Bioorganic & Medicinal Chemistry Letters 28 (2018) 1077–1083

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Synthetic strigolactone analogues reveal anti-cancer activities on hepatocellular carcinoma cells

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ARTICLE INFO

Article history:
Received 12 December 2017
Revised 7 February 2018
Accepted 8 February 2018
Available online 9 February 2018

Keywords:
Strigolactones
Liver cancer
Apoptosis
Cell proliferation
Hepatocellular carcinoma

ABSTRACT

Hepatocellular carcinoma (HCC) remains one of the leading causes of death worldwide. The complex etiology is attributed to many factors like heredity, cirrhosis, hepatitis infections or the dysregulation of the different molecular pathways. Nevertheless, the current treatment regimens have either severe side effects or tumors gradually acquire resistance upon prolonged use. Thus, developing a new selective treatment for HCC is the need of the hour. Many anticancer agents derived from plants have been evaluated for their cytotoxicity towards many human cancer cell lines. Strigolactones (SLs)-a newly discovered class of phytohormones, play a crucial role in the development of plant-root and shoot. Recently, many synthetic analogues of SLs have demonstrated pro-apoptotic effects on different cancer cell lines like prostate, breast, colon and lung. In this study, we tested synthetic SLs analogues on HCC cell line-HepG2 and evaluated their capability to induce cell proliferation inhibition and apoptosis. Primary WST-1 assays, followed by annexin-V/7AAD staining, demonstrated the anti-proliferative effects. The SLs analogues **TIT3** and **TIT7** were found to significantly reduce HepG2 cell viability in a dose- and time-dependent manner and induce apoptosis. Interestingly, though **TIT3** and **TIT7** strongly affected cancer cell proliferation, both compounds showed moderate anti-proliferative effect on normal cells. Further, migration of cancer cells was suppressed upon treatment with **TIT3** and **TIT7** in a wound healing assay. In summary, these findings suggest that two SLs analogues **TIT3** and **TIT7** exert selective inhibitory effects on cancer cells most likely through targeting microtubules. SLs analogues could be used in future as potential anti-cancer candidates in chemotherapy.

Hepatocellular carcinoma (HCC) is the predominant form of primary malignant liver tumor accounting to 80–90% of all liver cancers.[1–3] Yearly, one million cases of HCC are diagnosed worldwide, and more than 690,000 of them consequently die.[4] HCC is the fifth most common type of cancer in men and eighth in women[5] and is considered as the third leading cause of cancer-related deaths globally.[6] Several factors could be involved in the

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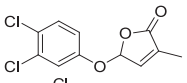
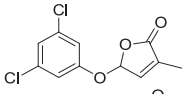
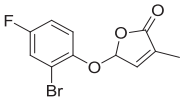
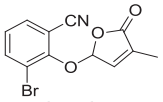
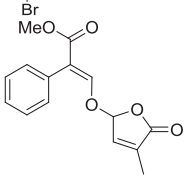
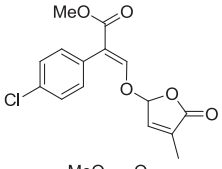
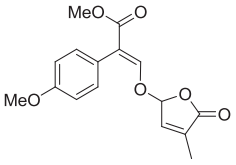
https://doi.org/10.1016/j.bmcl.2018.02.016
0960-894X/

Table 1
Structure and molecular weight of synthetic strigolactone analogues.

SL analogue	Molecular formula; weight	Structure
TSK13	$C_{11}H_8Cl_2O_3$; 259.09	
TSK14	$C_{11}H_8Cl_2O_3$; 259.09	
TSK15	$C_{11}H_8BrFO_3$; 287.08	
TSK16	$C_{12}H_8BrNO_3$; 294.10	
TIT3	$C_{15}H_{14}O_5$; 274.27	
TIT7	$C_{15}H_{13}ClO_5$; 308.71	
TIT14	$C_{16}H_{16}O_6$; 304.29	

development of hepatic tumors including chronic hepatitis B and C viral infections, diabetes mellitus and obesity.[3,7–9] Many studies have illustrated that patient survival rates can be significantly increased if tumors are detected at early stages,[10,11] and the subsequent treatments such as liver transplantation and resection are timely done.[12] Furthermore, chemotherapy is more frequently encountered with resistance, and nearly no effective cure is found in advanced HCC stages.[11]

Lack of understanding the molecular mechanisms of hepatic tumors limits the development of practical therapeutic approaches for it.[13–15] The significant drawbacks of the current treatment regimens like severe side effects, off-target toxicities and gradually acquired resistance by tumors upon prolonged use remains a challenge. Therefore, there is a pressing demand of developing new drugs and investigate their anti-proliferative effects on HCC to treat patients.

In the recent few years, many anticancer agents derived from plants have been evaluated for their potential to inhibit the proliferation of many human cancer cell lines.[16–21] Strigolactones (SLs) are a novel class of plant hormones, responsible for root and shoot development. Many synthetic analogues of SLs have demonstrated pro-apoptotic effects on a panel of cancer cell lines including osteosarcoma, leukaemia, lung, colon, prostate and breast.[22–24] These synthetic SLs analogues were found to induce a G2/M arrest and apoptosis in cancer cells.[22,24] Interestingly, the tested SLs analogues showed only a miniscule inhibition against normal cells (BJ fibroblasts).[24] SLs analogues have been shown to inhibit cell proliferation and induce apoptosis by targeting several signalling pathways. In this context, treatment of colon, prostate[22] and breast[24] cancer cell lines with synthetic SLs analogues caused the activation of p38 and JNK1/2 mitogen-activated protein kinases (MAPKs) leading to the inhibition of ERK1/2 and PI3K/AKT; the consequence was cell cycle arrest at G2 phase.[22,24] A recent study has reported

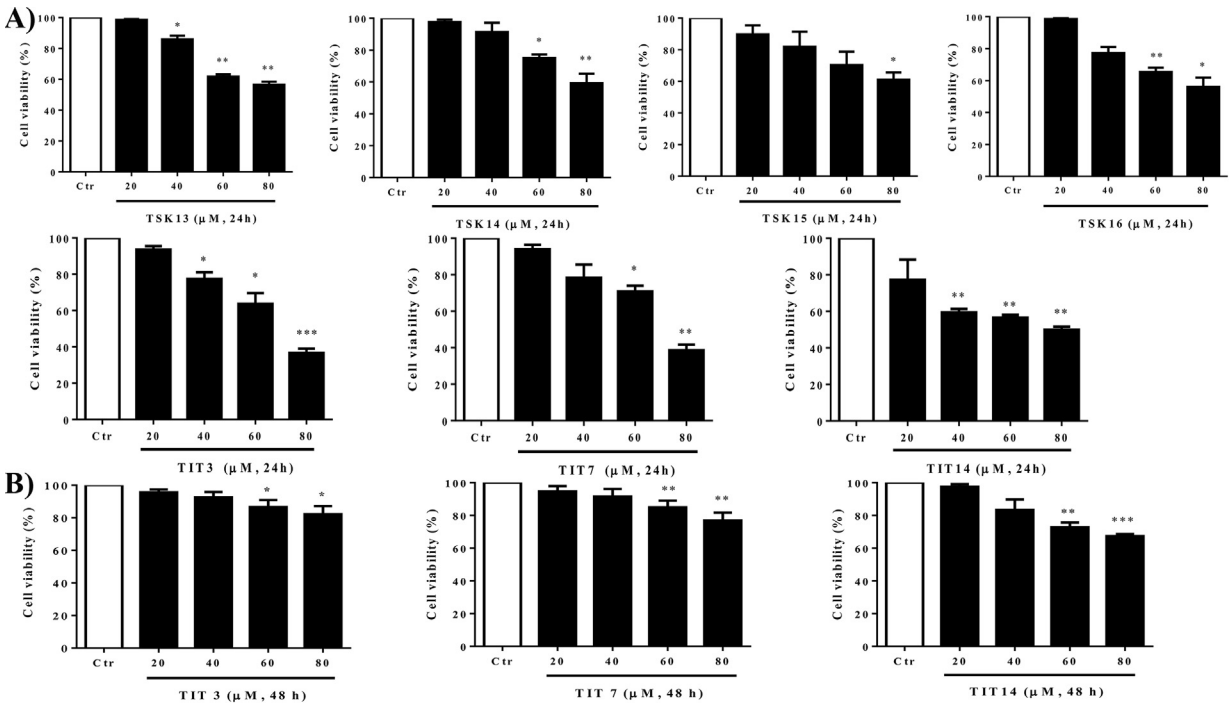


Fig. 1. (A) Dose-dependent antiproliferative effect of SL analogues on cell viability of HepG2. HepG2 cells were treated with several concentrations of SLs for 24 h. Cell viability was assessed using WST-1 assay as described in Supporting Information. The values here are represented as mean ± S.E.M. of two independent experiments in triplicates; statistically significant (unpaired '*t*' test; two-tailed): $^{*}p < 0.05$; $^{**}p < 0.001$; $^{***}p < 0.0001$; versus the corresponding untreated control. (B) Dose-dependent effect of SL analogues **TIT3**, **TIT7** and **TIT14** on cell viability of normal BHK cells. BHK cells were treated with several concentrations of SLs for 24 h. Cell viability was assessed using WST-1 assay as described in Supporting information. The values here are represented as mean ± S.E.M. of three independent experiments in triplicate; statistically significant (unpaired '*t*' test; two-tailed): $^{*}p < 0.05$; $^{**}p < 0.001$; $^{***}p < 0.0001$; versus the corresponding untreated control.