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ARTICLE TYPE

A concise formation of *N*-substituted 3,4-diarylpyrroles – synthesis and cytotoxic activity†

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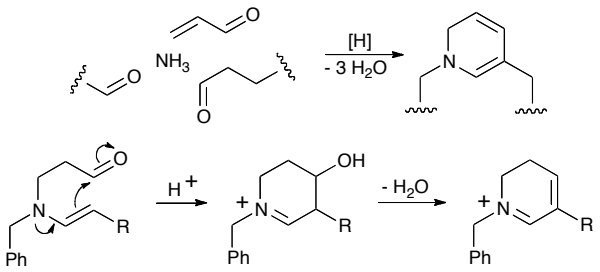
A short synthesis of *N*-substituted 3,4-diarylpyrroles by condensation of a phenacyl halide with a primary amine and a phenylacetaldehyde is reported. The key step is an intramolecular cyclization of an *in situ* generated enamine onto a ketone. Using differently substituted aromatic reactants and *N*-(3-aminopropyl)azatricyclodecane as the amine component, the preparation of analogs of the cytotoxic marine alkaloid halitulin could be achieved. The cytotoxicity of some of the compounds obtained by this method was studied, and one of them proved to be a very potent derivative, acting at a nanomolar concentration, in a caspase-independent cell death mechanism.

Introduction

In the context of a biomimetic approach toward manzamine alkaloids, we developed a method for the generation of 2,3-dihydropyridinium salts involving the intramolecular addition of an enamine onto an aldehyde (Scheme 1).[1] This procedure was based on a biogenetic proposal initially formulated by Baldwin and Whitehead.[2]

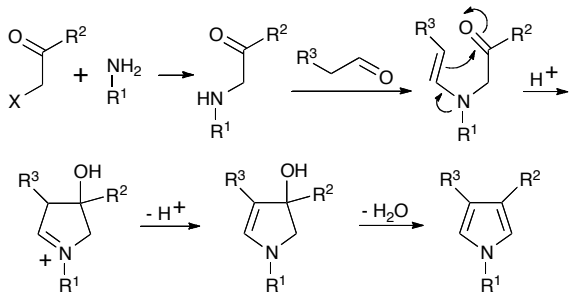


Scheme 1 Biomimetic formation of a 2,3-dihydropyridinium ion

Following this principle, it was anticipated that the cyclization of a β-ketoenamine could lead to a 1,3,4-trisubstituted pyrrole (Scheme 2), and more particularly to the 3,4-diarylpyrrole moiety of compounds such as the marine alkaloid halitulin (Figure 1).

This framework is also present in lamellarins and related derivatives obtained from marine organisms.[3] Halitulin, isolated from the marine sponge *Haliclona tulearensis*,[4] presents interesting biological properties, including cytotoxicity against several tumor cell lines at concentrations of 12–25 ng/mL. A total synthesis of halitulin has been reported by Steglich.[5]

Methods for the synthesis of pyrroles have been reviewed,[6] including those concerning compounds with two aryl groups on adjacent positions[7] and chiral molecules or natural products containing the pyrrole framework.[8] The process depicted in Scheme 2 is reminiscent of the Knorr and Hantzsch pyrrole syntheses,[6] but these reactions have been conducted mostly with active methylene compounds (β-diketones or β-ketoesters), leading to pyrroles substituted at position 3 by an acyl or an alkoxycarbonyl group. To the best of our knowledge, aralkyl ketones were used only for the formation of tri- or tetrasubstituted 1*H*-pyrroles.[9]



Scheme 2 A possible pathway toward 1,3,4-trisubstituted pyrroles

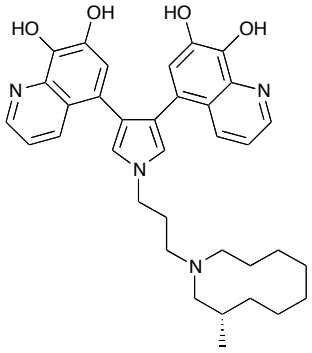


Figure 1 Structure of halitulin

It should be noted that the pathway shown in Scheme 2 might

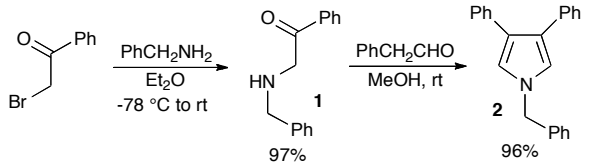
allow the formation of heterocycles with different R^2 and R^3 substituents, unlike the synthesis of symmetric 1,3,4-trisubstituted pyrroles by condensation of phenethylamines in the presence of $Pd(OAc)_2$ and $Cu(OAc)_2$[10] or via the one-pot AgOAc-mediated reaction of primary amines with aldehydes.[11]

As a part of a programme aiming at the synthesis of halitulin and analogs, we examined the formation of *N*-substituted 3,4-diarylpyrroles according to Scheme 2.

Results and discussion

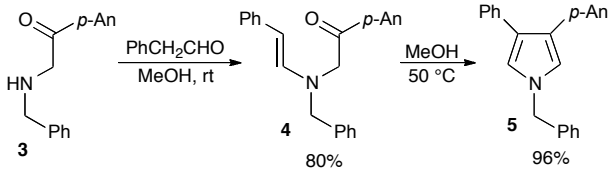
Chemistry

The formation of the precursor, for the desired cyclization, should result from the condensation of an α-haloketone, first with a primary amine, and then with an aldehyde. To test the feasibility of the reaction, even if α-alkylaminoketones are not very stable derivatives,[12] we first prepared separately compound **1** by reacting phenacyl bromide with benzylamine. By treatment of **1** with phenylacetaldehyde in methanol at room temperature, 1-benzyl-3,4-diphenylpyrrole **2**[13] was obtained in high yield (96%), showing the efficiency of the process (Scheme 3).



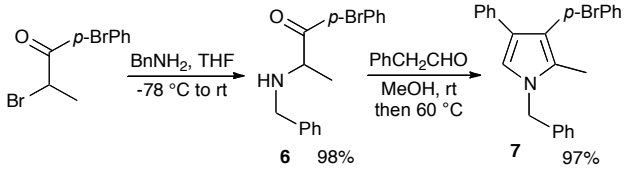
Scheme 3 Sequential formation of 1-benzyl-3,4-diphenylpyrrole **2**

The unstable intermediate enamine **4** with a *p*-methoxybenzoyl group, which could be isolated as a crystalline solid, starting from **3** (*p*-An = 4-methoxyphenyl), readily led to the corresponding pyrrole **5** when heated in methanol at 50 °C, strengthening the mechanistic proposal depicted in Scheme 2 (Scheme 4).



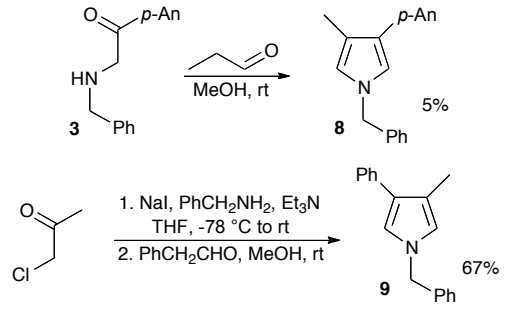
Scheme 4 Formation of a 1-benzyl-3,4-diarylpyrrole (**5**) from an isolated enaminoketone (**4**)

This strategy allows the preparation of 1,2,3,4-tetrasubstituted pyrroles, as exemplified by the formation of **7** via aminoketone **6** derived from 2,4'-dibromopropiophenone (Scheme 5).



Scheme 5 Sequential synthesis of a 1,2,3,4-tetrasubstituted pyrrole

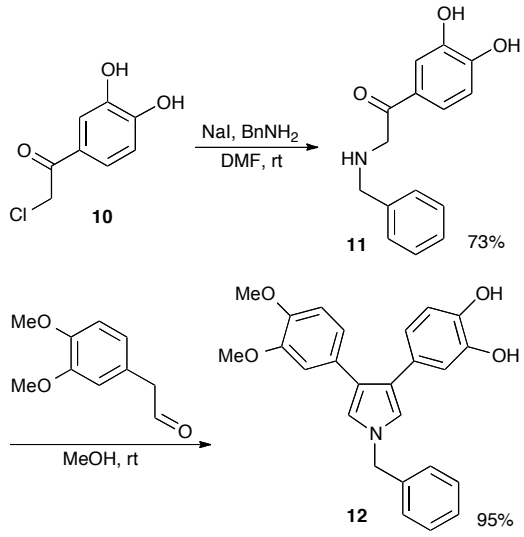
When aliphatic aldehydes are used, the procedure is not efficient, as indicated by the low yield of **8**[14] (Scheme 6), due to the decreased stability of the non-conjugated enamine. However, the same type of substitution for the pyrrole (compound **9**) can be obtained, starting from chloroacetone and phenylacetaldehyde. In this case, the product is best obtained using a one-pot procedure, due to the higher instability of the intermediate aminoketone.



Scheme 6 Formation of 1,3-dialkyl,4-arylpyrroles

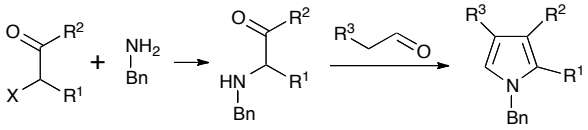
As halitulin presents catechol-type substituents, the formation of a pyrrole with a 3,4-dihydroxyphenyl group was envisaged, following the same methodology.

Condensation of benzylamine with the commercially available 2-chloro-3',4'-dihydroxyacetophenone **10**, in the presence of sodium iodide, led to the unstable aminoketone **11**, which was rapidly treated with 3,4-dimethoxyphenylacetaldehyde,[15] affording pyrrole **12** (Scheme 7).



Scheme 7 Synthesis of a pyrrole bearing catechol groups

The method has been extended to other derivatives and the results for the synthesis of substituted *N*-benzylpyrroles, according to the general Scheme 8, are summarized in Table 1. Bromo- or chloroketones were used as starting materials and, in the latter case, halogen exchange was achieved *in situ* with sodium iodide.

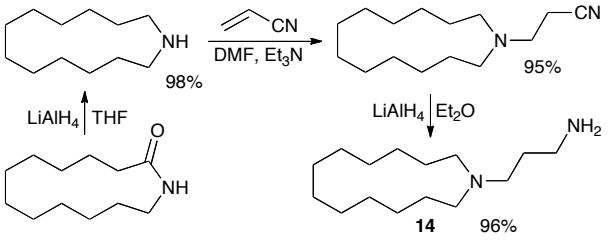


Scheme 8 General scheme for the synthesis of *N*-benzylpyrroles

Table 1 Yields of the compounds prepared according to Scheme 8

R^1	R^2	R^3	X	pyrrole	yield
H	Ph	Ph	Br	**2**	93%
H	4-$CH_3OC_6H_4$	Ph	Br	**5**	92%
CH_3	4-BrC_6H_4	Ph	Br	**7**	95%
H	4-$CH_3OC_6H_4$	CH_3	Br	**8**	5%
H	CH_3	Ph	Cl	**9**	60%
H	3,4-$(HO)_2C_6H_3$	3,4-$(CH_3O)_2C_6H_3$	Cl	**12**	69%
CH_3	4-BrC_6H_4	3,4-$(CH_3O)_2C_6H_3$	Br	**13**	82%

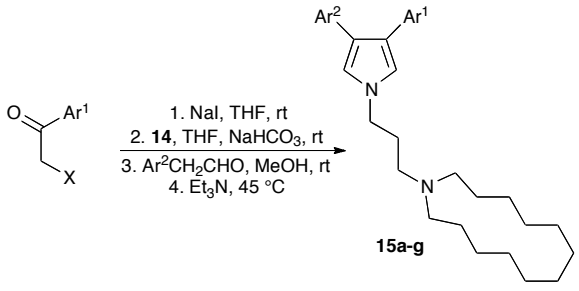
After the development of this new pyrrole synthesis, it was envisioned to apply it to the formation of halitulin analogs and to investigate some of their biological activities. We modified the hydrophobic moiety bound to the pyrrole nitrogen, which is present in the natural product, keeping the three-carbon linker between the two nitrogen atoms but not the azacyclodecane ring. For this, *N*-(3-aminopropyl)azatricyclodecane **14** was chosen as the primary amine component (see Scheme 2), instead of the isohaliclorensin moiety of halitulin.[16] The thirteen-membered macrocyclic amine was selected due to its rapid access starting from the commercially available laurolactam (Scheme 9),[17] and also because this achiral moiety is present in motuporamine A, another cytotoxic alkaloid isolated from the marine sponge *Xestospongia exigua* (Kirckpatrick).[18] In addition, it seemed interesting to see the role of this hydrophobic part of the molecule in the biological activity.



Scheme 9 Preparation of primary amine **14**

The aromatic moieties, characteristic of halitulin, were also simplified to examine the influence of the oxygens and of the quinoline part on the natural product activity.

Different conditions were tested for the formation of the pyrrole nucleus substituted by aryl groups, using **14** as the amine component, and the following one-pot procedure was found to be optimal for the preparation of compounds **15a-g** (Scheme 10 and Table 2).

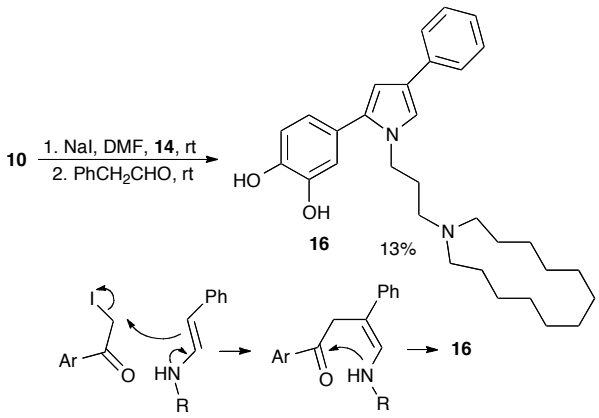


Scheme 10 One-pot synthesis of *N*-substituted 3,4-diarylpyrroles **15a-g**

Table 2 Yields of compounds **15a-g** prepared according to Scheme 10

Ar^1	Ar^2	X	pyrrole	yield
3,4-$(HO)_2C_6H_3$	Ph	Cl	**15a**	24%
3,4-$(HO)_2C_6H_3$	3,4-$OCH_2OC_6H_3$	Cl	**15b**	20%
3,4-$(HO)_2C_6H_3$	3,4-$(CH_3O)_2C_6H_3$	Cl	**15c**	19%
Ph	Ph	Br	**15d**	61%
4-$CH_3OC_6H_4$	Ph	Br	**15e**	52%
4-$CH_3OC_6H_4$	3,4-$OCH_2OC_6H_3$	Br	**15f**	29%
4-$CH_3OC_6H_4$	3,4-$(CH_3O)_2C_6H_3$	Br	**15g**	37%

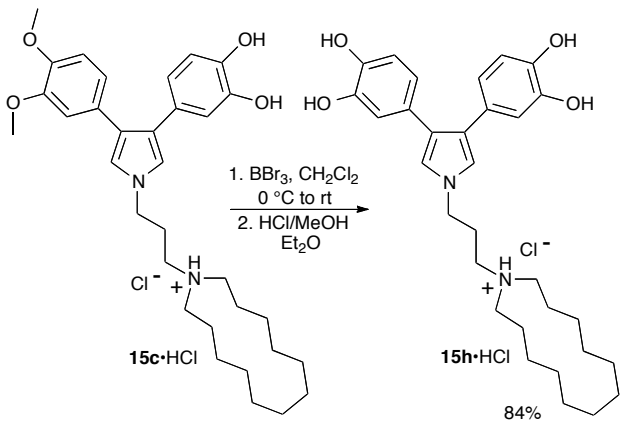
It was found, on one occasion, that a change of solvent (replacement of THF by DMF) and a shorter time of contact of phenacyl chloride **10** with sodium iodide, for the procedure shown in Scheme 10, led to the formation of *N*-substituted 2,4-diarylpyrrole **16**, albeit in a poor yield (Scheme 11). It is assumed that, in the latter case, the imine/enamine resulting from the condensation of phenylacetaldehyde and amine **14** reacted as the nucleophilic partner in the substitution reaction involving the iodoketone generated *in situ*.



Scheme 11 Formation of *N*-substituted 2,4-diarylpyrrole **16**

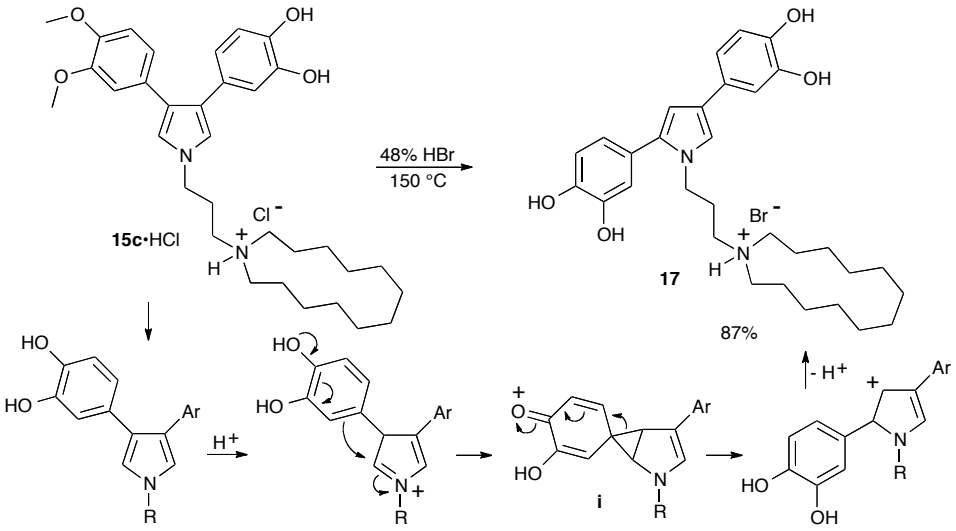
Hydrochlorides of derivatives **15a-g** and **16** were generally obtained by adding 2 M HCl in methanol to a chloroform solution of the pyrrolic tertiary amine.

BBr_3-Induced *O*-demethylation of **15c** led to the bis(catechol) analog **15h** (Scheme 12).

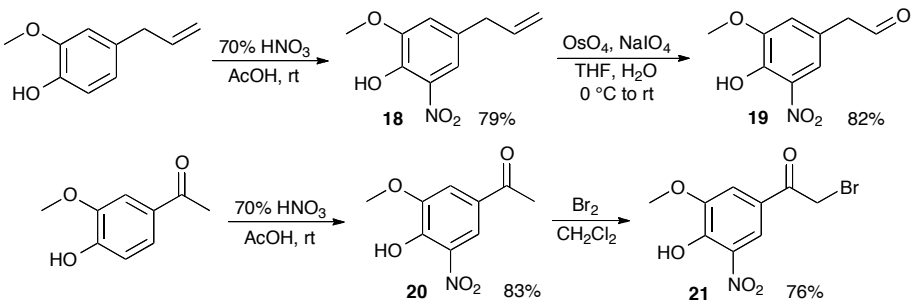


Scheme 12 Bis *O*-demethylation of **15c** to give **15h**

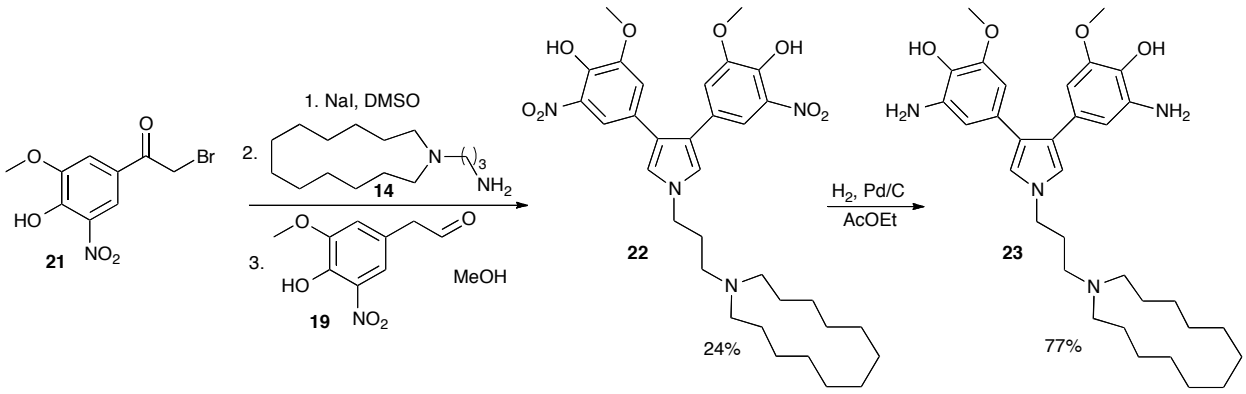
When harsher conditions were used for the demethylation of **15c** (48% HBr, 150 °C), a rearrangement was observed, leading to the 2,4-diarylpyrrole **17**, and a mechanistic proposal is given in Scheme 13. The electron-donating substituents on the phenyl group, and especially the *para*-hydroxyl, should make easier the migration of the aryl group via an intermediate such as **i**, and the formation of **17** could result from a steric decompression (release of the strain due to the two adjacent aryl substituents on the pyrrole nucleus). To the best of our knowledge, this type of rearrangement has not been reported but the migration of a substituent from position 2 to position 3 on the pyrrole ring is described as a more favoured process.[2]



Scheme 13 Demethylation of **15c** with rearrangement of a 3,4-diarylpyrrole into 2,4-diarylpyrrole **17**



Scheme 14 Preparation of phenylacetaldehyde **19** and phenacyl bromide **21**

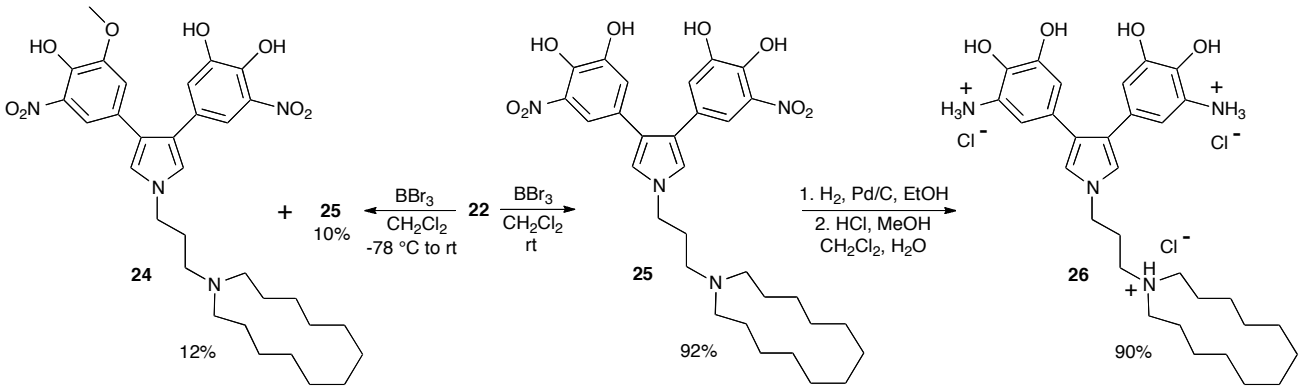


Scheme 15 Formation of pyrrole **22** by condensation of bromoketone **21** with amine **14** and aldehyde **19**, and reduction of the nitro functionalities

The formation of pyrroles substituted with two nitrocatechol groups at positions 3 and 4 was envisaged following Scheme 10, with the aim that these functionalities could be used as potential precursors for the dihydroxyquinoline moieties present in halitulin.[21] The aldehyde and the bromoketone, chosen as partners in the three-component reaction, were easily accessible, especially as the catechol monomethyl ethers **19** and **21**. These compounds were prepared, each in two steps, from

the commercially available and cheap eugenol and 4'-hydroxy-3'-methoxyacetophenone, respectively (Scheme 14). Both syntheses began with a regioselective nitration, leading to **18** and **20**, respectively. Oxidative cleavage of olefin **18** afforded aldehyde **19** and bromination of ketone **20** provided phenacyl bromide **21**.

For the key pyrrole synthesis, condensation of **21** with **14** and **19** was conducted in slightly modified conditions, compared to those of Scheme 10, the procedure being simplified and improved by using DMSO as the solvent (Scheme 15). This led to compound **22**, the nitro groups of which were reduced by catalytic hydrogenation, affording **23**.



Scheme 16 Demethylation of compound **22** with BBr_3 and reduction of the bis nitrocatechol derivative **25** by catalytic hydrogenation

For the demethylation of **22**, BBr_3 was used and, depending on the conditions, the monomethyl ether **24** and/or the bis nitrocatechol derivative **25** could be isolated. Reduction of the nitro functions of **25**, using catalytic hydrogenation, led to pyrrole **26** bearing two aminocatechol moieties.

Since halitulin is a toxic compound against different cell lines, the cytotoxicity of several pyrrolic products obtained by the presently reported methodology was examined.

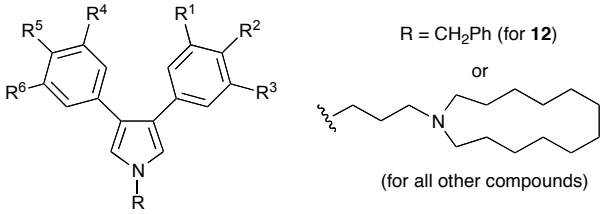
Cytotoxic studies

IC_{50} were measured for selected compounds, using the resorufin fluorescence test (72 h) and the values are reported in Table 3 (the structure of the pyrroles which have been tested is shown in Figure 2).

Table 3 Cytotoxicity of selected compounds against different cell lines with IC_{50} (μM) (see Figure 2 for the structures)

pyrrole[a]	HCT-116	U87	MDA-231	K562
12	20	nd[b]	nd[b]	nd[b]
15a	14	12	nd[b]	6
15b	15	nd[b]	nd[b]	nd[b]
15c	8	nd[b]	9	10
15d	20	20	na[c]	20
15e	20	nd[b]	nd[b]	nd[b]
15f	18	nd[b]	nd[b]	nd[b]
15g	35	nd[b]	nd[b]	nd[b]
15h	3	3	9	2
17[c]	30	nd[b]	nd[b]	nd[b]
22	20	na[d]	na[d]	na[d]
23	na[c] (> 30 μM)	na[c] (> 30 μM)	na[c] (> 30 μM)	na[c] (> 30 μM)
24	5	7	nd[b]	30
25	0.03	0.045	0.1	0.075
26	na[d]	na[d]	na[d]	na[d]

[a] as the hydrochloride salt, except for **12** and **17** (hydrobromide salt); [b] not determined; [c] 2,4-diarylpyrrole; [d] no activity



compound	R^1	R^2	R^3	R^4	R^5	R^6
12	H	OMe	OMe	H	OH	OH
15a	H	OH	OH	H	H	H
15b	H	OH	OH	H	O-CH_2-O	
15c	H	OH	OH	H	OMe	OMe
15d	H	H	H	H	H	H
15e	H	OMe	H	H	H	H
15f	H	OMe	H	H	O-CH_2-O	
15g	H	OMe	H	H	OMe	OMe
15h	H	OH	OH	H	OH	OH
17[a]	H	OH	OH	H	OH	OH
22	OMe	OH	NO_2	OMe	OH	NO_2
23	OMe	OH	NH_2	OMe	OH	NH_2
24	OMe	OH	NO_2	OH	OH	NO_2
25	OH	OH	NO_2	OH	OH	NO_2
26	OH	OH	NH_2	OH	OH	NH_2

[a] 2,4-diarylpyrrole

Figure 2 General structure of compounds which have been tested

From Table 3, it can be seen that the most potent compound is **25** with the 3-(azatricyclodecan-1-yl)propyl group as a substituent for the pyrrole nitrogen and bearing two nitrocatechol moieties. The cytotoxicity of **25** is in the nanomolar range, in the same order as for halitulin, and this questions the role of the quinoline part in the biological activity of the natural product. A loss of activity is observed when replacing one or two nitrocatechol groups by their monomethyl counterpart (compare compound **25** with **22** and **24**), as well as by substituting the nitro by an amino group (compare **25** with

26).

In vitro IC_{50} were therefore measured for **25** with another panel of human cancer cell lines, using colchicine as a reference (Table 4), and with another cell proliferation assay (MTS reagent).

Table 4 IC_{50} (μM) for compound **25** with different cell lines

cell line	**25**[a]	colchicine
KB	0.005/0.006	
HepG2*	0.001/0.002	0.007/0.017
HepG2* (2^{nd})	0.002/0.002	0.001/0.0009
PC3	0.048/0.077	~10/~10
HL60	0.013/0.010	0.0005/0.0012
HL60 (2^{nd})	0.022/0.034	<0.001/0.0007
HL60R	0.028/0.034	0.485/0.514
K562	0.015/0.012	0.0005/0.001
PaCa	0.0006/0.001	0.001/0.001
OVCAR8	0.013/0.018	0.003/0.003
MCF7	0.016/0.020	2.87/3.20

[a] as the hydrochloride salt

As shown in Table 4, IC_{50} for compound **25** remains in the nanomolar range, whatever the cell line (0.6 to 77 nM), with a 5 fold more sensitive absolute value with the MTS reagent used for this cell proliferation test than that obtained with resorufin (compare K562 cell line in Tables 3 and 4). With HL60R line, overexpressing the efflux pump P-gp in comparison with their counterpart HL60, a similar IC_{50} value is observed.

In an effort to elucidate the mechanism by which compound **25** can induce cell death, proapoptotic caspase 3–7 activity was performed. From the data presented in Figure 3, it can be concluded that **25** displayed no caspase-dependent apoptotic activity, compare to TNFα or doxorubicin on HL60 cells (not shown) used as a positive controls.

Therefore, in order to determine whether compound **25** induced other cell death mechanism, we investigated the autophagic response using the expression of LC3-II protein. As shown in Figure 4, expression of LC3-II proteins in HCT-116 cells was found to increase in a dose dependent manner after 24 h of treatment with **25**, starting at 25 nM. These results suggest that autophagic response is, at least in part, involved in the mechanism of cytotoxicity induced by **25**.

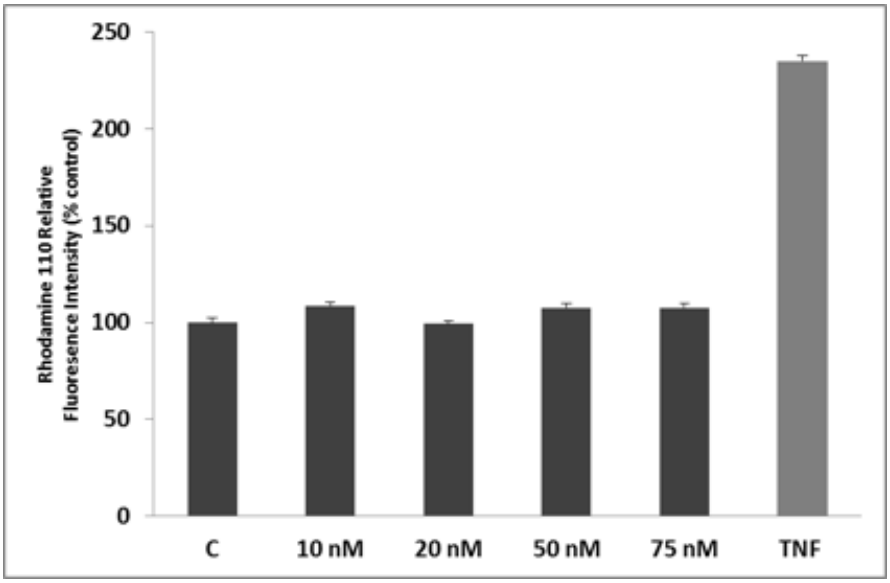


Figure 3 Apoptotic effects of compound **25** and TNFα in HCT-116 cells. Results are the accumulation of rhodamine in cells expressed as the percentage of control cells following 24 h of treatment with **25** at different concentrations and TNFα at 20 ng/mL.

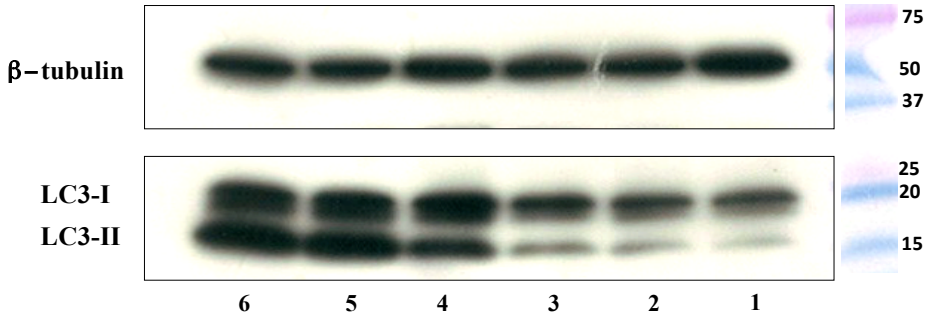


Figure 4 Western blot analysis of LC3 in compound **25**-treated HCT-116 cells. HCT-116 cells were treated without (column 1) or with **25** at concentrations of 5, 10, 25, 50 and 100 nM, respectively (columns 2 to 6). After drug treatment, HCT-116 cells were lysed and proteins were subjected to SDS-PAGE. An immunoblot was performed using anti-LC3 and anti-tubulin antibodies.

Conclusions

A concise one-pot synthesis of unsymmetrically substituted 3,4-diarylpyrroles, involving an intramolecular cyclization of *in situ* generated β-ketoenamines, is reported. The methodology is an alternative to the Hantzsch or Knorr pyrrole synthesis which is not limited to compounds bearing an electron-withdrawing substituent. If at least one aryl group could conveniently be introduced, since the formation of sufficiently stable enamines derived from phenylacetaldehyde or its substituted derivatives proved to be necessary, it was possible to obtain compounds with one alkyl group at position 3. The method could be extended to the synthesis of 2,4-diarylpyrroles either by reversing the order of introduction of the reactants or using an unprecedented rearrangement. Simplified analogs of halitulin were prepared using the present methodology and the cytotoxicity of some of the products obtained was studied. Compound **25**, with two nitrocatechol moieties as substituents of the pyrrole ring and a 3-(azatricyclodecan-1yl)propyl group on the nitrogen, was found to be the derivative with the highest cytotoxic activity of the series, the mechanism of which involved in part an autophagic response, without any caspase-dependent cell death mechanism. This compound might be a useful lead for anticancer drug development.

Notes and references

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