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Original article

Synthesis and evaluation of oxime derivatives as modulators for amyloid beta-induced mitochondrial dysfunction

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ABSTRACT

Starting from quinuclidinyl oxime **1** identified by preliminary screening, a series of azacycles-containing oxime derivatives was synthesized. Their mPTP blocking activities were evaluated by a JC-1 assay, measuring the change of mitochondrial membrane potential. The inhibitory activity of nine compounds against amyloid beta-induced mPTP opening was comparable or even superior to that of piracetam. Among them, **12d** effectively maintained mitochondrial function and cell viabilities on the ATP assay, the MTT assay, and the ROS assay. In addition, it exhibited favorable in vitro stability and pharmacokinetic characteristics, which hold a promise for further development of AD therapeutics.

1. Introduction

Alzheimer's disease (AD) is a progressive, neurodegenerative disorder, characterized by an age-dependent loss of memory and an impairment of multiple cognitive functions [1]. Although the mechanism of AD pathogenesis is largely unknown, deposition of extracellular amyloid beta (Aβ) plaques and formation of intracellular neurofibrillary tangles (NFT's) in brain of AD patients suggested that amyloid beta plays a pivotal role in the pathophysiology of AD [2]. It has been studied that amyloid beta is associated with a diverse range of neuronal properties including loss of neuron, synapses and synaptic function, mitochondrial abnormalities and inflammatory responses [3]. Despite its various impacts on neurons, increasing evidence indicated that amyloid beta is accumulated in mitochondria of the AD brain, which is responsible for mitochondrial dysfunction and oxidative damage ultimately resulting in structural and functional damage of AD neurons [4]. Therefore, modulation of mitochondrial proteins related to amyloid beta-induced mitochondrial dysfunction might be viable therapeutic strategies for the prevention and treatment of AD.

The effects of amyloid beta on mitochondria have not been fully elucidated, but recent reports show that mitochondrial permeability transition pore (mPTP) is involved in mitochondrial dysfunction induced by amyloid beta toxicity [5]. The mPTP is a multiprotein complex that is formed in the inner membrane of the mitochondria under certain pathological conditions such as oxidative stress, ischemia, stroke, and traumatic brain injury [6]. The opening of the mPTP allows uncontrolled transport in and out of mitochondria for molecules with molecular weight of less than 1.5 kDa. Structurally, it comprises three major components: a voltage-dependent anion channel (VDAC) in the outer membrane, the adenine nucleotide translocator (ANT) in the inner membrane, and cyclophilin D (CypD) in the mitochondrial matrix. In the

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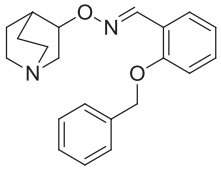
normal state of mPTP, reversible opening and closing of the mPTP is regulating the membrane potential, which maintains calcium homeostasis in the cell. However, an accumulation of soluble amyloid beta in AD neurons induces excessive calcium entry into cytosol resulting in elevated calcium level of mitochondria. High localization of calcium in mitochondria promotes the opening of the mPTP, which causes severe mitochondrial swelling, outer membrane rupture and incapability of ATP production. Finally, a release of proapoptotic proteins accompanied by mPTP opening leads to neuronal cell death [7–9].

Cyclosporin A (CsA), a cyclic nonribosomal peptide clinically used as an immunosuppressant, specifically inhibits the mPTP by binding to CypD in the matrix side of the inner mitochondrial membrane [10,11]. *N*-Methyl-4-isoleucin cyclosporin A (NIM811), a non-immunosuppressant analog of CsA, is also reported as a potent inhibitor of the mPTP in isolated liver mitochondria [12]. Although these compounds are effectively blocking the activity of the mPTP, they are not useful for therapeutics because the delivery of peptide to the brain is limited by poor bioavailability and low BBB (blood brain barrier) penetration. On the other hand, it has been reported that Dimebon, an antihistamine drug, blocks the mPTP opening and protects neurons against amyloid beta-induced cell death although the mechanism of action is not completely understood [13–15]. Currently, however, there are no safe and selective mPTP blockers available for therapeutic application to AD treatment. Therefore, given the increasing evidence of protective role of mPTP inhibition in regulating amyloid beta-induced mitochondrial dysfunction, nonpeptidyl mPTP blockers should be further developed for their potential as pharmacological therapeutics in clinical treatment of AD. Herein, we report the discovery of novel oxime derivatives that inhibit the activity of the mPTP, which is a potential drug target for treatment of AD.

2. Results and discussion

Initially, we identified quinuclidinyl oxime **1** as an mPTP blocker by screening the KIST chemical library (Fig. 1). The activity to block the mPTP opening induced by amyloid beta was evaluated using a cell-based JC-1 assay by measuring the change of mitochondrial membrane potential [16,17]. The color shift from green to red as the membrane potential increases indicates the recovery of mitochondrial function responding to applied amyloid beta toxicity. In fact, compound **1** exhibited 59% of increased green to red ratio, which means that it was able to reduce 41% of mitochondrial damage induced by amyloid beta. Along with this good in vitro inhibitory activity against mPTP opening, the in vitro stability of **1** on plasma and microsomes was examined to show that it has good plasma and metabolic stability. However, the pharmacokinetic parameters for compound **1** following intraperitoneal and oral administration in rat and mice suggested that the level of drug exposure (AUC) is not appropriate for therapeutic agents although compound **1** exhibited good permeability to the brain tissue.

On the basis of the preliminary data of the hit compound **1**, we decided to synthesize the analogs of compound **1** to improve pharmacokinetic profile as well as in vitro efficacy. To verify the effect of the 2-benzyloxyphenyl moiety on mPTP blocking activity, quinuclidinyl oxime derivatives containing a wide range of substituents on the aromatic region were initially synthesized as shown in Scheme 1. Quinuclidine hydroxylamine hydrochloride **4** was synthesized by Mitsunobu reaction and hydrazinolysis followed by salt formation. Next, we performed condensation reaction of **4** with either commercially available substituted benzaldehydes or the substituted benzyloxybenzaldehydes, easily prepared from O-alkylation of various benzyl halides with salicylaldehyde. The JC-1 assay data of the synthesized oxime derivatives **5** and **6** were



1

JC-1 assay: 59% (increased g/r ratio @ 5 μM)

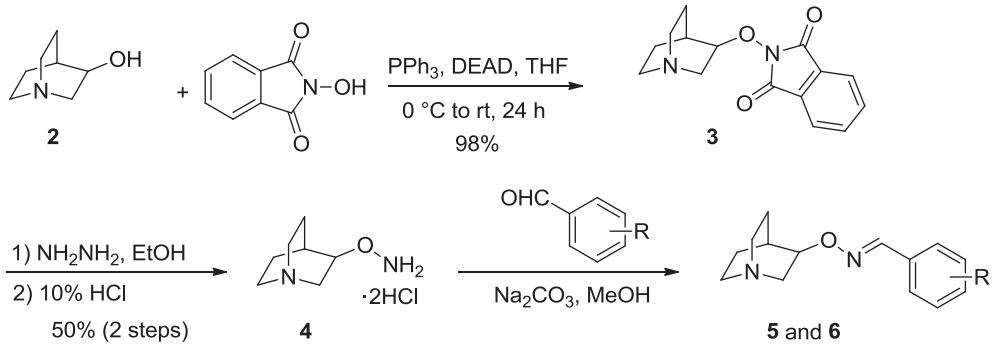
Plasma stability: < ±15% for 2 h

HLM stability: 85% (% remaining @ 1 h)

PK parameters	PO (10 mg/kg, ICR mice, n = 3)	IP (3 mg/kg, SD male rats, n = 3)
$AUC_{0-\infty}$(μg min/ml)	-	59.41±8.19
AUC_{last} (μg min/ml)	31.49	55.77±7.79
Terminal half-life (min)	-	365.8±1.0
C_{max} (μg/ml)	0.330	0.524±0.036
T_{max} (min)	5	25(19-31) [b]
B/P ratio (%)	273.0 ± 33.4	-

$AUC_{0-\infty}$, total area under the plasma concentration–time curve from time zero to time infinity; AUC_{last}, total area under the plasma concentration–time curve from time zero to last measured time; C_{max}, peak plasma concentration; T_{max}, time to reach C_{max}: PO, oral administration; IP, intraperitoneal administration; B/P ratio, brain to plasma ratio

Fig. 1. Structure and pharmacological profile of compound **1**.



Scheme 1. Synthesis of the quinuclidinyl oxime derivatives **5** and **6**.

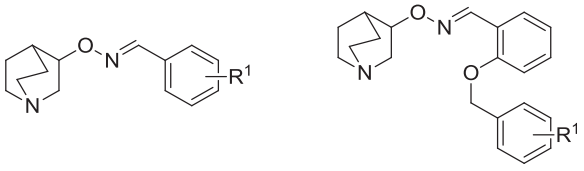
determined and listed in Table 1. Unfortunately, we observed that the lowest increased green/red ratio in the JC-1 assay was only 69% (**6j**, R^1 = 2,4-diCl), indicating the mPTP blocking activities of **5a**–**k** and **6a**–**m** are less potent than that of **1**. This result suggested that the aromatic moiety in this series may have a negative effect on the inhibitory activity against mPTP opening (Table 1).

In order to further investigate the structure activity relationship (SAR), we then decided to modify the other side of compound **1** by replacing the quinuclidine segment with monocyclic tertiary amines such as *N*-alkyl-pyrrolidines or piperidines. It was known that such a simple azacycle could be a stable precursor for quinuclidine synthesis or a common intermediate of quinuclidine metabolism [18]. Thus, the second class of oxime derivatives **10**–**13** was synthesized as shown in Scheme 2. Following the similar procedure as described above, we synthesized various pyrrolidine/piperidine hydroxyl amines **9a**–**d** as hydrogen chloride salt forms, which were subjected to condensation reaction with substituted benzaldehydes to afford the compounds **10**–**13**. In this event, considering the substituent effect of the phenyl ring moiety in **5** and **6** on the mPTP blocking activity, we selected six different benzaldehydes for this transformation. The result of JC-1 assay of the second series is summarized in Table 2. In addition to CsA, piracetam was also used as a control because it has been reported that it was able to restore mitochondrial dysfunction and neurite reduction associated with amyloid beta [19]. Compared to the quinuclidine oxime derivatives **5** and **6**, some pyrrolidine/piperidine analogs **10**–**13** showed high blocking activity against amyloid beta-induced mPTP opening. Among the tested compounds, the inhibitory activities of nine compounds were comparable or even superior to that of piracetam. While the compounds having the simple substituents such as methoxy and trifluoromethyl on the phenyl ring (**10**–**13a**/**b** series) showed the low inhibitory activities, the oxime derivatives derived from the substituted benzyloxybenzaldehydes (**10**–**13c**–**f** series) displayed excellent blocking activities up to 18% of increased green/red ratio (**10f**).

To complement the JC-1 assay, we performed a luciferase-based assay for cellular ATP levels to validate the effect of the selected compounds on mitochondrial function [20]. Because a main role for the mitochondria is the production of ATP, a compound which is able to block mPTP opening damaged by amyloid beta should eventually repair mitochondrial dysfunction by promoting ATP generation. As shown in Table 3, all the tested compounds did not exhibit significant cell toxicity. However, only compound **12d**, bearing two chlorine atoms at the 3,4-position of benzyloxy group, possessed highest inhibitory activity against amyloid beta-induced ATP reduction as well as reasonable cell viability, which are comparable to those of piracetam. Thus, we selected compound **12d** as a lead compound for further investigation.

In addition to the JC-1 assay and the luciferase-based assay, we executed the MTT assay for measuring mitochondrial dehydrogenase activity and a CM-H_2DCFDA-fluorescenet assay for detecting cellular reactive oxygen species (ROS) resulting from amyloid beta toxicity [21,22]. In fact, it was found that the viability of cells treated with amyloid beta was ameliorated by compound **12d**. We also

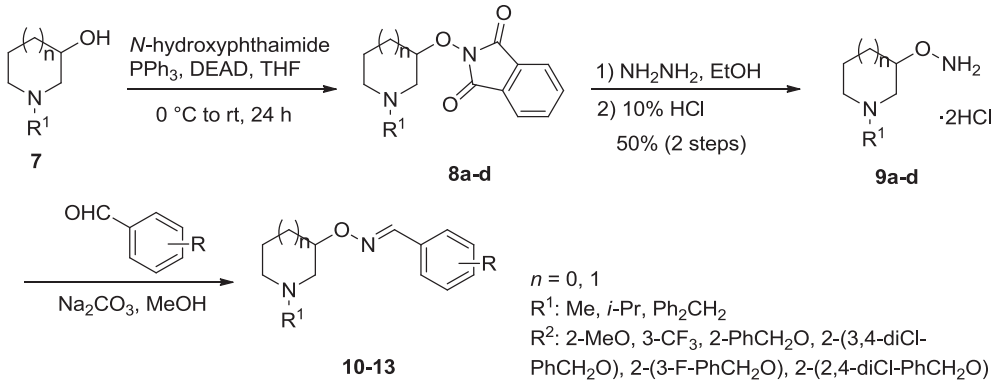
Table 1
In vitro blocking activity of quinuclidinyl oximes **5** and **6** against amyloid beta-induced mPTP opening (JC-1 assay).



5a-k **6a-m**

Compds	R^1	Increased g/r ratio (%)[a]	Compds	R^1	Increased g/r ratio (%)[a]	Compds	R^1	Increased g/r ratio (%)[a]
5a	3-PhO	138	**5i**	2-Br	93	**6f**	4-F	93
5b	3-F	92	**5j**	2-MeO	71	**6g**	4-MeO	96
5c	3-Br	95	**5k**	2-CF_3	86	**6h**	2,6-diCl	96
5d	3-MeO	86	**6a**	2-Cl	88	**6i**	3,4-diCl	77
5e	3-$PhCH_2O$	121	**6b**	3-Cl	101	**6j**	2,4-diCl	69
5f	3-CF_3	74	**6c**	4-Cl	85	**6k**	2-CF_3	91
5g	2-PhO	84	**6d**	2-F	82	**6l**	3-CF_3	90
5h	2-F	96	**6e**	3-F	75	**6m**	4-CF_3	85
CsA		46						

[a] % Increase of fluorescence-ratio (green/red) after treatment of each compound and amyloid beta with regard to that of amyloid beta alone (100%). See the text for more detailed information.



Scheme 2. Synthesis of pyrrolidinyl/piperidinyl oxime derivatives **10**–**13**.

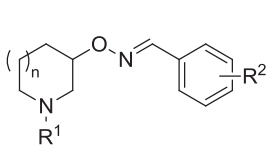
observed that **12d** reduced amyloid beta-induced ROS production with 82% inhibition value. These data suggested that compound **12d** is a potential mPTP blocker maintaining mitochondrial function and cell viability (Table 4).

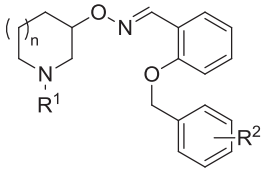
Finally, the pharmaceutical properties of compound **12d** were examined as shown in Tables 5 and 6. The stability assays showed that **12d** was not decomposed in rat plasma for 2 h and it remained up to 48% at 30 min after treatment of **12d** in pooled human hepatic microsomes. This result indicated that compound **12d** has good plasma and microsomal stability. The pharmacokinetic studies of **12d** on intravenous and oral administration in rats showed that all the PK parameters of this compound were highly improved in comparison of those of compound **1**. In particular, compound **12d** showed high level of drug exposure, moderate clearance, and good oral bioavailability. Furthermore, the high ratio of brain to plasma concentration at 2 h after iv or oral administration (14.58 and 0.29) turned out that **12d** penetrated into brain tissue effectively. Therefore, replacement of the quinuclidine ring in compound **1** by a pyrrolidine ring (compound **12d**) significantly enhanced the in vitro affinity while improving the stability and PK profile.

3. Conclusion

In this study, we identified compound **12d**, a potent mPTP blocker, starting from quinuclidinyl oxime hit compound **1** screened by the JC-1 assay. The replacement of substituents on the aromatic ring of compound **1** did not improve the inhibitory activity against amyloid beta-induced mPTP opening. However, the introduction of monocyclic azacycles such as pyrrolidine and piperidine as a quinuclidine surrogate served to increase the in vitro efficacy significantly. In particular, compound **12d** having *N*-benzylpyrrolidine showed good in vitro profiles with regard to the assays associated with mitochondrial functions and cell viabilities. Moreover, we found that the in vitro safety and PK properties of compound **12d** were dramatically improved by such a structural change. Therefore, compound **12d**, a potential mPTP blocker, can be

Table 2
The result of the JC-1 assay.





10a/b: n = 0, R^1 = Me
11a/b: n = 0, R^1 = *i*Pr
12a/b: n = 0, R^1 = $PhCH_2$
13a/b: n = 1, R^1 = Me

10c-f: n = 0, R^1 = Me
11c-f: n = 0, R^1 = *i*Pr
12c-f: n = 0, R^1 = $PhCH_2$
13c-f: n = 1, R^1 = Me

Compds	R^1	R^2	Increased g/r ratio (%)[a]	Compds	R^1	R^2	Increased g/r ratio (%)[a]
10a	Me	2-MeO	147	**12a**	$PhCH_2$	2-MeO	81
10b	Me	3-CF_3	108	**12b**	$PhCH_2$	3-CF_3	123
10c	Me	H	69	**12c**	$PhCH_2$	H	38
10d	Me	3,4-diCl	57	**12d**	$PhCH_2$	3,4-diCl	41
10e	Me	3-F	42	**12e**	$PhCH_2$	3-F	42
10f	Me	2,4-diCl	18	**12f**	$PhCH_2$	2,4-diCl	61
11a	*i*Pr	2-MeO	55	**13a**	Me	2-MeO	257
11b	*i*Pr	3-CF_3	54	**13b**	Me	3-CF_3	84
11c	*i*Pr	H	19	**13c**	Me	H	29
11d	*i*Pr	3,4-diCl	95	**13d**	Me	3,4-diCl	62
11e	*i*Pr	3-F	39	**13e**	Me	3-F	32
11f	*i*Pr	2,4-diCl	61	**13f**	Me	2,4-diCl	64
				Piracetam			40

[a] % Increase of fluorescence-ratio (green/red) after treatment of each compound and amyloid beta compared to that treated with amyloid beta alone (100%). See the text for more detailed information.

Table 3
The result of ATP assay of the selected compounds.

Compds	**1**	**10e**	**10f**	**11c**	**11e**	**12c**	**12d**	**12e**	**13c**	**13e**	Piracetam
% Recovery[a] (%)	13	20	−9	−93	−223	−137	104	−201	15	9	127
Viability	92	87	90	67	94	99	83	74	112	136	88

[a] % Recovery of ATP production at 5 μM of each compound against amyloid beta-suppressed mitochondrial ATP reduction.

considered as a promising lead for further development of new AD therapeutics.

4. Experimental section

4.1. Chemistry

General: All reactions were carried out under dry nitrogen unless otherwise indicated. Commercially available reagents were used without further purification. Solvents and gases were dried according to standard procedures. Organic solvents were evaporated with reduced pressure using a rotary evaporator. Analytical thin layer chromatography (TLC) was performed using glass plates precoated with silica gel (0.25 mm). TLC plates were visualized by exposure to UV light (UV), and then were visualized with a *p*-anisaldehyde stain followed by brief heating on hot plate. Flash column chromatography was performed using silica gel 60 (230–400 mesh, Merck) with the indicated solvents. ^{1}H and ^{13}C spectra were recorded on Bruker 300, Bruker 400 or Varian 300 NMR spectrometers. ^{1}H NMR spectra are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, and coupling constant (*J*) in Hertz (Hz). ^{1}H NMR chemical shifts are reported relative to $CDCl_3$ (7.26 ppm). ^{13}C NMR was recorded relative to the central line of $CDCl_3$ (77.0 ppm).

4.1.1. Synthesis of hydroxylamine hydrogen chloride

*4.1.1.1. Representative procedure for synthesis of 2-(quinuclidin-3-yloxy)isoindoline-1,3-dione (**3**).* To a solution of 3-quinuclidinol **2** (1.00 g, 7.86 mmol) in THF (39 mL) cooled to 0 °C were added diethyl azodicarboxylate (2.47 mL, 15.7 mmol), *N*-hydroxyphthalimide (2.05 g, 12.6 mmol), and triphenylphosphine (4.12 g, 15.7 mmol). After the reaction mixture was stirred for 6 h (monitored by TLC), it was treated with H_2O (40 mL) and extracted with chloroform (3 × 30 mL). The combined organic layer was washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting crude oil was purified by column chromatography on silica gel (ethyl acetate/hexane = 15:1) to yield 2-(quinuclidin-3-yloxy)isoindoline-1,3-dione **3** (1.80 g, 85%) as an oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.80 (m, 2H), 7.74 (m, 2H), 4.15 (m, 1H), 3.21 (m, 1H), 2.97–3.05 (m, 2H), 2.79–2.85 (m, 2H), 2.66 (m, 1H), 2.11 (m, 1H), 1.41 (m, 1H), 1.23 (m, 3H).

*4.1.1.2. Representative procedure for synthesis of O-(quinuclidin-3-yl) hydroxylamine hydrogen chloride (**4**).* To a solution of 2-(quinuclidin-3-yloxy)isoindoline-1,3-dione **3** (10.6 g, 39.3 mmol) in ethanol (131 mL) was added hydrazine monohydrate (3.57 mL, 59.0 mmol). The reaction mixture was stirred at 80 °C for 3 h and cooled to room temperature. The precipitate was filtered off through a pad of Celite® and the filtrate was washed with brine. The organic layer was treated with 10% HCl solution and concentrated under reduced pressure. The residual solid was filtered and recrystallized in ethanol to give *O*-(quinuclidin-3-yl)hydroxylamine hydrogen chloride **4** (3.86 g, 46%) as a solid. ^{1}H NMR (CD_3OD, 400 MHz) δ 4.67 (m, 1H), 3.78 (m, 1H), 3.30–3.40 (m, 5H), 2.60 (m, 1H), 2.15 (m, 2H), 1.92 (m, 2H).

*4.1.1.3. 2-(1-Methylpyrrolidin-3-yloxy)isoindoline-1,3-dione (**8a**).* Following the same procedure used for the synthesis of **3**, the reaction of 1-methyl-3-hydroxypyrrolidine (0.54 mL, 4.94 mmol), diisopropyl azodicarboxylate (1.95 mL, 9.89 mmol), *N*-hydroxyphthalimide (1.29 g, 7.91 mmol), and triphenylphosphine (2.59 g, 9.89 mmol) in THF (24 mL) at 0 °C gave the title compound **8a** (1.17 g, 97%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.51 (m, 2H), 7.42 (m, 2H), 3.94 (m, 1H), 3.67 (m, 1H), 3.42 (m, 2H), 2.99 (s, 3H), 2.97 (m, 1H), 2.41 (m, 1H).

*4.1.1.4. 2-(1-Isopropylpyrrolidin-3-yloxy)isoindoline-1,3-dione (**8b**).* Following the same procedure used for the synthesis of **3**, the reaction of 1-isopropyl-3-pyrrolidinol (0.52 mL, 3.87 mmol), diisopropyl azodicarboxylate (1.52 mL, 7.74 mmol), *N*-hydroxyphthalimide (1.01 g, 6.19 mmol), and triphenylphosphine (2.03 g, 7.74 mmol) in THF (19 mL) at 0 °C gave the title compound **8b** (990 mg, 93%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.79 (m, 2H), 7.72 (m, 2H), 4.88 (m, 1H), 3.09 (m, 1H), 2.99 (m, 2H), 2.94 (m, 1H), 2.92 (m, 1H), 2.15 (m, 2H), 1.14 (dd, J = 3.2, 6.3 Hz, 6H).

*4.1.1.5. 2-(1-Benzylpyrrolidin-3-yloxy)isoindoline-1,3-dione (**8c**).* Following the same procedure used for the synthesis of **3**, the reaction of 1-benzyl-3-pyrrolidinol (0.47 mL, 2.82 mmol), diethyl azodicarboxylate (0.89 mL, 5.64 mmol), *N*-hydroxyphthalimide (740 mg, 4.51 mmol), and triphenylphosphine (1.48 g, 5.64 mmol) in THF (14 mL) at 0 °C gave the title compound **8c** (766 mg, 84%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.78 (m, 2H), 7.70 (m, 2H), 7.18–7.33 (m, 5H), 4.90 (m, 1H), 2.89 (d, J = 4.2 Hz, 2H), 2.84 (m, 1H), 2.58 (m, 1H), 2.14 (m, 2H).

*4.1.1.6. 2-((1-Methylpiperidin-3-yl)oxy)isoindoline-1,3-dione (**8d**).* Following the same procedure used for the synthesis of **3**, the reaction of *N*-methyl-3-piperidinol (0.5 mL, 4.34 mmol), diisopropyl azodicarboxylate (1.71 mL, 8.68 mmol), *N*-hydroxyphthalimide (1.13 g, 6.95 mmol), and triphenylphosphine (2.28 g, 8.68 mmol) in THF (22 mL) at 0 °C gave the title compound (1.00 g, 88%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.51 (m, 2H), 7.42 (m, 2H), 3.94 (m, 1H), 3.67 (m, 1H), 3.42 (m, 2H), 2.99 (s, 3H), 2.97 (m, 1H), 2.41 (m, 1H).

*4.1.1.7. O-(1-Methylpyrrolidin-3-yl)hydroxylamine hydrogen chloride (**9a**).* Following the same procedure used for the synthesis of **4**, the

Table 4
The result of MTT assay and ROS assay of **12d**.

	MTT		ROS
	% Inhibition (against Aβ induced toxicity)	Viability	% Inhibition (against Aβ induced ROS)
1	0%	84%	64%
12d	149%	129%	82%
Piracetam	29%	132%	129%

Table 5
Plasma and microsomal stability of **12d**.

	Plasma stability (rat, % remaining at 2 h)	Microsomal stability (HLM,[a] % remaining at 30 min)
12d	111.17% (±3.0)	47.81% (±1.92)

[a] HLM, human liver microsomes.

Table 6
Mean (±SD[a]) pharmacokinetic parameters after intravenous ($n = 3$) and oral ($n = 4$) administration (10 mg/kg) of **12d** to SD male rats.

Plasma	Intravenous	Oral
$AUC_{0-\infty}$ (μg min/mL)	376.55 ± 98.10	143.30 ± 36.56
AUC_{last} (μg min/mL)	353.17 ± 89.08	117.33 ± 41.99
Terminal half-life (min)	140.97 ± 41.01	175.35 ± 48.99
C_{max} (μg/mL)	44.53 ± 4.59	0.57 ± 0.30
T_{max} (min)	–	120 ± 0
CL (mL/min/kg)	28.05 ± 8.58	72.13 ± 18.40
MRT (min)[b]		–
V_{ss} (mL/kg)	2870.90 ± 528.42	–
Brain to plasma ratio at 2 h	14.58	0.29
F (%)	38.06%	

$AUC_{0-\infty}$, total area under the plasma concentration–time curve from time zero to time infinity; AUC_{last}, total area under the plasma concentration–time curve from time zero to last measured time; C_{max}, peak plasma concentration; T_{max}, time to reach C_{max}; Cl, time-averaged total body clearance; MRT, mean residence time; V_{ss}, apparent volume of distribution at steady state; F, bioavailability.
[a] SD: standard deviations.
[b] Median (range) for T_{max}.

reaction of 2-(1-methylpyrrolidin-3-yloxy)isoindoline-1,3-dione **8a** (1.17 g, 4.75 mmol) and hydrazine monohydrate (0.53 mL, 7.13 mmol) in ethanol (15 mL) at 80 °C followed by treatment of 10% HCl (2.74 mL, 9.51 mmol) gave the title compound **9a** (880 mg, 97%). ^{1}H NMR (CD_3OD, 400 MHz) δ 4.67 (m, 1H), 3.67 (m, 1H), 3.42 (m, 2H), 2.99 (s, 3H), 2.97 (m, 1H), 2.41 (m, 1H).

*4.1.1.8. O-(1-Isopropylpyrrolidin-3-yl)hydroxylamine hydrogen chloride (**9b**).* Following the same procedure used for the synthesis of **4**, the reaction of 2-(1-isopropylpyrrolidin-3-yloxy)isoindoline-1,3-dione **8b** (145 mg, 0.53 mmol), and hydrazine monohydrate (0.06 mL, 0.79 mmol) in ethanol (1.7 mL) at 80 °C followed by treatment of 10% HCl (0.30 mL, 1.06 mmol) gave the title compound **9b** (100 mg, 87%). ^{1}H NMR (CD_3OD, 400 MHz) δ 4.65 (m, 1H), 3.09 (m, 1H), 2.99 (m, 2H), 2.94 (m, 1H), 2.92 (m, 1H), 2.15 (m, 2H), 1.14 (dd, $J = 3.2$, 6.3 Hz, 6H).

*4.1.1.9. O-(1-Benzylpyrrolidin-3-yl)hydroxylamine hydrogen chloride (**9c**).* Following the same procedure used for the synthesis of **4**, the reaction of 2-(1-benzylpyrrolidin-3-yloxy)isoindoline-1,3-dione **8c** (380 mg, 1.18 mmol) and hydrazine monohydrate (0.08 mL, 1.77 mmol) in ethanol (3.93 mL) at 80 °C followed by treatment of 10% HCl (0.16 mL, 2.36 mmol) gave the compound **9c** (386 mg, 62%). ^{1}H NMR (CD_3OD, 400 MHz) δ 7.18–7.33 (m, 5H), 4.65 (m, 1H), 2.89 (d, $J = 4.2$ Hz, 2H), 2.84 (m, 1H), 2.58 (m, 1H), 2.14 (m, 2H).

*4.1.1.10. O-(1-Methylpiperidin-3-yl)hydroxylamine hydrogen chloride (**9d**).* Following the same procedure used for the synthesis of **4**, the reaction of 2-((1-methylpiperidin-3-yl)oxy)isoindoline-1,3-dione **8d** (1.96 g, 7.57 mmol) and hydrazine monohydrate (0.85 mL, 11.3 mmol) in ethanol (25 mL) at 80 °C followed by treatment of 10% HCl (4.34 mL, 15.1 mmol) gave the title compound **9d** (960 mg, 63%). ^{1}H NMR (CD_3OD, 400 MHz) δ 4.65 (m, 1H), 3.94 (m, 1H), 3.67 (m, 1H), 3.42 (m, 2H), 2.99 (s, 3H), 2.97 (m, 1H), 2.41 (m, 1H).

*4.1.2. Synthesis of quinuclidinyl oxime derivatives **1**, **5** and **6***

*4.1.2.1. Representative procedure for synthesis of O-quinuclidin-3-yl oxime (**1**).* To a solution of *O*-(quinuclidin-3-yl)hydroxylamine hydrogen chloride **4** (642 mg, 2.98 mmol) in methanol (30 mL) were added 2-(benzyloxy)benzaldehyde (949 mg, 4.47 mmol) and Na_2CO_3 (474 mg, 4.47 mmol). The reaction mixture was stirred at room temperature for 3 h, quenched with water (25 mL) and extracted with chloroform (3 × 30 mL). The combined organic layer was washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The crude oil was purified by column chromatography on silica gel ($CHCl_3$/MeOH = 10:1) to give the title compound **1** (924 mg, 92%) as a solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.56 (s, 1H), 7.81 (dd, $J = 7.9$, 1.7 Hz, 1H), 7.28–7.44 (m, 6H), 6.98 (m, 2H), 5.10 (s, 2H), 4.37 (m, 1H), 3.18 (m, 1H), 2.75–2.93 (m, 6H), 2.23 (dd, $J = 6.3$, 3.1 Hz, 1H), 1.85 (m, 1H), 1.70 (m, 1H), 1.56 (m, 1H), 1.35 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.6, 144.9, 136.6, 131.0, 128.6, 128.1, 127.4, 126.5, 121.4, 121.1, 112.5, 78.9, 70.4, 54.4, 47.7, 47.0, 25.3, 24.4, 19.2; LC/MS (ESI$^+$): *m*/*z*: calcd for $C_{21}H_{24}N_2O_2$: 336.18, $[M + H]^+$; found: 337.49.

*4.1.2.2. 3-Phenoxybenzaldehyde O-quinuclidin-3-yl oxime (**5a**).* Following the general procedure, the reaction of *O*-(quinuclidin-3-yl)hydroxylamine hydrogen chloride **4** (108 mg, 0.50 mmol), 3-phenoxybenzaldehyde (0.12 mL, 0.75 mmol) and Na_2CO_3 (80 mg, 0.75 mmol) in methanol (5.0 mL) gave the title compound **5a** (97 mg, 60% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.09 (s, 1H), 7.27–7.42 (m, 5H), 7.11 (t, $J = 7.3$ Hz, 1H), 6.97–7.07 (m, 3H), 4.37 (m, 1H), 3.20 (dd, $J = 14.0$, 9.0 Hz, 1H), 2.71–2.97 (m, 5H), 2.22 (m, 1H), 1.85 (m, 1H), 1.70 (m, 1H), 1.55 (m, 1H), 1.35 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.5, 157.0, 148.4, 134.2, 130.1, 129.9, 123.5, 122.1, 120.2, 118.9, 117.1, 79.1, 54.3, 47.7, 47.0, 25.3, 24.2, 19.1; LC/MS (ESI$^+$): *m*/*z*: calcd for $C_{20}H_{22}N_2O_2$: 322.17, $[M + H]^+$; found: 323.68.

*4.1.2.3. 3-Fluorobenzaldehyde O-quinuclidin-3-yl oxime (**5b**).* Following the general procedure, the reaction of *O*-(quinuclidin-3-yl)hydroxylamine hydrogen chloride **4** (100 mg, 0.46 mmol), 3-fluorobenzaldehyde (74 μL, 0.69 mmol), and Na_2CO_3 (74 mg, 0.69 mmol) in methanol (4.67 mL) gave the title compound **5b** (99 mg, 85%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.09 (s, 1H), 7.27–7.36 (m, 3H), 7.01–7.08 (m, 1H), 4.39 (m, 1H), 3.20 (dd, $J = 14.0$, 9.0 Hz, 1H), 2.77–3.20 (m, 5H), 2.23 (m, 1H), 1.77 (m, 2H), 1.57 (m, 1H), 1.23 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.9 (d, $^1J = 244.7$ Hz), 147.8 (d, $^4J = 2.9$ Hz), 134.5 (d, $^3J = 8.0$ Hz), 130.3 (d, $^3J = 8.3$ Hz), 123.2 (d, $^4J = 4.2$ Hz), 116.8 (d, $^2J = 21.3$ Hz), 113.2 (d, $^2J = 22.7$ Hz), 79.1, 54.3, 47.6, 46.9, 25.3, 24.1, 19.1; LC/MS (ESI$^+$): *m*/*z*: calcd for $C_{14}H_{17}FN_2O$: 248.13, $[M + H]^+$; found: 249.43.

*4.1.2.4. 3-Bromobenzaldehyde O-quinuclidin-3-yl oxime (**5c**).* Following the general procedure, *O*-(quinuclidin-3-yl)hydroxylamine hydrogen chloride **4** (100 mg, 0.46 mmol) 3-bromobenzaldehyde (81 μL, 0.69 mmol), and Na_2CO_3 (74 mg, 0.69 mmol) in methanol (4.67 mL) gave the title compound **5c** (126 mg, 88%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.05 (s, 1H), 7.75 (s, 1H), 7.44–7.52 (m, 2H), 7.20–7.30 (m, 1H), 4.39 (m, 1H), 3.20 (dd, $J = 14.0$, 9.0 Hz, 1H), 2.79–2.93 (m, 5H), 2.25 (m, 1H), 1.78 (m, 2H), 1.59 (m, 1H), 1.35 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 147.6, 134.4, 132.7, 130.3, 129.5, 125.9, 122.9, 79.1, 54.2, 47.6, 46.9, 25.2, 24.0, 19.0; LC/MS (ESI$^+$): *m*/*z*: calcd for $C_{14}H_{17}BrN_2O$: 308.05, $[M + H]^+$; found: 309.38.

*4.1.2.5. 3-Methoxybenzaldehyde O-quinuclidin-3-yl oxime (**5d**).* Following the general procedure, the reaction of *O*-(quinuclidin-3-yl)hydroxylamine hydrogen chloride **4** (100 mg, 0.46 mmol), 3-methoxybenzaldehyde (85 μL, 0.69 mmol), and Na_2CO_3 (74 mg, 0.69 mmol) in methanol (4.6 mL) gave the title compound **5d** (96 mg, 79%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.11 (s, 1H), 7.28 (m, 1H), 7.14 (m, 2H), 6.91–6.95 (m, 1H), 4.41 (m, 1H), 3.84 (s, 3H), 3.22 (dd, $J = 14.0$, 9.0 Hz, 1H), 2.80–2.92 (m, 5H), 2.26 (m, 1H), 1.74 (m, 2H), 1.59 (m, 1H), 1.40 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.9, 149.0, 133.8, 129.8, 120.1, 116.2, 111.3, 78.9, 55.4, 54.4, 47.7, 47.0, 25.3, 24.2, 19.2; LC/MS (ESI$^+$): *m*/*z*: calcd for $C_{15}H_{20}N_2O_2$: 260.15, $[M + H]^+$; found: 261.39.

*4.1.2.6. 3-(Benzyloxy)benzaldehyde O-quinuclidin-3-yl oxime (**5e**).* Following the general procedure, the reaction of *O*-(quinuclidin-3-

yl)hydroxylamine hydrogen chloride **4** (87 mg, 0.46 mmol), 3-(benzyloxy)benzaldehyde (129 mg, 0.60 mmol), and Na_2CO_3 (64 mg, 0.60 mmol) in methanol (4.0 mL) gave the title compound (86 mg, 63%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.11 (s, 1H), 7.36–7.46 (m, 7H), 7.29 (dd, J = 14.1, 6.7 Hz, 1H), 7.07 (m, 1H), 5.09 (s, 2H), 4.43 (m, 1H), 3.25 (dd, J = 14.0, 9.0 Hz, 1H), 2.84–2.99 (m, 5H), 2.29 (m, 1H), 1.78 (m, 2H), 1.64 (m, 1H), 1.63 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.1, 149.1, 136.8, 133.7, 129.8, 128.7, 128.1, 127.6, 120.4, 116.9, 112.5, 78.5, 70.2, 54.2, 47.6, 46.9, 25.2, 23.9, 18.9; LC/MS (ESI$^+$): m/z: calcd for $C_{21}H_{24}N_2O_2$: 336.18, $[M + H]^+$; found: 337.79.

*4.1.2.7. 3-(Trifluoromethyl)benzaldehyde O-quinuclidin-3-yl oxime (**5f**).* Following the general procedure, the reaction of *O*-(quinuclidin-3-yl)hydroxylamine hydrogen chloride **4** (103.2 mg, 0.48 mmol), 3-(trifluoromethyl)benzaldehyde (96 μL, 0.72 mmol), and Na_2CO_3 (76 mg, 0.72 mmol) in methanol (4.8 mL) gave the title compound **5f** (95 mg, 66%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.15 (s, 1H), 7.84 (s, 1H), 7.73 (d, J = 7.7 Hz, 1H), 7.61 (d, J = 7.8 Hz, 1H), 7.49 (t, J = 7.7 Hz, 1H), 4.41 (m, 1H), 3.22 (dd, J = 14.0, 9.0 Hz, 1H), 2.79–2.94 (m, 5H), 2.26 (m, 1H), 1.85 (m, 2H), 1.74 (m, 1H), 1.59 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 147.6, 133.4, 131.4 (q, ^2J = 32.7 Hz), 130.3, 129.3, 126.3 (q, ^3J = 3.6 Hz), 124.0 (q, ^1J = 270.1 Hz), 123.6 (q, ^3J = 3.7 Hz), 122.1, 79.3, 54.3, 47.7, 47.0, 25.4, 24.2, 19.1; LC/MS (ESI$^+$): m/z: calcd for $C_{15}H_{17}F_3N_2O$: 298.13, $[M + H]^+$; found: 299.45.

*4.1.2.8. 2-Phenoxybenzaldehyde O-quinuclidin-3-yl oxime (**5g**).* Following the general procedure, the reaction of *O*-(quinuclidin-3-yl)hydroxylamine hydrogen chloride **4** (128 mg, 0.59 mmol), 2-phenoxybenzaldehyde (178 mg, 0.89 mmol), and Na_2CO_3 (95 mg, 0.89 mmol) in methanol (4.8 mL) gave the title compound **5g** (130 mg, 68%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.48 (s, 1H), 7.90 (dd, J = 7.8, 1.3 Hz, 1H), 7.28–7.35 (m, 3H), 7.07–7.14 (m, 2H), 6.87–6.96 (m, 3H), 4.40 (m, 1H), 3.22 (dd, J = 9.4, 5.0 Hz, 1H), 2.79–2.95 (m, 5H), 2.24 (m, 1H), 1.70–1.86 (m, 2H), 1.58 (m, 1H), 1.37 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.4, 154.9, 144.7, 131.2, 129.9, 126.7, 124.0, 123.9, 123.4, 119.5, 118.3, 78.7, 54.3, 47.6, 46.9, 25.3, 24.1, 19.0; LC/MS (ESI$^+$): m/z: calcd for $C_{20}H_{22}N_2O_2$: 322.17, $[M + H]^+$; found: 323.69.

*4.1.2.9. 2-Fluorobenzaldehyde O-quinuclidin-3-yl oxime (**5h**).* Following the general procedure, the reaction of *O*-(quinuclidin-3-yl)hydroxylamine hydrogen chloride **4** (130 mg, 0.60 mmol), 2-fluorobenzaldehyde (95 μL, 0.90 mmol), and Na_2CO_3 (96 mg, 0.90 mmol) in methanol (6.0 mL) gave the title compound **5h** (113 mg, 75%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.36 (s, 1H), 7.79 (t, J = 7.4 Hz, 1H), 7.32 (q, J = 7.0 Hz, 1H), 7.01–7.17 (m, 2H), 4.40 (m, 1H), 3.22 (dd, J = 14.5, 8.3 Hz, 1H), 2.73–2.98 (m, 5H), 2.23 (m, 1H), 1.69–1.87 (m, 2H), 1.57 (m, 1H), 1.38 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.8 (d, ^1J = 250.5 Hz), 142.7 (d, ^3J = 4.2 Hz), 131.3 (d, ^3J = 8.2 Hz), 126.7 (d, ^4J = 2.7 Hz), 124.3 (d, ^3J = 3.4 Hz), 120.2 (d, ^2J = 10.8 Hz), 115.9 (d, ^2J = 20.9 Hz), 79.0, 54.2, 47.6, 46.9, 25.3, 24.1, 19.0; LC/MS (ESI$^+$): m/z: calcd for $C_{14}H_{17}FN_2O$: 248.13, $[M + H]^+$; found: 249.41.

*4.1.2.10. 2-Bromobenzaldehyde O-quinuclidin-3-yl oxime (**5i**).* Following the general procedure, the reaction of *O*-(quinuclidin-3-yl)hydroxylamine hydrogen chloride **4** (102 mg, 0.47 mmol), 2-bromobenzaldehyde (83 μL, 0.71 mmol), and Na_2CO_3 (75 mg, 0.71 mmol) in methanol (4.7 mL) gave the title compound (106 mg, 72%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.52 (s, 1H), 7.86 (dd, J = 7.6, 1.6 Hz, 1H), 7.60 (m 1H), 7.19–7.35 (m, 2H), 4.43 (m, 1H), 3.26 (m, 1H), 2.84–2.95 (m, 5H), 2.28 (m, 1H), 1.73–1.91 (m, 2H), 1.61 (m, 1H), 1.41 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 148.3, 133.1, 131.6, 131.0, 127.4, 123.7, 79.0, 54.1, 47.5, 46.8, 25.2, 24.0, 18.9; LC/MS (ESI$^+$): m/z: calcd for $C_{14}H_{17}BrN_2O$: 308.05, $[M + H]^+$; found: 309.52.

*4.1.2.11. 2-Methoxybenzaldehyde O-quinuclidin-3-yl oxime (**5j**).* Following the general procedure, the reaction of *O*-(quinuclidin-3-yl)hydroxylamine hydrogen chloride (107 mg, 0.50 mmol), 2-methoxybenzaldehyde (90 μL, 0.74 mmol), and Na_2CO_3 (79 mg, 0.74 mmol) in methanol (5.0 mL) gave the title compound **5j** (122 mg, 94%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.52 (s, 1H), 7.77 (d, J = 7.7 Hz, 1H), 7.32 (m 1H), 6.87–6.95 (m, 2H), 4.39 (m, 1H), 3.84 (s, 3H), 3.21 (m, 1H), 2.78–2.95 (m, 5H), 2.24 (m, 1H), 1.89 (m, 1H), 1.68–1.77 (m, 1H), 1.59 (m, 1H), 1.38 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.5, 145.1, 131.0, 126.3, 120.9, 120.7, 111.0, 78.5, 55.5, 54.3, 47.6, 46.9, 25.2, 24.1, 19.1; LC/MS (ESI$^+$): m/z: calcd for $C_{15}H_{20}N_2O_2$: 260.15, $[M + H]^+$; found: 261.58.

*4.1.2.12. 2-(Trifluoromethyl)benzaldehyde O-quinuclidin-3-yl oxime (**5k**).* Following the general procedure, the reaction of *O*-(quinuclidin-3-yl)hydroxylamine hydrogen chloride **4** (103 mg, 0.48 mmol) in methanol (4.8 mL), 2-(trifluoromethyl)benzaldehyde (95 μL, 0.72 mmol), and Na_2CO_3 (76 mg, 0.72 mmol) gave the title compound **5k** (112 mg, 78%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.49 (d, J = 2.1 Hz, 1H), 8.03 (d, J = 7.7 Hz, 1H), 7.64–7.72 (m 1H), 7.42–7.57 (m, 2H), 4.42 (m, 1H), 3.21 (m, 1H), 2.77–2.94 (m, 5H), 2.23 (m, 1H), 1.69–1.87 (m, 2H), 1.56 (m, 1H), 1.38 (m, 1H); ^{13}C NMR (CD_3OD, 100 MHz) δ 146.7, 132.2, 130.1, 129.6, 127.8 (q, ^2J = 30.6 Hz), 127.2, 126.7 (q, ^1J = 271.2 Hz), 125.6 (q, ^3J = 5.68 Hz), 75.4, 52.1, 46.5, 45.7, 24.0, 19.7, 16.1, 19.0; LC/MS (ESI$^+$): m/z: calcd for $C_{15}H_{17}F_3N_2O$: 298.13, $[M + H]^+$; found: 299.47.

*4.1.2.13. 2-(2-Chlorobenzyloxy)benzaldehyde O-quinuclidin-3-yl oxime (**6a**).* Following the general procedure, the reaction of *O*-(quinuclidin-3-yl)hydroxylamine hydrogen chloride **4** (68 mg, 0.32 mmol), 2-(2-chlorobenzyloxy)benzaldehyde (118 mg, 0.48 mmol), and Na_2CO_3 (51 mg, 0.48 mmol) in methanol (3.2 mL) gave the title compound **6a** (117 mg, 99%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.58 (s, 1H), 7.81 (dd, J = 7.7, 1.5 Hz, 1H), 7.53 (m, 1H), 7.41 (m, 1H), 7.27–7.35 (m 3H), 6.93–7.04 (m, 2H), 5.19 (s, 2H), 3.21 (m, 1H), 2.78–2.96 (m, 5H), 2.26 (m, 1H), 1.87–1.91 (m, 1H), 1.70–1.78 (m, 1H), 1.56–1.62 (m, 1H), 1.33–1.40 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.3, 145.0, 134.3, 132.6, 131.0, 129.4, 129.1, 128.8, 127.0, 126.6, 121.3, 112.6, 78.6, 67.6, 54.2, 47.5, 46.8, 25.2, 24.1, 19.0; LC/MS (ESI$^+$): m/z: calcd for $C_{21}H_{23}ClN_2O_2$: 370.14, $[M + H]^+$; found: 371.59.

*4.1.2.14. 2-(3-Chlorobenzyloxy)benzaldehyde O-quinuclidin-3-yl oxime (**6b**).* Following the general procedure, the reaction of *O*-(quinuclidin-3-yl)hydroxylamine hydrogen chloride **4** (66 mg, 0.31 mmol), 2-(3-chlorobenzyloxy)benzaldehyde (114 mg, 0.46 mmol), and Na_2CO_3 (49 mg, 0.46 mmol) in methanol (3.1 mL) gave the title compound **6b** (60 mg, 52%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.54 (s, 1H), 7.80 (dd, J = 7.7, 1.5 Hz, 1H), 7.28–7.42 (m, 5H), 6.89–6.99 (m, 2H), 5.07 (s, 2H), 4.41 (m, 1H), 3.23 (m, 1H), 2.74–3.00 (m, 5H), 2.26 (m, 1H), 1.89 (m, 1H), 1.74 (m, 1H), 1.59 (m, 1H), 1.38 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.3, 144.9, 138.3, 131.0, 129.9, 128.2, 127.4, 126.7, 125.3, 121.3, 112.4, 78.6, 69.6, 54.3, 47.6, 46.9, 25.2, 24.1, 19.0; LC/MS (ESI$^+$): m/z: calcd for $C_{21}H_{23}ClN_2O_2$: 370.14, $[M + H]^+$; found: 371.46.

*4.1.2.15. 2-(4-Chlorobenzyloxy)benzaldehyde O-quinuclidin-3-yl oxime (**6c**).* Following the general procedure, the reaction of *O*-(quinuclidin-3-yl)hydroxylamine hydrogen chloride **4** (83 mg, 0.38 mmol), 2-(4-chlorobenzyloxy)benzaldehyde (143 mg, 0.58 mmol), and Na_2CO_3 (61 mg, 0.58 mmol) in methanol (3.8 mL) gave the title compound **6c** (142 mg, 96%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.52 (s, 1H), 7.80 (dd, J = 7.7, 1.6 Hz, 1H), 7.27–7.36 (m, 5H), 6.89–6.98 (m, 2H), 5.07 (s, 2H), 4.39 (m, 1H), 3.21 (m, 1H), 2.78–2.95 (m, 5H), 2.24 (m, 1H), 1.88 (m, 1H), 1.72 (m, 1H), 1.58 (m,

1H), 1.37 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.3, 144.8, 135.0, 133.9, 131.0, 128.8, 128.7, 126.6, 121.3, 121.2, 112.5, 78.7, 69.6, 54.3, 47.6, 46.9, 25.2, 24.1, 19.0; LC/MS (ESI^+): *m/z*: calcd for $C_{21}H_{23}ClN_2O_2$: 370.14, $[M + H]^+$; found: 371.53.

*4.1.2.16. 2-(2-Fluorobenzyloxy)benzaldehyde O-quinuclidin-3-yl oxime (**6d**).* Following the general procedure, the reaction of *O*-(quinuclidin-3-yl)hydroxylamine hydrogen chloride **4** (65 mg, 0.30 mmol), 2-(2-fluorobenzyloxy)benzaldehyde (105 mg, 0.45 mmol), and Na_2CO_3 (48 mg, 0.45 mmol) in methanol (3.0 mL) gave the title compound **6d** (107 mg, 99%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.54 (s, 1H), 7.81 (dd, J = 5.7, 1.2 Hz, 1H), 7.47–7.51 (m, 1H), 7.30–7.35 (m, 2H), 7.18 (td, J = 5.6, 0.7 Hz, 1H), 7.10 (td, J = 6.9, 0.8 Hz, 1H), 6.95–6.99 (m, 2H), 5.17 (s, 2H), 4.38 (m, 1H), 3.20 (m, 1H), 2.77–2.94 (m, 5H), 2.24 (m, 1H), 1.86 (m, 1H), 1.72 (m, 1H), 1.57 (m, 1H), 1.36 (m, 1H); ^{13}C NMR (CD_3OD, 75 MHz) δ 160.8 (d, ^1J = 244.5 Hz), 156.7, 146.1, 131.6, 130.2 (d, ^3J = 3.7 Hz), 126.2, 124.1 (d, ^3J = 3.7 Hz), 123.5 (d, ^2J = 14.2 Hz), 121.0, 120.4, 115.0 (d, ^2J = 21.0 Hz), 112.8, 74.6, 129.8, 129.7, 126.5, 124.3, 121.4, 121.2, 115.4 (d, ^2J = 21.0 Hz), 112.4, 74.6, 64.4, 52.3, 46.5, 45.7, 23.9, 19.7, 16.5; LC/MS (ESI^+): *m/z*: calcd for $C_{21}H_{23}FN_2O_2$: 354.17, $[M + H]^+$; found: 353.77.

*4.1.2.17. 2-(3-Fluorobenzyloxy)benzaldehyde O-quinuclidin-3-yl oxime (**6e**).* Following the general procedure, the reaction of *O*-(quinuclidin-3-yl)hydroxylamine hydrogen chloride **4** (72 mg, 0.33 mmol), 2-(3-fluorobenzyloxy)benzaldehyde (115 mg, 0.49 mmol), and Na_2CO_3 (53 mg, 0.49 mmol) in methanol (3.3 mL) gave the title compound **6e** (117 mg, 97%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.55 (s, 1H), 7.81 (d, J = 7.7 Hz, 1H), 7.28–7.39 (m, 2H), 7.18 (t, J = 9.7 Hz, 2H), 6.90–7.06 (m, 3H), 5.10 (s, 2H), 4.40 (m, 1H), 3.22 (m, 1H), 2.75–3.00 (m, 5H), 2.25 (m, 1H), 1.88 (m, 1H), 1.73 (m, 1H), 1.58 (m, 1H), 1.35 (m, 1H); ^{13}C NMR (CD_3OD, 100 MHz) δ 162.9 (d, ^1J = 243.1 Hz), 156.6, 146.2 (d, ^3J = 18.5 Hz), 139.6 (d, ^4J = 7.3 Hz), 131.5 (d, ^3J = 14.8 Hz), 130.1, 126.2, 122.8, 120.9, 120.3, 114.4 (d, ^2J = 20.6 Hz), 113.8 (d, ^2J = 22.5 Hz), 112.7, 74.6, 69.3, 52.3, 46.5, 45.7, 24.0, 19.7, 16.2; LC/MS (ESI^+): *m/z*: calcd for $C_{21}H_{23}FN_2O_2$: 354.17, $[M + H]^+$; found: 355.2.

*4.1.2.18. 2-(4-Fluorobenzyloxy)benzaldehyde O-quinuclidin-3-yl oxime (**6f**).* Following the general procedure, the reaction of *O*-(quinuclidin-3-yl)hydroxylamine hydrogen chloride **4** (83 mg, 0.38 mmol), 2-(4-fluorobenzyloxy)benzaldehyde (134 mg, 0.58 mmol), and Na_2CO_3 (62 mg, 0.58 mmol) in methanol (3.8 mL) gave the title compound **6f** (137 mg, 98%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.52 (s, 1H), 7.80 (d, J = 7.6 Hz, 1H), 7.39 (dd, J = 8.2, 5.6 Hz, 2H), 7.31 (t, J = 7.3 Hz, 1H), 7.08 (t, J = 8.6 Hz, 2H), 6.91–7.10 (m, 2H), 5.05 (s, 2H), 4.39 (m, 1H), 3.22 (m, 1H), 2.75–3.00 (m, 5H), 2.25 (m, 1H), 1.88 (m, 1H), 1.74 (m, 1H), 1.59 (m, 1H), 1.38 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.5 (d, ^1J = 245.1 Hz), 156.4, 144.9, 132.3, 131.0, 129.2 (d, ^3J = 8.0 Hz), 126.5, 121.2 (d, ^3J = 8.5 Hz), 115.5 (d, ^2J = 21.4 Hz), 112.5, 78.5, 69.8, 54.2, 47.5, 46.8, 25.2, 24.0, 18.9; LC/MS (ESI^+): *m/z*: calcd for $C_{21}H_{23}FN_2O_2$: 354.17, $[M + H]^+$; found: 355.2.

*4.1.2.19. 2-(4-Methoxybenzyloxy)benzaldehyde O-quinuclidin-3-yl oxime (**6g**).* Following the general procedure, the reaction of *O*-(quinuclidin-3-yl)hydroxylamine hydrogen chloride **4** (67 mg, 0.31 mmol), 2-(4-methoxybenzyloxy)benzaldehyde (113 mg, 0.46 mmol), and Na_2CO_3 (49 mg, 0.46 mmol) in methanol (3.1 mL) gave the title compound **6g** (104 mg, 92%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.53 (s, 1H), 7.80 (dd, J = 7.7, 1.7 Hz, 1H), 7.28–7.36 (m, 3H), 6.89–6.97 (m, 4H), 5.02 (s, 2H), 4.38 (m, 1H), 3.82 (s, 3H), 3.19 (m, 1H), 2.77–2.89 (m, 5H), 2.23 (m, 1H), 1.88 (m, 1H), 1.72 (m, 1H), 1.58 (m, 1H), 1.38 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.5, 156.7, 145.0, 131.0, 129.2, 128.6, 126.4, 121.2, 120.9, 114.0, 112.5, 78.6, 70.2, 55.3, 54.3, 47.6, 46.9, 25.2, 24.1, 19.0; LC/MS (ESI^+): *m/z*: calcd for $C_{22}H_{26}N_2O_3$: 366.19, $[M + H]^+$; found: 367.2.

*4.1.2.20. 2-(2,6-Dichlorobenzyloxy)benzaldehyde O-quinuclidin-3-yl oxime (**6h**).* Following the general procedure, the reaction of *O*-(quinuclidin-3-yl)hydroxylamine hydrogen chloride **4** (72 mg, 0.33 mmol), 2-(2,6-dichlorobenzyloxy)benzaldehyde (141 mg, 0.50 mmol), and Na_2CO_3 (53 mg, 0.50 mmol) in methanol (3.3 mL) gave the title compound **6h** (135 mg, 98%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.45 (s, 1H), 7.83 (d, J = 7.7 Hz, 1H), 7.38 (t, J = 6.5 Hz, 3H), 7.28 (t, J = 8.0 Hz, 1H), 7.12 (d, J = 8.3 Hz, 1H), 7.01 (t, J = 7.5 Hz, 1H), 5.31 (s, 2H), 4.36 (m, 1H), 3.20 (m, 1H), 2.72–2.97 (m, 5H), 2.23 (m, 1H), 1.85 (m, 1H), 1.72 (m, 1H), 1.57 (m, 1H), 1.36 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.7, 144.9, 137.0, 131.8, 130.9, 130.5, 128.5, 126.3, 121.8, 121.5, 113.0, 78.7, 65.8, 54.3, 47.6, 46.9, 25.2, 24.2, 19.0; LC/MS (ESI^+): *m/z*: calcd for $C_{21}H_{22}Cl_2N_2O_2$: 404.11, $[M + H]^+$; found: 405.1.

*4.1.2.21. 2-(3,4-Dichlorobenzyloxy)benzaldehyde O-quinuclidin-3-yl oxime (**6i**).* Following the general procedure, the reaction of *O*-(quinuclidin-3-yl)hydroxylamine hydrogen chloride **4** (71 mg, 0.32 mmol), 2-(3,4-dichlorobenzyloxy)benzaldehyde (140 mg, 0.49 mmol), and Na_2CO_3 (53 mg, 0.49 mmol) in methanol (3.2 mL) gave the title compound **6i** (121 mg, 90%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.52 (s, 1H), 7.80 (d, J = 7.7 Hz, 1H), 7.48 (m, 2H), 7.25–7.34 (m, 2H), 6.98 (t, J = 7.5 Hz, 1H), 6.89 (d, J = 8.4 Hz, 1H), 5.04 (s, 2H), 4.40 (m, 1H), 3.22 (m, 1H), 2.73–2.99 (m, 5H), 2.24 (m, 1H), 1.89 (m, 1H), 1.73 (m, 1H), 1.58 (m, 1H), 1.37 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.0, 144.7, 136.8, 131.0, 130.6, 129.2, 126.8, 126.5, 121.5, 112.4, 78.8, 69.0, 54.3, 47.6, 46.9, 25.2, 24.2, 19.1; LC/MS (ESI^+): *m/z*: calcd for $C_{21}H_{22}Cl_2N_2O_2$: 404.11, $[M + H]^+$; found: 405.1.

*4.1.2.22. 2-(2,4-Dichlorobenzyloxy)benzaldehyde O-quinuclidin-3-yl oxime (**6j**).* Following the general procedure, the reaction of *O*-(quinuclidin-3-yl)hydroxylamine hydrogen chloride **4** (76 mg, 0.35 mmol), 2-(2,4-dichlorobenzyloxy)benzaldehyde (148 mg, 0.52 mmol), and Na_2CO_3 (56 mg, 0.52 mmol) in methanol (3.5 mL) gave the title compound **4** (137 mg, 97%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.54 (s, 1H), 7.81 (dd, J = 7.7, 1.7 Hz, 1H), 7.45 (m, 2H), 7.27–7.34 (m, 2H), 6.98 (t, J = 7.5 Hz, 1H), 6.92 (d, J = 8.3 Hz, 1H), 5.14 (s, 2H), 4.38 (m, 1H), 3.19 (m, 1H), 2.74–2.92 (m, 5H), 2.24 (m, 1H), 1.85 (m, 1H), 1.72 (m, 1H), 1.57 (m, 1H), 1.36 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.0, 144.7, 134.3, 133.2, 132.9, 131.0, 129.6, 129.3, 127.3, 126.8, 121.5, 121.4, 112.5, 78.8, 67.1, 54.3, 47.6, 46.9, 25.3, 24.2, 19.1; LC/MS (ESI^+): *m/z*: calcd for $C_{21}H_{22}Cl_2N_2O_2$: 404.11, $[M + H]^+$; found: 405.1.

*4.1.2.23. 2-(2-(Trifluoromethyl)benzyloxy)benzaldehyde O-quinuclidin-3-yl oxime (**6k**).* Following the general procedure, the reaction of *O*-(quinuclidin-3-yl)hydroxylamine hydrogen chloride **4** (89 mg, 0.41 mmol), 2-(2-(trifluoromethyl)benzyloxy)benzaldehyde (175 mg, 0.62 mmol), and Na_2CO_3 (66 mg, 0.62 mmol) in methanol (4.1 mL) gave the title compound **6k** (167 mg, 99%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.58 (s, 1H), 7.82 (dd, J = 7.7, 1.6 Hz, 1H), 7.71 (m, 2H), 7.58 (t, J = 7.5 Hz, 1H), 7.44 (t, J = 7.6 Hz, 1H), 7.30 (m, 1H), 6.98 (t, J = 7.6 Hz, 1H), 6.90 (d, J = 8.3 Hz, 1H), 5.30 (s, 2H), 4.40 (m, 1H), 3.21 (ddd, J = 8.5, 14.4, 1.8 Hz, 1H) 2.77–2.95 (m, 5H), 2.25 (m, 1H), 1.87 (m, 1H), 1.72 (m, 1H), 1.58 (m, 1H), 1.36 (m, 1H); ^{13}C NMR (CD_3OD, 75 MHz) δ 156.4, 146.1, 134.6, 132.3, 131.6, 129.8, 128.4, 127.5 (q, ^2J = 30.7 Hz), 126.3, 125.9 (q, ^3J = 6.0 Hz), 124.4 (q, ^1J = 271.5 Hz), 121.1, 120.3, 112.4, 74.7, 66.9, 52.3, 46.5, 45.7, 24.0, 19.7, 16.2; LC/MS (ESI^+): *m/z*: calcd for $C_{22}H_{23}F_3N_2O_2$: 404.17, $[M + H]^+$; found: 405.2.

*4.1.2.24. 2-(3-(Trifluoromethyl)benzyloxy)benzaldehyde O-quinuclidin-3-yl oxime (**6l**).* Following the general procedure, the reaction of

O-(quinuclidin-3-yl)hydroxylamine hydrogen chloride **4** (75 mg, 0.34 mmol), 2-(3-(trifluoromethyl)benzyloxy)benzaldehyde (147 mg, 0.52 mmol), and Na_2CO_3 (55 mg, 0.52 mmol) in methanol (3.4 mL) gave the title compound **6l** (136 mg, 96%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.54 (s, 1H), 7.82 (d, J = 7.7 Hz, 1H), 7.50–7.67 (m, 4H), 7.32 (m, 1H), 6.96 (m, 2H), 5.14 (s, 2H), 4.39 (m, 1H), 3.21 (m, 1H), 2.80–2.99 (m, 5H), 2.24 (m, 1H), 1.86 (m, 1H), 1.73 (m, 1H), 1.58 (m, 1H), 1.37 (m, 1H); ^{13}C NMR (CD_3OD, 100 MHz) δ 156.5, 146.1, 138.2, 131.6, 130.9, 130.4 (q, ^2J = 31.9 Hz), 129.1, 126.2, 124.4 (q, ^3J = 3.7 Hz), 124.2 (q, ^1J = 269.7 Hz), 123.7 (q, ^3J = 3.7 Hz), 121.0, 120.3, 112.8, 74.7, 69.3, 52.3, 46.5, 45.7, 24.0, 19.7, 16.1; LC/MS (ESI$^+$): m/z: calcd for $C_{22}H_{23}F_3N_2O_2$: 404.17, $[M + H]^+$; found: 405.2.

*4.1.2.25. 2-(4-(Trifluoromethyl)benzyloxy)benzaldehyde O-quinuclidin-3-yl oxime (**6m**).* Following the general procedure, the reaction of *O*-(quinuclidin-3-yl)hydroxylamine hydrogen chloride **4** (87 mg, 0.40 mmol), 2-(4-(trifluoromethyl)benzyloxy)benzaldehyde (170 mg, 0.60 mmol), and Na_2CO_3 (64 mg, 0.60 mmol) in methanol (4.0 mL) gave the title compound **6m** (146 mg, 90%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.55 (s, 1H), 7.82 (dd, J = 7.7, 1.6 Hz, 1H), 7.66 (d, J = 8.2 Hz, 2H), 7.55 (d, J = 8.1 Hz, 2H), 7.31 (m, 1H), 6.97 (t, J = 3.8 Hz, 1H), 6.91 (d, J = 8.3 Hz, 1H), 5.16 (s, 2H), 4.40 (m, 1H), 3.21 (m, 1H), 2.78–2.95 (m, 5H), 2.25 (m, 1H), 1.86 (m, 1H), 1.73 (m, 1H), 1.58 (m, 1H), 1.37 (m, 1H); ^{13}C NMR (CD_3OD, 100 MHz) δ 156.5, 146.1, 141.3, 131.6, 129.6 (q, ^2J = 32.1 Hz), 127.5, 126.2, 125.1 (q, ^3J = 3.6 Hz), 124.6 (q, ^1J = 269.6 Hz), 121.0, 120.3, 112.6, 74.7, 69.2, 52.3, 46.5, 45.7, 24.0, 19.7, 16.2; LC/MS (ESI$^+$): m/z: calcd for $C_{22}H_{23}F_3N_2O_2$: 404.17, $[M + H]^+$; found: 405.2.

*4.1.3. Synthesis of pyrrolidinyl/piperidinyl oxime derivatives **10–13***

*4.1.3.1. 2-Methoxybenzaldehyde O-(1-methylpyrrolidin-3-yl) oxime (**10a**).* Following the general procedure, the reaction of *O*-(1-methylpyrrolidin-3-yl)hydroxylamine hydrogen chloride **9a** (74 mg, 0.39 mmol), *O*-anisaldehyde (71 μL, 0.58 mmol), and Na_2CO_3 (62 mg, 0.58 mmol) in methanol (3.9 mL) gave the title compound **10a** (13 mg, 14%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.48 (s, 1H), 7.76 (dd, J = 7.7, 1.7 Hz, 1H), 7.32 (m, 1H), 6.93 (t, J = 7.5 Hz, 1H), 6.88 (d, J = 8.4 Hz, 1H), 4.88 (m, 1H), 3.82 (s, 3H), 2.73–2.94 (m, 3H), 2.47 (m, 1H), 2.42 (s, 3H), 2.23 (m, 1H), 2.05 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.6, 145.4, 131.0, 126.3, 120.9, 120.7, 111.0, 82.8, 61.6, 55.5, 55.0, 42.1, 31.6; LC/MS (ESI$^+$): m/z: calcd for $C_{13}H_{18}N_2O_2$: 234.17, $[M + H]^+$; found: 235.2.

*4.1.3.2. 3-(Trifluoromethyl)benzaldehyde O-(1-methylpyrrolidin-3-yl) oxime (**10b**).* Following the general procedure, the reaction of *O*-(1-methylpyrrolidin-3-yl)hydroxylamine hydrogen chloride **9a** (64 mg, 0.38 mmol), 3-(trifluoromethyl)benzaldehyde (68 μL, 0.50 mmol), and Na_2CO_3 (54 mg, 0.50 mmol) in methanol (3.4 mL) gave the title compound **10b** (42 mg, 45%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.11 (s, 1H), 7.84 (bs, 1H), 7.73 (d, J = 7.7 Hz, 1H), 7.61 (d, J = 7.9 Hz, 1H), 7.49 (t, J = 7.8 Hz, 1H), 4.91 (m, 1H), 2.93 (m, 2H), 2.79 (m, 1H), 2.50 (m, 1H), 2.45 (s, 3H), 2.25 (m, 1H), 2.05 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 147.7, 133.1, 130.2, 129.1, 126.2, 123.5, 83.3, 61.4, 54.9, 42.0, 31.5; LC/MS (ESI$^+$): m/z: calcd for $C_{13}H_{15}F_3N_2O$: 272.11, $[M + H]^+$; found: 273.2.

*4.1.3.3. 2-(Benzyloxy)benzaldehyde O-(1-methylpyrrolidin-3-yl) oxime (**10c**).* Following the general procedure, the reaction of *O*-(1-methylpyrrolidin-3-yl)hydroxylamine hydrogen chloride **9a** (66 mg, 0.35 mmol), 2-(benzyloxy)benzaldehyde (100 mg, 0.52 mmol), and Na_2CO_3 (55 mg, 0.52 mmol) in methanol (3.2 mL) gave the title compound **10c** (15 mg, 14%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.53 (s, 1H), 7.81 (dd, J = 7.9, 1.7 Hz, 1H), 7.28–7.42 (m, 6H), 6.95 (m, 2H), 5.08 (s, 2H), 4.88 (m, 1H), 2.77–2.96 (m, 3H), 2.49 (m, 1H), 2.44 (s, 3H), 2.25 (m, 1H), 2.06 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.7, 145.3, 136.5, 131.0, 128.6, 128.0, 127.4, 126.5, 121.2, 121.0, 112.4, 82.8, 70.3, 61.5, 55.0, 42.1, 31.6; LC/MS (ESI$^+$): m/z: calcd for $C_{19}H_{22}N_2O_2$: 310.17, $[M + H]^+$; found: 311.2.

*4.1.3.4. 2-((3,4-Dichlorobenzyl)oxy)benzaldehyde O-(1-methylpyrrolidin-3-yl) oxime (**10d**).* Following the general procedure, the reaction of *O*-(1-methylpyrrolidin-3-yl)hydroxylamine hydrogen chloride **9a** (75 mg, 0.39 mmol), 2-((3,4-dichlorobenzyl)oxy)benzaldehyde (160 mg, 0.59 mmol), and Na_2CO_3 (63 mg, 0.59 mmol) in methanol (4 mL) gave the title compound **10d** (21 mg, 14%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.49 (s, 1H), 7.80 (dd, J = 7.7, 1.7 Hz, 1H), 7.48 (m, 2H), 7.23–7.33 (m, 2H), 6.98 (t, J = 7.5 Hz, 1H), 6.88 (d, J = 8.3 Hz, 1H), 5.02 (s, 2H), 4.88 (m, 1H), 2.84–2.94 (m, 2H), 2.65 (dd, J = 10.8, 5.6 Hz, 1H), 2.38 (s, 3H), 2.36 (m, 1H), 2.22 (m, 1H), 2.04 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.1, 144.8, 136.8, 132.7, 132.1, 130.9, 130.6, 129.2, 126.8, 126.5, 121.4, 112.3, 83.1, 69.0, 61.7, 55.0, 42.1, 31.6; LC/MS (ESI$^+$): m/z: calcd for $C_{19}H_{20}Cl_2N_2O_2$: 378.09, $[M + H]^+$; found: 379.1.

*4.1.3.5. 2-((3-Fluorobenzyl)oxy)benzaldehyde O-(1-methylpyrrolidin-3-yl) oxime (**10e**).* Following the general procedure, the reaction of *O*-(1-methylpyrrolidin-3-yl)hydroxylamine hydrogen chloride **9a** (76 mg, 0.40 mmol), 2-((3-fluorobenzyl)oxy)benzaldehyde (138 mg, 0.60 mmol), and Na_2CO_3 (64 mg, 0.60 mmol) in methanol (4 mL) gave the title compound **10e** (19 mg, 14% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.52 (s, 1H), 7.81 (dd, J = 7.7, 1.7 Hz, 1H), 7.27–7.38 (m, 2H), 7.15 (m, 2H), 6.89–7.02 (m, 3H), 5.06 (s, 2H), 4.88 (m, 1H), 2.84–2.93 (m, 2H), 2.66 (dd, J = 10.8, 5.6 Hz, 1H), 2.38 (s, 3H), 2.36 (m, 1H), 2.23 (m, 1H), 2.03 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.9 (d, ^1J = 244.8 Hz), 156.3, 145.0, 139.1 (d, ^3J = 7.3 Hz), 130.9, 130.1 (d, ^3J = 8.1 Hz), 126.7, 122.7 (d, ^4J = 3.0 Hz), 121.4, 121.2, 114.9 (d, ^2J = 21.0 Hz), 114.2 (d, ^2J = 21.9 Hz), 112.3, 83.1, 69.5, 61.7, 55.0, 42.1, 31.6; LC/MS (ESI$^+$): m/z: calcd for $C_{19}H_{21}FN_2O_2$: 328.16, $[M + H]^+$; found: 329.2.

*4.1.3.6. 2-((2,4-Dichlorobenzyl)oxy)benzaldehyde O-(1-methylpyrrolidin-3-yl) oxime (**10f**).* Following the general procedure, the reaction of *O*-(1-methylpyrrolidin-3-yl)hydroxylamine hydrogen chloride **9a** (75 mg, 0.39 mmol), 2-((2,4-dichlorobenzyl)oxy) benzaldehyde (160 mg, 0.59 mmol), and Na_2CO_3 (63 mg, 0.59 mmol)in methanol (3.9 mL) gave the title compound **10f** (17 mg, 12%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.52 (s, 1H), 7.80 (dd, J = 7.7, 1.7 Hz, 1H), 7.48 (d, J = 8.3 Hz, 1H), 7.42 (d, J = 2.1 Hz, 1H), 7.27–7.35 (m, 2H), 6.98 (t, J = 7.6 Hz, 1H), 6.92 (d, J = 8.3 Hz, 1H), 5.13 (s, 2H), 4.89 (m, 1H), 2.86–2.97 (m, 2H), 2.69 (dd, J = 10.9, 5.6 Hz, 1H), 2.41 (s, 3H), 2.40 (m, 1H), 2.24 (m, 1H), 2.06 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.1, 144.9, 134.3, 133.1, 132.9, 131.0, 129.6, 129.2, 127.4, 126.8, 121.49, 121.41, 112.4, 83.0, 67.0, 61.7, 55.0, 42.1, 31.6; LC/MS (ESI$^+$): m/z: calcd for $C_{19}H_{20}Cl_2N_2O_2$: 378.09, $[M + H]^+$; found: 379.1.

*4.1.3.7. 2-Methoxybenzaldehyde O-(1-isopropylpyrrolidin-3-yl) oxime (**11a**).* Following the general procedure, the reaction of *O*-(1-isopropylpyrrolidin-3-yl)hydroxylamine hydrogen chloride **9b** (48 mg, 0.22 mmol), *O*-anisaldehyde (40 μL, 0.33 mmol), and Na_2CO_3 (35 mg, 0.33 mmol) in methanol (2.2 mL) gave the title compound **11a** (33 mg, 57%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.47 (s, 1H), 7.76 (dd, J = 7.7, 1.6 Hz, 1H), 7.32 (m, 1H), 6.93 (t, J = 7.5 Hz, 1H), 6.88 (d, J = 8.4 Hz, 1H), 4.87 (m, 1H), 3.81 (s, 3H), 2.92 (d, J = 4.3 Hz, 1H), 2.81–2.93 (m, 2H), 2.60 (m, 1H), 2.45 (m, 1H), 2.22 (m, 1H), 2.04 (m, 1H), 1.14 (dd, J = 3.2, 6.3 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.5, 145.3, 131.0, 126.3, 120.9, 120.7, 111.0, 82.1, 57.5, 55.5, 55.1, 50.6, 31.1, 21.3; LC/MS (ESI$^+$): m/z: calcd for $C_{15}H_{22}N_2O_2$: 262.17, $[M + H]^+$; found: 263.2.

*4.1.3.8. 3-(Trifluoromethyl)benzaldehyde O-(1-isopropylpyrrolidin-3-yl) oxime (**11b**).* Following the general procedure, the reaction of *O*-(1-isopropylpyrrolidin-3-yl)hydroxylamine hydrogen chloride **9b** (49 mg, 0.23 mmol), 3-(trifluoromethyl)benzaldehyde (45 μL, 0.33 mmol), and Na_2CO_3 (35 mg, 0.33 mmol) in methanol (2.3 mL) gave the title compound **11b** (35 mg, 51%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.09 (s, 1H), 7.83 (s, 1H), 7.72 (d, J = 7.7 Hz, 1H), 7.60 (d, J = 7.8 Hz, 1H), 7.48 (t, J = 7.7 Hz, 1H), 4.89 (m, 1H), 2.81–2.98 (m, 3H), 2.39–2.57 (m, 2H), 2.23 (m, 1H), 2.02 (m, 1H), 1.13 (dd, J = 4.2, 6.3 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 147.5, 133.2, 131.2 (q, ^2J = 32.4 Hz), 130.1, 129.1, 126.1 (q, ^3J = 3.6 Hz), 123.8 (q, ^1J = 270.7 Hz), 123.5 (q, ^3J = 3.8 Hz), 82.9, 57.6, 55.0, 50.6, 31.0, 21.3; LC/MS (ESI$^+$): m/z: calcd for $C_{15}H_{19}F_3N_2O$: 300.14, $[M + H]^+$; found: 301.2.

*4.1.3.9. 2-(Benzyloxy)benzaldehyde O-(1-isopropylpyrrolidin-3-yl) oxime (**11c**).* Following the general procedure, the reaction of *O*-(1-isopropylpyrrolidin-3-yl)hydroxylamine hydrogen chloride **9b** (43 mg, 0.19 mmol), 2-(benzyloxy)benzaldehyde (63 mg, 0.29 mmol), and Na_2CO_3 (31 mg, 0.29 mmol) in methanol (1.9 mL) gave the title compound **11c** (25 mg, 37%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.53 (s, 1H), 7.81 (dd, J = 7.9, 1.7 Hz, 1H), 7.28–7.42 (m, 6H), 6.95 (m, 2H), 5.08 (s, 2H), 4.88 (m, 1H), 2.84–2.95 (m, 3H), 2.62 (m, 1H), 2.49 (quin, J = 6.3 Hz, 1H), 2.23 (m, 1H), 2.05 (m, 1H), 1.15 (dd, J = 3.5, 6.3 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.7, 145.2, 136.5, 131.0, 128.6, 128.0, 127.4, 126.5, 121.3, 121.0, 112.4, 82.2, 70.3, 57.5, 55.2, 50.6, 31.0, 21.2; LC/MS (ESI$^+$): m/z: calcd for $C_{21}H_{26}N_2O_2$: 338.2, $[M + H]^+$; found: 339.2.

*4.1.3.10. 2-((3,4-Dichlorobenzyl)oxy)benzaldehyde O-(1-isopropylpyrrolidin-3-yl) oxime (**11d**).* Following the general procedure, the reaction of *O*-(1-isopropylpyrrolidin-3-yl)hydroxylamine hydrogen chloride **9b** (43 mg, 0.19 mmol), 2-((3,4-dichlorobenzyl)oxy)benzaldehyde (83 mg, 0.29 mmol), and Na_2CO_3 (31 mg, 0.29 mmol) in methanol (1.9 mL) gave the title compound **11d** (39 mg, 48%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.48 (s, 1H), 7.80 (dd, J = 7.7, 1.7 Hz, 1H), 7.47 (m, 2H), 7.23–7.34 (m, 2H), 6.98 (t, J = 7.5 Hz, 1H), 6.88 (d, J = 8.3 Hz, 1H), 5.02 (s, 2H), 4.89 (m, 1H), 2.85–2.99 (m, 3H), 2.60 (m, 1H) 2.47 (m, 1H), 2.23 (m, 1H), 2.03 (m, 1H), 1.15 (dd, J = 3.8, 6.3 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.1, 144.9, 136.8, 132.7, 132.1, 131.0, 130.6, 129.2, 126.8, 126.5, 121.5, 121.4, 112.3, 82.3, 69.0, 57.5, 55.2, 50.6, 31.0, 21.2; LC/MS (ESI$^+$): m/z: calcd for $C_{21}H_{24}Cl_2N_2O_2$: 406.12, $[M + H]^+$; found: 407.1.

*4.1.3.11. 2-((3-Fluorobenzyl)oxy)benzaldehyde O-(1-isopropylpyrrolidin-3-yl) oxime (**11e**).* Following the general procedure, the reaction of *O*-(1-isopropylpyrrolidin-3-yl)hydroxylamine hydrogen chloride **9b** (45 mg, 0.20 mmol), 2-((3-fluorobenzyl)oxy)benzaldehyde (72 mg, 0.31 mmol), Na_2CO_3 (33 mg, 0.31 mmol) in methanol (2 mL) gave the title compound **11e** (27 mg, 36%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.52 (s, 1H), 7.81 (dd, J = 7.7, 1.7 Hz, 1H), 7.28–7.38 (m, 2H), 7.15 (m, 2H), 6.89–7.05 (m, 3H), 5.07 (s, 2H), 4.89 (m, 1H), 2.85–2.96 (m, 3H), 2.63 (m, 1H), 2.49 (m, 1H), 2.24 (m, 1H), 2.0 (m, 1H), 1.16 (dd, J = 3.6, 6.3 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.9 (d, ^1J = 244.5 Hz), 156.4, 145.1, 139.2, 139.0, 131.1, 130.2 (d, ^3J = 8.1 Hz), 126.7, 122.7 (d, ^4J = 2.7 Hz), 121.3, 114.9 (d, ^2J = 21.0 Hz), 114.1 (d, ^2J = 22.0 Hz), 112.3, 82.2, 69.5, 57.4, 55.2, 50.6, 31.0, 21.2; LC/MS (ESI$^+$): m/z: calcd for $C_{21}H_{25}FN_2O_2$: 356.19, $[M + H]^+$; found: 357.2.

*4.1.3.12. 2-((2,4-Dichlorobenzyl)oxy)benzaldehyde O-(1-isopropylpyrrolidin-3-yl) oxime (**11f**).* Following the general procedure, the reaction of *O*-(1-isopropylpyrrolidin-3-yl)hydroxylamine hydrogen chloride **9b** (47 mg, 0.21 mmol), 2-((2,4-dichlorobenzyl)oxy)benzaldehyde (91 mg, 0.32 mmol), and Na_2CO_3 (35 mg, 0.32 mmol) in methanol (2.1 mL) gave the title compound **11f** (28 mg, 31%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.51 (s, 1H), 7.81 (dd, J = 7.7, 1.7 Hz, 1H), 7.48 (d, J = 8.3 Hz, 1H), 7.42 (d, J = 2.1 Hz, 1H), 7.27–7.35 (m, 2H), 6.98 (t, J = 7.6 Hz, 1H), 6.92 (d, J = 8.3 Hz, 1H), 5.13 (s, 2H), 4.89 (m, 1H), 2.85–3.00 (m, 3H), 2.58 (m, 1H), 2.47 (quin, J = 6.3 Hz, 1H), 2.25 (m, 1H), 2.05 (m, 1H), 1.15 (dd, J = 4.1, 6.3 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.1, 145.0, 134.3, 133.2, 132.9, 131.0, 129.6, 129.2, 127.4, 126.8, 121.5, 121.4, 112.4, 82.3, 67.0, 57.6, 55.1, 50.6, 31.0, 21.3; LC/MS (ESI$^+$): m/z: calcd for $C_{21}H_{24}Cl_2N_2O_2$: 406.12, $[M + H]^+$; found: 407.1.

*4.1.3.13. 2-Methoxybenzaldehyde O-(1-benzylpyrrolidin-3-yl) oxime (**12a**).* Following the general procedure, the reaction of *O*-(1-benzylpyrrolidin-3-yl)hydroxylamine hydrogen chloride **9c** (45 mg, 0.17 mmol), *O*-anisaldehyde (31 μL, 0.25 mmol), and Na_2CO_3 (27 mg, 0.25 mmol) in methanol (1.7 mL) gave the title compound **12a** (23 mg, 44%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.47 (s, 1H), 7.75 (dd, J = 7.7, 1.7 Hz, 1H), 7.23–7.36 (m, 6H), 6.93 (t, J = 7.6 Hz, 1H), 6.88 (d, J = 8.4 Hz, 1H), 4.89 (m, 1H), 3.83 (s, 3H), 3.66 (d, J = 4.7 Hz, 2H), 2.79 (m, 3H), 2.50 (m, 1H), 2.21 (m, 1H), 2.00 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.5, 145.1, 130.9, 128.9, 128.2, 126.9, 126.3, 120.7, 111.0, 82.4, 60.4, 59.6, 55.5, 52.8, 31.2; LC/MS (ESI$^+$): m/z: calcd for $C_{19}H_{22}N_2O_2$: 310.17, $[M + H]^+$; found: 311.2.

*4.1.3.14. 3-(Trifluoromethyl)benzaldehyde O-(1-benzylpyrrolidin-3-yl) oxime (**12b**).* Following the general procedure, the reaction of *O*-(1-benzylpyrrolidin-3-yl)hydroxylamine hydrogen chloride **9c** (41 mg, 0.15 mmol), 3-(trifluoromethyl)benzaldehyde (31 μL, 0.23 mmol), and Na_2CO_3 (25 mg, 0.23 mmol)in methanol (1.5 mL) gave the title compound **12b** (26 mg, 49%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.11 (s, 1H), 7.84 (s, 1H), 7.72 (d, J = 7.7 Hz, 1H), 7.60 (d, J = 7.8 Hz, 1H), 7.49 (t, J = 7.7 Hz, 1H), 7.23–7.36 (m, 5H), 4.93 (m, 1H), 3.69 (q, J = 11.6 Hz, 2H) 2.83 (m, 3H), 2.51 (m, 1H), 2.25 (m, 1H), 2.03 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 147.3, 138.6, 133.3, 130.1, 129.1, 128.9, 128.2, 127.0, 126.1, 123.5, 83.1, 60.3, 59.5, 52.7, 31.1; LC/MS (ESI$^+$): m/z: calcd for $C_{19}H_{19}F_3N_2O$: 348.14, $[M + H]^+$; found: 349.1.

*4.1.3.15. 2-(Benzyloxy)benzaldehyde O-(1-benzylpyrrolidin-3-yl) oxime (**12c**).* Following the general procedure, the reaction of *O*-(1-benzylpyrrolidin-3-yl)hydroxylamine hydrogen chloride **9c** (46 mg, 0.17 mmol), 2-(benzyloxy)benzaldehyde (55 mg, 0.26 mmol), and Na_2CO_3 (28 mg, 0.26 mmol) in methanol (1.7 mL) gave the title compound **12c** (17 mg, 26%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.53 (s, 1H), 7.80 (dd, J = 7.9, 1.7 Hz, 1H), 7.22–7.41 (m, 11H), 6.95 (m, 2H), 5.08 (s, 2H), 4.90 (m, 1H), 3.67 (q, J = 6.3 Hz, 2H), 2.79 (m, 3H), 2.21 (m, 1H), 2.50 (m, 1H), 2.05 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.6, 144.9, 138.7, 136.5, 130.9, 128.9, 128.6, 128.2, 128.0, 127.4, 126.9, 126.5, 121.4, 121.0, 112.4, 82.5, 70.3, 60.4, 59.6, 52.8, 31.2; LC/MS (ESI$^+$): m/z: calcd for $C_{25}H_{26}N_2O_2$: 386.2, $[M + H]^+$; found: 387.2.

*4.1.3.16. 2-((3,4-Dichlorobenzyl)oxy)benzaldehyde O-(1-benzylpyrrolidin-3-yl) oxime (**12d**).* Following the general procedure, the reaction of *O*-(1-benzylpyrrolidin-3-yl)hydroxylamine hydrogen chloride **9c** (52 mg, 0.19 mmol), 2-((3,4-dichlorobenzyl)oxy)benzaldehyde (68 mg, 0.29 mmol), and Na_2CO_3 (31 mg, 0.29 mmol)in methanol (1.9 mL) gave the title compound **12d** (24 mg, 22%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.48 (s, 1H), 7.79 (dd, J = 7.7, 1.7 Hz, 1H), 7.49 (m, 2H), 7.21–7.36 (m, 7H), 6.97 (t, J = 7.5 Hz, 1H), 6.88 (d, J = 8.3 Hz, 1H), 5.02 (s, 2H), 4.89 (m, 1H), 3.66 (q, J = 11.0 Hz, 2H), 2.75–2.85 (m, 3H), 2.48 (m, 1H) 2.23 (m, 1H), 2.01 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.1, 144.7, 138.7, 136.8, 130.9, 130.6, 129.2, 128.9, 128.2, 126.9, 126.8, 126.5, 121.4, 112.3, 82.6, 69.0, 60.4, 59.6, 52.8, 31.2; LC/MS (ESI$^+$): m/z: calcd for $C_{25}H_{24}Cl_2N_2O_2$: 454.12, $[M + H]^+$; found: 455.1.

*4.1.3.17. 2-((3-Fluorobenzyl)oxy)benzaldehyde O-(1-benzylpyrrolidin-3-yl) oxime (**12e**).* Following the general procedure, the reaction of *O*-(1-benzylpyrrolidin-3-yl)hydroxylamine hydrogen

chloride **9c** (39 mg, 0.14 mmol), 2-((3-fluorobenzyl)oxy)benzaldehyde (51 mg, 0.22 mmol), and Na_2CO_3 (24 mg, 0.22 mmol) in methanol (1.4 mL) gave the title compound (19 mg, 32%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.52 (s, 1H), 7.81 (dd, J = 7.7, 1.7 Hz, 1H), 7.28–7.38 (m, 7H), 7.15 (m, 2H), 6.89–7.05 (m, 3H), 5.12 (s, 2H), 4.89 (m, 1H), 3.67 (q, J = 11.3 Hz, 2H), 2.85–2.96 (m, 3H), 2.49 (m, 1H), 2.24 (m, 1H), 2.0 (m, 1H); ^{13}C NMR (CD_3OD, 75 MHz) δ 163.0 (d, ^1J = 243.8 Hz), 156.7, 146.6, 139.6 (d, ^3J = 7.5 Hz), 131.6, 130.2, 130.0 (d, ^3J = 8.2 Hz), 126.2, 122.8 (d, ^4J = 3.0 Hz), 120.8, 114.3 (d, ^2J = 21.0 Hz), 113.8 (d, ^2J = 22.5 Hz), 112.6, 80.0, 69.2, 67.6, 38.7, 30.2, 28.7; LC/MS (ESI$^+$): m/z: calcd for $C_{25}H_{25}FN_2O_2$: 404.19, $[M + H]^+$; found: 405.2.

*4.1.3.18. 2-((2,4-Dichlorobenzyl)oxy)benzaldehyde O-(1-benzylpyrrolidin-3-yl) oxime (**12f**).* Following the general procedure, the reaction of *O*-(1-benzylpyrrolidin-3-yl)hydroxylamine hydrogen chloride **9c** (42 mg, 0.16 mmol), 2-((2,4-dichlorobenzyl)oxy)benzaldehyde (67 mg, 0.24 mmol), and Na_2CO_3 (25 mg, 0.24 mmol) in methanol (1.6 mL) gave the title compound **12f** (20 mg, 29%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.51 (s, 1H), 7.79 (dd, J = 7.7, 1.7 Hz, 1H), 7.48 (d, J = 8.3 Hz, 1H), 7.42 (d, J = 2.1 Hz, 1H), 7.24–7.43 (m, 7H), 6.98 (t, J = 7.6 Hz, 1H), 6.92 (d, J = 8.3 Hz, 1H), 5.13 (s, 2H), 4.90 (m, 1H), 3.67 (q, J = 11.3 Hz, 2H), 2.80 (m, 3H), 2.49 (m, 1H), 2.24 (m, 1H), 2.03 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.1, 144.7, 138.7, 134.3, 133.1, 132.9, 131.0, 129.6, 129.2, 128.9, 128.2, 127.4, 126.9, 126.8, 121.4, 112.4, 82.6, 67.0, 60.4, 59.6, 52.8, 31.2; LC/MS (ESI$^+$): m/z: calcd for $C_{25}H_{24}Cl_2N_2O_2$: 454.12, $[M + H]^+$; found: 455.1.

*4.1.3.19. 2-Methoxybenzaldehyde O-(1-methylpiperidin-3-yl) oxime (**13a**).* Following the general procedure, the reaction of *O*-(1-methylpiperidin-3-yl)hydroxylamine hydrogen chloride **9d** (70 mg, 0.34 mmol), *O*-anisaldehyde (62 μL, 0.52 mmol), and Na_2CO_3 (54 mg, 0.52 mmol) in methanol (3.4 mL) gave the title compound **13a** (33 mg, 57%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.50 (d, J = 7.8 Hz, 1H), 7.70 (dd, J = 7.7, 1.7 Hz, 1H), 7.31 (m, 1H), 6.89 (m, 2H), 4.30 (m, 1H), 4.17 (dd, J = 11.0, 5.2 Hz, 1H), 3.83 (d, J = 3.5 Hz, 3H), 3.17 (m, 1H), 2.71 (m, 1H), 2.30 (s, 3H), 1.60–2.01 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.5, 144.8, 130.9, 126.3, 120.7, 111.0, 64.5, 59.6, 57.5, 41.3, 28.4, 22.6; LC/MS (ESI$^+$): m/z: calcd for $C_{14}H_{20}N_2O_2$: 248.15, $[M + H]^+$; found: 249.2.

*4.1.3.20. 3-(Trifluoromethyl)benzaldehyde O-(1-methylpiperidin-3-yl) oxime (**13b**).* Following the general procedure, the reaction of *O*-(1-methylpiperidin-3-yl)hydroxylamine hydrogen chloride **9d** (74 mg, 0.36 mmol), 3-(trifluoromethyl)benzaldehyde (73 μL, 0.54 mmol), and Na_2CO_3 (58 mg, 0.54 mmol) in methanol (3.6 mL) gave the title compound **13b** (35 mg, 51%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.13 (d, J = 5.1 Hz, 1H), 7.83 (s, 1H), 7.73 (d, J = 7.6 Hz, 1H), 7.59 (m, 1H), 7.49 (m, 1H), 4.35 (m, 1H), 4.17 (dd, J = 11.0, 5.2 Hz, 1H), 3.14 (m, 1H), 2.66 (m, 1H), 2.30 (s, 3H), 1.61–2.03 (m, 5H); ^{13}C NMR (CD_3OD, 75 MHz) δ 149.5, 132.9, 132.7, 130.5, 129.4 (q, ^3J = 3.75 Hz), 126.4 (q, ^3J = 6.0 Hz), 123.9 (q, ^1J = 270.0 Hz), 123.2 (q, ^3J = 4.5 Hz), 77.8, 74.4, 55.6, 43.0, 26.1, 21.8; LC/MS (ESI$^+$): m/z: calcd for $C_{14}H_{17}F3N_2O$: 286.13, $[M + H]^+$; found: 287.2.

*4.1.3.21. 2-(Benzyloxy)benzaldehyde O-(1-methylpiperidin-3-yl) oxime (**13c**).* Following the general procedure, the reaction of *O*-(1-methylpiperidin-3-yl)hydroxylamine hydrogen chloride **9d** (70 mg, 0.34 mmol), 2-(benzyloxy)benzaldehyde (110 mg, 0.52 mmol), Na_2CO_3 (55 mg, 0.52 mmol) in methanol (3.4 mL) gave the title compound **13c** (25 mg, 37%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.56 (d, J = 5.8 Hz, 1H), 7.82 (m, 1H), 7.25–7.42 (m, 6H), 6.96 (m, 2H), 5.09 (d, J = 4.4 Hz, 2H), 4.31 (m, 1H), 4.18 (m, 1H), 3.14 (m, 1H), 2.66 (m, 1H), 2.32 (s, 3H), 1.61–1.78 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.6, 144.8, 144.5, 136.5, 130.9, 128.6, 128.0, 127.4, 126.5, 121.0, 112.5, 70.3, 64.5, 59.5, 57.4, 41.2, 28.4, 22.6; LC/MS (ESI$^+$): m/z: calcd for $C_{20}H_{24}N_2O_2$: 324.18, $[M + H]^+$; found: 325.2.

*4.1.3.22. 2-((3,4-Dichlorobenzyl)oxy)benzaldehyde O-(1-methylpiperidin-3-yl) oxime (**13d**).* Following the general procedure, the reaction of *O*-(1-methylpiperidin-3-yl)hydroxylamine hydrogen chloride **9d** (69 mg, 0.34 mmol), 2-((3,4-dichlorobenzyl)oxy) benzaldehyde (143 mg, 0.51 mmol), and Na_2CO_3 (54 mg, 0.51 mmol) in methanol (3.4 mL) gave the title compound **13d** (39 mg, 48%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.51 (d, J = 6.4 Hz, 1H), 7.82 (m, 1H), 7.23–7.53 (m, 4H), 6.98 (t, J = 7.3 Hz, 1H), 6.88 (d, J = 8.3 Hz, 1H), 5.03 (d, J = 4.3 Hz, 2H), 4.31 (m, 1H), 4.16 (m, 1H), 3.15 (m, 1H), 2.69 (m, 1H), 2.30 (s, 3H), 1.60–1.98 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.1, 144.5, 144.2, 136.8, 131.0, 130.6, 129.2, 126.8, 126.7, 126.6, 126.5, 121.5, 112.4, 69.0, 64.5, 59.5, 57.5, 41.3, 28.3, 22.7; LC/MS (ESI$^+$): m/z: calcd for $C_{20}H_{22}Cl_2N_2O_2$: 392.11, $[M + H]^+$; found: 393.1.

*4.1.3.23. 2-((3-Fluorobenzyl)oxy)benzaldehyde O-(1-methylpiperidin-3-yl) oxime (**13e**).* Following the general procedure, the reaction of *O*-(1-methylpiperidin-3-yl)hydroxylamine hydrogen chloride **9d** (76 mg, 0.37 mmol), 2-((3-fluorobenzyl)oxy)benzaldehyde (129 mg, 0.56 mmol), and Na_2CO_3 (59 mg, 0.56 mmol) in methanol (3.7 mL) gave the title compound **13e** (27 mg, 38%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.55 (d, J = 6.6 Hz, 1H), 7.82 (m, 1H), 7.11–7.38 (m, 4H), 6.99 (m, 3H), 5.07 (d, J = 4.3 Hz, 2H), 4.27 (m, 1H), 4.14 (m, 1H), 3.13 (m, 1H), 2.72 (m, 1H), 2.31 (s, 3H), 1.60–1.86 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.8 (d, ^1J = 231.7 Hz), 144.5, 144.3, 130.8 (d, ^3J = 9.3 Hz), 130.1 (d, ^3J = 8.0 Hz), 126.6 (d, ^4J = 4.7 Hz), 122.7, 121.2, 114.7, 114.2 (d, ^2J = 21.8 Hz), 114.1 (d, ^2J = 21.8 Hz), 112.4, 112.3, 69.5, 64.4, 59.6, 57.6, 41.4, 28.5, 22.6,; LC/MS (ESI$^+$): m/z: calcd for $C_{20}H_{23}FN_2O_2$: 342.17, $[M + H]^+$; found: 343.2.

*4.1.3.24. 2-((2,4-Dichlorobenzyl)oxy)benzaldehyde O-(1-methylpiperidin-3-yl) oxime (**13f**).* Following the general procedure, the reaction of *O*-(1-methylpiperidin-3-yl)hydroxylamine hydrogen chloride **9d** (67 mg, 0.37 mmol), 2-((2,4-dichlorobenzyl)oxy) benzaldehyde (139 mg, 0.49 mmol), Na_2CO_3 (53 mg, 0.49 mmol) in methanol (3.3 mL) gave the title compound **13f** (28 mg, 31%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.55 (d, J = 6.3 Hz, 1H), 7.82 (m, 1H), 7.48 (dd, J = 8.3, 5.8 Hz, 1H), 7.43 (d, J = 2.0 Hz, 1H), 7.25–7.35 (m, 2H), 6.99 (t, J = 7.5 Hz, 1H), 6.92 (d, J = 8.2 Hz, 1H), 5.14 (d, J = 3.3 Hz, 2H), 4.33 (m, 1H), 4.23 (m, 1H), 3.14 (m, 1H), 2.66 (m, 1H), 2.31 (s, 3H), 1.61–1.99 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 144.5, 144.3, 134.3, 133.2, 132.9, 131.0, 130.9, 129.7, 129.3, 127.4, 126.7, 121.5, 112.5, 67.0, 64.5, 59.5, 57.6, 41.4, 28.4, 22.6; LC/MS (ESI$^+$): m/z: calcd for $C_{20}H_{22}Cl_2N_2O_2$: 392.11, $[M + H]^+$; found: 393.1.

4.2. Biological evaluation

4.2.1. Cell culture

HT-22 (mouse hippocampal cells) cells were grown in Dulbecco's Modified Eagle's Medium (DMEM, GIBCO) supplemented with 10% (vol/vol) FBS and antibiotics (100 μg/mL penicillin/streptomycin mix) in a humidified atmosphere at 37 °C with 5% CO_2.

4.2.2. JC-1 mitochondrial membrane potential assay

HT-22 cells (30,000 per well) were seeded into a clear 96-well plate (FALCON) at 200 μL per well one day prior to assay. 750 μM of JC-1 (Stratagene) in DMSO stock solution was dissolved into phenol red-free Opti-MEM (GIBCO) medium to make final concentration of 7.5 μM JC-1 per well. Medium was removed from the plate, and 100 μL per well of JC-1 was added. Plates were incubated for 1 h and 15 min at 37 °C and washed twice with 100 μL per well PBS. Subsequently, cells were treated with 25 μL solution of each compound at 10 μM in Opti-MEM and incubated at 37 °C for

10 min followed by addition of 25 μL of amyloid Beta (American peptide, 1–42) solution at 10 μM. Fluorescence was measured at every 1 h for 3 h at ex/em 530 nm/580 nm ('red') and ex/em 485 nm/530 nm ('green'). The ratio of green to red fluorescence was recorded and the percent changes in ratio from each compound were calculated and normalized using vehicle control as 100%.

4.2.3. Assay for cellular ATP levels

10,000 HT-22 cells per well were seeded into a clear 96-well plate (FALCON) at 200 μL per well one day prior to assay. Medium was removed from the plate, and cells were treated with 25 μL solution of each compound at 10 μM and incubated at 37 °C for 10 min followed by addition of 25 μL of amyloid Beta (American peptide, 1–42) solution at 10 μM. Cells were incubated at 37 °C for 7 h and washed twice with PBS. Cells were lysed by using 1% Triton-X 100 in TBST buffer solution and protein concentrations of each well were determined via BCA protein determination kit (Thermo scientific). Equal amount of cell lysates from each well were plated into a white 96-well plate (NUNC) and the amount of ATP levels in each sample was determined by using ATP determination kit (Invitrogen). The ATP levels of each sample were subtracted with vehicle control and percent inhibition were calculated based on the ATP levels of the vehicle control treated with amyloid Beta. Cell viability was also calculated based on the ATP levels of each sample without the treatment of amyloid Beta solution.

4.2.4. MTT assay

5000 HT-22 cells per well were seeded and treated as above described method. Cells were incubated at 37 °C for 24 h 10 μL of MTT solution (Thiazolyl blue tetrazolium bromide, Sigma) was added directly to each well and incubated at 37 °C for 2 h. After confirming the formation of blue formazan precipitates under microscope, 140 μL of solubilizing solution (10% Triton-X 100 in Isopropanol with 0.1 M HCl) was added to each well and incubate for another hour at room temperature. Absorbance at 570 nM was measured and OD values from each well were subtracted with vehicle control and percent inhibition and cell viability were calculated by using the same method described for the ATP assay.

4.2.5. ROS assay

10,000 HT-22 cells per well were seeded in black/clear bottom plate and treated with each compound and amyloid Beta in Opti-MEM for 6 h. Cells were washed once with HBSS. 100 μL of CM-H_2DCFDA (Invitrogen C6827) solution, prepared from dilution of 2 μL of the 1 mM stock solution into 2 mL media (HBSS), was added into each well. Cells were incubated at 37 °C for 30 min and washed twice with HBSS. 100 μL of nuclear staining (Hoechst), prepared from dilution of 1 μL of nuclear staining into 1 mL HBSS, were added into each well. ROS production was measured by capturing fluorescent images from each well, then calculated the total signal intensity from each well by using Operetta high content screening system (Perkin Elmer). Percent inhibition against amyloid beta-induced ROS production was determined by calculating percent ratio of the increased total signal intensity from compounds treated cells to untreated cells in the presence of $A\beta_{1-42}$.

4.3. Evaluation of stability and pharmacokinetics

4.3.1. Plasma stability

To determine the stability of the selected compounds in plasma, a stock solution of each compound in acetonitrile (50 μg/mL) was spiked into polyethylene tubes containing drug free rat plasma to produce a concentration of 0.5 μg/mL. Each tube was incubated in a water-bath shaker kept at 37 °C for 0, 15, 30, 60, and 120 min, respectively. At each time point, 2× volume of acetonitrile containing carbamazepine (internal standard) was added to the plasma sample. The plasma samples were then centrifuged and the supernatants were analyzed by LC–MS/MS.

4.3.2. HLM (human liver microsomes) stability assay

To determine the microsomal stability of the selected compounds, pooled human liver microsomes (HLM's) containing 20 mg/mL of total protein were used and purchased from BD Biosciences (Bedford, MA). A compound was incubated with HLM at 37 °C, in the presence of an NADPH, in a final incubation volume of 200 μL. The final incubation solutions contain 1 μM of the compound, 1.2 mM NADPH, 0.5 mg/mL (total protein) microsomes, 100 mM phosphate buffer (pH 7.4). The incubation tubes were then incubated in a water-bath shaker at 37 °C for 30 min. At the time point, two incubation tubes were removed from the water-bath for duplicate and the reaction was terminated immediately. The 400 μL of ice-cold acetonitrile containing 0.1 μg/mL of internal standard was added to microsomal incubate to terminate the reaction and precipitate the proteins. The incubation solutions were then centrifuged and the supernatants were analyzed by LC–MS/MS.

4.3.3. Pharmacokinetic studies

Each compound at a dose of 10 mg/kg was administered intravenously or orally to male Sprague Dawley rats. Blood samples were collected via carotid artery at 0 (to serve as a control), 1′ (IV only), 5′, 15′, 0.5, 1, 2, 4, 6, and 8 h after administration of each compound. After centrifugation at 3000 rpm for 10 min, a 50-μL aliquot of plasma samples were stored at −70 °C until analysis. Pharmacokinetic parameters were determined by a non-compartmental analysis using WinNonlin® (Pharsight Corporation, Mountain View, CA) program. The total area under the plasma concentration–time curve from time zero to last measured time (AUC_{last}) was calculated by the trapezoidal rule–extrapolation method. Standard methods were used to calculate the following pharmacokinetic parameters [23]; the time-averaged total body clearance (CL), total area under the first moment of plasma concentration–time curve from time zero to time infinity ($AUC_{0-\infty}$), terminal half-life, mean residence time (MRT), apparent volume of distribution at steady state (V_{ss}). Animal experimentation was performed according to Guidelines for Accommodation and Care of Animals.

4.3.4. Quantitative analysis

Concentrations of each compound in the above samples were analyzed using LC-MS/MS. To a 50 μL aliquot of plasma sample, a 100 μL aliquot of acetonitrile containing 0.1 μg/mL of internal standard was added. After vortex mixing and centrifugation at 10,000 rpm for 10 min, a 5 μL of supernatant was injected onto LC–MS/MS system. The LC–MS/MS system consisted of a HP1100® HPLC system (Agilent, Santa Clara, CA) and API3200® triple-quadrupole mass spectrometer (Applied Biosystems-SCIEX, Concord, Canada). The HPLC mobile phases consisted of 0.1% formic acid (A) and 0.1% formic acid in 90% acetonitrile (B). Chromatographic separation was achieved on a reversed-phase Xterra® C_{18} column (50 × 2.1 mm, 3.5 μm, Waters Corporation, Milford, MA) using gradient elution at a flow rate of 0.3 mL/min. The lower limit of quantitation of each compound in rat plasma was 5 ng/mL. The values of coefficients of correlation (R) were more than 0.997.

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