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# Design, Synthesis, Cytotoxicity, Physicochemical and *In Vivo* Studies of New Thalidomide Dithiocarbamate Analogs as Anticancer

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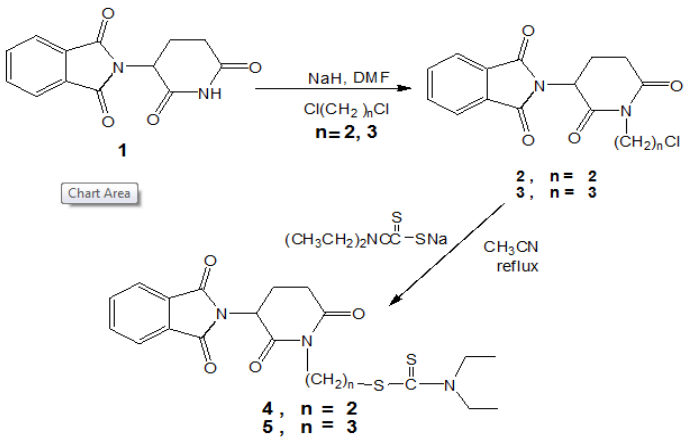
**ABSTRACT**

*Novel thalidomide dithiocarbamate analogs were synthesized in good yield. A two-step synthesis was utilized to obtain the new thalidomide dithiocarbamate analogs by reaction of thalidomide with 1,2 dichloroethane or 1,3 dichloropropane producing chloroethyl thalidomide 2 or chloropropyl thalidomide 3 compounds respectively, which reacts with Sodium diethyl dithiocarbamate to afford thalidomide dithiocarbamate 4 or 5.*

*The chemical structures of all synthesized compounds were elucidated on the basis of their spectral IR, 1H NMR, 13C NMR, Mass spectroscopy and elemental analysis. The anticancer nature of thalidomide and thalidomide analogs 2-5 was evaluated by screening the in vitro activity on three human cancer cell lines; human lung cancer cells (A-549), human liver cancer cells (HEGP-2) and human breast cancer cells (MCF-7). Also the in vivo activity of analogs towards lung cancer was evaluated. Moreover, the physicochemical properties of Thalidomide and their dithiocarbamate analogs were also determined using Mastersizer X.*

*Therefore, thalidomide dithiocarbamate analogs 4 and 5 possess a potential anticancer activity to be formulated as inhaler for lung cancer treatment.*




*Synthesis of new thalidomide dithiocarbamate analogs with anticancer activity and improved physicochemical properties. Thalidomide and thalidomide analogs 2-5 were evaluated for anticancer potency against A-549, MCF-7, HEGP-2 and were also evaluated in vivo towards lung*

*cancer. Moreover, their physicochemical properties were presented as their particle size. These new thalidomide dithiocarbamate analogs 4 and 5 have cytotoxicity against lung cancer cells with IC50 10.4 ± 0.2 µg/ml for compound 4 and IC50 12.4 ± 0.2 µg/ml for compound 5. Also they have small particle size, their improved physicochemical properties together with their anticancer activity, enhance their potential to be formulated as inhaler for lung cancer treatment.*

**Keywords:** Thalidomide, Dithiocarbamate, Cytotoxicity, Inhaler, Anticancer activity.

## INTRODUCTION

Thalidomide was originally marketed as a hypnotic/sedative agent in the late of 1950s and the early 1960s; Thalidomide had caused severe congenital malformations in children whose mothers took this medicinal product during pregnancy. As a result, it was withdrawn from the market due to its teratogenic effect [1-3]. Subsequently, Thalidomide was discovered to have various biological effects against some diseases including Acquired Immunodeficiency Syndrome (AIDS) [4], Graft versus Host Disease (GvHD) [5], leprosy [6] and other related diseases [7]. The Effectiveness of thalidomide in these diseases has been attributed to its regulatory activity on Tumor Necrosis Factor-alpha (TNF-α) production [8] and has been identified as an effective agent for the treatment of Multiple Myloma (MM) [9,10] and cancer related pathologic angiogenesis [11]. Thalidomide teratogenicity was partially explained by its anti-angiogenic activity [12]. In addition, thalidomide may have suppression effects on the human lung fibroblasts [13]. On the other hand, thalidomide analogs have found recent application in the treatment of cancer [14-17]. Thalidomide is currently used in therapy as a racemate. It is expected to play an important and effective role in medicine so we should develop its physicochemical properties to enhance its bioavailability via using it in different dosage forms. In the current study, using a two-step synthesis, new thalidomide dithiocarbamate compounds were synthesized and tested for their cytotoxic activity against human cell line. These new compounds may be formulated as inhaler due to their better physicochemical properties (particle size).

## MATERIALS AND METHODS

1,2 dichloroethane and Sodium hydride (Merck-Schuchardt), 1,3 dichloropropane (ACROS organics), silica gel GF254 (type 60) for thin layer chromatography (Merck), dimethyl formamide, Chloroform and Methylene Chloride (Fischer Scientific UK Limited). The reagents RPMI-1640 medium, SRB (SulphoRhodamine-B), Sodium diethyl dithiocarbamate and DMSO (Dimethyl sulfoxide) were purchased from (Sigma-Aldrich). 1HNMR and 13C NMR spectra were recorded on a Varian Gemini 300 MHZ spectrometer, Cairo University. Elemental analyses were determined on a Yanaca CHN Corder MT-3 elemental analyzer in microanalysis laboratory at Cairo University. IR spectra were recorded (KBr) on a Perkin-Elmer FT-IR Spectrum One spectrophotometer, Arab Drug Company. MS spectra were run on GC MS-QP 1000 EX (SHIMADZU) Mass Spectrometer, Micro analytical Laboratory, Faculty of Science, Cairo University.

### Melting Point Determination

The melting point was determined by using optimelt Automated Melting Point System SRS (Stanford Research Systems) model MPA100, at Arab Drug Company.

### Geometric Particle Size Determination

Geometric particle size was determined for powder and Spray by Mastersizer X using lens 100 mm and beam length 14.3 or 2.4. Sample unit is MSX64 dry powder feeder in case of dry powder and is MS5 inhalers mounting unit in case of spray.
**Apparatus**: Mastersizer x ver.2.15 serial no.33337-22, Malvern Instruments Ltd., Malvern, UK, at Arab Drug Company

### General Synthesis Method for Chloroethyl Thalidomide and Chloropropyl Thalidomide

A solution of (4 mmol) sodium hydride (60 %) in 15 ml of absolute dimethyl formamide was reacted with (4 mmol) thalidomide while cooling, after the gas formation has ceased; (4 mmol) dichloro compounds (1, 2 dichloroethane or 1,3 dichloropropane) were added slowly and stirred for further 8 h, Insoluble materials were filtered off and the filtrate was evaporated under reduced pressure. The residue was purified by preparative TLC using methylene chloride and the yield is 52 % and 54 % for compounds 2 and 3 respectively.

### General Synthesis Method for Compounds 4 and 5

Two mmol of compound 2 or 3 with a stoichiometric amount of sodium diethyl dithiocarbamate in 20 ml acetonitrile was heated under reflux with stirring at 120-130°C for 4 h, the solvent was evaporated under reduced pressure. The residue was purified by preparative TLC with chloroform and the yield is 79 % and 83 % for compounds 4 and 5 respectively.

**2-(1-(2-Chloroethyl)-2,6-dioxo-piperidine-3-yl)-1,3-dihydro-2H-isoindole-1,3-dione (2):** Yield (52 %), m.p. 148°C, white powder, IR (KBr) 2919, 1790, 1775, 1717, 1677, 1467, 1392, 1158, 719 $cm^{-1}$; 1H NMR (DMSO-d6) δ: 2.09-2.13 (m, 1H, H-4´), 2.51-2.63 (m, 1H, H-5´), 2.85-2.88 (m, 1H, H-4´), 3.00-3.08 (m, 1H, H-5´ CO), 3.88-3.91 (t, 2H, N-CH2CH2), 4.21-4.25 (t, 2H, N-CH2), 5.19-5.25 (m, 1H, H-3´), 7.8-7.84 (m, 4H, H aryl.); 13C NMR (DMSO-d6) δ: 21.97 (C-4´). 30.91 (C-5´), 40.68 (CH2CH2CL), 46.52, (N-CH2), 48.98 (C-3'), 123.37, 123.43 (C-4, C-7), 131.19 (C-3a, C-7a), 134.83, 134.88 (C-5, C-6), 167.04, 167.12 (C-1, C-3) 169.79 (C-2´) 172.71 (C-6´). EIMS m/z=322 [M+] Anal. Calc. for C15H13N2O4Cl: C, 56.17; H, 4.08; N, 8.73; Found: C, 55.95; H, 4.02; N, 8.65.

**2-(1-(3-Chloropropyl)-2,6-dioxo-piperidine-3-yl)-1,3-dihydro-2H-isoindole-1, 3-dione (3):** Yield (54 %), m.p. 133°C, off white powder, IR (KBr) 3098, 2912, 1785, 1772, 1711, 1692, 1610, 1386, 1341, 1113, 728 $cm^{-1}$; 1H NMR (DMSO-d6) δ: 1.88-1.93 (m, N-CH2CH2), 2.07-2.10 (m, 1H, H-4´), 2.50-2.63 (m, 1H, H-5´), 2.84-2.86 (m, 1H, H-4´), 2.88-2.96 (m, 1H, H-5´ CO), 3.75-3.77 (m, 2H, N-CH2CH2CH2), 3.95-4.03 (m, 2H, N-CH2), 5.23-5.29 (m, 1H, H-3´), 7.88-7.97 (m, 4H, H aryl.); 13C NMR (DMSO-d6): 21.81 (C-4´). 29.92 (C-5´), 31.78 (N-CH2CH2), 40.81 (CH2 CH2CH2Cl), 43.57 (N-CH2), 48.95 (C-3'), 123.31, 123.42 (C-4, C-7), 131.09 (C-3a, C-7a), 134.73, 134.77 (C-5, C-6), 167.1,167.19 (C-1, C-3),169.42 (C-2´), 172.81 (C-6´). EIMS m/z=335 [M+]. Anal. Calc. for C16H15N2O4Cl: C, 57.40; H, 4.51; N, 8.36; Found: C, 57.23; H, 4.36; N, 8.32.

**[3-(1,3-Dioxo-1,3-dihydro-2H-isoindol-2-yl)-2,6-dioxopiperidin-1-yl] ethyl diethyldithiocarbamate (4):** Yield (79 %), m.p. 125°C,white powder; IR (KBr) 2974, 2930, 1789, 1775, 1717, 1677, 1497, 1418, 1392, 1195, 1092, 966, 912, 718 $cm^{-1}$; 1H NMR (DMSO-d6) δ: 1.23-1.28 (t, 3H, CH3), 2.11 (m, 1H, H-4´), 2.55-2.57 (m, 1H, H-5´), 2.79-2.91 (m, 1H, H-4´), 2.93-3.02 (m, 1H, H-5´ CO), 3.41-3.47 (q, 2H, CH2), 3.59-3.63 (t, 2H, N-CH2CH2), 3.77-3.82 (t, 2H, N-CH2), 5.22-5.28 (m, 1H, H3´), 7.91-7.93 (m, 4H, H aryl.); 13C NMR (DMSO-d6) δ 13.65 (CH3), 21.92 (C4´), 30.72 (C5´), 36.08 (NCH2), 39.58 (NCH2 CH2S), 44.07 (CH2), 48.92 (C3´), 123.45, 123.52 (C4, C7), 131.22 (C3a, C7a), 134.97, 135.03 (C5, C6), 167.16,167.25 (C1, C3), 169.67 ( C2´), 172.89 ( C6´), 195.87 (C=S). EIMS m/z=433 [M+]. Anal. Calc. for C20H23N3O4S2: C, 55.41; H, 5.34; N, 9.69; S, 14.76. Found: C, 55.28; H, 5.29; N, 9.53; S, 14.71.

**[3-(1,3-Dioxo-1,3-dihydro-2H-isoindol-2-yl)-2,6-dioxopiperidin-1-yl] propyl diethyldithiocarbamate (5):** Yield (83 %), m.p. 117°C, off white powder; IR (KBr) 3098, 2986, 2917, 1787, 1773, 1716, 1682, 1391, 1198, 1158, 1113, 1090, 727 $cm^{-1}$; 1H NMR (DMSO-d6) δ: 1.24-1.28 (t, 3H, CH3), 1.91 (m, 2H, N-CH2CH2 ), 2.09-2.13 (m, 1H, H-4´), 2.55-2.64 (m, 1H, H-5´), 2.78-2.83 (m, 1H, H-4´), 2.95-3.00 (m, 1H, H-5´ CO), 3.37-3.44 (m, 2H, N-CH2CH2CH2), 3.63-3.65 (q, 2H, CH2), 3.97-4.05 (m, 2H, N-CH2), 5.23-5.28 (m, 1H, H3´), 7.88-7.93 (m, 4H, H aryl.);13C NMR (DMSO-d6) δ 13.70 (CH3), 21.95 (C4´), 27.85 (N-CH2CH2), 30.15 (C5´), 33.45 (N-CH2CH2CH2), 41.75 (N-CH2), 44.25 (CH2), 48.90 (C3´), 123.22, 123.31 (C4, C7), 131.28 (C3a, C7a), 134.80, 134.89 (C5, C6), 167.35, 167.46 (C1, C3), 169.85 ( C2´), 172.95 ( C6´), 195.95 (C=S). EIMS m/z=448 [M+]. Anal. Calc. for C21H25N3O4S2: C, 56.36; H, 5.63; N, 9.39; S, 14.33. Found: C, 56.19; H, 5.49; N, 9.22; S, 14.22.

**Anticancer Screening**

***In vitro* study:** Thalidomide and its new dithiocarbamate derivatives have been tested for their cytotoxic activity against human hepato carcinoma (HEPG-2), lung carcinoma (A-549), and breast adenocarcinoma (MCF-7) cell line in the National Cancer Institute, Cairo University. Potential cytotoxicity of compounds was tested using the described method [18-21].

The cytotoxic evaluation of all compounds (0, 5, 12.5, 25 and 50 µg/ml) against normal cells was carried out to explore the toxicity and selectivity of the tested compounds. Fetal bovine serum was obtained from (GIBCO, UK). The cells were cultured in RPMI-1640 medium with 10 % fetal bovine serum. Antibiotics (penicillin 100 units/ml and streptomycin 100 mg/ml) were added at 37 ºC in a 5 % CO2 incubator. The cells were seeded in a 96-well plate at a density of 1.0 x104 cells/well at 37°C For 48 hrs. under 5 % CO2. After incubation, the cells were treated with different concentration of compounds and incubated for 24 hrs. The medium was discarded. Fix with 10 % trichloroacetic acid (TCA) 150 mL/well for 1 h at 4°C. Wash by water 3 times (TCA reduce SRB protein binding). Wells were stained by SRB 70 ml/well for 10 min. at room temperature with 0.4 % 70 mL/well (keep in dark place). Then washed with acetic acid 1 % to remove unbound dye (end point: colorless drain age). The plates were subjected to air drying for 24 hrs. The dye was solubilized with 50 ml/well of 10 mM tris base (PH 7.4) for 5 min. on a shaker at 1600 rpm. The optical density (OD) of each well was measured at 570 nm with an ELISA microplate reader (EXL 800 USA). The relative cell viability in percentage was calculated as (A570 of treated samples/A570 of untreated sample) X 100 and The IC50 values were calculated using the Microsoft Excel. The data were recorded and analyzed to estimate the effects of the tested compounds on cell viability and growth; IC50 values for the tested compounds are reported in below table, three independent experiments for each concentration were performed.

***In vivo* study:** Lung cancer was processed in rats by using Diethylnitrosamine (rats injected intraperitoneal with Diethyl nitrosamine (DEN) (70 mg/2 ml/kg body weight/rat, once a week for eight weeks). Then rats were treated by compounds through intraperitoneal injection daily for 6 weeks then rats were scarified, and lung tissue was preserved in formalin and processed in an automated tissue processor. The processing consisted of an initial 2 step fixation and dehydration. Fixation comprising tissue immersion in 10 % buffered formalin for 48 hrs, followed by removal of fixative in distilled water for 30 minutes. Dehydration was then carried out by running the tissues through a graded series of alcohol (70 %, 90 %, and 100 %). The tissue was initially exposed to 70 % alcohol for 120 minutes followed by 90 % alcohol for 90 minutes and then two cycles of absolute alcohol, each for one hour. Dehydration was then followed by clearing the samples in several changes of xylene. It consisted of tissue immersion for an hour in a mixture comprising 50 % alcohol and 50 % xylene, followed by pure xylene for one and a half hour. Samples were then impregnated with molten paraffin wax, then embedded and blocked out. Paraffin sections (4–5 um) were stained with hematoxylin and eosin. Stained sections were examined for pathological lesions in the lungs of the examined rats.

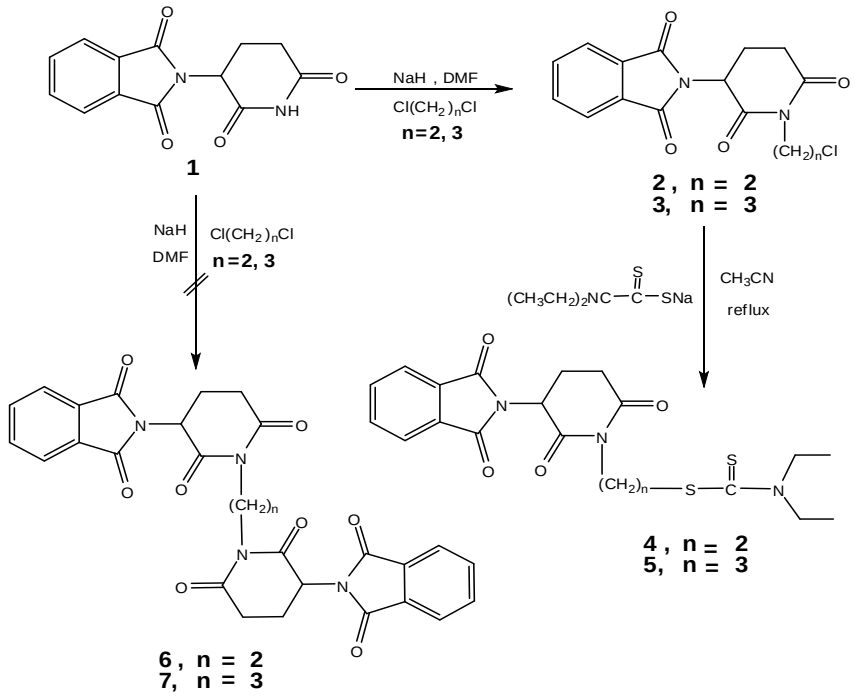
## RESULTS AND DISCUSSION

**Chemistry**

The synthesis of target compounds is summarized in the scheme 1. Thalidomide was reacted with sodium hydride and 1, 2 dichloroethane or 1, 3 dichloropropane in dimethyl formamide to give chloroethyl thalidomide 2 or chloropropyl thalidomide 3 in a reasonable yield (52 % or 54 %). Normally the reaction of 1, 2 dichloroethane or 1, 3 dichloropropane reacted to yield the bis-derivatives. The bis-analogs 6,7 were synthesized under severe conditions rather than the condition applied to synthesize analogs 2,3. The bis-analogs 6,7 right now are under biological investigation and will be published later.

On the other, hand thalidomide dithiocarbamate analogs 4 or 5 were synthesized in good yield (79 % or 83 %) by reaction of chloroethyl thalidomide 2 or chloropropyl thalidomide 3 with sodium diethyl dithiocarbamate in acetone.

The chemical structure of all synthesized compounds was elucidated on the basis of their spectral data IR, 1H NMR, 13C NMR, MS and Elemental Analysis (Scheme 1).




**Scheme 1 : Synthesis of thalidomide analogs 2-5**

The IR spectra of compounds (2-5) show absorption bands in the region (1610-1790 $cm^{-1}$) due to presence of C=O function and that for compounds 4, 5 shows absorption bands in the region (1090-1198 $cm^{-1}$) due to presence of C=S function.

The 1H NMR spectrum of Thalidomide analog 2, [2-(1-(2-Chloroethyl)-2,6-dioxo-piperidine-3-yl)-1,3-dihydro-2H-isoindole-1,3-dione] shows a triplet of each of δ 3.9 and 4.21 due to the methylene protons of the ethylene moiety.

Thalidomide analog 4, [3-(1,3-Dioxo-1,3-dihydro-2H-isoindol-2-yl)-2,6-dioxopiperidin-1-yl] ethyl diethyldithiocarbamate] shows in addition to the signal of compound 2 nucleus a quartet at δ 3.5 due to the methylene protons and a triplet at δ 1.23 due to the methyl group of the ethyl moiety

.

The 1H NMR spectrum of Thalidomide analog 3, [2-(1-(3-Chloropropyl)-2,6-dioxo-piperidine-3-yl)-1,3-dihydro-2H-isoindole-1,3-dione] shows a multiplet of each of δ 3.95, 1.88 and 3.78 due to the methylene protons of the propylene moiety.

Thalidomide analog 5, [3-(1,3-Dioxo-1,3-dihydro-2H-isoindol-2-yl)-2,6-dioxopiperidin-1-yl] propyl diethyldithiocarbamate] shows in addition to the signal of compound 3 nucleus a quartet at δ 3.65 due to the methylene protons and triplet at δ 1.24 due to the methyl group of the ethyl moiety.

The physicochemical properties have been studied for Thalidomide dithiocarbamate analogs (4, 5); the particle size was represented as 10 %, 50 % and 90 % of the sample in micron (µm), using Mastersizer X ver.2.15, Malvern Instruments Ltd., Malvern.

**Table 1**: Summarizes the physicochemical properties of thalidomide and its analogs (4, 5)

| Compound 5 | Compound 4 | Thalidomide | Physical parameter |
|---|---|---|---|
| 0.55 ± 0.05 | 1.39 ± 0.22 | 4.55 ± 0.25 | Particle size of 10 % (µm) |
| 1.27 ± 0.12 | 2.55 ± 0.20 | 17.49 ± 0.30 | Particle size of 50 % (µm) |
| 3.57 ± 0.21 | 4.83 ± 0.37 | 45.66 ± 0.55 | Particle size of 90 % (µm) |
| 117 ± 0.40 | 125 ± 0.25 | 270 ± 0.35 | Melting temperature |
| | | | m.p.(°C ) ± SD |

Table 1 shows that compound 4 has small particle size 10 %=1.39 ± 0.22 µm, 50 %=2.55 ± 0.20 µm and 90 %=4.83 ± 0.37 µm. Also compound 5 has small particle size 10 %=0.55 ± 0.05 µm, 50 %=1.27 ± 0.12 µm and 90 %=3.57 ± 0.21 µm. So these analogs (4, 5) possess better physicochemical properties compared to thalidomide itself which has larger particle size 10 %=4.55 ± 0.25 µm, 50 %=17.49 ± 0.30 µm and 90%=45.66 ± 0.55 µm.

Therefore, these new compounds (4, 5) can be formulated as inhalers (pressurized metered dose inhaler and dry powder inhaler), due to the fact that optimum aerodynamic particle size distribution for most inhalation aerosols has generally been recognized as being in the range of 1-5 µm. [18-20].

**In vitro study**

Thalidomide dithiocarbamate analogs (4, 5) have been tested for their cytotoxic activity against human hepatocarcinoma (HEPG-2), lung carcinoma (A-549) and breast carcinoma (MCF-7). Table 2 summarizes the anticancer activity of thalidomide and its derivatives (2-5) against human lung cancer cells (A-549) (Figure 1), human breast cancer cells (MCF-7) and human liver cancer cells (HEGP-2).

From Tables 3 and 4 we can notice that there is significant difference in IC50 between thalidomide and its analogs against human lung cancer cells (A-549).

**Table 2:** Summarize anticancer activity against cell lines

| Compound | $IC_{50}$ (µg/ml) | | |
|---|---|---|---|
| Number | A-549 | HEPG-2 | MCF-7 |
| 1 | 36.8 ± 0.3 | 38.2 ± 0.5 | - |
| 2 | 23.4 ± 0.2 | 23.5 ± 0.3 | - |
| 3 | 23.9 ± 0.2 | 35.3 ± 0.2 | - |
| 4 | 10.4 ± 0.1 | 48.0 ± 0.4 | 41.4 ± 0.5 |
| 5 | 12.4 ± 0.2 | 27.9 ± 0.2 | 50.0 ± 0.4 |

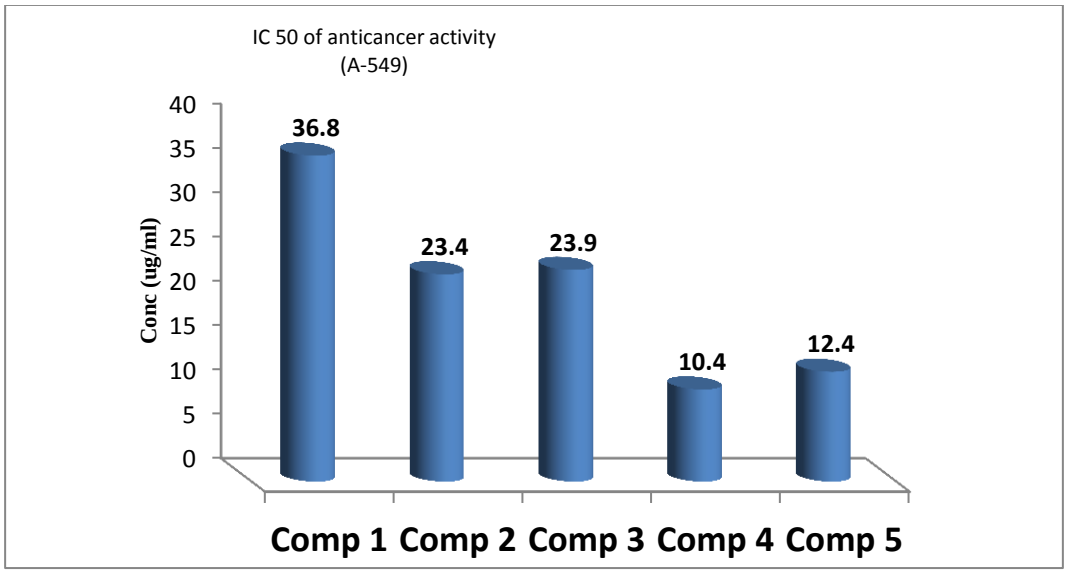
**Table 3:** ANOVA test of IC50 of thalidomide and thalidomide dithiocarbamate analogs (4,5) against lung cancer cells (A-549)

| *Groups* | *Count* | *Sum* | *Average* | *Variance* | | |
|---|---|---|---|---|---|---|
| Compound 1 | 6 | 221 | 36.83333 | 0.090667 | | |
| Compound 4 | 6 | 62.35 | 10.39167 | 0.010417 | | |
| Compound 5 | 6 | 74.7 | 12.45 | 0.043 | | |
| ***Source of Variation*** | ***SS*** | ***df*** | ***MS*** | ***F*** | ***P-value*** | ***F crit*** |
| Between Groups | 2595.891 | 2 | 1297.945 | 27024.89 | 2.11E-27 | 3.68232 |
| Within Groups | 0.720417 | 15 | 0.048028 | | | |
| Total | 2596.611 | 17 | | | | |

**Table 4**: Tuckey test of IC50 of thalidomide and and thalidomide dithiocarbamate analogs (4,5) against lung cancer cells (A-549)

| **Treatments** pair | **Tukey HSD** Q statistic | **Tukey HSD** p-value |
|---|---|---|
| Comp 1 vs. Comp 4 | 295.5413 | 0.0010053 |
| Comp 1 vs. Comp 5 | 272.5351 | 0.0010053 |
| Comp 4 vs. Comp 5 | 23.0062 | 0.0010053 |

**Figure1;** Histogram of IC50 of thalidomide and derivative against lung cancer cells.




**Histopathological Changes (*In Vivo* Study)**

A characteristic lymphomatous reaction was an outstanding feature in most of the examined cases. Lymphoid proliferation was wide spread in the pulmonary tissue; representing the positive control characteristic peribronchial nodular lymphoid hyperplasia and chronic inflammatory

reaction with focal thickening of the interalveolar septa. But Photomicrograph of rat's lung after being treated with compound 5 shows bronchial epithelial hyperplasia, lymphoid proliferation around the bronchi, Focal bronchial wall destruction and inflammatory cells (Figures 2-4) while Photomicrograph of rat's lung after being treated with compound 4 shows dilated blood vessels, bronchial and bronchiolar hyperplasia (Figure 5). The Photomicrograph of rat's lung after being treated with compound 1 shows a thickened interalveolar septa by proliferated or infiltrated lymphoblasts and or lymphocytes beside compensatory over inflation of air sacs (compensatory alveolar emphysema) (Figure 6). The Photomicrograph of rat's lung after being treated with compound 2 shows moderately to severely dilated, partially or completely blood engorged arteries and veins. Some of the arteries show diverticulosis, thick wall with hyaline degeneration and narrow lumen (Figure 7). The Photomicrograph of rat's lung after being treated with compound 3 shows perivascular edema, severe vacuolation and unclear bronchial mucosa (Figure 8).

**Figure 2:** Photomicrograph of the control negative normal rat's pulmonary tissue with preserved bronchial, bronchiolar and alveolar tissues.

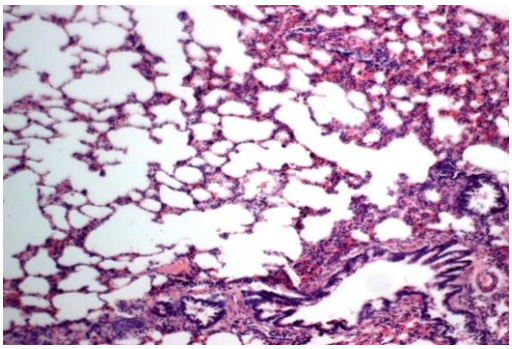


**Figure 3:** Photomicrograph of the control positive one with characteristic peribronchial nodular lymphoid hyperplasia and chronic inflammatory reaction with focal thickening of the interalveolar septa.

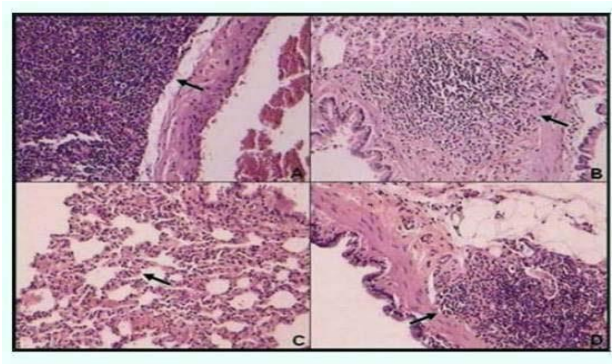



**Figure 4:** Photomicrograph of rat's lung after being treated with compound 5 showing bronchial epithelial hyperplasia, lymphoid proliferation around the bronchi, Focal bronchial wall destruction and inflammatory cells. H&E X100.

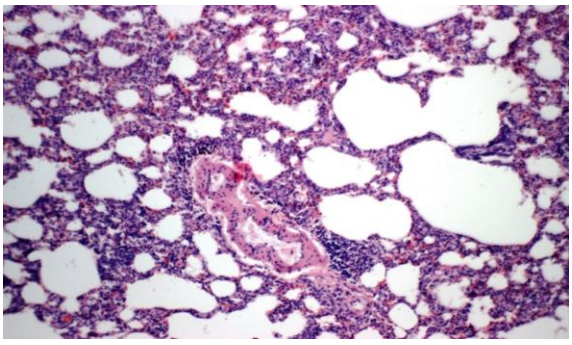


**Figure 5:** Photomicrograph of rat's lung after being treated with compound 4 showing dilated blood vessels, bronchial and bronchiolar hyperplasia. H&E X400.

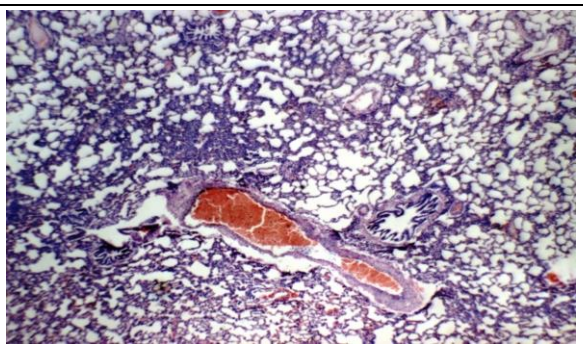


**Figure 6:** Photomicrograph of rat's lung after being treated with compound 1 showing thickened interalveolar septa by proliferated or infiltrated lymphoblasts and or lymphocytes beside compensatory over inflation of air sacs (compensatory alveolar emphysema). H&E X400.

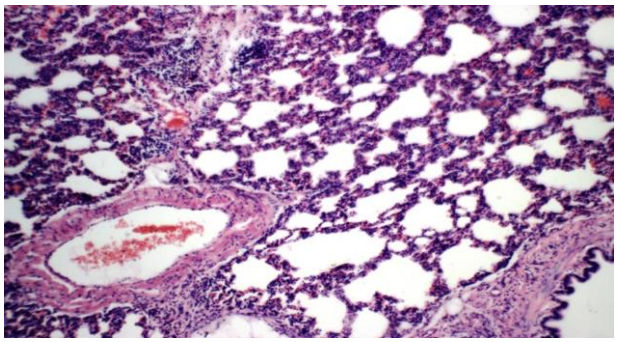


**Figure 7:** Photomicrograph of rat's lung after being treated with compound 2 showing moderately to severely dilated, partially or completely blood engorged arteries, veins. Some of the arteries showing diverticulosis, thick wall with hyaline degeneration and narrow lumen. H&E X100.

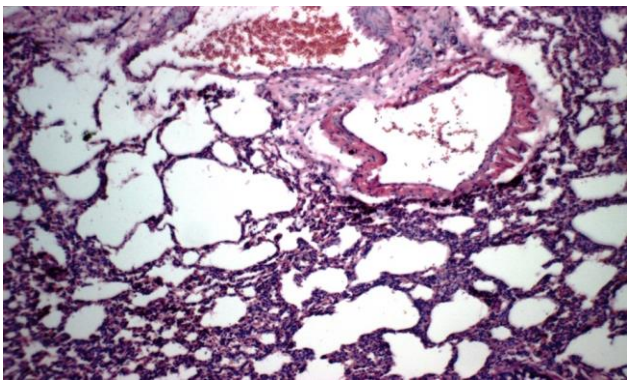
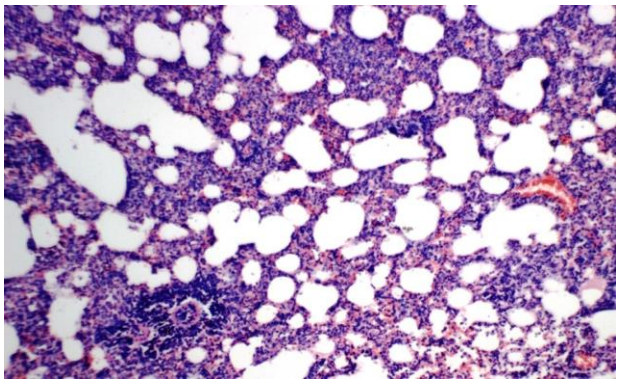


**Figure 8:** Photomicrograph of rat's lung after being treated with compound 3 showing perivascular edema and sever vacuolation and unclear bronchial mucosa. H&E X400.



**CONCLUSIONS**

A two-step synthesis of novel thalidomide dithiocarbamate analogs (4, 5) was evaluated. These new analogs were found to possess anticancer activity against human lung cancer with significant difference. Moreover, these analogs possess improved physicochemical properties, therefore; they may be formulated as inhalers for lung cancer treatment.

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