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Synthesis and *in vitro* evaluation of potential anticancer activity of mono- and bis-1,2,3-triazole derivatives of bis-alkynes

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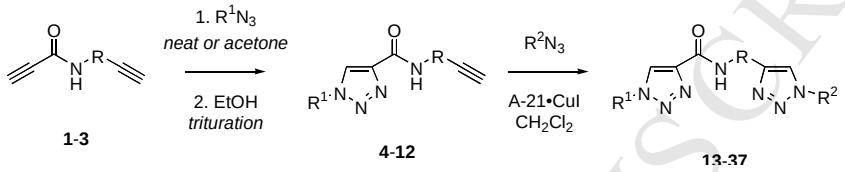
CNRS UMR8151, INSERM U1022, Unité de Pharmacologie Chimique, Génétique & Imagerie, Ecole Nationale Supérieure de Chimie de Paris and Université Paris Descartes, Paris, France



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Preliminary communication

Synthesis and *in vitro* evaluation of potential anticancer activity of mono- and bis-1,2,3-triazole derivatives of bis-alkynes

Hichem Elamari[a] , Riadh Slimi[a] , Guy G. Chabot[b,] ** , Lionel Quentin[b] , Daniel Scherman[b] and Christian Girard[a,] *

[a]*CNRS UMR8151, INSERM U1022, Unité de Pharmacologie Chimique, Génétique & Imagerie, Ecole Nationale Supérieure de Chimie de Paris (Chimie ParisTech), PSL,11 rue Pierre & Marie Curie, Paris 75005, France*

[b] *CNRS UMR8151, INSERM U1022, Faculté de Pharmacie, Université Paris Descartes, Sorbonne Paris Cité, 4 avenue de l'Observatoire, 75006 Paris, France*

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ABSTRACT

In order to find new molecules with cytotoxic activity against cancer cells, we prepared bis-akyne amides derived from propiolic acid. The bis-alkynes were then transformed in their mono-1,2,3-triazole analogs onto the amide side, due to its greater reactivity, using a catalyst-free Huisgen's reaction. The mono-triazoles were then subjected to the copper (I)-catalyzed version of the previous reaction (CuAAC), using a supported catalyst, to produce bis-triazoles. All products were obtained pure after simple trituration or filtration procedures. All synthetic compounds were tested *in vitro* for their cytotoxic activity using B16 melanoma cells. Four compounds (**7**, **23**, **25** and **33**) showed activities in the micromolar range (< 21 µM) whereas three compounds (**3**, **22** and **38**) presented activity at low micromolar concentrations (< 10 µM), and two analogues (**2** and **13**) were active at nanomolar levels (< 1 µM).

1. Introduction

Cancer is already the leading cause of death in many high-income countries and is set to become a major cause of morbidity and mortality in the next decades in every region of the world [1]. Death rate for cancer remains approximately the same worldwide and did not appear to decrease in recent years. Indeed, it is predicted that by 2030, approximately 20 million new cancer cases will be diagnosed worldwide and that about 13 million cancer patients will die from this disease [1,2]. Therefore, there is an urgent need for novel and more efficacious compounds in order to try to reduce the cancer mortality rate.

In our sustained endeavor to find new methods for the synthesis of biologically active compounds against cancer [3-13], based on our experience in the synthesis of 1,4-disubstituted bis-1,2,3-triazole [14] and previous results of triazolic analogs of Combretastatin A4 [15], we became interested in the evaluation of other triazolic derivatives. Since 1,2,3-triazoles are recognized as important and efficient pharmacophores, investigation of new structures incorporating this nucleus as mono- and bis-triazoles prepared from bis-alkynes was undertaken [16].

This communication reports our findings following the *in vitro* biological evaluation of all derivatives synthesized in this study using the murine B16 melanoma cell line. The choice of the B16 melanoma model is based on the urgent need to find new active compounds against metastatic melanoma which is particularly resistant to chemotherapy in humans [17]. The B16 melanoma is considered a good model of the human disease because it is highly invasive and can metastasize when grafted into syngeneic mice [18]. This melanoma model is also particularly refractory to chemotherapy, just like the human disease [19]. This model has also recently been shown to express alpha v beta 3 and E-selectin which are particularly important targets for antiangiogenic cancer therapy [20]. In addition, B16 melanoma has been used extensively in preclinical studies worlwide including the National Cancer Institute, and therefore allows a good comparison basis to numerous other published preclinical studies. Another important point is that first line interesting results obtained with this cell line *in vitro* can readily

* C. Girard. Tel.: +3-144-276-748; e-mail: christian-girard@chimie-paristech.fr

** G. G. Chabot. Tel.: +33-153-739-571; e-mail: guy.chabot@parisdescartes.fr

be tested *in vivo* in mice to further evaluate the lead compounds detected *in vitro*.

In the present study, we found out that the triazolic derivatives possessed biological activity, some in the micromolar and nanomolar range, and that, surprisingly, some of the starting bis-alkynes themselves showed interesting cytotoxicity against B16 melanoma cells.

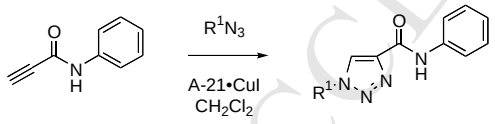
2. Chemistry

The compounds required for this study were synthesized according to our previously published procedure [14]. Briefly, the starting bis-alkyne amides **1**-**3** were prepared by classical DCC coupling between propiolic acid and propargyl amine for **1**, and *m*- and *p*-ethynylanilines for **2** and **3**, respectively (Scheme 1).

The bis-alkynes **1**-**3** were then reacted with various organic azides to afford the corresponding mono 1,4-disubstituted 1,2,3-triazoles **4**-**12**. This first Huisgen's reaction was conducted without catalyst and without solvent for the propiolic acid propargyl amide (**1**), or in acetone under reflux for the propiolic acid *m*-ethynylphenyl (**2**) and *m*-ethynylphenyl (**3**) amides [21,22]. All reactions gave good yields of a mixture of the 1,4- and 1,5-isomers of the triazole in ratio around 80 : 20, respectively. The reaction was selective for the alkyne conjugated with the carbonyl group (activated alkyne). The 1,4-isomers **4**-**12** were obtained pure and in fair yields after a simple trituration in ethanol, leaving the 1,5-isomers, together with a few 1,4-ones, in the filtrate.

The mono-triazole-alkynes **4**-**12** were then subjected to a second Huisgen's reaction using its copper (I)-catalyzed version [23-26], or copper-catalyzed alkyne-azide coupling (CuAAC), using our polymer-supported catalyst Amberlyst A-21•CuI in methylene chloride at room temperature [27,28]. This reaction gave exclusively the 1,4-isomers of the second triazole ring onto the inactivated alkyne in very good yield. The products **13**-**37** being obtained pure after a simple filtration and evaporation procedure.

In order to make some comparison between the different products and to study the influence of the second triazole ring, we also synthesized propiolic acid phenyl amide (**38**) from propiolic acid and aniline (Scheme 2). The alkyne **38** was then reacted with organic azides using the A-21•CuI CuAAC procedure to afford the triazoles **39**-**41** with the same selectivity and good yields.



Scheme 2. Copper(I)-catalyzed synthesis of triazoles **39**-**41** from propiolamide of aniline (**38**) and azides.

3. Biological activity

The cytotoxic activity of compounds **1**-**41** on B16 melanoma cells is presented in Table 1.

We first analyzed our biological results with the bis-alkynes **1**-**3** and the mono-alkyne **38**, in order to include the starting materials. To our surprise, the alkynes did possess interesting activities. The amide derived from propargyl amine **1** presented an IC_{50} of 38 µM. The replacement of the propargyl side chain in **1** by a *m*-ethynylphenyl to yield compound **2** caused a 127-fold increase in biological activity with an IC_{50} of 0.3 µM. The presence of an aromatic "linking" ring also increased the cytotoxic activity of **1**, as shown for the *para*-analog **3** and the phenyl substituted derivative **38**, which both presented a cytotoxic activity of 6 µM. Although compounds **3** and **38** showed a 6-fold increase in cytotoxicity compared to **1**, these IC_{50} values were twenty times lower than the IC_{50} value obtained with compound **2**.

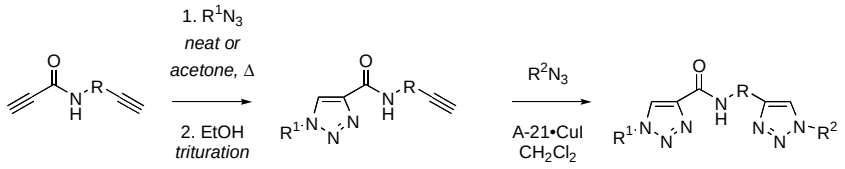
Introduction of the first triazole ring had a deleterious effect on the activities of the four precited compounds (**1**-**3** and **38**). The propargyl derivative **1** (38 µM) was about two times more potent than the benzyl-substituted triazole at the R^1 position of **4** (65 µM).

The presence at this position of a benzyloxycarbonylmethyl in **5**, and acetoxyethyl in **6**, gave compounds with activities higher than 100 µM. The same series of couplings on the *meta*-derivative **2** (0.3 µM) gave also mono-triazoles with lower activities: around fifty to three-hundred times decrease for compounds **7**, **8** and **9**, with IC_{50} of 14.5, 91.0 and 25.1 µM, respectively.

This effect was also observed for the *para*-derivative **3** and the phenyl substituted **38**. For the bis-alkyne **3** (6.3 µM), the cytotoxic activity was over 100 µM for **10** and **11**, and was 79 µM for **12**. The phenyl substituted propiolamide **38** (6.2 µM) exhibited the same decrease in activities with an IC_{50} of 93 µM for **39**, and over 100 µM for **40** and **41**.

When considering the results for the introduction of the second triazole ring in molecules **13**-**37**, some interesting modifications of the biological activity of the mono-triazoles derivatives **4**-**12** were observed.

In the R^1 = benzyl series (molecules **4**, **7** and **10**), we were surprised to observe an amelioration of activity when going from **4** to **13** (with R^2 = benzyl). The bis-triazole **13** had an IC_{50} = 0.3 µM, which was two-hundred and thirty times the activity of **4** and the same as the one of the bis-alkyne **2**. Introduction of this R^1 = benzyl in **22**, starting from **7**, gave also an increase in activity going from 14.5 to 4.5 µM (three times).



1 : R = CH_2
2 : R = *m*-Ph
3 : R = *p*-Ph

4 : R = CH_2, R^1 = Bn
5 : R = CH_2, R^1 = CH_2CO_2Bn
6 : R = CH_2, R^1 = $(CH_2)_2OAc$
7 : R = *m*-Ph, R^1 = Bn
8 : R = *m*-Ph, R^1 = CH_2CO_2Et
9 : R = *m*-Ph, R^1 = $(CH_2)_2OAc$
10 : R = *p*-Ph, R^1 = Bn
11 : R = *p*-Ph, R^1 = CH_2CO_2Et
12 : R = *p*-Ph, R^1 = $(CH_2)_2OAc$

13 : R = CH_2, R^1 = R^2 = Bn
14 : R = CH_2, R^1 = Bn, R^2 = CH_2CO_2Et
15 : R = CH_2, R^1 = Bn, R^2 = $(CH_2)_2OAc$
16 : R = CH_2, R^1 = CH_2CO_2Bn, R^2 = Bn
17 : R = CH_2, R^1 = CH_2CO_2Bn, R^2 = CH_2CO_2Et
18 : R = CH_2, R^1 = CH_2CO_2Bn, R^2 = $(CH_2)_2OAc$
19 : R = CH_2, R^1 = $(CH_2)_2OAc$, R^2 = Bn
20 : R = CH_2, R^1 = $(CH_2)_2OAc$, R^2 = CH_2CO_2Et
21 : R = CH_2, R^1 = R^2 = $(CH_2)_2OAc$

22 : R = *m*-Ph, R^1 = R^2 = Bn
23 : R = *m*-Ph, R^1 = Bn, R^2 = CH_2CO_2Et
24 : R = *m*-Ph, R^1 = Bn, R^2 = $(CH_2)_2OAc$
25 : R = *m*-Ph, R^1 = CH_2CO_2Et, R^2 = Bn
26 : R = *m*-Ph, R^1 = R^2 = CH_2CO_2Et
27 : R = *m*-Ph, R^1 = CH_2CO_2Et, R^2 = $(CH_2)_2OAc$
28 : R = *m*-Ph, R^1 = $(CH_2)_2OAc$, R^2 = Bn
29 : R = *m*-Ph, R^1 = $(CH_2)_2OAc$, R^2 = CH_2CO_2Et
30 : R = *m*-Ph, R^1 = R^2 = $(CH_2)_2OAc$,
31 : R = *p*-Ph, R^1 = R^2 = Bn
32 : R = *p*-Ph, R^1 = Bn, R^2 = CH_2CO_2Et
33 : R = *p*-Ph, R^1 = Bn, R^2 = $(CH_2)_2OAc$
34 : R = *p*-Ph, R^1 = CH_2CO_2Et, R^2 = $(CH_2)_2OAc$
35 : R = *p*-Ph, R^1 = $(CH_2)_2OAc$, R^2 = Bn
36 : R = *p*-Ph, R^1 = $(CH_2)_2OAc$, R^2 = CH_2CO_2Et
37 : R = *p*-Ph, R^1 = R^2 = $(CH_2)_2OAc$

Scheme 1. Two steps synthesis triazoles: Uncatalyzed first step to form mono-triazoles **4**-**12** and polymer-supported copper(I)-catalyzed second step (A-21•CuI) to access bis-triazoles **13**-**37**, strating from the bis-alkynes **1**-**3** and corresponding azides.

Table 1. *In vitro* biological activity (IC_{50}) against B16 melanoma cells for molecules **1**-**41** produced *via* Schemes 1 and 2[a]

N°	R	R^1	R^2	IC_{50} (µM)[b]	N°	R	R^1	R^2	IC_{50} (µM)[b]
1	CH_2	–	–	38.0 ± 0.4	**22**	*m*-Ph	Bn	Bn	4.5 ± 0.3
2	*m*-Ph	–	–	0.3 ± 0.008	**23**	*m*-Ph	Bn	CH_2CO_2Et	21.0 ± 2
3	*p*-Ph	–	–	6.3 ± 0.3	**24**	*m*-Ph	Bn	$(CH_2)_2OAc$	25.1 ± 03
4	CH_2	Bn	–	65 ± 5	**25**	*m*-Ph	CH_2CO_2Et	Bn	20.4 ± 0.4
5	CH_2	CH_2CO_2Bn	–	> 100	**26**	*m*-Ph	CH_2CO_2Et	CH_2CO_2Et	> 100
6	CH_2	$(CH_2)_2OAc$	–	> 100	**27**	*m*-Ph	CH_2CO_2Et	$(CH_2)_2OAc$	> 100
7	*m*-Ph	Bn	–	14.5 ± 0.7	**28**	*m*-Ph	$(CH_2)_2OAc$	Bn	> 100
8	*m*-Ph	CH_2CO_2Et	–	91.0 ± 6	**29**	*m*-Ph	$(CH_2)_2OAc$	CH_2CO_2Et	63.0 ± 9
9	*m*-Ph	$(CH_2)_2OAc$	–	25.1 ± 0.1	**30**	*m*-Ph	$(CH_2)_2OAc$	$(CH_2)_2OAc$	> 100
10	*p*-Ph	Bn	–	> 100	**31**	*p*-Ph	Bn	Bn	> 100
11	*p*-Ph	CH_2CO_2Et	–	> 100	**32**	*p*-Ph	Bn	CH_2CO_2Et	36.3 ± 0.8
12	*p*-Ph	$(CH_2)_2OAc$	–	79.0 ± 2	**33**	*p*-Ph	Bn	$(CH_2)_2OAc$	13.2 ± 0.3
13	CH_2	Bn	Bn	0.3 ± 0.003	**34**	*p*-Ph	CH_2CO_2Et	$(CH_2)_2OAc$	> 100
14	CH_2	Bn	CH_2CO_2Et	35.0 ± 1	**35**	*p*-Ph	$(CH_2)_2OAc$	Bn	> 100
15	CH_2	Bn	$(CH_2)_2OAc$	28.0 ± 1	**36**	*p*-Ph	$(CH_2)_2OAc$	CH_2CO_2Et	> 100
16	CH_2	CH_2CO_2Bn	Bn	22.4 ± 0.5	**37**	*p*-Ph	$(CH_2)_2OAc$	$(CH_2)_2OAc$	> 100
17	CH_2	CH_2CO_2Bn	CH_2CO_2Et	> 100	**38**	Ph[c]	–	–	6.2 ± 0.05
18	CH_2	CH_2CO_2Bn	$(CH_2)_2OAc$	> 100	**39**	Ph[c]	Bn	–	93.0 ± 2
19	CH_2	$(CH_2)_2OAc$	Bn	> 100	**40**	Ph[c]	CH_2CO_2Et	–	> 100
20	CH_2	$(CH_2)_2OAc$	CH_2CO_2Et	> 100	**41**	Ph[c]	$(CH_2)_2OAc$	–	> 100
21	CH_2	$(CH_2)_2OAc$	$(CH_2)_2OAc$	> 100					

[a] B16 melanoma cells were exposed for 48 h to the test compound and cytotoxicity was assayed using the MTT assay, as described in the General Procedures section.

[b] Compound concentration (µM) required to kill 50% of B16 murine melanoma cells (IC_{50}). Mean ± SEM of at least 3 determinations.

[c] Propiolic acid phenyl amide (**38**) derivatives, without a second ethynyl substituent.

However, the same effect was not observed when introducing this second triazole in **31**, obtained from **10**, since they had both IC_{50} > 100 µM. Also in this R^1 = benzyl series, the introduction of another type of chain like ethoxycarbonylmethyl and acetoxyethyl, had positive effects on the biological activity, but not as important as for **13**. Bis-triazoles **14**, **15**, **23**, **24**, **32** and **33**; synthesized from molecules **4**, **7** and **10**, presented activities in the range of 15-35 µM. Increase in activity was observed for propargylic-issued molecules **5** and **6** (both over 100 µM), giving **14** (38 µM) and **15** (28 µM), respectively. The same increased activity was not encountered in the *meta* derivative for the transformation from **7** (14 µM) to **23** (21 µM) and **24** (25 µM). However, the *para*-ethynyl derivative **10** (> 100 µM) also gave more active bis-triazoles **32** (36 µM) and **33** (13 µM).

In the R^1 = benzyl / ethyloxycarbonyl (**5**, **8** and **11**) and acetoxyethyl (**6**, **9**, **12**) series, the introduction of another triazole

ring only yielded compounds with IC_{50} > 100 µM. The only exceptions were the followings: preparation of **16** (22 µM) showed an increased biological activity from **5** (> 100 µM); compound **25** (20 µM) was 4.6-fold more cytotoxic than **8** (91 µM); and, **29** (63 µM) presented a 2.5-fold decreased in activity from **9** (25 µM).

4. Discussion

When considering the unexpected results obtained for the bis-alkynes **1**-**3** and **38**, it appears that the presence of a phenyl ring between the two alkynes yielded compounds with higher cytotoxic activities (Figure 1). However, the presence of the phenyl ring itself does not seem to be the only influence in this dramatic increase in activity. When the ethynyl group was in a *para* position like in **3** (6.3 µM), or absent like in **38** (6.2 µM), the activity was better than for **1** (38 µM), but lower than **2** (0.3 µM), where the ethynyl was in *meta* position. It thus seems that the presence of an ethynyl group in a *meta* position was necessary for a strong activity.

By comparing the structure of the more potent compounds, a further tentative of structure-activity relationship can be drawn for this small series of molecules. The bis-triazole **13** (0.3 µM), in which two benzyl substituents were on the triazoles gave an activity similar to **2** (0.3 µM), without any structural correlations. However, the same double substitution by benzylic substituents was found in the bis-triazole **22** (4.5 µM) derived from **2**. Replacement of one of the benzyl groups by another one, *e.g.* ethoxycarbonylmethyl like in **23** (21 µM) and **25** (20.4 µM), also issued from **2**, increased the IC_{50}. Interestingly for these two compounds, the replacement of the benzylic substituent on one or the other triazole gave products with the same activity. Introduction of a triazole bearing a benzyl substituent, onto the activated alkyne of **2**, gave the triazole-alkyne **7** with a good activity (14.5 µM). Once again, the benzylic part was found in the derivative, as well as a *meta* substitution. The benzyl group was also present in **33** (13.2 µM), derived from the *para*-bis-alkyne **3**.

From this preliminary study, we can hypothesize that for the bis-alkynes, an aromatic "spacer" as well as a *meta*-substitution was required for the highest activity, as seen for **2**. When one or two triazoles were formed on the starting bis-alkynes, it seemed that the presence of a benzylic part onto the nitrogen-1 of the cycle was responsible for an activity ranging from good to excellent as for **2**. This was observed for compounds **13**, **22**, **23**, **25** and **33**, for bis-triazole, and **7** for the mono-triazoles.

Considering the drug-like properties of our best compounds **2** and **13**, they were shown to meet the Lipinski's rule of 5 criteria, *i.e.*, a molecular mass ≤ 500, a log P ≤ 5 and a H donor count ≤ 5, indicating favorable properties for drug development [29]. Furthemore, potential molecular targets were also searched for, using the *in silico* bioactivity score developed by Molinspiration [30]. By comparison to large databases, the results showed that three potential pathways could significantly be involved in compound **2** mechanism of action (but not for **13**): G protein coupled receptor (GPCR) ligand, kinase inhibitor and enzyme inhibitor. Of course, those potential targets identified *in silico* would need further *in vitro* validation.

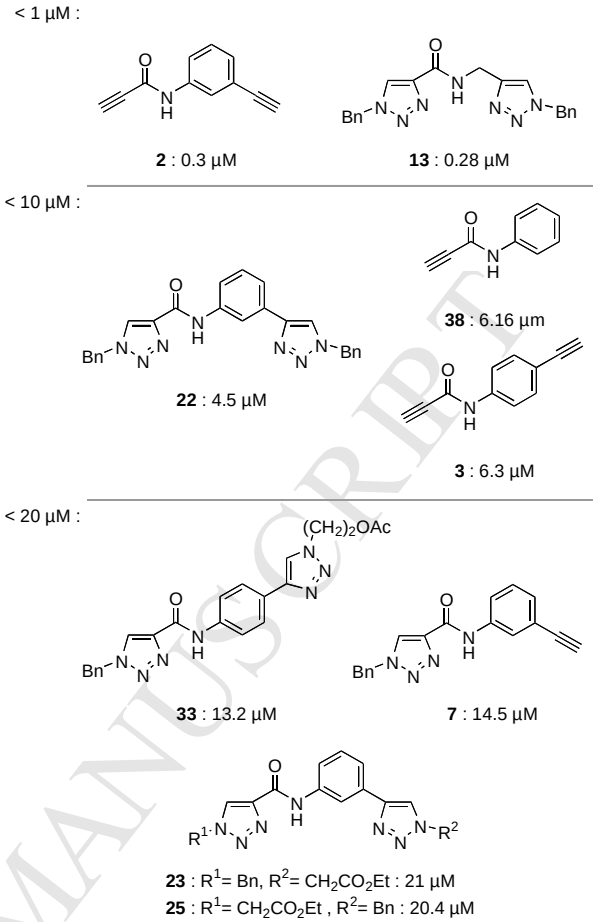


Figure 1. Representative active compounds (**2**, **3**, **7**, **13**, **22**, **23**, **25**, **33** and **38**) against B16 melanoma included in the range inferior to 1 µm to inferior or equal to 20 µM.

5. Conclusion

In this preliminary communication we presented our findings on the potential anticancer activity of bis-alkyne amides and their mono- and bis-triazolic derivatives. Some of the synthesized products showed noteworthy activity against B16 melanoma cells. Interestingly, one of the bis-alkynes was very potent, as well as a bis-triazole prepared from another less active mono-triazole. A tentative SAR was formulated as a starting point aiming at better understanding the required substituents for biological activity in this series of compounds. Further work onto the activity and mechanism of action of these compounds is warranted.

6. General Procedures

6.1. Catalyst free Huisgen's reaction (for the R^1 group)

To the neat bis-alkyne **1** (0.5 mmol), in an opened test tube, was added the needed organic azide (0.55 mmol). The mixture was stirred at room temperature for 18 h. The crude products were triturated in EtOH (8 mL) and filtrated to obtain the solid 1,4-isomer of the mono-triazoles **4**-**6**. For the reactions ran in solution, *i.e.* for bis-alkynes **2**-**3**, the alkyne was dissolved in acetone (4 mL), the azides added, and the solution was heated under reflux (65°C) for 24 h. The same work-up was conducted after acetone removal under vacuum to afford mono-triazoles **7**-**12**.

6.2. Amberlyst A-21•CuI CuAAC reaction (for the R^2 group)

The mono-triazoles **4**-**12** – or mono-alkyne **38** – (0.2 mmol) were dissolved in CH_2Cl_2 (2 mL) and treated with the desired azide (0.22 mmol) in the presence of Amberlyst A-21•CuI (12 mg, 8 mol%). The suspension was gently stirred at room temperature in a closed vessel until complete reaction (16-48 h), filtered and the polymer rinsed with CH_2Cl_2 (2 x 1 mL). Evaporation of the solvent gave the bis-triazoles **13**-**41**.

6.3. Cytotoxicity evaluation on B16 melanoma cells

Murine B16 melanoma cells were grown in DMEM medium containing 2 mM L-glutamine, 10% foetal bovine serum, 100 U/mL penicillin and 100 µg/mL streptomycin (37°C, 5% CO_2). All compounds were initially dissolved in DMSO at a stock concentration of 2.5 mg/mL and were further diluted in cell culture medium. Exponentially growing cells were plated onto 96-well plates at 5000 cells per well in 100 µl of culture medium. Twenty-four h after plating, 100 µl of medium containing the compound at final concentrations ranging from 0.01 to 100 µM were added to the wells (in triplicate) containing the cells, and incubated for 48 h at 37 °C and 5% CO_2. After the 48 h exposure period to the test compounds, cell viability was assayed using the MTT test [31] and absorbance was read at 562 nm in a microplate reader (BioKinetics Reader, EL340). Appropriate controls with DMEM only and MTT were run to subtract background absorbance. The concentration of compound that inhibited cell viability by 50% (inhibitory concentration for 50% of cells, or IC_{50}) was determined using the GraphPad Prism software.

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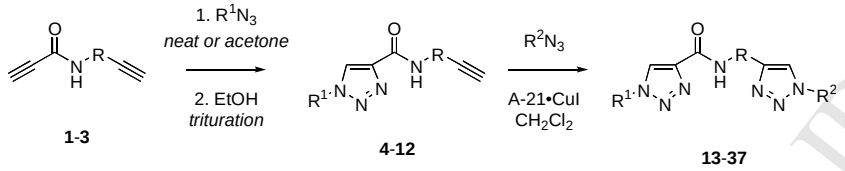
Synthesis and *in vitro* evaluation of potential anticancer activity of mono- and bis-1,2,3-triazole derivatives of bis-alkynes

H. Elamari, R. Slimi, G. G. Chabot⁎⁎ , L Quentin, D. Scherman and C. Girard⁎
CNRS UMR8151, INSERM U1022, Unité de Pharmacologie Chimique, Génétique & Imagerie, Ecole Nationale Supérieure de Chimie de Paris and Université Paris Descartes, Paris, France



- The compounds were prepared by a regioselective synthesis using click chemistry
- This was done by a solvent / catalyst free and a solid phase supported steps
- All synthetic compounds were tested: alkynes, mono and bistriazoles
- Some compounds reached micro to nanomolar cytotoxicities agains B13 melanoma
- We made a Structure-Activity Relationship tentative for the series