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Graphical Abstract

Synthesis, characterization and *in vitro* anticancer evaluation of novel 1,2,4-triazolin-3-one derivatives

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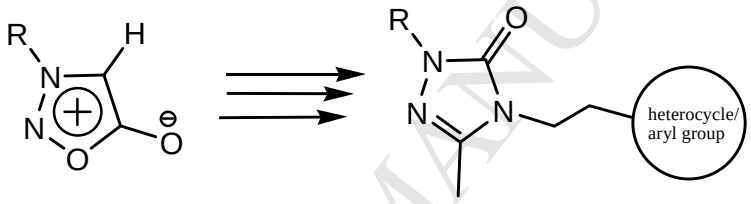
A series of novel 1,2,4-triazol-3-one appended to different heterocyclic/aryl moieties (**5a-t**) were synthesized and *in vitro* anticancerous action was studied against NCI-60 Human Tumor Cell Lines. The compound **5g** comprising 1,2,4-triazolin-3-one appended to 4-methylcoumarin ring has shown potent anticancer activity against various cell lines.



1 **5a-t**

Highlights

- Novel 1,2,4-triazolin-3-one derivatized with various heterocycles/aryl groups were synthesized.
- *In vitro* anticancer activity against NCI-60 human tumor cell lines was done.
- The compound **5g** comprising 4-methylcoumarin ring has shown potent anticancer activity.

Synthesis, characterization and *in vitro* anticancer evaluation of novel 1,2,4-triazolin-3-one derivatives

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A B S T R A C T

A series of novel 2-(4-chlorophenyl)-5-methyl-4-(2-amine/oxy-ethyl)-2,4-dihydro-[1,2,4]triazol-3-one (**5a-t**) were synthesized and the *in vitro* anticancerous action of the resulting compounds was studied against NCI-60 Human Tumor Cell Line at a single high dose (10^{-5} M) concentration for primary cytotoxicity assay. Among the tested compounds (**5a-e**, **5g-h**, **5k**, **5p**), the compound **5g** (NSC: 761736/1) was further evaluated for five dose criteria at five different minimal concentrations against the full panel of 60 human tumor cell lines which exhibited activity against *Leukemia* (GI_{50}: 1.10 μM), *Non-Small Cell Lung Cancer* (GI_{50}: 1.00 μM), *Renal Cancer* (GI_{50}: 1.00 μM), *Colon Cancer* (GI_{50}: 1.66 μM), *CNS Cancer* (GI_{50}: 1.36 μM), *Melanoma* (GI_{50}: 1.82 μM), *Ovarian Cancer* (GI_{50}: 1.64 μM) and *Breast Cancer* (GI_{50}: 1.69 μM).

1. Introduction

Cancer still remains a potentially life threatening disease and the number of cancer related deaths are increasing alarmingly. Literature clearly indicated that more than 90% of cancer patients die due to chronic tumor metastases - the spread and invasion of other organs [1]. Considering this, the development of newer chemotherapeutic scaffolds which selectively act on the target without side effects has became a primary objective of medicinal chemists. Recently, 1,2,4-triazole derivatives have been incorporated into wide variety of therapeutically interesting molecules to transform them into better drugs and exhibited significant biological activity for wide range of therapeutic properties *viz.*, antimicrobial [2], anti-tumour [3], antiinflammatory [4], antihypertensive [5], analgesic [6], anticonvulsant [7], antiviral [8], antidepressant [9], antitubercular [10], sedative [11] and plant growth regulatory activities [12]. Several compounds possessing 1,2,4-triazole nucleus are proved as drugs such as ribavirin

(antiviral agent) [13], terconazole and flucanozole (antifungal agent) [14]. The heterocyclic derivatives of 1,2,4-triazole exhibit a broad spectrum of pharmacological properties, for example 1,2,4-triazoles bearing coumarin, quinoline and morpholine [15-17] **Fig. 1**, have been reported as potential antimicrobial agents. Itraconazole, a potent antifungal agent, possess 1,2,4-triazole bearing piperazine substituent [18].

We opted to synthesize 1,2,4-triazolin-3-one derivatives (**5a-t**) from 3-arylsydnone (**1**) as it is proved to be useful precursor since it undergoes ring transformation *via* 1,3-dipolar cycloaddition reaction into various pharmacologically active heterocycles [19-22]. Also, we have recently demonstrated the anticancer activity of carbazole derivatives synthesized from 3-arylsydnone as synthon [23]. All these factors prompted us to synthesize 1,2,4-triazolin-3-ones appended to different bio-potent moieties in order to explore their *in vitro* anticancer activity against 60 human cancer cell lines at National Cancer Institute (NCI), National Institute of Health (NIH), Bethesda, USA.

2. Results and discussion

2.1. Chemistry

Initially, *N*-(4-chlorophenyl)sydnone (**1**) was ring transformed into 3-(4-chlorophenyl)-5-methyl-2-oxo-Δ^4-1,3,4-oxadiazole (**2**) which was further refluxed with ethanolamine to get 4-(2-hydroxy-ethyl)-2-(4-chlorophenyl)-5-methyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (**3**) through ring insertion. This (**3**) upon reaction with methanesulphonyl chloride in presence of triethylamine gave the mesilate **4**. Finally, the title compounds (**5a-t**) were obtained by reacting mesilate (**4**) with various secondary amines and/or hydroxyl substituted heterocycles/aromatic hydroxy compounds (**a-t, Scheme 1**) under mild basic condition. All the newly synthesized compounds were characterized by IR, ^{1}H and ^{13}C NMR, mass spectral and elemental analyses. In case of IR studies, all the compounds have shown a sharp intense band at 1698-1716 cm^{-1} which corresponds to carbonyl group of 1,2,4-triazolin-3-one ring. A medium intense band

appeared around 1595-1624 cm^{-1} was attributed to C=N stretching. In case of ^{1}H NMR, the C_5 methyl of 1,2,4-triazolin-3-one ring appeared at 1.86-2.68 ppm. The protons of ethyl chain resonated as two triplets in the upfield region *viz.*, 2.60-4.60 ppm. The signals appeared at 6.61-8.95 ppm were attributed to aromatic protons. For ^{13}C NMR, the C_5 methyl carbon of 1,2,4-triazolin-3-one ring resonated in the range 10.86-12.39 ppm. The ethyl carbons showed signals at 37.70-66.58 ppm. A signal resonated at 144-145 ppm was attributed to C_5 carbon of 1,2,4-triazolin-3-one ring. The carbonyl carbon of 1,2,4-triazolin-3-one ring was resonated in the range 149-152 ppm. The other rings attached to alkyl chain have shown signals at their respective positions. The mass spectral analyses of all the title compounds have shown the *m/z* values which corresponds to their molecular mass.

2.2. Pharmacology

2.2.1. Anticancer activity at a single high dose concentration (10^{-5}M)

All the newly synthesized compounds were subjected to *in vitro* anticancer screening in a single high dose (10^{-5} M) concentration against full 60 human cancer cell lines at NCI under DTP drug discovery programme. Output from the single dose screen is reported as a graph of mean growth percent of the treated cells. This allows detecting both growth inhibition values (between 0 and 100) and cytotoxicity values (less than 0). The results of the single dose screening were analyzed by COMPARE program [24]. Compounds **5a** (NSC: 761735/1), **5b** (NSC: 761741/1), **5c** (NSC: 761737/1), **5d** (NSC: 761740/1), **5e** (NSC: 761739/1), **5g** (NSC: 761736/1), **5h** (NSC: 761742/1), **5k** (NSC: 765439/1), **5p** (NSC: 765438/1) have been screened for single high dose (10^{-5} M) concentration on all the 60 human cancer cell lines organized into nine sub-panels derived from nine different human cancer types: leukemia, lung, colon, CNS, melanoma, ovarian, renal, prostate and breast cancer cell lines. The following are the percentage growth inhibition (GI%) of the treated cells at 10^{-5} M concentration with the compound **5b** (comprising 1,2,4-triazolin-3-one bearing morpholine substituent): *CNS Cancer*

SNB-75 (GI% 92.35); *Colon cancer* (GI% 70.54); compound **5g** (comprising 1,2,4-triazolin-3-one bearing 4-methylcoumarin substituent, **Table 1**): *Colon Cancer* HT 29 (GI% 99.30), COLO 205 (GI% 89.42), HCT 116 (GI% 84.88), HCT 15 (82.26); *Melanoma* SK-MEL-2 (GI% 96.45), SK-MEL-5 (GI% 89.24), M14 (GI% 85.28), UACC-257 (GI% 77.48); *Leukemia* CCRF-CEM (GI% 86.59), K-562 (GI% 83.73), SR 21.22 (GI% 78.78); *Non-Small Cell Lung Cancer* NCI-H460 (GI% 82.79); *CNS Cancer* SF-295 (GI% 85.97); *Ovarian Cancer* OVCAR-3 (GI% 85.18), OVCAR-8 (GI% 82.32); *Renal Cancer* CAKI-1 (GI% 80.52); *Prostate Cancer* DU-145 (GI% 78.36) and *Breast Cancer* MCF7 (GI% 84.21), MDA-MB-468 (GI% 83.92) and has shown cytotoxic effect against *Leukaemia* HL-60 (TB) and *Melanoma* MDA-MB-435 cancer cell lines. All other compounds (**5a**, **5c-e**, **5h**, **5k**, **5p**) have shown negligible GI%.

2.2.2. Anticancer activity at five dose concentrations

The methodology followed comprised *in vitro* screening of the compounds against full 60 cell lines divided into nine sub panels at five different minimal concentrations (0.01, 0.1, 1, 10 and 100 μM). The percentage of growth was evaluated spectrophotometrically versus controls not treated with test agents. The 48 h continuous drug exposure protocol was followed and SRB (sulforodamine B) protein assay was used to estimate cell viability or growth. The results were represented by graph of log concentration *vs* GI% and three dose response parameters (GI_{50}, TGI and LC_{50}) were calculated for each cell line. The GI_{50} value (growth inhibitory activity) corresponds to the molar concentration of the compound that inhibits 50% net cell growth; TGI value (cytostatic activity) is the molar concentration of the compound resulting in total growth inhibition and LC_{50} value (cytotoxic activity) is the molar concentration of the compound causing 50% net cell death. Furthermore, mean graph midpoints (MGMID) were calculated for GI_{50} parameter, giving an average activity parameter over all cell panels for tested compounds.

Among the tested compounds *viz.*, **5a-e**, **5g-h**, **5k**, **5p** the derivative possessing 4-methylcoumarin ring (**5g**) has shown significant growth inhibition against variety of cell lines at a single high dose (10^{-5} M) concentration and has been further evaluated for five dose screening at five different minimal concentrations. The compound **5g** has exhibited broad spectrum of growth inhibition activity against eight tumor cell lines with average GI_{50} values (MGMID) 2.97-3.65 μM namely, *Leukemia* K-562 (GI_{50}: 1.29 μM), RPMI-8226 (GI_{50}: 1.10 μM); *Non-Small Cell Lung Cancer* EKVX (GI50: 1.00 μM), HOP-92 (GI_{50}: 1.61 μM); *Colon Cancer* KM 12 (GI_{50}: 1.66 μM); *CNS Cancer* SF-268 (GI_{50}: 1.36 μM); *Melanoma* SK-MEL-2 (GI_{50}: 1.82 μM), UACC-62 (GI_{50}: 1.99 μM); *Ovarian Cancer* (GI_{50}: 1.64 μM); *Renal Cancer* A498 (GI_{50}: 1.13 μM) CAKI-1 cell line (GI50: 1.00 μM), TK-10 (GI_{50}: 1.34 μM), UO-31 (GI_{50}: 1.27 μM) and *Breast Cancer* BT-549 (GI_{50}: 1.69 μM) cell lines. The dose response curve of eight sub-panel cell lines for compound **5g** is represented in **Fig 2**.

3. Conclusions

In this communication, we report the synthesis of heterocyclic derivatives of 1,2,4-triazolin-3-one (**5a-t**) and their *in vitro* anticancer activity at NCI/NIH, Bethesda, USA. Out of twenty compounds, nine compounds (**5a-e**, **5g-h**, **5k**, **5p**) have been screened at a single high dose (10^{-5} M) concentration. Among these, the 1,2,4-triazolin-3-one bearing 4-methylcoumarin ring (**5g**) has shown nearly 50-99% growth inhibition of the tumor cells against various cell lines at 10^{-5} M concentration. It has also exhibited marked anticancer activity even at micro molar (μM) concentration against Leukemia, Non-Small Cell Lung Cancer, Renal Cancer, Colon Cancer, CNS Cancer, Melanoma, Ovarian Cancer, Renal Cancer and Breast Cancer cell panels. Structural modifications of these title compounds may lead to the discovery of more effective anticancer agents in future.

4. Experimental

4.1. Materials and methods

The purity of the compounds was checked by TLC on a silica gel plate using ethyl acetate and hexane (30%) as eluent. Melting points were determined in open capillaries. IR spectra (KBr) were recorded on a Nicolet Impact-410 FTIR spectrometer. ^{1}H (300 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on a Bruker Avance FT NMR spectrometer with TMS as an internal standard. Mass spectra were recorded using a Finnegan MAT (Model MAT 8200) spectrometer and elemental analysis was carried out using a Heraus CHN rapid analyzer. Compound **3** and corresponding mesilate **4** from *N*-(4-chlorophenyl)sydnone (**1**) were prepared according to the reported methods [25-27].

*4.2. General procedure for the preparation of title compounds (**5a-t**)*

A mixture of compound **4** (0.331 g, 0.001 M), appropriate secondary amine (**a-f,** 0.001 M) or hydroxyl substituted compound (**g-t,** 0.001 M) and anhydrous potassium carbonate (0.002 M) in dry DMF (20 ml) was stirred at 100 ºC. The completion of the reaction was checked by TLC using ethyl acetate and hexane (30%) as eluent. The reaction mixture was then poured into ice cold water and neutralized with dil. HCl (few drops). The precipitate thus formed was filtered and dried. All the newly prepared compounds were purified by column chromatography using ethyl acetate and hexane (10%) as eluent.

*4.2.1. 4-(2-(1H-1,2,4-Triazol-1-yl)ethyl)-2-(4-chlorophenyl)-5-methyl-2H-1,2,4-triazol-3(4H)-one (**5a**)*

Yield: 85%; m.p: 170-172 ºC; IR (KBr, cm^{-1}): 1710 (C=O), 1615 (C=N); ^{1}H NMR ($CDCl_3$, δ ppm): 1.86 (s, 3H, C_5-CH_3), 4.04 (t, 2H, N-CH_2), 4.50 (t, 2H, N-CH_2), 7.47-7.50 (d, 2H, *J* = 9 Hz, Ar-H), 7.86-7.89 (d, 2H, *J* = 9 Hz, Ar-H), 7.98 (s, 1H, triazole C_3-H), 8.52 (s, 1H, triazole C_5-H); ^{13}C NMR ($CDCl_3$, δ ppm): 12.39, 43.05, 48.38, 120.98, 130.50, 132.11, 137.55, 145.52, 151.38, 153.17, 154.45; MS (m/z): 306 (M^{+2}), 304 (M^{+}), 238, 236, 211, 209, 127, 125; Anal.

Calcd. for $C_{13}H_{13}N_6ClO$ (304.08): C, 51.24%; H, 4.30%; N, 27.58%; Found: C, 51.23%; H, 4.28%; N, 27.56%.

*4.2.2. 2-(4-Chlorophenyl)-5-methyl-4-(2-morpholinoethyl)-2H-1,2,4-triazol-3(4H)-one (**5b**)*

Yield: 60%; m.p: 110-112 ºC; IR (KBr, cm^{-1}): 1703 (C=O), 1624 (C=N); ^1H NMR ($CDCl_3$, δ ppm): 2.36 (s, 3H, C_5-CH_3), 2.53 (t, 4H, morpholine CH_2-N-CH_2), 2.64 (t, 2H, N-CH_2), 3.74 (t, 4H, morpholine CH_2-O-CH_2), 3.76 (t, 2H, N-CH_2), 7.35-7.39 (d, 2H, *J* = 12 Hz, Ar-H), 7.92-7.96 (d, 2H, *J* = 12 Hz, Ar-H), ^{13}C NMR ($CDCl_3$, δ ppm): 12.02, 39.11, 53.90, 57.04, 66.94, 119.46, 129.22, 130.24, 136.55, 144.63, 152.04; MS (m/z): 324 (M^{+2}), 322 (M^+), 238, 236, 211, 209, 127, 125; Anal. Calcd. for $C_{15}H_{19}N_4ClO_2$ (322.12): C, 55.81%; H, 5.93%; N, 17.36%; Found: C, 55.79%; H, 5.90%; N, 17.38%.

*4.2.3. 4-(2-(1H-Benzo[d][1,2,3]triazol-1-yl)ethyl)-2-(4-chlorophenyl)-5-methyl-2H-1,2,4-triazol-3(4H)-one (**5c**)*

Yield: 82%; m.p: 168-170 ºC; IR (KBr, cm^{-1}): 1702 (C=O), 1612 (C=N); ^1H NMR ($CDCl_3$, δ ppm): 1.92 (s, 3H, C_5-CH_3), 4.28 (t, 2H, N-CH_2), 5.07 (t, 2H, N-CH_2), 7.40-7.42 (m, 2H, Ar-H), 7.44-7.49 (d, 2H, *J* = 15 Hz, Ar-H), 7.80-7.85 (d, 2H, *J* = 15 Hz, Ar-H), 7.88-7.91 (m, 2H, Ar-H); ^{13}C NMR ($CDCl_3$, δ ppm): 10.86, 41.84, 53.90, 118.02, 119.52, 126.61, 126.93, 128.94, 130.37, 136.30, 143.89, 144.66, 151.69; MS (m/z): 356 (M^{+2}), 354 (M^+), 238, 236, 211, 209, 127, 125; Anal. Calcd. for $C_{15}H_{19}N_4ClO_2$ (354.10): C, 57.55%; H, 4.26%; N, 23.69%; Found: C, 57.58%; H, 4.23%; N, 23.66%.

*4.2.4. 3-(2-(1-(4-Chlorophenyl)-3-methyl-5-oxo-1H-1,2,4-triazol-4(5H-yl)ethyl)thiazolidine-2,4-dione (**5d**)*

Yield: 62; m.p: 278-280 ºC; IR (KBr, cm^{-1}): 1739 (C=O), 1705 (C=O), 1611 (C=N); ^1H NMR (DMSO, δ ppm): 2.50 (s, 3H, C_5-CH_3), 2.73 (t, 2H, N-CH_2), 2.89 (t, 2H, N-CH_2), 3.63 (s, 1H, C_5-H of thiazolidine), 7.47-7.50 (d, 2H, *J* = 9 Hz, Ar-H), 7.90-7.93 (d, 2H, *J* = 9 Hz, Ar-H); ^{13}C NMR ($CDCl_3$, δ ppm): 11.31, 33.85, 37.70, 41.60, 119.00, 128.36, 128.92, 136.66, 145.74,

151.50, 164.51, 167.90; MS (m/z): 354 (M^{+2}), 352 (M^{+}), 281, 278, 238, 236, 254, 251, 211, 209, 127, 125; Anal. Calcd. for $C_{14}H_{13}N_4ClO_3S$ (352.04): C, 47.66%; H, 3.71%; N, 15.88%; Found: C, 47.68%; H, 3.74%; N, 15.86%.

*4.2.5. 4-(2-(1H-Benzo[d]imidazol-1-yl)ethyl)-2-(4-chlorophenyl)-5-methyl-2H-1,2,4-triazol-3(4H)-one (**5e**)*

Yield: 76%; m.p: 78-80 ºC; IR (KBr, cm^{-1}): 1699 (C=O), 1598 (C=N); ^{1}H NMR ($CDCl_3$, δ ppm): 2.16 (s, 3H, C_5-CH_3), 4.05 (t, 2H, N-CH_2), 4.59 (t, 2H, N-CH_2), 7.27-7.29 (m, 2H, Ar-H), 7.32-7.37 (d, 2H, *J* = 15 Hz, Ar-H), 7.39-7.81 (m, 2H, Ar-H), 7.83-7.88 (d, 2H, *J* = 15 Hz, Ar-H), 7.90 (s, 1H, C_2-H of benzimidazole); ^{13}C NMR ($CDCl_3$, δ ppm): 11.20, 40.80, 44.92, 112.21, 115.41, 119.11, 125.66, 125.91, 128.71, 128.89, 131.46, 131.96, 136.16, 142.19, 145.25, 151.34; MS (m/z): 355 (M^{+2}), 353 (M^{+}), 237, 235, 211, 209, 127, 125; Anal. Calcd. for $C_{18}H_{16}N_5ClO$ (353.10): C, 61.10%; H, 4.56%; N, 19.79%; Found: C, 61.12%; H, 4.53%; N, 19.77%.

*4.2.6. 2-(4-Chlorophenyl)-5-methyl-4-(2-(4-methylpiperazin-1-yl)ethyl)-2H-1,2,4-triazol-3(4H)-one (**5f**)*

Yield: 65%; semisolid; IR (KBr, cm^{-1}): 1706 (C=O), 1599 (C=N); ^{1}H NMR ($CDCl_3$, δ ppm): 2.24 (s, 3H, C_5-CH_3), 2.32 (s, 3H, N-CH_3), 2.52-2.56 (m, 8H, piperazine), 2.66 (t, 2H, N-CH_2), 3.68 (t, 2H, N-CH_2), 7.25-7.28 (d, 2H, *J* = 9 Hz, Ar-H), 7.85-7.88 (d, 2H, *J* = 9 Hz, Ar-H); ^{13}C NMR ($CDCl_3$, δ ppm): 12.05, 45.60, 52.95, 54.76, 119.34, 128.78, 130.08, 136.37, 145.32, 151.85; MS (m/z): 337 (M^{+2}), 335 (M^{+}), 238, 236, 211, 209, 127, 125; Anal. Calcd. for $C_{16}H_{22}N_5ClO$ (335.15): C, 57.22%; H, 6.60%; N, 20.85%; Found: C, 57.23%; H, 6.58%; N, 20.87%.

*4.2.7. 2-(4-Chlorophenyl)-5-methyl-4-(2-(4-methyl-2-oxo-2H-chromen-7-yloxy)ethyl)-2H-1,2,4-triazol-3(4H)-one (**5g**)*

Yield: 76%; m.p: 238-240 ºC; IR (KBr, cm^{-1}): 1712 (C=O), 1615 (C=N); ^{1}H NMR ($CDCl_3$, δ ppm): 2.34 (s, 3H, coumarin CH_3), 2.38 (s, 3H, C_5-CH_3), 4.11 (t, 2H, N-CH_2), 4.30 (t, 2H, O-CH_2), 6.14 (s, 1H, C_4-H of coumarin), 6.77-7.26 (m, 2H, Ar-H), 7.34-7.37 (d, 2H, *J* = 9 Hz, Ar-H), 7.47-7.49 (m, 1H, Ar-H), 7.89-7.91 (d, 2H, *J* = 9 Hz, Ar-H); ^{13}C NMR ($CDCl_3$, δ ppm): 12.05, 18.61, 41.26, 65.78, 101.84, 106.22, 111.76, 112.55, 119.61, 125.81, 128.99, 130.44, 136.28, 144.79, 151.81, 152.26, 155.31, 160.72, 160.95; MS (m/z): 413 (M^{+2}), 411 (M^{+}), 238, 236, 211, 209, 127, 125; Anal. Calcd. for $C_{21}H_{18}N_3ClO_4$ (411.10): C, 61.24%; H, 4.41%; N, 10.20%; Found: C, 61.25%; H, 4.44%; N, 10.17%.

*4.2.8. 2-(4-Chlorophenyl)-4-(2-(5-chloroquinolin-8-yloxy)ethyl)-5-methyl-2H-1,2,4-triazol-3(4H)-one (**5h**)*

Yield: 72%; m.p: 308-310 ºC; IR (KBr, cm^{-1}): 1710 (C=O), 1599 (C=N); ^{1}H NMR ($CDCl_3$, δ ppm): 2.68 (s, 3H, C_5-CH_3), 4.26 (t, 2H, N-CH_2), 4.46 (t, 2H, O-CH_2), 6.94-6.97 (d, 1H, *J* = 9 Hz, Ar-H), 7.33-7.36 (d, 1H, *J* = 9 Hz, Ar-H), 7.48-7.51 (d, 2H, *J* = 9 Hz, Ar-H), 7.54-7.56 (m, 1H, Ar-H), 7.88-7.91 (d, 2H, *J* = 9 Hz, Ar-H), 8.51-8.92 (m, 2H, Ar-H); ^{13}C NMR ($CDCl_3$, δ ppm): 12.06, 41.43, 66.62, 108.95, 119.53, 122.50, 126.28, 128.95, 130.26, 132.98, 136.43, 144.58, 149.73, 152.37, 158.91; MS (m/z): 418 (M^{+4}), 416 (M^{+2}), 414 (M^{+}), 238, 236, 206, 204, 127, 125; Anal. Calcd. for $C_{20}H_{16}N_4Cl_2O_2$ (414.07): C, 57.84%; H, 3.88%; N, 13.49%; Found: C, 57.85%; H, 3.87%; N, 13.47%.

*4.2.9. 2-(4-Chlorophenyl)-5-methyl-4-(2-(2-oxo-2H-chromen-4-yloxy)ethyl)-2H-1,2,4-triazol-3(4H)-one (**5i**)*

Yield: 81%; m.p: 230-232 ºC; IR (KBr, cm^{-1}): 1716 (C=O), 1605 (C=N); ^{1}H NMR ($CDCl_3$, δ ppm): 2.41 (s, 3H, C_5-CH_3), 4.22 (t, 2H, N-CH_2), 4.49 (t, 2H, O-CH_2), 5.95 (s, 1H, C_4-H of coumarin), 7.36-7.38 (m, 2H, Ar-H), 7.50-7.53 (d, 2H, *J* = 9 Hz, Ar-H), 7.62-7.81 (m, 2H, Ar-H), 7.92-7.95 (d, 2H, *J* = 9 Hz, Ar-H); ^{13}C NMR ($CDCl_3$, δ ppm): 11.53, 40.01, 62.48, 91.11, 115.45, 116.47, 119.04, 122.74, 124.21, 128.95, 129.04, 132.81, 137.45, 145.01, 150.09,

154.21, 160.10, 164.23; MS (m/z): 399 (M^{+2}), 397 (M^{+}), 238, 236, 211, 209, 127, 125; Anal. Calcd. for $C_{20}H_{16}N_3ClO_4$ (397.08): C, 60.38%; H, 4.05%; N, 10.56%; Found: C, 60.35%; H, 4.04%; N, 10.59%.

*4.2.10. 2-(4-Chlorophenyl)-5-methyl-4-(2-(o-tolyloxy)ethyl)-2H-1,2,4-triazol-3(4H)-one (**5j**)*

Yield: 81%; m.p: 138-140 ºC; IR (KBr, cm^{-1}): 1711 (C=O), 1608 (C=N); ^1H NMR ($CDCl_3$, δ ppm): 2.15 (s, 3H, C_5-CH_3), 2.41 (s, 3H, CH_3), 4.09 (t, 2H, N-CH_2), 4.23 (t, 2H, O-CH_2), 6.61-6.99 (m, 4H, Ar-H), 7.09-7.11 (d, 2H, *J* = 6 Hz, Ar-H), 7.88-7.90 (d, 2H, *J* = 6 Hz, Ar-H); ^{13}C NMR ($CDCl_3$, δ ppm): 12.11, 24.51, 40.71, 66.05, 114.78, 119.72, 121.23, 124.60, 126.04, 128.65, 130.54, 136.61, 144.81, 151.65, 155.68; MS (m/z): 345 (M^{+2}), 343 (M^{+}), 238, 236, 211, 209, 127, 125; Anal. Calcd. for $C_{18}H_{18}N_3ClO_2$ (343.11): C, 62.88%; H, 5.28%; N, 12.22%; Found: C, 62.84%; H, 5.26%; N, 12.19%.

*4.2.11. 2-(4-Chlorophenyl)-5-methyl-4-(2-(p-tolyloxy)ethyl)-2H-1,2,4-triazol-3(4H)-one (**5k**)*

Yield: 80%; m.p: 156-158 ºC; IR (KBr, cm^{-1}): 1714 (C=O), 1611 (C=N); ^1H NMR ($CDCl_3$, δ ppm): 2.19 (s, 3H, C_5-CH_3), 2.43 (s, 3H, CH_3), 3.90 (t, 2H, N-CH_2), 4.27 (t, 2H, O-CH_2), 6.65-6.69 (d, 2H, *J* = 12 Hz, Ar-H), 7.11-7.14 (d, 2H, *J* = 12 Hz, Ar-H), 7.48-7.52 (d, 2H, *J* = 12 Hz, Ar-H), 7.88-7.92 (d, 2H, *J* = 12 Hz, Ar-H); ^{13}C NMR ($CDCl_3$, δ ppm): 11.98, 24.63, 40.74, 66.35, 113.64, 119.76, 128.86, 129.63, 130.65, 131.29, 136.52, 144.73, 152.09, 156.32; MS (m/z): 345 (M^{+2}), 343 (M^{+}), 238, 236, 211, 209, 127, 125; Anal. Calcd. for $C_{18}H_{18}N_3ClO_2$ (343.11): C, 62.88%; H, 5.28%; N, 12.22%; Found: C, 62.89%; H, 5.27%; N, 12.25%.

*4.2.12. 2-(4-Chlorophenyl)-5-methyl-4-(2-(m-tolyloxy)ethyl)-2H-1,2,4-triazol-3(4H)-one (**5l**)*

Yield: 78%; m.p: 162-164 ºC; IR (KBr, cm^{-1}): 1701 (C=O), 1598 (C=N); ^1H NMR ($CDCl_3$, δ ppm): 2.15 (s, 3H, C_5-CH_3), 2.35 (s, 3H, CH_3), 4.11 (t, 2H, N-CH_2), 4.26 (t, 2H, O-CH_2), 6.75-6.85 (m, 4H, Ar-H), 7.38-7.41 (d, 2H, *J* = 9 Hz, Ar-H), 7.88-7.91 (d, 2H, *J* = 9 Hz, Ar-H); ^{13}C NMR ($CDCl_3$, δ ppm): 12.01, 24.58, 40.78, 66.26, 111.49, 113.67, 119.69, 120.37, 128.63, 130.31, 136.74, 139.09, 144.87, 152.06, 156.79; MS (m/z): 345 (M^{+2}), 343 (M^{+}), 238, 236,

211, 209, 127, 125; Anal. Calcd. for $C_{18}H_{18}N_3ClO_2$ (343.11): C, 62.88%; H, 5.28%; N, 12.22%; Found: C, 62.86%; H, 5.27%; N, 12.21%.

*4.2.13. 2-(4-Chlorophenyl)-5-methyl-4-(2-(4-nitrophenoxy)ethyl)-2H-1,2,4-triazol-3(4H)-one (**5m**)*

Yield: 72%; m.p: 292-294 ºC; IR (KBr, cm^{-1}): 1709 (C=O), 1595 (C=N), 1498, 1340 (NO_2); ^1H NMR ($CDCl_3$, δ ppm): 2.37 (s, 3H, C_5-CH_3), 4.06 (t, 2H, N-CH_2), 4.27 (t, 2H, O-CH_2), 6.86-6.88 (d, 2H, *J* = 6 Hz, Ar-H), 7.28-7.30 (d, 2H, *J* = 6 Hz, Ar-H), 7.82-7.84 (d, 2H, *J* = 6 Hz, Ar-H), 8.12-8.14 (d, 2H, *J* = 6 Hz, Ar-H); ^{13}C NMR ($CDCl_3$, δ ppm): 12.08, 40.65, 66.37, 115.32, 121.72, 119.81, 128.85, 130.56, 136.42, 138.69, 144.92, 151.78, 160.03; MS (m/z): 376 (M^{+2}), 374 (M^+), 238, 236, 211, 209, 127, 125; Anal. Calcd. for $C_{17}H_{15}N_4ClO_4$ (374.08): C, 54.48%; H, 4.03%; N, 14.95%; Found: C, 54.46%; H, 4.05%; N, 14.97%.

*4.2.14. 4-(2-(4-Bromophenoxy)ethyl)-2-(4-chlorophenyl)-5-methyl-2H-1,2,4-triazol-3(4H)-one (**5n**)*

Yield: 74%; m.p: 178-180 ºC; IR (KBr, cm^{-1}): 1711 (C=O), 1610 (C=N); ^1H NMR ($CDCl_3$, δ ppm): 2.18 (s, 3H, C_5-CH_3), 4.02 (t, 2H, N-CH_2), 4.12 (t, 2H, O-CH_2), 6.66-6.70 (d, 2H, *J* = 12 Hz, Ar-H), 7.38-7.42 (d, 2H, *J* = 12 Hz, Ar-H), 7.44-7.48 (d, 2H, *J* = 12 Hz, Ar-H), 7.79-7.83 (d, 2H, *J* = 12 Hz, Ar-H); ^{13}C NMR ($CDCl_3$, δ ppm): 12.06, 41.42, 65.56, 113.80, 116.06, 119.53, 128.97, 130.37, 132.48, 136.35, 144.91, 151.82, 157.02; MS (m/z): 411 (M^{+4}), 409 (M^{+2}), 407 (M^+), 238, 236, 211, 209, 155, 153, 127, 125; Anal. Calcd. for $C_{17}H_{15}N_3BrClO_2$ (407.00): C, 49.96%; H, 3.70%; N, 10.28%; Found: C, 49.93%; H, 3.73%; N, 10.30%.

*4.2.15. 4-(2-(4-Chlorophenoxy)ethyl)-2-(4-chlorophenyl)-5-methyl-2H-1,2,4-triazol-3(4H)-one (**5o**)*

Yield: 68%; m.p: 166-168 ºC; IR (KBr, cm^{-1}): 1702 (C=O), 1596 (C=N); ^1H NMR ($CDCl_3$, δ ppm): 2.46 (s, 3H, C_5-CH_3), 4.08 (t, 2H, N-CH_2), 4.23 (t, 2H, O-CH_2), 6.65-6.69 (d, 2H, *J* = 12 Hz, Ar-H), 7.27-7.31 (d, 2H, *J* = 12 Hz, Ar-H), 7.41-7.45 (d, 2H, *J* = 12 Hz, Ar-H), 7.81-7.85

(d, 2H, *J* = 12 Hz, Ar-H); ^{13}C NMR ($CDCl_3$, δ ppm): 12.03, 40.89, 65.48, 113.85, 115.75, 119.55, 128.79, 130.28, 132.56, 137.57, 144.98, 151.95, 155.62; MS (m/z): 367 (M^{+4}), 365 (M^{+2}), 363 (M^{+}), 238, 236, 211, 209, 155, 153, 127, 125; Anal. Calcd. for $C_{17}H_{15}N_3Cl_2O_2$ (363.05): C, 56.06%; H, 4.15%; N, 11.54%; Found: C, 56.03%; H, 4.12%; N, 11.56%.

*4.2.16. 4-(2-(2-Chlorophenoxy)ethyl)-2-(4-chlorophenyl)-5-methyl-2H-1,2,4-triazol-3(4H)-one (**5p**)*

Yield: 65%; m.p: 188-190 ºC; IR (KBr, cm^{-1}): 1705 (C=O), 1597 (C=N); ^{1}H NMR ($CDCl_3$, δ ppm): 2.46 (s, 3H, C_5-CH_3), 4.06 (t, 2H, N-CH_2), 4.25 (t, 2H, O-CH_2), 6.93-7.38 (m, 4H, ArH), 7.46-7.49 (d, 2H, *J* = 9 Hz, Ar-H), 7.84-7.87 (d, 2H, *J* = 9 Hz, Ar-H); ^{13}C NMR ($CDCl_3$, δ ppm): 12.11, 40.76, 65.78, 115.80, 119.74, 121.09, 122.56, 127.11, 128.81, 129.98, 130.29, 136.11, 144.88, 152.01; 155.68; MS (m/z): 367 (M^{+4}), 365 (M^{+2}), 363 (M^{+}), 238, 236, 211, 209, 155, 153, 127, 125; Anal. Calcd. for $C_{17}H_{15}N_3Cl_2O_2$ (363.05): C, 56.06%; H, 4.15%; N, 11.54%; Found: C, 56.05%; H, 4.18%; N, 11.52%.

*4.2.17. 2-(4-Chlorophenyl)-4-(2-(2,3-dimethylphenoxy)ethyl)-5-methyl-2H-1,2,4-triazol-3(4H)-one (**5q**)*

Yield: 68%; m.p: 183-185 ºC; IR (KBr, cm^{-1}): 1712 (C=O), 1610 (C=N); ^{1}H NMR ($CDCl_3$, δ ppm): 2.17 (s, 3H, C_5-CH_3), 2.31 (s, 6H, CH_3), 4.06 (t, 2H, N-CH_2), 4.14 (t, 2H, O-CH_2), 6.65-7.06 (m, 3H, ArH), 7.47-7.51 (d, 2H, *J* = 12 Hz, Ar-H), 7.81-7.85 (d, 2H, *J* = 12 Hz, Ar-H); ^{13}C NMR ($CDCl_3$, δ ppm): 11.89, 11.97, 20.07, 41.71, 65.50, 109.04, 119.73, 123.21, 124.92, 126.01, 128.96, 130.30, 136.43, 138.22, 144.92, 151.87, 156.03; MS (m/z): 359 (M^{+2}), 357 (M^{+}), 238, 236, 211, 209, 155, 153, 127, 125; Anal. Calcd. for $C_{19}H_{20}N_3ClO_2$ (357.12): C, 63.77%; H, 5.63%; N, 11.74%; Found: C, 63.75%; H, 5.60%; N, 11.76%.

*4.2.18. 2-(4-Chlorophenyl)-4-(2-(3,5-dimethylphenoxy)ethyl)-5-methyl-2H-1,2,4-triazol-3(4H)-one (**5r**)*

Yield: 68%; m.p: 186-188 ºC; IR (KBr, cm^{-1}): 1708 (C=O), 1598 (C=N); ^1H NMR ($CDCl_3$, δ ppm): 2.20 (s, 3H, C_5-CH_3), 2.33 (s, 6H, CH_3), 4.14 (t, 2H, N-CH_2), 4.24 (t, 2H, O-CH_2), 6.58-6.77 (m, 3H, Ar-H), 7.61-7.65 (d, 2H, *J* = 12 Hz, Ar-H), 7.85-7.89 (d, 2H, *J* = 12 Hz, Ar-H); ^{13}C NMR ($CDCl_3$, δ ppm): 12.02, 24.87, 40.86, 66.01, 110.65, 119.81, 122.56, 128.94, 130.41, 136.57, 138.06, 144.89, 151.79, 157.03; MS (m/z): 359 (M^{+2}), 357 (M^+), 238, 236, 211, 209, 155, 153, 127, 125; Anal. Calcd. for $C_{19}H_{20}N_3ClO_2$ (357.12): C, 63.77%; H, 5.63%; N, 11.74%; Found: C, 63.74%; H, 5.65%; N, 11.75%.

*4.2.19. 2-(4-Chlorophenyl)-5-methyl-4-(2-(naphthalen-1-yloxy)ethyl)-2H-1,2,4-triazol-3(4H)-one (**5s**)*

Yield: 71%; m.p: 163-165 ºC; IR (KBr, cm^{-1}): 1700 (C=O), 1598 (C=N); ^1H NMR ($CDCl_3$, δ ppm): 2.32 (s, 3H, C_5-CH_3), 4.05 (t, 2H, N-CH_2), 4.20 (t, 2H, O-CH_2), 6.75-8.25 (m, 11H, ArH); ^{13}C NMR ($CDCl_3$, δ ppm): 12.13, 40.77, 66.41, 106.32, 119.67, 121.09, 122.27, 125.13, 125.98, 126.48, 127.01, 127.52, 128.96, 130.74, 135.61, 136.72, 144.87, 151.63, 156.71; MS (m/z): 381 (M^{+2}), 379 (M^+), 238, 236, 211, 209, 155, 153, 127, 125; Anal. Calcd. for $C_{21}H_{18}N_3ClO_2$ (379.11): C, 66.40%; H, 4.78%; N, 11.06%; Found: C, 66.42%; H, 4.80%; N, 11.03%.

*4.2.20. 2-(4-Chlorophenyl)-5-methyl-4-(2-(naphthalen-2-yloxy)ethyl)-2H-1,2,4-triazol-3(4H)-one (**5t**)*

Yield: 68%; m.p: 157-159 ºC; IR (KBr, cm^{-1}): 1698 (C=O), 1595 (C=N); ^1H NMR ($CDCl_3$, δ ppm): 2.30 (s, 3H, C_5-CH_3), 4.03 (t, 2H, N-CH_2), 4.16 (t, 2H, O-CH_2), 6.81-8.22 (m, 11H, ArH); ^{13}C NMR ($CDCl_3$, δ ppm): 12.12, 40.52, 66.58, 105.89, 117.68, 119.87, 124.41, 125.78, 126.31, 127.63, 128.14, 128.94, 129.54, 130.84, 134.80, 136.58, 144.77, 151.64, 157.30; MS (m/z): 381 (M^{+2}), 379 (M^+), 238, 236, 211, 209, 155, 153, 127, 125; Anal. Calcd. for $C_{21}H_{18}N_3ClO_2$ (379.11): C, 66.40%; H, 4.78%; N, 11.06%; Found: C, 66.42%; H, 4.77%; N, 11.04%.

4.3. Methodology of the in vitro anticancer screen

The human tumor cell lines of the cancer screening panel were grown in RPMI 1640 medium containing fetal bovine serum (5%) and L-glutamine (2 mM). For a typical screening experiment, cells were inoculated into 96 well microtiter plates in 100 µL at plating densities ranging from 5,000 to 40,000 cells/well depending on the doubling time of individual cell lines. After cell inoculation, the microtiter plates are incubated at 37 ℃, 5% CO_2, 95% air and 100 % relative humidity for 24 h prior to addition of experimental drugs. After 24 h, two plates of each cell line are fixed *in situ* with TCA to represent a measurement of the cell population for each cell line at the time of drug addition (Tz). Experimental drugs were solubilized in dimethyl sulfoxide at 400 fold the desired final maximum test concentration and stored frozen prior to use. At the time of drug addition, an aliquot of frozen concentrate was thawed and diluted to twice the desired final maximum test concentration with complete medium containing 50 µg/ml gentamicin. Additional four, 10 fold or ½ log serial dilutions were made to provide a total of five drug concentrations plus control. Aliquots of 100 µl of these different drug dilutions were added to the appropriate microtiter wells already containing 100 µl of medium, resulting in the required final drug concentrations. Following drug addition, the plates were incubated for an additional 48 h at 37 °C, 5% CO_2, 95% air, and 100% relative humidity. For adherent cells, the assay was terminated by the addition of cold TCA. Cells were fixed *in situ* by the gentle addition of 50 µl of cold 50% (w/v) TCA (final concentration, 10% TCA) and incubated for 60 minutes at 4 °C. The supernatant was discarded, and the plates were washed five times with tap water and air dried. Sulforhodamine B (SRB) solution (100 µl) at 0.4% (w/v) in acetic acid (1%) was added to each well, and plates were incubated for 10 minutes at room temperature. After staining, unbound dye was removed by washing five times with acetic acid (1%) and the plates were air dried. Bound stain was subsequently solubilized with trizma (10 mM) base, and the absorbance was read on an automated plate reader at a

wavelength of 515 nm. For suspension cells, the methodology was the same except that the assay was terminated by fixing settled cells at the bottom of the wells by gently adding 50 µl of 80% TCA (final concentration, 16% TCA). Using the seven absorbance measurements [time zero (Tz), control growth (C) and test growth in the presence of drug at the five concentration levels (Ti)], the percentage growth is calculated at each of the drug concentrations levels. Percentage growth inhibition was calculated as:

$[(Ti-Tz)/(C-Tz)] \times 100$ (for concentrations for which $Ti \geq Tz$)

$[(Ti-Tz)/Tz] \times 100$ (for concentrations for which $Ti < Tz$)

Three dose response parameters were calculated for each experimental agent. Growth inhibition of 50% (GI_{50}) was calculated from $[(Ti-Tz)/(C-Tz)] \times 100 = 50$, which was the drug concentration resulting in a 50% reduction in the net protein increase (as measured by SRB staining) in control cells during the drug incubation. The drug concentration resulting in total growth inhibition (TGI) is calculated from $Ti = Tz$. The LC_{50} (concentration of drug resulting in a 50% reduction in the measured protein at the end of the drug treatment as compared to that at the beginning) indicating a net loss of cells following treatment was calculated from $[(Ti-Tz)/Tz] \times 100 = 50$. Values were calculated for each of these three parameters if the level of activity was reached; however, if the effect was not reached or was exceeded, the value for that parameter was expressed as greater or less than the maximum or minimum concentration tested [28-30].

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Scheme 1 Synthetic route for title compounds **5a-t**

Table 1 Growth percent and growth inhibition (GI%) in single dose assay (10^{-5} M concentration) for compound **5g** (NSC: 761736/1)

Table 2 GI_{50}, TGI and LC_{50} values against 60 human cancer cell lines for compound **5g**

Fig. 1 Reported 1,2,4-triazole derivatives bearing heterocyclic substituent

Fig. 2 Dose response curve of eight sub-panel cell lines for compound **5g**

Scheme 1 Synthetic route for the title compounds **5a-t**

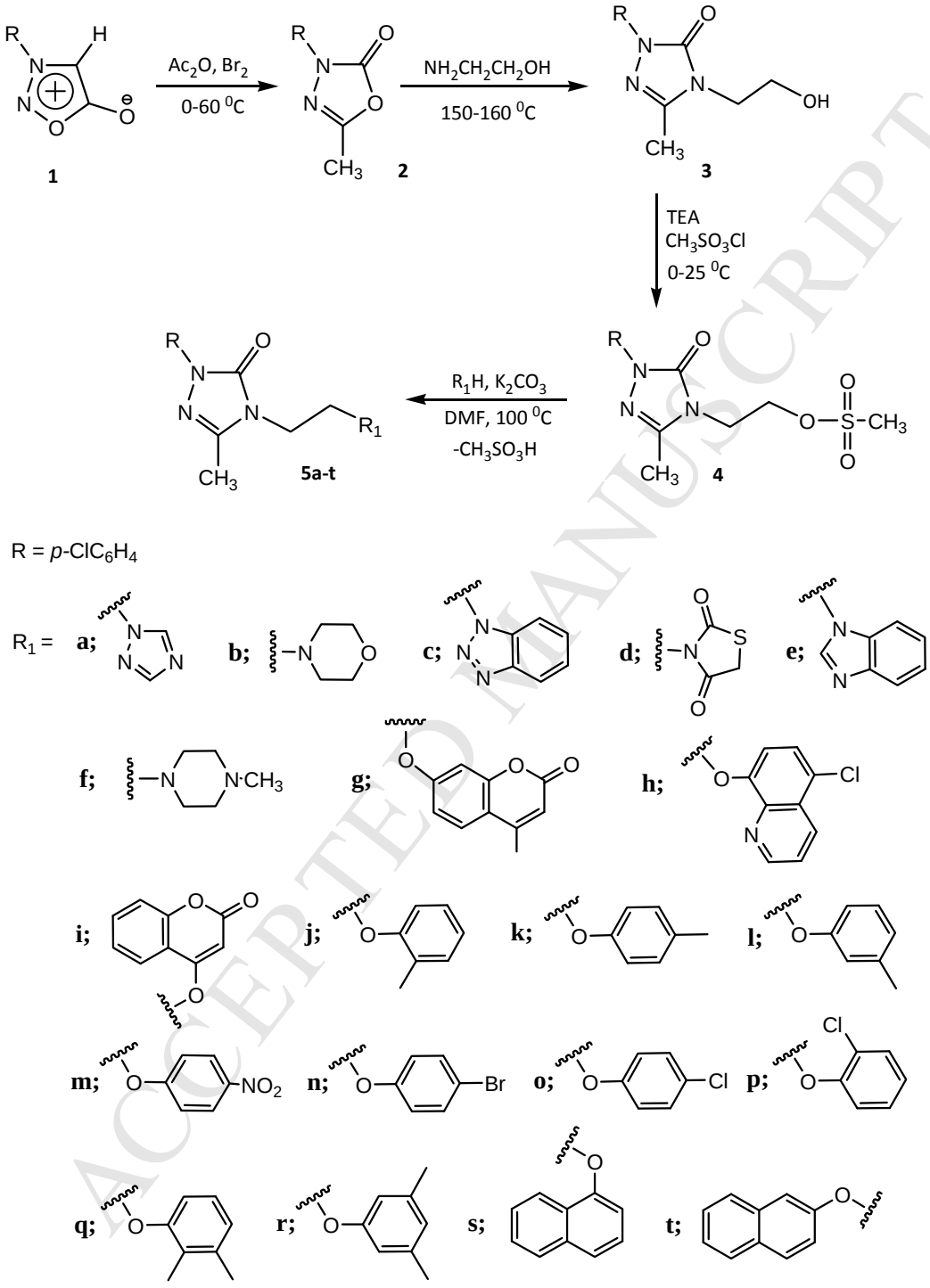


Table 1 Growth percent and growth inhibition (GI%) in single dose assay (10^{-5} M concentration) for compound **5g** (NSC: 761736/1)

Panel/ Cell line	Growth percent	Growth inhibition (GI%)
Leukemia		
CCRF-CEM	13.41	86.59
HL-60 (TB)	-5.70	cytotoxic
K-562	16.27	83.73
MOLT-4	37.58	62.42
RPMI-8226	31.00	69.00
SR	21.22	78.78
Non-Small Cell Lung Cancer		
A549/ATCC	30.22	69.78
EKVX	58.73	41.27
HOP-62	27.35	72.65
HOP-92	47.38	52.62
NCI-H226	50.09	49.91
NCI-H23	45.82	54.18
NCI-H322M	58.72	41.28
NCI-H522	17.21	82.79
Colon Cancer		
COLO 205	10.58	89.42
HCC-2998	46.66	53.34
HCT-116	15.12	84.88
HCT-15	17.74	82.26
HT29	0.70	99.30
KM12	31.42	68.58
CNS Cancer		
SF-268	50.30	49.70
SF-295	14.03	85.97
SF-539	29.47	70.53
SNB-19	54.49	45.51
SNB-75	20.38	79.62
U251	31.40	68.60
Melanoma		
LOX IMVI	48.02	51.98
MALME-3M	32.87	67.13
M14	14.72	85.28
MDA-MB-435	-38.55	cytotoxic
SK-MEL-2	3.55	96.45
SK-MEL-28	40.80	59.20
SK-MEL-5	10.76	89.24
UACC-257	22.52	77.48
UACC-62	43.33	56.67

Continued Table 1

Panel/ Cell line	Growth percent	Growth inhibiton (GI%)
Ovarian Cancer		
IGROV-1	59.69	40.31
OVCAR-3	14.82	85.18
OVCAR-4	67.10	32.90
OVCAR-5	38.80	61.20
OVCAR-8	17.68	82.32
NCI/ADR-RES	24.67	75.33
SK-OV-3	41.12	58.89
Renal Cancer		
786-D	32.86	67.14
A498	25.70	74.30
ACHN	41.87	58.13
CAKI-1	19.48	80.52
RXF-393	37.43	62.57
SN12C	51.82	48.18
TK-10	59.63	40.37
UO-31	42.80	57.20
Prostate Cancer		
PC-3	48.50	51.50
DU-145	21.64	78.36
Breast Cancer		
MCF-7	15.79	84.21
MDA-MB-231/ATCC	47.48	52.52
HS 578T	34.82	65.18
BT-549	56.66	43.34
T-47D	47.43	52.57
MDA-MB-468	16.08	83.92

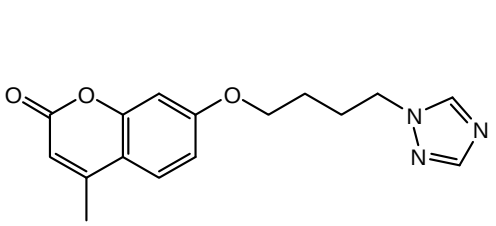
Table 2 GI_{50}, TGI and LC_{50} values against 60 human cancer cell lines for compound **5g**

Panel/ Cell line	GI_{50} μM	MGMID μM	TGI μM	LD_{50} μM
Leukemia				
HL-60 (TB)	2.80		-----	
K-562	1.29		>1.00	>1.00
MOLT-4	4.71	2.97	>1.00	>1.00
RPMI-8226	1.10		>1.00	>1.00
SR	4.97		6.67	>1.00
Non-Small Cell Lung Cancer	6.07		>1.00	>1.00
A549/ATCC	1.00		>1.00	>1.00
EKVX	3.05		3.29	>1.00
HOP-62	1.61	3.03	>1.00	>1.00
HOP-92	2.83		>1.00	>1.00
NCI-H23	2.80		>1.00	>1.00
NCI-H460	3.85		3.82	>1.00
NCI-H522				
Colon Cancer				
COLO 205	2.39		7.34	>1.00
HCC-2998	3.59		>1.00	>1.00
HCT-116	3.57		>1.00	>1.00
HCT-15	3.20	2.91	>1.00	>1.00
HT29	3.82		>1.00	>1.00
KM12	1.66		>1.00	>1.00
SW-620	2.20		>1.00	>1.00
CNS Cancer				
SF-268	1.36		>1.00	>1.00
SF-295	4.73		>1.00	>1.00
SF-539	4.06	3.65	4.74	>1.00
SNB-19	5.37		>1.00	>1.00
SNB-75	2.21		1.51	>1.00
U251	4.18		7.23	>1.00
Melanoma				
LOX IMVI	4.83		>1.00	>1.00
MALME-3M	3.85		>1.00	>1.00
M14	2.36		>1.00	>1.00
MDA-MB-435	2.69	3.64	8.37	>1.00
SK-MEL-2	1.82		>1.00	>1.00
SK-MEL-28	3.13		>1.00	>1.00
SK-MEL-5	8.48		>1.00	>1.00
UACC-257	-----		>1.00	>1.00
UACC-62	1.99		>1.00	>1.00

Continued Table 2

Panel/ Cell line	GI_{50} μM	MGMID μM	TGI μM	LD_{50} μM
Ovarian Cancer				
IGROV-1	3.50		>1.00	
OVCAR-3	3.25		1.52	>1.00
OVCAR-4	2.68	3.11	----	>1.00
OVCAR-5	2.19		>1.00	>1.00
OVCAR-8	5.17		>1.00	>1.00
NCI/ADR-RES	1.64		>1.00	>1.00
SK-OV-3	3.36		4.88	>1.00
Renal Cancer				
786-D	5.70		>1.00	>1.00
A498	1.13		3.19	>1.00
ACHN	5.59		>1.00	>1.00
CAKI-1	1.00	3.04	>1.00	>1.00
RXF-393	2.76		3.00	>1.00
SN12C	5.54		>1.00	>1.00
TK-10	1.34		8.84	>1.00
UO-31	1.27		>1.00	>1.00
Prostate Cancer				
PC-3	8.13	6.01	>1.00	>1.00
DU-145	3.90		>1.00	>1.00
Breast Cancer				
MCF-7	2.70		>1.00	>1.00
MDA-MB-231/ATCC	4.53		>1.00	>1.00
HS 578T	2.82	3.65	>1.00	>1.00
BT-549	1.65		9.94	>1.00
T-47D	7.55		>1.00	>1.00
MDA-MB-468	2.69		5.76	>1.00

Fig. 1 Reported 1,2,4-triazole derivatives bearing heterocyclic substituent



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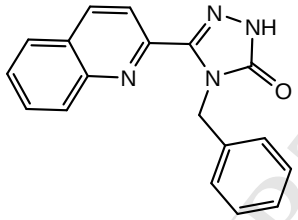

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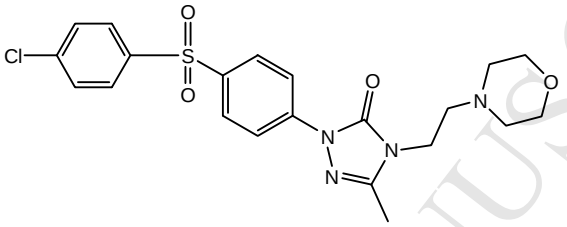
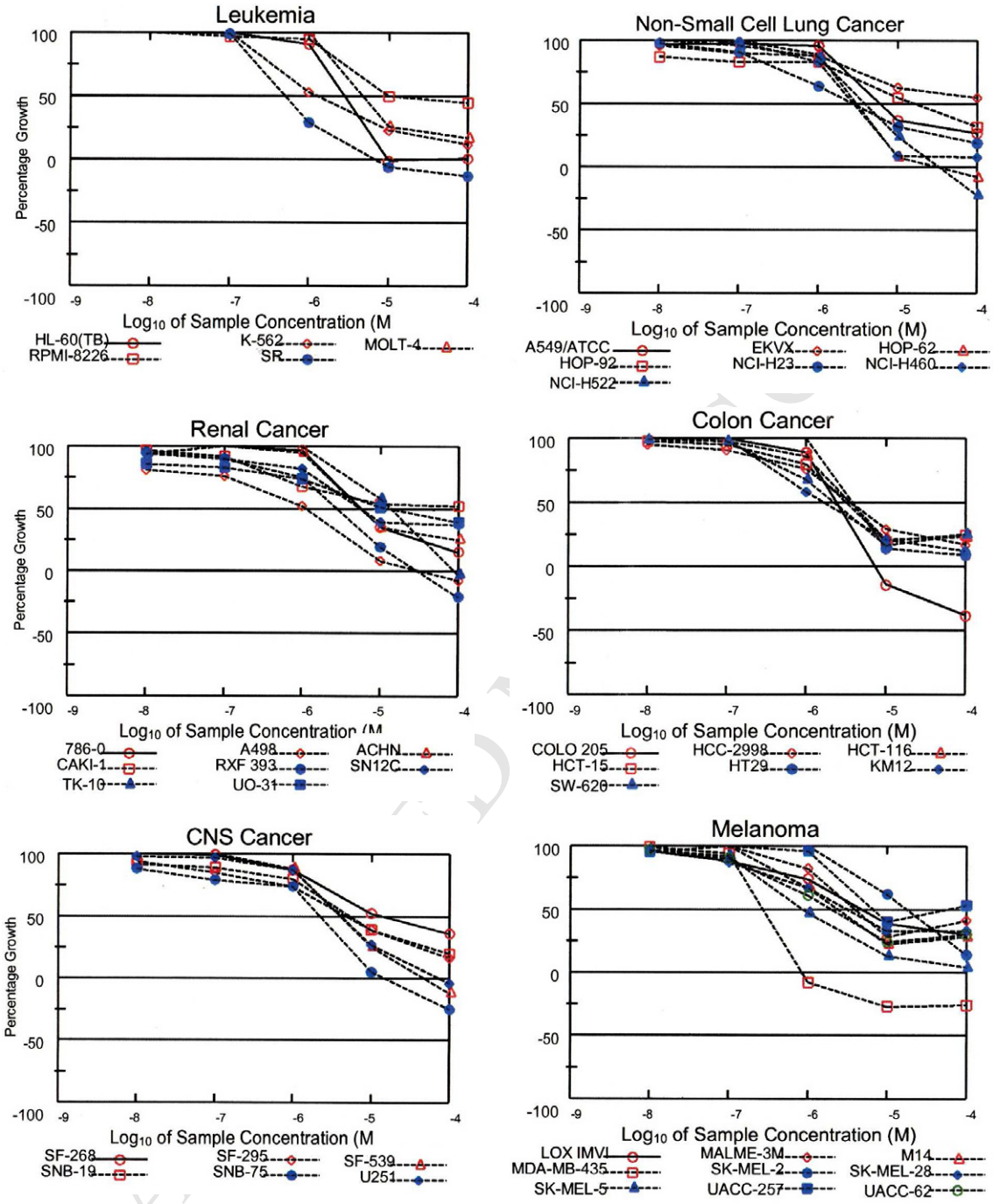


c

Fig. 2 Dose response curve of eight sub-panel cell lines for compound **5g**



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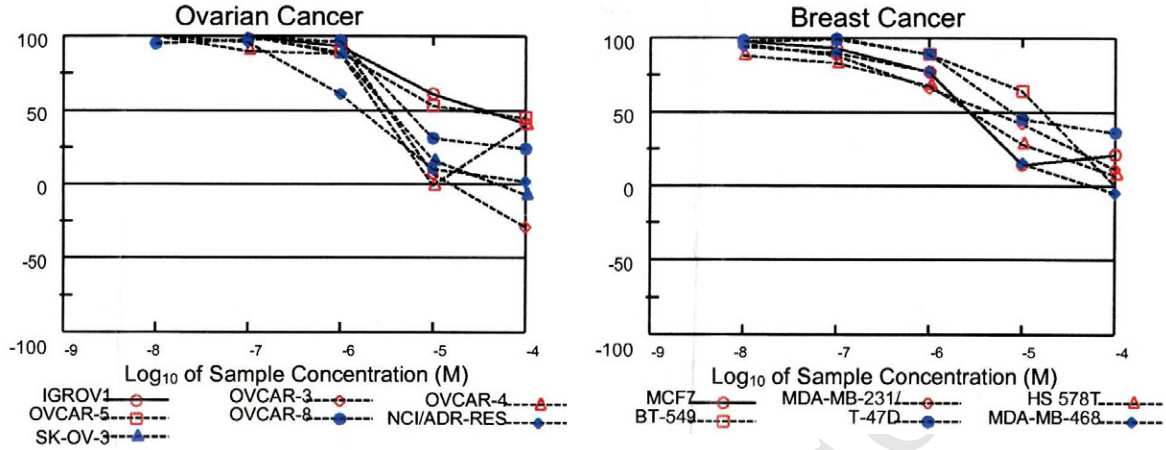
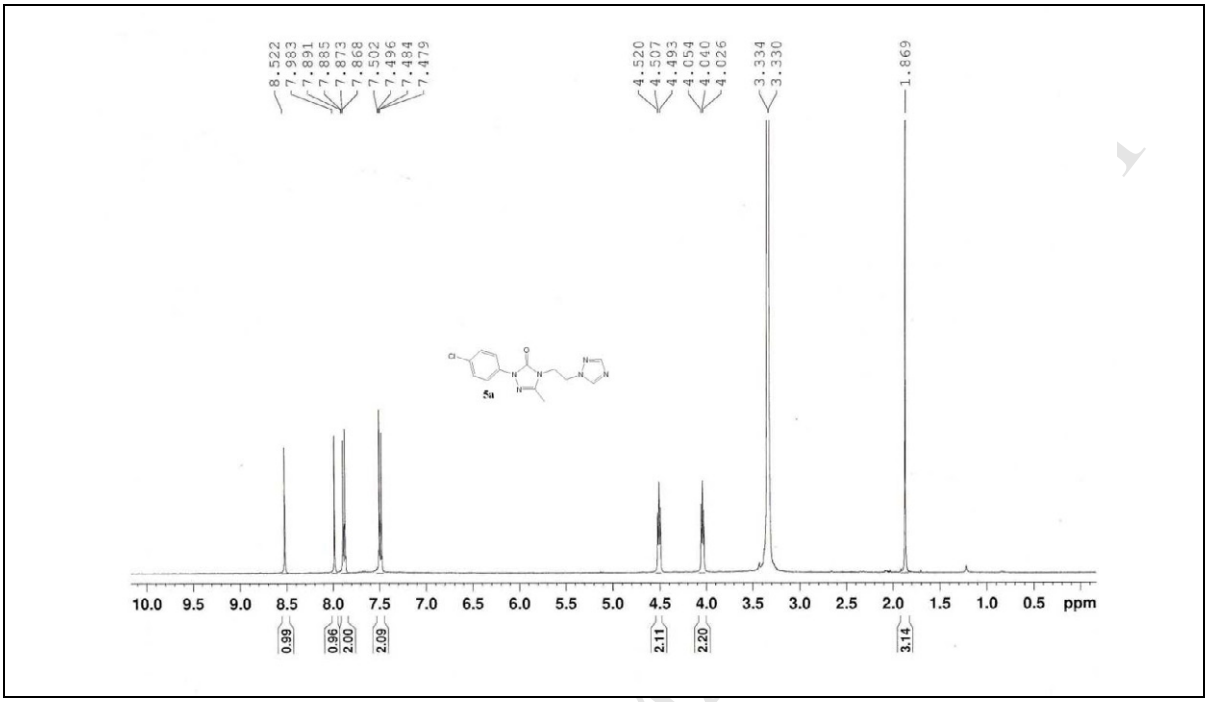
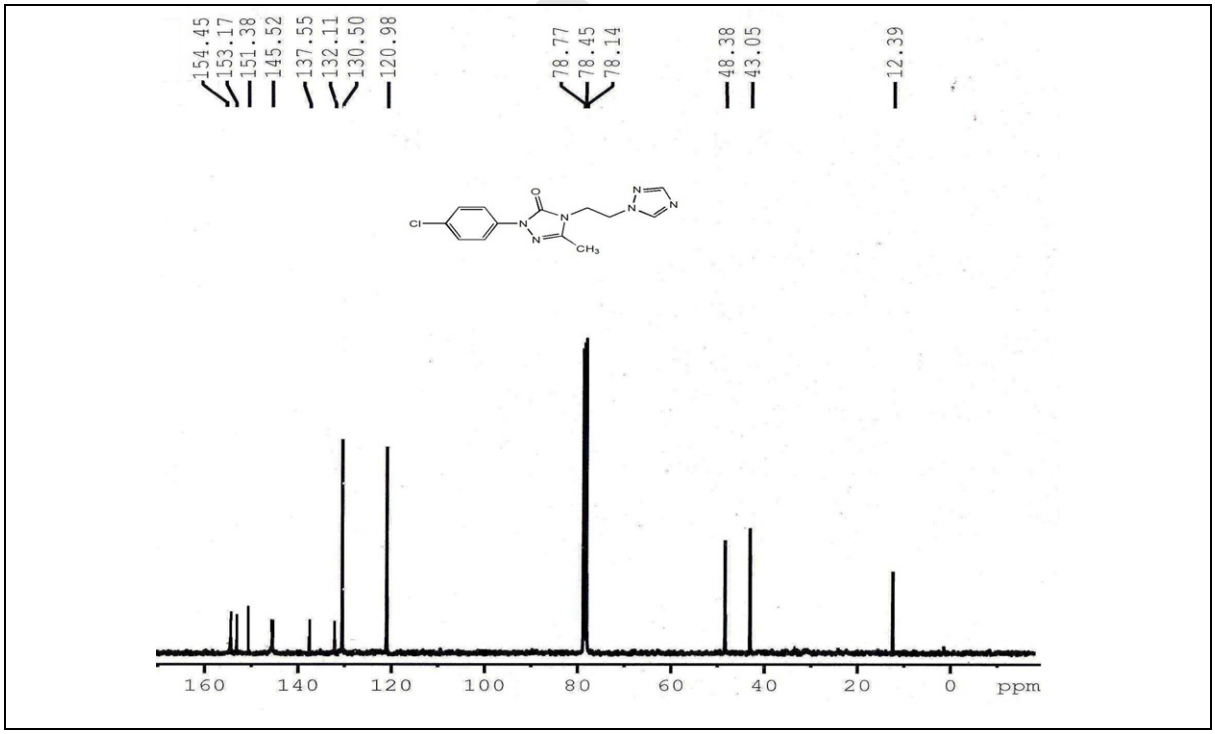


Supplementary information: Spectral data of synthesized compounds

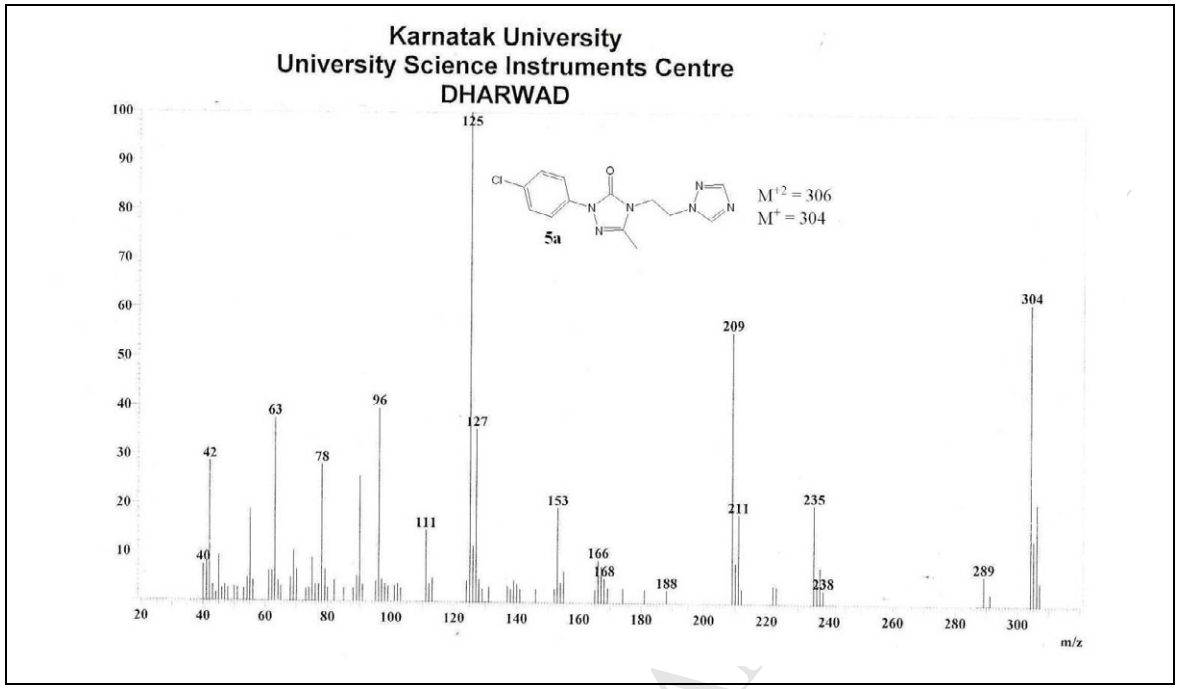
^{1}H-NMR spectrum of compound **5a**



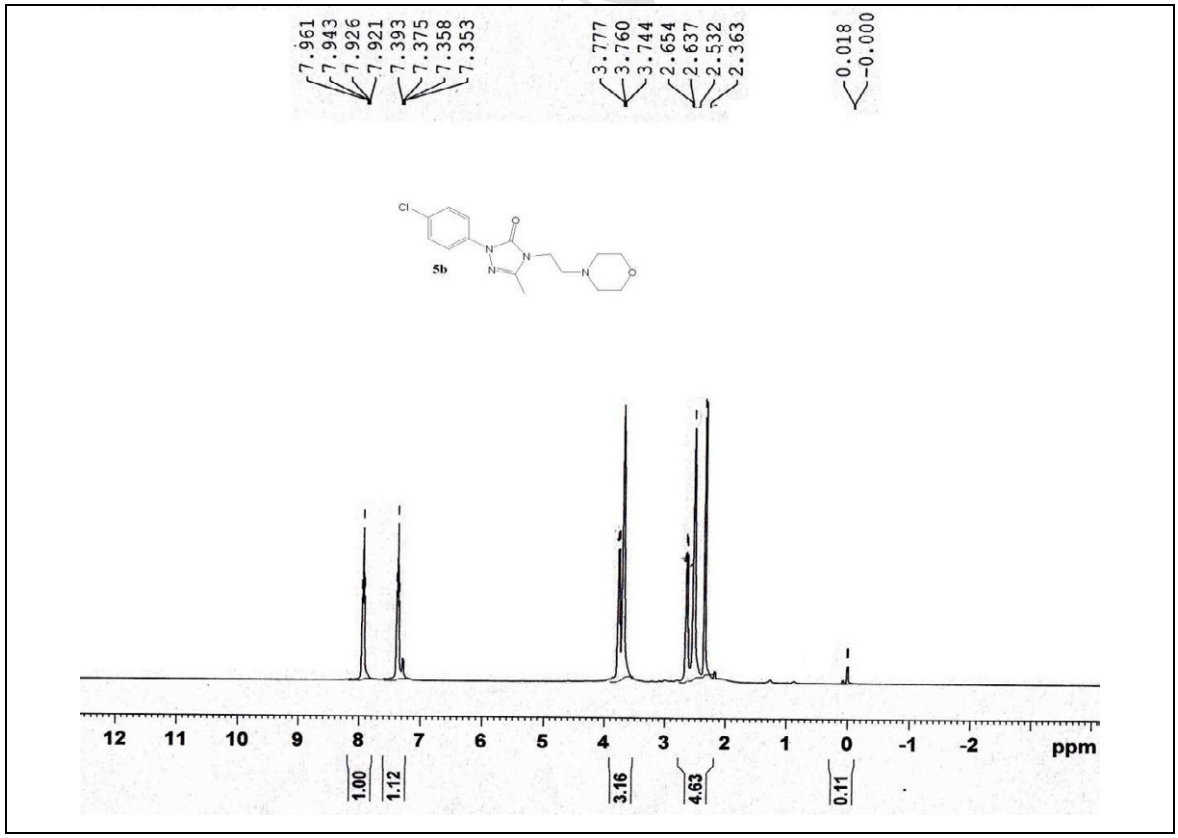
^{13}C-NMR spectrum of compound **5a**



Mass Spectrum of compound **5a**

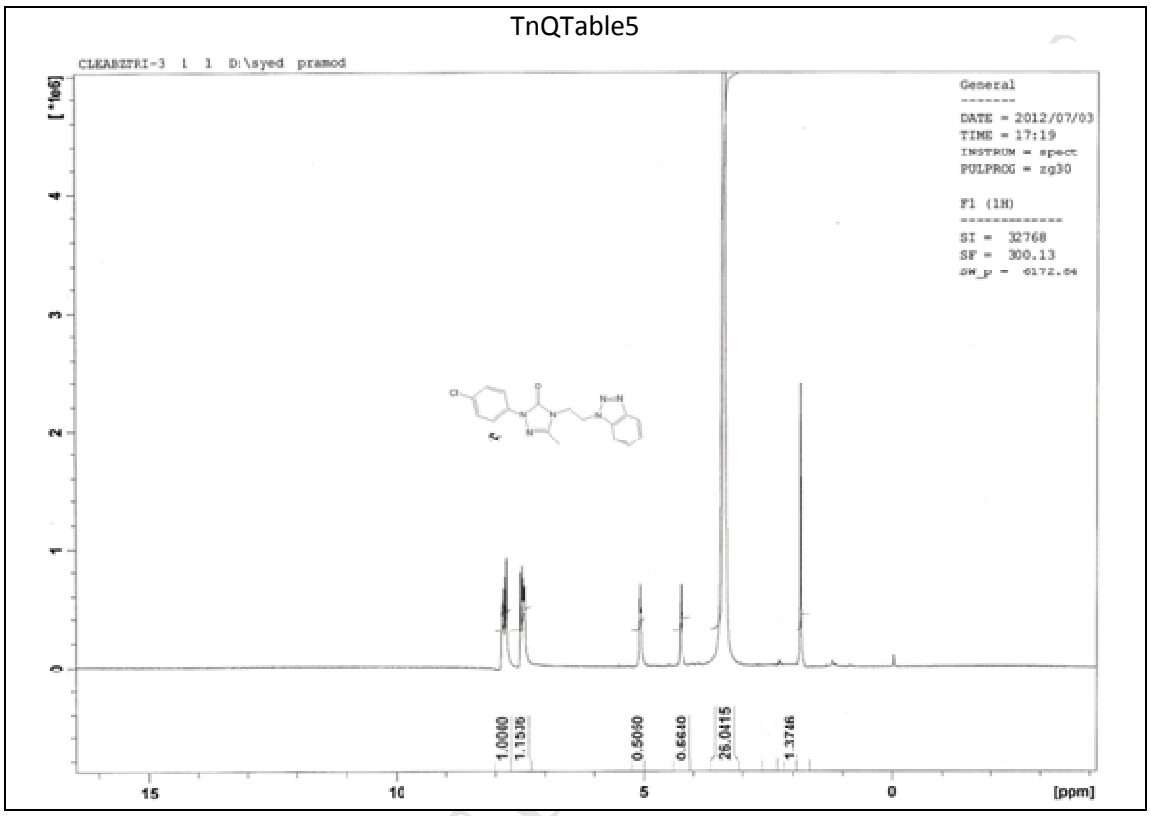


^{1}H-NMR spectrum of compound **5b**



^{13}C-NMR spectrum of compound **5b**

^{1}H-NMR spectrum of compound **5c**



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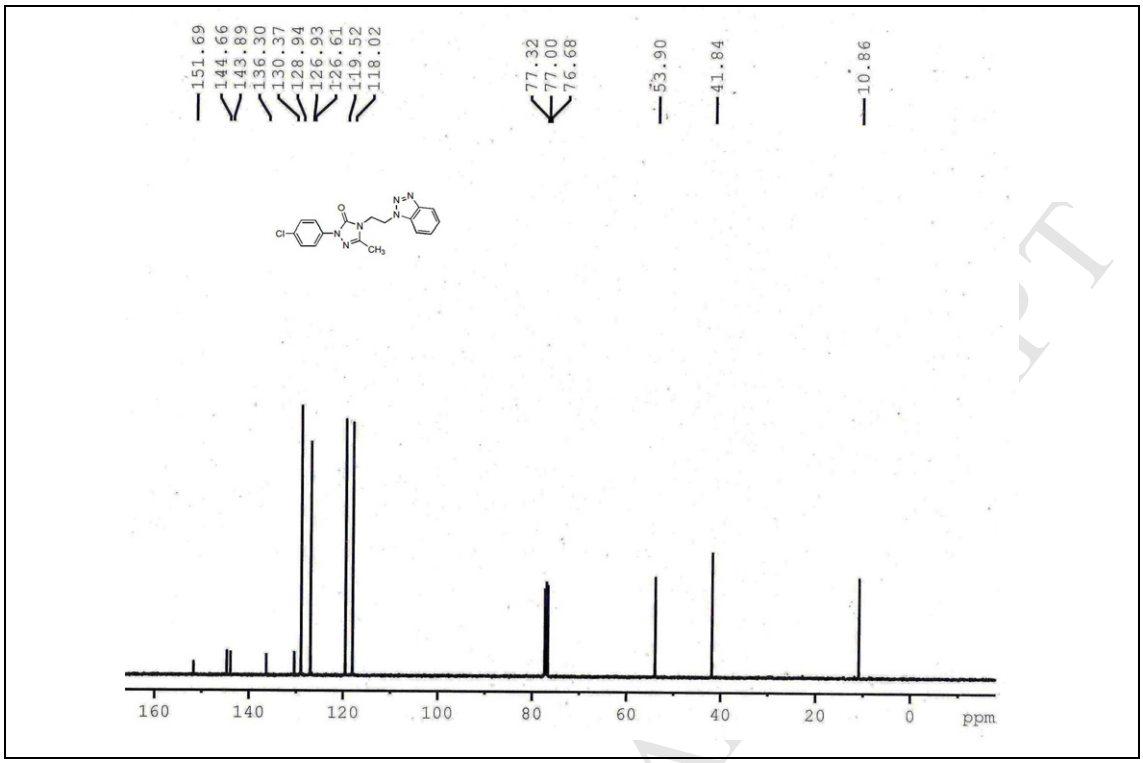
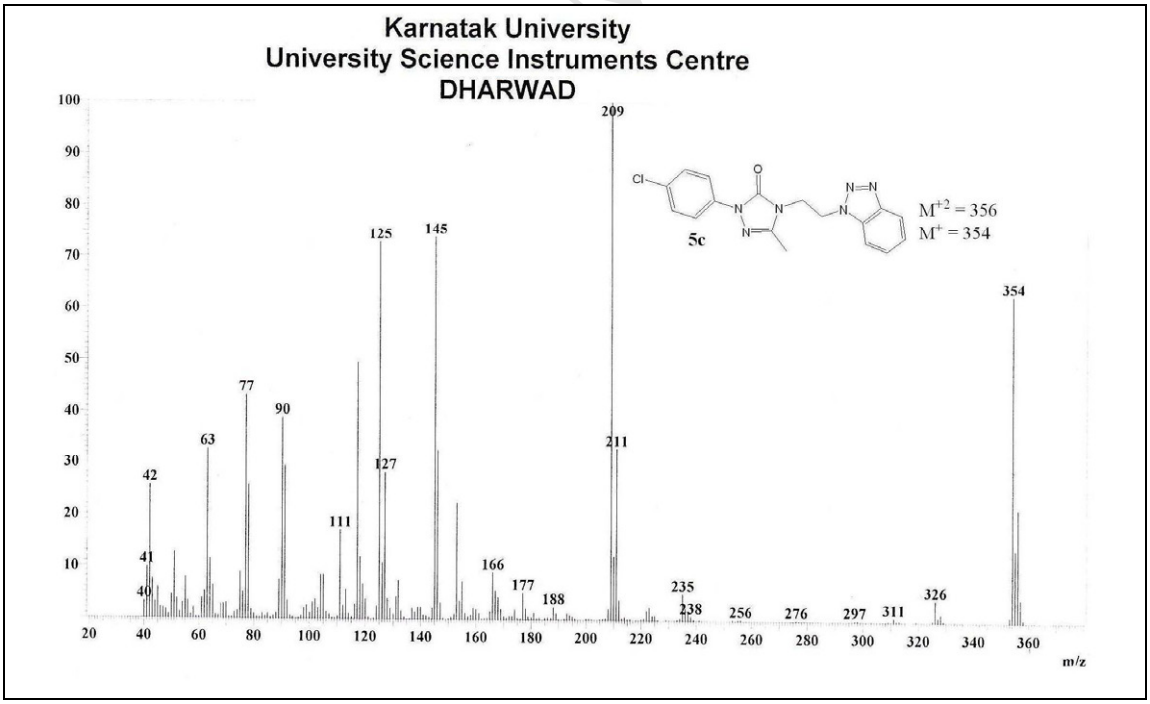
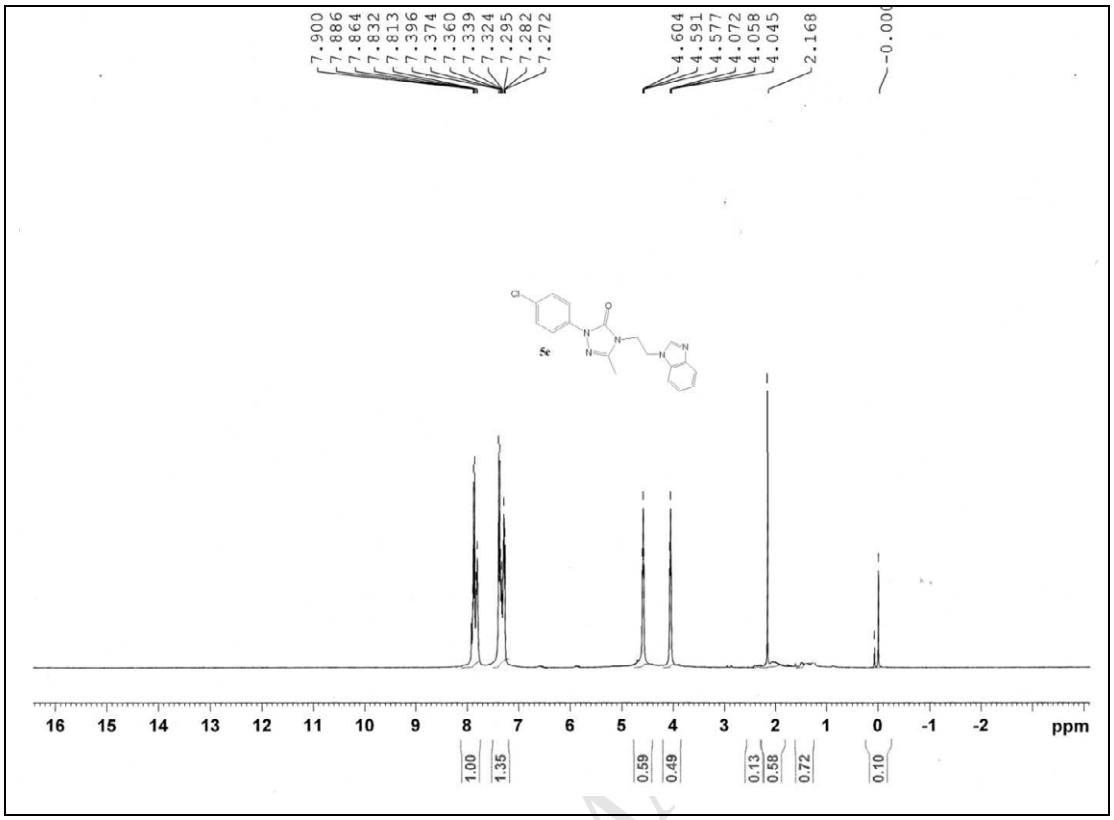


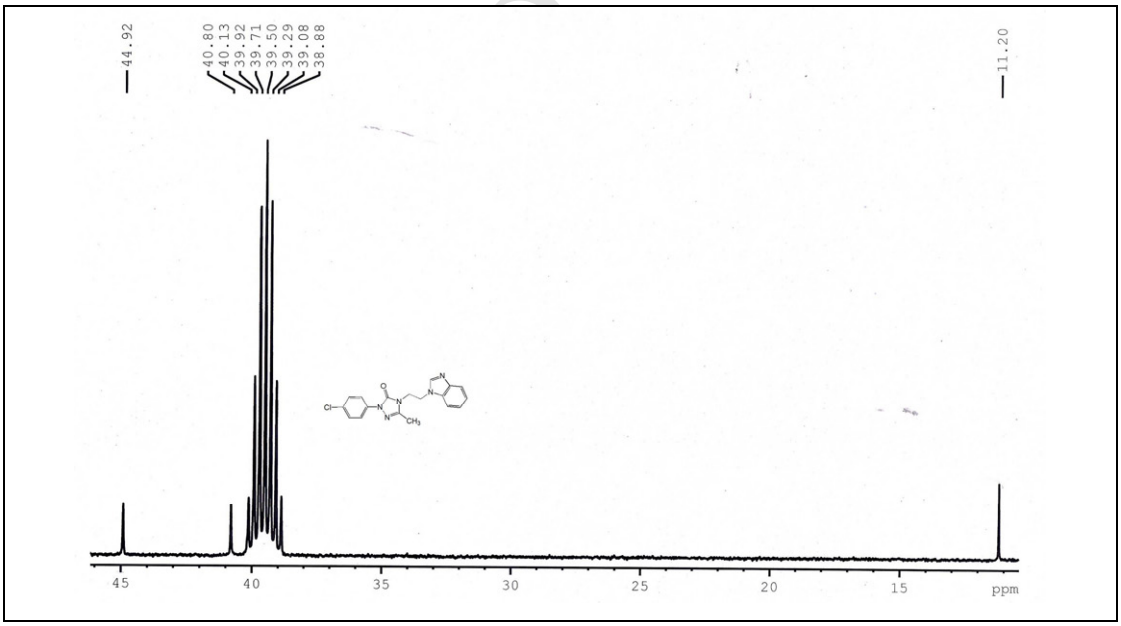
Mass spectrum of compound **5c**



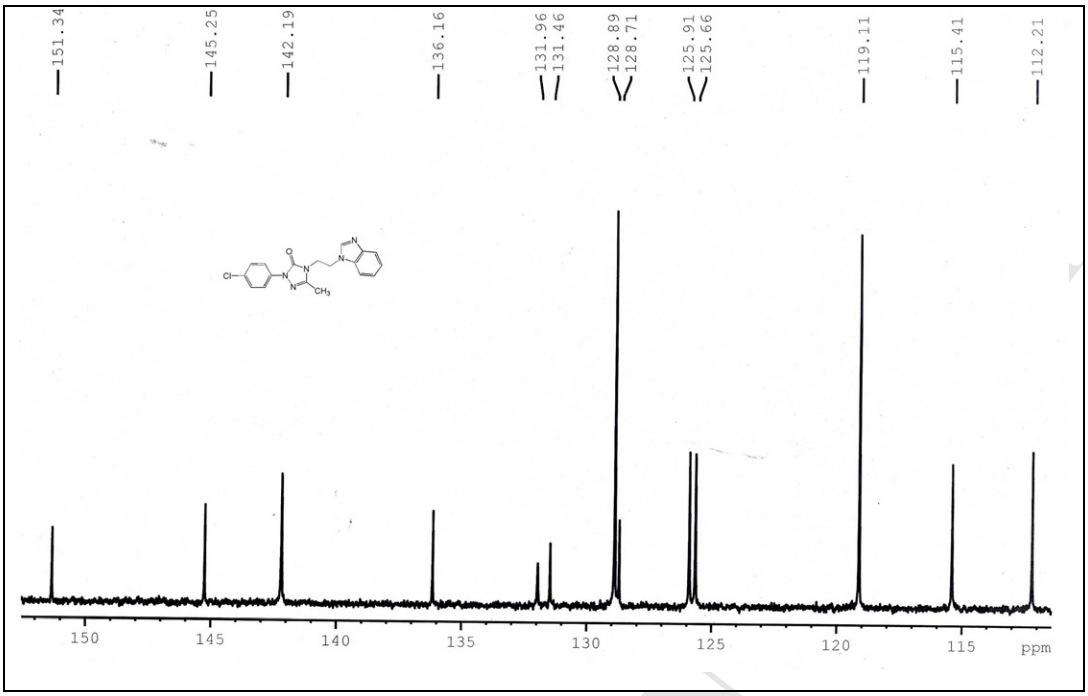
^{1}H-NMR spectrum of compound **5e**



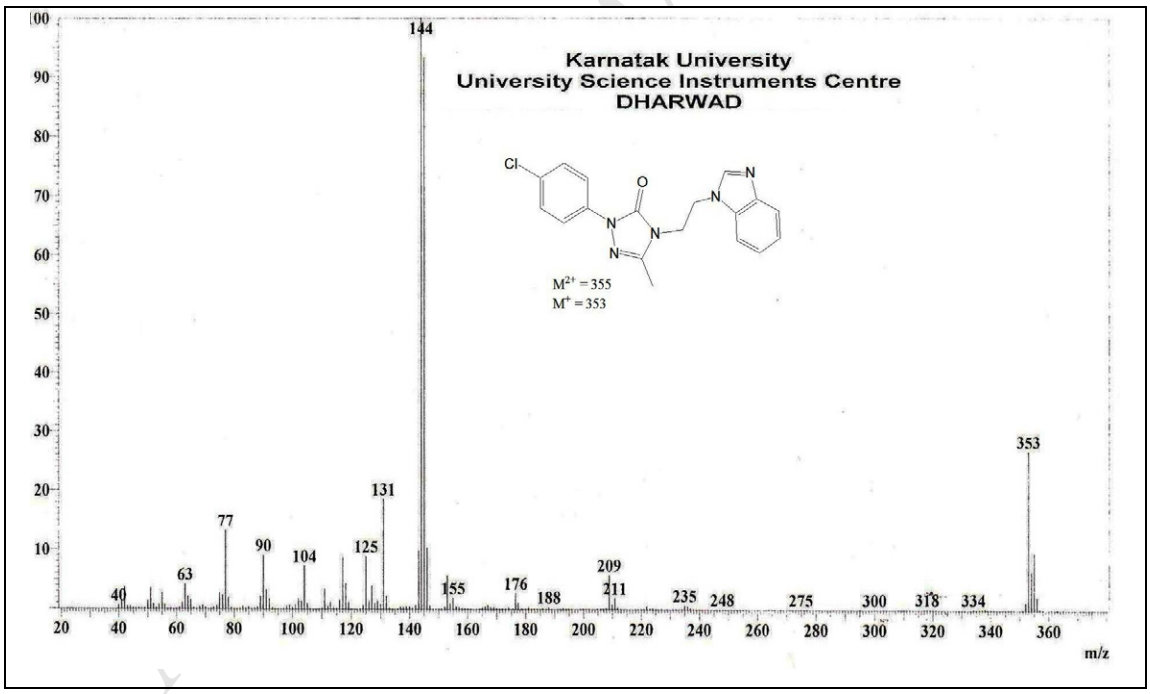
^{13}C-NMR spectrum of compound **5e**



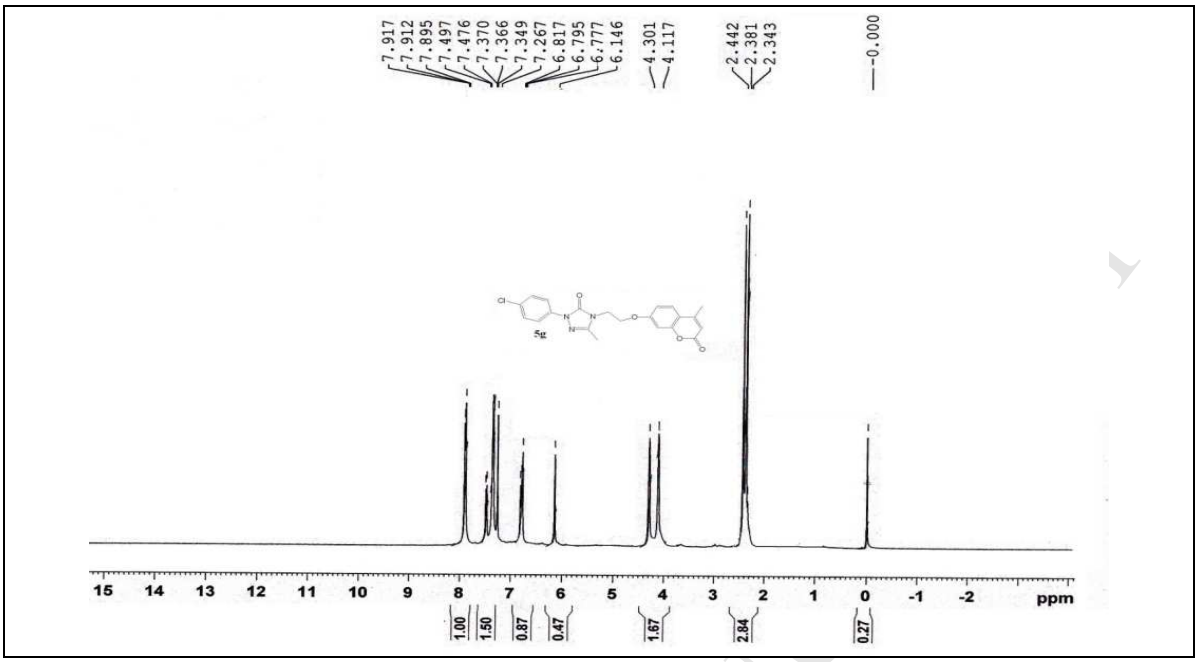
^{13}C-NMR spectrum of compound **5e**



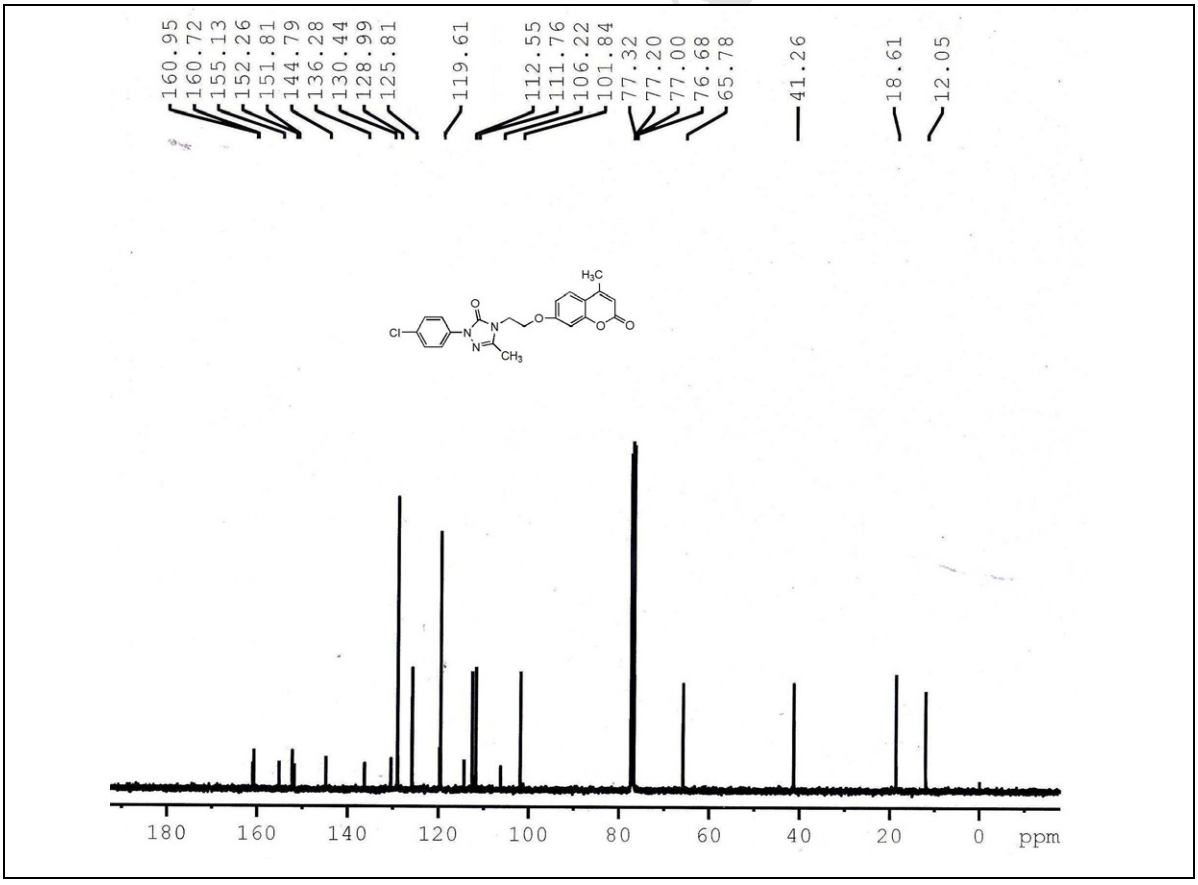
Mass spectrum of compound **5e**



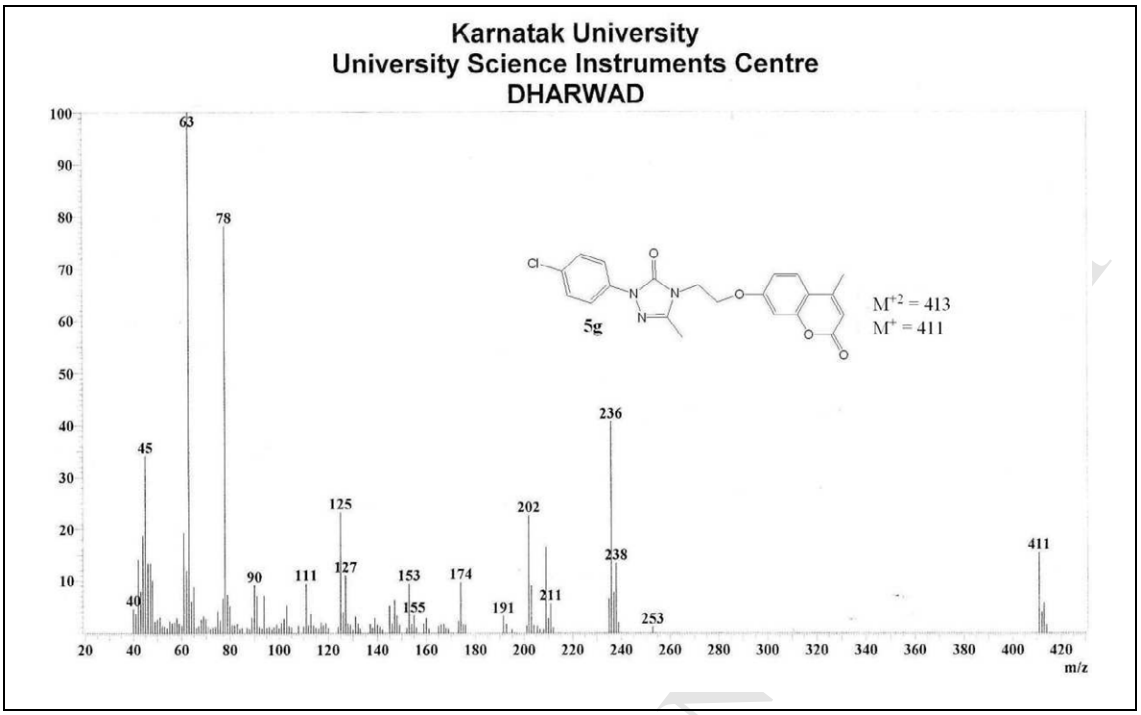
^{1}H-NMR spectrum of compound **5g**



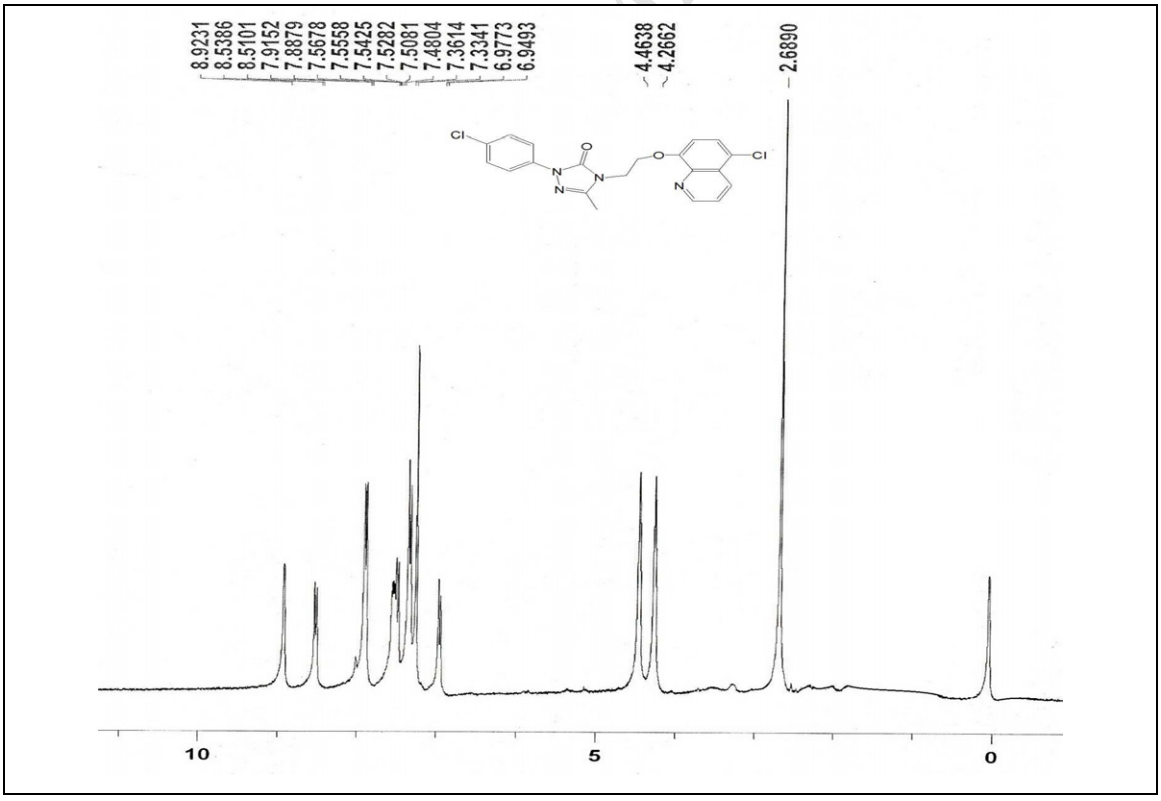
^{13}C-NMR spectrum of compound **5g**



Mass spectrum of compound **5g**



^{1}H-NMR spectrum of compound **5h**



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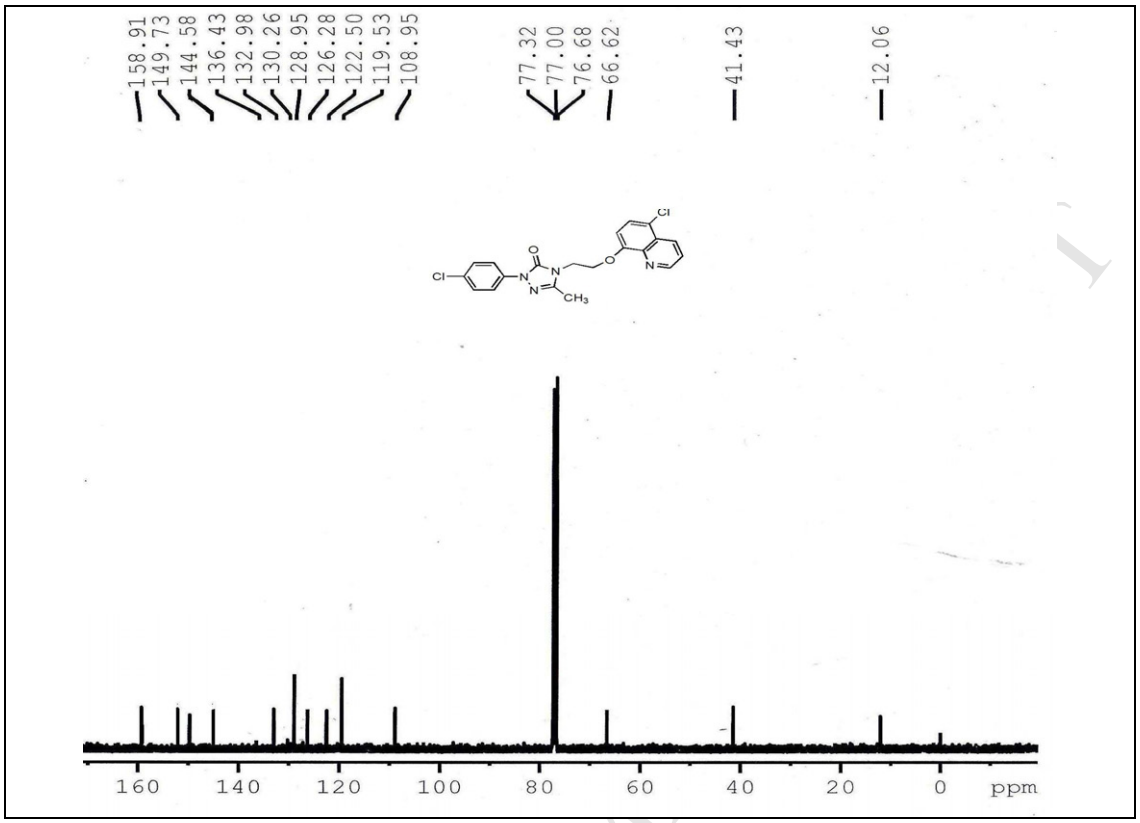
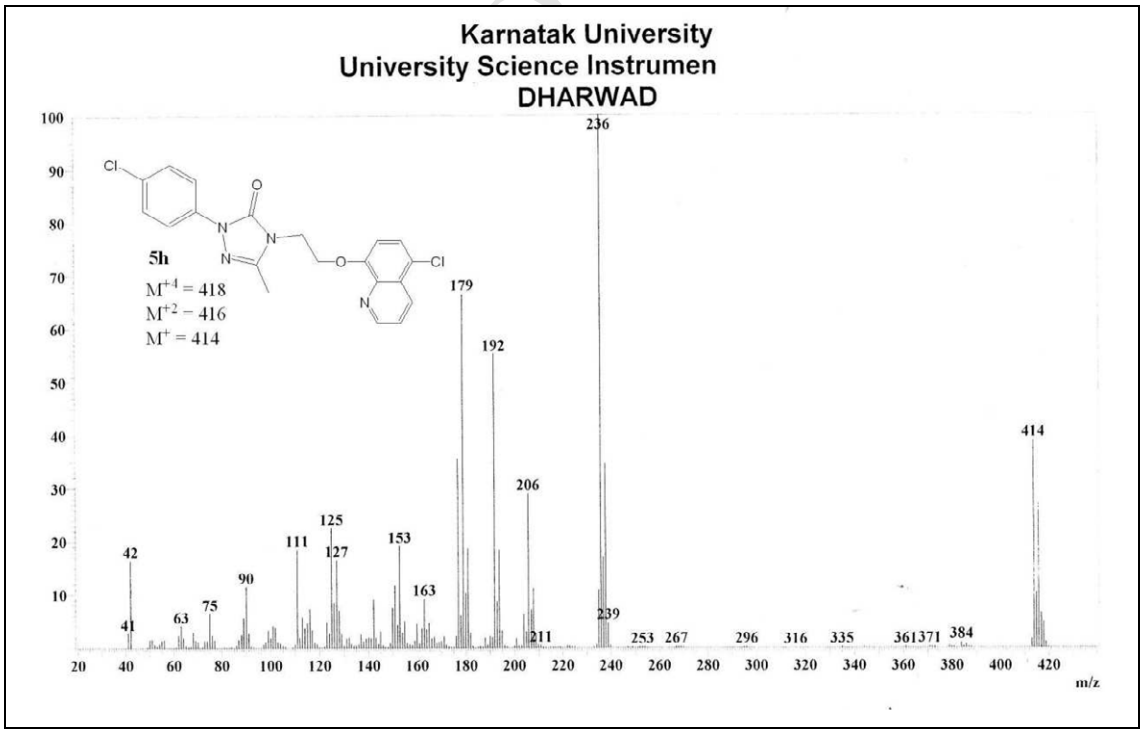
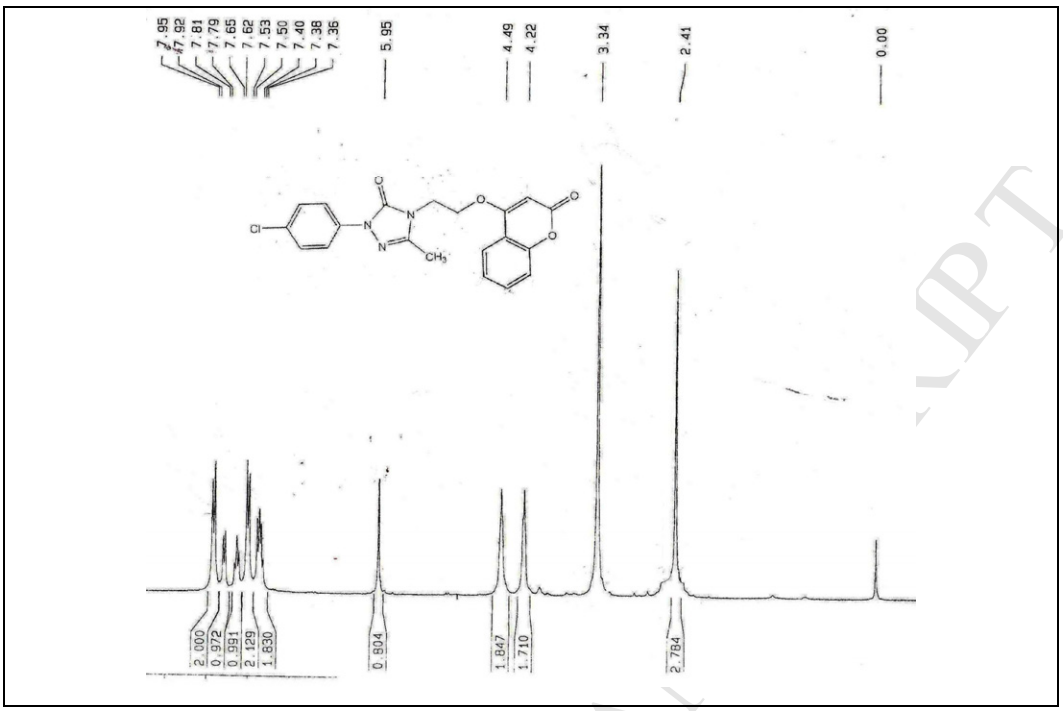


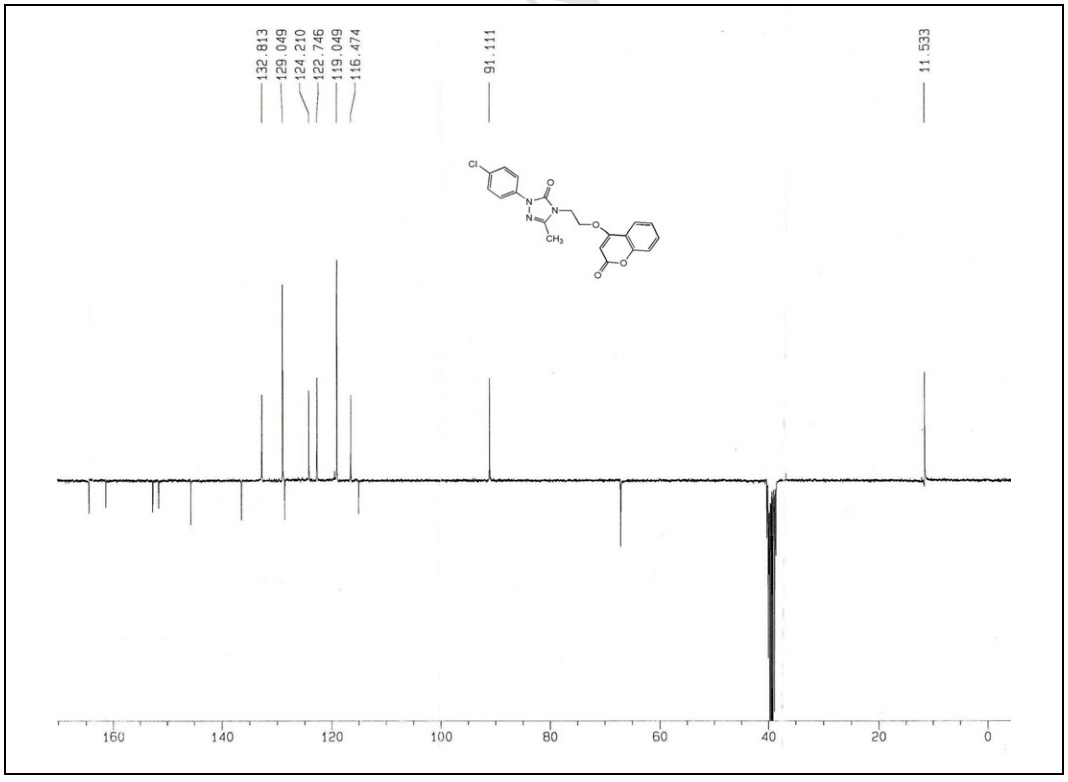
Mass spectrum of compound **5h**



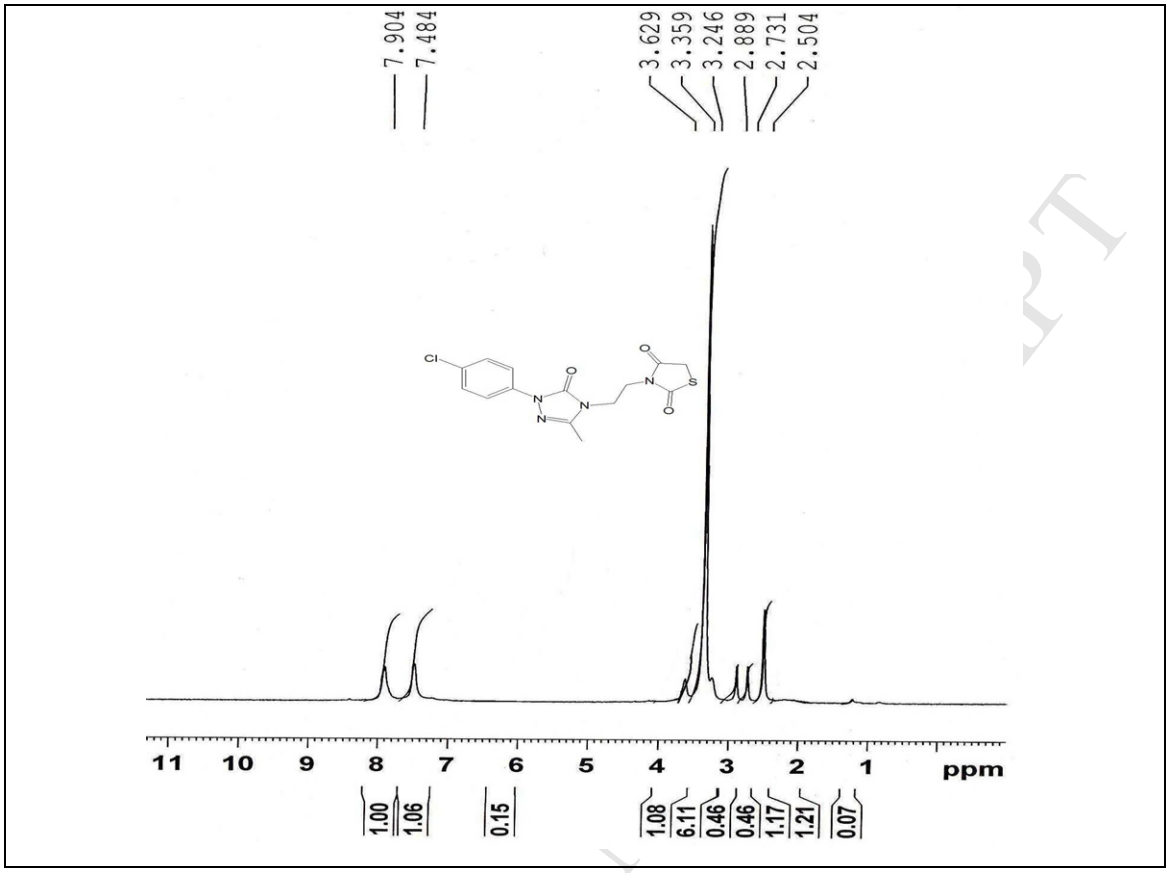
^{1}H-NMR spectrum of compound **5i**



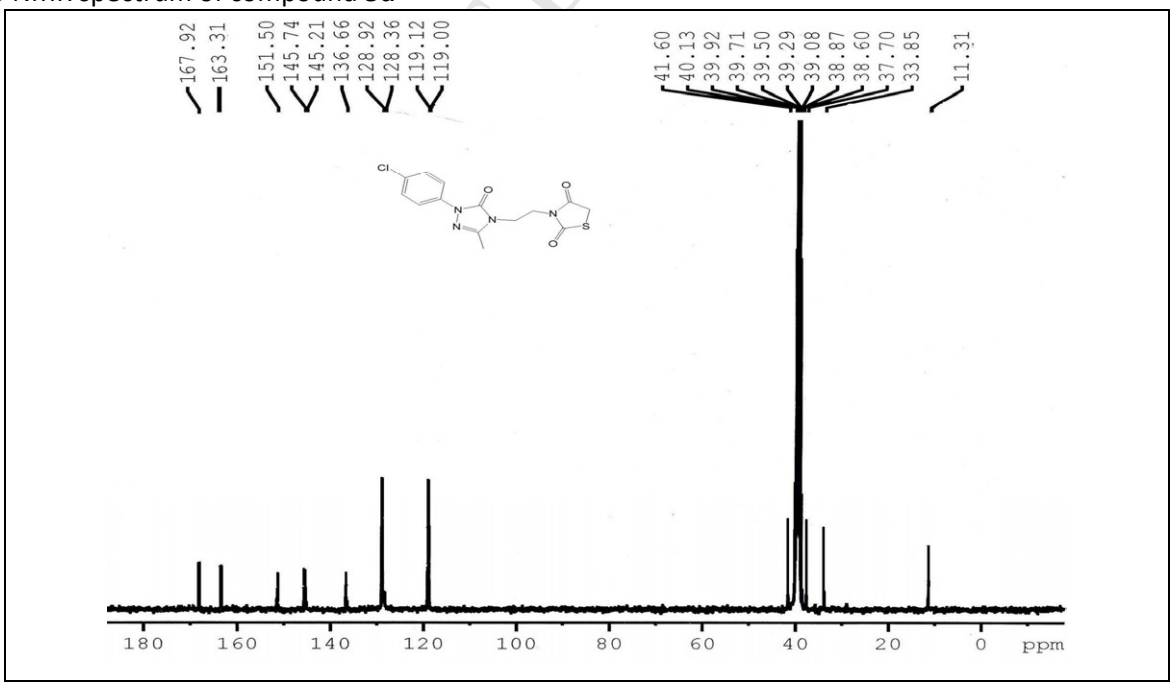
^{13}C-NMR spectrum of compound **5i**



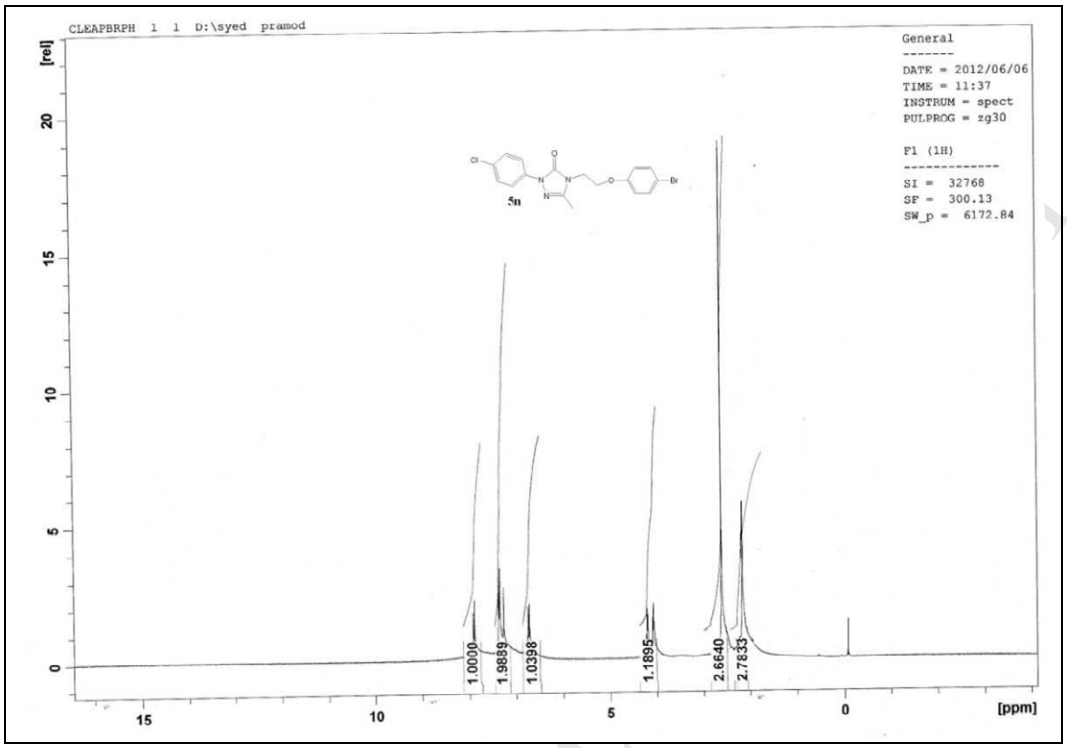
^{1}H-NMR spectrum of compound **5d**



^{13}C-NMR spectrum of compound **5d**



^{1}H-NMR spectrum of compound **5n**



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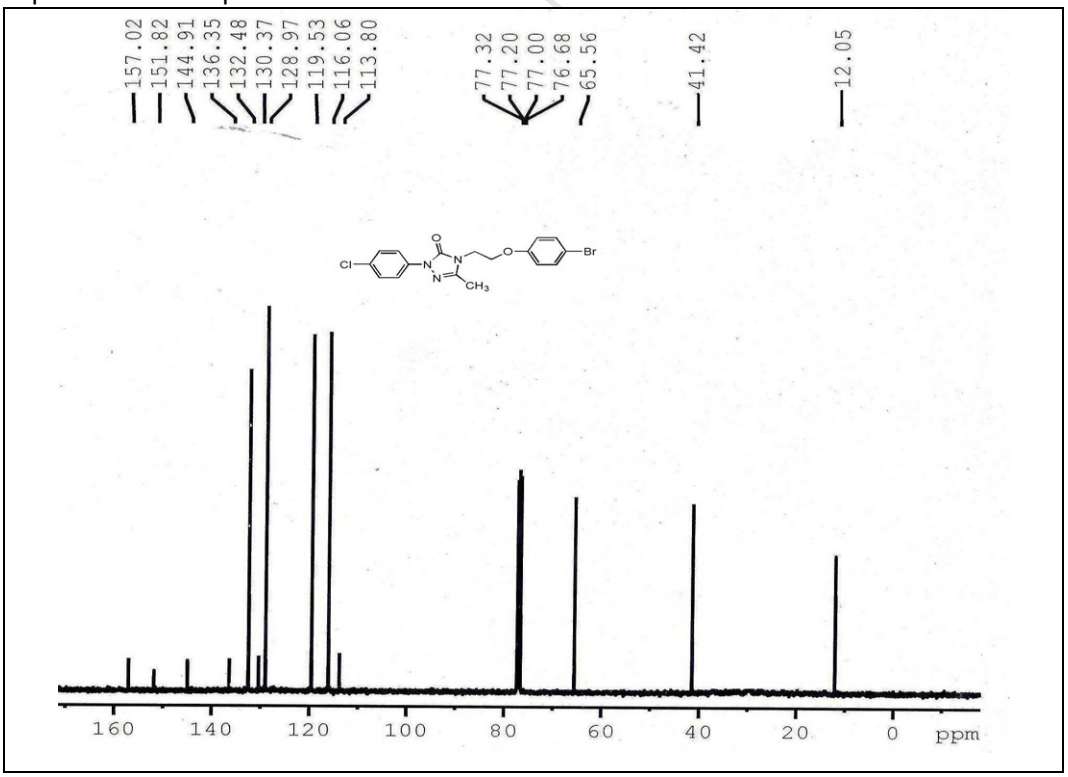
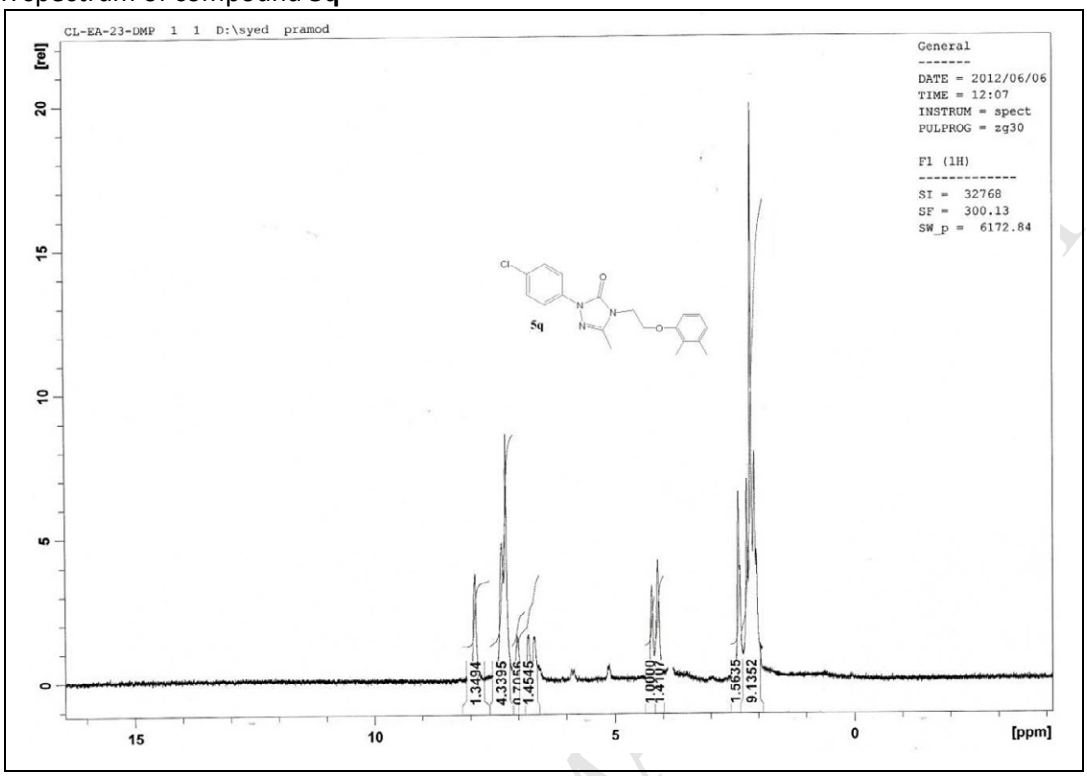
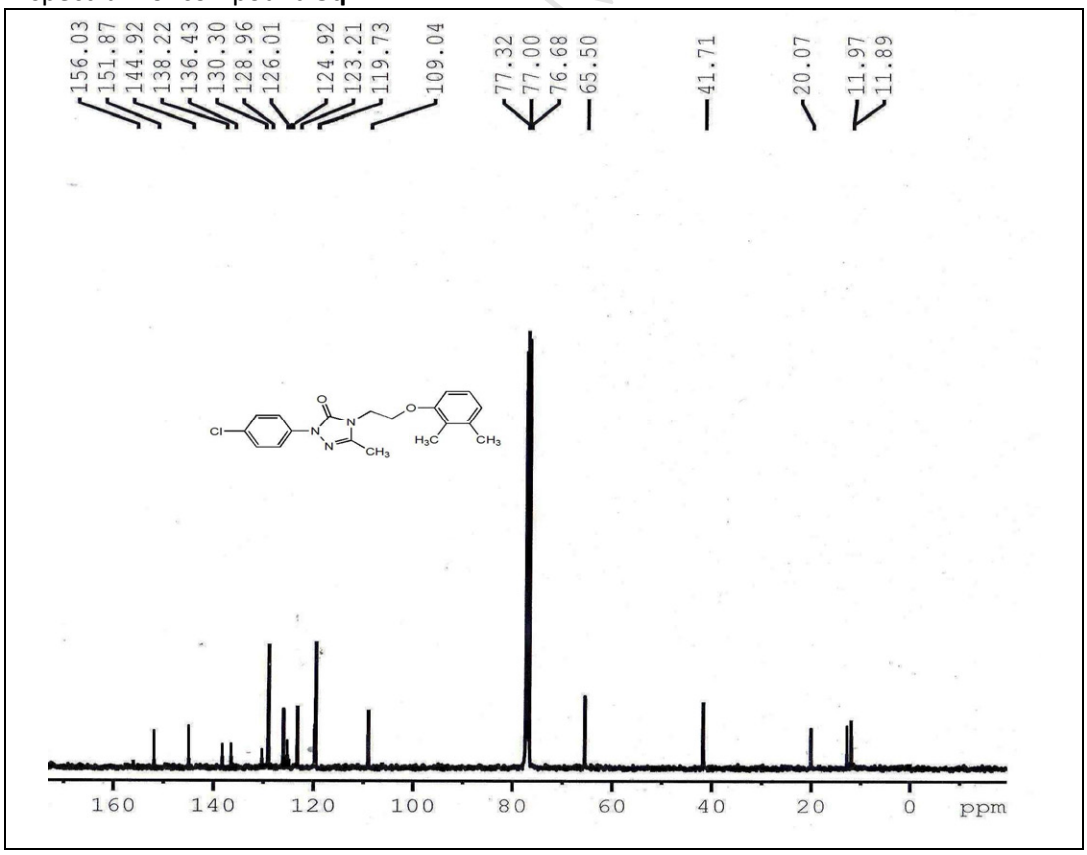


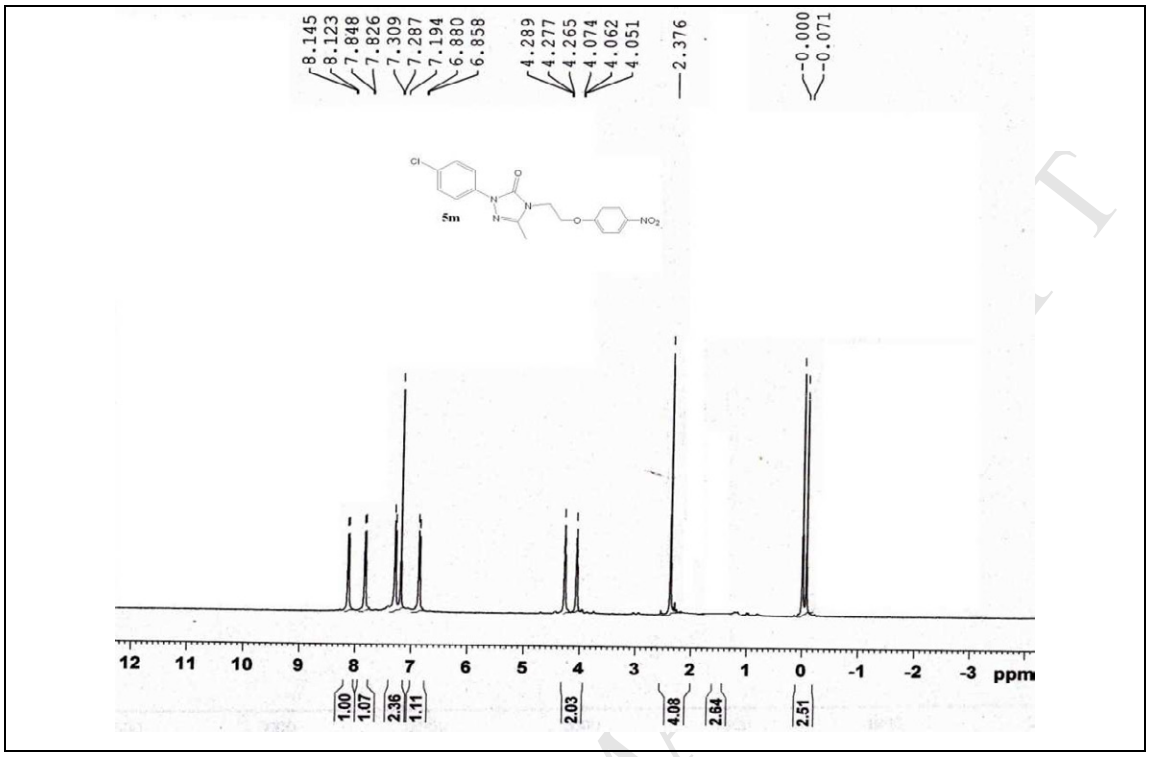
^{1}H-NMR spectrum of compound **5q**



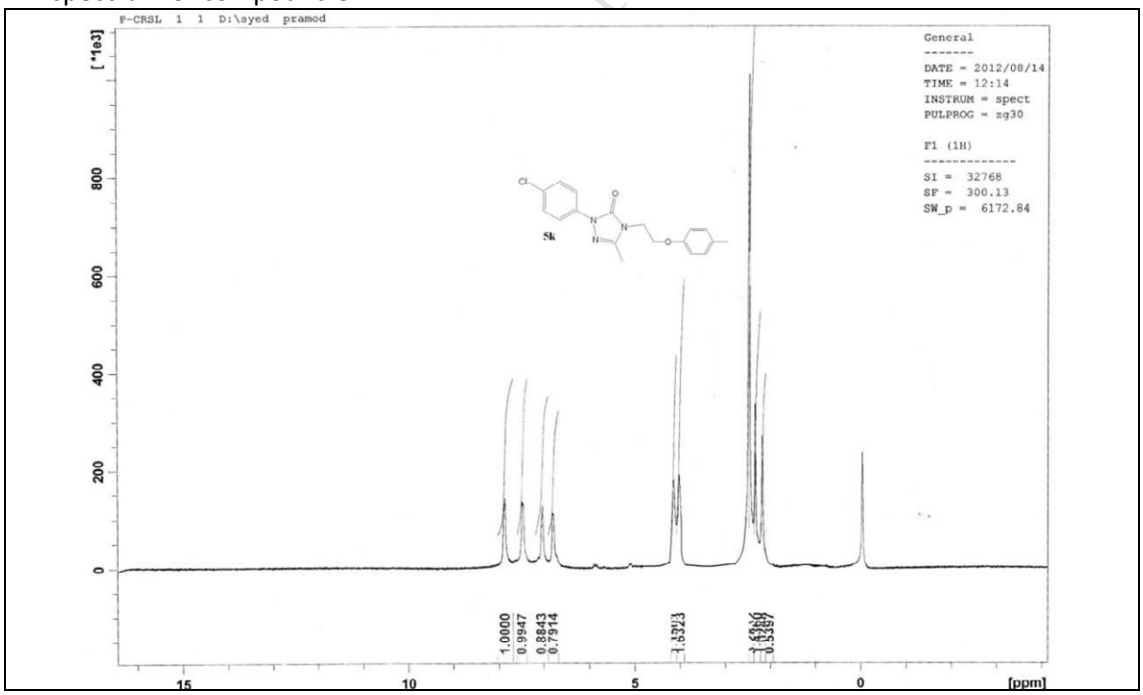
^{13}C-NMR spectrum of compound **5q**



^{1}H-NMR spectrum of compound **5m**



^{1}H-NMR spectrum of compound **5k**



^{1}H-NMR spectrum of compound **5p**

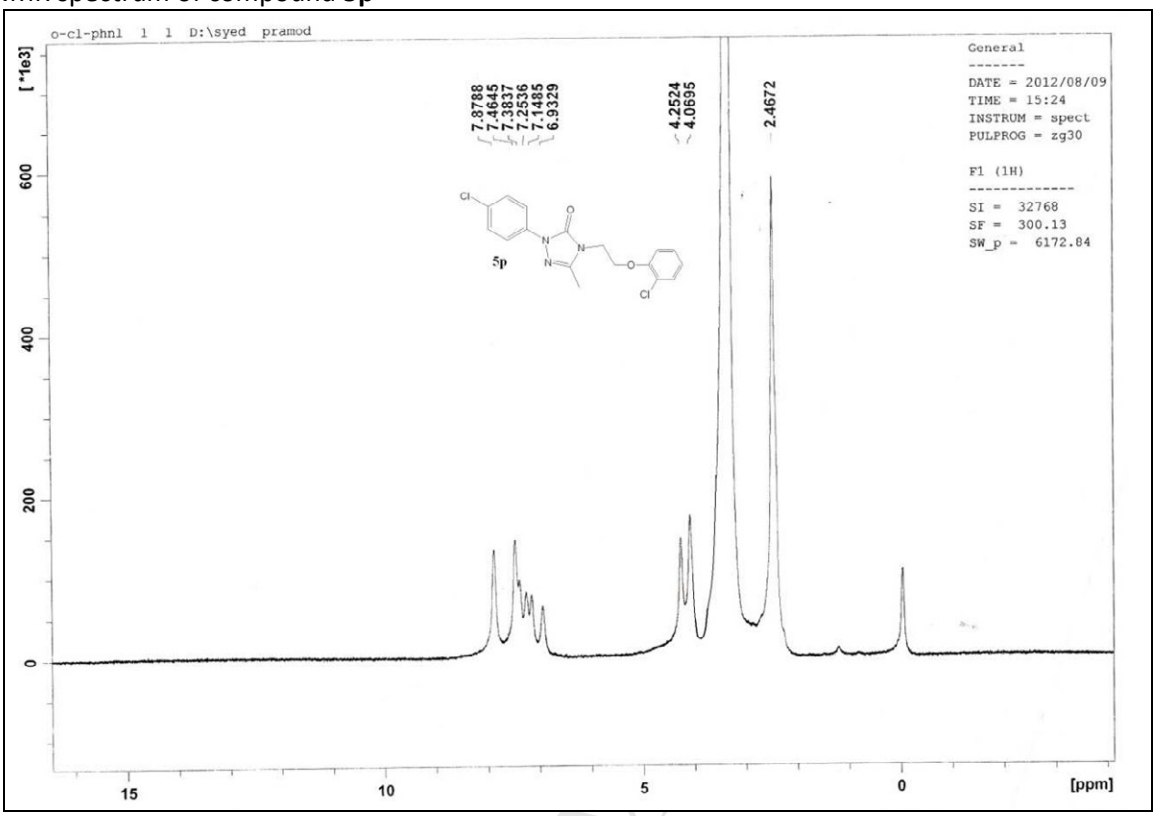
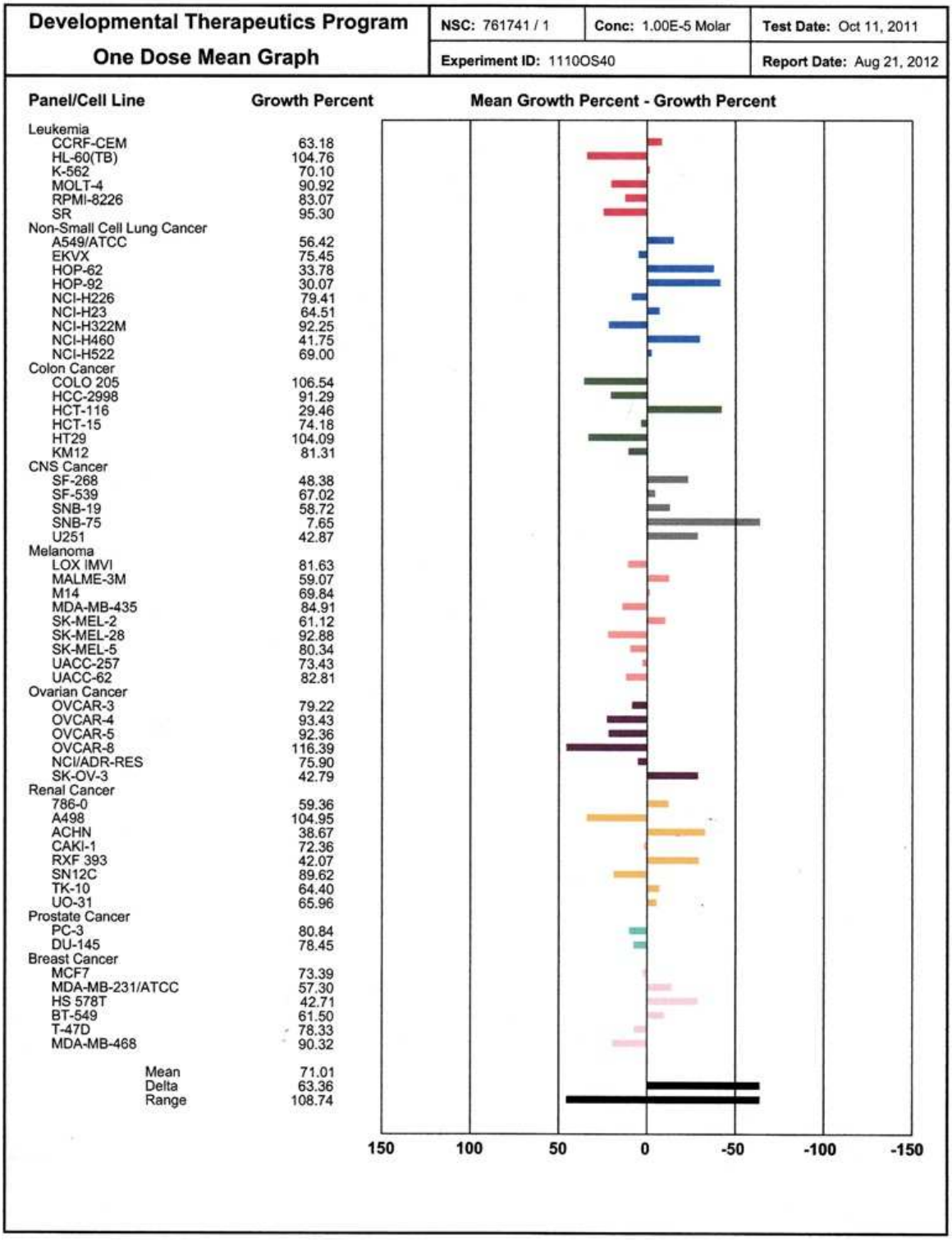


Fig. 1 *In vitro* anticancer screening data (growth percentage) on the 60 human cancer cell line in single dose assay (10^{-5} M concentration) for compound **5b**



Developmental Therapeutics Program
One Dose Mean Graph

NSC: 761741 / 1 | Conc: 1.00E-5 Molar | Test Date: Oct 11, 2011
Experiment ID: 1110OS40 | Report Date: Aug 21, 2012

Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	63.18
HL-60(TB)	104.76
K-562	70.10
MOLT-4	90.92
RPMI-8226	83.07
SR	95.30
Non-Small Cell Lung Cancer	
A549/ATCC	56.42
EKVX	75.45
HOP-62	33.78
HOP-92	30.07
NCI-H226	79.41
NCI-H23	64.51
NCI-H322M	92.25
NCI-H460	41.75
NCI-H522	69.00
Colon Cancer	
COLO 205	106.54
HCC-2998	91.29
HCT-116	29.46
HCT-15	74.18
HT29	104.09
KM12	81.31
CNS Cancer	
SF-268	48.38
SF-539	67.02
SNB-19	58.72
SNB-75	7.65
U251	42.87
Melanoma	
LOX IMVI	81.63
MALME-3M	59.07
M14	69.84
MDA-MB-435	84.91
SK-MEL-2	61.12
SK-MEL-28	92.88
SK-MEL-5	80.34
UACC-257	73.43
UACC-62	82.81
Ovarian Cancer	
OVCAR-3	79.22
OVCAR-4	93.43
OVCAR-5	92.36
OVCAR-8	116.39
NCI/ADR-RES	75.90
SK-OV-3	42.79
Renal Cancer	
786-0	59.36
A498	104.95
ACHN	38.67
CAKI-1	72.36
RXF 393	42.07
SN12C	89.62
TK-10	64.40
UO-31	65.96
Prostate Cancer	
PC-3	80.84
DU-145	78.45
Breast Cancer	
MCF7	73.39
MDA-MB-231/ATCC	57.30
HS 578T	42.71
BT-549	61.50
T-47D	78.33
MDA-MB-468	90.32
Mean	71.01
Delta	63.36
Range	108.74

Mean Growth Percent - Growth Percent

150 100 50 0 -50 -100 -150

Fig. 2 *In vitro* anticancer screening data (growth percentage) on the 60 human cancer cell line in single dose assay (10^{-5} M concentration) for compound **5g**

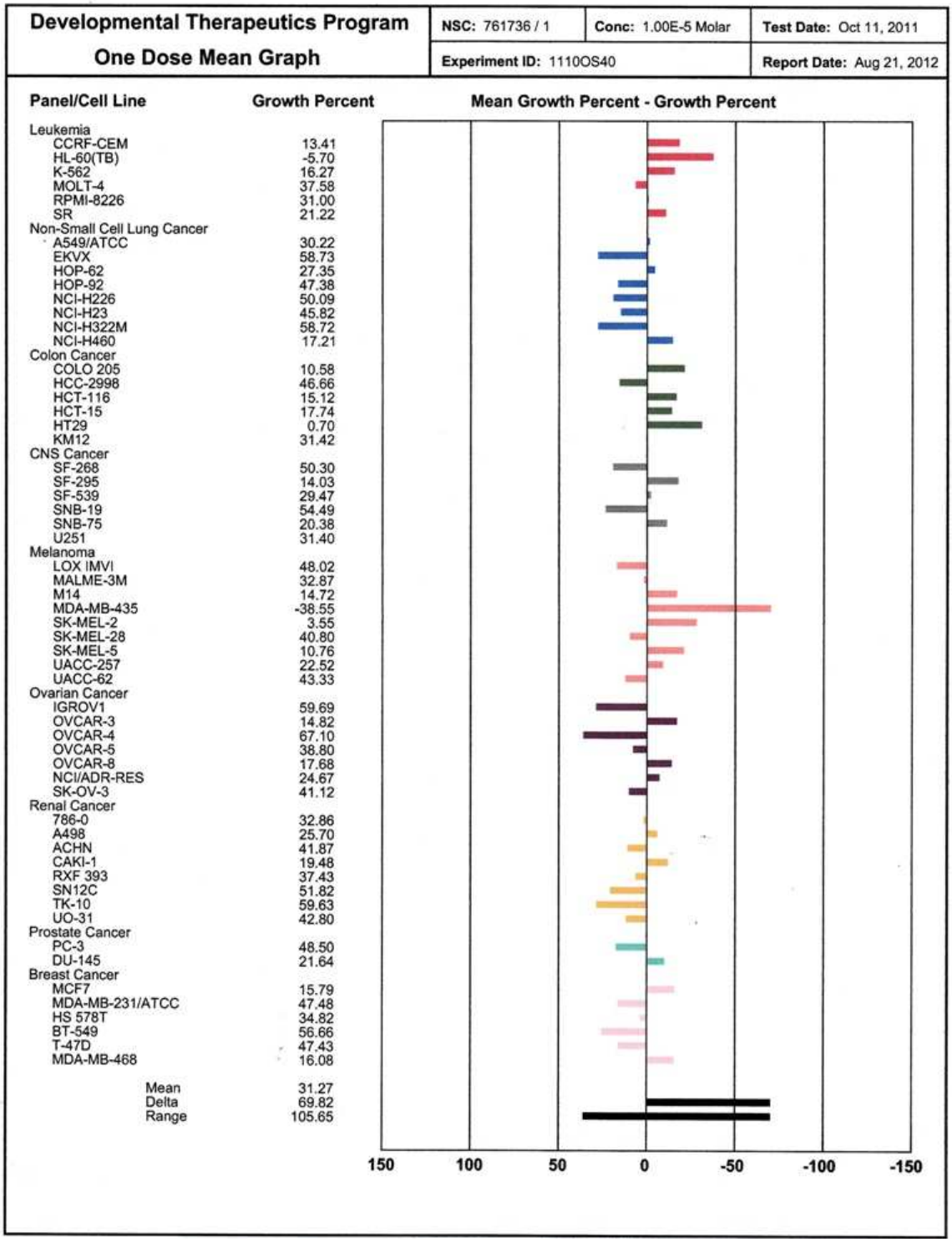


Fig. 3 Log_{10} values of GI_{50}, TGI_{50} and LC_{50} for compound **5g**

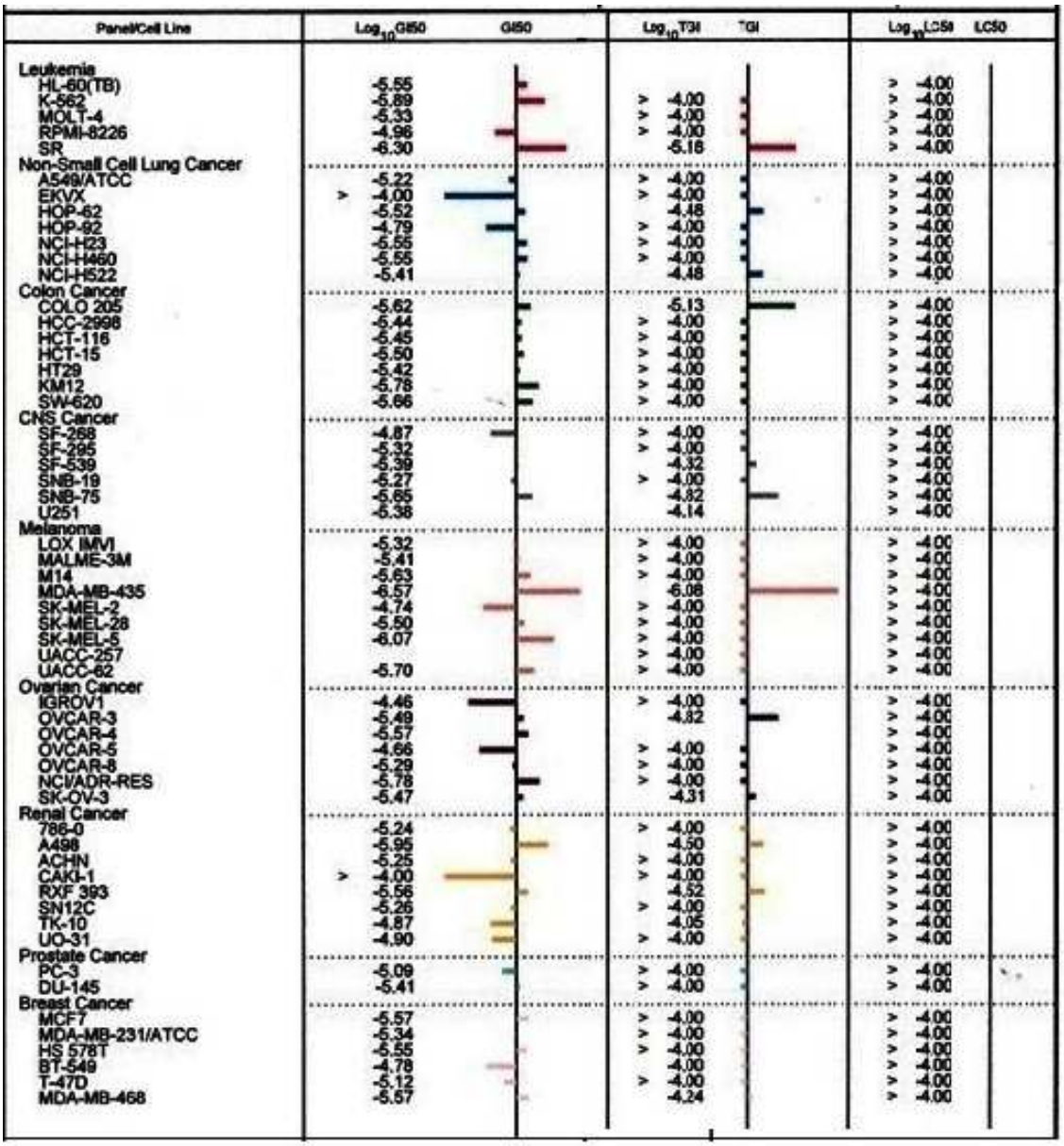


Table 2 GI50, TGI and LC50 values against 60 human cancer cell lines for compound **5g**

National Cancer Institute Developmental Therapeutics Program
In-Vitro Testing Results

NSC : 761736 / 1 | Experiment ID : 1110NS53 | Test Type : 08 | Units : Molar

Report Date : August 21, 2012 | Test Date : October 31, 2011 | QNS : | MC :

COMI : CI-EA-COU (110655) | Stain Reagent : SRB Dual-Pass Related | SSPL : 0YGI

		Log10 Concentration													
	Time	Mean Optical Densities						Percent Growth							
Panel/Cell Line	Zero	Ctrl	-8.0	-7.0	-6.0	-5.0	-4.0	-8.0	-7.0	-6.0	-5.0	-4.0	GI50	TGI	LC50
Leukemia															
HL-60(TB)	0.824	2.665	2.689	2.744	2.501	0.818	0.847	101	104	91	-1	1	2.80E-6	.	> 1.00E-4
K-562	0.235	1.605	1.697	1.686	0.966	0.553	0.400	107	106	53	23	12	1.29E-6	> 1.00E-4	> 1.00E-4
MOLT-4	0.787	2.408	2.475	2.559	2.402	1.207	1.068	104	109	100	26	17	4.71E-6	> 1.00E-4	> 1.00E-4
RPMI-8226	0.980	2.860	2.882	2.811	2.767	1.924	1.820	101	97	95	50	45	1.10E-5	> 1.00E-4	> 1.00E-4
SR	0.238	0.704	0.711	0.701	0.371	0.224	0.207	101	99	29	-6	-13	4.97E-7	6.67E-6	> 1.00E-4
Non-Small Cell Lung Cancer															
A549/ATCC	0.300	1.827	1.782	1.802	1.762	0.870	0.717	97	98	96	37	27	6.07E-6	> 1.00E-4	> 1.00E-4
EKVX	0.909	2.010	1.966	1.898	1.878	1.602	1.515	96	90	88	63	55	1.00E-4	> 1.00E-4	> 1.00E-4
HOP-62	0.333	0.925	0.933	0.942	0.862	0.382	0.308	101	103	89	8	-8	3.05E-6	3.29E-5	> 1.00E-4
HOP-92	1.173	1.765	1.686	1.666	1.662	1.497	1.361	87	83	83	55	32	1.61E-5	> 1.00E-4	> 1.00E-4
NCI-H23	0.596	1.826	1.796	1.711	1.390	0.995	0.830	98	91	64	32	19	2.83E-6	> 1.00E-4	> 1.00E-4
NCI-H460	0.248	1.960	2.023	1.947	1.672	0.401	0.394	104	99	83	9	8	2.80E-6	> 1.00E-4	> 1.00E-4
NCI-H522	0.706	2.087	2.088	2.038	1.912	1.032	0.553	100	96	87	24	-22	3.85E-6	3.32E-5	> 1.00E-4
Colon Cancer															
COLO 205	0.451	2.080	2.113	2.119	1.896	0.389	0.278	102	102	89	-14	-38	2.39E-6	7.34E-6	> 1.00E-4
HCC-2998	0.573	2.196	2.108	2.055	1.807	1.047	0.854	95	91	76	29	17	3.59E-6	> 1.00E-4	> 1.00E-4
HCT-116	0.235	1.681	1.702	1.650	1.472	0.543	0.562	101	98	86	21	23	3.57E-6	> 1.00E-4	> 1.00E-4
HCT-15	0.400	2.176	2.137	2.092	1.825	0.762	0.842	98	95	80	20	25	3.20E-6	> 1.00E-4	> 1.00E-4
HT29	0.275	1.711	1.762	1.803	1.704	0.481	0.401	104	106	100	14	9	3.82E-6	> 1.00E-4	> 1.00E-4
KM12	0.474	2.034	2.089	2.114	1.383	0.800	0.666	104	105	58	21	12	1.66E-6	> 1.00E-4	> 1.00E-4
SW-620	0.282	1.464	1.454	1.437	1.084	0.468	0.579	99	98	68	16	25	2.20E-6	> 1.00E-4	> 1.00E-4
CNS Cancer															
SF-268	0.588	1.758	1.810	1.751	1.605	1.198	1.013	104	99	87	52	36	1.36E-5	> 1.00E-4	> 1.00E-4
SF-295	0.818	2.647	2.540	2.381	2.163	1.526	1.119	94	85	74	39	16	4.73E-6	> 1.00E-4	> 1.00E-4
SF-539	0.684	1.848	1.873	1.887	1.712	0.980	0.601	102	103	88	25	-12	4.06E-6	4.74E-5	> 1.00E-4
SNB-19	0.608	1.917	1.816	1.774	1.652	1.119	0.872	92	89	80	39	20	5.37E-6	> 1.00E-4	> 1.00E-4
SNB-75	0.597	1.223	1.146	1.093	1.057	0.631	0.448	88	79	74	5	-25	2.21E-6	1.51E-5	> 1.00E-4
U251	0.402	1.881	1.848	1.842	1.692	0.805	0.384	98	97	87	27	-4	4.18E-6	7.23E-5	> 1.00E-4
Melanoma															
LOX IMVI	0.233	1.738	1.673	1.555	1.349	0.818	0.690	96	88	74	39	30	4.83E-6	> 1.00E-4	> 1.00E-4
MALME-3M	0.676	1.206	1.233	1.228	1.108	0.823	0.891	105	104	82	28	41	3.85E-6	> 1.00E-4	> 1.00E-4
M14	0.397	1.429	1.443	1.437	1.085	0.625	0.685	101	101	67	22	28	2.36E-6	> 1.00E-4	> 1.00E-4
MDA-MB-435	0.433	1.952	1.944	1.856	0.399	0.318	0.322	99	94	-8	-27	-26	2.69E-7	8.37E-7	> 1.00E-4
SK-MEL-2	0.758	1.329	1.351	1.369	1.395	1.115	0.840	104	107	112	62	14	1.82E-5	> 1.00E-4	> 1.00E-4
SK-MEL-28	0.604	1.666	1.719	1.525	1.315	0.952	0.958	105	87	67	33	33	3.13E-6	> 1.00E-4	> 1.00E-4
SK-MEL-5	0.418	2.140	2.089	1.998	1.224	0.634	0.485	97	92	47	13	4	8.48E-7	> 1.00E-4	> 1.00E-4
UACC-257	0.887	1.964	1.906	1.976	1.923	1.321	1.454	95	101	96	40	53	.	> 1.00E-4	> 1.00E-4
UACC-62	0.561	2.047	2.004	1.891	1.471	0.913	1.014	97	90	61	24	30	1.99E-6	> 1.00E-4	> 1.00E-4
Ovarian Cancer															
IGROV1	0.608	1.544	1.622	1.660	1.480	1.181	0.988	108	112	93	61	41	3.50E-5	> 1.00E-4	> 1.00E-4
OVCAR-3	0.611	1.641	1.754	1.742	1.595	0.679	0.431	111	110	96	7	-29	3.25E-6	1.52E-5	> 1.00E-4
OVCAR-4	0.605	1.200	1.198	1.143	1.130	0.599	0.841	100	90	88	-1	40	2.68E-6	.	> 1.00E-4
OVCAR-5	0.544	1.275	1.310	1.267	1.198	0.929	0.871	105	102	89	53	45	2.19E-5	> 1.00E-4	> 1.00E-4
OVCAR-8	0.310	1.335	1.288	1.312	1.306	0.629	0.558	95	98	97	31	24	5.17E-6	> 1.00E-4	> 1.00E-4
NCI/ADR-RES	0.466	1.545	1.571	1.502	1.125	0.569	0.484	102	96	61	10	2	1.64E-6	> 1.00E-4	> 1.00E-4
SK-OV-3	0.578	1.207	1.279	1.226	1.129	0.680	0.536	111	103	88	16	-7	3.36E-6	4.88E-5	> 1.00E-4
Renal Cancer															
786-0	0.674	2.090	2.127	2.150	2.046	1.168	0.890	103	104	97	35	15	5.70E-6	> 1.00E-4	> 1.00E-4
A498	1.238	1.905	1.779	1.743	1.587	1.290	1.144	81	76	52	8	-8	1.13E-6	3.19E-5	> 1.00E-4
ACHN	0.341	1.322	1.430	1.377	1.274	0.682	0.589	111	106	95	35	25	5.59E-6	> 1.00E-4	> 1.00E-4
CAKI-1	0.955	2.534	2.482	2.411	2.034	1.812	1.784	97	92	68	54	52	1.00E-4	> 1.00E-4	> 1.00E-4
RXF 393	0.630	1.269	1.234	1.206	1.106	0.750	0.501	95	90	75	19	-21	2.76E-6	3.00E-5	> 1.00E-4
SN12C	0.481	1.960	1.871	1.815	1.690	1.058	1.021	94	90	82	39	37	5.54E-6	> 1.00E-4	> 1.00E-4
TK-10	0.567	1.145	1.107	1.153	1.226	0.901	0.549	94	101	114	58	-3	1.34E-5	8.84E-5	> 1.00E-4
UO-31	0.554	1.463	1.340	1.307	1.225	1.020	0.913	86	83	74	51	39	1.27E-5	> 1.00E-4	> 1.00E-4
Prostate Cancer															
PC-3	0.645	1.959	1.921	1.826	1.619	1.271	1.095	97	90	74	48	34	8.13E-6	> 1.00E-4	> 1.00E-4
DU-145	0.338	1.351	1.462	1.433	1.311	0.522	0.437	111	108	96	18	10	3.90E-6	> 1.00E-4	> 1.00E-4
Breast Cancer															
MCF7	0.337	1.533	1.515	1.444	1.263	0.504	0.585	98	93	77	14	21	2.70E-6	> 1.00E-4	> 1.00E-4
MDA-MB-231/ATCC	0.431	1.029	1.005	0.957	0.824	0.681	0.498	96	88	66	42	11	4.53E-6	> 1.00E-4	> 1.00E-4
HS 578T	1.009	1.742	1.652	1.620	1.507	1.215	1.060	88	83	68	28	7	2.82E-6	> 1.00E-4	> 1.00E-4
BT-549	0.943	1.800	1.844	1.832	1.702	1.491	0.942	105	104	89	64	.	1.65E-5	9.94E-5	> 1.00E-4
T-47D	0.770	1.923	1.897	1.913	1.796	1.284	1.185	98	99	89	45	36	7.55E-6	> 1.00E-4	> 1.00E-4
MDA-MB-468	0.544	1.205	1.165	1.140	1.051	0.641	0.519	94	90	77	15	-5	2.69E-6	5.76E-5	> 1.00E-4