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### Tryptophan 2,3-Dioxygenase (TDO) Inhibitors as Anticancer Immunomodulators

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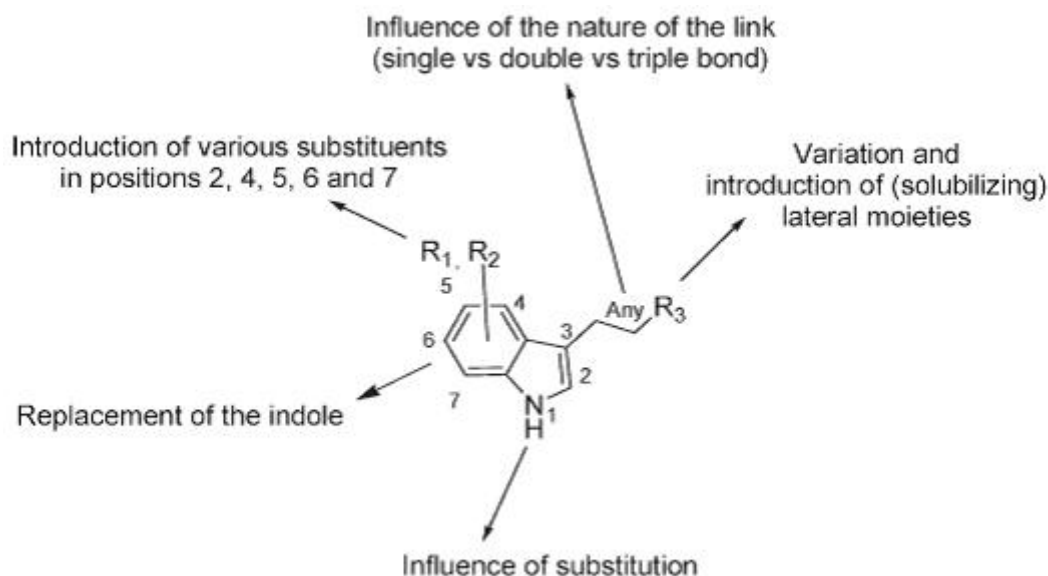
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## TRYPTOPHAN 2,3-DIOXYGENASE (TDO) INHIBITORS AS ANTICANCER IMMUNOMODULATORS

**Eduard Dolušić (1), Pierre Larrieu (2), Laurence Moineaux (1), Vincent Stroobant (2), Luc Pilotte (2), Didier Colau (2), Lionel Pochet (1), Etienne De Plaen (2), Catherine Uyttenhove (2), Benoît Van den Eynde (2), Johan Wouters (1), Bernard Masereel (1), Raphaël Frédérick (1)**

*1) Namur Medicine & Drug Innovation Center (NAMEDIC), Namur Research Institute for Life Sciences (NARILIS), University of Namur, B-5000 Namur, Belgium; 2) Ludwig Institute for Cancer Research, Brussels Branch, and de Duve Institute, Université Catholique de Louvain, B-1200 Brussels, Belgium*

Tryptophan catabolism mediated by indoleamine 2,3-dioxygenase (IDO) is an important mechanism of peripheral immune tolerance contributing to tumoral immune resistance.<sup>1</sup> IDO inhibition has been an active area of research in drug development for a number of years.<sup>2</sup> Recently, our group has shown that tryptophan 2,3 dioxygenase (TDO), an unrelated hepatic enzyme also catalyzing the first step of tryptophan degradation, is as well expressed in many tumors preventing their rejection by locally depleting tryptophan.<sup>3</sup> The role of tryptophan catabolites was demonstrated by another group.<sup>4</sup>



Herein, we report the syntheses and structure-activity studies around a series of 3-(2-(pyridyl)ethenyl)indoles.<sup>5</sup> Some 80 novel heterocyclic compounds were synthesized. Their TDO inhibitory potency was evaluated and rationalized by molecular modeling studies. The best candidate in terms of potency, selectivity, solubility and oral bioavailability was evaluated in a preclinical model in mice. Upon systemic treatment, the compound reversed TDO-mediated tumoral immune resistance.<sup>6</sup>

### References

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