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Drug resistance in cancer:
from biology to molecular
targets and drugs

ABSTRACTS

New potential anti-hepatocellular carcinoma (HCC) agents: *in vitro* evaluation of anti-HCC activity and hepatotoxicity of 6-substituted methyl 3-aminothieno[3,2-b]pyridine-2-carboxylates and QSAR studies.

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Hepatocellular carcinoma (HCC) is a major health problem with more than 660,000 new cases per year worldwide [1]. HCC is resistant to commonly used treatments like chemotherapy and radiotherapy and new anti-HCC therapies are urgently needed. Sorafenib was the first approved small molecule against HCC and underlines the importance of identifying potential new anti-HCC drugs [2].

Thirty-two 6-substituted methyl 3-aminothieno[3,2-b]pyridine-2-carboxylates, previously prepared by some of us [3,4], were evaluated as potential new anti-HCC agents by studying their *in vitro* cell growth inhibition on human HepG2 cells, generally regarded as a good HCC model, and hepatotoxicity using a porcine liver primary cell culture (PLP1). The presence of amino groups linked to a benzene moiety on the substituent of the 6-position emerged as the key element for the anti-HCC activity.

The methyl 3-amino-6-[(3-aminophenyl)ethynyl]thieno[3,2-b]pyridine-2-carboxylate was the most potent compound presenting HepG2 GI₅₀ = 1.2 µM against 2.9 µM of the positive control ellipticine, with no observed hepatotoxicity (PLP1 GI₅₀ > 125 µM against 3.3 µM of ellipticine). QSAR studies were also performed to provide mechanistic insights for the anti-HCC activity and hepatotoxicity of the compounds. The correlations obtained using molecular and 1D descriptors revealed the importance of the presence of amino groups and other hydrogen bond donors for anti-HCC activity, and hydrogen bond acceptors for hepatotoxicity. The best correlations were obtained with 3D descriptors belonging to different subcategories for anti-HCC activity and hepatotoxicity, respectively. These results point to different molecular mechanisms of action of the compounds for anti-HCC activity and hepatotoxicity. This work presents some promising 6-substituted methyl 3-aminothieno[3,2-b]pyridine-2-carboxylates for potential use in chemotherapy against HCC. Moreover these compounds may also be used as scaffolds for further synthesis of more potent and less toxic analogues.

- 1 Jemal A, Murray T, Ward E, Samuels A, Tiwari RC, Ghafour A, Feuer EJ, Thun MJ. Cancer statistics, 2005 (2005). CA Cancer Journal for Clinicians, 55: 10-30.
- 2 Keating GM, Santoro A. Sorafenib: a review of its use in advanced hepatocellular carcinoma (2009). Drugs 69: 223-240.
- 3 Queiroz M-JRP, Calhela RC, Vale-Silva LA, Pinto E, Lima R, Vasconcelos MH. Efficient synthesis of 6-(hetero)arylthieno[3,2-b]pyridines by Suzuki-Miyaura coupling. Evaluation of growth inhibition in human tumor cell lines, SARs and effects on the cell cycle (2010). European Journal Medicinal Chemistry 45: 5628-5634.
- 4 Queiroz M-JRP, Calhela RC, Vale-Silva LA, Pinto E, Almeida G, Vasconcelos MH. Synthesis and Evaluation of Tumor Cell Growth Inhibition of Methyl 3-Amino-6-[(hetero)arylethynyl]thieno[3,2-b]pyridine-2-carboxylates. Structure-Activity Relationships, Effects on the Cell Cycle and Apoptosis (2011). European Journal Medicinal Chemistry 46: 236-240.

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