THIOSEMICARBAZONES AS INHIBITORS OF TRYPTOPHAN 2,3-DIOXYGENASE (TDO), AN EMERGING TARGET FOR CANCER TREATMENT

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Thiosemicarbazones have received a great deal of attention due to their antineoplastic, antibacterial, antiviral, and antifungal activity. Their biological activity has been attributed to metal chelating properties in general and to the inhibitory activity on ribonucleotide reductase in particular. Compounds of this class, such as marboran and triapine, are already used in medical practice.

Indoleamine 2,3-dioxygenase (IDO) is an extrahepatic heme dioxygenase catalysing tryptophan oxidation in the so-called kynurenine pathway of this amino acid catabolism. IDO is involved in tumoral immune resistance: various human tumours express the enzyme constitutively and the development and synthesis of IDO inhibitors has been an active area of research in the recent years. A structurally unrelated hepatic enzyme catalysing the same reaction, tryptophan 2,3-dioxygenase (TDO), has lately also been linked to cancer immunopathology. Our group very recently described a series of ethenyl indole-based TDO inhibitors yielding LM 10, a potent (IC₅₀ = 2 uM in a cellular test), selective, orally bioavailable compound which, furthermore, shows anti-cancer activity in preclinical in vivo models in mice.

In this work, the synthesis of a small library of aromatic thiosemicarbazones as well as their evaluation and SAR as TDO inhibitors is described. The best compound (ED 135) is roughly equipotent to LM 10 in the cellular test. A new pharmacological profile for aromatic thiosemicarbazones with a potential in an emerging way of cancer treatment is thus demonstrated.

References
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