Chemoselective Hydrogenation of 6-Alkynyl-3-fluoro-2-pyridinaldoximes: Access to First-in-Class 6-Alkyl-3-Fluoro-2-pyridinaldoxime Scaffolds as New Reactivators of Sarin-Inhibited Human Acetylcholinesterase with Increased Blood–Brain Barrier Permeability

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Chemoselective Hydrogenation of 6-alkynyl-3-fluoro-2-pyridinaldoximes: Access to *first-in-class* 6-alkyl-3-Fluoro-2-pyridinaldoxime scaffolds, as New Reactivators of Sarin-Inhibited *human*-Acetylcholinesterase with increased Blood Brain Barrier Permeability

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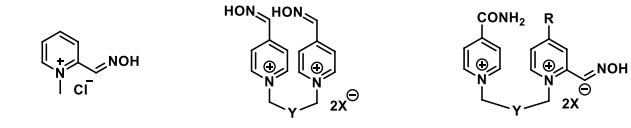
Abstract: Novel 6-alkyl- and 6-alkenyl-3-fluoro-2-pyridinaldoximes have been synthesized using a mild and efficient chemoselective hydrogenation of 6-alkynyl-3-fluoro-2-pyridinaldoxime scaffolds, without altering the reducible unprotected sensitive oxime functionality, and the C-F bond. These novel 6-alkyl-3-fluoro-2-pyridinaldoximes may find medicinal application as antidotes for organophosphates poisoning. Indeed, low molecular weight compound **12d** exhibited increased affinity for sarin inhibited acetylcholinesterase (*h*-AChE), and greater reactivation efficiency or resurrection for sarin-inhibited *h*-AChE, compared to 2-pyridinaldoxime (2-PAM) and HI-6, two pyridinium salts currently used as antidote by several countries. In addition, the uncharged 3-fluorinated bifunctional hybrid **12d** showed increased *in vitro* BBB permeability as compared to 2-PAM, HI-6 and obidoxime. These promising features of novel low molecular weight alkylfluoropyridinaldoxime open a new era for the design, synthesis and discovery of central non-quaternary broad spectrum reactivators for OP-inhibited cholinesterases.

1. Introduction

Currently, pyridinium- and bispyridiniumaldoximes are medically approved as antidotes for the treatment of acute organophosphate poisoning (Figure 1).[1] It is estimated that 3 millions of unintentional and intentional intoxications occur each year, accounting for an estimated 300 000 death per year.[2] Organophosphorous nerve agents (OPNA) developed initially as pesticides,[3] have been used as chemical warfare agent (CWA) in asymmetric conflicts, terrorist attacks, and recently criminal acts.[4] OPNA are extremely toxic as they phosphorylate the catalytic serine residue of acetylcholinesterase (AChE), an enzyme essential to humans and other species for neurotransmission.[5] They act as potent irreversible inhibitors of AChE and consequently lead to a cholinergic syndrome, and ultimately to death.[5] Several reports and clinical studies mention that the current antidotal treatment based on pyridinium aldoximes are not efficient enough.[5] Beside this limitation, they have low tendency to cross the blood-brain barrier (BBB) due to their permanent positive charge, and exhibit limited bioavailability in the central nervous system (CNS).[1,6,7]



Pralidoxime (2-PAM) : **1**

Trimedoxime : **2** (Y = CH_2, X = Br)
Obidoxime : **3** (Y = O, X = Cl)

Asoxime or HI-6 : **4** (R = H, X = Cl)
HLo-7 : **5** (R = C=NOH, X = CH_3SO_3)

Figure 1: Pyridiniumaldoxime reactivators in the market and currently developed as antidotes.

These drawbacks are one of the major limitations for the clinical development of centrally active quaternary pyridinium-based reactivators of OPNA inhibited AChE. Moreover, unequal efficacy of pyridinium oximes against different type of OPNA, CWA and pesticides is well known and reported.[6d] The recent intentional use of Novichock, a fourth generation OP,[8] against Serguei Skripal in Salisbury shows the growing importance to develop new broad spectrum antidotes, with superior reactivating potencies, and central therapeutic effectiveness, to counteract OPNA poisoning, and protect and treat both civilian and military populations.

To increase accessibility to CNS of reactivators and overcome their low bioavailability and limited pharmaco-distribution, non-symmetrical uncharged hybrid AChE reactivators bearing 3-hydroxy-2-pyridinaldoxime moiety **6**[9] and a peripheral site ligand (PSL), have been developed over the past few years (Figure 2).[10,11] This original approach led to the discovery of *in vitro* potent reactivators of OPNA inhibited AChE compared to positively charged 2-PAM and HI-6 that are currently fielded. For example, neutral hybrids **7**-**10** (Figure 2) exhibited a broad spectrum, and enhanced reactivation efficacy towards tabun, VX, sarin and paraoxon inhibited AChE.[10,11]

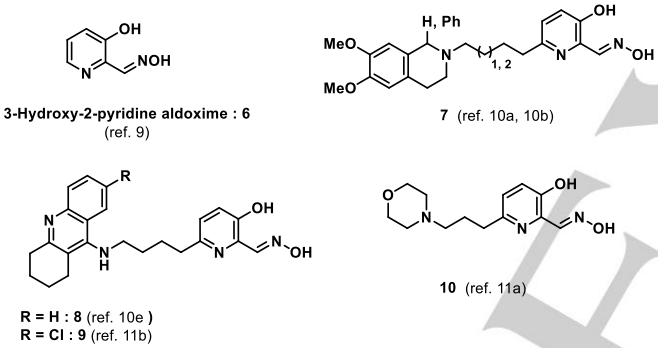


Figure 2: Selected structures of non-quaternary *h*AChE hybrid reactivators.

2. Results and Discussion

Furthermore, based on their physicochemical properties, the potency of some of these oximes to cross the BBB was predicted by *in silico* studies (compound **10,** Figure 2), and by *in vitro* parallel artificial membrane permeation assays.[11a] These data support the fact and demonstrate that non-quaternary hybrid reactivators based on 3-hydroxy-2-pyridinaldoxime are promising candidates for the optimization of new antidotes for OPNA poisoning, for the future.[10-11] Notably, tremendous efforts have been devoted recently to the development of synthetic approaches toward the synthesis of novel reactivators, including the use of PSL ligand-oxime conjugates and Ugi MCR reactions,[12] the use of chloropyridinium oximes,[13] and the development of non-oxime based reactivators.[14] Nevertheless, the narrow therapeutic window of some of these reactivators limits their use *in vivo* because of the lack of comprehensive biological profiling, which is largely hampered by synthetic accessibility. Despite the recently reported strategies, efforts toward the development of more efficient synthetic routes to create centrally active reactivators have been scarce**.**

In this context, and following our investigations on the synthesis of 6-alkyl-3-hydroxy-2-pyridinaldoxime as non-quaternary hybrid reactivators (Fig. 2),[10-11] we hypothesized that the substitution of the polar 3-hydroxy group on the pyridine ring, with a more electronegative and electron-withdrawing group such as fluorine, would provide reactivator with greater lipophilicity and BBB permeability, compared to pyridinium salts. Incorporation of fluorine atom into drugs often leads to a significant improvement of their medicinal properties, resulting in increased bioavailability and enhanced metabolic and biological membranes permeability.[15] In addition, fluorine is known to modulate the pk_a of the proximal oxime, the conformational bias and the binding properties *via* molecular interactions.[16] One of the most notable aspects of this synthetic strategy is that, the substitution of the 3-hydroxy group with fluorine would also prevent the extensive use of orthogonal hydroxyl protecting groups, shortening the overall synthetic processes.[10-11] Finally, we emphasized that the use of non-ionic bifunctional hybrids bearing fluoropyridinaldoxime may give access to novel reactivators with increased therapeutic performances.

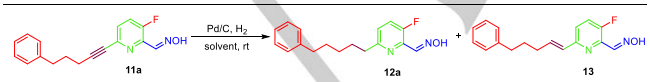
Herein we report the successful development of a chemoselective hydrogenation and semi-hydrogenation of 6-alkynyl-3-fluoro-2-pyridinaldoximes that affords first-in-class new 6-alkyl- and 6-alkenyl-3-fluoro-2-pyridinaldoximes. These new scaffolds may found a medicinal application as reactivators of OP-inhibited *h*AChE as demonstrated by the efficiency of **12d**, to reactivate selectively *in vitro* sarin-inhibited *h*AChE. The observed results for **12d** surpassed the efficiency of both 2-PAM and HI-6. In addition, we also report on the ability of **12d** to cross the BBB *in vitro*, better that 2-PAM, HI-6 and obidoxime. This unique synthetic strategy allows the expedient and efficient synthesis of new fluorinated hybrid reactivators for biological profiling and improved therapeutic window compared to medically approved pyridinium aldoximes.

2.1. Chemical Synthesis 6-alkyl-3-fluoro-2-pyridinaldoximes

Having set our hypothesis from a structural standpoint, the next challenge was to find an efficient access to 6-alkyl-3-fluoro-2-pyridinadoxime scaffolds, eventually from the corresponding 6-alkynyl-3-fluoro-2-pyridinadoxime recently described.[17] While the metallic reduction and metal-catalyzed (Pd, Ni, Pt) hydrogenation reactions of pyridyloxime derivatives, leading to the corresponding hydroxylamine or amine are known,[18] hydrogenation of fluoropyridinaldoximes are rare.[17] In particular, selective hydrogenation of more functionalized alkynylfluoropyridinaldoxime[17] represents an attractive goal for method development because of the prevalence of alkylpyridines in natural products and pharmaceutical agents.[19] One strategy to achieve chemoselective alkyne hydrogenation in

such substrates is to fine-tune the reaction conditions that govern the reduction kinetics of the oxime and the alkyne functionalities. Therefore, challenges with this strategy lies to some extent by adjustment of the reaction time, solvent, reaction temperature, and palladium catalyst nature and loading. In this context of recent efforts from our laboratory on the hydrogenation of alkynylfluoropyridinaldoximes, we found that the alkyne functionality could be reduced or semi-reduced, under palladium catalysis and in neutral conditions, using unoptimized conditions.[17] While we could have expected the concomitant reduction of the oxime to the amine and/or the reduction of C-F bond, in our unoptimized reaction conditions (Pd/C, MeOH, H_2 1 atmosphere, rt), the reported two examples of alkylfluoropyridinaldoximes, were obtained in low to moderate yields. It is evident that despite the significant advances outlined above, a mild scalable and general synthetic method to provide selectively alkylfluoropyridinaldoxime and/or alkenylfluoropyridinaldoxime was still lacking. Herein we disclose, to the best of our knowledge, the first chemoselective Pd-catalyzed hydrogenation and semi-hydrogenation of alkynylfluoropyridinaldoxime. The method is notable in that (i) it is selective; (ii) it prevents the concomitant over reduction of the oxime function to the primary amine or hydroxylamine, (iii) it prevents the reduction of the C-F bond; and (iv) a wide range of functional groups are tolerated. The origin of the selectivity for the semi-hydrogenation is still unknown and it seems that it is sensitive and dependent to the nature of the substrate. Further exploration on the hydrogenation reaction mechanism is still in progress in our laboratory.

With the above analysis in mind, we first investigated the hydrogenation of model substrate **11a**, as shown in Table 1. Taking inspiration from previous work, we decided to use alcohols as solvent and 5 mol% Pd/C(w/w) as the catalyst under one hydrogen atmosphere at room temperature, in the hope of accessing serviceable chemoselectivity. When EtOH was used, a mixture of the desired alkyl product **12a** was formed along with the semi-hydrogenated (*E*)-alken **13** in a 4/1 ratio, with a high conversion of the starting alkynyl reagent (92%), and after quite a long reaction time (Entry 1). The use of methanol, in the same experimental conditions gave exclusively the alkyl **12a**, after 5 h of reaction, at 66% conversion of **11a** (entry 2). Attempts to prolong the reaction time in MeOH did not improve significantly the conversion of **11a**. Exhaustive experiments revealed that the use of a 1/1 (v/v) MeOH/EtOAc mixture as solvent drastically promoted the hydrogenation providing the desired product in 96% of isolated yield after 2h of reaction (entry 3).



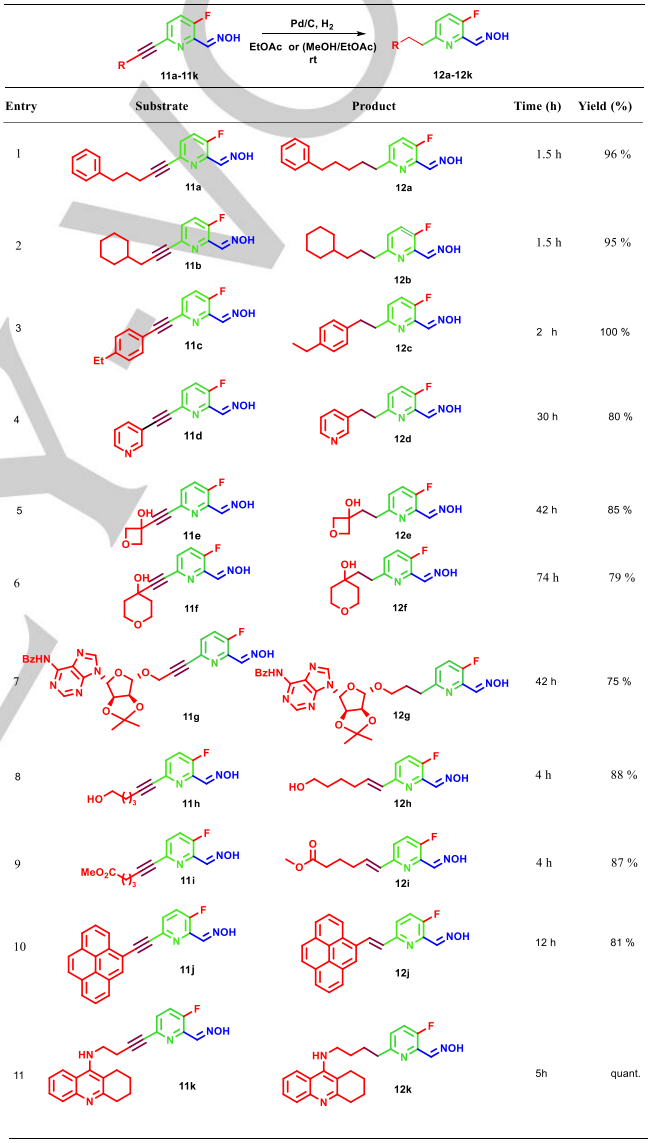
Entry	Solvent	Reaction time	Products (12a : 12b)	conversion of 11a
1	EtOH	48h	4 : 1	92 %
2	MeOH	5h	1 : 0	66 %
3	MeOH/EtOAc	2h	1 : 0	96 %[a]
4	EtOAc	1.5h	1 : 0	96 %[a]

a : isolated yield of **12a**

Table 1: Optimization of the hydrogenation conditions for **11a**

Further screening of palladium catalysts showed that the combination of Pd/C and EtOAc could promote the fast alkyne reduction of **11a** to give chemoselectively the product **12a** in almost quantitative yield in 90 min, without altering the oxime function and with no trace of the semi-reduced (*E*)-alken **13** (entry 4). With the optimized reaction condition in hand, substrate scope was examined, and the results are summarized in Table 2.

Table 2. Pd/C-catalyzed hydrogenation of 6-alkynyl-3-fluoro-2-pyridinaldoximes



Substrate **11b** was suitable for the transformation to give **12b** in 95% yield (entry 2). Similarly, the substrate **11c** with the aromatic ring was also compatible to the reaction conditions, affording product **12c** in quantitative yield (entry 3). Furthermore, substrates with different heterocycles were surveyed. Reaction of pyridyl derivative **11d** (entry 4) occurred smoothly with increased reaction time (30 h), and the corresponding alkylpyridine product **12d** was observed as the major compound in high yield. In the case of the congested and sterically

hindered cycloalkyl reagents such as hydroxyl-oxetane **11e** and hydroxyl-tetrahydropyran **11f** substrates, the reactions proceeded with longer reaction time at room temperature to reach full conversion, and afforded respectively products **12e** and **12f** in good isolated yields 85% and 79% respectively (entry 5, 6). For **11e** and **11f**, the extended reaction time, ascribed to the steric hindrance, was privileged instead of increasing the temperature of the reaction.The functional group tolerance was also evaluated and included, amide, acetonide, and sugar acetal in the reaction conditions for **11g** (entry 7), **12g** was obtained in 75% yield. Unexpectedly, when substrate having unprotected primary alcohol **11h**, ester **11i** and pyrene derivative **11j** were used (entry, 8, 9, 10), the corresponding semi-hydrogenated alkenyl **12h**, **12i**, and **12j** were formed exclusively, in quite high yield, without any traces of the fully hydrogenated alkyl compounds. The origin of this selectivity is still unknown and further studies are underway in our laboratory for the rationalization of these results. Further, we extended the synthetic potential of this current protocol to substrate **11k**, which afforded the desired product **12k** in quantitative yield (entry 11). **12k** is the 3-fluorinated analogue of **8** (Fig. 2), that is a known broad spectrum reactivator reported by our group recently.[10e]

Having in hands the new 3-fluoro-5-alkyl-2-pyrinaldoximes we decided to evaluate their ability to reactivate OPNA-inhibited AChE *in vitro*. As a proof of principle and for practical reasons, we investigated first the reactivity of compounds **12d** and **12k** which were greatly soluble in water, as hydrochloride form, and because of their structural design that is reminiscent of PSL-ligand oxime reactivators[10e]

2.2. In vitro reactivation of 12d and 12k

The abilities of 3-fluoro-2-pyridinaldoxime **12d** and **12k** as hydrochlorides to reactivate *in vitro* VX-, tabun- and sarin inhibited human AChE were investigated by spectrophotometry using the Ellman's reaction. Reactivation kinetics were compared to those of known reactivators 2-PAM and HI-6. We investigated first the potency of **12k**, for additional comparison with the known 3-hydroxy-2-pyridinaldoxime analogue 8 (Figure 2). Surprisingly, for **12k** the substitution of the 3-OH by a 3-F was accompanied with a dramatic loss of affinity for OP-inhibited *h*AChE compared to **8**, and no reactivation was observed in the range of the tested concentrations, for VX-, sarin and tabun inhibited *h*AChE. In contrast, **12d** was found to display higher affinity (K_D in µM) and lower reactivation rate (k_r in min^{-1}), leading to lower reactivation efficiency (k_{r2} in $mM^{-1}.min^{-1}$) towards VX-inhibited *h*AChE, in comparison with both 2-PAM and HI-6. In the case of sarin-inhibited *h*AChE, **12d** showed greater affinity and higher reactivation efficiency (kr_2 = 83 $mM^{-1}.min^{-1}$) than 2-PAM and HI-6. **12d** is found to be 7 times more efficient in the reactivation of sarin inhibited AChE compared to 2-PAM, and 6 times more efficient than HI-6. However, **12d** was found totally inefficient in reactivating tabun inhibited *h*AChE (Table 3) like HI-6. The *in vitro* efficacy of **12d** is evidenced for the first time for uncharged hybrid 3-fluoro-2-pyridinaldoxime. In order to shed light on the impact and the importance of the 3-fluorine atom proximal to the oxime functionality of non-elongated reactivator **12d**, compared to the 3-OH group on the pyridine moiety, we evaluated the efficacy of the substrate analogue **14**, [20] bearing a 3-OH group in place of the 3-F, to reactivate OPNA-inhibited AChE (Figure 3).

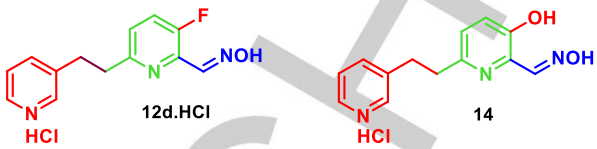


Figure 3 : Structure of **13** the 3-hydroxy analogue of **12d.HCl**.

Interestingly, the overall efficacy (k_{r2}) of **12d** as compared to **14** was 2 times (k_{r2}= 2) higher for VX (k_{r2} = 4) and 6 times (k_{r2} = 83) greater for sarin inhibited AChE, while compound **14** could reactivate tabun inhibited *h*AChE 2 times (k_{r2} = 0.5) higher than 2-PAM, in contrast to **12d**.

Table 3: Reactivation of OP-inhibited human hAChE by oximes 2-PAM, HI-6, **12d** and **14**

OP	Oxime	k_r (min^{-1})	K_D (µM)	k_{r2} (mM^{-1} min^{-1})
VX				
	2-PAM	0.2 ± 0.013	26 ± 7	7
	HI6	0.4 ± 0.02	19 ± 4	20
	8	0.72±0.07	31±6	22[11b]
	12k	0	0	0
	12d	0.04 ± 0.001	10 ± 2	4
	14	0.5 ± 0.04	250 ± 50	2
Sarin				
	2-PAM	0.3 ± 0,02	25 ± 7	11
	HI6	0.8 ± 0.06	57 ± 11	13
	8	0.33±0.01	20±3	16.5[11b]
	12k	0	0	0
	12d	**0.15 ± 0.006**	**2 ± 0.5**	**83**
	14	0.10 ± 0.003	9 ± 1	11
Tabun				
	2-PAM	0.5 ± 0.2	210 ± 110	2
	HI6	0	0	0
	8	0.021±0.001	7.1±1.5	3[11b]
	12k	0	0	0
	12d	0	0	0
	14	nd	nd	0.5

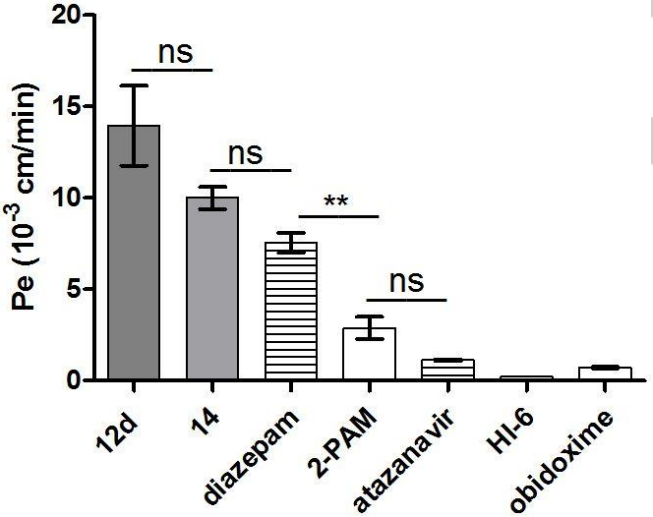
These *in vitro* results demonstrated that the substitution of a 3-OH by a 3-F on neutral hybrid reactivators may be a valid strategy for the development of new generation antidotes for OP-poisoning. According to the results observed for the fluorinated reactivator **12d** and **12k**, compared to their

respective 3-OH analogues, the overall efficacy remains dependant on the length and on the chemical structure of the PSL hybride.

Having demonstrated the efficacy of **12d** to reactivate sarin-inhibited *h*AChE compared to 2-PAM, HI-6, and the 3-hydroxylated analog **14**, we then investigated its ability to cross efficiently the BBB using a human *in vitro* essay.

2.3. BBB permeability

To evaluate the ability of the uncharged fluoropyridinaldoxime **12d** and the analogue **13** to cross the blood-brain barrier in order to reach the brain parenchyma, we made use of our *in vitro* model of human brain-like endothelial cells (BLECs), in which cord blood stem cell–derived endothelial cells cocultured with pericytes express mature BBB features such as a continuous network of tight junctions between endothelial cells, the expression of specific transporters and a low permeability to small molecular weight tracers.[21,22] We first assessed the toxicity of **12d** and **14**, 2-PAM, HI-6 and obidoxime on the *in vitro* BBB endothelium as compared to control condition (RH + 0.125% DMSO) in evaluating the diffusion of Lucifer Yellow (LY), a fluorescent hydrophilic small molecular weight (0.45kDa) integrity tracer, upon 1h- oxime treatment at 50µM. Endothelial permeability coefficient (Pe) of LY was thus generated as described earlier,[23] and expressed in cm/min ± SD. We could not detect any toxic effect of any of the tested aldoxime as no significant difference in the permeability coefficient value (Pe) of



LY was observed between groups (control: 0.68 ± 0.15 x 10^{-3} cm/min; +**12d**: 0.99 ± 0.10 x 10^{-3} cm/min; **+14**: 0.53 ± 0.05 x 10^{-3} cm/min; +HI-6:0.60 ± 0.10 x 10^{-3} cm/min; +2-PAM:0.65 ± 0.17 x 10^{-3} cm/min; +obidoxime: 0.45 ± 0.07 x 10^{-3} cm/min).

Figure 4 : BBB permeability. Endothelial permeability coefficients (Pe, expressed in cm/min ± SD) of new reactivators (**12d** and **14)**, compared to current aldoximes 2-PAM, HI-6, obidoxime and to diazepam and atazanavir. Pe were measured in the human *in vitro* BBB model at 50µM. Data were analyzed by the GraphPad Prism software. Statistical comparisons were performed using an unpaired t-test (Mann-Whitney). **p<0.01, n=3 at least.

Then, the BBB permeability to **12d** and **14** were compared to the BBB permeability to 2-PAM, HI-6 and obidoxime at 50 µM upon 1h-treatment. A LC-M/MS system (AB SCIEX TripleTOF® 5600 mass spectrometer) was used for the quantification and so that the calculation of the permeability coefficients of these molecules. Diazepam and atazanavir for which transports across the BBB are described in the litterature have also been tested in the *in vitro* BBB model at 50µM. Diazepam is a lipophilic drug which, thanks to passive diffusion, rapidly crosses the BBB[24] while protease inhibitors such as atazanavir may not enter into the CNS easily.[25]

Pe of the current aldoxime 2-PAM ($Pe_{2\text{-}PAM}$=2.88 ± 1.81 x 10^{-3} cm/min) (Figure 4) was not significantly different of Pe of atazanavir ($Pe_{atazanavir}$=1.13 ± 0.08 x 10^{-3} cm/min) known to cross relatively slowly the BBB. Pe of obidoxime ($Pe_{obidoxime}$=0.72 ± 0.08 x 10^{-3} cm/min) and HI-6 ($Pe_{HI\text{-}6}$=0.23 ± 0.01 x 10^{-3} cm/min) were lower than those of 2-PAM. 2-PAM and diazepam Pe values presented a significant difference and diazepam ($Pe_{diazepam}$= 7.54 ± 0.95 x10^{-3} cm/min) is usually described to cross rapidly the BBB. The diffusion of **12d** ($Pe_{\mathbf{12d}}$=13.96 ± 5.35 x 10^{-3} cm/min) and **14** ($Pe_{\mathbf{13}}$=10.00 ± 1.06 x 10^{-3} cm/min) across the hBLEC monolayer was higher as compared to the BBB permeability to the current pyridinium aldoximes 2-PAM, obidoxime and HI-6 (Figure 4). The rate of diffusion of **14** was in the same range of the one of diazepam while $Pe_{\mathbf{12d}}$ presented a slightly increased Pe value compared to diazepam.

3. Conclusion

A highly chemoselective hydrogenation reaction of 6-alkynyl-3-fluoro-2-pyridinaldoximes has been developed, giving access to novel 6-alkyl-3-fluoro-2-pyridinaldoxime and 6-alkenyl-3-fluoro-2-pyridinaldoxime scaffolds.This method offers significant advantages such as mild reaction conditions, broad substrate scope, high conversions, and excellent yields. Fluoropyridinaldoxime hybrids, such as compound **12d** may found an application as low molecular weight central antidote for OPNA poisoning, as demonstrated by its ability to selectively reactivate *in vitro,* sarin-inhibited *h*AChE, and to exhibit an increased *in vitro* BBB permeability, 10 to 135 fold, compared to 2-PAM and HI-6, respectively. The study of the biological properties of the synthesized library of compounds is under progress in our laboratories, as well as structure activity relationship (SAR) investigations.

Experimental Section

All starting materials and reagents were purchased from commercial sources, and used as received without further purification. Air and H_2O sensitive

reactions were performed in flame dried glassware under Ar atmosphere. Moisture sensitive reagents were introduced via a dry syringe. Anhydrous solvents were supplied over molecular sieves, and used as received. Petroleum ether (PE) refers to the 40-60 °C boiling fraction. Reactions were monitored by thin-layer chromatography (TLC) with silica gel 60 F_{254} 0.25 mm pre-coated glass plates. Compounds were visualized by using UV_{254} and/or phosphomolybdic acid stain [3 g $12MoO_3.H_3PO_4.xH_2O$ in 100 mL EtOH] followed by heating with a heat gun. Flash column chromatography was performed using Macherey-Nagel silica gel 60 (15–40 µm). NMR experiments were recorded with a Bruker Avance 400 spectrometer at 400 MHz for ^{1}H nuclei and at 100 MHz for ^{13}C nuclei. The chemical shifts are expressed in part per million (ppm) relative to TMS (δ = 0 ppm) and the coupling constant *J* in Hertz (Hz). NMR multiplicities are reported using the following abbreviations: br = broad, s = singlet, d = doublet, t = triplet, q = quadruplet, m = multiplet. HRMS were recorded on a Bruker micrOTOF spectrometer.

3-fluoro-6-(5-phenylpentyl)picolinaldehyde oxime 12a: To a degassed solution of fluorooxime **11a** (50 mg, 0.177 mmol, 1 equiv) in dry EtOAc (3 mL), 10% Pd/C (4.7 mg, 0.0177 mmol, 0.25 equiv) was added. After flushing with H_2 three times, the reaction mixture was stirred at room temperature under H_2 (1 atm.) for 90 min. Upon completion (monitored by TLC), the catalyst was removed by filtration through a short column of celite, the solvent was evaporated, and the residue was purified by column chromatography (EtOAc/PE, 1/9) to afford oxime **12a** as a white solid (50 mg, 96%); R_f (20 % EA+PE) 0.50; IR (neat): ν_{max} 3281, 3026, 2929, 2856, 1603, 1468, 1454, 1247, 1112, 980, 834, 745, 698, 642, 543, 499 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$); δ (ppm) 9.94 (br s, 1H), 8.30 (s, 1H), 7.31-6.98 (m, 7H), 2.72 (t, *J* = 7.7 Hz, 2H), 2.52 (t, *J* = 7.7 Hz, 2H), 1.67 (quintet, *J* = 7.7 Hz, 2H),1.58 (quintet, *J* = 7.7 Hz, 2H);1.31 (quintet, *J* = 7.3, 7.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 158. 80, *158.67, 157.70, *155.10, 144.98, *144.94, 142.58, 138.26, *138.16, 128.34, 128.23, 128.16, 125.55, 124.36, 124.33, *124.16, 37.37, 35.72, 31.16, 29.64, 28.77 (*doubling of the peaks were observed due to the coupling of carbons with fluorine atom); ^{19}F NMR (400 MHz, $CDCl_3$): δ (ppm) -128.97; HRMS (ESI$^+$): *m/z* calcd for $C_{17}H_{20}F_1N_2O_1^+$287.1554 found 287.1542.

6-(3-cyclohexylpropyl)-3-fluoropicolinaldehyde oxime 12b: To a degassed solution of fluorooxime **11b** (30mg, 0.115 mmol, 1 equiv) in dry EtOAc (3 mL), 10% Pd/C (6 mg, 0.058 mmol, 0.5 equiv) was added in two portions. After flushing with H_2 three times, the reaction mixture was stirred at room temperature under H_2 (1 atm.) for 90 min. Upon completion (monitored by TLC), the catalyst was removed by filtration through a short column of celite, the solvent was evaporated, and the residue was purified by preparative TLC (EtOAc/PE, 1/4) to afford oxime **12b** as a light yellowish solid (29 mg, 95%); R_f (20% EA+PE) 0.60; IR (neat): ν_{max}3277, 2923, 2849, 1588, 1472, 1441, 1244, 1124, 987, 947, 841, 805, 754, 736, 719, 666, 585 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.69 (br s, 1H, OH), 8.36 (s, 1H), 7.33 (dd, *J* = 8.6, 10.0 Hz, 1H), 7.12 (dd, *J* = 3.8, 8.6 Hz, 1H), 2.75 (t, *J* = 7.8 Hz, 2H), 1.73-1.57 (m, 7H), 1.25-1.12 (m, 6H), 0.88-0.78 (m, 2H); **^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 158.99, *158.94, 157.74, *155.14, 145.17, *145.14, 138.23, *138.13, 124.34, 124.14, 37.84, 37.50, 37.06, 33.31, 27.25, 26.66, 26.36 (* doubling of the peaks were observed due to the coupling of carbons with fluorine atom); ^{19}F NMR (400 MHz, $CDCl_3$) δ (ppm) -128.32, -129.07 {1:15 ratio of *cis-trans* oxime isomers}; HRMS (ESI$^+$) *m/z* calcd for $C_{15}H_{22}F_1N_2O_1^+$265.1711 found 265.1703.

6-(4-ethylphenethyl)-3-fluoropicolinaldehyde oxime 12c: To a degassed solution of fluorooxime **11c** (35 mg, 0.130 mmol, 1 equiv) in dry EtOAc (3 mL), 10% Pd/C (7 mg, 0.065 mmol, 0.5 equiv) was added. After flushing with H_2 three times, the reaction mixture was stirred at room temperature under H_2 (1 atm.) for 2 h. Upon completion (monitored by TLC), the catalyst was removed by filtration through a short column of celite, the solvent was evaporated, and the residue was purified by preparative TLC (EtOAc/PE1:4) to afford oxime **12c** as a light yellowish solid (35 mg, quant. yield); R_f (20 % EA+PE) 0.45;IR (neat) ν_{max}3273, 2961, 2926, 2864, 1512, 1472, 1455, 1241, 1180, 984, 836, 724, 657, 577, 512, 467 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.41 (s, 1H), 7.31 (dd, *J* = 8.6, 9.8 Hz, 1H), 7.15-6.99 (m, 6H), 3.10 (m, 2H), 3.01 (m, 2H), 2.60 (q, *J* = 7.6 Hz, 2H), 1.21 (t, *J* = 7.6 Hz, 3H);^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 157.82, *155.22, 157.72, *157.68, 145.01, *144.98, 141.85, 138.47, *138.37, 138.31, 128.39, 127.81, 124.70, *124.66, 124.30, *124.11, 39.27, 35.39, 28.39, 15.58 (* doubling of the peaks were observed due to the coupling of carbons with fluorine atom); ^{19}F NMR (400 MHz, $CDCl_3$) δ (ppm) -128.62; HRMS (ESI$^+$) *m/z* calcd for $C_{16}H_{18}F_1N_2O_1^+$273.1398 found 273.1388.

3-fluoro-6-(2-(pyridin-3-yl)ethyl)picolinaldehyde oxime 12d: To a degassed solution of fluorooxime **11d** (30 mg, 0.124 mmol, 1 equiv) in dry EtOAc (3 mL), 10% Pd/C (10 mg, 0.093 mmol, 0.75 equiv) was added in three portions. After flushing with H_2 three times, the reaction mixture was stirred at room temperature under H_2 (1 atm.) for 30 h. Upon completion (monitored by TLC), the catalyst was removed by filtration through a short column of celite, the solvent was evaporated, and the residue was purified by preparative TLC (EtOAc/PE, 4/1) to afford oxime **12d** as a white solid (25 mg, 82%); R_f (80% EA+PE) 0.20; IR (neat): ν_{max} 2925, 2853, 2713, 1738, 1579, 1469, 1244, 1176, 1119, 979, 823, 809, 709, 669, 642, 506 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 11.04 (br s, 1H), 8.45 (br d, *J* = 1.8 Hz, 1H), 8.30 (dd, *J* = 1.5, 4.5 Hz, 1H), 8.22 (s, 1H), 7.62 (dt, *J* = 1.8, 7.8 Hz, 1H), 7.53 (dd, *J* = 8.5, 10.4 Hz, 1H), 7.31-7.20 (m, 2H), 3.16-3.07 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 158.61, *156.0, 157.54, *157.49, 150.97, 148.32, 147.22, *147.16, 137.76, 136.70, 125.42, *125.33, 125.29, 125.*23, 124.14, 39.08, 33.03 (* doubling of the peaks were observed due to the coupling of carbons with fluorine atom); ^{19}F NMR (400 MHz, $CDCl_3$): δ (ppm) -127.24; HRMS (ESI$^+$): *m/z* calcd for $C_{13}H_{13}F_1N_3O_1^+$246.1037 found 246.1032.

3-(2-(5-fluoro-6-((hydroxyimino)methyl)pyridin-2-yl)ethyl)pyridin-1-ium chloride 12d.HCl: To the compound **12d** (1 equiv) in methanol (0.5 mL), was added 1.2 N HCl (0.5 mL). The reaction mixture was agitated for 10 min at rt, and then was concentrated under reduced pressure to get the HCl salt of **12d.HCl** as a white solid in quantitative yield. ^{1}H NMR (400 MHz, D_2O): δ (ppm) 8.66-8.62 (m, 2H), 8.47-8.39 (m, 2H), 8.01-7.94 (m, 2H), 7.62 (dd, *J* = 4.2, 8.8 Hz, 1H), 3.38-3.30 (m, 4H); ^{13}C NMR (100 MHz, D_2O): δ (ppm) 158.78, *156.20, 155.15, *155.11, 147.89, 142.05, 141.27, 141.10, 139.89, 136.97, *1136.78, 131.08, *130.89, 128.31, *128.25, 127.80, 35.18, 32.17 (* doubling of the peaks were observed due to the coupling of carbons with fluorine atom); ^{19}F NMR (400 MHz, D_2O): δ (ppm) -119.42, -124.91 (*cis-trans* oxime isomers); HRMS (ESI$^+$) *m/z* calcd for $C_{13}H_{13}F_1N_3O_1^+$ 246.1037 found 246.1019.

3-fluoro-6-(2-(3-hydroxyoxetan-3-yl)ethyl)picolinaldehyde oxime 12e: To a degassed solution of fluorooxime **11e** (45mg, 0.191 mmol, 1 equiv) in dry EtOAc (3 mL), 10% Pd/C (20 mg, 0.076 mmol, 1equiv) was added in two portions. After flushing with H_2 three times, the reaction mixture was stirred at room temperature under H_2 (1 atm.) for 42 h. Upon completion(monitored by TLC), the catalyst was removed by filtration through a short column of celite, the solvent was evaporated, and the residue was purified by preparative TLC (pure EtOAc) to afford oxime **12e** as a light yellowish solid (40 mg, 85%); R_f (pure EA) 0.35;IR (neat): ν_{max} 3352, 2948, 2876, 1592, 1472, 1450, 1311, 1260 , 1223, 1110, 948, 964, 833, 643, 542, 526, 469 cm^{-1}; **^{1}H NMR (400

MHz, $CDCl_3$): δ (ppm) 11.38 (br s, 1H), 8.39 (s, 1H), 7.39 (dd, *J* = 8.6, 9.4 Hz, 1H), 7.21 (dd, *J* = 3.8, 8.6 Hz, 1H), 7.06 (br s, 1H, OH), 4.69 (d, *J* = 6.7 Hz, 2H), 4.40 (d, *J* = 6.8 Hz, 2H), 3.0 (t, *J* = 6.2 Hz, 2H), 2.36 (t, *J* = 6.2 Hz, 2H); **^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 157.55, *154.96, 157.12, *157.08, 141.61, 138.22, *138.11, 125.26, *125.13, 125.08, 83.88, 73.82, 36.23, 31.50 (* doubling of the peaks were observed due to the coupling of carbons with fluorine atom); ^{19}F NMR (400 MHz, $CDCl_3$): δ (ppm) -127.36, -131.22 {1:10 ratio of cis-trans oxime isomers}; HRMS (ESI^+) *m/z* calcd for $C_{11}H_{14}F_1N_2O_3^+$241.0983 found 241.0971.

3-fluoro-6-(2-(4-hydroxytetrahydro-2H-pyran-4-yl)ethyl)picolinaldehyde oxime 12f: To a degassed solution of fluorooxime **11f** (40 mg, 0.151 mmol, 1 equiv) in dry EtOAc (3 mL), 10% Pd/C (8 mg, 0.076 mmol, 0.5 equiv) was added. After flushing with H_2 three times, the reaction mixture was stirred at room temperature under H_2 (1 atm.) for 74 h. Upon completion (monitored by TLC), the catalyst was removed by filtration through a short column of celite, the solvent was evaporated, and the residue was purified by preparative TLC (MeOH/EtOAc, 5/95) to afford oxime **12f** as a light yellowish liquid (32 mg, 79%); R_f (5% MeOH+EA) 0.40; IR (neat): ν_{max}3271, 2948, 2866, 1591, 1469, 1239, 1180, 1095, 982, 840, 730, 645, 543, 493 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 11.41 (br s, 1H, OH), 8.39 (s, 1H), 7.35 (dd, *J* = 8.6, 9.5 Hz, 1H), 7.17 (dd, *J* = 3.8, 8.6 Hz, 1H), 5.34 (br s, 1H, OH), 3.85 (td, *J* = 3.4, 10.2 Hz, 2H), 3.74 (m, 2H), 3.0 (t, *J* = 6.9 Hz, 2H), 1.98 (t, *J* = 6.9 Hz, 2H), 1.69-1.61 (m, 4H); **^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 157.96, *157.92, 157.50, *154.92, *155.97, *155.92, 155.26, *152.65,* 141.93, *139.04, *138.93,* 138.22, *138.11, *135.39, *135.37,126.05, *126.00, 125.57, *125.39,* 125.01, *124.98, 124.86, *124.67, *68.62,* 68.19, 63.96, *63.70,42.31*, 41.01, 38.17, *37.57,* 30.56, *30.07* (* doubling of the peaks were observed due to the coupling of carbons with fluorine atom); ^{19}F NMR (400 MHz, $CDCl_3$): δ (ppm) -127.74, -131.68 {1:5 ratio of cis-trans oxime isomers}; HRMS (ESI^+): *m/z* calcd for $C_{13}H_{18}F_1N_2O_3^+$269.1296 found 269.1285.

***N*-(9-((3a*R*,4*R*,6*R*,6a*R*)-6-((3-(5-fluoro-6-(-(hydroxyimino)methyl)pyridin-2-yl)propoxy)methyl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)-9H-purin-6-yl)benzamide 12g**: To a degassed solution of fluorooxime **11g** (40mg, 0.068 mmol, 1 equiv) in dry EtOAc (3 mL), 10% Pd/C (7.2 mg, 0.068 mmol, 1equiv) was added in two portions. After flushing with H_2 three times, the reaction mixture was stirred at room temperature under H_2 (1 atm.) for 42 h. Upon completion(monitored by TLC), the catalyst was removed by filtration through a short column of celite, the solvent was evaporated, and the residue was purified by preparative TLC (pure EtOAc) to afford oxime **12g** as a light yellowish thick syrup (30 mg, 75%); R_f (pure EA) 0.55; IR (neat): ν_{max}3260, 2925, 2857, 1698, 1612, 1582, 1456, 1248, 1211, 1073, 849, 709, 643, 623, 511 cm^{-1}; **^{1}H NMR (400 MHz, Acetone-d_6) δ (ppm) 8.71 (s, 1H), 8.57 (s, 1H), 8.20 (s, 1H), 8.11 (br d, *J* = 7.6 Hz, 2H), 7.63 (m, 1H), 7.56-7.44 (m, 3H), 7.25 (dd, *J* = 3.7, 8.5 Hz, 1H), 6.33 (br d, *J* = 2.2 Hz, 1H), 5.47 (dd, *J* = 2.2, 6.1 Hz, 1H), 5.09 (dd, *J* = 2.5, 6.1 Hz, 1H), 4.48 (m, 1H), 3.70 (dd, *J* = 4, 10.6 Hz, 1H), 3.61 (dd, *J* = 4.4, 10.6 Hz, 1H), 3.52-3.43 (m, 2H), 2.73 (t, *J* = 7.5 Hz, 2H), 1.89 (p, *J* = 7.5 Hz, 2H), 1.59 (s, 3H), 1.38 (s, 3H); **^{13}C NMR (100 MHz, Acetone-d_6): δ (ppm) 166.57, 166.53, 158.57, *158.53, 158.48, *155.88, 152.85, 151.06, 146.61, *146.55, 143.64, 143.59, 139.87, *139.77, 136.51, 136.50, 134.93, 133.41, 130.53, 129.76, 129.46, 129.27, 127.49, 126.67, 126.48, 125.45, *125.41, 125.22, *125.19, 114.34, 92.14, 92.08, 87.19, 85.71, 82.93, 82.88, 71.75, 71.62, 71.31, 71.06, 34.40, 33.94, 32.06, 30.67, 27.57, 25.62 (* doubling of the peaks were observed due to the coupling of carbons with fluorine atom); ^{19}F NMR (400 MHz, Acetone-d_6): δ (ppm): -128.36, -129.16 {1:3 ratio of cis-trans oxime isomers}; HRMS (ESI^+) *m/z* calcd for $C_{29}H_{31}F_1N_7O_6^+$592.2314 found 592.2281.

3-fluoro-6-(-6-hydroxyhex-1-en-1-yl)picolinaldehyde oxime 12h: To a degassed solution of fluorooxime **11h** (45 mg, 0.190 mmol, 1 equiv) in dry EtOAc (3 mL), 10% Pd/C (5 mg, 0.048 mmol, 0.25 equiv) was added. After flushing with H_2 three times, the reaction mixture was stirred at room temperature under H_2 (1 atm.) for 4 h. Upon completion (monitored by TLC), the catalyst was removed by filtration through a short column of celite, the solvent was evaporated, and the residue was purified by column chromatography (EtOAc/PE, 4/6) to afford oxime **12h** as a white solid (40 mg, 88%); R_f (pure EA) 0.75; IR (neat): ν_{max} 3275, 2929, 2857, 1644, 1587, 1468, 1252, 1210, 1056, 976, 845, 726, 639, 534 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 10.61 (br s, 1H, OH), 8.37 (s, 1H), 7.35 (t, *J* = 8.8 Hz, 1H), 7.16 (dd, *J* = 3.8, 8.8 Hz, 1H), 6.38 (br d, *J* = 11.8 Hz, 1H), 5.87 (dt, *J* = 7.6, 11.8 Hz,1H), 3.66 (t, *J* = 6.0 Hz, 2H), 2.61 (q, *J* = 7.6 Hz, 2H), 1.64-1.49 (m, 4H); **^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 157.40, *154.77, 153.21, 153.16, 144.74, 138.35, *138.26, 138.02, 126.66, 125.74, 125.70, 124.06, *123.87, 67.91, 31.76, 28.00, 25.14 (* doubling of the peaks were observed due to the coupling of carbons with fluorine atom);^{19}F NMR(400 MHz, $CDCl_3$): δ (ppm) -127.77; [There is some impurity observed in the NMR spectra along with compound **12i**, which is inseparable with **12h**]; HRMS (ESI^+): *m/z* calcd for $C_{12}H_{16}F_1N_2O_2^+$239.1190 found 239.1199.

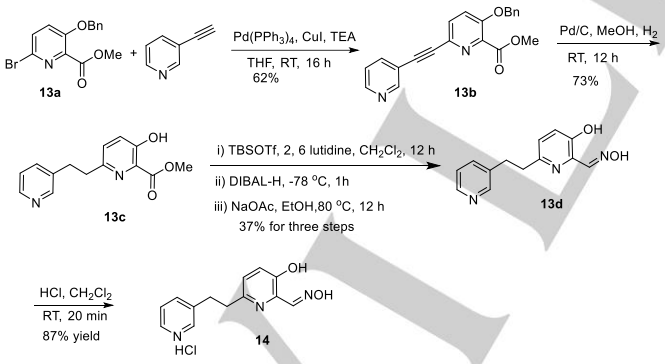
Methyl 6-(5-fluoro-6-(-(hydroxyimino)methyl)pyridin-2-yl)hex-5-enoate 12i: To a degassed solution of fluorooxime **11i** (34 mg, 0.128 mmol, 1 equiv) in dry EtOAc (3 mL), 10% Pd/C (3.4 mg, 0.032 mmol, 0.25 equiv) was added. After flushing with H_2 three times, the reaction mixture was stirred at room temperature under H_2 (1 atm.) for 4 h. Upon completion (monitored by TLC), the catalyst was removed by filtration through a short column of celite, the solvent was evaporated, and the residue was purified by column chromatography (EtOAc/PE, 1/3) to afford oxime **12i** as a white solid (30 mg, 87 %); R_f (20 % EA+PE) 0.65; IR (neat): ν_{max} 3256, 2937, 1727, 1582, 1466, 1249, 1189, 1169, 1005, 973, 865, 844, 733, 710, 629, 611, 520 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 9.62 (br s, 1H), 8.33 (s, 1H), 7.34 (dd, *J* = 8.6, 10.0 Hz, 1H), 7.19 (dd, *J* = 3.8, 8.6 Hz, 1H), 6.43 (dt, *J* = 1.6, 11.7 Hz, 1H), 5.86 (dt, *J* = 7.5, 11.7 Hz,1H), 3.60 (s, 3H), 2.62 (qd, *J* = 1.6, 7.6 Hz, 2H), 2.62 (t, *J* = 7.6 Hz, 2H), 1.82 (p, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 174.18, 157.45, *154.81, 152.92, 152.88, 146.09, *146.04, 138.39, *138.29, 136.79, 127.42, 125.56, 125.51, 124.23, *124.04, 51.52, 33.62, 28.10, 24.72 (* doubling of the peaks were observed due to the coupling of carbons with fluorine atom); ^{19}F NMR (400 MHz, $CDCl_3$): δ (ppm) -126.11; HRMS (ESI^+) *m/z* calcd for $C_{13}H_{16}F_1N_2O_3^+$267.1139 found 267.1114.

3-fluoro-6-((*E*)-2-(pyren-4-yl)vinyl)picolinaldehyde oxime 12j: To a degassed solution of fluorooxime **11j** (50 mg, 0.136 mmol, 1 equiv) in dry EtOAc (3 mL), 10% Pd/C (7.2 mg, 0.068 mmol, 0.5 equiv) was added in two portions. After flushing with H_2 three times, the reaction mixture was stirred at room temperature under H_2 (1 atm.) for 12 h. Upon completion (monitored by TLC), the catalyst was removed by filtration through a short column of celite, the solvent was evaporated, and the residue was purified by washings with DCM and EtOAc to afford oxime **12j** as a yellow solid (40 mg, 81%); R_f (30 % EA+PE) 0.50; IR (neat): ν_{max} 2958, 2926, 2856, 1721, 1585, 1461, 1266, 1248, 1117, 1102, 974, 955, 839, 729, 694, 540 cm^{-1}; ^{1}H NMR (500 MHz, DMSO): δ (ppm) 12.00 (s, 1H), 8.73 (d, *J* = 16 Hz, 1H), 8.67 (d, *J* = 9.4 Hz, 1H), 8.56 (d, *J* = 8.2 Hz, 1H), 8.36-8.29 (m, 5H), 8.21 (s, 2H), 8.10 (t, *J* = 7.7 Hz, 1H), 7.95

(dd, *J* = 3.8, 8.6 Hz, 1H), 7.87 (dd, *J* = 8.6, 10.3 Hz, 1H), 7.63 (d, *J* = 16 Hz, 1H);^{13}C NMR (125 MHz, DMSO): δ (ppm) 157.30, *155.20, 151.66, *151.64, 145.65, *145.60, 139.32, *139.24, 130.99, 130.90, 130.38, 130.34, 129.57, 128.84, 128.24, 127.99, 127.65, 127.41, 126.47, 125.66, 125.38, 125.30, *125.14, 124.25, *124.00, 123.90, 123.87, 123.74, 122.87 (* doubling of the peaks were observed due to the coupling of carbons with fluorine atom); ^{19}F NMR (400 MHz, DMSO): δ (ppm) -123.84; HRMS (ESI$^+$) *m/z* calcd for $C_{24}H_{16}F_1N_2O_1^+$367.1241 found 367.1229.

3-fluoro-6-(4-((1,2,3,4-tetrahydroacridin-9-yl)amino)butyl)picolinaldehyde oxime 12k: To a degassed solution of fluorooxime **11k** (20 mg, 0.052mmol, 1equiv) in dry EtOAc/MeOH (2/1 mL), 10% Pd/C (5.5 mg, 0.052 mmol, 1equiv) was added. After flushing with H_2 three times, the reaction mixture was stirred at room temperature under H_2 (1 atm.) for 20 h. Upon completion (monitored by TLC), the catalyst was removed by filtration through a short column of celite, the solvent was evaporated, and the residue was purified by preparative TLC (EtOAc/PE, 4/1) to afford oxime **12k** as a white solid (20 mg, quant. yield); R_f (20 % MeOH+EA) 0.20;*^{1}H NMR (400 MHz, CD_3OD): δ (ppm) 8.19 (s, 1H), 8.09 (brd, *J* = 8.6 Hz, 1H), 7.73 (brd, *J* = 8.6 Hz, 1H), 7.62-7.57(m, 1H), 7.44-7.34 (m, 2H), 7.14 (dd, *J* = 3.8, 8.6 Hz, 1H), 3.62 (t, *J* = 6.9 Hz, 2H), 2.95 (brt, *J* = 5.9 Hz, 2H), 2.75 (t, *J* = 7.0 Hz, 2H), 2.67 (t, *J* = 5.9 Hz, 2H), 1.92-1.85 (m, 4H) 1.77-1.65 (m, 4H); *^{13}C NMR (100 MHz, CD_3OD): δ (ppm) 159.62, 159.57, 159.11, 157.80, 157.75, 157.44, 156.52, 154.27, 154.06, 146.04, 145.32, 145.29, 140.11, 140.01, 130.85, 126.60, 126.53, 126.41, 126.23, 126.16, 126.05, 126.02, 125.97, 125.86, 125.22, 124.95, 124.88, 120.54, 120.40, 116.22, 116.03, 148.94, 37.48, 37.20, 33.27, 33.21, 31.38, 31.24, 28.12, 27.52, 26.09, 26.02, 23.99, 23.93, 23.46, 23.37 (* doubling of the peaks were observed due to the coupling of carbons with fluorine atom); ^{19}F NMR (400 MHz, CD_3OD): δ (ppm) -123.32, -130.21; HRMS (ESI$^+$) *m/z* calcd for $C_{23}H_{21}F_1N_4O^+$388.1714 found 388.1732.

3-hydroxy-6-(2-(pyridin-3-yl)ethyl)picolinaldehydeoxime hydrochloride 14:



Scheme: Convergent synthesis of **14**

Methyl 3-(benzyloxy)-6-(pyridin-3-ylethynyl)picolinate 13 b: To a degassed solution of methyl 3-(benzyloxy)-6-bromopicolinate **13a** (687 mg, 2.135 mmol, 1.1 equiv) in THF/Et_3N (12 mL/4 mL), $Pd[PPh_3]_4$ (336 mg, 0.072 mmol, 0.15equiv) and CuI (110 mg, 0.577 mmol, 0.3 equiv) were added. After degassing the reaction mixture for 5 min at room temperature, 3-ethynylpyridine (200 mg, 1.941 mmol, 1 equiv) was added dropwise and the reaction mixture was stirred at room temperature for 16 h. Upon completion, the reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography (EtOAc/PE, 1:1) to afford methyl 3-(benzyloxy)-6-(pyridin-3-ylethynyl)picolinate **13b** as a pale yellow solid (420 mg, 62%). R_f (50% EtOAc/PE) 0.35; IR (neat): ν_{max} 3031, , 2949, 1729, 1560, 1447, 1095, 1020, 738, 695 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$):δ 8.78 (d, *J* = 1.36 Hz, 1H), 8.56 (dd, *J* = 4.8, 1.4 Hz, 1H), 7.84 (dt, *J* = 7.9, 1.9 Hz, 1H), 7.59 (d, *J* = 8.7 Hz, 1H), 7.45-7.31 (m, 6H), 7.28-7.26 (m, 1H), 5.24 (s, 2H), 3.99 (s, 3H).^{13}C NMR (101 MHz, $CDCl_3$): δ 164.61, 153.53, 152.50, 149.11, 140.56, 138.78, 135.26, 134.20, 130.47,128.78, 128.33, 126.89, 123.05, 121.64, 119.55, 90.75, 85.22, 70.87, 52.82. HRMS (ESI$^+$) *m/z* calcd for $C_{21}H_{17}N_2O_3^+$345.1240 found 345.1234.

Methyl 3-hydroxy-6-(2-(pyridin-3-yl)ethyl)picolinate 13c: To a solution of methyl 3-(benzyloxy)-6-(pyridin-3-ylethynyl)picolinate **13b** (380 mg, 1.103 mmol, 1 equiv) in MeOH (10 mL) was added 10% Pd/C (150 mg) at room temperature under Argon atmosphere. The resulting solution was stirred for 12h under H_2 atmosphere using balloon pressure. Upon completion, the mixture was filtered using small celite pad, concentrated under reduced pressure and purified by SiO_2 column chromatography (EtOAc/PE 1:1) to afford methyl 3-hydroxy-6-(2-(pyridin-3-yl)ethyl)picolinate **13c** as light brown syrup (210 mg, 73%); R_f (50% EtOAc+PE) 0.4;IR (neat): ν_{max} 3417, 3021, 2954, 1676, 1574, 1467, 1450, 1302, 1207, 1109, 713, 538 cm^{-1};^{1}H NMR (400 MHz, CD_3OD): δ 8.34-8.20 (m, 2H), 7.61 (dt, *J* = 7.9, 1.9 Hz, 1H), 7.30-7.20 (m, 3H), 3.93 (s, 3H), 3.03- 2.90 (m, 4H).^{13}C NMR (101 MHz, CD_3OD): δ 170.62, 158.20, 153.55, 150.27, 147.69, 139.01, 138.52, 131.01, 130.33, 128.08, 125.12, 53.36, 39.04, 33.83.HRMS (ESI$^+$) *m/z* calcd for $C_{21}H_{17}N_2O_3^+$ 345.1240 found 345.1234.

3-hydroxy-6-(2-(pyridin-3-yl)ethyl)picolinaldehyde oxime 13d: To a solution of methyl 3-hydroxy-6-(2-(pyridin-3-yl)ethyl)picolinate **13c** (210 mg, 0.813 mmol, 1 equiv) in anhydrous CH_2Cl_2 (5 mL) was added 2,6-lutidine (0.224 mL, 0.977 mmol, 2.4 equiv) and TBSOTf (0.226 mL, 1.950 mmol, 1.2 equiv) dropwise. The mixture was stirred at room temperature for 12 h. Upon completion, water (10 mL) was added, extracted with CH_2Cl_2 (10 mL x 3), dried over anhydrous Na_2SO_4 and concentrated by vacuo to give crude methyl 3-((tert-butyldimethylsilyl)oxy)-6-(2-(pyridin-3-yl)ethyl)picolinate as a brown colour syrup. To a solution of this residue in CH_2Cl_2 (6 mL) was added DIBAL-H (2.4 mL, 1M in THF, 3 equiv) at -78 °C and stirred over 1 h at the same temperature. The mixture was quenched with MeOH (2 mL) and concentrated by vacuo. The white aluminum salts were removed by filtration and concentrated to give the crude 3-((tert-butyldimethylsilyl)oxy)-6-(2-(pyridin-3-yl)ethyl)picolinaldehyde as a light brown colour syrup. To a solution of this crude 3-((tert-butyldimethylsilyl)oxy)-6-(2-(pyridin-3-yl)ethyl)picolinaldehyde in EtOH (5 mL) was added hydroxylamine hydrochloride (112 mg, 1.611 mmol, 2 equiv), NaOAc (199 mg, 2.429 mmol, 3 equiv). The solution was refluxed for 12 h. After concentration by vacuo, the crude product was purified by SiO_2 column chromatography (60:40, EtOAc/PE) to afford 3-hydroxy-6-(2-(pyridin-3-yl)ethyl)picolinaldehyde oxime as a white solid **13d** (70 mg, 37% yield for three steps). R_f (0.5 in EtOAc) 0.5. IR (neat): ν_{max} 3011, 2927, 2865, 2601, 1459, 1421,1264, 1178, 1026, 861, 827, 758, 723, 670, 642, 537, 507 cm^{-1}. ^{1}H NMR (400 MHz, CD_3OD): δ 8.27-8.20 (m, 2H), 8.18 (s, 1H), 7.57 (d, *J* = 7.7 Hz, 1H), 7.22 (dd, *J* = 7.6, 4.9 Hz, 1H), 7.12 (d, *J* = 8.4 Hz, 1H), 6.96 (d, *J* = 8.4 Hz, 1H), 2.98-2.86 (m, 4H). ^{13}C NMR (101 MHz, CD_3OD): δ 153.95, 152.83, 150.11, 147.59, 139.09, 138.52, 136.59, 125.85, 125.61, 125.12, 39.11, 33.95. HRMS (ESI$^+$): *m/z* calcd for $C_{13}H_{14}N_3O_2^+$ 244.1083 found 244.1080

3-hydroxy-6-(2-(pyridin-3-yl)ethyl)picolinaldehyde oxime hydrochloride 13: To a solution of 3-hydroxy-6-(2-(pyridin-3-yl)ethyl)picolinaldehyde oxime **13d** (15 mg, 0.061mmol, 1 equiv) in CH_2Cl_2 (3 ml) was added 2N HCl (2mL) at room temperature and stirred for 20 min at the same temperature. The solvents were distilled under reduced pressure and the resulted solid was washed twice with diethyl ether. The solid was dried under vacuum to give 3-hydroxy-6-(2-(pyridin-3-yl)ethyl)picolinaldehyde oxime hydrochloride **13** as a white solid (15 mg, 87 %). IR (neat): ν_{max} 3306, 3199, 2770, 2743, 1555, 1432, 1336, 1192, 975, 840, 685 cm^{-1}. ^1H NMR (400 MHz, CD_3OD): δ 8.92 (bs, 1H), 8.82 (d, *J* = 5.7 Hz, 1H), 8.66 (dt, *J* = 8.2, 1.7 Hz, 1H), 8.52 (s, 1H), 8.12 (dd, *J* = 8.1, 5.8 Hz, 1H), 7.97 (d, *J* = 8.8 Hz, 1H), 7.80 (d, *J* = 8.8 Hz, 1H). 3.45-3.36 (m, 4H). ^{13}C NMR (101 MHz, CD_3OD): δ 155.03, 148.48, 148.31, 142.63, 141.97, 141.31, 141.16, 133.98, 133.87, 128.76, 128.66, 34.02, 32.94. HRMS (ESI^+): *m/z* calcd for $C_{13}H_{14}N_3O_2^+$244.1071 found 244.1080.

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Keywords: Acetylcholinesterase (AChE), 3-fluoro-2-pyridinaldoxime, organophosphorous nerve agents (OPNA), chemical warefare agent (CWA), blood brain barrier permeability, chemoselective hydrogenation.

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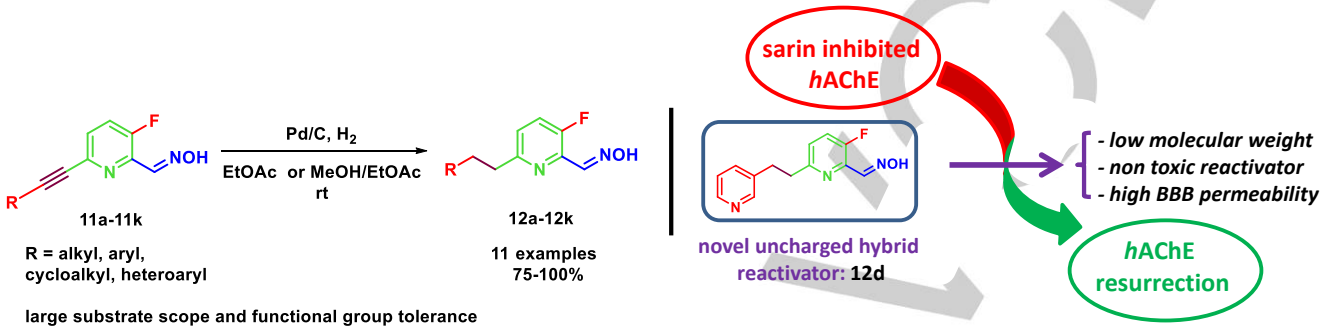
Graphical Abstract

Chemoselective Hydrogenation of 6-Alkynyl-3-Fluoro-2-Pyridinaldoxime: Access to First-in-Class 6-Alkyl-3-Fluoro-2-Pyridinaldoxime Scaffolds, as New Reactivators of Sarin-Inhibited *Human*-Acetylcholinesterase with Increased Blood Brain Barrier Permeability



We describe the chemoseletive hydrogenation of 6-alkynyl-3-fluoro-2-pyridinaldoxime **11a-11k** to afford 6-alkyl-3-fluoro-2-pyridinaldoxime **12a-12k** using mild hydrogenation conditions, without altering the C-F and oxime functionalities. The resulted 6-alkyl-3-fluoro-2-pyridinaldoxime **12d** acts as novel **low molecular weight non-quaternary fluorinated hybrid reactivator** of sarin-inhibited *human*-acetylcholinesterase, with unprecedented blood brain barrier permeability efficacy compared to currently used antidotes such as 2-PAM, HI-6 and obidoxime.