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Synthesis and Anticancer Assay of Novel Silyl-thiourea Derivatives

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ABSTRACT

The present work aims at the study of reaction of diphenyldiisothiocyanatosilane with amine ligands as a convenient pathway for synthesis of novel silyl-thiourea derivatives with silicon atom in a hyper coordinate environment. A rational mechanism of this reaction involves the coupling of isothiocyanate with amine through addition reaction and the involvement of lone pair of N/O hetero atoms in vicinity of silicon for creating hyper coordination around silicon atom. The structures of all the compounds were confirmed on the basis of spectroscopic techniques (FT-IR, ^{1}H NMR, ^{13}C NMR, UV spectroscopy) and elemental analyses. The synthesized compounds were screened for anticancer activity against HeLa cells using MTT colorimetric assay.

Keywords: diphenyldiisothiocyanatosilane, silyl-thiourea, hyper coordination, anticancer, MTT.

INTRODUCTION

Thiourea derivatives serve as a versatile class of organosulfur compounds due to their wide spectrum of biological activities. These compounds have been evaluated as efficient antimicrobial, anticancer, antidiabetic, anti-allergic and insecticidal agents [1-5]. Besides these, there are numerous laboratory and industrial applications of this class of compounds. Recently, thioureas have emerged as excellent oganocatalysts, chemosensors, corrosion inhibitors and thermoplastics in polymer industries [6-9]. Several methods of preparation of thiourea derivatives [10-13] have been documented in literature with the most common method reported as that of the addition reaction of amines with isothiocynates generating the -N(H)-C(=S)-N(H)-(thiourea) linkage. However, the use of silyl isothiocyanate as precursor for the formation of thiourea derivatives has remained unknown till now. In the light of above applications of thiourea derivatives, we have attempted the synthesis of novel silyl-thiourea derivatives by reacting diphenyldiisothiocyanatosilane with primary amines. Our results show that by executing this addition reaction of amine and isothiocyanate, silicon atom adopts a hyper coordinate environment in the final silyl-thiourea products. The synthesized silyl-thiourea compounds were tested for anticancer properties.

MATERIALS AND METHODS

All syntheses were carried out under dry nitrogen atmosphere using vacuum glassline. Solvents were dried and purified according to standard procedures prior to use. Diphenyldichlorosilane (Aldrich), 3-methylpyridin-2-amine (Himedia), 2-aminopyridin-2-ol (Himedia), furan-2-ylmethanamine (SDFCL), bis(2-aminoethyl)amine (Himedia), bis(3-aminopropyl)amine (Aldrich) were used as supplied. Potassium isothiocyanate (Qualigens) was vacuum dried before use. Diphenyldiisothiocyanatosilane was prepared by slight modification of a reported literature method [14]. Elemental analyses were performed using a Flash Organic Elemental (Model 2000) CHNS-O Analyzer. The % mass composition of isothiocyanate group and elemental silicon was determined by standard gravimetric methods [15]. FT-IR spectra were recorded in the range 4000-400 cm^{-1} on a Thermo Scientific Nicolet iS50 FT-IR Spectrophotometer. ^{1}H (300 MHz) and ^{13}C (75.5 MHz) spectra were obtained in DMSO-d_6/$CDCl_3$ or $CDCl_3$/CCl_4 on a Jeol AL 300 Spectrophotometer. Chemical shifts were reported as positive downfield shifts in ppm, as relative to tetramethylsilane.

Synthesis of Diphenyldiisothiocyanatosilane (1): To a benzene solution of diphenyldichlorosilane (5.00 mL, 24 mmol), potassium isothiocyanate (6.11 g, 63 mmol) was added in 30% excess. The reaction contents were stirred for 48 h at room temperature. After that the suspended potassium salts were filtered and washed with benzene. Removal of solvent from the filtrate by distillation gave the colorless title silane **1**. Yield: 6.20 g (85.6%); m.p 46°C, b.p 172-174°C (20 mm Hg). Anal. Calcd. (%) for $(C_6H_5)_2Si(NCS)_2$ (298): NCS, 38.93; Si, 9.40. Found (%): NCS, 37.80; Si, 9.00. FT-IR (cm^{-1}): 2066, 2017 (doublet, ν_{as} NCS), 1429 (ν_s C=C ar). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.00-7.61 (m, 5H, ar-C_6H_5). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 144.14 (N*C*S), 128.37, 128.56, 131.70, 134.18 (ar-C_6H_5).

General Procedure for Synthesis of Silyl-thiourea derivatives (2-6): A solution of diphenyldiisothiocyanatosilane (**1)** (1.00 mL, 4 mmol) in anhydrous CH_3CN (30 ml) was treated under vigorous stirring each time with a solution of 3-methylpyridin-2-amine (**7**) (0.80 mL, 8 mmol), 2-aminopyridin-3-ol (**8**) (0.88 g, 8 mmol), furan-2-ylmethanamine (**9**) (0.77 mL, 8 mmol), bis(2-aminoethyl)amine (**10**) (0.42 mL, 4 mmol) and bis(3-aminopropyl)amine (**11**) (0.56 mL, 4 mmol) in the same solvent. The mixtures were stirred for 24 h in case of reaction with **7**, **9**, **10** and **11**; however in case of reaction with **8**, the mixture was subjected to reflux at 80°C for 3 h followed by only stirring for another 21 h. Removal of solvent *in vacuo* gave the solid silyl-thiourea derivatives **2-6** respectively for reaction of silane **1** with amino ligands **7**-**11**. The product residues were washed with anhydrous *n*-hexane (2 mL) and vaccum dried.

Selected Physical and Spectral Data for 2-6

Bis(3-methylpyridyl)diphenylsilylthiourea (2): Yield: 1.3 g (63%); m.p 134-136°C. Anal. Calcd. (%) for $C_{26}H_{26}N_6S_2Si$ (514): C, 60.70; H, 5.06; N, 16.34; S, 12.45; Si, 5.45. Found (%): C, 60.68; H, 5.00; N, 16.24; S, 12.20; Si, 5.04. FT-IR (cm^{-1}): 595 (ν_{as} N→Si), 697 (ν_{as} Si-C_{ph}), 779 (ν_{as} Si-NH), 1466, 1567 (ν_s C=C ar), 1614 (ν_{as} C=N ar), 1651 (ν_{as} C=S), 3130 (ν_{as} C-H ar), 3334, 3468 (ν_{as} N-H). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.29 (s, 2 x 3H, C*H*$_3$), 6.61-7.59 (m, 2 x 8H, pyridyl-*H* + phenyl-*H*), 14.69 (bs, 4 x 1H, N*H*). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 16.49 (*C*H$_3$), 111.82-153.68 (pyridyl-*C* + phenyl-*C*), 161.07 (-N(H)*C*=S). UV (CH_3CN): λ_{max} (A) 302 nm (3.626).

Bis(3-hydroxypyridyl)diphenylsilylthiourea (3): Yield: 1.4 g (68%); m.p 188-190°C (decomp). Anal. Calcd. (%) for $C_{24}H_{22}N_6S_2O_2Si$ (518): C, 55.60; H, 4.25; N, 16.22; S, 12.35; Si, 5.40. Found (%): C, 55.48; H, 4.20; N, 16.00; S, 12.05; Si, 5.32. FT-IR (cm^{-1}): 696 (ν_{as} N→Si), 741 (ν_{as} Si-C_{ph}), 894 (ν_{as} Si-NH), 1463, 1569 (ν_s C=C ar), 1626 (ν_{as} C=N ar), 1655 (ν_{as} C=S), 3137 (ν_{as} C-H ar), 3248, 3297 (ν_{as} N-H, O-H). ^{1}H NMR (300 MHz, DMSO-d_6/$CDCl_3$): δ 3.00 (bs, 4 x 1H, N*H*), 6.53-7.52 (m, 2 x 8H, pyridyl-*H* + phenyl-*H*). ^{13}C NMR (75.5 MHz, DMSO-d_6/$CDCl_3$): δ 111.21-152.76 (pyridyl-*C* + phenyl-*C*), 164.79 (-N(H)*C*=S). UV (CH_3CN): λ_{max} (A) 307 nm (2.297).

Bis(2-furylmethyl)diphenylsilylthiourea (4): Yield: 1.2 g (61%); m.p 169-170°C (decomp). Anal. Calcd. (%) for $C_{24}H_{24}N_4S_2O_2Si$ (492): C, 58.54; H, 4.88; N, 11.38; S, 13.01; Si, 5.69. Found (%): C, 58.38; H, 4.86; N, 11.02; S, 12.96; Si, 5.40. FT-IR (cm^{-1}): 593 (ν_{as} O→Si), 754 (ν_{as} Si-C_{ph}), 820 (ν_{as} Si-NH), 1043 (ν_{as} C-O), 1566 (ν_s C=C ar), 1647 (ν_{as} C=S), 3096 (ν_{as} C-H ar), 3252 (ν_{as} N-H). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.05 (s, 2 x 2H, C*H*$_2$), 4.62 (bs, 4 x 1H, N*H*), 7.30 (d, 2 x 1H, furyl-*H*), 6.51 (dd, 2 x 1H, furyl-*H*), 6.31 (d, 2 x 1H, furyl-*H*), 7.19-7.51 (m, 2 x 5H, phenyl-*H*). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 41.16 (*C*H_2), 112.06-151.71 (furyl-*C* + phenyl-*C*), 160.72 (-N(H)*C*=S). UV (CH_3CN): λ_{max} (A) 302 nm (2.953).

1,1-diphenylsila-2,4,7,10,12-pentaza-3,11-dithione[5.5.0]bicyclododecane (5): Yield: 1.1 g (70%); m.p 120-122°C. Anal. Calcd. (%) for $C_{18}H_{23}N_5S_2Si$ (401): C, 53.86; H, 5.74; N, 17.45; S, 15.96; Si, 6.98. Found (%): C, 53.04; H, 5.62; N, 17.40; S, 15.20; Si, 6.44. FT-IR (cm^{-1}): 595 (ν_{as} N→Si), 696 (ν_{as} Si-C_{ph}), 780 (ν_{as} Si-NH), 1568 (ν_s C=C ar), 1651 (ν_{as} C=S), 3132 (ν_{as} C-H ar), 3403 (ν_{as} N-H). ^{1}H NMR (300 MHz, DMSO-d_6/$CDCl_3$): δ 2.51 (t, J = 4.8 Hz, 2 x 2H, HN-C*H*$_2$), 3.53 (t, J = 4.8 Hz, 2 x 2H, C*H*$_2$-NH), 7.05-7.57 (m, 2 x 5H, phenyl-*H*). ^{13}C NMR (75.5 MHz, DMSO-d_6/$CDCl_3$): δ 43.01 (HN-*C*H_2), 54.01 (*C*H_2-NH), 124.76-151.71 (phenyl-*C*), 160.26 (-N(H)*C*=S). UV (CH_3CN): λ_{max} (A) 307 nm (2.749).

1,1-diphenylsila-2,4,8,12,14-pentaza-3,13-dithione[6.6.0]bicyclotetradecane (6): Yield: 1.2 g (71%); m.p 200-202°C (decomp). Anal. Calcd. (%) for $C_{20}H_{27}N_5S_2Si$ (429): C, 55.94; H, 6.29; N, 16.32; S, 14.92; Si, 6.53. Found (%): C, 55.80; H, 6.12; N, 16.24; S, 14.86; Si, 6.40. FT-IR (cm^{-1}): 543 (ν_{as} N→Si), 733 (ν_{as} Si-C_{ph}), 755 (ν_{as} Si-NH), 1566 (ν_s C=C ar), 1648 (ν_{as} C=S), 3090 (ν_{as} C-H ar), 3256 (ν_{as} N-H). ^{1}H NMR (300 MHz, DMSO-d_6/$CDCl_3$): δ 3.55 (t, J = 6.9 Hz, 2 x 2H, HN-C*H*$_2$), 2.57 (m, J = 6.9 Hz, 2 x 2H, CH_2-C*H*$_2$-CH_2), 4.04 (t, J = 6.9 Hz, 2 x 2H, C*H*$_2$-NH), 7.66-7.82 (m, 2 x 5H, phenyl-*H*). ^{13}C NMR (75.5 MHz, DMSO-d_6/$CDCl_3$): δ 46.86 (HN-*C*H_2), 20.18 (CH_2-*C*H_2-CH_2), 55.67 (*C*H_2-NH), 126.16-150.98 (phenyl-*C*), 164.07 (-N(H)*C*=S). UV (CH_3CN): λ_{max} (A) 307 nm (1.953).

RESULTS AND DISCUSSION

Synthesis and Characterization of the Precursor Silane: Diphenyldiisothiocyanatosilane **1** was prepared from diphenyldichlorosilane and potassium isothiocyanate by following a modified literature method [14]. The synthesis of precursor Diphenyldiisothiocyanatosilane is outlined in the given equation.

$$Ph_2SiCl_2 + 2\ KNCS \xrightarrow[\text{stirr}\ 48\ h]{C_6H_6} \underset{\mathbf{1}}{Ph_2Si(NCS)_2} + 2\ KCl$$

Characterization of the diphenyldiisothiocyanatosilane **1** was performed by FT-IR, ^{1}H NMR and ^{13}C NMR spectroscopy. The neat FT-IR spectrum of neat colorless liquid silane **1** (Figure 1b) showed the appearance of a strong doublet at 2017 and 2066 cm^{-1} which was absent in the FT-IR spectrum of diphenyldichlorosilane (Figure 1a). Surely the peak corresponded to asymmetric stretching of two –N=C=S bonds covalently bonded to silicon atom in the isothiocyanate silane **1**. At the same time, FT-IR spectrum of neat solid KNCS (Figure 1c) revealed a broad band at 2038 cm^{-1} corresponding to symmetric stretching of N=C=S in the ionic salt.

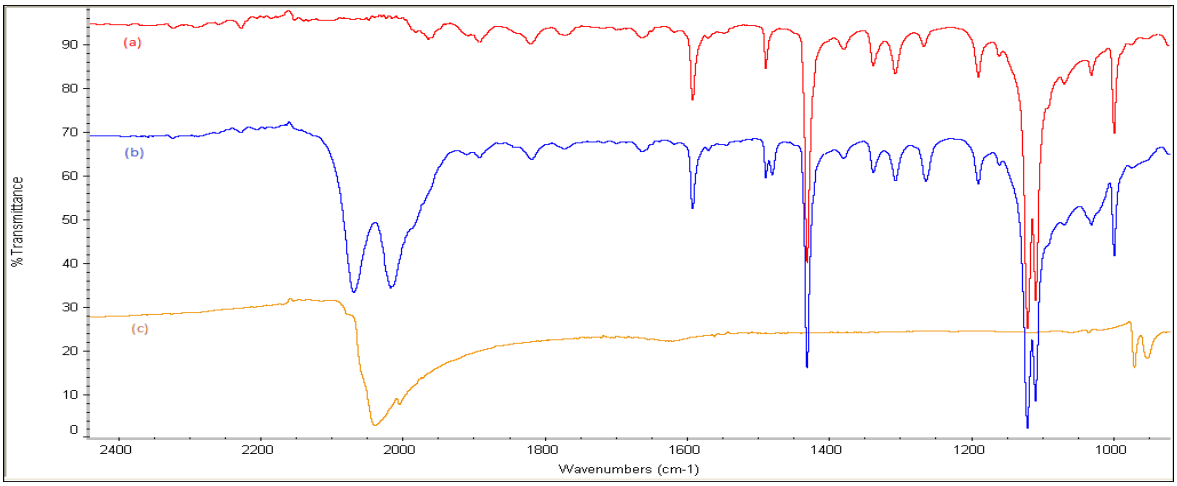

Figure 1. FT-IR Spectra of (a) Diphenyldichlorosilane, (b) Diphenyldiisothiocyanatosilane and (c) Potassium Isothiocyanate.

The ^{1}H NMR spectrum of silane **1** showed a multiplet in the region 7.00-7.61 ppm which was consistent with that of the phenyl protons. ^{13}C NMR spectrum of the silane in $CDCl_3$ showed a signal at 144.14 ppm due to NCS carbon and signals in the range 128.37-134.18 ppm due to phenyl ring carbon atoms.
The mass composition of elemental silicon and the isothiocyanate group were determined by gravimetric methods [15] and the results obtained were within the consistent range (Table 1).

Table 1. Analytical Data and Physical Properties of Compounds **1**-**6**.

Compound	m.p. (°C)	Analytical Data (%)					
		C Found (Calcd.)	H Found (Calcd.)	N Found (Calcd.)	S Found (Calcd.)	Si Found (Calcd.)	NCS Found (Calcd.)
1	46	-	-	-	-	9.00 (9.40)	37.80 (38.93)
2	134	60.68 (60.70)	5.00 (5.06)	16.24 (16.34)	12.20 (12.45)	5.04 (5.45)	-
3	188 (decomp.)	55.48 (55.60)	4.20 (4.25)	16.00 (16.22)	12.05 (12.35)	5.32 (5.40)	-
4	169 (decomp.)	58.38 (58.54)	4.86 (4.88)	11.02 (11.38)	12.96 (13.05)	5.40 (5.69)	-
5	120	53.04 (53.86)	5.62 (5.74)	17.40 (17.45)	15.20 (15.96)	6.44 (6.98)	-
6	200 (decomp.)	55.80 (55.94)	6.12 (6.29)	16.24 (16.32)	14.86 (14.92)	6.40 (6.53)	-

Synthesis and Characterization of Silyl-thiourea Compounds: Our objective was to prepare a small library of novel silyl-thiourea derivatives through a short and simple synthetic methodology. By choosing

the appropriate precursor diphenyldiisothiocyanatosilane **1** and corresponding amines **7**-**11**, silyl-thiourea products **2**-**6** were derived as outlined in figure 2.

It is noteworthy that as confirmed from FT-IR, multinuclei NMR, UV spectral data and elemental analysis, all the amine groups reacted with the isothiocyanate groups to yield the products with -N(H)-C(=S)-N(H)- (thiourea) linkage. The products obtained were white to pale yellow solids, soluble in acetonitrile, dimethyl sulphoxide and dimethyl formamide and were insoluble in *n*-hexane, benzene, carbon tetrachloride and water. The reaction took place at room temperature in acetonitrile, and was completed in 24 h in appreciable yields.

In the FT-IR spectra of all five thioureas **2**-**6**, the sharp band of –NCS group of silane **1** disappeared which clearly indicated the reaction of the silyl-NCS groups. Instead bands at around 1650 cm^{-1} and at around 3300 cm^{-1} arose which correspond to stretching frequencies of C=S and N-H of the -N(H)-C(=S)-N(H)- (thiourea) linkage. Bands at 800 cm^{-1} also appeared due to Si-NH linkage. Moreover, bands at 595, 696, 519 and 593 cm^{-1} appeared which could be assigned to N→Si and O→Si interactions due to presence of N/O heteroatoms in vicinity to silicon.

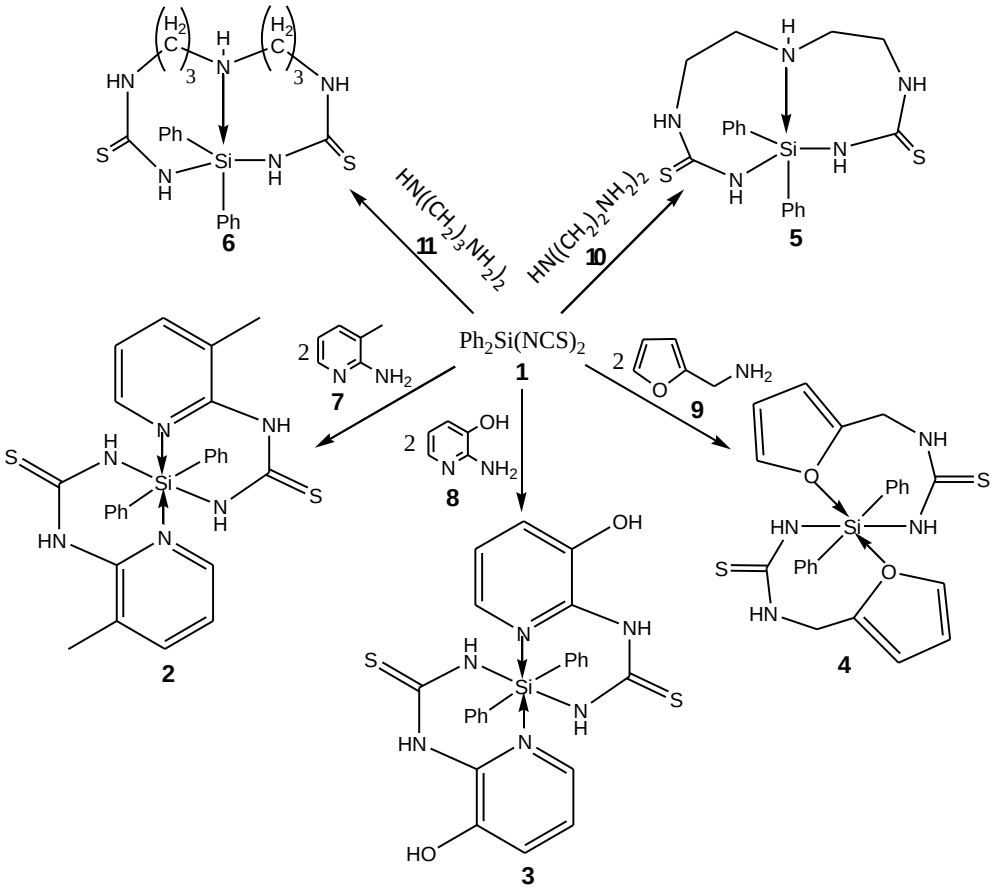

Figure 2. Synthesis of Silyl-thiourea derivatives.

The ^{1}H NMR spectra of the thiourea derivatives **2**-**6** were in agreement with the proposed structures of the synthesized compounds. The signals due to -CH_3 protons of **2** and -CH_2- protons of **4** appeared as singlets at 2.29 ppm and 4.04 ppm respectively whereas signals due to -CH_2- protons of **5** and **6** appeared as triplets and multiplet in the region 2.51-4.04 ppm. Signals due to pyridyl, furyl and phenyl protons for the thioureas were observed as multiplets in the region 6.30-7.82 ppm. A broad signal due to N-H of thiourea

linkage was observed at variable positions for all three compounds which is attributed to H-bonding effects with the NMR solvent DMSO-d_6 or due to intramolecular H-bonding when N-H and O-H both groups are present within the same compound i.e. for **3**.

The ^{13}C NMR spectra of **2-6** were also consistent with that of the proposed structures. It showed the signal for carbon of C=S bond in the region 160.26-164.07 ppm for all the thioureas. The appearance of the signal at about 160 ppm rather than at 180 ppm is attributed to the phenomenon of tautomerism of thiourea linkage which is responsible for interconversion of the N(H)C=S form to N=C-SH form in solutions, thereby giving the N=C carbon signal rather than the C=S carbon signal. The -CH_3 carbon of compound **2** appeared at 16.49 ppm and the aliphatic -CH_2- carbon atoms of compounds **4**, **5** and **6** appear at 41.16, 43.01, 54.01, 20.18, 46.86 and 55.67 ppm respectively. Signals due to carbon atoms of pyridyl, furyl and phenyl rings appeared in the region of 111.21-153.68 ppm.

The UV absorption spectra of the silyl-thiourea compounds were recorded as 2 x 10^{-4} M CH_3CN solutions between wavelength range of 200-400 nm. As shown in figure 3, the spectra of compounds showed a single absorption band at a λ_{max} of around 300 nm for all the compounds **2-6**. The data is ascribed to high energy ligand-centered n–π* electronic transition involving the thiourea group.

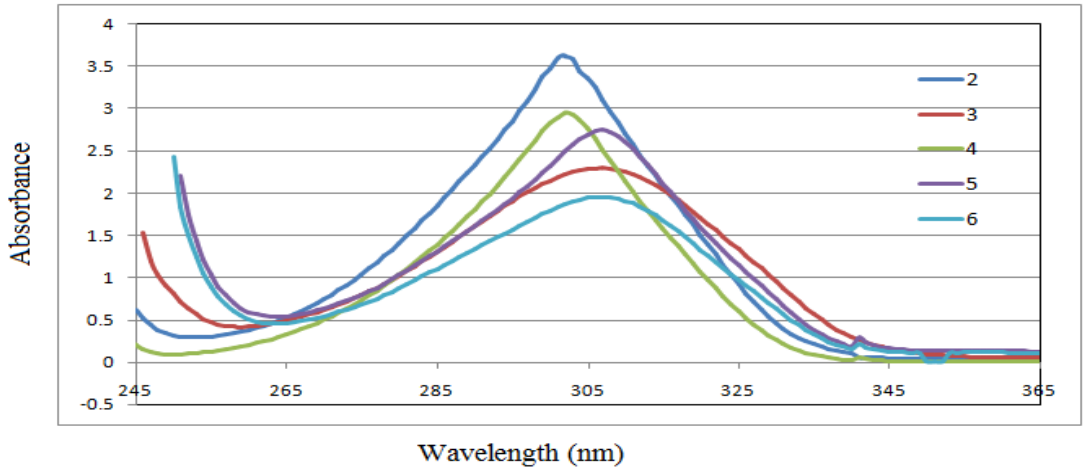

Figure 3. UV spectra of compounds **2-6** (2 x 10^{-4} M) in CH_3CN solution.

APPLICATIONS

Anticancer Assay: Cytotoxic activity of the five newly synthesized silyl-thiourea compounds **2-6** was screened at 50, 100 and 200 µM concentrations against HeLa cells using the MTT colorimetric assay. The MTT assay is based on the reduction of the yellow soluble 3-(4,5-methyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) into a blue-purple formazan product, mainly by mitochondrial succinic dehydrogenase enzyme activity inside living cells. The stock solutions of the synthesized compounds were prepared by dissolving in minimum volume of dimethyl sulfoxide (DMSO) and phosphate buffered saline (PBS) was then added to reach the appropriate volume. HeLa cells were cultured in RPMI 1640 medium that was supplemented with 50 mL heat-inactivated fetal calf serum (FCS) and sterilized by filtering through 0.22 µm filters. The HeLa cells were maintained in a humidified atmosphere of 5% CO_2, 95% air at 37°C. 180 µL of the cells (5×10^4 cells mL^{-1} of media) were plated in 96-multiwell plates and incubated for 24 h. 20 µL of different concentrations of the compounds (50, 100, 150, 200 µM) were added to each three wells (triplicate) to get final concentration of 50, 100, and 150 µM. Doxorubicin was used as positive control and the wells containing DMSO (1%) and cell suspension was regarded as the negative control.

The blank wells consisted of 200 µL of the RPMI medium. The microplates were further incubated for 48 h. To evaluate cell survival, each well was then incubated with 20 µL of MTT solution (5 mg mL^{-1} in PBS) and incubated for 4 h at 37°C. The media in each well was replaced with 200 µL DMSO and pipette up and down to dissolve the formazan crystals which were formed by the cellular reduction of MTT. The absorbance of each well was measured at 540 nm using an ELISA reader. Each experiment was repeated three times. The percentage of cell viability was calculated using the following formula:

$$\% \, Cell \, Survival = \frac{Mean \, absorbance \, in \, drug \, treated \, wells - Mean \, absorbance \, in \, blank}{Mean \, absorbance \, in \, control \, wells - Mean \, absorbance \, in \, blank} \times 100$$

The results were expressed as IC_{50}, which implied the induction of 50% inhibition of cell growth of treated cells when compared to the growth of control cells. The synthesized compounds showed mild cytotoxic activities, compound **3** reduced cell viability to about 50% at 90 µM concentration (Table 2). This may be attributed to the presence of electron withdrawing –OH group as the aromatic substituent at the pyridine nucleus along with the thiourea group which has already been reported to suppress various cancer cell lines [16].

Table 2. Assessment of the compounds for cytotoxicity in HeLa (cervical carcinoma) cell line after a 72 h exposure[a]

Cmpd	Mol. Wt.	IC_{50} (µM)
2	514	142±7.4
3	518	90±4.6
4	492	152±5.6
5	401	165±4.7
6	429	170+10.5

[a] 72 h IC_{50} values (in µM) as determined by MTT. Error is standard deviation of the mean; Cmpd = compound; IC_{50} = half maximal inhibitory concentration; MTT = 3-(4,5-methyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium bromide

From the anticancer assay, it is expected that the synthesized silyl-thiourea derivatives may emerge as chemotherapeutic agents in the field of medicinal chemistry.

CONCLUSIONS

We have designed a small library of novel silyl-thiourea derivatives through a simple pathway thus demonstrating the reactive potential of silyl-NCS functionality that opens up the scope for synthesis of useful hypervalent organosilicon derivatives which could find applications in material, agricultural and pharmaceutical sciences. In our present attempt, we have evaluated their inhibitory activity on HeLa cells using MTT colorimetric assay and found the silyl-thiourea derivatives as cytotoxic.

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