Organic & Biomolecular Chemistry

ROYAL SOCIETY OF CHEMISTRY

PAPER

View Article Online
View Journal

Cite this: DOI: 10.1039/d0ob00280a

Synthesis of propargylamines *via* the A^3 multicomponent reaction and their biological evaluation as potential anticancer agents†

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Received 7th February 2020,
Accepted 6th March 2020

DOI: 10.1039/d0ob00280a

rsc.li/obc

Propargylamines have gained importance in the area of anticancer research. We synthesized 1-substituted propargylic tertiary amines using the A^3-coupling as the key step. Both, solution and solid-phase protocols, were used to provide a library of 1-substituted propargylic tertiary amines with interesting structural diversity. The triple negative breast cancer subtype is the most aggressive and it lacks effective therapeutic options, while pancreatic cancer is one of the neoplasms with worse prognosis and limited therapeutic possibilities. The development of tumor-selective drugs has always been a major challenge in cancer treatment. From our library, two propargylamines displayed a high degree of cytotoxic selectivity. These levels of selectivity give a very interesting perspective for further development of 1-substituted propargylic tertiary amines as new potential chemotherapeutic antitumor agents.

Introduction

Over the past decades, propargylamines have become important structures for the synthesis of complex natural compounds and other bioactive substances, mainly of a myriad of nitrogen-containing heterocycles, such as pyrazines, pyridines, oxazoles, isoxazoles, imidazolidinones, triazoles and thiazoles, just to name a few.[1] Besides, the propargylamine moiety has been found in molecules of interesting biological and pharmacological properties; some of the examples are pargyline (**1**) and related structures, which have been reported as monoamine oxidase B (MAO-B) inhibitors,[2,3] as well as a selective GPIIb/IIIa antagonist that inhibits platelet aggregation, such as xemilofiban (**2**),[4,5] antibiotics like FR-90130 (**3**),[6] herbicides (**4**),[7] and acetyl-CoA carboxylase inhibitors (**5**),[8] among others (Fig. 1).

Furthermore, propargylamines have gained some importance in the area of anticancer research after the publication of reports showing antiproliferative activity in selegiline (**6**) [*R*-(−)-deprenyl, a well-known antiparkinsonian] and its derivatives,[9] and recently, the description of propargylamines, such as 7, that show histone deacetylase inhibitory effects.[10]

The public health demand for new antitumor agents is quite clear, due mostly to the lack of efficient therapies for the treatment of some types of cancer and metastasis progression,

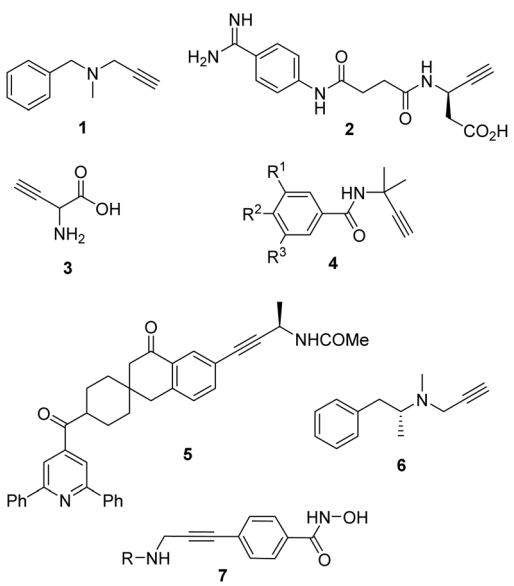

Fig. 1 Bioactive compounds containing a propargylamine moiety.

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†Electronic supplementary information (ESI) available. See DOI: 10.1039/d0ob00280a

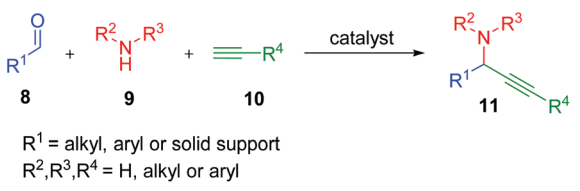
but also considering the side effects of known antineoplastic drugs and the development of drug resistance.[11]

Breast cancer is the most frequent cancer and one of the leading causes of cancer death in women. Among this sort of cancer, the triple negative subtype (characterized by the absence of expression of estrogen receptor [ER], progesterone receptor [PR] and epidermal growth factor receptor 2 [HER2/neu]) is the most aggressive one and, compared to other types of breast cancer, has worse prognosis. This type of tumor has high histological grade and high proliferation rates; it is also characterized by a high risk of recurrence and extreme malignancy.[12,13] Patients with this type of tumor have the disadvantage of not being able to receive hormonal therapies or therapies aimed at these cell targets so, the only treatment options they have are surgery, chemotherapy or combinations of both. On the other hand, pancreatic cancer, is also characterized by high malignity, poor prognosis and scarce therapeutic options.[14] The characteristics of both kinds of cancer underline the urgent need for treatments endowed with two equally important features: effectiveness and low toxicity.

Within the synthetic strategies for the construction of organic molecules, multicomponent reactions (MCRs) are of particular interest.[15,16] In MCRs, the desired product can be obtained in a single step using three or more starting materials, that is, two or more C–C and/or C–heteroatom bonds are formed in a simple manner. While a multi-step synthetic sequence requires multiple isolation and purification stages, similar diversity can be achieved in only a single stage in a multicomponent reaction. Although propargylamines can be obtained through a wide variety of methods,[1] the three-component coupling between an aldehyde, an alkyne and an amine, commonly called the A^3-coupling or Mannich-type reaction,[17] is particularly attractive for the generation of 1-substituted propargylic tertiary amines (**11**), an interesting core whose biological activity has not been extensively explored (Scheme 1).

We have also envisaged that the combination of MCRs and solid-phase organic synthesis could be very helpful by adding the advantages of solid-supported strategies (easy purification, parallelization and automatization)[18,19] to the high convergence of MCRs. In addition, the pseudo-dilution effect[20] could avoid purification problems associated with the homocoupling of terminal alkynes when copper catalysts are used (Glaser coupling).[21]

In this article, we wish to disclose our study regarding the different aspects related to the synthesis of 1-substituted propargylic tertiary amines by the A^3-coupling. The synthesized compounds were evaluated to establish their *in vitro* antiproliferative activity, providing encouraging preliminary results in the case of two derivatives.



Scheme 1 Generic A^3-coupling.

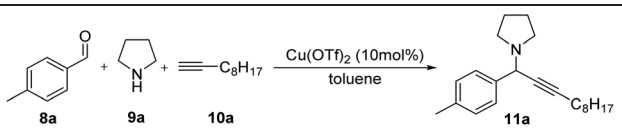
Results and discussion

Chemistry

Synthesis of propargylamines. Our first approach was to evaluate the reaction parameters by carrying out the MCR under different conditions. Thus, a short optimization was performed by testing the reaction among *p*-tolualdehyde (**8a**), pyrrolidine (**9a**) and 1-decyne (**10a**), some of the conditions evaluated are shown in Table 1. Traditionally, the A^3-coupling is carried out under copper catalysis, and the attack on the iminium ion is performed by the Cu-acetylide, instead of the enol, which is the main difference with the conventional Mannich reaction. Larsen *et al.* significantly extended the range of amines employed in this reaction by using Cu(OTf)$_2$, with remarkable Lewis acidity, that catalyzes tricomponent reactions among aldehydes, amines and terminal alkynes, regardless of the electronic properties of the imine intermediate.[22] When Cu(OTf)$_2$ was used at reflux of toluene for 6 h, product **11a** was obtained with 46% yield (entry 1). Under microwave heating for 1 h (entry 2), a mixture of **11a** and the corresponding 1,3-disubstituted allene **12a** was obtained, and the yields after purification by column chromatography were 43% and 26% respectively. A rationale for this transformation could imply that, after the generation of propargylamine, copper coordinates to the triple bond favouring a 1,5-hydride transfer and β-elimination to provide the allene product (Scheme 2).[23]

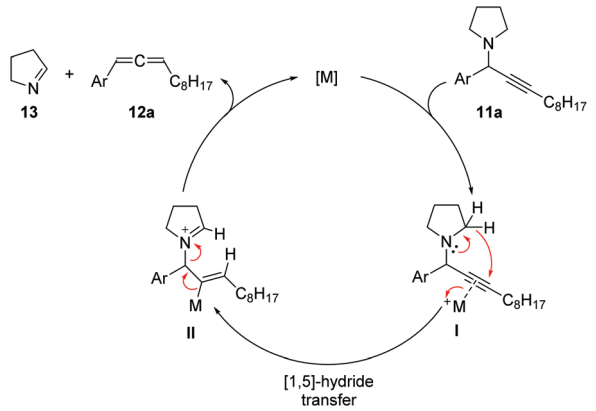
To our delight, when the reaction was performed under conventional heating at 120 °C in a sealed tube for 6 h, an almost quantitative isolated yield of the desired propargylamine was obtained (98%, entry 3, Table 1). Under similar conditions, but using diglyme as a solvent we obtained analogous results, however, work-up was more cumbersome due to the

Table 1 Optimization of the A^3 multicomponent reaction[a]



Entry	Conditions	Yield[b] (%)
1	Reflux, 6 h	46
2	MW[c] 120 °C, 1 h	43[d]
3	120 °C,[e] 6 h	98

[a] Reactions were carried out in toluene, with 10 mol% of Cu(OTf)$_2$, **8a** (1.1 equiv.), **9a** (1 equiv.) and **10a** (1.5 equiv.). [b] Yields were calculated after purification by column chromatography. [c] Microwave irradiation at 120 °C, 60 min, and 200 W max. power. [d] 26% of the corresponding allene was also isolated. [e] Closed vessel.



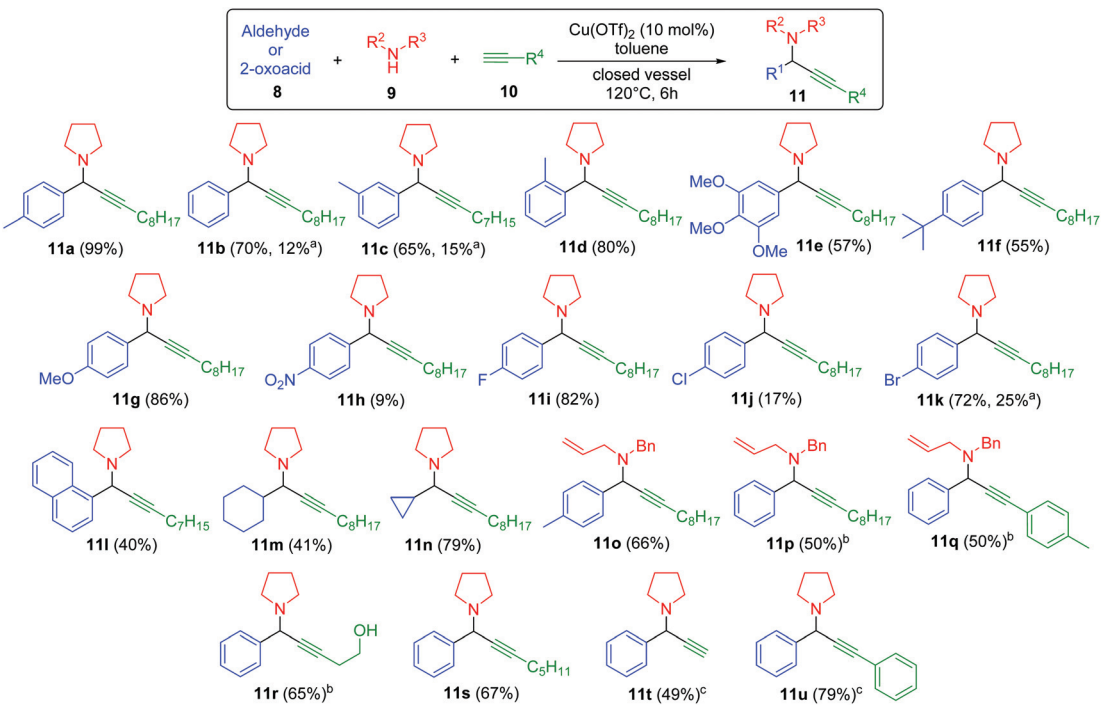
Scheme 2 Proposed mechanism for the formation of allenes from propargylamines.

very high boiling point of the solvent so, we decided to proceed with the conditions of entry 3.

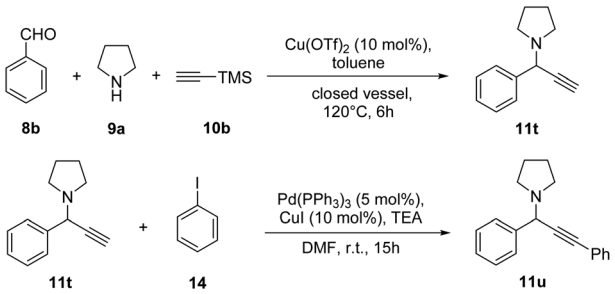
With these results in hand, a library of 1-substituted propargylic tertiary amines was obtained and the scope and limitations of the reaction were studied. Different amines, alkynes and aldehydes were tested (Scheme 3) and the respective propargylamines were obtained mostly in good yields, and in some cases, a minor amount of the corresponding 1,3-disubstituted allene was also isolated. We also noticed that the tricomponent reaction worked well under a decarboxylative approach using 2-oxoacid derivatives.[24] Thus, propargylamines **11p–r** were obtained in good yields using phenylglyoxylic acid (**8′b**).

At this stage, we thought that the Sonogashira coupling could be an interesting option for increasing the scope of the library. Thus, the strategy depicted in Scheme 4 was developed. First, we performed the A^3-component reaction under the optimized conditions using ethynyltrimethylsilane (**10b**) as the alkyne component, giving the propargylamine **11t** in 49% yield after purification using a chromatographic column. Hence, we obtained the Sonogashira precursor in a one-pot MCR-desilylation process. Desilylation was not surprising, since there are many examples in the literature of the cleavage of the Si–C bond in the presence of copper salts.[25–27] Then, the Sonogashira coupling was performed using aryl iodide and tetrakis(triphenylphosphine)palladium(0) as catalysts, to afford the phenyl derivative **11u.** This procedure is a good alternative for the generation of an arylalkynyl side chain in the propargylamine core. Although this was a promising strategy, no further examples were obtained since the aromatic ring in that position decreases the antitumor activity, according to the biological results shown below.

Solid-phase synthesis of propargylamines. Taking into account our experience on the combination of solid-phase organic chemistry and transition metal-catalyzed synthesis,[28–36] we decided to explore its application to the generation of 1-substituted propargylic tertiary amines.[37,38] We first synthesized the immobilized aldehyde **15** by anchoring the 4-formylbenzoic acid to Wang resin by a standard procedure. Then, we evaluated the behavior of the supported alde-



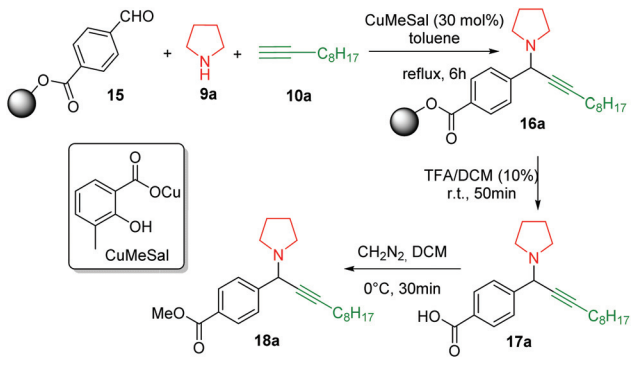
Scheme 3 Reactions were carried out in a closed vessel at 120 °C for 6 h in toluene, $Cu(OTf)_2$ (10 mol%), aldehyde (1.1 equiv.), amine (1 equiv.) and alkyne (1.5 equiv.). Yields were calculated after purification by column chromatography and are expressed in brackets. [a] Isolated allene yield. [b] Using phenylglyoxylic acid (**8′b**) instead of aldehyde **8b**. [c] The synthesis of these propargylamines is shown in Scheme 4.



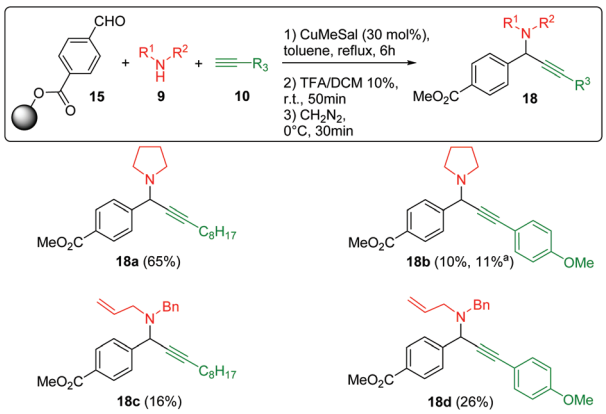
Scheme 4 MCR with ethynyltrimethylsilane (**10b**) and Sonogashira coupling.

hyde **15** under the optimized conditions in solution for the A^3-coupling. We foresaw that the strong Lewis acid conditions of the reaction due to $Cu(OTf)_2$ could lead to a premature cleavage of the immobilized compound from the resin. In fact, after suspending aldehyde **15** in toluene in the presence of 10 mol% of $Cu(OTf)_2$ and heating the mixture at 100 °C for 2 h, we verified that 75% of 4-formylbenzoic acid had been cleaved from the resin. Based on this, we proposed to find an alternative catalyst, to avoid premature cleavage of the ester bond between the substrate and the resin. We then focused on copper(I) carboxylates, such as copper(I) 3-methylsalicylate (CuMeSal)[39] and copper(I) thiophene-2-carboxylate (CuTC),[40–42] which have exhibited a rate of enhancement in different copper-catalyzed chemical reactions.

As a model, we tested the reaction among immobilized aldehyde **15**, pyrrolidine (**9a**) and 1-decyne (**10a**) (Scheme 5). Best results were obtained with 30 mol% of CuMeSal in toluene at reflux for 6 h, and the formation of the immobilized propargylamine was corroborated by IR and ^{13}C gel phase NMR. IR showed the disappearance of the aldehyde signals and the presence of an absorption band at 1716 cm^{-1} characteristic of an ester functional group. Among other signals, the ^{13}C gel-phase NMR spectrum showed the absence of an aldehyde carbonyl signal at 190.8 ppm, the presence of the pyrrolidine secondary carbons (50.1 and 23.5 ppm), and the sp carbons of the triple bond (87.8 and 76.2 ppm). No evidence of premature cleavage was observed during the reaction. The



Scheme 5 Solid-phase synthesis of propargylamines.



Scheme 6 Immobilized aldehyde **15** (1 equiv.), amine (2 equiv.), alkyne (3 equiv.), and CuMeSal (30 mol%) in toluene were heated at reflux for 6 h. After that, cleavage and methylation gave the propargylamines **18**. Yields were calculated after purification by column chromatography and are expressed in brackets [a] Isolated allene yield.

immobilized propargylamine was then subjected to TFA treatment to release **17a** from the polymeric support (Scheme 5). Finally, methylation was performed with diazomethane to obtain **18a** in a very good overall isolated yield of 65% after column chromatography, based on the theoretical loading of the starting Wang resin.

Then, we carried out a series of solid-phase experiments with different amines and alkynes (Scheme 6). When the alkyne with an aliphatic chain was changed to an aromatic derivative with a donor group in the *para* position, such as the 4-ethynylanisole, only 10% of the desired propargylamine **18b** was obtained, together with 11% of the corresponding allene. When an unsubstituted aromatic terminal alkyne was used (phenylacetylene), an inseparable mixture of unidentified products was obtained. Finally, *N*-allylbenzylamine and two different alkynes, 1-decyne and 4-ethynylanisole, were tested, giving yields of 16% and 26%, respectively (**18c** and **18d**). From these results, it seems to be clear that the combination of cyclic amines (pyrrolidine) and aliphatic terminal alkynes provided the best results.

Biological evaluation

Viability essay. A cell viability assay was initially developed to evaluate the *in vitro* antitumor activity of a library of propargylamines at 100 μM concentration against 4T1 (triple negative subtype) PANC-1 tumor cell lines (Fig. 2A and B, respectively). Compounds producing an inhibition of viability greater than 50% were considered to have an antitumor effect. We found that **11a**, **11b**, **11f**, **11g**, **11h**, **11i**, **11j**, **11k**, **11m**, **11n**, **11s** and **18a** inhibited more than 50% of viability of 4T1 and PANC-1 cells, while **18b** did it only in 4T1 cells. To evaluate the selectivity against tumor cells, the cytotoxic effect on the MC3T3e1 normal cell line was tested (Fig. 2C). Compounds producing less than 50% of cell viability inhibition were considered to be of low toxicity for normal cells. Propargylamines

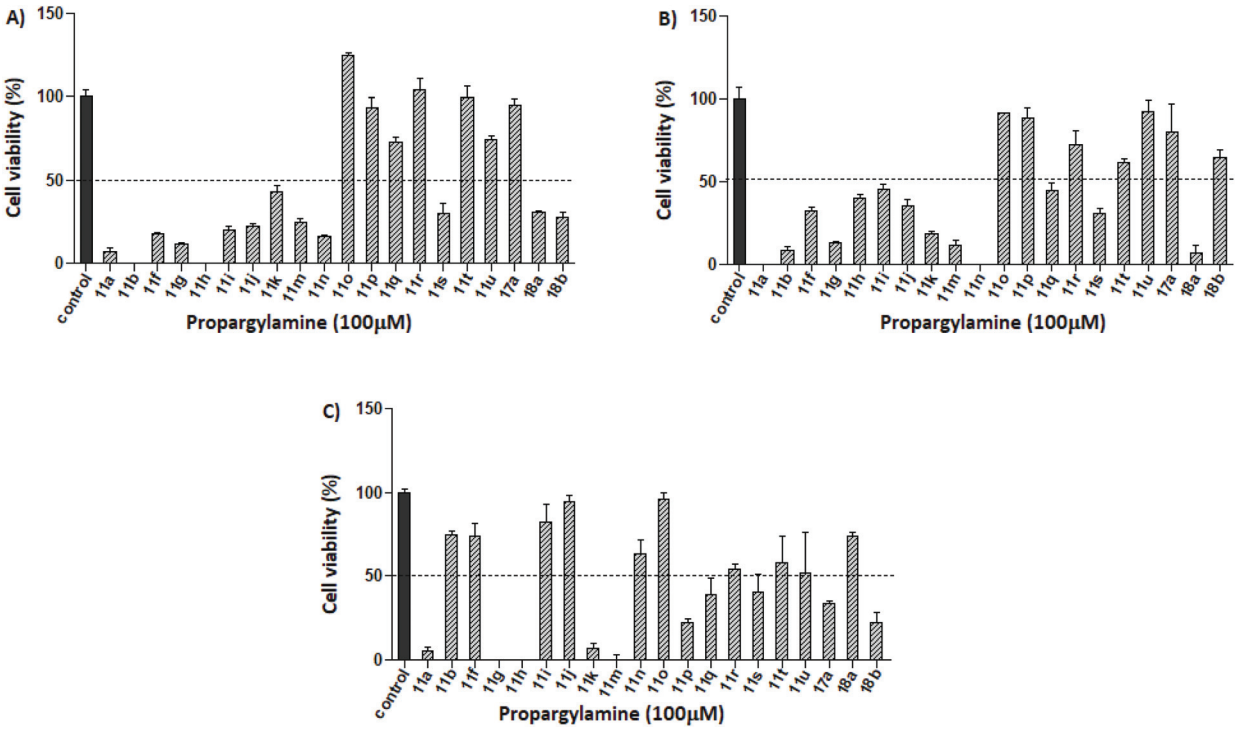


Fig. 2 Viability essays of propargylamines (100 μM) against different cell lines: (A) tumor cell line 4T1. (B) Tumor cell line PANC-1. (C) Normal cell line MC3T3e1.

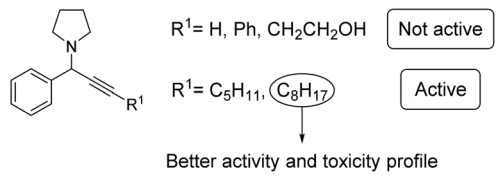


Fig. 3 Effect of the alkyne component of the propargylamine in cell viability assays.

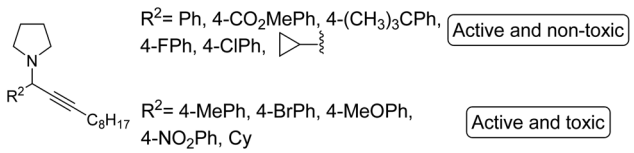


Fig. 4 Effect of the aldehyde component of the propargylamine in cell viability assays.

11b, **11f**, **11i**, **11j**, **11n**, **11o**, **11r**, **11t**, **11u** and **18a** inhibited viability by less than 50%.

From these results, some structure–activity relationships might be established. Propargylamines with an alkyl chain attached to the alkyne and cyclic amine (pyrrolidine) exhibit a better cell inhibitory effect. Compounds bearing an acyclic amine (**11o**, **11p** and **11q**) were mostly inactive, while aromatic substitution on the alkyne moiety also exhibited low activity (**11q**, **11u** and **18b**). Comparing the alkyl substituent on the alkyne side chain, we could realize that a certain chain length is necessary, since, for example, when R^1 is C_8H_{17} (**11b**) the activity and toxicity profile is better than that of the C_5H_{11} chain derivative (**11s**) (Fig. 3).

Then, the influence of the aldehyde component on the activity was analyzed, fixing the amine and alkyne (Fig. 4). All these compounds were active, which demonstrates the greater dependence of the amine and alkyne moiety on the activity, however, as can be seen in the figure, the aldehyde component is a determinant of the selectivity.

The steric differences between the 4-*t*BuPh (**11f**) and 4-CH_3Ph (**11a**) substituents could explain the better selectivity of the former; while, not surprisingly, aromatic substituents such as bromo (**11k**) or nitro (**11h**) could lead to more cytotoxicity. Eventually, compounds **11b**, **11f** and **18a** provided the best biological profile. Due to synthetic practicality, further studies were carried out on **11b** and **18a**.

Afterward, the effect on the cell viability of both compounds in cells with human background was tested: MDA MB 231 (triple negative breast cancer cells) and PANC-1 in a wide range of concentrations (MDA MB 231: 500–25 μM and PANC-1: 300–10 μM). We calculated the IC_{50} for each compound and cell type and, then, the selectivity index (Table 2).

The dose–response curves for both compounds against MDA MB 231 cells showed that **11b** had higher antitumor activity than **18a**, which was reflected in their respective IC_{50} values. In the case of PANC-1 cells, dose–response curves and IC_{50} values were similar for both compounds and lower than those obtained for the MDA MB 231 line. According to the IC_{50} values obtained in MC3T3e1 normal cells, both compounds

Table 2 Comparative IC_{50} values for compounds **11b** and **18a** against normal and cancer cells

Compound	Normal cell line IC_{50}	Tumor cell line IC_{50}	Selectivity index SI[a]
11b	*MC3T3e1*	MDA MB 231	3.38
	250.5 μM	74.05 μM	
		PANC-1	11.60
		21.59 μM	
18a	*MC3T3e1*	MDA MB 231	1.91
	558.4 μM	291.0 μM	
		PANC-1	41.17
		13.56 μM	

[a] IC_{50} for normal cells/IC_{50} for cancer cells.

showed selectivity for the tumor cell lines. The selected propargylamines reduced cell viability by around 50% over the entire range of concentrations studied, although at concentrations higher than 0.4 mM for **11b** and 0.5 mM for **18a** an increase in toxic effect was detected (see the ESI†).

High selectivity was obtained from **11b** and **18a**. The selectivity index (SI) is considered significant for values higher than 3. That is to say that the cytotoxicity caused by the compound to the tumor cells is more than three times higher than that caused to normal cells.[43] The SI of **11b** was higher than 3 in both tumor cell lines, while **18a** presented a high SI for PANC-1 cells (41.17) and a low SI for MDA MB 231 cells (1.91).

Conclusions

In summary, the synthesis of a series of 1-substituted propargylic tertiary amines by the A^3-coupling both in the solution and solid-phase was developed. The solution-phase approach allowed the generation of propargylamines mostly in good yields starting from different amines, alkynes and aldehydes. A minor amount of the corresponding allene was obtained in some cases. 2-Oxoacid derivatives were an interesting option for replacing the aldehyde in the synthesis of propargylamines with good yields. Besides, a tandem one-pot MCR-desilylation and Sonogashira coupling seems as an interesting option for the generation of an arylalkynyl side chain in the propargylamine core. In solid-phase chemistry, the synthesis was carried out using an immobilized aldehyde and the best results were achieved when cyclic secondary amines and terminal alkynes substituted with aliphatic chains were the other substrates.

The propargylamine library obtained possessed an interesting structural diversity and some structure–activity relationships were established after antiproliferative essays. The alkyl chain attached to the alkyne and cyclic amine exhibit a better cell inhibitory effect, while the aldehyde component is determinant on the selectivity related to normal cells. Further studies were carried out on two selected propargylamines, which exhibited a high degree of selectivity: compound **11b** showed a selectivity index higher than 3 for triple negative breast cancer cells and **18a** has a very interesting selectivity of 41.17 for pancreatic cancer cells. These levels of selectivity give a very promising perspective for further development of 1-substituted propargylic tertiary amines as new potential chemotherapeutic antitumor agents against cancers currently lacking effective treatments. Moreover, additional studies on the apoptosis, proliferation, clonogenicity and modulation of other antineoplastic drugs, among others, are currently in progress.

Experimental

Chemistry

General information and selected NMR spectra are reported in the ESI.†

(A) General procedure for solution-phase synthesis of propargylamines. Aldehyde **8** or phenylglyoxylic acid **8′b** (1.1 equiv.) was dissolved in toluene, then amine **9** (1 equiv.), alkyne **10** (1.5 equiv.) and $Cu(OTf)_2$ (0.1 equiv.) were added, and the vessel was capped and heated at 120 °C for 6 h. After that time, the reaction mixture was poured into a round-bottom flask and the solvent was removed by evaporation under reduced pressure. The crude product was purified by column chromatography.

*1-(1-(p-Tolyl)undec-2-yn-1-yl)pyrrolidine (**11a**).* Obtained following general procedure A: *p*-tolualdehyde (247 mg, 2.06 mmol), pyrrolidine (133 mg, 1.87 mmol), 1-decyne (388 mg, 2.81 mmol) and $Cu(OTf)_2$ (67 mg, 0.19 mmol) were dissolved in 5 mL of toluene and heated at 120 °C for 6 h. Silica gel column chromatography (98/2-hexane/EtOAc) provided 576 mg of the desired compound (99% yield) as a yellow oil. Characterization of **11a**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 0.83–0.94 (m, 3H), 1.24–1.34 (m, 8H), 1.37–1.45 (m, 2H), 1.49–1.60 (m, 2H), 1.69–1.84 (m, 4H), 2.27 (td, J = 7.0, 2.3 Hz, 2H), 2.33 (s, 3H), 2.55–2.67 (m, 4H), 4.60 (s, 1H), 7.13 (d, J = 7.8 Hz, 2H), 7.41 (d, J = 8.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 14.11, 18.79, 21.10, 22.68, 23.42, 28.90, 28.97, 29.09, 29.24, 31.84, 50.17, 58.52, 77.23, 87.03, 128.22, 128.82, 136.82, 137.06. HRMS (ESI) m/z found: 312.2684 ($M + H^+$); estimated for $C_{22}H_{34}N$: 312.2686.

*1-(1-Phenylundec-2-yn-1-yl)pyrrolidine (**11b**).* Obtained following general procedure A: benzaldehyde (98 mg, 0.93 mmol), pyrrolidine (60 mg, 0.85 mmol), 1-decyne (179 mg, 1.28 mmol) and $Cu(OTf)_2$ (30 mg, 0.09 mmol) were dissolved in 5 mL of toluene and heated at 120 °C for 6 h. Silica gel column chromatography (95/5-cyclohexane/EtOAc) provided 177 mg of the desired compound (70% yield) as a yellow oil. Characterization of **11b**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 0.80–0.94 (m, 3H), 1.18–1.34 (m, 8H), 1.36–1.48 (m, 2H), 1.43–1.63 (m, 2H), 1.68–1.86 (m, 4H), 2.28 (td, J = 6.9, 2.1 Hz, 2H), 2.52–2.66 (m, 4H), 4.60 (s, 1H), 7.15–7.41 (m, 3H), 7.47–7.57 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 14.10, 18.78, 22.67, 23.43, 28.89, 28.99, 29.08, 29.23, 31.83, 50.18, 58.81, 77.22, 87.10, 127.31, 128.09, 128.24, 140.2. HRMS (ESI) m/z found: 298.2527 ($M + H^+$); estimated for $C_{21}H_{32}N$: 298.2529.

*1-(1-(m-Tolyl)dec-2-yn-1-yl)pyrrolidine (**11c**).* Obtained following general procedure A: *m*-tolualdehyde (111 mg, 0.93 mmol),

pyrrolidine (60 mg, 0.85 mmol), 1-nonyne (159 mg, 1.28 mmol) and $Cu(OTf)_2$ (30 mg, 0.085 mmol) were dissolved in 3 mL of toluene and heated at 120 °C for 6 h. Silica gel column chromatography (96/4-cyclohexane/EtOAc) provided 164 mg of the desired compound (65% yield) as a yellow oil. Characterization of **11c**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 0.86–0.94 (m, 3H), 1.26–1.37 (m, 6H), 1.38–1.49 (m, 2H), 1.51–1.62 (m, 2H), 1.74–1.85 (m, 4H), 2.29 (td, J = 7.0, 2.1 Hz, 2H), 2.37 (s, 3H), 2.55–2.65 (m, 4H), 4.55 (s, 1H), 7.09 (d, J = 7.5 Hz, 1H), 7.20–7.25 (m, 1H), 7.31–7.37 (m, 2H). ^{13}C NMR ($CDCl_3$, 176 MHz) δ (ppm): 14.10, 18.81, 21.45, 22.64, 23.45, 28.82, 28.88, 28.99, 31.81, 31.85, 50.32, 58.92, 77.23, 87.06, 125.37, 127.99, 128.17, 128.97, 137.74. HRMS (ESI) m/z found: 298.2539 ($M + H^+$); estimated for $C_{21}H_{32}N$: 298.2529.

*1-(1-(o-Tolyl)undec-2-yn-1-yl)pyrrolidine (**11d**).* Obtained following general procedure A: *o*-tolualdehyde (112 mg, 0.93 mmol), pyrrolidine (60 mg, 0.85 mmol), 1-decyne (177 mg, 1.28 mmol) and $Cu(OTf)_2$ (30 mg, 0.085 mmol) were dissolved in 3 mL of toluene and heated at 120 °C for 6 h. Silica gel column chromatography (96/4-cyclohexane/EtOAc) provided 198 mg of the desired compound (75% yield) as a yellow oil. Characterization of **11d**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 0.83–0.93 (m, 3H), 1.23–1.32 (m, 8H), 1.37–1.45 (m, 2H), 1.45–1.62 (m, 2H), 1.67–1.78 (m, 4H), 2.27 (td, J = 7.0, 2.1 Hz, 2H), 2.41 (s, 3H), 2.47–2.65 (m, 4H), 4.70–4.77 (m, 1H), 7.07–7.20 (m, 3H), 7.57–7.66 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.12, 18.80, 19.07, 22.69, 23.54, 28.91, 29.06, 29.11, 29.26, 31.85, 50.10, 55.78, 77.23, 86.85, 125.49, 127.16, 128.11, 130.35, 136.54, 138.54. HRMS (ESI) m/z found: 312.2678 ($M + H^+$); estimated for $C_{22}H_{34}N$: 312.2686.

*1-(1-(3,4,5-Trimethoxyphenyl)undec-2-yn-1-yl)pyrrolidine (**11e**).* Obtained following general procedure A: 3,4,5-trimethoxybenzaldehyde (184.4 mg, 0.94 mmol), pyrrolidine (60 mg, 0.85 mmol), 1-decyne (177 mg, 1.28 mmol) and $Cu(OTf)_2$ (30 mg, 0.085 mmol) were dissolved in 3 mL of toluene and heated at 120 °C for 6 h. Silica gel column chromatography (85/15-cyclohexane/EtOAc) provided 188 mg of the desired compound (57% yield) as a yellow oil. Characterization of **11e**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 0.82–0.93 (m, 3H), 1.27 (m, 8H), 1.35–1.48 (m, 2H), 1.50–1.60 (m, 2H), 1.70–1.84 (m, 4H), 2.28 (td, J = 6.9, 2.1 Hz, 2H), 2.50–2.70 (m, 4H), 3.83 (s, 3H), 3.88 (s, 6H), 4.48 (t, J = 2.1 Hz, 1H), 6.79 (s, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.08, 18.79, 22.65, 23.48, 28.93, 28.99, 29.12, 29.22, 31.83, 50.46, 56.10, 59.23, 60.80, 77.22, 87.09, 105.18, 135.99, 137.13, 152.90. HRMS (ESI) m/z found: 388.2867 ($M + H^+$); estimated for $C_{24}H_{38}NO_3$: 388.2846.

*1-(1-(p-(tert-Butyl)phenyl)undec-2-yn-1-yl)pyrrolidine (**11f**).* Obtained following general procedure A: *p-tert*-butylbenzaldehyde (125 mg, 0.77 mmol), pyrrolidine (50 mg, 0.70 mmol), 1-decyne (145 mg, 1.05 mmol) and $Cu(OTf)_2$ (25 mg, 0.070 mmol) were dissolved in 3 mL of toluene and heated at 120 °C for 6 h. Silica gel column chromatography (95/5-hexane/EtOAc) provided 136 mg of the desired compound (55% yield) as a yellow oil. Characterization of **11f**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.88 (t, J = 6.8 Hz, 3H), 1.28–1.31 (m, 17H), 1.36–1.47 (m, 2H), 1.49–1.60 (m, 2H), 1.72–1.79 (m, 4H), 2.27 (td, J = 6.9, 2.1 Hz, 2H), 2.56–2.62 (m, 4H), 4.57 (s, 1H), 7.33 (d, J = 8.4 Hz, 2H), 7.44 (d, J = 8.3 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.11, 18.80, 22.69, 23.42, 28.92, 29.01, 29.10, 29.25, 31.39, 31.84, 34.47, 50.21, 58.46, 77.14, 86.88, 125.03, 127.89, 137.08, 150.18. HRMS (ESI) m/z found: 354.3162 ($M + H^+$); estimated for $C_{25}H_{40}N$: 354.3155.

*1-(1-(p-Methoxyphenyl)undec-2-yn-1-yl)pyrrolidine (**11g**).* Obtained following general procedure A: *p*-anisaldehyde (45 mg, 0.33 mmol), pyrrolidine (21 mg, 0.30 mmol), 1-decyne (62 mg, 0.45 mmol) and $Cu(OTf)_2$ (12 mg, 0.03 mmol) were dissolved in 2 mL of toluene and heated at 120 °C for 6 h. Silica gel column chromatography (80/20-hexane/EtOAc) provided 85 mg of the desired compound (86% yield) as a yellow oil. Characterization of **11g**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 0.82–0.94 (m, 3H), 1.22–1.34 (m, 8H), 1.36–1.47 (m, 2H), 1.48–1.60 (m, 2H), 1.69–1.88 (m, 4H), 2.27 (td, J = 6.9, 2.1 Hz, 2H), 2.55–2.69 (m, 4H), 3.80 (s, 3H), 4.64 (t, J = 2.2 Hz, 1H), 6.79–6.92 (m, 2H), 7.38–7.50 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 14.11, 18.78, 22.67, 23.41, 28.91, 28.95, 29.08, 29.24, 31.83, 49.97, 55.26, 57.99, 76.81, 87.24, 113.47, 129.51, 131.69, 159.00. HRMS (ESI) m/z found: 328.2618 ($M + H^+$); estimated for $C_{22}H_{34}NO$: 328.2635.

*1-(1-(p-Nitrophenyl)undec-2-yn-1-yl)pyrrolidine (**11h**).* Obtained following general procedure A: *p*-nitrobenzaldehyde (116 mg, 0.77 mmol), pyrrolidine (50 mg, 0.70 mmol), 1-decyne (145 mg, 1.05 mmol) and $Cu(OTf)_2$ (25 mg, 0.070 mmol) were dissolved in 3 mL of toluene and heated at 120 °C for 6 h. Silica gel column chromatography (95/5-hexane/EtOAc) provided 22 mg of the desired compound (9% yield) as a yellow oil. Characterization of **11h**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.83–0.94 (m, 3H), 1.22–1.36 (m, 8H), 1.39–1.46 (m, 2H), 1.48–1.63 (m, 2H), 1.70–1.86 (m, 4H), 2.30 (td, J = 6.9, 2.1 Hz, 2H), 2.51–2.65 (m, 4H), 4.75 (s, 1H), 7.74 (d, J = 8.6 Hz, 2H), 8.18 (d, J = 8.8 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.10, 18.73, 22.66, 23.52, 28.89, 29.05, 29.23, 31.82, 49.92, 57.97, 75.31, 88.69, 123.37, 128.98, 147.25, 147.72. HRMS (ESI) m/z found: 343.2384 ($M + H^+$); estimated for $C_{21}H_{31}N_2O_2$: 343.2380.

*1-(1-(p-Fluorophenyl)undec-2-yn-1-yl)pyrrolidine (**11i**).* Obtained following general procedure A: *p*-fluorobenzaldehyde (57 mg, 0.46 mmol), pyrrolidine (30 mg, 0.42 mmol), 1-decyne (87 mg, 0.63 mmol) and $Cu(OTf)_2$ (15 mg, 0.042 mmol) were dissolved in 3 mL of toluene and heated at 120 °C for 6 h. Silica gel column chromatography (95/5-hexane/EtOAc) provided 108 mg of the desired compound (82% yield) as a yellow oil. Characterization of **11i**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.88 (t, J = 6.9, 3H), 1.24–1.34 (m, 8H), 1.36–1.47 (m, 2H), 1.49–1.60 (m, 2H), 1.70–1.81 (m, 4H), 2.27 (td, J = 6.9, 2.1 Hz, 2H), 2.51–2.61 (m, 4H), 4.59 (s, 1H), 7.00 (t, J = 8.8 Hz, 2H), 7.50 (dd, J = 8.6, 5.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.09, 18.74, 22.66, 23.43, 28.89, 28.96, 29.07, 29.23, 31.82, 50.01, 57.98, 76.66, 87.42, 114.68, 114.96, 129.71, 129.81, 135.95, 135.99, 160.47, 163.72. HRMS (ESI) m/z found: 316.2431 ($M + H^+$); estimated for $C_{21}H_{31}NF$: 316.2435.

*1-(1-(p-Chlorophenyl)undec-2-yn-1-yl)pyrrolidine (**11j**).* Obtained following general procedure A: *p*-chlorobenzaldehyde (65 mg, 0.46 mmol), pyrrolidine (30 mg, 0.42 mmol), 1-decyne (87 mg,

0.63 mmol) and $Cu(OTf)_2$ (15 mg, 0.042 mmol) were dissolved in 3 mL of toluene and heated at 120 °C for 6 h. Silica gel column chromatography (95/5-hexane/EtOAc) provided 24 mg of the desired compound (17% yield) as a yellow oil. Characterization of **11j**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.82–0.93 (m, 3H), 1.19–1.35 (m, 8H), 1.38–1.47 (m, 2H), 1.49–1.58 (m, 2H), 1.72–1.79 (m, 4H), 2.27 (td, J = 7.0, 2.1 Hz, 2H), 2.52–2.60 (m, 4H), 4.59 (s, 1H), 7.28 (d, J = 8.5 Hz, 2H), 7.47 (d, J = 8.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.11, 18.75, 22.68, 23.45, 28.90, 28.96, 29.08, 29.24, 31.83, 50.04, 58.06, 76.43, 87.56, 128.21, 129.56, 132.99, 138.85. The spectra of the sample appear to contain traces amount of a side product/impurity. HRMS (ESI) m/z found: 332.2125 ($M + H^+$); estimated for $C_{21}H_{31}ClN$: 332.2140.

*1-(1-(p-Bromophenyl)undec-2-yn-1-yl)pyrrolidine (**11k**).* Obtained following general procedure A: *p*-bromobenzaldehyde (159 mg, 0.87 mmol), pyrrolidine (56 mg, 0.79 mmol), 1-decyne (164.5 mg, 1.19 mmol) and $Cu(OTf)_2$ (28 mg, 0.08 mmol) were dissolved in 3 mL of toluene and heated at 120 °C for 6 h. Silica gel column chromatography (93/7-hexane/EtOAc) provided 214 mg of the desired compound (72% yield) as a yellow oil. Characterization of **11k**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 0.82–0.94 (m, 3H), 1.19–1.35 (m, 8H), 1.35–1.47 (m, 2H), 1.48–1.61 (m, 2H), 1.64–1.84 (m, 4H), 2.27 (td, J = 7.0, 2.1 Hz, 2H), 2.49–2.65 (m, 4H), 4.58 (t, J = 2.1 Hz, 1H), 7.35–7.49 (m, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 14.12, 18.75, 22.68, 23.45, 28.90, 28.95, 29.08, 29.24, 31.84, 50.03, 58.10, 76.34, 87.60, 121.16, 129.94, 131.17, 139.36. HRMS (ESI) m/z found: 376.1643 ($M + H^+$); estimated for $C_{21}H_{31}BrN$: 376.1634.

*1-(1-(Naphthalen-1-yl)dec-2-yn-1-yl)pyrrolidine (**11l**).* Obtained following general procedure A: 1-naphthaldehyde (147 mg, 0.94 mmol), pyrrolidine (60 mg, 0.85 mmol), 1-nonyne (159 mg, 1.28 mmol) and $Cu(OTf)_2$ (30 mg, 0.085 mmol) were dissolved in 3 mL of toluene and heated at 120 °C for 6 h. Silica gel column chromatography (85/15-cyclohexane/EtOAc) provided 113 mg of the desired compound (40% yield) as a yellow oil. Characterization of **11l**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 0.82–0.97 (m, 3H), 1.24–1.37 (m, 8H), 1.41–1.50 (m, 2H), 1.55–1.64 (m, 2H), 1.73–1.85 (m, 4H), 2.34 (td, J = 7.0, 2.2 Hz, 2H), 2.56–2.81 (m, 4H), 5.34 (s, 1H), 7.44–8.13 (m, 7H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ (ppm): 14.15, 18.88, 22.67, 23.70, 28.85, 28.91, 29.09, 31.84, 50.19, 56.32, 87.55, 124.58, 125.02, 125.47, 125.77, 125.84, 128.22, 128.44, 131.56, 133.94, 136.08. The spectra of the sample appear to contain traces amount of a side product/impurity. HRMS (ESI) m/z found: 334.2550 ($M + H^+$); estimated for $C_{24}H_{32}N$: 334.2529.

*1-(1-Cyclohexylundec-2-yn-1-yl)pyrrolidine (**11m**).* Obtained following general procedure A: cyclohexanecarbaldehyde (98 mg, 0.87 mmol), pyrrolidine (56 mg, 0.79 mmol), 1-decyne (165 mg, 1.19 mmol) and $Cu(OTf)_2$ (28 mg, 0.08 mmol) were dissolved in 3 mL of toluene and heated at 120 °C for 6 h. Silica gel column chromatography (95/5-hexane/EtOAc) provided 98 mg of the desired compound (41% yield) as a yellow oil. Characterization of **11m**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 0.82–0.93 (m, 3H), 0.94–1.17 (m, 2H), 1.13–1.22 (m, 2H), 1.17–1.37 (m, 10H), 1.33–1.59 (m, 6H), 1.59–1.73 (m, 1H), 1.67–1.84 (m, 6H), 1.78–1.90 (m, 1H), 1.92–2.04 (m, 1H), 2.20 (td, J = 6.8, 2.1 Hz, 2H), 2.45–2.61 (m, 4H), 3.06 (dt, J = 8.0, 2.1 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 14.09, 18.68, 22.67, 23.45, 26.23, 26.28, 26.74, 28.84, 29.08, 29.14, 29.25, 29.94, 30.69, 31.83, 41.36, 50.05, 61.00, 77.71, 85.53. HRMS (ESI) m/z found: 304.3001 ($M + H^+$); estimated for $C_{21}H_{38}N$: 304.2999.

*1-(1-Cyclopropylundec-2-yn-1-yl)pyrrolidine (**11n**).* Obtained following general procedure A: cyclopropanecarbaldehyde (42 mg, 0.6 mmol), pyrrolidine (39 mg, 0.55 mmol), 1-decyne (114 mg, 0.825 mmol) and $Cu(OTf)_2$ (22 mg, 0.055 mmol) were dissolved in 3 mL of toluene and heated at 120 °C for 6 h. Silica gel column chromatography (95/5-hexane/EtOAc) provided 113 mg of the desired compound (79% yield) as a yellow oil. Characterization of **11n**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 0.30–0.53 (m, 3H), 0.82–0.94 (m, 3H), 1.00–1.12 (m, 1H), 1.23–1.32 (m, 8H), 1.34–1.41 (m, 2H), 1.42–1.54 (m, 2H), 1.71–1.89 (m, 4H), 2.18 (td, J = 6.8, 1.9 Hz, 2H), 2.71 (d, J = 28.7 Hz, 4H), 3.34–3.44 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 2.17, 3.11, 14.09, 14.25, 18.58, 22.66, 23.36, 28.80, 29.03, 29.06, 29.22, 31.82, 50.24, 58.02, 75.45, 85.58. HRMS (ESI) m/z found: 262.2523 ($M + H^+$); estimated for $C_{18}H_{32}N$: 262.2529.

*N-Allyl-N-benzyl-1-(p-tolyl)undec-2-yn-1-amine (**11o**).* Obtained following general procedure A: *p*-tolualdehyde (105 mg, 0.87 mmol), *N*-allylbenzylamine (116 mg, 0.79 mmol), 1-decyne (165 mg, 1.19 mmol) and $Cu(OTf)_2$ (28 mg, 0.08 mmol) were dissolved in 3 mL of toluene and heated at 120 °C for 6 h. Silica gel column chromatography (99/1-hexane/EtOAc) provided 202 mg of the desired compound (66% yield) as a yellow oil. Characterization of **11o**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 0.86–0.92 (m, 3H), 1.22–1.36 (m, 8H), 1.45–1.54 (m, 2H), 1.58–1.69 (m, 2H), 2.32 (s, 3H), 2.37 (td, J = 6.9, 2.2 Hz, 2H), 2.90–3.04 (m, 1H), 3.05–3.20 (m, 1H), 3.39 (d, J = 13.7 Hz, 1H), 3.74 (d, J = 13.7 Hz, 1H), 4.72 (s, 1H), 5.05–5.16 (m, 1H), 5.19–5.33 (m, 1H), 5.74–5.94 (m, 1H), 7.12 (d, J = 7.9 Hz, 2H), 7.16–7.24 (m, 1H), 7.26–7.41 (m, 4H), 7.52 (d, J = 7.9 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 14.11, 18.84, 21.07, 22.70, 28.97, 29.16, 29.22, 29.32, 31.88, 53.30, 54.41, 55.63, 75.29, 88.15, 116.98, 126.74, 128.15, 128.61, 128.79, 136.68, 136.92, 136.99, 140.05. HRMS (ESI) m/z found: 410.2807 ($M + Na^+$); estimated for $C_{28}H_{37}NNa$: 410.2818.

*N-Allyl-N-benzyl-1-phenylundec-2-yn-1-amine (**11p**).* Obtained following general procedure A: phenylglyoxylic acid (100 mg, 0.66 mmol), *N*-allylbenzylamine (88 mg, 0.6 mmol), 1-decyne (124 mg, 0.9 mmol) and $Cu(OTf)_2$ (24 mg, 0.06 mmol) were dissolved in 3 mL of toluene and heated at 120 °C for 6 h. Silica gel column chromatography (97/3-hexane/EtOAc) provided 112 mg of the desired compound (50% yield) as a yellow oil. Characterization of **11p**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 0.84–0.95 (m, 3H), 1.28–1.42 (m, 8H), 1.46–1.55 (m, 2H), 1.59–1.70 (m, 2H), 2.39 (td, J = 6.9, 2.1 Hz, 2H), 2.98 (dd, J = 14.0, 8.3 Hz, 1H), 3.07–3.20 (m, 1H), 3.40 (d, J = 13.7 Hz, 1H), 3.76 (d, J = 13.7 Hz, 1H), 4.77 (s, 1H), 5.06–5.17 (m, 1H), 5.20–5.34 (m, 1H), 5.75–5.95 (m, 1H), 7.15–7.42 (m, 8H), 7.64–7.67 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 14.12, 18.84, 22.70, 28.98, 29.16, 29.22, 29.33, 31.88, 53.36, 54.50, 55.90, 75.04, 88.41, 117.08, 126.80, 127.14, 127.91, 128.17,

128.26, 128.81, 136.85, 139.96, 140.02. HRMS (ESI) *m*/*z* found: 374.2838 ($M + H^+$); estimated for $C_{27}H_{36}N$: 374.2842.

N-Benzyl-N-(1-phenyl-3-(p-tolyl)prop-2-yn-1-yl)prop-2-en-1-amine ***(11q)***. Obtained following general procedure A: phenylglyoxylic acid (50 mg, 0.33 mmol), *N*-allylbenzylamine (44 mg, 0.3 mmol), 4-ethynyltoluene (53 mg, 0.45 mmol) and $Cu(OTf)_2$ (12 mg, 0.03 mmol) were dissolved in 2 mL of toluene and heated at 120 °C for 6 h. Silica gel column chromatography (95/5-hexane/EtOAc) provided 53 mg of the desired compound (50% yield) as a yellow oil. Characterization of **11q**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 2.36–2.40 (m, 3H), 2.98–3.28 (m, 2H), 3.50 (d, J = 13.6 Hz, 1H), 3.85 (d, J = 13.7 Hz, 1H), 5.00 (s, 1H), 5.09–5.36 (m, 2H), 5.78–5.96 (m, 1H), 7.18 (d, J = 7.9 Hz, 2H), 7.21–7.43 (m, 8H), 7.47 (d, J = 8.0 Hz, 2H), 7.71 (d, J = 7.6 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 21.51, 53.49, 54.66, 56.39, 84.29, 88.33, 117.37, 120.24, 126.92, 127.38, 128.08, 128.25, 128.28, 128.87, 129.11, 131.80, 136.64, 138.27, 139.47, 139.76. HRMS (ESI) *m*/*z* found: 352.2043 ($M + H^+$); estimated for $C_{26}H_{26}N$: 352.2060.

5-Phenyl-5-(pyrrolidin-1-yl)pent-3-yn-1-ol ***(11r)***. Obtained following general procedure A: phenylglyoxylic acid (131 mg, 0.87 mmol), pyrrolidine (56 mg, 0.79 mmol), 3-butyn-1-ol (83 mg, 1.19 mmol) and $Cu(OTf)_2$ (28 mg, 0.08 mmol) were dissolved in 3 mL of toluene and heated at 120 °C for 6 h. Silica gel column chromatography (95/5-hexane/EtOAc) provided 118 mg of the desired compound (65% yield) as a yellow oil. Characterization of **11r**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.70–1.80 (m, 4H), 2.42 (brs, 1H), 2.52–2.62 (m, 6H), 3.73 (t, J = 6.3 Hz, 2H), 4.56 (t, J = 2.1 Hz, 1H), 7.23–7.35 (m, 3H), 7.47–7.51 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 23.27, 23.34, 50.49, 59.02, 61.25, 79.40, 83.33, 127.62, 128.21, 128.26, 139.46. HRMS (ESI) *m*/*z* found: 230.1547 ($M + H^+$); estimated for $C_{15}H_{20}NO$: 230.1539.

1-(1-Phenyloct-2-yn-1-yl)pyrrolidine ***(11s)***. Obtained following general procedure A: benzaldehyde (49 mg, 0.46 mmol), pyrrolidine (30 mg, 0.42 mmol), 1-heptyne (40 mg, 0.42 mmol) and $Cu(OTf)_2$ (16 mg, 0.046 mmol) were dissolved in 3 mL of toluene and heated at 120 °C for 6 h. Silica gel column chromatography (95/5-hexane/EtOAc) provided 72 mg of the desired compound (67% yield) as a yellow oil. Characterization of **11s**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 0.88–0.93 (m, 3H), 1.32–1.49 (m, 4H), 1.50–1.58 (m, 2H), 1.74–1.80 (m, 4H), 2.27 (td, J = 7.0, 2.1 Hz, 2H), 2.52–2.66 (m, 4H), 4.60 (t, J = 2.2 Hz, 1H), 7.19–7.38 (m, 3H), 7.47–7.57 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 14.01, 18.76, 22.19, 23.43, 28.68, 31.11, 50.19, 58.83, 76.96, 87.10, 127.32, 128.10, 128.25, 140.15. HRMS (ESI) *m*/*z* found: 256.2055 ($M + H^+$); estimated for $C_{18}H_{26}N$: 256.2060.

1-(1-Phenylprop-2-yn-1-yl)pyrrolidine ***(11t)***. Obtained following general procedure A: benzaldehyde (49 mg, 0.46 mmol), pyrrolidine (30 mg, 0.42 mmol), trimethylsilylacetylene (44 mg, 0.63 mmol) and $Cu(OTf)_2$ (9 mg, 0.046 mmol) were dissolved in 3 mL of toluene and heated at 120 °C for 6 h. Silica gel column chromatography (95/5-hexane/EtOAc) provided 38 mg of the desired compound in 49% yield as a yellow oil. Characterization of **11t**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.47–1.66 (m, 4H), 2.27 (d, J = 2.3 Hz, 1H), 2.32–2.49 (m, 4H), 4.49 (d, J = 2.3 Hz, 1H), 7.00–7.19 (m, 3H), 7.28–7.38 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 23.44, 50.05, 58.37, 74.67, 80.68, 127.68, 128.15, 128.28, 138.83. HRMS (ESI) *m*/*z* found: 186.1270 ($M + H^+$); estimated for $C_{13}H_{16}N$: 186.1277.

(B) General procedure for the Sonogashira coupling. A round bottom flask was charged with propargylamine (1 equiv.), aryl iodide (1.2 equiv.), triethylamine (0.2 equiv.), $Pd(PPh_3)_3$ (0.05 equiv.) and CuI (0.1 equiv.) under an argon atmosphere. *N*,*N*-Dimethylformamide was added and the reaction mixture was stirred at room temperature for 15 h. After that time, the solvent was removed by evaporation under reduced pressure, and the crude product was purified by column chromatography.

1-(1,3-Diphenylprop-2-yn-1-yl)pyrrolidine ***(11u)***. Obtained following general procedure B: 1-(1-phenylprop-2-yn-1-yl)pyrrolidine (**11t**) (20 mg, 0.12 mmol), iodobenzene (**14**) (28 mg, 0.14 mmol), triethylamine (2 mg, 0.024 mmol), $Pd(PPh_3)_3$ (7 mg, 0.006 mmol) and CuI (2 mg, 0.012 mmol) were dissolved in 3 mL of *N*,*N*-dimethylformamide and stirred at room temperature for 15 h. Silica gel column chromatography (95/5-hexane/EtOAc) provided 25 mg of the desired compound (79% yield) as a yellow oil. Characterization of **11u**. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.76–1.83 (m, 4H), 2.65–2.72 (m, 4H), 4.89 (s, 1H), 7.22–7.39 (m, 6H), 7.41–7.55 (m, 2H), 7.60–7.62 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 23.50, 50.28, 59.13, 86.67, 86.93, 123.24, 127.58, 128.09, 128.27, 128.30, 131.80, 139.47. HRMS (ESI) *m*/*z* found: 262.1601 ($M + H^+$); estimated for $C_{19}H_{20}N$: 262.1590.

(C) Procedure for the synthesis of supported aldehyde 15. Wang resin (loading = 1.1 mmol g^{-1}, 366 mg, 0.4 mmol) was placed in a polypropylene cartridge; *p*-carboxybenzaldehyde (181 mg, 1.2 mmol), *N*,*N*′-diisopropylcarbodiimide (DIC) (0.19 mL, 1.2 mmol) and a catalytic amount of 4-dimethylaminopyridine (DMAP) were also added. Anhydrous DCM (20 mL) was added and the mixture was stirred at 250 rpm in the orbital shaker overnight at room temperature. It was then filtered and washed successively with DCM (3 × 10 mL), MeOH (3 × 10 mL), THF (3 × 10 mL), and DCM (1 × 10 mL). Finally, it was dried in a desiccator under reduced pressure. Theoretical loading of **15**: 0.96 mmol g^{-1}.[44]

(D) Procedure for the cleavage of compounds bound to Wang resin. The bound compound was placed in a round-bottom flask and a solution of TFA in DCM (10% v/v) was added. The mixture was magnetically stirred at room temperature for 50 minutes, then, filtered under reduced pressure and the resin was washed with MeOH (2 × 3 mL) and DCM (2 × 3 mL). The solvent was removed with a rotary evaporator and dried completely under reduced pressure.

(E) Procedure for methylation of carboxylic acids. The organic carboxylic acid was dissolved in DCM and, if necessary, MeOH was added, then the solution was cooled down to 0 °C and a solution of diazomethane in Et_2O was added dropwise until light yellow coloration. After 30 minutes of reaction, the excess of diazomethane was quenched with a few drops of glacial acetic acid and concentrated under reduced pressure.

(F) General procedure for solid phase synthesis of propargylamine 18. Supported aldehyde **15** (1 equiv., loading = 0.96 mmol g^{-1}), obtained using procedure C, was suspended in toluene. Amine **9** (2 equiv.), alkyne **10** (3 equiv.) and CuMeSal (30 mol%) were added. The reaction mixture was heated to reflux for 6 h with slow stirring. Then, the resin was filtered and washed with toluene (2 × 5 mL), MeCN (2 × 5 mL) and DCM (3 × 5 mL), and then dried under reduced pressure. Cleavage was carried out by procedure D, carboxylic acids were methylated according to procedure E and isolated **18** was obtained after silica gel column chromatography.

*Methyl 4-(1-(pyrrolidin-1-yl)undec-2-yn-1-yl)benzoate (**18a**).* Obtained following general procedure F: supported aldehyde (173.4 mg, 0.166 mmol), pyrrolidine (25.6 mg, 0.36 mmol), 1-decyne (62 mg, 0.45 mmol) and CuMeSal (10 mg, 0.046 mmol) were dissolved in 7 mL of toluene. After cleavage, methylation and purification by column chromatography (98/2-hexane/EtOAc) 38.3 mg of the desired compound was provided (65% yield) as a yellow oil. Characterization of **18a**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 0.83–0.91 (m, 3H), 1.22–1.34 (m, 8H), 1.35–1.47 (m, 2H), 1.49–1.61 (m, 2H), 1.72–1.79 (m, 4H), 2.28 (td, J = 6.9, 2.1 Hz, 2H), 2.53–2.60 (m, 4H), 3.91 (s, 3H), 4.67 (s, 1H), 7.52–7.70 (m, 2H), 7.90–8.11 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 14.10, 18.75, 22.67, 23.47, 28.89, 28.93, 29.07, 29.23, 31.83, 50.07, 52.04, 58.45, 76.17, 87.84, 128.20, 129.17, 129.48, 145.42, 167.04. HRMS (ESI) m/z found: 356.2567 ($M + H^+$); estimated for $C_{23}H_{34}NO_2$: 356.2584.

*Methyl 4-(3-(4-methoxyphenyl)-1-(pyrrolidin-1-yl)prop-2-yn-1-yl)benzoate (**18b**).* Obtained following general procedure F: supported aldehyde (210.8 mg, 0.2 mmol), pyrrolidine (28 mg, 0.4 mmol), 4-ethynylanisole (59.5 mg, 0.45 mmol) and CuMeSal (13 mg, 0.06 mmol) were dissolved in 7 mL of toluene. After cleavage, methylation and purification by column chromatography (85/15-hexane/EtOAc) provided 7 mg of the desired compound (10% yield) as an orange oil. Characterization of **18b**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.75–1.81 (m, 4H), 2.65–2.76 (m, 4H), 3.82 (s, 3H), 3.91 (s, 3H), 4.97 (s, 1H), 6.85 (d, J = 8.7 Hz, 2H), 7.42 (d, J = 8.7 Hz, 2H), 7.70 (d, J = 8.2 Hz, 2H), 8.02 (d, J = 8.2 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 23.55, 50.19, 52.11, 55.34, 58.79, 77.22, 92.88, 113.15, 113.98, 127.39, 128.40, 129.66, 129.98, 133.26, 159.71, 166.95. HRMS (ESI) m/z found: 350.1737 ($M + H^+$); estimated for $C_{22}H_{24}NO_3$: 350.1750.

*Methyl 4-(1-(allyl(benzyl)amino)undec-2-yn-1-yl)benzoate (**18c**).* Obtained following general procedure F: supported aldehyde (170 mg, 0.16 mmol), *N*-allylbenzylamine (47 mg, 0.32 mmol), 1-decyne (61 mg, 0.44 mmol) and CuMeSal (10 mg, 0.05 mmol) were dissolved in 7 mL of toluene. After cleavage, methylation and purification by column chromatography (90/10-hexane/EtOAc) provided 11 mg of the desired compound (16% yield) as a yellow oil. Characterization of **18c**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 0.70–0.88 (m, 3H), 1.11–1.40 (m, 8H), 1.41–1.50 (m, 2H), 1.51–1.65 (m, 2H), 2.32 (td, J = 6.9, 2.1 Hz, 2H), 2.84–3.08 (m, 2H), 3.32 (d, J = 13.6 Hz, 1H), 3.65 (d, J = 13.6 Hz, 1H), 3.83 (s, 3H), 4.70 (s, 1H), 4.97–5.26 (m, 2H), 5.65–5.86 (m, 1H), 7.07–7.32 (m, 5H), 7.61–7.65 (m, 2H), 7.88–7.97 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 14.11, 18.82, 22.69, 28.86, 28.97, 29.14, 29.32, 31.87, 52.02, 53.48, 54.66, 55.84, 74.34, 89.06, 117.41, 126.96, 128.26, 128.81, 129.08, 129.27, 136.50, 139.58, 145.51, 167.08. HRMS (ESI) m/z found: 432.2877 ($M + H^+$); estimated for $C_{29}H_{38}NO_2$: 432.2897.

*Methyl 4-(1-(allyl(benzyl)amino)-3-(4-methoxyphenyl)prop-2-yn-1-yl)benzoate (**18d**).* Obtained following general procedure F: supported aldehyde (154.4 mg, 0.15 mmol), *N*-allylbenzylamine (44 mg, 0.3 mmol), 4-ethynylanisole (59 mg, 0.45 mmol) and CuMeSal (10 mg, 0.05 mmol) were dissolved in 7 mL of toluene. After cleavage, methylation and purification by column chromatography (85/15-hexane/EtOAc) provided 17 mg of the desired compound (26% yield) as a yellow oil. Characterization of **18d**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 3.08 (dd, J = 14.1, 8.2 Hz, 1H), 3.15–3.26 (m, 1H), 3.50 (d, J = 13.6 Hz, 1H), 3.82 (d, J = 11.9 Hz, 1H), 3.85 (s, 3H), 3.91 (s, 3H), 5.01 (s, 1H), 5.16 (d, J = 9.5 Hz, 1H), 5.31 (d, J = 17.1 Hz, 1H), 5.77–5.97 (m, 1H), 6.91 (d, J = 8.8 Hz, 2H), 7.18–7.46 (m, 5H), 7.52 (d, J = 8.8 Hz, 2H), 7.79 (d, J = 7.8 Hz, 2H), 8.02 (d, J = 8.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 52.07, 53.60, 54.80, 55.38, 56.33, 82.64, 88.58, 114.04, 115.12, 117.66, 127.06, 128.29, 128.32, 128.86, 129.28, 129.41, 133.33, 136.32, 139.40, 145.01, 159.69, 167.04. HRMS (ESI) m/z found: 448.1861 ($M + Na^+$); estimated for $C_{28}H_{27}NNaO_3$: 448.1883.

Biological evaluation

Cell lines. The 4T1: TN murine mammary adenocarcinoma cell line, highly tumorigenic and invasive and can spontaneously metastasize from the primary tumor to multiple distant sites; the MDA-MB-231: TN human mammary adenocarcinoma cell line; the PANC-1: human cell line derived from pancreatic carcinoma, of ductal origin, with B phenotype for G6PD. The MC3T3e1: pre-osteoblastic cell line obtained from the calvaria of C57BL/6 mice embryos with fibroblast type morphology.

4T1 cells were cultured in RPMI supplemented with 10% fetal bovine serum (FBS), penicillin (10 U ml^{-1}), and streptomycin (10 μg ml^{-1}). MDA-MB-231, PANC-1 and MC3T3e1 cells were maintained in DMEM supplemented with 10% FBS, penicillin (10 U ml^{-1}), streptomycin (10 μg ml^{-1}) and L-glutamine (200 nM) (except for MC3T3e1). All types of cells were maintained in a humidified 5% CO_2 incubator at 37 °C.

4T1 cells were kindly provided by Dr N. Zwirner (IBYMECONICET), PANC-1 cells were kindly provided by Dr Daniel Bonfil (Department of Urology, Wayne State University USA), MDA MB 231 cells were kindly provided by Dr Javier Girardini (IBR CONICET) and MC3T3e1 cells were kindly provided by Dr Ricardo Boland (Universidad Nacional del Sur, Argentina).

Cell viability. For *in vitro* assessment, the effect of the different compounds on cancer cell viability, 2.5 × 10^3 4T1, MDA-MB-231 or PANC-1 cells per well were plated into 96-well cell culture plates. After attachment, different concentrations of the compounds were added and the cells were allowed to grow for 36 h. In order to know their effect on normal cells, MC3T3e1 cells (2.5 × 10^5 cells per well) were plated and treated

in the same way. The number of living cells was estimated indirectly by the tetrazolium salt reduction method (WST-1, Sigma Aldrich) as described by the manufacturer. The amount of formazan dye formed, directly correlates to the number of metabolically active cells in the culture. Cell viability was measured in a spectrophotometer (Rayto RT-2100C Microplate Reader) at 450 nm and expressed as the percentage of control untreated samples. All experiments were performed in triplicate. The viability of control untreated cells was considered as 100%.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

Support from CONICET, Agencia Nacional de Promoción Científica y Tecnológica (ANPCyT), Agencia Santafesina de Ciencia, Técnica e Innovación (ASACTEI) and Universidad Nacional de Rosario from Argentina is gratefully acknowledged. MM-A, CPS and DNPG thank CONICET and ANPCyT for fellowship.

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