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STUDY OF *BIS*CARBAMATES DERIVED FROM 2-AMINOBENZYLAMINES AS MODELS FOR ALCOHOL PRODRUGS

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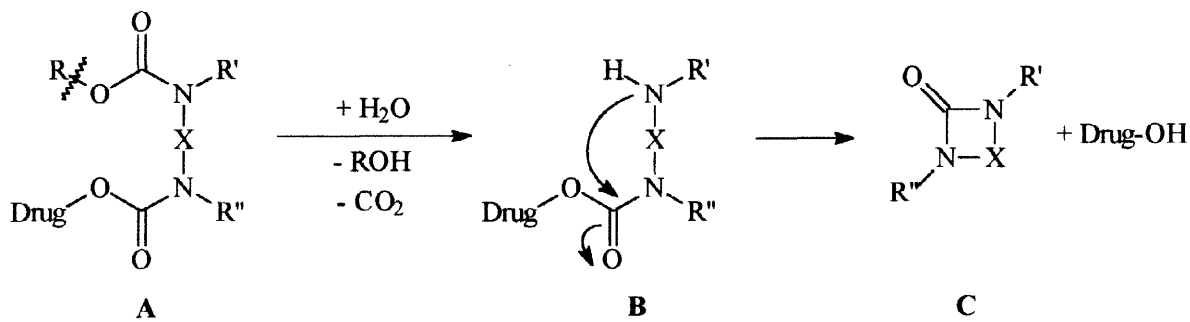
Abstract: Unsubstituted N-arylcarbamate of title compound does not cyclize to the corresponding cyclic urea, with ROH liberation, under mild conditions (40°C). Substitution of the benzylic position by two methyl groups promotes slow cyclisation while N-methylation of the N-aryl carbamate has a more important effect. Relative cyclisation rates are in agreement with barrier heights obtained from *ab initio* calculations. The calculations also suggest that the highest cyclisation rate of the latter is a consequence of the steric hindrance caused by the N-methyl substituent.

The efficiency of cancer chemotherapy is mainly limited by the lack of selectivity of cytotoxic agents for cancer cells. In order to avoid this drawback the use of non-toxic prodrugs, converted to the corresponding drug by an enzyme which is either targeted (ADEPT protocol)[1] or present in higher concentration in necrotic areas (*i.e.* β-glucuronidase), is an area of great current interest.[2,3] The required plasma stability of the prodrug rules out esters or carbonates as connecting groups between the active moiety and the enzyme substrate. Thus carbamates have been mainly studied, but few known anticancer agents have an amino group for this purpose (doxorubicin, mitomycin C,...) and thus it seems worthwhile to explore new approaches to prepare prodrugs linked to an hydroxyl, a more ubiquitous group among these drugs.

We now propose a *bis*carbamate structure such as **A** (Scheme 1). Cleavage of the first carbamate may be carried out as for amine prodrugs (eventually after a first spacer decomposition) and decarboxylation of the resulting carbamic acid should give aminocarbamate **B** which may then cyclize to cyclic urea **C** with elimination of Drug-OH.



A **B** **C**

Scheme 1

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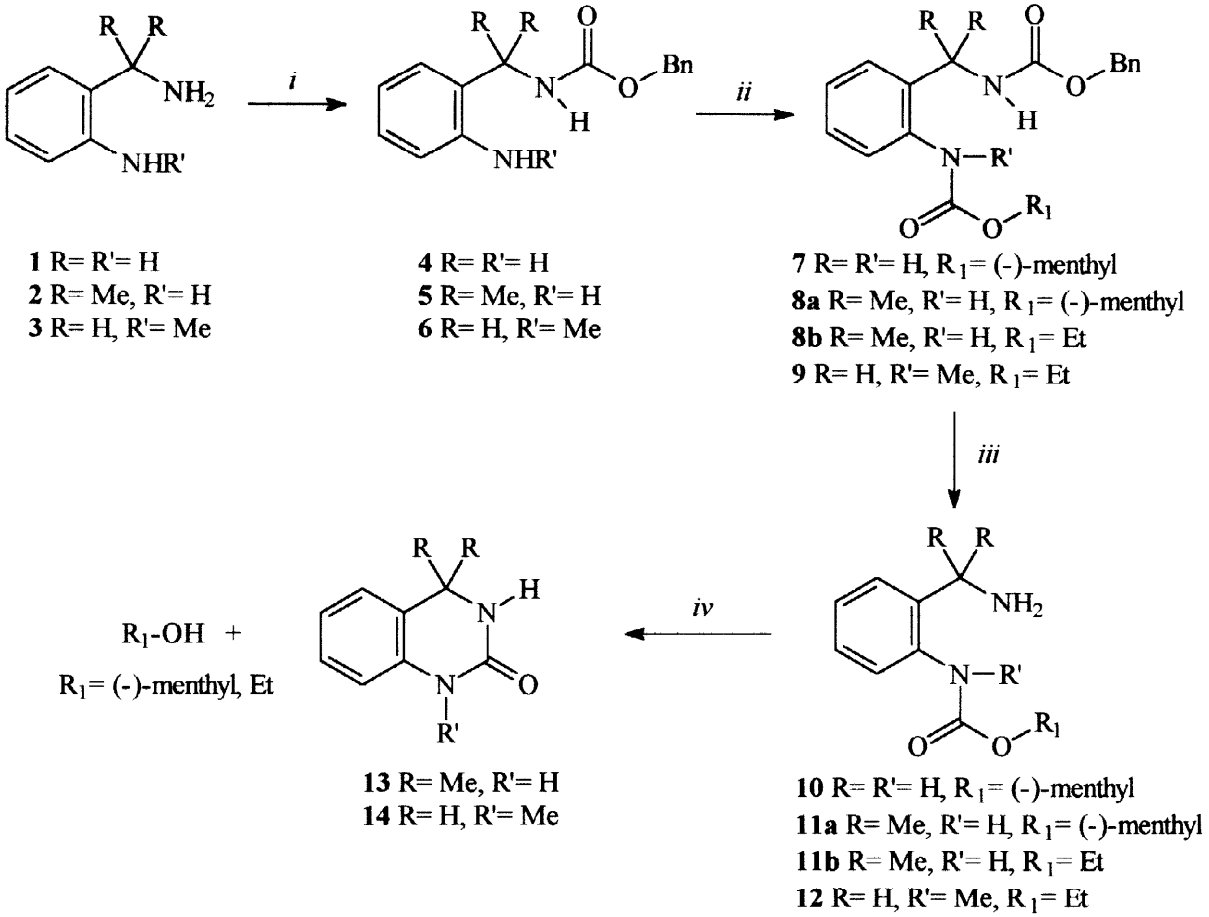
The spacer group X should be designed to induce fast decomposition of **B** under physiological conditions. Recently, a related approach has been published by Monneret[4] using the cyclisation of a phenol with an *ortho*-substituted carbamate (a process studied earlier by Hutchins[5] and Vigroux and Bergon[6]), thereby liberating a phenolic nitrogen mustard. Scheeren[7] and Haisma[3] have proposed a strategy based on the hydrolysis of a carbamate to generate an amine followed by an attempted internal nucleophilic displacement of another amine from an amide moiety. However no cyclisation was observed after carbamate hydrolysis with an aliphatic or an *ortho*-substituted benzyl spacer.[3]

These observations led us to study the preparation and behavior of model *bis*carbamates derived from substituted 2-aminobenzylamines. Key features of such structures are the presence of two structurally different amines and possible nitrogen, ring and benzyl substitutions for steric or electronic control.[8,9] These model studies were carried out with diamines **1-3** (Scheme 2).



1 R= R'= H
2 R= Me, R'= H
3 R= H, R'= Me

4 R= R'= H
5 R= Me, R'= H
6 R= H, R'= Me

7 R= R'= H, R_1= (-)-menthyl
8a R= Me, R'= H, R_1= (-)-menthyl
8b R= Me, R'= H, R_1= Et
9 R= H, R'= Me, R_1= Et

10 R= R'= H, R_1= (-)-menthyl
11a R= Me, R'= H, R_1= (-)-menthyl
11b R= Me, R'= H, R_1= Et
12 R= H, R'= Me, R_1= Et

13 R= Me, R'= H
14 R= H, R'= Me

Reagents and conditions: *i:* $BnOCOOpNO_2Ph$, Et_3N; *ii:* R_1OCOCl, pyridine; *iii:* H_2, 10% Pd/C, EtOH; *iv:* CH_2Cl_2, 20-40°C.

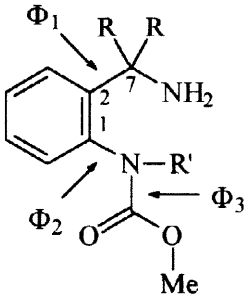
Scheme 2

The novel amine **2** was prepared from 2-aminobenzonitrile and MeMgI (6 eq.) by extension of the procedure of Laurent (in 59% yield as its hydrochloride salt)[10] and, amine **3**[11] was prepared by reduction (H_2, Pd/C, AcOH) of N-methyl-2-aminobenzonitrile. Condensation of benzyl *para*-nitrophenyl carbonate[12] with **1-3,**

respectively, afforded the *mono*carbamates **4-6** (60%, except for **5**: 25%) which upon treatment with either (-)-menthyl chloroformate or ethyl chloroformate[13] gave *bis*carbamates **7-9** (80-85%). Hydrogenolysis (10% Pd/C, EtOH, 20°C, 20-60 min) of the benzyl group afforded amines **10-11a,b** from *bis*carbamates **7-8a,b** in over 95% yield.

No cyclization was observed in CH_2Cl_2 or EtOH from **10** after 48 h at rt or after 24 h at 40°C (**10** was recovered unchanged). Slow cyclization of **11a,b** to **13**[14] was observed at 40°C in CH_2Cl_2 (**11/13** ratio: 3/2 after 20 h). Hydrogenolysis of **9** as above (1 h) gave a mixture of the expected amine **12** and the cyclized urea **14**[14] (2/1 to 2/3 ratio depending on experiments).[15] Cyclization of **12** to **14** (93% overall yield from **9**) was completed in 6.5 h at 40°C in CH_2Cl_2. Indeed, as expected, cyclization was found to proceed more rapidly under protic conditions : **12** was converted to **14** in EtOH/ 0.02M phosphate buffer (pH 4.5 and pH 7, 37°C) in 0.5 h.[16]

These results show that cyclization is induced by substitution at the benzylic position and more rapidly by N-methylation of the aromatic amine. The latter effect has been observed in the cyclization of a phenol with an *ortho*-substituted carbamate by Hutchins (although at high pH) and a conformational effect was tentatively proposed. To obtain a deepened understanding of the factors controlling the rates of cyclization (step iv in Scheme 2), we have performed *ab initio* calculations[17] on model reactions. From our experiments, these rates appear R- and R'- sensitive but R_1- nonsensitive. Thus, we have studied these cyclizations using **15**, **16** and **17** as model reactants respectively for **10**, **11** and **12** (figure 1).



15 R=R'= H
16 R= Me, R'= H
17 R= H, R'= Me

Torsion angles:

Φ_1: N-C(7)-C(2)-C(1)
Φ_2: C(=O)-N-C(1)-C(2)
Φ_3: O=C-N-C(1)

Figure 1

Table 1. 15-, 16- and 17-Cyclisation transition structures. Energetics and key geometrical parameters.

Transition Structure	RHF/3-21G[(a)]	B3LYP/6-31G* //RHF /3-21G[(a)(b)]	N–C[(c)]	N–H[(c)]	O–H[(c)]	C–O[(c)]
15-TS	–602.985953(60.7)	–610.062711(55.2)	1.602	1.231	1.329	1.357
16-TS	–680.631071(58.1)	–688.689088(52.8)	1.587	1.230	1.333	1.359
17-TS	–641.798277(52.6)	–649.365355(48.5)	1.592	1.232	1.334	1.358

(a) Energies in hartrees (Barrier heights in kcal/mol are indicated in parentheses).

(b) Density-functional energy calculations on RHF/3-21G geometries.

(c) Distances in Å. N, C, H and O atoms are those involved in the four center transition structures.

The transition structures (TS) were located at the RHF/3-21G level. The energetics and some geometrical parameters are reported in Table 1.

The examination of these TS reveals that the cyclization and the hydrogen migration are concerted (Figure 2). Such four-center transition states in carbonyl additions have already been obtained from *ab initio* calculations.[18] The barrier heights are slightly reduced upon including electron correlation at the density-functional B3LYP/6-31G* level of calculation,[19] but they remain in the same order. The calculated barrier heights are in good agreement with the experimental observations under aprotic conditions : the cyclization of **12** was complete in 6.5 h whereas **10** did not cyclize in 24 h.

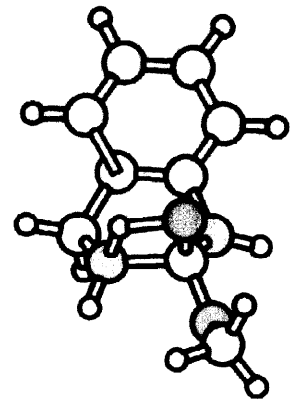


Figure 2 : **15** TS (Atoms : N : light grey ; O : grey ; C,H : white)

The predicted 8 kcal/mol difference in barrier heights is consistent with experimental observation regarding reactivity. The barrier to cyclization of **16** is intermediate in comparison with **15** and **17**. Thus, it would be expected that the rate of cyclization of **11** would also be intermediate. The 40% cyclization of **11** after 20 h supports this analysis. The satisfying agreement between the relative *ab initio* barrier heights and the experimentally observed rates is probably related to the fact that these experiments were conducted in an aprotic solvent (CH_2Cl_2). The examination of some key geometrical parameters (Table 1) show that the three TS are very similar. Therefore, the differences in the calculated barrier heights should originate in the reactant structures. The Φ_1, Φ_2 and Φ_3 torsion angles as defined in Figure 1 are expected to be key geometrical parameters for the reactants. Their values for the lowest energy conformer for each reactant are reported in Table 2.

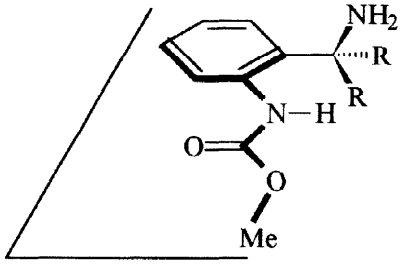
Table 2. 15, 16 and 17 model reactants. Energetics and geometrical parameters.

Reactant	RHF/3-21G[(a)]	B3LYP/6-31G* //RHF /3-21G[(a)(b)]	Φ_1[(c)]	Φ_2[(c)]	Φ_3[(c)]
15	–603.082603	–610.150713	53.6	168.4	–1.8
16	–680.723576	–688.773284	46.5	170.2	–1.9
17	–641.882168	–649.442610	90.9	–80.1	4.7

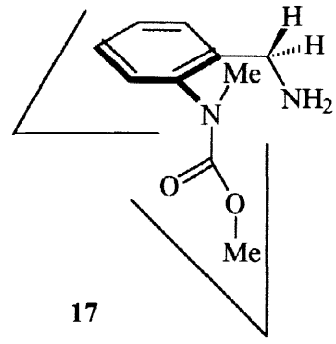
(a) Energies in hartrees.
(b) Density-functional energy calculations on RHF/3-21G geometries.
(c) Torsions angles in degrees.

A significant difference appears between **17** (Φ_2 = –80.1°) and **15** and **16** ($\Phi_2 \approx 170°$). The reason is probably the steric hindrance caused by the N-methyl group in **17**. Then, the conjugation between the benzenic

ring and the carbamate group in **15** and **16** no longer holds in **17** (Figure 3).[20] This effect induces a relative destabilisation of **17**.[21] Since the geometries of the TS's are very similar (Table 1), this explains the corresponding lower barrier height. This barrier height is indeed lower than the corresponding **15** and **16** barrier heights by 8 and 5.4 kcal/mol respectively.



15 R= H
16 R= Me



17

Figure 3

In conclusion, the liberation of an alcohol species from a *bis*carbamate after initial cleavage of the benzylic carbamate group is possible under mild conditions using compounds such as **12**. Introduction of an N-alkyl group on the aromatic amine appears essential for mild cyclization. Thus, for example, it is anticipated that formation of the benzylic amino group following glucuronide hydrolysis (the glycoside may be directly connected via a carbamate group[3] or via a suitable self-immolative spacer[22,23]) should result in ROH liberation. Further studies are underway.

Experimental section

Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR were recorded on a 300 MHz (Bruker Advance DPX300) spectrometer with TMS as internal standard. High resolution MS were performed by the "Service Central de Microanalyse" (CNRS, Lyon). Organic extract mixtures were dried over anhydrous $MgSO_4$, filtered and the solvent was then removed under reduced pressure. All separations were done under flash chromatography conditions on silica gel (Matrex, 25-40 mμ) and thin layer chromatography (TLC) were performed on silica gel plates (Merck, $60GF_{254}$).

2-(1-Amino-1-methylethyl)aniline (2). A solution of CH_3MgBr (50 mL, 3 M in Et_2O) was introduced in 80 mL of toluene at reflux. 2-Aminobenzonitrile (22.3 mmol) was then added and the reaction mixture was stirred at reflux for 3 h. Toluene was removed (rotavapor) and the residue was diluted with a saturated aqueous solution of sodium carbonate. The mixture was extracted with CH_2Cl_2. The residue was acidified with a solution of EtOH/HCl (5/0.8; v/v) to obtain the hydrochloride salt. After evaporation of the solvents under reduced pressure, dilution with MeOH and filtration of insoluble material, CH_2Cl_2 was added until the

hydrochloride salt precipitated as an oil. Yield : 59%; gum; ^{1}H NMR (CD_3SOCD_3) δ (ppm) : 1.69 (s, 6 H), 6.72 (dd, 1H, *J* 7.5 Hz), 6.90 (d, 1 H, *J* 7.5 Hz), 7.08 (dd, 1 H, *J* 7.5 Hz), 7.16 (d, 1 H, *J* 7.5 Hz); ^{13}C NMR (CD_3SOCD_3) δ (ppm) : 25.8, 56.0, 118.4, 120.0, 125.7, 127.2, 128.8, 144.7; HRMS: $C_9H_{14}N_2$ calculated: 150.1157, found: 150.1174.

General method for the synthesis of *mono*carbamates 4-6.

To a solution of substituted 2-aminobenzylamine (**1-3**) in DMF (3 mL/mmol) was added benzyl *para*-nitrophenyl carbonate (0.5 eq) and triethylamine (1.5 eq). The reaction mixture was stirred at room temperature for 12 h under nitrogen atmosphere. The solvent was removed and the residue dissolved in CH_2Cl_2. A saturated aqueous solution of sodium carbonate was added and the organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to afford the crude *mono*carbamate. Purification was done by flash-chromatography using ethyl acetate/petroleum ether.

Benzyl N-(2-aminobenzyl)carbamate (4). Yield : 60%; mp 74 °C; ^{1}H NMR ($CDCl_3$) δ (ppm) : 4.17 (broad s, 2 H), 4.30 (d, 2 H, *J* 6.0 Hz), 5.05 (broad s, 1 H), 5.12 (s, 2 H), 6.66 to 6.70 (m, 2 H), 7.02 to 7.13 (m, 2 H), 7.35 (s, 5 H); ^{13}C NMR ($CDCl_3$) δ (ppm) : 42.7, 67.0, 116.0, 118.2, 122.0, 128.1, 128.2, 128.5, 129.0, 130.0, 137.2, 145.2, 157.0; FABHR: $C_{15}H_{16}N_2O_2$ MH^+ calculated: 257.1290, MH^+ found: 257.1283.

Benzyl N-(1-(2-aminophenyl)-1-methylethyl)carbamate (5). Yield 25%; oil; ^{1}H NMR ($CDCl_3$) δ (ppm) : 1.71 (s, 1 H), 1.50 (broad s, 2 H), 5.01 (s, 2 H), 5.23 (broad s, 1 H), 6.59 (d, 1 H, *J* 7.8 Hz), 6.73 (dd, 1 H, *J* 7.8 Hz), 7.05 (dd, 1 H, *J* 7.8 Hz), 7.21 (d, 1 H, *J* 7.8 Hz), 7.28 (s, 5 H); ^{13}C NMR ($CDCl_3$) δ (ppm) : 27.0, 55.9, 66.7, 115.6, 117.8, 118.6, 126.4 to 128.9, 136.1, 144.1, 162.6; HRMS: $C_{17}H_{20}N_2O_2$ calculated: 284.1525, found: 284.1515.

Benzyl N-(2-(methylamino)benzyl)carbamate (6). Yield 60%; oil; ^{1}H NMR ($CDCl_3$) δ (ppm) : 2.81 (s, 3 H), 4.28 (d, 2 H, *J* 6.1 Hz), 4.68 (broad s, 1 H), 4.99 (broad s, 1 H), 5.12 (s, 2 H), 6.60 to 6.66 (m, 2 H), 7.02 (d, 1 H, *J* 7.3 Hz), 7.20 (dd, 1 H, *J* 7.5 Hz), 7.35 (s, 5 H); ^{13}C NMR ($CDCl_3$) δ (ppm) : 30.4, 42.7, 67.0, 109.8, 116.1, 122.4, 128.0, 128.1, 128.6, 129.5, 130.1, 136.4, 147.6, 157.1; HRMS: $C_{16}H_{18}N_2O_2$ calculated: 270.1368, found: 270.1350.

General method of preparation of *bis*carbamates 7-9.

To a solution of *mono*carbamate (**4-6**) in DMF (5 mL/mmol) was added ethyl chloroformate or menthyl chloroformate (1.3 eq) and pyridine (10 eq). After stirring for 2 h, at room temperature, under nitrogen atmosphere, the solvent was removed and the residue dissolved in CH_2Cl_2. After successive washings with a

solution of HCl (0.1 N) and water, the organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to afford the crude *bis*carbamate which was purified by flash column using ethyl acetate/petroleum ether.

Menthyl N-(2-(benzyloxycarbonylamino)benzyl)carbamate (7). Yield : 80%; mp 98 °C; ^{1}H NMR ($CDCl_3$) δ (ppm) : 0.83 (d, 3 H, *J* 7.1 Hz), 0.91 (d, 6 H, *J* 7.1 Hz), 1.00 to 2.20 (m, 9 H), 4.30 (d, 2 H, *J* 6.1 Hz), 4.67 (td, 1 H, *J* 10.8 and 4.3 Hz), 5.12 (s, 2 H), 5.29 (broad s, 1 H), 7.04 (dd, 1 H, *J* 8.0 Hz), 7.18 (d, 1 H, *J* 8.0 Hz), 7.29 (dd, 1 H, *J* 8.0 Hz), 7.33 (s, 5 H), 7.88 (d, 1 H, *J* 8.0 Hz), 8.08 (broad s, 1 H); ^{13}C NMR ($CDCl_3$) δ (ppm) : 16.8, 20.8, 22.1, 24.0, 26.7, 31.6, 34.5, 41.5, 42.1, 47.4, 67.3, 75.4, 122.8, 124.2, 128.2, 128.3, 128.6, 128.9, 130.1, 136.4, 136.8, 154.5, 157.1; FABHR: $C_{26}H_{34}N_2O_4$ MH^+calculated: 439.2599, MH^+found: 439.2610.

Menthyl N-(2-(1-benzyloxycarbonylamino-1-methylethyl)phenyl)carbamate (8a). Yield 85%; oil; ^{1}H NMR ($CDCl_3$) δ (ppm) : 0.80 (d, 3 H, *J* 7.1 Hz), 0.91 (d, 6 H, *J* 7.1 Hz), 1.70 (s, 6 H), 1.00 to 2.20 (m, 9 H), 4.67 (td, 1 H, *J* 10.8 and 4.3 Hz), 5.00 (s, 2 H), 5.12 (s, 1 H), 7.06 (dd, 1 H, *J* 7.6 Hz), 7.19 to 7.35 (m, 7 H), 7.71 (broad s, 1 H), 7.86 (d, 1 H, *J* 7.6 Hz); ^{13}C NMR ($CDCl_3$) δ (ppm) : 16.6, 20.7, 22.1, 23.7, 26.5, 27.9, 31.4, 34.3, 41.3, 47.1, 55.6, 66.8, 75.1, 123.9, 125.9, 126.1, 127.7 to 128.7, 135.7, 136.0, 153.7, 155.3; HRMS: $C_{28}H_{38}N_2O_4$ calculated: 466.2832, found: 466.2826.

Ethyl N-(2-(1-benzyloxycarbonylamino-1-methylethyl)phenyl)carbamate (8b). Yield 85%; oil; ^{1}H NMR ($CDCl_3$) δ (ppm) : 1.28 (t, 3 H, *J* 7.1 Hz), 1.70 (s, 6 H), 4.19 (q, 2 H, *J* 7.1 Hz), 5.01 (s, 2 H), 5.13 (s, 1 H), 7.06 (dd, 1 H, *J* 7.9 Hz), 7.20 to 7.36 (m, 7 H), 7.80 (broad s, 1 H), 7.86 (d, 1 H, *J* 7.9 Hz); ^{13}C NMR ($CDCl_3$) δ (ppm) : 14.7, 28.0, 55.6, 61.2, 66.8, 123.9, 125.9, 126.1, 127.7 to 128.7, 135.6, 136.0, 153.9, 155.3; HRMS: $C_{20}H_{24}N_2O_4$ calculated: 356.1737, found: 356.1736.

Ethyl N-(2-(benzyloxycarbonylamino)benzyl)-N-methylcarbamate (9). Yield 81%; oil; ^{1}H NMR ($CDCl_3$) δ (ppm) : 1.11 and 1.30 (2 broad s, 3 H), 3.21 (s, 3 H), 4.00 to 4.70 (m, 4 H), 5.12 (s, 2 H), 7.10 to 7.45 (m, 9 H); ^{13}C NMR ($CDCl_3$) δ (ppm) : 14.8, 37.8, 41.1, 61.9, 66.6, 126.0 to 130.0, 135.7, 137.0, 155.6, 156.5; HRMS: $C_{19}H_{22}N_2O_4$ calculated: 342.1580, found: 342.1582.

General procedure of hydrogenolysis.

B*is*carbamates **7-9** were diluted in EtOH (40 mL/mmol) with a catalytic amount of 10% Pd/C. The reaction mixture was stirred at room temperature under a hydrogen atmosphere until total hydrogenolysis of the benzyl group (20-60 min) was completed. After filtration of the catalyst, EtOH was removed and the residue dissolved in CH_2Cl_2. The cyclisation rate was followed by TLC and ^{1}H NMR.

Menthyl N-(2-(aminomethyl)phenyl)carbamate (10). Yield 100%; oil; ^{1}H NMR ($CDCl_3$) δ (ppm) : 0.83 (d, 3 H, *J* 7.1 Hz), 0.91 (d, 6 H, *J* 7.1 Hz), 1.00 to 2.20 (m, 9 H), 3.97 (s, 2 H), 4.67 (td, 1 H, *J* 10.8-4.3 Hz), 6.94 (dd, 1 H, *J* 8.0 Hz), 7.08 (d, 1 H, *J* 8.0 Hz), 7.27 (dd, 1 H, *J* 8.0 Hz), 8.03 (d, 1 H, *J* 8.0 Hz), 9.76 (broad s, 1 H); ^{13}C NMR ($CDCl_3$) δ (ppm) : 16.8, 20.8, 22.1, 24.0, 26.7, 31.6, 34.5, 41.5, 45.7, 47.4, 74.8, 120.3, 122.5, 125.2, 128.3, 128.9, 139.1, 154.0; HRMS: $C_{18}H_{28}N_2O_2$ calculated: 304.2151, found: 304.2143.

Menthyl N-(2-(1-amino-1-methylethyl)phenyl)carbamate (11a). Yield 100%; oil; ^{1}H NMR ($CDCl_3$) δ (ppm) : 0.82 (d, 3 H, *J* 7.0 Hz), 0.91 (d, 6 H, *J* 7.2 Hz), 1.70 (d, 6 H, *J* 8.3 Hz), 1.00 to 2.20 (m, 9 H), 4.67 (td, 1H, *J* 10.9 and 4.3 Hz), 6.96 (dd, 1 H, *J* 8.3 Hz), 7.22 to 7.27 (m, 2 H), 8.06 (d, 1 H, *J* 8.3 Hz), 11.30 (broad s, 1 H); ^{13}C NMR ($CDCl_3$) δ (ppm) : 16.8, 20.7, 22.1, 23.9, 26.6, 31.5, 32.2, 34.4, 41.5, 47.3, 53.6, 74.3, 121.2, 122.3, 125.8, 127.9, 134.0, 138.7, 153.9; HRMS: $C_{20}H_{32}N_2O_2$ calculated: 332.2464, found: 332.2450.

Ethyl N-(2-(1-amino-1-methylethyl)phenyl)carbamate (11b). Yield 100%; oil; ^{1}H NMR ($CDCl_3$) δ (ppm) : 1.32 (t, 3 H, *J* 7.1 Hz), 1.56 (s, 6 H), 4.22 (q, 2 H, *J* 7.1 Hz), 6.96 (m, 1 H), 7.22 to 7.27 (m, 2 H), 8.08 (d, 1H, *J* 8.2 Hz), 11.43 (broad s, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm) : 14.8, 31.8, 53.7, 60.6, 120.8, 122.2, 125.8, 127.9, 133.8, 138.6, 154.0; HRMS: $C_{12}H_{18}N_2O_2$ calculated: 222.1368, found: 222.1364.

4,4-Dimethyl-1,2,3,4-tetrahydro-2-quinazolinone (13). Yield : 27% from **11b** (recovered starting material : 33%); mp 148 °C (mp_{Litt}[14] 161°C); ^{1}H NMR ($CDCl_3$) δ (ppm) : 1.56 (s, 6 H); 5.41 (broad s, 1 H); 6.75 (d, 1 H, *J* 7.8 Hz); 6.98 (dd, 1 H, *J* 7.8 Hz); 7.14 to 7.19 (m, 2 H); 8.12 (broad s, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm) : 31.2, 54.7, 114.4, 122.5, 123.9, 126.9, 128.2, 135.3, 154.6; HRMS: $C_{10}H_{12}N_2O$ calculated: 176.0950, found: 176.0951.

1-Methyl-1,2,3,4-tetrahydro-2-quinazolinone (14). Yield : 93% from **9** (one pot); mp 134 °C (mp_{Litt}[11] 143°C); ^{1}H NMR ($CDCl_3$) δ (ppm) : 3.30 (s, 3 H), 4.43 (s, 2 H), 5.92 (broad s, 1 H), 6.87 (d, 1 H, *J* 7.0 Hz), 6.98 (dd, 1 H, *J* 7.0 Hz), 7.04 (d, 1 H, *J* 7.0 Hz), 7.25 (dd, 1 H, *J* 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ (ppm) : 29.6, 43.0, 112.9, 120.4, 122.0, 125.6, 128.1, 139.5, 156.2; HRMS: $C_9H_{10}N_2O$ calculated: 162.0793, found: 162.0793.

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16. Cyclisation was followed by HPLC : reverse phase column : Zorbax, 5 μ ODS, 25 x 4.6 mm) ; eluent : 1/1 acetonitrile/0.02 M phosphate buffer (pH 4.5 or 7), UV detection at 486 nm. Retention time: **12**: 14.7 min ; **14** : 5.2 min.

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