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Anti-Cytotoxic One Dose Response Study against NCI-60 Cancer Cell-lines of Synthesized Benzofuran Derivatives

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Abstract: In medicinal chemistry, benzofuran derivatives have drawn considerable devotion because of their diverse biological profiles including anti-cancer activity and many more.Aluxury combination of three compounds *i.e.*dimedone, 3-phenoxy benzaldehyde and phenacyl bromides in multi component reactions (MCR's) approach to synthesized *2-[(substitutedphenyl)carbonyl]-3-(3-phenoxyphenyl)-6,6-dimethyl-3,5,6,7-tetrahydro-1-benzofuran-4(2H)-one* derivatives (4a-4h).Structural diversity was identified by comparing^{1}H NMR coupling constant value of two chiral centers,and also by IR, Mass and ^{13}C NMR spectroscopic techniques.Of the synthesized molecules, three molecules were evaluated for their *Invitro* anti-cancer activity against a panel of NCI-60 human tumor cell linesderived from nine neoplastic diseases. On the basis of anti-cancer results, we concluded that out of 4a-4f, three compounds (4a, 4b and 4g) were found to be extra potent when compared to the remaining ones. Compounds 4a shows superfluous potency against T-47D cell line of breast cancer with growth percentage 05.71 % (GI_{50} Value).

Keywords: Benzofurans, Multicomponent reactions, Anti-cancer screening, NCI-60 cell-lines

1.0 Introduction

Since last few decades, cancer is one of the most important clinical problems worldwide and the chemists and pharmacists are continuously putting in efforts to cure it. It is a very complex disease which affects different organsand systems of the body. Most signal transduction ways are mediated by proteinkinases, and aberrant kinase signaling leads to proliferation ofcancer cells as well as angiogenesis and growth of solid tumorssuch as prostate, colon, breast, and gastric cancers [1]. Despite the presence of a variety of anticancer drugs as well as various therapies, there are no available agents which can currently exterminate cancer cells without causing injurious to normal tissues of the body. Therefore, it is a prime necessity to

develop novel anticancer agents and to generate a more specific treatment strategy [2].

Today's, effort is aimed for the improvement in process chemistry as well as atom economy and the one-pot transformations can be carried out through multistep sequential processes. Multicomponent reactionswhichare occur in one reaction vessel and involve more than two starting reagents that form a single product which contains the essential parts of the starting materials, with atom economy and ease of formation with minute or no formation of byproducts [3].

Benzofuran scaffolds and its reduced form (oxygen containing alicyclic heterocycles) have drawn considerable attention over the lastfew decades.Due to their profound physiological and chemotherapeutic properties as well astheir widespread occurrence in nature [4], it is of special interest for researchers owning to their applications as pharmacological molecules [5].Natural and synthetic compounds containing benzofuranfragmentshave been found to display a broad range of biological activities, such asanti-tumour [6], antiviral [7, 8], anti-microbial [9], anti-inflammatory [10],antioxidant [11], antiproliferative [12]and many more. In addition, 2-benzoylbenzofuran derivatives have beenidentified to possess anticytotoxic importance also [13].

Moreover, in previous work, we have designed tetrahydrobenzofuran derivatives which exhibited excellent anti-tubercular activities [14]. On the basis of these results, wewere interested in designing and synthesizing a number of novelhybrid compounds bearing 2-benzoyl benzofuran hybrid with3-aryloxysubtituents. In the present research, we reported the synthesis of a series ofnovel benzofuran compounds, a fusion between dimedone, and benzoyl group at 2nd position and a diverse oxygen connected biaryl substituents (3-phenoxy phenyl) at 3rd position in furan nucleus of benzofuran. These derivatives were evaluated for their *Invitro*anti-cancer activity against a panel of human tumor cell lines to uncover new potent anticancer agents.

2.0 Material and method

2.1 General

All the chemicals, reagents and solvents were purchased from the Sigma-Aldrich Chemical Co. and Spectrochem Ltd. Reaction progress was monitored by using precoated plates of silica gel G60 F254 (0.2 mm, Merck) thin-layer chromatography (TLC). Visualization of TLC was made under UV light (254 and 365nm) or with an iodine vapor flask. IR spectra were recorded on an IR Affinity-1S spectrophotometer (Shimadzu). For ^{1}H (400 MHz) and ^{13}C (101.1 MHz) NMR spectral analysis Bruker AVANCE II spectrometer was used. The position of signals was depicted in δ ppms value with reference to TMS as a standard using DMSO-$d_6$solvent. Mass spectra were carried out using liquid injection using GC: 7820A and MS: 5977B MSD (Agilent technology). Roteva rotary evaporator was used for the isolation of products and recovery of solvents. Melting points were measured in open capillaries.

2.2 Chemistry

Synthetic procedure for the 2-[(substitutedphenyl)carbonyl]-3-(3-phenoxyphenyl)-6,6-dimethyl-3,5,6,7-tetrahydro-1-benzofuran-4(2*H*)-one (4a-4h)

A mixture of dimedone **1** (1.1 mmole), substituted phenacyl bromide **2**(3.85 mmole), 3-phenoxy aldehyde **3** (3.0 mmole) and piperidine (7.14 mmole) were added to acetonitrile (2.0 ml) and heated at reflux temperature for 2.0 hrs. After 3.0 hrs reflux, add TEA and the reaction mixture was heated up to reflux temperature

for further 3.0 hrs. After completion of the reaction, the resulting mixture was cooled to room temperature, poured into ice cold water and was stirred at RT for 10 hrs. Filtered the separated solid mass and washed with water to give final products. Recrystallization was carried out using Ethanol: H_2O solvent mixture to afford analytically pure products **4a-4h**.

3-(3-Phenoxyphenyl)-6,6-dimethyl-2-(phenylcarbonyl)-3,5,6,7-tetrahydro-1-benzofuran-4(2*H*)-one (4a). This compound was isolated in oily light yellow colored. Mole. Formula $C_{29}H_{26}O_4$, Yield 80 %, mp 192 ^oC, IR (Direct method, cm^{-1}): 2956.87 (Aromatic –CH stretching), 1751.36 (Cyclic >C=O stretching), 1701.55 (Acyclic >C=O stretching), 1585.49, 1485.19, 1444.68 (Aromatic ring skeleton), 1371.39 (C-H Bending), 1171.70 (C-O stretching).; ^1H (400 MHz, $CDCl_3$) δ ppm: 7.84 – 7.50 (m, 4H), 7.41 – 7.39 (m, 4H), 7.17-6.92 (4H, m), 6.27 (1H, d), 4.23 (1H, d), 2.53 (2H, d), 2.18-2.05 (2H, dd), 1.05 (6H, s).; ^{13}C NMR (101 MHz, $CDCl_3$) δ: 202.20, 187.77, 161.45, 157.41, 154.90, 133.65, 131.24, 131.21, 130.27, 129.06, 129.06, 129.87, 128.17, 128.16, 128.51, 128.51, 121.32, 119.21, 118.20, 118.71, 119.76, 117.50, 84.49, 57.80, 51.48, 41.90, 32.40, 27.82, 28.81.; ms: *m/z*438.18 (M^+).

3-(3-Phenoxyphenyl)-6,6-dimethyl-2-(4-chlorophenylcarbonyl)-3,5,6,7-tetrahydro-1-benzofuran-4(2*H*)-one (4b). This compound was isolated in oily yellow colored. Mole. Formula $C_{29}H_{25}ClO_4$, Yield 86 %, mp 201 ^oC, IR (cm^{-1}): 2922.16 (Aromatic -CH stretching), 1755.43 (Cyclic >C=O stretching), 1651.23 (Acyclic >C=O stretching), 1529.55, 1483.26, 1446.61 (Aromatic ring skeleton), 1194.22 (C-O stretching), 829.39 (*p*-disubstituted ring), 694.37 (C-Cl starching).; ^1H (400 MHz, $CDCl_3$) δ ppm: 7.61-7.40 (m, 4H), 7.39-7.34 (m, 4H), 7.17-6.73 (m, 5H), 6.24 (1H, d), 4.25 (1H, d), 2.52 (2H, dd), 1.99 (2H, dd), 1.10 (3H, S), 1.02 (3H, S).; ^{13}C NMR (101 MHz, $CDCl_3$) δ: 200.61, 181.76, 162.18, 154.40, 153.88, 140.81, 136.81, 131.24, 131.26, 130.08, 130.06, 128.80, 128.85, 128.81, 127.91, 127.93, 122.34, 118.22, 118.21, 118.20, 118.20, 117.52, 84.51, 57.70, 50.48, 40.94, 30.39, 27.80, 26.80.; ms: *m/z*472.14 (M^+).

3-(3-Phenoxyphenyl)-6,6-dimethyl-2-(4-bromophenylcarbonyl)-3,5,6,7-tetrahydro-1-benzofuran-4(2*H*)-one (4c). This compound was isolated in solid light yellow colored. Mole. Formula $C_{29}H_{25}BrO_4$, Yield 88 % , mp 184 ^oC, IR (cm^{-1}): 2922.16 (Aromatic –CH stretching) , 2854.56 (Aliphatic –CH Stretching), 1782.23 (Cyclic >C=O stretching), 1711.89 (Acyclic >C=O stretching), 1595.43, 1537.56, 1491.09 (Aromatic ring skeleton), 1390.68 (C-H Bending), 1165.55 (C-O stretching), 866.04 (*p*-disubstituted aromatic ring), 752.24 (C-Br stretching); ^1H (400 MHz, $CDCl_3$) δ ppm: 7.78-7.73 (m, 4H), 7.42-7.35 (m, 3H), 7.18-7.14 (1H, m), 7.04-7.01 (2H, m), 6.95-6.92 (2H, m), 6.74-6.67 (1H, m), 4.24 (1H, d), 2.52 (2H, dd), 2.18 (2H, dd), 1.15 (3H, S), 1.05 (3H, S).; ^{13}C NMR (101 MHz, $CDCl_3$) δ: 205.68, 178.57, 160.14, 156.43, 155.95, 125.50, 132.02, 131.73 130.26, 130.06, 129.88, 129.78, 123.34, 119.24, 118.70, 118.55, 84.52, 57.72, 51.49, 40.91, 31.39, 28.82.; ms: *m/z*516.09 (M^+).

3-(3-Phenoxyphenyl)-6,6-dimethyl-2-(4-hydroxyphenylcarbonyl)-3,5,6,7-tetrahydro-1-benzofuran-4(2*H*)-one (4d). This compound was isolated in solid dark yellow colored. Mole. Formula $C_{29}H_{26}O_5$, Yield 84 %, mp 196 ^oC, IR (cm^{-1}): 3562.33 (-OH stretching), 2929.15 (Aromatic –CH stretching) , 2854.42 (Aliphatic –CH Stretching), 1788.20 (Cyclic >C=O stretching), 1721.48 (Acyclic >C=O stretching), 1591.43, 1537.36, 1458.22 (Aromatic ring skeleton), 1359.59 (C-H Bending), 1162.22 (C-O stretching), 871.00 (*p*-disubstituted aromatic ring).; ^1H (400 MHz, $CDCl_3$) δ ppm: 7.75-7.71 (m, 4H), 7.40-7.33 (m, 3H), 7.20-7.16 (1H, m), 7.10-7.07 (2H, m), 6.94-6.91 (2H,

m), 6.74-6.66 (1H, m), 5.01 (1H, S), 4.31 (1H, d), 2.45 (2H, dd), 2.17 (2H, dd), 1.13 (3H, S), 1.03 (3H, S); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 201.10, 188.70, 170.19, 163.50, 157.94, 156.40, 138.22, 132.64, 132.64, 130.07, 130.07, 129.69, 126.24, 123.36, 121.05, 120.78, 119.28, 119.28, 116.15, 115.77, 115.77, 115.54, 85.51, 50.65, 48.21, 41.53, 31.29, 28.50, 28.50..; ms: *m/z*516.09 (M^+).

3-(3-Phenoxyphenyl)-6,6-dimethyl-2-(4-methoxyphenylcarbonyl)-3,5,6,7-tetrahydro-1-benzofuran-4(2*H*)-one (4e). This compound was isolated in semi-solid light yellow colored. Mole. Formula $C_{30}H_{28}O_5$, Yield 81 %, mp 179 ^{o}C, IR (cm^{-1}): 2922.16 (Aromatic –CH stretching) , 2854.65 (Aliphatic –CH Stretching), 1687.71 (Cyclic >C=O stretching), 1637.88 (Acyclic >C=O stretching)1597.06, 1483.26, 1446.61 (Aromatic ring skeleton), 1309.67 (C-H Bending), 1170.79 (C-O stretching), 837.11 (*p*-disubstituted aromatic ring).; ^{1}H (400 MHz, $CDCl_3$) δ ppm: 7.84-7.82 (d, 2H), 7.41-7.32 (m, 3H), 7.17-7.10 (1H, m), 7.08-7.01 (4H, m), 6.95-6.92 (3H, m), 6.19 (1H, d), 4.22 (1H, d), 2.18-2.14 (2H, dd), 2.09-2.05 (2H, dd), 1.06 (3H, S), 1.03 (3H, S), 0.91 (3H, S).; ^{13}C NMR (101 MHz, $CDCl_3$) δ: 200.61, 188.71, 163.21, 163.19, 156.41, 154.91, 130.86, 130.80, 130.25, 130.27, 130.11, 130.07, 128.80, 127.40, 122.30, 118.21, 118.24, 118.81, 118.70, 118.50, 1123.80, 112.80, 83.49, 56.70, 56.04, 50.42, 41.91, 31.37, 28.88, 27.82.; ms: *m/z*468.19 (M^+).

3-(3-Phenoxyphenyl)-6,6-dimethyl-2-(4-ethoxyphenylcarbonyl)-3,5,6,7-tetrahydro-1-benzofuran-4(2*H*)-one (4f). This compound was isolated in oily light yellow colored. Mole. Formula$C_{31}H_{30}O_5$, Yield 83 %, mp 200 ^{o}C, IR (cm^{-1}):): 2923.15 (Aromatic –CH stretching), 2861.60 (Aliphatic –CH Stretching), 1690.52 (Cyclic >C=O stretching), 1595.10, 1482.30, 1451.40 (Aromatic ring skeleton), 1311.11 (C-H Bending), 1160.98 (C-O stretching), 838.10 (*p*-disubstituted aromatic ring).; ^{1}H (400 MHz, $CDCl_3$) δ ppm: 7.93 – 7.75 (m, 2H), 7.33 – 7.24 (m, 4H), 7.13 (s, 1H), 7.10 – 6.91 (m, 6H), 6.08 (d, 1H), 4.34 (d, 1H), 4.03 (t, 2H), 2.40 (dd, 2H), 2.12 (dd, 2H), 1.39 (q, 3H), 1.09 (s, 6H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ: 201.10, 188.70, 170.19, 164.71, 157.94, 156.40, 138.22, 131.90, 131.90, 130.07, 130.07, 129.69, 128.26, 123.36, 121.05, 120.78, 119.28, 119.28, 116.15, 115.54, 114.20, 114.20, 85.51, 63.99, 50.65, 48.21, 41.53, 31.29, 28.50, 28.50, 13.83.; ms: *m/z*482.20 (M^+).

3-(3-Phenoxyphenyl)-6,6-dimethyl-2-(4-methylphenylcarbonyl)-3,5,6,7-tetrahydro-1-benzofuran-4(2*H*)-one (4g). This compound was isolated in light yellow colored semi-liquid. Mole. Formula $C_{30}H_{28}O_4$, Yield 75 %, mp 171 ^{o}C, IR (cm^{-1}): 2924.09 (Aromatic –CH stretching), 2856.58 (Aliphatic –CH Stretching), 1691.57 (Cyclic >C=O stretching), 1637.56 (Acyclic >C=O stretching), 1555.49, 1483.26, 1446.61 (Aromatic ring skeleton), 1390.68 (C-H Bending), 1211.30 (C-O stretching), 869.93 (*p*-disubstituted aromatic ring).; ^{1}H (400 MHz, $CDCl_3$) δ ppm: 7.81-7.79 (d, 2H), 7.42-7.33 (m, 3H), 7.15-7.08 (1H, m), 7.09-7.02 (4H, m), 6.94-6.93 (3H, m), 6.21 (1H, d), 4.29 (1H, d), 2.19-2.15 (2H, dd), 2.11-2.07 (2H, dd), 1.08 (3H, S), 1.05 (3H, S), 0.95 (3H, S).; ^{13}C NMR (101 MHz, $CDCl_3$) δ: 201.10, 188.70, 170.19, 157.94, 156.40, 145.43, 138.22, 132.00, 130.07, 130.07, 129.69, 129.59, 129.59, 129.58, 129.58, 123.36, 121.05, 120.78, 119.28, 119.28, 116.15, 115.54, 85.51, 50.65, 48.21, 41.53, 31.29, 28.50, 28.50, 21.31.; ms: *m/z*452.19 (M^+).

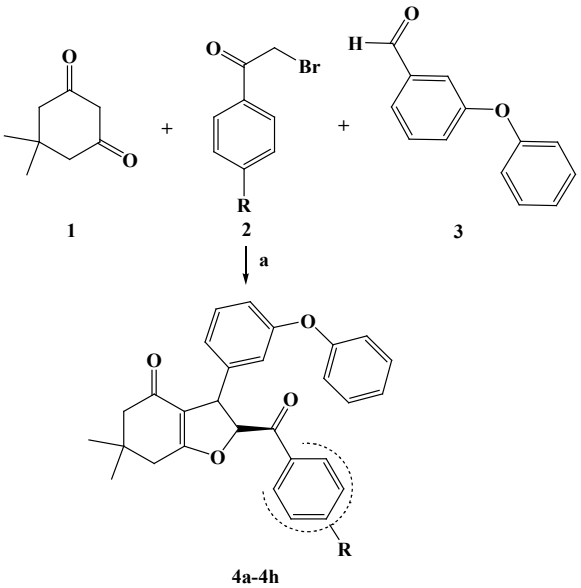
3-(3-Phenoxyphenyl)-6,6-dimethyl-2-(4-nitrophenylcarbonyl)-3,5,6,7-tetrahydro-1-benzofuran-4(2*H*)-one (4h). This compound was isolated in bright light yellow colored solid crystalline compound. Mole. Formula $C_{29}H_{25}NO_6$, Yield 78 %, mp 209 ^{o}C, IR (cm^{-1}): 2956.87 (Aromatic –CH stretching), 2858.51 (Aliphatic –CH Stretching), 1761.01 (Cyclic

>C=O stretching), 1707.00 (Acyclic >C=O stretching), 1550.77 (N-O stretching), 1585.49, 1485.19, 1446.61 (Aromatic ring skeleton), 1390.68 (C-H Bending), 1211.30 (C-O stretching), 877.61 (*p*-disubstituted aromatic ring).; ^{1}H (400 MHz, $CDCl_3$) δ ppm: 8.58 (d, 1H), 8.35-8.33 (m, 2H), 8.10-8.07 (2H, m), 7.41-7.36 (4H, m), 7.15 (1H, m), 7.04-7.02 (2H, m), 6.96-6.93 (2H, m), 6.76-6.75 (1H, m), 6.30 (1H, d), 4.03 (1H, d), 2.15 (2H, dd), 2.10 (2H, dd), 1.08 (6H, S).; ^{13}C NMR (101 MHz, $CDCl_3$) δ: 201.10, 188.70, 170.19, 157.94, 156.40, 150.85, 140.39, 138.22, 130.12, 130.12, 130.07, 130.07, 129.69, 124.52, 124.52, 123.36, 121.05, 120.78, 119.28, 119.28, 116.15, 115.54, 85.51, 50.65, 48.21, 41.53, 31.29, 28.50, 28.50.; ms: *m/z*483.16 (M^+).

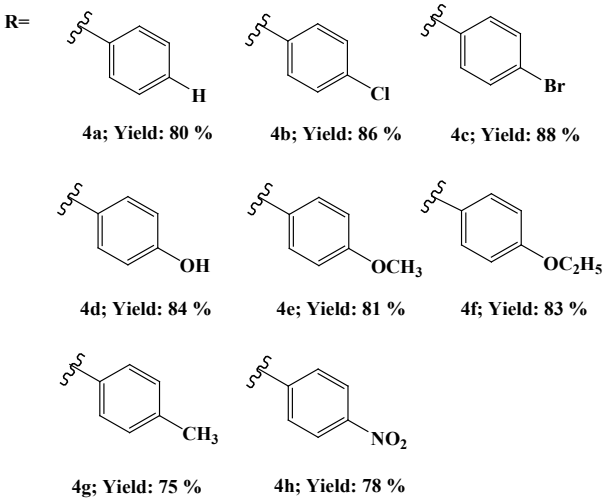
3.0 Results and Discussion

3.1 Chemistry

New benzofuran derivatives **(4a-4h)** were synthesized by a multicomponent procedure in a step economy way. Synthetic pathway and the progress of reaction for the compounds is sketched in reaction Schemes **1**.



Reaction conditions$: a) Acetonitrile, Pyridine, Reflux, 80 °C, 3.0 hrs; Triethylamine, Reflux, 80 °C



Reaction Scheme 1. Reaction pathway for compounds **4a-4h.**

$Each step was carried out in ***Insitu*** reaction condition.

A condensation reaction of pharmalogically and industrially important motif *i.e.* dimedone, novel aldehyde *i.e.* 3-phenoxy benzaldehyde and versatile phenacyl bromide, gave a diverse two chiral center containing benzofurans. These compounds **(4a-4h)** were produced by using two different base *i.e.* pyridine and *N*,*N*-triethylamine (TEA). The reactions proceeded with 75–90 % yield. The structures of the final compounds **(4a-4h)** were elucidated by using IR, ^{1}H-NMR, ^{13}C NMR and MS spectral data. In the IR spectra of the compounds, characteristic stretching bands were observed at ~1720, ~1750 and ~1250 cm^{-1} due to cyclic C=O, acyclic C=O, and C-O bonds. Halogen group in benzofurans also gave idea regarding the confirmation of desired functional and structural aspects.

By looking at ^{1}H-NMR spectra, proton of two chiral carbons C_2 and C_3 givesdoublet at ~ **4.0 δ ppm** and ~ **6.0 δ ppm** respectively. Moreover, the presence of two methyl group in dimedone ring was observed at ~ **1.10 δ ppm**. In addition the conversion to products was also confirmed by an ethylene proton **(~ 3.5 δ ppm)**, which was

between two carbonyl groups in dimedone ring has disappeared in the NMR of the product. The ^{13}C NMR spectrum of the product **4a-4h** exhibited two methyl carbon of benzofuran ring whose signal appeared at ~ **28.00 δ ppm**, two methylene carbons gave signal at ~ **38.00** and ~ **50.00 δ ppm** respectively. One methylene group signal appeared down filed due to the deshielding effect of cyclic carbonyl group.

According to reported values for ^{1}H chemical shifts, the geometry of 4a-4h are clearly assigned as the ***E-isomer*** with the help of the vicinal coupling constants of methine protons**(C2-C3)**, which showed ^{3}JHH values ~ **2.7 Hz**(Figure 1) and also from the literature [15].

An ES–MS spectrum of the compounds gave confirmative molecular peaks, and is well agreement with the fragmentation.

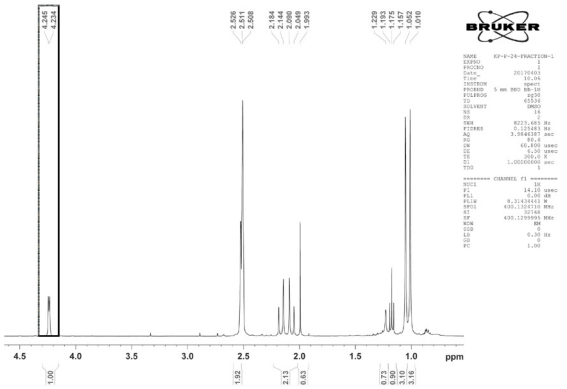


Figure 1. Identification of E-position of C2-C3 hydrogen on the basis of ^{1}H NMR **(Compound 4g; ^{3}JHH= 2.7 Hz)**.

3.2 Anti-cancer study

3.2.1 Method and protocol for screening

Anticancer screening was accomplished at the National Cancer Institute (NCI/NIH), Bethesda, Maryland, USA (https://dtp.cancer.gov/compsub/news.xhtml).

In the current protocol, the human tumor cell lines of the cancer screening panel are grown in RPMI 1640 medium containing 5% fetal bovine serum and 2 mM L-glutamine, inoculated into 96 well microtiter plates.The microtiter plates are incubated at 37°C, 5 %CO_2, 95% air and 100 % relative humidity for 24 hours. Experimental drugs are solubilized in DMSO 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 is thawed and diluted to twice the desired final maximum test concentration with complete medium containing 50µg/ml of gentamicin. Additional four, 10-fold or ½ log serial dilutions are made to provide a total of five drug concentrations plus control. Aliquots of 100 µl of these different drug dilutions are added to the appropriate microtiter wells already containing 100 µl of medium, resulting in the required final drug concentrations.

The plates were incubated for an additional 48 hours at same conditions.Addition is carried out in each well by Sulforhodamine B (SRB) solution (100 µl) at 0.4 % (w/v) in 1 % acetic acid. After 10 minutes staining, unbound dye is removed by washing with 1 % acetic acid and the plates are air dried. Bound stain is subsequently solubilized with 10 mM trizma base, and the absorbance is read on an automated plate reader at a wavelength of 515 nm.

Growth inhibition of 50 % (GI_{50}) is calculated from [(Ti-Tz)/(C-Tz)] x 100 = 50. Out of these experiments, if the effect is not reached or is exceeded, the value for that parameter is expressed as greater or less than the maximum or minimum concentration tested [16].

3.2.2 Activity Assay

Six of the synthesized compounds **(4a, 4b, 4c, 4e,4g , 4h)** were selected by the National

Cancer Institute (NCI) and evaluated for their *in vitro*anti-cancer activity against NCI-60 cell-line panel consisting of mainly nine panels *i.e.* leukemia , non-small cell lung cancer, colon cancer, CNS cancer, melanoma cancer, ovarian cancer, renal cancer, prostate cancer and breast cancer. Each panelconsists of more than three cell lines.One dose response parameters (GI_{50}) were calculated for each used NCI-60 cell lines. The GI_{50} value corresponds to the compound's concentration causing 50% decreases in net cell growth. The standard well marketed drug, cis-platin (Mean GI_{50} value: 1.4 mM) was taken as reference drug.

Compound **4a, 4c** and **4g**indicated promising anti-cancer activity. Compound **4a** reduced the growth of breast cancer cell line **(T-47D: 5.71 %)** and renal cancer cell line **(UO-31: 15.65 %)** **(Table 1)**. Compounds **4a** showed maximum activity when compared to other selected molecules**(Figure 2)**. It gives better results in leukemia, non-small cell lung cancer, renal cancer, breast cancer in the range of **5-15 %** and moderate results in colon cancer, CNS cancer, melanoma cancer, ovarian cancer andprostate cancer in the range of 23-33 %. It's interesting to mention here that all these three have shown activity in the same panel/cell lines.

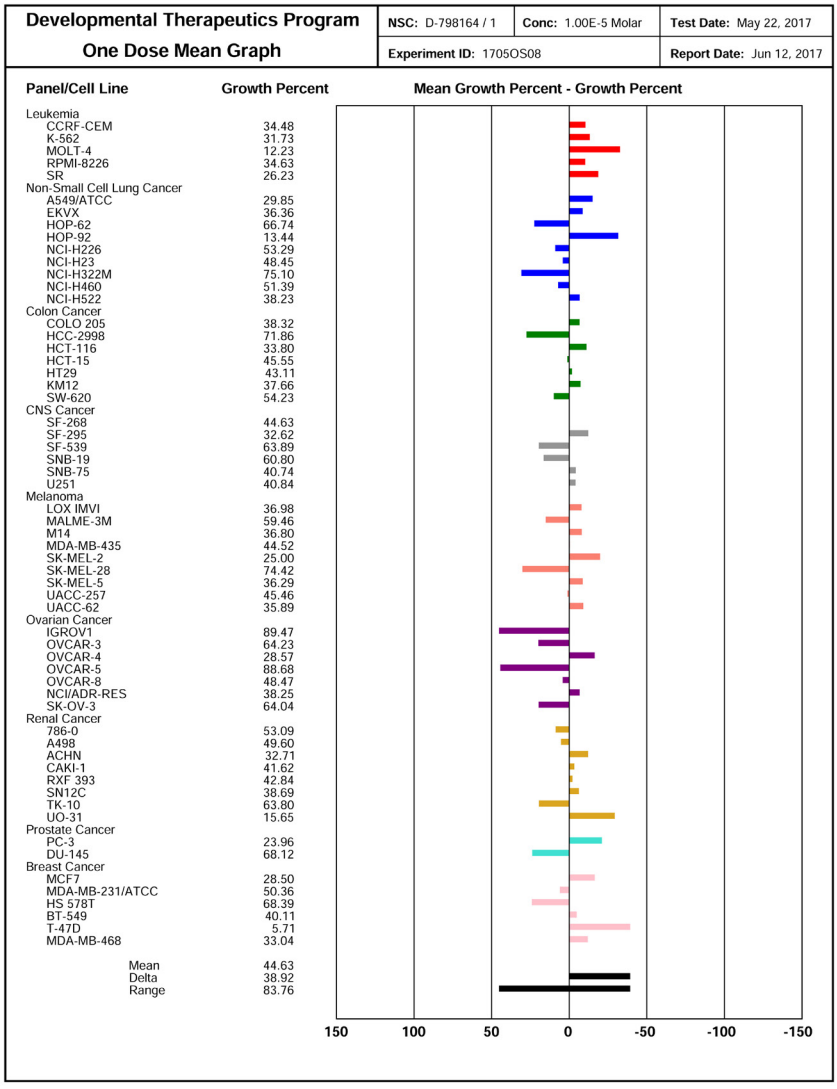


Figure 2. One dose response graph of compound **4a**.

Panels*	4a (NSC ID: D-798164)		4b (NSC ID: D-798165)		4g (NSC ID: D-798162)	
	Cell lines	GI_{50}(%)	Cell lines	GI_{50}(%)	Cell lines	GI_{50}(%)
I	MOLT-4	12.23	MOLT-4	35.73	CCRF-CEM	44.22
II	HOP-92	13.44	A549/ ATCC	51.71	HOP-92	35.75
III	HCT-116	33.80	HCT-116	41.61	HCT-116	26.74
IV	SF-295	32.62	SF-295	56.55	SF-295	51.14
V	SK-MEL-2	25.00	UACC-62	52.63	UACC-62	56.83
VI	OVCAR-4	28.57	OVCAR-4	56.89	OVCAR-4	46.57
VII	UO-31	15.65	UO-31	52.36	UO-31	44.61
VIII	PC-3	23.96	PC-3	41.79	PC-3	37.47
IX	T-47D	05.71	T-47D	37.14	T-47D	24.40

*I, Leukemia; II,non-small cell lung cancer; III, colon cancer; IV,CNS cancer; V, melanoma cancer; VI, ovarian cancer; VII, renal cancer;VIII, prostate cancer; IX, breast cancer.
Color Indication: *Light green color shows that two compounds gave response in similar cell lines and light purple color shows that all three compounds show response in same cell lines.*

Table1. Anti-cancer screening data at single dose assay as percent cell growth promotion of selected compounds**(4a, 4b and 4g)**(Range of <60 %).

The mean growth inhibitory concentrations (GI_{50}, µM) of in vitro subpanel tumor cell lines values are shown in Table 2. Among all tumorcell lines, compound **4a,** which is active against breast cancer cell, leukemia and non-small cell lung cancerhavebeen detected as themost sensitive one with growth percentages **05.71 %**, **12.23 %,** and **13.44 %**respectively. Compound **4g** hasalso caused **24.40 %** growth percentage against **T-47D** whichis a leukemia cell line. In short all the three most active compounds have shown better activity against breast cancer panel and most significance response is found in **T-47D** cell line. Remaining compounds gave average response in the range of **67.99 – 81.97 %** (Mean GI_{50} values) **(Table 2)**.

Compounds	Mean GI_{50} (µM)
4a	44.63
4b	67.99
4c	61.65
4e	90.46
4g	60.36
4h	81.97
Cis-platin	1.4

Table2. Median growth Inhibitory Concentrations (GI_{50}, µM) of *Invitro* subpanel tumor cell lines.

4.0 Conclusion

In this work, the synthesis of ***2-[(substitutedphenyl)carbonyl]-3-(3-phenoxyphenyl)-6,6-dimethyl-3,5,6,7-tetrahydro-1-benzofuran-4(2H)-one***derivatives (4a-4h) and anti-canceractivity of the selected compounds were investigated. The finalcompounds were obtained **insitu**in a single step synthetic procedure andthe structures of the final compounds were proved using IR,^{1}HNMR, ^{13}C NMR and MS spectral data. According to anti-cancer activityresults, compound **4a** exhibited the highest activity resulting ingrowth percentage of only05.71 % on **T-47D** cell lineof breast cancer.

Conflict of interest

The authors confirm that this article content has no conflict of interest.

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