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Synthesis of novel 7-oxo and 7-hydroxy trifluoroallocolchicinoids with cytotoxic effect

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ABSTRACT

The synthesis of 7-oxo and 7-hydroxy trifluoroallocolchicinoids was achieved through the intramolecular cyclization of *o*-phenyl-*β*-phenylalanines. The resulting compounds were evaluated for their cytotoxic activity against KB cells and their inhibitory effect towards the polymerization of tubulin. The results yielded some potent cytotoxic compounds with correlated partial antitubulin effect.

Allocolchicine **1**, as well as colchicine **2**, its supposed biogenetic precursor, is an alkaloid isolated from *Colchicum autumnale* L. (Fig. 1).[1–3] The tubulin polymerization inhibitory activity these two natural compounds exert confers on them a disturbing effect towards the microtubule-dependent cell functions and an antimitotic potentiality. These activities show also that the tropolone ring of colchicine is not absolutely necessary to the antitubulin effect and can be replaced by a benzene ring.[4] This discovery has led to numerous works aiming at synthesizing various allocolchicinoids, among which *N*-acetylcolchinol (NAC, **3**) and its methylether (NCME or NSC51046, **4**) which bind to the colchicine binding site of tubulin. These inhibitors have gained considerable attention by virtue of having been found to be active against a number of cancer cell lines and more interestingly against some multi-drug resistant lines expressing P-glycoprotein.[5–8] NAC further exhibits a potent antivascular effect resulting in disruption of the endothelial cells of tumor blood vessels, tumor ischemia and necrosis.[9] For this reason, the dihydrogenphosphate and prodrug of NAC (ZD6126, **5**) has reached the Phase II clinical trials in USA for the treatment of metastatic renal cell carcinoma, before these trails have been arrested due to a cardiac toxicity.

For a long time, allocolchicinoids were obtained by transformation of colchicine itself,[10–13] thus limiting the range of structural variations. Recently however, syntheses of novel allocolchicinoids were reported and some SAR studies have been realized.[5,14–19] The latter have noticeably established that, contrarily to the two benzene rings, the seven-membered central one does not seem to take part productively in the binding to tubulin but lies in an entropic contribution by suppressing free rotation around the pivot bond between the least square planes of the benzene rings.[20]

The antitubulin effect of the allocolchicinoids appearing thus correlated with the torsional angle between these rings, structural modifications affecting the cycloheptene ring of novel allocolchicinoids are requested to enhance the SAR knowledge and to potentially select novel antitubulin agents with therapeutic interest.

Within this context, we choose to synthesize 7-oxo **6** and 7-hydroxy **7** trifluoroallocolchicinoids in order to evaluate for the first time the incidence on the biological activity of a sp^2 configuration conferred to the carbon C7 of the dibenzocycloheptene system relatively to a sp^3 configuration. The synthesis of these compounds is herein reported through the intramolecular cyclization of *o*-phenyl-*β*-phenylalanines **8** together with an evaluation of

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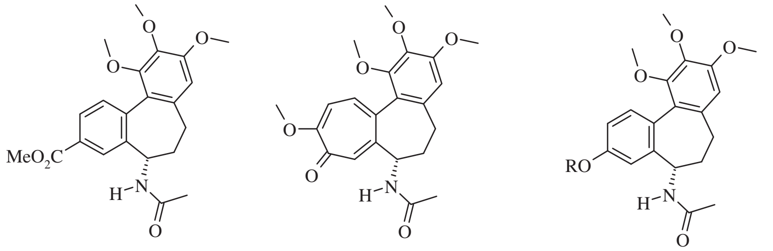


(-)-allocolchicine (**1**) (-)-colchicine (**2**)

NAC (R = H), (**3**)

NSC51046 or NCME (R = Me),(**4**)

ZD6126 (R = P(O)(OH)$_2$), (**5**)

Figure 1. Structure of (−)-allocolchicine (**1**), (−)-colchicine (**2**) and some allocolchicinoids (**3**–**5**).

their abilities to inhibit assembly of tubulin and the growth of KB cell lines (Fig. 2).

1. Results and discussion

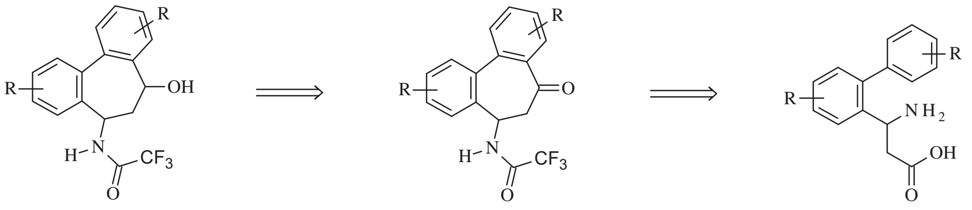
1.1. Chemistry

Despite their potential interest as useful building blocks in medicinal chemistry,[21] *o*-phenyl-*β*-phenylalanines **8** were at the beginning of our work almost unknown. In fact, only a 2′-carboxyphenyl derivative was described in literature and synthesized through the ring opening of an oxodibenzaze-pinylacetic acid.[22] We undertook the synthesis of these scaffolds firstly starting from racemic 2-bromo-3-amino-3-phenylpropionic acid **9** which we previously synthesized according to a Rodionov–Johnson procedure[23,24] applied to 2-bromobenzal-dehyde **10** (Scheme 1, Method A).[25] A subsequent Suzuki–Miyaura cross coupling was then achieved between **9**, previously *N*-protected as a trifluoroacetamide, and 3,4-dimethoxyphenyl-boronic acid, using Pd tetrakistriphenylphosphine as catalyst in DME and an aqueous solution of $NaHCO_3$ as a base. The sequence led to the *N*-deprotected *o*-(3′,4′-dimethoxyphenyl)-β-phenylalanine **8a** isolated under its hydrochloric salt which was precipitated at the end of the reaction by acidification and saturation of the aqueous solution. The overall yield to obtain **8a** starting from **10** was of 6%. This poor yield was the consequence of side products formation: 2-bromocinnamic acid during the Rodionov–Johnson step and 2-(3′,4′-dimethoxyphenyl)cinnamic acid **11** during the Suzuki–Miyaura reaction, respectively.

In order to enhance this yield, the sequence has been reversed, starting with the cross coupling of **10** with 3,4-dimethoxyphenylboronic acid according to the method we very recently described,[26] followed by the involvement of the resulting unknown biphenylcarboxaldehyde **12a** in a Rodionov–Johnson reaction (Scheme 1, Method B). According to this novel sequence, the overall yield with which the hydrochloric salt of **8a** was obtained starting from **10** was of 17%, the cinnamic acid **11** being concomitantly synthesized. This pathway was then applied to the coupling of **10** with 2,3,4-trimethoxyphenylboronic acid and to the coupling of its 3-methoxy **13** and 3-hydroxy derivatives **14** with 3,4-dimethoxy- and 2,3,4-trimethoxyphenyl-boronic acids under microwave irradiation (Scheme 2). According to this sequence, six biphenylcarboxaldehydes **12a**–**f** and the corresponding β-aminoacids **8a**–**f** were synthesized with yields ranging from 15% to 25%.

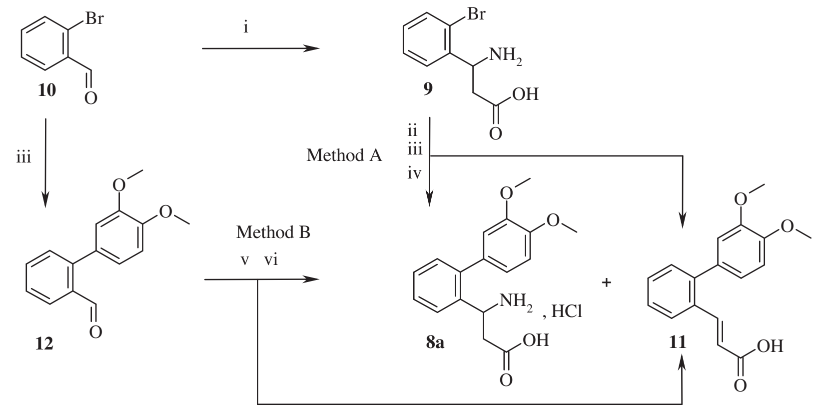
A mixture of TFA and TFA_2O was then used to achieve the one-pot intramolecular cyclization of **8a**–**f**, according to the method we have previously described for the cyclization of β-aminoacids in activated aromatic series into various indanones, thia-, oxa- and azaindanones (Scheme 3).[27–29] Applied to **8a**–**f**, the reaction led to the expected *N*-(7-oxo-6,7-dihydro-5*H*-dibenzo [*a*,*c*][7]cyclohepten-5-yl)-2,2,2-trifluoroacetamides **6a**–**f** with yields ranging from 50% to 60%. Only **8d** led concomitantly to the formation of the indanone derivative **15**. Fortunately, the cyclization of **8a**, **8c** and **8e** never took place on the 2′ position of the phenyl ring. This one-pot method of cyclization, already used by Boyé starting from biphenylpropionic acids,[30] further prevents the *O*-demethylation which usually occurs during Friedel–Crafts cyclisation of methoxy derivatives using Lewis acids. It also led to compounds whose trifluoracetylamino groups can exert some metabolic poisonous properties and thus can enhance their cytotoxic effect.

Finally, the reduction of the carbonyl group of **6a**–**f** was achieved using sodium borohydride in methanol (Scheme 3). The reaction led to the alcohols (**7a**–**f**) with yields ranging from 50% to 85%. The latter were formed as a mixture of their *cis* and *trans* diastereoisomers among which only the *trans* dimethoxy derivative (**7a**) has been separated by fractional crystallizations. Its configuration was established on the basis of 2D NMR data, completed

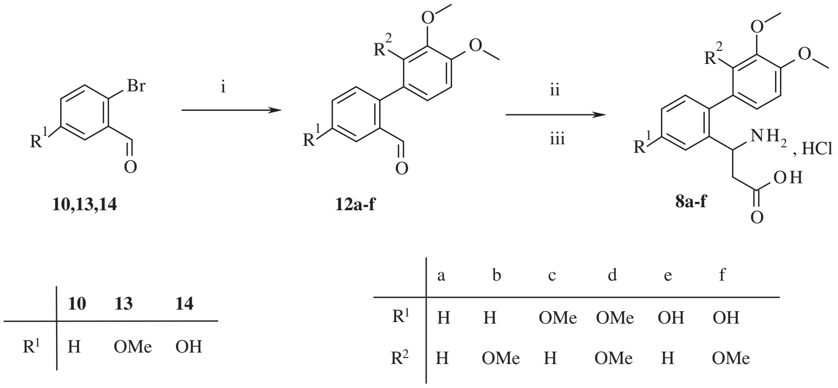


7 **6** **8**

Figure 2. Retrosynthetic access to 7-oxo (**6**) and 7-hydroxy (**7**) allocolchicinoids through intramolecular cyclization of *o*-phenyl-*β*-phenylalanines (**8**).



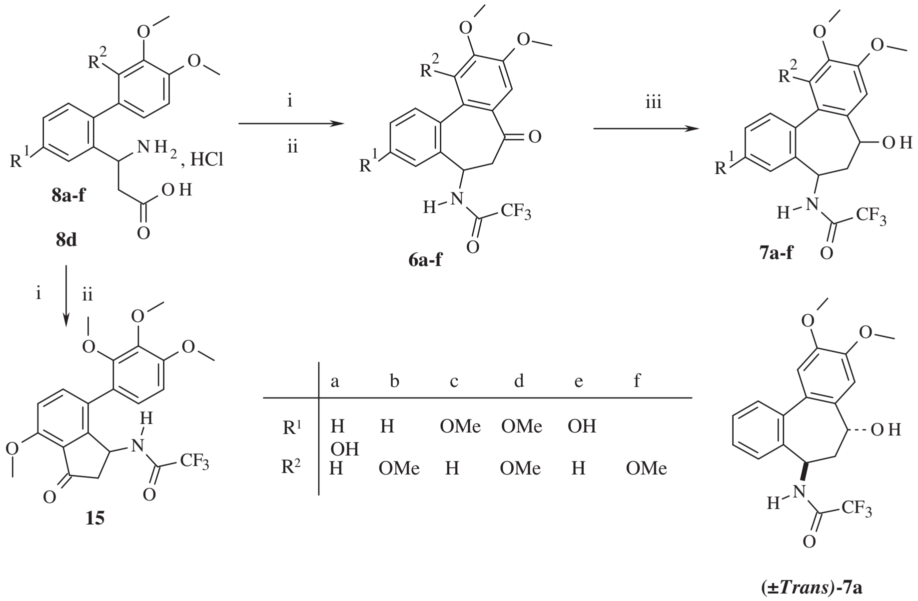
Scheme 1. Synthetic pathways for the synthesis of compounds **9**, **11**, **12a** and **8a.** Reagents: *Method A*, (i) $CH_2(CO_2H)_2$, $AcONH_4$, EtOH; (ii) $(CF_3CO)_2O$, Et_2O; (iii) 3,4-$(MeO)_2C_6H_3B(OH)_2$, $Pd(PPh_3)_4$, $NaHCO_3$, DME, H_2O; (iv) HCl, NaCl, H_2O; *Method B*, (v) $CH_2(CO_2H)_2$, $AcONH_4$, EtOH; (vi) HCl, H_2O.



	10	13	14
R^1	H	OMe	OH

	a	b	c	d	e	f
R^1	H	H	OMe	OMe	OH	OH
R^2	H	OMe	H	OMe	H	OMe

Scheme 2. Synthetic pathway for the synthesis of compounds **12a–f** and **8a–f** (Method B). Reagents: (i) 3,4-substituted $C_6H_3B(OH)_2$, $Pd(PPh_3)_4$, $K_3PO_4{\cdot}H_2O$, DME under microwave irradiation (6 bars, 80–150 watts); (ii) $CH_2(CO_2H)_2$, $AcONH_4$, EtOH; (iii) HCl, H_2O.



	a	b	c	d	e	f
R^1	H	H	OMe	OMe	OH	
	OH					
R^2	H	OMe	H	OMe	H	OMe

Scheme 3. Synthetic pathway for the synthesis of compounds **6a–f**, **7a–f** and **15**. Reagents: (i) TFA; (ii) TFA_2O; (iii) $NaBH_4$, MeOH.

by 1D NOESY experiments and was confirmed by X-ray crystallographic analysis (Fig. 3). The latter also showed a dihedral angle of 49.2° between the two aromatic rings of **7a**, in a similar manner as for colchicine itself.

1.2. Biology

Compounds synthesized in this work were tested for their in vitro cytotoxicity against KB cells at 10^{-5} and 10^{-6} M

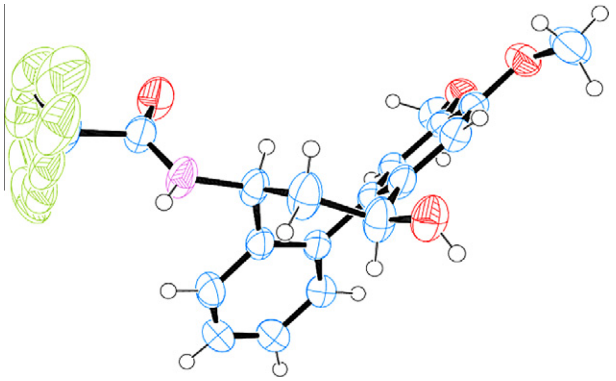


Figure 3. View of crystal structure of (±*Trans*)-**7a**. Displacement ellipsoids are drawn at the 50% probability level. H-atoms are shown as small spheres of arbitrary *radii*.

concentrations in triplicate, using docetaxel at 2.5 10^{-10} M as reference. The results are expressed in term of inhibition percentage at each concentrations and IC_{50} were measured for percentage greater than 80% at 10^{-5} M (Table 1). The inhibition of the polymerization of tubulin was also evaluated at 6.7 10^{-5} M in triplicate using deoxypodophyllotoxin (Dppt) as reference. The results are expressed in term of inhibition percentage and IC_{50} were measured for percentage greater than 45% (Table 1).

The results show that among the thirteen tested compounds, three exerted a cytotoxic activity towards KB cells with micromolar IC_{50} (**6b**, **7d** and **15**) and two with submicromolar values (**6d** and **6f**). The most potent compound was the tetramethoxy one (**6d**) with an IC_{50} of 45 nM in the same order of magnitude than those of NCME (IC_{50} = 19 nM).[8] This result appears particularly interesting since **6d** was prepared under its racemic mixture, whereas NCME is an optically active compound.

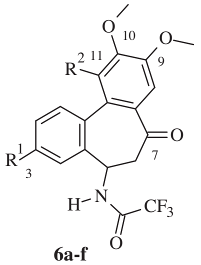
Inhibition of the polymerization of tubulin appears partially correlated with the cytotoxicity exerted towards KB and **6d**, the most cytotoxic derivative showed an IC_{50} against tubulin of 12 μM. This inhibitory effect remains however lower compared to NCME (IC_{50} = 0.7 μM).[8] On the other hand, the alcohol (**7b**), totally devoid of cytotoxic activity, surprisingly inhibits tubulin in a same order of magnitude than **6d**.

Concerning the SAR, 7-keto compounds appear always more cytototoxic comparatively to the corresponding 7-hydroxy compounds. In a similar manner, keto compounds inhibit more strongly tubulin than their hydrogenated analogs, except for the alcohol **7b**. On the other hand, the absence of a methoxy group in C1 position (R^2) appears detrimental for both cytotoxicity and tubulin inhibition since **6a**, **7a**, **7c**, **6e** and **7e** were devoid of activity (only **6c** weakly inhibits tubulin with IC_{50} = 60 μM). This result is consistent with the SAR established for colchicine and colchicinoids, this methoxy group being important in setting the correct conformation of the keto compounds.[30] Finally, for compounds with R^2 = OMe, an additional OMe group in C9 position (R^1) seems favorable to the activities (compound **6d** vs. **6b**). It can be replaced by a hydroxyl group but with a decrease of activity (compound **6f**). Interestingly, the indanone (**15**) bearing four methoxy groups showed also a moderate cytotoxic effect against KB cells.

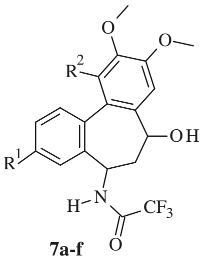
2. Conclusion

We have during this work developed a synthesis of novel 7-keto and 7-hydroxy trifluoroallocolchicinoids, some of which (compounds **6d** and **6f**) showing a good cytotoxic activity against KB cells, correlated with a partial tubulin inhibitory effect. This probably accounts for a multiple mechanism of action implying other

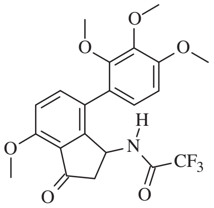
Table 1
Percentage of inhibition of KB cells growing at various concentrations and IC_{50} for deoxypodophyllotoxin (Dppt) and compounds **6a–f**, **7a–f** and **15**



6a-f



7a-f



15

R^1	R^2	Compd	KB cells inhibition			Tubulin inhibition	
			Inh% at 10^{-5} M	Inh% at 10^{-6} M	IC_{50} ± SD (μM)	Inh% at 6.7 10^{-5} M	IC_{50} ± SD (μM)
H	H	**6a**	92	0	–	12	–
		7a	9	0	–	23	–
H	OMe	**6b**	91	18	2.950 ± 0.650	48	80 ± 7
		7b	8	0	–	89	13 ± 4
OMe	H	**6c**	38	0	–	63	60 ± 5
		7c	9	0	–	2	–
OMe	OMe	**6d**	96	98	0.045 ± 0.005	89	12 ± 3
		7d	94	0	1.595 ± 0.410	18	–
OH	H	**6e**	40	0	–	24	–
		7e	2	0	–	13	–
OH	OMe	**6f**	96	37	0.330 ± 0.120	62	37 ± 2
		7f	60	0	–	29	–
–	–	**15**	97	0	1.250 ± 0.340	33	–
–	–	**Dppt**	100	100	0.003 ± 0.001	100	3.2 ± 0.2
–	–	**NCME**	–	–	0.019 ± 0.001[a]		0.7 ± 0.1[a]

[a] values for *N*-acetylcolchinol methylether (NCME) from.[8]

targets. Another compound (**7b**) exhibited also such an antitubulin effect but without cytotoxicity. If this lack of activity is not due to the incapacity of **7b** to reach into intracellular sites, this compound could also constitute an interesting hit to develop novel agents able to inhibit more specifically this target. The extension of this synthetic procedure to enantiomeric starting materials and also to heterocyclic series is currently under investigation. It could lead to novel original derivatives with enhanced properties.

3. Experimental section

3.1. Chemistry

Materials and methods: All commercial solvents and reagents were used as-received. The microwave reactions were performed using a Biotage Initiator Microwave oven; temperatures were measured with an IR-sensor and reaction times given as hold times. Flash chromatography was realized on a spot two apparatus; column: SiO_2; eluent: cyclohexane/ethyl acetate. Melting points were determined on a Kofler melting point apparatus and were uncorrected. IR spectra were recorded on KBr discs; only selected absorbances were quoted. TLC were carried out on 5 × 10 pre-coated plates with silica gel GF254 type 60 using an ethyl acetate cyclohexane mixture (1:1) as solvent; LC/MS (ESI) analyses were realized with a separating module using the following gradient: A (95%)/B (5%) to A (5%)/B (95%) in 5 min; this ratio was hold during 2 min before return to initial conditions in 1 min. Initial conditions were then maintained for 2 min (A: H_2O, B: CH_3CN; each containing HCOOH: 0.1%; Column: C18, flow: 0.4 mL min-1). MS detection was performed by positive or negative ESI. High resolution mass spectra were performed at 40 eV by electronic impact (HREIMS) or positive or negative electrospray (HRESIMS). ^1H and ^{13}C NMR spectra were recorded, respectively, at 400 and 100 MHz using $CDCl_3$, DMSO-d_6, CD_3OD or $(CD_3)_2CO$ as solvents. 2D NMR spectra and 1D NOESY experiments were recorded at 500 MHz. The apparent multiplicity is described as s (singlet), d (doublet), dd (doublet of doublets), t (triplet), m (multiplet); chemical shifts δ are reported in parts per million with the solvent resonance as the internal standard; coupling constants *J* are given in Hertz.

3.2. General procedure for the synthesis of biphenylcarbaldehydes (12a–f)

To degassed solutions of 1 equiv of substituted 2-bromo-benzaldehydes **10**, **13** or **14** in DME were added 1.5 equiv of boronic species, 3 equiv of $K_3PO_4{\cdot}H_2O$ and 0.05 equiv of $Pd(PPh_3)_4$; the suspensions were heated under microwave irradiation (6 bars, 80–150 watts) for 1 h 30 min at 150 °C. The resulting mixtures were filtered (washed with Et_2O or EtOAc) and concentrated under reduced pressure. The crude products were then purified by flash chromatography.

3.2.1. 3′,4′-Dimethoxybiphenyl-2-carbaldehyde (12a)

Starting from 2-bromobenzaldehyde (1 mmol, 185 mg, 117 μL), 3,4-dimethoxyphenyl boronic acid (1.5 mmol, 273 mg), $K_3PO_4{\cdot}H_2O$ (3 mmol, 637 mg) and $Pd(PPh_3)_4$ (0.05 mmol, 577 mg), **12a** was obtained as a colorless oil (173 mg, 71%); IR (KBr) λ (cm^{-1}) 1688 (CO), 1598, 1517, 1247, 1025; ^1H NMR (400 MHz, $CDCl_3$) δ 10.00 (s, 1H, CHO), 8.01 (d, 1H J_{ortho} = 7.8 Hz), 7.63 (dd, 1H, J_{ortho} = 7.8, J_{meta} = 1.9 Hz), 7.47 (m, 2H), 6.94 (d, 1H, J_{ortho} = 8.8 Hz), 6.91 (m, 2H), 3.95 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.7 (CHO), 149.3, 148.8, 146.2, 145.7, 133.9, 133.5, 130.7, 127.7, 127.6, 122.9, 113.2, 110.9, 55.9 (2C, OCH_3); LC–MS t_R = 10.63 min, [ESI^+] *m*/*z* $[M+H]^+$ 243, $[M+H-H_2O]^+$ 225; HREIMS [M^+] *m*/*z* 242.093876 (calcd for $C_{15}H_{14}O_3$ 242.094294).

3.2.2. 2′,3′,4′-Trimethoxybiphenyl-2-carbaldehyde (12b)

Starting from 2-bromobenzaldehyde (1.7 mmol, 315 mg, 199 μL), 2,3,4-trimethoxyphenylboronic acid (2.5 mmol, 540 mg), $K_3PO_4{\cdot}H_2O$ (5.1 mmol, 1.17 g) and $Pd(PPh_3)_4$ (0.085 mmol, 982 mg), **12b** was obtained as a pale yellow powder (323 mg, 70%); LC–MS t_R = 10.82 min, [ESI^+] *m*/*z* $[M+H]^+$ 273. Other spectral data are in agreement with those found in the literature.[18]

3.2.3. 3′,4,4′-Trimethoxybiphenyl-2-carbaldehyde (12c)

Starting from 2-bromo-5-methoxybenzaldehyde (3 mmol, 645 mg), 3,4-dimethoxyphenylboronic acid (4.5 mmol, 819 mg), $K_3PO_4{\cdot}H_2O$ (9 mmol, 1.91 g) and $Pd(PPh_3)_4$ (0.15 mmol, 1.73 g), **12c** was obtained as pale yellow solid (635 mg, 77%); mp 104–105c °C; ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.5 (CHO), 158.9, 148.9, 148.8, 138.9, 134.5, 132.0, 130.1, 122.9, 121.4, 113.1, 110.9, 109.7, 55.9 (2C, OCH_3), 55.6 (OCH_3); LC–MS t_R = 6.72 min, [ESI^+] *m*/*z* [M+H]+ 273. Other spectral data are in agreement with those found in the literature.[31]

3.2.4. 2′,3′,4,4′-Tetramethoxybiphenyl-2-carbaldehyde (12d)

Starting from 2-bromo-5-methoxybenzaldehyde (1.7 mmol, 365 mg), 2,3,4-trimethoxyphenylboronic acid (2.5 mmol, 540 mg), $K_3PO_4{\cdot}H_2O$ (5.1 mmol, 1.17 g) and $Pd(PPh_3)_4$ (0.085 mmol, 982 mg), **12d** was obtained as a pale yellow solid (443 mg, 86%); LC–MS t_R = 6.93 min, [ESI^+] *m*/*z* $[M+H]^+$ 303. Other spectral data are in agreement with those found in the literature.[18]

3.2.5. 4-Hydroxy-3′,4′-dimethoxybiphenyl-2-carbaldehyde (12e)

Starting from 2-bromo-5-hydroxybenzaldehyde (3 mmol, 603 mg), 3,4-dimethoxyphenylboronic acid (4.5 mmol, 819 mg), $K_3PO_4{\cdot}H_2O$ (9 mmol, 1.91 g) and $Pd(PPh_3)_4$ (0.15 mmol, 1.73 g), **12e** was obtained as a pale yellow solid (561 mg, 72%); mp 185–186 °C; IR (KBr) λ (cm^{-1}) 3424 (OH), 1679 (CO), 1605, 1498, 1253; ^1H NMR (400 MHz, $CDCl_3$) δ 9.94 (s, 1H, CHO), 7.44 (d, 1H, J_{meta} = 2.9 Hz), 7.36 (d, 1H, J_{ortho} = 8.8 Hz), 7.15 (dd, 1H, J_{ortho} = 8.8 Hz, J_{meta} = 2.9 Hz), 6.95 (d, 1H, J_{ortho} = 8.8 Hz), 6.87 (m, 2H), 5.21 (s, 1H, OH), 3.95 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.5 (CHO), 155.1, 148.9, 148.7, 138.9, 134.7, 132.3, 130.0, 122.9, 121.2, 113.1, 112.8, 110.9, 56.0 (2C, OCH_3); LC–MS t_R = 5.92 min, [ESI^-] *m*/*z* $[M-H]^-$ 257; HREIMS [M^+] *m*/*z* 258.08921 (calcd for $C_{15}H_{14}O_4$ 258.08919).

3.2.6. 4-Hydroxy-2′,3′,4′-trimethoxybiphenyl-2-carbaldehyde (12f)

Starting from 2-bromo-5-hydroxy-benzaldehyde (1.5 mmol, 301.5 mg), 2,3,4-trimethoxyphenylboronic acid (2.25 mmol, 477 mg), $K_3PO_4{\cdot}H_2O$ (4.5 mmol, 1.04 g) and $Pd(PPh_3)_4$ (0.075 mmol, 866 mg), **12f** was obtained as pale yellow solid (296 mg, 68%); mp 130–131 °C; IR (KBr) λ (cm^{-1}) 3454 (OH), 1680 (CO), 1602, 1486, 1286; ^1H NMR (400 MHz, $CDCl_3$) δ 9.78 (s, 1H, CHO), 7.56 (d, 1H, J_{meta} = 2.9 Hz, H3), 7.28 (d, 1H, J_{ortho} = 8.8 Hz, H6), 7.18 (dd, 1H, J_{ortho} = 8.8Hz, J_{meta} = 2.9 Hz, H5), 6.97 (d, 1H, J_{ortho} = 7.8 Hz), 6.78 (d, 1H, J_{ortho} = 7.8 Hz), 3.93 (s, 6H, OCH_3), 3.53 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.2 (CHO), 155.8, 153.7, 151.1, 141.9, 134.4, 133.8, 132.7, 125.7, 124.3, 121.6, 112.7, 107.5, 61.1 (OCH_3), 60.6 (OCH_3), 56.0 (OCH_3); LC–MS t_R = 6.04 min, [ESI^-] *m*/*z* $[M-H]^-$ 287; HREIMS [M^+] *m*/*z* 288.09936 (calcd for $C_{16}H_{16}O_5$ 288.09975).

3.2.7. 3-Amino-3-(2-bromophenyl)propanoic acid (9)

2-Bromo-benzaldehyde **10** (50 mmol, 9.25 g) was refluxed in EtOH (150 mL) with 1 equiv of malonic acid (50 mmol, 5.20 g) and 2 equiv of ammonium acetate (100 mmol, 7.70 g) for 6 h; the resulting precipitate was triturated in distilled water to separate the expected amino acid **9** from the corresponding diammonium 2-bromobenzylidene-propanedioate that was concomitantly formed and which remained in water. Compound **9** was obtained as a colorless solid (3.5 g, 29%) which was used without further purification; mp 200–201 °C; IR (KBr) λ (cm^{-1}) 2924, 2360, 1686 (CO), 1621, 1465, 1284, 1223, 1023. Other spectral data are in agreement with those found previously by us.[25]

3.2.8. 3-Amino-3-(3′,4′-dimethoxybiphenyl-2-yl)propanoic acid hydrochloride (8a) and 3-(3′,4′-di-methoxybiphenyl-2-yl)prop-2-enoic acid (11)

Method A; TFA_2O (100 mmol, 14 mL) was added dropwise to a suspension of 2-bromo-3-amino-3-phenylpropanoic acid **9** (10 mmol, 2.44 g) in Et_2O (30 mL). The reaction mixture was stirred for 1 h and then the solvent was concentrated under reduced pressure. The residue was triturated with distilled water to afford after filtration the expected 3-(2-bromophenyl)-3-trifluoro-acetylaminopropanoic acid which was obtained as a colorless solid (3.3 g, quant.) and used without further purification; IR (KBr) λ (cm^{-1}) 3300, 2360, 1706 (CO), 1559, 1261-1185-1156 (CF_3), 1023. Other spectral data are in agreement with those found in the literature.[25] To a degassed solution of the latest *N*-protected amino acid (9.4 mmol, 3.2 g) in DME (100 mL) were added 1.1 equiv of (3,4-dimethoxyphenyl)boronic acid (10 mmol, 1.88 g), 4 equiv of $NaHCO_3$ (37.6 mmol, 3.16 g) in H_2O (50 mL) and 0.05 equiv of $Pd(PPh_3)_4$ (0.47 mmol, 0.54 g); the suspension was refluxed for 48 h under nitrogen, filtered after cooling and evaporated to dryness in vacuum. The crude residue was then dissolved in water and washed with $CHCl_3$; the resulting aqueous layer was acidified with a solution of HCl 6 M until pH 1 and extracted with $CHCl_3$; after drying over $MgSO_4$ and filtration, the solvent was removed in vacuum and 2-(3′,4′-dimethoxybiphenyl) cinnamic acid (**11**) crystallized in the round flask as a colorless solid (10 mg <1%). Mp 166–167 °C; IR (KBr) λ (cm^{-1}) 3430, 1693 (CO), 1622, 1521, 1325, 1252, 1027; ^1H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, 1H, ^3J = 16.6 Hz, H*ethylen*.), 7.70 (d, 1H, J_{ortho} = 7.8 Hz), 7.42 (m, 3H), 6.94 (d, 1H, J_{ortho} = 8.8 Hz), 6.86 (m, 2H), 6.40 (d, 1H, ^3J = 16.6 Hz, H*ethylen*), 3.94 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0 (CO_2H), 148.6 (2C), 146.2, 142.9, 132.3, 132.2, 130.4, 130.2, 127.4, 127.0, 122.3, 118.1, 113.1, 110.9, 55.9 (2C); EIMS *m*/*z* 284 [M^+], 239 $[M-CO_2H]^{+\cdot}$., HREIMS [M^+] *m*/*z* 284.10542 (calcd for $C_{17}H_{16}O_4$ 284.10484).

The remaining aqueous layer was saturated with NaCl and stirred for 3 h at room temperature to give crystals of the expected deprotected biphenyl amino acid **8a**. The latter was obtained as colorless crystals which was used without further purification (600 mg, 19%); mp 242–243 °C; IR (KBr) λ (cm^{-1}) 3140, 2911, 1730 (CO), 1522, 1498, 1247, 1221, 1141, 1109, 1020; ^1H NMR (400 MHz, DMSO-d_6)* δ 8.75 (s, 2H, NH_2), 7.88 (d, 1H, J_{ortho} = 7.5 Hz, H_3), 7.47 (m, 1H, H4), 7.42 (m, 1H, H5), 7.27 (dd, 1H, J_{ortho} = 8.0 Hz, J_{meta} = 1.0 Hz, H6), 7.04 (d, 1H, J_{ortho} = 8.5 Hz, H5′), 7.02 (d, 1H, J_{meta} = 1.5 Hz, H2′), 6.91 (dd, 1H, J_{ortho} = 8.5 Hz, J_{meta} = 1.5 Hz, H6′), 4.60 (m, 1H, H3), 3.81 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.08 (dd, 1H, ^2J = 16 Hz, ^3J = 7.5 Hz, H2a), 2.94 (dd, 1H, ^2J = 16 Hz, ^3J = 7.5 Hz, H2b); ^{13}C NMR (100 MHz, DMSO-d_6)* δ 171.0 (C1), 148.7 (C3′), 148.5 (C4′), 142.3 (C1), 135.0 (C2), 132.7 (C1′), 130.9 (C6), 128.9 (C5), 128.3 (C4), 127.3 (C3), 121.9 (C6′), 113.6 (C2′), 112.0 (C5′), 56.0 (2C, OCH3), 47.6 (C3), 39.2 (C2); LC–MS t_R = 6.17 min, [ESI^+] *m*/*z* $[M+H]^+$ 302; HRESIMS $[M-H]^-$ *m*/*z* 300.1234 (calcd for $C_{17}H_{18}NO_4$ 300.1236).

*δ assignments according to 2D experiments (COSY, HMBC).

Method B; a solution of 3′,4′-dimethoxybiphenyl-2-carbaldehyde (**12a**) (2 mmol, 483 mg), 1 equiv of malonic acid (2 mmol, 208 mg) and 2 equiv of ammonium acetate (4 mmol, 308 mg) was refluxed in EtOH (20 mL) for 20 h. Water (10 mL) was then added to the reaction mixture and EtOH was removed under reduced pressure; the aqueous layer was then acidified with HCl 12 M and stirred until **11** was precipitated (10 mg <1%); after filtration, the aqueous layer was concentrated under reduced pressure; addition of acetone to the residue gave **8a** as a colorless precipitate (165 mg, 24%) which was used without further purification.

3.2.9. 3-Amino-3-(2′,3′,4′-trimethoxybiphenyl-2-yl)propanoic acid hydrochloride (8b)

The latter was obtained according to the method B used for **8a** starting from **12b** (2.28 mmol, 620 mg). Although the same work up was applied, **8b** could not be isolated from the starting material and was engaged under this form in the cyclisation step.

3.2.10. 3-Amino-3-(3′,4,4′-trimethoxybiphenyl-2-yl)propanoic acid hydrochloride (8c)

The latter was obtained according to the method B used for **8a**, starting from **12c** (2.3 mmol, 630 mg). At the end of the run time, distilled water was added to the reaction mixture and EtOH was removed under reduced pressure; the aqueous layer was then acidified with HCl 12 M and stirred until a bright yellow precipitate was obtained (cinnamic acid); after filtration, the aqueous layer was concentrated under reduced pressure; addition of acetone to the residue gave **8c** as a colorless precipitate (196 mg, 26%) which was used without further purification; mp 232–233 °C; IR (KBr) λ (cm^{-1}) 3033 (OH), 1716 (CO), 1615, 1497,1408, 1245, 1174, 1016; ^1H NMR (400 MHz, CD_3OD) δ 7.26 (d, 1H, J_{ortho} = 8.8 Hz), 7.18 (d, 1H, J_{meta} = 1.9 Hz), 7.02 (m, 2H), 6.93 (d, 1H, J_{meta} = 1.9 Hz), 6.86 (dd, 1H, J_{ortho} = 7.8 Hz, J_{meta} = 1.9 Hz), 4.79 (m, 1H, H3), 3.87 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 2.99 (m, 2H, H2a,b); ^{13}C NMR (100 MHz, CD_3OD) δ 172.7 (CO_2H), 161.2, 150.3, 150.1, 136.3, 135.5, 133.6, 133.4, 123.2, 115.6, 114.5, 113.0, 112.3, 56.5 (2C, OCH3), 56.1 (OCH_3), 49.0 (under solvent residual peaks), 39.4; LC–MS t_R = 4.36 min, [ESI^-] *m*/*z* $[M-H]^-$ 330; HREIMS [M^+] *m*/*z* 331.14131(calcd for $C_{18}H_{21}NO_5$ 331.14194).

3.2.11. 3-Amino-3-(2′,3′,4,4′-tetramethoxybiphenyl-2-yl)propanoic acid hydrochloride (8d)

The latter was obtained according to the method B used for **8a**, starting from **12d** (2.07 mmol, 625 mg). At the end of the run time, EtOH was evaporated until 2 mL left; distilled water was added until a yellow precipitate was obtained (cinnamic acid); after filtration, EtOH was removed in vacuum and the aqueous layer was acidified until pH 1; the resulting layer was washed three times with Et_2O to remove the corresponding benzylidene malonic acid; the aqueous layer was concentrated under reduced pressure; addition of acetone to the residue gave **8d** as a colorless precipitate (191 mg, 25%) which was used without further purification; mp 191–192 °C; IR (KBr) λ (cm^{-1}) 3154, 1724 (CO), 1608, 1489,1402, 1294, 1240, 1079; ^1H NMR (400 MHz, CD_3OD)* δ 7.26 (d, 1H, J_{ortho} = 8.8 Hz, H6), 7.20 (d, 1H, J_{meta} = 1.9 Hz, H3), 7.05 (dd, 1H, J_{ortho} = 8.8 Hz, J_{meta} = 1.9 Hz, H5), 6.98 (d, 1H, J_{ortho} = 8.8 Hz, H6′), 6.91 (m, 1H, H5′), 4.50 (dd, 1H, ^3J = 8.8 Hz, ^3J = 5.8 Hz, H3), 3.89 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.59 (s, 3H, OCH_3), 2.91 (dd, 1H, ^2J = 17.5 Hz, ^3J = 8.8 Hz, H2a), 2.75 (dd, 1H, ^2J = 17.6 Hz, ^3J = 5.9 Hz, H2b); ^{13}C NMR (100 MHz, CD_3OD)* δ 173.7 (C1), 161.4 (C4), 155.2 (C4′), 152.0 (C3′), 143.5 (C2′), 137.7 (C2), 133.5 (C6), 131.2 (C1), 127.4 (C1′), 127.1 (C6′), 115.6 (C5), 112.3 (C3), 109.8 (C5′), 61.8 (OCH_3), 61.5 (OCH_3), 56.6 (OCH_3), 56.1 (OCH_3), 50.4 (C3), 39.2 (C2); LC–MS t_R = 4.57 min, [ESI^-] *m*/*z* 360 $[M-H]^-$; HRESIMS $[M+H]^+$ *m*/*z* 362.1596 (calcd for $C_{19}H_{24}NO_6$ 362.1604).

*δ assignments according to 2D experiments (COSY, HMBC).

3.2.12. 3-Amino-3-(4-hydroxy-3′,4′-dimethoxybiphenyl-2-yl) propanoic acid hydrochloride (8e)

The latter was obtained according to the method B used for **8a**, starting from **12e** (2.13 mmol, 550 mg). At the end of the run time, EtOH was evaporated until 2 mL left; distilled water was added until a yellow precipitate was obtained (cinnamic acid); after filtration, EtOH was removed in vacuum and the aqueous layer was acidified until pH 1; the resulting phase was washed three times with Et_2O to remove the corresponding benzylidene malonic acid; the aqueous layer was evaporated to dryness under reduced pressure; addition of acetone to the residue gave **8e** as a colorless solid (75 mg, 10%) which was used without further purification; mp 240–241 °C; IR (KBr) λ (cm^{-1}) 3044 (OH), 1734 (CO), 1496, 1403, 1244; ^1H NMR (400 MHz, CD_3OD) δ 7.15 (d, 1H, J_{ortho} = 8.8 Hz), 7.06 (d, 1H, J_{meta} = 2.9 Hz), 7.02 (d, 1H, J_{ortho} = 7.8 Hz), 6.93 (d, 1H, J_{meta} = 1.9 Hz), 6.87 (m, 2H), 4.75 (dd, 1H, J = 5.8 Hz, H3), 3.87 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3,02 (dd, 1H, ^2J = 17.6 Hz, ^3J = 7.8 Hz, H2a), 2.94 (dd, 1H, ^2J = 17.6 Hz ^3J = 5.8 Hz, H2b); ^{13}C NMR (100 MHz, CD_3OD) δ 172.5 (CO_2H), 157.0, 148.3, 147.7, 139.1, 132.8, 131.4, 131.2, 121.3, 114.7, 113.2, 112.8, 111.6, 55.5 (2C, OCH_3), 48.7, 41.1; LC–MS t_R = 4.10 min, [ESI^-] m/z $[M-H]^-$ 316; HREIMS [M^+] m/z 317.12591 (calcd for $C_{17}H_{19}NO_5$ 317.12629).

3.2.13. 3-Amino-3-(4-hydroxy-2′,3′,4′-trimethoxybiphenyl-2-yl)pro-panoic acid (8f)

The latter was obtained according to the method B used for **8a** starting from **12f,** (1.96 mmol, 567 mg). At the end of the run time, **8f** has precipitated in the medium and was obtained after filtration as a colorless powder (160 mg, 23%) which was used without further purification; mp >260 °C; IR (KBr) λ (cm^{-1}) 3237 (OH), 1615 (CO), 1595, 1487,1410, 1292, 1094; ^1H NMR (400 MHz, DMSO-d_6, 90 °C) δ 6.99 (d, 1H, J_{meta} = 2.9 Hz, H3), 6.92 (d, 1H, J_{ortho} = 7.8 Hz), 6.80 (m, 2H), 6.70 (dd, 1H, J_{ortho} = 7.8 Hz, J_{meta} = 2.9 Hz, H5), 3.99 (m, 1H, CH), 3.83 (s, 6H, OCH_3), 3.78 (s, 3H, OCH_3), 2.29 (m, CH_2, H2); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.9 (CO_2H), 157.0, 152.8, 151.1, 141.7, 140.2, 131.4, 127.4, 126.5, 125.4, 114.5, 112.7, 108.0, 60.6 (OCH_3), 60.4 (OCH_3), 55.8 (OCH_3), 49.2, 40.1; LC–MS t_R = 4.24 min, [ESI^-] m/z $[M-H]^-$ 346; HRESIMS $[M+H]^+$ m/z 348.1435 (calcd for $C_{18}H_{22}NO_6$ 348.1447).

3.3. General procedure for the synthesis of dibenzocycloheptenones (6a–f) and phenylindanone (15)

A solution of β-amino acid **8a–f** in TFA was stirred at room temperature for 1 h; then, 25 equiv of TFA_2O were added and the mixture was refluxed for 3 h. The reaction mixture was evaporated to dryness under reduced pressure and water was added; the resulting precipitate was filtered and purified by flash chromatography.

3.3.1. *N*-(9,10-Dimethoxy-7-oxo-6,7-dihydro-5*H*-dibenzo[*a*,*c*-[7] cyclohepten-5-yl)-2,2,2-trifluoroacetamide (6a)

Starting from **8a** (1.8 mmol, 600 mg), **6a** was obtained as a colorless powder (410 mg, 61%); mp 205–206 °C; IR (KBr) λ (cm^{-1}) 3335, 2962, 1725 (CO),1702 (CO), 1518, 1359, 1273, 1215-1183-1167 (CF_3), 1026; ^1H NMR (400 MHz, $CDCl_3$)* δ 7.45 (m, 2H, H1, H2), 7.40 (m, 1H, H3), 7.30 (d, 1H, J_{ortho} = 7.8 Hz, H4), 7.28 (s, 1H, H8), 6.95 (s, 1H, H11), 6.73 (d, 1H, ^3J = 4.4 Hz, NH), 5.46 (m, 1H, H5), 4.01 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 3.22 (m, 2H, H6a,b); ^{13}C NMR (100 MHz, $CDCl_3$)* δ 199.1 (C7), 156.4 (q, ^2J = 38 Hz, $NHCOCF_3$), 153.1 (C10), 149.2 (C9), 137.0 (C11b), 136.5 (C4), 132.0 (C11a), 131.1 (C1), 130.4 (C7a), 129.2 (C2&C4a), 128.6 (C3), 115.4 (q, ^1J = 288 Hz, CF_3), 112.6 (C11), 111.4 (C8), 56.3 (OCH_3), 56.2 (OCH_3), 51.9 (C6), 49.1 (C5); LC–MS t_R = 9.18 min, [ESI^-] m/z $[M-H]^-$ 378; HRESIMS $[M-H]^-$ m/z 378.0938 (calcd for $C_{19}H_{15}F_3NO_4$ 378.0953).

*δ assignments according to 2D experiments (COSY, HMBC).

3.3.2. *N*-(9,10,11-Trimethoxy-7-oxo-6,7-dihydro-5*H*-dibenzo[*a*,*c*][7] cyclohepten-5-yl)-2,2,2-trifluoroacetamide (6b)

Starting from crude **8b**, **6b** was obtained as a colorless solid (103 mg, 11% overall yield from 12b); mp 82–83 °C; IR (KBr) λ (cm^{-1}) 2928, 1713–1682 (CO), 1586, 1336,1163, 1113; ^1H NMR (400 MHz, $(CD_3)_2CO$) δ 9.26 (br s, 1H, NH), 7.47 (m, 4H, H1-4), 6.90 (s, 1H, H8), 5.56 (m, 1H, H5), 3.94 (s, 6H, OCH_3), 3.58 (s, 3H, OCH_3), 3.31 (dd, 1H, ^2J = 17.6 Hz, ^3J = 3.9 Hz, H6a), 3.04 (dd, 1H, ^2J = 17.6 Hz, ^3J = 12.8 Hz, H6b); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 201.4 (C7), 159.6 (q, ^2J = 36 Hz, $NHCOCF_3$), 154.5, 151.9, 146.7, 139.1, 136.1, 132.7, 132.6, 128.9, 128.8, 128.1, 122.8, 116.2 (q, ^1J = 286 Hz, CF_3), 107.4, 61.6 (OCH_3), 61.2 (OCH_3), 56.4 (OCH_3), 53.2 (C6), 48.6 (C5); LC–MS t_R = 6.68 min, [ESI^-] m/z $[M-H]^-$ 408; HREIMS [M^+] m/z 409.11491 (calcd for $C_{20}H_{18}F_3NO_5$ 409.11367).

3.3.3. *N*-(3,9,10-Trimethoxy-7-oxo-6,7-dihydro-5H-dibenzo[*a*,*c*][7] cyclohepten-5-yl)-2,2,2-trifluoroacetamide (6c)

Starting from **8c** (0.46 mmol, 169 mg), **6c** was obtained as a pale yellow solid (100 mg, 53%); mp 178–179 °C; IR (KBr) λ (cm^{-1}) 3315, 2928, 2850, 1722 (CO), 1667 (CO), 1598, 1498, 1273, 1245-1210-1166 (CF_3), 1041; ^1H NMR (400 MHz, $(CD_3)_2CO$) δ 9.22 (br d, 1H, ^3J = 6.8 Hz, NH), 7.48 (d, 1H, J_{ortho} = 8.8 Hz, H1), 7.17 (s, 1H), 7.04 (s, 1H), 6.99 (dd, 1H, J_{ortho} = 8.8 Hz, J_{meta} = 2.9 Hz, H2), 6.94 (d, 1H, J_{meta} = 2.9 Hz, H4), 5.55 (m, 1H, H5), 3.98 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.25 (dd, 1H, ^2J = 18.5 Hz, ^3J = 2.9 Hz, H6a), 3.09 (dd, 1H, ^2J = 18.5 Hz, ^3J = 11.9 Hz, H6b); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 200.3 (C7), 160 (C3), 153.9, 153.7 (q, ^2J = 36 Hz, $NHCOCF_3$), 149.7, 140.5, 132.8, 132.5, 131.2, 129.6, 115.6 (q, ^1J = 288 Hz, CF_3), 113.7, 113.1, 112.1, 109.4, 56.2 (OCH_3), 56.1 (OCH_3), 55.6 (OCH_3), 52.6 (C6), 48.7 (C5); LC–MS t_R = 6.49 min, [ESI^-] m/z $[M-H]^-$ 408; HREIMS [M^+] m/z 409.11502 (calcd for $C_{20}H_{18}F_3NO_5$ 409.11367).

3.3.4. *N*-(3,9,10,11-Tetramethoxy-7-oxo-6,7-dihydro-5*H*-dibenzo [*a*,*c*][7]cyclohepten-5-yl)-2,2,2-trifluoroacetamide (6d)

Starting from **8d** (0.25 mmol, 90 mg), **6d** was obtained as a colorless solid (41 mg, 37%) which was separated from **15** using flash chromatography; mp 90–91 °C; IR (KBr) λ (cm^{-1}) 3430, 2925, 2849, 1727 (CO), 1679 (CO), 1613, 1579, 1485, 1336, 1210-1163-1111 (CF_3), 1088; ^1H NMR (400 MHz, $(CD_3)_2CO$) δ 9.25 (d, ^1H,^3J = 6.8 Hz, NH), 7.41 (d, 1H, J_{ortho} = 8.8 Hz, H1), 6.95 (m, 2H, H2&H4), 6.88 (s, 1H, H8), 5.56 (m, 1H, H5), 3.91 (s, 6H, OCH_3), 3.82 (s, 3H, OCH_3), 3.56 (s, 3H, OCH_3), 3.28 (dd, 1H, ^2J = 17.5 Hz, ^3J = 3.9 Hz, H6a), 3.02 (dd, 1H, ^2J = 17.5 Hz, ^3J = 13.6 Hz, H6b); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 201.5 (C7), 160.4 (C3), 157.1 (q, ^2J = 36 Hz, $HNCOCF_3$), 154.1, 151.8, 146.8, 140.7, 135.9, 134.1, 124.7, 124.5, 117 (q, ^1J = 285 Hz, CF_3), 113.2, 108.7, 107.6, 61.4 (OCH_3), 61.2 (OCH_3), 56.4 (OCH_3), 55.5 (OCH_3), 53.2 (C6), 48.5 (C5); LC–MS t_R = 6.40 min, [ESI^-] m/z $[M-H]^-$ 438; HREIMS [M^+] m/z 439.12413 (calcd for $C_{21}H_{20}F_3NO_6$ 439.12423).

3.3.5. *N*-[4-Methoxy-3-oxo-7-(2,3,4-trimethoxyphenyl)-2,3-dihydro-1H-inden-1-yl]-2,2,2-trifluoroacetamide (15)

Starting from **8d** (90 mg, 0.25 mmol), **15** was obtained as a colorless solid (27 mg, 24%) which was separated from **6d** using flash chroma-tography; mp 210–211 °C; IR (KBr) λ (cm^{-1}) 3295, 2940, 1724 (CO), 1702 (CO), 1486, 1462, 1204-1178-1100 (CF_3), 1090; ^1H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, 1H, J_{ortho} = 8.3 Hz), 7.00 (d, 1H, J_{ortho} = 8.3 Hz), 6.83 (d, 1H, J_{ortho} = 8.3 Hz), 6.72 (d, 1H, J_{ortho} = 8.3 Hz), 5.52 (br s, 1H, NH), 4.05 (m, 1H, H1), 3.99 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 3.66 (s, 3H, OCH_3), 3.19 (dd, 1H, ^2J = 18.5 Hz, ^3J = 7.8 Hz, H2a), 2.52 (dd, 1H, ^2J = 18.5 Hz, ^3J = 3.5 Hz, H2b);^{13}C NMR (100 MHz, $CDCl_3$) δ 200.4 (C3), 156.4 (q, $^2J_{CF}$ = 37 Hz,$NHCOCF_3$), 157.2, 154.1, 151.4, 150.4, 142.4, 138.7, 128.9, 124.8, 124.3, 124.2, 115.3 (q, $^1J_{CF}$ = 286 Hz, CF_3), 111.6, 107.9, 61.2 (OCH_3), 60.8 (OCH_3), 56.1 (OCH_3), 56.0 (OCH_3), 47.0, 44.7; LC–MS t_R = 6.07 min, [ESI^-] m/z $[M-H]^-$ 438; HREIMS m/z [M^+] 439.12638 (calcd for $C_{21}H_{20}F_3NO_6$ 439.12423).

3.3.6. *N*-(3-Hydroxy-9,10-dimethoxy-7-oxo-6,7-dihydro-5*H*-dibenzo[*a*,*c*][7]cyclohepten-5-yl)-2,2,2-trifluoroacetamide (6e)

Starting from **8e** (0.25 mmol, 80 mg), **6e** was obtained as a colorless solid (50 mg, 50%); mp 226–227 °C; IR (KBr) λ (cm^{-1}) 2924, 1727–1706 (CO), 1641, 1618, 1496, 1360, 1275, 1210, 1169; ^{1}H NMR (400 MHz, $(CD_3)_2CO$)* δ 9.22 (d, 1H, ^3J = 7.5 Hz, NH), 8.83 (s, 1H, OH), 7.39 (d, 1H, J_{ortho} = 8.8 Hz, H1), 7.18 (s, 1H, H8), 7.02 (s, 1H, H11), 6.90 (m, 2H, H2&H4), 5.50 (m, 1H, H5), 3.99 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 3.25 (dd, 1H, ^2J = 18.6 Hz, ^3J = 11.7 Hz, H6a), 3.10 (dd, 1H, ^2J = 18.6 Hz, ^3J = 2.9 Hz, H6b); ^{13}C NMR (100 M Hz, $(CD_3)_2CO$)* δ 200.4 (C7), 158.4 (C3), 156.1 (q, ^2J = 38 Hz, $NHCOCF_3$), 153.8 (C10), 149.5 (C9), 140.6 (C4a), 132.9 (C11a), 132.8 (C1), 131.0 (C7a), 128.5 (C11b), 116.2 (q, ^1J = 285 Hz, CF_3), 115.9 (C4), 113.1 (C11), 112.0 (C8), 110.1 (C2), 56.2 (OCH_3), 56.1 (OCH_3), 52.6 (C6), 48.7 (C5); LC–MS t_R = 5.84 min, [ESI$^-$] *m*/*z* 394 [M−H]$^-$; HREIMS [M$^+$] *m*/*z* 395.09889 (calcd for $C_{19}H_{16}F_3NO_5$ 395.09802).

*δ assignments according to 2D experiments (COSY, HMBC).

3.3.7. *N*-(3-Hydroxy-9,10,11-trimethoxy-7-oxo-6,7-dihydro-5*H*-dibenzo[*a*,*c*][7]cyclohepten-5-yl)-2,2,2-trifluoroacetamide (6f)

Starting from **8f** (0.29 mmol, 100 mg) **6f** was obtained as a colorless solid (57 mg, 46%); mp 122–123 °C; IR (KBr) λ (cm^{-1}) 2938, 1713 (CO), 1678 (CO), 1585, 1487, 1336, 1212-1163-1110 (CF_3), 999; ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 9.21 (br s 1H, NH), 8.70 (s, 1H, OH), 7.30 (d, 1H, J_{ortho} = 7.8 Hz, H1), 6.86 (m, 3H, H2, H4&H8), 5.52 (m, 1H, H5), 3.90 (s, 6H, OCH_3), 3.54 (s, 3H, OCH_3), 3.24 (dd, 1H, ^2J = 18.5 Hz, ^3J = 3.9 Hz, H6a), 3.01 (dd, 1H, ^2J = 18.5 Hz, ^3J = 13.6 Hz, H6b); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 201.6 (C7), 158.3, 157.1 (q, ^2J = 36 Hz, $HNCOCF_3$), 153.9, 151.9, 146.7, 140.7, 135.9, 134.1, 125.1, 123.3, 116.7 (q, ^1J = 286 Hz, CF_3), 115.2, 109.6, 107.5 (C8), 61.3 (OCH_3), 61.2 (OCH_3), 56.4 (OCH_3), 53.1 (C6), 48.6 (C5); LC–MS t_R = 6.08 min, [ESI$^-$] *m*/*z* 424 [M−H]$^-$; HRESIMS [M+H]$^+$ *m*/*z* 426.1153 (calcd for $C_{20}H_{19}F_3NO_6$ 426.1164).

3.4. General procedure for the synthesis of dibenzocycloheptenols (7a–f)

$NaBH_4$ (2 equiv) was added portion-wise to a solution of the dibenzocycloheptenones (**6a**–**f**) in MeOH (15 mL). The reaction mixture was then stirred for 2 h at room temperature before the solvent was removed under vacuum; addition of water led to the expected alcohols **7a**–**f** which were isolated by filtration and purified by recrystallization.

3.4.1. *N*-(7-Hydroxy-9,10-dimethoxy-6,7-dihydro-5*H*-dibenzo[*a*,*c*] [7]-cyclohepten-5-yl)-2,2,2-trifluoroacetamide (7a)

Starting from **6a** (0.37 mmol, 140 mg), **7a** (*cis* + *trans* diastereoisomers) was obtained as a colorless solid (120 mg, 85%); recrystallization from Et_2O gave the (+/−) *trans* diastereoisomers; mp 240–241 °C; IR (KBr) λ (cm^{-1}) 3547, 3297, 1707 (CO), 1566, 1506, 1217-1187-1142 (CF_3), 1023; ^{1}H NMR (400 MHz, DMSO-d_6)* δ 10.02 (d, 1H, ^3J = 7.8 Hz, NH), 7.37 (m, 3H, H1, H2&H3), 7.23 (m, 2H, H4,H8), 6.98 (s, 1H, H11), 5.47 (d, 1H, ^3J = 3.9 Hz, OH), 4.57 (m, 1H, H5), 4.20 (m, 1H, H7), 3.82 (s, 6H, OCH_3), 2.65 (td, 1H, ^2J = 12.1 Hz, ^3J = 7.3 Hz, H6a), 2.08 (td, 1H, ^2J = 11.7 Hz, ^3J = 7.3 Hz, H6b); ^{13}C NMR (100 MHz, DMSO-d_6)* δ 155.6 (q, ^2J = 36 Hz, $HNCOCF_3$), 148.6 (C9), 147.7 (C10), 137.9 (C4a), 137.4 (C11b), 134.4 (C7a), 128.2 (C1), 127.5 (C11a,C2), 127.4 (C3), 122.4 (C4), 115.9 (q, ^1J = 288 Hz, CF_3), 111.8 (C11), 107.3 (C8), 66.5 (C7), 55.7 (OCH_3), 55.5 (OCH_3), 48.4 (C5), 47.0 (C6); LC–MS t_R = 8.53 min, [ESI$^-$] *m*/*z* 380 [M−H]$^-$; HREIMS [M$^+$] *m*/*z* 381.11794 (calcd for $C_{19}H_{18}F_3NO_4$ 381.11876).

* The *trans* configuration was established on the basis of 2D NMR homonuclear (COSY) and heteronuclear (HSQC, HMBC) data, completed by 1D NOESY experiments using selective refocusing with a shaped pulse to observe dipolar coupling due to NOE with the irradiated peaks.

3.4.2. *N*-(7-Hydroxy-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo [*a*,*c*][7]-cyclohepten-5-yl)-2,2,2-trifluoroacetamide (7b)

Starting from **6b** (0.067 mmol, 28 mg), **7b** was obtained as a colorless solid (16 mg, 58%); mp 98–99 °C; IR (KBr) λ (cm^{-1}) 2923, 2849, 1712 (CO), 1599, 1485, 1404, 1329, 1215-1191-1145 (CF_3), 1077, 1004; ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ* 9.04 (brs, 1H, NH), 7.41 (m, 4H, H1-4), 7.18 (s, 1H, H8), 4.79 (m, 1H, H5), 4.57 (d, 1H, ^3J = 4.9 Hz, OH), 4.32 (m, 1H, H7), 3.90 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.53 (s, 3H, OCH_3), 2.64 (td, 1H, ^2J = 11.7 Hz, ^3J = 6.8 Hz, H6a), 2.22 (td,1H, ^2J = 11.7 Hz, ^3J = 6.8 Hz, H6b); ^{13}C NMR (100 MHz, $(CD_3)_2CO$)* δ 157.0 (q, ^2J = 36 Hz, $HNCOCF_3$), 154.3, 151.4, 142.3, 139.5, 139.1, 134.1, 131.0, 128.5, 128.3, 127.5, 122.8, 117.0 (q, ^1J = 285 Hz, CF3), 103.9, 68.3 (C7), 61.1 (OCH_3), 61.0 (OCH_3), 56.2 (OCH_3), 49.7 (C6), 47.5 (C5); LC–MS t_R = 6.25 min, [ESI$^-$] *m*/*z* 410 [M−H]$^-$; HREIMS [M$^+$] *m*/*z* 411.13031 (calcd for $C_{20}H_{20}F_3NO_5$ 411.12932).

***7b** is a mixture of 2 diastereoisomers (85% *trans*, 15% *cis*); only *trans* isomer NMR signals are described here.

3.4.3. *N*-(7-Hydroxy-3,9,10-trimethoxy-6,7-dihydro-5*H*-dibenzo [*a*,*c*][7]-cyclohepten-5-yl)-2,2,2-trifluoroacetamide (7c)

Starting from **6c** (0.06 mmol, 25 mg), **7c** was obtained as a colorless powder (17 mg, 68%); mp 246–247 °C; IR (KBr) λ (cm^{-1}) 3255, 3078, 2931, 1729 (CO), 1611, 1493, 1242, 1211-1178-1143 (CF_3), 1042; ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ∗ 9.03 (d, 1H, ^3J = 7.8 Hz, NH), 7.35 (d, 1H, J_{ortho} = 8.8 Hz, H1), 6.98 (m, 4H), 4.81 (m, 1H, H5), 4.56 (d, 1H, ^3J = 4.9 Hz, OH), 4.45 (m, 1H, H7), 3.89 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 2.73 (td, 1H, ^2J = 11.7 Hz, ^3J = 6.8 Hz, H6a), 2.33 (td, 1H, ^2J = 11.7 Hz, ^3J = 6.8 Hz, H6b); ^{13}C NMR (100 MHz, $(CD_3)_2CO$)* δ 160.1 (C3), 159.2 (q, ^2J = 36 Hz, $HNCOCF_3$) 149.9, 149.3, 140.4, 135.1, 131.1, 130.3 (C1), 128.8, 116.2 (q, ^1J = 286 Hz, CF_3),112.9, 112.8, 109.9, 108.4, 68.2 (C7), 56.3 (2C, OCH_3), 55.5 (OCH_3), 49.8 (C6), 48.3 (C5); LC–MS t_R = 6.09 min, [ESI$^-$] *m*/*z* 410 [M−H]$^-$; HRESIMS [M−H]$^-$ *m*/*z* 410.1201 (calcd for $C_{20}H_{19}F_3NO_5$ 410.1215).

***7c** is a mixture of 2 diastereoisomers (65% *trans*, 35% *cis*); only *trans* isomer NMR signals are described here.

3.4.4. *N*-(7-Hydroxy-3,9,10,11-tetramethoxy-6,7-dihydro-5*H*-dibenzo[*a*,*c*][7]cyclohepten-5-yl)-2,2,2-trifluoroacetamide (7d)

Starting from **6d** (0.045 mmol, 20 mg), **7d** was obtained as a colorless solid (13 mg, 65%); mp 190–191 °C; IR (KBr) λ (cm^{-1}) 2928, 2852, 1706, 1610, 1485, 1458, 1236-1189-1152 (CF_3), 1073; ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ* 8.91 (d, 1H, ^3J = 7.8 Hz NH), 7.24 (d, 1H, J_{ortho} = 7.8 Hz, H1), 7.04 (s, 1H, H8), 6.80 (m, 2H, H2&H4), 4.64 (td, 1H, ^2J = 11.7, ^3J = 7.8, H5), 4.44 (d, 1H, ^3J = 3.9 Hz, OH), 4.21 (m, 1H, H7), 3.77 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 2.51 (td, 1H, ^2J = 11.7 Hz, ^3J = 6.8 Hz, H6a), 2.08 (td, 1H, ^2J = 11.7 Hz, ^3J = 6.8 Hz, H6b); ^{13}C NMR (100 MHz, $(CD_3)_2CO$)* δ 160.1 (C3), 157.2 (q, ^2J = 38 Hz, $NHCOCF_3$), 154.1 (C10), 151.5 (C9), 142.3, 141.1, 139.0, 132.2 (C1), 126.2, 122.2, 115.8 (q, ^1J = 288 Hz, CF_3), 112.3 (C2), 109.2 (C4), 103.9 (C8), 68.4 (C7), 61.0 (2C, OCH_3), 56.2 (OCH_3), 55.4 (OCH_3), 49.8 (C6), 47.4 (C5); LC–MS t_R = 6.34 min, [ESI$^-$] *m*/*z* 440 [M−H]$^-$; HREIMS [M$^+$] *m*/*z* 441.13934 (calcd for $C_{21}H_{22}F_3NO_6$ 441.13988).

***7d** is a mixture of 2 diastereoisomers (90% *trans*, 10% *cis*); only *trans* isomer NMR signals are described here.

3.4.5. *N*-(3,7-Dihydroxy-9,10-dimethoxy-6,7-dihydro-5*H*-dibenzo[*a*,*c*][7]-cyclohepten-5-yl)-2,2,2-trifluoroacetamide (7e)

Starting from **6e** (20 mg, 0.05 mmol) **7e** was obtained as a colorless powder (13 mg, 65%); mp >260 °C; IR (KBr) λ (cm^{-1}) 3291, 2933, 1727, 1618, 1588, 1493, 1217-1191-1141 (CF_3), 1052, 1025; ^1H NMR (400 MHz, $(CD_3)_2CO$) δ* 9.00 (d, 1H, $^3J = 6.8$ Hz, NH), 8.63 (s, 1H, C3-OH), 7.31 (s, 1H, H8), 7.23 (d, 1H, $J_{ortho} = 7.8$ Hz, H1), 6.94 (s, 1H, H11), 6.88 (d, 1H, $J_{meta} = 2.9$ Hz, H4), 6.84 (dd, 1H, $J_{ortho} = 7.8$ Hz, $J_{meta} = 2.9$ Hz, H2), 4.76 (m, 1H, H5), 4.56 (d, 1H, $^3J = 4.9$ Hz, OH), 4.46 (m, 1H, H7), 3.87 (s, 6H, OCH_3), 2.72 (td, 1H, $^2J = 11.7$ Hz, $^3J = 6.8$ Hz, H6a), 2.29 (td, 1H, $^2J = 11.7$ Hz, $^3J = 6.8$ Hz, H6b); ^{13}C NMR (100 M Hz, $(CD_3)_2CO$) δ 158.0 (C3), 150.0 (C10), 149.7 (q, $^2J = 36$ Hz, $NHCOCF_3$), 149.6 (C9), 140.6, 135.4, 130.4 (C1), 130.1, 129.5, 115.6 (q, $^1J = 286$ Hz, CF_3), 115.1, 113.3, 110.9, 108.9 (C8), 68.3 (C7), 56.5 (OCH_3), 56.4 (OCH_3), 49.9 (C6), 48.5 (C5); LC–MS $t_R = 5.38$ min, [ESI^-] m/z 396 $[M-H]^-$; HREIMS [M^+] m/z 397.11267 (calcd for $C_{19}H_{18}F_3NO_5$ 397.11367).

***7e** is a mixture of 2 diastereoisomers (85% *trans*, 15% *cis*); only *trans* isomer NMR signals are described here.

3.4.6. *N*-(3,7-Dihydroxy-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a*,*c*][7]cyclohepten-5-yl)-2,2,2-trifluoroacetamide (7f)

Starting from **6f** (0.047 mmol, 20 mg) **7f** was obtained as a colorless solid (10 mg, 50%); mp >260 °C; IR (KBr) λ (cm^{-1}) 2931, 1725 (CO), 1586, 1485, 1401, 1337, 1220-1184-1143 (CF_3), 1067; ^1H NMR (400 MHz, $(CD_3)_2CO$) δ* 8.96 (br s, 1H, NH), 8.56 (s, 1H, OH), 7.26 (d, 1H, $J_{ortho} = 8.8$ Hz, H1), 7.15 (s, 1H, H8), 6.84 (m, 2H, H2,H4), 4.72 (m, 1H, H5), 4.53 (d, 1H, $^3J = 3.9$ Hz, OH), 4.35 (m, 1H, H7), 3.88 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.51 (s, 3H, OCH_3), 2.63 (m, 1H, H6a), 2.18 (m, 1H, H6b); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 157.8 (C3), 153.9 (q, $^2J = 38$ Hz, $NHCOCF_3$), 153.8, 151.4, 141.0, 138.9, 133.3, 132.2 (C1), 124.9, 122.3, 114.7 (q, $^1J = 282$ Hz, CF_3), 114.4 (C2), 110.1 (C4), 103.9 (C8), 68.4 (C7), 61.0 (OCH_3), 60.9 (OCH_3), 56.2 (OCH_3), 49.8 (C6), 47.4 (C5); LC–MS $t_R = 5.63$ min, [ESI^-] m/z 426 $[M-H]^-$; HRESIMS $[M+H]^+$ m/z 428.1309 (calcd for $C_{20}H_{21}F_3NO_6$ 428.1321).

***7f** is a mixture of 2 diastereoisomers (85% *trans*, 15% *cis*); only *trans* isomer NMR signals are described here.

4. Cristallographic study

Single crystals of **7a** suitable for X-ray crystallographic analysis were obtained by slow diffusion from diethyl ether solution. X-ray diffraction experiment for monocrystal of **7a** was performed with graphite–monochromatized Mo K_α radiation on a Bruker–Nonius Kappa CCD area detector diffractometer at 296 K. The data treatment was carried out with APEX II program.[32] The crystal structure was solved by direct methods using SHELXTL package[33] and refined using SHELX97.[34] All non-hydrogen atoms were refined anisotropically. Positions of all H-atoms, which were placed geometrically, were fixed during refinement.

Crystallographic data of **7a**: Crystal size: 0.35 × 0.21 × 0.18 mm. Formula $C_{19}H_{18}F_3NO_4$, formula weight 381.34, crystal system monoclinic, space group $P\ 21/n$, $a = 9.013(3)$ Å, $b = 11.993(4)$ Å, $c = 17.706\ (7)$ Å, $\alpha = 90°$, $\beta = 102.325\ (14)°$, $\gamma = 90°$, $V = 1869.7$ (11) Å3, $Z = 4$, calculated density = 1.355 g/cm^3, $\mu = 0.114\ mm^{-1}$, Rint = 0.0631, $R[F2 > 2\sigma(F2)] = 0.0631$, $wR(F2) = 0.1385$.

5. Cell culture and proliferation assay

The human epidermoid carcinoma KB cell lines were obtained from ECACC (Salisbury, UK) and grown in D-MEM medium supplemented with 10% fetal calf serum (Invitrogen), in the presence of penicilline, streptomycine and fungizone in 75 cm^3 flask under 5% CO_2. Cells were plated in 96-well tissue culture microplates at a density of 650 cells/well in 200 µl medium and treated 24 h later with compounds dissolved in DMSO with compound concentrations ranged 0.5–10 µM using a Biomek 3000 automate (Beckman). Controls received the same volume of DMSO (1% final volume). After 72 h exposure MTS reagent (Promega) was added and incubated for 3 h at 37 °C: the absorbance was monitored at 490 nm and results expressed as the inhibition of cell proliferation calculated as the ratio [(OD490 treated/OD490 control)×100]. For IC_{50} determinations (50% inhibition of cell proliferation) experiments were performed in separate duplicate.

6. Tubulin polymerization inhibition

Sheep brain microtubule proteins were purified by two cycles of assembly /disassembly at 37 °C/0 °C in MES buffer: 100 mM MES (2-[*N*-morpholino]ethane sulfonic acid, pH 6.6), 1 mM EGTA (ethyleneglycolbis[ß-aminoethyl ether]-*N*,*N*,*N*′,N′-tetracetic acid), 0.5 mM $MgCl_2$. All samples were dissolved in DMSO. Basically, inhibition of tubulin polymerization was conducted as initially described in[35] the evaluated compound (1 µL) was added to microtubule solution (150 µL) and incubated for 10 min at 37 °C followed by 5 min at 0 °C. The tubulin polymerization rate was measured by turbidimetry at 350 nm using deoxypodophyllotoxin (DPPT) as reference compound. Compounds were first tested at 6.7 10^{-5} M and results were given as the percentage of inhibition for the less active compounds. Compounds showing higher activities were then tested at concentrations ranged 33–2 µM to determine their IC_{50}.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2012.02.043.

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