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

Dolusic, Eduard; Larrieu, Pierre; Moineaux, Laurence; Strobant, Vincent; Pilotte, Luc; Colau, Didier; Pochet, Lionel; De Plaen, Etienne; Uyttenhove, Catherine; Van den Eynde, Benoît; Wouters, Johan; Masereel, Bernard; Frédérick, Raphael

Publication date:
2012

Document Version
Early version, also known as pre-print

[Link to publication](#)

Citation for published version (HARVARD):

Dolusic, E, Larrieu, P, Moineaux, L, Strobant, V, Pilotte, L, Colau, D, Pochet, L, De Plaen, E, Uyttenhove, C, Van den Eynde, B, Wouters, J, Masereel, B & Frédérick, R 2012, 'Tryptophan 2,3-Dioxygenase (TDO) Inhibitors as Anticancer Immunomodulators', BOSS XIII - 13th Belgian Organic Synthesis Symposium Louvain, 15 - 20 juillet 2012, Leuven, Belgium, 15/07/12 - 20/07/12 pp. Programme & Book of Abstracts, BOSS XIII, KU Leuven, Belgium, 15 - 20 July 2012, P292, p. 339.

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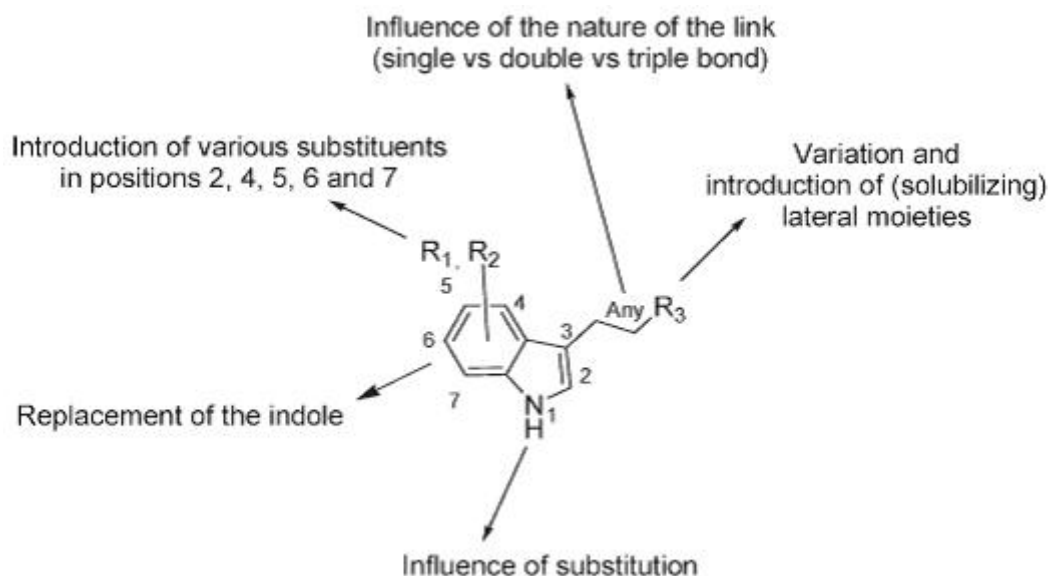
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TRYPTOPHAN 2,3-DIOXYGENASE (TDO) INHIBITORS AS ANTICANCER IMMUNOMODULATORS

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Tryptophan catabolism mediated by indoleamine 2,3-dioxygenase (IDO) is an important mechanism of peripheral immune tolerance contributing to tumoral immune resistance.¹ IDO inhibition has been an active area of research in drug development for a number of years.² 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.³ The role of tryptophan catabolites was demonstrated by another group.⁴



Herein, we report the syntheses and structure-activity studies around a series of 3-(2-(pyridyl)ethenyl)indoles.⁵ 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.⁶

References

This work was supported in part by FNRS-Télévie (7.4.543.07).

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