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Synthesis, antitumor activity and mechanism of action of novel 1,3-thiazole derivatives containing hydrazide–hydrazone and carboxamide moiety

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ABSTRACT

A series of novel 2,4,5-trisubstituted 1,3-thiazole derivatives containing hydrazide–hydrazine, and carboxamide moiety including 46 compounds **T** were synthesized, and evaluated for their antitumor activity in vitro against a panel of five human cancer cell lines. Eighteen title compounds **T** displayed higher inhibitory activity than that of 5-Fu against MCF-7, HepG2, BGC-823, Hela, and A549 cell lines. Especially, **T1**, **T26** and **T38** exhibit best cytotoxic activity with IC_{50} values of 2.21 μg/mL, 1.67 μg/mL and 1.11 μg/mL, against MCF-7, BCG-823, and HepG2 cell lines, respectively. These results suggested that the combination of 1,3-thiazole, hydrazide–hydrazone, and carboxamide moiety was much favorable to cytotoxicity activity. Furthermore, the flow cytometry analysis revealed that compounds **T1** and **T38** could induce apoptosis in HepG2 cells, and it was confirmed **T38** led the induction of cell apoptosis by S cell-cycle arrest.

1,3-Thiazole scaffold have attracted considerable attentions for decades due to their remarkable spectrum of biological activity, such as distinctive antifungal,[1,2] antimicrobial,[3–6] antitubercular[7,8] activity. Moreover, several 1,3-thiazole scaffolds were documented to contribute to a variety of antineoplastic potentials being employed as anticancer,[9–13] anti-angiogenic,[14] antiproliferative,[15,16] tubulin polymerization inhibiting,[17] and cytotoxic[18,19] agents. Recently, it was reported that the chemotherapeutic activity of 1,3-thiazoles

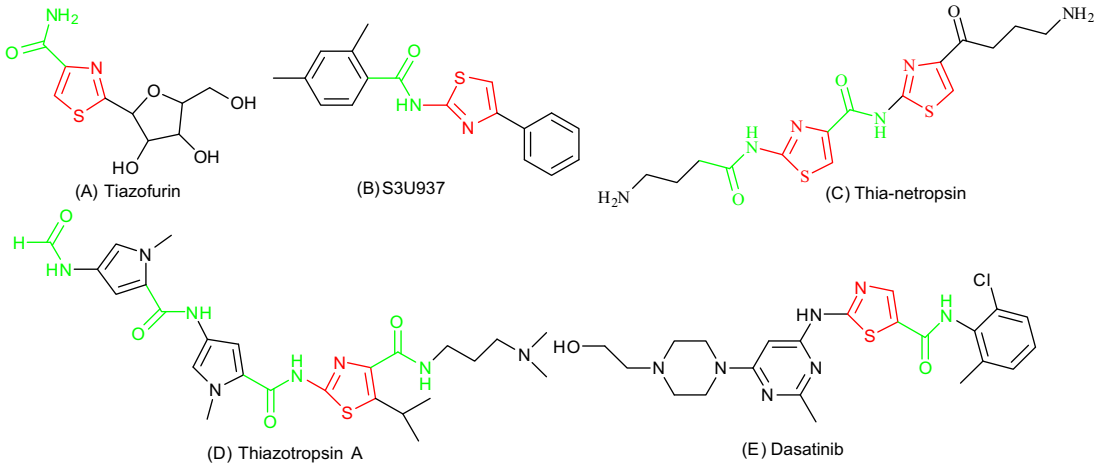

Figure 1. Antitumor agents containing 1,3-thiazole ring and carboxamide moiety.

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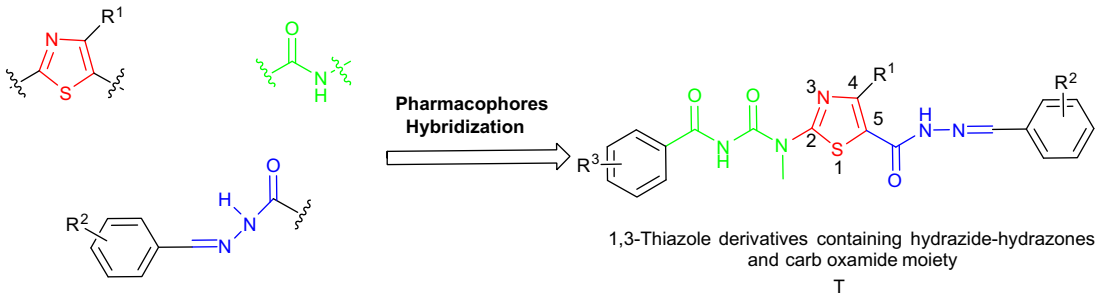
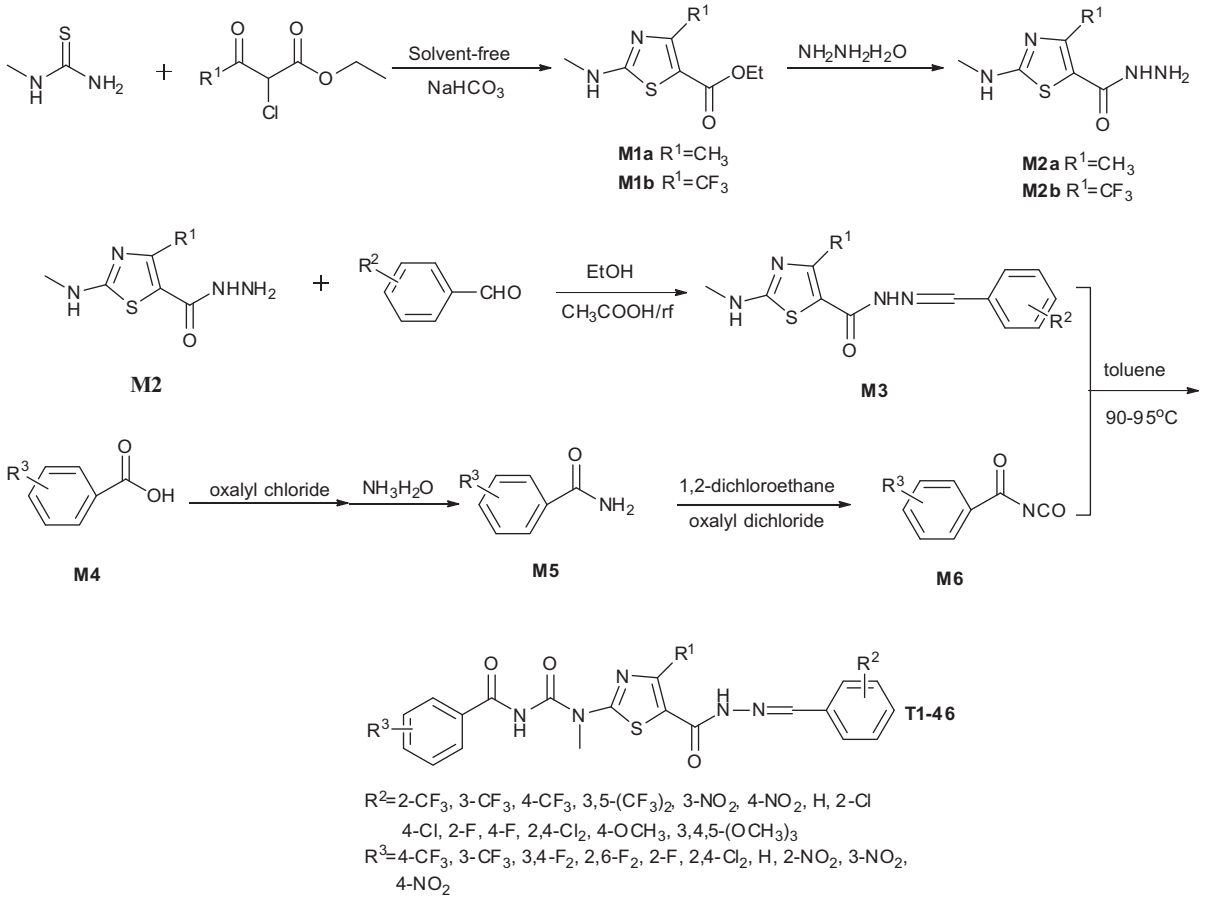


Figure 2. Design of **T** as antitumor agents.

derivatives are augmented by the discovery of tiazofurin (natural antineoplastic antibiotic) (Fig. 1, A),[20] and S3U937 (Fig. 1, B),[21] which exhibited potential antitumor activity against various cancer types.[22] The documented DNA minor groove binding property of 1,3-thiazole-netropsin, and thiazotropsin A (Fig. 1, C and D) are also payed attention.[23,24] Another 1,3-thiazole derivative dasatinib (Fig. 1, E) was reported to possess potential tyrosine kinase inhibitory activity, and proved to be efficient in the treatment of imatinib resistant mutants.[25] Most of antitumor agents in Figure 1 are distinguished by containing substituted 1,3-thiazole ring, and carboxamide groups. Furthermore, recently literatures revealed that the hydrazide-hydrazone (–CO–NH–N=CH–) moiety as a pharmacophore played a significant antitumor activity in some antitumor agents.[26–29] We noticed that some reported pharmacologically active 1,3-thiazole derivatives exhibited a narrow activity spectrum,[23,30] and their preparation method is not so effective, and easily due to lower yields, long reaction time or under microwave irradiation.[31] It seemed to be reasonable to improve the synthetic method, and find new 1,3-thiazole derivatives with broad-spectrum antitumor activity.

In view of the above mentioned facts, we report herein the synthesis, in vitro cytotoxic evaluation of some novel 1,3-thiazole derivatives based on pharmacophores hybridization. The corresponding carboxamide moiety, and hydrazide–hydrazone pharmacophore were integrated with structural unit of 1,3-thiazole into the novel structure **T** as shown in Figure 2, it was thought that these novel skeleton **T** bearing three pharmacological groups would be well synergistic antitumor effects, and broad-spectrum antitumor activity. Therefore a series of novel 2-(substituted(*N*-(methylcarbamoyl) benzamide))-4-substituted-5-(substituted(*N*-benzylideneacetohydrazide))1,3-thiazole derivatives **T** were designed and synthesized. It was expected that broad-spectrum



Scheme 1. Synthesis of title compounds **T1-46**.