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Original Article

Synthesis of Azide Functionalized Tetrahydrobenzofurans and their Antineoplastic Study

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Abstract

Background: In chemistry, the derivatives of benzofuran which are substituted on five-membered ring constitute one of the salient moieties in medicinal field and a survey of literature revealed that a good number of reports have shown that tetrahydrobenzofuran derivatives are of valuable biological activities.

Aim: On the basis of previous survey, we aimed to generate a series of 2-(4-azidobenzoyl)-3-substitutedaryl-6,6-dimethyl-2,3,6,7-tetrahydrobenzofuran-4(*5H*)-one bearing azide group which were identified by anti-cancer screening against sixteen cell-lines of NCI (National Cancer Institute) using nine different cancer cell panels.

Materials and methods: The tetrahydrobenzofuran derivatives were synthesized by multi-component reactions. It was achieved by coupling of dimedone (3.57 mmole), 4-azido phenacyl bromide (3.92 mmole) and various aromatic aldehydes (3.57 mmole) using two different bases i.e. pyridine and *N,N*- diethylethanamine under reflux condition. Anti-cancer activity was carried out by NCI-60 cell-lines using standard protocol by National Institute of Health.

Results: The results from anti-cancer study shows that the compound **4a** exhibited diverse cytotoxic activity against renal cancer panel (UO-31) with significant selectivity and had inhibitory effect on the generation of **UO-31** (growth percent= 69.36%) and the compound **4e** showed comparable activity in the same cell-line (UO-31: growth percent= 80.86%).

Conclusions: In summary, a series of azide group containing tetrahydrobenzofuran derivatives have been synthesized and were evaluated for their anticancer activity. It was concluded that the derivatives **4a** and **4e** exhibited promising anticancer activity. Nature of substituent on phenyl ring seems to be the crucial factor affecting the activity in both the compounds.

Key words

antineoplastic activity, azide phenacylbromides, NCI-60 cell-lines, tetrahydrobenzofuran

INTRODUCTION

It's well-known that we (humans) are currently passing from the era of non-curable disease i.e. cancer. Even till date, special efforts are being put in to find substantial anticancer agents. On-going study has identified that the analogues of "α,β-unsaturated Michael acceptor" have been an assaulted area for finding active scaffolds in this area.[1,2] Furthermore, alkylating agents as anticancer drug strictly bind with different cellular sites but they lack selectivity. Though, it can be abolished by using Michael acceptors by structural modifications and hence it might be easy to bind

to the targeted nucleophiles/sites with appropriate selectivity.[3,4]

It is widely known that benzo[*b*]furan derivatives substituted at C-2 (2nd numbered carbon of five membered rings in benzofuran) position show cytostatic and/or cytotoxic activity.[5] On scrutinizing the current research on tetrahydrobenzofurans, we can keep a record of the significant work carried out on it and can make a huge list on benzofuran derivatives (for example, ailanthoidol, a neolignan derivative) which makes it a "spectacular" in cancer therapy.[6] In addition, salvinal, isolated from *Salvia miltiorrhiza*, showed inhibitory activity against tumor growth and induced apoptosis in human cancer cells.[7] Recently, in the process of new drug discovery, the anticancer and antiviral activities of a variety of tetrahydrobenzofuran derivatives I[8], NSC725612 and NSC725616[9] have been reported (**Fig. 1**). In most of the drugs, nitrogen atom plays a versatile role for increasing the biological significance during drug designing and synthetic part.[10] Azide functionality is one of the most medicinally active groups which is widely used in the expansion of drug molecular design and used to formulate the basic structural units in medicines.[11] Hence, in this study we have chosen such a lead molecules for design and synthesis of a series of several tetrahydrobenzofuran derivatives substituted directly at C-2 with azide phenyl and C-3 (3rd numbered carbon of five membered rings in tetrahydrobenzofuran) with different aryl groups and such combinations may alter the biological significance in finding a lead drug molecule.[12] Besides, there is no strong evidence in the literature survey appraising the anticancer properties of azide bearing tetrahydrobenzofuran derivatives. These facts invigorated us to synthesize tetrahydrobenzofurans, substituted with azidophenylketone group at C-2 and to investigate the anticancer properties of these compounds.

The traditional method of the synthesis of benzo[*b*]furans involves multistep process and is a time consuming task. However, one of the major causes of waste in organic reaction chemistry is multi-stage synthesis. Thus, single-step syntheses are very attractive and possess high value in modern chemistry. In our previous work, we have reported that tetrahydrobenzofuran moieties exhibited potent antimicrobial activities[13], and we now aimed at designing and synthesizing new compounds 2-(4-azidobenzoyl)-3-substitutedaryl-6,6-dimethyl-2,3,6,7-tetrahydrobenzofuran-4(5H)-one (**4a-j**) with both tetrahydrobenzofuran and azide units in one molecule and exploratory anticancer activity of these newly synthesized molecules (**4a–j**) against nine different cancer panels of NIH (National Institute of Health) using various NCI-60 (National Cancer Institute) cell-lines (**Scheme 1**).

MATERIALS AND METHODS

General

Chemicals and solvents were purchased from Sigma-Aldrich Chemical Co., Merck chemical, Finar and Spectrochem Ltd. The entire chemicals were used without further purification unless otherwise noted. Thin-layer chromatography was accomplished on 0.2 mm precoated plates of Silica gel G60 F254 (Merck). Visualization was made with UV light (254 and 365 nm) or with an iodine chamber. Infrared spectra were recorded on an IR Affinity-1S spectrophotometer (Shimadzu). ^{1}H (400 MHz) and ^{13}C NMR spectra were recorded on a Bruker AVANCE II Spectrometer in DMSO-d_6. Chemical shifts are expressed in δppm downfield from TMS (Tetramethyl silane) as an internal standard. Mass spectra were determined using liquid injection using GC: 7820A and MS: 5977B MSD (Agilent technology). Solvent were evaporated with a ROTEVA rotary evaporator. Melting points were measured in open capillaries and are uncorrected. Elemental analysis of newly synthesized compounds was carried out on Euro Vector elemental analyzer using "Calibration type- linear regression" method.

Chemistry

General procedure for the preparation of 2-[(4-azidophenyl)carbonyl]-6,6-dimethyl-3-substitutedphenyl-3,5,6,7-tetrahydro-1-benzofuran-4(*2H*)-one (4a-4j).

To a 100 ml round bottom flask containing acetonitrile solvent (5.0 ml), a mixture of dimedone **1** (3.57 mmole), 4-azido phenacyl bromide **2** (3.92 mmole), aromatic aldehyde **3** (3.57 mmole) and pyridine (5.6 ml, 7.14 mmole) were refluxed for 3.0 hrs. TEA (*N,N*- diethylethanamine) (7.5 ml, 7.5 mmole) was added into the reaction mixture and was further refluxed for next 3.0 hrs. Completion of the reaction was monitored by thin layer chromatography. The resulting mixture was cooled to room temperature, poured into ice cold water and was stirred at room temperature (RT) for 10 hrs. The solid separated was filtered out and washed with water to give final products. Crystallization was carried out using ethanol to afford analytically pure products **4a-4j** (**Scheme 1**).

Spectral data of representative compounds

2-(4-azidobenzoyl)-6,6-dimethyl-3-(3-nitrophenyl)-2,3,6,7-tetrahydrobenzofuran-4(*5H*)-one (4a).

This compound was bright yellow colored solid material. Yield: 92%; mp: 209°C; IR (cm^{-1}): 3109.08 (Aromatic ring C-H stretching), 1689.54 (Ketonic group), 1393.17, 1418.24, 1468.61, 1519.07 (Aromatic ring skeleton), 1222.35 (C-O stretching), 840.57 (*p*-substituted ring); ^{1}H NMR: (400 MHz, DMSO-d_6)δ 8.24-8.22 (d, 2H, *J*= 8.8 Hz), 7.90-7.88 (d, 2H, *J*= 12 Hz), 7.48-7.46 (d, 2H, *J*= 8.0 Hz), 7.28-7.26 (d, 2H, *J*= 8 Hz), 6.34 (s, 1H), 4.51 (s, 1H), 2.15-2.12 (q, 4H), 1.085 (s, 6H); ^{13}C NMR: (101 MHz, DMSO-d_6)δ 192.00, 191.50, 176.67, 148.89, 146.65, 145.38, 131.06, 129.80, 128.89, 123.83, 119.51, 113.58, 89.89, 50.43, 47.18, 45.67, 38.82, 36.58, 34.03, 28.11, 27.81; MS (m/z): 432.23 (M^{+}); Anal Calcd for $C_{23}H_{20}N_4O_5$: C, 63.88; H, 4.66; N, 12.96; O, 18.50. Found: C, 63.80; H, 4.70; N, 12.98; O, 18.52.

2-(4-azidobenzoyl)-3-(furan-2-yl)-6,6-dimethyl-2,3,6,7-tetrahydrobenzofuran-4(*5H*)-one (4b).

This compound was dark reddish brown colored solid

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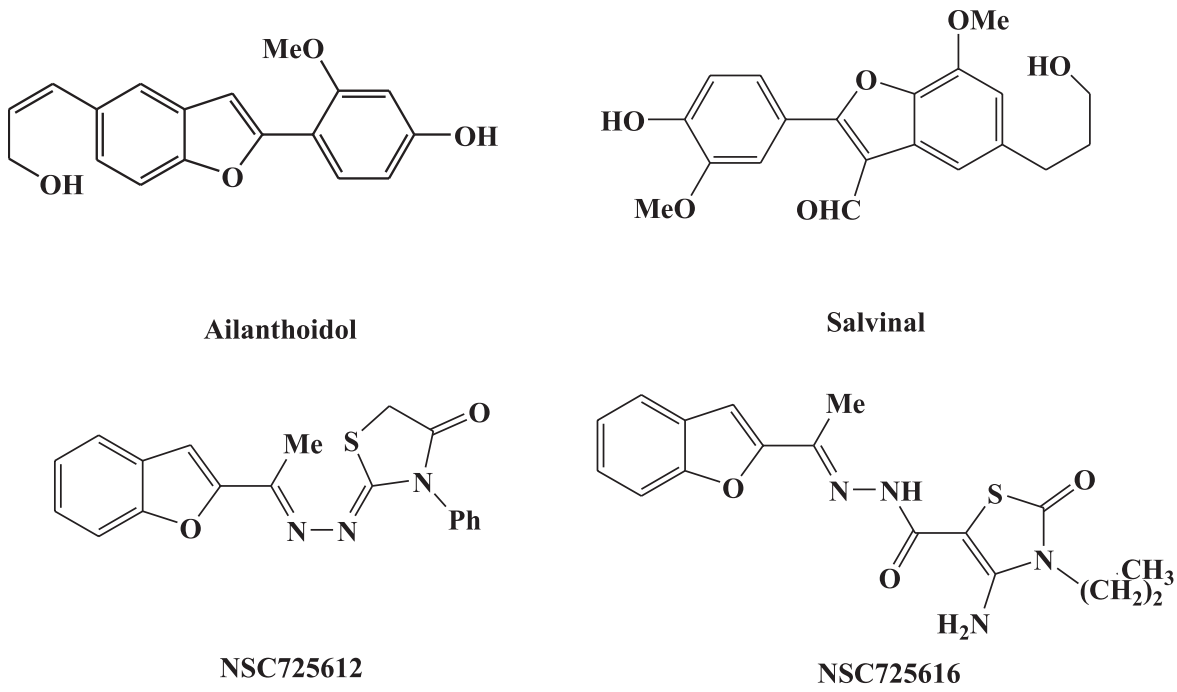
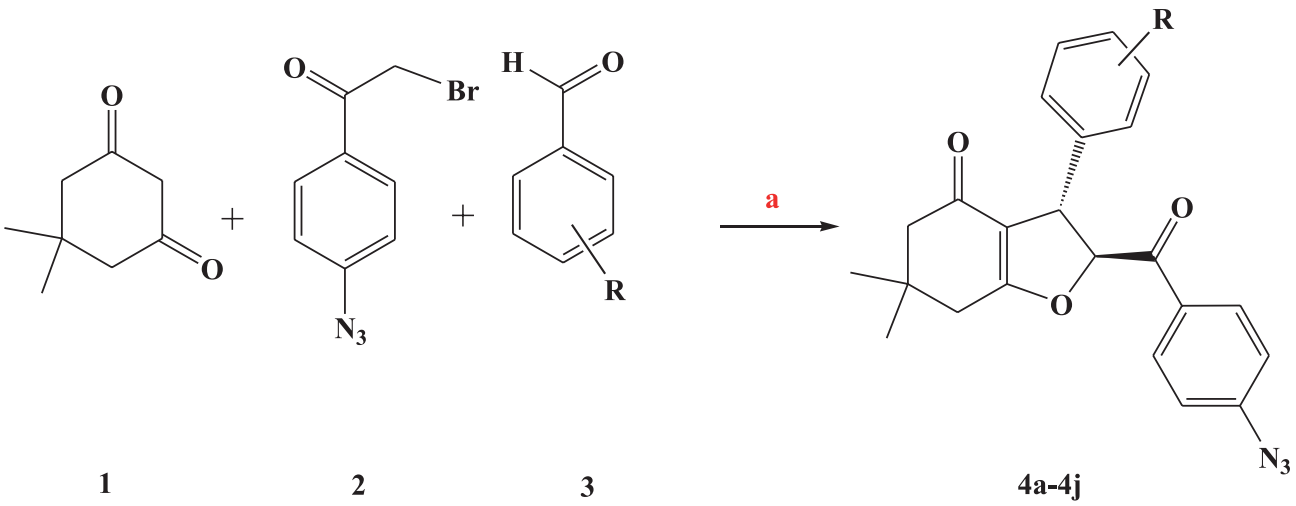


Figure 1. C-2 and C-3 substituted medicinally lead benzofuran analogues.



Reaction Scheme 1. Reaction and conditions: a) Acetonitrile, pyridine, 60-70°C 3.0 h; and A/3.0 h, TEA, 60-70°C, 3.0 h.

material. Yield: 88%; mp: 256°C; IR (cm^{-1}): 3116.14 (Aromatic ring C-H stretching), 1692.30 (Ketonic group), 1396.08, 1417.56, 1504.15, 1597.12 (Aromatic ring skeleton), 1222.53 (C-O stretching), 840.16 (*p*-substituted ring); ^{1}H NMR: (400 MHz, DMSO-d_6)δ 7.99-7.97 (d, 2H, *J*= 8.0 Hz), 7.62-7.61 (m, 1H), 7.31-7.28 (q, 2H), 6.42-6.41 (m, 1H), 6.31-6.29 (d, 1H, *J*= 4.4 Hz), 6.18-6.16 (d, 1H, *J*= 3.2 Hz), 4.42-4.40 (d, 1H, *J*= 4.0 Hz), 2.17-2.15 (d, 4H, *J*= 7.6 Hz), 1.23-1.21 (d, 3H, *J*= 3.2 Hz), 1.09-1.07 (d, 3H, *J*= 12 Hz); ^{13}C NMR: (101 MHz, DMSO-d_6)δ 192.52, 191.63, 176.77, 152.91, 145.37, 142.55, 131.06, 106.69, 87.87, 50.55, 41.08, 36.66, 33.99, 31.27, 28.98; MS (m/z): 377.39 (M^+); Anal Calcd for $C_{21}H_{19}N_3O_4$: C, 66.83; H, 5.07; N, 11.13; O, 16.96. Found: C, 66.78; H, 5.08; N, 11.15; O, 16.98.

2-(4-azidobenzoyl)-3-(2,5-dimethoxyphenyl)-6,6-dimethyl-2,3,6,7-tetrahydrobenzofuran-4(*5H*)-one (4c).

This compound was light yellow colored solid material. Yield: 79%; mp: 190°C; IR (cm^{-1}): 3156.56 (Aromatic ring C-H stretching), 1688.43 (Ketonic group), 1390.88, 1426.46, 1514.14, 1588.22 (Aromatic ring skeleton), 1278.67 (C-O stretching), 780.44,820.78 (*o, m*-substituted ring); ^{1}H NMR: (400 MHz, DMSO-d_6)δ 8.20-8.22 (d, 2H,

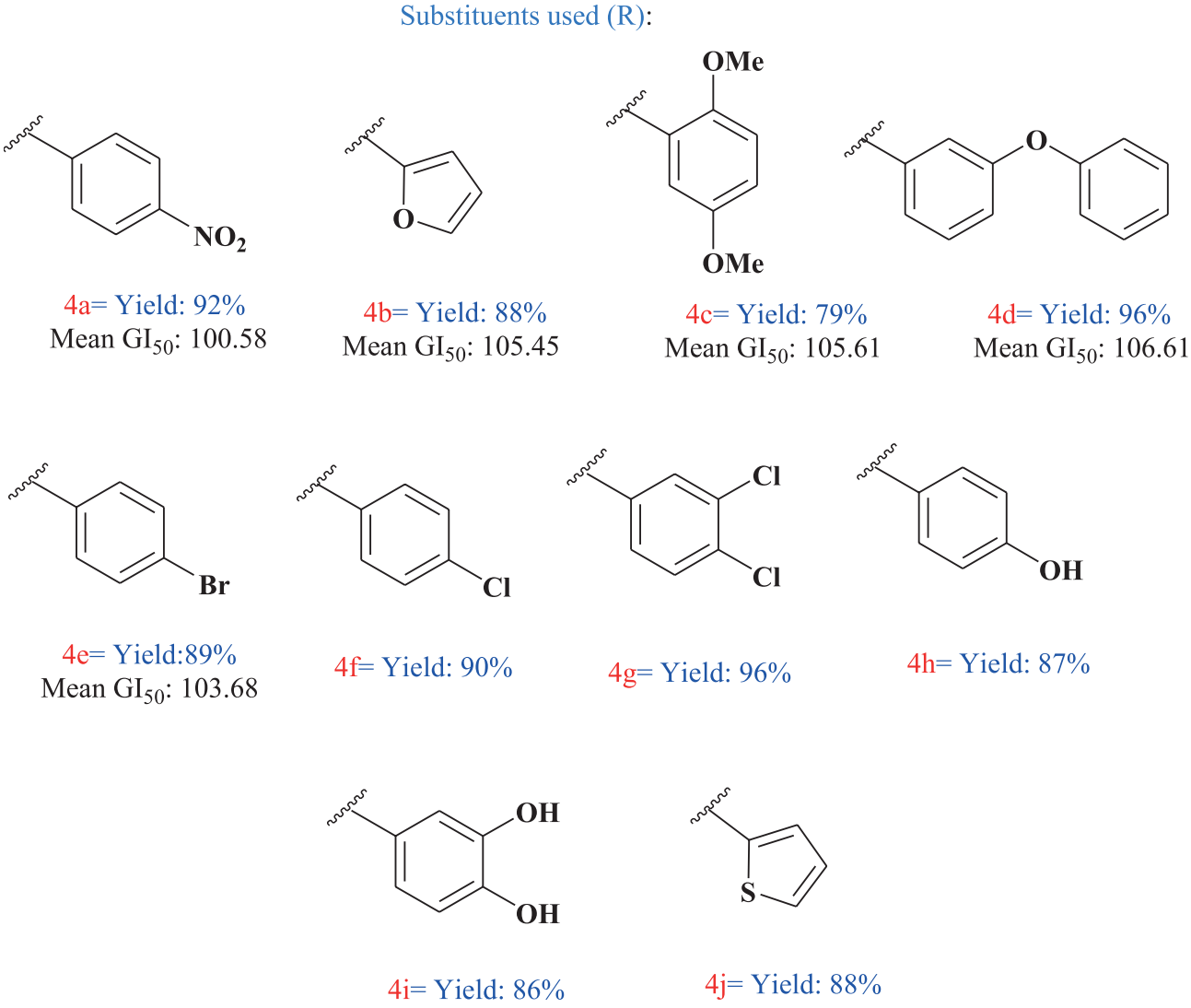


Figure 2. Synthesized structures related data of used substituents.

J= 8.8 Hz), 7.44-7.42 (d, 2H, *J*= 12 Hz), 7.30 (s, 1H), 7.26-7.24 (d, 2H, *J*= 8.0 Hz), 6.31 (s, 1H), 4.49 (s, 1H), 3.60 (s, 6H), 2.10-2.14 (q, 4H), 1.08 (s, 6H); ^{13}C NMR: (101 MHz, DMSO-d_6)δ 192.40, 191.10, 176.38, 148.60, 146.40, 145.18, 131.01, 129.45, 128.80, 123.40, 119.40, 113.50, 89.70, 56.67, 54.05, 50.35, 47.08, 45.15, 38.45, 36.30, 34.01, 28.05, 27.40; MS (m/z): 447.48 (M^+); Anal Calcd for $C_{25}H_{25}N_3O_5$: C, 67.08; H, 5.64; N, 9.41; O, 17.90. Found: C, 67.12; H, 5.62; N, 9.40; O, 17.89.

2-(4-azidobenzoyl)-6,6-dimethyl-3-(3-phenoxyphenyl)-2,3,6,7-tetrahydrobenzofuran-4(*5H*)-one (4d).

This compound was reddish brown colored solid material. Yield: 96%; mp: 260°C; IR (cm^{-1}): 3111.66 (Aromatic ring C-H stretching), 1687.57 (Ketonic group), 1377.89, 1456.56, 1544.17, 1580.25 (Aromatic ring skeleton), 1259.37 (C-O stretching), 773.64 (*m*-substituted ring); ^{1}H NMR: (400 MHz, DMSO-d_6)δ 8.22-8.20 (d, 2H, *J*= 8.8 Hz), 7.89-7.87 (d, 2H, *J*= 12 Hz), 7.40-7.38 (d, 2H, *J*= 8.0 Hz), 7.25-7.23 (d, 2H, *J*= 8.0 Hz), 7.21-7.19 (m, 2H), 6.91-6.80 (m, 3H), 6.31 (s, 1H), 4.40 (s, 1H), 2.135-2.110 (q, 4H), 1.01 (s, 6H); ^{13}C NMR: (101 MHz, DMSO-d_6)δ 192.40, 191.30, 176.40, 164.85, 148.40, 146.30, 145.15, 131.01, 129.55, 129.30, 128.90, 128.65, 123.40, 122.65, 119.40, 119.08, 118.05, 113.40, 89.80, 50.09, 47.08, 45.42, 38.05, 36.15, 34.01, 28.05, 27.40; MS (m/z): 479.53 (M^+); Anal Calcd for $C_{29}H_{25}N_3O_4$: C, 72.64; H, 5.25; N, 8.76; O, 13.35. Found: C, 72.70; H, 5.26; N, 8.73; O, 13.31.

2-(4-azidobenzoyl)-3-(4-bromophenyl)-6,6-dimethyl-2,3,6,7-tetrahydrobenzofuran-4(*5H*)-one (4e).

This compound was red colored solid material. Yield: 89%; mp: 210°C; IR (cm^{-1}): 3189.43 (Aromatic ring C-H stretching), 1691.90 (Ketonic group), 1380.02 1461.49, 1573.19, 1577.32 (Aromatic ring skeleton), 1233.75 (C-O stretching), 843.13 (*p*-substituted ring); ^{1}H NMR: (400 MHz, DMSO-d_6)δ 8.23-8.21 (d, 2H, *J*= 8.8 Hz), 7.83-7.81

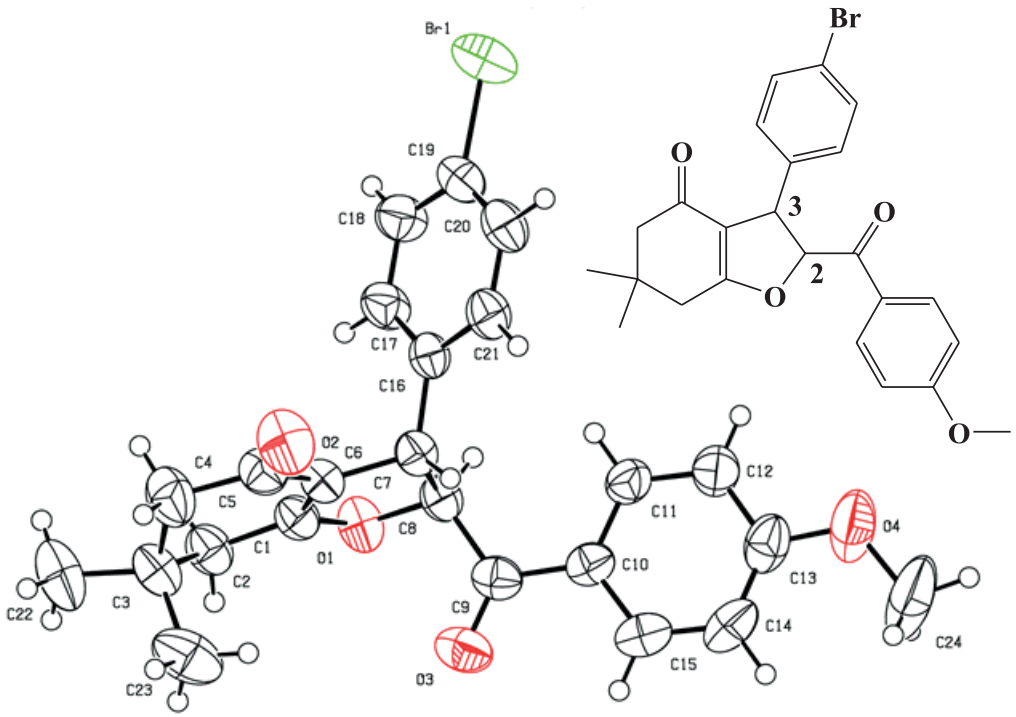
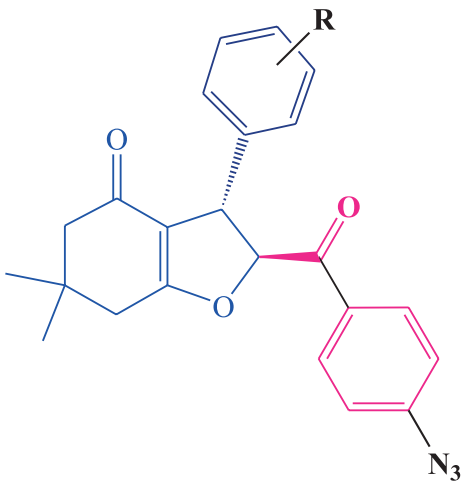


Figure 3. Oak ridge thermal ellipsoid plot (ORTEP) of the reference molecule at 50% probability (C-2 and C-3 positions in "S" configurations).[13]

Synthesis of Azide Functionalized Tetrahydrobenzofurans and their Antineoplastic Study

Graphical abstract



	Renal cancer panel (UO-31 cell-line)	
	4a (4-NO_2)	4e (4-Br)
Growth percent:	69.36%	80.86%

Benzofurans having Azide functionality

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Table 1. In vitro cytotoxicity study of selected compounds (**4a-4j**)

Compounds	Cancer panels and cell-lines (growth percent: < 80%)			
	Cancer panels	Cell-lines	Growth percent	Mean growth percent
4a	Renal cancer	UO-31	69.36	100.58
4b	-	-	-	105.45
4c	-	-	-	105.61
4d	-	-	-	106.61
4e	Renal cancer	UO-31	80.66	103.68

(d, 2H, *J*= 12 Hz), 7.45-7.43 (d, 2H, *J*= 8.0 Hz), 7.18-7.16 (d, 2H, *J*= 8.0 Hz), 6.32 (s, 1H), 4.50 (s, 1H), 2.16-2.12 (q, 4H), 1.05 (s, 1H); ^{13}C NMR: (101 MHz, DMSO-d_6)δ 192.33, 191.25, 176.34, 148.46, 146.36, 145.16, 129.40, 131.01, 128.56, 123.40, 119.35, 113.41, 89.98, 50.15, 47.06, 45.36, 38.44, 36.40, 34.01, 28.05, 27.75; MS (m/z): 466.33 (M^+); Anal Calcd for $C_{23}H_{20}BrN_3O_3$: C, 59.24; H, 4.32; Br, 17.13; N, 9.01; O, 10.29. Found: C, 59.22; H, 4.33; Br, 17.15; N, 9.00; O, 10.28.

RESULTS AND DISCUSSION

General chemistry

The overall synthetic route used to synthesize hybrid compounds is delineated in **Scheme 1**.

Treatment of commercial 5,5-dimethylcyclohexane-1,3-dione (**1**) with 1-(4-azidophenyl)-2-bromoethanone (**2**) and variety of phenyl aldehydes (**3a-j**) gave the 2-[(4-azidophenyl)carbonyl]-6,6-dimethyl-3-substitutedphenyl-3,5,6,7-tetrahydro-1-benzofuran-4(2H)-one (**4a-4j**) in the presence of pyridine and *N,N*- diethylethanamine base in refluxing acetonitrile. To get further insight into the *in vitro* analysis, the final products (4a-4j) were prepared with excellent yields by the reaction with various Ph-CHO and the biological activities of substituents on the phenyl ring were compared. Analysis data for the synthesized new molecules with respect to anticancer properties, structures and yields are provided in **Fig. 2**. All the synthesized compounds were characterized by IR, ^{1}H-NMR, ^{13}C-NMR and mass spectrometry. The spectra of title compounds are in Supplementary Materials.

Structural characterizations

In the IR spectra of 2-[(4-azidophenyl)carbonyl]-6,6-dimethyl-3-substitutedphenyl-3,5,6,7-tetrahydro-1-benzofuran-4(*2H*)-one (**4a-4j**), >C=O stretching vibration was observed at ~1690 cm^{-1} and absence of aldehydic >C=O stretching frequency shows the formation of tetrahydrobenzofuran derivatives. Moreover other functional groups like halogens, nitro, azide etc. were in well agreement to desired products in final molecules.

The ^{1}H NMR spectra of the synthesized tetrahydrobenzofurans (4a-4j) showed aromatic signals at δ 7.2-8.2 ppm corresponding to aromatic protons and two doublet peaks observed at ~6.2 and ~4.4 δ which correspond to the two chiral center at C-2 (H) and C-3 (H) respectively. ^{1}H NMR spectra of compounds (4a–4j) also revealed the appearance of the strong singlet of six protons of tetrahydrobenzofuran's six membered rings which occurs in the range of 1.0-1.2 ppm. The β and δ –CH_2 peak was observed at ~2.2 ppm with variable splitting sequence.

A stereochemical aspect of desired product was identified by our similar previous work. The major part of structural elucidation was to identify the configuration at C-2 and C-3 and it was identified that both the carbon shows "S" (sinister) configuration (**Fig. 3**).

***In vitro* cytotoxicity screening**

NCI-60 cell-lines were used for evaluation of *in vitro* anticancer activity of synthesized tetrahydrobenzofuran compounds synthesized at National Institute of Health (NIH) and nine cancer cell panels including Leukemia, Non-small cell lung cancer, colon cancer, Central Nervous System (CNS) cancer, Melanoma, Ovarian cancer, Renal cancer, Prostate cancer and Breast cancer. The screening was a two-stage process; beginning with the evaluation of all compounds against the 60 cell lines at a single dose of 10 μM. Data analysis is available by the "COMPARE program" and it was reported as the single dose screen. The data is reported as a mean graph of the percent growth of treated cells and were similar in appearance to mean graphs from the 5-dose assay (if data allowed from single dose study). Drug activity was determined by the DTP (Developmental Therapeutics Program) human cancer cell line screen and reported the values in terms of GI_{50} (Growth Inhibition of 50% of the cells) values. No control drug was used to identify a good anticancer agent by NCI as per protocol used in NIH.[14]

The cytotoxicity of the tested compounds (**4a-4j**) were determined on sixteen different human cancer cell lines (**Table 1**) on cell viability measured at 24 h after exposure. As per the protocol by NCI, computational studies were carried out to identify the probable active scaffolds out of screened molecules. Only when promising results are obtained are the in vitro studies performed.[15]

Data from **Table 1** revealed that the azide group containing tetrahydrobenzofuran derivatives showed promising response against in UO-31 cell lines (< 80%). Compounds **4a** and **4e** pointedly reduced the viability percentage of UO-31 cells at "10 μM concentrations". Among the synthesized tetrahydrobenzofurans compounds 4a and 4e were found to be most potent against UO-31 cell lines in renal cancer panel. As mentioned earlier there is no evidence for reporting the data for the anticancer activity of "azide-benzofurans". We have studied a bunch of NCI-60 cell-lines to exactly identify the effect of azide substituents on tetrahydrobenzofuran to recognize the anticancer properties.

As shown in **Table 1**, cytotoxic screening of the synthesized hybrid molecules showed palpable stimulus on cytotoxic activities. There were a single series of substituents at C-3 position of the tetrahydrobenzofuran ring, including azide functionalized aromatic ring with keto group at C-2 position. Compounds **4a** and **4e** were displaying better *in vitro* cytotoxic activity. However, the remaining tetrahydrobenzofuran analogues with substituted aromatic compounds **4b**, **4c** and **4d** had pathetic cytotoxic activity. In addition, the rational criteria due which structural part can be recognized that tetrahydrobenzofuran C-2 position could be more active either in the presence of electron withdrawing group or halide substituent, such as 4-NO_2 (**4a**) and 4-Br (**4e**). The novel compounds **4a** and **4e** displayed comparable anti-neoplastic activity and prominent selectivity against **UO-31** with growth percent, **69.36%** and **80.66%** respectively. In above discussion, it was generalized that out of the 10 synthesized molecules only a few compounds were revealed to possess antitumor activities but we could correlate the tendency of tetrahydrobenzofuran–azide compounds and research them further following the results obtained.

CONCLUSIONS

In this paper, a series of azide group containing tetrahydrobenzofuran derivatives which have been synthesized and evaluated for anticancer activity have been reported. Derivatives **4a** and **4e** exhibited promising anticancer activity. Nature of substituent on phenyl ring seems to be the crucial factor affecting the activity in both the compounds. In summary, additional studies on these new tetrahydrobenzofuran analogues on inspection of their therapeutic potentials can serve as the landmark in probing new therapies for the disease. We are also looking forward that the current work on synthesizing benzofuran by targeting C-3 positioned substituents and applying *in silico* study to find potent anticancer agents.

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Синтез функционализированных азидом тетрагидробензофуранов и их противоопухолевые свойства

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Абстракт

Введение: В химии производные бензофурана, которые замещены на пятичленное кольцо, представляют собой одну из интереснейших частиц в области лекарственных средств, а обзор доступной литературы показал, что в ряде исследований утверждается, что тетрагидробензофураны обладают ценными биологическими свойствами.

Цель: На основании нашего предыдущего исследования, наша цель состояла в том, чтобы генерировать серии 2- (4-азидобензоил) -3-замещенного арил-6,6-диметил-2,3,6,7-тетрагидробензофуран-4 (5H) – один, содержащие азидную группу, которые были идентифицированы с помощью противоракового скрининга в соответствии с шестнадцатью клеточными линиями НИР (Национального института рака) с использованием девяти различных панелей раковых клеток.

Материалы и методы: Производные тетрагидробензофурана были синтезированы с применением многокомпонентных реакций. Это было достигнуто путём сочетания димедона (3,57 mmole), 4-азидофенацилбромида (3,92 mmole) и различных ароматических альдегидов (3,57 mmole) с использованием двух разных основ, например, пиридина и N, N-диэтилэтанамина при кипячении. Противораковая активность была проверена клеточными линиями NCI-60 в соответствии со стандартным протоколом Национального института здоровья.

Результаты: Результаты противоопухолевого исследования показали, что ингредиент **4a** проявлял разнообразную цитотоксическую активность в отношении панели почечной карциномы (UO-31) со значительной селективностью и обладает ингибирующим эффектом на образование UO-31 (процент роста = 69,36%), а ингредиент **4e** показал сравнительный характер активности в той же клеточной линии (UO-31: процент роста = 80,86%).

Выводы: Синтезирован ряд производных тетрагидробензофурана, содержащих азидную группу, и оценен их противораковый эффект. Был сделан вывод, что производные 4a и 4e проявляют многообещающую противораковую активность. Доказано, что природа заместителя фенильного кольца является существенным фактором, влияющим на активность обоих компонентов.

Ключевые слова

тетрагидробензофуран, противоопухолевая активность, азид фенацилбромиды, NCI-60 клеточные линии