# 3-(4-chlorophenyl)-[1, 2, 3] oxadiazol-3-ium-5-olate and its 4-formyl analog-Ultrasound assisted synthesis and *in-vitro* anticancer evaluation against human tumor cell lines

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**Abstract**: The title compound, 3-(4-chlorophenyl)-4-formyl-[1, 2, 3] oxadiazol-3-ium-5-olate 5 was synthesized under ultrasonication by formylation of 3-(4-chlorophenyl)-[1, 2, 3] oxadiazol-3-ium-5-olate 4 and characterized by spectral studies. The ultrasonic method of synthesis was found to be simple, ecofriendly, economical, reduces reaction time and gave good yield when compared with traditional methods of synthesis. Anticancer activity of the compounds were tested against 60 human tumor cell lines and compared with standard drug vincristine sulphate. Compound 5 was found to be active against CNS (SNB-75, %GI=46.71), renal (UO-31, %GI=31.52), non small cell lung (NCI-H522, %GI=25.65), leukemia (MOLT-4, %GI=23.02) human tumor cell lines whereas, compound 4 against breast (MDA-MB-231/ATCC, %GI=19.90, T-47D %GI=16.50, MCF-7 15.10) and ovarian (IGROV1 %GI=19.30, OVCAR-4 %GI=17.90) human tumor cell lines. Compound 5 showed higher cytotoxicity against NCI-H23 cells (non small lung cancer cell panel) as compared to standard drug vincristine sulphate. Further structural modification of these compounds may lead to potent anticancer activity.

**Keywords**: Anticancer, sydnone, formylation, ultrasonication.

## INTRODUCTION

Mesoionic 1, 2, 3-oxadiazol-3-ium-5-olate (sydnone) derivatives have been described for a variety of medicinal activities including anticancer activity (Kier 1964, Dunkley 2003, Satyanarayana 1995, Kavali 2000, Dunkley 2003, Fregly 1964, Stewart 1965 and Roche 1965). It has been observed that the ionic resonance structures of 1, 2, 3-oxadiazol-3-ium-5-olate ring enhances interactions with biological molecules. A series of 4-substituted-3-nitrophenyl-1, 2, 3-oxadiazol-3-ium-5-olates has shown antitumor activity and the presence of 4-chloro and 4-pyrrolidino ring significantly enhanced the survival of tumor bearing mice (cell line S180, Ehrlich, B10MCII) (Dunkley *et al*., 2003). It is reported that piperidino and morpholino ring decreases anticancer potency (Kier *et al*., 1964, Dunkley *et al*., 2003). With the advent of green chemistry, the ultrasound assisted synthesis has become increasingly popular in recent years to improve the yields and shorten reaction times in a variety of chemical reactions. However, there are hardly any reports on ultrasound assisted synthesis of 1, 2, 3-oxadiazol-3-ium-5-olate derivatives in the literature. In view of all these, we describe herein the ultrasound assisted synthesis and anticancer activity of 3-*p*-chlorophenyl 1, 2, 3-oxadiazol-3-ium-5-olate (4) and its 4-formyl analog (5).

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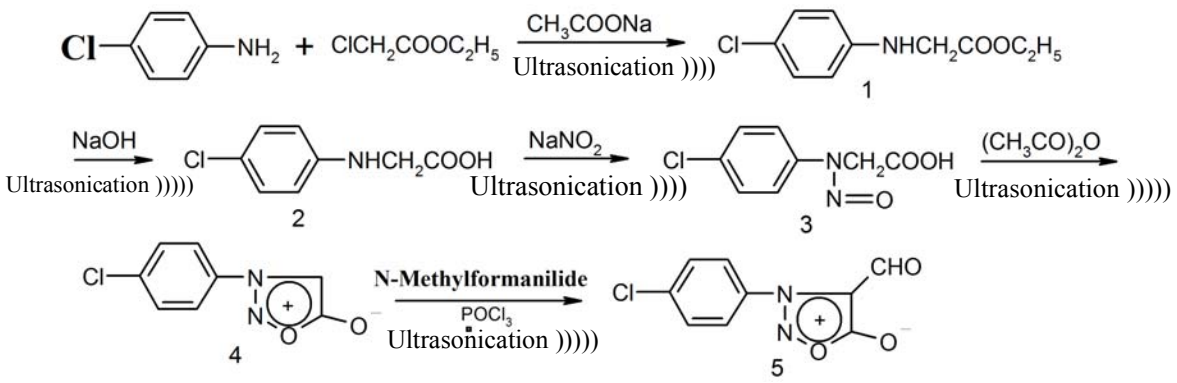
## MATERIALS AND METHODS

All chemicals and reagents were purchased from Sigma-Aldrich, Mumbai, India. Melting points of the intermediates and the final products were recorded on Systolic melting point apparatus and are uncorrected. TLC was carried out to monitor the completion of reaction by using E-Merck precoated 60 F254 plates. IR spectra were recorded by using KBr pellets on Jasco FTIR 1460 Plus spectrometer. NMR spectra were obtained on a BRUKER AVANCE II 400 NMR spectrometer at 400 MHz for $^{1}H$ and 40 MHz for $^{13}C$ (chemical shifts are expressed in δ, ppm). Mass spectra were recorded on WATERS, Q-TOF MICROMASS (LC-MS) instrument. The ultrasonic irradiation was performed by using a Biotechnics India (model-1510, frequency, 40 KHz).

***Synthesis of ethyl N-(4-chlorophenyl) aminoacetate (1)***

A mixture of *p*-Chloroaniline (2.80g, 0.02mol) and ethyl chloroacetate (2.12mL, 0.02mol) was added to the solution of ethyl alcohol (25ml) and anhydrous sodium acetate (3.27g, 0.04mol) under ultrasonication conditions and allowed to react for 2h. The contents was diluted with water and cooled in freezer for 24h. The solid separated is filtered and recrystallized by ethyl alcohol to yield 1 (83%), mp 114-116ºC. IR (KBr): 3327, 2950, 2934, 2879, 1756, 1069; $^{1}H$ NMR: δ 1.19 (t, 3H, COO-$CH_2$-$CH_3$), 3.75 (s, 1H, NH), 4.31 (s, 2H, $CH_2$), 4.53 (q, 2H, COO-$CH_2CH_3$), 6.79-7.19 (m, 4H, ArH); $^{13}C$ NMR: δ 13.95, 43.93, 62.07, 116.03, 124.02, 129.01, 145.96, 173.13.




**Scheme 1**: Synthesis of 3-(*p*-chlorophenyl)-4-sydnonecarboxaldehyde (**5**) under ultrasonication

***Synthesis of N-(4-chlorophenyl) aminoacetic acid (2)***

Ethyl *N*-(4-chlorophenyl) amino acetate (4.26g, 0.02mol) and ethanolic sodium hydroxide (1.2g, 0.03mol) was heated under ultrasonication conditions at 65°C for 15 min and allowed to cool and acidified with dil hydrochloric acid. The formed solid was filtered. Yield 87 %, mp 146-148ºC. IR (KBr): 3319, 3277, 2951, 2937, 2879, 1703, 1063; $^{1}$H NMR: δ 4.29 (s, 2H, $CH_2$), 6.39 (s, 1H, COOH), 6.55 (s, 1H, NH), 6.79-7.27 (m, 4H, ArH); $^{13}$C NMR: δ 45.08, 115.02, 124.16, 130.02, 145.97, 171.98

***Synthesis of N-nitroso (4-chlorophenyl) aminoacetic acid (3)***

Ice cold N-(4-chlorophenyl) aminoacetic acid (3.72g, 0.02mol) was added into crushed ice (40gm). Sodium nitrite solution (1.38g, 0.02mol) was added slowly under ultrasonication condition at 0°C for 10 min. The reaction contents were solidified by neutralising with hydrochloric acid. Solid was filtered and recrystallized by methanol to yield 3 (81%), mp 109-111ºC. IR (KBr): 3255-2521, 2923, 2849, 1711, 1569, 1325, 1062; $^{1}$H NMR: δ 4.99 (s, 2H, $CH_2$), 7.00-7.45 (m, 4H, ArH), 11.55 (s, 1H, COOH); $^{13}$C NMR: δ 50.02, 119.75, 130.09, 129.43, 137.78, 169.25

***Synthesis of 3-(4-chlorophenyl)-[1, 2, 3]-oxadiazol-3-ium-5-olate (4)***

Under ultrasonication condition at 25°C, reaction of compound 3 (5.40g, 0.0252 mol) and acetic anhydride (30 ml) was continued for 60 min. The contents of reaction were left overnight at room temperature. The contents were added slowly into crushed ice with stirring. The crude sydnone was filtered, dried and recrystallized by ethanol to yield 4 (93%), mp 139-141ºC. IR (KBr): 3181, 1748, 1053. $^{1}$H NMR: δ 7.23 (s, 1H, sydnone), 7.49-8.13 (m, 4H, ArH). $^{13}$C NMR: δ 123.15, 126.49, 131.53, 136.13, 141.13, 170.07.

***Synthesis of 3-(4-chlorophenyl)-4-formyl-[1, 2, 3] oxadiazol-3-ium-5-olate (5)***

N-Methylformanilide 2.84g (0.021mol) and phosphoryl chloride (3.17g, 0.0205mol) were mixed under ultrasonication conditions for 10min. After 30 min, compound 4, (3g, 0.0186mol) was added in parts with stirring in cold condition under ultrasonication. After 24 h, formed thick, sticky and brown mixture was added in 15 ml acetone and content poured into 75 gm crushed ice. The yellow precipitate gets separated and dried. Yield 56%, mp 75-77$^{0}$C. MS ($M^{+}$) (m/e) 223.99, 225.996, 225.002. IR (KBr): 1790 (C=O sydnone), 1640 (C=O aldehyde). $^{1}$H NMR: δ 7.2, 7.2, 7.3, 7.3 (Cl-Ph), 9.61 (CHO). $^{13}$C NMR: δ 127, 129, 129, 130, 130, 134 (Cl-Ph) 190 (CHO). Element analysis: C; 48.15, H; 2.22, N; 12.45, O; 21.37.

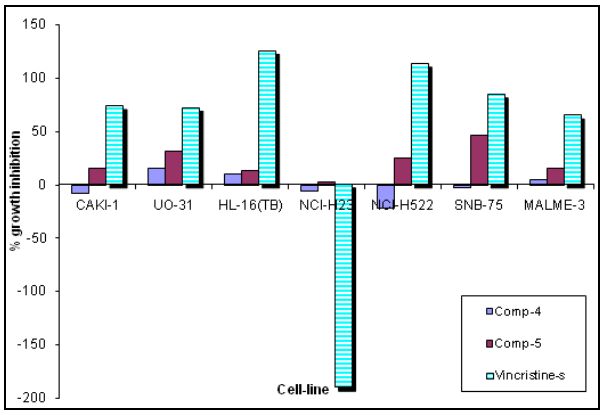



**Fig. 1**: % growth inhibition for anticancer activity evaluation of synthesized compounds

***Anticancer screening***

The synthesized compounds were evaluated for an *in-vitro* anticancer activity using human cancer cell lines (leukemia, lung, colon, CNS, melanoma, ovarian, renal, Prostrate and breast) at NCI, USA (Bethesda) (Roschke *et al*., 2003, Lorenzi *et al*., 2009, Mingyi *et al*., 2013, Al-Suwaidan *et al*., 2013, Senff-Ribeiro, 2004, Butkovic, 2011).

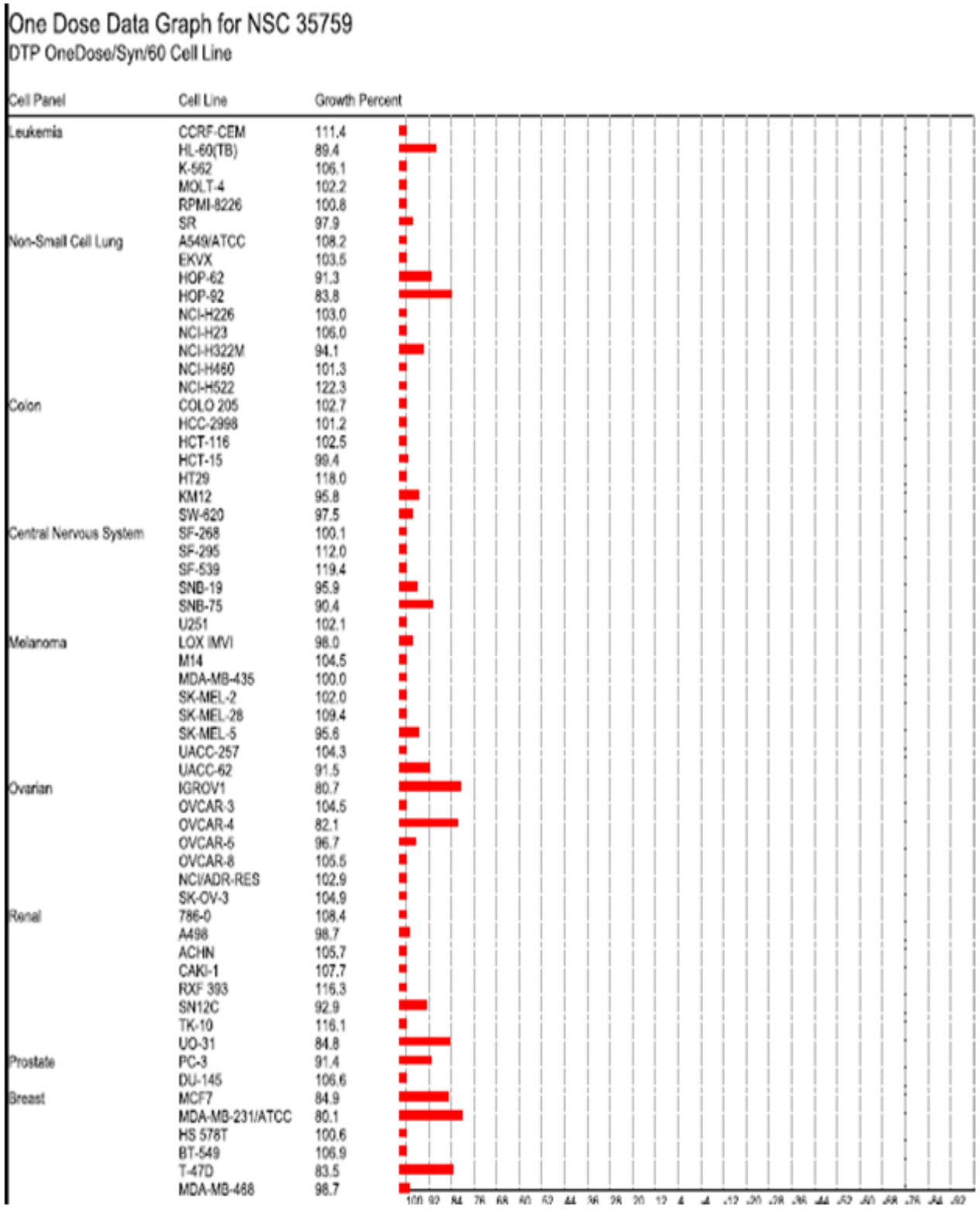



**Fig. 2**: Percentage growth inhibitions for anticancer activity evaluation of compound **4**

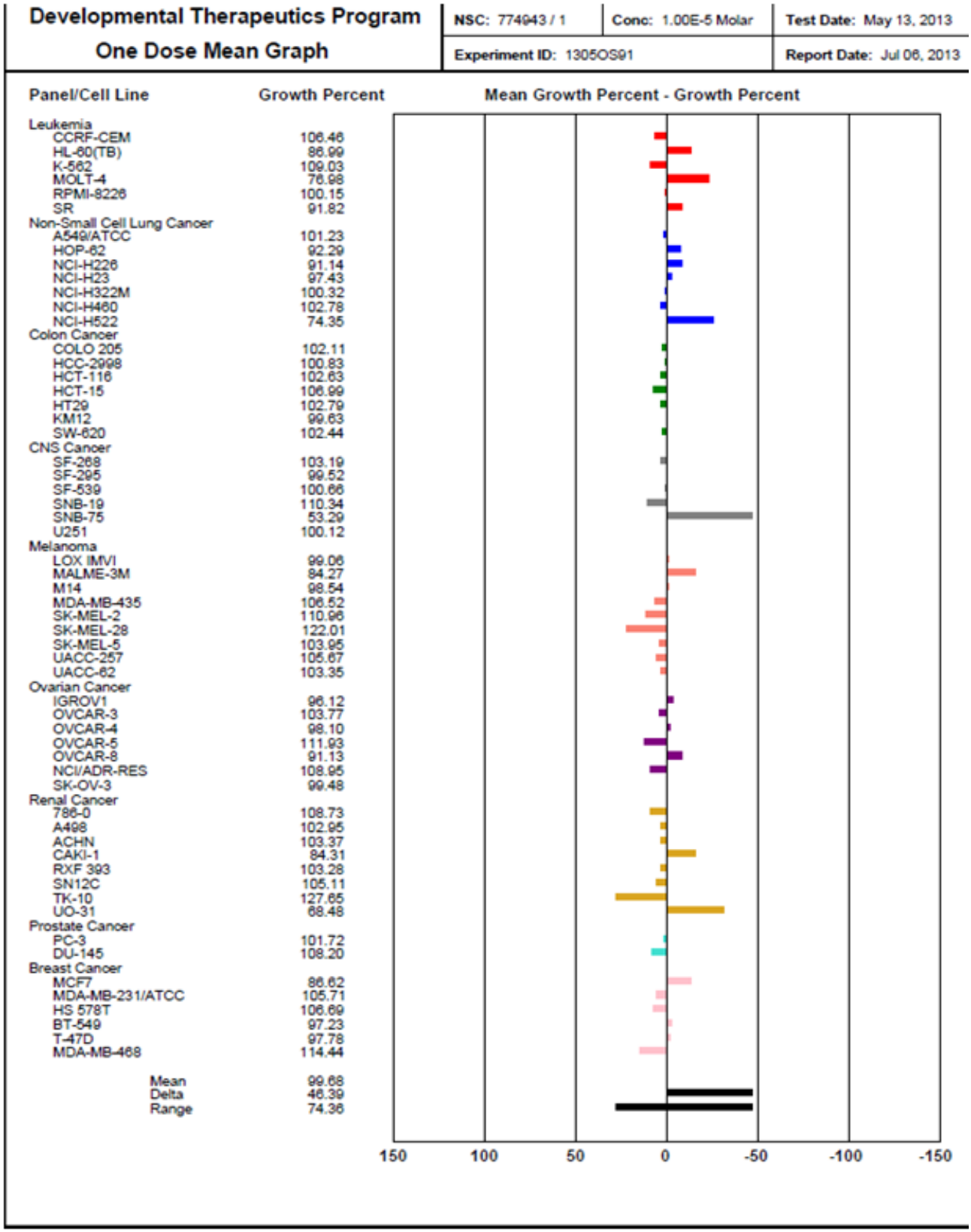



**Fig. 3**: Percentage growth inhibitions for anticancer activity evaluation of compound **5**

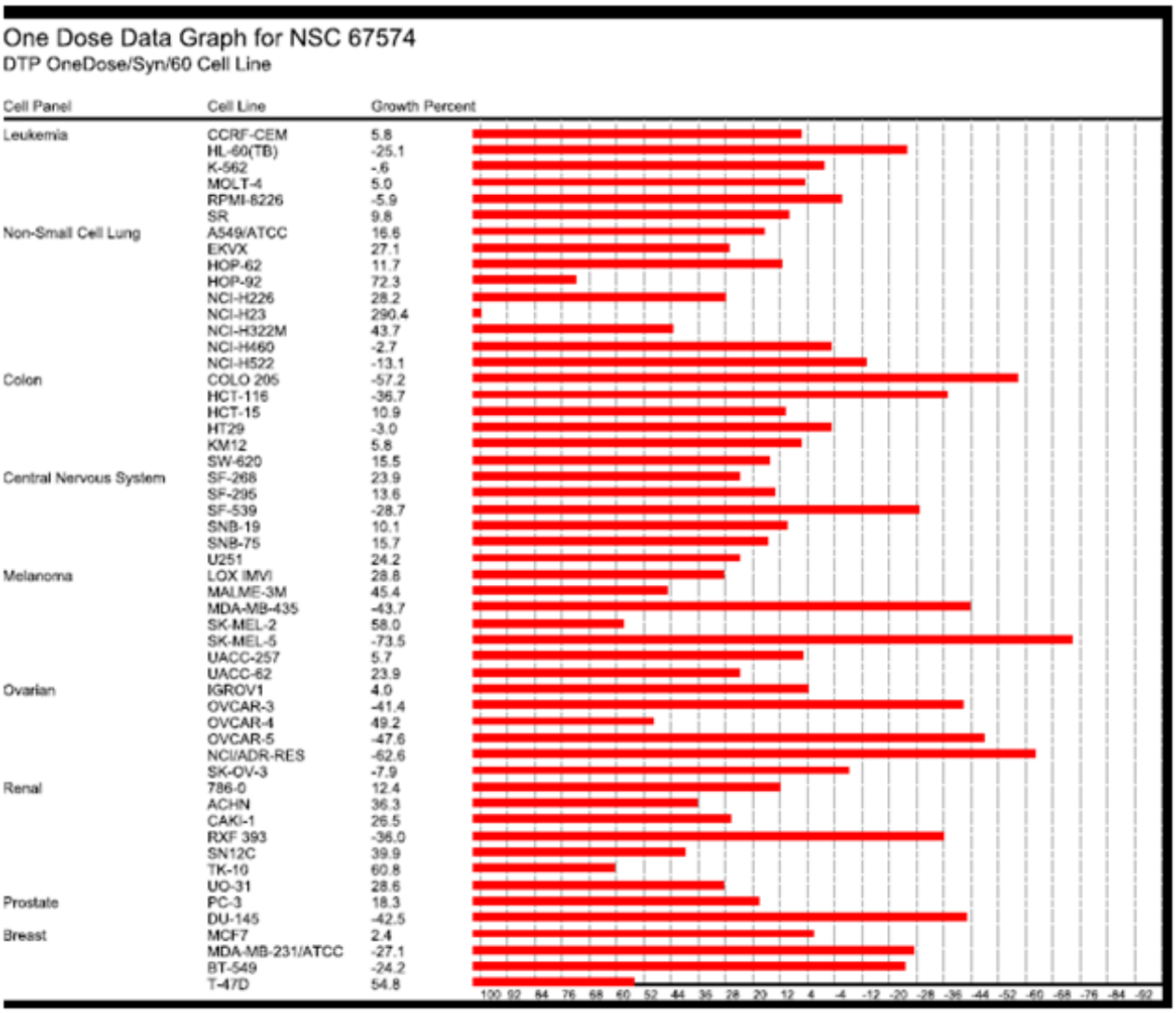



**Fig. 4**: Percentage growth inhibitions for anticancer activity evaluation of standard drug Vincristine sulphate.

**Table 1**: One dose mean graph for compound **4** (NSC: 35759) and compound **5** (NSC: 774943/1)

| Human tumor cell line | % Growth inhibition Comp. 4 (NSC 35759) | % Growth inhibition Comp. 5 (NSC 774943/1) |
|---|---|---|
| Leukemia | | |
| CCRF-CEM | -11.40 | -06.46 |
| HL-60 (TB) | 10.60 | 13.01 |
| K-562 | -06.10 | -09.03 |
| MOLT-4 | -02.20 | 23.02 |
| RPMI-8226 | -00.80 | -00.15 |
| SR | 02.10 | 08.18 |
| Non-Small Cell Lung Cancer | | |
| A549/ATCC | -08.20 | -01.23 |
| HOP-62 | 08.70 | 07.71 |
| NCI-H226 | -03.00 | 08.86 |
| NCI-H23 | -06.00 | 02.57 |
| NCI-H322M | 05.30 | -00.32 |

| Human tumor cell line | % Growth inhibition Comp. **4** (NSC 35759) | % Growth inhibition Comp. **5** (NSC 774943/1) |
|---|---|---|
| Colon Cancer | | |
| COLO 205 | -02.70 | -02.11 |
| HCC-2998 | -01.20 | -00.83 |
| HCT-116 | -02.50 | -02.63 |
| HCT-15 | 00.60 | -06.99 |
| HT29 | -18.00 | -02.79 |
| KM12 | 04.20 | 00.37 |
| SW-620 | 02.50 | -02.44 |
| CNS Cancer | | |
| SF-268 | -00.10 | -03.19 |
| SF-295 | -12.00 | 00.48 |
| SF-539 | -19.40 | -00.66 |
| SNB-19 | 04.10 | -10.34 |
| U251 | 09.60 | -00.12 |
| SNB-75 | -02.10 | 46.71 |
| Melanoma | | |
| LOX IMVI | 02.00 | 00.94 |
| MALME-3 | 04.72 | 15.73 |
| M M14 | -04.50 | 01.46 |
| MDA-MB-435 | 00.00 | -06.52 |
| SK-MEL-2 | -02.00 | -10.96 |
| SK-MEL-28 | -09.40 | -22.01 |
| SK-MEL-5 | 04.40 | -03.95 |
| UACC-257 | -04.30 | -05.67 |
| UACC-62 | 08.50 | -03.35 |
| Ovarian Cancer | | |
| IGROV1 | 19.30 | 05.88 |
| OVCAR-3 | -04.50 | -03.77 |
| OVCAR-4 | 17.90 | 01.90 |
| OVCAR-5 | 03.30 | -11.93 |
| OVCAR-8 | -05.50 | 08.87 |
| NCI/ADR-RES | -02.90 | -08.95 |
| SK-OV-3 | -04.90 | 00.52 |
| Renal Cancer | | |
| 786-0 | -08.40 | -08.73 |
| A498 | 01.30 | -02.95 |
| ACHN | -05.70 | -03.37 |
| CAKI-1 | -07.69 | 15.69 |
| RXF 393 | -16.28 | -03.28 |
| SN12C | 07.11 | -05.11 |
| TK-10 | -16.10 | -27.65 |
| UO-31 | 15.20 | 31.52 |
| Prostate Cancer | | |
| PC-3 | 08.60 | -01.72 |
| DU-145 | -06.60 | -08.20 |
| Breast Cancer | | |
| MCF7 | 15.10 | 13.38 |
| MDA-MB-231/ATCC | 19.90 | -05.71 |
| HS 578T | -00.60 | -06.69 |
| BT-549 97.23 | -06.90 | 02.77 |
| T-47D | 16.50 | 02.22 |
| MDA-MB-468 | 01.30 | -14.44 |
| Mean | - | 99.68 |
| Delta | - | 46.39 |
| Range | - | 74.36 |

**Table 2**: Percent Growth inhibition of synthesized compounds against most effective cancer cell lines

| Cell lines | Compound 4 (NSC: 35759) | Compound 5 (NSC 774943/1) | Standard drug Vincristine sulphate |
|---|---|---|---|
| CAKI-1 | -7.69 | 15.69 | 73.5 |
| UO-31 | 15.2 | 31.52 | 72 |
| HL-60 (TB) | 10.6 | 13.01 | 125.1 |
| NCI-H23 | -6 | 2.57 | -190.4 |
| NCI-H522 | -22 | 25.65 | 113.1 |
| SNB-75 | -2.1 | 46.71 | 84.3 |
| MALME-3 | 4.72 | 15.73 | 64.6 |

## RESULTS

We have attempted the synthesis of title compounds by ultrasonification as a move towards green synthesis. The compound 4 was synthesized as per reported protocol (Deshpande SR 2010) under ultrasonification. The formylation was carried out by the reported method Vilsemier Haack reaction (Thoman CJ 1964) under ultrasound irradiation at 40 KHz. The compounds were evaluated for their *in vitro* anticancer activity by NCI in one dose assay on a panel of 60 human cancer cell lines. The observed anticancer screening data of the compounds are given in tables 1 and 2. Compound 5 (NSC 774943/1) was found to be having broad spectrum of anticancer activity and highly active against SNB-75 (CNS cancer, % GI=46.71%), followed by UO-31 (renal cancer, % GI=31.52%), NCI-H522 (non-small cell lung cancer, %GI=25.65%), MOLT-4 (leukemia, % GI=23.02%), MALME-3 (melanoma, % GI=15.73%), CAKI-1 (renal cancer, % GI=15.69%) and MCF-7 (breast cancer, % GI=13.38%). Whereas, compound 4 exhibited higher anticancer activity than compound 5 against KM-12 (colon cancer), SK-MEL-5, UACC-62 (melanoma), IGROV1, OVCAR-4 (ovarian cancer), SN-12C (renal cancer), PC-3 (prostate cancer) MCF-7, MDA-MB-231/ATCC, T-47D (breast cancer). Compound 4 (NSC 35759) and compound 5 (NSC774943/1) exhibited higher cytotoxicity than standard vincristine sulfate against NCI-H23 cell line (non small cell lung cancer). The anticancer activities of compounds 4, 5 and vincristine sulfate are illustrated in fig. 1.

## DISCUSSION

The target molecules were synthesized under ultrasonication conditions as an approach towards green synthesis. As a part of ongoing development of efficient protocols for the green synthesis of compound 5, this study reports for the first time, a formylation of compound 4 at 4$^{th}$ carbon (by Vilsemier Haack reaction) under ultrasound irradiation. The use of ultrasonication technique makes enough advantages over conventional methods such as being simple, eco-friendly, economical, reduced reaction time and improved yields. The synthetic protocol based on conventional heating suffers from a long period and poor yields. Our present synthetic methodology under ultrasound irradiation developed to solve problems of conventional method. Anticancer evaluation of compound 5 revealed that, it is highly selective and effective towards SNB75 (CNS cancer), UO-31 (renal cancer) and NCI-H522 (non small cell lung cancer) human tumor cells. Compound 4 also displayed good activity than compound 5 against MDA-MB-231/ATCC (breast cancer) and ovarian cancer cell lines IGROV1 and OVCAR-4. Both Compounds 4 and 5 exhibited good activity against UO-31 (renal cancer) and MCF-7 (breast cancer) cancer cell lines. Formylation of compound 4 was found to increase and broaden the spectrum of anticancer activity against some cell lines. In general, compound 5 showed better anticancer activity than compound 4 against CAKI1/UO31 (renal cancer), HL16 (TB) (leukemia), NCI-H522/NCI-H226/NCI-H23 (non-small cell lung cancer), SNB75 (CNS cancer) and MALME-3M (melanoma). Formylation of compound 4 at carbon 4, reduces anticancer activity against KM-12 (Colon cancer), U251 (CNS cancer) SK-MEL-5, UACC-62 (Melanoma), IGROV1, OVCAR-4 (Ovarian cancer), SN-12C (Renal cancer), PC-3 (Prostate cancer), MCF-7, MDA-MB-231/ATCC, T-47D (Breast cancer) human tumor cell lines. The majority of drugs used for the treatment of cancer today are cytotoxic (cell killing) that work by interfering in some way with the operation of cells DNA.

***The structure activity relationship revealed that***

(1) Formylation on sydnone ring at 4$^{th}$ position gave potent activity against CAKI1/UO31 (renal cancer), MOLT-4, HL16TB (Leukemia), NCI-H522 (non small cell lung cancer), SNB-75 (CNS cancer) and MALME-3M (Melanoma).

(2) For same, formylation on sydnone ring at 4$^{th}$ position reduces cytotoxicity activity against KM-12 (Colon cancer), U251 (CNS cancer), SK-MEL-5, UACC-62 (Melanoma), IGROV1, OVCAR-4 (ovarian cancer), SN-12C (Renal cancer), PC-3 (Prostate cancer), MCF-7, MDA-MB-231/ATCC, T-47D (Breast cancer) human tumor cell lines. Compound 4 and 5 can be further evaluated for *in vivo* anticancer activities and more new compounds can be designed.

## CONCLUSION

Understanding the anticancer potential of sydnone compounds, we carried out green synthesis of molecules 4 and 5 under ultrasonication. The procedure proved to be more profitable than those previously reported in the literature. Hereby we examined compound 4 and 5 with anticancer screening against 60 human tumor cell lines ((leukemia, lung, colon, CNS, melanoma, ovarian, renal, Prostrate and breast). Compound 5 showed higher and broader spectrum of anticancer activity against human tumor cell lines. Compound 5 showed highest activity against SNB-75 with %GI=46.71(CNS cancer cell panel) and higher activity against NCI-H23 (non small cell lung cancer cell panel) than standard drug vincristine sulphate. Further research and development with designing necessary structural modifications of molecule 4 and 5 may lead to safer and effective potential anticancer drug candidates. The finding of the study inferred that the molecule 4 and 5 renders as a lead for further development of novel potent anticancer molecules against specific tumor cell line.

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