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SYNTHESIS OF SUBSTITUTED 1,4-BENZOXAZEPIN-3-ONE DERIVATIVES

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Abstract- A synthesis of substituted 1,4-benzoxazepin-3-one is described starting from salicylaldehyde, aniline and chloroacetyl chloride. Use of 2-bromo-3-phenylpropionyl chloride gave access to 2-benzyl-1,4-benzoxazepin-3-one; an addition/elimination sequence afforded the corresponding benzylidene derivative which structure has been confirmed by an X-Ray analysis. Biphenyl substituents were also introduced in position -4 of this scaffold.

The design of new scaffolds for mimicking peptidic backbone is always of interest for medicinal chemistry. Among the numerous heterocyclic structures which have been reported we can mention the pyrrolidone ring or the benzodiazepine skeleton. In a program devoted to the search for new factor Xa inhitors[1] we prepared 1,4-benzoxazepin-3-one bearing in position -2 a benzylidene and in position -4 aryl substituents. Similar structures but unsubstituted in position -2 (type **A** and **C**) have been briefly described in the literature.[2] Cyclic imides of type **B** have been also reported[3] (Figure 1).

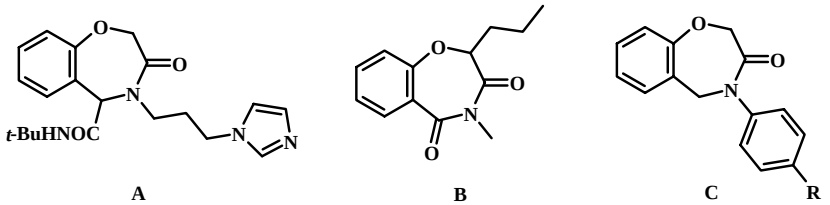
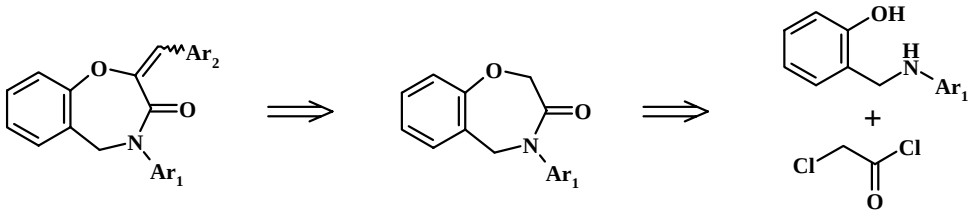


Figure 1

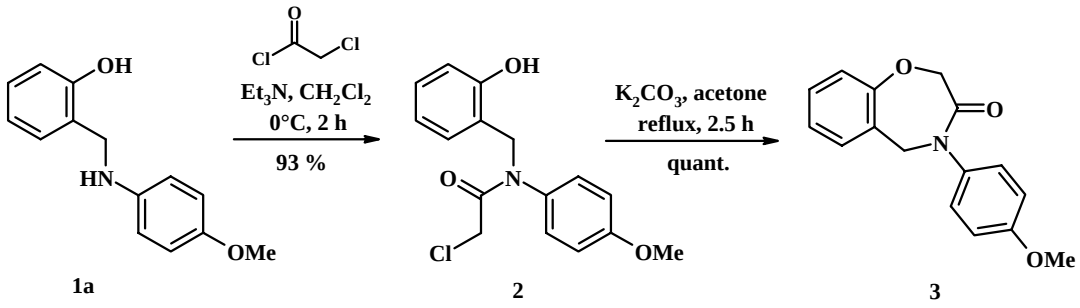
We recently published the synthesis of eight-membered ring derivatives of benzoxazocinone type.[4] In this paper we report our results concerning the synthesis of the seven-membered ring derivatives benzoxazepine.

Our retrosynthetic approach is outlined in Scheme 1.



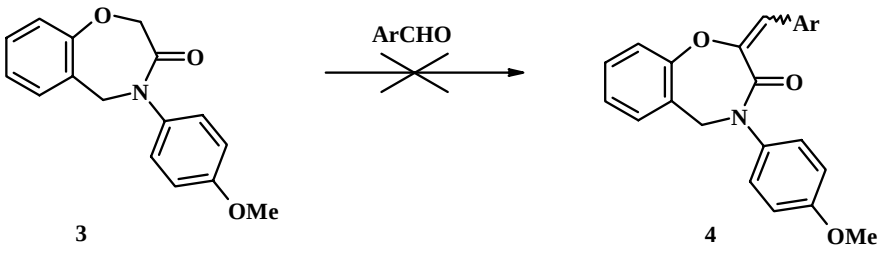
Scheme 1

Salicylaldehyde is first reacted with 4-methoxyaniline in refluxing ethanol followed directly at room temperature by sodium borohydride reduction of the obtained imine to give **1a** in 99% yield. **1a** is further reacted with chloroacetyl chloride[5] to provide the corresponding amide **(2)** in good yield (93%); the cyclic ether **(3)** is obtained in quantitative yield under basic treatment; these 2 steps can be performed "one pot" without isolation of **2** before cyclization.



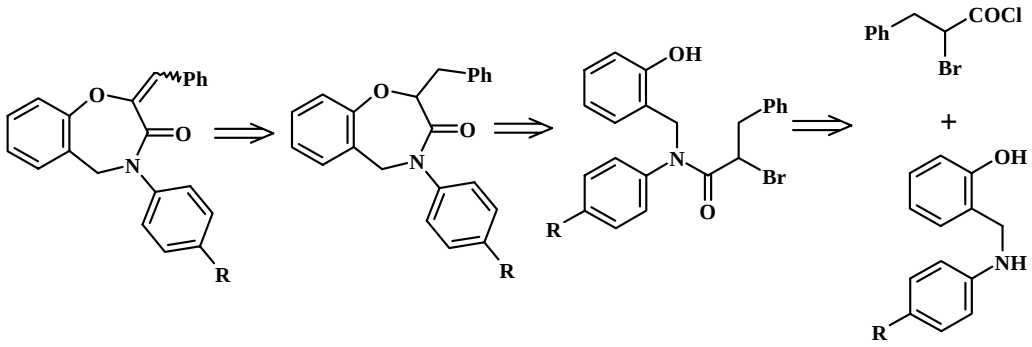
Scheme 2

Unfortunately we were not able to introduce the benzylidene moiety in position –2 *via* an aldol type reaction between compound **(3)** and piperonal using different set of reaction conditions and reagents (LDA/THF,[6] EtONa/EtOH or Ac_2O[7]) (Scheme 3).



Scheme 3

We turned then on to another synthetic approach for the preparation of **4**, benzyl group being introduced before cyclization as depicted in retrosynthetic Scheme 4.

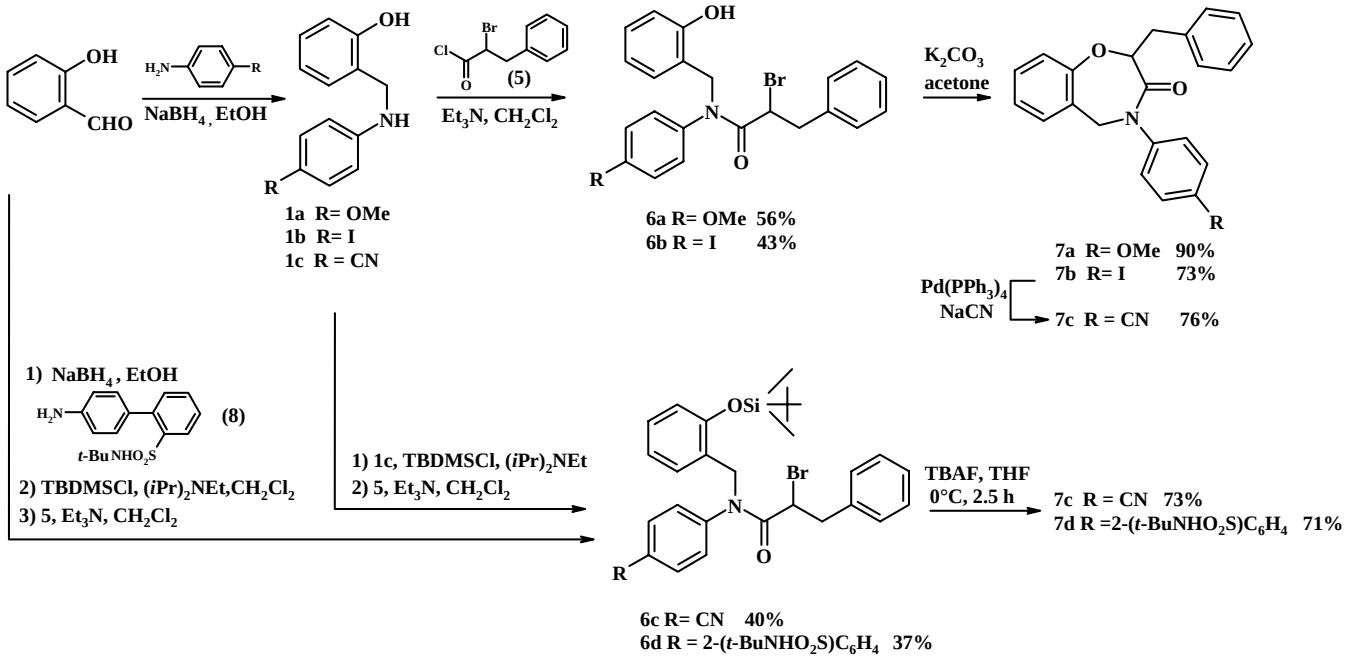


Scheme 4

In this approach the chloroacetyl chloride reagent is replaced by 2-bromo-3-phenylpropionyl chloride **(5)**[8] which was reacted on compounds **(1a,b)** affording the bromoamides **(6a,b)** in moderate yields (Scheme 5). **6a,b**, were cyclized to compounds **(7a,b)** in good yields using the same basic conditions as for conversion from **2** to **3** as reported above.

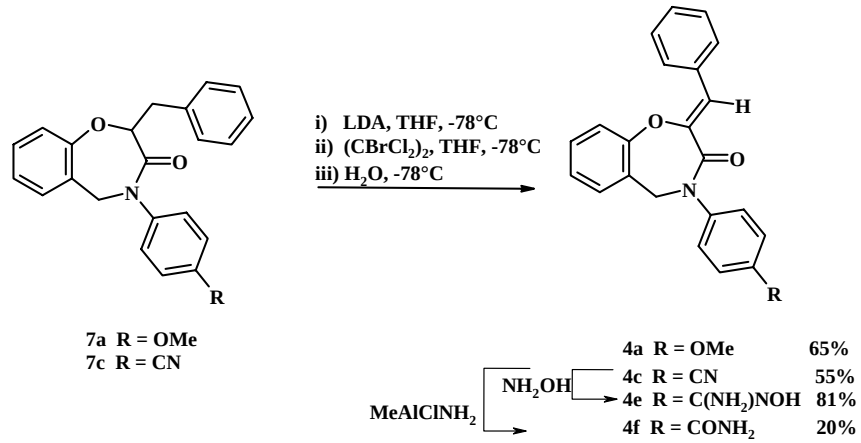
However when **1c** was reacted in the same conditions, a very low yield of the expected amide was obtained, therefore alternative access to **7c** was developed; **7c** was obtained by treating **7b** with sodium cyanide in acetonitrile in the presence of a catalytic amount of tetrakis(triphenylphosphine) palladium and copper(I) iodide in 76% yield (Scheme 5).

Alternatively phenol **(1c)** can be first protected with a *tert*-butyldimethylsilyl group and successfully converted to amide **(6c)** in reasonable yield (40%); further deprotection of **6c** with tetrabutylammonium fluoride (TBAF) at 0°C gave directly the expected cyclized compound (**7c)** in 73% yield. The structure of **7c** has been confirmed by an X-Ray analysis (not reported here).



Scheme 5

To further generate the exo double bond in position -2 we first investigated the radicalar bromination of **7a** with NBS, but no expected bromo derivative in position -2 was observed, so we moved to an electrophilic bromination[9,10] of the amide enolate of **7a**. Treatment of **7a** with LDA at low temperature followed by addition of iodine or 1,1,2,2-tetrachloro-1,2-dibromoethane at –78°C and quenching with a saturated ammonium chloride solution at –78°C or 0°C directly gave the ethylenic derivative **(4a)** (Scheme 6). The yield of **4a** was higher in the bromation/elimination sequence, 65% versus 51 % yield for the iodination/elimination sequence. No 2- iodo or 2-bromo derivative was isolated in those two reactions conditions.



Scheme 6

The stereochemistry of the ethylenic bond was assigned as *Z*, first by measuring the coupling constant $^3J_{CH}$ = 4.5 Hz.[11-13] (For an *E* configuration the $^3J_{CH}$ value would be greater than 7 Hz, Figure 2). Moreover an X-Ray analysis was performed on **4a** confirming the structure (Figure 3).

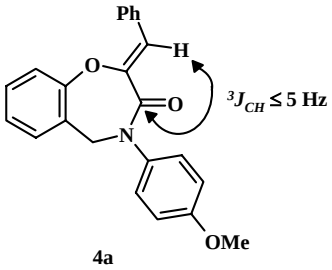


Figure 2

Compound **(7c)** similarly afforded **4c** in 55% yield. We were interested in converting the cyano group into an amidine using a Pinner reaction; but we were unable to sucessfully perform that transformation. We then moved to a two-step reaction by first preparing the amidoxime derivative **(7e)** by reacting **7c** with hydroxylamine hydrochloride in 55% yield; (Scheme 7). Hydrogenation[14] of **7e** over palladium on carbon in a mixture of acetic anhydride / acetic acid under an hydrogen pressure of 3.5 atm afforded **7f** in

80 % yield; the unsaturated cyano derivative **(4c)** similarly gave the amidoxime **(4e)** in 81% yield (Scheme 6).

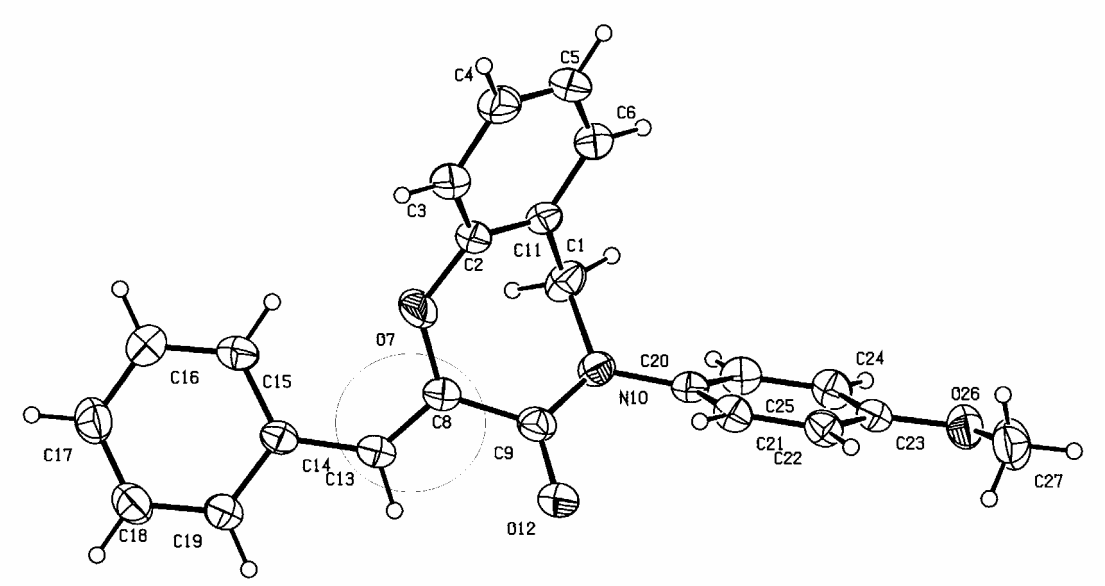
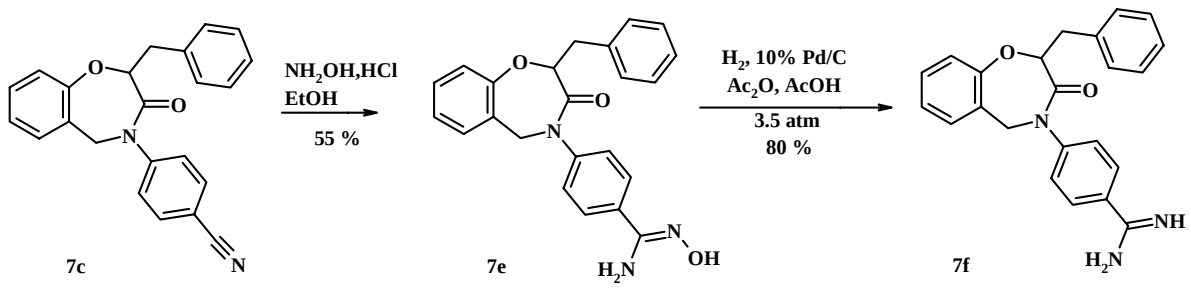


Figure 3. ORTEP structure of **4a**

Garipati[15] reported that the reaction of alkylchloroaluminium amide on benzonitrile afforded benzamidine;[16] in our case, only the benzamide **(4f)** was obtained in quite low yield (20 %) from **4c**.



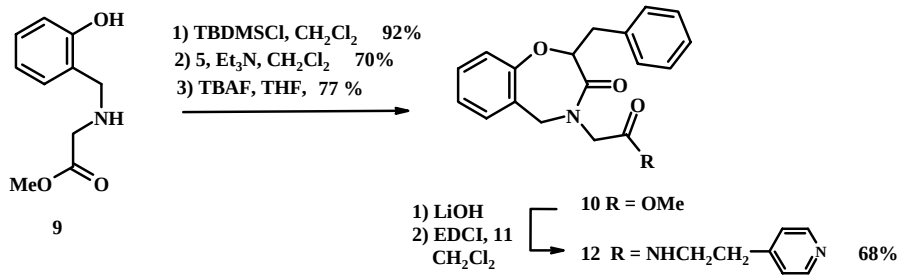
Scheme 7

We were also interested in introducing a 2'-SO_2NH*t*-Bu substituted 4-biphenyl moiety on the nitrogen of the oxazepinone since an improved activity toward inhibition of factor Xa has been reported by Wexler *et al.*[17] when the benzamidine moiety is replaced by a substituted biphenyl of that type.

Introduction of the biphenyl substituent was first done by reacting salicylaldehyde on the diphenylamine **(8)**[18,19] followed by sodium borohydride reduction of the intermediate imine to give the corresponding amine in 63 % yield; the protection of the hydroxy group of this amine with a *tert*-butyldimethylsilyl group afforded the *O*-protected derivative in 88 % yield; the reaction of the latter with 2-bromo-3-phenylpropionyl chloride **(5)** afforded **6d** in 68% yield, the global yield being 37 % from salicylaldehyde (Scheme 5). Once again, deprotection with tetrabutylammonium fluoride (TBAF) at 0°C gave directly the

cyclized derivative **(7d)** in good yield (71%).

Finally a methyl acetate substituent was also introduced on the 4-nitrogen starting from the glycine derivative **(9)**[20] which gave access to benzoxazepinone **(10)** (Scheme 8). Ester **(10)** was hydrolyzed into the corresponding acid, (LiOH/THF/H_2O/MeOH) in 99% yield, which was further reacted with 2-(4-pyridyl)ethylamine **(11)**[21] in presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) to afford **12** in 68% yield.



Scheme 8

Conclusions

We have synthesized 1,4-benzoxazepin-3-ones variously substituted in position –2 and -4; this scaffold can mimick peptidic backbone and therefore could be introduced as central scaffold in the synthesis of new potentially bioactive compounds.

EXPERIMENTAL

Melting points were determined using a Kofler hot stage apparatus and were uncorrected. NMR spectra were recorded on a Bruker instrument Avance DPX250 at 250 MHz (^{1}H) or 62.9 MHz (^{13}C NMR) in $CDCl_3$ or in DMSO-d_6. Chemical shifts (δ values) were reported in parts per million and coupling constants (*J* values) in Hz. IR spectra were recorded as a thin film on NaCl plates for the oils and in a KBr pellet for the solids on a Perkin-Elmer spectrophotometer FT Paragon 1000 PC. MS spectra were recorded on a Perkin-Elmer mass spectrometer Sciex API 300 (ionspray IS). Flash chromatography was performed on silica gel (Merk 60, 230-400 msh). TLC was performed on pre-coated silica gel plates (Merk 60, F_{254}, 0.25 mm). Organic solvents used were HPLC grade or were purified by standard procedure. All reagents were of commercial quality or were purified before use.

2-Chloro-*N*-(2-hydroxybenzyl)-*N*-(4-methoxyphenyl)acetamide (2) :To a mixture of **1a**[4] (694 mg, 3.03 mmol) and triethylamine (421 µL, 3.30 mmol) in dry dichloromethane (25 mL) at 0°C was added 2-chloroacetyl chloride (565 µL, 3.64 mmol) under argon atmosphere. The resulting solution was stirred at

0°C for 2 h and evaporated *in vacuo*. The residue was hydrolysed in water (10 mL) and extracted with ethyl acetate (2 x 10 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and evaporated *in vacuo*. The crude residue was chromatographed on silica gel, eluting with petroleum ether/ethyl acetate (70/30, v/v) affording compound **(2)** (858 mg, 93%) as a colorless solid; mp : 134°C (ethyl acetate–petroleum ether); IR (KBr, ν cm^{-1}) : 3154 (OH), 1611 (CO); ^{1}H NMR ($CDCl_3$) : δ 3.87 (s, 5H, CH_2Cl + OCH_3), 4.77 (s, 2H, CH_2N), 6.67 (dd, *J*= 1.9 Hz, *J*= 7.5 Hz, 1H, ArH), 6.73 (t, *J*= 7.5 Hz, 1H, ArH), 6.90-7.08 (m, 5H, ArH), 7.24 (dd, *J*= 1.9 Hz, *J*= 7.5 Hz, 1H, ArH), 9.04 (br s , 1H, OH); ^{13}C NMR ($CDCl_3$) : δ 41.4 (CH_2Cl), 51.7 (CH_2N), 55. 7 (CH_3O), 115.4 (2CH), 118.0 (CH), 119.6 (CH), 121.4 (C), 129.2 (2CH), 130.5 (CH), 132.0 (CH), 132.8 (C), 155.9 (C), 160.1 (C), 169.0 (CO). Anal. Calcd for $C_{16}H_{16}NO_3Cl$: C, 62.85; H, 5.27; N, 4.58. Found : C, 62.51; H, 5.15; N, 4.47; MS : m/z 306 (MH^+ [^{35}Cl]), 308 (MH^+ [^{37}Cl]).

4-(4-Methoxyphenyl)-2,3,4,5-tetrahydrobenz[*f*][1,4]oxazepin-3-one (3):

Procedure A (from compound **(2)** : To a stirred solution of **2** (713 mg, 2.33 mmol) in dry acetone (20 mL), was added potassium carbonate (964 mg, 6.99 mmol) and the resulting suspension was heated at reflux for 2 h under oxygen free argon atmosphere. After cooling, the reaction mixture was evaporated *in vacuo* and the residue diluted with water (20 mL) and extracted with ethyl acetate (2 x 10 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and evaporated *in vacuo*. The crude residue was chromatographed on silica gel, eluting with petroleum ether/ethyl acetate (60/40, v/v) to afford compound **(3)** (519 mg, quant.) as a colorless solid.

Procedure B (from compound **(1a)**: To a mixture of **1a**[4] (4.04 g, 17.6 mmol) and potassium carbonate (7.30 g, 52.9 mmol) in dry acetone (150 mL) at 0°C, was added 2-chloroacetyl chloride (1.6 mL, 19.4 mmol) under argon atmosphere. The resulting suspension was stirred at 0°C for 1 h and allowed to warm to rt and stirred for 18 h. Then the reaction mixture was heated to reflux for 2.5 h and after cooling, the precipitated product was filtered off. The filtrate was evaporated *in vacuo* and the residue taken up in dichloromethane (50 mL) and washed with water (50 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered and evaporated *in vacuo* to give **3** (4.50 g, 95%) as a colorless solid; mp : 175°C (methanol); IR (KBr, ν cm^{-1}) : 1665 (CO); ^{1}H NMR ($CDCl_3$) : δ 3.80 (s, 3H, OCH_3), 4.84 (s, 4H, CH_2N+CH_2O), 6.90 (dd, *J*= 2.8 Hz, *J*= 9.1 Hz, 2H, ArH), 7.06-7.18 (m, 4H, ArH), 7.32 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$) : δ 53.3 (OCH_2), 55.6 (OCH_3), 72.5 (NCH_2), 114.7 (2CH), 120.2 (CH), 123.8 (CH), 127.4 (2CH), 128.3 (C), 128.8 (CH), 130.4 (CH), 136.7 (C), 157.5 (C), 158.5 (C), 168.9 (CO). Anal. Calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found : C, 71.65; H, 5.50; N, 5.12; MS : m/z=270 (MH^+).

2-(*Z*)-Benzylidene-4-(4-methoxyphenyl)-2,3,4,5-tetrahydrobenz[*f*][1,4]oxazepin-3-one (4a): To a stirred solution of **7a** (303 mg, 0.84 mmol) in dry tetrahydrofuran (5 mL) at –78°C, was added dropwise 2M LDA (632 µL, 1.26 mmol) and the resulting solution was stirred for 1 h under argon atmosphere. At –

78°C was added dropwise 1,2-dibromo-1,1,2,2-tetrachloroethane (206 mg, 1.26 mmol) in dry tetrahydrofuran (5 mL) and the resulting mixture was further stirred at –78°C for 2.5 h. The reaction mixture was hydrolyzed with water (15 mL), extracted with ethyl acetate (2 x 10 mL) and washed with a solution of sodium hydrogensulfide (10 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and evaporated *in vacuo*. The crude residue was chromatographed on silica gel, eluting with petroleum ether/ethyl acetate (80/20, v/v) to afford compound **(4a)** (195 mg, 65%) as an yellow oil; IR (film, ν cm^{-1}) : 1658 (CO); ^{1}H NMR ($CDCl_3$) : δ 3.79 (s, 3H, OCH_3), 4.79 (s, 2H, NCH_2), 6.71 (s, 1H, =CH), 6.90 (dd, *J*= 2.0 Hz, *J*= 8.3 Hz, 2H, ArH), 7.06-7.16 (m, 4H, ArH), 7.23-7.42 (m, 5H, ArH), 7.84 (dd, *J*= 2.0 Hz, *J*= 8.3 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$) : δ 52.0 (CH_2N), 55.5 (OCH_3), 114.7 (2CH), 117.0 (CH), 120.4 (CH), 124.3 (CH), 127.4 (2CH), 127.9 (CH), 128.1 (CH), 128.5 (2CH), 129.4 (C), 130.1 (2CH), 130.2 (CH), 134.1 (C), 136.1 (C), 148.3 (C), 154.7 (C), 158.5 (C), 163.7 (CO). Anal. Calcd for $C_{23}H_{19}NO_3$: C, 77.29; H, 5.36; N, 3.92. Found : C, 77.60; H, 5.45; N, 4.06; MS : m/z 358 (MH^+), 380 ($M + Na^+$).

4-[{2-(*Z*)-Benzylidene-3-oxo-2,3,4,5-tetrahydrobenz[*f*][1,4]oxazepin-4-yl}]benzonitrile (4c): Similarly obtained as for **4a** starting from **7c**; reaction time 1.5 h; light brown solid m = 440 mg, 55%; mp : 186°C (ethyl acetate–petroleum ether); IR (KBr, ν cm^{-1}) : 2225 (CN), 1669 (CO); ^{1}H NMR ($CDCl_3$) : δ 4.90 (s, 2H, CH_2N), 6.75 (s, 1H, =CH), 7.10-7.36 (m, 4H, ArH), 7.39-7.45 (m, 5H, ArH), 7.69 (dd, *J*= 1.8 Hz, *J*= 8.1 Hz, 2H, ArH), 7.86 (dd, *J*= 1.8 Hz, *J*= 8.1 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$) : δ 51.4 (CH_2N), 110.6 (CN), 118.4 (C), 118.5 (CH), 120.6 (CH), 124.7 (CH), 126.7 (2CH), 127.9 (CH), 128.5 (C), 128.6 (CH), 128.7 (2CH), 130.2 (2CH), 130.8 (CH), 133.3 (2CH), 133.7 (C), 146.9 (C), 147.4 (C), 154.7 (C), 163.5 (CO). Anal. Calcd for $C_{23}H_{16}N_2O_2$: C, 78.39 ; H, 4.58 ; N, 7.95. Found : C, 78.45 ; H, 4.66 ; N, 8.06 ; MS : m/z 353 (MH^+), 375 ($M + Na^+$).

4-[2-(*Z*)-Benzylidene-3-oxo-2,3,4,5-tetrahydrobenz[*f*][1,4]oxazepin-4-yl]-*N'*-hydroxybenzamidine (4e): To a stirred solution of **4c** (866 mg, 2.45 mmol) in ethanol–water (300 mL, 1 : 1 v/v) was successively added hydroxylamine hydrochloride (768 mg, 11.1 mmol) and sodium carbonate (649 mg, 6.1 mmol). The resulting mixture was heated at reflux for 48 h and cooled to 0°C. The preciptated product was filtered off to give **4e** (566 mg) as a colorless solid. The filtrate was concentrated *in vacuo* and the crude residue was chromatographed on silica gel, eluting with dichloromethane/ethyl acetate (50/50, v/v) to give compound **(4e)** (182 mg) as a colorless solid in a total yield of 81%; mp : 223°C (methanol); IR (KBr, ν cm^{-1}) : 3424 (OH, NH), 1663 (CO); ^{1}H NMR (DMSO-d_6) : δ 4.98 (s, 2H, CH_2N), 5.85 (s, 2H, NH_2), 6.58 (s, 1H, =CH), 7.15 (dd, *J*= 1.1 Hz, *J*= 7.5 Hz, 1H, ArH), 7.25 (d, *J*= 8.5 Hz, 2H, ArH), 7.31-7.46 (m, 6H, ArH), 7.70 (d, *J*= 8.5 Hz, 2H, ArH), 7.86 (d, *J*= 7.5 Hz, 2H, ArH), 9.67 (s, 1H, OH); ^{13}C NMR (DMSO-d_6) : δ 50.3 (CH_2N), 115.7 (CH), 119.4 (CH), 124.3 (CH), 125.37 (CH), 125.44 (CH), 126.1 (CH), 128.2 (CH), 128.3 (CH), 128.4 (C), 128.7 (2CH), 128.8 (CH), 129.7 (2CH), 130.3 (CH), 131.7 (C), 133.6 (C),

142.7 (C), 148.1 (C), 150.3 (C), 153.9 (CN), 162.6 (CO). Anal. Calcd for $C_{23}H_{19}N_3O_3$: C, 71.68; H, 4.97; N, 10.90. Found : C, 71.39; H, 5.13; N, 11.04; MS : m/z 386.5 (MH^+).

4-[{2-(*Z*)-Benzylidene-3-oxo-2,3,4,5-tetrahydrobenz[*f*][1,4]oxazepin-4-yl}]benzamide (4f): To a stirred solution of **4c** (134 mg, 0.38 mmol) in dry toluene (1 mL) was added dropwise a freshly prepared solution of 1.25 M methylchloroaluminium amide (320 µL, 0.38 mmol) under argon atmosphere and the resulting solution was heated at reflux for 24 h. The cooled mixture was filtered to give **4f** (30 mg, 20%) as a light pink solid; mp: 194°C (ethyl acetate–petroleum ether); IR (KBr, ν cm^{-1}) : 3392 (NH), 1690 (CO); ^{1}H NMR (DMSO-d_6) : δ 4.88 (s, 2H, CH_2N), 6.81 (s, 1H, =CH), 7.16-7.37 (m, 4H, ArH), 7.40-7.51 (m, 5H, ArH), 7.65 (dd, *J*= 1.7 Hz, *J*= 8.3 Hz, 2H, ArH), 7.74 (dd, *J*= 1.7 Hz, *J*= 8.3 Hz, 2H, ArH), 7.98 (br s, 2H, NH_2); ^{13}C NMR (DMSO-d_6) : δ 52.4 (CH_2N), 118.4 (C), 118.6 (CH), 120.4 (CH), 121.6 (CH), 123.0 (C), 125.1 (2CH), 126.3 (CH), 128.1 (2CH), 128.2 (2CH), 129.3 (CH), 129.6 (CH), 129.7 (2CH), 132.0 (C), 137.6 (C), 145.1 (C), 156.2 (C), 167.2 (CO), 168.8 (CO). Anal. Calcd for $C_{23}H_{18}N_2O_3$: C, 74.58; H, 4.90; N, 7.56. Found : C, 74.87; H, 5.03; N, 7.68; MS : m/z 371 (MH^+), 393 ($M + Na^+$).

2-Bromo-*N*-(2-hydroxybenzyl)-*N*-(4-methoxyphenyl)-3-phenylpropionamide (6a): To a stirred solution of **1a**[4] (232 mg, 1.01 mmol) in dry dichloromethane (6 mL) at 0°C was added dropwise 2-bromo-3-phenylpropionyl chloride **(5)**[8] (625 mg, 2.52 mmol) in dry dichloromethane (10 mL) and triethylamine (141 µL, 1.01 mmol) under oxygen free argon atmosphere. The resulting solution was allowed to warm to rt and stirred for 24 h. The mixture was hydrolysed with water (20 mL) and the aqueous layer extracted with dichloromethane (2 x 10 mL). The combined extracts were dried over anhydrous magnesium sulfate, filtered and evaporated *in vacuo*. The crude residue was chromatographed on silica gel, eluting with petroleum ether/ethyl acetate (80/20, v/v) to afford compound **(6a)** (246 mg, 56%) as an yellow oil; IR (film, ν cm^{-1}) : 3205 (OH), 1690 (CO); ^{1}H NMR ($CDCl_3$) : δ 3.10 (dd, *J*= 4.7 Hz, *J*= 13.0 Hz, 1H, CH_2Ph), 3.59 (dd, *J*= 11.0 Hz, *J*= 13.0 Hz, 1H, CH_2Ph), 3.85 (s, 3H, OCH_3), 4.20 (dd, *J*= 4.7 Hz, *J*= 11.0 Hz, 1H, CHBr), 4.31 (d, *J*= 14.3 Hz, 1H, CH_2N), 5.02 (d, *J*= 14.3 Hz, 1H, CH_2N), 6.51 (dd, *J*= 1.6 Hz, *J*= 7.6 Hz, 1H, ArH), 6.62-6.64 (m, 1H, ArH), 6.89 (dd, *J*= 1.6 Hz, *J*= 7.6 Hz, 1H, ArH), 6.94 (d, *J*= 6.9 Hz, 1H, ArH), 7.03-7.33 (m, 8H, ArH), 9.38 (s, 1H, OH); ^{13}C NMR ($CDCl_3$) : δ 41.7 (CH_2Ph), 42.7 (CHBr), 51.3 (CH_2N), 55.5 (OCH_3), 114.9 (CH), 117.8 (2CH), 119.2 (2CH), 121.3 (C), 126.1 (CH), 127.4 (2CH), 129.5 (3CH), 130.3 (CH), 131.9 (CH), 132.6 (C), 136.6 (C), 155.9 (C), 159.7 (C), 171.1 (CO). Anal. Calcd for $C_{23}H_{22}NO_3Br$: C, 62.74; H, 5.04; N, 3.18. Found : C, 62.97; H, 4.91; N, 3.33; MS : m/z 440.5 (MH^+ [^{79}Br]), 442.5 (MH^+ [^{81}Br]), 462.5 (M[^{79}Br] + Na^+), 464.5 (M[^{81}Br] + Na^+).

2-Bromo-*N*-(2-hydroxybenzyl)-*N*-(4-iodophenyl)-3-phenylpropionamide (6b): Similarly obtained as for **6a** starting from **1b**.[4] Reaction time 3.5 h; yellow oil m =185 mg, 43%; IR (film, ν cm^{-1}) : 3174 (OH), 1642 (CO); ^{1}H NMR ($CDCl_3$) : δ 3.06 (dd, *J*= 4.6 Hz, *J*= 12.9 Hz, 1H, CH_2Ph), 3.56 (dd, *J*= 11.2 Hz, *J*= 12.9 Hz, 1H, CH_2Ph), 4.06 (dd, *J*= 4.6 Hz, *J*= 11.2 Hz, 1H, CHBr), 4.26 (d, *J*= 14.3 Hz, 1H, CH_2N), 4.98

(d, *J*= 14.3 Hz, 1H, CH_2N), 6.43 (dd, *J*= 1.4 Hz, *J*= 7.5 Hz, 1H, ArH), 6.63 (dd, *J*= 1.4 Hz, *J*= 7.5 Hz, 1H, ArH), 7.00-7.27 (m, 11H, ArH), 9.15 (s, 1H, OH); ^{13}C NMR ($CDCl_3$) : δ 41.7 (CH_2Ph), 42.5 (CHBr), 51.1 (CH_2N), 95.1 (C), 118.0 (CH), 119.4 (CH), 120.8 (C), 127.5 (2CH), 128.8 (3CH), 129.5 (3CH), 130.5 (CH), 131.8 (2CH), 136.5 (C), 139.7, (C), 155.9 (C), 170.6 (CO). Anal. Calcd for $C_{22}H_{19}NO_2BrI$: C, 49.28 ; H, 3.57 ; N, 2.61. Found : C, 49.66; H, 3.66; N, 2.73; MS : m/z 536 (MH^+ [^{79}Br]), 538 (MH^+ [^{81}Br]), 558 (M[^{79}Br] + Na^+), 560 (M[^{81}Br] + Na^+).

2-Bromo-*N*-[2-(*tert*-butyldimethylsilyloxy)benzyl]-*N*-(4-cyanophenyl)-3-phenylpropionamide (6c):

4-[2-(tert-Butyldimethylsilyloxy)benzylamino]benzonitrile : To a stirred solution of **1c**[4] (992 mg, 4.42 mmol) in dry dichloromethane (10 mL) at 0°C, was added diisopropylethylamine (857 mg, 6.64 mmol) and the resulting solution was stirred at 10°C for 10 min. At 0°C, was added a solution of *tert*-butyldimethylsilyl chloride (866 mg, 5.75 mmol) in dry dichloromethane (5 mL) and the reaction mixture was allowed to warm to rt and stirred for 18 h. Solvent was removed *in vacuo* and the crude residue was chromatographed on silica gel, eluting with petroleum ether/ ethyl acetate (90/10, v/v) to afford 4-[2-(*tert*-butyldimethylsilyloxy)benzylamino]benzonitrile (1.34 g, 96%) as a pale yellow oil; IR (film, ν cm^{-1}) : 3377 (NH), 2213 (CN); ^{1}H NMR ($CDCl_3$) : δ 0.26 (s, 6H, $Si(CH_3)_2$), 0.99 (s, 9H, $(CH_3)_3$), 4.33 (d, *J*= 5.7 Hz, 2H, CH_2N), 4.56 (br s, 1H, NH), 6.57 (dd, *J*= 2.2 Hz, *J*= 8.8 Hz, 2H, ArH), 6.85 (dd, *J*= 1.2 Hz, *J*= 7.7 Hz, 1H, ArH), 6.93 (dd, *J*= 1.2 Hz, *J*= 7.7 Hz, 1H, ArH), 7.15-7.27 (m, 2H, ArH), 7.41 (dd, *J*= 2.2 Hz, *J*= 8.8 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$) : δ -4.1 ($Si(CH_3)_2$), 18.2 ($\underline{C}(CH_3)_3$), 25.7 ($C(\underline{C}H_3)_3$), 43.0 (CH_2N), 98.4 (CN), 112.3 (2CH), 118.6 (CH), 120.6 (C), 121.3 (CH), 128.1 (C), 128.6 (CH), 128.9 (CH), 133.6 (2CH), 151.4 (C), 153.6 (C). Anal. Calcd for $C_{20}H_{26}N_2OSi$: C, 70.96; H, 7.74; N, 8.28. Found : C, 71.29; H, 7.60; N, 8.37; MS : m/z 339 (MH^+).

*2-Bromo N-[2-(tert-butyldimethylsilyloxy)benzyl]-N-(4-cyanophenyl)-3-phenylpropionamide (**6c**)* To a stirred solution of 4-[2-(*tert*-butyldimethylsilyloxy)benzylamino]benzonitrile (1.30 g, 3.84 mmol) in dry dichloromethane (15 mL) at 0°C was added dropwise *via* syringe, a solution of 2-bromo-3-phenylpropionyl chloride **(5)**[8] (1.42 g, 5.8 mmol) in dry dichloromethane (20 mL) and triethylamine (800 µL, 5.80 mmol) under argon atmosphere. The resulting solution was allowed to warm to rt and stirred for 24 h. The mixture was hydrolysed with water (20 mL) and aqueous layer extracted with dichloromethane (2 x 10 mL). The combined extracts were dried over anhydrous magnesium sulfate, filtered and evaporated *in vacuo*. The crude residue was chromatographed on silica gel, eluting with petroleum ether/ethyl acetate (80/20, v/v) to give compound **(6c)** (850 mg, 40%) as an orange oil; IR (film, ν cm^{-1}) : 2230 (CN), 1686 (CO); ^{1}H NMR ($CDCl_3$, rotamer A) : δ 0.03 (s, 3H, $Si(CH_3)_2$), 0.06 (s, 3H, $Si(CH_3)_2$), 0.82 (s, 9H, $(CH_3)_3$), 3.05 (dd, *J*= 4.1 Hz, *J*= 12.4 Hz, 1H, CH_2Ph), 3.51 (dd, *J*= 10.6 Hz, *J*= 12.4 Hz, 1H, CH_2Ph), 4.07-4.14 (m, 1H, CHBr), 4.75 (d, *J*= 14.8 Hz, 1H, CH_2N), 4.97 (d, *J*= 14.8 Hz, 1H, CH_2N), 6.65 (m, 3H, ArH), 6.81 (t, *J*= 7.3 Hz, 1H, ArH), 6.97-7.13 (m, 4H, ArH), 7.26-7.34 (m, 3H, ArH), 7.46 (d, *J*= 8.2 Hz, 2H, ArH); ^{1}H NMR

($CDCl_3$, rotamer B) : δ 0.04 (s, 3H, $Si(CH_3)_2$), 0.10 (s, 3H, $Si(CH_3)_2$), 0.83 (s, 9H, $(CH_3)_3$), 3.12 (dd, *J*= 4.1 Hz, *J*= 12.5 Hz, 1H, CH_2Ph), 3.62 (dd, *J*= 10.6 Hz, *J*= 12.5 Hz, 1H, CH_2Ph), 4.07-4.14 (m, 1H, CHBr), 4.77 (d, *J*= 14.5 Hz, 1H, CH_2N), 4.97 (d, *J*= 14.5 Hz, 1H, CH_2N), 6.65 (ml, 3H, ArH), 6.81 (t, *J*= 7.3 Hz, 1H, ArH), 6.97-7.13 (m, 4H, ArH), 7.26-7.34 (m, 3H, ArH), 7.46 (d, *J*= 8.2 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, rotamer A) : δ -4.5 ($Si(CH_3)_2$), 17.9 ($\underline{C}(CH_3)_3$), 25.5 ($C(\underline{C}H_3)_3$), 41.1 (CH_2), 42.9 (CHBr), 46.9 (CH_2Ph), 112.2 (CN), 117.6 (C), 118.2 (CH), 121.3 (CH), 127.3 (CH), 128.4 (CH), 128.5 (2CH), 128.6 (2CH), 129.0 (CH), 129.5 (CH), 129.6 (CH), 129.7 (CH), 133.1 (CH), 135.9 (C), 136.8 (C), 144.7 (C), 153.1 (C), 167.6 (CO); ^{13}C NMR ($CDCl_3$, rotamer B) : δ -4.5 ($Si(CH_3)_2$), 17.9 ($\underline{C}(CH_3)_3$), 25.5 ($C(\underline{C}H_3)_3$), 41.4 (CH_2), 42.9 (CHBr), 46.9 (CH_2Ph), 112.2 (CN), 117.6 (C), 118.2 (CH), 121.3 (CH), 127.3 (CH), 128.4 (CH), 128.5 (2CH), 128.6 (2CH), 129.0 (CH), 129.5 (CH), 129.6 (CH), 129.7 (CH), 133.1 (CH), 135.9 (C), 136.8 (C), 144.7 (C), 153.1 (C), 167.6 (CO). Anal. Calcd for $C_{29}H_{33}N_2O_2BrSi$: C, 63.38; H, 6.05; N, 5.10. Found : C, 63.66; H, 5.94; N, 5.23; MS : m/z 549.5 (MH^+ [^{79}Br]), 551.5 (MH^+ [^{81}Br]), 571.5 (M[^{79}Br] + Na^+), 573.5 (M[^{81}Br] + Na^+).

2-Bromo-*N*-[2-(*tert*-butyldimethylsilyloxy)benzyl]-*N*-2'-(*tert*-butylsulfamoylbiphenyl-4-yl)-3-phenyl-propionamide (6d):

4'-(2-Hydroxybenzylamino)biphenyl-2-N-tert-butylsulfonamide: To a stirred solution of salicylaldehyde (208 mg, 1.70 mmol) in dry ethanol (5 mL) was added 4'-amino[1,1-biphenyl]-2-*tert*-butylsulfonamide **8**[18,19] (519 mg, 1.70 mmol) in dry ethanol (5 mL) under argon atmosphere and the resulting mixture was heated at reflux for 30 min. Sodium borohydride (64.3 mg, 1.70 mmol) was added portionwise at 0°C, and the resulting solution was allowed to warm to rt and stirred for 16 h. After cooling, the reaction mixture was evaporated *in vacuo*. The residue was dissolved in ethyl acetate (20 mL) and washed with water (10 mL) and brine (10 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered and evaporated *in vacuo*. The crude residue was chromatographed on silica gel, eluting with petroleum ether/ethyl acetate (80/20, v/v) to give an yellow solid (440 mg, 63%); mp : 124°C (ethyl acetate–petroleum ether); IR (KBr, ν cm^{-1}) : 3444, 3395, 3349 (OH, NH); ^1H NMR ($CDCl_3$) : δ 0.97 (s, 9H, $(CH_3)_3$), 3.69 (s, 1H, NH or OH), 4.33 (br s, 1H, NH or OH), 4.43 (s, 2H, CH_2N), 6.84-6.91 (m, 4H, ArH), 7.17-7.23 (m, 2H, ArH), 7.28 (dd, *J*= 1.6 Hz, *J*= 7.5 Hz, 1H, ArH), 7.33 (d, *J*= 8.8 Hz, 2H, ArH), 7.44 (dd, *J*= 1.5 Hz, *J*= 7.5 Hz, 1H, ArH), 7.53 (dd, *J*= 1.5 Hz, *J*= 7.5 Hz, 1H, ArH), 7.87 (br s, 1H, NH or OH), 8.13 (dd, *J*= 1.5 Hz, *J*= 7.5 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$) : δ 29.8 ($C(\underline{C}H_3)_3$), 47.4 (CH_2N), 54.4 ($\underline{C}(CH_3)_3$), 114.8 (2CH), 116.5 (CH), 120.3 (CH), 123.2 (C), 127.5 (CH), 128.1 (CH), 129.0 (CH), 129.2 (CH), 130.6 (C), 130.9 (2CH), 131.9 (CH), 132.6 (CH), 139.9 (C), 142.2 (C), 147.7 (C), 156.1 (C). Anal. Calcd for $C_{23}H_{26}N_2O_3S$: C, 67.29; H, 6.38; N, 6.82. Found : C, 67.55; H, 6.54 ; N, 6.67; MS : m/z 411.5 (MH^+), 433.5 (M + Na^+).

4'-[2-(tert-Butyldimethylsilyloxy)benzylamino]biphenyl-2-N-tert-butylsulfonamide: To a stirred solution of

4'-(2-hydroxybenzylamino)biphenyl-2-*N*-*tert*-butylsulfonamide (55 mg, 0.13 mmol) in dry dichloromethane (2 mL) at 0°C, was added diisopropylethylamine (26 mg, 0.20 mmol) and the resulting solution was stirred at 10°C for 10 min under argon atmosphere. At 0°C, was added *tert*-butyldimethylsilyl chloride (26 mg, 0.17 mmol) in dry dichloromethane (0.5 mL) and the reaction mixture was allowed to warm to rt and stirred for 20 h. Solvents were removed *in vacuo* and the crude residue was chromatographed on silica gel, eluting with petroleum ether/ethyl acetate (90/10, v/v) to afford a colorless oil (62 mg, 88%); IR (film, ν cm^{-1}) : 3429 (NH); ^{1}H NMR ($CDCl_3$) : δ 0.28 (s, 6H, $Si(CH_3)_2$), 0.94 (s, 9H, $(CH_3)_3$), 1.02 (s, 9H, $(CH_3)_3$), 3.65 (s, 1H, NH), 4.27 (br s, 2H, CH_2), 4.35 (br s, 1H, NH), 6.70 (dd, *J*= 1.5 Hz, *J*= 7.8 Hz, 2H, ArH), 6.84 (dd, *J*= 1.5 Hz, *J*= 7.8 Hz, 1H, ArH), 6.90 (dd, *J*= 1.5 Hz, *J*= 7.8 Hz, 1H, ArH), 7.16 (dd, *J*= 1.5 Hz, *J*= 7.8 Hz, 1H, ArH), 7.25-7.37 (m, 4H, ArH), 7.42 (dd, *J*= 1.5 Hz, *J*= 7.8 Hz, 1H, ArH), 7.51 (dd, *J*= 1.5 Hz, *J*= 7.8 Hz, 1H, ArH), 8.13 (dd, *J*= 1.5 Hz, *J*= 7.8 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$) : δ -3.9 ($Si(CH_3)_2$), 18.4 ($\underline{C}(CH_3)_3$), 25.9 ($C(\underline{C}H_3)_3$), 29.8 ($C(\underline{C}H_3)_3$), 43.7 (CH_2N), 54.3 ($\underline{C}(CH_3)_3$), 112.6 (2CH), 118.7 (CH), 121.3 (CH), 127.2 (CH), 127.8 (C), 128.0 (CH), 128.4 (CH), 129.2 (CH), 130.9 (2CH), 131.8 (CH), 132.6 (CH), 132.7 (C), 140.2 (C), 142.3 (C), 148.4 (C), 153.8 (C). Anal. Calcd for $C_{29}H_{40}N_2O_3SSi$: C, 66.37; H, 7.68; N, 5.34. Found : C, 66.03; H, 7.87; N, 5.21; MS : m/z 525.5 (MH^+).

*2-Bromo-N-[2-(tert-butyldimethylsilyloxy)benzyl]-N-2'-(tert-butylsulfamoylbiphenyl-4-yl)-3-phenyl-propionamide (**6d**):* To a stirred solution of 4'-[2-(*tert*-butyldimethylsilyloxy)benzylamino]biphenyl-2-*N*-*tert*-butylsulfonamide (1.13 g, 2.14 mmol) in dry dichloromethane (20 mL) at 0°C was added dropwise 2-bromo-3-phenylpropionyl chloride **(5)**[8] (795 mg, 3.2 mmol) in dry dichloromethane (15 mL) and triethylamine (445 µL, 3.20 mmol) under argon atmosphere. The resulting solution was allowed to warm to rt and stirred for 16 h. The mixture was hydrolysed with water (40 mL) and aqueous layer extracted with dichloromethane (2 x 20 mL). The combined extracts were dried over anhydrous magnesium sulfate, filtered and evaporated *in vacuo*. The crude residue was chromatographed on silica gel, eluting with petroleum ether/ethyl acetate (90/10, v/v) to give compound **(6d)** (1.07 g, 68%) as a colorless solid; mp : 80°C (ethyle acetate–petroleum ether); IR (KBr, ν cm^{-1}) : 3280 (NH), 1671 (CO); ^{1}H NMR ($CDCl_3$) : δ 0.10 (s, 3H, $Si(CH_3)_2$), 0.12 (s, 3H, $Si(CH_3)_2$), 0.90 (s, 9H, $(CH_3)_3$), 0.93 (s, 9H, $(CH_3)_3$), 3.17 (dd, *J*= 5.3 Hz, *J*= 13.2 Hz, 1H, CH_2Ph), 3.35 (s, 1H, NH), 3.64 (dd, *J*= 10.1 Hz, *J*= 13.2 Hz, 1H, CH_2Ph), 4.31 (dd, *J*= 5.3 Hz, *J*= 10.1 Hz, 1H, CHBr), 4.85 (d, *J*= 15.0 Hz, 1H, CH_2N), 5.03 (d, *J*= 15.0 Hz, 1H, CH_2N), 6.65-6.86 (m, 4H, ArH), 6.97-7.10 (m, 2H, ArH), 7.16-7.20 (m, 2H, ArH), 7.25 (dd, *J*= 1.6 Hz, *J*= 7.7 Hz, 1H, ArH), 7.40-7.59 (m, 7H, ArH), 8.16 (dd, *J*= 1.6 Hz, *J*= 7.7 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$) : δ -4.2 ($Si(CH_3)_2$), 18.2 ($\underline{C}(CH_3)_3$), 25.8 ($C(\underline{C}H_3)_3$), 29.8 ($C(\underline{C}H_3)_3$), 41.6 (CHBr), 43.6 (CH_2Ph), 47.6 (CH_2N), 54.4 ($\underline{C}(CH_3)_3$), 118.5 (CH), 121.3 (CH), 126.5 (C), 127.4 (CH), 127.7 (2CH), 128.2 (2CH), 128.5 (CH), 128.8 (2CH), 129.5 (CH), 129.7 (2CH), 131.0 (2CH), 132.0 (CH), 132.0 (CH), 137.2 (C), 138.8 (C), 139.8 (C), 141.1 (C), 142.1 (C), 153.3 (C), 168.4 (CO). Anal. Calcd for $C_{38}H_{47}N_2O_4BrSSi$: C, 62.03; H, 6.44; N,

3.81. Found : C, 62.30; H, 6.59; N, 3.68; MS : m/z 735.5 (MH^+ [^{79}Br]), 737.5 (MH^+ [^{81}Br]), 757.5 (M[^{79}Br] + Na^+), 759.5 (M[^{81}Br] + Na^+).

2-Benzyl-4-(4-methoxyphenyl)-2,3,4,5-tetrahydrobenz[*f*][1,4]oxazepin-3-one (7a): To a vigourously stirred solution of **6a** (421 mg, 0.96 mmol) in dry acetone (20 mL) was added potassium carbonate (396 mg, 2.87 mmol) and the resulting solution was heated at reflux for 3 h. After cooling, the reaction mixture was evaporated *in vacuo* and the residue was taken up in ethyl acetate (10 mL) and washed with water (10 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered and evaporated *in vacuo*. The crude residue was chromatographed on silica gel, eluting with petroleum ether/ethyl acetate (90/10, v/v) affording compound **(7a)** (311 mg, 90%) as a beige solid; mp : 138°C (ethyl acetate–petroleum ether); IR (KBr, ν cm^{-1}): 1674 (CO); ^{1}H NMR ($CDCl_3$) : δ 3.39 (dd, *J*= 7.0 Hz, *J*= 14.2 Hz, 1H, CH_2Ph), 3.49 (dd, *J*= 4.6 Hz, *J*= 14.2 Hz, 1H, CH_2Ph), 3.80 (s, 3H, OCH_3), 4.48 (d, *J*= 15.8 Hz, 1H, CH_2N), 4.94 (d, *J*= 15.8 Hz, 1H, CH_2N), 5.27 (dd, *J*= 4.6 Hz, *J*= 7.0 Hz, 1H, CH), 6.89-7.10 (m, 6H, ArH), 7.24-7.49 (m, 7H, ArH); ^{13}C NMR ($CDCl_3$) : δ 38.6 (CH_2Ph), 53.5 (CH_2N), 55.6 (OCH_3), 80.3 (CH), 114.6 (2CH), 120.3 (CH), 122.9 (CH), 126.5 (C), 126.8 (CH), 127.3 (2CH), 128.3 (2CH), 128.7 (CH), 129.9 (CH), 130.2 (2CH), 136.7 (C), 137.6 (C), 156.9 (C), 158.4 (C), 169.6 (CO). Anal. Calcd for $C_{23}H_{21}NO_3$: C, 76.86; H, 5.89; N, 3.90. Found : 76.54; 5.78; 3.74; MS : m/z 360.5 (MH^+).

2-Benzyl-4-(4-iodophenyl)-2,3,4,5-tetrahydrobenz[*f*][1,4]oxazepin-3-one (7b): Similarly obtained as for **7a** starting from **6b**, reaction time 7 h; yellow solid; m =112 mg, 73%; mp : 160°C (ethyl acetate–petroleum ether); IR (KBr, ν cm^{-1}) : 1690 (CO); ^{1}H NMR ($CDCl_3$) : δ 3.38 (dd, *J*= 6.8 Hz, *J*= 16.0 Hz, 1H, CH_2Ph), 3.49 (dd, *J*= 4.5 Hz, *J*= 16.0 Hz, 1H, CH_2Ph), 4.53 (d, *J*= 15.8 Hz, 1H, NCH_2), 4.94 (d, *J*= 15.8 Hz, 1H, NCH_2), 5.25 (dd, *J*= 4.5 Hz, *J*= 6.8 Hz, 1H, CH), 6.94 (dd, *J*= 2.4 Hz, *J*= 8.8 Hz, 2H, ArH), 7.00-7.10 (m, 3H, ArH), 7.28-7.49 (m, 6H, ArH), 7.73 (dd, *J*= 2.4 Hz, *J*= 8.8 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$) : δ 38.4 (CH_2Ph), 53.0 (NCH_2), 80.1 (CH), 91.9 (C), 120.3 (CH), 123.0 (CH), 125.8 (C), 126.8 (CH), 128.1 (2CH), 128.3 (2CH), 128.5 (CH), 130.0 (CH), 130.1 (2CH), 137.3 (C), 138.3 (2CH), 143.2 (C), 156.7 (C), 169.2 (CO). Anal. Calcd for $C_{22}H_{18}NO_2I$: C, 58.04; H, 3.98; N, 3.08. Found : C, 57.81; H, 3.85; N, 2.94; MS : m/z 456 (MH^+), 478 (M + Na^+).

4-(2-Benzyl-3-oxo-2,3,4,5-tetrahydrobenz[*f*][1,5]oxazepin-4-yl)benzonitrile (7c):

*From **7b*** : To a stirred solution of **7b** (1.35 g, 2.97 mmol) in deoxygenated acetonitrile (100 mL) was successively added sodium cyanide (291 mg, 5.93 mmol), freshly prepared tetrakis-(triphenylphosphine)palladium (514 mg, 0.45 mmol) and copper(I) iodide (85 mg, 0.45 mmol) under argon atmosphere. The resulting solution was heated at reflux for 3.5 h and the mixture was cooled to room temperature and hydrolysed with water (50 mL). The aqueous layer was extracted with ethyl acetate (2 x 25 mL) and washed with brine (20 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and evaporated *in vacuo*. The crude residue was chromatographed on silica

gel, eluting with petroleum ether/ethyl acetate (70/30, v/v) to afford compound **(7c)** (798 mg, 76%) as light yellow solid.

*From **6c*** : To a stirred solution of **6c** (850 mg, 1.55 mmol) in dry dichloromethane (10 mL) at 0°C, was added dropwise 1M tetrabutylammonium fluoride (2.64 mL, 2.64 mmol) in dichloromethane under argon atmosphere and the resulting mixture was stirred at 0°C for 3.5 h. Solvents were removed *in vacuo* and the residue was taken up in dichloromethane (10 mL) and washed with water (10 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered and evaporated *in vacuo*. The crude residue was chromatographed on silica gel, eluting with petroleum ether/ethyl acetate (80/20, v/v) to give compound **(7c)** (402 mg, 73%) as a light yellow solid; mp : 159°C (ethyl acetate–petroleum ether); IR (KBr, ν cm^{-1}) : 2226 (CN), 1693 (CO); ^{1}H NMR ($CDCl_3$) : δ 3.32 (dd, *J*= 6.6 Hz, *J*= 14.3 Hz, 1H, CH_2Ph), 3.44 (dd, J_1= 4.8 Hz, J_2= 14.3 Hz, 1H, CH_2Ph), 4.53 (d, *J*= 16.0 Hz, 1H, CH_2N), 4.53 (d, *J*= 16.0 Hz, 1H, CH_2N), 5.24 (dd, *J*= 4.8 Hz, *J*= 6.6 Hz, 1H, CH), 6.96-7.08 (m, 3H, ArH), 7.24-7.31 (m, 8H, ArH), 7.63 (d, *J*= 8.5 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$) : δ 38.3 (CH_2Ph), 52.9 (CH_2N), 79.9 (CH), 110.3 (CN), 118.4 (C), 120.3 (CH), 123.1 (CH), 125.1 (C), 126.6 (2CH), 126.9 (CH), 128.4 (2CH), 128.6 (CH), 130.1 (2CH), 130.3 (CH), 133.1 (2CH), 137.1 (C), 147.2 (C), 156.7 (C), 169.3 (CO). Anal. Calcd for $C_{23}H_{18}N_2O_2$: C, 77.95; H, 5.12; N, 7.90. Found : C, 78.22; H, 5.23; N, 7.99; MS : m/z 355 (MH^+), 372 ($M + NH_4^+$), 377 ($M + Na^+$).

4'-(2-Benzyl-3-oxo-2,3,4,5-tetrahydrobenz[*f*][1,4]oxazepin-4-yl)biphenyl-2-*N*-*tert*-butylsulfonamide (7d): To a stirred solution of **6d** (1.07 g, 1.45 mmol) in dry dichloromethane (20 mL) at 0°C, was added slowly a 1M Bu_4NF in dry dichloromethane (1.45 mL, 1.45 mmol) under argon atmosphere and the resulting mixture was stirred at 0°C for 2.5 h. Solvents were removed *in vacuo* and the residue was taken up in dichloromethane (10 mL) and washed with water (10 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered and evaporated *in vacuo*. The crude residue was chromatographed on silica gel, eluting with petroleum ether/ethyl acetate (90/10, v/v) to give compound **(7d)** (552 mg, 71%) as a colorless solid; mp : 94°C (ethyl acetate–petroleum ether); IR (KBr, ν cm^{-1}) : 1682 (CO); ^{1}H NMR ($CDCl_3$) : δ 1.02 (s, 9H, $(CH_3)_3$), 3.36 (dd, *J*= 6.8 Hz, *J*= 14.3 Hz, 1H, CH_2Ph), 3.46 (dd, *J*= 4.5 Hz, *J*= 14.3 Hz, 1H, CH_2Ph), 3.75 (s, 1H, NH), 4.58 (d, *J*= 16.0 Hz, 1H, CH_2N), 5.00 (d, *J*= 16.0 Hz, 1H, CH_2N), 5.25 (dd, *J*= 4.5 Hz, *J*= 6.8 Hz, 1H, CH), 6.96-7.10 (m, 3H, ArH), 7.22-7.38 (m, 7H, ArH). 7.42-7.60 (m, 6H, ArH), 8.17 (dd, *J*= 1.6 Hz, *J*= 7.8 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$) : δ 29.9 ($C(\underline{C}H_3)_3$), 38.6 (CH_2Ph), 53.3 (CH_2N), 54.6 ($\underline{C}(CH_3)_3$), 80.3 (CH), 120.4 (CH), 123.1 (CH), 125.8 (2CH), 126.0 (C), 126.9 (CH), 128.1 (CH), 128.4 (3CH), 128.6 (CH), 130.1 (CH), 130.2 (2CH), 130.8 (2CH), 132.0 (CH), 132.4 (CH), 137.5 (C), 138.2 (C), 139.3 (C), 142.3 (C), 143.6 (C), 156.9 (C), 169.5 (CO). Anal. Calcd for $C_{32}H_{32}N_2O_4S$: C, 71.09; H, 5.97; N, 5.18. Found : 71.44; H, 6.15; N, 5.33; MS : m/z 541 (MH^+), 558.5 ($M + NH_4^+$), 563 ($M + Na^+$).

4-(2-Benzyl-3-oxo-2,3,4,5-tetrahydrobenz[*f*][1,4]oxazepin-4-yl)-*N*'-hydroxybenzamidine (7e): To a stirred solution of **7c** (700 mg, 1.81 mmol) in ethanol–water (200 mL, 1 : 1 v/v) was successively added hydroxylamine hydrochloride (465 mg, 6.7 mmol) and sodium carbonate (326 mg, 3.1 mmol). The resulting mixture was heated at reflux for 24 h and evaporated *in vacuo*. The crude residue was chromatographed on silica gel, eluting with dichloromethane/ethyl acetate (10/90, v/v) to afford compound **(7e)** (386 mg, 55%) as a colorless solid; mp : 189°C (methanol); IR (KBr, ν cm^{-1}) : 3353 (OH, NH), 1677 (CO); ^{1}H NMR (DMSO-d_6) : δ 2.45 (dd, *J*= 8.6 Hz, *J*= 14.5 Hz, 1H, CH_2Ph), 2.57 (dd, *J*= 3.8 Hz, *J*= 14.5 Hz, 1H, CH_2Ph), 3.80 (d, *J*= 17.0 Hz, 1H, CH_2N), 5.06 (d, *J*= 17.0 Hz, 1H, CH_2N), 4.98 (dd, *J*= 3.8 Hz, *J*= 8.6 Hz, 1H, CH), 6.18 (d, *J*= 7.8 Hz, 1H, ArH), 6.29 (t, *J*= 7.2 Hz, 1H, ArH), 6.52-6.78 (m, 9H, ArH), 7.02 (d, *J*= 8.5 Hz, 2H, ArH); ^{13}C NMR (DMSO-d_6) : δ 37.4 (CH_2Ph), 53.4 (CH_2N), 77.6 (CH), 119.4 (CH), 122.6 (2CH), 123.7 (C), 126.1 (2CH), 126.8 (2CH), 127.2 (CH), 128.9 (2CH), 130.2 (CH), 130.3 (2CH), 131.6 (C), 138.1 (C), 144.0 (C), 151.5 (C), 156.8 (CN), 169.7 (CO). Anal. Calcd for $C_{23}H_{21}N_3O_3$: C, 71.30; H, 5.46; N, 10.85. Found : C, 71.68; H, 5.33; N, 10.75 MS : m/z 388.5 (MH^+).

4-(2-Benzyl-3-oxo-2,3,4,5-tetrahydrobenz[*f*][1,4]oxazepin-4-yl)benzamidine (7f): To a stirred solution of **7e** (299 mg, 0.77 mmol) in acetic acid (9 mL) was added acetic anhydride (162 μL, 1.7 mmol), 10% palladium on carbon (111 mg, 37% w) and the resulting suspension was stirred at rt for 2 h under hydrogen (3.5 bars). The reaction mixture was filtered through Celite and the filtrate evaporated *in vacuo* to give **7f** (227 mg, 80%) as colorless solid; mp : 204°C (methanol); IR (KBr, ν cm^{-1}) : 3030 (NH), 1654 (CO), 1610 (CN); ^{1}H NMR (DMSO-d_6) : δ 3.16 (dd, *J*= 8.7 Hz, *J*= 14.5 Hz, 1H, CH_2Ph), 3.28 (dd, *J*= 4.0 Hz, *J*= 14.5 Hz, 1H, CH_2Ph), 3.42 (br s, 2H, NH_2), 4.62 (d, *J*= 17.3 Hz, 1H, CH_2N), 5.82 (dd, *J*= 4.0 Hz, *J*= 8.7 Hz, 1H, CH), 5.92 (d, *J*= 17.3 Hz, 1H, CH_2N), 6.88 (d, *J*= 6.9 Hz, 1H, ArH), 6.98 (t, *J*= 7.5 Hz, 1H, ArH), 7.23-7.31 (m, 3H, ArH), 7.38 (t, *J*= 7.5 Hz, 2H, ArH), 7.47-7.52 (m, 4H, ArH), 7.88 (d, *J*= 8.5 Hz, 2H, ArH); ^{13}C NMR (DMSO-d_6) : δ 36.7 (CH_2Ph), 52.4 (CH_2N), 76.6 (CH), 118.6 (CH), 121.6 (CH), 122.8 (C), 125.6 (2CH), 126.4 (CH), 127.2 (C), 128.1 (2CH), 128.4 (2CH), 129.4 (CH), 129.6 (CH), 129.7 (2CH), 137.6 (C), 146.5 (C), 156.2 (CN), 169.0 (CO).; Anal. Calcd for $C_{23}H_{21}N_3O_2$: C, 74.37; H, 5.70; N, 11.31. Found : C, 74.00; H, 5.59; N, 11.23; MS : m/z 372 (MH^+).

Methyl (2-benzyl-3-oxo-2,3,4,5-tetrahydrobenz[*f*][1,4]oxazepin-4-yl)acetate (10):

Methyl [2-(tert-butyldimethylsilyloxy)benzylamino]acetate: To a stirred solution of **9**[19] (3.36 g, 17.2 mmol) in dry dichloromethane (20 mL) at 0°C, was added diisopropylethylamine (4.5 mL, 25.8 mmol) and the resulting solution was stirred at 10°C for 10 min. After cooling at 0°C, *tert*-butyldimethylsilyl chloride (3.37 g, 22.4 mmol) in dry dichloromethane (10 mL) was added and the reaction mixture was allowed to warm to rt and stirred for 22 h. Solvents were removed *in vacuo* and the crude residue was chromatographed on silica gel, eluting with petroleum ether/ ethyl acetate (80/20, v/v) to give methyl [2-(*tert*-butyldimethylsilyloxy)benzylamino]acetate (4.91 g, 92%) as a pale yellow oil; IR (film, ν cm^{-1}) :

3347 (NH), 1747 (CO); ^{1}H NMR ($CDCl_3$) : δ 0.25 (s, 6H, $Si(CH_3)_2$), 1.02 (s, 9H, $(CH_3)_3$), 2.01 (br s, 1H, NH), 3.40 (s, 2H, CH_2), 3.69 (s, 3H, OCH_3), 3.80 (s, 2H, CH_2N), 6.80 (dd, *J*= 1.1 Hz, *J*= 7.6 Hz, 1H, ArH), 6.92 (dd, *J*= 1.1 Hz, *J*= 7.7 Hz, 1H, ArH), 7.13 (dd, *J*= 1.8 Hz, *J*= 7.6 Hz, 1H, ArH), 7.25 (dd, *J*= 1.8 Hz, *J*= 7.5 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$) : δ -4.2 ($Si(CH_3)_2$), 18.2 ($\underline{C}(CH_3)_3$), 25.8 ($C(\underline{C}H_3)_3$), 48.5 (CH_2), 50.0 (CH_2), 51.6 (OCH_3), 118.5 (CH), 121.1 (CH), 128.1 (CH), 129.9 (C), 130.0 (CH), 153.8 (C), 172.6 (CO); MS : m/z 310 (MH^+).

Methyl (2-bromo-3-phenylpropionyl)-[2-(tert-butyldimethylsilyloxy)benzyl]aminoacetate : To a stirred solution of methyl [2-(*tert*-butyldimethylsilyloxy)benzylamino]acetate (4.91 g, 15.9 mmol) in dry dichloromethane (30 mL) at 0°C was added dropwise 2-bromo-3-phenylpropionyl chloride **(5)**[8] (5.89 g, 23.8 mmol) in dry dichloromethane (40 mL) and triethylamine (3.3 mL, 23.8 mmol) under argon atmosphere. The resulting solution was allowed to warm to rt and stirred for 16 h. The mixture was hydrolyzed with water (50 mL) and aqueous layer was extracted with dichloromethane (2 x 25 mL). The combined extracts were dried over anhydrous magnesium sulfate, filtered and evaporated *in vacuo*. The crude residue was chromatographed on silica gel, eluting with petroleum ether/ethyl acetate (80/20, v/v) affording compound methyl (2-bromo-3-phenylpropionyl)-[2-(*tert*-butyldimethylsilyloxy)benzyl]amino-acetate (5.81 g, 70%) as a yellow oil; IR (film, ν cm^{-1}) : 1755, 1669 (CO); two rotamers A and B were observed in NMR in the ratio 70/30; ^{1}H NMR ($CDCl_3$, rotamer A) : δ 0.23 (s, 6H, $Si(CH_3)_2$), 0.98 (s, 9H, $(CH_3)_3$), 3.10 (dd, *J*= 5.3 Hz, *J*= 13.2 Hz, 1H, CH_2Ph), 3.30 (dd, *J*= 10.1 Hz, *J*= 13.2 Hz, 1H, CH_2Ph), 3.57 (s, 2H, CH_2CO_2), 3.70 (s, 3H, OCH_3), 4.32 (d, *J*= 16.3 Hz, 1H, CH_2N), 4.43-4.47 (m, 1H, CHBr), 4.81 (d, *J*= 16.3 Hz, 1H, CH_2N), 6.51 (dd, *J*= 1.1 Hz, *J*= 7.2 Hz, 1H, ArH), 6.70 (dd, *J*= 1.1 Hz, *J*= 7.2 Hz, 1H, ArH), 6.78 (d, *J*= 7.9 Hz, 1H, ArH), 7.08-7.14 (m, 2H, ArH), 7.23-7.30 (m, 4H, ArH); ^{1}H NMR ($CDCl_3$, rotamer B) : δ 0.24 (s, 6H, $Si(CH_3)_2$), 0.99 (s, 9H, $(CH_3)_3$), 3.20 (dd, *J*= 5.3 Hz, *J*= 13.2 Hz, 1H, CH_2Ph), 3.30 (dd, *J*= 10.1 Hz, *J*= 13.2 Hz, 1H, CH_2Ph), 3.57 (s, 2H, CH_2CO_2), 3.70 (s, 3H, OCH_3), 4.43-4.47 (m, 1H, CHBr), 4.52 (d, *J*= 16.3 Hz, 1H, CH_2N), 4.85 (d, *J*= 16.3 Hz, 1H, CH_2N), 6.51 (dd, *J*= 1.1 Hz, *J*= 7.2 Hz, 1H, ArH), 6.70 (dd, *J*= 1.1 Hz, *J*= 7.2 Hz, 1H, ArH), 6.78 (d, *J*= 7.9 Hz, 1H, ArH), 7.08-7.14 (m, 2H, ArH), 7.23-7.30 (m, 4H, ArH); ^{13}C NMR ($CDCl_3$, rotamer A) : δ -4.1 ($2CH_3$), 18.3 ($\underline{C}(CH_3)_3$), 25.8 ($C(\underline{C}H_3)_3$), 41.1 (CH_2Ph), 42.5 (CHBr), 48.1 (CH_2N), 48.6 ($\underline{C}H_2CO_2$), 52.2 ($CO_2\underline{C}H_3$), 118.4 (CH), 121.6 (CH), 125.9 (C), 127.1 (2CH), 128.6 (CH), 128.6 (2CH), 129.7 (2CH), 137.3 (C), 153.1 (C), 169.1 (CO), 169.7 (CO); ^{13}C NMR ($CDCl_3$, rotamer B) : δ -4.1 ($2CH_3$), 18.3 ($\underline{C}(CH_3)_3$), 25.8 ($C(\underline{C}H_3)_3$), 41.0 (CH_2Ph), 44.1 (CHBr), 44.7 (CH_2N), 48.7 ($\underline{C}H_2CO_2$), 52.4 ($CO_2\underline{C}H_3$), 118.6 (CH), 121.7 (CH), 126.4 (C), 126.6 (2CH), 128.5 (CH), 128.6 (2CH), 129.6 (CH), 129.7 (CH), 137.6 (C), 153.8 (C), 169.1 (CO), 169.3 (CO); MS : m/z 520.5 (MH^+ [^{79}Br]), 522.5 (MH^+ [^{81}Br]), 537.5 (M[^{79}Br] + NH_4^+), 539.5 (M[^{81}Br] + NH_4^+), 542.5 (M[^{79}Br] + Na^+), 544.5 (M[^{81}Br] + Na^+).

Methyl (2-benzyl-3-oxo-2,3,4,5-tetrahydrobenz[f][1,4]oxazepin-4-yl)acetate **(10)** : To a stirred solution of

methyl (2-bromo-3-phenylpropionyl)-[2-(*tert*-butyldimethylsilyloxy)benzyl]aminoacetate (6.43 g, 12.3 mmol) in dry tetrahydrofuran (20 mL) at 0°C, was added dropwise 1M Bu_4NF (12.3 mL, 12.3 mmol) in dichloromethane under argon atmosphere and the resulting mixture was stirred at 0°C for 2.5 h. Solvents were removed *in vacuo* and the residue was taken up in dichloromethane (10 mL) and washed with brine (5 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered and evaporated *in vacuo*. The crude residue was chromatographed on silica gel, eluting with petroleum ether/ethyl acetate (70/30, v/v) to give compound **(10)** (3.08 g, 77%) as an yellow solid; mp : 124-125°C (ethyl acetate–petroleum ether); IR (KBr, ν cm^{-1}) : 1761, 1690 (CO); ^{1}H NMR ($CDCl_3$) : δ 3.25 (dd, *J*= 8.2 Hz, *J*= 14.4 Hz, 1H, CH_2Ph), 3.37 (dd, *J*= 4.1 Hz, *J*= 14.4 Hz, 1H, CH_2Ph), 3.70 (s, 3H, OCH_3), 4.04 (d, *J*= 17.6 Hz, 1H, CH_2CO), 4.18 (d, *J*= 16.0 Hz, 1H, CH_2N), 4.50 (d, *J*= 17.6 Hz, 1H, CH_2CO), 4.82 (d, *J*= 16.0 Hz, 1H, CH_2N), 5.08 (dd, *J*= 4.1 Hz, *J*= 8.2 Hz, 1H, CH), 6.89 (dd, *J*= 1.4 Hz, *J*= 7.6 Hz, 1H, ArH), 6.94 (dd, *J*= 1.4 Hz, *J*= 7.6 Hz, 1H, ArH), 7.02 (dd, *J*= 1.4 Hz, *J*= 7.6 Hz, 1H, ArH), 7.15-7.33 (m, 6H, ArH); ^{13}C NMR ($CDCl_3$) : δ 38.1 (CH_2), 49.9 (CH_2), 51.9 (CH_2), 52.3 (OCH_3), 79.5 (CH), 120.1 (CH), 122.6 (CH), 125.1 (C), 126.6 (CH), 128.3 (2CH), 128.8 (CH), 129.7 (CH), 129.8 (2CH), 137.7 (C), 156.7 (C), 169.6 (CO), 170.6 (CO). Anal. Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.30. Found : C, 69.88; H, 5.61; N, 4.43; MS : m/z 326 (MH^+), 348 ($M + Na^+$).

2-(2-Benzyl-3-oxo-2,3,4,5-tetrahydrobenz[*f*][1,4]oxazepin-4-yl)-*N*-[2-(4-pyridyl)ethyl]acetamide (12):

2-(2-Benzyl-3-oxo-2,3,4,5-tetrahydrobenz[f][1,4]oxazepin-4-yl)acetic acid: To a stirred solution of **10** (1.26 g, 3.88 mmol) in THF–MeOH–H_2O (40 mL, 3 : 1 : 1 v/v/v) at 0°C, was added lithium hydroxide monohydrate (325 mg, 7.76 mmol) and the resulting solution was stirred at 0°C for 1 h, and further stirred at rt for 1 h. Solvent was removed *in vacuo* and the residue was taken up in dichloromethane–water (20 mL, 1 : 1 v/v) followed by an addition of conc. hydrochloric acid to pH=3. The organic layers was dried over anhydrous magnesium sulfate, filtered and evaporated *in vacuo* to give (2-benzyl-3-oxo-2,3,4,5-tetrahydrobenz[*f*][1,4]oxazepin-4-yl)acetic acid (1.19 g, 99%) as a white foam; mp : 144°C (methanol); IR (KBr, ν cm^{-1}) : 3061 (OH), 1740 (CO); ^{1}H NMR ($CDCl_3$) : δ 3.25 (dd, *J*= 8.0 Hz, *J*= 14.4 Hz, 1H, CH_2Ph), 3.36 (dd, *J*= 4.1 Hz, *J*= 14.4 Hz, 1H, CH_2Ph), 4.06 (d, *J*= 17.7 Hz, 1H, CH_2CO), 4.24 (d, *J*= 15.8 Hz, 1H, CH_2N), 4.52 (d, *J*= 17.7 Hz, 1H, CH_2CO), 4.73 (d, *J*= 15.8 Hz, 1H, CH_2N), 5.06 (dd, *J*= 4.1 Hz, *J*= 8.0 Hz, 1H, CH), 6.89 (d, *J*= 7.8 Hz, 1H, ArH), 6.96 (d, *J*= 7.3 Hz, 1H, ArH), 7.03 (dd, *J*= 1.7 Hz, *J*= 7.5 Hz, 1H, ArH), 7.01-7.25 (m, 6H, ArH), 7.73 (br s, 1H, OH); ^{13}C NMR ($CDCl_3$) : δ 38.2 (CH_2), 50.3 (CH_2), 51.6 (CH_2), 79.9 (CH), 120.2 (CH), 123.0 (CH), 125.6 (C), 126.7 (CH), 128.4 (2 CH), 129.0 (CH), 130.0 (3 CH), 137.5 (C), 156.7 (C), 171.4 (CO), 173.5 (CO). Anal. Calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found : C, 69.10; H, 5.32; N, 4.68; MS : m/z 312 (MH^+), 329 ($M + NH_4^+$), 334 ($M + Na^+$).

2-(2-Benzyl-3-oxo-2,3,4,5-tetrahydrobenz[f][1,4]oxazepin-4-yl)-N-[2-(4-pyridyl)ethyl]acetamide ***(12):*** To a stirred solution of (2-benzyl-3-oxo-2,3,4,5-tetrahydrobenz[*f*][1,4]oxazepin-4-yl)acetic acid (1.39 g, 4.47 mmol) in dry CH_2Cl_2 (15 mL) was added DMAP (46.8 mg, 0.38 mmol), 2-(4-pyridyl)ethylamine[20] (**11**)

(1.04 g, 8.40 mmol) under argon atmosphere. After cooling, EDCI (807 mg, 4.20 mmol) was added at 0°C and the resulting mixture was stirred at 0°C for 4 h and further stirred at rt for 20 h. Solvents were removed *in vacuo* and the residue was taken up in dichloromethane (10 mL) and washed with water (3 x 10 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered and evaporated *in vacuo*. The crude residue was chromatographed on silica gel, eluting with dichloromethane/methanol (100/2, v/v) affording compound **(12)** (1.08 g, 68%) as a colorless solid; mp : 108-109°C (methanol); IR (KBr, ν cm^{-1}) : 3298 (NH), 1683 (CO); ^{1}H NMR ($CDCl_3$) : δ 2.63 (t, *J*= 7.1 Hz, 2H, CH_2Py), 3.22 (dd, *J*= 7.3 Hz, *J*= 14.3 Hz, 1H, CH_2Ph), 3.29 (m, 1H, CH_2Ph), 3.34-3.43 (m, 2H, CH_2NH), 4.00 (d, *J*= 15.7 Hz, 1H, CH_2CO), 4.14 (d, *J*= 15.7 Hz, 1H, CH_2CO), 4.22 (d, *J*= 16.0 Hz, 1H, CH_2N), 4.70 (d, *J*= 16.0 Hz, 1H, CH_2N), 5.04 (dd, *J*= 4.4 Hz, *J*= 7.3 Hz, 1H, CH), 6.57 (t, *J*= 5.8 Hz, 1H, NH), 6.89-7.04 (m, 5H, ArH), 7.16-7.27 (m, 2H, ArH), 7.28-7.36 (m, 4H, ArH), 8.41 (d, *J*= 4.7 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$) : δ 34.7 (CH_2), 38.0 (CH_2), 39.4 (CH_2), 51.2 (CH_2), 52.4 (CH_2), 79.6 (CH), 120.0 (CH), 122.9 (CH), 124.1 (2CH), 125.2 (C), 126.7 (CH), 128.2 (2CH), 128.8 (CH), 129.7 (2CH), 129.9 (CH), 137.2 (C), 147.8 (C), 149.6 (2CH), 156.4 (C), 168.5 (CO), 170.7 (CO). Anal. Calcd for $C_{25}H_{25}N_3O_3$: C, 72.27; H, 6.06; N, 10.11. Found : C, 72.54; H, 5.92; N, 10.01; MS : m/z 416.5 (MH^+).

X-Ray Structure Analysis of **4a** : $C_{23}H_{19}NO_3$, Mr (g.mol^{-1}), 357.39; temperature 296(2) K; crystal size 0.37 x 0.22 x 0.05 mm; wavelength (λ) 1.54180 Å ; crystal system monoclinic; space group P 21/n; unit cell dimensions a = 12.427(2) Å, α = 90°, b = 8.478(1) Å, β = 94.42(1)°, c = 17.577(1) Å, γ= 90°; crystal volume 1846.3(4) $Å^3$; Z, calculated density 4, 1.286 $Mg.m^{-3}$, absorption coefficient 0.686 mm^{-1}; F(000) 752; θ range for data collection 4.21 to 64.93° ; index ranges -14 ≤ h ≤14, 0 ≤ k ≤9, 0 ≤l ≤ 20; measured reflections 3130 ; Max. and min. transmission 0.9665 and 0.7855; extinction coefficient 0.0050(5). R (all data) : R1 = 0.1053 ; wR2 = 0.1623 ; Goof 1.033.

Selected bond lenghts [Å] and torsional angles[°]:C(8)-C(13) 1.324(4), C(8)-C(9); 1.489(4)), O(7)-C(8) 1.385(3), O(7)-C(8)-C(13)-C(14) -7.2(5); O(7)-C(8)-C(9)-N(10) 46.0(4), C(9)-N(10)-C(11)-C(1) -70.8(4) C(2)-O(7)-C(8)-C(9) -6.9(5) (see indexation on Figure 1). Crystallographic data have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication no CCDC 227995.

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