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# A flexible approach for the preparation of substituted benzazepines: Application to the synthesis of tolvaptan☆

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Dedicated with respect to Professor Bernd Giese, recipient of last year's Tetrahedron Prize.

**Abstract**—A practical preparation of benzazepine derivatives using a series of radical and ionic reactions is reported. This approach was applied to the synthesis of tolvaptan, a very promising vasopressin $V_2$ receptor antagonist currently in clinical trials.


## 1. Introduction

Benzazepines and related compounds such as benzazepinones and benzodiazepines constitute a wide class of compounds with diverse and often important pharmacological properties. Paullones (**1**),[1] for example (Fig. 1), show important antitumor activity, while others behave as inhibitors of angiotensin converting enzyme[2] and as analgesics.[3] Recent studies revealed that *N*-substituted benzazepines can act as powerful vasopressin $V_2$ receptor antagonists and thus have a potential for the treatment of heart diseases.[4] Some of the most promising derivatives of this group are tolvaptan (**2**)[5] and OPC-31260 (**3**),[6] currently undergoing clinical trials (Fig. 1).

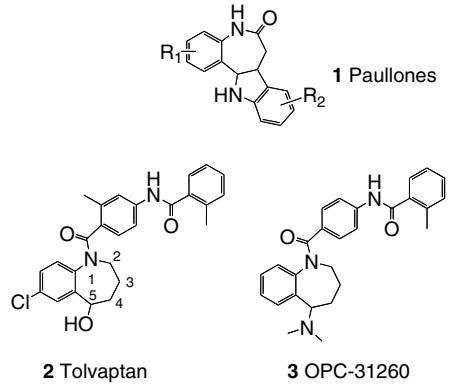


**Figure 1.** Some vasopressin $V_2$ receptor antagonists.

Even though benzazepines are well known and studied structures, difficulties arise in their preparation especially when a C5-substituent is required or if electron withdrawing groups are present in the aromatic ring. The preparation of tolvaptan, for example, required 11 linear steps, some involving harsh conditions that limit the generality of this approach (Scheme 1).[5] Besides, even if the final steps of this route seem trivial, the yields are low, thus resulting in a very low overall yield (<1%). In addition, the introduction of a C5-substituent other than oxygen would require extra steps in order to modify the ketone precursor. In other words, this route lacks flexibility, and cannot be easily transposed to the synthesis of analogues.

One practical method for the preparation of benzazepines is by application of the Beckmann rearrangement to tetralone ketoximes[7] followed by amide reduction. Although this transformation is very effective, the main problem lies in the preparation of substituted tetralones. A few years ago, we reported a new method for the preparation of α-tetralones by means of a tin-free radical chemistry.[8] This method allows the synthesis of a wide variety of substituted α-tetralones under neutral, mild conditions. More recently, this methodology was

*Keywords*: Xanthate; Benzazepines; Beckmann rearrangement; Tolvaptan.

☆ This work has been the subject of a patent. Cordero-Vargas, A.; Quiclet-Sire, B.; Zard, S. Z. Procédé utile pour la préparation de benzazépines et dérivés de celles-ci. France. French patent. FR-0450416. 02 March 2004.

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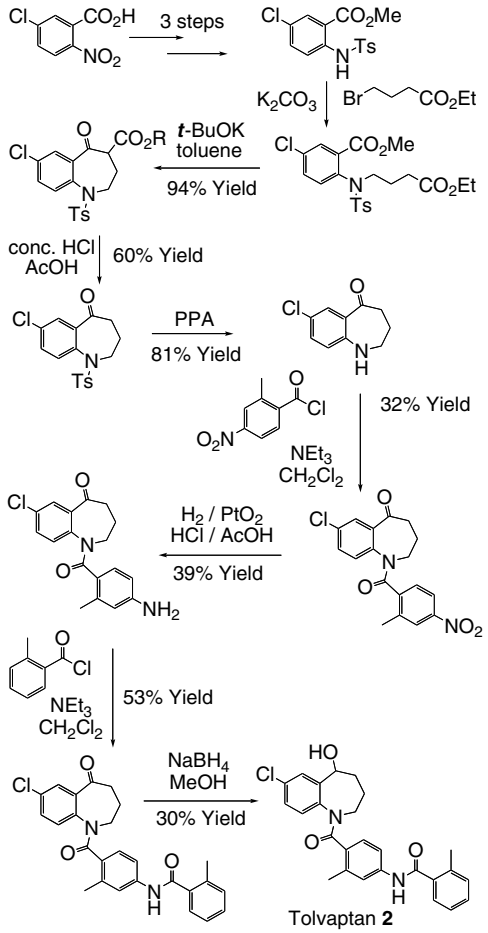
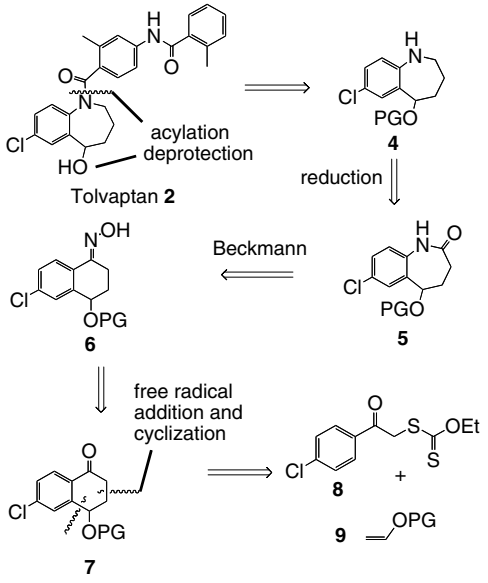



**Scheme 1.** Reported synthesis of tolvaptan.

employed for the preparation of substituted naphthalenes[9] and *C*-arylglycosides[10] as well as for the first total synthesis of the natural product 10-norparvulenone.[11] We have now found that this chemistry can be applied in an efficient practical synthesis of tolvaptan. More generally, it represents a flexible entry into benzazepines with various substitution patterns hitherto not easily accessible.

## 2. Results and discussion

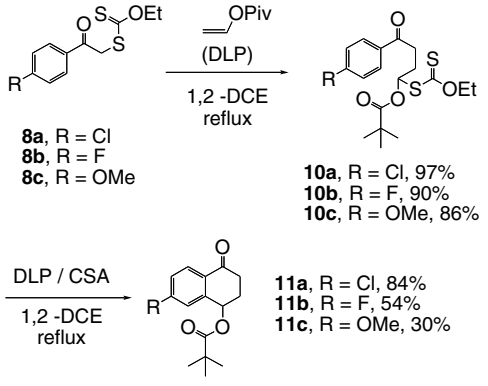
The main general features of our route are outlined in Scheme 2. Tolvaptan (**2**) could derive from benzazepine **4** by acylation and deprotection of the alcohol group. The latter can be derived, in the crucial step of the synthesis, by a Beckmann rearrangement and amide reduction from ketoxime **6**. The protected alcohol group has to resist the Beckmann rearrangement conditions. This is not an easily fulfilled requirement since we had shown that adducts **7** readily undergo aromatisation to naphthols upon exposure to acid.[9] Furthermore, the lability to acid increases as the lactam **5** stage is reached because of the electron releasing effect of the nitrogen lone pair. Finally, tetralone **7**, the direct precursor of **6**, would be easily prepared in a convergent manner from an acetophenone xanthate (**8**) and an appropriate olefin (**9**), the latter serving as the radical trap.



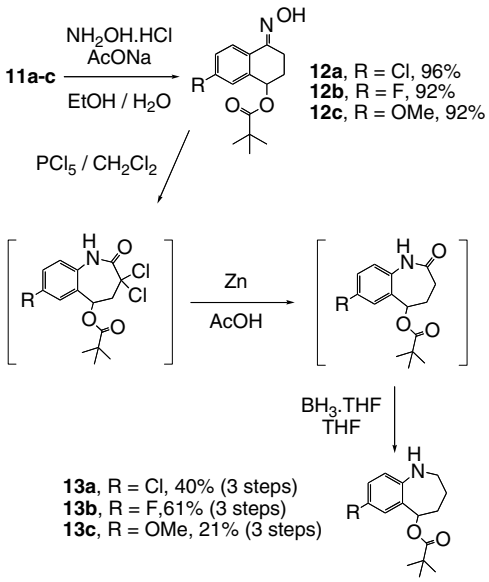

**Scheme 2.** Retrosynthetic analysis for tolvaptan.

Our synthesis starts with the preparation of the required tetralones **11a–c** as previously reported.[9] Thus, xanthate group transfer addition of xanthates **8a–c**,[12] using dilauroyl peroxide (DLP) as radical initiator and 1,2-dichloroethane (DCE) as the solvent, produces adducts **10a–c** in excellent yield. The latter were then subjected to the same free radical conditions in the presence of a catalytic amount of camphorsulfonic acid (CSA)[13] to generate tetralones **11a–c** by ring closure to the aromatic ring. This step requires stoichiometric quantities of the peroxide, which acts both as initiator for the radical cyclisation and as oxidant for the intermediate cyclohexadienyl radical (Scheme 3).

The preparation of the corresponding oximes **12a–c** was easily achieved by reaction of **11a–c** with $NH_2OH$–HCl and sodium acetate in ethanol/water (Scheme 4). Having obtained the required precursors for the Beckmann rearrangement, we proceeded to prepare key intermediates **13a–c**. Unfortunately, all standard conditions for mediating the ring expansion failed. Our worries concerning the lability of the benzylic ester as the main stumbling block of the synthesis were thus well founded.



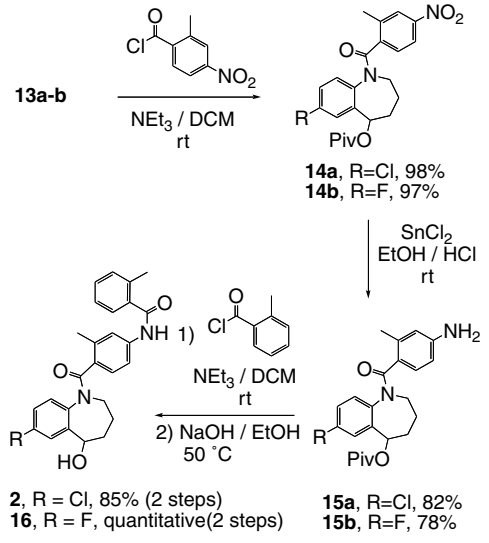

**Scheme 3.** Radical sequence for the preparation of tetralones.




**Scheme 4.** Beckmann rearrangement-reduction sequence.

Ultimately, after careful experimentation, we found that treatment of oximes **12a**–**c** with an excess of $PCl_5$ in $CH_2Cl_2$ produced an α,α-dichloro lactam,[14] which was then subjected to reduction with Zn powder in acetic acid. The amide carbonyl could then be selectively reduced[15] by $BH_3$–THF complex to give key benzazepines **13a**–**c** in good overall yields, except for the methoxy substituted derivative. This is not surprising since the presence of the electron donating group increases the sensitivity of the pivalate group to the presence of acid during the Beckmann rearrangement.

Completion of the synthesis of tolvaptan is shown in Scheme 5. With the benzazepine precursor in place, the next step toward tolvaptan was the acylation of the secondary amine with 2-methyl-4-nitro benzoyl chloride.[16] The high efficiency of this seemingly trivial step contrasts with the analogous acylation described by the Otsuka chemists (Scheme 1). In their route, the presence of the electron withdrawing ketone function deactivates the nitrogen and lowers considerably the efficiency of the acylation step. Reduction of the nitro group of **14a**–**b** with tin (II) chloride in ethanol/HCl afforded anilines **15a**–**b**. Finally, acylation of the latter with 2-methyl benzoyl chloride and saponification of the ester group under basic conditions allowed us to obtain tolvaptan (**2**) and its 5′-fluoro analogue (**16**) in excellent yield.

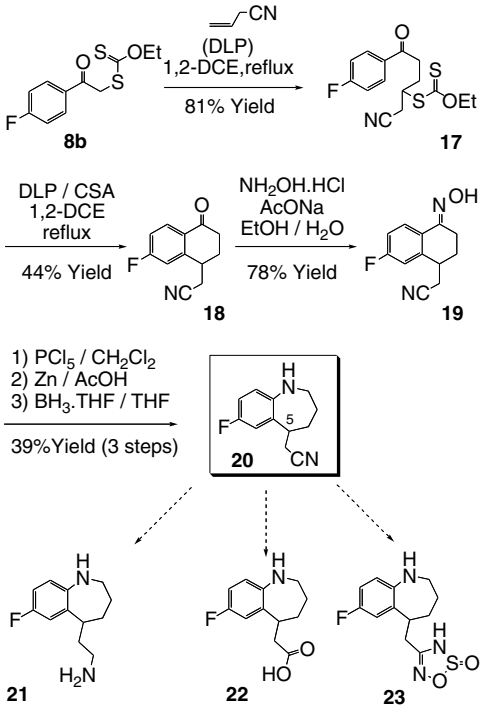



**Scheme 5.** Synthesis of tolvaptan and its fluoro analogue.

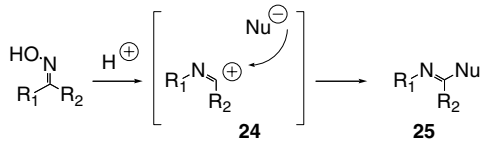
Our method for the synthesis of α-tetralones is quite flexible and several substituents can be introduced into the molecule just by choosing the appropriate radical trap. In order to show the scope and applicability of this method, we prepared some analogues possessing a hydrocarbon chain at C5 (Scheme 6). Thus, reaction of xanthate **8b** with a small amount of DLP in the presence of allyl cyanide afforded adduct **17** in 81% yield. Tetralone **18** was prepared from **17** in 44% yield after the CSA catalyzed cyclisation step. The final three-step sequence was then applied to oxime **19**, affording benzazepine **20** in good overall yield.

As seen in Scheme 6, the presence of the nitrile group in **20** is not arbitrary. This functional group is highly useful because it could be used as a starting point to prepare a series of other benzazepines possessing a primary amine (**21**), an acid (**22**),[4b] or an oxathiadiazole oxide (**23**).[17] The latter structure also exhibits interesting antihyperglycemic activity.[15]

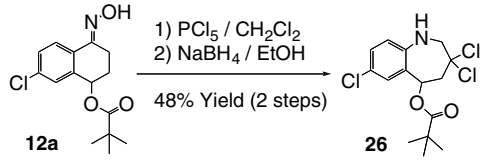
While α-halo lactams have been reported as important intermediates for the synthesis of C3-substituted




**Scheme 6.** Synthesis of further analogues.




**Scheme 7.** Trapping the intermediate in the Beckmann rearrangement.




**Scheme 8.** Synthesis of a dichlorobenzazepine.

benzazepinones,[2] benzazepines bearing this substitution pattern are rare. It is known[7] that the intermediate of the Beckmann reaction is an iminium ion (**24**) that can be trapped by a nucleophile in order to generate the corresponding imines (**25**) (Scheme 7).

We exploited this feature in order to prepare a novel benzazepine derivative possessing a halide in the 3-position, which would be difficult to access otherwise. When oxime **12a** was treated with an excess of $PCl_5$ in $CH_2Cl_2$ and quenched with a suspension of $NaBH_4$ in ethanol, compound **26** was obtained in 48% overall yield (Scheme 8). This molecule could, of course, be used as starting material for the synthesis of yet another tolvaptan analogue.

## 3. Conclusion

In summary, we have illustrated a useful application of the xanthate methodology. The mild conditions of this protocol allow the preparation of a great diversity of functionalized benzazepines tedious to obtain by more traditional routes. The efficiency of our approach to tolvaptan (**2**) is indicated by the good overall yield (21%), which contrasts with the low overall yield reported for the original route (<1%). In addition, the synthesis of the 5′-fluoro derivative **16** (20.6% overall yield) as well as the preparation of analogues **20** and **26** underscores its flexibility.

## 4. Experimental

### 4.1. General considerations

All reactions were carried out under an inert atmosphere. Commercial reagents were used as received without further purification. All products were purified by using silica gel SDS 60 C.C. 40–63 or by crystallisation. NMR spectra were recorded in $CDCl_3$ with TMS as an internal standard at room temperature on a Bruker AMX400 operating at 400 MHz for $^1H$ and 100 MHz for $^{13}C$. Infrared Absorption spectra were recorded as a solution in $CCl_4$ with a Perkin-Elmer 1600 Fourier Transform Spectrophotometer. Mass spectra were recorded with a HP 5989B mass spectrometer. Melting points were determined by Reichert microscope apparatus and were uncorrected.

**4.1.1. 2,2-Dimethyl-propionic acid 1-ethoxythiocarbonylsulfanyl-4-(4-methoxy-phenyl)-4-oxo-butyl ester (10c).** A solution of **8c** (0.5 g, 1.85 mmol) and of 0.55 mL (2.7 mmol) of vinyl pivalate in 1,2-dichloroethane (2 mL) was refluxed for 15 min under argon. Lauroyl peroxide (DLP) was then added (5 mol %) to the refluxing solution, followed by additional portions (2 mol % every 90 min). When starting material was totally consumed (after addition of 7.5 mol % of DLP), the crude mixture was cooled to room temperature, concentrated under reduced pressure and purified by flash column chromatography (silica gel, petroleum ether–ethyl acetate, 95:5) to give **10c** as a yellow oil (86% yield): $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 7.92 (d, 2H, C*H* arom, $J = 8.8$ Hz), 6.93 (d, 2H, C*H* arom, $J = 8.8$ Hz), 6.71 (t, 1H, C*H*–S, $J = 8.0$ Hz), 4.65–4.59 (m, 2H, O–C$H_2$), 3.87 (s, 3H, OC$H_3$), 3.08 (dq, 2H, CO–C$H_2$, $J = 7.2$, 4.4 Hz), 2.42–2.35 (m, 2H, CH–C$H_2$), 1.41 (t, 3H, $CH_2$–C$H_3$, $J = 6.0$ Hz), 1.19 (s, 9H, (C$H_3$)$_3$); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 210.3 (*C*S), 196.6 (*C*O), 176.9 (O–*C*O), 163.7 (*C*–OMe), 130.9 (*C*–CO), 130.4 (*C*H arom), 113.9 (*C*H arom), 80.4 (*C*H–S), 70.4 (O–*C*$H_2$), 55.6 (O*C*$H_3$), 43.5 (*C*–(CH$_3$)$_3$), 33.9 (CO–*C*$H_2$), 28.8 (CH–*C*$H_2$), 27.1 (3C, (*C*$H_3$)$_3$), 13.8 ($CH_2$–*C*$H_3$); MS (CI+$NH_3$) *m/z*: 416 ($MH^+$+$NH_3$), 399 ($MH^+$), 297 ($MH^+$–PivOH); IR ($cm^{-1}$, $CCl_4$): 1738 (O–*C*=*O*), 1683 (C=O), 1229 (C=S).

**4.1.2. Dithiocarbonic acid [1-cyanomethyl-4-(4-fluorophenyl)-4-oxo-butyl] ester ethyl ester (17).** A solution of **8b** (2.0 g, 7.74 mmol) and of 1.25 mL (1.03 g, 15.48 mmol) of allyl cyanide in 1,2-dichloroethane (8 mL) was refluxed for 15 min under argon. Lauroyl peroxide (DLP) was then added (5 mol %) to the refluxing solution, followed by additional portions (2 mol % every 90 min). When starting material was totally consumed (after addition of 15 mol % of DLP), the crude mixture was cooled to room temperature, concentrated under reduced pressure and purified by flash column chromatography (silica gel, petroleum ether–ethyl acetate, 9:1) to give **17** as a yellow oil (81% yield): $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 7.98 (dd, 2H, C*H* arom, $J = 8.4$, 5.2 Hz), 7.14 (t, 2H, C*H* arom, $J = 8.4$ Hz), 4.63 (m, 2H, O–C$H_2$), 4.01 (dddd, 1H, C*H*–S, $J = 15.2$, 5.3, 5.3, 5.3 Hz), 3.19 (t, 2H, CO–C$H_2$, $J = 7.2$ Hz), 2.96 (t, 2H, C$H_2$–CN), 2.39 (ddt, 1H, CO–CH$_2$–C$H_2$, $J = 10.9$, 7.2, 4.3 Hz), 2.15 (dddd, 1H, CO–CH$_2$–C$H_2$, $J = 18.0$, 7.2, 6.8, 6.8 Hz), 1.42 (t, 3H, $CH_2$–C$H_3$, $J = 7.0$ Hz); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 212.0 (*C*S), 196.5 (*C*O), 165.9 (d, 1C, *C*–F, $^1J_{C-F} = 255.2$ Hz), 132.9 (*C*–CO), 130.7 (d, 2C, *C*H arom, $^2J_{C-F} = 13.0$ Hz), 117.1 (*C*≡N), 115.9 (d, 2C, *C*H arom, $^3J_{C-F} = 22.0$ Hz), 70.7 (O–*C*$H_2$), 46.2 (*C*H–S), 35.4 (CO–*C*$H_2$), 26.7 (*C*$H_2$–CN), 24.5 (CO–CH$_2$–*C*$H_2$), 13.8 ($CH_2$–*C*$H_3$); MS (CI+$NH_3$) *m/z*: 343 ($MH^+$+$NH_3$), 326 ($MH^+$), 205 ($MH^+$–SC(S)OEt); IR ($cm^{-1}$, $CCl_4$): 2250 (C≡N), 1741 (C=O), 1236 (C=S).

**4.1.3. 2,2-Dimethyl-propionic acid 7-methoxy-4-oxo-1,2,3,4-tetrahydro-naphthalen-1-yl ester (11c).** A solution of **10c** (3.0 g, 7.50 mmol) in 1,2-dichloroethane (75 mL) was refluxed for 15 min under argon. Lauroyl peroxide (DLP) was then added portionwise (20 mol % per hour) to the refluxing solution. When starting material was totally consumed (after addition of 1.2 equiv DLP), the crude mixture was cooled to room temperature, concentrated under reduced pressure and purified by flash column chromatography (silica gel, petroleum ether–AcOEt, 9:1 to 8:2) and recrystallised with ethanol to give tetralone **11c** (30% yield) as white crystals (mp 80 °C): $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 8.06 (d, 1H, C*H* arom, $J$ = 8.0 Hz), 6.96 (dd, 1H, C*H* arom, $J$ = 8.0, 4.0 Hz), 6.89 (d, 1H, C*H* arom, $J$ = 4.0 Hz), 6.08 (dd, 1H, C*H*–OPiv, $J$ = 8.0, 4.0 Hz), 3.89 (s, 3H, OC$H_3$), 2.87 (ddd, 1H, CO–C$H_2$, $J$ = 18.0, 9.0, 6.0 Hz), 2.66 (ddd, 1H, CO–C$H_2$, $J$ = 16.0, 8.0, 4,0 Hz), 2.45–2.37 (m, 1H, CO–CH$_2$–C$H_2$), 2.29–2.21 (m, 1H, CO–CH$_2$–C$H_2$), 1.26 (s, 9H, (C$H_3$)$_3$); $^{13}$C NMR ($CDCl_3$, 100, 5 MHz) $\delta$ 195.8 (*C*O), 177.9 (O–*C*O), 164.0 (*C*–OMe), 143.7 (*C*–CO), 129.8 (*C*H arom), 125.5 (*C*–C–CO), 114.9 (*C*H arom), 111.9 (*C*H arom), 69.1 (*C*H–OPiv), 55.6 (OC$H_3$), 39.1 (*C*–(CH$_3$)$_3$), 34.6 (CO–C$H_2$), 28.8 (CO–CH$_2$–C$H_2$), 27.18 (3C, (C$H_3$)$_3$); MS (CI+$NH_3$) *m*/*z*: 294 ($MH^+$+$NH_3$), 277 ($MH^+$), 176 ($MH^+$–PivOH); IR (cm$^{-1}$, $CCl_4$): 1731 (O–*C*=*O*), 1687 (C=O), 1146 (*O*–*C*=O); Anal. calcd. for $C_{16}H_{20}O_4$: C, 69.54; H, 7.3. Found: C, 69.07; H, 7.27.

**4.1.4. 7-Fluoro-4-oxo-1,2,3,4-tetrahydro-naphthalen-1-yl)-acetonitrile (18).** A solution of **17** (2.0 g, 6.14 mmol) and of CSA (0.14 g, 0.61 mmol) in 1,2-dichloroethane (61 mL) was refluxed for 15 min under argon. Lauroyl peroxide (DLP) was then added portionwise (20 mol % per hour) to the refluxing solution. When starting material was totally consumed (after addition of 1.2 equiv DLP), the crude mixture was cooled to room temperature, concentrated under reduced pressure and purified by flash column chromatography (silica gel, petroleum ether–AcOEt, 8:2) and recrystallised with petroleum ether to give tetralone **18** (44% yield) as a yellow solid (mp 126–128 °C): $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 8.12 (dd, 1H, C*H* arom, $J$ = 9.0, 5.8 Hz), 7.1 (dt, 1H, C*H* arom, $J$ = 8.2, 2.4 Hz), 7.05 (d, 1H, C*H* arom, $J$ = 9.6 Hz), 3.38 (tt, 1H, C*H*, $J$ = 11.6, 6.1 Hz), 2.75–2.83 (m, 3H, CO–C$H_2$ and C$H_2$–CN), 2.68 (ddd, 1H, C$H_2$–CN, $J$ = 18.0, 7.4, 5.0 Hz), 2.45 (ddd, 1H, CO–CH$_2$–C$H_2$, $J$ = 19.0, 9.4, 4.6 Hz), 2.20–2.28 (m, 1H, CO–CH$_2$–C$H_2$); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 194.9 (*C*O), 166.06 (d, 1C, *C*–F, $^1J_{C-F}$ = 256 Hz), 146.1 (*C*–CO), 131.3 (d, 1C, *C*H arom, $^3J_{C-F}$ = 10.9 Hz), 122.0 (C≡N), 117.6 (*C*–CCO), 115.9 (d, 1C, *C*H arom, $^2J_{C-F}$ = 23 Hz), 114.2 (d, 1C, *C*H arom, $^2J_{C-F}$ = 22 Hz), 35.1 (*C*H), 34.9 (CO–*C*H$_2$), 27.6 (*C*H$_2$–CN), 22.9 (CO–CH$_2$–*C*H$_2$); MS (CI+$NH_3$) *m*/*z*: 221 ($MH^+$+$NH_3$), 204 ($MH^+$); IR (cm$^{-1}$, $CCl_4$): 2254 (C≡N), 1693 (C=O), 1250 (C–F); Anal. calcd. for $C_{12}H_{10}NOF$: C, 70.93; H, 4.96; N, 6.44. Found: C, 70.53 ; H, 5.03 ; N, 6.56.

**4.1.5. General procedure for the preparation of oximes.** To a stirred solution of the corresponding tetralone (1 mmol) in ethanol (0.75 mL) was added a solution of hydroxylamine hydrochloride (1.3 mmol) and anhyd sodium acetate (1.2 mmol) in 0.3 mL of water. The resulting mixture was then refluxed for 2 h. After consumption of all the starting material, ethanol was evaporated and the resulting mixture was diluted with water, extracted with ethyl acetate, dried over $Na_2SO_4$ and concentrated. The residue was purified by crystallisation to afford the desired oximes.

**4.1.6. 2,2-Dimethyl-propionic acid 4-[(E)-hydroxyimino]-7-chloro-1,2,3,4-tetrahydro-naphthalen-1-yl ester (12a).** According to the general procedure, a solution of 1.99 g (7.11 mmol) of tetralone **11a** in 5.3 mL of ethanol is treated with a solution of $NH_2OH \cdot HCl$ (0.6 g, 9.24 mmol) and anhyd sodium acetate (1.16 g, 8.53 mmol) in water (2.1 mL) to furnish oxime **12a** as a yellow solid (96%), mp 110–112 °C (petroleum ether): $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 9.19 (br, 1H, O*H*), 7.86 (d, 1H, C*H* arom, $J$ = 8.0 Hz), 7.35 (d, 1H, C*H* arom, $J$ = 4.0 Hz), 7.29 (dd, 1H, C*H* arom, $J$ = 8.0, 4.0 Hz), 5.89 (t, 1H, C*H*–OPiv, $J$ = 4.0 Hz), 2.93 (t, 2H, C(NOH)–C$H_2$, $J$ = 6.0 Hz), 2.07 (m, 2H, CH–C$H_2$), 1.22 (s, 9H, (C$H_3$)$_3$); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 178.0 (O–*C*O), 153.3 (*C*–NOH), 138.3 (*C*–C(NOH)), 135.6 (*C*–Cl), 129.0 (*C*H arom), 128.9 (*C*–CH), 128.0 (*C*H arom), 125.7 (*C*H arom), 69.0 (*C*H–OPiv), 39.1 (*C*–(CH$_3$)$_3$), 27.2 (3C, (*C*H$_3$)$_3$), 26.3 (C(NOH)–*C*H$_2$), 19.3 (CH–*C*H$_2$).

**4.1.7. 2,2-Dimethyl-propionic acid 4-[(E)-hydroxyimino]-7-fluoro-1,2,3,4-tetrahydro-naphthalen-1-yl ester (12b).** According to the general procedure, a solution of 1.14 g (4.31 mmol) of tetralone **11b** in 3.2 mL of ethanol is treated with a solution of $NH_2OH \cdot HCl$ (0.36 g, 5.6 mmol) and anhyd sodium acetate (0.43 g, 5.17 mmol) in water (1.3 mL) to furnish oxime **12b** as a yellow solid (92%), mp 125–128 °C (petroleum ether): $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 9.10 (br, 1H, O*H*), 7.92 (dd, 1H, C*H* arom, $J$ = 8.8, 6.0 Hz), 7.05 (dt, 1H, C*H* arom, $J$ = 8.5, 2.5 Hz), 7.02 (dd, 1H, C*H* arom, $J$ = 8.2, 3.0 Hz), 5.89 (dd, 1H, C*H*–OPiv, $J$ = 7.0, 3.8 Hz), 2.94 (m, 2H, C(NOH)–C$H_2$), 2.07 (m, 2H, CH–C$H_2$), 1.23 (s, 9H, C$H_3$); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 178.0 (O–*C*O), 164.7 (*C*–NOH), 163.5 (d, 1C, *C*–F, $^1J_{C-F}$ = 250 Hz 153.3 (*C*–C–(NOH)), 139.2 (d, 1C, *C*H arom, $^3J_{C-F}$ = 8.0 Hz), 126.5 (*C*–CH), 116.2 (d, 1C, *C*H arom, $^2J_{C-F}$ = 22 Hz), 114.3 (d, 1C, *C*H arom, $^2J_{C-F}$ = 23 Hz), 69.1 (*C*H–OPiv), 39.1 (*C*–(CH$_3$)$_3$), 27.2 (3C, (*C*H$_3$)$_3$), 26.4 (C(NOH)–*C*H$_2$), 19.5 (CH–*C*H$_2$); MS (CI+$NH_3$) *m*/*z*: 297 ($MH^+$+$NH_3$), 280 ($MH^+$), 179 ($MH^+$–OPiv); IR (cm$^{-1}$, $CCl_4$): 3593 (N–*O*H), 1730 (O–*C*=*O*), 1279 (*O*–*C*=O).

**4.1.8. 2,2-Dimethyl-propionic acid 4-[(E)-hydroxyimino]-7-methoxy-1,2,3,4-tetrahydro-naphthalen-1-yl ester (12c).** According to the general procedure, a solution of 2.2 g (0.78 mmol) of tetralone **11c** in 0.6 mL of ethanol is treated with a solution of $NH_2OH \cdot HCl$ (0.07 g, 1.0 mmol) and anhyd sodium acetate (1.13 g, 0.93 mmol) in water (0.2 mL) to furnish oxime **12c** as a yellow solid (92%), mp 114–115 °C (petroleum ether): $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 9.34 (br, 1H, O*H*), 7.86 (d, 1H, C*H* arom, $J$ = 8.0 Hz), 6.90 (d, 1H, C*H* arom, $J$ = 2.0 Hz), 6.87 (dd, 1H, C*H* arom, $J$ = 7.8, 2.2 Hz),

5.91 (dd, 1H, C*H*–OPiv, $J$ = 6.0, 4.0 Hz), 3.82 (s, 3H, OC$H_3$), 2.93 (t, 2H, C(NOH)–C$H_2$, $J$ = 6.8 Hz), 2.04–2.11 (m, 2H, CH–C$H_2$), 1.22 (s, 9H, (C$H_3$)$_3$); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 178.13 (O–*C*O), 160.7 (*C*–OMe), 153.8 (*C*–NOH), 138.4 (*C*–C(NOH)), 125.8 (*C*H arom), 123.0 (*C*–CH), 115.4 (*C*H arom), 112.2 (*C*H arom), 69.6 (*C*H–OPiv), 55.4 (OC$H_3$), 39.1 (*C*–(CH$_3$)$_3$), 27.2 (3C, (C$H_3$)$_3$), 26.6 (C(NOH)–*C*H$_2$), 19.4 (CH–*C*H$_2$); MS (CI+$NH_3$) *m*/*z*: 292 ($MH^+$), 191 ($MH^+$–OPiv); IR ($cm^{-1}$, $CCl_4$): 3596 (N–*OH*), 1727 (O–*C*=*O*), 1604 (*C*=*N*–OH), 1272 (*O*–*C*=O).

**4.1.9. {7-Fluoro-4-[(E)-hydroxyimino]-1,2,3,4-tetrahydro-naphthalen-1-yl}-acetonitrile (19).** According to the general procedure, a solution of 0.4 g (1.96 mmol) of tetralone **18** in 0.9 mL of ethanol is treated with a solution of $NH_2OH \cdot HCl$ (0.16 g, 2.55 mmol) and anhyd sodium acetate (0.32 g, 2.36 mmol) in water (0.4 mL) to furnish oxime **19** as a yellow solid (78%), mp 167–168 °C (ethyl acetate/petroleum ether): $^1$H NMR ($CDCl_3$/DMSO–$d_6$, 400 MHz) $\delta$ 9,94 (br, 1H, O*H*), 7.97 (dd, 1H, C*H* arom, $J$ = 8.8, 6.0 Hz), 6.93–7.0 (m, 2H, C*H* arom), 3.16–3.22 (m, 1H, C*H*), 2.96 (dt, 1H, C(NOH)–C$H_2$, $J$ = 18.8, 5.2 Hz), 2.73 (m, 1H, C(NOH)–C$H_2$), 2.58–2.66 (m, 1H, C$H_2$–CN), 2.05–2.12 (m, 2H, CH–C$H_2$); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 162.3 (d, 1C, *C*–F, $^1J_{C-F}$ = 250 Hz), 150.7 (*C*=NOH), 140.0 (*C*–C=NOH), 126.8 (*C*≡N), 126.2 (d, 1C, *C*H arom, $^3J_{C-F}$ = 7.7 Hz), 117.8 (*C*–CH), 114.4 (d, 1C, *C*H arom, $^2J_{C-F}$ = 15.0 Hz), 113.6 (d, 1C, *C*H arom, $^2J_{C-F}$ = 23 Hz), 34.7 (*C*H), 24.8 (C(NOH)–*C*H$_2$), 21.9 (*C*H$_2$–CN), 19.1 (CH–*C*H$_2$); MS (CI+$NH_3$) *m*/*z*: 236 ($MH^+$+$NH_3$), 219 ($MH^+$); IR ($cm^{-1}$, $CCl_4$): 3591 (N–*OH*), 1741 (*C*=*N*–OH), 1239 (*O*–*C*=O).

**4.1.10. General procedure for the preparation of benzazepines.** To a stirred suspension of $PCl_5$ (4 mmol) in dry $CH_2Cl_2$ (10 mL) at 0 °C was slowly added a solution of the corresponding oxime (1 mmol) in 10 mL of dry $CH_2Cl_2$. The mixture was stirred at room temperature for 2 h, neutralised with saturated aqueous $NaHCO_3$, extracted with $CH_2Cl_2$, dried over $NaSO_4$ and concentrated under reduced pressure. The residue was then dissolved in 10 mL of acetic acid and heated to reflux. Then, powdered Zn (6 mmol) was slowly added to the reaction mixture. The resulting mixture was then refluxed for further 30 min. When starting material was totally consumed, the crude mixture was diluted with ethyl acetate, filtered through Celite, washed with saturated aqueous $NaHCO_3$ and concentrated in vacuo. The residue was then dissolved in THF (1.5 mL) and added dropwise to a solution of $BH_3 \cdot THF$ (2 mmol) in THF (1.5 mL) at 0°C. The resulting solution was then refluxed for 30 min, acidified with saturated aqueous citric acid and the solvent was evaporated under reduced pressure. The residue was then basified with saturated aqueous $Na_2CO_3$, extracted with $CH_2Cl_2$, dried over $Na_2SO_4$ and concentrated under reduced pressure. The title compound is purified by flash chromatography.

**4.1.11. 2,2-Dimethyl-propionic acid 7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-5-yl ester (13a).** Following the general method, this compound was obtained from oxime **12a** as a white solid (40% over 3 steps), mp 65–66 °C (petroleum ether): $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.27 (d, 1H, C*H* arom, $J$ = 2.4 Hz), 7.02 (dd, 1H, C*H* arom, $J$ = 8.4, 2.4 Hz), 6.64 (d, 1H, C*H* arom, $J$ = 8.8 Hz), 5.84 (d, 1H, C*H*–OPiv, $J$ = 8.0 Hz), 3.83 (br, 1H, N*H*), 3.25 (dt, 1H, NH–C$H_2$, $J$ = 13.2, 4.2 Hz), 2.93 (ddd, 1H, NH–C$H_2$, $J$ = 13.2, 9.6, 3.2 Hz), 1.80–2.0 (m, 4H, CH–C$H_2$ and NH–CH$_2$–C$H_2$), 1.27 (s, 9H, (C$H_3$)$_3$); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 177.3 (O–*C*O), 147.5 (*C*–NH), 131.5 (*C*–Cl), 128.1 (*C*H arom), 127.7 (*C*H arom), 125.2 (*C*–CH), 120.8 (*C*H arom), 73.7 (*C*H–OPiv), 47.5 (NH–*C*H$_2$), 41.7 (*C*–(CH$_3$)$_3$), 31.3 (CH–C$H_2$), 27.3 (3C, (C$H_3$)$_3$), 27.0 (NH–CH$_2$–*C*H$_2$); MS (CI+$NH_3$) *m*/*z*: 284 ($MH^+$), 282 ($MH^+$), 184 ($MH^+$–PivOH) 181 ($MH^+$–PivOH); IR ($cm^{-1}$, $CCl_4$): 3386 (NH), 1729 (O–*C*=*O*), 1151 (*O*–*C*=O); Anal. calcd. $C_{15}H_{20}NO_2Cl$: C, 63.94; H, 7.15. Found: C, 63.75; H, 7.15.

**4.1.12. 2,2-Dimethyl-propionic acid 7-fluoro-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-5-yl ester (13b).** Following the general method, this compound was obtained from oxime **12b** as a white solid (61% over 3 steps), mp 58–60 °C (petroleum ether): $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.05 (dd, 1H, C*H* arom, $J$ = 9.4, 3.0 Hz), 6.78 (td, 1H, C*H* arom, $J$ = 8.3, 3.1 Hz), 6.68 (dd, 1H, C*H* arom, $J$ = 8.4, 4.8 Hz), 5.84 (d, 1H, C*H*–OPiv, $J$ = 10.0 Hz), 3.58 (br, 1H, N*H*), 3.26 (dt, 1H, NH–C$H_2$, $J$ = 13.2, 4.2 Hz), 2.79 (td, 1H, NH–C$H_2$, $J$ = 11.7, 2.8 Hz), 1.7–2.0 (m, 4H, CH–C$H_2$ and NH–CH$_2$–C$H_2$), 1.26 (s, 9H, (C$H_3$)$_3$); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 177.2 (O–*C*O), 157.7 (d, 1C, *C*–F, $^1J_{C-F}$ = 236 Hz), 144.4 (*C*–NH), 133.2 (*C*–CH), 120.9 (d, 1C, *C*H arom, $^2J_{C-F}$ = 7.0 Hz), 114.1 (d, 1C, *C*H arom, $^2J_{C-F}$ = 7.0 Hz), 113.7 (d, 1C, *C*H arom, $^3J_{C-F}$ = 24 Hz), 73.6 (*C*H–OPiv), 47.6 (NH–*C*H$_2$), 39.0 (*C*–(CH$_3$)$_3$), 32.0 (NH–CH$_2$–*C*H$_2$), 27.5 (CH–*C*H$_2$), 27.3 (3C, (C$H_3$)$_3$); MS (CI+$NH_3$) *m*/*z*: 266 ($MH^+$), 165 ($MH^+$–OPiv); IR ($cm^{-1}$, $CCl_4$): 3385 (NH), 1729 (O–*C*=*O*), 1152 (*O*–*C*=O); Anal. calcd. for $C_{15}H_{20}NO_2F$: C, 67.9; H, 7.6. Found: C, 67.93; H, 7.62.

**4.1.13. 2,2-Dimethyl-propionic acid 7-methoxy-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-5-yl ester (13c).** According to the general method, this compound was obtained from oxime **12c** as a yellow oil (21% over 3 steps): $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 6.93 (d, 1H, C*H* arom, $J$ = 2.4 Hz), 6.66–6.7 (m, 2H, C*H* arom), 5.87 (d, 1H, C*H*–OPiv, $J$ = 9.2 Hz), 3.76 (s, 3H, OC$H_3$), 3.24 (dt, 1H, NH–C$H_2$, $J$ = 12.8 et 4.2 Hz), 2.78 (td, 1H, NH–C$H_2$, $J$ = 11.7, 2.8 Hz), 1.75–2.0 (m, 4H, CH–C$H_2$ and NH–CH$_2$–C$H_2$), 1.28 (s, 9H, (C$H_3$)$_3$); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 189.1 (O–*C*O), 141.9 (*C*–OMe), 134.0 (*C*-NH), 130.2 (*C*–CH), 121.0 (*C*H arom), 112.9 (*C*H arom), 112.5 (*C*H arom), 74.1 (*C*H–OPiv), 55.6 (OC$H_3$), 48.2 (NH–*C*H$_2$), 39.1 (*C*–(CH$_3$)$_3$), 32.3 (NH–CH$_2$–*C*H$_2$), 27.7 (CH–*C*H$_2$), 27.4 (3C, (C$H_3$)$_3$); MS (CI+$NH_3$) *m*/*z*: 278 ($MH^+$), 177 ($MH^+$–PivOH); IR ($cm^{-1}$, $CCl_4$): 3450 (NH), 1727 (O–*C*=*O*), 1156 (*O*–*C*=O).

**4.1.14. (7-Fluoro-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-5-yl)-acetonitrile (20).** According to the general procedure, this compound was obtained from oxime **19** as a white solid

(39% over 3 steps), mp 74–75 °C (petroleum ether): $^1$H NMR ($CDCl_3$, 400 MHz) δ6.84 (dd, 1H, C*H* arom, *J* = 9.2, 2.4 Hz), 6.78 (td, 1H, C*H* arom, *J* = 8.2, 3.0 Hz), 6.67 (dd, 1H, C*H* arom, *J* = 8.4, 4.8 Hz), 3.59 (sl, 1H, N*H*), 3.19–3.29 (m, 2H, C*H* and NH–C$H_2$), 3.0 (dd, 1H, C$H_2$–CN, *J* = 16.6, 8.6 Hz), 2.81 (dd, 1H, C$H_2$–CN, *J* = 16.6, 7.4 Hz), 2.72 (ddd, 1H, NH–C$H_2$, *J* = 12.6, 10.8, 2.0 Hz), 2.05–2.1 (m, 1H, NH–CH$_2$–C$H_2$), 1.84–1.95 (m, 1H, NH–CH$_2$–C$H_2$), 1.71–1.79 (m, 2H, CH–C$H_2$); $^{13}$C NMR ($CDCl_3$, 100 MHz) δ 157.8 (d, 1C, *C*–F, $^1J_{C-F}$ = 241 Hz), 145.7 (*C*–NH), 134.4 (d, 1C, *C*H arom, $^3J_{C-F}$ = 6.0 Hz), 121.8 (*C*≡N), 119.2 (*C*–CH), 116.7 (d, 1C, *C*H arom, $^2J_{C-F}$ = 22.1 Hz), 114.2 (d, 1C, *C*H arom, $^2J_{C-F}$ = 19.1 Hz), 48.9 (NH–*C*H$_2$), 42.5 (*C*H), 29.9 (*C*H$_2$–CN), 26.1 (NH–CH$_2$–*C*H$_2$), 19.1 (CH–*C*H$_2$); MS (CI+$NH_3$) *m*/*z*: 205 ($MH^+$); IR ($cm^{-1}$, $CCl_4$): 3384 (NH), 2246 (C≡N), 1253 (*O*–*C*=O); Anal. calcd. for $C_{12}H_{13}N_2F$: C, 70.57; H, 6.42. Found: C, 70.42 ; H, 6.55.

**4.1.15. 2,2-Dimethyl-propionic acid 3,3,7-trichloro-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-5-yl ester (26).** To a stirred suspension of $PCl_5$ (0.28 g, 1.35 mmol) in dry $CH_2Cl_2$ (1,5 mL) at 0 °C was slowly added a solution of oxime **12a** (0.1 g, 0.34 mmol) in 1.5 mL of dry $CH_2Cl_2$. The mixture was stirred at room temperature for 2 h. The solution was then cooled at 0 °C and a suspension of $NaBH_4$ (0.13 g, 3.38 mmol) in ethanol (0.3 mL) was added dropwise. When starting material was completely consumed, water was added and the reaction mixture was extracted with $CH_2Cl_2$, dried over $Na^2SO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, petroleum ether–AcOEt, 95:5) and recrystallised with petroleum ether to give benzazepine **20** (48% yield over 2 steps) as a white solid (mp 103–104 °C): $^1$H NMR ($CDCl_3$, 400 MHz) δ 7.21 (d, 1H, C*H* arom, *J* = 2.0 Hz), 7.10 (dd, 1H, C*H* arom, *J* = 8.8, 2.4 Hz), 6.72 (d, 1H, C*H* arom, *J* = 8.4 Hz), 6.03 (t, 1H, C*H*–OPiv, *J* = 5.6 Hz), 4.22 (br, 1H, N*H*), 3.75 (dd, 1H, CH–C$H_2$, *J* = 14.8, 6.8 Hz), 3.57 (d, 1H, CH–C$H_2$, *J* = 14.0 Hz), 3.86 (d, 2H, NH–C$H_2$, *J* = 4.0 Hz), 1.29 (s, 9H, (C$H_3$)$_3$); $^{13}$C NMR ($CDCl_3$, 100 MHz) δ 177.0 (O–*C*O), 145.2 (*C*–NH), 142.3 (*C*–Cl), 128.5 (*C*H arom), 128.2 (*C*H arom), 126.6 (*C*–CH), 121.0 (*C*H arom), 88.4 (*C*$Cl_2$), 69.2 (*C*H–OPiv), 61.6 (NH–*C*H$_2$), 50.1 (CH–*C*H$_2$), 39.0 (*C*–(CH$_3$)$_3$), 27.3 (3C, (*C*H$_3$)$_3$); MS (CI+$NH_3$) *m*/*z*: 352 ($MH^+$), 350 ($MH^+$), 250 ($MH^+$–PivOH), 248 ($MH^+$–PivOH); IR ($cm^{-1}$, $CCl_4$): 3446 (NH), 1735 (O–*C*=*O*), 1139 (*O*–*C*=O); Anal. calcd. for $C_{15}H_{18}NO_2Cl_3$:C, 51.38; H, 5.17. Found: C, 51.31; H, 5.16.

**4.1.16. 2,2-Dimethyl-propionic acid 7-chloro-1-(2-methyl-4-nitro-benzoyl)-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-5-yl ester (14a).** A solution of 2-methyl-4-nitrobenzoyl chloride (0.21 g, 1.06 mmol) in $CH_2Cl_2$ (2 mL) was added dropwise to an ice-cooled solution of benzazepine **13a** (0.1 g, 0.35 mmol) and triethylamine (2 mL, 0.14 g, 1.41 mmol) in $CH_2Cl_2$. The mixture was stirred at room temperature for 1 h, neutralised with saturated aqueous $Na_2CO_3$, extracted with ethyl acetate, dried over $Na_2SO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, petroleum ether–AcOEt, 9:1) and recrystallised with petroleum ether to give benzazepine **20** (98% yield) as a white solid (mp 58–60 °C): $^1$H NMR ($CDCl_3$, 400 MHz) δ 7.92 (d,1H, C*H* arom, *J* = 2.0 Hz), 7.77 (dd, 1H, C*H* arom, *J* = 8.2, 2.2 Hz), 7.15 (d, 1H, C*H* arom, *J* = 8.4 Hz), 7.14 (s, 1H, C*H* arom), 6.85 (dd, 1H, C*H* arom, *J* = 8.0, 2.4 Hz), 6.51 (d, 1H, C*H* arom, *J* = 8.4 Hz), 5.95 (dd, 1H, C*H*–OPiv, *J* = 5.6, 2.6 Hz), 4.74 (dt, 1H, N–C$H_2$, *J* = 14.0, 4.1 Hz), 2.81 (ddd, 1H, N–C$H_2$, *J* = 12.0, 10.1, 2.1 Hz), 2.49 (s, 3H, Ar–C$H_3$), 2.09–2.19 (m, 2H, N–CH$_2$–C$H_2$), 1.67–1.82 (m, 2H, CH–C$H_2$), 1.29 (s, 9H, C$H_3$); $^{13}$C NMR ($CDCl_3$, 100 MHz) δ 177.2 (O–*C*O), 167.9 (N–*C*O), 147.7 (*C*–$NO_2$), 141.8 (*C*–N), 140.2 (*C*–CO), 137.6 (*C*–Cl), 137.4 (*C*–CH), 134.28 (*C*–$CH_3$), 128.9 (*C*H arom), 128.0 (*C*H arom), 127.6 (*C*H arom), 125.3 (*C*H arom), 124.6 (*C*H arom), 121.0 (*C*H arom), 71.8 (*C*H–OPiv), 46.6 (N–*C*H$_2$), 39.14 (*C*–(CH$_3$)$_3$), 32.0 (N–CH$_2$–*C*H$_2$), 27.3 (3C, (*C*H$_3$)$_3$), 25.4 (CH–*C*H$_2$), 20.2 (Ar–*C*H$_3$); MS (CI+$NH_3$) *m*/*z*: 465 ($MH^+$+$NH_3$), 463 ($MH^+$+$NH_3$), 447 ($MH^+$), 445 ($MH^+$), 346 ($MH^+$–PivOH), 344 ($MH^+$–PivOH); IR ($cm^{-1}$, $CCl_4$): 1735 (O–*C*=*O*), 1659 (N–*C*=*O*), 1529 ($NO_2$), 1139 (*O*–*C*=O).

**4.1.17. 2,2-Dimethyl-propionic acid 7-fluoro-1-(2-methyl-4-nitro-benzoyl)-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-5-yl ester (14b).** Using the same procedure as **14a**, benzazepine **14b** (97%) was obtained from **13b** (0.05 g, 0.18 mmol) as a yellow oil: $^1$H NMR ($CDCl_3$, 400 MHz) δ 7.98 (d, 1H, C*H* arom, *J* = 2.4 Hz), 7.82 (dd, 1H, C*H* arom, *J* = 8.6, 2.6 Hz), 7.22 (d, 1H, C*H* arom, *J* = 8.8 Hz), 6.94 (d, 1H, C*H* arom, *J* = 8.8 Hz), 6.63 (d, 1H, C*H* arom, *J* = 5.2 Hz), 6.63 (s, 1H, C*H* arom), 6.03 (dd, 1H, C*H*–OPiv, *J* = 11.4, 3.0 Hz), 4.81 (dt, 1H, N–C$H_2$, *J* = 13.6, 4.2 Hz), 2.88 (td, 1H, N–C$H_2$, *J* = 12.1, 2.0 Hz), 2.56 (s, 3H, Ar–C$H_3$), 2.16–2.25 (m, 2H, N–CH$_2$–C$H_2$), 1.75–1.9 (m, 2H, CH–C$H_2$), 1.36 (s, 9H, C$H_3$); $^{13}$C NMR ($CDCl_3$, 100 MHz) δ 177.2 (O–*C*O), 168.04 (N–*C*O), 162.04 (d, 1C, *C*–F, $^1J_{C-F}$ = 248 Hz), 147.7 (*C*–$NO_2$), 142.0 (*C*–N), 137.6 (*C*–CO), 134.8 (*C*–CH), 129.4 (d, 1C, *C*H arom, $^2J_{C-F}$ = 10.5 Hz), 127.5 (*C*H arom), 125.2 (d, 1C, *C*H arom, $^2J_{C-F}$ = 4.2 Hz), 120.9 (*C*H arom), 120.2 (*C*H arom), 114.8 (*C*–$CH_3$), 111.6 (d, 1C, *C*H arom, $^3J_{C-F}$ = 28.0 Hz), 72.0 (*C*H–OPiv), 46.6 (N–*C*H$_2$), 39.1 (*C*–(CH$_3$)$_3$), 32.1 (N–CH$_2$–*C*H$_2$), 27.3 (3C, (*C*H$_3$)$_3$), 25.5 (CH–*C*H$_2$), 19.9 (Ar–*C*H$_3$); MS (CI+$NH_3$) *m*/*z*: 446 ($MH^+$+$NH_3$), 429 ($MH^+$), 326 ($MH^+$–PivOH); IR ($cm^{-1}$, $CCl_4$): 1735 (O–*C*=*O*), 1659 (N–*C*=*O*), 1529 ($NO_2$), 1346 ($NO_2$), 1139 (*O*–*C*=O).

**4.1.18. 2,2-Dimethyl-propionic acid 1-(4-amino-2-methyl-benzoyl)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-5-yl ester (15a).** To a solution of **14a** (0.15 g, 0.34 mmol) and HCl (0.2 mL) in ethanol (6 mL) at reflux was added $SnCl_2$ (0.32 g, 1.68 mmol). The mixture was refluxed for 2 h, cooled at room temperature, basified with saturated aqueous $Na_2CO_3$, extracted with ethyl acetate, dried over $Na_2SO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, petroleum ether–AcOEt, 4:1) and recrystallised with petroleum ether to give compound **15a** (82% yield) as a white solid (mp 185–186 °C): $^1$H

NMR ($CDCl_3$, 400 MHz) $\delta$ 7.22 (s, 1H, C*H* arom), 6.93 (d, 1H, C*H* arom, $J$ = 8.0 Hz), 6.73 (d, 1H, C*H* arom, $J$ = 8.0 Hz), 6.56 (d, 1H, C*H* arom, $J$ = 8.0 Hz), 6.4–6.46 (m, 2H, C*H* arom), 6.22 (d, 1H, C*H* arom, $J$ = 8.0 Hz), 6.02 (d, 1H, C*H*–OPiv, $J$ = 7.4 Hz), 4.84 (d, 1H, N–C$H_2$, $J$ = 8.4 Hz), 3.7 (br, 2H, N*H*), 3.78 (t, 1H, N–C$H_2$, $J$ = 12.0 Hz), 2.37 (s, 3H, Ar–C$H_3$), 2.05–2.21 (m, 2H, N–$CH_2$–C$H_2$), 1.68–1.77 (m, 2H, CH–C$H_2$), 1.35 (s, 9H, C$H_3$); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 177.1 (O–*C*O), 170.4 (N–*C*O), 147.1 (*C*–NCO), 139.3 (*C*–$NH_2$), 137.7 (*C*–CO), 132.6 (*C*–Cl), 129.6 (*C*H arom), 128.7 (*C*H arom), 127.7 (*C*H arom), 125.6 (*C*–CH), 124.2 (*C*H arom), 116.6 (*C*H arom), 114.3 (*C*–$CH_3$), 111.9 (*C*H arom), 72.1 (*C*H–OPiv), 46.2 (N–*C*$H_2$), 39.0 (*C*–$(CH_3)_3$), 32.0 (N–$CH_2$–*C*$H_2$), 27.3 (3C, (*C*$H_3$)$_3$), 25.6 (CH–*C*$H_2$), 20.1 (Ar–*C*$H_3$); MS (CI+$NH_3$) *m*/*z*: 433 ($MH^+$+$NH_3$), 432 ($MH^+$+$NH_3$), 416 ($MH^+$), 414 ($MH^+$), 315 ($MH^+$–PivOH), 313 ($MH^+$–PivOH); IR ($cm^{-1}$, $CCl_4$): 3400 ($NH_2$), 1734 (O–*C*=*O*), 1651 (N–*C*=*O*), 1142 (*O*–*C*=O).

**4.1.19. 2,2-Dimethyl-propionic acid 1-(4-amino-2-methyl-benzoyl)-7-fluoro-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-5-yl ester (15b).** Using the same procedure as **15a**, compound **15b** (78%) was obtained from **14b** (0.05 g, 0.13 mmol) as a colourless oil: $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 6.95 (d, 1H, C*H* arom, $J$ = 9.6 Hz), 6.73 (d, 1H, C*H* arom, $J$ = 8.0 Hz), 6.56–6.66 (m, 2H, C*H* arom), 6.39 (s, 1H, C*H* arom), 6.20 (d, 1H, C*H* arom, $J$ = 8.4 Hz), 6.03 (d, 1H, C*H*–OPiv, $J$ = 10.4 Hz), 4.84 (d, 1H, N–C$H_2$, $J$ = 13.6 Hz), 3.71 (br, 2H, N$H_2$), 2.77 (t, 1H, N–C$H_2$, $J$ = 12.2 Hz), 2.36 (s, 3H, Ar–C$H_3$), 2.13–2.15 (m, 2H, N–$CH_2$–C$H_2$), 1.69–1.84 (m, 2H, CH–C$H_2$), 1.34 (s, 9H, C$H_3$); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 177.1 (O–*C*O), 170.5 (N–*C*O), 161.3 (d, 1C, *C*–F, $^1J_{C-F}$ = 247 Hz), 150.3 (*C*–NCO), 147.0 (*C*H arom), 140.1 (*C*–$NH_2$), 137.6 (*C*–CO), 129.9 (*C*–CH), 128.5 (*C*H arom), 116.5 (d, 1C, *C*H arom, $^2J_{C-F}$ = 12.6 Hz), 114.4 (d, 1C, *C*H arom, $^2J_{C-F}$ = 6.0 Hz), 112.2 (*C*–CH), 111.1 (*C*–$CH_3$), 110.7 (d, 1C, *C*H arom, $^3J_{C-F}$ = 26 Hz), 72.2 (*C*H–OPiv), 46.2 (N–*C*$H_2$), 39.0 (*C*–$(CH_3)_3$), 32.2 (N–$CH_2$–*C*$H_2$), 27.3 (3C, (*C*$H_3$)$_3$), 25.7 (CH–*C*$H_2$), 19.3 (Ar–*C*$H_3$); MS (CI+$NH_3$) *m*/*z*: 399 ($MH^+$), 298 ($MH^+$–PivOH); IR ($cm^{-1}$, $CCl_4$): 3399 ($NH_2$), 1734 (O–*C*=*O*), 1649 (N–*C*=*O*), 1148 (*O*–*C*=O).

**4.1.20. Tolvaptan (2).** A solution of 2-methylbenzoyl chloride (0.05 g, 0.30 mmol) in $CH_2Cl_2$ (1 mL) was added dropwise to an ice-cooled solution of benzazepine **15a** (0.05 g, 0.12 mmol) and triethylamine (0.07 mL, 0.05 g, 0.48 mmol) in $CH_2Cl_2$ (1 mL). The mixture was stirred at room temperature for 1 h, neutralised with saturated aqueous $Na_2CO_3$, extracted with ethyl acetate, dried over $Na_2SO_4$ and concentrated under reduced pressure. The crude mixture was then dissolved in ethanol (1.5 mL) and 2 mL of a 2 N NaOH aqueous solution was added to the solution. The resulting solution was then heated at 50 °C for 2 h and cooled to room temperature. Water was then added to the reaction mixture and the insoluble material was removed by filtration. The solid thus obtained was washed with cold water and recrystallised from methanol/diethyl ether to furnish compound 1 (85% over 2 steps) as a white solid: mp 220–221 °C (lit. 225.9 °C) whose spectroscopic and analytical data were identical to those reported in the literature.

**4.1.21. Fluoro-Tolvaptan (16).** Using the same procedure as **2**, compound **16** (quantitative yield) was obtained from **15b** (0.04 g, 0.10 mmol) as a white solid (mp 196–198 °C): $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 10.4 (br, 1H, N*H*), 7.70 (s,1H, C*H* arom), 7.4–7.63 (m, 6H, C*H* arom), 6.91–7.0 (m, 3H, C*H* arom), 5.92 (br, 1H, O*H*), 5.88 (d, 1H, C*H*–OH, $J$ = 4.0 Hz), 5.06 (d, 1H, N–C$H_2$, $J$ = 10.0 Hz), 4.81 (d, 1H, N–C$H_{2'}$, $J$ = 13.2 Hz), 2.83 (t, 1H, N–$CH_2$–C$H_2$, $J$ = 12.0 Hz), 2.53–2.56 (m, 1H, N–$CH_2$–C$H_2$), 2.50 (s, 6H, Ar–C$H_3$), 2.25–2.26 (m, 1H, CH–C$H_2$), 1.90–1.92 (m, 1H, CH–C$H_{2'}$); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 167.8 (N–*C*O), 167.3 (N–*C*O), 160.8 (d, 1C, *C*–F, $^1J_{C-F}$ = 243 Hz), 145.6 (*C*–NCO), 139.2 (*C*–NCO), 136.9 (*C*–C(O)N), 136.0 (*C*–C(O)N), 135.8 (*C*–CH), 135.2 (*C*–$CH_3$), 131.5 (*C*–$CH_3$), 130.4 (*C*H arom), 129.5 (d, 1C, *C*H arom, $^3J_{C-F}$ = 13.0 Hz), 128.2 (*C*H arom), 127.1 (*C*H arom), 126.3 (*C*H arom), 125.6 (*C*H arom), 120.8 (*C*H arom), 115.8 (*C*H arom), 113.3 (d, 1C, *C*H arom, $^2J_{C-F}$ = 23.1 Hz), 111.7 (d, 1C, *C*H arom, $^2J_{C-F}$ = 26.1 Hz), 69.5 (*C*H–OH), 45.8 (N–*C*$H_2$), 35.4 (N–$CH_2$–*C*$H_2$), 25.8 (CH–*C*$H_2$), 19.6 (Ar–*C*$H_3$), 19.2 (Ar–*C*$H_3$); MS (CI+$NH_3$) *m*/*z*: 433 ($MH^+$); IR ($cm^{-1}$, $CCl_4$): 3490 (OH), 1640 (N–*C*=*O*), 1623 (N–*C*=*O*).

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