Synthesis and SAR of 1,2,3,4-Tetrahydroisoquinoline-Based CXCR4 Antagonists

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S Supporting Information

ABSTRACT: CXCR4 is the most common chemokine receptor expressed on the surface of many cancer cell types. In comparison to normal cells, cancer cells overexpress CXCR4, which correlates with cancer cell metastasis, angiogenesis, and tumor growth. CXCR4 antagonists can potentially diminish the viability of cancer cells by interfering with CXCL12-mediated pro-survival signaling and by inhibiting chemotaxis. Herein, we describe a series of CXCR4 antagonists that are derived from (S)-5,6,7,8-tetrahydroquinolin-8-amine that has prevailed in the literature. This series removes the rigidity and chirality of the tetrahydroquinoline providing 2-(aminomethyl)pyridine analogs, which are more readily accessible and exhibit improved liver microsomal stability. The medicinal chemistry strategy and biological properties are described.

TIQ-15
CXCR4 Ca^{2+}Flux = 7 nM
in vitro Metabolic Stability:
Human 77%, Rat 37%, Mouse 17%

CXCR4 Ca^{2+} Flux = 21 nM
in vitro Metabolic Stability:
Human 86%, Rat 33%, Mouse 64%

KEYWORDS: CXCR4, GPCR, antagonist, chemokine, anticancer, tetrahydroisoquinoline, muscarinic, biotransformation
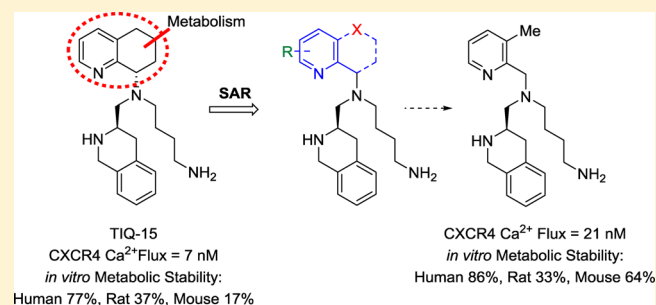
Chemokines and chemokine receptors are essential to immune cell trafficking.[1] The human chemokine system contains four types of ligands differentiated by their cysteine residue pattern at the amino termini.[2] Of particular interest is the C−X−C motif containing chemokine receptor type 4 (CXCR4). CXCR4 is a seven transmembrane G protein-coupled receptor (GPCR).[3] In normal embryonic and adult tissue, CXCR4 expression is primarily associated with hematopoietic and immune systems; however, it can be found in several other tissues including the thymus, brain, and small intestine. When CXCR4 is bound to its specific natural ligand CXCL12 (also known as stromal cell derived factor 1, SDF-1), downstream signals mediated by heterotrimeric G proteins trigger various cellular responses including increased intracellular calcium flux, gene transcription, chemotaxis, cell survival, and proliferation.[1] CXCR4 stands as the most widely overexpressed chemokine receptor in human tumor cells.[4−7] In several types of cancer, CXCR4 activation stimulates proliferation, angiogenesis, migration, adhesion, invasion, metastasis, and survival.[8] Because cancer cells utilize the CXCR4/CXCL12 mechanism for survival, metastasis, and immune evasion, identification of new and effective small molecule CXCR4 inhibitors would be beneficial.

Several small molecule CXCR4 antagonists exemplified by AMD3100 (Plerixafor, Mozobil),[9] AMD070 (X4P-001),[10,11] and GSK 812397[12,13] have been reported in the literature (Figure 1). The bicyclam AMD3100 was the first generation CXCR4 antagonist developed by AnorMED but exhibited poor oral
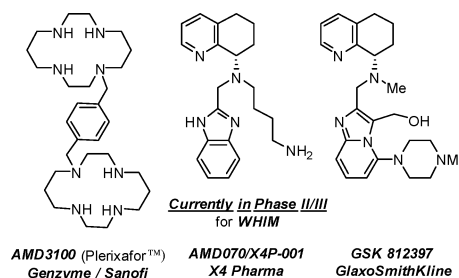

Figure 1. Literature examples of small molecule CXCR4 antagonists.

bioavailability and dose-limiting adverse events. Subsequently, AMD070 improved oral bioavailability and eliminated the adverse interactions associated with cyclams. However, this structure suffered from cytochrome P450 2D6 inhibition,[14] likely due to the 2-substituted benzimidazole.[15] The 2D6 isoform is primarily expressed in the liver and is responsible for the metabolism of nearly 25% of all drugs.[16] Strong inhibition of 2D6 leads to drug−drug interactions and detracts from future therapeutic value. Exchanging the benzimidazole moiety with other heterocycles was expected to reduce such off-target effects.

Recently, our group disclosed the discovery of TIQ-15, a potent small molecule 1,2,3,4-tetrahydroisoquinoline (THIQ)-based CXCR4 antagonist (Figure 2).[17] Subsequent synthetic
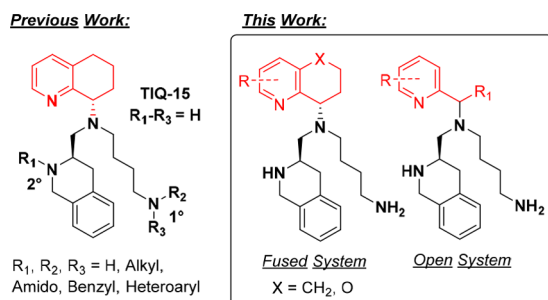

Figure 2. Derivatization of TIQ-15 and new approach to tetrahydroquinoline replacement.

efforts focused on increasing lipophilicity by attenuating the basicity of the 1° and 2° amine moieties of TIQ-15. Various analogs bearing alkyl, amido, benzyl, and heteroaryl substitutions on the 2° nitrogen or the 1° butyl amine of TIQ-15 were synthesized; nevertheless, the parent compound remained the most attractive analog. A critical aspect of this investigation was to improve upon TIQ-15 as an orally administrable compound. To address this, we conducted biotransformation studies of TIQ-15 in human liver microsomes (HLM). Interestingly, these studies revealed no metabolites over 120 min when monitored by LC−MS/MS. Upon incubation with mouse liver microsomes (MLM), rapid metabolism of the tetrahydroquinoline (THQ) ring was observed. In order for an accurate evaluation of our compounds in a mouse model, it was essential to determine the first pass metabolites in MLM for TIQ-15 and tune out that metabolic liability. The biotransformation study with MLM exposed oxidation metabolites of the THQ moiety (M1 and M2, Chart 1) and was monitored by LC−MS/MS.

Chart 1. Metabolism of TIQ-15 in MLM
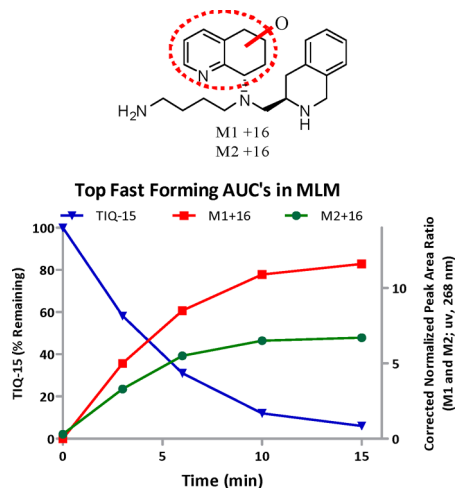
We sought to inhibit MLM metabolism of the THQ by incorporating an oxygen into the ring. Our goal was to improve upon the metabolic stability in both human and mouse liver microsomes while maintaining CXCR4 antagonist potency. Commercially available ketone **1** was transformed to pyran **8** in five synthetic steps (Scheme 1). Reductive amination of ketone **1** and (R)-1-(4-methoxyphenyl)ethan-1-amine **2** followed by

Scheme 1. Synthesis of Pyran Analog 8[a]
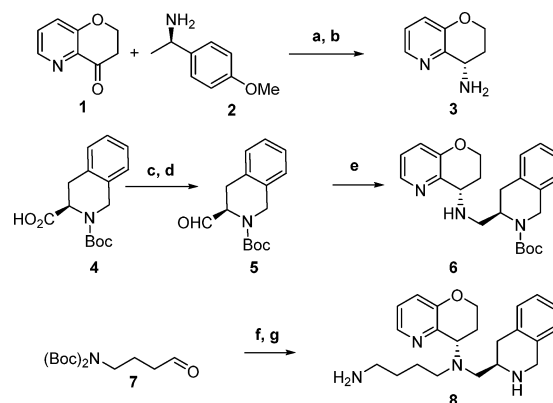
[a]Reagents: (a) Ti(OiPr)$_4$, NaBH(OAc)$_3$, THF, 35%; (b) TFA, DCM 85%, 39%; (c) BH$_3$·Me$_2$S, THF, 90%; (d) (COCl)$_2$, DMSO, Et$_3$N, CH$_2$Cl$_2$, 63%; (e) NaBH(OAc)$_3$, 1,2-DCE, **3**, 77%; (f) NaBH(OAc)$_3$, 1,2-DCE, **6**, 51%; (g) TFA, DCM, 39%.

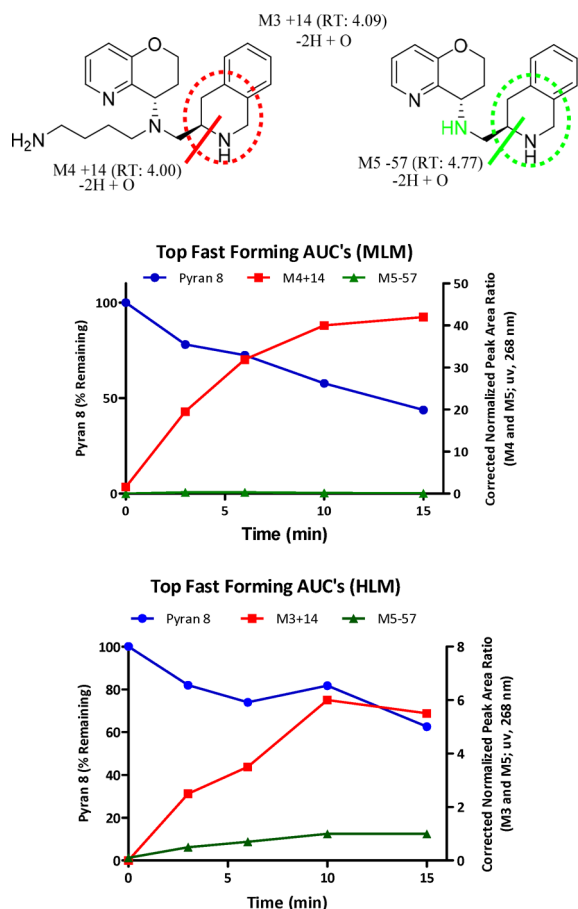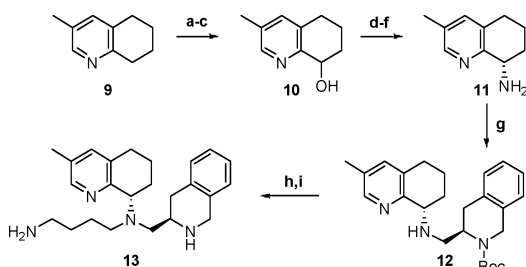trifluoroacetic acid (TFA) mediated removal of the para-methoxybenzyl (PMB) moiety delivered chiral amine **3**.[18,19] Aldehyde **5** was produced from commercially available carboxylic acid **4** via borane reduction to the alcohol and Swern conditions[20] for oxidation. Amine **3** and aldehyde **5** were treated with sodium triacetoxyborohydride in 1,2-dichloroethane to yield secondary amine **6**. A final reductive amination of butyraldehyde **7** and amine **6** with subsequent removal of the carbamate protecting groups revealed pyran analog **8**.

We discovered that our strategy to block metabolism in MLM with pyran **8** shifted the metabolic liability to the THIQ moiety (Chart 2a, MLM). However, comparing **TIQ-15** with pyran **8**, more parent compound remained at 15 min in Chart 2a vs Chart 1. Metabolism of pyran **8** with MLM generated a soft spot that was subjected to oxidation and dehydrogenation as identified by LC−MS fragmentation (**M4**). Incubation of pyran **8** in HLM revealed two distinct metabolites: **M3** and **M5**. **M3** formed due to oxidation and dehydrogenation of the THIQ ring. The formation of **M5** was due to oxidation and dehydrogenation of the THIQ, in combination with a dealkylation of the tertiary amine (**M5**, green circle). The observed metabolism of pyran **8** in MLM and additional HLM metabolites warranted a more extensive SAR to improve microsomal stability.

Incorporation of substituents onto the THQ required long synthetic sequences and limited our ability to conduct efficient SAR studies. For instance, in order to produce a methyl substitution at the 3-position we used the following strategy (Scheme 2). N-Oxidation of 3-methyl tetrahydroquinoline **9** followed by a Boekelheide rearrangement[21] and hydrolysis of the acetyl ester provided alcohol **10**. Swern oxidation followed by the Boggs[12] protocol delivered chiral amine **11**. Two consecutive reductive aminations, first with aldehyde **5** and then butyl aldehyde **7**, delivered the carbamate intermediate that was treated with TFA to afford the desired compound **13**. The final compound **13** was synthesized in nine total steps only to discover that, although CXCR4 potency was retained, mouse liver microsomal stability was significantly worse than TIQ-15 and pyran **8** (Table 1, entries 1−3).

Given the lengthy synthesis required to incorporate substitutions onto the conformationally restricted THQ moiety (**8** and **13**), we chose to access new molecules more rapidly by opening the THQ into substituted 2-(aminomethyl)pyridines,

Chart 2. Metabolism of Pyran 8 in MLM and HLM

Top Fast Forming AUC's (MLM)

Top Fast Forming AUC's (HLM)

Table 1. SAR for Benzylic Methyl (*S*,*R*) Analogs

entry	R	CXCR4	mAChR	LM %[a]		
		Ca^{2+} flux (IC$_{50}$) (nM)	Ca^{2+} flux (IC$_{50}$) (nM)	H	R	M
1	**TIQ-15**	7	>30000	77	37	17
2	**8**	6	>16700	91	3	39
3	**13**	11	>16700	84	7	2
4	H (**16a**)	62	28500	97	77	79
5	3-Me (**16b**)	1710	33000	100	22	11
6	5-Me (**16c**)	24	6100	79	1	5

[a]Liver microsomal stability measured as percent remaining by LC−MS/MS after 10 min in human (H), rat (R), and mouse (M).

ition, etc., as opposed to competition ligand binding assays, which convey no functional information. Since inhibition of CXCR4 signaling was desired, calcium flux assays were more appropriate for initial measurements of on-target activity. Second, allosteric binders can evade detection by competition ligand binding assays that employ labeled orthosteric binders, commonly leading to false negatives. The compounds described herein block the functional response of SDF-1/CXCR4 ligand/ receptor interactions as either orthosteric or allosteric antagonists.

Analogs with benzylic methyl substitution maintaining the same chiral configuration as TIQ-15 (*S*,*R*) were analyzed first (Scheme 3). These compounds were prepared using the

Scheme 2. Synthesis of 3-Methyl THQ Compound 13[a]

[a]Reagents: (a) AcOH, H$_2$O$_2$; (b) Ac$_2$O; (c) K$_2$CO$_3$, MeOH, 35% over 3 steps; (d) (COCl)$_2$, DMSO, Et$_3$N, CH$_2$Cl$_2$, 75%; (e) NaBH(OAc)$_3$, **2**, 1,2-DCE, 61%; (f) TFA, 93%; (g) NaBH(OAc)$_3$, **5**, 1,2-DCE, 70%; (h) NaBH(OAc)$_3$, **7**, 1,2-DCE; (i) TFA, CH$_2$Cl$_2$, 74% over 2 steps.

Scheme 3. Synthesis of Three (*S*,*R*) Analogs[a]

[a]Reagents: (a) NaBH(OAc)$_3$, CH$_2$Cl$_2$, **2** (27−45%); (b) TFA (49−98%); (c) NaBH(OAc)$_3$, **5**, 1,2-DCE (67−80%); (d) NaBH(OAc)$_3$, **7**, 1,2-DCE; (e) TFA, CH$_2$Cl$_2$ (36−61% over 2 steps).

quinolines, and isoquinolines, which were more readily available. Similar studies with pyridine analogs have been conducted using AMD070 as the parent structure, and we anticipated the CXCR4 activity of this new series of compounds to follow a similar trend.[22] However, there have been no reports on microsomal stability for these molecules. The properties that we sought to improve upon were (1) inhibition of SDF-1 induced Ca^{2+} flux and (2) liver microsomal stability while avoiding off target interactions, such as mAChR[23] inhibition. Intracellular calcium release is a basic functional assay that measures GPCR activity and inhibition thereof. Calcium flux assays were chosen over ligand binding assays as the primary on-target screen for several reasons. First, calcium flux assays are functional assays that give information regarding receptor activation, potentiation, inhib-
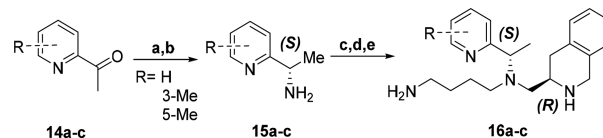
procedure adapted from Boggs et al.[12] Reductive aminations with **2** and 2-acetylpyridines **14a−c** provided a mixture of diastereomers with an approximate ratio of 4:1 favoring the desired (*S*,*S*) conformation. The (*S*,*S*) diastereomer was separated via column chromatography followed by recrystallization in hexanes to provide X-ray quality crystals, which were used to assign the absolute stereochemistry (see Supporting Information). TFA mediated removal of the PMB moiety revealed chiral amino pyridines with the desired (*S*) configuration **15a−c**. The chiral amines **15a−c** were reacted as described previously in successive reductive aminations with aldehyde **5**, then **7**, followed by carbamate deprotection protocol to furnish compounds **16a−c**.

The assay results from compounds **16a−c** (Table 1, entries 4−6) provided unexpected data. The potency (IC$_{50}$) for these compounds was defined as the concentration of the compound

required to inhibit 50% of the SDF-1 induced Ca^{2+} signaling. Unsubstituted pyridine **16a** revealed a 10-fold decrease in CXCR4 potency in comparison to **TIQ-15**, while significantly increasing microsomal stability (Table 1, entry 4). The 3-methylpyridine **16b** exhibited nearly a 100-fold loss in CXCR4 potency and a substantial reduction in RLM and MLM stability. The loss in CXCR4 potency could be due to steric clash between the benzylic methyl and the 3-methyl substituent, which might hinder the molecule from attaining the appropriate conformation for receptor binding. Conversely, the 5-methylpyridine **16c** showed a 3-fold improvement in potency compared to **16a**, but liver microsomal stability suffered. Initially, the pyridine moiety **16a** validated that an open framework could improve metabolic stability and maintain decent potency; however, introducing additional methyl groups onto this framework (**16b** and **16c**) proved to be deleterious to RLM and MLM stability. Compound **13** corroborates this result by showing a marked decrease in mouse liver microsomal stability compared to pyran **8**. Continuing with our analysis of pyridine substituents, we chose to remove the (S) chiral center and utilized substituted pyridine-2-carboxaldehyde moieties as starting materials. These building blocks provided access to monosubstituted 2-(aminomethyl)-pyridines, eliminating two synthetic steps and providing a more rapid production and analysis pipeline.

In our open scaffold series, compounds **19a−s** could be obtained after a simple reductive amination with commercially available pyridine carboxaldehydes **17a−s** and butyl amine **18** using STAB-H in 1,2-dichloroethane (Scheme 4). A subsequent

Scheme 4. Synthetic Sequence To Access Open Scaffold[a]
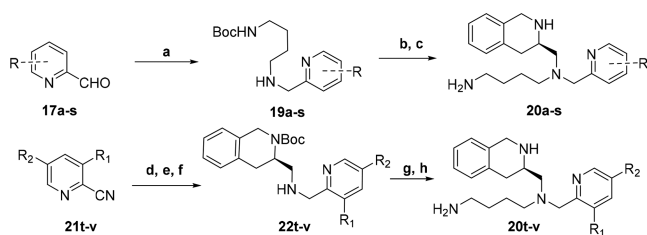
[a]Reagents: (a) NaBH(OAc)$_3$, H$_2$N(CH$_2$)$_4$NHBoc (**18**), 1,2-DCE (29−83%); (b) **5**, NaBH(OAc)$_3$, 1,2-DCE; (c) TFA, CH$_2$Cl$_2$ (56−86% over 2 steps); (d) NiCl$_2$·6H$_2$O, NaBH$_4$, Boc$_2$O, MeOH, 0 °C to rt; (e) TFA, CH$_2$Cl$_2$ (55−78% over 2 steps); (f) **5**, NaBH(OAc)$_3$, 1,2-DCE (57−82%); (g) NaBH(OAc)$_3$, **7**, 1,2-DCE; (h) TFA, CH$_2$Cl$_2$ (31−58% over 2 steps).

reductive amination with the secondary amines **19a−s** and aldehyde **5** followed by carbamate removal furnished final compounds **20a−s**. The 3,5-disubstituted pyridine series **20t−v** was obtained via the 2-cyano-pyridine derivatives **21t−v**. The cyano group was reduced using nickel boride prepared *in situ* in the presence of di-*tert*-butyl dicarbonate to yield the Boc-protected primary amines.[24] TFA mediated deprotection followed by consecutive reductive aminations with **5**, then **7**, and a final deprotection provided the finished compounds **20t−v**.

Overall, 22 molecules with various functional group substitutions on the pyridine moiety were synthesized and screened for (1) improved potency in a CXCR4 Ca^{2+} flux assay, (2) limited off-target interaction with mAChR receptor, and (3) increased liver microsomal stability (Table 2). In comparison to the constrained moieties (Table 1, entries 1−3), the open

Table 2. Open Scaffold SAR

compound	R	CXCR4 Ca^{2+} flux (IC$_{50}$) (nM)[a]	mAChR Ca^{2+} flux (IC$_{50}$) (nM)	LM %[b] H	R	M
20a	H	230	11500	100	33	77
20b	2-quin	5751	>16700	88	8	35
20c	1-isoquin	8721	4350	88	5	62
20d	3-isoquin	3307	>16700	100	31	45
20e	6-Me	2902	10700	100	34	ND
20f	5-Me	71	23200	100	3	67
20g	4-Me	698	3000	87	30	74
20h	3-Me	21	5900	86	33	64
20i	5-Cl	631	>16700	89	5	56
20j	4-Cl	>33000	>33000	89	31	ND
20k	3-Cl	1855	>16700	100	14	43
20l	5-F	260	>33000	88	10	76
20m	3-F	2116	>16700	83	9	64
20n	5-OMe	>23000	>27000	92	13	69
20o	3-OMe	>33000	>33000	100	38	99
20p	5-CF$_3$	>33000	>21000	98	8	85
20q	3-CF$_3$	406	>33000	100	66	82
20r	3-cPr	163	>16700	90	29	56
20s	3-vinyl	484	>16700	86	4	44
20t	3,5-diMe	69	>33000	100	39	79
20u	3-Me-5-F	127	>33000	100	36	91
20v	5-Me-3-F	323	11,630	86	18	51

[a]See Supporting Information for standard deviation. [b]Liver microsomal stability measured as percent remaining by LC−MS/MS after 10 min in human (H), rat (R), and mouse (M). ND = not determined.

scaffold markedly improved upon metabolic stability albeit with a slight drop in CXCR4 antagonist activity, exemplified by **20h**.

When comparing the unsubstituted pyridine analog **20a** with the unsubstituted quinoline analogs **20b−20d**, the pyridine was determined to be the superior antagonist. Establishing the pyridine as higher priority, we began by substituting a methyl group at each position of the pyridine **20e−20h**. We observed that the 5-methyl (**20f**, 71 nM) and 3-methyl (**20h**, 21 nM) substituents demonstrated the greatest potency and improved MLM stability. At this point, our focus was to test different functional groups (electron donating and electron withdrawing) at the 3- and 5-positions to evaluate the effect on CXCR4 potency. Halogen (Cl, F) substitution was best suited at the 5-position (**20i**, **20l**), whereas 3- or 5-methoxy (**20n**, **20o**) and 5-trifluoromethyl **20p** substituted analogs were inactive. Interestingly, a 3-trifluoromethyl **20q** substituent retained moderate activity as well as 3-vinyl **20s** and 3-cyclopropyl **20r**, which were alkyl modifiers, in an attempt to improve upon the properties associated with the 3-methyl substituted compound **20h**. The 3,5-dimethyl analog **20t** was equipotent to **20f** but elicited weaker inhibition of muscarinic acetylcholine receptor compared to **20h**. Compound **20t** also had an enhanced stability in HLM and MLM. It was posited that a synergistic effect would be observed between analogs **20h** and **20l** if the 5-methyl group was exchanged with a fluorine **20u**. We observed a 5-fold reduction in CXCR4 activity for **20u**, compared to **20h**, but we benefitted from a loss in muscarinic activity and increased microsomal

stability. Substituted thiazoles were also tested, but compounds containing these moieties were inactive in the CXCR4 Ca^{2+} flux assay (see Supporting Information).

Additional parameters including parallel artificial membrane permeability assay (PAMPA) and cytochrome P450 (CYP450) inhibition were analyzed. Unfortunately, we observed little to no passive membrane permeability. In the CYP450 assays, inhibition resulting from this chemotype was solely observed on isoform 2D6 (see Supporting Information). Overall, the open methyl-substituted pyridine analogs showed a modest decrease in CXCR4 activity; however, they showed promise due to the increased microsomal stability compared to TIQ-15. This suggests that a more robust compound could be derived from an open pyridine analog.

In summary, we have developed a series of CXCR4 antagonists that possess increased liver microsomal stability in human and mouse models compared to the parent molecule TIQ-15. Specifically, compounds **20c**, **20e**, and **20t** bearing methyl substituents around a pyridylmethyl moiety seem to be the most promising. Ultimately, we have significantly progressed this scaffold and intend to continue to improve upon the membrane permeability (PAMPA, Caco-2) and reduce CYP450 activity of this series. This and other studies will be presented in due course.

■ ASSOCIATED CONTENT

ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmedchemlett.7b00381.

Experimental and characterization data for all new compounds and all biological data (PDF)

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■ ABBREVIATIONS

CXCR4, CXC chemokine receptor type 4; GPCR, G protein-coupled receptor; CXCL12, CXC chemokine ligand type 12; THQ, 5,6,7,8-tetrahydroquinoline; THIQ, 1,2,3,4-tetrahydroisoquinoline; HLM, human liver microsomes; RLM, rat liver microsomes; MLM, mouse liver microsomes; PMB, *para*-methoxybenzyl; TFA, trifluoroacetic acid; DCE, 1,2-dichloroethane; mAChR, muscarinic acetylcholine receptor; STAB-H, sodium triacetoxyborohydride; PAMPA, parallel artificial membrane permeability assay

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