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Bridged 5,6,7,8-Tetrahydro-1,6-naphthyridines, Analogues of Huperzine A: Synthesis, Modelling Studies and Evaluation as Inhibitors of Acetylcholinesterase

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Derivatives of 6,8-bridged 5,6,7,8-tetrahydro-1,6-naphthyridines, designed as analogues of huperzine A, were synthesised and evaluated as inhibitors of acetylcholinesterase. In a first approach, C_3-bridged naphthyridines were constructed by internal nucleophilic aromatic substitution of 2-chloro-3-(1-piperidinylmethyl)pyridine precursors containing a 3-CO_2Me group on the 1-piperidinyl ring moiety. Alternatively, ring-closing metathesis on 6,8-diallyl-substituted tetrahydro-1,6-naphthyridines was applied to construct an unsaturated C_4 bridge. Some of the target compounds showed inhibition of acetylcholinesterase but lower than that of huperzine A. The relative order of inhibition activities could be rationalised by comparative docking simulation studies on the basis of the known crystal structure of the acetylcholinesterase–huperzine A complex.

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Introduction

The enzyme acetylcholinesterase (AChE) currently is the most important target for the treatment of Alzheimer's disease (AD). The principal role of this enzyme is the hydrolysis of acetylcholine (ACh). According to the "cholinergic hypothesis", AD patients have a lack of cholinergic neurotransmission. Consequently, AChE inhibitors can be used for the symptomatic treatment of AD, which is aimed at restoring acetylcholine levels and enhancing memory in AD patients. Four inhibitors, i.e. tacrine, donepezil, rivastigmine and galanthamine have been approved for this symptomatic treatment (Figure 1).

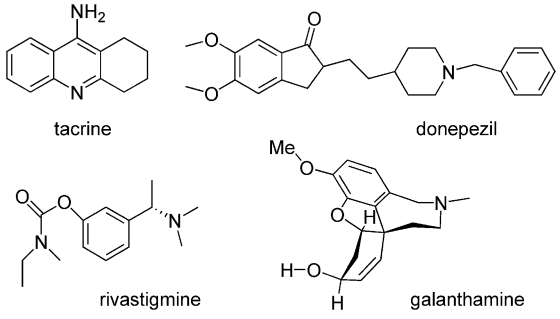

Figure 1. Four inhibitors of AChE that have been approved for the symptomatic treatment of AD.

Huperzine A (HA, Figure 2), isolated from the Chinese herb Huperzia Serrata, is being used in China already for many years for the treatment of several diseases.[1] This compound is a potent, reversible and selective inhibitor of AChE, which has a unique structure compared to other AChE inhibitors. Its inhibiting activity and the duration of its action are better than those of the four approved inhibitors.[2] Furthermore, HA is very selective for AChE compared to BuChE,[3] which might result in less side effects. HA has a high bioavailability and crosses the blood-brain barrier very easily. Clinical studies in China showed that treatment with HA results in a significant improvement of the memory of older people and patients suffering from AD or vascular dementia, without appreciable side effects. HA also shows neuroprotective effects against H_2O_2, β-amyloid and oxygen glucose deprivation that are not correlated with its AChE inhibiting activity.[4] Total syntheses of HA[5] and various analogues[6] have been reported.

More recently, huprines have been introduced as a new class of very potent and selective AChE inhibitors.[7] These structures, e.g. Huprine X (Figure 2), are synthetic hybrids of HA and tacrine, which are able to interact with the binding sites of both HA and tacrine at the same time, resulting in a very high AChE inhibition potency.[8]

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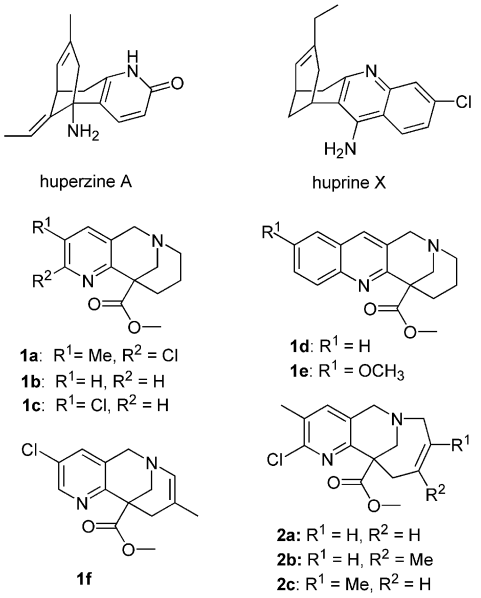


Figure 2. Structures of huperzine A, huprine X and target compounds.

Our target compounds **1a**–**c**, **1f** and **2a**–**c** are 5,6,7,8-tetrahydro-1,6-naphthyridines having either a C_3 or C_4 bridge between the 6- and the 8-position, which can be viewed as analogues of HA (Figure 2). Suitable variation of the bridge components and substituents on the pyridine ring can provide a series of HA analogues to be tested for AChE inhibition activity. Targets **1d**,**e** encompassing a quinoline- instead of a pyridine-ring moiety were meant to mimick the bridged tricyclic structure of Huprine X.

An overlay of the geometrically optimised model structures of HA and target **1f** illustrates the good overall superposibility of the basic skeleton of HA with that of the bridged naphthyridine targets. Variable substituents and bridge components will serve to explore favourable or adverse interactions with the active binding site of the enzyme and to determine the structure/activity relationship of the naphthyridine analogues of HA as possible AChE inhibitors (Figure 3).

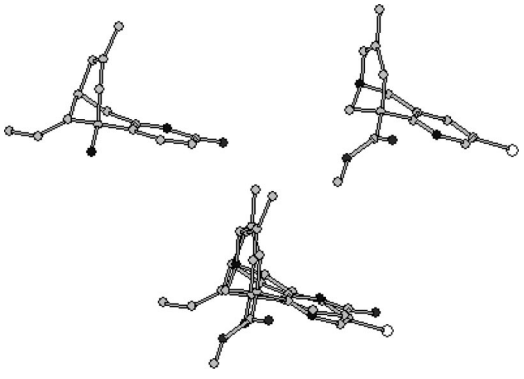
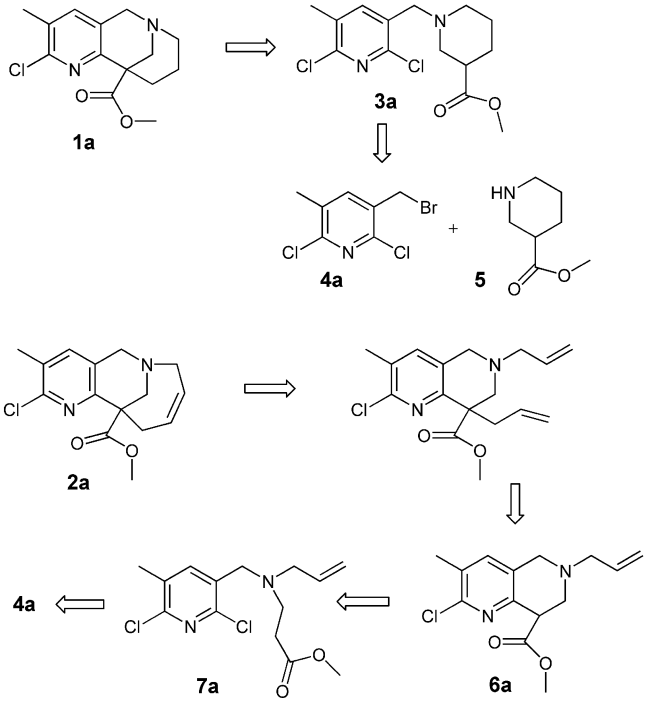


Figure 3. Geometrically optimised (Hyperchem MM+) model structures of HA, target **1f** and overlay of structures HA and **1f**.

Retrosynthetic Analysis

In a first approach aimed at the synthesis of the C_3-bridged target compound **1a**, the key step involves an internal nucleophilic aromatic substitution (NAS) on an appropriate 3-substituted 2-chloropyridine **3a** (Scheme 1). Precursor **3a** can be prepared by amination of 3-(bromomethyl)pyridine **4a** with piperidine **5**.



Scheme 1. Synthetic strategies for targets **1a** and **2a**.

A second approach proceeds by allylation of the 8-position of tetrahydronaphthyridine **6a** followed by ring-closing metathesis on the 6,8-diallyl-substituted product to form the C_4-bridged target **2a**. Naphthyridine **6a** can be constructed by internal NAS of **7a**, which in turn is accessible from 3-(bromomethyl)pyridine **4a** (Scheme 1).

After testing these two synthetic strategies, substituents on the pyridine ring and bridge components can be diversified.

Results and Discussion

First Synthetic Approach: Ring Closure by Nucleophilic Aromatic Substitution

Our first approach started with the synthesis of ring-closing precursor **3a** by amination of 3-(bromomethyl)pyridine **4a**[9] with methyl 3-piperidinecarboxylate (**5**) (Scheme 2). The latter was prepared by esterification of the commercially available acid **8**. Subsequent ring closure of precursor **3a** was effected through base-promoted α-deprotonation of the ester group and concomitant NAS reaction on the 2-Cl position of the pyridine-ring moiety. This conversion proceeded smoothly by heating **3a** with $KN(SiMe_3)_2$ in toluene to afford the bridged naphthyridine target **1a** in 30% yield.

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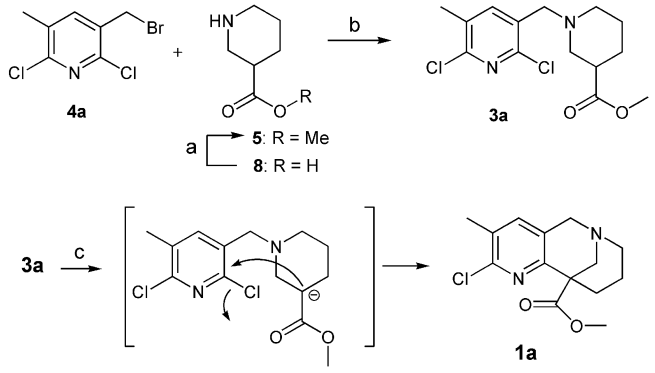
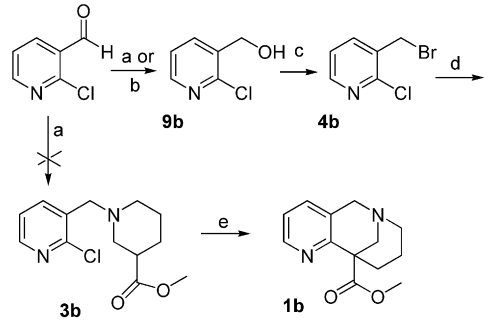


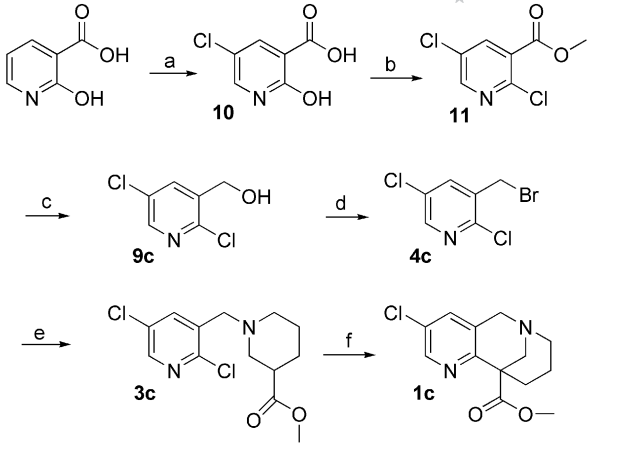
Scheme 2. Reagents and conditions: (a) oxalyl chloride (3 equiv.), MeOH, 0 °C, 1 h (98%); (b) K_2CO_3 (1 equiv.), MeOH, 60 °C, overnight (85%); (c) $KN(SiMe_3)_2$ (1.2 equiv.), toluene, 80 °C, 30 min. (30%).

After developing a suitable method for the construction of the bridged system **1a**, we next envisaged the introduction of various substituents on the pyridine-ring moiety. Our first modified target was compound **1b**, in which the annulated pyridine ring contains no further substituents. To prepare the corresponding ring-closing precursor **3b**, we first tried a reductive amination of 2-chloropyridine-3-carbaldehyde with piperidine **5** using $NaCNBH_3$ as the reducing agent (Scheme 3). Unfortunately, no reductive coupling was observed; instead, the aldehyde was reduced to alcohol **9b**. Therefore, we followed another route starting with reduction of the aldehyde to alcohol **9b**, which was converted to bromide **4b**. Subsequent amination with piperidine **5** furnished precursor **3b** in 60% yield. Final ring closure was effected in the same manner as described for the conversion of **3a** to **1a** to afford the analogous bridged target compound **1b** in 28% yield.



Scheme 3. Reagents and conditions: (a) $NaCNBH_4$, **5** (1 equiv.), MeOH, pH = 5, room temp.; (b) $NaBH_4$ (1 equiv.), MeOH, 0 °C, 15 min (90%); (c) PBr_3 (1 equiv.), CH_2Cl_2, room temp., 1 h (85%); (d) **5** (1 equiv.), K_2CO_3 (1 equiv.), MeOH, 60 °C, overnight (60%); (e) $KN(SiMe_3)_2$ (1.2 equiv.), toluene, 80 °C, 30 min. (28%).

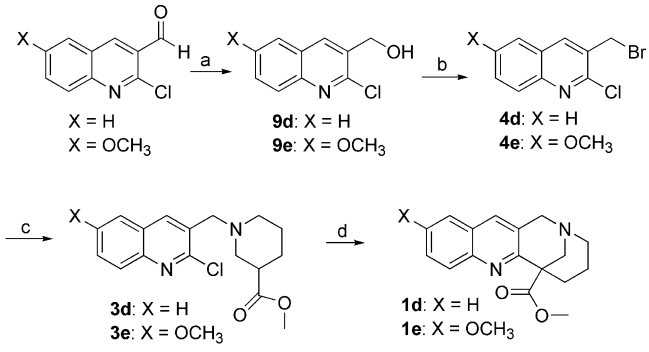
For our next modified target **1c**, we envisaged the introduction of a chlorine substituent in the 5-position of the pyridine ring in order to mimick the carbonyl group of HA. The corresponding precursor **3c** was assembled by amination of 3-(bromomethyl)pyridine **4c** with piperidine **5** (Scheme 4).



Scheme 4. Reagents and conditions: (a) NCS (1 equiv.), DMF, room temp., 2 d (60%); (b) (i) thionyl chloride, cat. DMF, reflux, 2 h, (ii) 0 °C, MeOH (30%); (c) $NaBH_4$ (1 equiv.), MeOH, room temp, 2 h (35%); (d) PBr_3 (1 equiv.), CH_2Cl_2, room temp., 1 h (72%); (e) **5** (1 equiv.), K_2CO_3 (1 equiv.), MeOH, 60 °C, overnight (53%); (f) $KN(SiMe_3)_2$ (1.2 equiv.), toluene, 80 °C, 30 min. (33%).

The synthesis of trihalopyridine **4c** started with chlorination of 2-hydroxynicotinic acid to produce 5-chloro-2-hydroxynicotinic acid (**10**). The electron-donating 2-OH group proved to be necessary for this conversion because 2-chloronicotinic acid was not reactive under the chlorination conditions (*N*-chlorosuccinimide in DMF). Further (2-OH → 2-Cl) substitution and concomitant esterification were accomplished by reaction with thionyl chloride catalysed by DMF, followed by methanolic workup of the acyl chloride intermediate. The resulting ester, methyl 2,5-dichloronicotinate (**11**), was reduced by $NaBH_4$ to produce alcohol **9c**, which was converted into the corresponding bromide **4c**. Subsequent amination of bromide **4c** with piperidine **5** furnished precursor **3c**, which finally underwent base-promoted ring closure providing target **1c** in 33% yield.

Quinoline targets **1d**,**e** can be viewed as analogues of huprine X, in which the pyridine-ring moiety of targets **1a**–**c** is extended with an additional benzene ring. To synthesise compounds **1d**,**e**, a similar approach was applied as that



Scheme 5. Reagents and conditions: (a) $NaBH_4$ (1 equiv.), MeOH, 0 °C, 15 min (95%, 90%); (b) PBr_3 (1 equiv.), CH_2Cl_2, room temp., 1 h (55%, 52%); (c) **5** (1 equiv.), K_2CO_3 (1 equiv.), MeOH, 60 °C, overnight (70%, 68%); (d) $KN(SiMe_3)_2$ (1.2 equiv.), toluene, 80 °C, 30 min. (35%, 37%).

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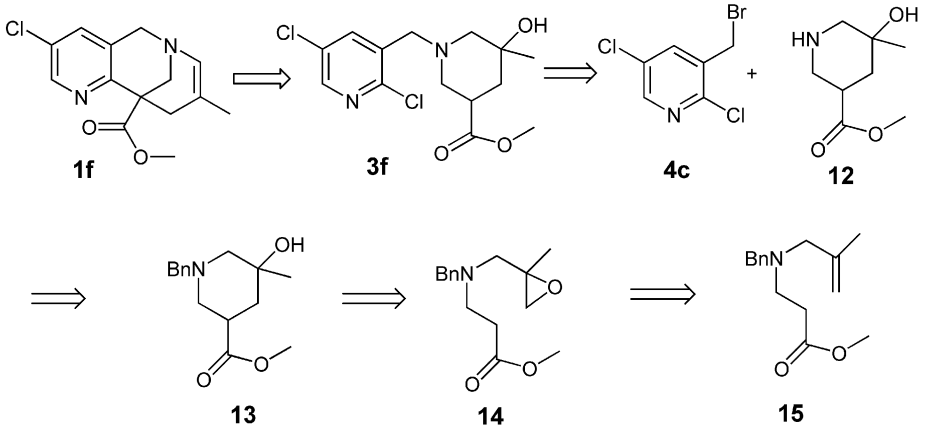
used for **1b**. Our synthesis started with the reduction of 2-chloro-3-quinolinecarbaldehyde and its 6-OMe derivative, followed by conversion of alcohols **9d**,**e** into 3-(bromomethyl)quinolines **4d**,**e** (Scheme 5). Amination of bromides **4d**,**e** furnished ring-closing precursors **3d**,**e**. These were submitted to the base-promoted NAS procedure to provide the bridged quinoline analogues **1d**,**e** in 35% and 37% yields.

Because target **1c** exhibits pronounced AChE inhibition activity (see below), we wanted to further improve the structural similarity with HA by an appropriate change of the bridge components, i.e. introduction of an Me-substituted alkene linkage (target **1f**). According to the retrosynthetic sequence depicted in Scheme 6, target **1f** could be obtained by amination of bromide **4c** with a substituted piperidine **12**, followed by ring closure and elimination of the tertiary OH group. Piperidine **12** in its turn could form by epoxidation of alkene **15**, followed by internal attack of the enolate anion of ester **14** on the epoxide group and *N*-debenzylation.

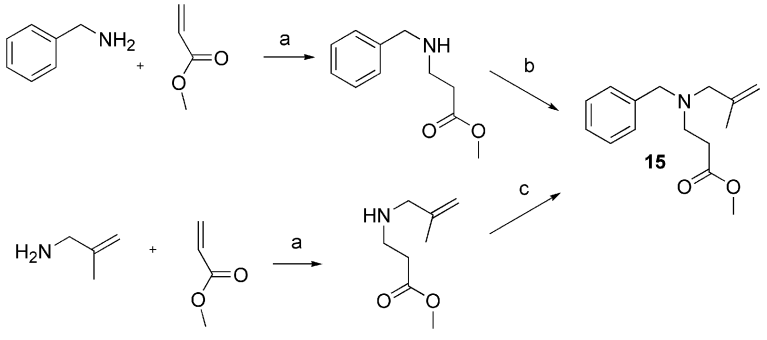
Our sequence started with the synthesis of amine **15**, which could be prepared in two different manners starting with conjugate addition of benzylamine or methallylamine to methyl acrylate (Scheme 7). Subsequent alkylation of the secondary amine intermediates with methallyl chloride or benzyl bromide furnished amine **15** in comparable yields (68% and 62% over 2 steps).

Direct epoxidation of the alkene linkage of amine **15** by reaction with *m*CPBA did not succeed. The desired epoxide **14** could, however, be obtained indirectly through dihydroxylation of the alkene group (**15** → **16**) by using catalytic OsO_4 and NMO. Chemoselective sulfonylation of the primary alcohol group afforded monotosylate **17**,[10] which was converted to epoxide **14** by treatment with base (Scheme 8).

Our synthesis plan required opening of the epoxide group by internal attack of the ester enolate anion to form the six-membered ring, i.e. piperidine **12**. However, treatment of epoxide **14** with various bases, e.g. KO*t*Bu in THF and $KN(SiMe_3)_2$ in toluene, left the epoxide group unchanged. Finally, epoxide opening and concomitant ring closure could be effected by reaction with LDA and Et_2AlCl at low temperature. When the latter reagent is applied in intermolecular reactions of ester enolate ions with terminal epoxides, the epoxide group is opened exclusively at the primary site in preference to the secondary site.[11] However, in our case, which involves internal attack on a terminal epoxide with a tertiary carbon center, pyrrolidine **18** was generated instead of piperidine **12**. In the ^{13}C NMR spectrum, pyrrolidine structure **18** was revealed by signals corresponding to the CH_2OH group (δ = 73.7 ppm) and the quaternary carbon atom (δ = 46.2 ppm). By contrast, the signal of the tertiary alcohol center C-5 of piperidine **12** expectedly would appear at δ = 80 ppm or higher. The as-



Scheme 6. Synthesis plan for target **1f**.



Scheme 7. Reagents and conditions: (a) dioxane, 100 °C, 1 d; (b) methallyl chloride, 100 °C, 1 d (68% over 2 steps); (c) benzyl bromide, 100 °C, 1 d (62% over 2 steps).

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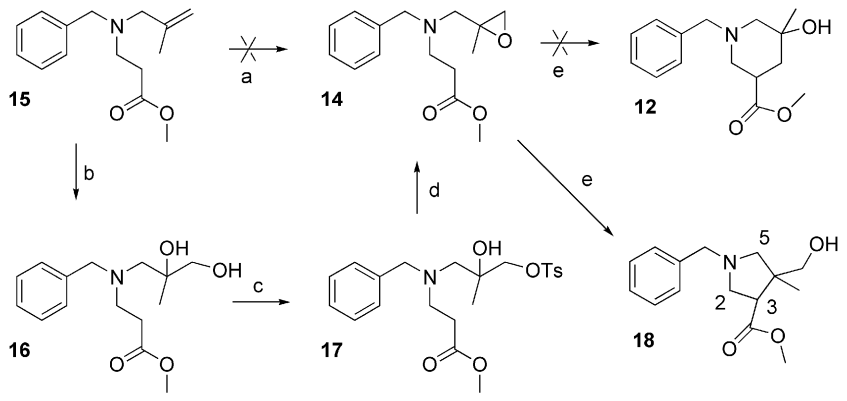


Scheme 8. Reagents and conditions: (a) *m*CPBA (b) OsO_4, (cat.), NMO (3 equiv.), H_2O, Et_2O, *tert*-butyl alcohol, room temp., 2 d (48%); (c) toluenesulfonyl chloride (2 equiv.), Bu_2SnO (0.5 equiv.), DMAP (1 equiv.), NEt_3, room temp., overnight (d) K_2CO_3 (1 equiv.), MeOH, room temp, 1 h (61% over 2 steps); (e) (i) LDA (1 equiv.), THF, –78 °C, 15 min, (ii) Et_2AlCl (1 equiv.) (iii) –50 °C, 4 h (10%).

signment of **18** was confirmed by the HMBC correlations found between the methyl group (δ = 0.9 ppm) on the quaternary carbon center and 4 carbon atoms, i.e. C-4 (δ = 46.2 ppm), C-3 (δ = 48.4 ppm), C-5 (δ = 64.9 ppm) and CH_2OH (δ = 73.7 ppm). Similar correlations with 4 carbon atoms would not be possible for the methyl group located at the tertiary alcohol center C-5 of piperidine **12**.

The stereochemical structure of compound **18** was determined by NOESY analysis, which revealed the *trans* disposition of the ester and hydroxymethylene groups (Figure 4). In particular, the 3-H proton (δ = 3.14 ppm) showed an important cross peak with the hydroxymethylene proton (δ = 3.49 ppm). This assignment was confirmed by the high-field ^{13}C chemical shift value (δ = 17.8 ppm) observed for the methyl group, which is due to the γ-*cis* effect exerted by the ester group.[12]

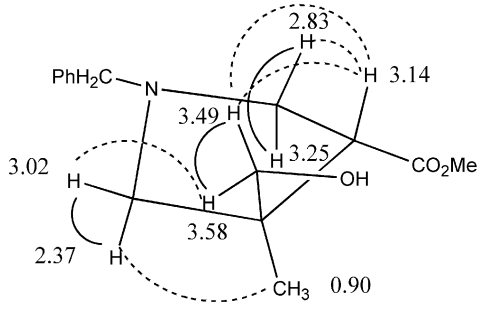
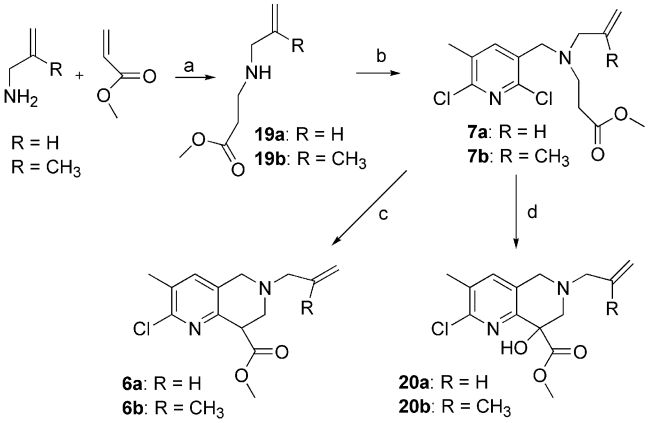


Figure 4. NOESY analysis of compound **18**: correlations between geminal and non-geminal protons are indicated by plain and dashed curves, respectively.

One may conclude that coordination of the epoxide group with the Al reagent provides a considerable cation character to the tertiary carbon center, which enhances the kinetic preference to form the five-membered ring. Further attempts to synthesise piperidine **12**, e.g. through the formation and subsequent ring closure of the THP-protected derivative of tertiary alcohol **17**, also failed.

Second Synthetic Approach: Ring Closure Proceeding by Ring-Closing Metathesis

The second approach in our general synthesis plan (Scheme 1) implies the construction of a C_4 bridge between the 6- and 8-position of a suitable tetrahydro-1,6-naphthyridine precursor. The latter bicyclic system can again be synthesised through amination of 3-(bromomethyl)pyridine **4a**. In this case, the amination is carried out with noncyclic secondary amines **19a**,**b** to produce the corresponding 3-(aminomethyl)pyridines **7a**,**b**. Amines **19a**,**b** were obtained by conjugate addition of allylamine and methallylamine to methyl acrylate. Compounds **7a**,**b** smoothly underwent internal NAS cyclisation under conventional heating conditions to form tetrahydronaphthyridines **6a**,**b** (Scheme 9); 2 equiv. of base are required to effect complete conversion into compounds **6a**,**b**, which are generated as the corresponding anions. The latter turned out to be very sensitive to oxidation; hence, air must be rigorously excluded. Final workup of the reaction mixture was carried out by cooling



Scheme 9. Reagents and conditions: (a) dioxane, 100 °C, 1 d; (b) **4a** (1 equiv.), K_2CO_3, 60 °C, overnight (80%, 60% over 2 steps); (c) (i) $KN(SiMe_3)_2$ (2.2 equiv.), toluene, 80 °C, 10 min, (ii) –78 °C, saturated NH_4Cl, 5 min (77%, 66%); (d) (i) $KN(SiMe_3)_2$ (2.2 equiv.) toluene, 80 °C, 10 min, (ii) O_2, overnight (88%, 70%).

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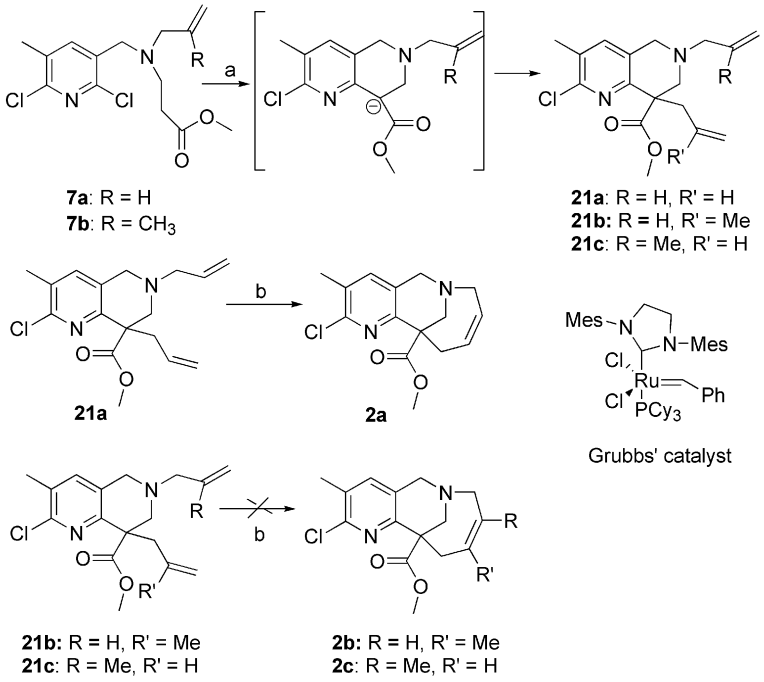

Scheme 10. Reagents and conditions: (a) (i) $KN(SiMe_3)_2$ (2.2 equiv.) toluene, 80 °C, 10 min, (ii) allyl bromide or methallyl chloride (3 equiv.), 80 °C, 15 min (32%, 42%, 46%); (b) 2nd generation Grubbs's catalyst (0.3 equiv.), CH_2Cl_2, room temp., overnight (40%).

to –78 °C, followed by careful addition of a saturated solution of NH_4Cl. When the reaction was carried out in the presence of air, oxidation of the anion intermediate resulted in detection of alcohol **20** as a side product. Finally, alcohols **20a**,**b** could be isolated as the sole product in high yield when oxygen was admitted to the reaction mixture.

In the next step an allyl or methallyl group was introduced at the 8-position of naphthyridines **6a**,**b** to give 6,8-substituted compounds **21a**–**c**, serving as precursors for RCM (Scheme 10). The alkylation of **6a**,**b** preferably is carried out in situ by adding the (meth)allyl halide reagents to the anion intermediates generated upon NAS cyclisation of **7a**,**b**. When submitted to RCM using Grubbs' second generation catalyst, diallyl precursor **21a** was converted into target **2a** with an acceptable yield (40%). However, addition of 0.3 equiv. of the catalyst was required for complete consumption of the starting material. A possible explanation for the necessity of using this large amount of catalyst is the formation of a stable chelate complex (six-membered ring) involving the 8-allyl and the ester carbonyl groups. Addition of $Ti(OiPr)_4$ to prevent co-ordination of the ester carbonyl group with the ruthenium catalyst[13] did not improve this situation. In contrast to the successful conversion of precursor **21a** into target **2a**, RCM on the analogous 6- and 8-methallyl-substituted precursors **21b**,**c** failed. This failure might be due to both steric hindrance and inactivation of the Grubbs' catalyst by a basic amine function.[14]

Enzyme Kinetic Experiments

The ability of the new ligands to inhibit the enzymatic activity of acetylcholinesterase was measured spectrophotometrically and is expressed as values for inhibition constants K_I. These values were calculated from the equation for competitive inhibition relating the reaction velocity in the presence of inhibitor to the substrate concentration, by using the relevant K_M value. The assays were carried out according to Ellman's colorimetric method.[15] Some of the tested compounds showed AChE inhibition activity (K_I = 1369 μM for **1a**; K_I = 305 μM for **1c**; K_I = 972 μM for **2a**; compounds **1b**,**d**,**e** showed no activity). Compound **1c** shows the best activity, suggesting that its chlorine substituent is able to mimic the carbonyl function of HA. However, the inhibition constants for the compounds tested are much lower than those reported for huperzine A (4.6 nM) and huprine X (0.026 nM),[16] hence these SAR deductions must be further scrutinised.

Modelling

The influence of the structural varation on inhibition activities was investigated by comparative modelling studies and docking simulations of huperzine A, huprine X and the structural analogues presented in this work. Molecular modelling was performed by using the Molecular Operating Environment (MOE).[17] Docking experiments were based on the crystal structures of complexes of acetylcholinesterase with huperzine A, huperzine B and huprine X retrieved from the pdb databank (pdb entries 1VOT, 1GPN and 1E66, respectively). By using MOE, target molecules of type **1** and **2** were modelled in complex with the three diverse crystal structures. Similar modelling experiments on huperzine A, huperzine B and huprine X were used to validate our approach. In a first step, the binding site was de-

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fined by using the site-finder algorithm implemented in MOE. This site was filled with alpha spheres. The centres of these spheres were used for the placement of the ligands by using the Alpha Triangle placement method. The different conformations used for docking were calculated by using a stochastic conformational search. A total number of 100 different binding modes were allowed. London ΔG was used as a scoring function during the docking process to calculate the estimated free energy of binding. Compounds showing inhibition activity were able to reproduce a binding mode according with that of the original huprin/huperzine. Compounds that could not reproduce a similar binding mode were docked with restrictions in order to fulfil this binding mode. After completing the docking protocol, selected binding modes were submitted for rescoring by using the DrugScore algorithm via the DS-online server. This scoring function also allows for visualisation of the good and bad contacts per atom. From this analysis it was clear that the huprine X analogues **1d** and **1e** cannot adopt a binding mode similar to that of huprine X, due to steric repulsion with the ester group (Figure 5, A, B). These compounds also are unable to adopt a binding mode similar to that of huperzine A, since in this case binding is prevented by steric repulsion with the additional aromatic ring (Figure 5, C, D).

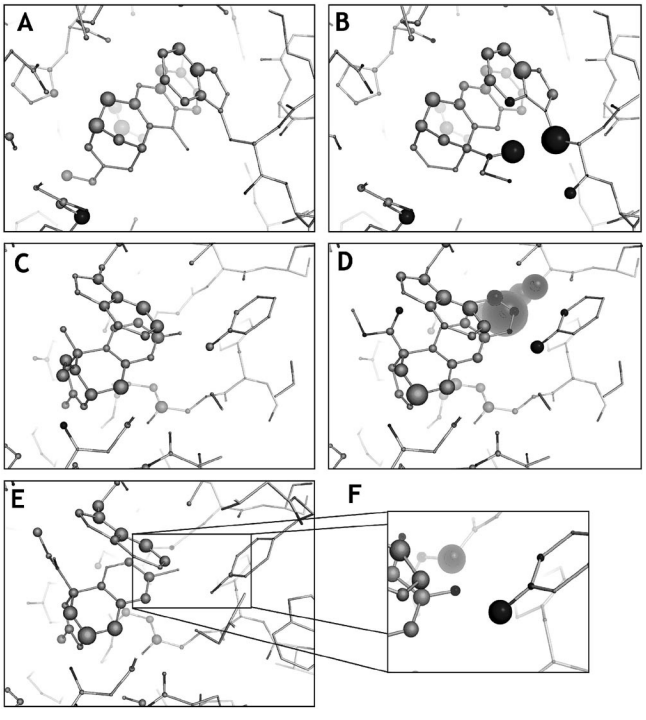

Figure 5. (A) Huprine X in AChE (1E66). (B) Clash of the ester group of **1d** with Trp-84 (binding mode as for huprine X). (C) HA in AChE (1GPN). (D) Clash of **1d** with Ser-122, Gly-123 and Ser-124 (binding mode as for HA). (E) Compound **1c** shows few clashes; the Cl substituent is able to mimick the C=O group of HA. (F) The methyl group of compound **1a** is not compatible with the OH group of Tyr-131.

However, in docking simulations of modified models, effective binding at the huprine X site was observed when the ester group of **1d** and **1e** was replaced by a hydrogen atom. For the 1-H analogue of **1d**, similar binding energies were estimated for the (1*S*) and the (1*R*) enantiomer (–9.7 and –9.5 kcal/mol). The value found for huprine X was –12.7 kcal/mol. Interestingly, in the case of the 1-H analogue of 7-OMe compound **1e**, a potential strong binding activity (–11.2 kcal/mol) was found ony for the (1*R*) enantiomer having the C_3 bridge in a similar fashion as the bioactive (–)-huprine X. Apparently, the extended methoxyquinoline substructure of the (1*R*) enantiomer is able to mimic the Cl-substituted quinoline part of huprine X (Figure 6 and Supporting Information).

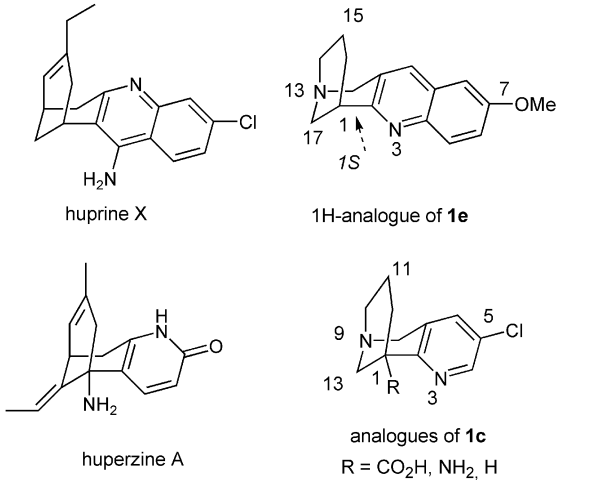

Figure 6. 3D structures of modified 1H-analogue of **1e** compared to (–)-huprine X and of modified analogues of **1c** compared to huperzine A (for detailed results of docking simulations, see Supporting Information).

In contrast to the quinoline compounds **1d**,**e**, substituted pyridine compounds without additional aromatic ring (**1a**, **1c** and **2a**) show activity and are able to bind in the AChE pocket. The results of the docking simulations are in accord with the observed differences in activity. The best scoring compound (**1c**) has the most complementary structure, comparable with that of huperzine A. Presumably, the Cl substituent in **1c** is able to mimic a hydrogen-bonding interaction of the carbonyl group of HA with the OH group of Tyr-131 (Figure 5, C, E). In the less active compounds **1a** and **2a**, this position is occupied by the hydrophobic methyl group (Figure 5F). Hence, an electronegative substituent at this position is favourable for the interaction with the active site.

In future work this insight can be used to design new molecules, which explore other interactions in the pocket but still contain the chloro or another electronegative substituent at this position. For example, docking simulations of modified models, in which the ester group of **1c** was replaced by small and/or polar groups (H, CO_2H, NH_2), resulted in effective solvent-oriented binding at the site of HA: carboxylate ion –11.6 kcal/mol, protonated amine –11.9 kcal/mol, hydrogen –9.5 kcal/mol (compare to value

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found for HA: –13.3 kcal/mol). The increased binding affinities observed for the carboxylate and ammonium ions can be ascribed to solvation by water. Only enantiomers corresponding to HA showed potential binding activity (Figure 6 and Supporting Information).

Conclusions

In this work bridged tetrahydro-1,6-naphthyridines **1a**–**e** and **2a**, designed as analogues of the alkaloid huperzine A, have been synthesised and evaluated as inhibitors of acetylcholinesterase. Two different strategies were utilised, in which internal nucleophilic aromatic substitution and ring-closing metathesis, respectively, served as the key cyclisation step.

Experimental Section

General Remarks: Analytical and preparative thin-layer chromatography was performed on TLC plates coated with Alugram Sil G/UV254. Column chromatography was carried out by using 70–230 mesh silica gel 60 (E. M. Merck) as the stationary phase. ^{1}H and ^{13}C NMR spectra were recorded with Bruker AMX 400 and Bruker Avance 300 spectrometers, chemical shifts (δ) are given in ppm relative to tetramethylsilane as an internal reference. Mass spectra were recorded with a Hewlett–Packard MS Engine 5989 apparatus for EI and CI spectra and a Kratos MS 50 TC instrument by using a DS90 data system for exact mass measurements performed in the EI mode at a resolution of 10000. IR spectra were recorded with a Perkin–Elmer 1720 Fourier-transform spectrometer. All melting points are uncorrected and were measured with an Electrothermal IA 9000 digital melting point apparatus.

Enzyme Kinetic Experiments: The following solutions were used: acetylthiocholine iodide (substrate; Sigma): 30 mM (43.3 mg in 5 mL of water), 15 mM, 6 mM, 3 mM, 1.5 mM; 5,5′-dithiobis-2-nitrobenzoic acid (reagent; Aldrich): 10 mM (39.6 mg in 10 mL of 0.1 M sodium phosphate buffer, pH = 7.0); AChE from electric eel (enzyme; Sigma, lyophilised powder): 5 units/mL (0.20 mg in 11.4 mL of 0.1 M sodium phosphate buffer, pH = 7.0); 0.1 M sodium phosphate buffer, pH = 8.0; inhibitors dissolved in DMSO (approximately 2 mg/mL). Measurements were performed at 25 °C with a Shimadzu UV-1601 spectrophotometer, equipped with a temperature-controlled cuvette holder and PC for data storage by using 1 cm polystyrene cuvettes; 0.725 mL of buffer solution (pH = 8), 12.5 μL of substrate, 25 μL of reagent, 12.5 μL of inhibitor (or DMSO in tests without inhibitor) were mixed; after autozero, 12.5 μL of enzyme was added. The absorbance at 412 nm was measured for 5 min, allowing to determine the initial velocity (ΔA/s). Tests were done without inhibitor, and with compounds **1a**–**e** and **2a** as inhibitor. Inhibitors were tested at 3–5 different substrate concentrations.

1. Synthesis of Alcohols 9b–e

(2-Chloro-3-pyridinyl)methanol (9b): $NaBH_4$ (81 mg, 2.14 mmol) was added to a stirred and cooled (0 °C) solution of 2-chloropyridine-3-carbaldehyde (300 mg, 2.14 mmol) in MeOH (30 mL). After reaction for 15 min, water (30 mL) was added slowly. The mixture was extracted with CH_2Cl_2 (3 × 50 mL). The organic layers were dried with $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel, eluent heptane/EtOAc, 80:20 to 70:30). Yield 0.275 g, 90% (oil). IR (NaCl): $\tilde{\nu}$ = 2920 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.27 (d, J = 4.6 Hz, 1 H), 7.92 (d, J = 7.2 Hz, 1 H), 7.28 (dd, J = 7.2, J = 4.6 Hz, 1 H), 4.79 (s, 2 H), 3.18 (br. s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 149.4, 148.4, 137.3, 135.7, 123.2, 61.7 ppm. MS (EI): m/z (%) = 143 (100), 114 (63), 108 (99). HRMS: calcd. for C_6H_6ClNO 143.0138; found 143.0134.

(2,5-Dichloro-3-pyridinyl)methanol (9c): $NaBH_4$ (292 mg, 9.76 mmol) was added to a solution of methyl 2,5-dichoronicotinate (1 g, 4.88 mmol) in MeOH (50 mL). The mixture was stirred at room temp. for 2 h, then water (50 mL) was added slowly. The mixture was extracted with CH_2Cl_2 (3 × 50 mL). The organic layers were dried with $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel, eluent heptane/EtOAc, 95:5 to 80:20). Yield 0.311 g, 36% (oil). IR (NaCl): $\tilde{\nu}$ = 3609, 2986 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.25 (d, J = 1.9 Hz, 1 H), 7.94 (d, J = 1.9 Hz, 1 H), 4.76 (d, J = 5.7 Hz, 2 H), 2.74 (t, J = 5.7 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 146.9, 146.9, 136.8, 136.8, 131.9, 61.2 ppm. MS (EI): m/z (%) = 177 (71), 148 (14), 142 (99). HRMS: calcd. for $C_6H_5Cl_2NO$ 176.9748; found 176.9754.

(2-Chloro-3-quinolinyl)methanol (9d): $NaBH_4$ (199 mg, 5.23 mmol) was added to a stirred and cooled (0 °C) solution of 2-chloroquinoline-3-carbaldehyde (1 g, 5.23 mmol) in MeOH (50 mL). After reaction for 15 min, water (30 mL) was added slowly. The mixture was extracted with CH_2Cl_2 (3 × 50 mL). The organic layers were dried with $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel, eluent heptane/EtOAc, 70:30). Yield 0.959 g, 95% (oil). IR (NaCl): $\tilde{\nu}$ = 2918 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.46 (s, 1 H), 8.07 (d, J = 8.1 Hz, 1 H), 7.94 (d, J = 8.1 Hz, 1 H), 7.78 (t, J = 8.1 Hz, 1 H), 7.64 (t, J = 7.9 Hz, 1 H), 5.73 (t, J = 5.5 Hz, 1 H), 4.69 (d, J = 5.5 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.7, 146.4, 136.2, 134.3, 130.5, 128.3, 127.8, 127.6, 127.5, 60.3 ppm. MS (EI): m/z (%) = 193 (100), 164 (33), 128 (33). HRMS: calcd. for $C_{10}H_8ClNO$ 193.0294; found 193.0302.

(2-Chloro-6-methoxy-3-quinolinyl)methanol (9e): $NaBH_4$ (172 mg, 5.52 mmol) was added to a stirred and cooled (0 °C) solution of 2-chloro-6-methoxyquinoline-3-carbaldehyde (1 g, 4.52 mmol) in MeOH (50 mL). After reaction for 15 min, water (30 mL) was added slowly. The mixture was extracted with CH_2Cl_2 (3 × 50 mL). The organic layers were dried with $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel, eluent heptane/EtOAc, 70:30). Yield 0.907 g, 90% (oil). IR (NaCl): $\tilde{\nu}$ = 2918 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13 (s, 1 H), 7.86 (d, J = 9.2 Hz, 1 H), 7.32 (dd, J = 9.2, J = 2.7 Hz, 1 H), 6.99 (d, J = 2.7 Hz, 1 H), 4.88 (s, 2 H), 3.90 (s, 3 H), 3.15 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.6, 146.7, 143.0, 135.4, 133.1, 129.7, 128.8, 123.2, 105.5, 62.2, 56.0 ppm. MS (EI): m/z (%) = 223 (100), 194 (21), 158 (5). HRMS: calcd. for $C_{11}H_{10}ClNO$ 223.0400; found 223.0401.

2. Synthesis of 3-(Bromomethyl)pyridines 4b–e

General Procedure: PBr_3 (0.47 mL, 5 mmol) was added to a stirred solution of alcohol **9b**–**e** (5 mmol) in CH_2Cl_2 (50 mL) at room temp. After reaction for 1 h, the mixture was cooled to 0 °C. Then water was added slowly followed by a solution of K_2CO_3 until the mixture was neutral. The mixture was extracted with CH_2Cl_2 (3 × 50 mL). The organic layers were dried with $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel, eluent heptane/EtOAc, 80:20).

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3-(Bromomethyl)-2-chloropyridine (4b): Yield 0.722 g, 85% (oil). IR (NaCl): $\tilde{\nu}$ = 2923 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.35 (d, J = 4.5 Hz, 1 H), 7.80 (d, J = 7.3 Hz, 1 H), 7.26 (dd, J = 7.3, J = 4.5 Hz, 1 H), 4.56 (s, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 149.6, 148.1, 142.3, 134.1, 124.2, 28.5 ppm. MS (EI): m/z (%) = 170 (12), 126 (13). HRMS: calcd. for C_6H_5BrN 169.9005; found 169.9003 [M^+ – Cl].

3-(Bromomethyl)-2,5-dichloropyridine (4c): Yield 0.860 g, 72% (oil). IR (NaCl): $\tilde{\nu}$ = 2920 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.31 (d, J = 2.2 Hz, 1 H), 7.80 (d, J = 2.4 Hz, 1 H), 4.51 (s, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 149.0, 148.4, 139.5, 133.7, 131.6, 28.6 ppm. MS (EI): m/z (%) = 239 (7), 204 (6), 160 (100). HRMS: calcd. for $C_6H_4BrCl_2N$ 238.8904; found 238.8904.

3-(Bromomethyl)-2-chloroquinoline (4d): Yield 0.701 g, 55% (oil). IR (NaCl): $\tilde{\nu}$ = 2919 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.44 (s, 1 H), 8.05 (d, J = 8.0 Hz, 1 H), 7.92 (d, J = 8.4 Hz, 1 H), 7.76 (td, J = 7.7, J = 1.4 Hz, 1 H), 7.62 (td, J = 7.5, J = 1.2 Hz, 1 H), 4.67 (s, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 148.7, 146.3, 136.2, 134.2, 130.5, 128.2, 127.8, 127.6, 127.5, 60.2 ppm. MS (EI): m/z (%) = 255 (51), 220 (63), 176 (90), 140 (100). HRMS: calcd. for $C_{10}H_7BrClN$ 254.9450; found 254.9466.

3-(Broommethyl)-2-chloro-6-methoxyquinoline (4e): Yield 0.741 g, 52% (oil). IR (NaCl): $\tilde{\nu}$ = 2919 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.13 (s, 1 H), 7.91 (d, J = 9.2 Hz, 1 H), 7.38 (dd, J = 9.2, J = 2.7 Hz, 1 H), 7.05 (d, J = 2.7 Hz, 1 H), 4.70 (s, 2 H), 3.3 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.9, 147.7, 143.8, 138.5, 130.1, 130.0, 128.7, 124.2, 105.4, 56.1, 30.3 ppm. MS (EI): m/z (%) = 285 (14), 206 (100). HRMS: calcd. for $C_{11}H_9BrClNO$ 284.9556; found 284.9567.

3. Synthesis of Ring-Closing Precursors 3a–e

General Procedure: Methyl 3-piperidinecarboxylate (430 mg, 3 mmol) and K_2CO_3 (274 mg, 2 mmol) were added to a solution of 3-(bromomethyl)pyridine **4a–e** (2 mmol) in MeOH (50 mL). The reaction mixture was stirred at 75 °C for 1 h and then cooled to room temp. Following the addition of water (30 mL), the mixture was extracted with CH_2Cl_2 (3 × 50 mL). The organic layers were dried with $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel, eluent heptane/EtOAc, 90:10).

Methyl 1-[(2,6-Dichloro-5-methyl-3-pyridinyl)methyl]-3-piperidinecarboxylate (3a): Yield 0.537 g, 85% (oil). IR (NaCl): $\tilde{\nu}$ = 2950, 2855, 2805, 1734 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69 (s, 1 H), 3.65 (s, 3 H), 3.51 (s, 2 H), 2.82 (d, J = 10.2 Hz, 1 H), 2.68–2.62 (m, 1 H), 2.60–2.54 (m, 1 H), 2.38 (t, J = 10.2 Hz, 1 H), 2.33 (s, 3 H), 2.24–2.16 (m, 1 H), 1.90–1.82 (m, 1 H), 1.76–1.68 (m, 1 H), 1.60–1.48 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.3, 148.2, 146.6, 141.9, 131.7, 131.4, 58.2, 55.3, 53.9, 51.7, 41.6, 26.5, 24.4, 18.9 ppm. MS (EI): m/z (%) = 316 (100), 301 49), 285 (50), 257 (73). HRMS: calcd. for $C_{14}H_{19}Cl_2N_2O_2$ 316.0745; found 316.0753.

Methyl 1-[(2-Chloro-3-pyridinyl)methyl]-3-piperidinecarboxylate (3b): Yield 0.322 g, 60% (oil). IR (NaCl): $\tilde{\nu}$ = 2949, 2854, 2803, 1734 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.28 (dd, J = 4.6, J = 1.6 Hz, 1 H), 7.85 (d, J = 7.7 Hz, 1 H), 7.24 (dd, J = 7.7, J = 4.6 Hz, 1 H), 3.67 (s, 3 H), 3.60 (s, 2 H), 2.89 (d, J = 10.6 Hz, 1 H), 2.73–2.67 (m, 1 H), 2.65–2.58 (m, 1 H), 2.42 (t, J = 10.0 Hz, 1 H), 2.28–2.22 (t, J = 9.8 Hz, 1 H), 1.95–1.88 (m, 1 H), 1.80–1.73 (m, 1 H), 1.65–1.52 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.7, 151.3, 148.2, 139.2, 133.5, 122.9, 59.3, 55.8, 54.3, 52.0, 42.1, 26.9, 24.8 ppm. MS (EI): m/z (%) = 268 (100), 253 (63), 137 (61), 209 (72). HRMS: calcd. for $C_{13}H_{17}ClN_2O_2$ 268.0979; found 268.0989.

Methyl 1-[(2,5-Dichloro-3-pyridinyl)methyl]-3-piperidinecarboxylate (3c): Yield 0.320 g, 53% (oil). IR (NaCl): $\tilde{\nu}$ = 2949, 2852, 2801, 1734 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.23 (d, J = 2.0 Hz, 1 H), 7.87 (d, J = 2.0 Hz, 1 H), 3.70 (s, 3 H), 3.56 (s, 2 H), 2.81 (d, J = 9.9 Hz, 1 H), 2.69–2.59 (m, 2 H), 2.50 (t, J = 10.1 Hz, 1 H), 3.31 (t, J = 8.5 Hz, 1 H), 1.92–1.86 (m, 1 H), 1.82–1.78 (m, 1 H), 1.68–1.58 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.6, 148.9, 146.7, 138.5, 135.0, 131.5, 59.0, 55.8, 54.5, 52.2, 42.9, 26.8, 24.7 (C-5′) ppm. MS (EI): m/z (%) = 302 (100), 287 (96), 271 (87). HRMS: calcd. for $C_{13}H_{16}Cl_2N_2O_2$ 302.0589; found 302.0590.

Methyl 1-[(2-Chloro-3-quinolinyl)methyl]-3-piperidinecarboxylate (3d): Yield 0.445 g, 70% (oil). IR (NaCl): $\tilde{\nu}$ = 2950, 2852, 2804, 1733 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.74 (s, 1 H), 8.00 (d, J = 8.3 Hz, 1 H), 7.89 (d, J = 7.8 Hz, 1 H), 7.74 (t, J = 7.5 Hz, 1 H), 7.54 (t, J = 7.4 Hz, 1 H), 4.20 (s, 2 H), 3.67 (s, 3 H), 3.45–3.32 (m, 1 H), 3.27–3.16 (m, 1 H), 3.06–2.94 (m, 1 H), 2.78–2.68 (m, 1 H), 2.61–2.51 (m, 1 H), 2.15–2.03 (m, 1 H), 2.00–1.84 (m, 2 H), 1.63–1.50 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.2, 150.7, 147.3, 140.9, 131.0, 128.2, 128.0, 127.9, 127.4, 127.3, 58.2, 54.4, 53.2, 51.9, 40.5, 26.3, 23.4 ppm. MS (EI): m/z (%) = 318 (100), 303 (40), 287 (41), 259 (85). HRMS: calcd. for $C_{17}H_{19}ClN_2O_2$ 318.1135; found 318.1131.

Methyl 1-[(2-Chloro-6-methoxy-3-quinolinyl)methyl]-3-piperidinecarboxylate (3e): Yield 0.473 g, 68% (oil). IR (NaCl): $\tilde{\nu}$ = 2950, 2850, 2803, 1732 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13 (s, 1 H), 7.89 (d, J = 9.0 Hz, 1 H), 7.33 (dd, J = 9.0, J = 2.7 Hz, 1 H), 7.08 (d, J = 2.7 Hz, 1 H), 3.93 (s, 3 H), 3.71 (s, 2 H), 3.67 (s, 3 H), 2.99 (d, J = 10.8 Hz, 1 H), 2.83–2.78 (m, 1 H), 2.71–2.64 (m, 1 H), 2.47 (t, J = 10.1 Hz, 1 H), 2.30 (t, J = 9.5 Hz, 1 H), 2.00–1.93 (m, 1 H), 1.84–1.78 (m, 1 H), 1.72–1.60 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.9, 158.5, 148.8, 143.1, 137.1, 131.0, 129.6, 128.9, 122.9, 105.4, 59.7, 56.0, 55.9, 54.4, 52.0, 42.2, 27.1, 24.9 ppm. MS (EI): m/z (%) = 348 (100), 289 (33). HRMS: calcd. for $C_{18}H_{21}ClN_2O_3$ 348.1241; found 348.1239.

4. Synthesis of Bridged Compounds 1a–e

General Procedure: $KN(SiMe_3)_2$ (0.5 M solution in toluene, 1.2 mL, 0.6 mmol) was added to a solution of ring-closing precursor **3a–e** (0.5 mmol) in dried toluene (5 mL). The reaction mixture was stirred at 80 °C for 30 min and then cooled to room temp. Following the addition of a saturated NH_4Cl solution (10 mL), the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were dried with $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by reversed phase HPLC (gradient of MeOH and H_2O with 0.1% formic acid).

1a: Yield 0.042 g, 30% (oil). IR (NaCl): $\tilde{\nu}$ = 2925, 1653 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21 (s, 1 H), 4.36 (d, J = 17.2 Hz, 1 H), 3.74 (d, J = 17.2 Hz, 1 H), 3.71 (s, 3 H), 3.43 (d, J = 13.0 Hz, 1 H), 3.21 (d, J = 13.0 Hz, 1 H), 3.03–2.95 (m, 2 H), 2.31 (s, 3 H), 2.15–2.10 (m, 2 H), 1.44–1.38 (m, 1H′), 1.18–1.10 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.9, 153.6, 149.2, 135.7, 130.8, 130.8, 55.0, 54.6, 53.3, 52.2, 46.0, 31.6, 19.4, 19.4 ppm. MS (EI): m/z (%) = 280 (72), 221 (100). HRMS: calcd. for $C_{14}H_{17}ClN_2O_2$ 280.0979; found 280.0973.

1b: Yield 0.032 g, 28% (oil). IR (NaCl): $\tilde{\nu}$ = 2950, 2938, 1647 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.48 (d, J = 4.6 Hz, 1 H), 7.43 (d, J = 7.6 Hz, 1 H), 7.19 (dd, J = 7.6, J = 4.6 Hz, 1 H), 4.57 (d, J = 17.6 Hz, 1 H), 3.87 (d, J = 17.6 Hz, 1 H), 3.78 (s, 3 H), 3.61 (d, J = 13.0 Hz, 1 H), 3.31 (d, J = 13.0 Hz, 1 H), 3.12–3.08 (m, 2 H), 2.24–2.20 (m, 1 H), 2.16 (td, J = 13.4, J = 4.2 Hz, 1 H), 1.60–

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1.50 (m, 1 H), 1.29–1.22 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.0, 155.5, 148.8, 133.3, 130.6, 122.8, 54.2, 54.0, 53.2, 52.7, 46.9, 31.9, 19.2 ppm. MS (EI): *m*/*z* (%) = 232 (61), 173 (100). HRMS: calcd. for $C_{13}H_{16}N_2O_2$ 232.1212; found 239.1219.

1c: Yield 0.044 g, 33% (oil). IR (NaCl): $\tilde{\nu}$ = 2923, 1684 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.40 (s, 1 H), 7.42 (s, 1 H), 4.50 (d, *J* = 17.6 Hz, 1 H), 3.83 (d, *J* = 17.6 Hz, 1 H), 3.74 (s, 3 H), 3.52 (d, *J* = 13.2 Hz, 1 H), 3.27 (d, *J* = 13.2 Hz, 1 H), 3.10–3.04 (m, 2 H), 2.18–2.10 (m, 2 H), 1.58–1.50 (m, 1 H), 1.25–1.15 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.5, 153.7, 147.2, 132.4, 131.9, 130.3, 53.9, 53.9, 52.9, 52.3, 46.2, 22.6, 18.9 ppm. MS (EI): *m*/*z* (%) = 266 (71), 207 (100). HRMS: calcd. for $C_{13}H_{15}ClN_2O_2$ 266.0822; found 266.0836.

1d: Yield 0.049 g, 35% (oil). IR (NaCl): $\tilde{\nu}$ = 2921, 1653 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 (d, *J* = 8.3 Hz, 1 H), 7.88 (s, 1 H), 7.76 (d, *J* = 8.3 Hz, 1 H), 7.67 (t, *J* = 7.6 Hz, 1 H), 7.52 (t, *J* = 7.4 Hz, 1 H), 4.81 (d, *J* = 17.4 Hz, 1 H), 4.15 (d, *J* = 17.4 Hz, 1 H), 3.80 (d, *J* = 13.5 Hz, 1 H), 3.78 (s, 3 H), 3.42 (d, *J* = 13.5 Hz, 1 H), 3.28–3.18 (m, 2 H), 2.40–2.31 (m, 1 H), 2.20 (td, *J* = 13.7, *J* = 4.5 Hz, 1 H), 1.64–1.56 (m, 1 H), 1.36–1.26 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.3, 156.3, 147.3, 131.6, 129.4, 129.3, 127.2, 127.0, 127.0, 126.8, 53.9, 53.9, 53.4, 52.3, 47.4, 32.4, 19.0 ppm. MS (EI): *m*/*z* (%) = 282 (91), 223 (100). HRMS: calcd. for $C_{17}H_{18}N_2O_2$ 282.1368; found 282.1376.

1e: Yield 0.058 g, 37% (oil). IR (NaCl): $\tilde{\nu}$ = 2920, 1653 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91 (d, *J* = 9.1 Hz, 1 H), 7.73 (s, 1 H), 7.30 (dd, *J* = 9.1, *J* = 2.8 Hz, 1 H), 7.00 (d, *J* = 2.8 Hz, 1 H), 4.66 (d, *J* = 17.6 Hz, 1 H), 4.02 (d, *J* = 17.6 Hz, 1 H), 3.92 (s, 3 H), 3.78 (s, 3 H), 3.68 (d, *J* = 12.8 Hz, 1 H), 3.34 (d, *J* = 12.8 Hz, 1 H), 3.16–3.07 (m, 2 H), 2.34–2.26 (m, 1 H), 2.17 (td, *J* = 13.2, *J* = 4.5 Hz, 1 H), 1.50–1.43 (m, 1 H), 1.28–1.20 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.5, 157.8, 154.9, 143.3, 130.8, 129.9, 129.4, 128.3, 121.7, 104.3, 55.6, 54.9, 54.3, 54.1, 52.1, 47.1, 32.9, 19.7 ppm. MS (EI): *m*/*z* (%) = 312 (88), 253 (100). HRMS: calcd. for $C_{18}H_{20}N_2O_3$ 312.1474; found 312.1468.

5. Attempted Synthesis of 12

Methyl 3-[Benzyl(2-methyl-2-propenyl)amino]propanoate (15). Procedure A: Methyl acrylate (8.2 mL, 92 mmol) was added to a solution of benzylamine (10 mL, 92 mmol) in dioxane (100 mL). The reaction mixture was stirred at 100 °C overnight. After cooling the mixture to room temp., methallyl chloride (8.9 mL, 92 mmol) was added, and the reaction mixture ws again stirred at 100 °C overnight. After the reaction was finished, the solvent was removed under reduced pressure, and the residue was purified by column chromatography (silica gel, heptane/EtOAc, 97:3). **Procedure B:** Methyl acrylate (0.95 mL, 10 mmol) was added to a solution of methallylamine (0.8 mL, 10 mmol) in dioxane (100 mL). The reaction mixture was stirred at 100 °C overnight. After cooling the mixture to room temp., benzyl bromide (1.9 mL, 10 mmol) was added, and the reaction mixture was again stirred at 100 °C overnight. Workup of the reaction mixture and purification of the product were carried out as described in Procedure A. Yield (Procedure A): 17 g, 68%; (Procedure B): 1.53 g, 62% (oil). IR (NaCl): $\tilde{\nu}$ = 2951, 2806, 1701 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.30–7.26 (m, 5 H), 4.90 (s, 1 H), 4.84 (s, 1 H), 3.61 (s, 3 H), 3.51 (s, 2 H), 2.92 (s, 2 H), 2.73 (t, *J* = 7.2 Hz, 2 H), 2.46 (t, 2*J* = 7.2 Hz, 2 H), 1.72 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.4, 144.1, 139.9, 128.9, 128.6, 127.3, 61.4, 58.5, 51.9, 49.6, 32.9, 21.0 ppm. MS (EI): *m*/*z* (%) = 247 (15), 206 (35), 192, (16), 174 (92), 156 (30), 91 (100). HRMS: calcd. for $C_{15}H_{21}NO_2$ 247.1572; found 247.1580.

Methyl 3-[Benzyl(2,3-dihydroxy-2-methylpropyl)amino]propanoate (16): *N*-Methylmorpholine *N*-oxide (4.2 g, 36 mmol) and a catalytic amount OsO_4 were added to a solution of amine **13** (3 g, 12 mmol) in a mixture of water (45 mL), Et_2O (45 mL) and *tert*-butyl alcohol (10 mL). The reaction mixture was stirred at room temp. for 2 d. Following addition of water (50 mL), the mixture was extracted with CH_2Cl_2 (3 × 100 mL). The organic layers were dried with $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel, heptane/EtOAc, 50:50). Yield 1.5 g, 48% (oil). IR (NaCl): $\tilde{\nu}$ = 3406, 2951, 1733 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.24 (m, 5 H), 3.83 (d, *J* = 13.4 Hz, 1 H), 3.68 (s, 3 H), 3.48 (d, *J* = 13.4 Hz, 1 H), 3.33 (s, 2 H), 3.12–3.05 (m, 1 H), 2.82–2.74 (m, 1 H), 2.71 (d, *J* = 14.0 Hz, 1 H), 2.56–2.50 (m, 3 H), 1.03 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.7, 138.6, 129.2, 128.5, 127.5, 72.3, 70.2, 62.4, 61.0, 52.4, 52.2, 33.1, 21.2 ppm. MS (EI): *m*/*z* (%) = 281 (1), 250 (33), 206 (5), 91 (100). HRMS: calcd. for $C_{15}H_{23}NO_4$ 281.1627; found 281.1625.

Methyl 3-{Benzyl[(2-methyl-2-oxiranyl)methyl]amino}propanoate (14): *para*-Toluenesulfonyl chloride (404 mg, 2.12 mmol), Bu_2SnO (131 mg, 0.53 mmol), DMAP (129 mg, 1.06 mmol) and NEt_3 (2 mL) were added to a solution of diol **14** (300 mg, 1.06 mmol) in toluene (50 mL). The reaction mixture was stirred at room temp. overnight. Following the addition of water (50 mL), the mixture was extracted with CH_2Cl_2 (3 × 100 mL). The organic layers were dried with $MgSO_4$, and the solvent was removed under reduced pressure. The residue was dissolved in MeOH (50 mL), and K_2CO_3 (292 mg, 2.12 mmol) was added. The mixture was stirred at room temp for 1 h. Following the addition of water (50 mL), the mixture was extracted with CH_2Cl_2 (3 × 50 mL). The organic layers were dried with $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel, heptane/EtOAc, 70:30). Yield 0.167 g, 61% (oil). IR (NaCl): $\tilde{\nu}$ = 3054, 2987, 1733 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.24 (m, 5 H), 3.71 (d, *J* = 13.9 Hz, 1 H), 3.66 (s, 3 H), 3.54 (d, *J* = 13.9 Hz, 1 H), 2.96–2.76 (m, 2 H), 2.64–2.40 (m, 6 H), 1.33 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.4, 139.5, 129.4, 129.0, 128.8, 59.8, 59.3, 56.6, 52.5, 52.0, 50.4, 32.8, 19.6 ppm. MS (EI): *m*/*z* (%) = 263 (5), 206 (100), 190 (28), 91 (91). HRMS: calcd. for $C_{15}H_{21}NO_3$ 263.1521; found 263.1523.

Methyl 1-Benzyl-4-(hydroymethyl)-4-methyl-3-pyrrolidinecarboxylate (18): A solution of epoxide **16** (100 mg, 0.38 mmol) in THF (0.5 mL) was added to a stirred and cooled (–78 °C) solution of LDA (2 M solution, 0.2 mL, 0.40 mmol) in dried THF (2 mL). After reaction at –78 °C for 15 min, Et_2AlCl (0.9 M solution, 0.42 mL, 0.38 mmol) was added. The reaction mixture was stirred between –50 °C and –35 °C for 6 h. After cooling the mixture to –78 °C, a saturated NH_4Cl solution (1 mL) was added. The mixture was warmed to room temp. After decantation, the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were dried with $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel, heptane/EtOAc, 50:50). Yield 0.010 g, 10% (oil). IR (NaCl): $\tilde{\nu}$ = 2951, 2919, 1733 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.23 (m, 5 H), 3.71 (s, 3 H), 3.69 (s, 2 H), 3.58 (d, *J* = 10.0 Hz, 1 H), 3.44 (dd, *J* = 10.0, *J* = 1.5 Hz, 1 H) 3.25 (dd, *J* = 8, *J* = 6.7 Hz, 1 H), 3.14 (t, *J* = 6.7 Hz, 1 H), 3.02 (d, *J* = 9.2 Hz, 1 H) 2.83 (dd, *J* = 8, *J* = 6.7 Hz, 1 H), 2.37 (dd, *J* = 9.2, *J* = 1.5 Hz, 1 H), 0.90 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.4, 138.1, 128.6, 128.5, 127.3, 73.7, 64.9, 59.7, 56.7, 51.6, 48.5, 46.2, 17.8 ppm. MS (EI): *m*/*z* (%) = 263 (16), 246 (6), 232 (11), 172 (52), 91 (100). HRMS: calcd. for $C_{15}H_{21}NO_3$ 263.1521; found 263.1522.

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6. Synthesis of Amines 7a,b. General Procedure: Amine **19a**,**b** (4.7 mmol) and K_2CO_3 (540 mg, 3.9 mmol) were added to a solution of 3-(bromomethyl)pyridine **4a** (1 g, 3.9 mmol) in acetonitrile (40 mL). The reaction mixture was stirred at 60 °C overnight. Following addition of water (50 mL), the mixture was extracted with CH_2Cl_2 (3 × 100 mL). The organic layers were dried with $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel, heptane/EtOAc, 80:20).

Methyl 3-{Allyl[(2,6-dichloro-5-methyl-3-pyridinyl)methyl]amino}-propanoate (7a): Yield 0.876 g, 80% (oil). IR (NaCl): $\tilde{\nu}$ = 2986, 1735 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.72 (s, 1 H), 5.84–5.80 (m, 1 H), 5.21 (d, J = 17.8 Hz, 1 H), 5.17 (d, J = 5.3 Hz, 1 H), 3.66 (s, 3 H), 3.61 (s, 2 H), 3.12 (br. s, 2 H), 2.82 (t, J = 7.1 Hz, 2 H), 2.47 (t, J = 7.1 Hz, 2 H), 2.37 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.6, 148.2, 146.3, 141.9, 134.7, 132.7, 131.4, 118.2, 56.9, 53.6, 51.6, 49.4, 32.5, 18.8 ppm. MS (EI): *m*/*z* (%) = 281 (9), 275 (13), 229 (6), 172 (100). HRMS: calcd. for $C_{14}H_{18}ClN_2O_2$ 281.1057; found 281.1057 [M^+ – Cl].

Methyl 3-{[(2,6-Dichloro-5-methyl-3-pyridinyl)methyl](2-methyl-2-propenyl)amino}propanoate (7b): Yield 0.772 g, 60% (oil). IR (NaCl): $\tilde{\nu}$ = 2955, 2924, 1734 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.73 (s, 1 H), 4.92 (s, 1 H), 4.87 (s, 1 H), 3.66 (s, 3 H), 3.58 (s, 2 H), 2.98 (s, 2 H), 2.79 (t, J = 7.0 Hz, 2 H), 2.49 (t, J = 7.0 Hz, 2 H), 2.36 (s, 3 H), 1.70 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.7, 148.1, 146.3, 142.7, 141.8, 132.7, 131.4, 113.7, 61.1, 53.8, 51.5, 49.6, 32.3, 20.6, 18.9 ppm. MS (EI): *m*/*z* (%) = 330 (6), 289 (50), 275 (37), 257 (100), 256 (88). HRMS: calcd. for $C_{15}H_{20}Cl_2N_2O_2$ 330.0902; found 330.0909.

7. Synthesis of Tetrahydronaphthyridines 6a,b. General Procedure: $KN(SiMe_3)_2$ (0.5 M solution in toluene, 6.8 mL, 3.41 mmol) was added to a solution of amines **7a**,**b** (1.55 mmol) in dried toluene (10 mL). The reaction mixture was stirred at 80 °C for 10 min and then cooled to –78 °C. Following addition of a saturated NH_4Cl solution (10 mL), the mixture was warmed to room temp. The reaction mixture was extracted with CH_2Cl_2 (3 × 20 mL). The organic layers were dried with $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel, heptane/EtOAc, 95:5).

Methyl 6-Allyl-2-chloro-3-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine-8-carboxylate (6a): Yield: 0.334 g, 77% (oil). IR (NaCl): $\tilde{\nu}$ = 2986, 1736 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.25 (s, 1 H), 5.93–5.88 (m, 1 H), 5.26 (d, J = 17.7 Hz, 1 H), 5.22 (d, J = 9.9 Hz, 1 H), 3.96 (t, J = 4.6 Hz, 1 H), 3.76 (d, J = 15.2 Hz, 1 H), 3.74 (s, 3 H), 3.50 (d, J = 15.2 Hz, 1 H), 3.28 (dd, J = 12.0, J = 5.0 Hz, 1 H), 3.25–3.13 (m, 2 H), 2.88 (dd, J = 12.0, J = 5.0 Hz, 1 H), 2.35 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.5, 149.6, 149.1, 137.6, 134.4, 130.8, 129.5, 118.3, 60.4, 53.9, 52.8, 52.3, 47.8, 19.3 ppm. MS (EI): *m*/*z* (%) = 280 (26), 239 (100). HRMS: calcd. for $C_{14}H_{17}ClN_2O_2$ 280.0979; found 280.0977.

Methyl 2-Chloro-3-methyl-6-(2-methyl-2-propenyl)-5,6,7,8-tetrahydro-1,6-naphthyridine-8-carboxylate (6b): Yield 0.286 g, 66% (oil). IR (NaCl): $\tilde{\nu}$ = 2984, 2954, 1738 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.25 (s, 1 H), 4.91 (s, 2 H), 3.91 (t, J = 4.5 Hz, 1 H), 3.75 (d, J = 15.0 Hz, 1 H), 3.70 (s, 3 H), 3.39 (d, J = 15.0 Hz, 1 H), 3.27 (dd, J = 11.7, J = 4.5 Hz, 1 H), 3.10 (d, J = 12.8 Hz, 1 H), 2.99 (d, J = 12.8 Hz, 1 H), 2.74 (dd, J = 11.7, J = 4.5 Hz, 1 H), 2.34 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.0, 150.1, 149.4, 142.5, 138.1, 131.2, 130.2, 114.2, 64.7, 54.6, 53.1, 52.6, 48.3, 20.8, 19.7 ppm. MS (EI): *m*/*z* (%) = 294 (37), 253 (100), 249 (68), 235 (40). HRMS: calcd. for $C_{14}H_{17}ClN_2O_2$ 294.0979; found 294.0996.

8. Synthesis of 8-Hydroxy-tetrahydronaphthyridines 20a,b. General Procedure: $KN(SiMe_3)_2$ (0.5 M solution in toluene, 6.8 mL, 3.41 mmol) was added to a solution of amines **7a**,**b** (1.55 mmol) in dried toluene (10 mL). The reaction mixture was stirred at 80 °C for 10 min, then the inert gas was replaced by oxygen. The mixture was stirred at 80 °C overnight, then cooled to room temp. Following addition of a saturated NH_4Cl solution (10 mL), the reaction mixture was extracted with CH_2Cl_2 (3 × 20 mL). The organic layers were dried with $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel, heptane/EtOAc, 80:20).

Methyl 6-Allyl-2-chloro-8-hydroxy-3-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine-8-carboxylate (20a): Yield 0.403 g, 88% (oil). IR (NaCl): $\tilde{\nu}$ = 2986, 1734 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.31 (s, 1 H), 5.96–5.86 (m, 1 H), 5.28 (d, J = 17.3 Hz, 1 H), 5.24 (d, J = 10.4 Hz, 1 H), 3.79 (s, 3 H), 3.76 (d, J = 15.7 Hz, 1 H), 3.63 (d, J = 15.7 Hz, 1 H), 3.27 (dd, J = 6.0, J = 5.0 Hz, 2 H), 3.23 (d, J = 12.0 Hz, 1 H), 3.04 (d, J = 12.0 Hz, 1 H), 2.37 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.2, 151.9, 149.9, 137.8, 134.0, 132.3, 129.1, 118.9, 74.8, 60.2, 59.0, 53.7, 53.0, 19.4 ppm. MS (EI): *m*/*z* (%) = 296 (39), 278 (30), 255 (86), 227 (100). HRMS: calcd. for $C_{14}H_{17}ClN_2O_3$ 296.0928; found 296.0937.

Methyl 2-Chloro-8-hydroxy-3-methyl-6-(2-methyl-2-propenyl)-5,6,7,8-tetrahydro-1,6-naphthyridine-8-carboxylate (20b): Yield 0.336 g, 70% (oil). IR (NaCl): $\tilde{\nu}$ = 2953, 1741 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.30 (s, 1 H), 4.94 (br. s, 2 H), 3.77 (s, 3 H), 3.63 (s, 2 H), 3.16–3.10 (m, 3 H), 2.90 (d, J = 11.8 Hz, 1 H), 2.3 (s, 3 H), 1.75 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.7, 152.4, 150.1, 142.2, 138.2, 132.7, 129.8, 114.6, 75.2, 64.6, 59.3, 54.6, 53.4, 20.9, 19.8 ppm. MS (EI): *m*/*z* (%) = 310 (34), 255 (100), 227 (20). HRMS: calcd. for $C_{15}H_{19}ClN_2O_3$ 310.1084; found 310.1062.

9. Synthesis of 6,8-Diallyl-tetrahydronaphthyridines 21a–c. General Procedure: $KN(SiMe_3)_2$ (0.5 M solution in toluene, 4.4 mL, 2.2 mmol) was added to a solution of amines **7a**,**b** (1 mmol) in dried toluene (10 mL). The reaction mixture was stirred at 80 °C for 10 min, then allyl bromide or methallyl chloride (3 mmol) was added. The mixture was stirred at 80 °C for 15 min, then it was cooled to room temp. Following addition of a saturated NH_4Cl solution (10 mL), the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The organic layers were dried with $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel, heptane/EtOAc, 90:10).

Methyl 6,8-Diallyl-2-chloro-3-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine-8-carboxylate (21a): Yield 0.102 g, 32% (oil). IR (NaCl): $\tilde{\nu}$ = 2982, 2953, 2926, 1733 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.21 (s, 1 H), 5.91–5.78 (m, 1 H), 5.74–5.62 (m, 1 H), 5.22 (dd, J = 17.0, J = 15 Hz, 1 H), 5.18 (d, J = 9.6 Hz, 1 H), 5.07 (dd, J = 17.7, J = 1.7 Hz, 1 H), 5.00 (d, J = 10.0 Hz, 1 H), 3.71 (d, J = 14.9 Hz, 1 H), 3.66 (s, 3 H), 3.42 (d, J = 14.9 Hz, 1 H), 2.27 (d, J = 11.3 Hz, 1 H), 3.18 (dd, J = 13.7, J = 6.3 Hz, 1 H), 3.10 (dd, J = 13.7, J = 6.4 Hz, 1 H), 2.93 (dd, J = 13.9, J = 6.5 Hz, 1 H), 2.81 (dd, J = 13.9, J = 7.4 Hz, 1 H), 2.57 (d, J = 11.5 Hz, 1 H), 2.33 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.9, 153.2, 149.3, 137.9, 135.1, 134.6, 130.8, 130.1, 118.7, 118.5, 61.1, 57.7, 55.0, 53.4, 52.7, 40.1, 19.7 ppm. MS (EI): *m*/*z* (%) = 320 (16), 279 (75). HRMS: calcd. for $C_{17}H_{21}ClN_2O_2$ 320.1292; found 320.1292.

Methyl 6-Allyl-2-chloro-3-methyl-8-(2-methyl-2-propenyl)-5,6,7,8-tetrahydro-1,6-naphthyridine-8-carboxylate (21b): Yield 0.140 g, 42% (oil). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.21 (s, 1 H), 5.90–5.83 (m, 1 H), 5.24 (d, J = 18.7 Hz, 1 H), 5.20 (d, J = 11.3 Hz, 1 H), 4.77 (s, 1 H), 4.69 (s, 1 H), 3.75 (d, J = 14.9 Hz, 1 H), 3.37 (s,

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3 H), 3.39 (d, J = 14.9 Hz, 1 H), 3.39 (d, J = 13.6 Hz, 1 H), 3.22 (dd, J = 13.8, J = 5.9 Hz, 1 H), 3.14 (d, J = 13.6 Hz, 1 H), 3.09 (dd, J = 13.8, J = 6.8 Hz, 1 H), 2.87 (d, J = 13.6 Hz, 1 H), 2.52 (d, J = 13.6 Hz, 1 H), 2.35 (s, 3 H), 1.43 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.3, 153.1, 149.0, 142.2, 137.9, 135.2, 130.8, 130.2, 118.4, 115.9, 61.2, 57.8, 55.2, 53.2, 52.9, 42.8, 24.4, 19.7 ppm. MS (EI): *m*/*z* (%) = 334 (13), 303 (7), 293 (32), 279 (100). HRMS: calcd. for $C_{18}H_{23}ClN_2O_2$ 334.1448; found 334.1449.

Methyl 8-Allyl-2-chloro-3-methyl-6-(2-methyl-2-propenyl)-5,6,7,8-tetrahydro-1,6-naphthyridine-8-carboxylate (21c): Yield 0.153 g, 46% (oil). IR (NaCl): $\tilde{\nu}$ = 2980, 2952, 2923, 1734 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.21 (s, 1 H), 5.67 (m, 1 H), 5.06 (d, J = 17.0 Hz, 1 H), 4.99 (d, J = 10.1 Hz, 1 H), 4.97 (s, 2 H), 3.68 (d, J = 15.5 Hz, 1 H), 3.64 (s, 3 H), 3.35 (d, J = 15.5 Hz, 1 H), 3.24 (d, J = 11.6 Hz, 1 H), 3.06 (d, J = 12.6 Hz, 1 H), 2.97 (dd, J = 13.7, J = 5.7 Hz, 1 H), 2.96 (d, J = 12.6 Hz, 1 H), 2.79 (dd, J = 13.7, J = 5.7 Hz, 1 H), 2.55 (d, J = 11.6 Hz, 1 H), 2.33 (s, 3 H), 1.71 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.0, 153.2, 149.3, 142.6, 137.9, 134.6, 130.7, 130.1, 118.7, 114.2, 65.2, 58.2, 55.0, 53.5, 52.7, 39.8, 20.8, 19.7 ppm. MS (EI): *m*/*z* (%) = 334 (16), 293 (32), 261 (86). HRMS: calcd. for $C_{18}H_{23}ClN_2O_2$ 334.1448; found 334.1436.

10. Synthesis of Bridged Compound 2a: Grubbs' 2nd generation catalyst (10 mg) was added to a solution of **21a** (30 mg, 0.093 mmol) in dried CH_2Cl_2 (5 mL). The reaction mixture was stirred at room temp. overnight. After filtration of the catalyst, the solvent was removed under reduced pressure. The residue was purified by reversed phase HPLC (gradient of MeOH and H_2O with 0.1% formic acid).

2a: Yield 0.010 g, 40% (oil). IR (NaCl): $\tilde{\nu}$ = 2953, 2925, 1732 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.14 (s, 1 H), 5.68–5.62 (m, 1 H), 5.43–5.38 (m, 1 H), 4.32 (d, J = 17.3 Hz, 1 H), 3.86 (d, J = 13.8 Hz, 1 H), 3.72 (s, 3 H), 3.71 (d, J = 17.3 Hz, 1 H), 3.61 (dd, J = 16.8, J = 2.8 Hz, 1 H), 3.53 (dd, J = 16.8, J = 6.5 Hz, 1 H), 3.42 (d, J = 13.8 Hz, 1 H), 3.12 (ddd, J = 16.0, J = 8.7, J = 2.0 Hz, 1 H), 2.79 (dd, J = 15.8, J = 2.7 Hz, 1 H), 2.31 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.7, 153.6, 149.2, 136.4, 131.8, 131.1, 130.2, 130.2, 60.5, 55.8, 53.0, 52.8, 48.7, 38.2, 19.8 ppm. MS (EI): *m*/*z* (%) = 292 (70), 233 (100). HRMS: calcd. for $C_{15}H_{17}ClN_2O_2$ 292.0979; found 292.0981.

Supporting Information (see footnote on the first page of this article): (1) Coloured version of Figure 5 showing detailed results for docking experiments on Huprine X, Huperzine A and compounds **1a**, **1c** and **1d**. (2) Extended Figure 6 showing spatial structures of modified models of compounds **1d**,**e** and **1c** compared to Huprine X and Huperzine A. (3) Docking simulations on modified models of compounds **1d**,**e** and **1c** superimposed on those obtained for Huprine X and Huperzine A.

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