Synthesis and development of novel small molecules targeting Rac1 signaling as new potential leads for antitumor agents

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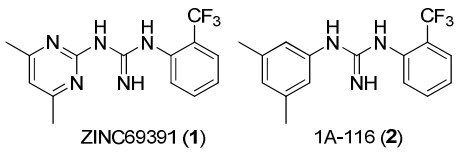
INTRODUCTION

Rho GTPases are a family of small GTP-binding proteins involved in cell cytoskeleton organization, migration, transcription, and proliferation. They act as molecular switches that cycle between an inactive GDP-bound and an active GTP-bound form. Guanine nucleotide exchange factors (GEFs) highly regulates this process. The active GTP-bound state binds preferentially to downstream effectors proteins and actively transduces signals.[1] The aberrant activation of Rac1, one of the most studied Rho GTPases, is involved in tumor progression, invasion and metastasis and it is considered a promising target for novel anticancer drug development.[2]

We present the identification of a hit structure, ZINC69391 (**1**) and the synthesis and evaluation of new analogues.

RESULTS AND DISCUSSION

ZINC69391 (**1**) was found by docking-based virtual library screening targeting the surface of Rac1 involved in GEF interactions. It showed significant antiproliferative effect on different cancer cell lines and inhibited Rac1-Tiam1 interaction *in vitro*. Moreover, it significantly reduced lung metastasis in a syngeneic animal model. A first group of related analogues with variations at the aromatic rings were designed and synthesized (Scheme 1). 1A-116 (**2**) showed a significant increase in antiproliferative activity compared to **1** on F3II cells, showing an IC_{50} value of 4 µM, a 10-fold reduction compared to the parental ZINC69391 (Figure 2b).

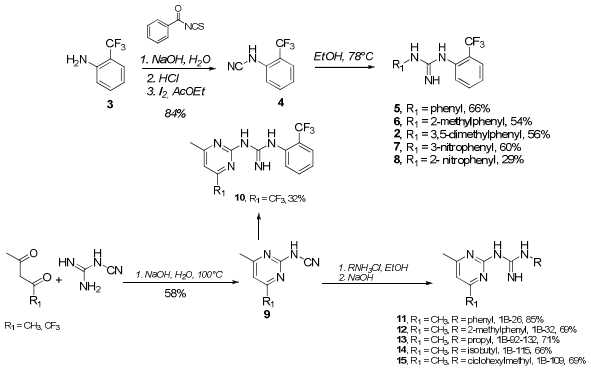


ZINC69391 (**1**) 1A-116 (**2**)

Figure 1. Structures of ZINC69391 (**1**) and 1A-116 (**2**).

Molecular docking studies and the synthesis of analogues substituted with sulfonamide groups at the aromatic rings and with variations in the linker region will be presented.

Scheme 1. Synthesis of ZINC69391 (**1**) analogues



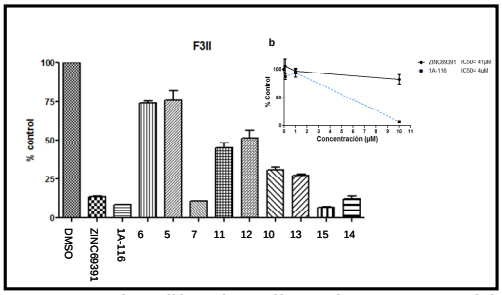


Figure 2. a. Anti-proliferative effect of ZINC69391 (**1**) and its analogues measured in F3II cells that were treated with 100 µM solution of the drugs during 72 h; **b**. IC_{50} of ZINC69391 and 1A-116 GraphPrism®, n = 3).

CONCLUSION

Compound **2** emerged as the best candidate for further preclinical studies and was identified as a new lead compound. It was prepared on gram scale for *in vivo* preclinical studies that are in progress. Molecular docking simulations predicted the observed enhanced affinity of analogue **2** *vs* **1.**.

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REFERENCES

[1] Etienne-Manneville, S.; Hall, A. *Nature*, **2002** *420(6916),*629.
[2] Fritz, G.; Kaina, B. *Curr Cancer Drug Targets*, **2006**. *6(1)*,1.