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An innovative strategy for the synthesis of a new series of potent aminopeptidase (APN or CD13) inhibitors derived from the oxepin-4-one family

Lionel Roux, Cédric Charrier, Emmanuel Salomon, Meral Ilhan, Philippe Bisseret *, Céline Tarnus *

FRE 3253, Laboratoire de Chimie Organique et Bioorganique associé au CNRS, ENSCMu, 3 rue A. Werner, 68093 Mulhouse Cedex, France

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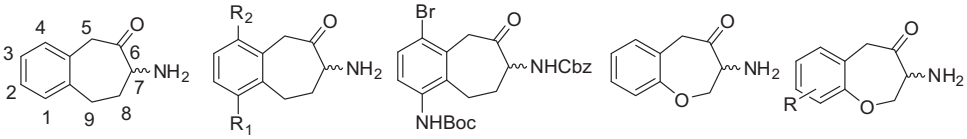
ABSTRACT

Derivatives from the aminobenzosuberone family have been recently synthesized and recognized as highly selective inhibitors of aminopeptidase N (APN)/CD13 (EC 3.4.11.2), an important target for cell migration processes involved in particular in tumor invasion. We present here a much more straightforward synthesis of analogues belonging to a novel isosteric oxo series which also possesses excellent inhibitory potential against APN. Their synthesis, as reported here, relied on an interesting iodine(III)-mediated rearrangement originally described by Koser and Justik as the key step. This represents the second application of this rearrangement in medicinal chemistry.

Among proteolytic enzymes, the ubiquitous aminopeptidase N (APN)/CD13 (EC 3.4.11.2)[1] has been shown to play an important role in tumor angiogenesis and metastasis.[2] Although many inhibitors of this ectopeptidase are available, most of them are poorly selective.[3] The development of highly specific and potent inhibitors remains a challenge since most aminopeptidases are zinc-dependent enzymes that share a broad substrate specificity. Structural requirements for APN inhibition were previously determined[4,5] and led to the discovery of (±)-7-amino-6-benzosuberone scaffold **1** as a lead structure, which demonstrated a remarkable inhibitory potency and selectivity toward APN, with a K_i value of 1 μM.



1 **2** **3** **4** **5**

This scaffold therefore appeared as an excellent candidate for further chemical elaboration and derivatization and we already pointed out the outstanding inhibitory activity and selectivity toward APN of (±)-1,4-difunctionalized derivatives **2**. This series of aminobenzosuberones was easily obtained from the protected derivative **3**.[5] This latter compound could be synthesized in about 15 steps from L-tryptophane[6] highlighting, as a key step, an iodine(III)-mediated ring expansion originally described by Justik and Koser on simple 1-tetralone.[7] Although our synthesis relied, for the first time in medicinal chemistry, on this efficient rearrangement, it remained somewhat tedious because of its number of steps. We present here a much more straightforward synthesis of the 9-oxo isostere **4** of aminobenzosuberone **1**, as well as the preparation of a key protected precursor **10** ideally substituted for the synthesis of oxepin-4-one derivatives **5**. Our strategy is described in Figure 1. In both cases simple iodo-phenol-derivatives as well as 2-benzyloxycarbonylamino-but-3-en-1-ol **6** are used as starting reagents.

In the first place, we needed an efficient preparation of 2-benzyloxycarbonylamino-but-3-en-1-ol **6**. This compound was readily obtained in an overall yield of 41% from DL-serine methyl ester hydrochloride as indicated in Scheme 1, taking advantage of a new short and quick synthesis.[8,9] After protection as a *N*-benzyloxycarbonyl derivative and as a *O*-*tert*-butyldimethylsilyl derivative,[10] intermediate **13** was reduced with Dibal-*H*. Alcohol **14** was then converted into aldehyde **15** after an oxidation with Dess-Martin periodinane, which in turn was transformed into alkene **16** via a Wittig reaction in good yield.[11,12] Removal of the *O*-*tert*-butyldimethylsilyl protection was accomplished with TBAF and yielded the desired racemic compound **6**.[13]

* Corresponding authors.
E-mail address: philippe.bisseret@uha.fr (P. Bisseret).

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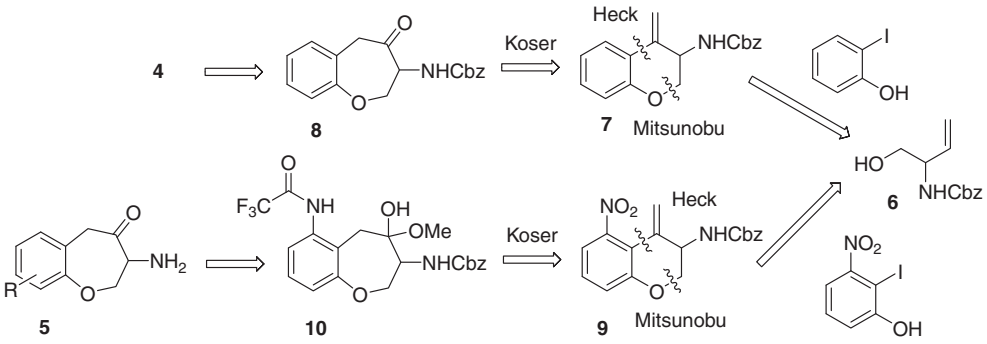
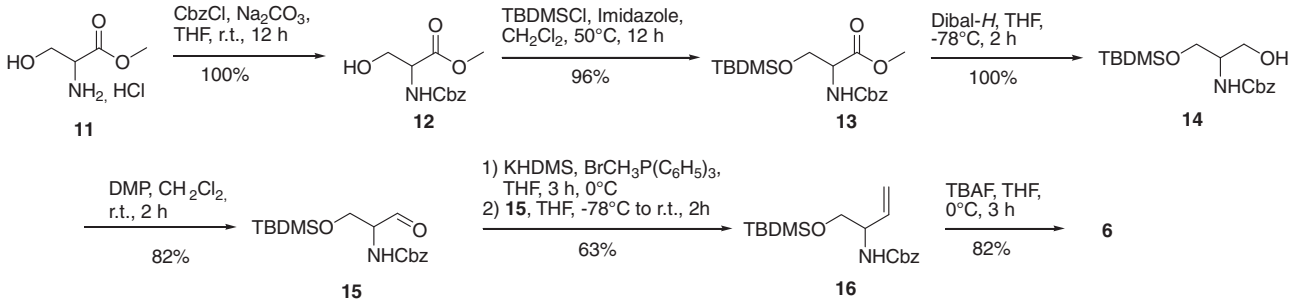


Figure 1. Retrosynthetic pathway.



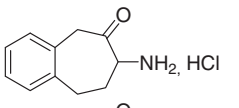
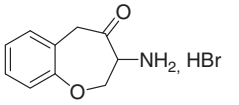
Scheme 1. Synthesis of 2-benzyloxycarbonylamino-but-3-en-1-ol **6**.

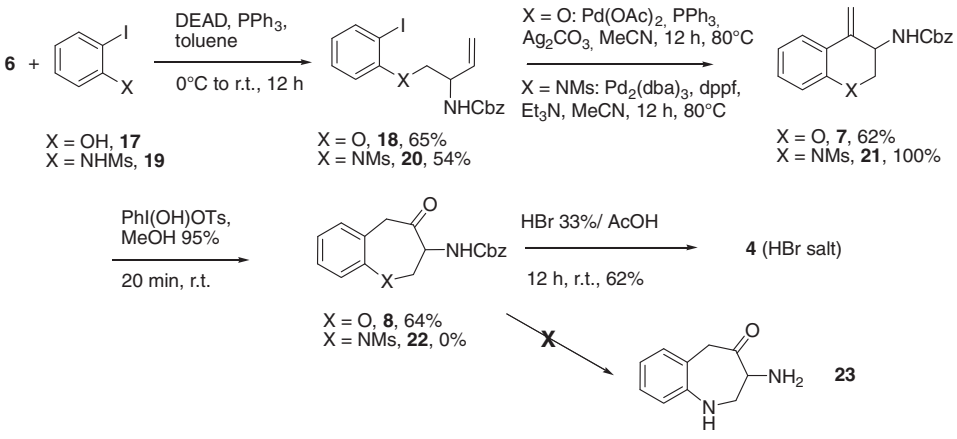
As shown in Scheme 2, the preparation of 3-benzyloxycarbonylamino-4-methylene-chromane **7**[14] was accomplished in good overall yield using a Mitsunobu reaction[15] between alcohol **6** and 2-iodophenol **17**, followed by an intramolecular Heck reaction.[16,17] The resulting methylenic derivative **7** was then treated with [hydroxy(tosyloxy)iodo]benzene HTIB in methanol at room temperature according to Koser and Justik.[7] Under these conditions, we were pleased to isolate after 20 min the desired benzo[*b*]oxepin-4-one **8** in good yield. The removal of the *N*-*tert*-butylcarbamate protection was accomplished under acidic conditions (HBr 33% in acetic acid) leading the desired inhibitor **4**, as a racemic mixture.

The inhibitory activity of **4** on APN was evaluated and compared to the one of the parent isostere **1**. As presented in Table 1, both compounds exhibited similar K_i.

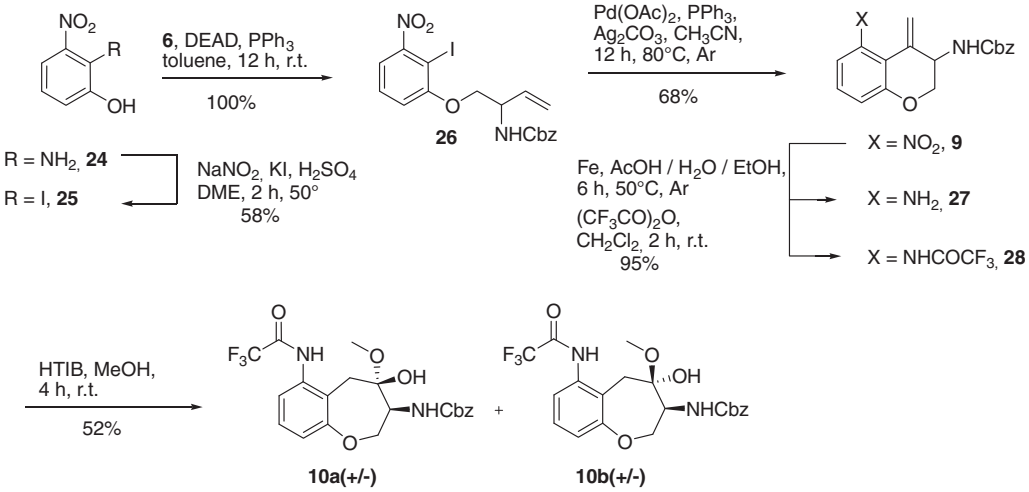
Encouraged by these promising results, we then investigated the preparation of 9-amino isostere **23**, starting from 2-iodo-*N*-(methylsulfonyl)-aniline **19**. As outlined in Scheme 2, although both the Mitsunobu coupling and Heck cyclization went uneventfully, we could not perform the key ring expansion: by making use

Table 1
Inhibition of aminopeptidase N

Compounds		K_i (μM)	*c* log *P*
		APN EC 3.4.11.2	
	**1**	l	1.08
	**4**	l	0.39



Scheme 2. Synthesis of 9-oxo derivative **4** and tentative preparation of its 9-aza isostere **23**.



Scheme 3. Synthesis of 6-benzyloxycarbonylamino-4-hydroxy-4-methoxy-6-(2,2,2-trifluoroacetamido)-2,3,4,5-tetrahydrobenzo[*b*]oxepine **10**.

of the conditions previously described, we only got a complex mixture.

Instead of pursuing experiments starting from other protected anilines, we focussed our attention on the oxepinone series in view of preparing analogues substituted on the aromatic ring. Commercial 3-nitro-2-amino-phenol **24** was first submitted to a Sandmeyer reaction leading to derivative **25**.[18] Like previously, the preparation of 3-benzyloxycarbonylamino-4-methylene-5-nitrochromane **9** required two steps: a Mitsunobu reaction between alcohol **6** and compound **25**, followed by an intramolecular Heck reaction (Scheme 3). The resulting methylenic derivative **9** was then submitted to Koser and Justik's conditions without success. Realizing that the nitro function could be responsible for this failure, we decided to repeat the experiment starting from *N*-trifluoroacetyl derivative **28**, easily obtained in two steps from **9**.[19,20] We were pleased to observe that, in this case, the iodine (III)–mediated ring expansion worked with a correct yield. Indeed, after chromatography, we could isolate, in place of the expected keto derivative, the pair of hemi-ketals **10a** and **10b** (Scheme 3).[21]

In conclusion, we synthesized 3-amino-2-hydro-*5H*-benzo[*b*]oxepin-4-one **4** as a new lead structure for the preparation of APN inhibitors. Indeed, compared to its 9-methylenic isostere **1,** this compound exhibited a similar inhibitory activity but could be prepared in a much more efficient way from simple starting materials, by making use of an iodine (III)-mediated ring expansion as a key-step.[7] Although we could not apply this reaction for the preparation of the 9-aza isostere **23**, the relevance of our synthetic strategy was highlighted by its extension to the preparation of a key functionalized precursor **10** to substituted oxepin-4-one derivatives of type **5**.

Acknowledgments

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14. *Selected analytical data*: 3-Benzyloxycarbonylamino-4-(2-iodo-phenoxy)-but-1-ene **18**:
^{1}H NMR ($CDCl_3$, 400 MHz, 295 K): δ 7.75 (dd, J = 1.5, 7.8 Hz, 1H, H_{3ar}), 7.34 (m, 6H, $5H_{Cbz}$ and H_{5ar}), 6.78 (d, J = 8.1 Hz, 1H H_{6ar}), 6.73 (t, J = 7.8 Hz, 1H, H_{4ar}), 6.04 (ddd, J = 5.8, 10.6, 17.4 Hz, 1H, H_2), 5.38 (br d, J = 17.4 Hz, 1H, H_{1trans} + NH), 5.28 (br d, J = 10.6 Hz, 1H, H_{1cis}), 5.15 (br s, 2H, H $CH_{2\ Cbz}$), 4.63 (m, 1H, H_3), 4.11 (br s, 2H, H_4). ^{13}C NMR ($CDCl_3$, 100.6 MHz, 295 K): δ 156.8 ($C_{q\ carbamate}$), 155.8 (C_q), 139.4 (C_{3ar}), 136.4 ($C_{q\ Cbz}$), 135.2 (C_2), 129.5 (C_{5ar}), 128.5, 128.2 and 128.1 ($5C_{Cbz}$), 123.1 (C_{4ar}), 117.0 (C_1), 112.3 (C_{6ar}), 86.8 (C_q), 71.1 (C_4), 66.9 (CH_2 Cbz), 52.8 (C_3). IR (cm^{-1}, KBr): 3295, 2924, 1680, 1541, 1458, 1247, 1052, 747, 699. HRMS calcd for [$C_{18}H_{18}INO_3$, Na^+] = 446.0224; found: 446.0224.
3-Benzyloxycarbonylamino-4-methylen-chromane **7**:
^{1}H NMR ($CDCl_3$, 400 MHz, 295 K): δ 7.56 (d, J = 8.0 Hz, 1H, H_5), 7.34 (m, 5H, H_{Cbz}), 7.20 (t, J = 8.3 Hz, 1H, H_7), 6.95 (t, J = 8.3 Hz, 1H, H_6), 6.87 (br d, J = 8.1 Hz, 1H, H_8), 5.55 (br s, 1H, $1H_{methylene}$), 5.25 (br s, 1H, $1H_{methylene}$), 5.11 (m, 3H, H $CH_{2\ Cbz}$ + NH), 4.61(m, 1H, H_3), 4.26 (dd, J = 3.8, 10.9 Hz, 1H, H_{2b}), 4.18 (dd, J = 2.5, 10.9 Hz, 1H, H_{2a}). ^{13}C NMR ($CDCl_3$, 100.6 MHz, 295 K): δ 155.7 ($C_{q\ carbamate}$), 153.6 (C_q), 137.3 (C_q), 136.2 ($C_{q\ Cbz}$), 129.9 (C_7), 128.5, 128.2 and 128.2 ($5C_{Cbz}$), 125.2 (C_5), 121.6 (C_6), 119.6 (C_q); 117.5 (C_8), 109.2 ($C_{methylene}$), 69.2 (C_2), 67.0 (CH_2 Cbz), 50.0 (C_3). IR (cm^{-1}, KBr): 3417, 3342, 2928, 1698, 1541, 1222, 1068, 752, 697. HRMS calcd for [$C_{18}H_{17}NO_3$, Na]$^+$: 318.1100; found: 318.1094.
3-Benzyloxycarbonylamino-2-hydro-5*H*-benzo[*b*]oxepin-4-one **8**:
^{1}H NMR ($CDCl_3$, 400 MHz, 295 K): δ 7.35 (m, 5H, H_{Cbz}), 7.23 (d, J = 7.6 Hz, 1H, H_6), 7.17 (br d, J = 7.3 Hz, 1H, H_9), 7.10–7.06 (2t, J = 7.6 Hz, 2H, H_7 and H_8), 5.65 (br d, J = 5.1 Hz, 1H, NH), 5.11 (br s, 2H, H $CH_{2\ Cbz}$), 4.92 (dt, J = 6.6, 9.6 Hz, 1H, H_3), 4.76 (dd, J = 6.6, 11.4 Hz, 1H, H_{2a}), 4.14 (d, J = 14.0 Hz, 1H, H_{5b}), 3.74 (dd, J = 9.6, 11.4 Hz, 1H, H_{2a}), 3.60 (d, J = 14.0 Hz, 1H, H_{5a}). ^{13}C NMR ($CDCl_3$, 100.6 MHz, 295 K): δ 202.2 (C_4), 158.2 (C_q),155.6 ($C_{q\ carbamate}$), 136.0 ($C_{q\ Cbz}$), 130.4 (C_9), 129.2 (C_6), 128.6, 128.3 and 128.2 (5C Cbz), 124.9 and 121.4 (C_7 and C_8), 124.5 (C_q), 73.4 (C_2),67.2 (CH_2 Cbz),60.4 (C_3), 45.8 (C_5). IR (cm^{-1}, KBr) : 3421, 2926, 2361, 1688, 1527, 1457, 1262, 1081, 754, 695, 474. HRMS calcd for [$C_{18}H_{17}NO_4$, Na]$^+$: 334.1050; found: 334.1047.
3-Amino-2,2-dihydro-5*H*-benzo[*b*]oxepin-4-one, hydrobromide **4**:
^{1}H NMR (CD_3OD, 400 MHz, 295 K): δ 7.21 (d, J = 7.1 Hz, 1H, H_6), 7.21 (t, J = 7.6 Hz, 1H, H_8), 7.07 (t, J = 7.6 Hz, 1H, H_7), 7.00 (br d, J = 7.3 Hz, 1H, H_9), 4.56 (d, J = 14.1 Hz, 1H, H_{5b}), 4.23 (dd, J = 4.0, 13.6 Hz, 1H, H_{2a}), 4.09 (dd, J = 2.0, 13.6 Hz, 1H, H_{2b}), 3.64 (d, J = 14.1 Hz, 1H, H_{5a}), 3.44 (m, 1H, H_3). ^{13}C NMR (CD_3OD, 100.6 MHz, 295 K): δ 200.05 (C_4), 160.8 (C_q), 133.1 (C_6), 129.7 (C_8), 125.9 (C_7), 122.0 (C_9), 96.0 (C_q), 69.7 (C_2), 59.9 (C_3), 46.1 (C_5). IR (cm^{-1}, KBr): 3446, 2927, 2361, 1732, 1653, 1559, 1541, 1506, 1488, 1457, 1258, 1075, 763. HRMS calcd for [$C_{10}H_{12}NO_2$, H]$^+$: 178.0863; found: 178.071.
3-Benzyloxycarbonylamino-4-(2-iodo-3-nitro-phenoxy)-but-1-ene **26**:

^{1}H NMR ($CDCl_3$, 400 MHz, 295 K): δ 7.36 (m, 7H, 5H_{Cbz}, H_{5ar}, H_{4ar}), 6.94 (d, J = 8.1 Hz, 1H, H_{6ar}), 6.04 (ddd, J = 5.8, 10.3, 17.4 Hz, 1H, H_2), 5.38 (d, J = 17.4 Hz, 1H, H_{1trans}), 5.34 (br s, 1H, NH), 5.30 (br d, J = 10.3 Hz, 1H, H_{1cis}), 5.14 (br s, 2H, H $CH_{2\ Cbz}$), 4.67 (m, 1H, H_3), 4.18 (br s, 2H, H_4). ^{13}C NMR ($CDCl_3$, 100.6 MHz, 295 K): δ 158.3 ($C_{q\ carbamate}$), 155.8 and 136.1 (C_q), 134.5 (C_2), 130.1 (C_{ar}), 128.5, 128.3 and 128.2 (5C Cbz), 118.7 (C_q), 117.6 and 117.5 (C_1 and C_{ar}), 114.6 (C_{6ar}), 80.7 (C_q), 71.9 (C_4), 67.1 (CH_2 Cbz), 52.5 (C_3). IR (cm^{-1}, KBr): 3309, 3246, 1697, 1533, 1350, 1281, 1251, 734. HRMS calcd for $[C_{18}H_{17}IN_2O_5, Na]^+$: 491.0074; found: 491.0068.

3-Benzyloxycarbonylamino-4-methylen-5-nitro-chromane **9**:
^{1}H NMR ($CDCl_3$, 400 MHz, 295 K): δ 7.35 (m, 5H, H_{Cbz}), 7.27 (dd, J = 8.6, 7.8 Hz, 1H, H_7), 7.09 (br d, J = 7.8 Hz, 1H, H_8), 7.02 (d, J = 8.6 Hz, 1H, H_6), 5.43 (br s, 1H, $1H_{methylene}$), 5.30 (br s, 1H, $1H_{methylene}$), 5.13 (m, 3H, H $CH_{2\ Cbz}$ + NH), 4.63(m, 1H, H_3), 4.26 (br d, J = 11.1 Hz, 1H, H_{2b}), 4.25 (dd, J = 2.5, 11.1 Hz, 1H, H_{2a}). ^{13}C NMR ($CDCl_3$, 100.6 MHz, 295 K): δ 155.5 ($C_{q\ carbamate}$), 135.9 ($C_{q\ Cbz}$), 130.0 (C_q), 129.4 (C_7), 128.6, 128.3 and 128.2 (5C Cbz), 128.1 (C_q), 120.8 (C_q), 120.3 (C_6), 117.4 (C_q), 116.3 (C_8), 116.1 ($C_{methylene}$), 70.2 (C_2),67.2 (CH_2 Cbz), 50.3 (C_3). IR (cm^{-1}, KBr): 3421, 3305, 2931, 1699, 1531, 1249, 738. HRMS calcd for $[C_{18}H_{16}N_2O_5, Na]^+$: 363.0951; found: 363.0946.

3-Benzyloxycarbonylamino-4-methylen-5-trifluoroacetamide-chromane **28**:
^{1}H NMR ($CDCl_3$, 400 MHz, 295 K): δ 8.29 (s, 1H, NH), 7.69 (d, J = 8.1 Hz, 1H, H_6), 7.34 (m, 5H, H_{Cbz}), 7.25 (dd, J = 8.1, 8.3 Hz, 1H, H_7), 6.79 (br d, J = 7.8 Hz, 1H, H_8), 5.61 (br s, 1H, $1H_{methylene}$), 5.46 (br s, 1H, $1H_{methylene}$), 5.11 (m, 3H, H $CH_{2\ Cbz}$ + NH); 4.60 (m, 1H, H_3), 4.42 (br d, J = 11.3 Hz, 1H, H_{2b}), 4.29 (dd, J = 2.3, 11.3 Hz, 1H, H_{2a}). ^{13}C NMR ($CDCl_3$, 100.6 MHz, 295 K): δ 155.5 ($C_{q\ carbamate}$), 154.0 ($C_{q\ amide}$), 136.2 (C_q), 135.9 ($C_{q\ Cbz}$), 132.8, 128.7, 119.5 and 114.08 ($4C_q$), 130.1 (C_7), 128.6, 128.3 and 128.2 (5C Cbz), 115.7 (C_6), 115.2 (C_8), 114.3 ($C_{methylene}$), 70.2 (C_2), 67.2 (CH_2 Cbz), 51.0 (C_3). ^{19}F NMR ($CDCl_3$, 376.5 MHz, 295 K): δ −68.2 ppm. IR (cm^{-1}, KBr): 330, 3247, 1706, 1541, 1339, 1180, 740. HRMS calcd for $[C_{20}H_{17}F_3N_2O_4, Na]^+$: 429.1033; found: 429.1033.

6-Benzyloxycarbonylamino-4-hydroxy-4-methoxy-6-(2,2,2-trifluoroacetamido)-2,3,4,5-tetrahydrobenzo[*b*]oxepine **10**:
10a: ^{1}H NMR ($CDCl_3$, 400 MHz, 295 K): δ 7.63 (d, J = 8.1 Hz, 1H, H_7), 7.34 (m, 7H, NH, H_{Cbz} and H_8), 6.73 (d, J = 8.3 Hz, 1 H, H_9), 5.30 (br d, 1H, NH), 5.11 (s, 2H, H $CH_{2\ Cbz}$), 4.56 (d, J = 12.3 Hz, 1H, H_{5a}), 4.28 (m, 2H, H_3 and H_{2a}), 4.11 (m, 2H, H_{5b} and H_{2b}), 3.13 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 100.6 MHz, 295 K): δ 155.7 ($C_{q\ carbamate}$), 153.6 ($C_{q\ amide}$, q, J = 38.1 Hz), 153.1, 143.3, 135.8 ($3C_q$), 133.6 (C_8), 128.7, 128.5 and 128.3 (5C Cbz), 115.8 ($C_{q\ CF3}$, q, J = 288 Hz), 112.7 (C_7), 111.6 (C_q), 109.5 (C_9), 75.1 (C_q), 67.4 (CH_2 Cbz), 65.3 (C_2), 58.6 (C_5), 51.3 (C_2), 51.0 (C_{OMe}). ^{19}F NMR ($CDCl_3$, 376.5 MHz, 295 K): δ −68.2 ppm.
Compound **10b**: ^{1}H NMR ($CDCl_3$, 400 MHz, 295 K): δ 7.65 (d, 1H, H_7, J = 7.8 Hz), 7.34 (m, 7H, NH, H_{Cbz} and H_8), 6.73 (d, J = 8.3 Hz, 1H, H_9), 5.09 (s, 2H, H $CH_{2\ Cbz}$), 4.71 (br d, 1H, NH), 4.67 (d, J = 12.0, 1.8 Hz, 1H, H_{2a}), 4.56 (br d, J = 12.9 Hz, 1H, H_{5a}), 4.33 (m, 1H, H_3), 4.32 (d, J = 12.0, 1.8 Hz, 1H, H_{2b}), 4.04 (br d, J = 12.9 Hz, 1H, H_{5a}), 3.17 (s, 3H, CH_3). RMN ^{13}C ($CDCl_3$): 155.7 ($C_{q\ carbamate}$), 153.6 ($C_{q\ amide}$, q, J = 38.1 Hz), 152.4, 143.8, 135.5 ($3C_q$), 133.5 (C_8), 128.7, 128.6 and 128.4 (5C Cbz), 115.8 ($C_{q\ CF3}$, q, J = 288 Hz), 112.6 (C_7), 111.2 (C_q), 110.1 (C_9), 76.1 (C_q), 67.7 (CH_2 Cbz), 67.6 (C_2), 55.7 (C_5), 51.1 (C_2), 47.2 (C_{OMe}). RMN ^{19}F ($CDCl_3$): −68.2 ppm. HRMS calcd for $[C_{22}H_{23}F_3N_2O_5, Na]^+$: 477.1457; found: 477.1463.

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