NOVEL REARRANGEMENT OF PYRROLO[2,1-*c*][1,4]BENZODIAZEPINES INTO PYRROLO[2,1-*b*]QUINAZOLINONES, ANALOGOUS OF ALKALOID, VASICINONE

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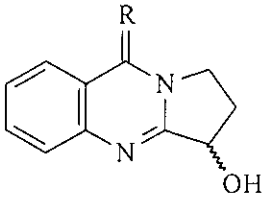
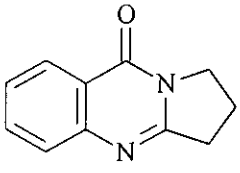
Abstract —Tetrahydropyrrolo[2,1-*c*][1,4]benzodiazepin-5,11-diones **(4)** and **(22-24)** in concentrated hydrochloric acid rearranged after 30 min into new oxohexahydropyrrolo[2,1-*b*][1,4]quinazolinecarboxylic acids **(5)** and **(25-27)** in good yields. Quinazolinone **(5)** was then treated in various conditions to lead to the corresponding esters and carboxamides **(28-34)**.

INTRODUCTION

Vasicinone **(1)** is known as one of the pyrrolo[2,1-*b*]quinazoline alkaloids isolated from the leaves and the inflorescence of *Justicia Adhatoda* Nees which was used in medicine as a remedy for cold, cough, bronchitis and asthma.[1] Due to their pharmacological properties, compound **(1)** and its derivatives such as vasicine **(1')**, desoxyvasicinone **(2)** and dihydrovasicinone **(3)** (Scheme 1) arouse a constant interest and are always the subject of many reports.[2-4] However their activities such as bronchodilators[5] or anticholinesterasic[6] are always the subject of controversies.



1 : R = O
1' : R = H_2



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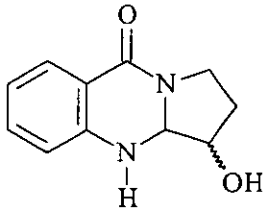
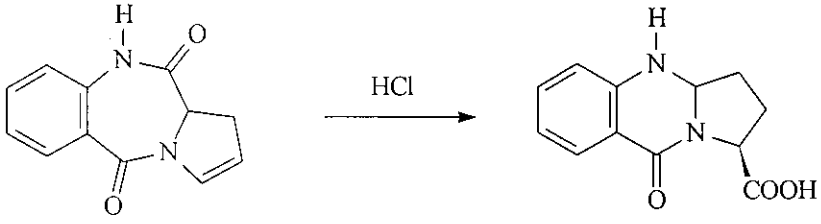


3

Scheme 1

As part of our program to study new rearrangements of pyrrolo[2,1-*c*][1,4]benzodiazepines, we have recently reported the synthesis of new cyclopenta[*b*][1,4]benzodiazepines[7,8] and new pyrrolo[2,1-*b*]quinazolinones.[9] This new type of compound, analogous of vasicinone derivatives mentioned above, was the unexpected result of treatment of compound **(4)** in acidic medium (Scheme 2).

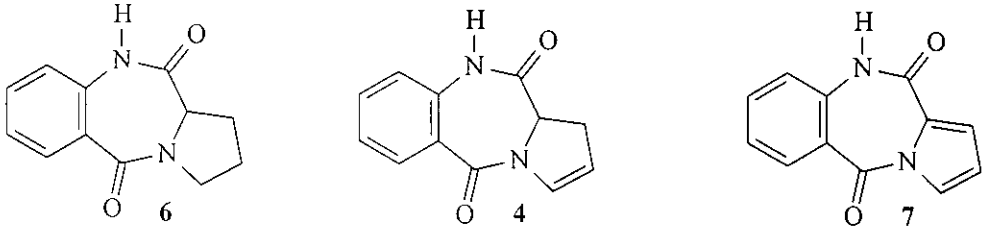


4 **5**

Scheme 2

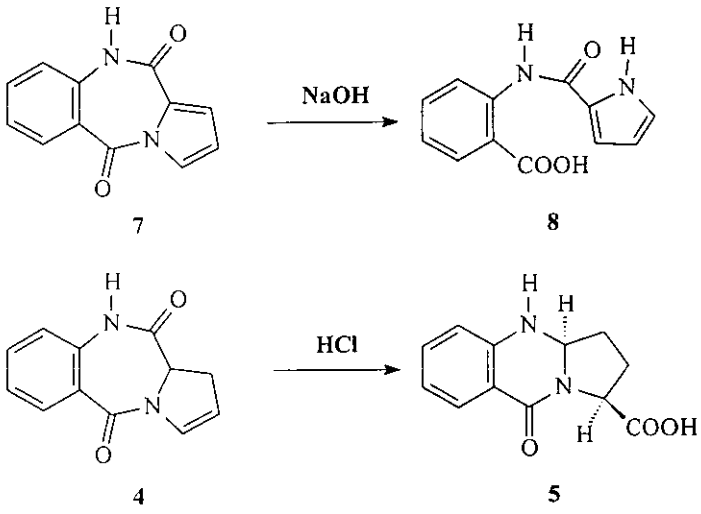
RESULTS AND DISCUSSION

We first studied the stability of benzodiazepines **(4), (6)** and **(7)** in acidic or alkaline medium (Scheme 3).



Scheme 3

First of all, we noted that no change occurred on compound **(6)**[10] whatever the nature of the medium. Then, it appeared that in alkaline medium, compound **(7)**[8] opened spontaneously at room temperature affording the known *N*-(2-pyrrolylcarbonyl)anthranilic acid **(8)**[11] (Scheme 4). This result confirmed a previous report in which 7 led to the corresponding aldehyde by treatment with $LiAlH_4$.[12] In contrary, in acidic medium such as concentrated hydrochloric acid, only compound **(4)** has shown a different behavior and rearranged into a new compound **(5)**.

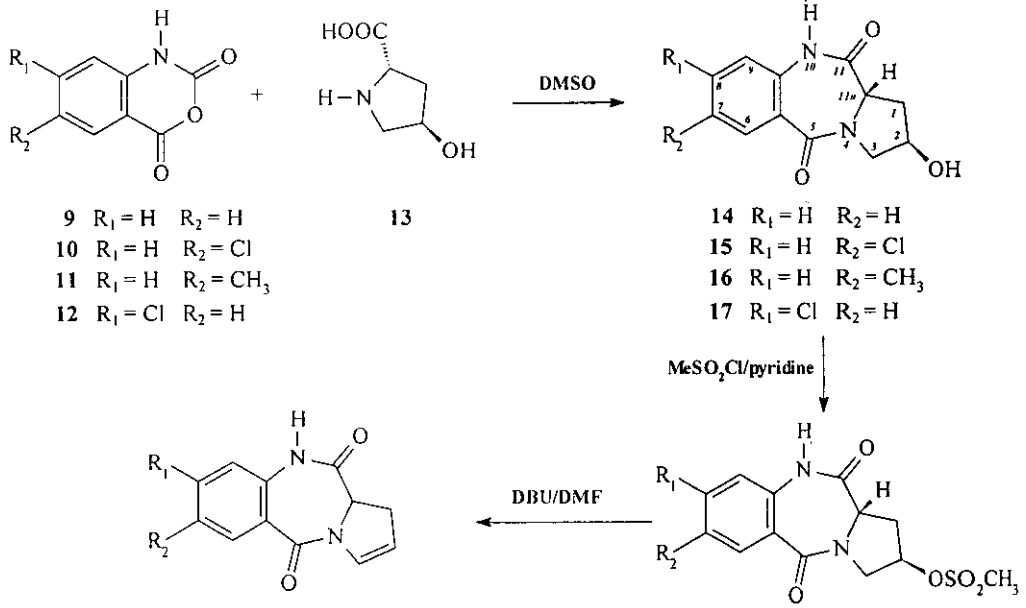


7 8

4 5

Scheme 4

The benzodiazepine **(4)** was synthesized from the condensation of isatoic anhydride **(9)** with the *trans*-4-hydroxy-L-proline **(13)** in dimethyl sulfoxide[13] under microwave heating. The resulted benzodiazepine **(14)** was treated with methanesulfonic chloride as described in 1996 by Gillard *et al.*[14] to lead to the mesylate **(18)** which one, heated in presence of DBU, gave the benzodiazepine **(4)** (Scheme 5). Racemisation proceeded under this reaction conditions due to H-11a deprotonation with DBU.



9 $R_1 = H$ $R_2 = H$
10 $R_1 = H$ $R_2 = Cl$
11 $R_1 = H$ $R_2 = CH_3$
12 $R_1 = Cl$ $R_2 = H$

13

14 $R_1 = H$ $R_2 = H$
15 $R_1 = H$ $R_2 = Cl$
16 $R_1 = H$ $R_2 = CH_3$
17 $R_1 = Cl$ $R_2 = H$

18 $R_1 = H$ $R_2 = H$
19 $R_1 = H$ $R_2 = Cl$
20 $R_1 = H$ $R_2 = CH_3$
21 $R_1 = Cl$ $R_2 = H$

4 $R_1 = H$ $R_2 = H$
22 $R_1 = H$ $R_2 = Cl$
23 $R_1 = H$ $R_2 = CH_3$
24 $R_1 = Cl$ $R_2 = H$

Scheme 5

Then, when compound (4) was heating a few min in concentrated hydrochloric acid, a new tricyclic system (5) was obtained in good yield (80%). To our knowledge, in spite of our first results briefly described,[9] there is no report of such a rearrangement. The structure and stereochemistry of compound (5) has been established by X-Ray analysis (Figure 1) on compound (29). Moreover, the analysis of ^{1}H NMR spectra permitted us to show that the reaction was diastereoselective. We have not yet found any satisfactory explanation about the diastereoselectivity of the cyclisation. This study is under investigation.

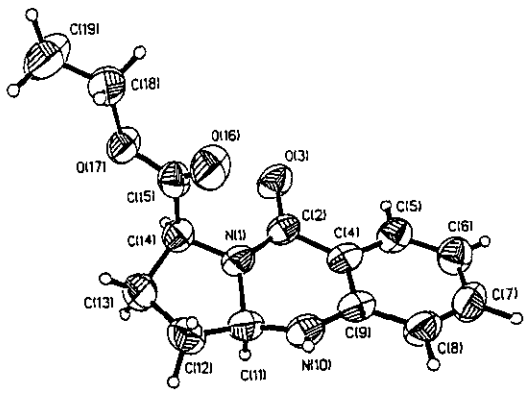
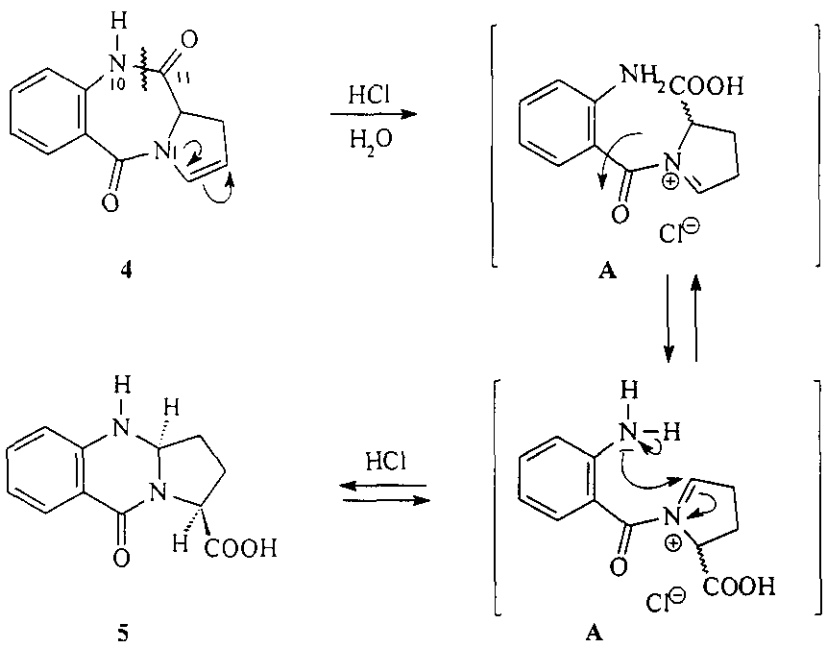


Figure 1 : ORTEP diagram of compound (29)

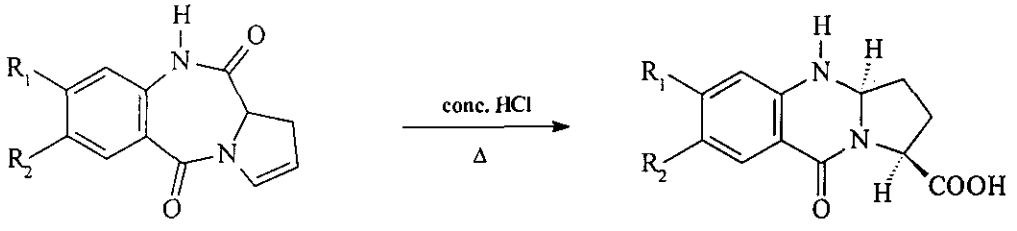
The mechanism of formation of 5 could be explained by the following pathway : under acidic conditions, the lactam N10-C11 bond of 4 would be cleaved to lead to an acyl-iminium form **A** which would rearrange to give the quinazolinone (5) as in Scheme 6.



4 A 5 A

Scheme 6

In an attempt of generalization to obtain various quinazolinones **(25-27)**, we synthesized other benzodiazepines **(22-24)** differently substituted on the aromatic nucleus by the same way as precedently described in Scheme 5. We submitted the obtained tetrahydropyrolo[2,1-*c*][1,4]benzodiazepines **(22-24)** to the same conditions than for compound **(4)** (Scheme 7). Our results are summarized in Table I. The quinazolinones **(25-27)** were obtained in good yields after heating a few min in concentrated hydrochloric acid.



22-24 **25-27**

Scheme 7

Table I : Synthesis of pyrrolo[2,1-*b*]quinazolinones **(25-27)**.

Compound	Product	R_1	R_2	Reaction time (min.)	Yield (%)
22	**25**	H	Cl	30	70
23	**26**	H	CH_3	30	75
24	**27**	Cl	H	30	70

At last, we decided to carry out the acid **(5)** (R_1=R_2=H) in various conditions to give the corresponding esters and carboxamides **(28-33)** as reported in Scheme 8 and Table II.

5 **28-33**

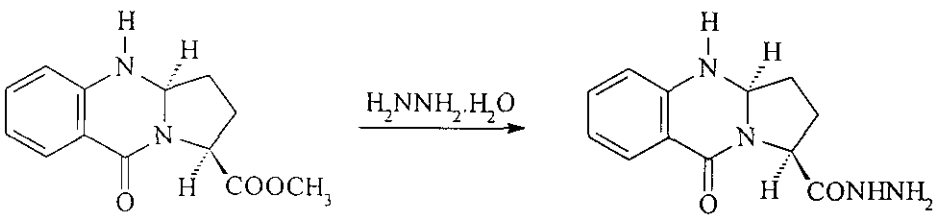
Scheme 8

Table II : Synthesis of esters and carboxamides **(28-33)**.

Product	Reactant	R	T (°C)	Reaction time	Yield* (%)
28	CH_3OH	OCH_3	65	1h	80
29	C_2H_5OH	OC_2H_5	80	1h	80
30	$(CH_3)_2CHOH$	$OCH(CH_3)_2$	80	1h	70
31	$(CH_3)_2CHCH_2NH_2$	$NHCH_2CH(CH_3)_2$	20	3h	50
32	$C_6H_5CH_2NH_2$	$NHCH_2C_6H_5$	20	3h	70
33	$(CH_3)_2CHNH_2$	$NHCH(CH_3)_2$	20	3h	70

* Pure isolated product.

The new derivatives of quinazolinones were obtained with good yields. Only compound **(34)** was synthesized by the condensation of ester **(28)** with one equivalent of hydrazine hydrate as in Scheme 9. The expected quinazolinone **(34)** was obtained rapidly with 60% yield.



28 **34**

Scheme 9

CONCLUSION

Studying the stability of various pyrrolo[2,1-*c*][1,4]benzodiazepines, we have brought to the formation of new pyrrolo[2,1-*b*]quinazolinecarboxylic acids. These compounds allowed us to develop several syntheses leading to esters and carboxamides derivatives.

ACKNOLEDGEMENTS

This work was supported by « Conseil Régional de Basse-Normandie ».

EXPERIMENTAL SECTION

General. Melting points were determined on a Kofler melting point apparatus and are uncorrected. IR spectra were taken with a Genesis Series FTIR spectrophotometer. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) were recorded on a JEOL Lambda 400 spectrometer. Chemical shifts are expressed in parts

per million downfield from tetramethylsilane as an internal standard. The MS spectra were taken on a JEOL JMS GCMate spectrometer at an ionizing potentiel of 70eV. Elemental analyses were performed at the "Institut de Recherche en Chimie Organique Fine" (Rouen). Reaction times were monitored by TLC until no starting material remained. TLC were performed on 0.2-mm precoated plates of silica gel 60F-264 (Merck). Visualization was made with UV light. Reactions under microwave heating were performed into Normatron® (Normalab) microwave reactor[15]. All solvents and reagents were purchased from Acros and Aldrich Chimie and used without further purification. Isatoic anhydride **(9)** is commercially available by Acros. 5-Chloroisatoic anhydride **(13)** is commercially available by Aldrich. 5-Methylisatoic anhydride **(14)** and 6-Chloroisatoic anhydride **(15)** were prepared from literature methods.[16,17]

Preparation of dilactams (14), (15), (16) and (17)

General procedure for compounds (14), (15), (16) and (17)

The anhydride **(9)**, **(10)**, **(11)** or **(12)** was diluted in 100 mL of dimethyl sulfoxide. After addition under stirring of *trans*-4-hydroxy-L-proline **(13)** (1.1 eq.), the mixture was refluxed under microwave heating (500W) for 30 min. The solution was then cooled and taken up in a mixture of ice and water. The precipitate was filtered, dried and crystallized from appropriate solvent.

(2R,11aS)-2-Hydroxy-1,2,3,10,11,11a-hexahydropyrrolo[2,1-c][1,4]benzodiazepin-5,11-dione **(14)**

See general procedure : anhydride **(9)** (56 g; 0.38 mol), *trans*-4-hydroxy-L-proline **(13)** (54 g ; 0.41 mol). **(14)** : pale crystals, 80% yield; mp 220°C (H_2O). *Anal.* Calcd for $C_{12}H_{12}N_2O_3$: C, 62.06 ; H, 5.21 ; N, 12.06. Found : C, 62.54 ; H, 5.19 ; N, 12.13. MS (m/z) : M^+ 232 (24). IR (cm^{-1}) : 3300-3600 (NH-OH) ; 1680 (CO) ; 1610 (CO). ^1H NMR (DMSO-d_6) δ: 1.93 (m, 1H, H*1*), 2.63 (m, 1H, H*1*), 3.45 (dd, 1H, J=12.2 and 4.3 Hz, H*3*), 3.65 (dd, 1H, J=12.2 and 2.5 Hz, H*3*), 4.21 (t, 1H, J=6.8 Hz, H*11a*), 4.34 (s, 1H, H*2*), 5.19 (d, 1H, J=3.9 Hz, OH), 7.12 (d, 1H, J=8 Hz, H*9*), 7.22 (t, 1H, J=8 Hz, H*7*), 7.51 (t, 1H, J=8 Hz, H*8*), 7.80 (d, 1H, J=8 Hz, H*6*), 10.54 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 34.3 (C*1*), 3.9 (C*3*), 55.1 (C*11a*), 67.3 (C*2*), 121.2 (C*9*), 123.8 (C*7*), 125.9 (C*5a*), 130.3 (C*6*), 132.0 (C*8*), 136.2 (C*9a*), 165.0 (C*5*), 170.2 (C*11a*). $[\alpha]_D$ = +374° (*c* =0.01, MeOH).

(2R,11aS)-7-Chloro-2-hydroxy-1,2,3,10,11,11a-hexahydropyrrolo[2,1-c][1,4]benzodiazepin-5,11-dione **(15)**

See general procedure : anhydride **(10)** (10 g; 50 mmol), *trans*-4-hydroxy-L-proline **(13)** (7.2 g ; 55 mmol). **(15)** : white crystals, 60% yield; mp 154°C (ethyl acetate). *Anal.* Calcd for $C_{12}H_{11}N_2O_3Cl$: C, 54.05 ; H, 4.16 ; N, 10.50. Found : C, 53.88 ; H, 4.10 ; N, 10.32. MS (m/z) : M^+ 266 (19). IR (cm^{-1}) :

3300-3600 (NH-OH) ; 1680 (CO) ; 1610 (CO). ^{1}H NMR (DMSO-d_6) δ: 1.93 (m, 1H, H*1*), 2.61 (m, 1H, H*1*), 3.48 (dd, 1H, J=12.0 and 4.8 Hz, H*3*), 3.60 (dd, 1H, J=12.0 and 3.5 Hz, H*3*), 4.27 (t, 1H, J=7 Hz, H*11a*), 4.31 (m, 1H, H*2*), 5.20 (d, 1H, J=4 Hz, OH), 7.15 (d, 1H, J=8.6 Hz, H*9*), 7.59 (dd, 1H, J=8.6 and 2.2 Hz, H*8*), 7.74 (d, 1H, J=2.2 Hz, H*6*), 10.67 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 34.2 (C*1*), 53.9 (C*3*), 55.1 (C*11a*), 67.2 (C*2*), 123.2 (C*Ar*), 127.3 (C*Ar*), 127.8 (C*Ar*), 129.4 (C*Ar*), 131.8 (C*Ar*), 135.2 (C*Ar*), 163.7 (C*5*), 170.0 (C*11a*). $[\alpha]_D$ = +353° (c =0.01, MeOH).

***(2R,11aS)-7-Methyl-2-hydroxy-1,2,3,10,11,11a-hexahydropyrrolo[2,1-c][1,4]benzodiazepin-5,11-dione* (16)**

See general procedure : anhydride **(11)** (2.15 g; 12 mmol), *trans*-4-hydroxy-L-proline **(13)** (1.75 g ; 13 mmol). **(16)** : white crystals, 55% yield; mp 208°C (ethyl acetate). *Anal.* Calcd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.72 ; N, 11.37. Found : C, 63.29 ; H, 5.53 ; N, 11.45. MS (m/z) : M^+ 246 (50), 228 (- H_2O, 3). IR (cm^{-1}) : 3460 (OH) ; 3220 (NH) ; 1670 (CO) ; 1620 (CO). ^{1}H NMR (DMSO-d_6) δ: 1.92 (m, 1H, H*1*), 2.31 (s, 3H, CH_3), 2.62 (m, 1H, H*1*), 3.45 (dd, 1H, J=12 and 4.5 Hz, H*3*), 3.62 (dd, 1H, J=12 and 3.4 Hz, H*3*), 4.13 (t, 1H, J=6.6 Hz, H*11a*), 4.31 (m, 1H, H*2*), 5.13 (d, 1H, J=3.2 Hz, OH), 7.01 (d, 1H, J=8.0 Hz, H*9*), 7.31 (d, 1H, J=8.0 Hz, H*8*), 7.58 (s, 1H, H*6*), 10.41 (br s, 1H, NH).^{13}C NMR (DMSO-d_6) δ: 20.1 (CH_3), 34.3 (C*1*), 53.8 (C*3*), 55.1 (C*11a*), 67.3 (C*2*), 121.2 (C*Ar*), 125.7 (C*Ar*), 130.2 (C*Ar*), 132.7 (C*Ar*), 133.0 (C*Ar*), 133.8 (C*Ar*), 165.1 (C*5*), 170.1 (C*11a*). $[\alpha]_D$ = +362° (c =0.01, MeOH).

***(2R,11aS)-8-Chloro-2-hydroxy-1,2,3,10,11,11a-hexahydropyrrolo[2,1-c][1,4]benzodiazepin-5,11-dione* (17)**

See general procedure : anhydride **(12)** (20 g; 0.1 mol), *trans*-4-hydroxy-L-proline **(13)** (14.15 g ; 0.11 mol). **(17)** : pale crystals, 82% yield; mp 244°C (ether). *Anal.* Calcd for $C_{12}H_{11}N_2O_3Cl$: C, 54.05 ; H, 4.16; N, 10.50. Found : C, 53.76 ; H, 4.20 ; N, 10.52. MS (m/z) : M^+ 266 (45). IR (cm^{-1}) : 3600 (OH) ; 3470 (NH) ; 1695 (CO) ; 1610 (CO). ^{1}H NMR (DMSO-d_6) δ: 1.92 (m, 1H, H*1*), 2.61 (m, 1H, H*1*), 3.45 (dd, 1H, J=12 and 4.4 Hz, H*3*), 3.60 (dd, 1H, J=12 and 3.3 Hz, H*3*), 4.25 (m, 1H, H*11a*), 4.25 (m, 1H, H*2*), 5.15 (d, 1H, J=3.5 Hz, OH), 7.16 (s, 1H, H*9*), 7.27 (d, 1H, J=8.0 Hz, H*7*), 7.78 (d, 1H, J=8.0 Hz, H*6*), 10.62 (br s, 1H, NH).^{13}C NMR (DMSO-d_6) δ: 34.2 (C*1*), 53.9 (C*3*), 55.1 (C*11a*), 67.2 (C*2*), 123.2 (C*Ar*), 127.3 (C*Ar*), 127.8 (C*Ar*), 129.4 (C*Ar*), 131.8 (C*Ar*), 135.2 (C*Ar*), 163.7 (C*5*), 170.0 (C*11*). $[\alpha]_D$ = +398° (c =0.01, MeOH).

Preparation of mesylates (18), (19), (20) and (21)

General procedure for compounds (18), (19), (20) and (21)

To an ice-cooled (0°C) solution of methanesulfonyl chloride (5 eq.) in 100 mL of pyridine, we added in small portions the dilactam **(14)**, **(15)**, **(16)** or **(17)**. Stirring was continued for 20 min at 0°C and 14 h at rt. The solution mixture was pourred into ice-water and the resulting solution was extracted with ethyl acetate. After evaporation under reduced pressure, the residue was taken up again in water. The precipitate was filtered, dried and purified with appropriate solvent.

(2R,11aS)-2-Methylsulfonyloxy-1,2,3,10,11,11a-hexahydropyrrolo[2,1-c][1,4]benzodiazepin-5,11-dione **(18)**

See general procedure : dilactam **(14)** (20 g; 86.2 mmol), methanesulfonyl chloride (33.3 mL ; 0.43 mol). **(18)** : white crystals, 75% yield; mp 230°C (ether). *Anal.* Calcd for $C_{13}H_{14}N_2O_5S$: C, 50.32 ; H, 4.55 ; N, 9.03. Found : C, 50.09 ; H, 4.63 ; N, 9.21. MS (m/z) : M^+ 310 (100). IR (cm^{-1}) : 3220 (NH) ; 1710 (CO) ; 1610 (CO). ^{1}H NMR (DMSO-d_6) δ: 2.35 (m, 1H, H*1*), 2.93 (m, 1H, H*1*), 3.26 (s, 3H, CH_3), 3.71 (dd, 1H, J=13.4 and 4.4 Hz, H*3*), 4.10 (d, 1H, J=13.4 and 3.2 Hz, H*3*), 4.34 (t, 1H, J=7.2 Hz, H*11a*), 5.35 (br s, 1H, H*2*), 7.15 (d, 1H, J=8.2 Hz, H*9*), 7.27 (dd, 1H, J=8.2 and 7.9 Hz, H*8*), 7.54 (dd, 1H, J=8.2 and 7.9 Hz, H*7*), 7.81 (d, 1H, J=7.9 Hz, H*6*), 10.70 (br s, 1H, NH).^{13}C NMR (DMSO-d_6) δ: 32.7 (CH_3), 37.7 (C*1*), 52.0 (C*3*), 54.8 (C*11a*), 78.6 (C*2*), 121.5 (C*Ar*), 124.3 (C*Ar*), 125.4 (C*Ar*), 130.5 (C*Ar*), 132.6 (C*Ar*), 136.3 (C*Ar*), 164.9 (C*5*), 169.6 (C*11*). $[\alpha]_D$ = +302° (c =0.01, MeOH).

(2R,11aS)-7-Chloro-2-methylsulfonyloxy-1,2,3,10,11,11a-hexahydropyrrolo[2,1-c][1,4]benzodiazepin-5,11-dione **(19)**

See general procedure : dilactam **(15)** (3.5 g; 14 mmol), methanesulfonyl chloride (5.4 mL ; 70 mmol). **(19)** : white crystals, 75% yield; mp 235°C (ether). *Anal.* Calcd for $C_{13}H_{13}N_2O_5ClS$: C, 45.29 ; H, 3.80 ; N, 8.13. Found : C, 45.17 ; H, 3.75 ; N, 8.36. MS (m/z) : M^+ 344 (100), 345 (12), 346 (28). IR (cm^{-1}) : 3210 (NH) ; 1700 (CO) ; 1610 (CO). ^{1}H NMR (DMSO-d_6) δ: 2.32 (m, 1H, H*1*), 2.93 (m, 1H, H*1*), 3.26 (s, 3H, CH_3), 3.71 (dd, 1H, J=13.3 and 3.0 Hz, H*3*), 4.08 (d, 1H, J=13.3 Hz, H*3*), 4.38 (t, 1H, J=7.0 Hz, H*11a*), 5.33 (br s, 1H, H*2*), 7.15 (d, 1H, J=8.6 Hz, H*9*), 7.60 (d, 1H, J=8.6 Hz, H*8*), 7.76 (s, 1H, H*6*), 10.78 (br s, 1H, NH).^{13}C NMR (DMSO-d_6) δ: 32.6 (CH_3), 37.7 (C*1*), 52.1 (C*3*), 54.8 (C*11a*), 78.4 (C*2*), 123.5 (C*Ar*), 126.8 (C*Ar*), 128.3 (C*Ar*), 129.7 (C*Ar*), 132.3 (C*Ar*), 135.3 (C*Ar*), 163.6 (C*5*), 169.3 (C*11*). $[\alpha]_D$ = +287° (c =0.01, MeOH).

(2R,11aS)-7-Methyl-2-methylsulfonyloxy-1,2,3,10,11,11a-hexahydropyrrolo[2,1-c][1,4]benzodiazepin-5,11-dione **(20)**

See general procedure : dilactam **(16)** (1 g; 4 mmol), methanesulfonyl chloride (1.6 mL ; 20 mmol). **(20)** : white crystals, 75% yield; mp 240°C (ether). *Anal.* Calcd for $C_{14}H_{16}N_2O_5S$: C, 51.84 ; H, 4.97 ; N, 8.64. Found : C, 51.53 ; H, 4.58 ; N, 8.70. MS (m/z) : M^+ 324 (33), 228 (M^+- OSO_2Me, 45). IR (cm^{-1}): 3260 (NH) ; 1690 (CO) ; 1630 (CO). ^1H NMR (DMSO-d_6) δ: 2.30 (m, 1H, H*1*), 2.31 (s, 3H, CH_3), 2.91 (m, 1H, H*1*), 3.25 (s, 3H, OSO_2CH_3), 3.67 (dd, 1H, J=12 and 4.4 Hz, H*3*), 4.08 (dd, 1H, J=12 and 3.4 Hz, H*3*), 4.38 (t, 1H, J=6.7 Hz, H*11a*), 5.32 (m, 1H, H*2*), 7.04 (d, 1H, J=8.1 Hz, H*9*), 7.36 (d, 1H, J=8.1 Hz, H*8*), 7.60 (s, 1H, H*6*), 10.58 (br s, 1H, NH).^{13}C NMR (DMSO-d_6) δ: 20.1 (CH_3), 32.6 (OSO_2CH_3), 37.7 (C*1*), 51.9 (C*3*), 54.7 (C*11a*), 78.5 (C*2*), 121.5 (C*Ar*), 125.2 (C*Ar*), 130.3 (C*Ar*), 133.2 (C*Ar*), 133.4 (C*Ar*), 133.9 (C*Ar*), 164.9 (C*5*), 169.4 (C*11*). $[\alpha]_D$ = +292° (c =0.01, MeOH).

(2R,11aS)-8-Chloro-2-methylsulfonyloxy-1,2,3,10,11,11a-hexahydropyrrolo[2,1-c][1,4]benzodiazepin-5,11-dione **(21)**

See general procedure : dilactam **(17)** (20 g; 75 mmol), methanesulfonyl chloride (29 mL ; 0.375 mol). **21** : white crystals, 80% yield; mp 245°C (ether). *Anal.* Calcd for $C_{13}H_{13}N_2O_5ClS$: C, 45.29 ; H, 3.80 ; N, 8.13. Found : C, 45.14 ; H, 3.70 ; N, 8.42. MS (m/z) : M^+ 344 (100), 345 (13), 346 (28). IR (cm^{-1}) : 3210 (NH) ; 1690 (CO) ; 1620 (CO). ^1H NMR (DMSO-d_6) δ: 2.32 (m, 1H, H*1*), 2.90 (m, 1H, H*1*), 3.26 (s, 3H, CH_3), 3.69 (dd, 1H, J=13.4 and 4.0 Hz, H*3*), 4.08 (d, 1H, J=13.4 Hz, H*3*), 4.39 (t, 1H, J=7.4 Hz, H*11a*), 5.32 (br s, 1H, H*2*), 7.19 (s, 1H, H*9*), 7.31 (d, 1H, J=8.4 Hz, H*7*), 7.81 (d, 1H, J=8.4 Hz, H*6*), 10.78 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 32.6 (CH_3), 37.7 (C*1*), 52.1 (C*3*), 54.8 (C*11a*), 78.4 (C*2*), 120.7 (C*Ar*), 124.1 (C*Ar*), 124.2 (C*Ar*), 132.6 (C*Ar*), 136.7 (C*Ar*), 137.7 (C*Ar*), 164.1 (C*5*), 169.5 (C*11*). $[\alpha]_D$ = +322° (c =0.01, acetone).

Preparation of alkenes (4), (22), (23) and (24)

General procedure for compounds (4), (22), (23) and (24)

Compound **(18)**, **(19)**, **(20)** or **(21)** in solution in dimethylformamide (100 mL) in presence of 2 equivalents of diazabicyclo[5.4.0]undec-7-ene (DBU) was refluxed for 2 h under microwave heating. The mixture was then cooled, taken up in a mixture of ice and water and extracted with ethyl acetate. After evaporation under reduced pressure, the residue was taken up again in water. The precipitate was filtered, dried and purified with an appropriate solvent.

5,10,11,11a-Tetrahydropyrrolo[2,1-c][1,4]benzodiazepin-5,11-dione **(4)**

See general procedure : mesylate **(18)** (15 g; 48 mmol), DBU (11.5 mL; 96 mmol). **(4)** : white crystals, 70% yield; mp 230°C (ethyl alcohol). *Anal.* Calcd for $C_{12}H_{10}N_2O_2$: C, 67.28; H, 4.70 ; N, 13.08. Found :

C, 67.15 ; H, 4.67 ; N, 12.88. MS (m/z) : M^+ 214 (100). IR (cm^{-1}) : 3220 (NH) ; 1710 (CO) ; 1610 (CO). ^1H NMR (DMSO-d_6) δ: 2.77 (m, 1H, H*1*), 3.44 (m, 1H, H*1*), 4.60 (dd, 1H, J=11.0 and 3.7 Hz, H*11a*), 5.45 (m, 1H, H*2*), 6.89 (d, 1H, J=4.2 Hz, H*3*), 7.15 (d, 1H, J=8.0 Hz, H*9*), 7.26 (t, 1H, J=8.0 Hz, H*8*), 7.54 (t, 1H, J=8 Hz, H*7*), 7.88 (d, 1H, J=8 Hz, H*6*), 10.66 (br s, 1H, NH).^{13}C NMR (DMSO-d_6) δ: 30.3 (C*1*), 55.5 (C*11a*), 112.7 (C*2*), 121.6 (C*Ar*), 124.2 (C*Ar*), 125.7 (C*Ar*), 127.2 (C*3*), 130.5 (C*Ar*), 132.5 (C*Ar*), 136.1 (C*Ar*), 161.5 (C*5*), 169.1 (C*11*).

***7-Chloro-5,10,11,11a-tetrahydropyrrolo[2,1-c][1,4]benzodiazepin-5,11-dione* (22)**

See general procedure : mesylate **(19)** (2 g; 6 mmol), DBU (1.8 mL ; 12 mmol). **(22)** : white crystals, 77% yield; mp 230°C (ethyl alcohol). *Anal.* Calcd for $C_{12}H_9N_2O_2Cl$: C, 57.96 ; H, 3.65 ; N, 11.26. Found : C, 57.85 ; H, 3.62 ; N, 11.12. MS (m/z) : M^+ 248 (100), 249 (12), 250 (31). IR (cm^{-1}) : 3230 (NH) ; 1720 (CO) ; 1610 (CO). ^1H NMR (DMSO-d_6) δ: 2.85 (m, 1H, H*1*), 3.45 (m, 1H, H*1*), 4.71 (dd, 1H, J=11.0 and 3.8 Hz, H*11a*), 5.55 (m, 1H, H*2*), 6.94 (br s, 1H, H*3*), 7.24 (d, 1H, J=7.8 Hz, H*9*), 7.66 (d, 1H, J=7.8 Hz, H*8*), 7.81 (s, 1H, H*6*), 10.79 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 30.3 (C*1*), 55.5 (C*11a*), 113.4 (C*2*), 123.7 (C*Ar*), 127.1 (C*Ar*), 127.2 (C*3*), 128.2 (C*Ar*), 129.7 (C*Ar*), 132.3 (C*Ar*), 135.1 (C*Ar*), 160.3 (C*5*), 168.8 (C*11*).

***7-Methyl-5,10,11,11a-tetrahydropyrrolo[2,1-c][1,4]benzodiazepin-5,11-dione* (23)**

See general procedure : mesylate **(20)** (1 g; 3 mmol), DBU (0.9 mL ; 6 mmol). **(23)** : white crystals, 73% yield; mp 210°C (ethyl alcohol). *Anal.* Calcd for $C_{13}H_{12}N_2O_2$: C, 68.41 ; H, 5.30 ; N, 12.27. Found : C, 68.12 ; H, 5.26 ; N, 12.15. MS (m/z) : M^+ 228 (100). IR (cm^{-1}) : 3220 (NH) ; 1710 (CO) ; 1620 (CO). ^1H NMR (DMSO-d_6) δ: 2.32 (s, 3H, CH_3), 2.79 (m, 1H, H*1*), 3.38 (m, 1H, H*1*), 4.55 (dd, 1H, J=11.2 and 3.6 Hz, H*11a*), 5.43 (br s, 1H, H*2*), 6.88 (br s, 1H, H*3*), 7.06 (d, 1H, J=8.2 Hz, H*9*), 7.34 (d, 1H, J=8.2 Hz, H*8*), 7.61 (s, 1H, H*6*), 10.36 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 20.1 (CH_3), 30.3 (C*1*), 55.5 (C*11a*), 113.2 (C*2*), 123.7 (C*Ar*), 127.1 (C*Ar*), 127.2 (C*3*), 128.2 (C*Ar*), 129.7 (C*Ar*), 132.3 (C*Ar*), 135.1 (C*Ar*), 160.5 (C*5*), 167.8 (C*11*).

***8-Chloro-5,10,11,11a-tetrahydropyrrolo[2,1-c][1,4]benzodiazepin-5,11-dione* (24)**

See general procedure : mesylate **(20)** (15 g; 43 mmol), DBU (12.8 mL ; 86 mmol). **(24)** : pale crystals, 70% yield; mp 260°C (ether). *Anal.* Calcd for $C_{12}H_9N_2O_2Cl$: C, 57.96 ; H, 3.65 ; N, 11.26. Found : C, 57.72 ; H, 3.61 ; N, 11.12. MS (m/z) : M^+ 248 (100), 249 (13), 250 (30). IR (cm^{-1}) : 3210 (NH) ; 1690 (CO) ; 1620 (CO). ^1H NMR (DMSO-d_6) δ: 2.80 (m, 1H, H*1*), 3.39 (m, 1H, H*1*), 4.64 (dd, 1H, J=10.9 and 3.4 Hz, H*11a*), 5.46 (br s, 1H, H*2*), 6.87 (br s, 1H, H*3*), 7.19 (s, 1H, H*9*), 7.29 (d, 1H, J=8.3 Hz, H*7*), 7.81

(d, 1H, J=8.3 Hz, H*6*), 10.74 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 30.3 (C*1*), 55.5 (C*11a*), 113.0 (C*2*), 120.9 (C*Ar*), 124.1 (C*Ar*), 124.5 (C*Ar*), 127.1 (C*3*), 132.5 (C*Ar*), 136.5 (C*Ar*), 137.5 (C*Ar*), 160.7 (C*5*), 168.9 (C*11*).

Preparation of quinazolinones (5), (25), (26) and (27)

General procedure for compounds (5), (25), (26) and (27)

Compound (**4**), (**22**), (**23**) or (**24**) in concentrated hydrochloric acid (5 mL) was heated in an oil bath (60°C) for 30 min. After elimination of HCl under reduced pressure, the residue was taken up in a saturated aqueous solution of sodium hydrogencarbonate. The aqueous layer was reacidified by conc. HCl and the precipitate collected by filtration. The product was dried and purified with an appropriate solvent.

***9-Oxo-1,2,3,3a,4,9-hexahydropyrrolo[2,1-b]quinazoline-1-carboxylic acid* (5)**

See general procedure : alkene (**4**) (10 g; 46.7 mmol). (**5**) : white crystals, 80% yield; mp 260°C (ether). *Anal.* Calcd for $C_{12}H_{12}N_2O_3$: C, 62.06 ; H, 5.21 ; N, 12.06. Found : C, 61.66 ; H, 5.28 ; N, 11.98. MS (m/z) : M^+ 232 (42), 204 (M^+ - CO, 100), 188 (M^+ - CO_2, 57). IR (cm^{-1}) : 3230 (NH) ; 1710 (CO) ; 1640 (CO) ; 1440. ^{1}H NMR (DMSO-d_6) δ: 1.95 (m, 2H, CH_2), 2.23 (m, 2H, CH_2), 4.31 (d, 1H, J=4.8 Hz, H-C-COOH), 4.95 (t, 1H, J=4.6 Hz, H-C-NH), 6.73 (m, 2H, H*Ar*), 6.98 (br s, 1H, NH), 7.26 (t, 1H, J=7.2 Hz, H*Ar*), 7.57 (d, 1H, J=7.2 Hz, H*Ar*), 12.6 (br s, 1H, COOH). ^{13}C NMR (DMSO-d_6) δ: 26.5 (CH_2), 31.1 (CH_2), 56.6 (H-C-COOH), 69.8 (H-C-NH), 114.8 (C*Ar*), 116.5 ($C_{(Ar)}$-CO), 117.8 (C*Ar*), 127.4 (C*Ar*), 133 (C*Ar*), 149.1 (=$C_{(Ar)}$-NH), 161.2 (N-CO), 172.8 (COOH).

***7-Chloro-9-oxo-1,2,3,3a,4,9-hexahydropyrrolo[2,1-b]quinazoline-1-carboxylic acid* (25)**

See general procedure : alkene (**22**) (1 g; 4 mmol). (**25**) : white crystals, 70% yield; mp >260°C (ether). *Anal.* Calcd for $C_{12}H_{11}N_2O_3Cl$: C, 54.05 ; H, 4.16 ; N, 10.50. Found : C, 53.83 ; H, 3.96 ; N, 10.24. MS (m/z) : M^+ 266 (47), 267 (M^+ +1, 19), 268 (M^+ +2, 14), 238 (M^+ - CO, 100). IR (cm^{-1}) : 3220 (NH) ; 1710 (CO) ; 1630 (CO) ; 1440. ^{1}H NMR (DMSO-d_6) δ: 1.95 (m, 2H, CH_2), 2.23 (m, 2H, CH_2), 4.32 (d, 1H, J=8.8 Hz, H-C-COOH), 4.96 (m, 1H, H-C-NH), 6.76 (d, 1H, J=8.5 Hz, H*Ar*), 7.22 (br s, 1H, NH), 7.30 (d, 1H, J=8.5 Hz, H*Ar*), 7.49 (s, 1H, H*Ar*), 12.64 (br s, 1H, COOH). ^{13}C NMR (DMSO-d_6) δ: 26.5 (CH_2), 30.9 (CH_2), 56.6 (H-C-COOH), 69.7 (H-C-NH), 116.7 (C*Ar*), 117.6 ($C_{(Ar)}$-CO), 121.4 (C*Ar*), 126.5 (C*Ar*), 132.7 (C*Ar*), 147.1 (=$C_{(Ar)}$-NH), 160.1 (N-CO), 172.5 (COOH).

***7-Methyl-9-oxo-1,2,3,3a,4,9-hexahydropyrrolo[2,1-b]quinazoline-1-carboxylic acid* (26)**

See general procedure : alkene **(23)** (1 g; 4.4 mmol). **(26)** : white crystals, 65% yield; mp >260°C (ether). *Anal.* Calcd for $C_{13}H_{14}N_2O_3$: C, 63.40 ; H, 5.73 ; N, 11.37. Found : C, 63.24 ; H, 5.65 ; N, 11.45. MS (m/z) : M^+ 246 (45). IR (cm^{-1}) : 3240 (NH) ; 1710 (CO) ; 1630 (CO) ; 1440. ^1H NMR (DMSO-d_6) δ: 1.93 (m, 2H, CH_2), 2.18 (m, 3H, CH_3), 2.20 (m, 2H, CH_2), 4.31 (d, 1H, J=7.4 Hz, H-C-COOH), 4.89 (m, 1H, H-C-NH), 6.65 (d, 1H, J=7.0 Hz, H*Ar*), 6.8 (br s, 1H, NH), 7.08 (d, 1H, J=7.0 Hz, H*Ar*), 7.39 (br s, 1H, H*Ar*), 12.49 (br s, 1H, COOH). ^{13}C NMR (DMSO-d_6) δ: 20.1 (CH_3), 26.5 (CH_2), 31.1 (CH_2), 56.5 (H-C-COOH), 69.9 (H-C-NH), 114.9 (C*Ar*), 116.6 ($C_{(Ar)}$-CO), 126.6 (C*Ar*), 127.3 (C*Ar*), 133.8 (C*Ar*), 146.9 ($=C_{(Ar)}$-NH), 161.3 (N-CO), 172.8 (COOH).

***6-Chloro-9-oxo-1,2,3,3a,4,9-hexahydropyrrolo[2,1-b]quinazoline-1-carboxylic acid* (27)**

See general procedure : alkene **(24)** (2 g; 8 mmol). **(27)** : white crystals, 75% yield; mp >260°C (ether). *Anal.* Calcd for $C_{12}H_{11}N_2O_3Cl$: C, 54.05 ; H, 4.16 ; N, 10.50. Found : C, 53.85 ; H, 4.02 ; N, 10.23. MS (m/z) : M^+ 266 (38), 267 (M^+ +1, 23), 268 (M^+ +2, 16), 238 (M^+ - CO, 100). IR (cm^{-1}) : 3220 (NH) ; 1710 (CO) ; 1630 (CO) ; 1440. ^1H NMR (DMSO-d_6) δ: 1.93 (m, 2H, CH_2), 2.24 (m, 2H, CH_2), 4.30 (d, 1H, J=8.7 Hz, H-C-COOH), 4.98 (m, 1H, H-C-NH), 6.76 (m, 2H, H*Ar*), 7.29 (br s, 1H, NH), 7.56 (d, 1H, J=8.0 Hz, H*Ar*), 12.63 (br s, 1H, COOH). ^{13}C NMR (DMSO-d_6) δ: 26.5 (CH_2), 30.9 (CH_2), 56.5 (H-C-COOH), 69.7 (H-C-NH), 113.8 (C*Ar*), 115.2 ($C_{(Ar)}$-CO), 117.6 (C*Ar*), 129.3 (C*Ar*), 137.5 (C*Ar*), 150 ($=C_{(Ar)}$-NH), 160.3 (N-CO), 172.6 (COOH).

Preparation of quinazolinones (28-30)

General procedure for compounds (28), (29) and (30)

Quinazolinone **(5)** (2 g; 8.6 mmol) was solubilized in the alcohol (100 mL) in presence of a catalytic amount of concentrated sulfuric acid. The mixture was then allowed to reflux for 1 h. After evaporation of the alcohol under reduced pressure, the oily residue was taken up in water. The precipitate was filtered, dried and recrystallized from an appropriate solvent.

***Methyl-9-oxo-1,2,3,3a,4,9-hexahydropyrrolo[2,1-b]quinazoline-1-carboxylate* (28)**

See general procedure : Methyl alcohol. **(28)** : pale crystals, 80% yield; mp 182°C (methyl alcohol). *Anal.* Calcd for $C_{13}H_{14}N_2O_3$: C, 63.40 ; H, 5.73 ; N, 11.38. Found : C, 63.29 ; H, 5.88 ; N, 11.19. MS (m/z) : 244 (M^+ - H_2, 35), 185 (- CO_2CH_3, 100). IR (cm^{-1}) : 3280 (NH) ; 1750 (CO) ; 1650 (CO) ; 1440. ^1H NMR (DMSO-d_6) δ: 1.95 (m, 2H, CH_2), 2.25 (m, 2H, CH_2), 3.60 (s, 3H, CO_2CH_3), 4.40 (d, 1H, J=8.8 Hz, H-C-CO_2CH_3), 4.95 (dd, 1H, J=9.3 and 4.9 Hz, H-C-NH), 6.70 (m, 2H, H*Ar*), 7.00 (br s, 1H, NH), 7.25 (t, 1H, J=7.2 Hz, H*Ar*), 7.56 (d, 1H, J=7.2 Hz, H*Ar*).^{13}C NMR (DMSO-d_6) δ: 26.3 (CH_2), 31.1 (CH_2), 51.9

($CO_2\underline{C}H_3$), 56.3 (H-$\underline{C}$-CO_2CH_3), 69.7 (H-$\underline{C}$-NH), 114.8 (C*Ar*), 116.3 ($\underline{C}_{(Ar)}$-CO), 117.8 (C*Ar*), 127.3 (C*Ar*), 133 (C*Ar*), 149 (=$\underline{C}_{(Ar)}$-NH), 161.2 (N-$\underline{C}$O), 171.8 ($\underline{C}O_2CH_3$).

***Ethyl-9-oxo-1,2,3,3a,4,9-hexahydropyrrolo[2,1-b]quinazoline-1-carboxylate* (29)**

X-Ray Crystallographic Analysis Data for $C_{14}H_{16}N_2O_3$ **(29)**, Mr = 260.3, orthorombic, Pbca (n 61), a = 13.572 (3), b = 12.083 (2), c = 15.918 (3) Å, V = 2610.4 (9) Å^3, Z = 8, D_{calc} = 1.325 g.cm^{-3}, μ (CuKα) = 0.774 cm^{-1}, F(000) = 1104, T = 293 K, final R = 0.0364 for 2321 observations. The sample (0.25, 0.25, 0.52 mm) is studied on a NONIUS MACH 3 diffractometer with graphite monochromatized CuKα radiation. The structure was solved with direct methods (SIR92) and refined with anisotropic thermal parameters for all non-hydrogen atoms using SHELX93. A riding model was employed for the treatment of hydrogen atoms, the distance X-H being free to refine. The final R values Are R_1 = 0.0364 (I>2σ(I)) and wR_2 = 0.0958 with 2054 out of 2321 reflections with $F^2>0$ and 186 parameters. The reflection (416) was omitted from refinement. The maximal residual density is 0.16e/Å^3. Tables of structure factors, atomic coordinates, bond lenghts and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Center. See general procedure : Ethyl alcohol. **(29)** : pale crystals, 80% yield; mp 138°C (ethyl alcohol). *Anal.* Calcd for $C_{14}H_{16}N_2O_3$: C, 64.60 ; H, 6.20 ; N, 10.76. Found : C, 64.19 ; H, 6.08 ; N, 10.72. MS (m/z) : M^+ 260 (23), 258 (M^+ - H_2, 22), 187 (M^+ - $CO_2CH_2CH_3$, 61). IR (cm^{-1}) : 3310 (NH) ; 1750 (CO) ; 1640 (CO) ; 1440. ^{1}H NMR (DMSO-d_6) δ: 1.17 (t, 3H, J=7.0 Hz, $CO_2CH_2C\underline{H}_3$), 1.93 (m, 2H, CH_2), 2.25 (m, 2H, CH_2), 4.08 (q, 2H, J=7.0 Hz, $CO_2\underline{C}H_2CH_3$), 4.38 (d, 1H, J=9.0 Hz, $\underline{H}$-C-$CO_2CH_2CH_3$), 4.95 (dd, 1H, J=8.9 and 4.8 Hz, $\underline{H}$-C-NH), 6.73 (m, 2H, H*Ar*), 7.00 (br s, 1H, NH), 7.27 (t, 1H, J=7.4 Hz, H*Ar*), 7.56 (d, 1H, J=7.4 Hz, H*Ar*). ^{13}C NMR (DMSO-d_6) δ: 14 ($CO_2CH_2\underline{C}H_3$), 26.3 (CH_2), 31.1 (CH_2), 56.4 (H-$\underline{C}$-$CO_2CH_2CH_3$), 60.5 ($CO_2\underline{C}H_2CH_3$), 69.7 (H-$\underline{C}$-NH), 114.8 (C*Ar*), 116.3 ($\underline{C}_{(Ar)}$-CO), 117.8 (C*Ar*), 127.3 (C*Ar*), 133.1 (C*Ar*), 149 (=$\underline{C}_{(Ar)}$-NH), 161.2 (N-$\underline{C}$O), 171.3 ($\underline{C}O_2CH_2CH_3$).

***Isopropyl-9-oxo-1,2,3,3a,4,9-hexahydropyrrolo[2,1-b]quinazoline-1-carboxylate* (30)**

See general procedure : Isopropyl alcohol. **(30)** : pale crystals, 80% yield; mp 120°C (acetonitrile). *Anal.* Calcd for $C_{15}H_{18}N_2O_3$: C, 65.68 ; H, 6.61 ; N, 10.21. Found : C, 65.21 ; H, 6.55 ; N, 10.30. MS (m/z) : M^+ 274 (2), 272 (M^+ - H_2, 22), 185 (M^+ - $CO_2CH(CH_3)_2$, 100). IR (cm^{-1}) : 3280 (NH) ; 1750 (CO) ; 1650 (CO) ; 1440. ^{1}H NMR (DMSO-d_6) δ: 1.08 (d, 3H, J=6.0 Hz, $CO_2CH(C\underline{H}_3)_2$,), 1.11 (d, 3H, J=6 Hz, $CO_2CH(C\underline{H}_3)_2$,), 1.90 (m, 2H, CH_2), 2.15 (m, 2H, CH_2), 4.30 (br d, 1H, J=10 Hz, $\underline{H}$-C-$CO_2CH(CH_3)_2$), 4.80 (hept, 1H, J= 6.0 Hz, $CO_2C\underline{H}(CH_3)_2$,), 4.90 (dd, 1H,J=8.7 and 4.0 Hz, $\underline{H}$-C-NH), 6.70 (m, 2H, H*Ar*), 7.00 (br s, 1H, NH), 7.20 (td, 1H,J=8.0 and 1.5 Hz, H*Ar*), 7.50 (dd, 1H,J=8.0 and 1.5 Hz, H*Ar*). ^{13}C NMR

(DMSO-d_6) δ: 21.4 ($CO_2CH(\underline{C}H_3)_2$), 21.5 ($CO_2CH(\underline{C}H_3)_2$), 26.3 ($CH_2$), 31.1 ($CH_2$), 56.6 (H-$\underline{C}$-$CO_2CH(CH_3)_2$), 67.9 ($CO_2\underline{C}H(CH_3)_2$), 69.7 (H-$\underline{C}$-NH), 114.8 (C*Ar*), 116.4 ($\underline{C}_{(Ar)}$-CO), 117.8 (C*Ar*), 127.3 (C*Ar*), 133 (C*Ar*), 149 (=$\underline{C}_{(Ar)}$-NH), 161.0 (N-$\underline{C}$O), 170.8 ($\underline{C}O_2CH(CH_3)_2$).

Preparation of quinazolinones (31-33)

General procedure for compounds (31), (32) and (33)

Quinazolinone **(5)** (1 g; 4.3 mmol) was solubilized in 300 mL of acetone. The mixture under stirring was cooled in an ice/acetone bath to obtain an internal temperature equal to 0°C. Triethylamine (0.6 mL; 4.3 mmol), ethyl chloroformate (0.41 mL; 4.3 mmol) and the corresponding amine (4.3 mmol) were added at 0°C successively every 20 min. The mixture was then allowed to stand at rt for 2 h. The precipitate of triethylammonium chloride was eliminated by filtration. Acetone was evaporated under reduced pressure and the residual crystals were taken up in water, filtered, dried and recrystallized or washed with an appropriate solvent.

***9-Oxo-1,2,3,3a,4,9-hexahydropyrrolo[2,1-b]quinazoline-1-isobutylcarboxamide* (31)**

See general procedure : Isobutylamine (0.43 mL, 4.3 mmol). **(31)** : pale crystals, 40% yield; mp 258°C (methyl alcohol). *Anal.* Calcd for $C_{16}H_{21}N_3O_2$: C, 66.88 ; H, 7.37 ; N, 14.62. Found : C, 66.53 ; H, 7.27 ; N, 14.78. MS (m/z) : M^+ 287 (16), 285 (M^+ - H_2, 11), 187 (M^+ - $CONHCH_2CH(CH_3)_2$, 100). IR (cm^{-1}) : 3305 (NH) ; 1670 (CO) ; 1640 (CO) ; 1440. ^{1}H NMR (DMSO-d_6) δ: 0.80 (d, 6H, J=6.6 Hz, $CH(\underline{C}H_3)_2$), 1.65 (sept, 1H, J=6.6 Hz, $\underline{C}H(CH_3)_2$), 1.95 (m, 2H, CH_2), 2.15 (m, 2H, CH_2), 2.87 (t, 2H, J=6.3 Hz, NH-$\underline{C}H_2$-CH), 4.34 (d, 1H, J=8.5 Hz, $\underline{H}$-C-$CONHCH_2$), 4.90 (dd, 1H, J=9.2 and 4.9 Hz, $\underline{H}$-C-NH), 6.72 (m, 2H, H*Ar*), 6.98 (br s, 1H, N$\underline{H}$-C-N), 7.27 (t, 1H, J=8.0 Hz, H*Ar*), 7.59 (d, 1H, J=8.0 Hz, H*Ar*), 7.77 (br t, 1H, J=5.5 Hz, CON$\underline{H}CH_2$). ^{13}C NMR (DMSO-d_6) δ: 19.9 ($CH(\underline{C}H_3)_2$), 26.9 (CH_2), 28 ($NH\underline{C}H_2CH(CH_3)_2$), 30.8 ($CH_2$), 45.9 ($CH_2\underline{C}H(CH_3)_2$), 57.6 (H-$\underline{C}$-$CONHCH_2CH(CH_3)_2$), 70 (H-$\underline{C}$-NH), 114.8 (C*Ar*), 116.8 ($\underline{C}_{(Ar)}$-CO), 117.8 (C*Ar*), 127.4 (C*Ar*), 132.9 (C Ar), 149.1 (=$\underline{C}_{(Ar)}$-NH), 161.6 (N-$\underline{C}$O), 170.7 ($\underline{C}ONHCH_2CH(CH_3)_2$).

***9-Oxo-1,2,3,3a,4,9-hexahydropyrrolo[2,1-b]quinazoline-1-benzylcarboxamide* (32)**

See general procedure : Benzylamine (0.47 mL, 4.3 mmol). **(32)** : pale crystals, 70% yield; mp 234°C (ether). *Anal.* Calcd for $C_{19}H_{19}N_3O_2$: C, 71.01 ; H, 5.96 ; N, 13.07. Found : C, 70.82 ; H, 5.83 ; N, 12.88. MS (m/z) : M^+ 321 (50), 319 (M^+ - H_2, 100), 187 (M^+ - $CONHCH_2C_6H_5$, 100). IR (cm^{-1}) : 3310 (NH) ; 3290 (NH) ; 1660 (CO) ; 1640 (CO). ^{1}H NMR (DMSO-d_6) δ: 1.95 (m, 2H, CH_2), 2.15 (m, 2H, CH_2), 4.28 (d, 2H, J=4.0 Hz, NH-$\underline{C}H_2$), 4.41 (d, 1H, J=8.9 Hz, $\underline{H}$-C-$CONHCH_2$), 4.93 (dd, 1H, J=8.2 and 3.7 Hz, $\underline{H}$-

C-NH), 6.74 (m, 2H, H*Ar*), 7.01 (br s, 1H, NH-C-N), 7.19-7.29 (m, 5H, C_6H_5), 7.27 (m, 1H, H*Ar*), 7.62 (d, 1H, J=7.6 Hz, H*Ar*), 8.39 (t, 1H, J=5.4 Hz, CONHCH$_2$). ^{13}C NMR (DMSO-d_6) δ: 27.1 (CH$_2$), 30.9 (CH$_2$), 42 (CH$_2$), 57.6 (H-C-CONHCH$_2$), 70.1 (H-C-NH), 114.8 (CAr), 116.7 (CAr), 117.7 (CAr), 126.6 ($C_{(Ar)}$-CO), 126.9 (CAr), 127.4 (CAr), 128.2 (CAr), 132.9 (=$C_{(Ar)}$-NH), 149.1 (N-CO), 161.8 (CONHCH$_2$C$_6$H$_5$).

***9-Oxo-1,2,3,3a,4,9-hexahydropyrrolo[2,1-b]quinazoline-1-isopropylcarboxamide* (33)**

See general procedure : Isopropylamine (0.37 mL, 4.3 mmol). **(33)** : pale crystals, 70% yield; mp 250°C (ether). *Anal.* Calcd for $C_{15}H_{19}N_3O_2$: C, 65.91 ; H, 7.01 ; N, 15.37. Found : C, 65.82 ; H, 6.95 ; N, 15.14. MS (m/z) : M$^+$ 273 (100), 271 (M$^+$ - H$_2$, 99), 187 (M$^+$ - CONHCH(CH$_3$)$_2$, 100). IR (cm^{-1}) : 3310 (NH) ; 3290 (NH) ; 1650 (CO) ; 1640 (CO). ^{1}H NMR (DMSO-d_6) δ: 1.06 (d, 6H, J=6.4 Hz, CH(CH$_3$)$_2$), 1.90-2.20 (m, 4H, CH$_2$), 3.80 (hept, 1H, J=6.4 Hz, CH(CH$_3$)$_2$), 4.30 (d, 1H, J=8.6 Hz, H-C-CONH), 4.90 (dd, 1H, J=5.0 and 3.1 Hz, H-C-NH), 6.74 (m, 2H, H*Ar*), 6.83 (br s, 1H, NH-C-N), 7.27 (t, 1H, J=7.6 Hz, H*Ar*), 7.50 (br s, 1H, CONHCH), 7.61 (d, 1H, J=7.6 Hz, H*Ar*). ^{13}C NMR (DMSO-d_6) δ: 22.3 (CH(CH$_3$)$_2$), 27.1 (CH$_2$), 30.9 (CH$_2$), 40.5 (CH(CH$_3$)$_2$), 57.6 (H-C-CONHCH(CH$_3$)$_2$), 70.1 (H-C-NH), 114.8 (C*Ar*), 116.8 ($C_{(Ar)}$-CO), 117.8 (C*Ar*), 127.5 (C*Ar*), 133.0 (C*Ar*), 149.1 (=$C_{(Ar)}$-NH), 161.7 (N-CO), 169.9 (CONHCH(CH$_3$)$_2$).

Preparation of *9-Oxo-1,2,3,3a,4,9-hexahydropyrrolo[2,1-b]quinazoline-1-hydrazinocarboxamide* (34)

Quinazolinone **(28)** (1 g; 4.06 mmol) was solubilized in methyl alcohol (20 mL) in presence of 98% hydrate hydrazine (0.98 mL; 20.3 mmol). The mixture was then allowed to reflux for 4 h. Methyl alcohol was evaporated under reduced pressure and the residue was taken up in water. Washing with methyl alcohol and then recrystallisation in a mixture of water/ethyl alcohol (1/1) gave **34** as white crystals, 0.6g (60%); mp 252°C. *Anal.* Calcd for $C_{12}H_{13}N_4O_2$: C, 58.53 ; H, 5.73 ; N, 22.75. Found : C, 58.82 ; H, 5.78 ; N, 22.55. MS (m/z) : M$^+$ 246 (34), 215 (M$^+$ - NHNH$_2$, 31), 187 (M$^+$ - CONHNH$_2$, 59). IR (cm^{-1}) : 3330 (NH) ; 3230 (NH) ; 1640 (CO) ; 1510 (CO) ; 1440. ^{1}H NMR (DMSO-d_6) δ: 1.80-2.20 (m, 4H, 2 CH$_2$), 4.20 (br s, 2H, CONHNH$_2$), 4.28 (d, 1H, J=8.2 Hz, H-C-CONHNH$_2$), 4.91 (m, 1H, H-C-NH), 6.73 (m, 2H, H*Ar*), 6.98 (br s, 1H, NH-C-N), 7.25 (t, 1H, J=7.4 Hz, H*Ar*), 7.57 (d, 1H, J=7.4 Hz, H*Ar*), 9.00 (br s, 1H, CONHNH$_2$). ^{13}C NMR (DMSO-d_6) δ: 26.9 (CH$_2$), 30.9 (CH$_2$), 56.1 (H-C-CONHNH$_2$), 69.9 (H-C-NH), 114.8 (C*Ar*), 116.7 ($C_{(Ar)}$-CO), 117.8 (C*Ar*), 127.4 (C*Ar*), 132.9 (C*Ar*), 149.1 (=$C_{(Ar)}$-NH), 161.7 (N-CO), 170.4 (CONHNH$_2$).

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