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SYNTHESIS OF 5-(4-ARYL)-2-PHENYL-5,6-DIHYDROBENZO[*b*][1,5]-OXAZOCIN-4-ONES

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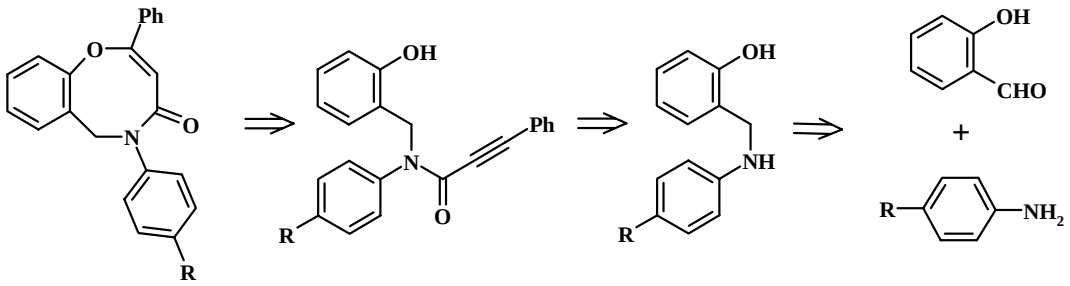
Abstract - Cyclization of *N*-aryl-*N*-(2-hydroxybenzyl)-3-phenylpropynamide in basic medium under the influence of a catalytic amount of Pd(0) afforded the eight-membered framework 5-(4-aryl)-2-phenyl-5,6-dihydrobenzo[*b*][1,5]-oxazocin- 4-ones.

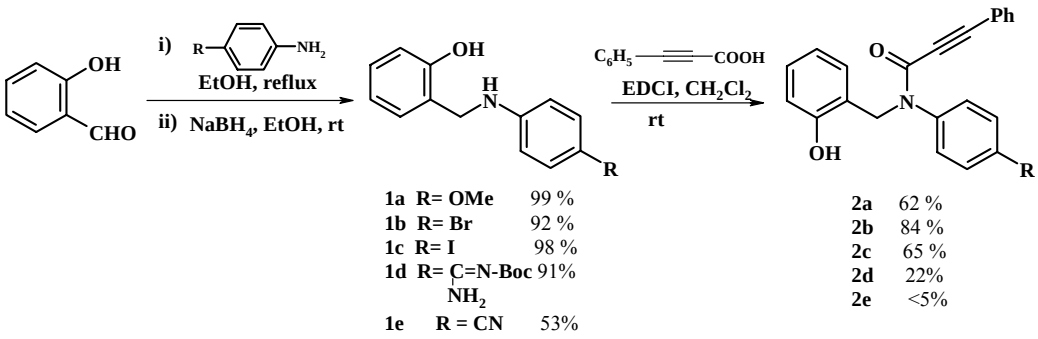
The well-documented drawbacks of peptides as drugs have prompted a search for heterocyclic peptidomimetics[1,2] with better oral bioavailability and higher stability against enzymatic degradation. Several scaffolds such as sugars, pyrrolidone or benzodiazepines[3-6] mimicking the peptide secondary structure have been reported in the literature. New structures that hold the peptide side chains in a similar conformation than in the natural peptides are off importance. In our search for non-peptidic factor Xa inhibitors,[7] we designed new benzoxazocines which may possess these properties. To the best of our knowledge, targeted heterocyclic skeleton has not been widely described; we can mention reactions of isocyanides and salicylic aldehyde which gave substituted benzoxazocin-4-ones.[8] Benzo-fused oxazocinones[9] and benzoxazines [10] were also described. In this paper we reported our results obtained in the synthesis of this eight-membered scaffold.

The retrosynthetic approach of targeted structure is outlined in Scheme 1.



Scheme 1

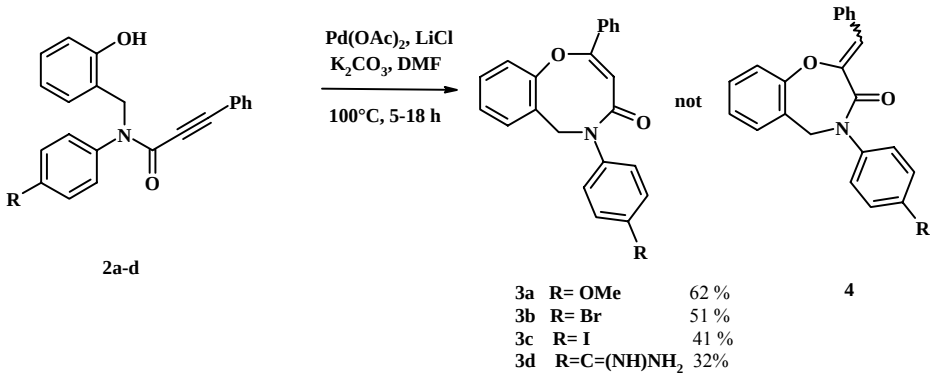
Condensation of salicylic aldehyde with 4-substituted anilines in refluxing ethanol gave the corresponding imines which by reduction with sodium borohydride at room temperature afforded amines (**1a-e)** in an excellent yield (91-99 %), except for **1e** (53%). Treatment of **1a-e** with phenylpropiolic acid was achieved in presence of EDCI in dichloromethane at room temperature to give amides **(2a-e)** in 22-84 % yield, except for **2e** (<5%) (Scheme 2). The amidino substituent of compounds **(1d)** and **(2d)** was selectively introduced on the heterocycle based on its potential role (binding with aspartic residue 189 in the catalytic site) for inhibiting factor Xa.[7,11]



Scheme 2

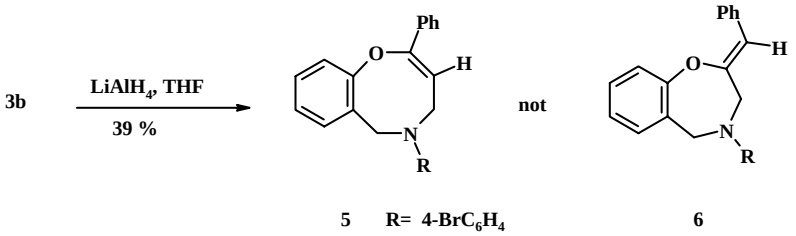
When **2** was treated with potassium carbonate, the internal cyclization of the formed phenolate on the acetylenic amide moiety *via* a pseudo-Michael reaction did not occurred, even with addition of cuprous iodide; a same approach was already applied for the synthesis of six-membered 1,4-benzodioxine derivatives.[12] However when applying the palladium methodology developped by Kundu[13] *et al.*, a single product **(3)** (eight- membered ring) was obtained in a reasonable yield 32-62 % (Scheme 3). We postulated that a complexation of the triple bond with Pd(II) salt occurred, facilitating the nucleophilic attack of the phenolate moiety on the acetylenic bond (8-endo-dig cyclization).[14]

Even if the compound **(3)** is the expected cyclized product of this palladium-assisted pseudo-Michael cyclization, we cannot totally exclude the formation of seven-membered derivative **(4)**, the 2D NMR data were no conclusive.



Scheme 3

A reduction of **3b** with lithium aluminium hydride in THF afforded the only compound **(5)** (Scheme 4); this has been proved by ^{1}H NMR spectrum data (*inter alia* the allyl CH_2 signal was a doublet with a coupling constant J = 6.2 Hz).



Scheme 4

In addition, the X-Ray diffraction study of **3a** confirmed the eight-membered ring type structure (Figure 1); the crystal cohesion was due to H-bond and Van der Waals forces between oxygen atom 21 (O21) and hydrogen 27 (H27) (dashed line).

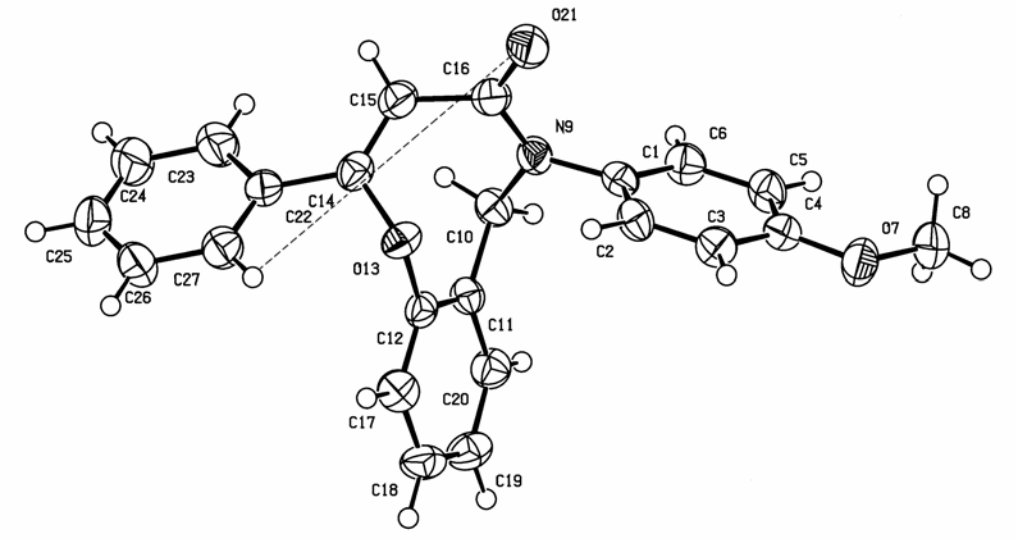
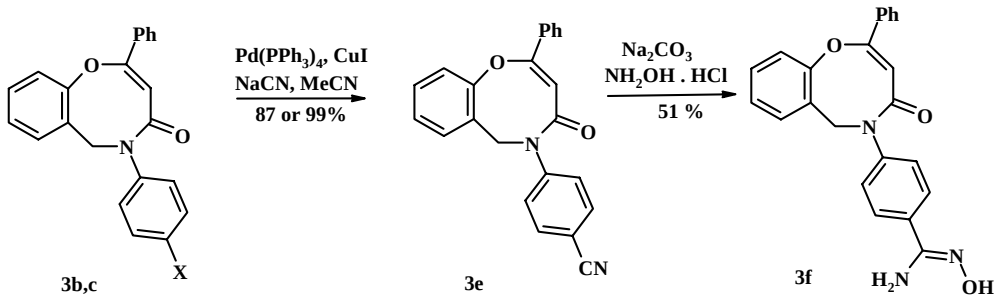


Figure 1. ORTEP representation of **3a**

By using the Boc-4-aminobenzamidine, we could obtain the amine **(1d)** in 91% yield; nevertheless, condensation of **1d** with phenylpropiolic acid in the same condition as for **2a-c** afforded **2d** in an only 22 % yield. An activation of the carboxylic acid [e.g. acid chloride, mixed anhydride] did not improve the yield. A slight improvement (up to 28%) was only observed when hydroxybenzotriazole (HOBt) was added. Cyclization of **2d** afforded the benzoxazocine **(3d)** in 32 % yield, the amidine deprotection occurring during the cyclization.

The amidification of the cyano derivative **(1e)** (R = CN) was even more disappointing (<5% yield). An alternative approach was then investigated starting with the bromo- or iodobenzoxazocine **(3b,c)**. Introduction of the cyano substituent was achieved with sodium cyanide in presence of palladium(0) catalyst. Thus heating **3b** and sodium cyanide in acetonitrile in presense of cuprous iodide and palladium tetrakistriphenylphosphine gave the cyano derivative **(3e)** in 87 % yield. The iodo derivative **(3c)** gave an even better yield of 99 % for **3a**. Treatment of **3e** with hydroxylamine hydrochloride in basic medium afforded the hydroxamidine **(3f)** in 51% yield (Scheme 5).



Scheme 5

In this paper we have designed and prepared a new family of substituted eight-membered heterocycles whose properties as peptidic mimics could be further explored. Thus, by employing judiciously substituted anilines and / or phenylpropiolic acid, we could have access to benzoxacin-4-ones.

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-[(4-Methoxyphenylamino)methyl]phenol (1a): To a stirred solution of salicylic aldehyde (2.69 g, 21.8 mmol) in dry ethanol (30 mL) was added a solution of 4-methoxyaniline (2.71 g, 21.8 mmol) in dry ethanol (50 mL) under argon atmosphere. The resulting mixture was heated at reflux for 30 min. After cooling, sodium borohydride (836 mg, 22 mmol) was added portionwise at 5°C with care, and the solution was further stirred for 10 min at 5°C. The reaction mixture was allowed to warm to rt and stirred for 2 h. The preciptated product was filtered off to give compound **(1a)** (3.72 g) as a colorless solid. The filtrate was evaporated *in vacuo*, and the residue was taken up in ethyl acetate (15 mL) and washed with water (15 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered and evaporated *in vacuo*. The resultant solid was combined with the precipitated material to give the title compound **(1a)** (4.98 g, 99 %) as a colorless solid; mp : 133-134°C (ethanol); IR (KBr, ν cm^{-1}) : 3261 (NH, OH); ^{1}H NMR ($CDCl_3$) : δ 3.74 (s, 3H, OCH_3), 3.85 (s, 1H, NH or OH), 4.35 (s, 2H, CH_2N), 6.80-6.89 (m, 6H, ArH), 7.11 (d, *J*= 6.3 Hz, 1H, ArH), 7.20 (td, J_1= 1.6 Hz, J_2= 7.7 Hz, 1H, ArH), 9.12 (s, 1H, NH or OH); ^{13}C NMR ($CDCl_3$) : δ 50.3 (CH_2N), 55.7 (OCH_3), 114.9 (2CH), 116.8 (CH), 117.9 (2CH), 119.9 (CH), 123.0 (C), 128.6 (CH), 129.2 (CH), 140.6 (C), 154.6 (C), 157.3 (C); Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found : C, 73.14; H, 6.75; N, 6.23; MS : m/z 230 (MH^+).

2-[(4-Bromophenylamino)methyl]phenol (1b): Similarly obtained as for **1a** starting from 4-bromoaniline; pale yellow solid; yield (7.18 g, 92 %); mp : 121°C (ethanol); IR (KBr, ν cm^{-1}) : 3262 (NH, OH); ^{1}H NMR (DMSO-d_6) : δ 4.17 (br s, 2H, CH_2N), 6.23 (br s, 1H, NH or OH), 6.53 (d, *J*= 6.9 Hz, 2H, ArH), 6.71 (td, *J*= 1.3 Hz, *J*= 7.5 Hz, 1H, ArH), 6.82 (dd, *J*= 1.3 Hz, *J*= 7.5 Hz, 1H, ArH), 7.04 (td, *J*= 1.3 Hz, *J*= 7.5 Hz, 1H, ArH), 7.13-7.19 (m, 3H, ArH), 9.25 (br s, 1H, NH or OH); ^{13}C NMR (DMSO-d_6) : δ 41.3 (CH_2N), 106.1 (C), 114.0 (2CH), 115.0 (CH), 118.6 (CH), 125.3 (C), 127.6 (CH), 128.1 (CH), 131.3 (2CH), 148.1 (C), 155.3 (C); Anal. Calcd for $C_{13}H_{12}NOBr$: C, 56.14; H, 4.35; N, 5.04. Found : C, 55.96; H, 4.20; N, 5.10; MS : m/z 278 (MH^+ [^{79}Br]), 280 (MH^+ [^{81}Br]).

2-[(4-Iodophenylamino)methyl]phenol (1c): Similarly obtained as for **1a** starting from 4-iodoaniline except refluxing time: 7 h instead of 30 min; yield (8.92 g, 98 %); beige solid; mp : 130°C (ethanol); IR (KBr, ν cm^{-1}) : 3262 (NH, OH) ; ^{1}H NMR ($CDCl_3$) : δ 3.99 (br s, 1H, NH or OH), 4.34 (s, 2H, CH_2N), 6.58 (d, *J*= 9.1 Hz, 2H, ArH), 6.84-6.91 (m, 2H, ArH), 7.13-7.24 (m, 2H, ArH), 7.48 (d, *J*= 9.1 Hz, 2H, ArH), 7.78 (br s, 1H, NH or OH); ^{13}C NMR ($CDCl_3$) : δ 48.0 (CH_2N), 82.3 (C), 116.7 (CH), 117.8 (2CH), 120.4

(CH), 122.8 (C), 129.0 (CH), 129.5 (CH), 138.2 (2CH), 147.1 (C), 156.3 (C); Anal. Calcd for $C_{13}H_{12}NOI$: C, 48.02; H, 3.72; N, 4.31. Found : C, 48.21; H, 3.55; N, 4.43; MS : m/z 199 (MH^+ – I), 232 (MH^+ – C_6H_5-OH), 326 (MH^+).

***tert*-Butyl-*N*-{amino-[4-(2-hydroxybenzylamino)phenyl]methylene}carbamate (1d):** Similarly obtained as for **1a** from 4-amino-*tert*-butyl-*N*-[amino-(4-aminophenyl)methylene]carbamate; yield (4.50 g, 91%); yellow solid; mp : 170°C (methanol); IR (KBr, ν cm^{-1}) : 3494, 3458 (OH, NH), 1674 (CO); ^{1}H NMR (DMSO-d_6) : δ 1.44 (s, 9H, $(CH_3)_3$), 4.25 (s, 2H, CH_2N), 6.34 (t, *J*= 7.3 Hz, 1H, ArH), 6.61 (d, *J*= 8.8 Hz, 2H, ArH), 6.69 (d, *J*= 7.5 Hz, 1H, ArH), 6.87 (t, *J*= 7.5 Hz, 1H, ArH), 7.00 (d, *J*= 7.5 Hz, 1H, ArH), 7.76 (d, *J*= 8.8 Hz, 2H, ArH), 9.04 (br s, 2H, NH_2); ^{13}C NMR (DMSO-d_6) : δ 26.2 ($C(\underline{C}H_3)_3$), 40.4 (CH_2N), 75.1 ($\underline{C}(CH_3)_3$), 109.1 (2CH), 111.1 (CH), 114.7 (CH), 117.8 (C), 123.5 (C), 125.5 (CH), 125.6 (CH), 127.1 (2CH), 150.6 (C), 160.5 (C), 162.0 (CN), 161.4 (CO); Anal. Calcd for $C_{19}H_{23}N_3O_3$: C, 66.84; H, 6.79; N,12.31. Found : C, 67.16; H, 6.71; N, 12.22; MS : m/z 286 (MH^+ – $C(CH_3)_3$), 342.5 (MH^+).

4-(2-Hydroxybenzylamino)benzonitrile (1e): Similarly obtained as for **1a** starting from 4-cyanoaniline except reflux 20 h instead of 30 min; yield (11.3 g, 53%) as a beige solid ; mp : 116°C (ethanol); IR (KBr, ν cm^{-1}) : 3404 (OH, NH), 2200 (CN) ; ^{1}H NMR ($CDCl_3$) : δ 4.40 (d, *J*= 5.5 Hz, 2H, CH_2N), 4.65 (br s, 1H, NH or OH), 6.51 (br s, 1H, NH or OH), 6.69 (d, *J*= 8.8 Hz, 2H, ArH), 6.86-6.93 (m, 2H, ArH), 7.17-7.26 (m, 2H, ArH), 7.43 (d, *J*= 8.8 Hz, 2H, ArH) ; ^{13}C NMR (DMSO-d_6) : δ 40.8 (CH_2), 95.7 (CN), 112.0 (CH), 115.1 (CH), 119.0 (CH), 120.8 (C), 124.5 (C), 128.0 (CH), 128.4 (CH), 133.4 (3CH), 152.3 (C), 155.2 (C); Anal. Calcd for $C_{14}H_{12}N_2O$: 74.98 ; H, 5.39 ; N, 12.49. Found : C, 75.05 ; H, 5.34 ; N, 12.53 ; MS : m/z 225 (MH^+), 247 ($M + Na^+$).

***N*-(2-Hydroxybenzyl)-*N*-(4-methoxyphenyl)-3-phenylpropynamide (2a):** To a stirred solution of **1a** (451 mg, 1.98 mmol) in dry dichloromethane (30 mL) were successively added phenylpropiolic acid (289 mg, 1.98 mmol) and EDCI (381 mg, 1.98 mmol) under argon atmosphere. The reaction mixture was stirred at rt for 17 h and evaporated *in vacuo*. The crude residue was chromatographed on silica gel, eluting with petroleum ether/ethyl acetate (80/20, v/v) to give **2a** (439 mg, 62 %) as a yellow oil; IR (film, ν cm^{-1}) : 3184 (OH), 2214 (C≡C), 1616 (CO); ^{1}H NMR ($CDCl_3$) : δ 3.85 (s, 3H, OCH_3), 4.84 (s, 2H, CH_2N), 6.71-6.74 (m, 2H, ArH), 6.92-6.99 (m, 2H, ArH), 7.00 (d, *J*= 8.1 Hz, 1H, ArH), 7.07-7.14 (m, 4H, ArH), 7.20-7.26 (m, 3H, ArH), 7.30-7.36 (m, 1H, ArH), 9.06 (br s, 1H, OH); ^{13}C NMR ($CDCl_3$) : δ 50.2 (CH_2N), 55.5 (OCH_3), 81.6 (Csp), 93.6 (Csp), 114.4 (2CH), 117.8 (CH), 119.5 (CH), 119.8 (C), 121.6 (C), 128.4 (2CH), 129.5 (2CH), 130.1 (CH), 130.3 (CH), 131.8 (CH), 132.5 (2CH), 133.8 (C), 155.8 (C), 156.3 (C), 159.6 (CO); Anal. Calcd for $C_{23}H_{19}NO_3$: C, 77.29; H, 5.36; N, 3.92. Found : C, 77.02; H, 5.54; N, 3.78; MS : m/z 358 (MH^+).

***N*-(4-Bromophenyl)-*N*-(2-hydroxybenzyl)- 3-phenylpropynamide (2b):** Similarly obtained as for **2a**; time reaction 48 h; yield (8.38 g, 84 %); brown solid; mp : 105°C (ether). IR (KBr, ν cm^{-1}) : 3157 (OH), 2201 (C≡C), 1621 (CO); ^{1}H NMR ($CDCl_3$) : δ 4.86 (s, 2H, CH_2N), 6.69-6.77 (m, 2H, ArH), 7.00 (d, *J*= 7.9 Hz, 1H, ArH), 7.05-7.10 (m, 4H, ArH), 7.21-7.40 (m, 4H, ArH), 7.58 (d, *J*= 8.8 Hz, 2H, ArH), 8.95 (br s, 1H, OH); ^{13}C NMR ($CDCl_3$) : δ 50.1 (CH_2N), 81.4 (Csp), 94.3 (Csp), 118.2 (CH), 119.6 (C), 119.8 (CH), 121.3 (C), 123.0 (C), 128.6 (2CH), 130.4 (2CH), 130.7 (2CH), 131.8 (CH), 132.6 (2CH), 132.8 (2CH), 140.3 (C), 155.9 (C), 156.0 (CO); Anal. Calcd for $C_{22}H_{16}NO_2Br$: C, 65.04; H, 3.97; N, 3.45; Found : C, 65.30; H, 4.03; N, 3.62; MS : m/z 406 (MH^+ [^{79}Br]), 408 (MH^+ [^{81}Br]), 428 (M[^{79}Br] + Na^+), 430 (M[^{81}Br] + Na^+).

***N*-(2-Hydroxybenzyl)-*N*-(4-iodophenyl)-3-phenylpropynamide (2c):** Similarly obtained as for **2b**; yield (222 mg, 65 %); yellow solid; mp : 175°C (ether). IR (KBr, ν cm^{-1}) : 3118 (OH), 2208 (C≡C), 1623 (CO); ^{1}H NMR ($CDCl_3$) : δ 4.85 (s, 2H, CH_2N), 6.71-6.73 (m, 2H, ArH), 6.94 (d, *J*= 8.8 Hz, 2H, ArH), 6.99 (d, *J*= 8.2 Hz, 1H, ArH), 7.08-7.13 (m, 2H, ArH), 7.18-7.46 (m, 4H, ArH), 7.77 (d, *J*= 8.8 Hz, 2H, ArH), 8.88 (br s, 1H, OH); ^{13}C NMR ($CDCl_3$) : δ 50.0 (CH_2N), 81.4 (C), 94.2 (Csp), 94.5 (Csp), 118.1 (CH), 119.6 (C), 119.8 (CH), 121.3 (C), 128.6 (2CH), 130.6 (2CH), 130.7 (2CH), 131.8 (CH), 132.6 (2CH), 138.8 (2CH), 141.0 (C), 155.8 (C), 155.9 (CO); Anal. Calcd for $C_{22}H_{16}NO_2I$: C, 58.30; H, 3.56; N, 3.09. Found : C, 58.63; H, 3.48; N, 3.25; MS : m/z 454 (MH^+), 476 (M + Na^+).

***tert*-Butyl-*N*-(amino-{4-[(2-hydroxybenzyl)-(3-phenylpropynoyl)amino]phenyl}methylene)carbamate (2d):** Similarly obtained as for **2b** starting from **1d**; yield (45 mg, 22%); light yellow solid; mp : 172°C; IR (KBr, ν cm^{-1}) : 3501 (OH, NH), 2209 (C≡C), 1668 (CO); ^{1}H NMR ($CDCl_3$) : δ 1.55 (s, 9H, $(CH_3)_3$), 4.88 (s, 2H, CH_2N), 6.62 (dd, *J*= 1.9 Hz, *J*= 7.5 Hz, 1H, ArH), 6.66 (td, J_1= 1.2 Hz, J_2= 7.5 Hz, 1H, ArH), 6.98 (dd, J_1= 1.1 Hz, J_2= 8.2 Hz, 1H, ArH), 7.09 (dd, *J*= 1.1 Hz, *J*= 8.2 Hz, 2H, ArH), 7.18-7.37 (m, 6H, ArH), 7.96 (d, *J*= 8.8 Hz, 2H, ArH), 8.88 (br s, 1H, OH); (signals (br s) at 9.03 (NH_2) and 9.57 (OH) in DMSO-d_6) ^{13}C NMR ($CDCl_3$) : δ 28.3 (C($\underline{C}H_3)_3$), 50.1 (CH_2N), 53.6 (C), 80.2 (Csp), 81.4 (Csp), 94.2 ($\underline{C}(CH_3)_3$), 118.1 (CH), 119.5 (C), 119.9 (CH), 121.2 (2C), 128.6 (4CH), 128.9 (2CH), 130.7 (2CH), 131.7 (CH), 132.6 (2CH), 135.4 (C), 144.2 (CN), 155.7 (CO), 155.8 (CO); Anal. Calcd for $C_{28}H_{27}N_3O_4$: C, 71.63; H, 5.80; N, 8.95. Found : C, 71.55; H, 5.88; N, 8.87; MS : m/z 370 (MH^+ – Boc), 470.5 (MH^+).

5-(4-Methoxyphenyl)-2-phenyl-5,6-dihydrobenzo[*b*][1,5]oxazocin-4-one (3a): To a stirred solution of **2a** (145 mg, 0.41 mmol) in dry *N*,*N*-dimethylformamide (5 mL) were added successively palladium acetate (5 mg, 0.02 mmol), lithium chloride (8.6 mg, 0.20 mmol) and potassium carbonate (140 mg, 1.01 mmol)

under oxygen free argon atmosphere. The resulting solution was stirred at 100°C for 5 h. The mixture was evaporated *in vacuo* and the residue was taken up in ethyl acetate (10 mL) and washed with water (3 x 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 (50/50, v/v) affording compound **(3a)** (90 mg, 62%) as a yellow solid; mp : 156°C (dichloromethane); IR (KBr, ν cm^{-1}) : 1659 (CO); ^{1}H NMR ($CDCl_3$) : δ 3.76 (s, 3H, OCH_3), 5.06 (br s, 2H, CH_2N), 6.49 (s, 1H, =CH), 6.85 (dt, *J*= 2.7 Hz, *J*= 9.1 Hz, 2H, ArH), 6.90 (br s, 1H, ArH), 6.95-7.01 (m, 1H, ArH), 7.10 (dt, *J*= 2.7 Hz, *J*= 9.1 Hz, 2H, ArH), 7.28-7.31 (m, 2H, ArH), 7.33-7.43 (m, 3H, ArH), 7.72-7.76 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$) : δ 55.0 (CH_2N), 55.4 (OCH_3), 111.5 (=CH), 114.6 (2CH), 122.5 (CH), 124.4 (CH), 126.7 (2CH), 127.6 (C), 128.0 (2CH), 128.8 (2CH), 130.0 (CH), 130.2 (CH), 130.4 (CH), 133.4 (C), 134.7 (C), 152.0 (C), 153.3 (C), 158.5 (C), 168.0 (CO); Anal. Calcd for $C_{23}H_{19}NO_3$: C, 77.29; H, 5.36; N, 3.92. Found : C, 76.93; H, 5.48; N, 4.07; MS : m/z 358 (MH^+), 380 ($M + Na^+$).

5-(4-Bromophenyl)-2-phenyl-5,6-dihydrobenzo[*b*][1,5]oxazocin-4-one (3b): Similarly obtained as **3a** from **2b**; time reaction 18 h; yield (1.55 g, 51%); orange solid; mp : 176-177°C (ethyl acetate/petroleum ether); IR (KBr, ν cm^{-1}) : 1667 (CO); ^{1}H NMR ($CDCl_3$) : δ 5.07 (br s, 2H, CH_2N), 6.46 (s, 1H, =CH), 6.90 (dd, *J*= 1.0 Hz, *J*= 7.5 Hz, 1H, ArH), 7.00-7.04 (m, 1H, ArH), 7.11 (dt, *J*= 2.4 Hz, *J*= 8.8 Hz, 2H, ArH), 7.29-7.31 (m, 2H, ArH), 7.36-7.41 (m, 3H, ArH), 7.43 (dt, *J*= 2.4 Hz, *J*= 8.8 Hz, 2H, ArH), 7.71-7.76 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$) : δ 54.6 (CH_2N), 111.2 (=CH), 120.8 (C), 122.7 (CH), 124.7 (2CH), 126.8 (2CH), 127.4 (C), 128.4 (2CH), 128.9 (2CH), 130.3 (2CH), 130.4 (CH), 132.5 (CH), 133.2 (C), 141.0 (C), 152.9 (C), 153.8 (C), 167.9 (CO); Anal. Calcd for $C_{22}H_{16}NO_2Br$: C, 65.04; H, 3.97; N, 3.45. Found : C, 65.37; H, 4.05; N, 3.59; MS : m/z 406 (MH^+ [^{79}Br]), 408 (MH^+ [^{81}Br]), 428 (M[^{79}Br] + Na^+), 430 (M[^{81}Br] + Na^+).

5-(4-Iodophenyl)-2-phenyl-5,6-dihydrobenzo[*b*][1,5]oxazocin-4-one (3c): Similarly obtained as **3b** from **2c**; yield (163 mg, 41%); brown solid; mp : 190°C (ethyl acetate–petroleum ether); IR (KBr, ν cm^{-1}) : 1667 (CO); ^{1}H NMR ($CDCl_3$) : δ 5.05 (br s, 2H, CH_2N), 6.45 (s, 1H, =CH), 6.89 (dd, *J*= 1.0 Hz, *J*= 7.7 Hz, 1H, ArH), 6.94-7.01 (m, 3H, ArH), 7.27-7.29 (m, 2H, ArH), 7.35-7.39 (m, 3H, ArH), 7.61 (dt, *J*= 2.4 Hz, *J*= 8.8 Hz, 2H, ArH), 7.70-7.74 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$) : δ 54.4 (CH_2N), 92.1 (C), 111.4 (=CH), 122.6 (CH), 124.6 (2CH), 126.7 (2CH), 127.3 (C), 128.6 (2CH), 128.8 (2CH), 130.2 (CH), 130.4 (2CH), 133.1 (C), 138.3 (CH), 141.7 (C), 152.8 (C), 153.7 (C), 167.7 (CO); Anal. Calcd for $C_{22}H_{16}NO_2I$: C, 58.30; H, 3.56; N, 3.09. Found : C, 58.64; H, 3.39; N, 3.11; MS : m/z 454 (MH^+), 476 ($M + Na^+$).

4-(4-Oxo-2-phenyl-4*H*,6*H*-benzo[*b*][1,5]oxazocin-5-yl)benzamidine (3d): Similarly obtained from **2d**

as for **3a**; time reaction 15 h; yield (80 mg, 32%); yellow oil; IR (film, ν cm^{-1}) : 3062 (NH), 1644 (CO), 1620 (CN); ^{1}H NMR (DMSO-d_6) : δ 5.26 (br s, 2H, CH_2N), 6.78 (s, 1H, =CH), 7.04 (t, *J*= 7.5 Hz, 1H, ArH), 7.20 (br d, *J*= 6.9 Hz, 1H, ArH), 7.30 (br t, *J*= 7.5 Hz, 1H, ArH), 7.41-7.52 (m, 6H, ArH), 7.79-7.88 (m, 4H, ArH); ^{13}C NMR (DMSO-d_6) : δ 52.1 (CH_2N), 108.2 (C), 112.6 (=CH), 118.5 (C), 122.5 (CH), 124.7 (CH), 125.9 (2CH), 126.8 (2CH), 127.9 (C), 128.9 (2CH), 130.1 (CH), 130.3 (CH), 130.7 (CH), 132.6 (C), 133.1 (2CH), 145.8 (C), 151.7 (C), 152.3 (CN), 167.5 (CO); Anal. Calcd for $C_{23}H_{19}N_3O_2$: C, 74.78; H, 5.18; N, 11.37. Found : C, 74.32; H, 5.36; N, 11.21; MS : m/z 353 (M – NH_2).

4-(4-Oxo-2-phenyl-4*H*,6*H*-benzo[*b*][1,5]oxazocin-5-yl)benzonitrile (3e): To a stirred solution of **3b** (142 mg, 0.35 mmol) in deoxygenated acetonitrile (10 mL) were successively added sodium cyanide (35 mg, 0.71 mmol), freshly prepared tetrakis(triphenylphosphine)palladium (21 mg, 0.018 mmol) and copper iodide (I) (7 mg, 0.035 mmol) under oxygen free argon atmosphere, and the resulting solution was heated at reflux for 3 h. After cooling, the mixture was filtered through Celite and the filtrate was taken up with ethyl acetate (10 mL) and washed with water (5 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered and evaporated *in vacuo*. The crude product was chromatographed on silica gel, eluting with petroleum ether/ethyl acetate (70/30, v/v), affording compound **(3e)** (107 mg, 87%) as an orange solid; mp : 86°C (ethyl acetate–petroleum ether); IR (KBr, ν cm^{-1}) : 2227 (CN), 1676 (CO); ^{1}H NMR ($CDCl_3$) : δ 5.14 (br s, 2H, CH_2N), 6.47 (s, 1H, =CH), 6.98 (br d, *J*= 7.2 Hz, 1H, ArH), 7.05 (m, 1H, ArH), 7.31 (br d, *J*= 4.4 Hz, 2H, ArH), 7.36-7.40 (m, 3H, ArH), 7.43 (dt, J_1= 2.0 Hz, J_2= 8.8 Hz, 2H, ArH), 7.56 (dt, J_1= 2.0 Hz, J_2= 8.8 Hz, 2H, ArH), 7.72-7.76 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$) : δ 53.8 (CH_2N), 109.8 (CN), 110.8 (=CH), 118.3 (C), 122.6 (CH), 124.7 (CH), 126.3 (2CH), 126.6 (2CH), 127.1 (C), 128.7 (2CH), 129.9 (CH), 130.3 (CH), 130.4 (CH), 132.7 (C), 132.9 (2CH), 145.9 (C), 152.6 (C), 153.9 (C), 167.6 (CO); Anal. Calcd for $C_{23}H_{16}N_2O_2$: C, 78.39; H, 4.58; N, 7.95. Found : C, 78.03; H, 4.65; N, 8.03; MS : m/z 353 (MH^+). Similarly obtained from **3c**; yield 99%.

***N*-Hydroxy-4-(4-oxo-2-phenyl-4*H*,6*H*-benzo[*b*][1,5]oxazocin-5-yl)benzamidine (3f):** To a stirred solution of **3e** (1.18 g, 3.35 mmol) in ethanol–water (360 mL, 50/50, v/v), were added successively hydroxylamine hydrochloride (860 mg, 12.40 mmol) and sodium carbonate (604 mg, 5.70 mmol). The mixture was heated at reflux for 48 h and after cooling, the precipitated product was filtered off to give compound **(3f)** (551 mg) as a colorless solid. The filtrate was evaporated *in vacuo* and the residue was taken up in dichloromethane (15 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 dichloromethane/ethyl acetate (10/90, v/v) affording compound **(3f)** (100 mg) as a colorless solid with a total yield of 51 %; mp : 249°C (dichloromethane); IR (KBr, ν cm^{-1}) : 3402 (OH, NH),

1666 (CO); ^{1}H NMR ($CDCl_3$) : δ 5.18 (br s, 2H, CH_2N), 5.78 (br s, 2H, NH_2), 6.77 (s, 1H, =CH), 7.02 (td, J_1= 1.2 Hz, J_2= 7.6 Hz, 1H, ArH), 7.13 (dd, *J*= 1.5 Hz, *J*= 6.8 Hz, 1H, ArH), 7.22 (br d, *J*= 8.7 Hz, 2H, ArH), 7.28-7.35 (m, 1H, ArH), 7.42-7.45 (m, 4H, ArH), 7.62 (br d, *J*= 8.7 Hz, 2H, ArH), 7.86-7.90 (m, 2H, ArH), 9.64 (s, 1H, OH); ^{13}C NMR ($CDCl_3$) : δ 53.1 (CH_2N), 112.8 (=CH), 122.4 (CH), 124.5 (CH), 125.7 (2CH), 126.1 (2CH), 126.7 (2CH), 128.0 (C), 128.9 (2CH), 130.0 (CH), 130.2 (CH), 130.7 (CH), 131.5 (C), 132.6 (C), 142.2 (C), 150.4 (C), 151.4 (C), 152.4 (CN), 167.2 (CO); Anal. Calcd for $C_{23}H_{19}N_3O_3$: C, 71.68; H, 4.97; N, 10.90. Found : C, 71.32; H, 5.13; N, 11.03; MS : m/z 386.5 (MH^+), 408 ($M + Na^+$).

5-(4-Bromophenyl)-2-phenyl-5,6-dihydro-4*H*-benzo[*b*][1,5]oxazocine (5): To a solution of **3b** (108 mg, 0.27 mmol) in dry tetrahydrofuran (3 mL) at 0°C, was added lithium aluminium hydride (20.2 mg, 0.53 mmol) and the resulting solution was further stirred at 0°C for another 1 h under oxygen free argon atmosphere. The mixture was hydrolysed with water (5 mL) and extracted with ethyl acetate (2 x 5 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and evaporated *in vacuo*. The crude product was chromatographed on silica gel, eluting with petroleum ether/ethyl acetate (90/10, v/v) affording compound (**5)** (41 mg, 39%) as a yellow solid ; mp : 160°C (ethyl acetate–petroleum ether); IR (KBr, ν cm^{-1}) : 1650 (C=C); ^{1}H NMR ($CDCl_3$) : δ 3.93 (d, *J*= 6.2 Hz, 2H, CH_2N), 4.57 (s, 2H, NCH_2), 5.81 (t, *J*= 6.2 Hz, 1H, =CH), 6.59 (dd, *J*= 2.2 Hz, *J*= 6.9 Hz, 2H, ArH), 6.97 (dd, *J*= 1.3 Hz, *J*= 7.9 Hz, 1H, ArH), 7.04 (dd, *J*= 1.4 Hz, *J*= 7.4 Hz, 1H, ArH), 7.11 (dd, *J*= 2.0 Hz, *J*= 7.7 Hz, 1H, ArH), 7.15-7.32 (m, 6H, ArH), 7.55-7.59 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$) : δ 44.9 (NCH_2), 52.0 (CH_2N), 108.7 (C), 109.9 (=CH), 114.3 (2CH), 122.6 (CH), 125.0 (CH), 126.2 (2CH), 128.5 (2CH), 128.9 (CH), 129.7 (CH), 131.0 (CH), 131.2 (C), 132.0 (2CH), 136.1 (C), 147.2 (C), 155.9 (C), 157.5 (C); Anal. Calcd for $C_{22}H_{18}NOBr$: C, 67.36; H, 4.62; N, 3.57. Found : C, 67.65; H, 4.45; N, 3.64; MS : m/z 392 (MH^+ [^{79}Br]), 394 (MH^+ [^{81}Br]).

X-Ray Structure Analysis of 3a : $C_{23}H_{19}NO_3$, Mr ($g.mol^{-1}$), 357.39; temperature 296(2) °K; crystal size 0.37x0.15x0.10 mm; wavelength (λ) 1.54180 Å ; cristal system monoclinic; space group P 21/c ; unit cell dimensions a = 13.731(1) Å, α = 90°, b = 10.178(2) Å, β = 108.54(2)°, c = 13.765(3) Å, γ= 90°; crystal volume 1823.9(6) $Å^3$; Z, calculated density 4, 1.302 $Mg.m^{-3}$, absorption coefficient 0.694 mm^{-1}; F(000) 752; θ range for data collection 3.39 to 54.96° ; index ranges -14 ≤ h ≤13, 0 ≤ k ≤10, 0 ≤l ≤ 14; measured reflections 2277 ; Max. and min. transmission 0.9338 and 0.7833; extinction coefficient 0.0063(7). R (all data) : R1 = 0.0820 ; wR2 = 0.1527 ; Goof 1.098**.**

Selected bond lenghts [Å] and torsional angles[°]: C14-C15 1.328(5), C15-C16 1.478(5), C16-N9 1.366(4), C10-C11 1.513(4), C14-C15-C16-O21 -121.5(4), C14-C15-C16-N9 58.0(5), N9-C10-C11-C12 49.1(4), C11-C12-O13-C14 57.5(4) (see indexation on Figure 1). Crystallographic data have been deposited at the

Cambridge Crystallographic Data Centre as supplementary publication no CCDC 207399.

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