

A Simple Two-Step Sequence for the Synthesis of Novel 4-Aryl-4,5-dihydro-6*H*-[1,3]dioxolo[4,5-*h*]pyrrolo[1,2-*a*][1]benzazepin-6-ones from 6-Amino-3,4-methylenedioxyacetophenone

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Keywords: Phosphoric acid / Michael addition / Chalcones / Cyclization / Heterocycles

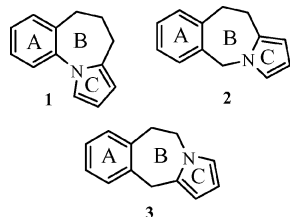
Herein is provided an efficient and two-step short procedure for the synthesis of novel 6*H*-[1,3]dioxolobenzo[4,5-*h*]pyrrolo[1,2-*a*][1]benzazepin-6-one derivatives promoted by commercial phosphoric acid. In a parallel approach some

pyrrolyl chalcones were isolated that proved to behave as intermediates for the title compounds.

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Introduction

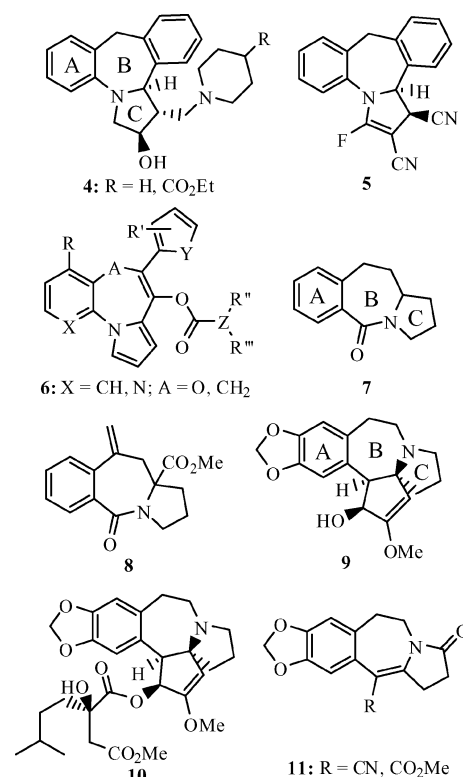
The biological activity of compounds containing a modified azepine ring towards different diseases has been intensively studied, both in vitro and in vivo.^[1] Within this context, compounds containing the benzo-pyrrolo-fused azepin framework have gained significant attention in recent years because of the possibility of finding it as part of naturally occurring materials or constructing it by synthetic approaches. In both cases such structures exhibit interesting biological activities.^[2] Pyrrolo-benzazepines can exist in the three isomeric forms **1**, **2** or **3** (see Scheme 1).



Scheme 1. General structures for the three possible benzo-pyrrolo-fused azepin systems.

Biological or synthetic modifications of any of the three rings will originate diverse derivatives of the structures **1**, **2** and **3** in varied and interesting fashions. Scheme 2 shows some examples of such compounds. For example, compounds **4**, obtained through an asymmetric 1,3-dipolar re-

action, showed moderate activities in several in vitro assays for adrenergic, dopaminergic and serotonergic receptors.^[2a] Fluorinated compound **5** was synthesized by a 1,3-dipolar cycloaddition domino sequence because of its potential biological activity.^[2b] Compounds **6** were prepared for screening as novel and selective peripheral-type benzodiazepine receptor (PBR) ligands and to evaluate their ability



Scheme 2. Some pyrrolobenzazepine derivatives of chemical and practical interest.

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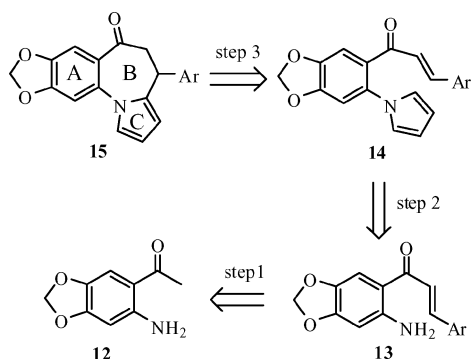
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to modulate steroid biosynthesis in rats.^[2c] Structures **7** and **8** were obtained from an intramolecular Schmidt reaction^[2d] and from a Pd-catalyzed intramolecular cyclization of some amides,^[2e] respectively. Cephalotaxine **9** is reported as the major alkaloid found in the evergreen plum yews *Cephalotaxus*, which is indigenous in South-East Asia. Compound **9** by itself shows no pronounced biological activity, but its 2-alkylhydroxysuccinate, known as deoxyharingtonine (**10**), has displayed the highest IC₅₀ value against leukaemic cells.^[2f–2k] Finally, compounds **11** were obtained by a KH-induced cyclization of thioimides in a new approach to the ABC core of cephalotaxine **9**.^[2l]

Results and Discussion

Continuing with our studies directed towards the synthesis and chemical transformation of 1-(6-amino-1,3-benzodioxol-5-yl)-3-arylprop-2-en-1-ones **13**,^[3] we describe herein a short two-step protocol aimed at obtaining the novel 4-aryl-4,5-dihydro-6*H*-[1,3]dioxolobenz[4,5-*h*]pyrrolo[1,2-*a*]-[1]benzazepin-6-one of type **15**, compounds closely related to the pharmacologically active structures **6**, sharing the same ABC core.

Before beginning with the experiments, the synthesis of the target compounds **15** was visualized according to the retrosynthetic analysis shown in Scheme 3. A three-step sequence was proposed, which includes the synthesis and isolation of the chalcone and pyrrolyl chalcone intermediates **13** and **14**, respectively.

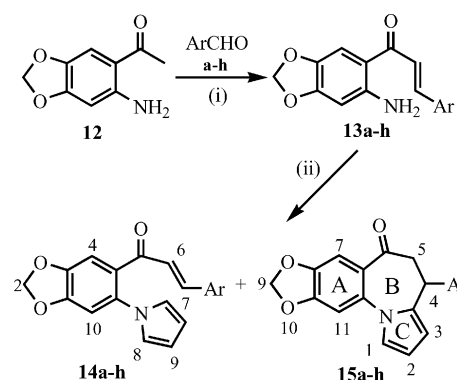


Scheme 3. Retrosynthetic analysis of the synthesis of the target compounds **15**.

Following this synthetic scheme, chalcones **13a–h** were readily obtained from acetophenone **12** and aldehydes **a–h** (see Table 1) according to the procedure we described previously.^[3f]

Continuing with the second step and seeking to obtain the pyrrolyl chalcone intermediates **14**, a mixture of chalcone **13a** (1 equiv.) and 2,5-dimethoxytetrahydrofuran (3 equiv.) in AcOH (5 mL, as solvent and catalyst) was heated at 80 °C for 1 h, according to a reported procedure for the synthesis of arylpyrroles.^[4a] Unfortunately, this well-known procedure was unsuccessful in our case and no product was formed even after 2 h of heating.

To overcome this failed attempt, we decided to repeat the same reaction under reflux in toluene (5 mL) with AcOH (1.5 mL) as catalyst. This time the reaction proceeded quite well and after complete consumption of the chalcone **13a** (TLC control), a mixture of two products was obtained and separated by column chromatography by using a mixture of CHCl₃/AcOEt as eluent. This will be referred to as approach A (Scheme 4). Spectroscopic analysis of the isolated compounds showed that the first eluted fraction corresponded to the expected pyrrolyl chalcone **14a** in 13% yield and the second one, surprisingly, corresponded to our cyclized target product **15a** in 37% yield.



Scheme 4. Reaction products obtained by approach A. Reagents and conditions: i. EtOH (15 mL), 20% NaOH (1 mL), reflux; ii. 2,5-dimethoxytetrahydrofuran (3 equiv.), toluene (5 mL), AcOH (1.5 mL), reflux.

Taking into account the relative success of the above approach, it was extended to the other chalcones **13b–h** with similar results, that is, the formation of mixtures of both

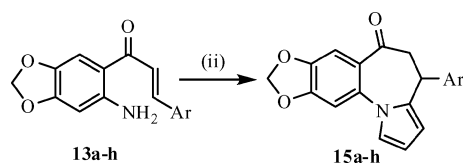
Table 1. Analytical data for intermediates **14** and products **15**.

Entry	Ar	% Yield of 14	Approach A M.p. [°C]	Approach B		
				% Yield of 15	% Yield of 15 ^[a]	M.p. [°C]
a	<i>p</i> -BrC ₆ H ₄	13 ^[a]	170–171	37 ^[a]	93	200–202
b	<i>p</i> -ClC ₆ H ₄	8 ^[a]	144–145	40 ^[a]	90	191–192
c	3,4,5-(MeO) ₃ C ₆ H ₂	26 ^[b]	–	20 ^[b]	87	167–169
d	<i>p</i> -NO ₂ C ₆ H ₄	43 ^[a]	185–186	27 ^[a]	96	250–251
e	<i>p</i> -CF ₃ C ₆ H ₄	29 ^[a]	161–163	48 ^[a]	89	256–257
f	pyridin-3-yl	22 ^[a]	155–157	34 ^[a]	91	193–194
g	1,3-benzodioxol-5-yl	12 ^[b]	–	57 ^[b]	85	162–164
h	naphthalen-2-yl	7 ^[b]	–	50 ^[b]	86	192–193

[a] Isolated yield. [b] Determined by ¹H NMR spectroscopy.

compounds **14** and **15**, some of them separable by column chromatography, as shown in Table 1. According to these results, the conversion process from **13** to **15** may proceed mainly in only one step in which the chalcone **14** thus formed could behave as an intermediate, partially cyclizing to the final product **15** in the reaction medium. Attempts to complete the conversion of **14** into **15** by heating for longer times caused the formation of resinous materials and a lowering of the yields.

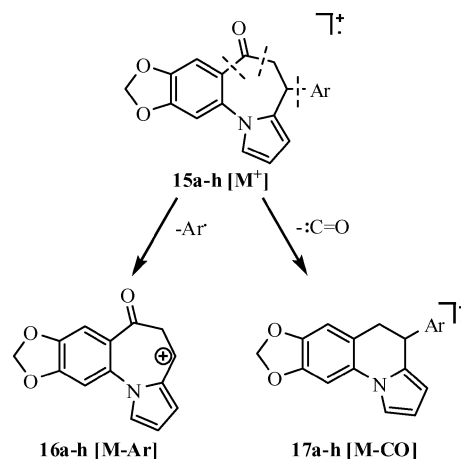
The latter results prompted us to search for a more efficient and selective procedure to chalcone intermediates **14** as the only product or, preferably, the target compounds **15** directly from chalcones **13** in a single step. After several attempts using different reaction conditions (i.e., TsOH/MeOH/reflux, Amberlyst-15®/AcOH/60 °C, sulfamic acid/ACN/60 °C or microwave irradiation without solvent), we found that when chalcones **13** were mixed with 2,5-dimethoxytetrahydrofuran (3 equiv.) and gently heated at 70 °C for about 5 min adding a drop of 85% H₃PO₄, compounds **15** were obtained as unique products (TLC control) in excellent yields, as depicted in Scheme 5 and Table 1. This will be referred to as approach B.



Scheme 5. Direct synthesis of the target compounds **15** by procedure B. Reagents and conditions: ii. 2,5-dimethoxytetrahydrofuran (3 equiv.), 85% H₃PO₄ (1 drop), 70 °C, 5 min.

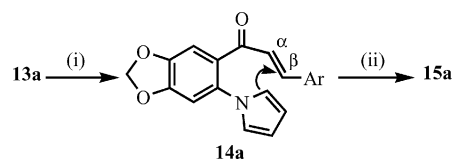
All the obtained pyrrolyl chalcones **14** were yellow solids, pyrrolbenzazepines **15** were pale-yellow solids, whereas the starting chalcones **13** were orange-to-dark-red solids. These characteristics permitted us to follow the reaction progress easily by TLC and to check the purity of compounds **14** and **15**. All compounds **14** and **15** were fully characterized by analytical and spectroscopic methods (IR, ¹H and ¹³C NMR, elemental analysis and MS). The main characteristic of the IR spectra of both **14** and **15** is the lack of NH₂ absorption bands. This agrees with their assigned structures. It is relevant that the ¹H NMR spectra of compounds **14** show two sets of doublets at 6.11–6.23 and 7.27–7.34 ppm with coupling constants of 15.7–16.4 Hz, which correspond to the vinylic protons of the α,β-unsaturated moiety. There are also two additional sets of signals at 6.15–6.17 and 6.89–6.92 ppm assigned to the four protons of the new pyrrole ring formed. For compounds **15**, the most relevant feature in the ¹H NMR spectra is the disappearance of the signals corresponding to the α,β-unsaturated moiety protons, whilst the appearance of three new aliphatic sets of doublet of doublets at 3.03–3.29, 3.35–3.56 and 4.36–4.73 ppm support the AMX system of the new azepinic ring formed. A set of three signals at 5.37–5.61, 6.11–6.19 and 6.90–7.19 ppm for the now 2-substituted pyrrolyl moiety is also consistent with the proposed structure. On the other hand, loss of the Ar ring leads to the typical base peak **16**

in the MS spectra of the target compounds **15** (Scheme 6). The loss of the aryl ring is accompanied by other common ring-contraction processes for the azepinic moiety. In this way, a decarbonylation process with the loss of 28 a.m.u. furnished the quite stable pyrroloquinolinic species **17** with relative stabilities of between 30–76%.



Scheme 6. Main MS fragmentations for compounds **15**.

Finally, to confirm the above assertion that chalcones **14** behave as intermediates for compounds **15**, a sample of the isolated compound **14a** (0.2 g) and a drop of 85% H₃PO₄ were heated at 70 °C for 3 min. In this way compound **15a** was readily obtained in quantitative yield, as depicted in Scheme 7.



Scheme 7. Synthesis of target compound **15a** from chalcone intermediate **14a**. Reagents and conditions: i. 2,5-dimethoxytetrahydrofuran (3 equiv.), toluene (5 mL), AcOH (1.5 mL), reflux; ii. 85% H₃PO₄ (1 drop), 70 °C, 3 min.

According to Scheme 7 the conversion of intermediates **14** into the target compounds **15** occurred by an intramolecular Michael-type addition from the 2-position of the pyrrolyl moiety towards the β-carbon atom of the α,β-unsaturated chalcone moiety in **14**. At this point it is worth mentioning that like other authors,^[4a–4d] we have previously reported^[4e] the utility of the pronounced nucleophilic character of the 2-position of the pyrrolyl moiety in the intermolecular formation of diverse six- and seven-membered rings mediated by Mannich-type reactions. However, we are not aware of other reports that describe the involvement of this pyrrolyl moiety in the formation of the above rings by an intramolecular Michael-type addition, with the exception of one report in which some pyrrolohydropyridine intermediates were obtained in the total synthesis of (–)-tashiramine.^[5] Thus these results provide new and useful synthetic possibilities for the widely studied pyrrole chemistry.

Conclusions

We have implemented an efficient and selective procedure for the synthesis of novel 6*H*-[1,3]dioxolobenzo[4,5-*h*]pyrrolo[1,2-*a*][1]benzazepin-6-one-11-one derivatives **15** in high yields from a short two-step sequence promoted by commercial phosphoric acid. In this approach, pyrrolyl chalcones **14** were proven to behave as intermediates for compounds **15**. To the best of our knowledge, this is the first report involving an intramolecular Michael-type addition mediated by a pyrrolyl moiety for the construction of pyrrolo-azepin frameworks. The commercial availability of numerous benzaldehydes, along with some amino ketones **12**, confers a general character on this method that allows libraries of azepins **15** to be constructed for structure–activity relationship studies.

Experimental Section

General: Melting points were determined on a Büchi melting point apparatus and are uncorrected. IR spectra were recorded with a Shimadzu FTIR 8400 on KBr disks. ¹H and ¹³C NMR spectra were recorded with Bruker 500, AMX 400, DPX 300 and Varian Gemini 200 instruments; chemical shifts (δ) are reported in ppm relative to internal tetramethylsilane and coupling constants in Hz. CDCl₃ and [D₆]DMSO were used as solvents. Silica gel plates (Merck F₂₅₄) were used for analytical TLC. Mass spectra were recorded with Varian Model MAT MS-311 and SHIMADZU-GCMS 2010-DI-2010 spectrometers at 70 eV. Microanalyses were performed with a LECO CHNS-932 elemental analyzer and the values are within ±0.4% of the theoretical values. The starting 2,5-dimethoxytetrahydrofuran, aldehydes **a–h** and 6-amino-3,4-methylenedioxyacetophenone (**12**) were purchased from Aldrich, Fluka and Acros (analytical reagent grades) and were used without further purification.

General Procedure for the Synthesis of Mixtures of Compounds 14 and 15. Approach A: By gentle warming, chalcone **13** (0.58 mmol) was dissolved in toluene (5 mL) and then 2,5-dimethoxytetrahydrofuran (1.74 mmol) and AcOH (1.5 mL) were added. The mixture was heated at reflux for 2 h until no presence of the starting chalcone **13** was detected (monitored by TLC). Removal of the solvent under reduced pressure afforded the crude product, which was purified by column chromatography on silica gel by using a mixture of CHCl₃/AcOEt (5:1) as eluent. The first chromatographic fraction corresponded to compound **14** in all cases and the second one corresponded to compound **15**.

3-(*p*-Bromophenyl)-1-[6-(pyrrol-1-yl)-1,3-benzodioxol-5-yl]prop-2-en-1-one (14a): Yield 30 mg. IR (KBr): $\tilde{\nu}$ = 1650 (C=O), 1237 (OCH₂O) cm⁻¹. ¹H NMR (400 MHz, [D₆]DMSO): δ = 6.12 (d, *J* = 15.9 Hz, 1 H, 6-H), 6.15 (t, *J* = 2.2 Hz, 2 H, 9-H), 6.19 (s, 2 H, 2-H), 6.89 (t, *J* = 2.2 Hz, 2 H, 8-H), 7.13 (br. s, 2 H, 4-H and 10-H), 7.27 (d, *J* = 15.9 Hz, 1 H, 7-H), 7.33 (d, *J* = 8.6 Hz, 2 H, Ar-H), 7.52 (d, *J* = 8.6 Hz, 2 H, Ar-H) ppm. ¹³C NMR (100 MHz, [D₆]DMSO): δ = 102.7 (OCH₂O), 106.7, 108.1, 110.2 (C-9), 122.8 (C-8), 123.5, 124.6 (C-6), 128.6, 130.1, 131.7, 133.8, 135.1, 140.5 (C-7), 146.8, 152.0, 190.6 (C=O) ppm. MS (70 eV, EI): *m/z* (%) = 395/397 (28/27) [M]⁺, 366/367 (31/30), 212 (83). C₂₀H₁₄BrNO₃ (396.23): calcd. C 60.62, H 3.56, N 3.53; found C 60.50, H 3.67, N 3.45.

3-(*p*-Chlorophenyl)-1-[6-(pyrrol-1-yl)-1,3-benzodioxol-5-yl]prop-2-en-1-one (14b): Yield 16 mg. IR (KBr): $\tilde{\nu}$ = 1652 (C=O), 1239

(OCH₂O) cm⁻¹. ¹H NMR (400 MHz, [D₆]DMSO): δ = 6.11 (d, *J* = 15.8 Hz, 1 H, 6-H), 6.15 (t, *J* = 2.2 Hz, 2 H, 9-H), 6.19 (s, 2 H, 2-H), 6.89 (t, *J* = 2.2 Hz, 2 H, 8-H), 7.13 (br. s, 2 H, 4-H and 10-H), 7.27 (d, *J* = 16.1 Hz, 1 H, 7-H), 7.41 (br. d, 4 H, Ar-H) ppm. ¹³C NMR (100 MHz, [D₆]DMSO): δ = 102.6 (OCH₂O), 106.7, 108.1, 110.2 (C-9), 122.8 (C-8), 124.6 (C-6), 128.6, 128.7, 129.9, 133.5, 134.7, 135.1, 140.5 (C-7), 146.8, 150.3, 190.6 (C=O) ppm. MS (70 eV, EI): *m/z* (%) = 351/353 (85/28) [M]⁺, 322/324 (28/9), 212 (85). C₂₀H₁₄ClNO₃ (351.78): calcd. C 68.28, H 4.01, N 3.98; found C 68.43, H 3.87, N 4.07.

3-(*p*-Nitrophenyl)-1-[6-(pyrrol-1-yl)-1,3-benzodioxol-5-yl]prop-2-en-1-one (14d): Yield 90 mg. IR (KBr): $\tilde{\nu}$ = 1656 (C=O), 1511, 1341 (NO₂), 1253 (OCH₂O) cm⁻¹. ¹H NMR (400 MHz, [D₆]DMSO): δ = 6.15 (t, *J* = 2.1 Hz, 2 H, 9-H), 6.21 (s, 2 H, 2-H), 6.23 (d, *J* = 16.3 Hz, 1 H, 6-H), 6.92 (t, *J* = 2.06 Hz, 2 H, 8-H), 7.17 (s, 1 H, 10-H), 7.18 (s, 1 H, 4-H), 7.34 (d, *J* = 15.9 Hz, 1 H, 7-H), 7.64 (d, *J* = 8.7 Hz, 2 H, Ar-H), 8.15 (d, *J* = 8.7 Hz, 2 H, Ar-H) ppm. ¹³C NMR (100 MHz, [D₆]DMSO): δ = 102.7 (OCH₂O), 106.7, 108.1, 110.4 (C-9), 122.9 (C-8), 123.8, 127.4 (C-6), 128.6, 129.1, 135.3, 138.5 (C-7), 141.1, 146.8, 147.7, 150.6, 190.5 (C=O) ppm. MS (70 eV, EI): *m/z* (%) = 362 (100) [M]⁺, 333 (26), 212 (91). C₂₀H₁₄N₂O₅ (362.34): calcd. C 66.30, H 3.89, N 7.73; found C 66.13, H 3.97, N 7.88.

1-[6-(Pyrrol-1-yl)-1,3-benzodioxol-5-yl]-3-[*p*-(trifluoromethyl)phenyl]prop-2-en-1-one (14e): IR (KBr): $\tilde{\nu}$ = 1654 (C=O), 1241 (OCH₂O) cm⁻¹. ¹H NMR (300 MHz, [D₆]DMSO): δ = 6.16 (s, 2 H, 2-H), 6.17 (t, *J* = 2.2 Hz, 2 H, 9-H), 6.19 (d, *J* = 16.2 Hz, 1 H, 6-H), 6.92 (t, *J* = 2.2 Hz, 2 H, 8-H), 7.16 (br. s, 2 H, 4-H and 10-H), 7.34 (d, *J* = 15.9 Hz, 1 H, 7-H), 7.59 (d, *J* = 8.0 Hz, 2 H, Ar-H), 7.68 (d, *J* = 8.2 Hz, 2 H, Ar-H) ppm. ¹³C NMR (75 MHz, [D₆]DMSO): δ = 102.7 (OCH₂O), 106.7, 108.1, 110.4 (C-9), 122.9 (C-8), 126.3 (C-6), 128.4, 128.8, 129.0, 135.3, 138.6, 139.6 (C-7), 146.8, 145.6, 150.5, 190.6 (C=O) ppm. MS (70 eV, EI): *m/z* (%) = 385 (100) [M]⁺, 357 (54), 212 (83). C₂₁H₁₄F₃NO₃ (385.34): calcd. C 65.46, H 3.66, N 3.63; found C 65.56, H 3.75, N 3.54.

3-(Pyridin-3-yl)-1-[6-(pyrrol-1-yl)-1,3-benzodioxol-5-yl]prop-2-en-1-one (14f): Yield 40 mg. IR (KBr): $\tilde{\nu}$ = 1657 (C=O), 1239 (OCH₂O) cm⁻¹. ¹H NMR (500 MHz, [D₆]DMSO): δ = 6.15 (t, *J* = 2.1 Hz, 2 H, 9-H), 6.20 (s, 2 H, 2-H), 6.23 (d, *J* = 15.9 Hz, 1 H, 6-H), 6.91 (t, *J* = 2.1 Hz, 2 H, 8-H), 7.15 (s, 1 H, 10-H), 7.16 (s, 1 H, 4-H), 7.31 (d, *J* = 16.0 Hz, 1 H, 7-H), 7.35 (dd, *J* = 7.3, 4.8 Hz, 1 H, Py-H), 7.76 (dd, *J* = 8.0, 1.6 Hz, 1 H, Py-H), 8.50 (dd, *J* = 4.8, 1.6 Hz, 1 H, Py-H), 8.57 (s, 1 H, Py-H) ppm. ¹³C NMR (125 MHz, [D₆]DMSO): δ = 102.7 (OCH₂O), 106.7, 108.1, 110.2 (C-9), 122.9 (C-8), 123.7, 125.6 (C-6), 128.5, 130.3, 134.5, 135.2, 138.3 (C-7), 146.8, 149.7, 150.4, 150.6, 190.5 (C=O) ppm. MS (70 eV, EI): *m/z* (%) = 318 (83) [M]⁺, 289 (37), 212 (100). C₁₉H₁₄N₂O₃ (318.33): calcd. C 71.69, H 4.43, N 8.80; found C 71.90, H 4.57, N 8.66.

General Procedure for the Direct Synthesis of Compounds 15. Approach B: A mixture of chalcone **13** (0.58 mmol), 2,5-dimethoxytetrahydrofuran (1.74 mmol) and H₃PO₄ (85%, 1 drop) was gently heated at 70 °C for 5 min. After no presence of chalcone **13** was detected (TLC control), the reaction mixture was cooled to room temperature, aq. NaHCO₃ (10%, 5 mL) was added and the mixture extracted with AcOEt (3 × 5 mL). The combined extracts were dried with anh. Na₂SO₄ and the solvent was removed under vacuum. The crudes thus obtained were purified by column chromatography on silica gel and DCM as eluent to yield compounds **15** as unique products.

4-(*p*-Bromophenyl)-4,5-dihydro-6*H*-[1,3]dioxolobenzo[4,5-*h*]pyrrolo-[1,2-*a*][1]benzazepin-6-one (15a): Yield 213 mg. IR (KBr): $\tilde{\nu}$ = 1665

(C=O), 1251 (OCH₂O) cm⁻¹. ¹H NMR (400 MHz, [D₆]-DMSO): δ = 3.05 (dd, J = 2.7, 18.8 Hz, 1 H, 5-H), 3.42 (dd, J = 11.4, 18.8 Hz, 1 H, 5-H), 4.49 (dd, J = 2.1, 11.4 Hz, 1 H, 4-H), 5.43 (br. s, 1 H, 3-H), 6.12 (t, J = 3.3 Hz, 1 H, 2-H), 6.16 (s, 2 H, 9-H), 7.08 (s, 1 H, 11-H), 7.12 (s, 1 H, 7-H), 7.16 (t, J = 2.9 Hz, 1 H, 1-H), 7.28 (d, J = 8.5 Hz, 2 H, Ar-H), 7.51 (d, J = 8.5 Hz, 2 H, Ar-H) ppm. ¹³C NMR (100 MHz, [D₆]DMSO): δ = 36.6 (C-4), 50.2 (C-5), 102.7 (OCH₂O), 104.5, 107.2, 108.2, 109.3, 119.9, 121.9, 124.9, 130.3, 131.2, 134.4, 135.4, 139.7, 145.5, 152.0, 199.3 (C=O) ppm. MS (70 eV, EI): m/z (%) = 395/397 (27/28) [M]⁺, 367/369 (31/30) [M – CO]⁺, 240 (100) [M – C₆H₄Br]⁺. C₂₀H₁₄BrNO₃ (396.23): calcd. C 60.62, H 3.56, N 3.53; found C 60.44, H 3.67, N 3.41.

4-(*p*-Chlorophenyl)-4,5-dihydro-6*H*-[1,3]dioxolobenzo[4,5-*h*]pyrrolo[1,2-*a*][1]benzazepin-6-one (15b): Yield 183 mg. IR (KBr): $\tilde{\nu}$ = 1665 (C=O), 1250 (OCH₂O) cm⁻¹. ¹H NMR (200 MHz, CDCl₃): δ = 3.14 (dd, J = 2.6, 18.7 Hz, 1 H, 5-H), 3.38 (dd, J = 11.4, 18.7 Hz, 1 H, 5-H), 4.41 (dd, J = 2.2, 11.4 Hz, 1 H, 4-H), 5.53 (br. s, 1 H, 3-H), 6.06 (s, 2 H, 9-H), 6.17 (t, J = 3.2 Hz, 1 H, 2-H), 6.78 (s, 1 H, 11-H), 6.90 (t, J = 2.4 Hz, 1 H, 1-H), 7.18 (d, J = 8.6 Hz, 2 H, Ar-H), 7.27 (s, 1 H, 7-H), 7.30 (d, J = 8.6 Hz, 2 H, Ar-H) ppm. ¹³C NMR (50 MHz, CDCl₃): δ = 37.4 (C-4), 50.5 (C-5), 102.3 (OCH₂O), 104.3, 107.4, 109.1, 109.7, 121.4, 125.2, 128.6, 129.2, 132.8, 135.1, 136.0, 138.3, 145.8, 152.3, 199.3 (C=O) ppm. MS (70 eV, EI): m/z (%) = 351/353 (62/21) [M]⁺, 323/325 (50/17) [M – CO]⁺, 240 (100) [M – C₆H₄Cl]⁺. C₂₀H₁₄ClNO₃ (351.78): calcd. C 68.28, H 4.01, N 3.98; found C 68.46, H 4.22, N 4.00.

4-(3,4,5-Trimethoxyphenyl)-4,5-dihydro-6*H*-[1,3]dioxolobenzo[4,5-*h*]pyrrolo[1,2-*a*][1]benzazepin-6-one (15c): Yield 205 mg. IR (KBr): $\tilde{\nu}$ = 1667 (C=O), 1251 (OCH₂O) cm⁻¹. ¹H NMR (400 MHz, [D₆]-DMSO): δ = 3.03 (dd, J = 2.7, 18.8 Hz, 1 H, 5-H), 3.46 (dd, J = 12.2, 19.0 Hz, 1 H, 5-H), 3.64 (s, 3 H, OCH₃), 3.72 (s, 6 H, OCH₃ × 2), 4.44 (dd, J = 2.1, 12.0 Hz, 1 H, 4-H), 5.52 (br. s, 1 H, 3-H), 6.11 (t, J = 3.1 Hz, 1 H, 2-H), 6.18 (s, 2 H, 9-H), 6.66 (s, 2 H), 7.10 (s, 1 H, 11-H), 7.13 (s, 1 H, 7-H), 7.14 (t, J = 3.3 Hz, 1 H, 1-H) ppm. ¹³C NMR (100 MHz, [D₆]DMSO): δ = 37.6 (C-4), 50.9 (C-5), 55.8, 59.9, 102.6 (OCH₂O), 104.5, 105.6, 107.1, 108.2, 109.3, 121.6, 125.3, 134.3, 135.9, 135.9, 136.2, 145.5, 151.9, 152.7, 200.0 (C=O) ppm. MS (70 eV, EI): m/z (%) = 407 (100) [M]⁺, 379 (39) [M – CO]⁺, 240 (43) [M – C₉H₁₁O₃]⁺. C₂₃H₂₁NO₆ (407.42): calcd. C 67.80, H 5.20, N 3.44; found C 67.74, H 5.31, N 3.27.

4-(*p*-Nitrophenyl)-4,5-dihydro-6*H*-[1,3]dioxolobenzo[4,5-*h*]pyrrolo[1,2-*a*][1]benzazepin-6-one (15d): Yield 202 mg. IR (KBr): $\tilde{\nu}$ = 1666 (C=O), 1350, 1520 (NO₂), 1249 (OCH₂O) cm⁻¹. ¹H NMR (400 MHz, [D₆]DMSO): δ = 3.12 (dd, J = 2.7, 18.6 Hz, 1 H, 5-H), 3.52 (dd, J = 11.2, 18.8 Hz, 1 H, 5-H), 4.73 (dd, J = 2.1, 11.2 Hz, 1 H, 4-H), 5.45 (br. s, 1 H, 3-H), 6.14 (t, J = 3.3 Hz, 1 H, 2-H), 6.16 (s, 2 H, 9-H), 7.10 (s, 1 H, 11-H), 7.13 (s, 1 H, 7-H), 7.19 (t, J = 2.9 Hz, 1 H, 1-H), 7.61 (d, J = 8.7 Hz, 2 H, Ar-H), 8.18 (d, J = 8.9 Hz, 2 H, Ar-H) ppm. ¹³C NMR (100 MHz, [D₆]DMSO): δ = 37.0 (C-4), 49.8 (C-5), 102.7 (OCH₂O), 104.5, 107.4, 108.2, 109.4, 122.2, 123.4, 125.0, 129.4, 134.3, 134.7, 145.5, 146.4, 148.2, 152.0, 199.0 (C=O) ppm. MS (70 eV, EI): m/z (%) = 362 (52) [M]⁺, 334 (66) [M – CO]⁺, 240 (100) [M – C₆H₄NO₂]⁺. C₂₀H₁₄N₂O₅ (362.34): calcd. C 66.30, H 3.89, N 7.73; found C 66.48, H 3.73, N 7.85.

4-[*p*-(Trifluoromethyl)phenyl]-4,5-dihydro-6*H*-[1,3]dioxolobenzo[4,5-*h*]pyrrolo[1,2-*a*][1]benzazepin-6-one (15e): Yield 199 mg. IR (KBr): $\tilde{\nu}$ = 1665 (C=O), 1253 (OCH₂O) cm⁻¹. ¹H NMR (200 MHz, CDCl₃): δ = 3.18 (dd, J = 2.6, 18.7 Hz, 1 H, 5-H), 3.44 (dd, J = 11.0, 18.7 Hz, 1 H, 5-H), 4.52 (dd, J = 2.1, 11.4 Hz, 1 H, 4-H), 5.51 (br. s, 1 H, 3-H), 6.08 (s, 2 H, 9-H), 6.19 (t, J = 3.2 Hz, 1 H, 2-H), 6.81 (s, 1 H, 11-H), 6.93 (t, J = 2.4 Hz, 1 H, 1-H), 7.29 (s, 1 H, 7-H),

7.33 (d, J = 8.2 Hz, 2 H, Ar-H), 7.61 (d, J = 8.2 Hz, 2 H, Ar-H) ppm. ¹³C NMR (50 MHz, CDCl₃): δ = 37.9 (C-4), 50.3 (C-5), 102.4 (OCH₂O), 104.4, 107.6, 109.2, 109.8, 121.6, 125.2, 125.5, 125.6, 128.3, 129.4, 135.2, 135.5, 143.9, 145.9, 152.4, 199.1 (C=O) ppm. MS (70 eV, EI): m/z (%) = 385 (52) [M]⁺, 357 (58) [M – CO]⁺, 240 (100) [M – C₇H₄F₃]⁺. C₂₁H₁₄F₃NO₃ (385.34): calcd. C 65.46, H 3.66, N 3.63; found C 65.54, H 3.73, N 3.52.

4-(Pyridin-3-yl)-4,5-dihydro-6*H*-[1,3]dioxolobenzo[4,5-*h*]pyrrolo[1,2-*a*][1]benzazepin-6-one (15f): Yield 168 mg. IR (KBr): $\tilde{\nu}$ = 1665 (C=O), 1251 (OCH₂O) cm⁻¹. ¹H NMR (400 MHz, [D₆]-DMSO): δ = 3.09 (dd, J = 2.7, 18.8 Hz, 1 H, 5-H), 3.49 (dd, J = 11.7, 18.8 Hz, 1 H, 5-H), 4.60 (dd, J = 2.4, 11.8 Hz, 1 H, 4-H), 5.37 (br. s, 1 H, 3-H), 6.12 (t, J = 3.13 Hz, 1 H, 2-H), 6.18 (d, J = 1.6 Hz, 2 H, 9-H), 7.10 (s, 1 H, 11-H), 7.13 (s, 1 H, 7-H), 7.18 (t, J = 2.4 Hz, 1 H, 1-H), 7.38 (dd, J = 7.8, 4.7 Hz, 1 H, Py-H), 7.80 (td, J = 8.0, 1.8 Hz, 1 H, Py-H), 8.47 (dd, J = 4.7, 1.6 Hz, 1 H, Py-H), 8.52 (d, J = 2.2 Hz, 1 H, Py-H) ppm. ¹³C NMR (100 MHz, [D₆]DMSO): δ = 34.9 (C-4), 50.0 (C-5), 102.7 (OCH₂O), 104.5, 107.2, 108.2, 109.4, 122.0, 123.4, 125.1, 134.2, 135.3, 135.5, 135.8, 145.5, 148.2, 149.4, 152.0, 199.4 (C=O) ppm. MS (70 eV, EI): m/z (%) = 318 (80) [M]⁺, 290 (76) [M – CO]⁺, 240 (100) [M – C₅H₄N]⁺. C₁₉H₁₄N₂O₃ (318.33): calcd. C 71.69, H 4.43, N 8.80; found C 71.59, H 4.38, N 8.92.

4-(1,3-Benzodioxol-5-yl)-4,5-dihydro-6*H*-[1,3]dioxolobenzo[4,5-*h*]pyrrolo[1,2-*a*][1]benzazepin-6-one (15g): Yield 178 mg. IR (KBr): $\tilde{\nu}$ = 1667 (C=O), 1248 (OCH₂O) cm⁻¹. ¹H NMR (200 MHz, CDCl₃): δ = 3.14 (dd, J = 2.8, 18.7 Hz, 1 H, 5-H), 3.35 (dd, J = 11.4, 18.9 Hz, 1 H, 5-H), 4.36 (dd, J = 2.6, 11.4 Hz, 1 H, 4-H), 5.59–5.62 (m, 1 H, 3-H), 5.95 (s, 2 H, 9-H), 6.06 (s, 2 H, 9-H), 6.18 (t, J = 3.4 Hz, 1 H, 2-H), 6.72 (br. d, 1 H), 6.75 (br. d, 1 H), 6.76 (s, 1 H), 6.79 (s, 1 H, 11-H), 6.90 (t, J = 2.3 Hz, 1 H, 1-H), 7.29 (s, 1 H, 7-H) ppm. ¹³C NMR (50 MHz, CDCl₃): δ = 37.7 (C-4), 50.9 (C-5), 100.9 (OCH₂O), 102.3 (OCH₂O), 104.3, 107.3, 108.1, 108.4, 109.1, 109.6, 120.9, 121.2, 125.2, 133.6, 135.2, 136.6, 145.7, 146.4, 147.6, 152.2, 199.6 (C=O) ppm. MS (70 eV, EI): m/z (%) = 361 (61) [M]⁺, 333 (48) [M – CO]⁺, 240 (100) [M – C₇H₅O₂]⁺. C₂₁H₁₅NO₅ (361.35): calcd. C 69.80, H 4.18, N 3.88; found C 69.97, H 4.12, N 4.02.

4-(Naphthalen-2-yl)-4,5-dihydro-6*H*-[1,3]dioxolobenzo[4,5-*h*]pyrrolo[1,2-*a*][1]benzazepin-6-one (15h): Yield 183 mg. IR (KBr): $\tilde{\nu}$ = 1666 (C=O), 1251 (OCH₂O) cm⁻¹. ¹H NMR (200 MHz, CDCl₃): δ = 3.29 (dd, J = 2.8, 18.9 Hz, 1 H, 5-H), 3.56 (dd, J = 11.6, 18.9 Hz, 1 H, 5-H), 4.62 (dd, J = 2.4, 11.8 Hz, 1 H, 4-H), 5.53–5.55 (m, 1 H, 3-H), 6.08 (s, 2 H, 9-H), 6.18 (t, J = 3.2 Hz, 1 H, 2-H), 6.83 (s, 1 H, 11-H), 6.93 (t, J = 2.4 Hz, 1 H, 1-H), 7.31 (s, 1 H, 7-H), 7.31 (s, 1 H, 7-H), 7.39–7.50 (m, 3 H), 7.71–7.85 (m, 4 H) ppm. ¹³C NMR (50 MHz, CDCl₃): δ = 38.1 (C-4), 50.7 (C-5), 102.3 (OCH₂O), 104.4, 107.6, 109.2, 109.7, 121.3, 125.4, 125.8, 126.0, 126.4, 127.5, 127.7, 128.1, 132.5, 133.3, 136.5, 137.3, 145.8, 152.3, 200.0 (C=O) ppm. MS (70 eV, EI): m/z (%) = 367 (51) [M]⁺, 339 (72) [M – CO]⁺, 240 (100) [M – C₁₀H₇]⁺. C₂₄H₁₇NO₃ (367.4): calcd. C 78.46, H 4.66, N 3.81; found C 78.60, H 4.53, N 3.93.

Supporting Information (see also the footnote on the first page of this article): All ¹H, ¹³C and DEPT spectra for compounds **14** and **15**.

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- [1] a) A. Guzikowsky, S. Espitia, J. Hawkinson, J. Huettner, D. Nogales, R. Wodward, E. Weber, C. Keana, *J. Med. Chem.* **1996**, *39*, 4643–4653; b) A. Link, C. Kunick, *J. Med. Chem.* **1998**, *41*, 1299–1305.
- [2] a) J. García, J. Andrés, A. Fraile, A. Martín, M. Martín, *Tetrahedron Lett.* **2004**, *45*, 4653–4656; b) M. Novikov, A. Khlebnikov, M. Shevchenko, *J. Fluorine Chem.* **2003**, *123*, 177–181; c) G. Campiani, A. Ramunno, I. Fiorini, V. Nacci, E. Morelli, E. Novellino, M. Goegan, T. Mennini, S. Sullivan, D. Zisterer, C. Williams, *J. Med. Chem.* **2002**, *45*, 4276–4281; d) G. Milligan, C. Mossman, J. Aube, *J. Am. Chem. Soc.* **1995**, *117*, 10449–10459; e) M. Ikeda, S. Akamatsu, Y. Kugo, T. Sato, *Heterocycles* **1996**, *42*, 155–158; f) L. Huang, Z. Xue in *The Alkaloids* (Ed.: A. Brossi), Academic Press, New York, **1984**, vol. 23, pp. 157–226; g) M. Jalil Miah, T. Hudlicky, J. Reed in *The Alkaloids* (Ed.: A. Brossi), Academic Press, New York, **1998**, vol. 51, pp. 199–269; h) P. Benderra, H. Morjani, A. Trussardi, M. Manfait, *Leukemia* **1998**, *12*, 1539–1544; i) S. Sacchi, H. Kantarjian, S. O'Brien, J. Cortes, M. Rios, F. Giles, M. Beran, C. Koller, M. Keating, M. Talpaz, *Cancer* **1999**, *86*, 2632–2641; j) L. Tietze, H. Braun, P. Steck, S. El Bialy, N. Tölle, A. Düfert, *Tetrahedron* **2007**, *63*, 6437–6445; k) J. Koseki, H. Sato, Y. Watanabe, T. Nagasaka, *Org. Lett.* **2002**, *4*, 885–888; l) E. de Oliveira, F. Dumas, J. d'Angelo, *Tetrahedron Lett.* **1997**, *38*, 3723–3726.
- [3] a) J. Low, J. Cobo, M. Nogueras, P. Cuervo, R. Abonia, Ch. Glidewell, *Acta Crystallogr., Sect. C* **2004**, *60*, 744–750; b) J. Low, J. Cobo, P. Cuervo, R. Abonia, Ch. Glidewell, *Acta Crystallogr., Sect. C* **2004**, *60*, 827–829; c) J. Low, J. Cobo, A. Ortiz, P. Cuervo, R. Abonia, Ch. Glidewell, *Acta Crystallogr., Sect. E* **2004**, *60*, 1057–1059; d) J. Low, J. Cobo, M. Nogueras, A. Sánchez, A. Albornoz, R. Abonia, *Acta Crystallogr., Sect. E* **2002**, *58*, 42–45; e) P. Cuervo, R. Abonia, J. Cobo, J. Low, Ch. Glidewell, *Acta Crystallogr., Sect. C* **2007**, *63*, 99–101; f) R. Abonia, P. Cuervo, B. Insuasty, J. Quiroga, M. Nogueras, J. Cobo, H. Meier, E. Lotero, *Open Org. Chem. J.* **2008**, *2*, 26–34.
- [4] a) G. Cheeseman, M. Rafiq, *J. Chem. Soc. C* **1971**, 2732–2734; b) S. Raines, S. Chai, F. Palopoli, *J. Heterocycl. Chem.* **1976**, *13*, 711–716; c) S. Massa, A. Mai, R. Di Santo, M. Artico, *J. Heterocycl. Chem.* **1993**, *30*, 897–903; d) F.-W. Sum, J. Dusz, E. Delos Santos, G. Grosu, M. Reich, X. Du, J. Albright, P. Chan, J. Coupet, X. Ru, H. Mazandarani, T. Saunders, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2195–2198; e) R. Abonia, B. Insuasty, J. Quiroga, H. Kolshorn, H. Meier, *J. Heterocycl. Chem.* **2001**, *38*, 671–674.
- [5] M. Banwell, D. Beck, J. Smith, *Org. Biomol. Chem.* **2004**, *2*, 157–159.

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