European Journal of Medicinal Chemistry 45 (2010) 5428–5437

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

Synthesis and biological activities of new furo[3,4-*b*]carbazoles: Potential topoisomerase II inhibitors

Youssef Hajbi [a], Cléopatra Neagoie [a,b], Bérenger Biannic [a], Aurélie Chilloux [a], Emeline Vedrenne [a], Brigitte Baldeyrou [c], Christian Bailly [c], Jean-Yves Mérour [a], Sorin Rosca [b], Sylvain Routier [a,*], Amélie Lansiaux [c,**]

[a] *Institut de Chimie Organique et Analytique, Université d'Orléans, CNRS UMR 6005, B.P. 6759, 45067 Orléans Cedex 2, France*
[b] *Universitatea Politehnica, 313, Splaiul Independentei, 77206 Bucuresti, Romania*
[c] *INSERM U-837, Centre Oscar Lambret, Université Lille Nord de France, Faculté de Médecine de Lille, IRCL, 59045 Lille, France*

ARTICLE INFO

Article history:
Received 4 June 2010
Received in revised form
27 August 2010
Accepted 1 September 2010
Available online 15 September 2010

Keywords:
Carbazoles
Synthesis
Azatoxin
Microwave
Topoisomérase II
Inhibition cytotoxicity

ABSTRACT

New 1,5-Dihydro-4-(substituted phenyl)-3*H*-furo[3,4-*b*]carbazol-3-ones were synthesised via a key step Diels–Alder reaction under microwave irradiation. 3-Formylindole was successfully used in a 6-step synthesis to obtain those complex heterocycles. The Diels–Alder reaction generating the carbazole ring was optimised under thermal conditions or microwave irradiation. After cleavage of functional groups, DNA binding, topoisomerase inhibition and cytotoxic properties of the new-formed furocarbazoles were investigated. These carbazoles do not present a strong interaction with the DNA, and do not modify the relaxation of the DNA in the presence of topoisomerase I or II except for one promising compound. This compound is a potent topoisomerase II inhibitor, and its cellular activity is not moderated compared to etoposide. The synthesis of these molecules allowed the generalisation of the method using indole and 5-OBn indole and several benzaldehydes. The synthesis of these molecules produced chemical structures endowed with promising cytotoxic and topoisomerase II inhibition activities.

1. Introduction

Lignans are natural products which can be isolated from a wide range of plants. The synthesis of such scaffolds is important as they exhibit great antiviral activities [1]. Some of them proved to be promising tools for the fight against cancer: podophyllotoxin and its glycosylated analogues etoposide and teniposide, for instance, are pro-apoptotic drugs strongly inhibiting tubulin polymerisation and topoisomerase II [2–4].

This enzyme has raised considerable attention due to its crucial role in the cell cycle and DNA replication. A lot of well-known compounds, such as mitoxantrone, inhibit its activity, but drug resistance prompted chemists to design new inhibitors by exchanging the quinonic chromophore for another. In lignans chemical series, naphthalenic analogues such as **I**, where the non-aromatic central ring was suppressed, were developed; they exhibit a good activity against the topoisomerase II (Fig. 1) [7].

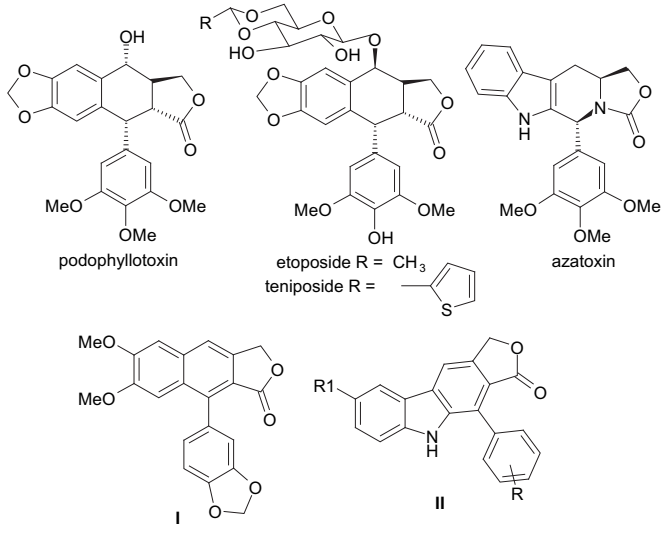


Fig. 1. The most representative lignans and derivatives.

* Corresponding author. Tel.: +33 238 49 48 53; fax: +33 238 41 72 81.
** Corresponding author. Tel.: +33 320 29 59 53; fax: +33 320 16 92 29.
E-mail addresses: sylvain.routier@univ-orleans.fr (S. Routier), a-lansiaux@o-lambret.fr (A. Lansiaux).

0223-5234/$ – see front matter © 2010 Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.ejmech.2010.09.003

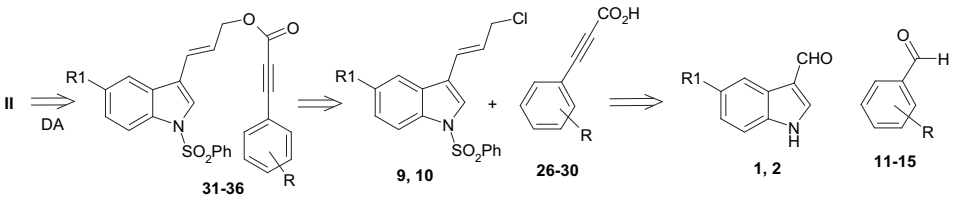


Fig. 2. Retrosynthetic scheme.

Azatoxin, an indolic heterolignan, has also proved to be a good topoisomerase II inhibitor [5,6]. Based on our interests in designing indolocarbazole analogues as topoisomerase I inhibitors, we aimed to develop new DNA topoisomerase II inhibitors [8]. We thought that the frameworks of azatoxin and compound of type **I** could be combined to generate tetrahydrofuro[3,4-*b*] carbazole such as **II**, in which the indole ring is fused to the aromatic central ring.

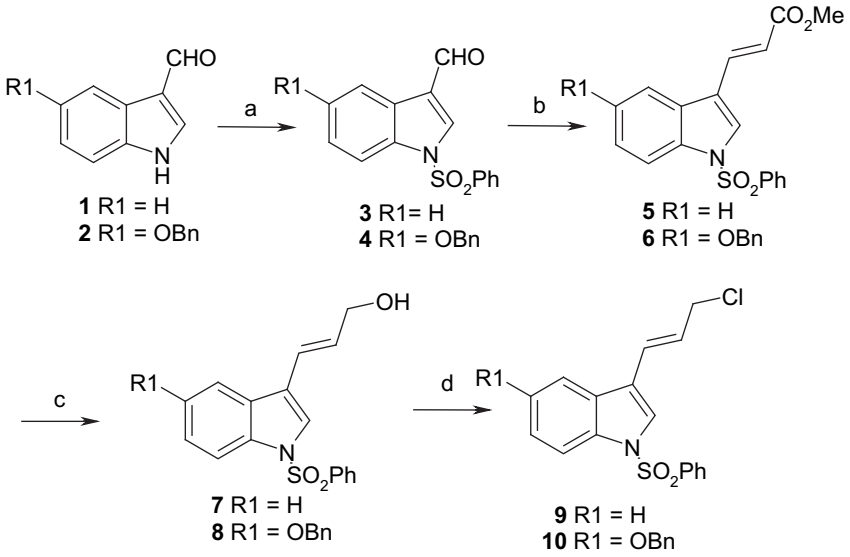
We hoped that this structure could result from an intramolecular Diels–Alder reaction (DA, Fig. 2) [9]. Precursors **31**–**36** could be obtained from indolic chloro derivatives (R = Cl) and alkynes **26**–**30**. Therefore, indoles **1**–**2** and benzaldehydes **11**–**15** constituted the starting materials. The first issue was the choice of an appropriate indolic protecting group. As the target **II** exhibits a base-sensitive lactone, synthesis involving a Boc group or even better, no protecting group was first envisaged.

Unfortunately, the synthesis of indoles **IV** without any protecting group failed in our work, and the Boc group was prematurely released during the synthetic pathway. These results prompted us to use the robust benzenesulphonyl group. The first studies were realised with 3-formylindole and 2,4,5-trimethoxybenzaldehyde. Herein, we present the results of our method applied to indole reacting with a wide range of benzaldehydes. Results obtained with 5-OBn indole **2** are also discussed.

2. Chemistry

2.1. Preparation of the indolic skeletons type *IV*

3-Formylindole **1** and 3-formyl-5-benzyloxyindole **2** [10] were first protected with a benzenesulphonyl group using benzenesulphonyl chloride (1.2 eq.) in the presence of $BnEt_3N^+Cl^-$ and NaOH. The protection of **1** was carried out at room temperature, whereas reflux conditions were necessary for indole **2**: compounds **3** [11] and **4** were both obtained in good yield (Scheme 1).



Scheme 1. (a) $BnEt_3N^+$, Cl^- (cat.), NaOH (3.0 eq.), $PhSO_2Cl$ (1.2 eq.), CH_2Cl_2, r.t., 2 h, from **1**: 0 °C to r.t., **3** 84%, from **2**: 0 °C to reflux, **4** 81%; (b) $PPh_3 = CHCOOCH_3$ (3 eq.), toluene, reflux, 12 h, from **3**: 5 98%, from **4**: 6 93%; (c) DibalH (2.5 eq.), toluene, 0 °C to r.t., from **5**: 2 h, **7** quant., from **6**: 2 h 30, **8** quant.; (d) $SOCl_2$ (1.9 eq.), benzotriazole (1.9 eq.), CH_2Cl_2, r.t., 15 min., from **7**: **9** quant, from **8**: **10** quant.

A Wittig reaction was next performed in toluene under reflux conditions using a slight excess of (carbethoxymethylene) triphenylphosphorane (3.0 eq.) to give compounds **5** [12] and **6** in 98 and 93% yields respectively. The ester moieties were then reduced with DibalH, affording alcohols **7** and **8** in quantitative yields [13]. Chlorination was then realised using thionyl chloride in the presence of benzotriazole, quantitatively affording compounds **9** and **10** [14].

2.2. Preparation of the propynoic acids type *V*

We then focused our efforts on the Corey–Fuchs alkyne methodology [15]. Benzaldehydes **10**–**15** were treated with PPh_3 and CBr_4 to afford geminated dibromo alkenes **16**–**20** in very good

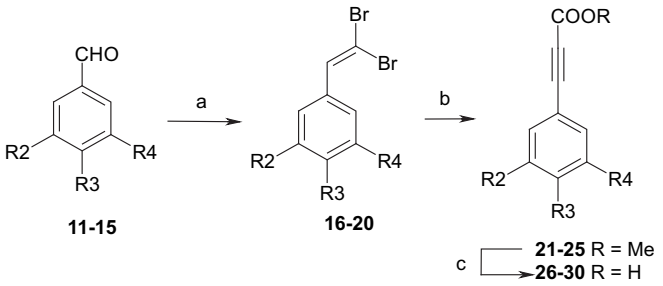
yields (Table 1, entries 1–5, Scheme 2). The triple bond formation was then obtained via a twofold elimination using *n*-BuLi at −78 °C. The lithium acetylide intermediates were quenched *in situ* with methyl chloroformate at the same temperature, leading to methyl esters **21**–**25** in excellent yields (entries 6–10).

These esters were then saponified, yielding propiolic acids **26**–**30** (entries 11–15). Reactions were achieved using LiOH at r.t. in a mixture of THF/MeOH/H_2O. Starting materials **21**–**25** completely disappeared after 1 h. HCl (1 N) was then slowly added at 0 °C to reach pH = 4. The desired carboxylic acids were isolated, without any difficulty, in nearly quantitative yields. Acids **26**–**30** were thus obtained from aldehydes **11**–**15** through a three-step sequence in overall yields of 67–89%. This pathway proved to be highly efficient as reactions could be performed in a multigram-scale with similar yields.

Table 1
Preparation of **16**–**30**.

Entry	Compounds	R^2	R^3	R^4	R	Product	Yield (%)
1	**11**	H	OMe	H	–	**16**	94 [16]
2	**12**	OMe	H	OMe	–	**17**	88 [17]
3	**13**	H	OMe	OMe	–	**18**	89 [18]
4	**14**	H	$-OCH_2O-$		–	**19**	82 [18]
5	**15**	OMe	H	OMe	–	**20**	95 [19]
6	**16**	H	OMe	H	Me	**21**	83 [20]
7	**17**	OMe	H	OMe	Me	**22**	85
8	**18**	H	OMe	OMe	Me	**23**	88 [21]
9	**19**	H	$-OCH_2O-$		Me	**24**	87 [22]
10	**20**	OMe	OMe	OMe	Me	**25**	96 [23]
11	**21**	H	OMe	H	H	**26**	95, 74[a] [24]
12	**22**	H	H	OMe	H	**27**	98, 73[a]
13	**23**	H	OMe	OMe	H	**28**	97, 76[a] [22]
14	**24**	H	$-OCH_2O-$		H	**29**	95, 67[a] [25]
15	**25**	OMe	OMe	OMe	H	**30**	98, 89[a] [26]

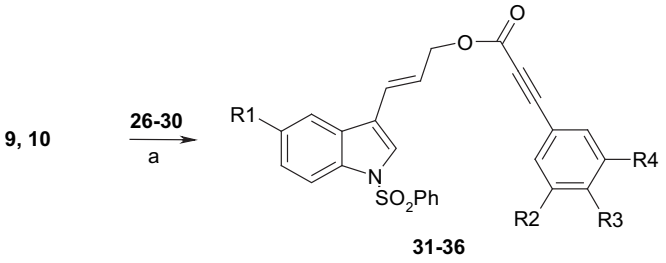
[a] Overall yield calculated from aldehydes **11**–**15**.



Scheme 2. For substitutions and yields see also Table 1. (a) PPh_3 (3.0 eq.), CBr_4 (1.5 eq.), CH_2Cl_2, 0 °C, 1 h then **11**–**15**, r.t. 2 h; (b) *n*-BuLi (2.2 eq.), THF, −78 °C, 1 h then $ClCO_2Me$ (1.2 eq.), −78 °C, 1 h; (c) LiOH (1.4 eq.), r.t., 1 h then HCl (1 N), 0 °C, 1 h.

2.3. Preparation of the esters of type *III*

The subsequent step involved a nucleophilic reaction between chlorinated compounds **9** and **10** and the sodium salts of acids **26**–**30** (Scheme 3). These reactions were performed in the dark using $NaHCO_3$ in dry DMF, and appeared to be very sluggish. After 48 h, rapid neutralisation, extraction and purification afforded compounds **31**–**36** in good yields (Table 2, entries 1–6). Unfortunately, compound **36** proved to be too unstable to be fully characterised.



Scheme 3. For substitutions and yields see Table 2. (a) $NaHCO_3$ (1.5 eq.), DMF, 48 h, r.t., 26–30 (1.5 eq.).

Table 2
Preparation of **31**–**36**.

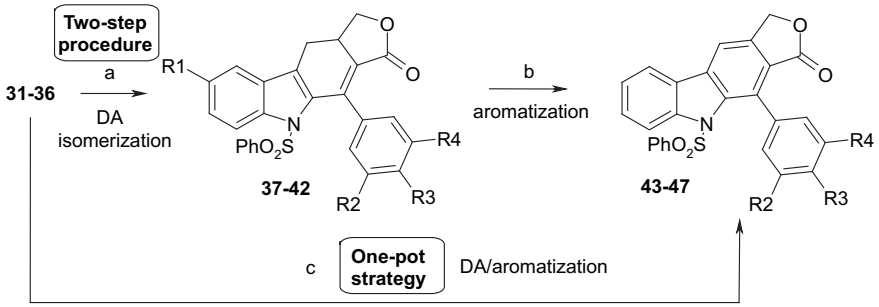
Entry			Compounds		R^1	R^2	R^3	R^4
							Product	Yield[a] (%)
1	**9**	**26**	H	H	OMe	H	**31**	80
2	**9**	**27**	H	OMe	H	OMe	**32**	74
3	**9**	**28**	H	H	OMe	OMe	**33**	85
4	**9**	**29**	H	H	$-OCH_2O-$		**34**	81
5	**9**	**30**	H	OMe	OMe	OMe	**35**	98
6	**10**	**27**	OBn	OMe	H	OMe	**36**	71

[a] Yields are given for isolated products.

2.4. Synthesis of 4-phenyl-3H-furo[3,4-b]carbazoles *II*

2.4.1. DA and aromatisation steps

The DA reactions were first carried out under thermal conditions in a sealed tube protected from light and under inert atmosphere (Scheme 4) to provide the cycloadducts **37**–**41** in moderate yields. Alternatively, the electrocyclisation was realised under microwave irradiation at 150 °C for 2 h 30. After precipitation, the desired compounds **37**–**41** were isolated in good to quantitative yields (Table 3, entries 1–5). The NMR data of **37**–**41** showed that isomerisation of the new double bonds occurred, allowing the formation of the indole core. Despite our efforts, we were unable to obtain compound **42**.



Scheme 4. For substitutions and yields see Table 3. (a) Toluene, MW, 150 °C, 2 h 30; (b) Toluene, sealed tube, 150 °C, MW, *o*-chloranil (2.0 eq.), 1 h 30; (c) one-pot reaction: (i) toluene, MW, 150 °C 1 h, (ii) *o*-chloranil (2.5 eq.), MW, 150 °C, 35 min.

Table 3
Preparation of **43**–**47** via the two-step procedure.

Entry	Compounds	R^1	R^2	R^3	R^4	DA product (Yield (%))[a]	Arom. product (Yield (%))[a]
1	**31**	H	H	OMe	H	**37** (81)	**43** (76, 81[b])
2	**32**	H	OMe	H	OMe	**38** (74)	**44** (77)
3	**33**	H	H	OMe	OMe	**39** (87)	**45** (70)
4	**34**	H	H	$-OCH_2O-$		**40** (70%)	**46** (66)
5	**35**	H	OMe	OMe	OMe	**41** (99)	**47** (75)
6	**36**	OBn	OMe	H	OMe	**42** (–)	(–)

[a] Yields are given for isolated products.
[b] By heating in toluene 24 h.

Cycloadducts **37**–**41** (entries 1–5) were then aromatised in refluxing toluene using *o*-chloranil. Starting from **37**, the reaction afforded the cyclised furocarbazole **43** in 81% yield but yields dropped with **32**–**35**. Aromatisation was thus performed under microwave irradiation for 1 h 30 and the furocarbazoles **43**–**46** were isolated in 66–77% yield (entries 1–5). As an alternative, we realised a one-pot electrocyclisation–aromatisation step under microwave irradiation starting from **31** to **35**, without isolating intermediates **37**–**41** (Table 4). Brief optimisation of the conditions afforded the fully aromatised compounds **43**–**47** after 1 h 35 in pretty good yields (entries 1–5). Compound **46** was obtained in only 26% yield, as its purification remained problematic.

Table 4
Preparation of **43**–**47** via the one-pot strategy.

Entry	Compounds	R^1	R^2	R^3	R^4	Product	Yield[a] (%)
1	**31**	H	H	OMe		**43**	88
2	**32**	H	OMe		OMe	**44**	70
3	**33**	H	H	OMe	OMe	**45**	75
4	**34**	H	H	$-OCH_2O-$		**46**	26
5	**35**	H	OMe	OMe	OMe	**47**	95

[a] Yields are given for isolated products.

2.4.2. Cleavage of benzenesulphonyl groups

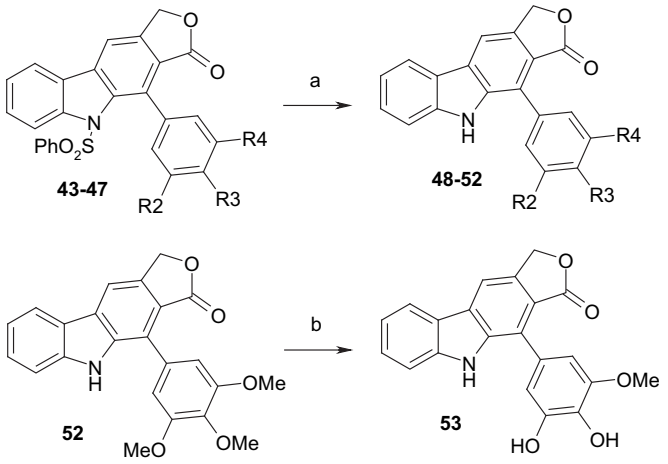
Benzenesulphonyl groups were cleaved using a 6% Hg/Na amalgam in the presence of a large excess of Na_2HPO_4 at −78 °C (Table 5, entries 1–5). After 1 h, the reaction mixtures were allowed to reach −50 °C for 30 min to finally give the desired compounds **48**–**52** in good yields [27]. As an alternative, treatment of **43**–**47** with a Bu_4NF solution in toluene at 100 °C for 1 h led to the same derivatives **48**–**52** in similar yields [28] (Scheme 5).

In order to mime the etoposide pendular aromatic ring, we tried the demethylation of the R^3 methyl ether group but each assay failed. Demethylation of the 3,4,5-trimethoxy derivative **52** (entry 6) was only performed using an equimolar amount of BBr_3 at room temperature to afford a mixture of demethylated compounds. When the reaction was carried out at −78 °C, a double demethylation of hydroxy groups occurred, yielding **53** in an amount of 55% (Table 5).

Table 5

Entry	Compounds	R^1	R^2	R^3	R^4	Product	Yield[a] (%)
1	**43**	H	H	OMe	H	**48**	71,[b] 81[c]
2	**44**	H	OMe	H	OMe	**49**	74,[b] 70[c]
3	**45**	H	H	OMe	OMe	**50**	70,[b] 72[c]
4	**46**	H	H	$-OCH_2O-$		**51**	70,[b] 79[c]
5	**47**	H	OMe	OMe	=OMe	**52**	82,[b] 75[c]
6	**52**	H	OH	OH	OMe	**53**	55

[a] Yields are given for isolated products.
[b] Method A: Na_2HPO_4 (excess), 6% Na/Hg amalgam, −78 °C, 1 h to −50 °C, 30 min., THF/MeOH 1/1.
[c] Method B: Bu_4NF, toluene, 90 °C, 1 h.



Scheme 5. For substitutions and yields see Table 4. (a) Method A or Method B; (b) BBr_3 (1.0 eq.), CH_2Cl_2, −78 °C, 1 h, 55%.

3. Biological activities

3.1. Topoisomerase inhibition and DNA binding

The structure of newly synthesised compounds **48**–**53** is close to azatoxin, an indolic heterolignan, which has proven to be a topoisomerase II inhibitor. For these reasons these compounds were tested for topoisomerase II inhibition and DNA binding. As shown in Fig. 3, supercoiled plasmid DNA was treated with human topoisomerase II in the presence of the reference compound (etoposide) or compounds **48**–**53** at different concentrations. The DNA relaxation/cleavage products were resolved by electrophoresis. Inhibition of topoisomerase II was clearly specifically detected with the reference compound (etoposide), which produced a marked level of DNA double stranded breaks (Fig. 3A), corresponding to linear DNA (lin). Among all 6 tested compounds only **53** was found to stabilise the drug–DNA complex with an increase of the band corresponding to linear DNA (double stranded breaks). Fig. 3B shows that **53**, tested at different concentrations from 1 to 100 μM, appeared to be less active than etoposide.

Fig. 3A and B also shows that, in high concentrations, **53** presents a supercoiled form (Sc) which represents a weak interaction with DNA, while etoposide presents stabilisation of DNA topoisomerase II covalent complexes. But the drug showed minimal if any interaction with DNA in the absence of the enzyme. In the same way, **50,** which differs from **53** by the absence of OMe in R^4, did not inhibit topoisomerase II, while it presented an interaction with the DNA visualised by an increase in the supercoiled form at high concentration. This weak DNA interaction is not bound to an intercalation mechanism because any modification of the DNA topology is visualised on relaxation agarose gels in the absence of ethidium bromide in presence of **50** and **53** and any variation of the melting temperature of calf thymus DNA is visualised (data not shown). The result from this topoisomerase assay established that compound **53** is a highly potent topoisomerase II poison *in vitro*, with a weak interaction with DNA, and that the OMe in R^4 is necessary for this inhibition.

3.2. Cytotoxic activity

To gain an insight into the involvement of topoisomerase II inhibition in the cytotoxicity of the compounds, their antiproliferative activity was assessed using the HL60/MX2 cell line resistant to mitoxantrone, which displays altered catalytic activity

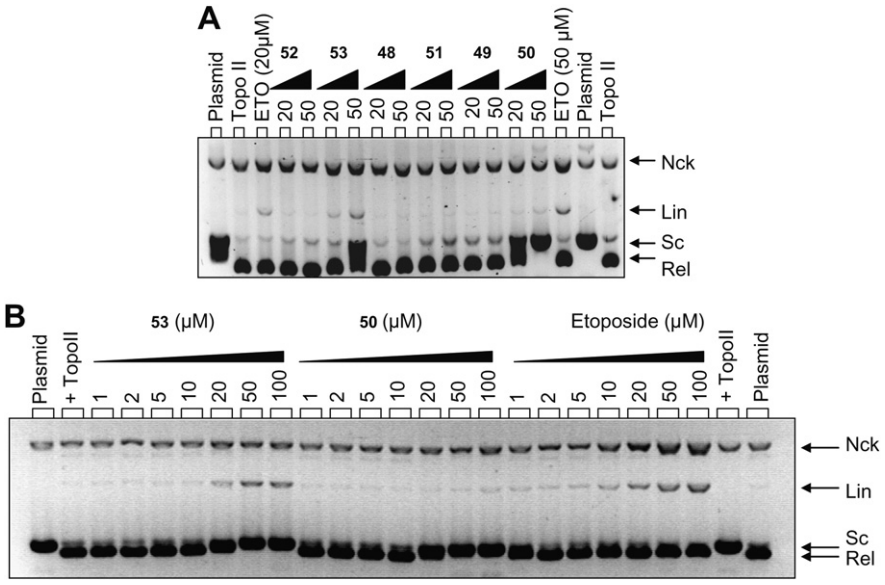


Fig. 3. Effect of compounds on the relaxation of plasmid DNA by human topoisomerase II. Native supercoiled PUC19 (350 ng, lane plasmid) was incubated with 4 units topoisomerase II in the absence (lane Topo II) or presence of tested compound at the indicated concentration. (A) Selected compounds displaying detectable DNA breaks at 20 and 50 μM. Etoposide was used at 20 (left) and 50 μM (right). (B) Comparison of most potent compound **53** with **50** and reference compound (etoposide) from 1 to 100 μM. DNA samples were separated by electrophoresis on a 1% agarose gel containing 1 μg/mL ethidium bromide. Gels were photographed under UV light. Nck: nicked; Sc: supercoiled; Lin: linear; Rel: relaxed.

and reduced levels of topoisomerase II [28]. The HL60/MX2 cell line displays an atypical multidrug resistance profile with a decreased expression and activity of topoisomerase II. When evaluated on the HL60 cell line, compound **53** displayed a high cytotoxicity in the submicromolar range ($IC_{50} = 150$ nM), higher than etoposide ($IC_{50} = 490$ nM). Compound **53** was also cytotoxic on HL60/MX2 ($IC_{50} = 170$ nM). This weak resistance index may be explained by its binding to the enzyme at a different site from that of mitoxantrone or by a specific kinetics. No obvious relationship was found between cytotoxicity and topoisomerase II inhibition. This was also demonstrated for other topoisomerase II inhibitors in the literature [29,30] and could be a contribution of different cellular activities.

4. Conclusion

In this paper we described the preparation of new furocarbazoles starting from formylindoles and various benzaldehydes. Our straightforward and efficient synthesis gave access to esters which were then readily used in a 6π-electrocyclisation/aromatisation reaction. This key step was performed under microwave irradiations and could be realised through a one-pot process. After the furocarbazoles deprotection and the methyl ether cleavage, the compounds obtained were evaluated as potent anticancer agents. Compared to azatoxin, where the benzylic asymmetric carbon confers a T-shape to the molecule, the rigidity of our models was enhanced and the pendular phenyl ring appeared to be orthogonal to the central furocarbazole. This difference of structure could explain the lack of activity of **52**.

Finally, compound **53**, which bears more donor/acceptor hydrogen bonds on the pendular phenyl ring, is a particularly interesting compound. It strongly inhibits the topoisomerase II *in vitro*, but less than etoposide, and interacts differently with the DNA. To remove substitutions from the phenyl group of the molecule probably decreases the steric dimensions of the compound and facilitates the interaction with the topoisomerase II. On the other hand, compound **53** presents a more significant cytotoxic effect than etoposide and seems independent to the topoisomerase II inhibition (weak index of resistance). Additional mechanisms and/or targets could be involved. The development of this molecule could be interesting because of the different spectrum of actions from etoposide, which is frequently prescribed in oncology and for which toxicities and resistance have been observed.

5. Experimental section

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DPX 250 or 400 MHz instrument using $CDCl_3$ or DMSO-d_6. The chemical shifts are reported in ppm (δ scale) and all coupling constants (J) values are in hertz (Hz). The splitting patterns are designated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and dd (doublet doublet). Melting points are uncorrected. IR absorption spectra were obtained on a Perkin–Elmer PARAGON 1000 PC and values were reported in cm^{-1}. MS spectra (Ion Spray) were performed on a Perkin–Elmer Sciex PI 300. HRMS were performed by the Centre Commun de Spectrométrie de Masse (Clermont Ferrand, France). Monitoring of the reactions was performed using silica gel TLC plates (silica Merck 60 F254). Spots were visualised by UV light at 254 nm and 356 nm. Column chromatography was performed using silica gel 60 (0.063–0.200 mm, Merck).

5.1. 1-Benzenesulphonyl-5-benzyloxy-3-formylindole (*4*)

Benzyltriethylammonium chloride (0.12 g, 0.5 mmol) and fine powdered sodium hydroxide (2.8 g, 70 mmol) were added to 1,2-dichloroethane (30 mL) under argon at r.t. A solution of 5-benzyloxy-3-formylindole **2** (5.63 g, 22.4 mmol) in 1,2-dichloroethane (30 mL) was added at 0 °C. Benzenesulphonyl chloride (3.33 mL, 26 mmol) was then added dropwise at 0 °C and the reaction mixture was stirred under reflux for 2 h. The mixture was cooled to r.t. and filtered. Water (50 mL) was added to the filtrate, which was extracted with CH_2Cl_2 (30 mL). The organic layer was dried over $MgSO_4$ and the expected product **4** was crystallised from EtOAc as a white solid (4.29 g, 81%). Mp 145–147 °C; IR (KBr, cm^{-1}) ν 3120, 3100, 2830, 1680, 1446, 909, 725; ^{1}H NMR (DMSO-d_6, 250 MHz) δ 5.09 (s, 2H),

7.07 (dd, 1H, $J = 2.5$ Hz, $J = 8.7$ Hz), 7.20–7.70 (m, 8H), 7.85 (d, 2H, $J = 7.5$ Hz), 7.93 (d, 2H, $J = 8.8$ Hz), 8.18 (s, 1H), 10.06 (s, 1H, CHO); ^{13}C NMR (DMSO-d_6, 62.5 MHz) δ 70.7 (CH_2), 105.3 (CH), 114.1 (CH), 116.7 (CH), 122.4 (Cq), 127.0 (2CH), 127.3 (Cq), 127.6 (2CH), 128.0 (2CH), 128.3 (Cq), 128.6 (CH), 129.7 (2CH), 134.6 (CH), 136.2 (Cq), 136.5 (CH), 137.4 (Cq), 156.9 (Cq), 185.4 (CHO); MS (IS) 392 ($M + H^+$).

5.2. (E)-3-(1-Benzenesulphonyl-1H-indol-3-yl)-acrylic acid methyl ester (**5**)

To a solution of **3** (4.7 g, 16.5 mmol) in dry toluene (100 mL) was portionwise added carbethoxymethylene triphenylphosphorane (16.55 g, 49.5 mmol). The reaction mixture was heated overnight under reflux. The solvent was removed under reduced pressure and the crude residue was purified by flash chromatography (petroleum ether/EtOAc 5/5) to afford compound **5** as a white solid (5.52 g, 98%). All spectral data were in agreement with previous reports [12].

5.3. (E)-3-(1-Benzenesulphonyl-1H-5-benzyloxyindol-3-yl)-acrylic acid methyl ester (**6**)

Compound **6** was isolated as a white solid (93%) starting from **4** and using the procedure described for the preparation of compound **5**. Mp 225–227 °C; IR (KBr, cm^{-1}) ν 3097, 1675, 1425, 1204, 953; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 3.81 (s, 3H, CH_3), 5.09 (s, 2H), 6.42 (d, 1H, $J = 16.0$ Hz), 7.06 (dd, 1H, $J = 2.5$ Hz, $J = 16.0$ Hz), 7.23–7.41 (m, 3H), 7.42–7.72 (m, 5H), 7.81–7.92 (m, 3H), 8.02 (d, 2H, $J = 7.0$ Hz), 8.50 (s, 1H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 51.0 (CH_3), 69.8 (CH_2), 104.5 (CH), 114.3 (CH), 115.2 (CH), 117.5 (CH), 117.8 (Cq), 126.8 (CH), 127.7 (2CH), 127.8 (Cq), 128.4 (2CH), 128.7 (2CH), 129.3 (CH), 129.9 (Cq), 131.4 (2CH), 131.5 (CH), 134.9 (Cq), 135.5 (CH), 137.0 (Cq), 155.8 (Cq), 166.8 (CO); MS (IS) 336 ($M + Na^+$).

5.4. 3-(Benzenesulphonyl-1H-indol-3-yl)-prop-2-en-1-ol (**7**)

To a solution of **5** (4.5 g, 13 mmol) in dry toluene under argon was added dropwise at 0 °C a solution of DibalH (20% in toluene, 29.8 mL, 32.5 mmol). The reaction mixture was stirred at r.t. for 2 h and the reaction mixture was slowly hydrolysed at 0 °C with water (30 mL). Aluminium salts were filtered and the solvent was removed under reduced pressure. The aqueous phase was extracted with EtOAc (2×20 mL). The organic layer was dried with $MgSO_4$, filtered and evaporated to dryness. A flash chromatography (petroleum ether/EtOAc 7/3) afforded the compound **7** as a yellow solid (3.91 g, quant.). Mp 102–104 °C; IR (KBr, cm^{-1}) ν 3397, 1655, 1447, 1176, 973; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 4.12 (d, 2H, $J = 6.4$ Hz), 6.47 (dt, 1H, $J = 6.4$ Hz, $J = 16.1$ Hz), 6.69 (d, 1H, $J = 16.1$ Hz), 7.43–7.60 (m, 6H), 7.73 (d, 1H, $J = 7.2$ Hz), 7.87 (d, 2H, $J = 9.5$ Hz), 7.99 (d, 1H, $J = 7.2$ Hz); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 64.0 (CH_2), 113.9 (CH), 120.3 (Cq), 120.5 (CH), 121.8 (CH), 123.8 (CH), 124.0 (CH), 125.2 (CH), 126.9 (CH), 129.1 (Cq), 129.4 (CH), 130.1 (CH), 134.0 (CH), 135.6 (Cq), 138.1 (Cq); MS (IS) 336.5 ($M + Na^+$).

5.5. 3-(1-Benzenesulphonyl-1H-5-benzyloxyindol-3-yl)-prop-2-en-1-ol (**8**)

Compound **8** was isolated as a yellow solid (quant.) starting from **6** and using the procedure described for the preparation of compound **7**. Mp 211–212 °C; IR (KBr, cm^{-1}) ν 3364, 1658, 1435, 1171, 968; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 4.33 (d, 2H, $J = 5.0$ Hz), 5.06 (s, 2H), 6.33 (dt, 1H, $J = 5.0$ Hz, $J = 17.0$ Hz), 6.62 (d, 1H, $J = 17.0$ Hz), 7.01–7.62 (m, 14H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 61.7 (CH_2), 69.7 (CH_2), 104.3 (CH), 114.3 (CH), 114.4 (Cq), 108.8 (CH), 120.4 (Cq), 126.6 (2CH), 127.7 (CH), 127.8 (CH), 128.4 (2CH), 128.6 (Cq), 128.8 (2CH), 129.4 (Cq), 129.7 (2CH), 131.4 (CH), 132.1 (CH), 134.5 (CH), 137.0 (Cq), 155.5 (Cq); MS (IS) 420.5 $(M + H)^+$; 442.5 ($M + Na^+$).

5.6. 1-Benzenesulphonyl-3-chloropropenyl-1H-indole (**9**)

A solution 1.5 M of benzotriazole (1.786 g, 15 mmol) and $SOCl_2$ (1.09 mL, 15 mmol) in dry CH_2Cl_2 (10 mL) was prepared. This solution (6.7 mL) was added dropwise at 0 °C to a solution of **7** (2.5 g, 8.0 mmol) in dry CH_2Cl_2 (50 mL). The reaction mixture was stirred at r.t. for 15 min and filtered. The filtrate was dried *in vacuo* to afford compound **9** as an orange solid (2.60 g, quant.). Degradation was observed during the flash chromatography operation. Mp 139–141 °C; IR (KBr, cm^{-1}) ν 1659, 1447, 1363, 1177, 953, 743; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 4.26 (d, 2H, $J = 7.2$ Hz), 6.40 (dt, 1H, $J = 7.2$ Hz, $J = 16.0$ Hz), 6.73 (d, 1H, $J = 16.0$ Hz), 7.26–7.48 (m, 5H), 7.62 (s, 1H), 7.72 (d, 1H, $J = 7.5$ Hz), 7.88 (d, 2H, $J = 8.6$ Hz), 8.00 (d, 1H, $J = 7.3$ Hz); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 44.5 (CH_2), 118.2 (Cq), 112.6 (CH), 119.2 (CH), 122.6 (CH), 124.0 (CH), 125.0 (CH), 125.6 (2CH), 127.2 (CH), 127.5 (CH), 128.2 (2CH), 131.0 (CH), 132.8 (Cq), 134.3 (CH), 136.8 (Cq); MS (IS) 331.5 ($M + H^+$, ^{35}Cl) and 333.5 ($M + H^+$, ^{37}Cl).

5.7. 1-Benzenesulphonyl-5-benzyloxy-3-chloropropenyl-1H-indole (**10**)

Compound **10** was isolated as a yellow solid (quant.) starting from **8** and using the procedure described for the preparation of compound **9**. Mp 184–186 °C; IR (KBr, cm^{-1}) ν 2961, 1518, 1435, 1171, 968; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 4.33 (dd, 2H, $J = 1.0$ Hz, $J = 6.5$ Hz), 5.06 (s, 2H), 6.33 (dt, 1H, $J = 6.5$ Hz, $J = 17.0$ Hz), 6.62 (d, 1H, $J = 17.0$ Hz), 76.99–7.01 (m, 1H), 7.21 (d, 1H, $J = 2.5$ Hz), 7.31–7.82 (m, 8H), 7.83–7.89 (m, 3H), 8.12 (dd, 1H, $J = 3.1$ Hz, $J = 6.6$ Hz); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 44.3 (CH_2), 69.5 (CH_2), 104.6 (CH), 113.7 (CH), 118.5 (Cq), 112.8 (CH), 119.7 (CH), 122.6 (CH), 125.0 (CH), 125.6 (2CH), 127.2 (2CH), 127.5 (Cq), 128.2 (2CH), 128.8 (2CH), 129.8 (Cq), 131.3 (CH), 133.1 (Cq), 133.0 (CH), 136.8 (Cq), 153.9 (Cq); MS (IS) 438.5 ($M + H^+$, ^{35}Cl) and 440.5 ($M + H^+$, ^{37}Cl).

5.8. General procedure for the preparation of 2,2-dibromovinyl benzenes **16–20**

A solution of CBr_4 (1.5 eq.) in dry CH_2Cl_2 was stirred under argon at r.t. PPh_3 (3.0 eq.) was added portionwise slowly. The reaction mixture was stirred for 1 h and then cooled to 0 °C. A solution of benzaldehydes **11–15** (1.0 eq.) in dry CH_2Cl_2 was then added and the mixture was stirred for 2 h at r.t. The reaction mixture was filtered. The filtrate was hydrolysed with water. After extraction, the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and solvent was removed under reduced pressure. The crude product was purified by flash chromatography to afford compounds **16–20**. All spectral data were in agreement with previous reports [16–20].

5.9. General procedure for the preparation of propynoic methyl esters **21–25**

A solution of 2,2-(dibromovinyl)-benzenes **16–20** in dry THF (1 eq.) was stirred under argon at r.t. A solution of *n*-BuLi (2.5 M in hexane, 2.2 eq.) was added dropwise at −78 °C and the reaction mixture was next stirred at r.t. for 1 h and then cooled to −78 °C. At that point, methyl chloroformate (1.2 eq.) was added to the solution. After 1 h at r.t., the solvent was concentrated under reduced pressure. EtOAc and a saturated aqueous solution of ammonium chloride were added. After extractions with EtOAc, the combined organic layers were dried over $MgSO_4$ and the solvent removed under reduced pressure. The crude product was purified by flash

chromatography (petroleum ether/EtOAc 8/2) to afford compounds **21**–**25**. All spectral data were in agreement with previous reports [21–24].

5.10. (3,5-Dimethoxybenzene)-propynoic acid methyl ester (**22**)

Compound **22** was obtained starting from **17** as a yellow solid in 85% yield. Mp 104–106 °C; IR (KBr) cm^{-1} 3022, 2202, 1732, 1215, 1046, 767, 669, 508; ^1H NMR (DMSO, 250 MHz) δ 3.35 (s, 3H), 3.78 (s, 6H), 6.69 (t, 1H, $J = 2.5$ Hz), 6.81 (d, 2H, $J = 2.5$ Hz); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 54.8 (CH_3), 54.9 ($2CH_3$), 79.5 (Cq), 81.9 (Cq), 104.9 (2CH), 106.9 (CH), 140.8 (Cq), 142.4 (2Cq), 160.7 (CO); MS (IS) 221 ($M + H^+$).

5.11. General procedure to obtain the propynoic acids **26**–**30**

To a solution of propynoic methyl esters **21**–**25** in THF/H_2O/MeOH (4/1/1) at r.t., was added $LiOH \cdot H_2O$ (1.4 eq.). The reaction mixture was stirred overnight at r.t. EtOAc was added and the reaction mixture was acidified at pH = 4 with an aqueous solution of HCl (1 N). After extraction of the aqueous layers by EtOAc, the combined organic layers were dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure to afford compounds **21**–**25**. These compounds, which appeared to be very pure, were used in the next step without further purification. All spectral data were in agreement with previous reports [25–27].

5.12. (3,5-Dimethoxybenzene)-propynoic acid (**27**)

Compound **27** was obtained starting from **22** as a yellow solid in 98% yield. Mp 131–133 °C; IR (KBr, cm^{-1}) ν 3019, 2947, 2602, 2217, 1709, 1587, 1451, 1348, 1208, 1160, 1068, 832; ^1H NMR ($CDCl_3$, 250 MHz) δ 3.79 (s, 6H), 6.56 (t, 1H, $J = 2.5$ Hz), 6.74 (d, 2H, $J = 2.5$ Hz), 8.91 (s, 1H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 55.6 ($2CH_3$), 79.5 (Cq), 89.1 (Cq), 104.8 (CH), 110.9 (2CH), 120.3 (Cq), 158.3 (2Cq), 160.7 (CO); MS (IS) 205.0 ($M - H^+$).

5.13. General procedure for the preparation of esters **31**–**36**

A solution of acids **21**–**25** (3.0 eq.) and $NaHCO_3$ (1.5 eq.) in dry DMF was stirred under argon and in the dark at r.t. for 1 h. 3-chloropropenyl **9** or **10** (1.0 eq.) was added in one portion and the reaction mixture was stirred for 48 h. Water was then added and the solution was extracted with EtOAc and purified quickly on a pad of silica gel (petroleum ether/AcOEt 7/3) to afford the esters **31**–**36**, which were immediately used in the DA step.

5.14. 4-Methoxyphenylpropynoic-3-(1-benzenesulphonyl-1H-indol-3-yl)-allyl ester (**31**)

Compound **31** was isolated after purification by flash chromatography (petroleum ether/EtOAc 8:2) as a yellow solid starting from **26** in 96% yield. Mp 95–97 °C; IR (KBr, cm^{-1}) ν 2954, 2210, 1697, 1603, 1446, 1364, 1156, 948, 739, 684; ^1H NMR ($CDCl_3$, 250 MHz) δ 3.83 (s, 3H), 4.90 (d, 2H, $J = 6.5$ Hz), 6.35 (dt, 1H, $J = 6.5$ Hz, $J = 16.0$ Hz), 6.76 (d, 1H, $J = 16.0$ Hz), 6.86 (d, 2H, $J = 8.7$ Hz), 7.26–7.56 (m, 7H), 7.59 (s, 1H), 7.75 (d, 1H, $J = 7.0$ Hz), 7.87 (d, 2H, $J = 7.2$ Hz), 7.99 (d, 1H, $J = 7.7$ Hz); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 55.5 (CH_3), 66.7 (CH_2), 77.3 (Cq), 80.0 (Cq), 87.8 (Cq), 111.3 (Cq), 113.9 (CH), 114.4 (CH), 119.7 (Cq), 120.5 (CH), 123.6 (CH), 123.8 (CH), 124.9 (2CH), 125.3 (2CH), 126.1 (CH), 126.9 (2CH), 128.8 (Cq), 129.4 (2CH), 134.1 (CH), 135.1 (CH), 138.1 (Cq), 154.2 (Cq), 161.7 (CO); MS (IS) 472.5 ($M + H^+$).

5.15. 3,5-Dimethoxyphenylpropynoic-3-(1-benzenesulphonyl-1H-indol-3-yl)-allyl ester (**32**)

Compound **32** was isolated as a yellow solid starting from **27** in 74% yield after purification by flash chromatography (petroleum ether/EtOAc 9:1). Mp 149–151 °C; IR (KBr, cm^{-1}) ν 3111, 3019, 2376, 1714, 1642, 1307, 1243, 1150, 1110, 765; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.70 (s, 6H), 4.82 (d, 2H, $J = 6.6$ Hz), 6.30 (dt, 1H, $J = 6.6$ Hz, $J = 16$ Hz), 6.47 (t, 1H, $J = 2.4$ Hz), 6.70 (d, 1H, $J = 16$ Hz), 7.19–7.30 (m, 3H), 7.35 (t, 2H, $J = 8.0$ Hz), 7.45–7.48 (m, 1H), 7.57 (s, 1H), 7.65 (d, 1H, $J = 8.0$ Hz), 7.80 (d, 2H, $J = 8.0$ Hz), 7.92 (d, 2H, $J = 8.0$ Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 55.6 ($2CH_3$), 66.9 (CH_2), 79.8 (Cq), 86.8 (Cq), 104.4 (CH), 110.7 (CH), 113.9 (CH), 119.6 (Cq), 120.5 (CH), 120.7 (Cq), 123.4 (CH), 123.8 (CH), 124.9 (CH), 125.3 (2CH), 126.3 (CH), 126.9 (2CH), 128.8 (Cq), 129.4 (2CH), 135.6 (Cq), 138.1 (Cq), 153.8 (Cq), 160.7 (2Cq), 162.6 (CO); HRMS (ESI) calculated for $C_{28}H_{24}NO_6S$ 502.1324, found 502.1315 ($M + H^+$).

5.16. 3,4-Dimethoxyphenylpropynoic-3-(1-benzenesulphonyl-1H-indol-3-yl)-allyl ester (**33**)

Compound **33** was isolated as a yellow solid starting from **28** in 85% yield after purification by flash chromatography (petroleum ether/EtOAc 8:2). Mp 63–65 °C; IR (KBr, cm^{-1}) ν 2935, 2206, 1701, 1596, 1512, 1445, 1370, 1248, 1225, 1133, 978, 744, 685; ^1H NMR ($CDCl_3$, 250 MHz) δ 3.85 (s, 3H), 3.88 (s, 3H), 4.88 (d, 2H, $J = 6.5$ Hz), 6.34 (dt, 1H, $J = 6.5$ Hz, $J = 16$ Hz), 6.75–6.84 (m, 2H), 7.06 (d, 1H, $J = 1.7$ Hz), 7.20–7.60 (m, 6H), 7.64 (s, 1H), 7.70 (d, 1H, $J = 7.0$ Hz), 7.86 (d, 2H, $J = 7.0$ Hz), 7.99 (d, 1H, $J = 7.7$ Hz); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 56.0 (CH_3), 66.6 (CH_2), 79.7 (Cq), 87.7 (Cq), 111.0 (CH), 111.2 (Cq), 113.7 (CH), 115.3 (CH), 119.6 (Cq), 120.4 (CH), 123.4 (CH), 123.7 (CH), 124.8 (2CH), 125.2 (CH), 126.0 (CH), 126.8 (2CH), 127.3 (CH), 128.7 (Cq), 129.3 (CH), 134.0 (CH), 135.5 (Cq), 137.9 (Cq), 148.7 (Cq), 151.6 (Cq), 154.0 (CO); HRMS (ESI) calculated for $C_{28}H_{23}NO_6SNa$ 524.1144, found 524.1128 ($M + Na^+$).

5.17. 3,4-Methylenedioxyphenylpropynoic-3-(1-benzenesulphonyl-1H-indol-3-yl)-allyl ester (**34**)

Compound **34** was isolated as a yellow solid starting from **29** in 81% yield after purification by flash chromatography (petroleum ether/EtOAc 9:1). Mp 71–73 °C; IR (KBr, cm^{-1}) ν 2938, 2196, 1710, 1449, 1339, 1242, 678; ^1H NMR ($CDCl_3$, 250 MHz) δ 4.87 (d, 2H, $J = 6.4$ Hz), 6.00 (s, 2H), 6.34 (dt, 1H, $J = 6.4$ Hz, $J = 16.0$ Hz), 6.75–681 (m, 2H), 6.98 (d, 1H, $J = 1.5$ Hz), 7.13 (dd, 1H, $J = 1.5$ Hz, $J = 8.0$ Hz), 7.26–7.52 (m, 5H), 7.64 (s, 1H), 7.71 (d, 1H, $J = 7.2$ Hz), 7.86 (d, 2H, $J = 7.2$ Hz), 7.98 (d, 1H, $J = 7.7$ Hz); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 66.7 (CH_2), 79.5 (Cq), 87.3 (Cq), 101.8 (CH_2), 108.8 (CH), 112.4 (Cq), 112.5 (CH), 113.7 (CH), 119.6 (Cq), 120.4 (CH), 123.4 (CH), 123.8 (2CH), 124.8 (CH), 125.2 (CH), 126.0 (CH), 126.8 (2CH), 128.7 (Cq), 128.9 (CH), 129.3 (CH), 134.0 (CH), 135.5 (Cq), 137.9 (Cq), 147.6 (Cq), 150.1 (Cq), 153.9 (CO); HRMS (ESI) calculated for $C_{27}H_{19}NO_6SNa$ 508.0847, found 508.0831 ($M + Na^+$).

5.18. 3,4,5-Trimethoxyphenylpropynoic-3-(1-benzenesulphonyl-1H-indol-3-yl)-allyl ester (**35**)

Compound **35** was isolated as a white solid starting from **30** in 98% yield after purification by column chromatography (petroleum ether/EtOAc 8:2). Mp 153–155 °C; IR (KBr, cm^{-1}) ν 3450, 3100, 3000, 2220, 1750, 1715, 1640, 1245, 1300, 1150, 1100, 760; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.84 (s, 6H), 3.88 (s, 3H), 4.90 (d, 2H, $J = 6.4$ Hz), 6.41 (dt, 1H, $J = 6.4$ Hz, $J = 16$ Hz), 6.76–683 (m, 1H),

6.84 (s, 2H), 7.26–7.55 (m, 5 H), 7.65 (s, 1H), 7.72 (d, 1H, $J = 8.0$ Hz), 7.80 (d, 2H, $J = 7.6$ Hz), 8.00 (d, 1H, $J = 8.0$ Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 56.3 ($2CH_3$), 61.1 (CH_3), 66.8 (CH_2), 79.8 (Cq), 87.3 (Cq), 110.5 (CH), 113.8 (CH), 114.1 (Cq), 119.6 (Cq), 120.4 (CH), 123.4 (CH), 123.8 (2CH), 124.9 (CH), 125.3 (CH), 126.3 (CH), 126.9 (2CH), 128.7 (Cq), 129.4 (2CH), 134.0 (CH), 135.5 (Cq), 138.0 (Cq), 141.1 (Cq), 153.2 (2Cq), 153.9 (CO); HRMS (ESI) calculated for $C_{29}H_{26}NO_7S$ 532.1424, found 532.1430 ($M + H^+$).

5.19. General procedure for the preparation of N-benzenesulphonyl furocarbazol-3(4H,5H,10H)-ones **37**–**41**

A solution of esters **31**–**36** (0.17 mmol) in toluene (2.5 mL) was heated at 150 °C for 2 h 30 under microwave irradiation. After cooling at 0 °C overnight, the precipitate was filtered and washed with pentane to give the desired products **37**–**41**.

5.20. 4-(4-Methoxyphenyl)-5-benzenesulphonyl-1H-furo[3,4-b] carba zol-3(4H,5H,10H)-one (**37**)

Compound **37** was isolated as a pale beige solid starting from **31** in 81% yield. Mp 225–227 °C; IR (KBr, cm^{-1}) ν 3105, 2985, 1751, 1247, 1130, 1131, 756; ^{1}H NMR (DMSO-d_6, 250 MHz) δ 2.56 (t, 1H, $J = 16.6$ Hz), 3.00 (dd, 1H, $J = 7.7$ Hz, $J = 16.6$ Hz), 3.38–3.52 (m, 1H), 3.83 (s, 3H), 4.02 (dd, 1H, $J = 7.5$ Hz, $J = 9.1$ Hz), 4.69 (t, 1H, $J = 9.1$ Hz), 6.81 (d, 2H, $J = 8.7$ Hz), 7.18–7.45 (m, 10H), 8.09 (d, 1H, $J = 8.4$ Hz); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 25.0 (CH_2), 36.1 (CH), 55.0 (CH_3), 69.7 (CH_2), 112.0 (CH), 117.3 (CH), 120.4 (CH), 120.6 (CH), 125.5 (2CH), 126.4 (2CH), 126.7 (2CH), 127.2 (2CH), 128.9 (Cq), 129.3 (Cq), 131.6 (Cq), 131.9 (Cq), 134.1 (Cq), 134.3 (CH), 138.7 (Cq), 140.4 (Cq), 140.4 (Cq), 159.1 (Cq), 167.4 (CO); HRMS (ESI) calculated for $C_{27}H_{22}NO_5S$ 472.1219, found 472.1223 ($M + H^+$).

5.21. 5-Benzenesulphonyl-4-(3,5-dimethoxyphenyl)-1H-furo[3,4-b] carbazol-3(4H,5H,10H)-one (**38**)

Compound **38** was isolated as a white solid starting from **32** in 74% yield. Mp 235–237 °C; IR (KBr, cm^{-1}) ν 3064, 3007, 1739, 1607, 1589, 1446, 1362, 1203, 1150, 1026, 759, 685; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.60 (t, 1H, $J = 17.2$ Hz), 3.11 (dd, 1H, $J = 8.0$ Hz, $J = 17.2$ Hz), 3.34–3.56 (m, 1H), 3.70 (s, 6H), 4.06 (dd, 1H, $J = 7.6$ Hz, $J = 9.0$ Hz), 4.67 (t, 1H, $J = 9.0$ Hz), 6.46–6.52 (m, 3H), 7.30–7.46 (m, 6H), 7.50–7.56 (m, 2H), 7.94 (d, 1H, $J = 8.4$ Hz); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 24.5 (CH_2), 35.9 (CH), 54.8 ($2CH_3$), 69.1 (CH_2), 100.1 (Cq), 109.1 (CH), 116.6 (CH), 120.0 (CH), 121.3 (Cq), 124.7 (CH), 125.7 (2CH), 126.5 (2CH), 128.3 (2CH), 128.6 (Cq), 130.0 (Cq), 133.3 (Cq), 135.0 (CH), 135.4 (Cq), 137.9 (CH), 139.7 (Cq), 139.9 (Cq), 158.5 (2Cq), 167.4 (CO); HRMS (ESI) calculated for $C_{28}H_{23}NO_6SNa$ 524.1132, found 524.1136 ($M + Na^+$).

5.22. 5-Benzenesulphonyl-4-(3,4-dimethoxyphenyl)-1H-furo[3,4-b] carbazol-3(4H,5H,10H)-one (39)

Compound **39** was isolated as a yellow solid starting from **33** in 87% yield. Mp 205–207 °C; IR (KBr, cm^{-1}) ν 2940, 1737, 1580, 1445, 1361, 1235, 1173, 1023, 755, 686; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 2.50 (t, 1H, $J = 17.0$ Hz), 3.02 (dd, 1H, $J = 7.5$ Hz, $J = 17.0$ Hz), 3.39–3.55 (m, 1H), 3.83 (s, 3H), 3.87 (s, 3H), 4.02–4.13 (m, 1H), 4.68 (t, 1H, $J = 9.0$ Hz), 6.71 (d, 1H, $J = 8.5$ Hz), 6.94 (d, 1H, $J = 8.5$ Hz), 7.04 (s, 1H), 7.21–7.44 (m, 8H), 8.07 (d, 1H, $J = 8.5$ Hz); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 26.3 (CH_2), 36.9 (CH), 55.7 (CH_3), 56.0 (CH_3), 69.9 (CH_2), 109.1 (CH), 114.6 (CH), 117.7 (CH), 119.3 (Cq), 120.0 (CH), 123.8 (2CH), 125.1 (CH), 126.3 (2CH), 127.2 (CH), 128.4 (CH), 129.0 (Cq), 129.6 (Cq), 133.4 (CH), 133.5 (Cq), 136.6 (Cq), 139.1 (Cq), 141.1 (Cq), 142.2 (Cq), 147.4 (Cq), 149.5 (Cq), 167.6 (CO); HRMS calculated for $C_{28}H_{23}NO_6SNa$ 524.1144, found 524.1147 ($M + Na^+$).

5.23. 4-(Benzo[d][1,3]dioxol-5-yl)-5-benzenesulphonyl-1H-furo [3,4-b]carbazol-3(4H,5H,10H)-one (**40**)

Compound **40** was isolated as a yellow solid starting from **34** in 70% yield. Mp 234–236 °C; IR (KBr, cm^{-1}) ν 2903, 1737, 1603, 1445, 1366, 1243, 1227, 1175, 1087, 753, 686; ^{1}H NMR (DMSO-d_6, 250 MHz) δ 2.55 (t, 1H, $J = 16.9$ Hz), 3.00 (dd, 1H, $J = 7.7$ Hz, $J = 16.9$ Hz), 3.34–3.51 (m, 1H), 4.02 (dd, 1H, $J = 7.5$ Hz, $J = 9.2$ Hz), 4.67 (t, 1H, $J = 9.2$ Hz), 5.97 (s, 2H), 6.69 (d, 1H, $J = 8.0$ Hz), 6.80–6.94 (m, 2H), 7.11–7.57 (m, 8H), 8.09 (d, 1H, $J = 8.0$ Hz); ^{13}C NMR (DMSO-d_6, 62.9 MHz) δ 26.4 (CH), 36.8 (CH_2), 69.9 (CH_2), 101.2 (CH_2), 107.1 (CH), 111.5 (CH), 117.9 (CH), 119.5 (CH), 120.0 (CH), 125.0 (2CH), 125.3 (2CH), 126.4 (CH), 127.3 (CH), 127.8 (Cq), 128.3 (Cq), 128.5 (CH), 129.1 (CH), 129.9 (Cq), 133.4 (CH), 136.5 (Cq), 139.0 (Cq), 141.2 (Cq), 146.5 (Cq), 148.1 (Cq), 167.4 (CO); HRMS (ESI) calculated for $C_{27}H_{20}NO_6S$ 486.1011, found 486.0993 ($M + H^+$).

5.24. 5-Benzenesulphonyl-4-(3,4,5-trimethoxyphenyl)-1H-furo [3,4-b]carbazol-3(4H,5H,10H)-one (**41**)

Compound **41** was isolated as a yellow solid starting from **35** in 99% yield. Mp 215–217 °C; IR (KBr, cm^{-1}) ν 2941, 1737, 1606, 1445, 1362, 1215, 1174, 1089, 756, 686; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 2.58 (t, 1H, $J = 17.0$ Hz), 3.09 (dd, 1H, $J = 7.7$ Hz, $J = 17.0$ Hz), 3.43–3.59 (m, 1H), 3.76 (s, 6H), 3.89 (s, 3H), 4.06 (dd, 1H, $J = 7.7$ Hz, $J = 9.0$ Hz), 4.73 (t, 1H, $J = 9.0$ Hz), 6.64 (s, 2H), 7.26–7.47 (m, 8H), 8.08 (d, 1H, $J = 8.2$ Hz); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 26.2 (CH_2), 37.0 (CH), 56.2 ($2CH_3$), 61.0 (CH_3), 69.9 (CH_2), 108.7 (CH), 117.5 (CH), 120.1 (CH), 120.2 (Cq), 125.1 (2CH), 126.2 (CH), 127.2 (2CH), 128.5 (2CH), 128.8 (Cq), 128.8 (Cq), 129.1 (Cq), 133.5 (CH), 137.0 (Cq), 138.6 (Cq), 138.9 (Cq), 141.0 (Cq), 142.2 (Cq), 151.9 (2Cq), 167.4 (CO); HRMS (ESI) calculated for $C_{29}H_{26}NO_7S$ 532.1430, found 532.1423 ($M + H^+$).

5.25. General procedures for the preparation of furocarbazoles **43**–**47**

Method A: A solution of derivatives **37**–**42** (0.41 mmol) and *o*-chloranil (0.2 g, 0.82 mmol) in toluene was irradiated under microwave for 1 h 30. After cooling at 4 °C for 12 h, the reaction mixture was filtered and the precipitate washed with pentane, then dried under vacuum. *Method B*: A solution of **31**–**36** (0.19 mmol) in toluene was heated at 150 °C for 1 h under microwave irradiation (Biotage initiator apparatus), then *o*-chloranil (0.48 mmol) was added and the mixture irradiated at 150 °C for an additional 35 min. After evaporation of the solvent, the residue was dissolved in a small amount of Et_2O, and the precipitate was filtered and dried under reduced pressure.

5.26. 9-Benzenesulphonyl-4-(4-methoxyphenyl)-1,5-dihydro-3H-furo [3,4-b]carbazol-3-one (**43**)

Compound **43** was isolated as a white solid from **37** (*Method A*) in 76% yield or from **31** (*Method B*) in 88% yield. Mp 234–236 °C; IR (KBr, cm^{-1}) ν 2934, 1746, 1610, 1514, 1446, 1349, 1239, 1177, 1023, 763, 685; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.86 (s, 3H), 5.31 (s, 2H), 6.84 (d, 2H, $J = 8.8$ Hz), 7.12–7.21 (m, 4H), 7.33–7.43 (m, 4H), 7.53 (t, 1H $J = 8.8$ Hz), 7.77 (s, 1H), 7.81 (d, 1H, $J = 7.6$ Hz), 8.16 (d, 1H, $J = 8.0$ Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 55.2 (CH_3), 67.5 (CH_2), 111.7 (CH), 112.9 (CH), 119.7 (CH), 120.7 (CH), 125.7 (2CH), 126.0 (Cq), 126.3 (2CH), 127.5 (Cq), 128.4 (2CH), 129.3 (2CH), 131.9 (Cq), 132.0 (CH), 133.2 (CH), 135.0 (Cq), 136.4 (Cq), 136.8 (Cq), 140.1 (Cq), 143.4

(Cq), 144.9 (Cq), 159.6 (Cq), 169.2 (CO); HRMS calculated for $C_{27}H_{20}NO_5S$ 470.1062, found 470.1063 ($M + H^+$).

5.27. 9-Benzenesulphonyl-4-(3,5-dimethoxyphenyl)-1,5-dihydro-3H-furo[3,4-b]carbazol-3-one (**44**)

Compound **44** was isolated as a pale grey solid from **38** (*Method A*) in 77% yield or from **32** (*Method B*) in 70% yield. Mp 235–237 °C; IR (KBr, cm^{-1}) ν 2940, 1737, 1582, 1446, 1360, 1212, 1088, 945, 756, 684; ^1H NMR (DMSO-d_6, 250 MHz) δ 3.73 (s, 6H), 5.42 (s, 2H), 6.46 (t, 1H, $J = 2.2$ Hz), 6.62 (d, 2H, $J = 2.2$ Hz), 7.15 (d, 2H, $J = 7.2$ Hz), 7.24 (t, 2H, $J = 8.2$ Hz), 7.44–7.51 (m, 2H), 7.58–7.65 (m, 1H), 8.06 (dd, 2H, $J = 4.5$ Hz, $J = 7.2$ Hz), 8.24 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 55.0 ($2CH_3$), 67.4 (CH_2), 99.5 (CH), 109.2 (CH), 113.5 (CH), 119.1 (CH), 121.4 (2CH), 125.9 (2CH), 126.0 (Cq), 127.2 (Cq), 128.8 (2CH), 128.9 (Cq), 129.3 (CH), 133.3 (CH), 133.8 (Cq), 135.2 (CH), 135.5 (Cq), 135.8 (Cq), 138.6 (Cq), 142.3 (Cq), 145.9 (Cq), 159.1 (2Cq), 168.4 (CO); HRMS calculated for $C_{28}H_{22}NO_6S$ 500.1168, found 500.1151 ($M + H^+$).

5.28. 9-Benzenesulphonyl-4-(3,4-dimethoxyphenyl)-1,5-dihydro-3H-furo[3,4-b]carbazol-3-one (**45**)

Compound **45** was isolated as a pale brown solid from **39** (*Method A*) in 70% yield or from **33** (*Method B*) in 75% yield. Mp >250 °C; IR (KBr, cm^{-1}) ν 3024, 1747, 1327, 1212, 1041, 751, 670, 514; ^1H NMR ($CDCl_3$, 250 MHz) δ 3.83 (s, 3H), 3.92 (s, 3H), 5.32 (s, 2H), 6.74 (d, 1H, $J = 8.7$ Hz), 6.99 (d, 2H, $J = 8.7$ Hz), 7.16–7.28 (m, 4H), 7.36–7.44 (m, 2H), 7.53 (t, 1H, $J = 7.7$ Hz), 7.82 (t, 2H, $J = 7.7$ Hz), 8.15 (d, 1H, $J = 8.0$ Hz); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 55.7 (CH_3), 56.0 (CH_3), 67.5 (CH_2), 109.8 (CH), 111.8 (CH), 114.5 (CH), 119.4 (CH), 120.8 (CH), 122.3 (Cq), 123.7 (CH), 125.5 (2CH), 126.0 (Cq), 126.1 (2CH), 127.2 (Cq), 128.4 (CH), 129.3 (CH), 133.2 (CH), 134.6 (Cq), 136.2 (Cq), 137.3 (Cq), 140.0 (Cq), 143.4 (Cq), 144.7 (Cq), 147.9 (Cq), 149.1 (Cq), 169.1 (CO); HRMS calculated for $C_{28}H_{22}NO_6S$ 500.1168, found 500.1167 ($M + H^+$).

5.29. 9-Benzenesulphonyl-4-(3,4-methylenedioxyphenyl)-1,5-dihydro-3H-furo[3,4-b]carbazol-3-one (**46**)

Compound **46** was isolated as a yellow solid from **40** (*Method A*) in 66% yield or from **34** (*Method B*) in 26% yield. Mp 240–242 °C; IR (KBr, cm^{-1}) ν 3019, 1215, 1045, 761, 669, 505; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.31 (s, 2H), 6.00 (s, 2H), 6.72 (d, 1H, $J = 12.8$ Hz), 6.91 (dd, 1H, $J = 2.4$ Hz, $J = 12.8$ Hz), 7.00 (d, 1H, $J = 2.4$ Hz), 7.17–7.29 (m, 4H), 7.38–7.45 (m, 2H), 7.53 (t, 1H, $J = 8.0$ Hz), 7.79–7.84 (m, 2H), 8.17 (d, 1H, $J = 13.2$ Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 67.5 (CH_2), 101.6 (CH_2), 107.6 (CH), 111.6 (CH), 112.0 (CH), 119.6 (CH), 120.8 (CH), 122.3 (Cq), 124.7 (CH), 125.7 (2CH), 126.3 (2CH), 126.5 (Cq), 127.2 (Cq), 128.5 (CH), 129.3 (CH), 133.3 (CH), 134.6 (Cq), 136.4 (Cq), 136.8 (Cq), 140.0 (Cq), 143.4 (Cq), 144.8 (Cq), 146.9 (Cq), 147.8 (Cq), 169.1 (CO); HRMS calculated for $C_{27}H_{18}NO_6S$ 484.0855, found 484.0854 ($M + H^+$).

5.30. 9-Benzenesulphonyl-4-(3,4,5-trimethoxyphenyl)-1,5-dihydro-H-furo[3,4-b]carbazol-3-one (**47**)

Compound **47** was isolated as a yellow solid from **41** (*Method A*) in 75% yield or from **35** (*Method B*) in 95% yield. Mp 204–206 °C; IR (KBr, cm^{-1}) ν 2936, 1736, 1581, 1511, 1446, 1361, 1224, 1174, 1123, 1012, 746, 685; ^1H NMR ($CDCl_3$, 250 MHz) δ 3.72 (s, 6H), 3.88 (s, 3H), 5.59 (s, 2H), 7.21–7.28 (m, 6H), 7.36–7.42 (m, 2H), 7.51 (t, 1H, $J = 8.0$ Hz), 7.83 (d, 2H, $J = 8.5$ Hz), 8.12 (d, 1H, $J = 8.5$ Hz); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 56.1 ($2CH_3$), 61.1 (CH_3), 67.5 (CH_2), 108.7 (CH), 112.1 (CH), 118.9 (Cq), 119.2 (CH), 120.8 (CH), 125.4 (2CH), 126.0 (2CH), 126.9 (Cq), 128.5 (2CH), 128.8 (Cq), 129.4 (CH), 133.3 (CH), 134.1 (Cq), 136.0 (Cq), 137.7 (Cq), 138.2 (Cq), 140.2 (Cq), 143.3 (Cq), 144.5 (Cq), 152.2 (2Cq), 169.1 (CO); HRMS calculated for $C_{29}H_{23}NO_7SNa$ 552.1093, found 552.1088 ($M + Na^+$).

5.31. General procedure for the preparation of NH-furocarbazoles **48**–**52**

Method A: see also reference [9]. *Method B*: A solution of **43**–**47** (0.21 mmol) and TBAF (1 M solution in THF, 0.42 mmol) in toluene (5 mL) was heated at 90 °C for 1 h. The resulting solution was cooled to room temperature and solvent was removed *in vacuo*. The crude product was purified by flash column chromatography (petroleum ether/EtOAc 8/2), to give the desired compounds.

5.32. 4-(4-Methoxyphenyl)-1,5-dihydro-3H-furo[3,4-b]carbazol-3-one (**48**)

Compound **48** was isolated as a yellow solid from **43** following *Method A* in 71% yield or following *Method B* in 81% yield. Mp >250 °C; IR (KBr, cm^{-1}) ν 3326, 2936, 1732, 1580, 1410, 1237, 1111, 828, 756; ^1H NMR (DMSO-d_6, 250 MHz) δ 3.87 (s, 3H), 5.46 (s, 2H), 7.12 (d, 2H, $J = 8.7$ Hz), 7.19–7.25 (m, 1H), 7.47–7.56 (m, 4H), 8.24 (d, 1H, $J = 7.7$ Hz), 8.30 (s, 1H), 11.07 (s, 1H); ^{13}C NMR (acetone-d_6, 62.9 MHz) δ 55.1 (CH_3), 68.0 (CH_2), 111.9 (CH), 112.1 (CH), 113.6 (CH), 117.8 (Cq), 119.2 (CH), 121.2 (2CH), 124.0 (Cq), 125.0 (Cq), 127.5 (2CH), 128.1 (Cq), 131.4 (CH), 137.7 (Cq), 138.4 (Cq), 142.2 (Cq), 159.1 (Cq), 165.7 (Cq), 170.0 (CO); HRMS calculated for $C_{21}H_{16}NO_3$ 330.1130, found 330.1115 ($M + H^+$).

5.33. 4-(3,5-Dimethoxyphenyl)-1,5-dihydro-3H-furo[3,4-b]carbazol-3-one (**49**)

Compound **49** was isolated as a yellow solid from **44** following *Method A* in 74% yield or following *Method B* in 70% yield. Mp >250 °C; IR (KBr, cm^{-1}) ν 2936, 1701, 1596, 1512, 1414, 1369, 1303, 1175, 1133, 1021, 744; NMR (acetone-d_6, 400 MHz) δ 3.83 (s, 6H), 5.45 (s, 2H), 6.57 (t, 1H, $J = 2.2$ Hz), 6.74 (d, 2H, $J = 2.2$ Hz), 7.24–7.28 (m, 1H), 7.47–7.51 (m, 1H), 7.57 (d, 1H, $J = 8.0$ Hz), 8.26 (d, 1H, $J = 8.0$ Hz), 8.30 (s, 1H), 10.43 (s, 1H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 55.7 ($2CH_3$), 68.9 (CH_2), 101.0 (CH), 108.9 (CH), 112.6 (CH), 113.1 (CH), 119.5 (Cq), 120.4 (CH), 122.0 (2CH), 122.8 (Cq), 125.3 (Cq), 128.5 (CH), 129.6 (Cq), 136.2 (Cq), 138.9 (Cq), 139.7 (Cq), 143.2 (Cq), 161.6 (2Cq), 170.3 (CO); HRMS calculated for $C_{22}H_{18}NO_4$ 360.1236, found 360.1219 ($M + H^+$).

5.34. 4-(3,4-Dimethoxyphenyl)-1,5-dihydro-3H-furo[3,4-b]carbazol-3-one (**50**)

Compound **50** was isolated as a yellow solid from **45** following *Method A* in 70% yield or following *Method B* in 72% yield. Mp 212–214 °C; IR (KBr, cm^{-1}) ν 2944, 1712, 1588, 1513, 1367, 1301, 1167, 1143, 1017, 712; NMR (acetone-d_6, 400 MHz) δ 3.84 (s, 3H), 3.92 (s, 3H), 5.45 (s, 2H), 7.01 (d, 1H, $J = 12.6$ Hz), 7.08–7.11 (m, 2H), 7.22 (t, 1H, $J = 12.6$ Hz), 7.45–7.56 (m, 2H), 8.26 (d, 1H, $J = 12.6$ Hz), 8.31 (s, 1H), 11.11 (s, 1H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 55.7 (CH_3), 56.0 (CH_3), 68.1 (CH_2), 108.2 (CH), 110.7 (CH), 111.9 (CH), 112.3 (CH), 118.0 (Cq), 119.3 (CH), 121.2 (Cq), 121.3 (CH), 123.7 (Cq), 123.8 (CH), 126.5 (CH), 127.6 (Cq), 128.2 (Cq), 137.6 (Cq), 138.5 (Cq), 142.2 (Cq), 147.0 (Cq), 147.1 (Cq), 169.9 (CO); HRMS calculated for $C_{22}H_{18}NO_4$ 360.1236, found 360.1245 ($M + H^+$).

5.35. 4-(3,4-Methylenedioxyphenyl)-1,5-dihydro-3H-furo[3,4-b] carba zol-3-one (**51**)

Compound **51** was isolated as a yellow solid from **46** following *Method A* in 70% yield or following *Method B* in 79% yield. Mp >250 °C; IR (KBr, cm^{-1}) ν 3308, 2900, 1735, 1499, 1442, 1325, 1226, 1111, 1031, 858, 745; ^1H NMR (DMSO-d_6, 250 MHz) δ 5.46 (s, 2H), 6.14 (s, 2H), 7.00 (dd, 1H, $J = 1.5$ Hz, $J = 8.0$ Hz), 7.08–7.11 (m, 2H), 7.19–7.26 (m, 1H), 7.45–7.56 (m, 2H), 8.25 (d, 1H, $J = 7.8$ Hz), 8.31 (s, 1H), 11.11 (s, 1H); ^{13}C NMR (DMSO-d_6, 62.9 MHz) δ 68.1 (CH_2), 101.1 (CH), 108.2 (CH_2), 110.7 (CH), 111.9 (Cq), 112.3 (CH), 118.0 (Cq), 119.2 (Cq), 121.2 (CH), 121.3 (CH), 123.7 (CH), 123.8 (CH), 126.5 (Cq), 127.6 (CH), 128.2 (Cq), 137.6 (Cq), 138.4 (Cq), 142.2 (Cq), 147.0 (Cq), 147.1 (Cq), 169.9 (CO); HRMS calculated for $C_{21}H_{13}NO_4Na$ 366.0742, found 366.0747 ($M + Na^+$).

5.36. 4-(3,4,5-Trimethoxyphenyl)-1,5-dihydro-3H-furo[3,4-b]car bazol-3-one (**52**)

Compound **50** was isolated as a white solid from **47** following *Method A* in 82% yield or following *Method B* in 75% yield [9].

5.37. 4-(3,4-Hydroxy-5-methoxyphenyl)-1,5-dihydro-3H-furo[3,4-b]carbazol-3-one (**53**)

A solution of BBr_3 (2.5 M in CH_2Cl_2, 17 μL) was added to a solution of **52** (50 mg, 0.128 mmol) in CH_2Cl_2(5 mL) at −78 °C. Water (5 mL) and CH_2Cl_2 (20 mL) were added after 1 h and the reaction mixture was allowed to warm to r.t. After extraction, the organic layer was washed with water (10 mL) and concentrated under reduced pressure. The crude residue was purified by flash chromatography (petroleum ether to petroleum ether/EtOAc 7/3) to afford compound **53** as a white solid (26 mg, 55%). Mp >250 °C; IR (KBr, cm^{-1}) ν 3512, 2932, 1714, 1532, 1437, 1317, 1123, 1034, 746; ^1H NMR ($CDCl_3$, 250 MHz) δ 3.93 (s, 3H), 5.44 (s, 2H), 7.17 (t, 1H, $J = 7.9$ Hz), 7.22 (t, 1H, $J = 7.9$ Hz), 7.26–7.34 (m, 2H), 7.43–7.60 (m, 2H), 7.80 (s, 1H), 8.36 (br s, 1H); ^{13}C HSQC NMR ($CDCl_3$, 62.9 MHz) δ 56.4, 68.1, 106.3, 111.1, 111.4, 118.2, 119.9, 122.1, 122.4; HRMS calculated for $C_{21}H_{16}NO_5$ 362.1028, found 362.1016 ($M + H^+$).

5.38. DNA binding measurements

They were performed as previously described [31].

5.39. Topoisomerases inhibition assays

They were performed as previously described [32].

5.40. Cell culture and survival assay

They were performed as previously described [33].

Acknowledgements

This work was supported by grants from the Ligue Nationale Française contre le Cancer (Comités du Nord et de l'inter-Région Grand Ouest) and the Canceropôle Grand Ouest.

References

[1] (a) J.L. Charlton, J. Nat. Prod. 61 (1998) 1447–1451;
(b) W.D. Mac Rae, G.H.N. Towers, Phytochemistry 23 (1984) 1207–1220.
[2] L.S. Thurston, H. Irie, S. Tani, F.S. Han, Z.C. Liu, Y.C. Cheng, K.H. Lee, J. Med. Chem. 29 (1986) 1547–1550.
[3] D.A. Burden, P.S. Kingma, S.J. Froelich-Ammon, M.A. Bjornsti, M.W. Patchan, R.B. Thompson, N. Osheroff, J. Biol. Chem. 271 (1996) 29238–29244.
[4] J.S. Madalengoitia, J.J. Tepe, K.A. Werbovetz, R.K. Lehnert, T.L. MacDonald, Bioorg. Med. Chem. 5 (1997) 1807–1815.
[5] F. Leteurtre, D.L. Sackett, J. Madalengoitia, G. Kohlhagen, T. MacDonald, E. Hamel, K.D. Paull, Y. Pommier, Biochem. Pharmacol. 49 (1995) 1283–1290.
[6] (a) B. Madrigal, P. Puebla, R. Pelaez, E. Caballero, M. Medarde, J. Org. Chem. 68 (2003) 854–864;
(b) J. Routier, M. Calancea, M. David, Y. Vallée, J.-N. Denis, Eur. J. Org. Chem. (2008) 5687–5691.
[7] (a) S.R. Flanagan, D.C. Harrowven, M. Bradley, Tetrahedron 58 (2002) 5989–6001;
(b) T. Kuroda, K. Kondo, T. Iwasaki, A. Ohtani, K. Takashima, Chem. Pharm. Bull. 45 (1997) 678–684.
[8] S. Routier, J.-Y. Mérour, N. Dias, A. Lansiaux, C. Bailly, O. Lozach, L. Meijer, J. Med. Chem. 49 (2006) 789–799.
[9] A. Chilloux, B. Biannic, S. Routier, J.-Y. Mérour, Lett. Org. Chem. 4 (2007) 198–202.
[10] K.-H. Buchheit, R. Gamse, R. Giger, D. Hoyer, F. Klein, E. Kloeppner, H.-J. Pfannkuche, H. Mattes, J. Med. Chem. 38 (1995) 2331–2338.
[11] V.O. Illi, Synthesis (1979) 136–139.
[12] (a) J.S. Madalengoira, T.L. Macdonald, Tetrahedron Lett. 34 (1993) 6237–6240;
(b) T. Ithara, K. Kawasaki, F. Ouseto, Synthesis (1984) 236–237.
[13] H. Sai, T. Ogiku, T. Nishitani, H. Hiramatsu, H. Horikawa, T. Iwasaki, Synthesis (1994) 582–586.
[14] Y. Sato, T. Tamura, M. Mori, Angew. Chem. Int. Ed. 43 (2004) 2436–2440.
[15] S.S. Chaudhari, K.G. Akamanchi, Synlett (1999) 1763–1765.
[16] R.B. Upasani, K.C. Yang, M. Acosta-Burruel, C.S. Konkoy, J.A. McLellan, R.M. Woodward, N.C. Lan, R.B. Carter, J.E. Hawkinson, J. Med. Chem. 40 (1997) 73–84.
[17] D.P. Papahatjis, T. Kourouli, V. Abadji, A. Goutopoulos, A. Makriyannis, J. Med. Chem. 41 (1998) 1195–1200.
[18] A. Pelter, R.S. Ward, G.M. Little, J. Chem. Soc., Perkin Trans I (1990) 2775–2790.
[19] H.J. Bestmann, H. Frey, Liebigs Ann. Chem. (1980) 2061–2071.
[20] D.H. Wadsworth, S.M. Geer, M.R. Detty, J. Org. Chem. 52 (1987) 3662–3668.
[21] S.J. O'Malley, K.L. Tan, A. Watzke, R.G. Bergman, J.A. Ellman, J. Am. Chem. Soc. 127 (2005) 13496–13497.
[22] C.M. Bonnin, P.A. Calby, C.G. Freeman, A.D. Waerd, Aust. Chem. J 32 (1979) 833–847.
[23] H. Sai, T. Ogiku, H. Ohmizu, A. Ohtani, Chem. Pharm. Bull. 54 (2006) 1686–1693.
[24] J.P. Das, U.K. Roy, S. Roy, Organometallics 24 (2005) 6136–6140.
[25] X. Lu, G. Zhu, Synlett (1993) 68–70.
[26] M. Tanoguchi, T. Kashima, H. Saika, T. Inoue, M. Raimoto, H. Yamagushi, Chem. Pharm. Bull. 37 (1989) 68–72.
[27] L. Rivas, L. Quintero, J.L. Fourrey, Tetrahedron Lett. 43 (2002) 7639–7641.
[28] A. Yasuhara, T. Sakamoto, Tetrahedron Lett. 39 (1998) 595–596.
[29] W.G. Harker, D.L. Slade, R.L. Parr, P.W. Feldhoff, D.M. Sullivan, M.H. Holguin, Cancer Res. 55 (1995) 1707–1716.
[30] A. Ryckebusch, D. Garcin, A. Lansiaux, J.-F. Goossens, B. Baldeyrou, N. Dias, R. Houssin, C. Bailly, J.-P. Hénichart, J. Med. Chem. 51 (2008) 3617–3629.
[31] J.-M. Barret, A. Kruczynski, S. Vispé, J.-P. Annereau, V. Brel, Y. Guminski, J.G. Delcros, A. Lansiaux, N. Guilbaud, T. Imbert, C. Bailly, Cancer Res. 68 (2008) 9845–9853.
[32] A. Bourderioux, V. Bénéteau, J.-Y. Mérour, B. Baldeyrou, C. Ballot, A. Lansiaux, C. Bailly, R. Le Guével, C. Guillouzo, S. Routier, Org. Biomol. Chem. 6 (2008) 2108–2117.
[33] C. Bailly, Methods Enzymol. 340 (2001) 610–623.