Molecular Diversity
https://doi.org/10.1007/s11030-022-10493-7

ORIGINAL ARTICLE

Rational synthesis, anticancer activity, and molecular docking studies of novel benzofuran liked thiazole hybrids

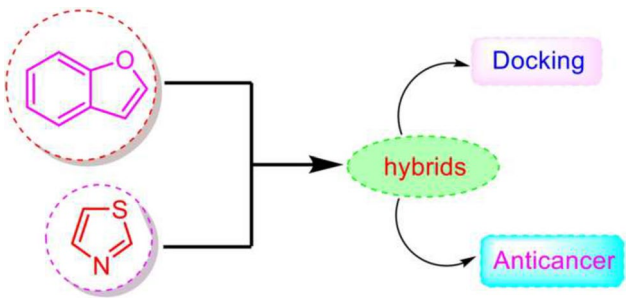
Sanjay D. Hadiyal[1,2] · Jaydeep N. Lalpara[2] · Bhavin B. Dhaduk[2] · H. S. Joshi[1]

Received: 28 March 2022 / Accepted: 2 July 2022

Abstract

A novel series of benzofuran bearing thiazole hybrids were synthesized by the multistep reaction approach. All synthesized molecules were selected by the National Cancer Institute, USA for one-dose anticancer activity against 60 various human cancer cell lines indicating nine types of cancer. Among thirteen compounds, two compounds showed higher lethality, so, it was selected for five-dose anticancer screening against all cancer cell lines. Compound 8g and 8h were displayed remarkable antiproliferative activity with GI_{50} values ranging from 0.295 to 4.15 µM and LC_{50} values ranging from 4.43 to > 100 µM. All data are compared with standard drugs fluorouracil and doxorubicin. Compound 8g showed higher potency as a cytotoxic molecule then fluorouracil. Furthermore, all new hybrids were studied for molecular docking into the active binding sites of 1HOV protein.

Graphical abstract



Keywords Thiazole · Benzofuran · Anticancer activity · Molecular docking · NCI-60

Introduction

Investigation of new pharmacophores is demanding in the current scenario. Several protocols have been established over the past few years. Using of a new building block to synthesize a numerous heterocyclic scaffold which shows a significant and diverse biological response. The heterocyclic compounds having diverse clubbed moieties show a diverse significant activity [1–3]. Cancer has long been documented as one of the common reasons for death [4]. Therefore, numerous different systems have been utilized to construct new therapies or to enhance prevailing treatment. The investigation of more potent, newly functionalized, and least toxic anticancer agents is the prime target for a researcher as of its widespread and severe infection.

Thiazole and its analogs are promising scaffolds in medicinal chemistry and many of them were reported to show a diversity of biological responses such as anti-Alzheimer, anti-hypolipidemic, anticancer, anti-HIV, anti-inflammatory, antihypertensive, antimicrobial, anticonvulsant, antiviral, antimalarial, and antidiabetic activities [5–15]. Furthermore,

✉ H. S. Joshi
drhsjoshichem@gmail.com

[1] Department of Chemistry, Saurashtra University, Rajkot, Gujarat 360005, India

[2] Department of Chemistry, RK University, Rajkot, Gujarat 360020, India

Published online: 19 July 2022

their heterocyclic fused analogs have gained extensive attention due to their significant biological response. Thiazole ring-containing compounds have marked their existence in several clinically available anticancer drugs like dasatinib (tyrosine kinase inhibitor Bcr-Abl) [16], tiazofurin (IMP dehydrogenase inhibitor) [17], and dabrafenib (B-RAF enzyme inhibitor) [18].

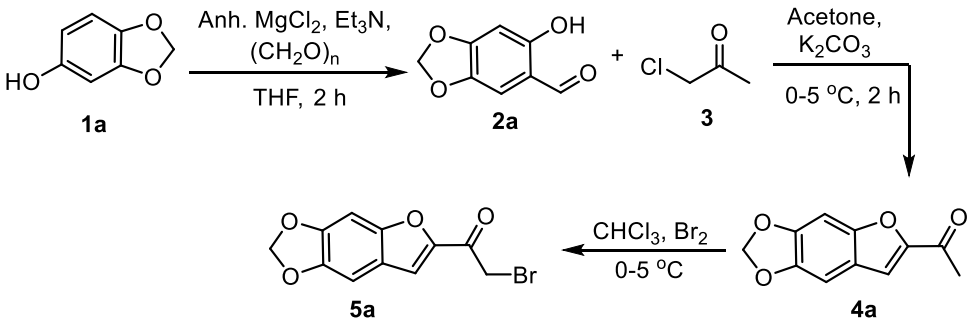
Furthermore, benzofuran is an important class of heterocyclic moiety of the fused heterocycle. Benzofuran analogs exhibit a diverse biological response such as kinase inhibitor, antitumor, analgesic, and antimicrobial [19–22]. Additionally, benzofuran derivatives find applications including fluorescent sensors [23] and polymer-supported reagents [24]. The most renowned and recognized natural products containing benzofuran ring structure are amiodarone, ailanthoidol, and bufuralol compounds [25]. Moreover, some of the 2-arylbenzofuran compounds derived from natural products also have significant biological responses [26]. Recently, blood–brain permeable and oral active benzofuran derivatives have been found to exhibit potent anti-amyloid aggregation activity, which can make available an alternative treatment for Alzheimer's disease [27].

Additionally, the hybridization of the molecule has gained much attention in the drug design area in the past decade. It includes the combination of two pharmacophore moieties with diverse bioactivity to form a new hybrid molecule directing at enhancing their biological efficacy and overcoming drug resistance [28]. Molecular docking is a powerful tool to identify and design biologically active compounds. Here, we performed a docking study on 1HOV (MMP-2) protein. MMP-2 is a member of the matrix metalloproteinase family that has been implicated in tumor cell metastasis and angiogenesis. Solution structure of a catalytic domain of MMP-2 complexed with a hydroxamic acid inhibitor (SC-74020) [29]. 1HOV is associated mostly in pathogenesis of colorectal cancer. In continuation of our efforts toward synthesis of bioactive molecules [30, 31]; herein, we wish to report a synthesis of hybrid molecules comprising benzofuran linked with thiazole and their corresponding derivatives.

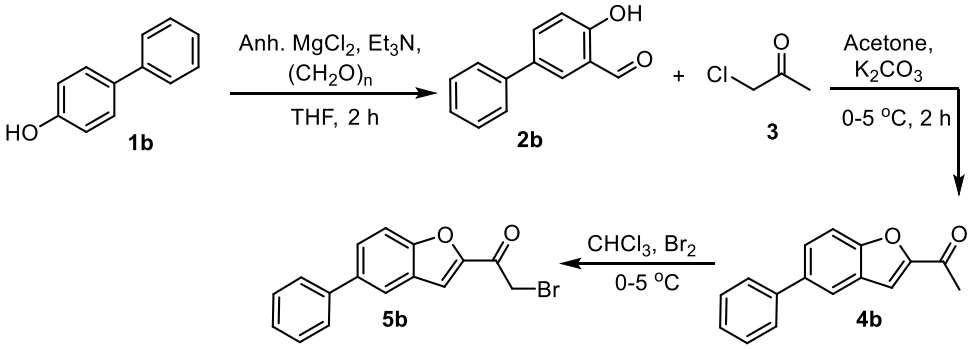
Results and discussion

Chemistry

The starting materials required in the synthesis of our aimed molecules are prepared as outlined in Scheme 1 and Scheme 2. Thus, 2-bromo-1-(2*H*-furo[2,3-*f*][1,3]benzodioxol-6-yl)ethan-1-one **5a** and 1-([1,3]dioxolo[4,5-*f*]benzofuran-6-yl)-2-bromoethan-1-one **5b** were, respectively, obtained in high yields by the reaction of the corresponding phenol derivatives sesamol **1a** and [1,1′-biphenyl]-4-ol **1b** with paraformaldehyde under a basic condition in the presence of anhydrous $MgCl_2$ to form the corresponding salicylaldehyde **2a** and **2b**. Followed by the cyclization of salicylaldehyde with chloroacetone in the presence of K_2CO_3 at 0–5 °C for 2 h to get a product as **4a** and **4b**. Further bromination on acetyl carbon in the presence of Br_2



Scheme 1 Synthesis of 1-([1,3]dioxolo[4,5-*f*]benzofuran-6-yl)-2-bromoethan-1-one from sesamol



Scheme 2 Synthesis of 2-bromo-1-(5-phenylbenzofuran-2-yl)ethan-1-one from [1,1'-biphenyl]-4-ol

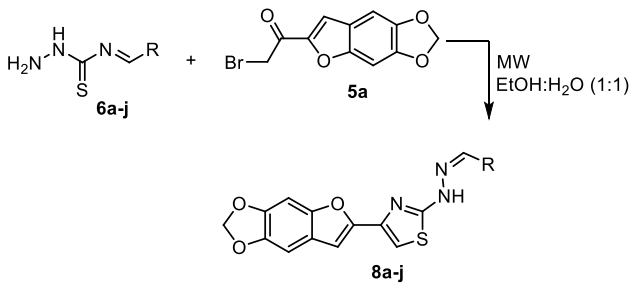
Table 1 Reaction optimization for compound **8a** using conventional heating and microwave irradiation method

Entry	Solvent	Conventional heating			Microwave irradiation		
		Temp (°C)	Time (min)	Yield (%)	Temp (°C)	Time (min)	Yield (%)
1	PEG-400	60	90	75	60	10	76
2	MeCN	70	90	54	70	10	58
3	THF	60	90	57	60	10	57
4	EtOH	Reflux	90	80	80	10	85
5	H_2O	rt	180	Trace	–	–	–
6	H_2O	Reflux	90	63	90	10	65
7	EtOH: H_2O (1:1)	70	90	83	70	10	92

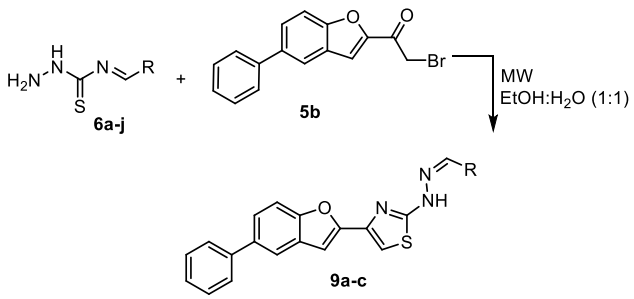
in chloroform at 0–5 °C to get desired adducts **5a** and **5b** (Scheme 1, Scheme 2).

The present work aims to synthesize 4-([1,3]dioxolo[4,5-*f*]benzofuran-6-yl)-2-(2-(substitutedbenzylidene)hydrazinyl)thiazole **(8a–j)** and 4-(5-phenylbenzofuran-2-yl)-2-(2-(substitutedbenzylidene)hydrazinyl)thiazole **(9a–c)**. To achieve this target, we firstly synthesized 2-bromo-1-(2*H*-furo[2,3-*f*][1,3]benzodioxol-6-yl)ethan-1-one **5a** and 1-([1,3]dioxolo[4,5-*f*]benzofuran-6-yl)-2-bromoethan-1-one **5b**. Further it reacts with substituted hydrazinecarbothioamide **(6a–j)** to get final adducts. Several reaction conditions have been applied for the synthesis of desired adducts. One-pot reaction of *N*-(3,4,5-trimethoxybenzylidene)hydrazinecarbothioamide **6a**, and 2-bromo-1-(2*H*-furo[2,3-*f*][1,3]benzodioxol-6-yl)ethan-1-one **5a** was chosen as a model reaction. This reaction was screened against various solvents such as polar protic and polar aprotic. It was carried out by conventional heating method as well as microwave-assisted method (Table 1). From reaction optimization, we found that aqueous ethanol (1:1) was the best solvent in terms of yield, and the reaction was carried out without a catalyst. We tried to complete the reaction in aqueous media, but we did not get a good yield, after that the reaction was also performed at room temperature eventually no trace of the products was achieved even though a long time. Comparing the time of completion for the reaction by conventional method and microwave irradiation method, we found that the microwave method was better than conventional heating method, because reaction was completed within 10 min and conventional heating method required 1.5–2 h.

The diversity of this reaction and substrate scope were evaluated by synthesizing a series of 4-([1,3]dioxolo[4,5-*f*]benzofuran-6-yl)-2-(2-(substitutedbenzylidene)hydrazinyl)thiazole (**8a–j**). The final adducts were achieved by the cyclocondensation reaction of substituted hydrazinecarbothioamide **(6a–j)** with 1-([1,3]dioxolo[4,5-*f*]benzofuran-6-yl)-2-bromoethan-1-one **5a** under the final optimal condition in good yield (Scheme 3). Similarly, compound 1-([1,3]dioxolo[4,5-*f*]benzofuran-6-yl)-2-bromoethan-1-one **5b** react with substituted hydrazinecarbothioamide **(6a–c)** under the same condition to get



Scheme 3 Microwave irradiated synthesis of thiazole-based dioxol ring fused benzofuran derivatives under aqueous ethanolic media



Scheme 4 Synthesis of thiazole-based benzofuran analogs in aqueous EtOH under microwave irradiation

4-(5-phenylbenzofuran-2-yl)-2-(2-(substitutedbenzylidene) hydrazinyl)thiazole **9a–c** derivatives in good yields (Scheme 4).

Biology

The five-dose anticancer evaluation data showed that two compounds, **8g** and **8h** exhibited excellent activity with significant low values of GI_{50} (0.295 to 4.15 μM), TGI (1.45 to > 100 μM) and LC_{50} (4.43 μM to > 100 μM) against numerous cancer cell lines, some of them have lower than 1.0 μM. The mean graph of $Log_{10}GI_{50}$, $Log_{10}TGI$, and $Log_{10}LC_{50}$ for all two compounds are displayed in Fig. 2 and compared with the reference drugs fluorouracil and doxorubicin. From the data, all two compounds specifically

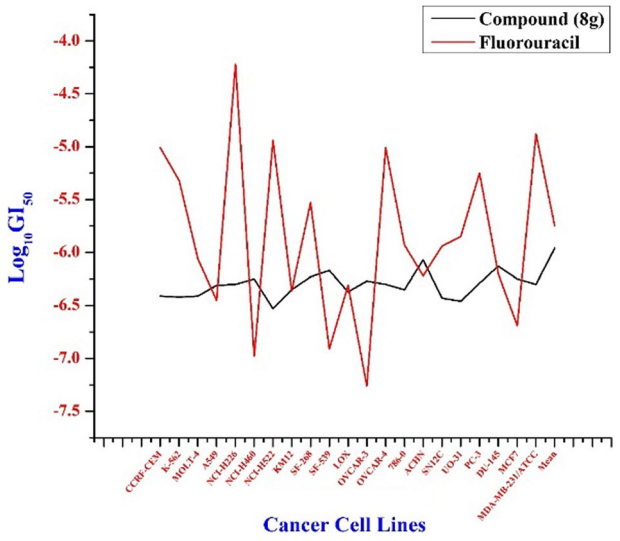


Fig. 1 Comparative value of GI_{50} for 8g and fluorouracil for specific cell lines

8g and **8h** emerged with important $GI_{50} < 1.0$ µM. The most potent compound **8g** exhibited excellent GI_{50} values for some specific cell lines and it compares with the reference drug fluorouracil (Fig. 1).

Results revealed that compound **8g** (NSC D-804988/1) was the most active compound of the series with a very low value of $GI_{50} = 0.392$ µM for CCRF-CEM, 0.382 µM for K-562 and 0.382 µM for MOLT-4 in Leukemia. $GI_{50} = 0.295$ for NCI-H522, 0.486 for A549, 0.506 for NCI-H226, 0.563 for NCI-H460 in Non-Small Cell Lung Cancer (Table 2). Some of the other lower GI_{50} values are mentioned in Table 3. Synthesized compound **8g** showed more potency than reference drug fluorouracil but it was less potent than doxorubicin. Compound 8h has equivalent potency toward fluorouracil. Mean graph plotted for $Log_{10}GI_{50}$, $Log_{10}TGI$ and $Log_{10}LC_{50}$ for compounds 8g, 8h and reference drugs fluorouracil and doxorubicin (Fig. 2). Five-dose data of compounds revealed that synthesized molecule 8g showed good potency against leukemia and renal cancer cell lines (Fig. 3).

Molecular docking study

The matrix metalloproteinases (MMPs) are a family of zinc-dependent enzymes that are required for extracellular matrix degradation and tissue remodeling. Many metalloproteins are reported to interact with benzofuran derivatives [32, 33]. All ligands were screened against the solution structure of a catalytic domain of mmp-2 complexed with sc-74020, 1HOV protein. The protein (PDB ID: 1HOV) was retrieved from RCS Protein Data Bank (http://www.rcsb.org). The interactions between protein docking binding sites are very compatible with ligands 8g and 8h, according to docking

Table 2 Percentage of growth of subpanel of tumor cell lines at single-dose (10 µM) concentration

Cell line	Growth percentage	
	8g (NSC: D-814251/1)	8h (NSC: D-814252/1)
Leukemia		
CCRF-CEM	2.87	17.48
HL-60(TB)	2.27	16.25
K-562	4.08	21.66
MOLT-4	−23.76	9.91
RPMI-8226	−22.42	30.88
Non-small cell lung cancer		
A549	−38.60	−10.08
EKVX	5.32	59.31
HOP-62	−18.38	62.08
HOP-92	−0.22	63.15
NCI-H226	−56.27	58.37
NCI-H23	−25.76	20.95
NCI-H322M	26.69	77.31
NCI-H460	−27.24	13.34
NCI-H522	−42.18	8.73
Colon cancer		
COLO 205	−28.83	6.46
HCC-2998	−3.45	62.71
HCT-116	−1.24	−13.57
HCT-15	6.56	18.44
HT29	23.24	36.88
KM12	−29.75	15.81
SW-620	−33.95	2.26
CNS cancer		
SF-268	−34.61	39.25
SF-295	−41.06	84.76
SF-539	−80.04	7.00
SNB-19	3.35	53.94
SNB-75	−0.26	51.16
U251	−10.01	36.95
Melanoma		
LOX IMVI	−93.97	−48.84
MALME-3 M	−45.63	24.97
M14	16.58	52.47
MDA-MB-435	−31.62	69.03
SK-MEL-2	51.34	90.79
SK-MEL-28	30.89	81.03
SK-MEL-5	5.79	87.40
UAAC-257	3.52	80.08
UAAC-62	1.76	88.83
Ovarian cancer		
IGROV1	−43.75	30.22
OVCAR-3	−44.37	8.65
OVCAR-4	−12.92	32.54
OVCAR-5	9.56	58.01
OVCAR-8	−12.09	23.69

Table 2 (continued)

Cell line	Growth percentage	
	8g (NSC: D-814251/1)	8h (NSC: D-814252/1)
NCI/ADR-RES	10.65	34.74
Renal cancer		
786-0	− 40.05	1.77
A498	− 3.19	71.11
ACHN	− 31.41	11.09
CAKI-1	− 43.28	9.09
SN12C	− 12.28	38.94
TK-10	22.69	50.66
UO-31	− 96.53	− 43.38
RFX393	–	17.06
Prostate cancer		
PC-3	1.87	33.57
DU-145	− 41.26	12.45
Breast cancer		
MCF7	− 0.83	13.69
MDA-MB-231/ATCC	− 27.03	42.42
HS 578T	− 6.98	70.55
BT-549	− 56.91	48.56
T-47D	− 3.93	35.24
MDA-MB-468	0.52	27.31

Negative value indicates lethality of compound for specific cancer line

"–" sign indicates not tested

findings analysis (Figs. 4, 5). Results of docking study for active molecules into the active size of enzyme displayed various interactions especially Van der Waals, conventional hydrogen bond, π-cation, π-donor hydrogen bond, π-sulfur, π–π T-shaped, Amine-π stacked, and π-alkyl. The protein 1HOV established two hydrogen bonds A: LEU124, A: GLY153 in ligand 8g on site dioxol ring and N=N, respectively. Also, π-sulfur was established with A: TYR180 on thiazole ring and π-cation was generated with amino acid A: ARG126. The fused furan ring showed interaction with A: ALA149 and A: TYR180 via π–π T-shaped. Indole, furan and phenyl rings interacted with A: LEU124, A: ARG150, A: ARG126 and A: VAL154 by π-alkyl interaction. In ligand 8h, two conventional hydrogen bond interactions were found with A: ARG122 on N of thiazole ring and N=N. The π–π T-shaped interaction was established with A: ALA149 and A: TYR180 on the phenyl ring of benzofuran. The phenyl ring and both furan rings interact with amino acids A: ARG122, A: LEU124, A: ARG150 and A: ARG126 via π-alkyl interaction. The result of docking such as hydrophobicity and H-bonds, interpolated charge, and aromaticity attached as supplementary material.

Conclusion

In conclusion, we have synthesized thirteen novel compounds as benzofuran and thiazole hybrids by the multistep reaction. Compounds were confirmed by the ^{1}H NMR, ^{13}C NMR, IR, and mass spectrometry. All synthesized compounds were studied for molecular docking against 1HOV protein and further evaluated for single dose in vitro anticancer activity. Among them, two compounds were selected for further five-dose screening. Data of anticancer screening revealed that the compound 8g has a higher potential than the reference drug fluorouracil, whereas compound 8h is equipotent to standard drug. It is expected that these synthesized molecules will be evaluated for further medical applications.

Materials and methods

General

All melting points are uncorrected. Commercial chemicals, reagents, and solvents were used without further purification. The purity of the reaction products was monitored by TLC on Merck Silica Gel G60 F254 plates with spot visualization with UV light (254 and 365 nm), iodine vapor, and aqueous $KMnO_4$. The ^{1}H and ^{13}CNMR spectra were recorded on a Bruker Advanced 400 MHz spectrometer at 400 (^{1}H) and 101 MHz (^{13}C) in DMSO-d_6 and $CDCl_3$. The ^{1}H NMR chemical shifts were measured in ppm relative to internal TMS. Mass spectra were recorded on a Shimadzu GC-MSQP-2010 mass spectrometer in EI (70 eV) model using the direct inlet probe technique and m/z is reported in atomic units per elementary charge.

General procedure for synthesis of 4-hydroxybenzo[*d*][1,3] dioxole-5-carbaldehyde *(2a)* and 4-hydroxy-[1,1′-biphenyl]-3-carbaldehyde *(2a and 2b)*

To a stirred solution of **1a** and **1b** (10 gm, 72.4 mmol) in THF (150 mL) Et_3N (20.5 mL, 144 mmol) was added followed by $MgCl_2$ (13.7 gm, 144 mmol). The mixture was stirred for 20 min at RT, and then paraformaldehyde (45.2 gm, 217 mmol) was added. The resultant mixture was refluxed for 3 h. The progress of the reaction was monitored by TLC. The reaction mixture was cooled at room temperature and then poured in 1 N HCl (100 mL) and the product was extracted with ethyl acetate (3 × 30 mL), washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to obtain a crude product.

Table 3 Results of five-dose anticancer activity[a] (cytotoxic activities of compounds expressed as GI_{50}, TGI, LC_{50} (μM) for compounds 8g and 8h against full NCI-60 cell lines)

Cell line	Compound					
	8g (NSC: D-814251/1)			8h (NSC: D-814252/1)		
	GI_{50}	TGI	LC_{50}	GI_{50}	TGI	LC_{50}
Leukemia						
CCRF-CEM	*0.392*	> 100	> 100	*0.551*	16.2	> 100
HL-60(TB)	2.18	14.4	> 100	2.70	7.59	> 100
K-562	*0.382*	> 100	> 100	2.10	> 100	> 100
MOLT-4	*0.385*	9.49	> 100	*0.946*	14.5	> 100
RPMI-8226	1.55	> 100	> 100	3.08	13.3	> 100
SR	*0.912*	> 100	> 100	1.29	25.3	> 100
Non-small cell lung cancer						
A549	*0.486*	3.10	> 100	1.79	6.87	> 100
EKVX	1.27	6.44	> 100	2.25	10.9	71.6
HOP-62	1.60	7.95	> 100	3.04	12.6	> 100
HOP-92	1.49	5.34	> 100	1.94	8.99	43.3
NCI-H226	*0.506*	2.45	-	3.67	18.9	> 100
NCI-H23	1.77	5.19	> 100	1.51	4.22	32.4
NCI-H322M	3.37	15.7	68.0	4.15	24.2	> 100
NCI-H460	*0.563*	2.43	–	2.59	10.3	> 100
NCI-H522	*0.295*	1.45	–	*0.625*	2.97	67.7
Colon cancer						
HCC-2998	2.06	5.13	30.3	3.52	12.9	57.7
HCT-116	2.13	10.2	> 100	1.57	4.03	> 100
HCT-15	1.14	3.25	9.29	1.10	3.03	-
HT29	3.32	> 100	> 100	2.99	7.62	> 100
KM12	*0.449*	2.04	7.74	1.85	5.14	23.5
SW-620	1.20	3.00	7.51	*0.681*	2.48	7.58
CNS cancer						
SF-268	*0.589*	2.86	> 100	2.67	23.1	> 100
SF-295	1.82	4.31	12.2	2.78	11.5	53.5
SF-539	*0.669*	1.98	4.65	1.58	3.96	9.91
SNB-19	1.57	6.25	29.5	4.73	23.1	> 100
SNB-75	1.40	2.89	5.96	1.86	11.4	38.2
U251	1.32	-	> 100	2.90	14.5	> 100
Melanoma						
LOX IMVI	*0.426*	1.70	5.22	1.35	2.76	5.64
MALME-3M	1.40	4.02	18.5	1.92	6.18	31.7
M14	3.34	12.7	> 100	2.90	11.6	> 100
MDA-MB-435	1.74	4.44	15.2	2.86	10.2	40.2
SK-MEL-2	2.60	8.07	> 100	3.11	11.3	> 100
SK-MEL-28	3.17	12.2	42.5	3.42	12.3	50.2
SK-MEL-5	1.66	3.23	6.28	2.08	4.60	10.9
UAAC-257	2.57	7.77	> 100	3.83	23.2	> 100
UAAC-62	1.75	3.72	7.92	3.81	14.5	42.3
Ovarian cancer						
IGROV1	1.17	3.32	–	2.60	8.09	> 100
OVCAR-3	*0.536*	1.89	5.33	1.66	3.29	-
OVCAR-4	*0.503*	4.11	23.9	1.27	12.2	66.9
OVCAR-5	1.66	3.85	–	2.71	8.67	89.6
OVCAR-8	1.66	> 100	> 100	2.80	> 100	> 100
NCI/ADR-RES	2.25	–	> 100	2.21	> 100	> 100

Table 3 (continued)

Cell line	Compound					
	8g (NSC: D-814251/1)			8h (NSC: D-814252/1)		
	GI_{50}	TGI	LC_{50}	GI_{50}	TGI	LC_{50}
Renal cancer						
786-0	*0.445*	1.88	–	1.97	4.94	21.3
ACHN	*0.860*	2.61	7.25	1.85	11.3	35.8
CAKI-1	1.18	3.21	8.70	*0.854*	6.69	55.9
RFX393	1.33	2.78	5.84	1.80	5.13	19.6
SN12C	*0.374*	3.98	> 100	2.97	12.7	53.3
TK-10	2.40	5.59	18.20	3.38	24.7	> 100
UO-31	*0.348*	1.57	4.43	*0.590*	3.68	23.7
Prostate cancer						
PC-3	*0.519*	6.20	> 100	1.79	12.4	> 100
DU-145	*0.739*	3.31	17.2	2.02	5.49	21.8
Breast cancer						
MCF7	*0.566*	5.39	> 100	0.*683*	7.19	> 100
MDA-MB-231/ATCC	*0.502*	2.42	–	1.64	3.83	8.97
HS 578T	2.02	6.02	> 100	2.74	22.2	> 100
BT-549	1.32	7.55	> 100	3.43	15.2	69.8
T-47D	2.09	> 100	> 100	1.27	9.47	> 100
MDA-MB-468	1.01	6.06	> 100	2.14	7.14	> 100

For the compound GI_{50} value less than 1.0 μM were in italics

"–" means not tested

[a]Data derived from NCI-60 human cell lines

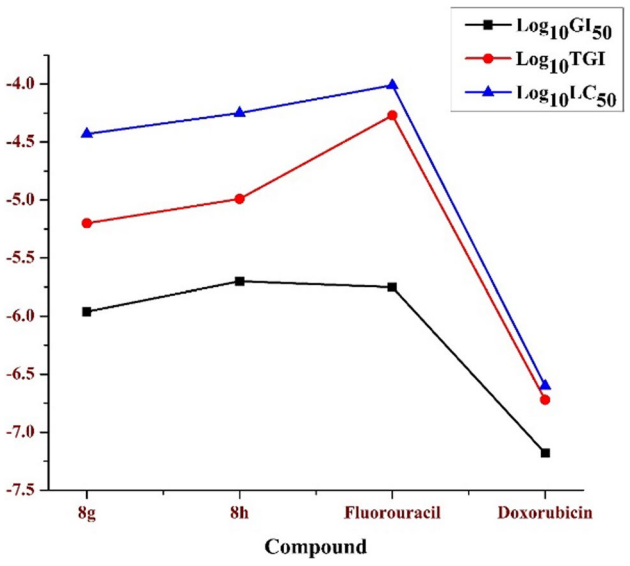


Fig. 2 Mean $Log_{10}GI_{50}$, $Log_{10}TGI$ and $Log_{10}LC_{50}$ values of 8g, 8h and reference drug

The crude product was purified by column chromatography using 60–120 silica gel and toluene as mobile phase, and the product was eluted in 100% toluene to get a product as **2a** and **2b** with 65–68% yield.

General procedure for synthesis of 1-([1,3]dioxolo[4,5-*f*]benzofuran-6-yl)ethan-1-one *(4a)* and 1-(5-phenylbenzofuran-2-yl) ethan-1-one *(4a and 4b)*

To stir compounds **2a/2b** (5 gm) in dry acetone (40 mL) and K_2CO_3 (8.31 gm, 60.2 mmol). The reaction mixture was stirred for 10 min at 0 °C. After that, 1-chloropropan-2-one (3.34 gm, 36.1 mmol) was added dropwise. Then the reaction mixture was stirred at room temperature (27 °C) for 4 h. The progress of the reaction was monitored by TLC. After the completion of reaction, the mixture was poured into ice-cold water; a solid product was separated by filtration and washed with water, dried under vacuum to obtain products as **4a/4b** with 93–95% yield.

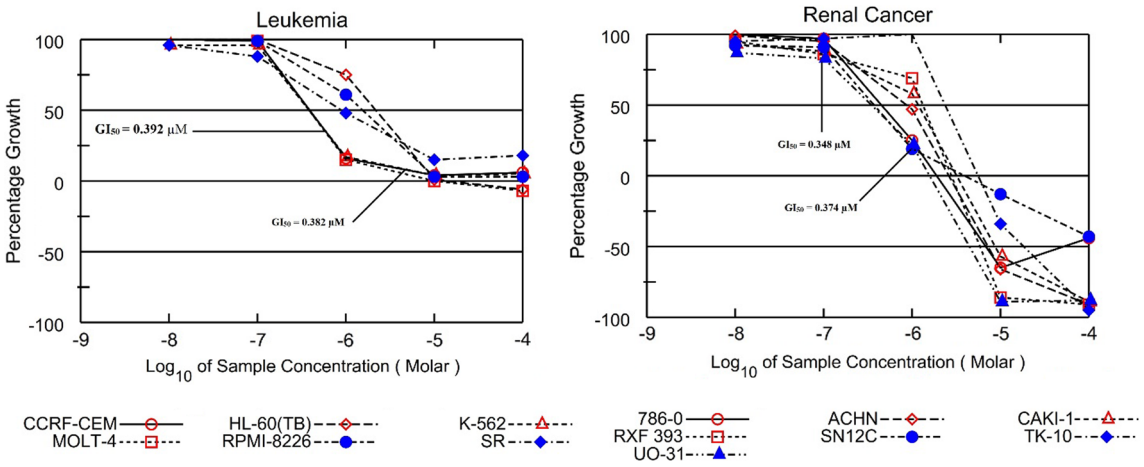


Fig. 3 Five-dose anticancer graph of compound 8g for leukemia and renal cancer

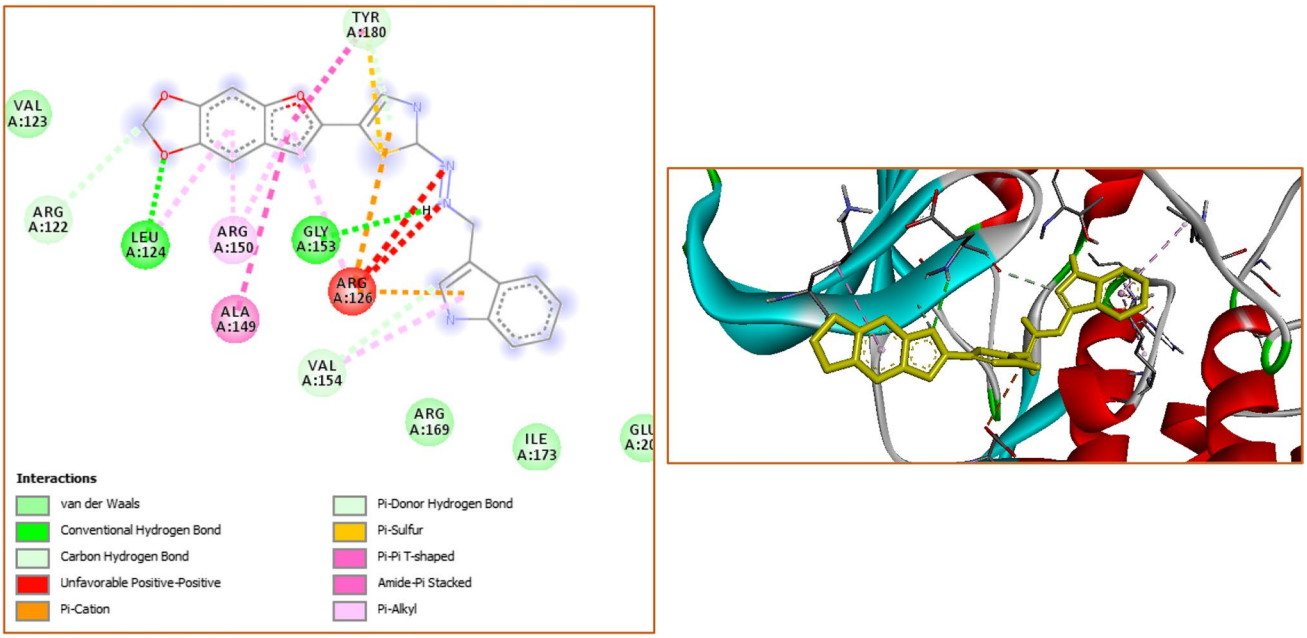


Fig. 4 2D and 3D visualization of ligand (8g) and amino acid residues of protein by using Discovery studio

General procedure for synthesis of 1-([1,3]dioxolo[4,5-*f*] benzofuran-6-yl)-2-bromoethan-1-one *(5a)* and 2-bromo-1-(5-phenylbenzofuran-2-yl) ethan-1-one *(5a and 5b)*

A stirred solution of **4a/4b** (5 gm, 24.5 mmol) in dry chloroform (30 mL) was stirred at 0 °C. Then freshly prepared bromine solution (1.5 mL in 30 mL $CHCl_3$, 29.4 mmol) was added dropwise by addition funnel. The reaction mixture was stirred at room temperature (27 °C) for 5 h. The progress of the reaction was monitored by TLC. After the completion of reaction, a saturated solution of $Na_2S_2O_3$ (25 mL) was added. Unreacted bromine was removed by the addition of $CHCl_3$ (3 × 30 mL) and organic layer dried over Na_2SO_4 then filtered and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography using 60-120 silica gel (stationary phase) and toluene (mobile solvent) to achieved a product as 2**a** and 2**b** with 65-68% yield.

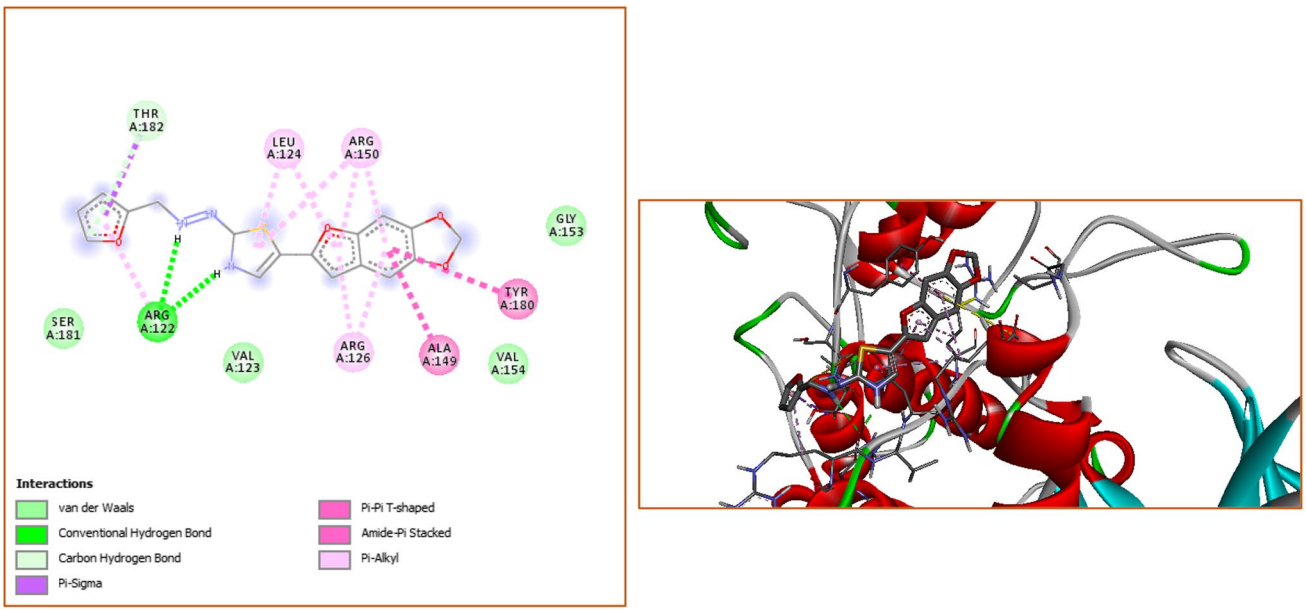


Fig. 5 2D and 3D visualization of ligand (8h) and amino acid residues of protein by using Discovery studio

General procedure for synthesis of 4-([1,3]dioxolo[4,5-*f*]benzofuran-6-yl)-2-(2-(substitutedbenzylidene)hydrazinyl)thiazole (8a–j) and 2-(2-(substitutedbenzylidene) hydrazinyl)-4-(5-phenylbenzofuran-2-yl) thiazole (9a–c)

To stirred a compound 2**a**/2**b** (5 gm)in dry acetone (40 mL) followed by addition of K_2CO_3 (8.31 gm). The progress of the reaction was monitored by TLC. After the completion of reaction, the resulting mixture was poured into ice-cold water. The solid material was filtered and wash with water. The crude product was purified by recrystallized method from 95% EtOH to an obtained pure solid product. Yield: 80–92%.

Spectral analysis

6-hydroxybenzo[*d*][1,3]dioxole-5-carbaldehyde (2a): ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.72 (s, 1H), 3.55 (s, 1H), 6.78 (s, 1H), 6.39 (s, 2H), 5.92 (s, 2H).

1-([1,3]dioxolo[4,5-*f*]benzofuran-6-yl)-2-bromoethan-1-one (5a): ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.88 (d, J = 0.8 Hz, 1H), 7.194 (d, J = 5.6 Hz, 2H), 6.01 (s, 2H), 4.31 (s, 2H).

5-([1,3]dioxolo[4,5-f]benzofuran-6-yl)-2-(2-(3,4,5-trimethoxybenzylidene)hydrazinyl)thiazole (8a): IR (KBr, ν_{max}, cm^{-1}) 3471 (–N–H aliphatic), 3086 (C–H, str., aromatic), 2939 (C–H, str., alkene), 2877 (C–H, str.,alkane),1612 (–NH–, bend., sec. amine), 1573 (C=C, str., Ar), 1504 (C=C, ben., Ar), 1458(–C–S, str., aromatic), 1319 (C–N str., aromatic), 1234 (C–H, bend., –CH_3), 1172 (C–O str., alip. ether), 1033 (C=C bend.), 840 (p-disubstituted aromatic). 779–725 (m-disubstituted aromatic). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.31 (s, 1H), 7.97 (s, 1H), 7.28 (s, 1H), 7.18 (s, 1H), 7.13 (s, 1H), 6.99 (s, 1H), 6.93 (d, J = 4 Hz, 2H), 6.06 (s, 2H), 3.83 (s, 6H), 3.67 (s, 3H). mass m/z: 453.

5-([1,3]dioxolo[4,5-*f*]benzofuran-6-yl)-2-(2-(anthracen-9-ylmethylene)hydrazinyl)thiazole (8b): IR (KBr, ν_{max}, cm^{-1}) 3417 (–N–H aliphatic), 3047 (C–H, str., aromatic), 2901 (C–H, str., alkene), 2777 (C–H, str., alkane), 1627 (–NH–, bend., sec. amine), 1566 (C=C, str., Ar), 1450 (C=C, ben., Ar), 1365 (–C–S., str., aromatic), 1311 (C–N str. aromatic), 1242 (C–H, bend., –CH_3), 1172 (C-O str., alip.ether), 1033 (C=C bend.), 840 (p-disubstituted aromatic). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.53 (s, 1H), 9.27 (s, 1H), 8.69 (d, J = 10.0 Hz, 3H), 8.16 (d, J = 8.4 Hz, 2H), 7.57–7.68 (m, 4H), 7.30 (s, 1H), 7.22 (s, 1H), 7.16 (s, 1H), 7.00 (s, 1H), 6.07 (s, 2H), Mass m/z: 463.

5-([1,3]dioxolo[4,5-*f*]benzofuran-6-yl)-2-(2-(thiophen-2-ylmethylene)hydrazinyl)thiazole (8c): IR (KBr, ν_{max}, cm^{-1}) 3333 (–N–H aliphatic), 3117 (C–H, str., aromatic), 3032 (C–H, str., alkene), 2805 (C–H, str., alkane), 1635 (-NH-, bend., sec. amine), 1566 (C=C, str., Ar), 1458 (C=C, ben., Ar), 1411 (–C–S, str. aromatic), 1311 (C–N str. aromatic), 1242 (C–H, bend., –CH_3), 1172 (C–O str., alip. ether), 1033 (C=C bend.), 856 (p-disubstituted aromatic). ^{1}H

NMR (400 MHz, DMSO-d_6) δ 12.64 (s, 1H), 8.24 (s, 1H), 7.60 (d, J = 5.2 Hz, 1H), 7.39 (d, J = 3.2 Hz, 1H), 7.28 (s, 1H), 7.10–7.17 (m, 3H), 6.95 (s, 1H), 6.07 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.37, 151.46, 149.27, 146.03, 144.41, 141.79, 138.95, 137.14, 129.40, 127.85, 121.58, 104.46, 102.97, 101.31, 99.60, 93.46. Mass m/z: 369.

4-((2-(5-([1,3]dioxolo[4,5-*f*]benzofuran-6-yl)thiazol-2-yl) hydrazono)methyl)benzonitrile (8d): IR (KBr, ν_{max}, cm^{-1}) 3410 (-N–H aliphatic), 3279 (C–H, str., aromatic), 3124 (C–H, str., alkene), 2901 (C–H, str., alkane), 2214 (–CN str., aromatic), 1728 (-NH, bend., sec. amine), 1566 (C=C, str., Ar), 1496 (C=C, ben., Ar), 1450 (–C–S, str., aromatic), 1311 (C–N str., aromatic), 1242 (C–H, bend., –CH_3), 1165 (C-O str., alip. ether), 1033 (C=C bend.), 825 (p-disubstituted benzene). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.48 (s, 1H), 8.05 (s, 1H), 7.81 (dd, J = 21.2, 8.4 Hz, 4H), 7.21 (d, J = 10.0 Hz, 2H), 7.10 (s, 1H), 6.94 (s, 1H), 6.02 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.41, 151.35, 149.26, 146.02, 144.39, 139.58, 138.65, 132.70, 126.71, 121.58, 118.79, 110.90, 105.09, 103.12, 101.29, 99.63, 93.41. Mass m/z: 388.

5-([1,3]dioxolo[4,5-*f*]benzofuran-6-yl)-2-(2-(2,4-dichlorobenzylidene)hydrazinyl)thiazole (8e): IR (KBr, ν_{max}, cm^{-1}) 3279 (–N–H aliphatic), 3132 (C–H, str., aromatic), 3063 (C–H, str., alkene), 2993 (C–H, str., alkane), 1573 (–NH–, bend., sec. amine), 1473 (C=C, str., Ar), 1450 (C=C, ben., Ar), 1365 (–C–S, str., aromatic), 1311 (C–N str., aromatic), 1242 (C–H, bend., –CH3), 1165 (C-O str., alip. ether), 1041 (C=C bend.), 879 (p-disubstituted). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.56 (s, 1H), 7.58 (d, J = 13.1 Hz, 2H), 7.31 (s, 1H), 7.19 (s, 1H), 7.12 (d, J = 3.8 Hz, 2H), 6.98 (s, 1H), 6.56 (s, 1H), 6.05 (s, 2H). Mass m/z: 431.

5-([1,3]dioxolo[4,5-*f*]benzofuran-6-yl)-2-(2-(4-fluorobenzylidene)hydrazinyl)thiazole (8f): IR (KBr, ν_{max}, cm^{-1}) 3495 (–N–H aliphatic), 3286 (C–H, str., aromatic), 3109 (C–H, str., alkene), 2885 (C–H, str., alkane), 1735 (–NH, bend., sec. amine), 1558 (C=C, str., Ar), 1404 (C=C, ben., Ar), 1450 (–C–S., str., aromatic), 1365 (C–N str., aromatic), 1226 (C–H, bend., –CH3), 1165 (C-O str., alip. ether), 1033 (C=C bend.), 825 (p-disubstituted benzene). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.98 (s, 1H), 8.02 (s, 1H), 7.72 (m, 2H), 7.26 (m, 3H), 7.17 (s, 1H), 7.12 (s, 1H), 6.94 (s, 1H), 6.03 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.77, 163.87, 161.42, 151.48, 149.23, 145.99, 144.37, 141.96, 140.72, 130.76, 128.32, 121.60, 116.00, 115.78, 104.53, 103.01, 101.28, 99.63, 93.41. Mass m/z: 381.

2-(2-((1*H*-indol-3-yl)methylene)hydrazinyl)-5-([1,3] dioxolo[4,5-*f*]benzofuran-6-yl)thiazole (8g): IR (KBr, ν_{max}, cm^{-1}) 3371 (–N–H aliphatic), 3093 (C–H, str., aromatic), 3055 (C–H, str., alkene), 2893 (C–H, str., alkane), 1627 (–NH–, bend., sec. amine), 1535 (C=C, str., Ar), 1489 (C=C, ben., Ar), 1458 (–C–S, str., aromatic), 1303 (C–N str., aromatic), 1246 (C–H, bend., –CH_3), 1165 (C–O str., alip. ether), 1033 (C=C bend.), 825 (p-disubstituted benzene). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.60 (s, 1H), 8.33 (s, 1H), 8.27 (d, J = 7.5 Hz, 1H), 7.82 (d, J = 2.7 Hz, 1H), 7.52 (d, J = 7.5 Hz, 1H), 7.32 (s, 1H), 7.26 (m, 2H), 7.20 (d, J = 4.0 Hz, 2H), 7.02 (s, 1H), 6.10 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 169.20, 151.46, 149.22, 145.97, 144.37, 141.52, 140.09, 137.01, 129.70, 123.90, 122.68, 121.63, 121.50, 120.55, 111.95, 111.43, 103.69, 102.93, 101.28, 99.65, 93.41.

5-([1,3]dioxolo[4,5-*f*]benzofuran-6-yl)-2-(2-(furan-2-ylmethylene)hydrazinyl)thiazole (8h): IR (KBr, ν_{max}, cm^{-1}) 3431 (–N–H aliphatic), 3117 (C–H, str., aromatic), 2901 (C–H, str., alkene), 2777 (C–H, str., alkane), 1635 (–NH–, bend., sec. amine), 1566 (C=C, str., Ar), 1496 (C=C, ben., Ar), 1458 (–C–S, str., aromatic), 1365 (C-N str., aromatic), 1311 (C–H, bend., –CH_3), 1242 (C-O str., alip. ether), 1018 (C=C bend.), 879 (p-disubstituted benzene). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.48 (s, 1H), 7.92 (s, 1H), 7.81 (d, J = 1.2 Hz, 1H), 7.28 (s, 1H), 7.17 (s, 1H), 7.12 (s, 1H), 6.93 (s, 1H), 6.82 (d, J = 3.3 Hz, 1H), 6.61 (dd, J = 3.3, 1.8 Hz, 1H), 6.05 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.40, 151.51, 149.27, 149.13, 146.02, 144.64, 144.41, 141.85, 131.99, 121.58, 112.58, 112.07, 104.41, 102.98, 101.31, 99.60, 93.48.

5-([1,3]dioxolo[4,5-*f*]benzofuran-6-yl)-2-(2-(pyridin-3-ylmethylene)hydrazinyl)thiazole (8i): IR (KBr, ν_{max}, cm^{-1}) 3417 (–N–H aliphatic), 3263 (C–H, str., aromatic), 3124 (C–H, str., alkene), 2916 (C–H, str., alkane), 1666 (–NH–, bend., sec. amine), 1566 (C=C, str., Ar), 1465 (C=C, ben., Ar), 1411 (- C-S., str., aromatic), 1365 (C–N str., aromatic), 1311 (C–H, bend., –CH_3), 1242 (C–O str., alip. ether), 1033 (C=C bend.), 840 (p-disubstituted benzene). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.46 (s, 1H), 9.03 (d, J = 1.5 Hz, 1H), 8.83–8.73 (m, 1H), 8.54 (d, J = 8.1 Hz, 1H), 8.15 (s, 1H), 7.88 (dd, J = 8.0, 5.4 Hz, 1H), 7.29 (d, J = 4.1 Hz, 2H), 7.14 (s, 1H), 6.96 (s, 1H), 6.06 (d, J = 4.4 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.26, 151.37, 149.31, 146.10, 144.45, 142.90, 138.12, 136.42, 132.56, 126.07, 121.55, 105.25, 103.12, 101.34, 99.62, 93.49.

5-([1,3]dioxolo[4,5-*f*]benzofuran-6-yl)-2-(2-(3-nitrobenzylidene)hydrazinyl)thiazole (8j): IR (KBr, ν_{max}, cm^{-1}) 3225 (–N–H aliphatic), 3132 (C–H, str., aromatic), 3093 (C–H, str., alkene), 2916 (C–H, str.,alkane), 1654 (–NH–, bend., sec. amine), 1566 (C=C, str., Ar), 1524 (C=C, ben., Ar), 1458 (–NO_2, str., aromatic), 1411 (–C–S, str., aromatic), 1350 (C–N str., aromatic), 1234 (C–H, bend., –CH3),

1172 (C–O str., alip.ether), 1041 (C=C bend.), 840 & 732 (m-disubstituted aromatic). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.46 (s, 1H), 8.41 (t, J = 4.0, 1H), 8.16 (m, 1H), 8.13 (s, 1H), 8.04 (d, J = 7.9 Hz, 1H), 7.70 (t, J = 8.0 Hz, 1H), 7.23 (s, 1H), 7.19 (s, 1H), 7.11 (s, 1H), 6.94 (s, 1H), 6.03 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.48, 151.38, 149.24, 148.15, 145.99, 144.37, 139.22, 136.02, 132.30, 130.40, 123.42, 121.58, 120.13, 104.97, 103.07, 101.28, 99.62, 93.39.

5-(5-phenylbenzofuran-2-yl)-2-(2-(3,4,5-trimethoxybenzylidene)hydrazinyl)thiazole (9a): IR (KBr, ν_{max}, cm^{-1}) 3417 (–N–H aliphatic), 2931 (C–H, str., aromatic), 2823 (C–H, str., alkene), 2762 (C–H, str.,alkane), 1627 (–NH, bend., sec. amine), 1573 (C=C, str., Ar), 1496 (C=C, ben., Ar),1450 (–C–S, str., aromatic), 1319 (C–N str., aromatic),1242 (C–H, bend., $–CH_3$), 1134 (C–O str., alip. ether), 1049 (C=C bend.), 825 (p-disubstituted aromatic). 756–941 (m-disubstituted aromatic). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.33 (s, 2H), 7.99 (s, 3H), 7.92 (d, J = 1.5 Hz, 3H), 7.68 (dd, J = 12.4, 5.1 Hz, 10H), 7.59 (dd, J = 8.6, 1.8 Hz, 3H), 7.47 (t, J = 7.7 Hz, 7H), 7.35 (m, 6H), 7.12 (s, 3H), 7.00 (s, 6H), 3.84 (d, J = 9.3 Hz, 19H), 3.70 (s, 9H). Mass m/z: 485.

2-(2-(anthracen-9-ylmethylene)hydrazinyl)-5-(5-phenylbenzofuran-2-yl)thiazole (9b): IR (KBr, ν_{max}, cm^{-1}) 3471 (–N–H aliphatic), 3117 (C–H, str., aromatic), 3047 (C–H, str., alkene), 2890 (C-H, str.,alkane), 1643 (–NH, bend., sec. amine), 1573 (C=C, str., Ar), 1512 (C=C, ben., Ar), 1450 (–C–S., str., aromatic), 1303 (C–N str., aromatic), 1249 (C–H, bend., $–CH_3$), 1180 (C–O str., alip.ether), 1049 (C=C bend.), 879 (p-disubstituted benzene), ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.50 (s, 1H), 9.28 (s, 1H), 8.70 (d, J = 10.0 Hz, 3H), 8.17 (d, J = 8.4 Hz, 2H), 7.95 (d, J = 1.6 Hz, 1H), 7.70 (dd, J = 8.3, 3.1 Hz, 3H), 7.66 (d, J = 8.6 Hz, 2H), 7.60 (m, 3H), 7.49 (t, J = 12 Hz, 2H), 7.42 (s, 1H), 7.37 (t, J = 16 Hz, 1H), 7.19 (s, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.87, 153.78, 152.60, 140.65, 140.50, 135.89, 130.97, 129.31, 129.17, 129.08, 128.92, 127.19, 126.93, 125.56, 124.80, 124.55, 123.90, 119.44, 111.30, 106.40, 102.69. Mass m/z: 495.

5-(5-phenylbenzofuran-2-yl)-2-(2-(thiophen-2-ylmethylene)hydrazinyl)thiazole (9c): IR (KBr, ν_{max}, cm^{-1}) 3441 (–N–H aliphatic), 3109 (C–H, str., aromatic), 3063 (C–H, str., alkene), 2910 (C–H, str., alkane), 1635 (–NH–, bend., sec. amine), 1566 (C=C, str., Ar), 1504 (C=C, ben., Ar), 1450 (–C–S., str., aromatic), 1357 (C–N str., aromatic), 1273 (C–H, bend., $–CH_3$), 1126 (C-O str., alip. ether), 1049 (C=C bend.), 872 (p-disubstituted benzene). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.17 (s, 1H), 8.25 (s, 1H), 7.93 (d, J = 1.6 Hz, 1H), 7.71 (d, J = 1.2 Hz, 1H), 7.68 (d, J = 8.8 Hz, 2H), 7.61 (m, 2H), 7.48 (t, J = 7.7 Hz, 2H), 7.39 (dt, J = 14.7, 4.3 Hz, 3H), 7.12 (dd, J = 5.6, 2.9 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.53, 153.74, 152.58, 141.74, 140.50, 138.95, 137.17, 135.86, 129.44, 129.14, 128.90, 127.88, 127.04, 126.91, 123.84, 119.40, 111.27, 106.37, 102.53. Mass m/z: 401.

Biology

Anticancer screening at a one-dose (10 μM) concentration

The anticancer screening of the newly prepared compounds 8a–j and 9a–c was carried out at NCI, USA under the screening project at the National Cancer Institute (NCI), USA for primary in vitro one-dose anticancer screening against full NCI-60 cell line panels representing nine different kinds of cancer including leukemia, lung, colon, melanoma, ovary, kidney, brain, prostate, and breast cancers in accordance with the protocol (http://dtp.nci.nih.gov). All newly synthesized hybrids were selected by NCI, USA for the single dose (10 μM) and screening results of all the ten molecules displayed excellent anticancer activity with a broad spectrum of cytotoxic activity (cytotoxicity ranging from 0–100%) against sixty cancer cell lines and results represented in Table 3.

In vitro anticancer screening at five-dose full NCI-60 cell lines

The single-dose screening results showed that two compounds including 8g and 8h were found to be more potent in a preliminary test on sixty human cancer cell lines and were selected for an advanced assay against a panel of sixty cancer cell lines at tenfold dilutions of five concentrations (100 μM, 10 μM, 1 μM, 0.1 μM, and 0.01 μM) [34, 35]. The results of the five-dose screening of all nine compounds are presented in terms of response parameters GI_{50}, TGI, and LC_{50} for each cell line tested.

Molecular docking

All docking tests used the AutoDock Vina program, using the optimized model as the docking target [36]. The screening technique is limited to molecular docking, and there is no molecular dynamics modeling. The protein (PDB ID: 1HOV) was retrieved from RCS Protein Data Bank (http://www.rcsb.org). All the molecules were sketched using Chem-Draw ultra-14.0, and molecules in CDX format have been converted to MOL format using ChemBio3D ultra-14.0. All MOL files are converted into pdb format using openbabel. Molecules in pdb format projected to AutoDock vina and selected as ligand molecules and saved as pdbqt format. The Protein preparation was completed by AutoDock Vina software. From the protein, deleted water molecules,

added polar hydrogen and added Kollman charge. After completing the described process, all molecules were saved in pdbqt format. The structures of the small compounds were improved using the classical MM2 force field before testing against 1HOV target proteins; the active site aspartates of targets were regarded as rigid. The 3D crystal structure of a protein, Matrix Metalloproteinase-2 (1HOV), was obtained from the Protein database and is associated mostly with the pathogenesis of colorectal cancer [37]. The active or binding sites of the receptors were determined using online servers.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11030-022-10493-7.

Acknowledgements The authors are grateful to the Department of Chemistry, Saurashtra University and Department of Chemistry, School of Science, RK University (Rajkot) for providing laboratory facilities. Authors also thankful to National facility for drug discovery (NFDD) for providing spectral data.

Data availability The data that support the findings of this study are available in "figshare" at https://doi.org/10.6084/m9.figshare.19367219.

Declarations

Conflict of interest The authors declare no conflict of interest.

References

1. Hadiyal SD, Parmar ND, Kalavadiya PL, Lalpara JN, Joshi HS (2020) Microwave-assisted three-component domino synthesis of polysubstituted 4*H*-pyran derivatives and their anticancer activity. Russ J Org Chem 56:671–678
2. Radia AJ, Lalpara JN, Modasiya IJ, Dubal GG (2021) Design and synthesis of novel 1, 3, 4-oxadiazole based azaspirocycles catalyzed by NaI under mild condition and evaluated their antidiabetic and antibacterial activities. J Heterocycl Chem 58:612–621
3. Hadiyal SD, Lalpara JN, Parmar ND, Joshi HS (2021) Microwave irradiated targeted synthesis of pyrrolobenzodiazepine embrace 1,2,3-triazole by click chemistry synthetic aspect and evaluation of anticancer and antimicrobial activity. Polycycl Aromat Compd. https://doi.org/10.1080/10406638.2021.1913425
4. Varmus H (2006) The new era in cancer research. Science 312:1162–1165
5. Hemaida AY, Hassan GS, Maarouf AR, Joubert J, El-Emam AA (2021) Synthesis and biological evaluation of thiazole-based derivatives as potential acetylcholinesterase inhibitors. ACS Omega 6:19202–19211
6. Santosh NM, Priyanka TS, Devanand BS (2010) Synthesis and hypolipidemic activity of novel 2-(4-(2-substituted aminothiazole-4-yl) phenoxy) acetic acid derivatives. Eur J Med Chem 45:3096–3100
7. Ayati A, Emami S, Moghimi S, Foroumadi A (2019) Thiazole in the targeted anticancer drug discovery. Fut Med Chem 11:1929–1952
8. Venkatachalam TK, Sudbeck EA, Mao C, Uckun FM (2001) Anti-HIV activity of aromatic and heterocyclic thiazolyl thiourea compounds. Bioorg Med Chem Lett 11:523–528
9. Deb PK, Kaur R, Chandrasekaran B (2014) Synthesis, anti-inflammatory evaluation, and docking studies of some new thiazole derivatives. Med Chem Res 23:2780–2792
10. Andreani A, Rambaldi M, Locatelli A, Cristoni A, Malandrino S, Pifferi G (1992) Synthesis and antihypertensive activity of imidazo[2,1-*b*]-thiazoles bearing a 2,6-dichlorophenyl group. Acta Pharm Nord 4:93–96
11. Sadek B, Al-Tabakha MM, Fahelelbom KM (2011) Antimicrobial prospect of newly synthesized 1,3-thiazole derivatives. Molecules 16:9386–9396
12. Deng XQ, Song MX, Wei CX, Li FN, Quan ZS (2010) Synthesis and anticonvulsant activity of 7-alkoxy-triazolo-[3,4-*b*]benzo[*d*]thiazoles. Med Chem 6:313–320
13. Singh IP, Gupta S, Kumar S (2020) Thiazole compounds as antiviral agents: an update. Med Chem 16:4–23
14. Kumawat MK (2018) Thiazole containing heterocycles with antimalarial activity. Curr Drug Discov Technol 15:196–200
15. Chirag HR, Nariya PB, Deepika M, Raghuvir RSP, Naval KP, Anilkumar SP (2021) Design, synthesis and antidiabetic activity of biphenylcarbonitrile-thiazolidinedione conjugates as potential α-amylase inhibitors. ChemistrySelect 6:2464–2469
16. Li X, He Y, Ruiz CH, Koenig M, Cameron MD (2009) Characterization of dasatinib and its structural analogs as CYP3A4 mechanism-based inactivators and the proposed bioactivation pathways. Drug Metab Dispos 37:1242–1250
17. Wright DG, Boosalis M, Malek K, Waraska K (2004) Effects of the IMP-dehydrogenase inhibitor, Tiazofurin, in bcr-abl positive acute myelogenous leukemia. Part II. In vitro studies. Leuk Res 28:1137–1143
18. Hu-Lieskovan S, Mok S, Homet Moreno B, Tsoi J, Robert L, Goedert L, Pinheiro EM, Koya RC, Graeber TG, Comin-Anduix B, Ribas A (2015) Improved antitumour activity of immunotherapy with B-RAF and MEK inhibitors in BRAF(V600E) melanoma. Sci Transl Med 7:279ra41
19. Kwiecień H, Goszczyńska A, Rokosz P (2016) Benzofuran small molecules as potential inhibitors of human protein kinases. A review. Curr Pharm Des 22:879–894
20. Napiórkowska M, Cieślak M, Kaźmierczak-Barańska J, Królewska-Golińska K, Nawrot B (2019) Synthesis of new derivatives of benzofuran as potential anticancer agents. Molecules 24:1529
21. Khalil HS, Sedky NK, Amin KM, Abd Elhafez OM, Arafa RK (2019) Visnagin and benzofuran scaffold-based molecules as selective cyclooxygenase-2 inhibitors with anti-inflammatory and analgesic properties: design, synthesis and molecular docking. Fut Med Chem 11:659–676
22. Jiang X, Liu W, Zhang W (2011) Synthesis and antimicrobial evaluation of new benzofuran derivatives. Eur J Med Chem 46:3526–3530
23. Ozlem O, Kadriye E, Cumhur K, Murat K, Misir A (2007) Characterization of a newly synthesized fluorescent benzofuran derivative and usage as a selective fiber optic sensor for Fe(III). Sens Actuators B 2:450–456
24. Jorg H, Steven VL, Rene S (1999) Three-step synthesis of an array of substituted benzofurans using polymer-supported reagents. J Chem Soc Perkin Trans 1(17):2421–2423
25. Cha-Lin K, Ji-Wang C (2001) A convenient synthesis of naturally occurring benzofuran ailanthoidol. Tetrahedron Lett 42:1111–1113
26. Upendra S, Togati N, Arun M, Srimanta M, Debabrata M (2013) Palladium-catalyzed synthesis of benzofurans and coumarins from phenols and olefins. Angew Chem 52:12669–12673
27. Hee-Jin H, Dong WK, Hyuk-Min K, Jin-Mi K (2018) Discovery of an orally bioavailable benzofuran analogue that serves as a β-amyloid aggregation inhibitor for the potential treatment of Alzheimer's disease. J Med Chem 61:396–402

28. Arias CA, Murray BE (2009) Antibiotic-resistant bugs in the 21st century–a clinical super-challenge. N Engl J Med 360(5):439–443
29. Feng Y, Likos JJ, Zhu L, Woodward H, Munie G, McDonald JJ, Stevens AM, Howard CP, De Crescenzo GA, Welsch D, Shieh HS, Stallings WC (2002) Solution structure and backbone dynamics of the catalytic domain of matrix metalloproteinase-2 complexed with a hydroxamic acid inhibitor. Biochim Biophys Acta 1598:10–23
30. Lalpara JN, Vachhani MD, Hadiyal SD, Goswami S, Dubal GG (2021) Synthesis and in vitro antidiabetic screening of novel dihydropyrimidine derivatives. Russ J Org Chem 57:241–246
31. Lalpara JN, Hadiyal SD, Radia AJ, Dhalani JM, Dubal GG (2020) Design and Rapid Microwave Irradiated One-Pot Synthesis of Tetrahydropyrimidine Derivatives and Their Screening In Vitro Antidiabetic Activity. Polycyclic Aromat Compd. https://doi.org/10.1080/10406638.2020.1852586
32. Naglaa FE, Marwa E, Ewies FE, Mohamed FE, Hanem MA, Marwa AF (2021) Design, synthesis, biological evaluation, and molecular docking of new benzofuran and indole derivatives as tubulin polymerization inhibitors. Drug Dev Res 83:485–500
33. Praveen K, Chinnappa AU, Santhosha SM, Nayak DS, SubbaRao VM, Hulikal SS, Rajeshwara A (2020) Antiproliferative potential, quantitative structure-activity relationship, cheminformatic and molecular docking analysis of quinoline and benzofuran derivatives. Eur J Chem 11:223–234
34. Boyd MR, Paull KD (1995) Some practical considerations and application of the national cancer institute in vitro anticancer drug discovery screen. Drug Dev Res 34:91–109
35. Shoemaker RH (2006) The NCI60 human tumor cell line anticancer drug screen. Nat Rev Cancer 6:813–823
36. Oleg T, Olson AJ (2010) AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. J Comput Chem 31:455–461
37. Mydhili G, Shalini G, Mohammad AA, Mohammad NA, Sami A, Saad A, Mazen A, Govindasamy R, Muthu T, Manju V (2021) In silico modeling and molecular docking insights of kaempferitrin for colon cancer-related molecular targets. J Saudi Chem Soc 25:101319