New modular structures constructed by click chemistry

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INTRODUCTION

Inspired by diferent natural compounds with cytotoxic activity, we synthesised new modular compounds by Click Chemistry,[1] using two kinds of building blocks which can be easily coupled. The Cu(I) catalyzed version of the Huisgen reaction, was the tool selected for the coupling of the building blocks. These compounds have been tested to determine their antiproliferative activity against five human solid tumor cell lines.

RESULTS AND DISCUSSION

During our studies of hybrid compounds, we synthesized compound **1a** (Figure 1) which showed moderate antiproliferative activity.

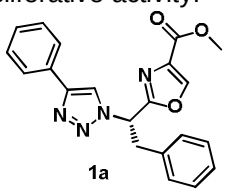

Figure 1. First cytotoxic structure obtained

In order to improve this result, we focused our efforts into the synthesis of compounds with a general structure **1** (Figure 2), based in two diferents building blocks. The first building block corresponds to an aromatic ethynyl compound, which was synthesized from aromatic aldehydes by means of Corey-Fuchs reaction.[2] The second building block, corresponds to an oxazole or thiazole ring, and was synthesized from serine dipeptides.[3] Using this aproach, we proposed 4 zones which can be appropiate for modifications.

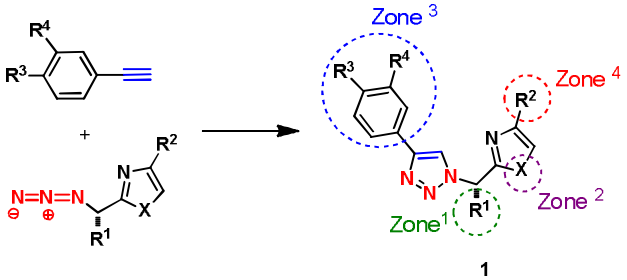

Figure 2. Synthesis of related compounds

Zone 1 can be modified using diferent aminoacids as starting material. Zone 2 corresponds to the synthesis of oxazole or thiazole rings. Zone 3 can be modified changing the starting aldehyde. Zone 4 corresponds to modifications of the methyl ester of **1a**.

This way, we synthesized 16 new compounds, and they were assayed *in vitro* to determine their antiproliferative activity against five human solid tumor cell lines. Only two of the new compounds showed a better profile than the parent compound. Apparently modifications of Zones 2 and 4, produce loss of activity, and Zones 1 and 3, admit only few changes.

CONCLUSION

We have developed the synthesis of new modular products, created a small library of related compounds and assayed them to determine their antiproliferative activity. Besides only two of the new compouns show activity, we think that it's still possible to improve the activities obtained so far, with new compounds.

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REFERENCES

[1] Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2001**, *40*, 2004.
[2] Fuchs, P. L.; Corey, E. J. *Tetrahedron Lett.* **1972**, *13*, 3769.
[3] Phillips, A. J.; Uto, Y.; Wipf, P.; Reno, M. J.; Williams, D. R. *Org. Lett.* **2000**, *2*, 1165.