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Original article

Synthesis of novel 2, 5-dihydrofuran derivatives and evaluation of their anticancer activity

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ABSTRACT

According to metal-catalyzed [3 + 2] cycloaddition reaction, we synthesized a series of novel 2, 5-dihydrofuran derivatives and evaluated their *in vitro* anti-cancer activities via MTT method. The bioassay showed that the majority of the resultant compounds exerted anti-tumor effect against four human cancer cell lines to various extents, which supported the rationale of the design. Compounds **9e** and **10g** showed the highest activity with broad anti-cancer spectrum, which were good candidates for further evaluation.

1. Introduction

The development of new anti-tumor agents is an important field in medicinal chemistry, due to the increasing problems of toxic side effects of recent marketed drugs. For example, 5-fluorouracil and doxorubicin (Fig. 1) anti-cancer drugs are a class of broad-spectrum anti-tumor agents. However, the drawback is that the effective dose and toxic dose medication are similar, which results in that they could kill both cancer cells and normal cells [1,2]. Accordingly, it is meaningful for us to find a novel kind of structure with safe and effective properties in the progress of cancer treatment.

In the last decades, medicinal chemists have paid great attention to the development of novel lead from natural products. Most interestingly, existence of heterocyclic unit in numerous natural products often plays an essential role in their biological activity, particularly in anti-cancer effect [3–7]. Among these heterocycles reported, some five-membered oxygen heterocycles derivatives found or synthesized represent wide range of biological activities and thus they could be used as versatile intermediates [8–13]. Therefore, our focus was on the design and synthesis of five-membered oxygen heterocycles.

According to domino reaction [14,15], metal-catalyzed [3 + 2] cycloaddition reaction is one of the most efficient approaches in the synthesis of five-membered heterocycles [16–20]. In general, strategies for substituted 2, 5-dihydrofuran reported need expensive catalysts and harsh reaction conditions, which include RCM reaction, Ag (I)-catalyzed rearrangement cyclization and Prins reaction. Nevertheless, our group has developed an efficient and mild approach for synthesizing functionalized 2, 5-dihydrofuran derivatives. By this method, we have introduced a wide range of substituents on the 2-, 3- and 4-positions, especially carboxylic acid group on the 3-position, of 2, 5-dihydrofuran. Herein, we reported an efficient and straightforward method for the syntheses of a series of substituted 2, 5-dihydrofuran derivatives and we also investigated the anti-cancer activities of the desired compounds.

2. Chemistry

The chemical synthesis of 2, 5-dihydrofuran derivatives was achieved by a 3-step protocol, as illustrated in Scheme 1. Compound **3** was synthesized through a conventional Knoevenagel Condensation between compound **1** and compound **2** refluxing in toluene with the catalytic piperidine and glacial acetic acid [21]. Compound **3** was reacted with 1, 4-butynediol in the presence of NaH and CuI at 40 °C in THF, within 15–22 h and product **5** with 77–92% yield was formed sequentially after compound **4** as an intermediate (compound **4c** was separated successfully and determined via X-

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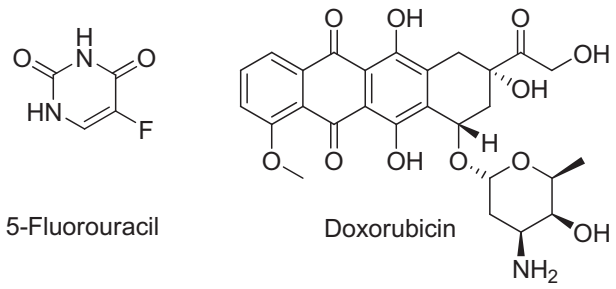


Fig. 1. Chemical structures of 5-fluorouracil and doxorubicin.

ray crystallographic structure - Fig. 2). This step could be accelerated with electron-withdrawing aryl-substituted group (Table 1, entries 1, 2), while decelerated with electron-donating aryl-substituted one (Table 1, entries 3, 4). On the contrary, the yield of electron-rich group was higher than that of electron-deficient one. Compounds **5** acid chloride formed by thionyl chloride were reacted with substituted amines to afford compounds **6a - 6s**, **7a - 7g**, **8a - 8s** and **9a**–**9f** and with substituted piperazines to afford compounds **10a**–**10g**. The chemical structures of these compounds were confirmed by ESIMS, NMR spectroscopic analysis, IR and elemental analyses. The purity of final compounds was assessed on the basis of analytical HPLC (≥95%). (see Supplementary Data).

Additionally, the structure of compounds **4c** and **5c** was further confirmed by X-ray diffraction. Their crystal data are presented in Table 2, and Fig. 2 gives ORTEP III views of both compounds.

3. Results and discussion

3.1. Reaction mechanism

Based on the fact that intermediate **4c** was successfully separated and determined, we could propose a tentative reaction mechanism (Scheme 2). First of all, 1, 4-butyne-diol was treated with NaH to produce alcohol sodium which could attack double bond of the substrate alkynylmalonate to yield the intermediate **A**, followed by cyclization reaction promoted via CuI connecting at triple bond and then intermediate **C** was formed. Subsequently, the other ring was cyclized with an ethanol molecule leaving via an intramolecular ester exchange reaction to form intermediate **D**. Furthermore, the Cu atom took off to yield compound **4** which then undergone a [3,3]-sigmatropic reaction to produce product **5**.

3.2. Pharmacology

All the synthesized compounds (**5**–**10**) were evaluated for their *in vitro* cytotoxic activities against four human cancer cell lines via MTT method, including A-549 (human lung adenocarcinoma cell line), HeLa (human cervical carcinoma cell line), SW480 (human colon carcinoma cell line) and QGY-7701 (human hepatoma cell line). 5-Fluorouracil (5-Fu) and doxorubicin were used as positive controls.

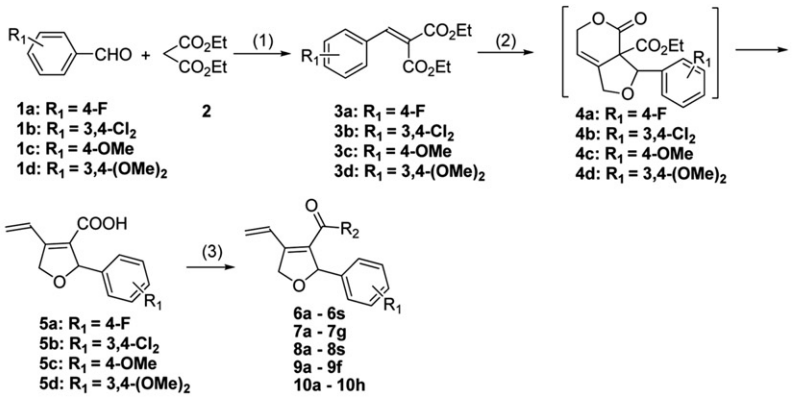
The results of the assay are summarized in Table 3 (where the IC_{50} value is defined as the concentration of a compound that corresponds to 50% growth inhibition). Data in the table showed the most of the synthesized compounds displayed certain anti-tumor activities against the four human cancer cell lines.

Compounds **5a**–**5d** have different patterns of substituted benzene that attach to the C-2 of 2, 5-dihydrofurans. As shown in Table 3, these compounds generally exhibited moderate to good potency against HeLa cell line, especially compound **5b** (IC_{50} = 10.26 μM) and **5d** (IC_{50} = 18.00 μM) exhibited comparable inhibitory effect to 5-Fu (IC_{50} = 16.32 μM) but lower activity than doxorubicin (IC_{50} = 1.12 μM). It could suggest that the 3, 4-disubstituted benzene at position-2 could increase the activity for inhibiting HeLa cell line. However, these four compounds displayed poor activities against other three cell lines.

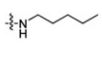
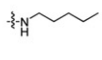
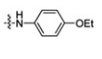
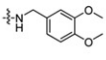
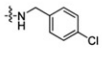
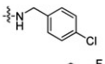
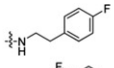
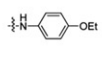
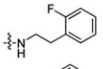
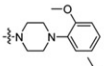
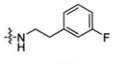
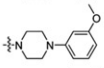
The introduction of amide group on position-3 of the 2, 5-dihydrofuran led to the different situation of anti-cancer activity. Firstly, the carboxylic acid group of compound **5a** was changed into substituted amide group (compounds **6a**–**6s**). Interestingly, the anti-tumor activities in HeLa cell was totally disappear, while moderate inhibitory activity in QGY-7701 cell was observed in compounds **6a**–**6o** whose side chains on C-3 were substituted benzene rings or cyclohexane. Compared with the ring group, the introduction of an aliphatic side chain (compounds **6p**–**6s**) resulted in the loss of activity against the four cancer cell lines. Among compounds **6**, **6k** was not only the best one with the IC_{50} value of 29.66 μM against QGY-7701 but also it was the only one found effective against the cell line SW480 (IC_{50} = 35.95 μM). Likewise, we also modified the compound **5b** at position-3 with a series of amide groups, but the result was another story. In this subseries, amides linked with ring groups were negative of all four cell lines. On the country, the compounds with aliphatic side chains, compounds **7d**, **7e** and **7f**, have moderate effect on QGY-7701, SW480 and HeLa cell line, respectively.

Moreover, postion-3 substituent groups on compounds **8a**–**8s** derived from compound **5c** were exactly the same as the subseries **6**. Nevertheless, the bioactivities of these compounds displayed some dissimilarity, which means the influence of changing 4-fluoro benzene to 4-methoxyl benzene is obvious. In A-549 cell line, almost all the tested compounds showed no anti-tumor effect except compounds **8e** and **8q** which exhibited moderate inhibitory effect (IC_{50} = 17.55 μM and IC_{50} = 36.48 μM). This could suggest that these two compounds had unique mechanism for inhibiting A-549 cell line. Subseries **6** did exert moderate activity against QGY-7701 cell line. Nevertheless, compounds **8** demonstrated a stronger decrease in growth inhibitory activity except compound **8g** (IC_{50} = 43.14 μM). Synthesized compounds **8g**, **8l**, **8m, 8o** and **8p** demonstrated moderate to good activity against HeLa cell line, of which **8g** (IC_{50} = 15.85 μM) and **8p** (IC_{50} = 13.98 μM) had the similar activity to the 5-Fu (IC_{50} = 16.32 μM) but not as good as doxorubicin (IC_{50} = 1.12 μM). Investigation of anti-tumor activities in SW480 cells suggested that benzyl amide with electron-donating group (compounds **8f**, **8g** and **8h**) may play a pivotal role in the modulation of cytotoxic activity and the effect could increase with the stronger ability of the electron donation. In addition, in order to further investigate the compound **5d**, compounds **9a**–**9f** were synthesized as well and the bioactivities result was exhilarating us. Compound **9e** presented remarkable activity against three human tumor cell lines, being the most sensitive to growth inhibition of HeLa with IC_{50} value of 5.54 μM which is similar to the doxorubicin. Besides, compared with the reference drugs, it had homogeneous activities against QGY-7701 cell line and SW480 cell line, respectively. Both **9a** and **9e** had much better anti-HeLa effect than the compound **5d**, which means our modification is successful.

The most encouraging result to us was the compounds with substituted piperazinyl amide group at C-3 of 2, 5-dihydrofuran (compounds **10a**–**10g**). The most potent compound in this subseries was compound **10g** that presented good activity against four human tumor cell lines, being the most sensitive to growth inhibition QGY-7701 of cancer panel with IC_{50} value of 4.96 μM and HeLa cancer panel displaying a IC_{50} value of 4.00 μM. Moreover, compound **10d** and **10f** showed best activity against SW480 and A-549, respectively. The result indicated that the benzyl group with electron-withdrawing connecting to piperazinyl amide was important for the anti-cancer activity.



Reagents and conditions: (1) Piperidine, CH_3COOH, Toluene, Reflux, 6h; (2) 1, 4-butyne-diol, NaH, CuI, THF, 40℃, 15 - 22h; (3) a. $SOCl_2$, Reflux, 4h; b. Substituted amines or piperazidines, THF, r.t., Overnight.

Compd.	R_1	R_2	Compd.	R_1	R_2	Compd.	R_1	R_2
6a	4-F		**7b**	3,4-Cl_2		**8o**	4-OMe	
6b	4-F		**7c**	3,4-Cl_2		**8p**	4-OMe	
6c	4-F		**7d**	3,4-Cl_2		**8q**	4-OMe	
6d	4-F		**7e**	3,4-Cl_2		**8r**	4-OMe	
6e	4-F		**7f**	3,4-Cl_2		**8s**	4-OMe	
6f	4-F		**7g**	3,4-Cl_2		**9a**	3,4-$(OMe)_2$	
6g	4-F		**8a**	4-OMe		**9b**	3,4-$(OMe)_2$	
6h	4-F		**8b**	4-OMe		**9c**	3,4-$(OMe)_2$	
6i	4-F		**8c**	4-OMe		**9d**	3,4-$(OMe)_2$	
6j	4-F		**8d**	4-OMe		**9e**	3,4-$(OMe)_2$	
6k	4-F		**8e**	4-OMe		**9f**	3,4-$(OMe)_2$	
6l	4-F		**8f**	4-OMe		**10a**	4-OMe	
6m	4-F		**8g**	4-OMe		**10b**	4-OMe	
6n	4-F		**8h**	4-OMe		**10c**	4-OMe	
6o	4-F		**8i**	4-OMe		**10d**	4-OMe	
6p	4-F		**8j**	4-OMe		**10e**	4-OMe	
6q	4-F		**8k**	4-OMe		**10f**	4-OMe	
6r	4-F		**8l**	4-OMe		**10g**	4-OMe	
6s	4-F		**8m**	4-OMe				
7a	3,4-Cl_2		**8n**	4-OMe				

Scheme 1. Synthesis of title compounds. Reagents and conditions: (1) Piperidine, CH_3COOH, Toluene, Reflux, 6 h; (2) 1, 4-butyne-diol, NaH, CuI, THF, 40 °C, 15–22 h; (3) a. $SOCl_2$, Reflux, 4 h; b. Substituted amines or piperazidines, THF, r.t., Overnight.

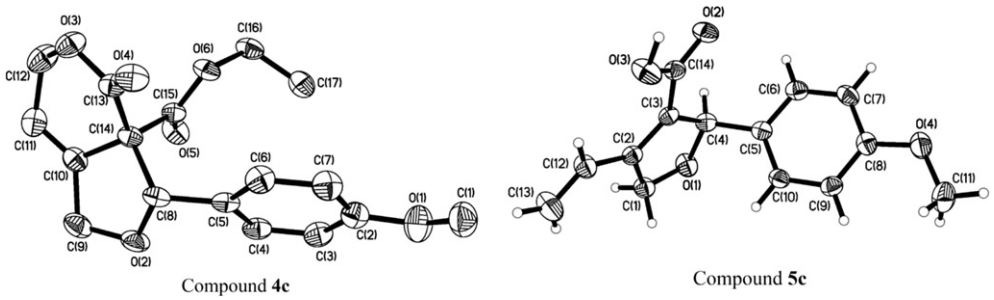
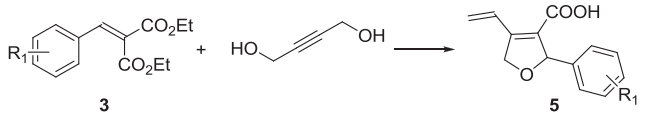


Fig. 2. ORTEP drawing of **4c** and **5c**.

Table 1
Synthesis of 2, 5-dihydrofuran derivatives.[a]



Entry	Compd.	Substrate R_1=	Temp (°C)	Time (h)	Yield[b] (%)
1	**5a**	4-F	40	15	77
2	**5b**	3,4-Cl_2	40	15	78
3	**5c**	4-OMe	40	22	92
4	**5d**	3,4-$(OMe)_2$	40	22	87

[a] Reaction conditions: Alkylidene malonate (20 mmol), 1,4-butyne-diol (30 mmol), CuI (2 mmol), NaH (24 mmol), THF (35 ml).
[b] Isolated yield.

Table 2
Crystallographical and experimental data for compounds **4c** and **5c**.

Data	Compound	
	4C	**5C**
CCDC deposition no.	780473	842494
Empirical Formula	C_{17} H_{19} O_6	C_{14} H_{14} O_4
Formula weight	319.32	246.25
Temperature (k)	293(2)	293(2)
Wavelength (Å)	0.71073	0.71073
Crystal system	Monoclinic	Monoclinic
Space group, *Z*	*P2(1)/n*	*P2(1)/c*
a (Å)	10.124(4)	9.049(12)
b (Å)	11.754(4)	18.06(2)
c (Å)	13.792(5)	7.994(11)
α (°)	90	90
β (°)	111.533(3)	106.340(16)
γ (°)	90	90
D_{calc}. (Mg/m^3)	1.389	1.305
F(000)	676	520
θ range (°)	2.16–26.01	2.26–25.02
Crystal size (mm^3)	0.30 × 0.26 × 0.23	0.20 × 0.10 × 0.02
Reflections collected/unique	6721/2993 [*R(int)* = 0.0842]	4325/2173 [*R(int)* = 0.0435]
Max. & min. transmission	0.9762 & 0.9691	0.9981 & 0.9811
Data/restraints/parameters	2993/0/208	2173/0/169
R, Rw[I>2σ(I)]	0.0449/0.1250	0.0449/0.1250
Goodness-of-fit on F^2	1.043	1.040

4. Conclusion

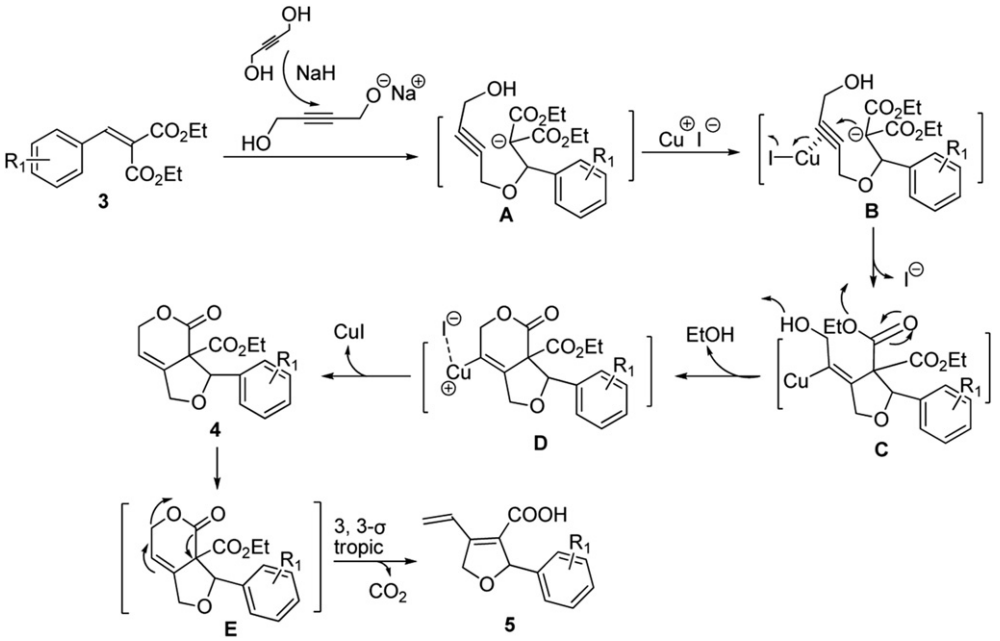
We have developed an efficient and mild stepwise reaction of 1, 4-butyne-diol and alkylidene malonates that allows controlled acquisition of highly substituted 2, 5-dihydrofuran derivatives with good yields. The results of preliminary anti-cancer assays of 2, 5-dihydrofuran derivatives indicated that introduction of benzene ring with electron-rich group at position-3 and piperazinyl amide group at position-2 could improve the anti-cancer activities effectively. Among all the tested compounds, compounds **9e** and **10g** showed the highest activity with broad anti-cancer spectrum, which were good candidates for further evaluation. Studies on the mechanism of action; influence of chirality; whether a given compound exerts cytotoxic, anti-adhesive or cytostatic effects; *in vivo* anti-tumor effects of this novel structure are still going on.

5. Experimental protocols

Melting points were measured on an uncorrected X-5 digital melting point apparatus (Gongyi City Yuhua Instrument Co., Ltd.; China). ^{1}H NMR and ^{13}C NMR spectra were recorded on a BRUKER AVANCE 300 spectrometer (Bruker Company, Germany), using TMS as an internal standard and $CDCl_3$ (99.8% D, Cambridge Isotope Laboratories) or DMSO-d^6 (99.9% D, Cambridge Isotope Laboratories) as solvents. Chemical shifts (δ values) and coupling constants (*J* values) are given in ppm and Hz, respectively. Elemental analyses were performed with a MOD-1106 instrument and were consistent with theoretical values within 0.4%. The mass spectra were recorded on an Esquire 3000 LC-MS mass spectrometer. Crystal structure was determined on a Bruker SMART CCD (Bruker Company, Germany). Purity analysis was determined on Agilent 1100 Serial HPLC (Agilent Company, US); A C_{18} column (ZORBAX™ 4.6 × 150 mm, 5 μm, PN: 993967906 SN: USRK042041). TLC analysis was carried out on silica gel plates GF254 (Qindao Haiyang Chemical, China). Silica gel thin-layer chromatography was performed with Silica gel 60G (Qindao Haiyang Chemical, China). All solvents and reagents were analytically pure, and no further purification was needed. All starting materials were commercially available.

5.1. General procedure for the synthesis of compounds *5*

NaH (60% in mineral oil, 24 mmol) was added to a solution of but-2-yne-1,4-diol (2.58 g, 30 mmol) in THF (50 mL) under nitrogen, and the solution was stirred for 5 min at room temperature. Alkylidene malonate (**1**, 20 mmol) and CuI (0.38 g, 2 mmol) were then added successively. When consumption of the starting materials was observed by TLC, the reaction mixture was quenched by dropwise addition of a 20% solution of HCl, immediately cooled to room temperature. The mixture was further diluted and extracted twice with CH_2Cl_2, and the organic layer was washed successively with saturated solution of brine, and water. The organic extracts were dried over $MgSO_4$, filtered, concentrated, and the residue purified by flash column chromatography to afford compound **5**.



Scheme 2. Putative reaction mechanism.

Table 3
In vitro anti-cancer activity of target compounds.

Compd.	Cytotoxicity IC_{50} (μM)[b]				Compd.	Cytotoxicity IC_{50} (μM)[b]			
	A-549[a]	QGY-7701	HeLa	SW480		A-549	QGY-7701	HeLa	SW480
5a	>100	>100	67.37	>100	**8c**	>100	>100	>100	>100
5b	>100	>100	10.26	>100	**8d**	>100	>100	>100	>100
5c	>100	>100	44.26	>100	**8e**	17.55	>100	>100	>100
5d	>100	>100	18.00	>100	**8f**	>100	>100	>100	39.47
6a	>100	46.74	>100	>100	**8g**	>100	43.14	15.85	31.68
6b	>100	56.44	NA[d]	>100	**8h**	>100	>100	>100	13.49
6c	>100	59.16	>100	>100	**8i**	>100	>100	>100	>100
6d	>100	52.82	>100	>100	**8j**	>100	>100	>100	>100
6e	NA[d]	61.58	>100	>100	**8k**	>100	>100	>100	>100
6f	>100	67.57	>100	>100	**8l**	>100	>100	37.46	>100
6g	>100	62.13	>100	>100	**8m**	>100	>100	31.36	>100
6h	>100	87.32	>100	>100	**8n**	>100	>100	>100	>100
6i	>100	51.37	>100	>100	**8o**	>100	>100	24.75	>100
6j	>100	36.93	>100	>100	**8p**	>100	>100	13.98	>100
6k	>100	29.66	>100	35.95	**8q**	36.48	>100	>100	>100
6l	>100	35.05	>100	>100	**8r**	>100	>100	>100	>100
6m	>100	59.80	>100	>100	**8s**	>100	>100	>100	>100
6n	>100	87.25	NA[d]	>100	**9a**	>100	>100	5.03	45.11
6o	>100	40.47	>100	>100	**9b**	>100	>100	>100	>100
6p	>100	>100	>100	>100	**9c**	>100	69.10	>100	>100
6q	>100	>100	>100	>100	**9d**	>100	>100	>100	>100
6r	>100	>100	>100	>100	**9e**	>100	7.49	5.54	19.13
6s	>100	>100	>100	>100	**9f**	>100	>100	>100	>100
7a	>100	>100	>100	>100	**10a**	22.96	23.55	>100	>100
7b	>100	>100	>100	>100	**10b**	20.67	17.95	15.30	25.02
7c	>100	>100	>100	>100	**10c**	10.26	>100	>100	44.15
7d	>100	31.29	>100	>100	**10d**	35.34	>100	>100	13.14
7e	>100	>100	>100	27.54	**10e**	26.83	>100	>100	>100
7f	>100	>100	60.07	>100	**10f**	8.31	10.98	9.86	>100
7g	>100	>100	>100	>100	**10g**	8.86	4.96	4.00	29.24
8a	>100	>100	>100	>100	**5-Fu**[c]	5.64	14.30	16.32	15.71
8b	>100	>100	>100	>100	**Doxorubicin**[c]	6.61	8.65	1.12	65.25

[a] Abbreviations: A-549: human lung adenocarcinoma cell line; HeLa: human cervical carcinoma cell line; QGY-7701: human hepatoma cell line; SW480: human colon carcinoma cell line.
[b] The IC_{50} value was defined as the concentration at which 50% survival of cells was observed.
[c] Used as a positive control.
[d] NA: Not active.

*5.1.1. Ethyl 3-(4-methoxyphenyl)-4-oxo-3,3a,4,6-tetrahydro-1H-furo[3,4-c]pyran-3a-carboxylate (**4c**)*

Color: White; m.p. 95.4–95.9 °C; Yield: 11%; IR: 3462, 3435, 3074, 3007, 2986, 2964, 2937, 2917, 2860, 2840, 2360, 2045, 1940, 1908, 1723, 1610, 1583, 1511, 1452, 1421, 1386, 1358, 1303, 1246, 1175, 1112, 1083, 1032, 983, 967, 921, 852, 837, 816, 797, 775, 74 cm^{-1}; ^1H NMR: (300 MHz, DMSO) δ: 7.61(d, 2H, J = 9.0 Hz), 6.86(d, 2H, J = 9.0 Hz), 6.02–6.06 (m, 1H), 5.40 (s, 1H), 4.95 (d, 1 H, J = 11.7 Hz), 4.81–4.84 (m, 2H), 4.61(d, 1 H, J = 11.7 Hz), 3.78–3.85 (m, 5H), 0.9(t, 3H, J = 7.2 Hz); ^{13}C NMR (300 MHz, DMSO) δ: 167.51, 164.94, 159.45, 141.98, 128.18, 115.55, 113.16, 83.93, 68.59, 67.56, 64.17, 62.16, 55.15, 13.51 ppm; ESIMS: *m/s* (%): 317.71 $[M - H]^-$; Anal. calcd for $C_{17}H_{18}O_6$: C 64.14, H 5.70. Found: C 54.33, H 5.67%.

*5.1.2. 2-(4-Fluorophenyl)-4-vinyl-2,5-dihydrofuran-3-carboxylic acid (**5a**)*

Color: White; m.p. 155.1–155.7 °C; Yield: 77%; IR: 3456, 2860, 2580, 2015, 1671, 1603, 1509, 1450, 1384, 1331, 1282, 1218, 1158, 1132, 1099, 1072, 1014, 946, 854, 824, 746 cm^{-1}; ^1H NMR: (300 MHz, DMSO) δ: 12.83 (br, 1H), 7.24–7.34 (m, 3H), 7.11–7.18 (m, 2H), 5.87 (dd, 1H, J = 5.1, 3.0 Hz), 5.60 (d, 1H, J = 14.4 Hz), 5.50 (d, 1H, J = 18.0 Hz), 5.13 (dd, 1H, J = 14.4, 5.1 Hz), 4.95 ppm (dd, 1H, J = 14.4, 3.0 Hz); ^{13}C NMR (300 MHz, DMSO) δ: 163.8, 163.4, 160.2, 146.5, 137.9, 129.2, 127.7, 123.5, 115.1, 87.5, 74.8 ppm; ESIMS: *m/s* (%): 233.42 $[M - H]^-$; Anal. calcd for $C_{13}H_{11}FO_3$: C 66.66, H 4.73. Found: C 66.69, H 4.76%.

*5.1.3. 2-(3,4-Dichlorophenyl)-4-vinyl-2,5- dihydrofuran-3-carboxylic acid (**5b**)*

Color: White; m.p. 102.6–103.0 °C; Yield: 78%; IR: 3440, 2900, 2859, 2621, 1687, 1667, 1637, 1589, 1468, 1429, 1406, 1384, 1319, 1282, 1202, 1132, 1070, 1029, 1014, 940, 926, 883, 824, 789, 747, 705 cm^{-1}; ^1H NMR: (300 MHz, DMSO) δ: 12.94 (s, 1H), 7.53–7.60 (m, 2H), 7.24–7.34 (m, 2H), 5.89 (dd, 1H, J = 5.4, 3.0 Hz), 5.61 (d, 1H, J = 11.1 Hz), 5.51 (d, 1H, J = 18.0 Hz), 5.21 (dd, 1H, J = 14.4, 5.4 Hz), 4.95 ppm (dd, 1H, J = 14.4, 3.0 Hz); ^{13}C NMR (300 MHz, DMSO) δ: 163.7, 147.1, 130.9, 130.5, 129.3, 128.3, 127.7, 127.5, 124.8, 123.9, 69.0, 75.2 ppm; ESIMS: *m/s* (%): 285.54 $[M - H]^-$; Anal. calcd for $C_{13}H_{10}Cl_2O_3$: C 54.76, H 3.54. Found: C 55.11, H 4.74%.

*5.1.4. 2-(4-Methoxyphenyl)-4-vinyl-2,5- dihydrofuran-3-carboxylic acid (**5c**)*

Color: White; m.p. 160.1–160.4 °C; Yield: 92%; IR: 3446, 3035, 3964, 2889, 2855, 2839, 2670, 2621, 2574, 2360, 2340, 1672, 1612, 1588, 1440, 1384, 1513, 1440, 1384, 1320, 1303, 1273, 1248, 1174, 1125, 1113, 1073, 1034, 1019, 947, 852, 824, 809, 742 cm^{-1}; ^1H NMR: (300 MHz, DMSO) δ: 12.71 (s, 1H), 7.29 (dd, 1H, J = 18.0, 11.1 Hz), 7.14–7.19 (m, 2H), 6.84–6.89 (m, 2H), 5.82 (dd, 1H, J = 5.4, 3.0 Hz), 5.58 (d, J = 11.1 Hz, 1H), 5.48 (d, 1H, J = 18.0 Hz), 5.07 (dd, 1H, J = 14.4, 5.4 Hz), 4.89 (dd, 1H, J = 14.4, 3.0 Hz), 3.72 ppm (s, 3H); ^{13}C NMR (300 MHz, DMSO) δ: 163.8, 158.9, 146.0, 133.5, 129.3, 128.3, 127.7, 123.1, 113.5, 87.7, 74.3, 55.0 ppm; ESIMS: *m/s* (%): 245.70 $[M - H]^-$; Anal. calcd for $C_{14}H_{14}O_4$: C 68.28, H 5.73. Found: C 68.46, H 7.89%.

*5.1.5. 2-(3,4-Dimethoxyphenyl)-4-vinyl-2,5- dihydrofuran-3-carboxylic acid (**5d**)*

Color: White; m.p. 180.3–180.9 °C; Yield: 87%; IR: 3446, 3009, 2961, 2946, 2836, 1868, 1072, 1646, 1592, 1558, 1520, 1467, 1423, 1384, 1357, 1310, 1264, 1237, 1193, 1161, 1141, 1114, 1062, 1019, 932, 871, 807, 795, 768, 705 cm^{-1}; ^1H NMR: (300 MHz, DMSO) δ: 12.76 (s, 1H), 7.30 (dd, 1H, J = 18.0, 11.1 Hz), 6.76–6.91 (m, 3H), 5.82 (dd, 1H, J = 5.4, 3.0 Hz), 5.60 (d, 1H, J = 11.1 Hz), 5.50 (d, 1H, J = 18.0 Hz), 5.09 (dd, 1H, J = 14.4, 5.4 Hz), 4.90 (dd, 1H, J = 14.4, 3.0 Hz), 3.72 (s, 3H), 3.71 ppm (s, 3H); ^{13}C NMR (300 MHz, DMSO) δ: 164.0, 152.7, 146.3, 137.2, 137.0, 129.0, 127.7, 123.3, 104.4, 88.3, 74.6, 59.9, 55.8 ppm; ESIMS: *m/s* (%): 275.70 $[M - H]^-$; Anal. calcd for $C_{15}H_{16}O_5$: C 65.21, H 5.84. Found: C 65.31, H 5.90%.

*5.2. General procedure for the synthesis of compounds **6**–**10***

To a solution of compounds **5** (2 mmol) in the $SOCl_2$ (15 ml) were stirred in refluxing for 4 h. The solvent was then removed under reduced pressure and white solids were obtained. The solids dissolving in THF (10 ml) was added dropwise to the solution of substituted amine or piperazidine (3 mmol) in THF (10 ml) with stirring at room temperature overnight. The mixture was poured into 10% HCl ice-water (150 ml) with stirring. The resulting solid was filtered, dried and purified by flash column chromatography to yield compounds **6**–**10**.

*5.2.1. 2-(4-Fluorophenyl)-N-phenyl-4-vinyl-2,5-dihydrofuran-3-carboxamide (**6a**)*

Color: White; m.p. 140.3–140.8 °C; Yield: 92%; ^1H NMR: (300 MHz, $CDCl_3$) δ: 7.34 (m, 9H), 7.05 (m, 2H), 6.61 (m, 1H), 5.60 (d, 1H), 5.52 (d, 1H), 5.21 (dd, 1H), 5.08 ppm (dd, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ: 163.8, 160.2, 155.1, 141.0, 137.2, 130.5, 129.2, 128.8, 128.7, 128.1, 120.3, 117.4, 115.1, 86.1, 74.6 ppm; ESIMS: *m/s* (%): 309.39 $[M - H]^-$; Anal. calcd for $C_{19}H_{16}FNO_2$: C 73.77, H 5.21 N 4.53. Found: C 73.29, H 5.69, N 4.32%.

*5.2.2. 2-(4-Fluorophenyl)-N-m-tolyl-4-vinyl-2,5-dihydrofuran-3-carboxamide (**6b**)*

Color: White; m.p. 115.1–115.7 °C; Yield: 92%; ^1H NMR: (300 MHz, $CDCl_3$) δ: 7.41 (m, 6H), 7.09 (m, 4H), 6.61 (m, 1H), 5.60 (d, 1H), 5.45 (d, 1H), 5.23 (dd, 1H), 5.05 (dd, 1H), 2.36 ppm (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ: 163.8, 156.1, 159.1, 138.2, 141.2, 138.2, 137.8, 130.5, 129.2, 128.8, 128.7, 126.9, 124.1, 120.3, 117.6, 115.1, 86.5, 75.6, 23.2 ppm; ESIMS: *m/s* (%): 323.58 $[M - H]^-$; Anal. calcd for $C_{20}H_{18}FNO_2$: C 74.29, H 5.61 N 4.33. Found: C 74.02, H 5.39, N 4.37%.

*5.2.3. 2-(4-Fluorophenyl)-N-p-tolyl-4-vinyl-2,5-dihydrofuran-3-carboxamide (**6c**)*

Color: White; m.p. 160.1–161.0 °C; Yield: 92%; ^1H NMR: (300 MHz, $CDCl_3$) δ: 7.50 (m, 3H), 7.29 (m, 4H), 7.07 (m, 3H), 6.69 (m, 2H), 5.59 (d, 1H), 5.39 (d, 1H), 5.19 (dd, 1H), 5.03 (dd, 1H), 2.30 ppm (s, 3H); ESIMS: *m/s* (%): 323.58 $[M - H]^-$; Anal. calcd for $C_{20}H_{18}FNO_2$: C 74.29, H 5.61 N 4.33. Found: C 74.14, H 5.43, N 4.32%.

*5.2.4. 2-(4-Fluorophenyl)-N-(2-methoxyphenyl)-4-vinyl-2,5-dihydrofuran-3-carboxamide (**6d**)*

Color: White; m.p. 108.7–109.1 °C; Yield: 92%; ^1H NMR: (300 MHz, $CDCl_3$) δ: 7.32 (m, 8H), 6.93 (s, 1H), 6.81 (m, 2H), 6.59 (m, 1H), 5.59 (d, 1H), 5.39 (d, 1H), 5.19 (dd, 1H), 5.05 (dd, 1H), 3.80 ppm (m, 3H); ESIMS: *m/s* (%): 338.12 $[M - H]^-$; Anal. calcd for $C_{20}H_{18}FNO_3$: C 70.78, H 5.35 N 4.13. Found: C 70.65, H 5.30, N 4. 26%.

*5.2.5. N-(4-Ethoxyphenyl)-2-(4-fluorophenyl)-4-vinyl-2,5-dihydrofuran-3-carboxamide (**6e**)*

Color: White; m.p. 155.2–155.9 °C; Yield: 92%; ^1H NMR: (300 MHz, $CDCl_3$) δ: 7.39 (m, 6H), 6.93 (b, 1H), 6.81 (m, 2H), 6.60 (m, 1H), 5.59 (d, 1H), 5.39 (d, 1H), 5.19 (dd, 1H), 5.05 (dd, 1H), 3.99 (m, 2H), 1.39 ppm (m, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ: 163.3, 162.7, 155.6, 155.1, 141.0, 131.5129.2, 128,3, 128.5, 121.7, 117.4, 115.4, 115.2, 86.1, 74.6, 64.7, 15.2 ppm; ESIMS: *m/s* (%): 352.14 $[M - H]^-$; Anal. calcd for $C_{21}H_{20}FNO_3$: C 71.37, H 5.70 N 3.96. Found: C 71.11, H 5.56, N 4.74%.

*5.2.6. N-Benzyl-2-(4-fluorophenyl)-4-vinyl-2,5-dihydrofuran-3-carboxamide (**6f**)*

Color: White; m.p. 119.1–119.8 °C; Yield: 93%; ^1H NMR: (300 MHz, $CDCl_3$) δ: 7.29 (m, 7H), 6.93 (m, 1H), 6.49 (m, 1H), 5.56 (m, 2H), 5.36 (d, 2H), 5.18 (dd, 1H), 4.99 (dd, 1H), 4.39 (m, 2H) ppm ^{13}C NMR (300 MHz, $CDCl_3$) δ: 163.9, 160.7, 150.8, 141.0, 137.2, 131.5,

129.2, 128.8, 127.7, 127.0, 125.6, 117.7, 115.1, 85.6, 74.1, 44.8 ppm; ESIMS: *m/s* (%): 322.34 [M − H]$^-$; Anal. calcd for $C_{20}H_{18}FNO_2$: C 74.29, H 5.61 N 4.33. Found: C 74.01, H 5.56, N 4.50%.

*5.2.7. 2-(4-Fluorophenyl)-N-(4-methylbenzyl)-4-vinyl-2,5-dihydrofuran-3-carboxamide (**6g**)*

Color: White; m.p. 113.9–114.6 °C; Yield: 91%; ^{1}H NMR: (300 MHz, $CDCl_3$) δ: 8.56 (m, 1H), 7.41 (m, 4H), 6.90 (m, 5H), 6.49 (m, 1H), 5.49 (d, 1H), 5.25 (d, 1H), 4.96 (m, 2H), 4.21 (m, 2H), 2.23 ppm (s,3H); ESIMS: *m/s* (%): 336.12 [M − H]$^-$; Anal. calcd for $C_{20}H_{18}FNO_3$: C 74.76, H 5.97 N 4.15. Found: C 74.59, H 5.77, N 4. 31%.

*5.2.8. N-(3,4-Dimethoxybenzyl)-2-(4-fluorophenyl)-4-vinyl-2,5-dihydrofuran-3-carboxamide (**6h**)*

Color: White; m.p. 98.2–98.8 °C; Yield: 92%; ^{1}H NMR: (300 MHz, $CDCl_3$) δ: 7.30 (m, 5H), 6.83 (m, 1H), 6.54 (m, 2H), 6.49 (m, 1H), 5.73 (b, 1H), 5.54 (d, 1H), 5.38 (d, 1H), 5.18 (dd, 1H), 4.99 (dd, 1H), 4.30 (m, 2H), 3.83 (m,3H), 3.78 ppm (m,3H); ESIMS: *m/s* (%): 382.85 [M − H]$^-$; Anal. calcd for $C_{22}H_{22}FNO_4$: C 68.92, H 5.78 N 3.65. Found: C 70.04, H 5.73, N 3.63%.

*5.2.9. N-(2-Fluorobenzyl)-2-(4-fluorophenyl)-4-vinyl-2,5-dihydrofuran-3-carboxamide (**6i**)*

Color: White; m.p. 106.5–107.0 °C; Yield: 93%; ^{1}H NMR: (300 MHz, $CDCl_3$) δ: 7.30 (m, 6H), 6.96 (m, 3H), 6.49 (m, 1H), 5.79 (b, 1H), 5.52(d, 1H), 5.34 (d, 1H), 5.18 (dd, 1H), 4.99 (dd, 1H), 4.41 ppm (m, 2H); ESIMS: *m/s* (%): 340.11 [M − H]$^-$; Anal. calcd for $C_{20}H_{17}F_2NO_2$: C 70.37, H 5.02 N 4.10. Found: C 70.18, H 5.02, N 4.13%.

*5.2.10. N-(4-Chlorobenzyl)-2-(4-fluorophenyl)-4-vinyl-2,5-dihydrofuran-3-carboxamide (**6j**)*

Color: White; m.p. 137.5–138.0 °C; Yield: 92%; ^{1}H NMR: (300 MHz, $CDCl_3$) δ: 7.30 (m, 5H), 6.89 (m, 4H), 6.49 (m, 1H), 5.74 (b, 1H), 5.54 (d, 1H), 5.38 (d, 1H), 5.18 (dd, 1H), 4.99 (dd, 1H), 4.41 (m, 1H), 4.28 ppm (m,1H); ESIMS: *m/s* (%): 356.33 [M − H]$^-$; Anal. calcd for $C_{20}H_{17}ClFNO_2$: C 67.14, H 4.79 N 3.91. Found: C 67.01, H 4.56, N 3.52%.

*5.2.11. N-(4-Fluorophenethyl)-2-(4-fluorophenyl)-4-vinyl-2,5-dihydrofuran-3-carboxamide (**6k**)*

Color: White; m.p. 120.3–120.8 °C; Yield: 91%; ^{1}H NMR: (300 MHz, $CDCl_3$) δ: 7.31 (m, 4H), 6.91 (m, 4H), 6.39 (m, 1H), 5.51 (d, 1H), 5.32 (m, 2H), 5.09 (dd, 1H), 4.99 (dd, 1H), 3.48 (m, 2H), 2.73 ppm (m,2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ: 168.1, 160.2, 150.5, 141.0, 136.7, 131.7, 130.5, 129.1, 128.7, 117.4, 115.1, 114.6, 86.1, 74.6, 41.5, 37.2 ppm; ESIMS: *m/s* (%): 354.28 [M − H]$^-$; Anal. calcd for $C_{21}H_{19}F_2NO_2$: C 70.97, H 5.39 N 3.94. Found: C 71.00, H 5.92, N 3.62%.

*5.2.12. N-(2-Fluorophenethyl)-2-(4-fluorophenyl)-4-vinyl-2,5-dihydrofuran-3-carboxamide (**6l**)*

Color: White; m.p. 92.1–92.9 °C; Yield: 97%; ^{1}H NMR: (300 MHz, $CDCl_3$) δ: 7.29 (m, 6H), 6.96 (m, 3H), 6.40 (m, 1H), 5.49 (d, 1H), 5.36 (m, 2H), 5.18 (dd, 1H), 4.99 (dd, 1H), 3.49 (m, 2H), 2.73 ppm (m,2H); ESIMS: *m/s* (%): 354.21 [M − H]$^-$; Anal. calcd for $C_{21}H_{19}F_2NO_2$: C 70.97, H 5.39 N 3.94. Found: C 71.01, H 5.85, N 3.75%.

*5.2.13. N-(3-Fluorophenethyl)-2-(4-fluorophenyl)-4-vinyl-2,5-dihydrofuran-3-carboxamide (**6m**)*

Color: White; m.p. 96.8–97.5 °C; Yield: 96%; ^{1}H NMR: (300 MHz, $CDCl_3$) δ: 7.29 (m, 6H), 6.90 (m, 1H), 6.88 (m, 2H), 6.39 (m, 1H), 5.51 (d, 1H), 5.35 (m, 2H), 5.18 (dd, 1H), 4.99 (dd, 1H), 3.49 (m, 2H), 2.79 ppm (m, 2H); ESIMS: *m/s* (%): 354.16 [M − H]$^-$; Anal. calcd for $C_{21}H_{19}F_2NO_2$: C 70.97, H 5.39 N 3.94. Found: C 71.01, H 5.47, N 3.93%.

*5.2.14. 2-(4-Fluorophenyl)-N-(3-methoxyphenethyl)-4-vinyl-2,5-dihydrofuran-3-carboxamide (**6n**)*

Color: White; m.p. 109.6–110.4 °C; Yield: 93%; ^{1}H NMR: (300 MHz, $CDCl_3$) δ: 7.29 (m, 6H), 6.92 (m, 2H), 6.49 (m, 1H), 5.78 (b, 1H), 5.53 (d, 1H), 5.39 (d, 1H), 5.18 (dd, 1H), 4.99 (dd, 1H), 4.39 (m, 2H), 3.78 ppm (m, 2H); ESIMS: *m/s* (%): 366.28 [M − H]$^-$; Anal. calcd for $C_{22}H_{22}FNO_3$: C 71.92, H 6.04 N 3.81. Found: C 71.89, H 5.99, N 3.92%.

*5.2.15. N-Cyclohexyl-2-(4-fluorophenyl)-4-vinyl-2,5-dihydrofuran-3-carboxamide (**6o**)*

Color: White; m.p. 72.3–72.8 °C; Yield: 93%; ^{1}H NMR: (300 MHz, $CDCl_3$) δ: 7.33 (m, 5H), 6.49 (m, 1H), 5.49 (d, 1H), 5.32 (m, 2H), 5.18 (dd, 1H), 4.97 (dd, 1H), 3.19 (m, 1H), 1.29 (m, 6H), 1.05 (m, 2H), 0.83 ppm (m, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ: 166.3, 162.6, 150.6, 138.0, 130.1, 129.2, 128.7, 117.4, 115.1, 82.5, 52.3, 31.8, 25,4, 25.9 ppm; ESIMS: *m/s* (%): 314.74 [M − H]$^-$; Anal. calcd for $C_{19}H_{22}FNO_2$: C 72.36, H 7.03 N 4.44. Found: C 72.35, H 7.11, N 4.37%.

*5.2.16. 2-(4-Fluorophenyl)-N-propyl-4-vinyl-2,5-dihydrofuran-3-carboxamide (**6p**)*

Color: White; m.p. 87.5–88.2 °C; Yield: 93%; ^{1}H NMR: (300 MHz, $CDCl_3$) δ: 7.33 (m, 5H), 6.49 (m, 1H), 5.51 (d, 1H), 5.31 (m, 2H), 5.12 (dd, 1H), 4.97 (dd, 1H), 3.16 (m, 2H), 1.29 (m, 2H), 0.82 ppm (m, 3H); ESIMS: *m/s* (%): 274.54 [M − H]$^-$; Anal. calcd for $C_{16}H_{18}FNO_2$: C 69.80, H 6.59 N 5.09. Found: C 69.99, H 6.55, N 5.03%.

*5.2.17. 2-(4-Fluorophenyl)-N-pentyl-4-vinyl-2,5-dihydrofuran-3-carboxamide (**6q**)*

Color: White; m.p. 78.5–78.9 °C; Yield: 94%; ^{1}H NMR: (300 MHz, $CDCl_3$) δ: 7.33 (m, 5H), 6.49 (m, 1H), 5.49 (d, 1H), 5.32 (m, 2H), 5.18 (m, 2H), 4.97 (dd, 1H), 3.78 (m, 2H), 1.54 (m, 4H), 1.09 (m, 2H), 0.83 ppm (m, 3H); ESIMS: *m/s* (%): 302.20 [M − H]$^-$; Anal. calcd for $C_{18}H_{22}FNO_2$: C 71.26, H 7.31, N 4.62. Found: C 71.45, H 7.25, N 4.60%.

*5.2.18. 2-(4-Fluorophenyl)-N-isobutyl-4-vinyl-2,5-dihydrofuran-3-carboxamide (**6r**)*

Color: White; m.p. 91.1–91.7 °C; Yield: 93%; ^{1}H NMR: (300 MHz, $CDCl_3$) δ: 7.33 (m, 5H), 6.49 (m, 1H), 5.48 (d, 1H), 5.32 (d, 1H), 5.09 (m, 3H), 1.18 ppm (m, 9H); ^{13}C NMR (300 MHz, $CDCl_3$) δ: 166.3, 162.6, 150.6, 138.0, 130.1, 129.2, 128.7, 117.4, 115.1, 85.8, 82.5, 41.3, 28.1, 21.4 ppm; ESIMS: *m/s* (%): 288.34 [M − H]$^-$; Anal. calcd for $C_{17}H_{20}FNO_2$: C 70.57, H 6.97 N 4.84. Found: C 70.44, H 7.96, N 4.80%.

*5.2.19. N-tert-Butyl-2-(4-fluorophenyl)-4-vinyl-2,5-dihydrofuran-3-carboxamide (**6s**)*

Color: White; m.p. 84.9–85.6 °C; Yield: 94%; ^{1}H NMR: (300 MHz, $CDCl_3$) δ: 7.33 (m, 5H), 6.49 (m, 1H), 5.51 (d, 1H), 5.31 (m, 2H), 5.12 (dd, 1H), 4.97 (dd, 1H), 3.09 (m, 1H), 2.91 (m, 1H), 1.56 (m, 1H), 0.62 ppm (m, 6H); ESIMS: *m/s* (%): 288.21 [M − H]$^-$; Anal. calcd for $C_{17}H_{20}F_2NO_2$: C 70.57, H 6.97 N 4.84. Found: C 70.66, H 6.85, N 4.75%.

*5.2.20. 2-(3,4-Dichlorophenyl)-N-phenyl-4-vinyl-2,5-dihydrofuran-3-carboxamide (**7a**)*

Color: White; m.p. 179.4–179.8 °C; Yield: 85%; ^{1}H NMR: (300 MHz, $CDCl_3$) δ: 7.50 (m, 2H, Ph-H); 7.34 (m, 5H, Ph-H); 7.17 (m, 1H, Ph-H); 7.11 (m, 1H, C=CH–); 7.01 (s, 1H, –CONH); 6.08 (t, 1H, –CH–Ph); 5.59 (d, 1H, CH_2=C–); 5.43 (d, 1H, CH_2=C–); 5.21 (dd, 1H, –CH_2–O); 5.02 ppm (dd, 1H, –CH_2–O); ^{13}C NMR (300 MHz, $CDCl_3$) δ: 163.8, 143.4, 133.5, 130.3, 130.0, 129.8, 129.2, 128.0, 127.8, 127.5, 127.2, 126.4, 125.3, 124.7, 123.4, 68.7, 75.9 ppm; ESIMS: *m/s* (%): 358.28 [M − H]$^-$; Anal. calcd for $C_{19}H_{15}Cl_2NO_2$: C 63.35, H 4.20 N 3.89. Found: C 63.66, H 4.43, N 3.68%.

*5.2.21. 2-(3,4-Dichlorophenyl)-N-(2-methoxyphenyl)-4-vinyl-2,5-dihydrofuran-3-carboxamide (**7b**)*

Color: White; m.p. 142.9–144.1 °C; Yield: 88%; ^{1}H NMR: (300 MHz, $CDCl_3$) δ: 8.30 (m, 1H, –CONH); 7.53 (m, 1H, Ph-H); 7.42 (m, 1H, Ph-H); 7.33 (q, 1H, C=CH–); 7.28 (m, 2H, Ph-H); 7.03 (m, 1H, Ph-H); 6.93 (m, 1H, Ph-H); 6.81 (m, 1H, Ph-H); 6.04 (t, 1H, –CH–Ph); 5.59 (d, 1H, CH_2=C–); 5.43 (m, 1H, CH_2=C–); 5.18 (dd, 1H, –CH_2–O); 5.02 (dd, 1H, –CH_2–O); 3.74 ppm (m, 3H, –OCH_3); ESIMS: *m/s* (%): 390.07 $[M + H]^+$; Anal. calcd for $C_{20}H_{17}Cl_2NO_3$: C 61.55, H 4.39 N 3.59. Found: C 61.59, H 4.40, N 3.57%.

*5.2.22. N-Benzyl-2-(3,4-dichlorophenyl)-4-vinyl-2,5-dihydrofuran-3-carboxamide (**7c**)*

Color: White; m.p. 149.3–149.5 °C; Yield: 80%; ^{1}H NMR: (300 MHz, $CDCl_3$) δ: 7.41 (m, 2H, Ph-H); 7.31 (m, 1H, Ph-H); 7.25 (m, 4H, Ph-H); 7.18 (m, 1H, Ph-H); 7.06 (q, 1H, C=CH-); 6.95 (m, 1H, Ph-H); 5.99 (t, 1H, –CH–Ph); 5.52 (d, 1H, CH_2=C–); 5.38 (s, 1H, CH_2=C–); 5.32 (s, 1H, –CONH); 5.15 (dd, 1H, –CH_2–O); 4.97 (dd, 1H, –CH_2–O); 4.40 ppm (m, 2H, –N–CH_2); ^{13}C NMR (300 MHz, $CDCl_3$) δ: 165.8, 147.2, 134.3, 131.5, 130.0, 129.3, 128.2, 128.0, 127.8, 127.3, 126.9, 126.4, 125.3, 124.7, 122.3, 68.7, 75.9, 45.2 ppm; ESIMS: *m/s* (%): 374.07 $[M + H]^+$; Anal. calcd for $C_{20}H_{17}Cl_2NO_2$: C 64.18, H 4.58 N 3.74. Found: C 64.11, H 4.53, N 3.73%.

*5.2.23. 2-(3,4-Dichlorophenyl)-N-propyl-4-vinyl-2,5-dihydrofuran-3-carboxamide (**7d**)*

Color: White; m.p. 149.2–149.6 °C; Yield: 80%; ^{1}H NMR: (300 MHz, $CDCl_3$) δ: 7.44 (m, 2H, Ph-H); 7.24 (m, 1H, Ph-H); 7.04 (q, 1H, C=CH–); 5.99 (s, 1H, –CH–Ph); 5.52 (d, 1H, CH_2=C–); 5.37 (s, 1H, CH_2=C–); 5.31 (s, 1H, –CONH); 5.14 (dd, 1H, –CH_2–O); 4.97 (dd, 1H, –CH_2–O); 3.19 (m, 2H, -N-CH_2); 1.40 (m, 2H, CH_2); 0.85 ppm (m, 3H, CH_3); ESIMS: *m/s* (%): 324.17 $[M - H]^-$; Anal. calcd for $C_{16}H_{17}Cl_2NO_2$: C 58.91, H 5.25 N 4.29. Found: C 58.90, H 5.32, N 4.21%.

*5.2.24. 2-(3,4-Dichlorophenyl)-N-pentyl-4-vinyl-2,5-dihydrofuran-3-carboxamide (**7e**)*

Color: White; m.p. 126.9–127.6 °C; Yield: 80%; ^{1}H NMR: (300 MHz, $CDCl_3$) δ: 7.43 (m, 2H, Ph-H); 7.23 (m, 1H, Ph-H); 7.04 (q, 1H, C=CH–); 5.98 (t, 1H, –CH–Ph); 5.51 (d, 1H, CH_2=C–); 5.35 (m, 1H, CH_2=C–); 5.30 (m, 1H, –CONH); 5.14 (dd, 1H, –CH_2–O); 4.95 (dd, 1H, –CH_2–O); 3.20 (m, 2H, -N-CH_2); 1.29 (m, 4H, CH_2); 1.11 (m, 2H, CH_2); 1.06 (m, 2H, CH_2); 0.84 ppm (m, 3H, CH_3); ESIMS: *m/s* (%): 352.12 $[M - H]^-$; Anal. calcd for $C_{18}H_{21}Cl_2NO_2$: C 61.02, H 5.97 N 3.95. Found: C 61.00, H 5.94, N 3.98%.

*5.2.25. 2-(3,4-Dichlorophenyl)-N-isobutyl-4-vinyl-2,5-dihydrofuran-3-carboxamide (**7f**)*

Color: White; m.p. 158.5–159.2 °C; Yield: 87%; ^{1}H NMR: (300 MHz, $CDCl_3$) δ: 7.45 (m, 2H, Ph-H); 7.24 (m, 1H, Ph-H); 7.07 (q, 1H, C=CH–); 5.99 (t, 1H, –CH–Ph); 5.52 (d, 1H, CH_2=C–); 5.38 (s, 1H, CH_2=C–); 5.31 (m, 1H, –CONH); 5.15 (dd, 1H, –CH_2–O); 4.97 (dd, 1H, –CH_2–O); 3.05 (m, 2H, –N–CH_2); 1.63 (m, 1H, –N–CH); 0.81 ppm (m, 6H, CH_3); ESIMS: *m/s* (%): 338.08 $[M - H]^-$; Anal. calcd for $C_{17}H_{19}Cl_2NO_2$: C 60.01, H 5.63 N 4.12. Found: C 60.34, H 5.56, N 4.24%.

*5.2.26. N-tert-Butyl-2-(3,4-dichlorophenyl)-4-vinyl-2,5-dihydrofuran-3-carboxamide (**7g**)*

Color: White; m.p. 108.8–109.3 °C; Yield: 75%; ^{1}H NMR: (300 MHz, $CDCl_3$) δ: 7.45 (m, 2H, Ph-H); 7.23 (m, 1H, Ph-H); 6.95 (q, 1H, C=CH–); 5.97 (t, 1H, –CH–Ph); 5.48 (d, 1H, CH_2=C–); 5.30 (d, 1H, CH_2=C–); 5.14 (m, 1H, –CONH); 5.10 (m, 1H, –CH_2–O); 4.95 (dd, 1H, –CH_2–O); 1.26 ppm (m, 9H, CH_3); ^{13}C NMR (300 MHz, $CDCl_3$) δ: 165.8, 147.1, 131.5, 130.5, 129.3, 128.3, 127.2, 127.5, 124.8, 123.9, 69.0, 75.2, 64.3, 26,9 ppm; ESIMS: *m/s* (%): 338.16 $[M - H]^-$; Anal. calcd for $C_{17}H_{19}Cl_2NO_2$: C 60.01, H 5.63 N 4.12. Found: C 60.06, H5.73, N 4.21%.

*5.2.27. 2-(4-Methoxyphenyl)-N-phenyl-4-vinyl-2,5-dihydrofuran-3-carboxamide (**8a**)*

Color: White; m.p. 116.5–116.8 °C; Yield: 85%; ^{1}H NMR: (300 MHz, $CDCl_3$) δ: 7.40 (q, 1H, C=CH–); 7.37 (m, 2H, Ph-H); 7.24 (m, 2H , Ph-H); 7.21 (m, 2H , Ph-H); 7.07 (m, 1H, Ph-H); 6.98 (m, 2H, Ph-H); 6.87 (s, 1H, –CONH); 5.99 (t, 1H, –CH–Ph); 5.56 (d, 1H, CH_2=C–); 5.40 (d, 1H, CH_2=C–); 5.15 (dd, 1H, –CH_2–O); 4.99 (dd, 1H, –CH_2–O); 3.84 ppm (s, 3H, –OCH_3); ^{13}C NMR (300 MHz, $CDCl_3$) δ: 163.8, 158.2, 148.4, 135.3, 136.7, 129.3, 128.2, 128.3, 128.0, 127.7, 123.1, 121.4, 113.5, 87.7, 74.3, 55.0 ppm; ESIMS: *m/s* (%): 320.14 $[M - H]^-$; Anal. calcd for $C_{20}H_{19}NO_3$: C 74.75, H 5.96 N 4.36. Found: C 74.48, H 5.75, N 4.32%.

*5.2.28. 2-(4-Methoxyphenyl)-N-m-tolyl-4-vinyl-2,5-dihydrofuran-3-carboxamide (**8b**)*

Color: White; m.p. 138.6–140.4 °C; Yield: 95%; IR (KBr, cm^{-1}): 3294, 2923, 2853, 1637, 1611, 1591, 1528, 1515, 1456, 1383, 1301, 1281, 1253, 1173, 1110, 1069, 1020, 918, 836, 808, 773, 738, 688, 603, 551, 439; ^{1}H NMR: (300 MHz, $CDCl_3$) δ: 7.49 (q, 1H, C=CH–); 7.39 (m, 2H, Ph-H); 7.26 (s, 1H, Ph-H); 7.07 (m, 1H, Ph-H); 6.99 (m, 2H, Ph-H); 6.88 (m, 2H, Ph-H); 6.81 (s, 1H, –CONH); 5.99 (t, 1H, –CH–Ph); 5.55 (d, 1H, CH_2=C–); 5.40 (d, 1H, CH_2=C–); 5.15 (dd, 1H, –CH_2–O); 4.99 (dd, 1H, –CH_2–O); 3.84 (s, 3H, –OCH_3); 2.28 ppm (s, 3H, –CH_3); ESIMS: *m/s* (%): 334.53 $[M - H]^-$; Anal. calcd for $C_{21}H_{21}NO_3$: C 75.20, H 6.31 N 4.18. Found: C 75.12, H 6.39, N 4.26%.

*5.2.29. 2-(4-Methoxyphenyl)-N-p-tolyl-4-vinyl-2,5-dihydrofuran-3-carboxamide (**8c**)*

Color: White; m.p. 201–201.3 °C; Yield: 88%; IR (KBr, cm^{-1}): 3299, 2923, 2852, 1635, 1596, 1517, 1459, 1402, 1383, 1317, 1253, 1173, 1110, 1069, 1024, 994, 945, 920, 894, 803, 778, 743, 702, 570, 545, 509, 458; ^{1}H NMR: (300 MHz, $CDCl_3$) δ: 7.50 (q, 1H, C=CH–); 7.40 (m, 2H, Ph-H); 7.07 (m, 4H, Ph-H); 6.97 (m, 2H, Ph-H); 6.80 (s, 1H, –CONH); 5.98 (t, 1H, –CH–Ph); 5.55 (d, 1H, CH_2=C–); 5.36 (m, 1H, CH_2=C–); 5.14 (dd, 1H, –CH_2–O); 4.99 (dd, 1H, –CH_2–O); 3.84 (s, 3H, –OCH_3); 2.27 ppm (s, 3H, CH_3); ESIMS: *m/s* (%): 334.55 $[M - H]^-$; Anal. calcd for $C_{21}H_{21}NO_3$: C 75.20, H 6.31 N 4.18. Found: C 75.12, H 6.41, N 4.20%.

*5.2.30. N-(2-Methoxyphenyl)-2-(4-methoxyphenyl)-4-vinyl-2,5-dihydrofuran-3-carboxamide (**8d**)*

Color: White; m.p. 110–110.5 °C; Yield: 82%; ^{1}H NMR: (300 MHz, $CDCl_3$) δ: 8.35 (q, 1H, –CONH); 7.53 (m, 2H, Ph-H); 7.34 (m, 2H, Ph-H); 6.95 (m, 4H, Ph-H); 6.75 (m, 1H, C=CH–); 6.02 (m, 1H, –CH–Ph); 5.55 (d, 1H, CH_2=C–); 5.40 (d, 1H, CH_2=C–); 5.14 (dd, 1H, –CH_2–O); 4.98 (dd, 1H, –CH_2–O); 3.85 (s, 3H, –OCH_3); 3.61 ppm (s, 3H, –OCH_3); ESIMS: *m/s* (%): 350.12 $[M - H]^-$; Anal. calcd for $C_{21}H_{21}NO_4$: C 71.78, H 6.02 N 3.99. Found: C 71.66, H 6.11, N 3.91%.

*5.2.31. N-(4-Ethoxyphenyl)-2-(4-methoxyphenyl)-4-vinyl-2,5-dihydrofuran-3-carboxamide (**8e**)*

Color: White; m.p. 188.1–188.4 °C; Yield: 90%; IR (KBr, cm^{-1}): 3334, 2955, 2924, 2851, 1635, 1598, 1517, 1476, 1409, 1384, 1303, 1249, 1174, 1116, 1073, 1048, 1026, 932, 817, 805, 662, 592, 519; ^{1}H NMR: (300 MHz, $CDCl_3$) δ: 7.50 (q, 1H, C=CH–); 7.38 (m, 2H, Ph-H); 7.27 (s, 1H, –CONH); 7.10 (m, 2H, Ph-H); 6.98 (m, 2H, Ph-H); 6.76 (m, 2H, Ph-H); 5.99 (t, 1H, –CH–Ph); 5.54 (d, 1H, CH_2=C–); 5.36 (t, 1H, CH_2=C–); 5.14 (dd, 1H, –CH_2–O); 4.98 (dd, 1H, –CH_2–O); 3.97 (m, 2H, O–CH_2–); 3.84 (s, 3H, –OCH_3); 1.40 ppm (m, 3H, CH_3); ^{13}C NMR (300 MHz, $CDCl_3$) δ: 169.2, 158.1, 156.2, 143.8, 139.3, 136.7, 129.3, 128.0, 127.8, 127.4, 123.1, 121.1, 113.5, 85.3, 74.3, 70.0, 53.5, 13.4 ppm; ESIMS: *m/s* (%): 364.49 $[M - H]^-$; Anal. calcd for $C_{22}H_{23}NO_4$: C 72.31, H 6.34 N 3.83. Found: C 72.01, H 6.56, N 3.77%.

*5.2.32. N-Benzyl-2-(4-methoxyphenyl)-4-vinyl-2,5-dihydrofuran-3-carboxamide (**8f**)*

Color: White; m.p. 165.1–165.5 °C; Yield: 93%; IR (KBr, cm^{-1}): 3300, 3062, 3032, 3002, 2925, 2848, 1658, 1624, 1588, 1510, 1454, 1424, 1384, 1354, 1314, 1247, 1175, 1148, 1112, 1077, 1030, 986, 945, 934, 914, 849, 813, 768, 737, 723, 697, 602, 566, 537, 484; ^{1}H NMR: (300 MHz, $CDCl_3$) δ: 7.40 (q, 1H, C═CH–); 7.26 (d, 2H, Ph-H); 6.88 (d, 2H, Ph-H); 5.92 (m, 1H, –CH–Ph); 5.50 (d, 1H, CH_2═C–); 5.41 (s, 1H, –CONH); 5.34 (d, 1H, CH_2═C–); 5.11 (dd, 1H, –CH_2–O); 4.94 (dd, 1H, –CH_2–O); 4.36 (m, 2H, -N–CH_2–); 3.80 ppm (s, 3H, –OCH_3); ^{13}C NMR (300 MHz, $CDCl_3$) δ: 163.8, 158.9, 150.8, 141.0, 133.2, 131.5, 128.1, 128.9, 127.7, 125.8, 125.6, 116.7, 115.1, 85.6, 74.2, 53.6, 44.8 ppm; ESIMS: *m/s* (%): 334.14 $[M - H]^-$; Anal. calcd for $C_{21}H_{21}NO_3$: C 75.20, H 6.31 N 4.18. Found: C 75.02, H 6.43, N 4.30%.

*5.2.33. 2-(4-Methoxyphenyl)-N-(4-methylbenzyl)-4-vinyl-2,5-dihydrofuran-3-carboxamide (**8g**)*

Color: White; m.p. 150.4–150.7 °C; Yield: 92%; ^{1}H NMR: (300 MHz, $CDCl_3$) δ: 7.40 (q, 1H, C═CH–); 7.25 (m, 2H, Ph-H); 7.02 (t, 2H, Ph-H); 6.86 (m, 2H, Ph-H); 6.77 (d, 2H, Ph-H); 5.91 (t, 1H, –CH–Ph); 5.50 (d, 1H, CH_2═C–); 5.51 (s, 1H, –CONH); 5.49 (d, 1H, CH_2═C–); 5.11 (dd, 1H, –CH_2–O); 4.94 (dd, 1H, –CH_2–O); 4.29 (m, 2H, –N–CH_2–); 3.81 (s, 3H, –OCH_3); 2.31 ppm (s, 3H, –CH_3); ESIMS: *m/s* (%): 348.12 $[M - H]^-$; Anal. calcd for $C_{22}H_{23}NO_3$: C 75.62, H 6.63 N 4.01. Found: C 75.59, H 6.77, N 4. 08%.

*5.2.34. N-(3,4-Dimethoxybenzyl)-2-(4-methoxyphenyl)-4-vinyl-2,5-dihydrofuran-3-carboxamide (**8h**)*

Color: White; m.p. 162.4–162.5 °C; Yield: 92%; ^{1}H NMR: (300 MHz, $CDCl_3$) δ: 7.37 (q, 1H, C═CH–); 7.25 (m, 2H , Ph-H); 6.84 (m, 2H, Ph-H); 6.70 (d, 1H, Ph-H); 6.46 (m, 2H, Ph-H); 5.91 (t, 1H, –CH–Ph); 5.50 (d, 1H, CH_2═C–); 5.39 (s, 1H, –CONH); 5.37 (d, 1H, CH_2═C–); 5.10 (dd, 1H, –CH_2–O); 4.94 (dd, 1H, –CH_2–O); 4.26 (m, 2H, –N–CH_2–); 3.86 (s, 3H, –OCH_3); 3.76 ppm (m, 6H, –OCH_3); ESIMS: *m/s* (%): 394.55 $[M - H]^-$; Anal. calcd for $C_{23}H_{25}NO_5$: C 69.86, H 6.37 N 3.54. Found: C 70.00, H 6.16, N 3.53%.

*5.2.35. N-(2-Fluorobenzyl)-2-(4-methoxyphenyl)-4-vinyl-2,5-dihydrofuran-3-carboxamide (**8i**)*

Color: White; m.p. 142.3–142.9 °C; Yield: 87%; ^{1}H NMR: (300 MHz, $CDCl_3$) δ: 7.37 (q, 1H, C═CH–); 7.27 (m, 2H, Ph-H); 7.20 (m, 1H, Ph-H); 6.98 (m, 2H, Ph-H); 6.88 (m, 2H, Ph-H); 5.90 (t, 1H, –CH–Ph); 5.50 (d, 1H, CH_2═C–); 5.34 (d, 1H, CH_2═C–); 5.10 (dd, 1H, –CH_2–O); 4.93 (dd, 1H, –CH_2–O); 4.37 (d, 2H, –N–CH_2–); 3.85 ppm (s, 3H, –OCH_3); ESIMS: *m/s* (%): 352.67 $[M - H]^-$; Anal. calcd for $C_{21}H_{20}FNO_3$: C 71.37, H 5.70 N 3.96. Found: C 71.18, H 5.59, N 4.02%.

*5.2.36. N-(4-Chlorobenzyl)-2-(4-methoxyphenyl)-4-vinyl-2,5-dihydrofuran-3-carboxamide (**8j**)*

Color: White; m.p. 166.8–167.2 °C; Yield: 92%; ^{1}H NMR: (300 MHz, $CDCl_3$) δ: 7.39 (q, 1H, C═CH–); 7.25 (d, 2H , Ph-H); 7.15 (d, 2H , Ph-H); 6.87 (d, 2H , Ph-H); 6.77 (d, 2H, Ph-H); 5.90 (t, 1H, –CH–Ph); 5.51 (d, 1H, CH_2═C–); 5.41 (s, 1H, –CONH); 5.31 (d, 1H, CH_2═C–); 5.11 (dd, 1H, –CH_2–O); 4.94 (dd, 1H, –CH_2–O); 4.30 (m, 2H, –N–CH_2–) 3.81 ppm (s, 3H, –OCH_3); ESIMS: *m/s* (%): 368.28 $[M - H]^-$; Anal. calcd for $C_{21}H_{20}ClNO_3$: C 68.20, H 5.45 N 3.79. Found: C 68.07, H 5.56, N 3.80%.

*5.2.37. N-(4-Fluorophenethyl)-2-(4-methoxyphenyl)-4-vinyl-2,5-dihydrofuran-3-carboxamide (**8k**)*

Color: White; m.p. 120.3–120.8 °C; Yield: 91%; ^{1}H NMR: (300 MHz, $CDCl_3$) δ: 7.34 (q, 1H, C═CH–); 7.20 (m, 2H, Ph-H); 6.89 (m, 6H, Ph-H); 5.80 (t, 1H, –CH–Ph); 5.48 (d, 1H, CH_2═C–); 5.32 (m, 1H, CH_2═C–); 5.12 (s, 1H, –CONH); 5.06 (dd, 1H, –CH_2–O); 4.90 (dd, 1H, –CH_2–O); 3.81 (s, 3H, –OCH_3); 3.40 (m, 2H, –N–CH_2–); 2.61 ppm (m, 2H, –CH_2-Ph); ESIMS: *m/s* (%): 366.38 $[M - H]^-$; Anal. calcd for $C_{22}H_{22}FNO_3$: C 71.92, H 6.04 N 3.81. Found: C 71.88, H 6.10, N 3.72%.

*5.2.38. N-(2-Fluorophenethyl)-2-(4-methoxyphenyl)-4-vinyl-2,5-dihydrofuran-3-carboxamide (**8l**)*

Color: White; m.p. 123.3–123.6 °C; Yield: 94%; ^{1}H NMR: (300 MHz, $CDCl_3$) δ: 7.30 (q, 1H, C═CH–); 7.20 (m, 2H, Ph-H); 7.00 (m, 2H, Ph-H); 6.90 (m, 1H, Ph-H); 6.84 (m, 2H, Ph-H); 5.82 (t, 1H, –CH–Ph); 5.46 (d, 1H, CH_2═C–); 5.30 (d, 1H, CH_2═C–); 5.19 (s, 1H, –CONH); 5.06 (dd, 1H, –CH_2–O); 4.90 (dd, 1H, –CH_2–O); 3.80 (s, 3H, –OCH_3); 3.42 (m, 2H, –N–CH_2–); 2.68 ppm (m, 2H, –CH_2-Ph); ESIMS: *m/s* (%): 366.05 $[M - H]^-$; Anal. calcd for $C_{22}H_{22}FNO_3$: C 71.92, H 6.04 N 3.81. Found: C 71.85, H 6.10, N 3.79%.

*5.2.39. N-(3-Fluorophenethyl)-2-(4-methoxyphenyl)-4-vinyl-2,5-dihydrofuran-3-carboxamide (**8m**)*

Color: White; m.p. 114.9–115.8 °C; Yield: 90%; IR (KBr, cm^{-1}): 3310, 3064, 3013, 2953, 2924, 2858, 1621, 1588, 1540, 1511, 1486, 1446, 1383, 1249, 1195, 1173, 1139, 1110, 1062, 1032, 1004, 935, 919, 857, 830, 807, 787, 747, 690, 561, 520, 456; ^{1}H NMR: (300 MHz, $CDCl_3$) δ: 7.33 (m, 1H, C═CH–); 7.20 (m, 1H, Ph-H); 7.14 (m, 2H, Ph-H); 6.92 (m, 1H, Ph-H); 6.86 (m, 2H, Ph-H); 6.70 (m, 2H, Ph-H); 5.80 (t, 1H, –CH–Ph); 5.48 (m, 1H, CH_2═C–); 5.32 (d, 1H, CH_2═C–); 5.17 (s, 1H, –CONH); 5.06 (dd, 1H, –CH_2–O); 4.91 (dd, 1H, –CH_2–O); 3.85 (s, 3H, –OCH_3); 3.43 (m, 2H, –N–CH_2–); 2.64 (m, 2H, –CH_2-Ph); ESIMS: *m/s* (%): 366.06 $[M - H]^-$; Anal. calcd for $C_{22}H_{22}FNO_3$: C 71.92, H 6.04 N 3.81. Found: C 71.76, H 6.07, N 3.77%.

*5.2.40. N-(3-Methoxyphenethyl)-2-(4-methoxyphenyl)-4-vinyl-2,5-dihydrofuran-3-carboxamide (**8n**)*

Color: White; m.p. 145.5–145.7 °C; Yield: 91%; ^{1}H NMR: (300 MHz, $CDCl_3$) δ: 7.30 (q, 1H, C═CH–); 7.20 (m, 2H, Ph-H); 7.00 (m, 2H, Ph-H); 6.90 (m, 1H, Ph-H); 6.84 (m, 2H, Ph-H); 5.82 (t, 1H, –CH–Ph); 5.46 (d, 1H, CH_2═C–); 5.30 (d, 1H, CH_2═C–); 5.19 (s, 1H, –CONH); 5.06 (dd, 1H, –CH_2–O); 4.90 (dd, 1H, –CH_2–O); 3.80 (s, 3H, –OCH_3); 3.42 (m, 2H, -N–CH_2–); 2.68 ppm (m, 2H, –CH_2-Ph); ^{13}C NMR (300 MHz, $CDCl_3$) δ: 168.0, 160.6, 159.7, 150.3, 138.6, 137.2, 130.3, 129.0, 128.4, 123.3, 118.4, 114.5, 113.4, 115.2, 88.3, 80.4, 55.8, 40.3, 35.4 ppm; ESIMS: *m/s* (%): 378.29 $[M - H]^-$; Anal. calcd for $C_{23}H_{25}NO_4$: C 72.80, H 6.64 N 3.69. Found: C 72.89, H 6.59, N 3.72%.

*5.2.41. N-Cyclohexyl-2-(4-methoxyphenyl)-4-vinyl-2,5-dihydrofuran-3-carboxamide (**8o**)*

Color: White; m.p. 167.2–167.5 °C; Yield: 91%; ^{1}H NMR: (300 MHz, $CDCl_3$) δ: 7.38 (q, 1H, C═CH–); 7.28 (m, 2H, Ph-H); 6.92 (m, 2H, Ph-H); 5.88 (t, 1H, –CH–Ph); 5.48 (d, 1H, CH_2═C–); 5.31 (m, 1H, CH_2═C–); 5.11 (m, 1H, –CH_2–O); 5.06 (m, 1H, –CONH); 4.92 (dd, 1H, –CH_2–O); 3.81 (s, 3H, –OCH_3); 1.24 ppm (m, 10H, CH_2); ^{13}C NMR (300 MHz, $CDCl_3$) δ: 164.2, 158.9, 146.1, 133.5, 129.3, 128.3, 127.7, 123.2, 114.5, 85.7, 74.3, 55.1, 52.5, 31.9, 27.3, 24.2 ppm; ESIMS: *m/s* (%): 326.76$[M - H]^-$; Anal. calcd for $C_{20}H_{25}NO_3$: C 73.37, H 7.70 N 4.28. Found: C 73.16, H 7.84, N 4.44%.

*5.2.42. 2-(4-Methoxyphenyl)-N-propyl-4-vinyl-2,5-dihydrofuran-3-carboxamide (**8p**)*

Color: White; m.p. 128.4–128.7 °C; Yield: 93%; IR (KBr, cm^{-1}): 3286, 3083, 2958, 2924, 2853, 1625, 1540, 1513, 1462, 1383, 1301, 1279, 1251, 1174, 1154, 1110, 1066, 1030, 995, 946, 919, 820, 773, 709, 571, 542; ^{1}H NMR: (300 MHz, $CDCl_3$) δ: 7.40 (q, 1H, C═CH–); 7.28 (m, 2H, Ph-H); 6.91 (m, 2H, Ph-H); 5.88 (t, 1H, –CH–Ph); 5.48 (d, 1H, CH_2═C–); 5.32 (d, 1H, CH_2═C–); 5.10 (m, 1H, –CONH); 5.06 (m, 1H, –CH_2–O); 4.93 (dd, 1H, –CH_2–O); 3.81 (s, 3H, –OCH_3); 3.09 (m, 2H, –N–CH_2); 1.28 (m, 2H, CH_2); 0.85 ppm (m, 3H, CH_3); ESIMS: *m/s* (%): 288.16 $[M + H]^+$; Anal.

calcd for $C_{17}H_{21}NO_3$: C 71.06, H 7.37 N 4.87. Found: C71.01, H 7.45, N 4.71%.

*5.2.43. 2-(4-methoxyphenyl)-N-pentyl-4-vinyl-2,5-dihydrofuran-3-carboxamide (**8q**)*

Color: White; m.p. 112.4–112.8 °C; Yield: 91; IR (KBr, cm^{-1}): 3319, 3078, 3013, 2954, 2929, 2852, 1621, 1546, 1514, 1464, 1438, 1383, 1351, 1305, 1245, 1172, 1151, 1108, 1071, 1034, 1005, 949, 922, 840, 811, 769, 729, 692, 575, 537; ^{1}H NMR: (300 MHz, $CDCl_3$) δ: 7.43 (q, 1H, C═CH–); 7.29 (m, 2H, Ph-H); 6.92 (m, 2H, Ph-H); 5.89 (t, 1H, –CH–Ph); 5.49 (d, 1H, CH_2═C–); 5.33 (d, 1H, CH_2═C–); 5.11 (m, 1H, –CONH); 5.07 (m, 1H, $-CH_2-O$); 4.93 (dd, 1H, $-CH_2-O$); 3.81 (s, 3H, $-OCH_3$); 3.14 (m, 2H, $-N-CH_2$); 1.22 (m, 4H, CH_2); 0.95 (m, 2H, CH_2); 0.84 ppm (m, 3H, CH_3); ESIMS: *m/s* (%): 314.47 $[M-H]^-$; Anal. calcd for $C_{19}H_{25}NO_3$: C 72.35, H 7.99, N 4.44. Found: C 72.43, H 7.25, N 4.40%.

*5.2.44. N-Isobutyl-2-(4-methoxyphenyl)-4-vinyl-2,5-dihydrofuran-3-carboxamide (**8r**)*

Color: White; m.p. 140.2–140.4 °C; Yield: 93%; IR (KBr, cm^{-1}): 3280, 3089, 3005, 2960, 2925, 2855, 1621, 1591, 1547, 1513, 1468, 1434, 1384, 1311, 1293, 1277, 1252, 1175, 1157, 1061, 1030, 1006, 923, 829, 816, 764, 700, 598, 543, 471; ^{1}H NMR: (300 MHz, $CDCl_3$) δ: 7.43 (q, 1H, C═CH–); 7.29 (m, 2H, Ph-H); 6.92 (m, 2H, Ph-H); 5.88 (t, 1H, –CH–Ph); 5.48 (d, 1H, CH_2═C–); 5.32 (m, 1H, CH_2═C–); 5.13 (m, 1H, –CONH); 5.09 (m, 1H, $-CH_2-O$); 4.93 (dd, 1H, $-CH_2-O$); 3.80 (s, 3H, $-OCH_3$); 2.95 (m, 2H, -N-CH_2); 1.52 (m, 1H, CH); 0.85 ppm (m, 6H, CH_3); ESIMS: *m/s* (%): 300.24 $[M-H]^-$; Anal. calcd for $C_{18}H_{23}NO_3$: C 71.73, H 7.69 N 4.65. Found: C 71.64, H 7.56, N 4.37%.

*5.2.45. N-tert-Butyl-2-(4-methoxyphenyl)-4-vinyl-2,5-dihydrofuran-3-carboxamide (**8s**)*

Color: White; m.p. 151.2–151.4 °C; Yield: 80%; IR (KBr, cm^{-1}): 3341, 3039, 2999, 2966, 2925, 2836, 1628, 1589, 1533, 1512, 1452, 1384, 1365, 1301, 1278, 1242, 1174, 1108, 1076, 1035, 997, 923, 911, 836, 810, 779, 736, 625, 570, 543, 505; ^{1}H NMR: (300 MHz, $CDCl_3$) δ: 7.37 (q, 1H, C═CH–); 7.28 (m, 2H, Ph-H); 6.91 (m, 2H, Ph-H); 5.84 (t, 1H, –CH–Ph); 5.45 (d, 1H, CH_2═C–); 5.29 (m, 1H, CH_2═C–); 5.07 (dd, 1H, $-CH_2-O$); 4.93 (m, 1H, –CONH); 4.89 (m, 1H, $-CH_2-O$); 3.81 (s, 3H, $-OCH_3$); 1.13 ppm (m, 9H, CH_3); ESIMS: *m/s* (%): 300.11 $[M-H]^-$; Anal. calcd for $C_{18}H_{23}NO_3$: C 71.73, H 7.69 N 4.65. Found: C 71.66, H 7.75, N 4.51%.

*5.2.46. 2-(3,4-Dimethoxyphenyl)-N-phenyl-4-vinyl-2,5-dihydrofuran-3-carboxamide (**9a**)*

Color: White; m.p. 161.1–161.8 °C; Yield: 91%; ^{1}H NMR: (300 MHz, $CDCl_3$) δ: 7.51 (q, 1H, C═CH–); 7.25 (m, 2H, Ph-H); 7.19 (m, 2H, Ph-H); 7.06 (m, 2H, Ph-H); 6.94 (m, 2H, Ph-H); 5.98 (s, 1H, –CH–Ph); 5.57 (d, 1H, CH_2═C–); 5.41 (d, 1H, CH_2═C–); 5.32 (s, 1H, –CONH); 5.14 (dd, 1H, $-CH_2-O$); 5.02 (m, 1H, $-CH_2-O$); 3.91 (m, 3H, $-OCH_3$); 3.75 ppm (m, 3H, $-OCH_3$); ^{13}C NMR (300 MHz, $CDCl_3$) δ: 164.0, 152.7, 146.3, 138.7, 136.2, 135.7, 129.0, 128.5, 128.0, 127.7, 123.3, 121.5, 104.4, 88.5, 74.6, 59.5, 55.4 ppm; ESIMS: *m/s* (%): 350.29 $[M-H]^-$; Anal. calcd for $C_{21}H_{21}NO_4$: C 71.78, H 6.02 N 3.99. Found: C 71.88, H 6.11, N 3.82%.

*5.2.47. N-Benzyl-2-(3,4-dimethoxyphenyl)-4-vinyl-2,5-dihydrofuran-3-carboxamide (**9b**)*

Color: White; m.p. 143.1–143.7 °C; Yield: 89%; ^{1}H NMR: (300 MHz, $CDCl_3$) δ: 7.44 (q, 1H, C═CH–); 7.23 (m, 3H, Ph-H); 6.89 (m, 3H, Ph-H); 6.79 (m, 2H, Ph-H); 5.89 (t, 1H, –CH–Ph); 5.53 (s, 1H, CH_2═C–); 5.50 (s, 1H, –CONH); 5.36 (d, 1H, CH_2═C–); 5.12 (dd, 1H, $-CH_2-O$); 4.95 (m, 1H, $-CH_2-O$); 4.33 (m, 2H, $-N-CH_2$); 3.87 (s, 3H, $-OCH_3$); 3.80 ppm (s, 3H, $-OCH_3$); ESIMS: *m/s* (%): 364.93 $[M-H]^-$; Anal. calcd for $C_{22}H_{23}NO_4$: C 72.31, H 6.34 N 3.83. Found: C 72.54, H 6.27, N 3.81%.

*5.2.48. 2-(3,4-Dimethoxyphenyl)-N-(4-methylbenzyl)-4-vinyl-2,5-dihydrofuran-3-carboxamide (**9c**)*

Color: White; m.p. 153.6–153.8 °C; Yield: 94%; ^{1}H NMR: (300 MHz, $CDCl_3$) δ: 7.44 (q, 1H, C═CH–); 7.02 (m, 2H, Ph-H); 6.89 (m, 1H, Ph-H); 6.78 (m, 4H, Ph-H); 5.89 (t, 1H, –CH–Ph); 5.51 (d, 1H, CH_2═C–); 5.45 (s, 1H, –CONH); 5.35 (d, 1H, CH_2═C–); 5.12 (dd, 1H, $-CH_2-O$); 4.94 (m, 1H, $-CH_2-O$); 4.28 (m, 2H, -N-CH_2); 3.88 (s, 3H, $-OCH_3$); 3.81 (s, 3H, $-OCH_3$); 2.30 ppm (s, 3H, CH_3); ESIMS: *m/s* (%): 378.53 $[M-H]^-$; Anal. calcd for $C_{23}H_{25}NO_4$: C 72.80, H 6.64 N 3.69. Found: C 72.77, H 6.58, N 3.68%.

*5.2.49. N-(4-Chlorobenzyl)-2-(3,4-dimethoxyphenyl)-4-vinyl-2,5-dihydrofuran-3-carboxamide (**9d**)*

Color: White; m.p. 157.4–157.9 °C; Yield: 90%; ^{1}H NMR: (300 MHz, $CDCl_3$) δ: 7.45 (q, 1H, C═CH–); 6.97 (m, 2H, Ph-H); 6.89 (m, 3H, Ph-H); 6.78 (m, 2H, Ph-H); 5.88 (t, 1H, –CH–Ph); 5.52 (m, 1H, CH_2═C–); 5.47 (s, 1H, –CONH); 5.36 (d, 1H, CH_2═C–); 5.12 (dd, 1H, $-CH_2-O$); 4.94 (dd, 1H, $-CH_2-O$); 4.28 (m, 2H, $-N-CH_2$); 3.87 (s, 3H, $-OCH_3$); 3.81 ppm (s, 3H, $-OCH_3$); ESIMS: *m/s* (%): 398.63 $[M-H]^-$; Anal. calcd for $C_{22}H_{22}ClNO_4$: C 66.08, H 5.55 N 3.50. Found: C 66.21, H 5.24, N 3.43%.

*5.2.50. 2-(3,4-Dimethoxyphenyl)-N-phenyl-4-vinyl-2,5-dihydrofuran-3-carboxamide (**9e**)*

Color: White; m.p. 165.0–165.8 °C; Yield: 91%; ^{1}H NMR: (300 MHz, $CDCl_3$) δ: 7.42 (q, 1H, C═CH–); 6.95 (m, 1H, Ph-H); 6.88 (m, 1H, Ph-H); 6.84 (m, 1H, Ph-H); 5.87 (t, 1H, –CH–Ph); 5.49 (d, 1H, CH_2═C–); 5.33 (m, 1H, CH_2═C–); 5.13 (s, 1H, –CONH); 5.10 (m, 1H, $-CH_2-O$); 4.93 (m, 1H, $-CH_2-O$); 3.89 (s, 6H, $-OCH_3$); 3.75 (m, 1H, -N-CH); 1.33 ppm (m, 10H, CH_2); ^{13}C NMR (300 MHz, $CDCl_3$) δ: 164.0, 153.9, 146.4, 137.2, 135.8, 129.0, 127.7, 125.3, 104.9, 88.5, 74.6, 63.6, 59.9, 55.8, 34.5, 26.4, 22.0 ppm; ESIMS: *m/s* (%): 356.29 $[M-H]^-$; Anal. calcd for $C_{21}H_{27}NO_4$: C 70.56, H 7.61 N 3.92. Found: C 70.68, H 7.71, N 3.88%.

*5.2.51. 2-(3,4-Dimethoxyphenyl)-N-propyl-4-vinyl-2,5-dihydrofuran-3-carboxamide (**9f**)*

Color: White; m.p. 134.2–134.6 °C; Yield: 90%; ^{1}H NMR: (300 MHz, $CDCl_3$) δ: 7.42 (q, 1H, C═CH–); 6.94 (m, 1H, Ph-H); 6.88 (s, 1H, Ph-H); 6.84 (m, 1H, Ph-H); 5.88 (t, 1H, –CH–Ph); 5.50 (d, 1H, CH_2═C–); 5.33 (d, 1H, CH_2═C–); 5.19 (s, 1H, –CONH); 5.10 (dd, 1H, $-CH_2-O$); 4.93 (m, 1H, $-CH_2-O$); 3.88 (s, 6H, $-OCH_3$); 3.10 (m, 2H, $-N-CH_2$); 1.85 (m, 2H, CH_2); 0.68 ppm (m, 3H, CH_3); ESIMS: *m/s* (%): 316.57 $[M-H]^-$; Anal. calcd for $C_{18}H_{23}NO_4$: C 68.12, H 7.30 N 4.41. Found: C 68.04, H 7.45, N 4.43%.

*5.2.52. (2-(4-Methoxyphenyl)-4-vinyl-2,5-dihydrofuran-3-yl)(4-(2-methoxyphenyl)piperazin-1-yl)methanone (**10a**)*

Color: White; m.p. 109.6–110.4 °C; Yield: 80%; ^{1}H NMR: (300 MHz, $CDCl_3$) δ: 7.29 (m, 2H, Ph-H); 7.01 (m, 1H, Ph-H); 6.88 (m, 1H, Ph-H); 6.85 (m, 3H, Ph-H); 6.67 (m, 1H, Ph-H); 6.40 (q, 1H, C═CH–); 6.14 (t, 1H, –CH–Ph); 5.38 (m, 1H, CH_2═C–); 5.24 (m, 1H, CH_2═C–); 5.20 (m, 1H, $-CH_2-O$); 4.99 (dd, 1H, $-CH_2-O$); 4.03 (m, 2H, $N-CH_2-$); 3.85 (s, 3H, $-OCH_3$); 3.74 (s, 3H, $-OCH_3$); 3.44 (m, 3H, $N-CH_2-$); 3.34 (d, 1H, $N-CH_2-$); 2.52 ppm (d, 2H, $N-CH_2-$); ESIMS: *m/s* (%): 419.73 $[M-H]^-$; Anal. calcd for $C_{25}H_{28}N_2O_4$: C 71.41, H 6.71 N 6.66. Found: C 71.34, H 6.75, N 6.55%.

*5.2.53. (2-(4-Methoxyphenyl)-4-vinyl-2,5-dihydrofuran-3-yl)(4-(3-methoxyphenyl)piperazin-1-yl)methanone (**10b**)*

Color: White; m.p. 105.8–106.9 °C; Yield: 86%; IR (KBr, cm^{-1}): 3421, 3087, 3002, 2974, 2941, 2892, 2852, 2815, 1621, 1512, 1490,

1461, 1437, 1382, 1342, 1303, 1278, 1248, 1196, 1169, 1150, 1112, 1068, 1056, 1028, 1007, 988, 946, 845, 812, 766, 692, 609, 547; ^{1}H NMR: (300 MHz, $CDCl_3$) δ: 7.28 (m, 2H, Ph-H); 7.26 (m, 1H, Ph-H); 6.85 (m, 2H, Ph-H); 6.41 (m, 3H, Ph-H); 6.33 (m, 1H, C═CH–); 6.12 (t, 1H, –CH–Ph); 5.38 (m, 1H, CH_2═C–); 5.25 (m, 1H, CH_2═C–); 5.19 (dd, 1H, –CH_2–O); 4.99 (dd, 1H, –CH_2–O); 4.02 (d, 2H, N–CH_2–); 3.79 (s, 3H, –OCH_3); 3.71 (s, 3H, –OCH_3); 3.30 (m, 4H, N–CH_2–); 2.88 (d, 1H, N–CH_2–); 2.73 ppm (m, 2H, N–CH_2–); ^{13}C NMR (300 MHz, $CDCl_3$) δ: 163.8, 160.1, 154.6, 150.5, 146.3, 133.5, 129.9, 129.8, 128.3, 127.7, 123.1, 113.5, 110.4, 110.0, 103.4, 84.7, 75.1, 55.8, 55.0, 55.4, 54.7 ppm; ESIMS: *m/s* (%): 419.25 [M – H]$^-$; Anal. calcd for $C_{25}H_{28}N_2O_4$: C 71.41, H 6.71 N 6.66. Found: C 71.48, H 6.70, N 6.62%.

*5.2.54. (4-(2,3-Dimethylphenyl)piperazin-1-yl)(2-(4-methoxyphenyl)-4-vinyl-2,5-dihydrofuran-3-yl)methanone (**10c**)*

Color: White; m.p. 176.3–176.5 °C; Yield: 96%; ^{1}H NMR: (300 MHz, $CDCl_3$) δ: 7.32 (m, 2H, Ph-H); 7.06 (m, 1H, Ph-H); 6.92 (m, 1H, Ph-H); 6.89 (m, 2H, Ph-H); 6.61 (m, 1H, Ph-H); 6.40 (q, 1H, C═CH–); 6.15 (t, 1H, –CH–Ph); 5.39 (d, 1H, CH_2═C–); 5.25 (m, 1H, CH_2═C–); 5.20 (m, 1H, –CH_2–O); 4.99 (dd, 1H, –CH_2–O); 3.79 (s, 3H, –OCH_3); 3.37 (m, 4H, N–CH_2–); 2.84 (m, 2H, N–CH_2–); 2.52 (d, 2H, N–CH_2–); 2.25 (s, 3H, CH_3); 2.18 ppm (s, 3H, CH_3); ESIMS: *m/s* (%): 417.16 [M – H]$^-$; Anal. calcd for $C_{26}H_{30}N_2O_3$: C 74.61, H 7.22 N 6.69. Found: C 74.55, H 7.27, N 6.63%.

*5.2.55. (4-(2-Chlorophenyl)piperazin-1-yl)(2-(4-methoxyphenyl)-4-vinyl-2,5-dihydrofuran-3-yl)methanone (**10d**)*

Color: White; m.p. 118.7–119.4 °C; Yield: 85%; IR (KBr, cm^{-1}): 3423, 3093, 2971, 2942, 2912, 2847, 2829, 1665, 1632, 1592, 1564, 1508, 1482, 1462, 1435, 1382, 1334, 1302, 1275, 1244, 1169, 1151, 1102, 1068, 1023, 1003, 990, 930, 849, 812, 783, 741, 692, 637, 612, 545, 451; ^{1}H NMR: (300 MHz, $CDCl_3$) δ: 7.31 (m, 2H, Ph-H); 7.27 (m, 1H, Ph-H); 7.19 (m, 1H, Ph-H); 6.99 (m, 2H, Ph-H); 6.75 (m, 1H, Ph-H); 6.39 (q, 1H, C═CH–); 6.14 (t, 1H, –CH–Ph); 5.38 (m, 1H, CH_2═C–); 5.23 (m, 1H, CH_2═C–); 5.19 (m, 1H, –CH_2–O); 4.99 (m, 1H, –CH_2–O); 4.13 (d, 2H, N–CH_2–); 3.76 (s, 3H, –OCH_3); 3.36 (m, 2H, N–CH_2–); 3.03 (d, 2H, N–CH_2–); 2.66 ppm (d, 2H, N–CH_2–); ^{13}C NMR (300 MHz, $CDCl_3$) δ: 169.7, 159.7, 150.8, 150.0, 138.3, 133.3, 130.2, 129.4, 129.1, 127.2, 123.9, 117.6, 114.2, 113.1, 86.1, 80.9, 55.8, 52.8, 49.8 ppm; ESIMS: *m/s* (%): 425.16 [M + H]$^+$; Anal. calcd for $C_{24}H_{25}ClN_2O_3$: C 67.84, H 5.93 N 6.59. Found: C 67.87, H 5.90, N 6.62%.

*5.2.56. (4-(3-Chlorophenyl)piperazin-1-yl)(2-(4-methoxyphenyl)-4-vinyl-2,5-dihydrofuran-3-yl)methanone (**10e**)*

Color: White; m.p. 105.4–106.2 °C; Yield: 88%; ^{1}H NMR: (300 MHz, $CDCl_3$) δ: 7.28 (m, 2H, Ph-H); 7.16 (m, 1H, Ph-H); 6.86 (m, 3H, Ph-H); 6.72 (m, 1H, Ph-H); 6.65 (m, 1H, Ph-H); 6.38 (q, 1H, C═CH–); 6.12 (t, 1H, –CH–Ph); 5.38 (m, 1H, CH_2═C–); 5.28 (m, 1H, CH_2═C–); 5.20 (m, 1H, –CH_2–O); 4.99 (dd, 1H, –CH_2–O); 4.07 (m, 2H, N–CH_2–); 3.71 (s, 3H, –OCH_3); 3.30 (m, 4H, N–CH_2–); 2.87 (d, 1H, N–CH_2–); 2.74 ppm (m, 1H, N–CH_2–); ESIMS: *m/s* (%):425.16 [M + H]$^+$; Anal. calcd for $C_{24}H_{25}ClN_2O_3$: C 67.84, H 5.93 N 6.59. Found: C 67.79, H 5.93, N 6.62%.

*5.2.57. (4-(4-Fluorophenyl)piperazin-1-yl)(2-(4-methoxyphenyl)-4-vinyl-2,5-dihydrofuran-3-yl)methanone (**10f**)*

Color: White; m.p. 101.6–102.2 °C; Yield: 93%; ^{1}H NMR: (300 MHz, $CDCl_3$) δ: 7.28 (m, 2H, Ph-H); 6.97 (m, 1H, Ph-H); 6.93 (m, 1H, Ph-H); 6.86 (m, 2H, Ph-H); 6.75 (m, 2H, Ph-H); 6.38 (q, 1H, C═CH–); 6.12 (t, 1H, –CH–Ph); 5.38 (m, 1H, CH_2═C–); 5.25 (m, 1H, CH_2═C–); 5.20 (dd, 1H, –CH_2–O); 4.99 (dd, 1H, –CH_2–O); 4.07 (d, 2H, N–CH_2–); 3.75 (s, 3H, –OCH_3); 3.41 (m, 2H, N–CH_2–); 3.11 (d, 2H, N–CH_2–); 2.69 ppm (d, 2H, N–CH_2–); ^{13}C NMR (300 MHz, $CDCl_3$) δ: 164.0, 156.8, 152.7, 142.3, 146.1, 137.2, 137.0, 129.0, 127.7, 123.3, 117.3, 111.3, 104.3, 88.5, 74.6, 59.5, 55.8, 55.7, 53.25 ppm; ESIMS: *m/s* (%): 407.14 [M – H]$^-$; Anal. calcd for $C_{24}H_{25}FN_2O_3$: C 75.57, H 6.17 N 6.86. Found: C 75.42, H 6.33, N 6.60%.

*5.2.58. (4-(2,3-Dichlorophenyl)piperazin-1-yl)(2-(4-methoxyphenyl)-4-vinyl-2,5-dihydrofuran-3-yl)methanone (**10g**)*

Color: White; m.p. 149.8–149.3 °C; Yield: 92%; ^{1}H NMR: (300 MHz, $CDCl_3$) δ: 7.32 (m, 2H, Ph-H); 7.28 (m, 1H, Ph-H); 7.12 (m, 1H, Ph-H); 6.89 (m, 2H, Ph-H); 6.67 (m, 1H, Ph-H); 6.39 (q, 1H, C═CH–); 6.14 (t, 1H, –CH–Ph); 5.39 (m, 1H, CH_2═C–); 5.25 (m, 1H, CH_2═C–); 5.19 (dd, 1H, –CH_2–O); 4.99 (dd, 1H, –CH_2–O); 4.20 (d, 2H, N–CH_2–); 3.77 (s, 3H, –OCH_3); 3.37 (m, 2H, N–CH_2–); 3.05 (d, 2H, N–CH_2–); 2.69 ppm (d, 2H, N–CH_2–); ESIMS: *m/s* (%): 457.33 [M – H]$^-$; Anal. calcd for $C_{24}H_{24}Cl_2N_2O_3$: C 62.75, H 5.27 N 6.10. Found: C 62.71, H 5.26, N 6.12%.

5.3. Antitumor screening

5.3.1. Methodology of the in vitro cancer screen

In vitro anti-cancer activity was measured by means of the IC_{50} using the MTT [3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide] assay method [22–25]. Test cancer cell lines were obtained from the Navy Medical College. The IC_{50} determination was performed according to the National Committee for Clinical Laboratory Standards (NCCLS) recommendations. All compounds were dissolved in DMSO with the stock concentration of 10 g/L, and diluted with medium freshly before drug administration. Cell lines were seeded into 96-well plates at density of 8000 cells/well. 24 h after seeding, each compound dilution was added in duplicate and incubation continued at 37 °C in a humidified atmosphere containing 5% CO_2. After 24 h, add 20 μL MTT (Sigma) at 5 mg/mL in PBS (filter sterilized, light protected, and stored at 4 °C) per well, and after 4 h of incubation at 37 °C, MTT is converted to a blue formazan product by mitochondrial succinate dehydrogenase. This product was eluted from cells by addition of 150 mL of DMSO. The absorbance at 570 nm was determined by an ELISA using a ELX800 microplate spectrophotometer. The IC_{50} value was defined as the concentration at which 50% of the cells could survive.

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Appendix. Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejmech.2011.11.036.

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