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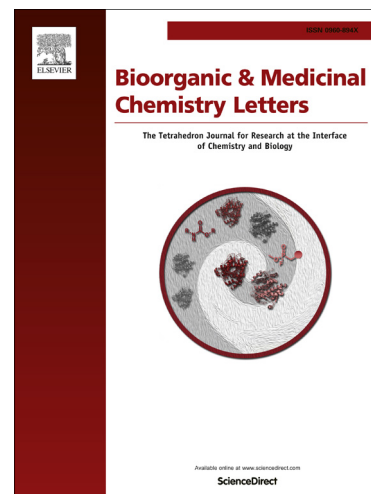
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Discovery of structurally simplified analogs of colchicine as an immunosuppressant

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ABSTRACT

We have discovered a new class of colchicine-derived therapeutic agents for immune diseases including rejection of organ-transplantation and autoimmune disease. Compound **2**, which had been developed to overcome poor pharmacokinetic properties of compound **1**, a first-generation colchicine analog, turned out to show toxicity such as intestinal toxicity and loss of weight during *in vivo* tests. The deletion of 7-carboxamide group and middle ring-truncation in colchicine allowed us to have structurally simplified analogs with strong immunosuppressive activity. Herein, we report non-alkaloid tricyclic compound **7** and **12** as immunosuppressants which exhibited a strong immunosuppressive *in vivo* efficacy on the T-dependent antibody response, the Zymosan A-induced arthritis model and the Carrageenan-induced edema model. Compound **7** and **12** revealed less toxicity than the previous lead compound **2**, and their minimum lethal doses (MLD) were proved to exceed 100 mg/kg.

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