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Synthesis and structure-activity relationships of a series 4-methoxy-3-(piperidin-4-yl)oxy benzamides as novel inhibitors of the presynaptic choline transporter

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Abstract

The synthesis and SAR of 4-methoxy-3-(piperidin-4-yl) benzamides identified after a high-throughput screen of the MLPCN library is reported. SAR was explored around the 3-piperidine substituent as well as the amide functionality of the reported compounds. Starting from the initial lead compounds, **1-7**, iterative medicinal chemistry efforts led to the identification of ML352 (**10m**). ML352 represents a potent and selective inhibitor of CHT based on a drug-like scaffold.

Keywords

MLPCN; ML352; Choline transporter; CHT; Structure-activity relationship

Acetylcholine (ACh) is a neurotransmitter that has effects as a neuromodulator on a variety of physiological and behavioral functions including movement, cardiovascular activity, gut motility, arousal, attention, mood and memory.¹ Accordingly, genetic variation and/or environmental perturbations in components of cholinergic signaling are associated with myasthenias, tachycardia, attention deficit hyperactivity disorder (ADHD), schizophrenia, depression and Alzheimer's disease.² Much of the research has been targeted at potentiation of the cholinergic signaling through the use of acetylcholinesterase inhibitors (AChE), which remains the standard of care for Alzheimer's disease.³ An important and

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underexplored protein that controls cholinergic signaling capacity is the presynaptic, high-affinity choline transporter (CHT), which, in humans, is encoded by the *SLC5A7* gene.^{4,5} Genetic alterations in CHT have been implicated in risk for neuromuscular, cardiovascular, cognitive, and mood disorders.^{6,7,8,9} CHT mediated choline transport is sodium- and chloride-dependent and is essential for the uptake of choline for ACh synthesis in neurons.^{10,11,12,13} Unfortunately, the only small molecule available that targets CHT is hemicholinium-3 (HC-3) (Figure 1), a highly toxic, quaternary ammonium containing molecule.¹⁴ HC-3 is less than ideal as a tool compound due to its poor CNS penetration, its off-target interactions, and, as a result of its competitive nature, the need to use high concentrations *in vivo* to overcome the high choline concentrations in extracellular fluid. Thus the development of novel tool compounds which afford noncompetitive CHT inhibition would be beneficial to the research community in order to further explore the role of CHT in cholinergic signaling.

We utilized a membrane depolarization assay developed in the Blakely lab, coupled with a human CHT LVAA (cytoplasmic C-terminus Leu530Ala and Val531Ala) cell line in an effort to identify small molecule inhibitors of CHT.¹⁵ The high-throughput screen¹⁶ was performed at the Johns Hopkins Ion Channel Center (JHICC) and used the >300000 NIH Molecular Library Small Molecule Repository (MLSMR) compound collection. Compounds were screened in a triple add protocol where depolarization responses were collected for compound or vehicle in the context of either: 1) no choline, 2) an EC₂₀ concentration of choline, or 3) an EC₈₀ concentration of choline. From this screen, a series of 4-methoxybenzamides were identified for transition into a lead optimization campaign (Table 1). This series and the rest of the compounds presented in this manuscript were tested in a radiolabeled choline uptake assay in a heterologous system utilizing HEK cells stably transfected with an endocytic mutant of human CHT to determine their potency.^{15b} In these assays, CHT is exposed to [³H]choline in the presence or absence of potential inhibitor compounds, CHT transports [³H]choline into the cells, and then the amount of choline transported is quantified by scintillation spectrometry. In Table 2, we present the % Activity remaining and IC₅₀s of compounds determined in the radiolabeled choline uptake assays at two concentrations of choline chloride. By testing at these concentrations, 100nM (low) and 10μM (high), a quick evaluation of the mechanism of inhibition of these compounds could be revealed. Potential noncompetitive compounds would decrease in the uptake of choline at the high and low substrate concentration whereas competitive inhibitors would show significant inhibition at the low concentration of substrate, indicating no change in the V_{max} of choline transport.

The synthesis of the lead scaffold followed known procedures and is outlined in Scheme 1. The commercially available 3-hydroxy-4-methoxybenzoic acid, **8**, was converted to the appropriate amide, **9**, via HATU coupling conditions.¹⁷ The common intermediate amide, **9**, could then be converted to the final compounds by either: a) standard Mitsunobu conditions (R₂OH, DEAD, PPh₃),¹⁸ or b) through a standard displacement reaction (R₂Br, Cs₂CO₃, KI, DMF). The final compounds, **10a-o**, were isolated in modest to good yield.

The SAR assessment started with the evaluation of the right-hand amide portion of the molecule (Table 2). As many of these compounds were available from commercial sources,

the SAR was performed via a combination of SAR by catalog and synthesis. The compounds were evaluated in a [^3H]choline transport assay with human CHT transfected HEK-293 cells utilizing a low (100 nM, sub- K_M) and high (10 μM , V_{max}) concentration of choline. All compounds were evaluated for % activity remaining at both concentrations of choline (with a standard 5 μM concentration of compound), and those compounds that <50% activity remaining were then progressed to CRC formats for IC_{50} determinations, again, at both concentrations. Since the lead compound from the HTS evaluation contained an isoxazole ring system, our first compounds evaluated similar 5-membered heteroaryl groups (**10a-h**). The thiazole and pyrazole compounds (**10a,b,d**) were active at both choline concentrations, albeit with modest potency ($> 1 \mu\text{M}$). Thiophene analog (**10c**) was inactive at the low concentration and displayed modest inhibitory activity at the high concentration. 3-Isopropylisoxazole methyl derivative, **10e**, a compound similar to the HTS hit compound was very potent at both concentrations (240 nM and 100 nM at the low and high choline concentrations, respectively). Moving to a six-membered heteroaryl (**10i**) or extending the chain length (**10j-k**) was only moderately tolerated.

Having evaluated and identified an optimal amide group, we next turned our attention to the 4-isopropylpiperidine ether moiety (Table 3). The synthesis of these compounds follows that outlined in Scheme 1. The SAR around this portion of the molecule was quite narrow as substituents such as the cyclohexyl, **10o**, and cyclopentyl, **10p**, were inactive. Replacements that were tolerated included the (2-piperidin-1-yl)ethoxy, **10q**, ($\text{IC}_{50} = 0.76$ and $0.53 \mu\text{M}$, respectively) and 2-morpholinoethoxy, **10r**, ($\text{IC}_{50} = 6.12$ and $1.77 \mu\text{M}$, respectively). However, the morpholine was ~10-fold less active than the piperidine analog. Removal of the isopropyl group from the piperidine ether led to a much less active compound (NH, **10l**). However, the methylpiperidine ether analog, **10m**, was an active compound – equipotent with the isopropyl analog. Moving the *N*-methylpiperidine from the 4-position to the 3-position, **10n**, was tolerated, but less active. Lastly, the unsubstituted phenol, **10v**, was inactive. Based on the potency at both concentrations of choline studied, **10m**, was declared an MLPCN probe compound, ML352 and further profiled as outlined below.¹⁹

Having identified a potent CHT inhibitor, we next profiled a number of the analogs in a variety of selectivity and DMPK assays in order to inform the community on the use of ML352 and its analogs. ML352 was tested in EuroFin's Lead Profiling Screen which is a binding assay panel of 68 GPCR's, ion channels and transporters screened at 10 μM . ML352 did not show any significant inhibition of any of the targets (significant activity constitutes $>50\%$ inhibition at 10 μM), highlighting a clean ancillary pharmacology profile.¹⁶ In addition, ML352 was tested against the dopamine transporter (DAT) and did not show any inhibitory activity at the highest concentration tested.¹⁶

Next, ML352 and its analogs were tested in a battery of pharmacokinetic assays (Table 4) including an assessment of intrinsic clearance (CL_{INT}) in liver microsomes and plasma protein binding in the mouse. The previous work on ML352 concentrated on rat PK properties.¹⁶ ML352 was shown to have low-to-moderate intrinsic clearance in the mouse ($\text{CL}_{\text{INT}} = 43.7 \text{ mL/min/kg}$ using 87.5 g liver/kg of body weight) with subsequent low predicted hepatic clearance ($\text{CL}_{\text{HEP}} = 29.4 \text{ mL/min/kg}$ using 90 mL/min/kg for mouse liver blood flow). Interestingly, the closely related analog, **10e** (isopropyl analog) was highly

cleared in liver microsomes, $CL_{INT} = 781$ mL/min/kg. Compound **10f** (pyrazole analog) also displayed low intrinsic clearance ($CL_{INT} = 29.9$ mL/min/kg) and predicted hepatic clearance ($CL_{HEP} = 22.4$ mL/min/kg). ML352 possesses excellent free fraction in mouse (0.48) as did all of the analogs tested ($>0.30, f_u$) in mouse equilibrium dialysis plasma protein binding studies. In addition, all of the analogs tested displayed low potential for human cytochrome P450 inhibition as demonstrated by IC_{50} values for 1A2, 2C9, 2D6, 3A4 being >10 μ M, except for compound **10f** against 2D6 (6.7 μ M). Moreover, ML352 was highly soluble in PBS (98.2 μ M).¹⁶ Lastly, ML352 and analogs were evaluated in a cassette tissue distribution study in mice. ML352 was shown to have low B:P (brain:plasma ratio) in this study (0.28), similar to results in the rat.¹⁶ Of all the analogs tested in mice, ML352 and **10k** had the highest B:P and total brain concentrations.

In conclusion, we have explored the SAR around a series of 3-methoxy-4-(piperidin-4-yl)oxy benzamides as inhibitors of the choline transporter. Within this series, it was noted that benzylic heteroaromatic amide moieties were the most potent. In addition, 3-(piperidin-4-yl)oxy substituents were favored over alkyl ether changes. From this work, ML352 was discovered as a potent inhibitor of CHT at both a low and high concentration of choline (100 nM and 10 μ M, respectively), which is consistent with noncompetitive inhibition.¹⁶ In addition, we have characterized ML352 and additional analogs in a variety of selectivity and *in vitro* and *in vivo* DMPK studies. Further studies to determine the reversibility and binding mode (orthosteric or allosteric), and the calculated free brain CHT inhibitor concentrations, are on-going and will be reported in due course.

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19. **3-hydroxy-N-((3-isopropylisoxazol-5-yl)methyl)-4-methoxybenzamide (9)**. To a round-bottomed flask was added 3-hydroxy-4-methoxybenzoic acid (**1**) (0.43 g, 2.55 mmol, 1.0 eq), (3-isopropylisoxazol-5-yl)methanamine hydrochloride (0.45 g, 2.55 mmol, 1.0 eq), Hünig's base (1.33 mL, 7.65 mmol, 3.0 eq) and DMF (15 mL) at rt. To the solution was added HATU (0.97 g, 2.55 mmol, 1.0 eq). After 8 h at rt, the rxn was added to EtOAc:H₂O (1:1, 150 mL). The separated organic layer was washed with 1N HCl (50 mL), H₂O (2 × 50 mL), Brine (50 mL) and dried (MgSO₄). The mixture was filtered and the solvent removed under reduced pressure. The material was taken forward without further purification. LCMS: R_T = 0.766 min, >98% @ 215 and 254 nM, m/z = 290.8 [M + H]⁺. **N-((3-isopropylisoxazol-5-yl)methyl)-4-methoxy-3-((1-methylpiperidin-4-yl)oxy)benzamide (10m, ML352)**. To a solution of PPh₃ (0.72 g, 2.76 mmol, 2.0 eq) in THF (15 mL) at 0°C was added diethyl azodicarboxylate (DEAD) (0.44 mL, 2.76 mmol, 2.0 eq), followed by 4-hydroxy-N-methylpiperidine (0.27 g, 2.33 mmol, 1.7 eq). After 15 min, a solution of **9** (0.40 g, 1.37 mmol, 1.0 eq) in THF (5 mL) was added and the ice bath was removed. After an additional 24 h at rt, the rxn was added to EtOAc:H₂O (1:1, 200 mL). The separated organic layer was washed with H₂O (50 mL), Brine (50 mL) and dried (MgSO₄). The mixture was filtered and the solvent removed under vacuo. The residue was purified by reverse-phase HPLC (15-55% acetonitrile: H₂O w/ 0.1% TFA) to afford **10m, ML352** (0.29 g, 55% yield over 2 steps). LCMS: R_T = 0.741 min, >98% @ 215 and 254 nM, m/z = 387.8 [M + H]⁺; ¹H NMR (500 MHz, 333K, DMSO-d₆): δ 8.81 (t, J = 5.8 Hz, 1 H), 7.60 (d, J = 8.4 Hz, 1 H), 7.56 (br s, 1 H), 7.10 (d, J = 8.5 Hz, 1 H), 6.24 (s, 1 H), 4.62-4.40 (m, 1 H), 4.54 (d, J = 5.7 Hz, 2 H), 3.85 (s, 3 H), 3.55-3.29 (m, 4 H), 2.96 (septet, J = 7.0 Hz, 1 H), 2.82 (br s, 3 H), 2.26-1.74 (m, 4 H), 1.20 (d, J = 7.0 Hz, 6 H); HRMS, calc'd for C₂₁H₃₀N₃O₄ [M + H]⁺, 388.2236; found 388.2238.

Figure 1.
Structure of hemicholinium-3 (HC-3).

Scheme 1.

Reagents and conditions: (a) R-NH₂, HATU, DIEA, DMF, rt; (b) R₂OH, DEAD, PPh₃, THF, 0 °C → rt, **41–59%**; (c) R₂Br, Cs₂CO₃, KI, DMF, 120 °C, 30 min, μ W, **23–93%**.

Table 1

Structures of initial benzamide scaffold.

Cmpd	R	R ¹	R ²	IC ₅₀ (μM) ^a
1		H		1.26
2	H			4.22
3	OMe			3.36
4	OMe			4.47
5	OMe			3.16
6	OMe			0.60
7	OMe			0.76

^aIC₅₀'s were generated from the membrane depolarization assay utilizing HEK 293 cells stably transfected with an endocytic mutant of human CHT. 10-point concentration response curves were performed at 100 nM choline concentration

Table 2

SAR of the right-hand amide analogs.

Cmpd	R ²	% Activity remaining ^d			Choline concentration			IC ₅₀ (μM) ^d	
		100 nM	10 μM	10 μM	100 nM	10 μM	10 μM	100 nM	10 μM
10a		42.2	13.2	3.48 ± 0.40	1.02 ± 0.06				
10b		42.6	18.9	4.93 ± 1.40	1.64 ± 0.30				
10c		76.4	36.7	-	-				
10d		49.9	29.4	8.09 ± 0.80	2.51 ± 0.22				
10e		10.9	-2.8	0.24 ± 0.05	0.10 ± 0.02				
10f		45.8	15.9	1.58 ± 0.29	0.91 ± 0.11				
10g		41.8	24.8	9.27 ± 1.83	1.85 ± 0.17

Cmpd	R ²	% Activity remaining ^a				IC ₅₀ (μM) ^a			
		Choline concentration							
		100 nM	10 μM	100 nM	10 μM	100 nM	10 μM	100 nM	10 μM
10h		64.8	47.5	-	-	-	-	-	-
10i		87.7	71.8	-	-	-	-	-	-
10j		37.4	9.9	2.13 ± 0.22	1.56 ± 0.14	-	-	-	-
10k		46.3	20.4	4.12 ± 1.36	1.73 ± 0.28	-	-	-	-

^aIC₅₀'s were generated from radiolabeled choline chloride uptake experiments in HEK 293 cells stably transfected with an endocytic mutant of human CHT. 10-point concentration response curves were performed in triplicate with 2-fold dilutions starting from the maximal concentration (20 μM). Inhibition definition: The compound will be defined as inactive if greater than 50% of basal activity remains at 5 μM compound concentration at 100nM choline chloride solution. Otherwise, the compound will be defined as an inhibitor with the calculated IC₅₀ value. IC₅₀ values are expressed as IC₅₀ ± SD, using estimated standard deviations provided by the fitting software (Origin 6.0).

Table 3

SAR evaluation of the piperidine replacements.

Cmpd	R ¹	% Activity remaining ^a				IC50 (μM) ^a			
		Choline concentration				Choline concentration			
		100 nM	10 μM	100 nM	10 μM	100 nM	10 μM	100 nM	10 μM
10l		51.5	18.6	-	-	-	-	-	-
10m ML352		3.1	-0.9	0.51 ± 0.83	0.09 ± 0.01				
10n		51.7	18.4	1.25 ± 0.27	4.54 ± 2.85				
10o		83.2	87.6	-	-				
10p		82.0	81.3	-	-				
10q		38.3	-0.2	0.76 ± 0.70	0.53 ± 0.40				
10r		36.7	32.1	6.12 ± 6.47	1.77 ± 0.25				
10s		59.7	28.2	-	-				
10t		50.1	29.8	-	-

Cmpd	R ¹	% Activity remaining ^a			IC ₅₀ (μM) ^a		
		Choline concentration					
		100 nM	10 μM	100 μM	100 nM	10 μM	10 μM
10u		99.8	89.4	-	-	-	-
10v	H	86.2	99.4	-	-	-	-

^aIC₅₀'s were generated from radiolabeled choline chloride uptake experiments in HEK 293 cells stably transfected with an endocytic mutant of human CHT. 10-point concentration response curves were performed in triplicate with 2-fold dilutions starting from the maximal concentration (20 μM). Inhibition definition: The compound will be defined as inactive if greater than 50% of basal activity remains at 5 μM compound concentration at 100nM choline chloride solution. Otherwise, the compound will be defined as an inhibitor with the calculated IC₅₀ value. IC₅₀ values are expressed as IC₅₀ ± SD, using estimated standard deviations provided by the fitting software (Origin 6.0).

Table 4

In vitro and *in vivo* pharmacokinetic properties of ML352 and analogs

	10m, ML352	10q	10b	10k	10e	10f
MW	387.2	401.5	403.2	411.3	415.2	428.3
cLogP	2.49	2.85	4.11	3.56	3.41	3.82
TPSA	77.1	77.1	63.7	63.7	77.1	68.6

<i>In vitro PK parameter, mouse^a</i>						
CL _{INT} (mL/min/kg)	43.7	167	979	106	781	29.9
CL _{HEP} (mL/min/kg)	29.4	58.4	82.4	48.8	80.7	22.4
PPB (f _u)	0.48	0.71	0.39	0.35	0.57	0.57

Cytochrome P450 inhibition (IC ₅₀ , μM)						
1A2	>30	>30	10.3	>30	>30	>30
2C9	>30	>30	>30	>30	>30	>30
2D6	>30	>30	>30	27.1	>30	6.7
3A4	>30	>30	>30	28.2	>30	>30

Tissue Distribution (1.0 mg/kg per compound intraperitoneal cassette dose to mice, 10%EtOH:85%PEG400:5%DMSO, n = 3)						
Plasma (ng/mL)	15.5	25.9	8.8	4.3	10.5	12.8
Brain (ng/g)	3.3	1.8	1.5	4.0	BLQ	BLQ
Mean B:P	0.28	0.07	0.19	1.1	<0.06	<0.05

BLQ=Below level of quantitation