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

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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.[1] Their biological activity has been attributed to metal chelating properties in general[2] and to the inhibitory activity on ribonucleotide reductase in particular.[3] 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[4] and the development and synthesis of IDO inhibitors has been an active area of research in the recent years.[5] A structurally unrelated hepatic enzyme catalysing the same reaction, tryptophan 2,3-dioxygenase (TDO), has lately also been linked to cancer immunopathology.[6] Our group very recently described a series of ethenyl indole-based TDO inhibitors yielding **LM 10**, a potent (IC_{50} = 2 uM in a cellular test), selective, orally bioavailable compound which, furthermore, shows anti-cancer activity in preclinical *in vivo* models in mice.[7]

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.[8]

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