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Synthesis of New Substituted 4,5-Dihydro-3*H*-spiro[1,5]-benzoxazepine-2,4′-piperidine and Biological Properties

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The reduction of substituted spiro-piperidinyl chromanone oximes with DIBAH reagents has been known to afford the corresponding substituted 4,5-dihydro-3*H*-spiro[1,5]-benzoxazepine-2,4′-piperidine. The position and electronic effects of the substituents on the aryl moiety control the observed rearrangement. Spiro-benzoxazepine analogue **5j** represents a key intermediate for the creation of a library of diverse potential bioactive drugs. With three functional groups that could be selectively and orthogonally protected, many different substituents can be introduced. The obtained analogues were assayed as the possible aspartyl protease inhibitors HIV protease (HIV-1), and β-secretase (BACE-1).

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Introduction

Certain privileged structures can provide useful ligands for more than one receptor, and judicious modifications of such structures might provide viable alternatives in the search for either new receptor agonists or antagonists, as well as protein active sites.[1] The selection and derivatization of scaffolds that recur in classes of bioactive compounds has become a strategy to complement diversity in the generation of chemical libraries for lead discovery. Among privileged structures, which are believed to be important for biological activity, spiro-piperidines[2] have been identified as a relevant scaffold for the design of bioactive compounds. More recently, it has been shown[3] that some criteria (the number of rotatable bonds and numbers of hydrogen bond acceptors and donors) appear to be determinative for a drug to have an acceptable oral bioavailability. Moreover, structure rigidity as well as the functional groups introduced on the different positions of a scaffold are essential for receptor or enzyme active-site affinity.

Taking into account these considerations, we selected the motive 4,5-dihydro-3*H*-spiro[1,5]-benzoxazepine-2,4′-piperidine as a privileged structure for the creation of a focussed library of bioactive drugs (Fig. 1).

New analogues of this focussed library will be tested for their inhibitory properties on two representative aspartyl proteases: HIV protease involved in the HIV viral replication cycle of infected cells,[4] and β-secretase (BACE-1) involved in the formation of senile plaque in Alzheimer's disease.[5–8] To reach this goal, an efficient method is needed for the synthesis of such scaffolds starting from spiro-piperidine chromanone oximes. The synthesis of this latter scaffold has been published,[9] but the described structures bear no substituents on the aryl moiety. Introduction of various substituents on this part of the structure presents two main interests: first to increase the structural diversity of the resulting analogues; and second to study substituent effects on the reductive rearrangement process (Beckmann rearrangement).

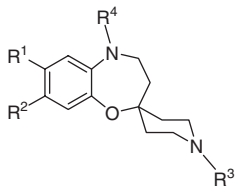

Fig. 1. General structure of spiro-benzoxazepine-piperidine.

Results and Discussion

As a preliminary objective, we developed a synthetic route which allowed the synthesis of a diversity of spiro-benzoxazepine bearing various substituents as shown in Scheme 1.[9,10] Some compounds **3a**, **3d**, **3f**, **3g**, **4f**, and **5f** of this scheme have been recently described.[9,11,12]

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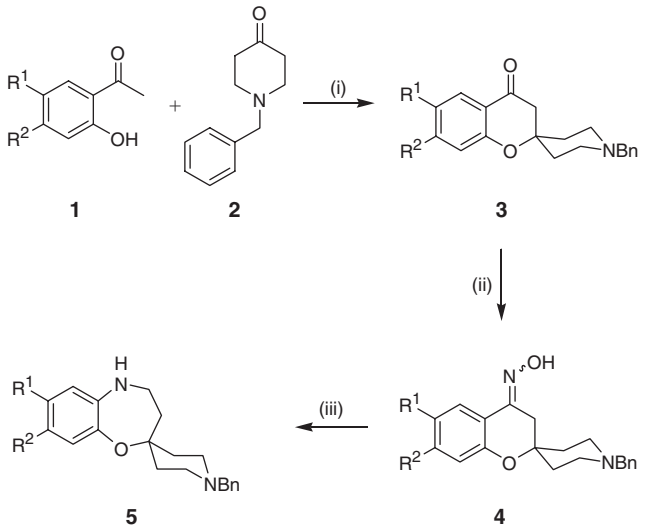


Scheme 1. Reagents and conditions: (i) pyrrolidine, MeOH, reflux; (ii) HCl·H_2N-OH, pyridine, EtOH, reflux; (iii) reductive rearrangement step (Beckmann rearrangement).

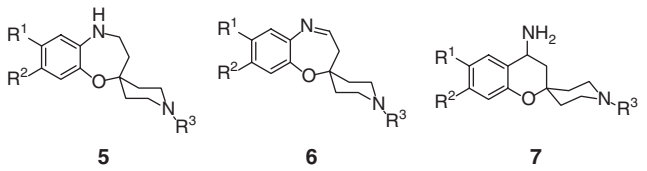


Fig. 2. Possible compounds obtained after reduction step (Beckman rearrangement).

Some of final spiro-benzoxyazepines, after selective deprotection, could be considered as possible starting building blocks for the construction of a chemical library.

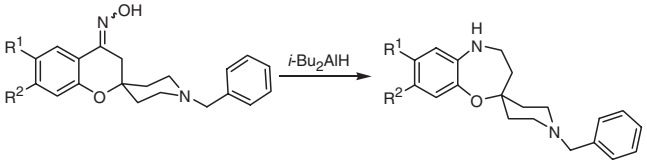
Introduction of substituents for R^3 and R^4 (Fig. 1) was standard chemistry. In contrast, introduction of various substituents on the aromatic ring appears more difficult since the reductive rearrangement (Beckmann rearrangement) step could lead to at least three possible products as shown in Fig. 2.

The yield of the primary aryl alkyl amines **7** with respect to the formation of secondary amine **5**, and imine **6** depends on the following parameters:

- The position and electronic effect of substituents R^1 and R^2 on the aryl nucleus.
- The protection or not of the oxime function by tosyl or other substituted silyl groups.[13,14]
- The size of the ring bearing the oxime function and the substituent on the heterocyclic ring fused to the aromatic ring (e.g. spiro-piperidine ring).
- The nature of the reductive agent used for the rearrangement of the oxime and the reaction conditions.

Catalytic reduction of aromatic oximes alkyl and aryl ethers with borane and organoboron reagents affords either hydroxyl amine, or amines that mainly depend on the structure of the starting oximes and the reaction conditions.[15,16] Free oximes have been reported to be converted into rearranged secondary amines through diisobutylaluminium hydride (DIBAH) reduction.[10]

Table 1. Reduction of aryl-substituted chromanone oximes



Oximes	R^1	R^2	Products	Yield [%]
4a	OMe	H	**5a**	61
4b	Me	H	**5b**	16
4c	OBn	H	**5c**	52
4d	Cl	H	**5d**	32
4e	F	H	**5e**	40
4f	H	H	**5f**	52
4g	H	OMe	**5g**	—[A]
4h	NO_2	H	**5h**	—[A]

[A] Not detected.

Introduction of specific substituents on the aryl moiety was considered as an important aspect to build a diversified focussed library of aryl-substituted 4,5-dihydro-3*H*-spiro[1,5]-benzoxazepine-2,4′-piperidine. We also synthesized a large variety of compounds starting directly from chromanone oximes. Then, we explored the effect of substituents R^1 and R^2 on the reductive rearrangement products using DIBAH in CH_2Cl_2 as a reducing agent. Results are reported in Table 1.

From these results it can observed that:

- When oximes (**4a**–**4f**) have been reduced by DIBAH, the only products obtained were the corresponding anilines (**5a**–**5f**) in various yields, without detection of either imine **6** or primary amines **7** (Fig. 2) in the reaction mixture. Only starting oxime derivatives were recovered.
- The electronic effects (donating or withdrawing) of the substituents on the aryl moiety greatly influence the progression of this reductive step. Strong electron-withdrawing substituents such as the nitro group (NO_2) at position 6 of the aromatic moiety are clearly unfavourable to the rearrangement since no reaction occurred under the experimental conditions. In contrast, either electron donating substituents, or less electron-withdrawing substituents than NO_2 (H, Cl, OCH_3), led to the expected secondary aniline **5** as major rearrangement product.
- Considering compounds **4a** and **4g** with a methoxy group at position 6 and 7 of the aromatic ring, respectively, it can be observed (Table 1) that the reductive rearrangement step is greatly influenced by the substitution position on this moiety. No reaction was observed with the oxime **4g**, and 95% of the starting oxime was recovered. Using mass spectrum and NMR analyses of the obtained side products, only the corresponding intracyclic 4-ene-benzoxazepine **6g** analogue was identified in 2% yield.

In contrast, for the oxime **4a** only the expected secondary aniline **5a** was obtained in 61% yield. These observations are in agreement with the proposed Yamamoto mechanism[10] for

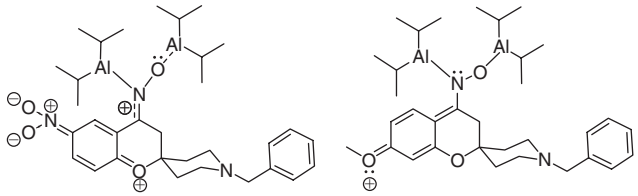


Fig. 3. Stabilizing effect on the cationic center by aryl substituents 6-NO_2 and 7-OMe.

Table 2. Catalyst effects on aryl-substituted chromanone oximes

Oximes	Reduction conditions	Yield **5**[A] [%]	Yield **6** [%]
4a	DIBAH·CH_2Cl_2/0°C/3 h	61	—[B]
4g	DIBAH·CH_2Cl_2/0°C/3 h	2.5	—[B]
4a	Red-Al·THF/Δ/18 h	No reaction	
4g	Red-Al·THF/Δ/18 h	No reaction	
4a	$LiAlH_4$·ether/rt/18 h	5	—[B]
4g	$LiAlH_4$·ether/rt/18 h	5	—[B]
4a	BMS·THF/rt/18 h	5	—[B]

[A] For each experiment the starting oximes were entirely recovered.
[B] Not isolated and not detected.

the reduction of oximes using DIBAH leading to rearrangement. Addition of DIBAH on the oxime substrate coordinates to nitrogen and oxygen lone pairs, leading to a complex in which the nitrogen positive charge is stabilized through resonance. A reaction mechanism different from classical Beckmann rearrangement has also been suggested.[17] In this case, first the reduction of the oxime double bond occurred, then the rearrangement proceeded.

When a methoxy substituent, which has a lower field effect than resonance effect, is introduced at position 7 of the aromatic ring **4g**, a direct resonance interaction with the cationic center occurs. This interaction stabilizes the reactive cationic center and impedes the reductive rearrangement. In contrast, introduction of this methoxy substituent at position 6 abolished direct interaction with the cationic center, which is thus less stabilized, and reductive rearrangement could occur. Similarly, when the strong electron-withdrawing NO_2 substituent is introduced at the 6 position on the aromatic ring, its high field withdrawing effect conjugated with its resonance effect destabilizes the cationic center, and therefore, prevents the reductive rearrangement as shown in Fig. 3.

We next performed the same reductive rearrangement reaction on free chromanone oxime **4a** as representative substrate, but using various aluminium containing catalysts (DIBAH, Red-Al, $LiAlH_4$) and non-aluminum reagents such as borane dimethyl sulfide (BMS). Results are reported in Table 2.

As shown, only DIBAH in CH_2Cl_2 leads to the secondary amine in satisfactory yield. Other aluminium catalysts either failed or gave very low yield, probably by forming a cationic complex, and thus confirming the electrophilic nature of the rearrangement. Strengthening this hypothesis, when BMS reductive reagent in THF was used, reduction of analogue **4a** did not proceed.

Following the results of Ortiz-Marciales et al.[15] that oxime rearrangement with borane reductive catalyst (BF_3–Et_2O/BH_3–DMSO) takes place only when the chromanone oximes were silylated, analogue **4g** bearing a methoxy substituent at position 7 was first silylated and then submitted to the reductive step using BF_3–Et_2O/BH_3–DMSO. Under these conditions, 95% of starting oxime was recovered, and among the isolated formed products, analogues **6g** and **7g** were isolated in less than 2% yield but clearly identified (Scheme 2).

These results show that, whatever the reagents used for this reductive step, this reductive process is mainly determined by the position and nature of the substituent (electronic effect) on the aryl moiety of the chromanone oxime.

Finally, in order to introduce a function suitable to link various side chains on the aryl moiety, we deprotected the methoxy and amine functions of compound **5a** into its corresponding compound **5j** (Scheme 3). The **5j** analogue has three positions which could be selectively protected or deprotected (two amino groups and one hydroxyl group), and which allow the introduction of diverse substituents. This analogue represents a versatile basic scaffold on which a library of potential bioactive analogues may be built.

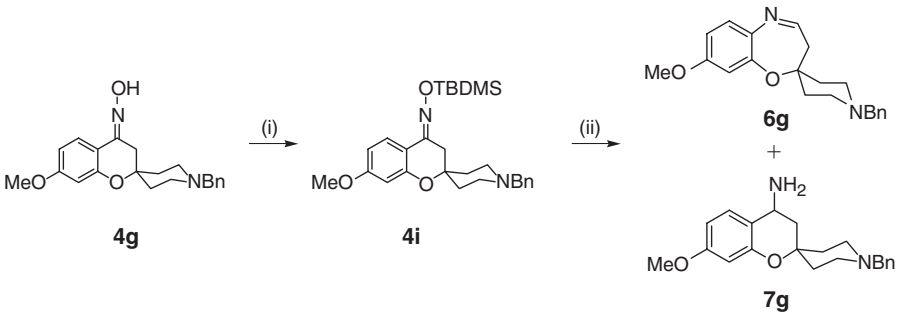
The whole synthesized compounds were assayed for inhibitory activity against HIV protease and BACE-1 (β-secretase). These evaluations were performed according standard procedures: BACE-1 inhibition measurements using the FRET Kit assay methodology[18] (PanVera Corp., Madison, WI), and recombinant HIV protease according to Bihel and Kraus.[19] However, neither whole derivative showed inhibitory activity, even at 10 μM concentration, for any enzymes tested under our assay conditions.

Conclusion

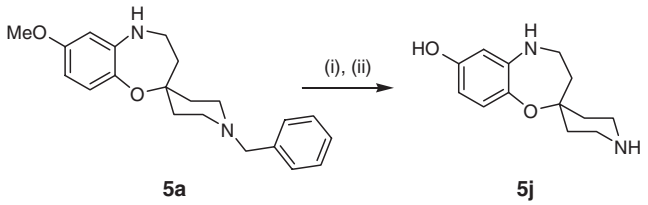
We have succeeded to elaborate a focussed library of 4,5-dihydro-3*H*-spiro[1,5]-benzoxazepine-2,4′-piperidine derivatives with various substituents on the aryl moiety, starting directly from free oxime chromanones by a reductive Beckmann rearrangement. Compound **5j** with three functional groups will be used as a versatile intermediate for the construction of a diverse library of bioactive analogues. Our results bring evidence that the position and electronic effects of the substituents on the aryl moiety greatly influence the formation of the spiro-benzoxazepine products. These results are also in agreement with reported studies that suggest a cationic rearrangement mechanism during the reductive rearrangement step of OH-free oxime chromanones using an aluminated catalyst. After biological evaluation of the inhibitory properties of the new analogues on two aspartyl protease enzymatic models, no significant inhibitory activity was found for these new analogues.

Experimental

Unless otherwise noted, starting materials and reagents were obtained from commercial suppliers and were used without purification. Tetrahydrofuran (THF) was distilled over sodium benzophenone ketyl immediately before use. Methylene dichloride (CH_2Cl_2) was distilled over P_2O_5 just before use. Nuclear magnetic resonance spectra were recorded at 250 MHz for ^1H and 62.9 MHz for ^{13}C on a Bruker AC-250 spectrometer. Chemical shifts are expressed as ppm downfield from TMS (tetramethylsilane). Electrospray mass spectra were obtained on a



Scheme 2. (i) TBDMS-Cl, CH_2Cl_2, rt; (ii) (a) BF_3-Et_2O, (b) BH_3-$S(CH_3)_2$, THF, rt.



Scheme 3. (i) BBr_3, CH_2Cl_2, rt; (ii) H_2, $Pd(OH)_2$ (10%), MeOH, rt.

Waters Micromass ZMD spectrometer by direct injection of the sample solubilized in acetonitrile. Microanalyses were carried out by the Service Central d'Analyses du CNRS (Venaison, France) and were within 0.4% of theoretical values. Analytical thin layer chromatography (TLC) and preparative thin layers chromatography (PLC) were performed using silica gel plates 0.2 mm thick and 1 mm thick respectively (60F254 Merck). Preparative flash column chromatography was carried out on silica gel (230–240 mesh, G60 Merck).

*Typical Procedure for Synthesis of 2,3-Dihydrochromanone: 1′-Benzylspiro[chromene-2,4′-piperidin]-4(3*H*)-one* ***3f***

Compound **3f** was obtained by refluxing 2′-hydroxyacetophenone **1f** (2 g, 14.6 mmol) with *N*-benzyl-piperidone **2** (3.3 mL, 14.6 mmol) in methanol (20 mL), in the presence of a catalytic amount of pyrrolidine (0.6 mL, 7.3 mmol). The resulting mixture was extracted with ethyl acetate (3 × 50 mL). The organic layer was dried ($MgSO_4$) and concentrated to give a yellow oil. Purification was carried out by flash silica gel chromatography using cyclohexane/ethyl acetate (3:1, v/v) as eluent to give product **3f** as yellow solid (4.1 g, 91%), mp 99–101°C. (Found: C 78.32, H 6.97, N 4.43. Calc. for $C_{20}H_{21}NO_2$: C 78.15, H 6.89, N 4.56%). δ_H ($CDCl_3$, 250 MHz) 1.75 (2H, ddd, *J* 13.5, 9.6, 4.6), 2.02–2.07 (2H, m), 2.46 (2H, td, *J* 11.4, 2.5), 2.61–2.66 (2H, m), 2.72 (2H, s), 3.56 (2H, s), 6.96–7.03 (2H, m), 7.26–7.38 (5H, m), 7.46–7.52 (1H, m), 7.86–7.90 (1H, m). *m/z* (ES) 308 $[M + H]^+$.

*1′-Benzyl-6-methoxyspiro[chromene-2,4′-piperidin]-4(3*H*)-one* ***3a***

Yellowish oil (60%). (Found: C 74.55, H 6.72, N 4.23. Calc. for $C_{21}H_{23}NO_3$: C 74.75, H 6.87, N 4.15%). δ_H ($CDCl_3$, 250 MHz) 1.75 (2H, ddd, *J* 13.5, 9.6, 4.6), 2.02–2.07 (2H, m), 2.46 (2H, td, *J* 11.4, 2.5), 2.63 (2H, dt, *J* 11.6, 3.8), 2.72 (2H, s), 3.56 (2H, s), 3.82 (3H, s), 6.94 (1H, d, *J* 9.0), 7.12 (1H, dd, *J* 8.9, 3.1), 7.29–7.36 (6H, m). *m/z* (ES–MS) 338 $[M + 1]^+$.

*1′-Benzyl-6-methylspiro[chromene-2,4′-piperidin]-4(3*H*)-one* ***3b***

Yellow solid (65%), mp 96–97°C. (Found: C 78.32, H 7.17, N 4.26. Calc. for $C_{21}H_{23}NO_2$: C 78.47, H 7.21, N 4.36%). δ_H ($CDCl_3$, 250 MHz) 1.69 (2H, ddd, *J* 13.5, 9.6, 4.6), 1.94 (2H, m), 2.22 (3H, s), 2.43 (2H, td, *J* 11.4, 2.5), 2.57–2.60 (2H, m), 2.69 (2H, s), 3.45 (2H, s), 6.81 (1H, d, *J* 8.4), 7.19–7.32 (5H, m), 7.68 (1H, d, *J* 8.7), 7.56 (1H, d, *J* 1.55). *m/z* (ES–MS) 322 $[M + 1]^+$.

*1′-Benzyl-6-(benzyloxy)spiro[chromene-2,4′-piperidin]-4(3*H*)-one* ***3c***

Yellow solid (90%), mp 133–134°C. (Found: C 78.26, H 6.32, N 3.47, Calc. for $C_{27}H_{27}NO_3$: C 78.42, H 6.58, N 3.39%). δ_H ($CDCl_3$, 250 MHz) 1.69 (2H, ddd, *J* 13.5, 9.6, 4.6), 2.04–2.10 (2H, m), 2.44 (2H, td, *J* 11.4, 2.5), 2.61–2.70 (2H, m), 2.73 (2H, s), 3.57 (2H, s), 5.06 (2H, s), 6.93 (1H, d, *J* 9.0), 7.17 (1H, dd, *J* 9.0, 3.1), 7.23–7.45 (11H, m). *m/z* (ES–MS) 414 $[M + 1]^+$.

*1′-Benzyl-6-chlorospiro[chromene-2,4′-piperidin]-4(3*H*)-one* ***3d***

Yellowish oil (95%). (Found: C 70.34, H 5.96, N 3.85. Calc. for $C_{20}H_{20}ClNO_2$: C 70.27, H 5.90, N 4.10%). δ_H ($CDCl_3$, 250 MHz) 1.69 (2H, ddd, *J* 13.5, 9.6, 4.6), 1.93–2.00 (2H, m), 2.38 (2H, td, *J* 11.4, 2.5), 2.53–2.61 (2H, m), 2.65 (2H, s), 3.48 (2H, s), 6.90 (1H, d, *J* 8.8), 7.19–7.27 (5H, m), 7.36 (1H, dd, *J* 2.6, 8.8), 7.75 (1H, d, *J* 2.7). *m/z* (ES–MS) 342 $[M + 1]^+$.

*1′-Benzyl-6-fluorospiro[chromene-2,4′-piperidin]-4(3*H*)-one* ***3e***

Yellow solid (38%), mp 88–89°C. (Found: C 73.85, H 6.14, N 4.42. Calc. for $C_{20}H_{20}FNO_2$: C 73.83, H 6.20, N 4.30%). δ_H ($CDCl_3$, 250 MHz) 1.70 (2H, ddd, *J* 13.5, 9.6, 4.6), 1.92–2.04 (2H, m), 2.46 (2H, td, *J* 11.4, 2.5), 2.52–2.59 (2H, m), 2.69 (2H, s), 3.47 (2H, s), 7.13 (2H, m), 7.21–7.29 (5H, m), 7.41 (1H, dd, *J* 8.8, 2.6). *m/z* (ES–MS) 326 $[M + 1]^+$.

*1′-Benzyl-7-methoxyspiro[chromene-2,4′-piperidin]-4(3*H*)-one* ***3g***

Yellow oil (86%). (Found: C 74.55, H 6.72, N 4.23. Calc. for $C_{21}H_{23}NO_3$: C 74.75, H 6.87, N 4.15%). δ_H ($CDCl_3$, 250 MHz) 1.75 (2H, ddd, *J* 13.5, 9.6, 4.6), 2.00–2.05 (2H, m), 2.46 (2H, td, *J* 11.4, 2.5), 2.58–2.61 (2H, m), 2.65 (2H, s), 3.54 (2H, s), 3.85 (3H, s), 6.45 (1H, d, *J* 2.4), 6.54 (1H, dd, *J* 8.6, 2.4), 7.25–7.32 (5H, m), 7.79 (1H, d, *J* 8.8). *m/z* (ES–MS) 338 $[M + 1]^+$.

*1′-Benzyl-6-nitrospiro[chromene-2,4′-piperidin]-4(3*H*)-one* ***3h***

Yellow oil (85%). (Found: C 68.01, H 5.94, N 8.19. Calc. for $C_{22}H_{20}N_2O_4$: C 68.17, H 5.72, N 7.95%). δ_H ($CDCl_3$, 250 MHz) 1.84 (2H, ddd, *J* 13.5, 9.6, 4.6), 2.03–2.09 (2H, m), 2.48 (2H, td, *J* 11.4, 2.5), 2.64–2.71 (2H, m), 2.81 (2H, s), 3.57 (2H, s), 7.12 (1H, dd, *J* 8.9, 3.1), 7.25–7.35 (5H, m), 8.36 (1H, dd, *J* 9.1, 2.8), 8.75 (1H, d, *J* 2.8). *m/z* (ES–MS) 353 $[M + 1]^+$.

*Typical Procedure for the Synthesis of Oximes: 1′-Benzylspiro[chromene-2,4′-piperidin]-4(3*H*)-one Oxime* ***4f***

Compound **3f** (3.1 g, 10 mmol) was refluxed for 3 h with hydroxylamine hydrochloride (1.4 g, 20 mmol), anhydrous ethanol (50 mL), and pyridine (1.6 mL, 20 mmol). After cooling, the reaction mixture was poured into water; the precipitate was then recrystallized from dilute ethanol to give the oxime almost quantitatively, mp 229–231°C. (Found: C 74.56, H 6.95, N 8.44. Calc. for $C_{20}H_{22}N_2O_2$: C 74.51, H 6.88, N 8.69%). δ_H ([D_6]DMSO, 250 MHz) 1.99–2.16 (4H, m), 2.78 (2H, s), 3.12–3.14 (4H, m), 4.31–4.35 (2H, m), 6.93–6.98 (2H, m), 7.24–7.33 (6H, m), 7.74 (1H, d, *J* 8.7), 11.16 (1H, s). *m/z* (ES–MS) 323 $[M + 1]^+$.

*1′-Benzyl-6-methoxyspiro[chromene-2,4′-piperidin]-4(3*H*)-one Oxime* ***4a***

White solid (72%), mp 279–280°C. (Found: C 71.61, H 6.92, N 8.05. Calc. for $C_{21}H_{24}N_2O_3$: C 71.57, H 6.86, N 7.95%). δ_H ([D$_6$]DMSO, 250 MHz) 1.93–2.13 (4H, m), 2.75 (2H, s), 3.02–3.16 (4H, m), 3.71 (3H, s), 4.39–4.42 (2H, m), 6.92–6.94 (2H, m), 7.22–7.26 (2H, m), 7.44 (3H, m), 7.70 (1H, m), 11.47 (1H, s). *m/z* (ES–MS) 353 $[M+1]^+$.

*1′-Benzyl-6-methylspiro[chromene-2,4′-piperidin]-4(3*H*)-one Oxime* ***4b***

White solid (93%), mp 268–269°C. (Found: C 75.23, H 7.17, N 8.61. Calc. for $C_{21}H_{24}N_2O_2$: C 74.97, H 7.19, N 8.33%). δ_H ([D$_6$]DMSO, 250 MHz) 1.95–2.07 (4H, m), 2.15 (3H, s), 2.39–2.43 (2H, m), 6.86 (2H, s), 2.97–3.10 (4H, m), 6.79 (1H, d, *J* 8.3), 7.01 (1H, dd, *J* 8.5, 1.9), 7.29–7.41 (3H, m), 7.48–7.50 (1H, m), 7.58 (2H, m), 12.03 (1H, s). *m/z* (ES–MS) 337 $[M+1]^+$.

*1′-Benzyl-6-(benzyloxy)spiro[chromene-2,4′-piperidin]-4(3*H*)-one Oxime* ***4c***

White solid (95%), mp 245–254°C. (Found: C 75.71, H 6.54, N 6.25. Calc. for $C_{27}H_{28}N_2O_3$: C 75.68, H 6.59, N 6.54%). δ_H ([D$_6$]DMSO, 250 MHz) 2.02–2.07 (2H, m), 2.39–2.50 (2H, m), 2.95 (2H, s), 2.99–3.13 (2H, m), 3.27–3.32 (2H, m), 4.20–4.21 (2H, m), 4.98 (2H, s), 6.74–6.77 (1H, m), 6.88–6.89 (1H, m), 7.29–7.52 (9H, m), 7.65–7.74 (2H, m), 12.03 (1H, s). *m/z* (ES–MS) 429 $[M+1]^+$.

*1′-Benzyl-6-chlorospiro[chromene-2,4′-piperidin]-4(3*H*)-one Oxime* ***4d***

White solid (76%), mp 259–260°C. (Found: C 67.07, H 5.66, N 7.98. Calc. for $C_{20}H_{21}ClN_2O_2$: C 67.32, H 5.93, N 7.85%). δ_H ([D$_6$]DMSO, 250 MHz) 1.94–2.08 (4H, m), 2.78 (2H, s), 3.10–3.17 (4H, m), 4.31–4.36 (2H, m), 7.00–7.04 (1H, m), 7.36–7.45 (4H, m), 7.64–7.69 (3H, m), 11.67 (1H, s). *m/z* (ES–MS) 357 $[M+1]^+$.

*1′-Benzyl-6-fluorospiro[chromene-2,4′-piperidin]-4(3*H*)-one Oxime* ***4e***

White solid (29%), mp 212–214°C. (Found: C 70.71, H 6.18, N 8.17. Calc. for $C_{20}H_{21}FN_2O_2$: C 70.57, H 6.22, N 8.23%). δ_H ([D$_6$]DMSO, 250 MHz) 1.91–2.08 (4H, m), 2.37 (2H, m), 2.64 (4H, m), 3.46 (2H, s), 7.12–7.57 (8H, m), 11.56 (1H, s). *m/z* (ES–MS) 341 $[M+1]^+$.

*1′-Benzyl-7-methoxyspiro[chromene-2,4′-piperidin]-4(3*H*)-one Oxime* ***4g***

White solid (88%), mp 279–280°C. (Found: C 71.49, H 6.76, N 8.23. Calc. for $C_{21}H_{24}N_2O_3$: C 71.57, H 6.86, N 7.95%). δ_H ([D$_6$]DMSO, 250 MHz) 1.93–2.14 (4H, m), 2.74 (2H, s), 3.10–3.25 (4H, m), 3.76 (3H, s), 4.33–4.43 (2H, m), 6.48–6.61 (2H, m), 7.43–7.47 (3H, m), 7.64–7.67 (3H, m), 11.16 (1H, s). *m/z* (ES–MS) 353 $[M+1]^+$.

*1′-Benzyl-6-nitrospiro[chromene-2,4′-piperidin]-4(3*H*)-one Oxime* ***4h***

White solid (81%), mp 230–231°C. (Found: C 65.57, H 5.69, N 11.62. Calc. for $C_{20}H_{21}N_3O_4$: C 65.38, H 5.76, N 11.44%). δ_H ([D$_6$]DMSO, 250 MHz) 2.00–2.25 (4H, m), 3.13–3.58 (8H, m), 7.25 (1H, d, *J* 9.1), 7.44–7.47 (3H, m), 7.65–7.74 (2H, m), 8.25 (1H, dd, *J* 9.1, 2.8), 8.56 (1H, d, *J* 2.7), 11.90 (1H, s). *m/z* (ES–MS) 368 $[M+1]^+$.

*Typical Procedure for the Silylation of Oximes: 1′-Benzyl-7-methoxyspiro[chromene-2,4′-piperidin]-4(3*H*)-one-*O-[tert-butyl(dimethyl)silyl] Oxime* ***4i***

To a stirred solution of **4g** (0.40 g, 1.1 mmol) and *tert*-butyldimethylsilyl chloride (TBDMS-Cl) (0.17 g, 1.1 mmol) in CH_2Cl_2 (10 mL) was added dropwise a solution of imidazole (0.15 g, 2.2 mmol) in CH_2Cl_2 at room temperature. The reaction was left overnight with stirring. Purification was carried out by flash silica gel chromatography using cyclohexane/ethyl acetate (3:1, v/v) as eluent to give product 1′-benzyl-7-methoxyspiro[chromene-2,4′-piperidin]- 4(3*H*)-one-*O*-[*tert*-butyl(dimethyl)silyl] oxime **4i** as yellow oil (0.4 g, 80%). (Found: C 69.76, H 8.44, N 5.68. Calc. for $C_{27}H_{38}N_2O_3Si$: C 69.49, H 8.21, N 6.00%). δ_H ($CDCl_3$, 250 MHz) 0.26 (6H, s), 1.00 (9H, m), 1.68–1.79 (2H, m), 1.88–2.04 (2H, m), 2.40–2.45 (2H, m), 2.61–2.68 (2H, m), 2.87 (2H, s), 3.59 (2H, s), 3.84 (3H, s), 6.46 (1H, d, *J* 2.2), 6.55 (1H, dd, *J* 8.7, 2.3), 7.26–7.38 (5H, m), 7.83 (1H, d, *J* 8.8). *m/z* (ES–MS) 467 $[M+1]^+$.

*Typical Procedure for the Synthesis of Secondary Anilines: 1′-Benzyl-4,5-dihydro-3*H*-spiro[1,5-benzoxazepine-2,4′-piperidine]* ***5f***

Oxime **4f** (3 g, 9.3 mmol) was solubilized in anhydrous dichloromethane (20 mL). The mixture was stirred at 0°C for 30 min, and diisobutylaluminium hydride in dichloromethane (54 mL, 1 M, 54 mmol) was added dropwise during 1 h. The mixture was stirred for 3 h under nitrogen at 0°C. The reaction was quenched by slowly adding MeOH (9 mL), followed by distilled water (9 mL) and 20% sulfuric acid (50 mL). The solution was stirred for a further 20 min. The solution was basified to pH 9 using 30% sodium hydroxide solution. The resulting mixture was extracted with ethyl acetate (2 × 100 mL). The organic layer was dried ($MgSO_4$) and concentrated to give a yellow oil. The residue was purified by chromatography on alumina with cyclohexane/ethyl acetate (1:1, v/v) to give product **5f** as yellow oil (1.5 g, 52%). (Found: C 78.04, H 7.88, N 9.25. Calc. for $C_{20}H_{24}N_2O$: C 77.89, H 7.84, N 9.08%). δ_H ($CDCl_3$, 250 MHz) 1.69 (2H, ddd, *J* 13.5, 9.6, 4.6), 1.96 (2H, t, *J* 5.4), 2.06–2.11 (2H, m), 2.55 (2H, td, *J* 11.4, 2.5), 2.65 (2H, dt, *J* 11.6, 3.8), 3.30 (2H, t, *J* 5.4), 3.62 (2H, s), 6.65 (1H, dd, *J* 1.5, 7.8), 6.78 (1H, td, *J* 7.8, 1.5), 6.91 (1H, td, *J* 7.8, 1.5), 7.20 (1H, dd, *J* 7.8, 1.5), 7.28–7.40 (5H, m). *m/z* (ES–MS) 309 $[M+1]^+$.

*1′-Benzyl-7-methoxy-4,5-dihydro-3*H*-spiro[1,5-benzoxazepine-2,4′-piperidine]* ***5a***

Yellow oil (61%). (Found: C 74.68, H 7.57, N 8.41. Calc. for $C_{21}H_{26}N_2O_2$: C 74.52, H 7.74, N 8.28%). δ_H ($CDCl_3$, 250 MHz) 1.52 (2H, ddd, *J* 13.5, 9.6, 4.6), 1.81 (2H, t, *J* 5.4), 1.86–1.91 (2H, m), 2.40 (2H, td, *J* 11.4, 2.5), 2.50–2.55 (2H, m), 3.21 (2H, t, *J* 5.4), 3.47 (2H, s), 3.64 (3H, s), 6.08 (1H, d, *J* 2.8), 6.16 (1H, dd, *J* 8.7, 2.9), 6.76 (1H, d, *J* 8.7), 7.16–7.25 (5H, m). *m/z* (ES–MS) 339 $[M+1]^+$.

*1′-Benzyl-7-methyl-4,5-dihydro-3*H*-spiro[1,5-benzoxazepine-2,4′-piperidine]* ***5b***

Yellow solid (16%), mp 64–65°C. (Found: C 78.32, H 8.38, N 8.77. Calc. for $C_{21}H_{26}N_2O$: C 78.22, H 8.13, N 8.69%). δ_H ($CDCl_3$, 250 MHz) 1.52 (2H, ddd, *J* 13.5, 9.6, 4.6), 1.81 (2H, t, *J* 5.4), 1.86–1.91 (2H, m), 2.16 (2H, s), 2.40 (2H, td, *J* 11.4, 2.5), 2.51–2.56 (2H, m), 3.21 (2H, t, *J* 5.4), 3.47 (2H, s), 6.10–6.18 (2H, m), 6.76–6.78 (1H, m), 7.24–7.32 (5H, m). *m/z* (ES–MS) 323 $[M+1]^+$.

*1′-Benzyl-7-(benzyloxy)-4,5-dihydro-3*H*-spiro[1,5-benzoxazepine-2,4′-piperidine]* ***5c***

Yellow solid (52%), mp 101–103°C. (Found: C 78.14, H 7.11, N 6.54. Calc. for $C_{27}H_{30}N_2O_2$: C 78.23, H 7.29, N 6.76%). δ_H ($CDCl_3$, 250 MHz) 1.66 (2H, ddd, *J* 13.5, 9.6, 4.6), 1.93 (2H, t, *J* 5.4), 2.02–2.06 (2H, m), 2.50–2.70 (2H, m), 2.29–2.39 (2H, m), 3.28 (2H, t, *J* 5.4), 3.61 (2H, s), 4.98 (2H, s), 6.29–2.30 (1H, d, *J* 2.8), 6.39 (1H, dd, *J* 8.5, 2.8), 6.91 (1H, d, *J* 8.7), 7.29–7.49 (10H, m). *m/z* (ES–MS) 415 $[M+1]^+$.

*1′-Benzyl-7-chloro-4,5-dihydro-3*H*-spiro[1,5-benzoxazepine-2,4′-piperidine]* ***5d***

Yellow oil (32%). (Found: C 70.19, H 6.82, N 8.37. Calc. for $C_{20}H_{23}ClN_2O$: C 70.06, H 6.76, N 8.17%). δ_H ($CDCl_3$, 250 MHz) 1.66 (2H, ddd, *J* 13.5, 9.6, 4.6), 1.92 (2H, t, *J* 5.4), 1.97–2.02 (2H, m), 2.50 (2H, td, *J* 11.4, 2.5), 2.63–2.68 (2H, m), 3.28 (2H, t, *J* 5.4), 3.60 (2H, s), 6.60 (1H, d, *J* 2.6), 6.68 (1H, dd, *J* 8.4, 2.4), 6.89 (1H, d, *J* 6.5), 7.30–7.39 (5H, m). *m/z* (ES–MS) 343 $[M+1]^+$.

*1′-Benzyl-7-fluoro-4,5-dihydro-3*H-*spiro[1,5-benzoxazepine-2,4′-piperidine]* ***5e***

Yellow oil (40%). (Found: C 73.42, H 6.89, N 8.22. Calc. for $C_{20}H_{23}FN_2O$: C 73.59, H 7.10, N 8.58%). δ_H ($CDCl_3$, 250 MHz) 1.68 (2H, ddd, *J* 13.5, 9.6, 4.6), 1.95 (2H, t, *J* 5.4), 1.99–2.07 (2H, m), 2.35 (2H, td, *J* 11.4, 2.5), 2.63–2.68 (2H, m), 3.28 (2H, t, *J* 5.4), 3.46 (2H, s), 6.95 (1H, dd, *J* 8.6, 4.8), 7.15 (1H, m), 7.22–7.31 (5H, m), 7.42 (1H, dd, *J* 9.6, 2.8), 11.64 (1H, s). *m/z* (ES–MS) 327 $[M + 1]^+$.

*1′-Benzyl-8-methoxy-4,5-dihydro-3*H-*spiro[1,5-benzoxazepine-2,4′-piperidine]* ***5g***

Yellow oil (2.5%). (Found: C 74.63, H 7.41, N 8.34. Calc. for $C_{21}H_{26}N_2O_2$: C 74.52, H 7.74, N 8.28%). δ_H ($CDCl_3$, 250 MHz) 1.63–1.75 (2H, m), 1.88–2.04 (4H, m), 2.44–2.57 (2H, m), 2.59–2.73 (2H, m), 3.15 (2H, t, *J* 5.4), 3.62 (2H, s), 3.72 (3H, s), 6.45 (1H, dd, *J* 9.6, 2.8), 6.53 (1H, d, *J* 2.6), 6.60 (1H, d, *J* 8.6), 7.24–7.37 (5H, m). *m/z* (ES–MS) 339 $[M + 1]^+$.

Typical Procedure for Lithium Aluminum Hydride Reduction

To a swirling suspension of 0.20 mg of $LiAlH_4$ in 10 mL of ether, a solution of oximes (**4a**, **4g**) (0.2 g, 0.5 mmol) in 10 mL of ether was added dropwise at room temperature. The solution was then allowed to stand overnight at room temperature. The reaction mixture was decomposed with water under cooling with ice. The ether layer was washed with 1 N sodium hydroxide and water, then dried ($MgSO_4$) and concentrated to give oil. The residue was purified by chromatography on alumina with cyclohexane/ethyl acetate (1:1, v/v) to give product **5a**, **5g** as yellow oil (**5a**, 5%; **5g**, 5%).

*4,5-Dihydro-3*H-*spiro[1,5-benzoxazepine-2,4′-piperidin]-7-ol* ***5j***

To a suspension of **5a** (0.62 mg, 1.8 mmol) in 15 mL of CH_2Cl_2 and cooled to 0°C a 1 M solution of BBr_3 in dichloromethane (5.5 mL) was slowly added dropwise, and the solution was stirred at room temperature for 48 h. The organic layer was washed successively by H_2O (10 mL), brine (10 mL), 5% aqueous $NaHCO_3$ (2 × 10 mL), then brine (10 mL), and was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (CH_2Cl_2/MeOH 95:5) to give the intermediate compound as white oil (204 mg, 34%). (Found: C 73.82, H 7.76, N 8.53. Calc. for $C_{20}H_{24}N_2O_2$: C 74.04, H 7.46, N 8.64%). δ_H ($CDCl_3$, 250 MHz) 1.64 (2H, ddd, *J* 13.5, 9.6, 4.6), 1.87 (2H, t, *J* 5.4), 1.93–2.03 (2H, m), 2.53 (2H, td, *J* 11.4, 2.5), 2.56–2.68 (2H, m), 3.17 (2H, t, *J* 5.4), 3.62 (2H, s), 6.13 (1H, dd, *J* 8.5, 2.8), 6.21 (1H, d, *J* 2.9), 6.66 (1H, d, *J* 8.6), 7.28–7.36 (5H, m). *m/z* (ES–MS) 325 $[M + 1]^+$.

To a stirred suspension of the previous *N*-benzyl compound (0.1 g, 0.42 mmol) in dry methanol (10 mL), was added an equal weight of 10% $Pd(OH)_2$ under H_2. The resulting mixture was stirred at room temperature, and the reaction was monitored by TLC. After completion, the catalyst was removed by filtration through Celite and washed with methylene chloride (10 mL). The residue was purified by flash chromatography (CH_2Cl_2/MeOH 95:5) to give the desired compound **5j** in quantitative yield. (Found: C 66.82, H 7.61, N 12.07%. Calc. for $C_{13}H_{18}N_2O_2$: C 66.64, H 7.74, N 11.96%). δ_H (CD_3OD, 250 MHz) 1.51 (2H, ddd, *J* 4.5, 11.5, 13.5), 1.87–1.94 (4H, m), 2.80 (2H, m), 3.05 (2H, ddd, *J* 2.8, 11.5, 12.3), 3.19 (2H, t, *J* 5.4), 6.14 (1H, dd, *J* 2.8, 8.5), 6.21 (1H, d, *J* 2.9), 6.72 (1H, d, *J* 8.6). *m/z* (ES–MS) 235 $[M + H]^+$.

Boron Trifluoride/Borane Reduction of O*-Silylated Oximes*

To a stirred solution of **4i** (0.3 g, 0.6 mmol) in ether (3 mL) under nitrogen was added boron trifluoride ethearate (253 μL, 2.0 mmol). Immediately following the addition, a solution of borane dimethyl sulfide in THF (66 μL, 2 M, 1.3 mmol) was added dropwise to the reaction flask at room temperature. The reaction mixture was refluxed for 18 h. At this time the solution was cooled to 0°C, and the reaction mixture cautiously quenched by addition of distilled water (3 mL). To complete the hydrolysis, a solution of hydrochloric acid (3 mL, 6 M) was slowly added, and the reaction mixture was refluxed at 70°C for 1 h. The reaction mixture was extracted with CH_2Cl_2 (3 × 10 mL), and the aqueous phase was basified with aqueous NaOH (2 N), extracted with CH_2Cl_2 (3 × 10 mL), washed with brine (7 mL), and dried with anhydrous $MgSO_4$. The solution was filtered and concentrated under reduced pressure. The crude product was analyzed by MS and purified by flash chromatography (CH_2Cl_2/MeOH 95:5) to give the compounds **6g**, **7g** in less than 2% yield. For **6g**, *m/z* (ESI–MS) 337 $[M + H]^+$, and **7g**, *m/z* (ESI–MS) 339 $[M + H]^+$.

Procedure for Inhibition Assay

HIV-1 Aspartate Protease Assay

In the assay for HIV-protease inhibition, the enzyme was preincubated for 10 min at 37°C with inhibitor by adding an aliquot (10 μL) of the inhibitor in DMSO to the enzyme (20 μL of a 0.294-μM solution) in buffer (370 μL, 0.05 M NaOAc, pH 4.9, 0.2 M NaCl, 0.005 M DTT, 10% v/v glycerol). Percentage of inhibition was spectrophotometrically measured (λ 300 nm) on a Uvikon 930 spectrophotometer by adding an aliquot of the substrate solution (20 μL of a 573-μM solution of H–His–Lys–Ala–Arg–Val–Leu–*p*NO_2Phe–Glu–Ala–Nle–Ser–NH_2) to the enzyme-inhibitor solution in a cuvette. Amprenavir was used as reference inhibitor.

BACE-1 Enzymatic Assay

These experiments were performed using a BACE-1 (β-secretase) FRET Kit assay (PanVera Corp.), according to the described protocol and using a multiwell spectrofluorometer with 530–545 nm excitation and 570–590 nm emission wavelengths (Victor2 1420, Wallac Perkin Elmer). The procedure was as follows: substrate and enzyme were diluted into the provided assay buffer (50×10^{-3} M Tris, pH 7.5, 10% glycerol) according to the described protocol. Each inhibitor was diluted in DMSO at the desired concentration. The substrate (Rh-EVNLDAEFK-Quencher, 10 μL of the main solution) and each inhibitor (1 μL of the corresponding solution) were introduced in a 96-well flat bottom black polystyrene plate (Corning). The resulting mixtures were gently mixed and 10 μL of the enzyme solution was then added to each well to start the reaction. The reaction mixtures were incubated at 25°C for 90 min and the fluorescence was monitored at 530–545 nm (excitation wavelength) and 570–590 nm (emission wavelength). The kinetic assays were performed in duplicate for each inhibitor, using BACE-1 inhibitor (H–Lys–Thr–Glu–Glu–Ile–Ser–Glu–Val–Asn–3*S*,4*S*–Stat–Val–Ala–Glu–Phe–OH, IC_{50} 30×10^{-9} M, Calbiochem) as reference (positive control, 100% inhibition at 1 μM), DMSO alone as negative control (no inhibition). The provided BACE-1 product standard (Rh-EVNL) was used as control for the enzyme cleavage, 15% cleavage of the substrate was obtained after 90 min of reaction at 37°C.

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