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Novel pyrrolobenzodiazepine and pyrroloquinazoline scaffolds synthesized by a simple and highly selective Ugi/cyclization sequence

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Pyrrolo[2,1-c][1,4]benzodiazepines (PBDs) and other benzo-fused *N*-heterocycles constitute privileged structures found in numerous bioactive compounds. Thus, developing simple and selective syntheses to furnish these derivatives from easily accessible starting materials is an important and challenging goal. In this work, novel pyrrolobenzodiazepine and pyrroloquinazoline derivatives have been synthesized following a common two step synthetic strategy. This strategy involves a *one-pot* Ugi/cyclization sequence followed by a reduction with spontaneous thermocontrolled cyclization. The control of the temperature in this second step allows the fully selective access to either pyrrolo[2,1-c][1,4]benzodiazepine-3-ones **6** or pyrrolo[2,1-*b*]quinazolines **7**. Density functional theory (DFT) calculations have been carried out to rationalize this reactivity, identifying the kinetic and thermodynamic reaction products and offering insights into the cyclization pathways. These synthetic methodologies show the versatility of the Ugi reaction as a tool in the synthesis of heterocyclic compounds with a pseudopeptidic skeleton.

Introduction

Benzo-fused *N*-heterocycles represent privileged scaffolds in the search for new bioactive compounds.[1] 1,4-Benzodiazepines, and in particular, 3*H*-1,4-benzodiazepin-2-ones, are one of the most studied structures due to their wide range of biological properties.[2] Similarly, quinazolines are also biologically relevant benzo-fused heterocycles with properties such as antimalarial, antimicrobial, anti-inflammatory or anticancer activities.[3] Fusion of these scaffolds with other heterocycles such as pyrrole gives rise to systems which in many cases present an improved activity.[4] This is the case of pyrrolo[2,1-c][1,4]benzodiazepines (PBDs), especially pyrrolo[2,1-c][1,4]benzodiazepine-5-ones (Fig. 1a), which show promising activities as antitumor agents.[5] This interest is reflected in the large number of synthetic methodologies developed to prepare these derivatives.[6]

Although the design of new families of PBDs usually implies the modification of the aromatic A or the pyrrolo C rings, the number of described PBDs with an additional carbonyl group at C-3, located in the pyrrolo C ring, is limited. Moreover, none of them presents the N10-C11 imine moiety,[5] but amine,[7] amide,[8] iminoether or amidine groups.[9] This N10-C11 imine moiety has been shown to play a key role in the biological activity of PDBs, as this electrophilic group forms a covalent bond with the C2-NH_2 group of a guanine in the DNA minor groove forming a covalent adduct that inhibit a large number of biological processes.[10] Furthermore, to the best of our knowledge, there are no examples of PBDs with only a single carbonyl group at C-3, since all the described PBD functionalized at this position have an additional carbonyl group in the C-5 position, located in the diazepine B ring. This fact could be explained by its predictable low stability, as it has been shown for 4,5-dihydro-3*H*-benzo[e][1,4]diazepines where the tautomerization of the desirable imine group to the most stable enamine tautomer[11] favored the oxidative cleavage of the heterocycle in presence of air. [12]

In order to give access to pyrrolo[2,1-c][1,4]benzodiazepine-3-ones bearing the N10-C11 imine group, we envisioned the possibility of installing a quaternary center at C11a, in order to prevent the tautomerization (Fig. 1b), enhancing their stability. This would give rise to a new family of PBDs with potential interesting pharmacological properties. Herein we report our efforts toward this goal using the Ugi reaction as the starting point, followed by different postcondensation reactions.

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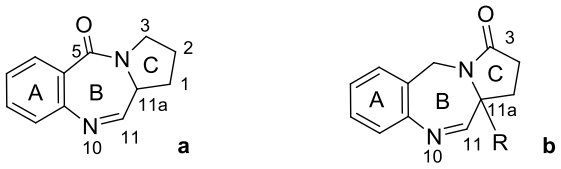
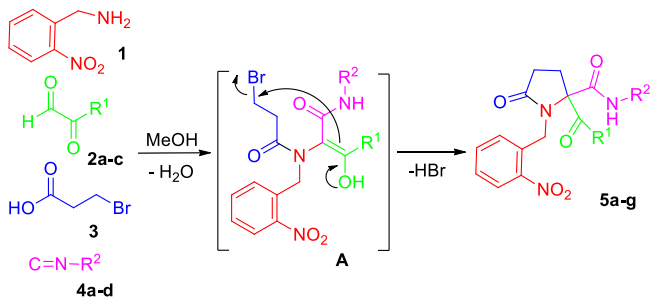


Fig. 1 (a) Pyrrolo[2,1-c][1,4]benzodiazepine-5-ones and (b) novel pyrrolo[2,1-c][1,4]benzodiazepine-3-ones described in this work.

Results and discussion

Recently, Ding *et al.* have reported the synthesis of pyrrolidones from 2-(bromomethyl)-3-aryl-2-propenoic acid and arylglyoxal derivatives via a tandem Ugi 4CC/SN cyclization in a one-pot sequence promoted in basic medium.[13] With these precedents, we decided to use as starting reactants for our planned Ugi/post-condensation strategy three doubly functionalized building blocks, in addition to the essential isocyanide component **4**. Thus, 3-bromopropionic acid **3** and different glyoxals **2** were selected to synthesize the pyrrolo nucleus C, whereas 2-nitrobenzylamine **1** would be used for the synthesis of the diazepine nucleus B fused to the benzo ring A in a posterior step.

The Ugi reaction was carried out in standard conditions. The corresponding imine was formed mixing the 2-nitrobenzylamine **1** (1 equiv) with a solution of glyoxal **2a-d** (1 equiv) in methanol. Alkyl isocyanides **4a-d** (1 equiv) and 3-bromopropionic acid **3** (1 equiv) were then added and the mixture was stirred at room temperature until precipitation of products **5a-g**. The use of 3-bromopropionic acid afforded the pyrrolidinones **5** in one-pot reaction in good yield, through a spontaneous cyclization from the Ugi adduct **A**, without the addition of a base (Table 1).



Scheme 1 Synthesis of pyrrolidinones **5a-g** by an Ugi/cyclization sequence.

Table 1 Results from the Ugi/cyclization sequence.

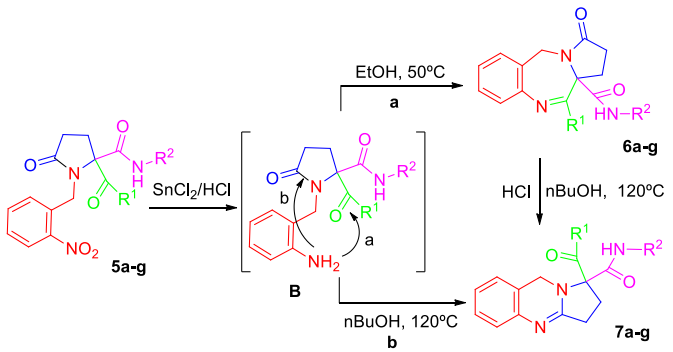
2 (R^1)	**4** (R^2)	**5**	Isolated Yield
2a (C_6H_5)	**4a** (cC_6H_{11})	**5a**	78
2a (C_6H_5)	**4b** ($CH_3(CH_2)_3$)	**5b**	75
2a (C_6H_5)	**4c** ($(CH_3)_3C$)	**5c**	85
2a (C_6H_5)	**4c** ($C_6H_5CH_2$)	**5d**	83
2b (4-$CH_3C_6H_4$)	**4a** (cC_6H_{11})	**5e**	81
2c (4-ClC_6H_4)	**4a** (cC_6H_{11})	**5f**	75
2d (CH_3)	**4a** (cC_6H_{11})	**5g**	53

The second stage was carried out employing the conditions previously essayed in our group for the construction of benzodiazepines from nitro derivatives.[11] Thus, *N*-(2-nitrobenzyl)pyrrolidinone **5a** was reduced using stannous chloride under acidic conditions in refluxing ethanol (70 °C). As expected, the corresponding amino intermediate **B** underwent a spontaneous cyclization. However, under these conditions, the amino group reacted not only with the most reactive carbonyl group of the ketone to yield the expected pyrrolobenzodiazepine **6a** but also with the carbonyl group of the amide to afford the pyrroloquinazoline **7a**, thus yielding a mixture of two isomers (**6a:7a**) in an approximate ratio of 1:1 (Scheme 2).

This result prompted us to explore different conditions for the reduction reaction in order to control the chemoselectivity of the cyclization step. When the reduction was carried out at moderate temperature (50 °C), pyrrolobenzodiazepines **6** were obtained exclusively (Scheme 2, *via* a). On the other hand, at higher temperature (120 °C) pyrroloquinazolines **7** were obtained as single products (Scheme 2, *via* b). Thus, controlling the reaction temperature, either scaffold can be easily obtained from the same Ugi adduct as single products (Table 2).

These results seem to indicate that the cyclization yielding the pyrrolobenzodiazepines is kinetically favorable, whereas the formation of the pyrroloquinazoline system is thermodynamically controlled. In fact, clean isomerization of pyrrolobenzodiazepines **6** to the corresponding pyrroloquinazolines **7** can be achieved by refluxing **6a-g** in the presence of hydrochloric acid in boiling n-butanol (120 °C). Interestingly, it should be noted that the PBDs **6** have a high stability in neutral conditions, and they were recovered quantitatively after heating for 2 hr in boiling n-butanol (120 °C).

The structures of these fused heterocycles were fully characterized by NMR and HRMS spectroscopy and unequivocally confirmed by single crystal X-ray diffraction analyses of compounds **6c** and 7**g** (Fig. 2).



Scheme 2 Synthesis of pyrrolobenzodiazepines **6** and pyrroloquinazolines **7** from Ugi adducts.

Table 2 Cyclization results at 50 °C (left) and at 120 °C (right).

5 (R^1, R^2)	Temp (°C)[a]	**6** (%)[b]
5a (C_6H_5, cC_6H_{11})	50	**6a** (75)
5b (C_6H_5, $CH_3(CH_2)_3$)	50	**6b** (63)
5c (C_6H_5, $(CH_3)_3C$)	50	**6c** (65)
5d (C_6H_5, $C_6H_5CH_2$)	50	**6d** (72)
5e (4-$CH_3C_6H_4$, cC_6H_{11})	50	**6e** (65)
5f (4-ClC_6H_4, cC_6H_{11})	50	**6f** (77)
5g (CH_3, cC_6H_{11})	50	**6g** (75)

5 (R^1, R^2)	Temp (°C)[a]	**7** (%)[b]
5a (C_6H_5, cC_6H_{11})	120	**7a** (68)
5b (C_6H_5, $CH_3(CH_2)_3$)	120	**7b** (55)
5c (C_6H_5, $(CH_3)_3C$)	120	**7c** (54)
5d (C_6H_5, $C_6H_5CH_2$)	120	**7d** (58)
5e (4-$CH_3C_6H_4$, cC_6H_{11})	120	**7e** (70)
5f (4-ClC_6H_4, cC_6H_{11})	120	**7f** (71)
5g (CH_3, cC_6H_{11})	120	**7g** (61)

[a] At the indicated temperature the other isomer was not detected by NMR in the reaction mixture. [b] Isolated yields.

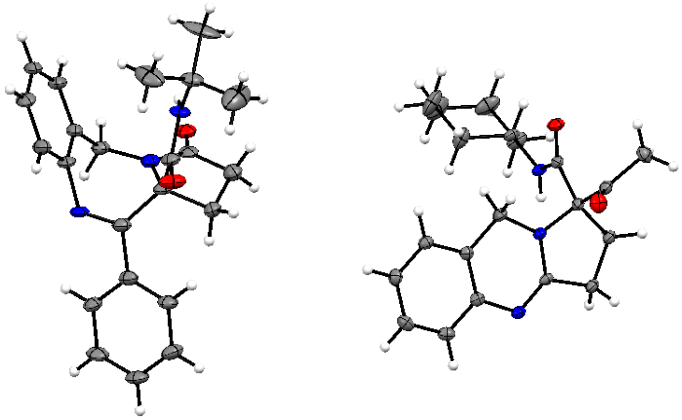
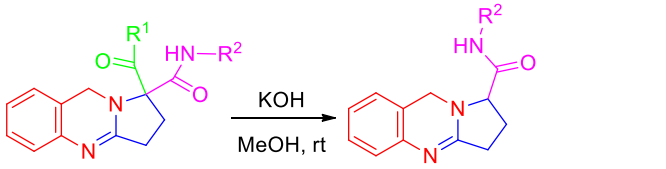


Fig. 2 X-ray diffraction structures of pyrrolobenzodiazepine **6c** and pyrroloquinazoline **7g**.

Due to the similitude of pyrroloquinazolines **7** with the linarinic acid, a natural product isolated from *Linaria vulgaris*,[14] we explored the debenzoylation of **7** to yield linarinic acid derivatives. Linarinic acid is used in the traditional Chinese medicine and its derivatives have been evaluated for their pharmacological properties.[15] Thus, treatment of derivatives **7a** and **7d** with a KOH solution in ethanol at room temperature yielded the corresponding amide derivatives **8a-b** in high yield. The amide was not hydrolyzed under these conditions and the use of harsher conditions caused the decomposition of the quinazoline scaffold (Scheme 3).



7a: R^1: C_6H_5, R^2: cC_6H_{11}
7d: R^1: C_6H_5, R^2: $CH_2C_6H_5$

8a R^2: cC_6H_{11} (91%)
8b R^2: $CH_2C_6H_5$ (87%)

Scheme 3 Debenzoylation reactions of pyrroloquinazoline derivatives.

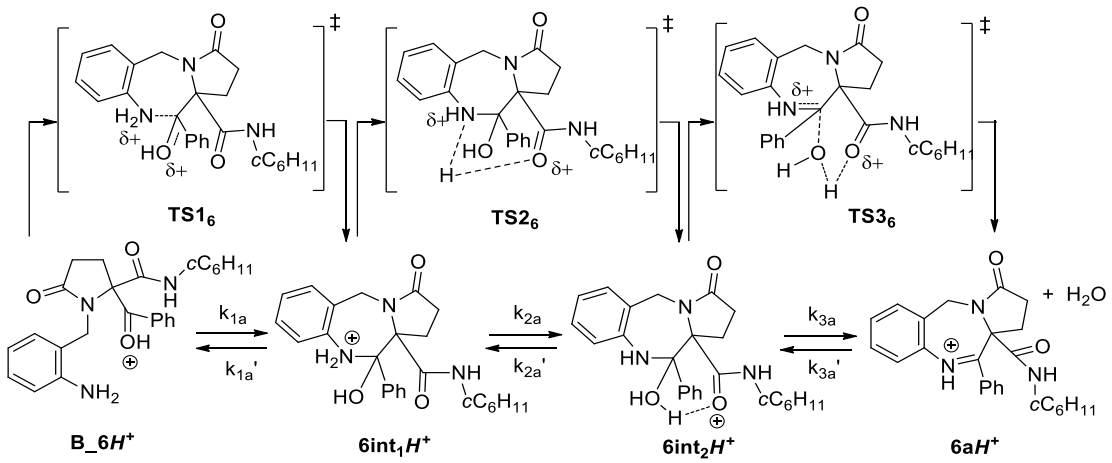
Computational studies

In order to rationalize the experimental results observed in the second cyclization step and shed light on the reaction mechanisms (Scheme 2), DFT quantum chemical calculations were carried out with Gaussian 09.[16] Compound **5a** was used as model for the cyclization reaction furnishing **6a** and **7a** from the corresponding B intermediate. The geometries of all species were fully optimized at the B3LYP/6-31G** level. The reaction schemes are depicted in Schemes 4 and 5 for the cyclization yielding **6a** and **7a**, respectively. The corresponding energy diagrams are shown in Figures 3 and 4. In both cases the reaction proceeds from the protonated **B** intermediate through a 3-step sequence, involving intramolecular formation of hemiaminal, proton migration and dehydration.

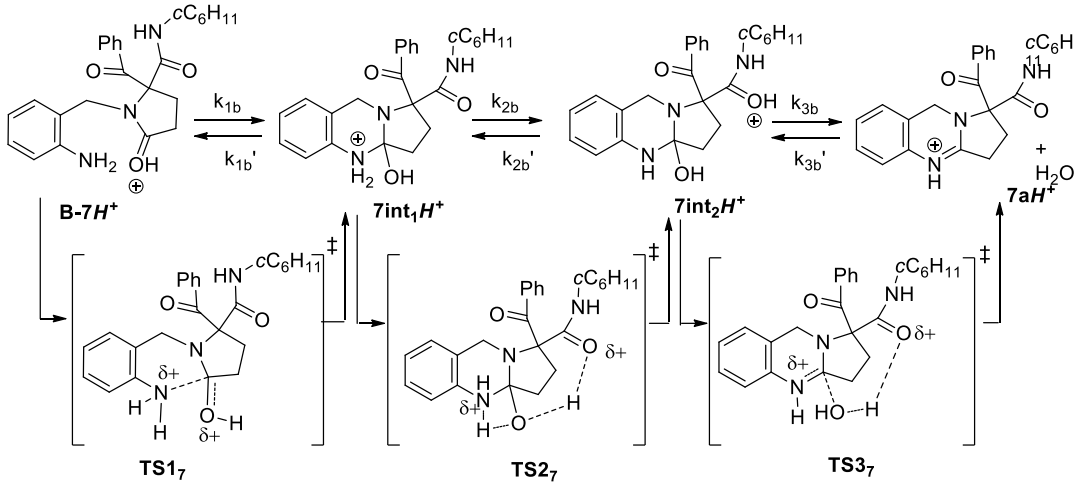
The calculated free energies for the syntheses of these fused heterocycles explain how the selectivity can be controlled by the temperature. In both syntheses, the reaction starts with the protonation of a carbonyl group. The charge distribution calculated for the neutral intermediate **B** by NBO analysis confirmed, as it was expected, a more negative charge on the oxygen of the lactam (-0.609 *e*) than on the oxygen of the benzoyl group (-0.595 *e*); this difference favors the protonation of the former group. However, comparing the barriers of cyclization from the protonated intermediates (**B-6***H*$^+$ and **B-7***H*$^+$) to the corresponding heterocycle, the cyclization to benzodiazepine is faster. Thus, while the activation energies for the synthesis of pyrrolobenzodiazepines **6** are considerably lower than the barriers for the synthesis of pyrroloquinazolines **7** (kinetic control), the latter are much more stable than the pyrrolobenzodiazepines (thermodynamic control) (Fig. 3 *vs* Fig. 4). In that way, the calculated activation energies for the synthesis of pyrrolobenzodiazepine **6a** in acidic medium in ethanol (5.8, 7.6 and 7.3 kcal mol^{-1} for the cyclization, proton migration and dehydration, respectively) are low enough to allow the fast conversion at moderate temperatures (kinetically favorable) with reaction rates at 50 °C of k_{1a} = 8.58 x 10^8 s^{-1}, k_{2a} = 5.05 x 10^7 s^{-1} and k_{3a} = 7.21 x 10^7 s^{-1} for each stage (Scheme 4). Furthermore, the calculated energies in the two first stages for the synthesis of pyrroloquinazoline **7a** are considerable higher (10.7, 20.3 and 0.6 kcal mol^{-1} for the cyclization, proton migration and

dehydration in acidic medium in ethanol) and the cyclization should be carried out at 120 °C to afford the pyrroloquinazoline derivative **7a**, with reaction rates at this temperature of k_{1b} = 9.81 x 10^6 s^{-1}, k_{2b} = 4.43 x 10^1 s^{-1} and k_{3b} = 3.82 x 10^{12} s^{-1} (Scheme 5). The syntheses of both systems are thermodynamically favorable (Fig. 3 and 4) with equilibrium constants of 3.96 x 10^3 and 5.78 x 10^{14} for the pyrrolobenzodiazepine **6a** and the pyrroloquinazoline **7a** synthesis, respectively (calculated using the Arrhenius equation). However, the higher stability of pyrroloquinazoline derivatives explains the chemical results when the cyclization reactions are carried out in acidic medium in boiling n-butanol (thermodynamic control).

These computational studies are also in good agreement with the observed experimental results regarding both the isomerization of **6a** to **7a** under acidic conditions at 120 °C and the stability of **6a** at high temperature in the absence of acid. Thus, the calculated free energies in gas phase for the two stages found in the hydrolysis of these systems, addition of water and ring opening, were 56.6 and 35.5 kcal mol^{-1} for the imine group in the pyrrolobenzodiazepine **6a**, and 47.3 and 36.3 kcal mol^{-1} for the amidine group in the pyrroloquinazoline **7a**. However, in an acidic medium these barriers drop dramatically, and when the pyrrolobenzodiazepines **6** were treated with hydrochloric acid in boiling n-butanol they were transformed in a quantitative way in their corresponding pyrroloquinazoline isomer **7**.



Scheme 4 Process of cyclization and opening for pyrrolobenzodiazepine **6a**.



Scheme 5. Process of cyclization and opening for pyrroloquinazoline **7a**.

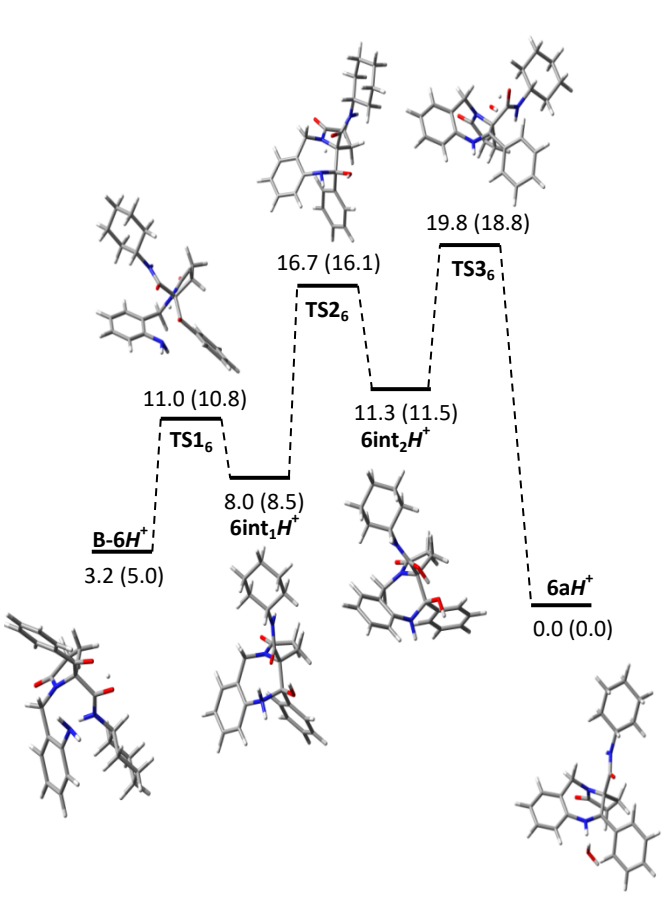


Fig. 3. Energy diagram for the synthesis (and opening) of pyrrolobenzodiazepine **6a** in acidic medium. The values reported in the diagram are in kcal mol^{-1} and refer to calculations performed in gas phase and ethanol (in brackets).

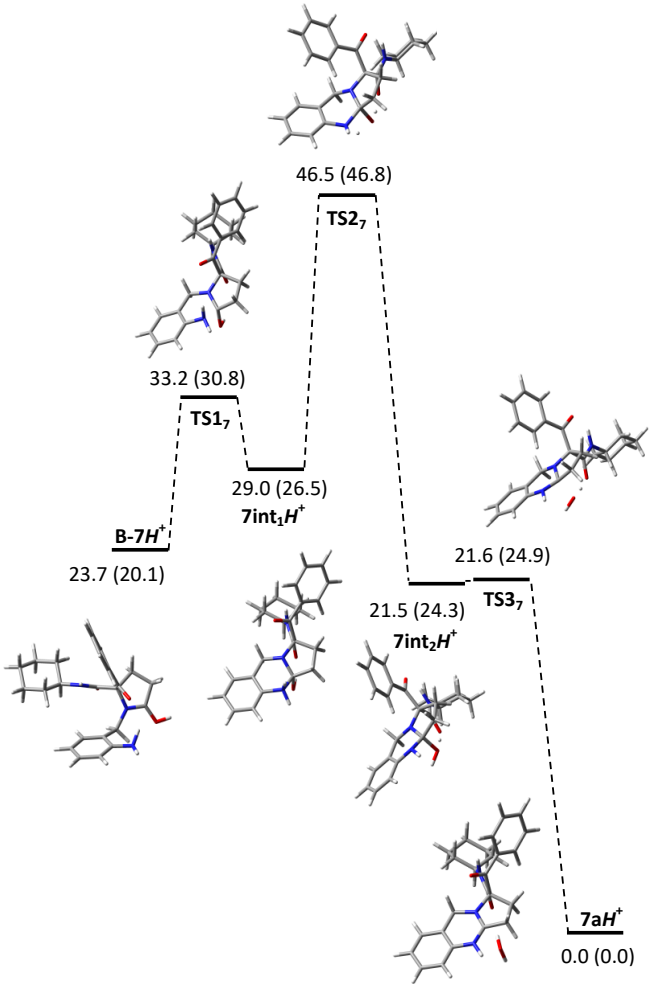


Fig. 4 Energy diagram for the synthesis (and opening) of pyrroloquinazoline **7a** in acidic medium. The values reported in the diagram are in kcal mol^{-1} and refer to calculations performed in gas phase and ethanol (in brackets).

These results are in agreement with the DFT results, as the calculated barriers of each stage (in gas phase) for the hydrolysis of the imine in the protonated pyrrolobenzodiazepine **6a** decrease to 19.8, 5.5 and 3.7 kcal mol^{-1} for the hydration, proton migration and ring opening respectively. Slightly lower barriers are found when the calculations are performed using ethanol as solvent (18.8, 4.6 and 2.3 kcal mol^{-1}) (Fig. 3). The reaction rates calculated from the Eyring-Polanyi equation from these last values indicate that the benzodiazepine opening is a slow process at room temperature (k_{3a}' = 1.01 x 10^{-1} s^{-1}, k_{2a}' = 2.94 x 10^{9} s^{-1}, k_{1a}' = 1.41 x 10^{11} s^{-1}) but it is affordable in boiling n-butanol (k_{3a}' = 2.85 x 10^{2} s^{-1}, k_{2a}' = 2.46 x 10^{10} s^{-1}, k_{1a}' = 4.64 x 10^{11} s^{-1}) (Scheme 4). These values, along with the free energies calculated for the synthesis of pyrroloquinazolines **7**, explain the isomerization reaction in acidic conditions.

Finally, it is interesting to note that although there is a third possibility of cyclization through the amide derived from the isocyanide compound, the corresponding benzodiazepine is not observed. Again, the high energetic barriers calculated for this reaction pathway is in agreement with the observed result.

Conclusion

In summary, we have developed a simple and versatile methodology for the synthesis of two different families of pyrrolo- fused heterocycles based on an Ugi/cyclization/condensation sequence. By controlling the chemoselectivity in the reduction/cyclization step with the temperature, selective access to pyrroloquinazolines and unprecedented pyrrolo[2,1-c][1,4]benzodiazepine-3-ones has been demonstrated. A comprehensive computational DFT study rationalized these results and shed light on the mechanisms involved in these transformations, identifying the pyrrolobenzodiazepines as the kinetic products and the pyrroloquinazolines as the thermodynamic ones. The synthetic usefulness of these reactions to prepare new derivatives of the linarinic acid alkaloid has been proved. Efforts to evaluate the biological activity of the new derivatives are currently underway in our laboratories.

Experimental

General experimental methods

Melting points are not corrected. Infrared spectra were registered in potassium bromide tablets. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 300 and 75 MHz, respectively, on Varian Mercury 300, or at 400 and 100 MHz on Varian Unity Inova 400. Chemical shifts are reported in parts per million with respect to residual solvent protons and coupling constants are reported in hertz. Low resolution mass spectra were recorded in positive ion mode by electronic impact (EI) at 70 eV and HRMS were recorded by electronic impact or by electrospray ionization (ESI).

Synthesis and characterization

General procedure for the synthesis of Ugi aducts 5a-5g

The *o*-nitrobenzylamine hydrochloride **1** (0.207 g, 1.1 mmol) was treated with a solution of KOH (1.0 mmol) in methanol for 10 min, after which the glyoxal **2** (1 mmol) was added. The mixture was stirred for 15 min at room temperature. Then, the 3-bromopropanoic acid **3** (1 mmol) and the isocyanide **4** (1 mmol) were added and the mixture was stirred for 2 days. When a solid was formed, the precipitate was filtered and washed. If no solid was observed, the solvent was removed, the raw product solved in dichloromethane and washed with a NaOH solution and then with a HCl solution. The organic extract was dried over Na_2SO_4 and concentrated to dryness. The crude residue was recrystallized from isopropyl alcohol/isopropyl ether mixtures.

5-Benzoyl-5-(*N*-cyclohexylcarbamoyl)-1-(2-nitrobenzyl)-2-pyrrolidinone (5a). White solid; m.p. 187-188 ^{o}C; IR (KBr, cm^{-1}): 3320, 3083, 1692, 1668, 1613; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93-7.91 (m, 1H), 7.83-7.80 (m, 2H), 7.58-7.51 (m, 2H), 7.44-7.31 (m, 4H), 5.77 (d, *J* = 7.9 Hz, 1H, NH), 5.24 (d, *J* = 18.0 Hz, 1H, $CH_{2\ benzyl}$), 4.73 (d, *J* = 18.0 Hz, 1H, $CH_{2\ benzyl}$), 3.41-3.24 (m, 2H), 2.81-2.72 (m, 1H), 2.53-2.40 (m, 2H), 1.41-0.50 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.1 (Cq), 176.8 (Cq), 166.1 (Cq), 147.7 (Cq), 134.3 (CH_{Ar}), 133.9 (CH_{Ar}), 133.3 (Cq), 133.0 (Cq), 129.4 (CH_{Ar}), 129.2 (CH_{Ar}), 129.0 (CH_{Ar}), 127.9 (CH_{Ar}), 124.9 (CH_{Ar}), 77.4 (Cq), 49.6 (CH), 44.1 (CH_2), 31.9 (CH_2), 31.7 (CH_2), 28.8 (CH_2), 28.3 (CH_2), 25.2 (CH_2), 24.7 (CH_2); MS (EI) *m/z* (%): 450 (M^++1, 0.7), 344 (100), 136 (83), 105 (72), 78 (37); HRMS (EI): calculated for $C_{25}H_{28}N_3O_5$ [M^++1] 450.2029, found 450.2026.

5-Benzoyl-5-(*N*-butylcarbamoyl)-1-(2-nitrobenzyl)-2-pyrrolidinone (5b). Sticky solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93-7.33 (m, 9H), 6.00 (t, *J* = 5.1 Hz, 1H, NH), 5.28 (d, *J* = 17.8 Hz, 1H, $CH_{2\ benzyl}$), 4.73 (d, *J* = 17.8 Hz, 1H, $CH_{2\ benzyl}$), 3.33-3.20 (m, 1H), 2.88-2.73 (m, 2H), 2.59-2.40 (m, 3H), 1.01-0.82 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.8 (Cq), 176.8 (Cq), 166.9 (Cq), 147.6 (Cq), 134.2 (CH_{Ar}), 133.7 (CH_{Ar}), 133.1 (Cq), 132.7 (Cq), 129.3 (CH_{Ar}), 129.2 (CH_{Ar}), 128.9 (CH_{Ar}), 127.8 (CH_{Ar}), 124.7 (CH_{Ar}), 77.2 (Cq), 43.5 (CH_2), 40.1 (CH_2), 30.5 (CH_2), 28.7 (CH_2), 28.0 (CH_2), 19.8 (CH_2), 13.6 (CH_3); HRMS (ESI): calculated for $C_{23}H_{26}N_3O_5$ [M^++1] 424.1867, found 424.1859.

5-Benzoyl-1-(2-nitrobenzyl)-5-(*N*-tertbutylcarbamoyl)-2-pyrrolidinone (5c). White solid; m.p. 112-113 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95-7.84 (m, 3H), 7.62-7.33 (m, 6H), 5.41 (s, 1H, NH), 5.31 (d, *J* = 18.0 Hz, 1H, $CH_{2\ benzyl}$), 4.69 (d, *J* = 18.0 Hz, 1H), 3.29-3.22 (m, 1H), 2.80-2.69 (m, 1H), 2.51-2.37 (m, 2H), 0.85 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.7 (Cq), 176.6 (Cq), 165.5 (Cq), 147.6 (Cq), 134.1 (CH_{Ar}), 133.7 (CH_{Ar}), 132.9 (Cq), 132.8 (Cq), 129.3 (CH_{Ar}), 129.0 (CH_{Ar}), 128.7 (CH_{Ar}), 127.8 (CH_{Ar}), 124.7 (CH_{Ar}), 78.1 (Cq), 52.6 (Cq), 43.6 (CH_2), 28.4 (CH_2), 27.8 (CH_2), 27.5 (CH_3); HRMS (ESI): calculated for $C_{23}H_{26}N_3O_5$ [M^++1] 424.1867, found 424.1866.

5-Benzoyl-5-(*N*-benzylcarbamoyl)-1-(2-nitrobenzyl)-2-pyrrolidinone (5d). White solid; m.p. 94-96 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93-7.08 (m, 12H), 6.94 (t, *J* = 5.7 Hz, 1H, NH), 6.82-6.79 (m, 2H), 5.25 (d, *J* = 17.9 Hz, 1H, $CH_{2\ benzyl}$), 4.76 (d, *J* = 17.9 Hz, 1H, $CH_{2\ benzyl}$), 4.09 (dd, *J* = 14.8, 6.3 Hz, 1H, $CH_{2\ benzyl}$), 3.67 (dd, *J* = 14.8, 5.0 Hz, 1H, $CH_{2\ benzyl}$), 3.35-3.20 (m, 1H), 2.82-2.67 (m, 1H), 2.53-2.40 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.4 (Cq), 177.0 (Cq), 167.0 (Cq), 147.7 (Cq), 136.9 (Cq), 134.0 (CH_{Ar}), 133.8 (CH_{Ar}), 133.2 (Cq), 133.0 (Cq), 129.4 (CH_{Ar}), 128.9 (CH_{Ar}), 128.6 (CH_{Ar}), 127.9 (CH_{Ar}), 127.9 (CH_{Ar}), 127.5 (CH_{Ar}), 124.9 (CH_{Ar}), 77.4 (Cq), 44.2 (CH_2), 43.9 (CH_2), 28.7 (CH_2), 28.0 (CH_2); MS (EI) *m/z* (%): 458 (M^+, 3), 352 (32), 136 (38), 106 (26), 105 (72), 91 (100), 77 (42); HRMS (EI): calculated for $C_{26}H_{24}N_3O_5$ [M^++1] 458.1723, found 458.1716.

5-(*N*-Cyclohexylcarbamoyl)-5-(4-methylbenzoyl)-1-(2-nitrobenzyl)-2-pyrrolidinone (5e). White solid; m.p. 137-138 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94-7.20 (m, 8H), 5.85 (d, *J* = 7.9 Hz, 1H, NH), 5.25 (d, *J* = 18.2 Hz, 1H, $CH_{2\ benzyl}$), 4.73 (d, *J* = 18.2 Hz, 1H, $CH_{2\ benzyl}$), 3.41-3.22 (m, 2H), 2.81-2.69 (m, 1H), 2.52-2.35 (m, 2H), 2.39 (s, 3H), 1.41-0.46 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.4 (Cq), 176.8 (Cq), 166.1 (Cq), 147.5 (Cq), 145.4 (Cq), 133.7 (CH_{Ar}), 133.0 (Cq), 130.5 (Cq), 129.6 (CH_{Ar}), 129.5 (CH_{Ar}), 129.0 (CH_{Ar}), 127.7 (CH_{Ar}), 124.8 (CH_{Ar}), 77.4 (Cq), 49.5 (CH), 44.1 (CH_2), 31.8 (CH_2), 31.6 (CH_2), 31.0 (CH_2), 28.7 (CH_2), 28.2 (CH_2), 25.1 (CH_2), 24.6 (CH_2), 21.8 (CH_3); MS (EI): 464 (M^++1, 5), 463 (M^+, 0.9), 344 (56), 136 (67), 120 (21), 119 (100), 91 (21), 78 (23); HRMS (EI): calculated for $C_{26}H_{30}N_3O_5$ [M^++1] 464.2185, found 464.2191.

5-(4-Chlorobenzoyl)-5-(*N*-cyclohexylcarbamoyl)-1-(2-nitrobenzyl)-2-pyrrolidinone (5f). White solid; m.p. 195-196 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02-7.90 (m, 1H), 7.77-7.74 (m, 2H), 7.56-7.51 (m, 1H), 7.41-7.32 (m, 4H), 6.02 (d, *J* = 7.8 Hz, 1H, NH), 5.21 (d, *J* = 18.1 Hz, 1H, $CH_{2\ benzyl}$), 4.74 (d, *J* = 18.1 Hz, 1H, $CH_{2\ benzyl}$), 3.49-3.10 (m, 2H), 2.88-2.69 (m, 1H), 2.54-2.34 (m, 2H), 1.52-0.47 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.5 (Cq), 176.7 (Cq), 165.6 (Cq), 147.4 (Cq), 140.5 (Cq), 133.7 (CH_{Ar}), 132.7 (Cq), 131.3 (Cq), 130.6 (CH_{Ar}), 129.0 (CH_{Ar}), 128.7 (CH_{Ar}), 127.7 (CH_{Ar}), 124.7 (CH_{Ar}), 77.2 (Cq), 49.4 (CH), 43.9 (CH_2), 31.6 (CH_2), 31.3 (CH_2), 28.4 (CH_2), 27.8 (CH_2), 24.9 (CH_2), 24.6 (CH_2); HRMS (ESI): calculated for $C_{25}H_{27}ClN_3O_5$ [M^++1] 484.1634, found 484.1633.

5-Acetyl-5-(*N*-cyclohexylcarbamoyl)-1-(2-nitrobenzyl)-2-pyrrolidinone (5g). White solid; m.p. 170-171 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03-7.91 (m, 1H), 7.66-7.52 (m, 2H), 7.46-7.35 (m, 1H), 6.98 (d, *J* = 7.7 Hz, 1H, NH), 4.95 (d, *J* = 16.8 Hz, 1H, $CH_{2\ benzyl}$), 4.80 (d, *J* = 16.8 Hz, 1H, $CH_{2\ benzyl}$), 3.63-3.47 (m, 1H),

2.75-2.62 (m, 1H), 2.60-2.41 (m, 2H), 2.31-2.20 (m, 1H), 2.16 (s, 3H), 1.80-0.83 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.1 (Cq), 177.5 (Cq), 166.8 (Cq), 133.8 (CH_{Ar}), 132.5 (Cq), 130.9 (CH_{Ar}), 128.5 (CH_{Ar}), 124.9 (CH_{Ar}), 49.0 (CH_2), 44.0 (CH), 32.6 (CH_2), 32.5 (CH_2), 29.4 (CH_2), 29.0 (CH_2), 27.1 (CH_3), 25.5 (CH_2), 24.8 (CH_2), 24.7 (CH_2); MS (EI) *m/z* (%): 388 (55, M^++1), 344 (100), 262 (38), 219 (49); HRMS (EI): calculated for $C_{20}H_{26}N_3O_5$ [M^++1] 388.1872, found 388.1870.

General procedure for the synthesis of pyrrolobenzodiazepines 6a-6g

To a suspension of pyrrolidinone **5a-g** (0.5 mmol) in ethanol (5 ml) and hydrochloric acid solution 0.6 M (1.5 mmol) was added stannous chloride (5 mmol). The reaction was heated at 50 °C during 45 min, cooled and concentrated under reduced pressure. The residue was dissolved in dichloromethane and washed with a diluted KOH solution and then with water. The organic extract was dried over Na_2SO_4 and concentrated to dryness. The crude residue was recrystallized from dichloromethane/isopropyl ether mixtures.

11a-(*N*-Cyclohexylcarbamoyl)-11-phenyl-2,3,5,11a-tetrahydro-1*H*-pyrrolo[2,1c][1,4]benzodiazepin-3-one (6a). White solid; m.p. 163-164 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57-7.54 (m, 2H), 7.43-7.30 (m,4H), 7.23-7.10 (m, 3H), 5.38 (d, *J* = 8.5 Hz, 1H, NH), 4.98 (d, *J* = 13.9 Hz, 1H, $CH_{2\ benzyl}$), 3.93 (d, *J* = 13.9 Hz, 1H, $CH_{2\ benzyl}$), 3.29-3.17 (m, 1H), 2.33-2.11 (m, 4H), 1.60-0.76 (m, 9H, H), 0.40-0.28 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.0 (Cq), 170.2 (Cq), 169.2 (Cq), 148.1 (Cq), 139.3 (Cq), 130.0 (CH_{Ar}), 129.6 (CH_{Ar}), 128.7 (CH_{Ar}), 128.6 (CH_{Ar}), 127.8 (CH_{Ar}), 126.8 (CH_{Ar}), 125.7 (CH_{Ar}), 122.8 (Cq), 71.6 (Cq), 48.7 (CH), 43.7 (CH_2), 33.8 (CH_2), 33.1 (CH_2), 32.4 (CH_2), 29.2 (CH_2), 25.4 (CH_2), 25.1 (CH_2), 24.9 (CH_2); MS (EI) *m/z* (%): 401 (M^+, 1.8), 275 (100), 277 (10), 193 (15); HRMS (EI): calculated for $C_{25}H_{27}N_3O_2$ [M^+] 401.2103, found 401.2109.

11a-(*N*-Butylcarbamoyl)-11-phenyl-2,3,5,11a-tetrahydro-1*H*-pyrrolo[2,1c][1,4]benzodiazepin-3-one (6b). White solid; m.p. > 230 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69-7.14 (m, 9H), 6.01 (t, *J* = 5.9 Hz, 1H, NH), 5.02 (d, *J* = 13.9 Hz, 1H, $CH_{2\ benzyl}$), 3.99 (d, *J* = 13.9 Hz, 1H, $CH_{2\ benzyl}$), 2.75 (q, *J* = 6.9 Hz, 2H), 2.39-2.04 (m, 4H), 1.52-0.83 (m, 4H), 0.78 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.7 (Cq), 171.0 (Cq), 170.0 (Cq), 147.9 (Cq), 138.9 (Cq), 129.7 (CH_{Ar}), 129.3 (CH_{Ar}), 128.4 (CH_{Ar}), 127.5 (CH_{Ar}), 126.5 (CH_{Ar}), 125.4 (CH_{Ar}), 122.6 (Cq), 71.4 (Cq), 43.5 (CH_2), 39.6 (CH_2), 33.3 (CH_2), 31.2 (CH_2), 29.0 (CH_2), 20.0 (CH_2), 13.6 (CH_3); HRMS (ESI): calculated for $C_{23}H_{26}N_3O_2$ [MH^+] 376.2020, found 376.2015.

11-Phenyl-11a-(*N*-tertbutylcarbamoyl)-2,3,5,11a-tetrahydro-1*H*-pyrrolo[2,1c][1,4]benzodiazepin-3-one (6c). White solid; m.p. 207-209 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68-7.10 (m, 9H), 5.36 (s, 1H, NH), 5.01 (d, *J* = 13.9 Hz, 1H, $CH_{2\ benzyl}$), 3.97 (d, *J* = 13.9 Hz, 1H, $CH_{2\ benzyl}$), 2.44-2.13 (m, 4H), 0.92 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.7 (Cq), 170.0 (Cq), 169.3 (Cq), 148.1 (Cq), 139.1 (Cq), 129.9 (CH_{Ar}), 129.3 (CH_{Ar}), 128.4 (CH_{Ar}), 128.3 (CH_{Ar}), 127.5 (CH_{Ar}), 126.5 (CH_{Ar}), 125.6 (CH_{Ar}), 122.8 (Cq), 71.7 (Cq), 51.2 (Cq), 43.5 (CH_2), 33.6 (CH_2), 28.9 (CH_2), 27.9 (CH_3); HRMS (ESI): calculated for $C_{23}H_{26}N_3O_2$ [M^++1] 376.2020, found 376.2014.

11a-(*N*-Benzylcarbamoyl)-11-phenyl-2,3,5,11a-tetrahydro-1*H*-pyrrolo[2,1c][1,4]benzodiazepin-3-one (6d). Sticky solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63-6.91 (m, 14H), 6.46 (t, *J* = 5.6 Hz, 1H, NH), 4.94 (d, *J* = 13.8 Hz, 1H, $CH_{2\ benzyl}$), 4.11 (dd, *J* = 14.5, 6.3 Hz, 1H, $CH_{2\ benzyl}$), 3.96 (d, *J* = 13.8 Hz, 1H, $CH_{2\ benzyl}$), 3.70 (dd, *J* = 14.5, 5.3 Hz, 1H, $CH_{2\ benzyl}$), 2.45-2.00 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.9 (Cq), 171.4 (Cq), 169.0 (Cq), 148.0 (Cq), 139.2 (Cq), 137.4 (Cq), 129.9 (CH_{Ar}), 129.6 (CH_{Ar}), 128.8 (CH_{Ar}), 128.8 (CH_{Ar}), 128.7 (CH_{Ar}), 128.2 (CH_{Ar}), 127.8 (CH_{Ar}), 126.7 (CH_{Ar}), 125.5 (CH_{Ar}), 122.6 (Cq), 71.6 (Cq), 44.2 (CH_2), 43.8 (CH_2), 33.5 (CH_2), 29.2 (CH_2); MS (EI) *m/z* (%): 409 (M^+, 2), 276 (25), 275 (79), 122 (50), 105 (100), 91 (64), 96 (225), 77 (62); HRMS (EI): calculated for $C_{26}H_{23}N_3O_2$ [M^+] 409.1790, found 409.1793.

11a-(*N*-Cyclohexylcarbamoyl)-11-tolyl-2,3,5,11a-tetrahydro-1*H*-pyrrolo[2,1c][1,4]benzodiazepin-3-one (6e). White solid; m.p. 208-210 °C; IR (KBr, cm^{-1}): 3321, 2928, 2849, 1695, 1647, 1525, 1392; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51-7.49 (m, 2H), 7.40-7.14 (m, 6H), 5.51 (d, *J* = 8.3 Hz, 1H, NH), 5.02 (d, *J* = 13.9 Hz, 1H, $CH_{2\ benzyl}$), 3.98 (d, *J* = 13.8 Hz, 1H, $CH_{2\ benzyl}$), 3.41-3.16 (m, 1H), 2.40 (s, 3H), 2.41-2.18 (m, 4H), 1.82-0.82 (m, 9H), 0.47-0.32 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.9 (Cq), 170.3 (Cq), 169.2 (Cq), 148.3 (Cq), 139.6 (Cq), 136.5 (Cq), 129.9 (CH_{Ar}), 129.2 (CH_{Ar}), 128.7 (CH_{Ar}), 127.8 (CH_{Ar}), 126.7 (CH_{Ar}), 125.7 (CH_{Ar}), 122.9 (Cq), 71.7 (Cq), 48.7 (CH), 43.7 (CH_2), 33.9 (CH_2), 33.1 (CH_2), 32.4 (CH_2), 29.2 (CH_2), 25.4 (CH_2), 25.1 (CH_2), 24.9 (CH_2), 21.6 (CH_3); MS (EI) *m/z* (%): 415 (M^+, 2), 291 (9), 290 (52), 289 (100), 207 (16), 83 (11); HRMS (EI): calculated for $C_{26}H_{29}N_3O_2$ [M^+] 415.2260, found 415.2259.

11-(4-Chlorophenyl)-11a-(*N*-cyclohexylcarbamoyl)-2,3,5,11a-tetrahydro-1*H*-pyrrolo[2,1c][1,4]benzodiazepin-3-one (6f). White solid; m.p. 199-200 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58-7.17 (m, 8H), 5.66 (d, *J* = 8.3 Hz, 1H, NH), 5.04 (d, *J* = 13.9 Hz, 1H, $CH_{2\ benzyl}$), 3.96 (d, *J* = 13.8 Hz, 1H, $CH_{2\ benzyl}$), 3.43-2.17 (m, 1H), 2.41-2.16 (m, 4H), 1.62-0.82 (m, 9H), 0.47-0.34 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.5 (Cq), 169.8 (Cq), 168.0 (Cq), 147.7 (Cq), 137.5 (Cq), 135.5 (Cq), 129.8 (CH_{Ar}), 129.1 (CH_{Ar}), 128.6 (CH_{Ar}), 128.5 (CH_{Ar}), 125.4 (CH_{Ar}), 122.5 (Cq), 71.2 (Cq), 48.5 (CH), 43.5 (CH_2), 33.7 (CH_2), 32.8 (CH_2), 32.1 (CH_2), 28.9 (CH_2), 25.2 (CH_2), 24.8 (CH_2), 24.7 (CH_2); HRMS (ESI): calculated for $C_{25}H_{27}ClN_3O_2$ [MH^+] 436.1786, found 436.1783.

11a-(*N*-Cyclohexylcarbamoyl)-11-methyl-2,3,5,11a-tetrahydro-1*H*-pyrrolo[2,1c][1,4]benzodiazepin-3-one (6g). Brown solid; m.p. 99-100 °C; IR (KBr, cm^{-1}): 3508, 3320, 2928, 2849, 1692, 1641, 1534, 1386; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.09 (m, 4H), 5.43 (d, *J* = 8.2 Hz, 1H), 4.87 (d, *J* = 13.8 Hz, 1H, $CH_{2\ benzyl}$), 3.82 (d, *J* = 13.8 Hz, 1H, $CH_{2\ benzyl}$), 3.26-3.15 (m, 1H), 2.75-2.61 (m, 1H), 2.49 (s, 3H), 2.44-2.33 (m, 3H), 1.75-0.24 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.8 (Cq), 170.0 (Cq), 167.3 (Cq), 148.3 (Cq), 129.8 (CH_{Ar}), 128.9 (CH_{Ar}), 126.3 (CH_{Ar}), 125.2 (CH_{Ar}), 123.3 (Cq), 70.9 (Cq), 48.4 (CH), 43.8 (CH_2), 33.0 (CH_2), 32.4 (CH_2), 31.5 (CH_2), 29.1 (CH_2), 27.1 (CH_3), 25.4 (CH_2), 25.0 (CH_2), 24.9 (CH_2); MS (EI) *m/z* (%): 339 (M^+, 4), 215

(11), 214 (78), 213 (100), 130 (13), 84 (25); HRMS (EI): calculated for $C_{20}H_{25}N_3O_2$ [M$^+$] 339.1947, found 339.1939.

General procedure for the synthesis of Ugi aducts 7a-7g

To a suspension of pyrrolidinone **5a-g** (0.5 mmol) in n-butanol (5 ml) and hydrochloric acid solution 0.6 M (1.5 mmol) was added stannous chloride (5 mmol). The reaction was refluxed at 120 °C during 45 min, cooled and concentrated under reduced pressure. The residue was dissolved in dichloromethane and washed with a diluted KOH solution and then with water. The organic extract was dried over Na_2SO_4 and concentrated to dryness. The crude residue was recrystallized from methanol.

1-Benzoyl-1-(*N*-cyclohexylcarbamoyl)-1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazoline (7a). White solid; m.p. 210-212 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88-7.85 (m, 2H), 7.74-7.53 (m, 2H), 7.45-7.40 (m, 2H), 7.20-7.14 (m, 1H), 7.10 (td, *J* = 7.7, 1.5 Hz, 1H), 7.00 (td, *J* = 7.3, 1.6 Hz, 1H), 6.86 (dd, *J* = 7.5, 1.3 Hz, 1H), 4.77 (d, *J* = 13.6 Hz, 1H, $CH_{2\ benzyl}$), 4.55 (d, *J* = 13.6 Hz, 1H, $CH_{2\ benzyl}$), 3.91-3.84 (m, 1H), 3.11-2.92 (m, 2H), 2.64 (ddd, *J* = 13.4, 9.6, 4.6 Hz, 1H), 2.55-2.17 (m, 1H), 2.11-1.05 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.7 (Cq), 166.4 (Cq), 162.4 (Cq), 133.8 (Cq), 133.6 (CH_{Ar}), 129.1 (CH_{Ar}), 128.6 (CH_{Ar}), 128.5 (CH_{Ar}), 126.2 (CH_{Ar}), 125.1 (CH_{Ar}), 122.4 (CH_{Ar}), 118.9 (Cq), 79.9 (Cq), 49.5 (CH), 45.0 (CH_2), 32.8 (CH_2), 32.6 (CH_2), 29.7 (CH_2), 29.3 (CH_2), 25.3 (CH_2), 25.0 (CH_2), 24.9 (CH_2); HRMS (ESI): calculated for $C_{25}H_{28}N_3O_2$ [M$^+$+1] 402.2176, found 402.2172.

1-Benzoyl-1-(*N*-butylcarbamoyl)-1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazoline (7b). Sticky solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91-7.88 (m, 2H), 7.61-7.42 (m, 4H), 7.23-7.09 (m, 2H), 7.01 (td, *J* = 7.3, 1.6 Hz, 1H), 6.85 (d, *J* = 7.4 Hz, 1H), 4.71 (d, *J* = 13.5 Hz, 1H, $CH_{2\ benzyl}$), 4.55 (d, *J* = 13.5 Hz, 1H, $CH_{2\ benzyl}$), 3.36 (td, *J* = 7.3, 5.6 Hz, 2H), 3.27-3.07 (m, 1H), 3.02-2.90 (m, 1H), 2.74 (ddd, *J* = 16.2, 9.7, 5.6 Hz, 1H), 2.48 (ddd, *J* = 13.2, 9.7, 5.9 Hz, 1H), 1.66-1.46 (m, 2H), 1.42-1.13 (m, 2H), 0.90 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.5 (Cq), 166.8 (Cq), 162.4 (Cq), 133.5 (CH_{Ar}), 133.4 (Cq), 128.8 (CH_{Ar}), 128.5 (CH_{Ar}), 128.4 (CH_{Ar}), 126.0 (CH_{Ar}), 125.1 (CH_{Ar}), 121.8 (CH_{Ar}), 118.5 (Cq), 79.4 (Cq), 44.9 (CH_2), 39.7 (CH_2), 31.0 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 19.9 (CH_2), 13.5 (CH_3); HRMS (ESI): calculated for $C_{23}H_{26}N_3O_2$ [M$^+$+1] 376.2020, found 376.2017.

1-Benzoyl-1-(*N*-tertbutylcarbamoyl)-1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazoline (7c). White solid; m.p. 186-187 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92-7.89 (m, 2H), 7.61-7.42 (m, 3H), 7.17 (td, *J* = 7.4, 1.4 Hz, 1H), 7.07 (dd, *J* = 7.9, 1.3 Hz, 1H), 6.98 (td, *J* = 7.4, 1.3 Hz, 1H), 6.82 (d, *J* = 7.5 Hz, 1H), 6.21 (s, 1H, NH), 4.62 (d, *J* = 12.9 Hz, 1H, $CH_{2\ benzyl}$), 4.54 (d, *J* = 12.9 Hz, 1H, $CH_{2\ benzyl}$), 3.00-2.87 (m, 1H), 2.76-2.65 (m, 2H), 2.48-2.38 (m, 1H), 1.36 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.4 (Cq), 166.3 (Cq), 161.9 (Cq), 134.3 (Cq), 133.8 (CH_{Ar}), 129.1 (CH_{Ar}), 128.7 (CH_{Ar}), 128.4 (CH_{Ar}), 125.8 (CH_{Ar}), 124.5 (CH_{Ar}), 124.2 (CH_{Ar}), 119.3 (Cq), 79.5 (Cq), 52.5 (Cq), 45.2 (CH_2), 30.2 (CH_2), 29.9 (CH_2), 28.5 (CH_3); HRMS (ESI): calculated for $C_{23}H_{26}N_3O_2$ [M$^+$+1] 376.2020, found 376.2015.

1-Benzoyl-1-(*N*-benzylcarbamoyl)-1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazoline (7d). White solid; m.p. 184-185 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88-6.94 (m, 14H), 6.75 (dd, *J* = 7.4, 1.3 Hz, 1H), 4.66-4.44 (m, 4H, $CH_{2\ benzyl}$), 2.97-2.85 (m, 1H), 2.77-2.61 (m, 2H), 2.50-2.39 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.4 (Cq), 168.0 (Cq), 162.2 (Cq), 138.1 (Cq), 134.1 (Cq), 133.8 (CH_{Ar}), 129.3 (CH_{Ar}), 128.9 (CH_{Ar}), 128.8 (CH_{Ar}), 128.6 (CH_{Ar}), 128.4 (CH_{Ar}), 127.9 (CH_{Ar}), 126.3 (CH_{Ar}), 125.0 (CH_{Ar}), 123.7 (CH_{Ar}), 119.6 (Cq), 79.4 (Cq), 45.2 (CH_2), 44.2 (CH_2), 29.7 (CH_2), 29.6 (CH_2); MS (EI) *m/z* (%): 409 (M$^+$, 9), 304 (17), 275 (18), 197 (33), 169 (30), 144 (100), 105 (26), 91 (51), 77 (25); HRMS (EI): calculated for $C_{26}H_{23}N_3O_2$ [M$^+$] 409.1790, found 409.1800.

1-(*N*-Cyclohexylcarbamoyl)-1-(4-methylbenzoyl)-1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazoline (7e). White solid; m.p. 212-214 °C; IR (KBr, cm^{-1}): 3239, 2931, 2855, 1720, 1658, 1537; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86-7.26 (m, 2H), 7.24-7.21 (m, 2H), 7.19-7.13 (m, 1H), 7.07 (dd, *J* = 7.9, 1.4 Hz, 1H), 6.97 (td, *J* = 7.4, 1.5 Hz, 1H), 6.81 (dd, *J* = 7.4, 1.4 Hz, 1H), 6.69 (d, *J* = 8.0 Hz, 1H, NH), 4.65 (d, *J* = 13.0 Hz, 1H, $CH_{2\ benzyl}$), 4.53 (d, *J* = 13.0 Hz, 1H), 3.92-3.80 (m, 1H), 2.94-2.83 (m, 1H), 2.77-2.62 (m, 2H), 2.43-2.33 (m, 1H), 2.39 (s, 3H), 1.97-1.06 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.5 (Cq), 166.9 (Cq), 162.1 (Cq), 145.0 (Cq), 142.1 (Cq), 131.7 (Cq), 129.6 (CH_{Ar}), 129.4 (CH_{Ar}), 128.6 (CH_{Ar}), 126.2 (CH_{Ar}), 124.7 (CH_{Ar}), 124.1 (CH_{Ar}), 119.7 (Cq), 79.3 (Cq), 49.5 (CH), 45.3 (CH_2), 33.3 (CH_2), 32.8 (CH_2), 30.0 (CH_2), 29.9 (CH_2), 25.6 (CH_2), 25.1 (CH_2), 25.0 (CH_2), 21.9 (CH_3); MS (EI) *m/z* (%): 415 (M$^+$, 6), 289 (21), 197 (32), 169 (28), 144 (100), 119 (41), 91 (27); HRMS (EI): calculated for $C_{26}H_{29}N_3O_2$ [M$^+$] 415.2260, found 415.2259.

1-(4-Chlorobenzoyl)-1-(*N*-cyclohexylcarbamoyl)-1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazoline (7f). White solid; m.p. > 230 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84-7.80 (m, 2H), 7.43-7.32 (m, 3H), 7.20-6.84 (m, 4H), 4.70 (d, *J* = 13.3 Hz, 1H, $CH_{2\ benzyl}$), 4.52 (d, *J* = 13.3 Hz, 1H, $CH_{2\ benzyl}$), 3.92-3.80 (m, 1H), 2.91-2.59 (m, 3H), 2.40-2.31 (m, 1H), 1.99-0.79 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.2 (Cq), 166.6 (Cq), 161.8 (Cq), 140.2 (Cq), 132.3 (Cq), 130.5 (CH_{Ar}), 129.0 (CH_{Ar}), 128.5 (CH_{Ar}), 126.1 (CH_{Ar}), 124.9 (CH_{Ar}), 123.5 (CH_{Ar}), 119.2 (Cq), 79.1 (Cq), 49.4 (CH), 45.0 (CH_2), 33.0 (CH_2), 32.7 (CH_2), 29.6 (CH_2), 29.4 (CH_2), 25.3 (CH_2), 24.9 (CH_2), 24.9 (CH_2); HRMS (ESI): calculated for $C_{25}H_{27}ClN_3O_2$ [M$^+$+1] 436.1786, found 436.1781.

1-Acetyl-1-(*N*-cyclohexylcarbamoyl)-1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazoline (7g). Brown solid; m.p. 199-200 °C; IR (KBr, cm^{-1}): 3165, 2935, 2852, 2721, 1666, 1622, 1593; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22-6.87 (m, 5H), 4.59 (d, *J* = 13.0 Hz, 1H, $CH_{2\ benzyl}$), 4.43 (d, *J* = 13.0 Hz, 1H, $CH_{2\ benzyl}$), 3.86-3.74 (m, 1H), 2.88 (ddd, *J* = 16.7, 9.0, 7.7 Hz, 1H), 2.70 (ddd, *J* = 16.7, 8.9, 6.4 Hz, 1H), 2.39 (s, 3H), 2.28-2.22 (m, 2H), 1.92-1.15 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.6 (Cq), 166.7 (Cq), 162.9 (Cq), 141.9 (Cq), 128.8 (CH_{Ar}), 126.1 (CH_{Ar}), 125.0 (CH_{Ar}), 124.3 (CH_{Ar}), 119.4 (Cq), 78.8 (Cq), 49.0 (CH), 45.2 (CH_2), 33.1 (CH_2), 33.0 (CH_2), 30.3 (CH_2), 29.8 (CH_2), 27.2 (CH_3), 25.6 (CH_2), 25.0 (CH_2); MS (EI) *m/z* (%): 339 (M$^+$, 8), 213 (18), 197 (20), 169 (18), 144 (100); HRMS (EI): calculated for $C_{20}H_{25}N_3O_2$ [M$^+$] 339.1947, found 339.1949.

General procedure for the synthesis of pyrroloquinazoline-1-carboxamides 8a and 8b[14]

To a suspension of pyrroloquinazoline derivative **7a**, **7d** (0.5 mmol) in methanol (5 ml) was added a solution of KOH (0.5 mmol) in methanol. The reaction was stirred at room temperature in an ultrasonic bath for 15 min. The reaction was concentrated under reduced pressure; the residue was dissolved in dichloromethane and washed with a diluted HCl solution and then with water. The organic extract was dried over Na_2SO_4 and concentrated to dryness. The crude residue was recrystallized from methanol/hexane mixtures.

***N*-Cyclohexylcarbamoyl-1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazoline (8a).** White solid; m.p. > 230 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26-6.85 (m, 4H), 5.93 (d, *J* = 8.4 Hz, 1H, NH), 4.41 (d, *J* = 13.3 Hz, 1H, $CH_{2\ benzyl}$), 4.35 (d, *J* = 13.3 Hz, 1H, $CH_{2\ benzyl}$), 3.82-3.69 (m, 2H), 2.75-2.56 (m, 2H), 2.48-2.33 (m, 1H), 1.96-0.76 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.7 (Cq), 163.6 (Cq), 142.5 (Cq), 129.0 (CH_{Ar}), 126.1 (CH_{Ar}), 125.0 (CH_{Ar}), 124.5 (CH_{Ar}), 119.6 (Cq), 66.6 (CH), 48.5 (CH), 46.6 (CH_2), 33.4 (CH_2), 33.2 (CH_2), 30.3 (CH_2), 25.6 (CH_2), 25.3 (CH_2), 25.1 (CH_2); MS (EI) *m/z* (%): 297 (M^+, 10), 216 (28), 157 (37), 144 (100), 97 (42), 83 (51), 69 (47); HRMS (EI): calculated for $C_{18}H_{23}N_3O$ [M^+] 297.1841, found 297.1844.

Computational methods

The geometries of all species were fully optimized at the B3LYP/6-31G** level. The environmental effects were taken into account by the Polarizable Continuum Model (PCM) using the integral equation formalism variant (IEFPCM).[17] The nature of all optimized structures was determined using harmonic frequency analysis as true minima with no imaginary frequencies or transition states with only one imaginary frequency. All transition state structures and reaction paths were further validated by intrinsic reaction coordinate (IRC) calculations in both forward and reverse directions. All reported energy differences correspond to Gibbs' free energies. All calculations were performed using the Gaussian 09 program.[15]

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Notes and references

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