter, we describe our systemic structure−activity relationship (SAR) study on the biarylurea series that led to identification of novel CNS penetrant CXCR2 antagonists with good developability profiles, whose in vivo efficacy in a cuprizone model supported the rationale that antagonizing CXCR2 with small molecules could be an attractive approach for the treatment of demyelinating diseases like MS.

To begin with exploration of CNS penetrant CXCR2 antagonists, we first investigated a urea compound **1**. Its brain-to-blood ratio (Br/Bl) of the area under the curve (AUC) was determined to be 0.14 after a single PO dose of 1.94 mg/kg in mice. While the ratio did not meet an internal criteria set for CNS penetrant compounds (Br/Bl > 0.3), it showed an acceptable starting point for further optimization. According to the previously established SAR, the 3-position of the urea scaffold was tolerated with moieties having various sizes and shapes. Therefore, initial SAR efforts were focused on the sulfonamide region with an aim of reducing the number of hydrogen bonding donors (HBD), which was usually considered to negatively impact CNS penetration. When the tertiary sulfonamide **4** was tested, it displayed a similar Br/Bl to the primary sulfonamide **1** (Br/Bl = 0.17). Methylation of **4** to convert peripheral secondary amine to tertiary amine further reduced one HBD, and the resulting compound **5** had a marked increase in Br/Bl from 0.17 to 0.50 (**4** vs **5**). The increase of Br/Bl was also observed for another compound **6**, which only differed from **5** in a halogen atom (e.g., Br/Bl = 0.47 for **6**). Encouraged by the CNS data of **5** and **6**, we varied alkyl groups on the piperazine nitrogen. Clearly, from methyl to ethyl to isopropyl (compounds **6**−**8**), their Br/Bls were continuously increased from 0.47 to 1.87, which were correlated with their cLogPs enhanced from 3.89 to 4.73, indicating that lipophilicity plays an important role in CNS penetration. Additionally, when the substituted morpholine was used to replace 4-methylpiperazine for maintaining comparable lipophilicity as well as HBD, this variation, however, produced lower CNS penetrant compounds **9** and **10**. While some sulfonamide compounds **5**−**8** displayed an acceptable Br/Bl through optimizing lipophilicity and HBD, their absolute exposures in brain (e.g., brain AUC) were within the range of 83−151 h·ng/g, which apparently needs to be further increased for better accessing the CNS target and exerting pharmacological effects subsequently. To this end, sulfone compounds with fewer hydrogen bonding acceptors (HBA) were explored. For alkyl sulfones, *t*-butyl sulfone **14** with highest lipophilicity displayed the best CNS penetration property with a Br/Bl of 1.04 compared to ethyl sulfone **11** and isopropyl sulfone **12**. Interestingly, cyclic alkyl sulfones, particularly **16** and **17**, were hardly detected from brain, largely due to their poor absorption and rapid clearance. Similar to piperazine sulfonamides (**5** and **6**), alkylation of the piperidine nitrogen (**21** and **22**) significantly improved the Br/Bl. More importantly, their brain exposures were also markedly increased (e.g., brain AUC: 358 h·ng/g for **21** compared to 29.8 h·ng/g for **20**), which was not seen from above sulfonamide compounds. With such promising CNS data, further SAR study centered on N-containing heterocyclic sulfones. Among pyrolidine, piperidine, and azepane sulfones, piperidine sulfones (**21** and **22**) showed the most favorable CNS penetration property (Br/Bl > 0.45). Subsequently, spirocompounds (**27**−**29**), structurally relevant to above N-containing heterocyclic sulfones, were also explored. While their blood exposures were noticeably high, these spirocompounds rarely crossed through into the brain (Br/Bl < 0.1). The non-CNS penetration property of these spirocompounds was presumably due to some transporter effects, which need to be elucidated in the future study as no explanation could be apparently made from the perspective of their physicochemical properties. Additionally, a couple of amides (**30** and **31**) were tested; however, they were metabolically unstable in our in vivo CNS study. Through systemic SAR study, sulfones with optimal HBD, HBA, and lipophilicity were found to be the most favorable for the urea series to incorporate reasonable brain penetration properties, compared to sulfonamides and amides. It should be also noted that IC_{50}s of all compounds (Table 1) measured in a CXCR2 Tango assay were below 10 nM (e.g., pIC_{50} > 8), confirming that the 3-position of urea scaffold is well tolerated with various functionalities and could be used for optimization of other drug-like properties such as solubility, permeability, free fraction, etc.

The general synthetic procedures for urea compounds containing sulfone moieties were described in Scheme 1. Thiol compound **32** was prepared according to a published procedure.[37] It reacted with methylsulfonate piperidine to generate thiol ether **33**, which was then oxidized to the sulfone **34** by *m*-chloroperoxybenzoic acid. Hydrolysis of the benzoxazole moiety yielded the aminophenol **35**, which further coupled with isocyanates to produce the urea **36**. Terminal piperidine amine was alkylated through a reduction amination reaction to give the products **21** and **22**.

On the basis of their good CNS penetration properties as well as reasonable cLogP and PSA values, several representative compounds **21**−**24** were conducted for pharmacokinetic study in mice following intravenous and oral administration. As described in Table 2, these compounds demonstrated a similar PK profile of moderate oral bioavailability (%*F*: 26−41%),

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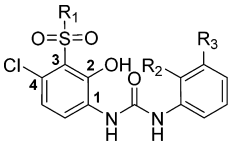
Table 1. SAR of the Diarylurea Series



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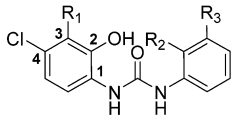

30-31

Compound	R_1	R_2	R_3	CXCR2 Tango (pIC_{50})[a]	Neutrophil Chemotaxis (pIC_{50})[a]	PSA[b]	cLogP[b]	Blood $AUC_{0\text{-}4h}$ (hr*ng/ml)	Brain $AUC_{0\text{-}4h}$ (hr*ng/g)	Br/Bl
1	NH_2	Cl	Cl	8.7	6.5	121.5	2.61	352[c]	49[c]	0.14[c]
4		Cl	Cl	9.2	5	110.8	3.77	855[d]	143[d]	0.17[d]
5		Cl	Cl	9.1	6	102.0	4.34	303	151	0.5
6		Cl	F	9.1	6.5	102.0	3.89	176	83	0.47
7		Cl	F	9	5.7	102.0	4.42	189	128	0.67
8		Cl	F	8.8	5.7	102.0	4.73	52.9	99	1.87
9		Cl	F	8.4	5.5	108.0	4.37	279	96	0.35
10		Cl	Cl	8	4.8	108.0	4.82	519	73	0.14
11		Cl	Cl	9.3	5.2	95.5	4.47	256	73.9	0.29
12		Cl	F	9.3	8.0	95.5	4.33	198	95	0.48
13		Cl	Cl	9.2	6.8	95.5	4.78	290	180	0.62
14		Cl	F	9.3	7.4	95.5	4.72	355	369	1.04
15		Cl	F	9.5	7.9	95.5	4.40	103	28.4	0.28
16		Cl	F	9.5	7.6	95.5	4.96	2.98	1.26	0.42
17		Cl	F	9.5	7.1	95.5	5.52	NA[e]	NA[e]	NA[e]
18		Cl	Cl	9.3	8.1	104.7	4.04	284	59	0.21
19		Cl	Cl	9.1	8.2	104.7	3.57	290	37	0.13
20		Cl	Cl	8.7	[f]	107.5	3.55	904	29.8	0.03
21		Cl	Cl	8.8	6.8	98.7	4.00	600	358	0.6
22		Cl	F	9.3	7.6	98.7	3.55	735	335	0.46
23		Cl	F	8.9	6.8	98.7	4.07	684	244	0.36
24		Cl	Cl	8.9	6.6	98.7	4.44	577	164	0.28
25		Cl	F	9.3	7.1	98.7	3.99	432	136	0.32
26		Cl	F	9.3	7	98.7	4.10	463	99.1	0.21
27		Cl	F	9.4	6.2	98.7	3.30	1049	22.9	0.02
28		Cl	F	8.7	8.7	98.7	4.42	1387	111	0.08
29		Cl	F	9.4	7.6	98.7	5.54	1479	69.3	0.05
30		Cl	F	9	8.1	81.7	3.36	NA[e]	NA[e]	NA[e]
31		Cl	F	9.3	8.2	81.7	3.92	NA[e]	NA[e]	NA[e]

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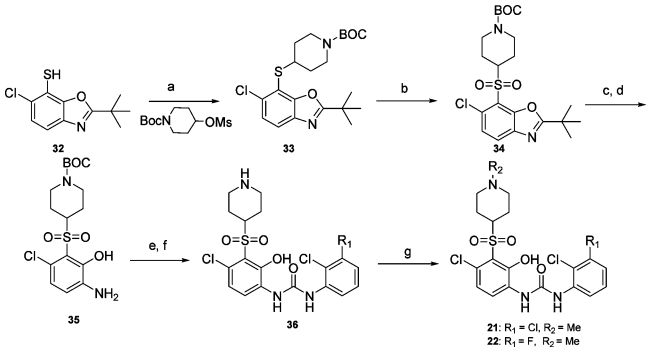
Table 1. continued

[a]pIC50 value is the average of at least two determinations. [b]Calculated from ChemBioDraw Ultra 14.0. [c]Obtained from actual PO dose of 1.9 mg/kg. [d]Obtained from actual PO dose of 3.4 mg/kg. All others in Table 1 were performed with a IP dose of 2 mg/kg in C57 BL/6 mice. [e]Not applicable because the concentration at time points measured was below the limit of quantification. [f]Not tested.

Scheme 1. Synthesis of Urea Compounds Containing a Urea Moiety[a]



[a]Reagents and conditions: (a) K_2CO_3, DMF, rt; (b) mCPBA, DCM, rt; (c) conc. H_2SO_4, dioxane, H_2O, 100 °C; (d) $(BOC)_2O$, rt; (e) aryl isocyanate, DCM, rt; (f) TFA, rt; (g) aldehyde/ketone, $NaBH_3CN$, AcOH, 0 °C.

Table 2. Mouse PK of CNS Penetrant CXCR2 Antagonists[a,38]

	iv, 1 mg/kg			po, 2 mg/kg		
compd	$T_{1/2}$	Cl_b	V_{ss}	C_{max}	$DNAUC_{0\sim\infty}$	%F
21	2.0	15.6	2.12	132	299	30
22	2.8	16.9	3.17	157	354	41
23	2.3	30.8	2.82	125	212	41
24	1.9	15.4	1.72	216	271	26

[a]Units: $T_{1/2}$, h; Cl_b, mL/min/kg; Vss, L/kg; C_{max}, ng/mL; $DNAUC_{0\sim\infty}$, ng·h/mL/mg/kg.

moderate clearance (Cl_b: 15.4−30.8 mL/min/kg), and acceptable oral exposure ($DNAUC_{0\sim\infty}$: 212−354 ng·h/mL/mg/kg), justifying further evaluation.

Some in vitro developability assays were conducted to evaluate their drug-like properties (Table 3). The plasma free fraction of all compounds tested here was very low, corresponding to their high plasma protein binding. Notably, **22** had the highest human plasma free fraction, largely attributed to its lowest lipophilicity as indicated by cLogP. They did not show inhibitory activity in the human CYP enzymes (pIC_{50} < 5 for 1A2, 2D6, 2C9, 2C19, and 3A4, respectively), indicating that there is no drug−drug interaction concern. Neither compound was observed for glutathione adducts and hERG binding, revealing good stability and low concern on the cardiac safety, respectively.

Table 3. Developability Profile of CNS Penetrant CXCR2 Antagonists

compd	Fu% plasma (human)	CYP inhibition (1A2, 2D6, 2C9, 2C19, 3A4)	GSH conjugate	hERG binding (pIC_{50})
21	0.1	pIC_{50} < 5	not observed	<4.1
22	0.13	pIC_{50} < 5	not observed	<4
23	0.036	pIC_{50} < 5	*a*	<4
24	0.021	pIC_{50} < 5	not observed	*a*

[a]Not tested.

Compound **22** was tested in a cuprizone-induced demyelination model due to its superior Fu%, evidence of brain penetration and reasonable developability profile (Figure 2). In this in vivo model, mice were fed with cuprizone for 5 weeks to cause demyelinating lesions in the CNS and then orally administrated with **22** for 9 consecutive days at doses of 30 and 100 mg/kg twice daily. When mice were sacrificed for CNS analysis, Black−Gold myelin staining revealed severe demyelination of the corpus callosum in forebrain of the control group, while the treatment groups showed accelerated significant remyelination at 100 mg/kg (b.i.d., p.o.) compound **22** dosing compared to the control vehicle group ($p < 0.05$).

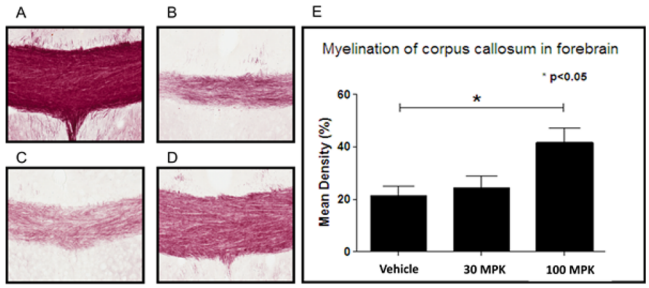


Figure 2. CNS penetrant CXCR2 antagonist **22** in a cuprizone model.[33] The corpus callosum in forebrain was selected for Black−Gold II staining. (A) From the control group without cuprizone feeding; (B) from the vehicle group with cuprizone feeding; (C) from the treatment group of oral b.i.d. dosing of 30 mg/kg for 9 consecutive days after cuprizone feeding; (D) from the treatment group of oral b.i.d. dosing of 100 mg/kg; (E) statistics results.

In summary, a set of novel CNS penetrant CXCR2 antagonists were identified from the historical urea series through systemic SAR study. To the best of our knowledge, these urea compounds are the first CNS penetrant CXCR2 antagonists reported to date, which demonstrated nanomolar potency (Tango assay), favorable PK profile, reasonable CNS penetration, and good developability potential. The key compound **22** showed efficacy in a cuprizone-induced demyelination model through oral administration, providing evidence to support CXCR2 to be a potential therapeutic target to treat demyelinating diseases such as multiple sclerosis. Future work will explore optimizing the series to help qualify the potential therapeutic potential of CNS penetrant CXCR2 antagonists.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmedchemlett.5b00489.

Biological assays and experimental procedures (PDF)

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Notes

The authors declare no competing financial interest.

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