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A Novel Molecule (1-(4-methoxyphenyl)-3,3-dimethyl- 1-(5-phenyl-1,3,4-thiadiazol-2-yl) Urea derivatives have Antiproliferative activities against A Leukemia Cell Line -K562"

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ABSTRACT

Cancer is deliberate to be caused by the interaction between genetic susceptibility and environmental toxins. Based on the DNA changes in cells, proliferating cycle of tumor cells can be divided into 4 phase's Pre-synthetic phase (Gap 1 phase or G1 phase). The antiproliferative activities of these compounds were evaluated against a Cytotoxicity analysis of compounds against leukemia cell line -K562 organism homo sapiens (human) organ bone - marrow.Tissue - lymphoblast, disease - chronic myelogenous leukemia (CML) one human tumor cell lines (K562) by applying the MTT colorimetric assay. The 1, 3-disubstituted urea derivatives show good antiproliferative activity against human cancer cell lines (K562). Generally, an aromatic ring on N-3 seems to be in favor of enhancing the inhibitory activity, compounds introduced a Nitro group substituted at C-3 position on the aromatic ring approved to generally decrease activity. Cells were incubated with different concentrations of the extract for 5 days in a 96 well plate, after which the liver cells which did not take in stain and dead cells which took in stain were counted. For counting the cell suspension was mixed with an equal volume of trypan blue and was counted. A concentration that inhibited the growth of cells at 50% (IC50) was computed. Substances with low IC50 indicate potential for cytotoxicity. (A) 1, 1-dimethyl-3-phenyl-3-(5-phenyl-1, 3, 4-thiadiazol-2-yl) urea was found higher activity

Keywords: Cancer, urea derivative, antiproliferative activities, malignant behavior.

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INTRODUCTION

Cancer is the uncontrolled growth of cells coupled with malignant behavior: invasion and metastasis. Cancer is thought to be caused by the interaction between genetic susceptibility and environmental toxins. Two types of tumors exist, benign and malignant. Benign tumors are not cancerous. They can usually be removed and generally don't grow back once they're gone. The cells in benign tumors don't spread and it is rare for a benign tumor to be life-threatening. DNA is found in every cell in the body and regulates all of its activities. Cancer is caused by damage to DNA. Genetic abnormalities found in cancer typically affect two general classes of genes. Cancer-promoting oncogenes are typically activated in cancer cells, giving those cells new properties, such as hyperactive growth and division, protection against programmed cell death, loss of respect for normal tissue boundaries, and the ability to become established in diverse tissue environments.

Definitive diagnosis requires the histology examination of a biopsy specimen, although the initial indication of malignancy can be symptomatic or radiographic imaging abnormalities. Most cancers can be treated and some forced into remission, depending on the specific type, location, and stage.

Phases of Oncogenesis

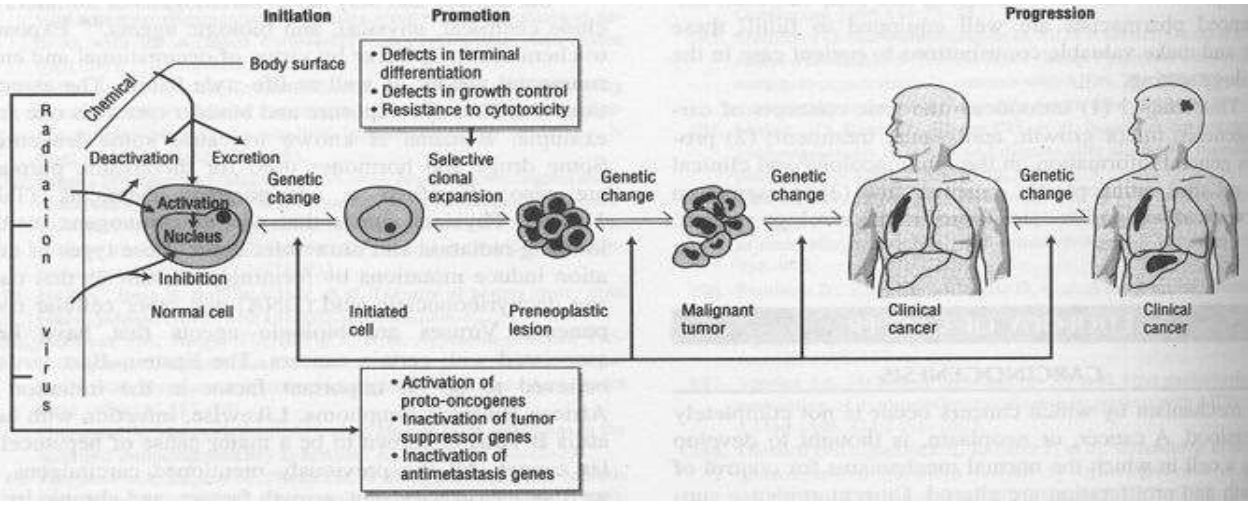
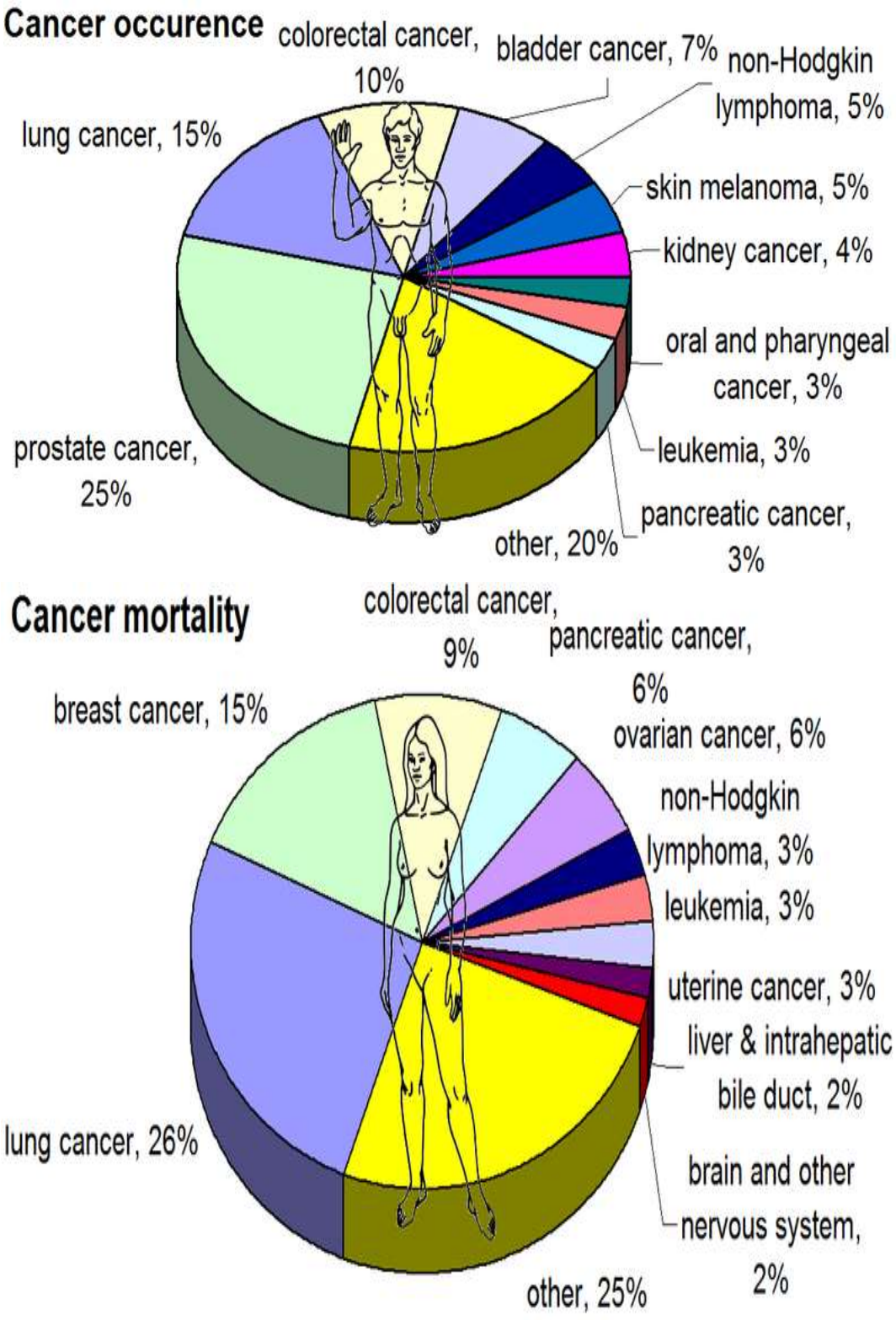


Figure 1: Phases of Oncogenesis

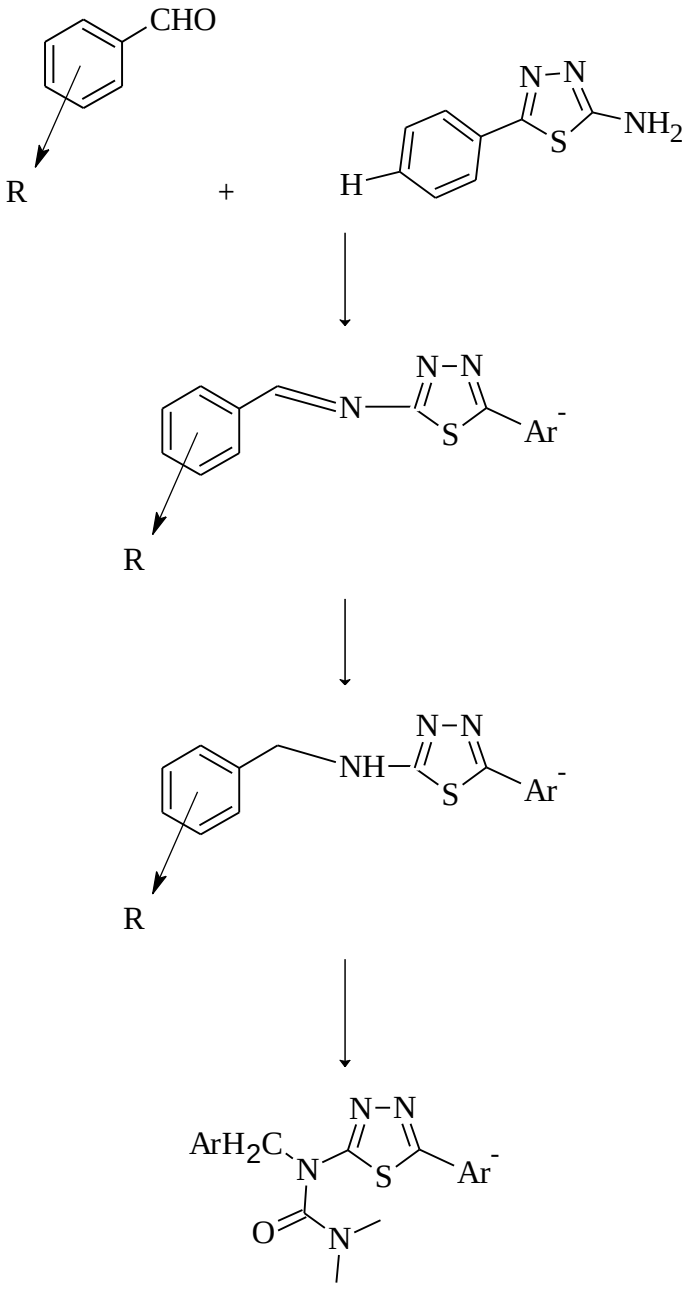
Cancers are classified by the type of cell that resembles the tumor and, therefore, the tissue presumed to be the origin of the tumor. These are the histology and the location, respectively. Examples of general categories include: Carcinoma, Sarcoma, Germ cell tumor, Blastic tumor or blastoma.

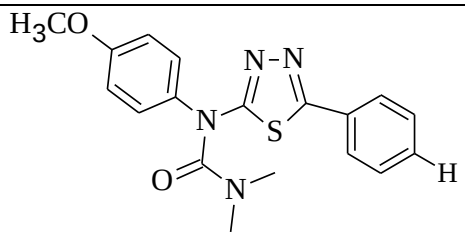


As of 2004, worldwide cancer caused 13% of all deaths (7.4 million). The leading causes were: lung cancer (1.3 million deaths/year), stomach cancer (803,000 deaths), colorectal cancer (639,000 deaths), liver cancer (610,000 deaths), and breast cancer (519,000 deaths). Greater than 30% of cancer is preventable via avoiding risk factors including: tobacco, overweight or obesity, low fruit

and vegetable intake, physical inactivity, alcohol, sexually transmitted infections, and air pollution.5,6

Scheme for synthesis compound:



Code	Compounds	Mol. Formula	Mol.Wt.	Melting Point°C	Crystals Nature	% Yield
S002	 1-(4-methoxyphenyl)-3,3-dimethyl-1-(5-phenyl-1,3,4-thiadiazol-2-yl)urea	$C_{18}H_{18}N_4O_2S$	354.42612	195-197	Reddish Brown color	67%

MATERIALS AND METHOD

(A)Aldehyde was dissolved in 25 ml of ethanol, and amine was added to the solution. The reaction mixture was refluxed for1 h.

(B) And then 0.05 mmol of NaBH4 was added to the reaction solution slowly, and stirred under 50 _C for 2e3 h. The mixture was evaporated under vacuum, and dissolved in EtOAc (30 ml). The solution was washed with 20 ml water twice, dried over anhydrous sodium sulfate, and evaporated. Purification by silica gel afforded pure products.

(C)The mixture of CH2Cl2 (15 ml) dry DMF (3 ml, 40 mmol) and SOCl2 (7 ml, 0.10 mol) was stirred to reflux at 70 _C for4 h and cooled. The solvents and excess SOCl2 were then removed under reduced pressure. The residue dissolved inCH2Cl2 (15 ml) was added dry pyridine (4 ml)

(D) And various amines (40 mmol). The reaction mixture was stirred at50e60 _C for 5e6 h, and then added to 20 ml ice-water, the organic layer was separated, and the aqueous layer was extracted with ethyl acetate (2 _ 10 ml). The organic layer was combined and washed with saturated NaHCO3, dried with anhydrous Na2SO4 for 0.5 h and concentrated under vacuum; ultimately the residue was purified by silica gel column (eluent EtOAc / petroleum ether, 1:2 - 2:1).

Experimental data:

a (solubility profile)

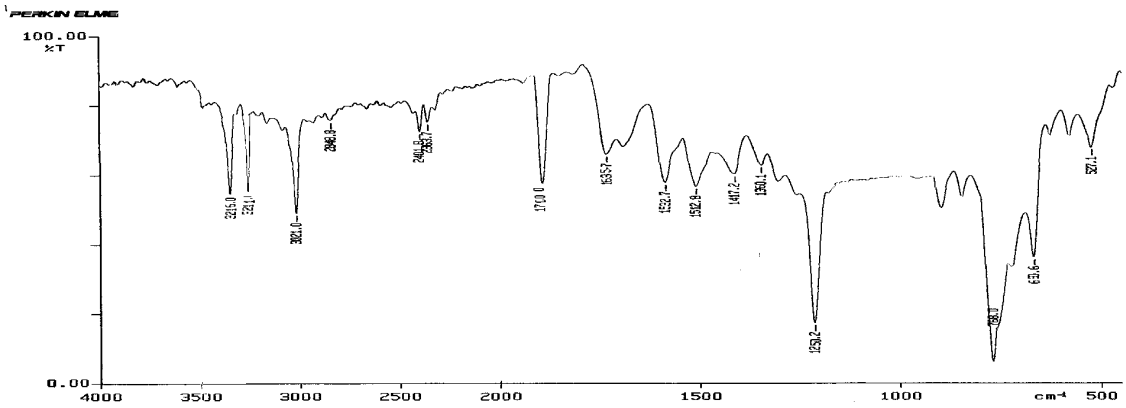
S.No.	Name of Solvents	Solubility Normal Tem.			Hot. Tem.		
		+	±	-	+	±	-
1.	Water			✓			
2	Ethanol		✓		✓		
3.	Methanol		✓		✓		
4.	Chloroform		✓		✓		
5.	Benzene			✓	✓		
6.	Carbon Tetrachloride	✓					

7.	Ethyl acetate	✓
8.	Pyridine	✓
9.	Dimethyl formamide	✓
10.	Dimethyl sulfoxide	✓

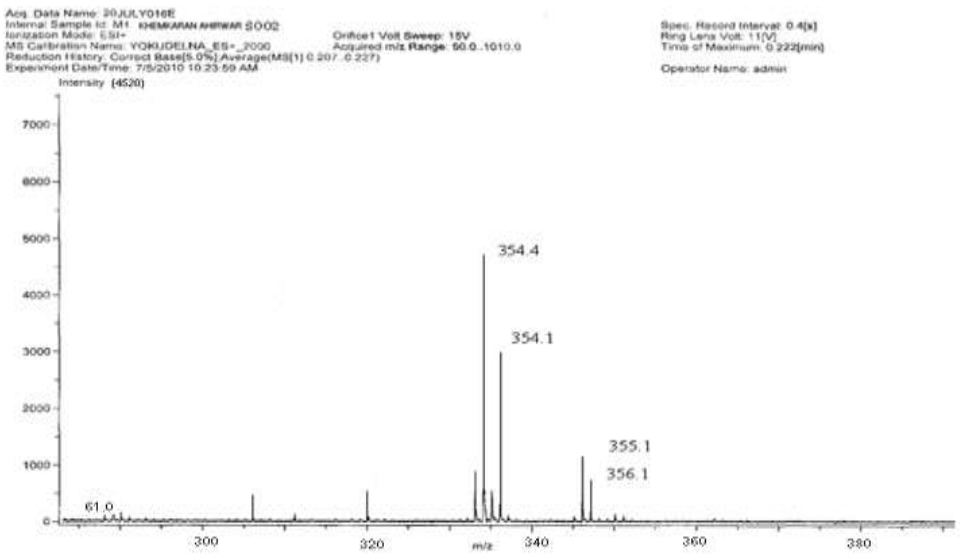
(B). Infra Red / 1H NMR (KBr) (cm-1) **spectral study of the synthesized compounds.**

SOO1- 1, 1-dimethyl-3-phenyl-3-(5- phenyl-1, 3, 4-thiadiazol-2-yl) urea.

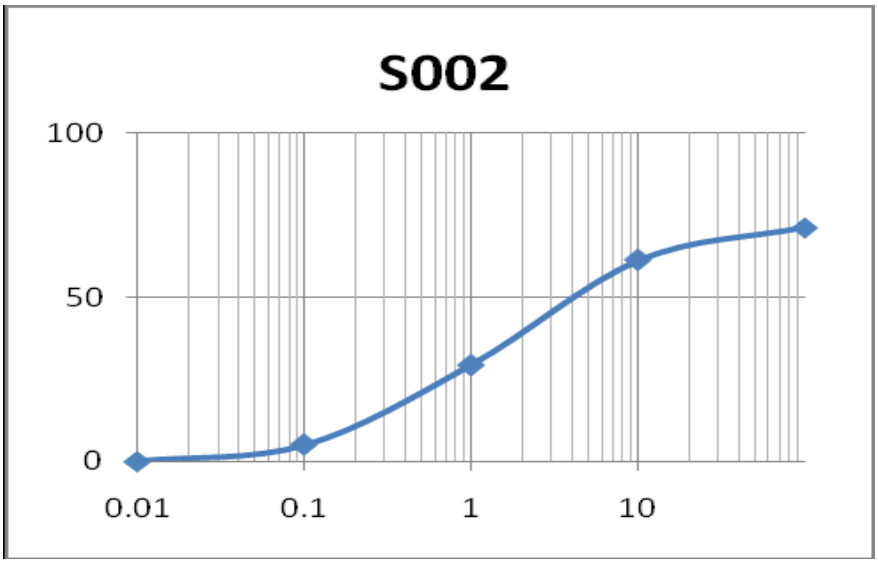
Peaks cm-1	Due to	Probable Group
1700.0 (Strong peak)	C=O , stretching	Amide
1250.2 (Strong peak)	C-C , stretching	Benzene
768.00 (Strong peak)	C-S ,stretching	Thiourea
3216.0 (Medium peak)	N-H str.(asymmetric stretching)	Primary Amide
690.6(Weak peak)	C-H , stretching	(Aromatic ring)
1635.7(Weak peak)	N=C, stretching	Nitrate



(C) **Mass Spectroscopy Analysis**



(D) **Dose Response Curves for Compounds against K 562.**



CONCLUSION

The objective of the present work was to synthesize, purify, characterize and evaluate the Antiproliferative activity of 1, 3 disubstituted urea compounds. The yield of different synthesized compounds was found to be in the range of 42-80% and the Characterization was done by melting point and TLC. Characteristic IR bands show several Functional vibrational modes which confirm the completion of the reaction. Some structures were confirmed by FTIR. All the five test compounds showed Antiproliferative activity against the human tumor cell line K-562. (Disease-chronic myelogenous leukemia (CML).

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