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ORIGINAL ARTICLE

ANTICANCER ACTIVITY OF SOME NOVEL 1-(3,5-DIPHENYL-1H-1,2,4- TRIAZOL-1-YL)-3-(SUBSTITUTED ARYL)PROP-2-EN-1-ONE

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ABSTRACT: In the present study anticancer activity of some formerly synthesized 1-(3,5-diphenyl-1H-1, 2, 4-triazol-1-yl)-3-(substituted aryl)prop-2-en-1-one (Chalcones) have been reported. Five selected compounds were subjected to National Cancer Institute (NCI) for in vitro human tumor cell lines screening. The compounds were evaluated at single concentration of 10-5M towards the panel of approximately 60 cancer cell lines derived from nine different cancer types: leukemia, lung, colon, CNS, melanoma, ovarian, renal, prostate and breast cancers. The tested compounds showed a broad spectrum of growth inhibitory activity against human tumor cells, as well as some distinctive pattern of selectivity toward CNS Cancer (SNB-75), Renal Cancer (UO-31), Non-Small Cell Lung Cancer (NCI-H522) and Leukemia (SR). The most efficient anticancer compound 3j was found to be active with selective influence on CNS Cancer cell lines especially on SNB-75 with a growth % of 80.21.
KEYWORDS: Chalcones, CNS Cancer, anticancer activity, Leukemia.

INTRODUCTION

The recent findings suggest that the 1,2,4-triazole nucleus is associated with diverse biological activities such as anticancer (Bhat *et al.,* 2009; Al-Soud *et al.,* 2003), antimicrobial (Lingappa *et al.,* 2008; Rao *et al.,* 2000; Jalilian *et al.,* 2000; Lazarevic *et al.,* 2001), anticonvulsant (Chimirri *et al.,* 1999), anti-inflammatory, analgesic (Hunashal *et al.,* 2011), antidepressant (Kane *et al.,* 1988), antitubercular (Husain *et al.,* 1987), antimalarial (Xiao *et al.,* 2001) and hypoglycemic (Deliwala *et al.,* 1971) activities. Chalcones are products of condensation of simple or substituted aromatic with simple or substituted acetophenones in presence of alkali (Schmidt, 1881; Claisen and Clapared, 1881). Chalcones are well known intermediates for synthesizing various heterocyclic compounds. Chalcones and its derivatives have attracted particular interest during the last few decades due to use of such ring system as the core structure in many drug substances covering wide range of pharmacological activities such as antimicrobial (Rajendra *et al.,* 2008; Tavares *et al.,* 2011), anticancer (Echeverria *et al.,* 2009; Kumar *et al.,* 2010; Reddy *et al.,* 2011; Vogel *et al.,* 2010), antitubercular (Shivakumar *et al.,* 2005), antimalarial (Tomar *et al.,* 2010; Eric *et al.,* 2010), antiviral (Churkin *et al.,* 1982), anticonvulsant (Bedia *et al.,* 2011), antiproliferative (Liu and Mei, 2006), anti-inflammatory activity (Herencia *et al.,* 1998; Won *et al.,* 2005), antileishmanial (Boeck *et al.,* 2006) and anti-oxidant (Hussain *et al.,* 2009) etc. Walton *et al.* (1945) during their chemical studies in the structure of clavicin found that a structural feature which was responsible for antibacterial activity in clavicin was α, β unsaturated keto functional group which is similar to the structure of chalcones. The diverse biological properties of chalcones have prompted us to evaluate some novel 1,2,4-triazole linked chalcones for their anticancer activity.

In view of these observations and in continuation of our work on biologically active heterocycles and their increasing importance in pharmaceutical and biological field, it was considered of interest to investigate the anticancer activity of 1-(3,5-diphenyl-1H-1,2,4-triazol-1-yl)-3-(substituted aryl)prop-2-en-1-one (Chalcones, Figure 1) against the panel of approximately 60 cancer cell lines derived from nine different cancer types: leukemia, lung, colon, CNS, melanoma, ovarian, renal, prostate and breast cancers. In case of recently synthesized 3,5-disubstituted 1,2,4-triazolyl chalcones, which have been recently reported

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for their potential analgesic (Khanage *et al.*, 2013) and antimicrobial (Khanage *et al.*, 2012a) activity and their structures have been earlier confirmed by spectral methods and elemental analysis (Khanage *et al.*, 2012b).

EXPERIMENTAL

2.1. Anticancer activity

In the present study, newly synthesized 1-(3,5-diphenyl-1H-1,2,4-triazol-1-yl)-3-(substituted aryl)prop-2-en-1-one (Chalcones) have been evaluated for anticancer screening. Compounds 3a, 3d, 3f, 3g and 3j were submitted to NCI for in vitro human tumor cell lines screening. The compounds were evaluated at single concentration of 10-5M towards the panel of approximately 60 cancer cell lines derived from nine different cancer types: leukemia, lung, colon, CNS, melanoma, ovarian, renal, prostate and breast cancers. Preliminary anticancer assay was performed according to the US NCI protocol. All the compounds were added to a previously prepared cell culture at a single concentration. The cell culture was incubated for 48 h. End point determinations were made with a protein binding dye, sulforhodamine B (SRB). The results for each compound were reported as the percent growth of treated cell lines or panel when compared to untreated control cells. The mean growth %, range of growth % and growth % relative to most sensitive cell line is depicted in Table 1.

RESULTS AND DISCUSSION

The compounds 3a, 3d, 3f, 3g and 3j were evaluated at single concentration of 10-5 M towards the panel of approximately 60 cancer cell lines derived from nine different cancer types. All tested compounds exhibited more selective antitumor pattern toward cell lines of renal, CNS, Leukemia and Non-Small Cell Lung Cancer (Figure 2), but tested compounds were exhibited moderate growth inhibitory property toward renal and CNS cancer cell lines. Compound with 2,4-dimethoxy substitution (3j) was found to be a highly active growth inhibitor of the CNS cancer cell line (SNB-75) with a growth % of most sensitive cell line to be -19.79, whilst least active over other cell lines (Figure 3). The mean growth % for compound 3j was observed 100.39 % and fall in a range of -19.79-34.66 (Table 1). Compounds 3d and 3g showed selectivity on renal cancer (UO-31) with a growth % of most sensitive cell line to be -19.26 and -15.91respectively and found to be moderate growth inhibitor of the renal cancer cell line (UO-31). These compounds showed varying range of growth % -19.26 to 35.77 for compound 3d and -15.91 to 35.13 for compound 3g. Compounds 3a and 3f showed selectivity on CNS cancer (SNB-75) with a growth % of most sensitive cell line to be -18.85 and -15.70 respectively and found to be sensible growth inhibitor of the CNS cancer (SNB-75). These compounds showed range of growth % -18.85 to 32.06 for compound 3a, -15.70 to 31.09 for compound 3f.

The SAR study reveals that anticancer activity of the tested compounds is sensitive to the nature of substituents on aromatic ring of triazole linked chalcone. Among the compounds tested, compounds with electron withdrawing groups like chloro and methoxy on phenyl ring of 1,2,4-triazolyl chalcone shows most marked effect and possessed significant activity (Figure 1). From the screening results the compound of 2-chloro substitution on phenyl ring (3f) was found to be least active anticancer agent. The results also states that chalcones of 1,2,4-triazole heterocycles might have support remarkably for the anticancer activity.

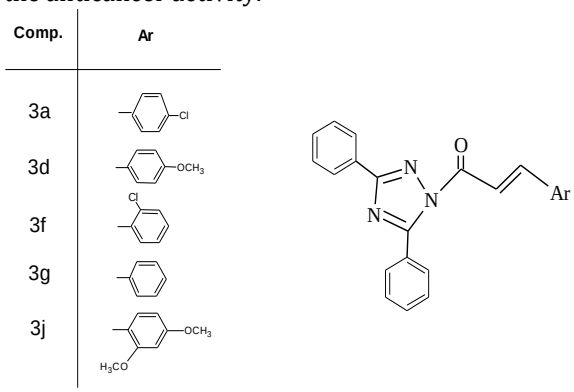

Figure 1: Structures of triazolyl chalcones tested for anticancer activity.

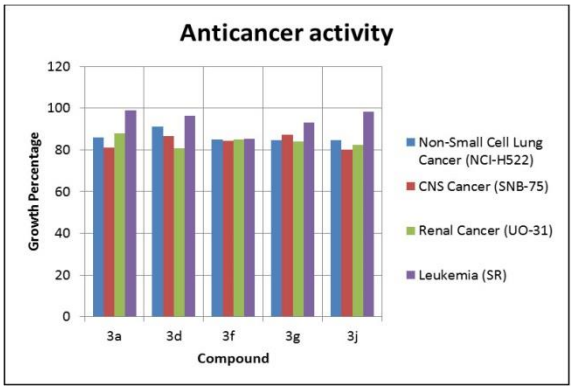

Figure 2: Anticancer activity of tested compounds against most selective human tumor cell lines.

Table 1: Anticancer screening data of compounds

Comp.	NSC code	60 Cell lines in assay in 1-dose 10^{-5} M concentration				
		Mean growth (%)	Range growth (%)	Most sensitive cancer type	Most sensitive cell line	Growth of Sensitive cell (%)
3a	767426	101.56	-18.85-32.06	CNS Cancer	SNB75	-18.85
			-14.19-32.06	N.S.C.L.C.*	NCI-H522	-14.19
			-12.25-32.06	Renal Cancer	UO-31	-12.25
3d	767427	101.94	-19.26-35.77	Renal Cancer	UO-31	-19.26
			-13.34-35.77	CNS Cancer	SNB75	-13.34
			-9.79-35.77	Leukemia	MOLT-4	-9.79
3f	767428	100.89	-15.70-31.09	CNS Cancer	SNB-75	-15.70
			-15.12-31.09	N.S.C.L.C.	NCI-H522	-15.12
			-14.86-31.09	Renal Cancer	UO-31	-14.86
			-14.66-31.09	Leukemia	SR	-14.66
			-15.91-35.13	Renal Cancer	UO-31	-15.91
3g	767429	100.66	-15.24-35.13	N.S.C.L.C.	NCI-H522	-15.24
			-12.60-35.13	CNS Cancer	SNB-75	-12.60
			-9.68-35.13	Leukemia	K-562	-9.68
3j	767430	100.39	-19.79-34.66	CNS Cancer	SNB-75	-19.79
			-17.69-34.66	Renal Cancer	UO-31	-17.69
			-15.28-34.66	N.S.C.L.C.	NCI-H522	-15.28

* Non-Small Cell Lung Cancer

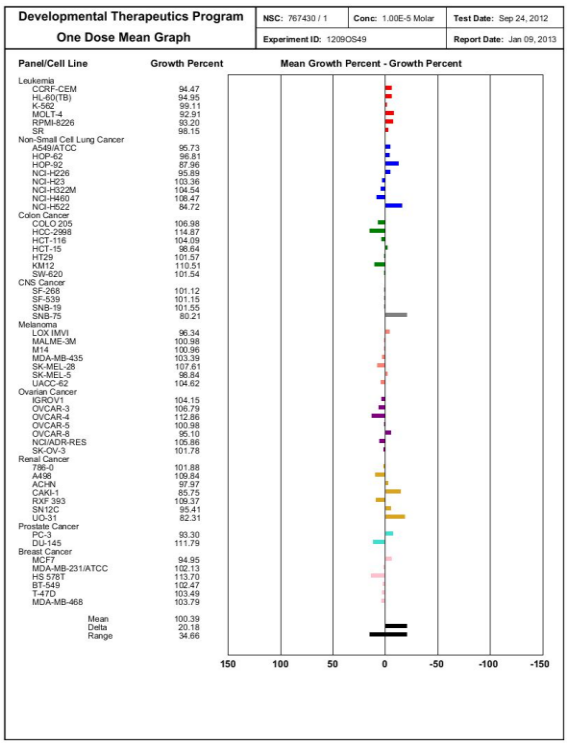

Figure 3: Selected NCI sixty cell screening data highlighting the potency of compound (3j: NSC: 767430) against CNS Cancer (SNB-75). Bars to the right of the mean line represent cell lines more sensitive to test compound compared to mean, whereas bars to the left represent less sensitive cell lines.

CONCLUSION

In conclusion, the results of the present study divulge that 1,2,4-triazolyl chalcones may have potential anticancer effects. None of the compounds have effective anticancer properties in human cancer cell line study. All tested compounds showed selective anticancer activity in cell lines of CNS Cancer (SNB-75), Renal Cancer (UO-31), Non-Small Cell Lung Cancer (NCI-H522) and Leukemia (SR). Whereas compound 3j exhibited selective influence on CNS Cancer cell lines especially on SNB-75.

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