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Studies on Some Novel (Z)-1-(5-chloro-furan-2-yl)-2-(4-nitrophenyl) ethene Analogues as Antiproliferative agents

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ABSTRACT

Malignant tumours are one of the world's most serious hazards to human health, and the clinical prognosis is still insufficient. As a result, it is necessary to develop new therapeutic strategies for the improvement of presently available medications.There has been a lot of interest in using natural products or their derivatives to produce more effective chemotherapeutic drugs in recent decades. Natural chemicals having a stilbene backbone have shown to have promise anticancer activity in recent years, targeting a wide range of intracellular pathways. In view of that some new analogues were synthesized and screened them for antiangiogenic activity. In the synthesized analogues one of the phenyl rings is replaced by substituted-furan ring. Majority of the synthesised compounds exhibited considerable antiangiogenic activity. Antiangiogenic action was discovered to be affected by the size of the bridge substituent (on the Ethylene Bridge). Most active compounds of the antiangiogenic screening were further subjected for anticancer activity.Compound 11h showed maximum anticancer activity with % growth inhibition of 28.78 and 16.28 against HCT-116 and MCF-7 cell lines respectively at concentration of 10 µM.Further derivatization of these molecules will be helpful in the hopes of obtaining more selective and potent anticancer medicines.

Keywords: *Stilbenes, Combretastatins, Antiangiogenic, Anticancer.*

INTRODUCTION

One of the most widely explored topics today is cancer prevention. Different techniques are required since the pathophysiology of cancer is complicated in so many ways. Although significant improvements in cellular and molecular biology have improved cancer chemotherapeutic therapy, more research into new anticancer drugs is still needed to overcome resistance and toxicity problems. Because natural products are a substantial source of lead compounds with varied mechanisms of cytostatic action [1], there has been a lot of interest in using natural products or their derivatives to produce more effective chemotherapeutic drugs in recent decades [2]. Natural chemicals having a stilbene backbone have shown to have promise anticancer activity in recent years, targeting a wide range of intracellular pathways [3a-b].Stilbene is a flexible scaffold with two aromatic rings connected by an ethylene bridge. Some plants create stilbenes as a defence mechanism in reply to pathogen spell and other stresses. Stilbenes are prevalent in natural stuffs [4] and have aextensivearray of biological roles [5]. They are classified as Z-type or E-type depending on the arrangement of their middle double bond, which can endure Z/E isomerization, resulting in a change in overall structure and a reduction in biological activity. In reality, photoisomerization is a typical obstacle

in optimization research, and much quantum chemistry calculation research has concentrated on the mechanisms behind it [6], rather than optimising these molecules to increase their stability and retain their biological action [7-9]. Stilbene-containing analogues have long piqued the interest of chemists and pharmacologists due to their key biological effects, which include antioxidant, hypolipidemic, anticancer, anti-inflammatory, and antiviral capabilities [14-18]. Among these, resveratrol is one of the most investigated, with anti-proliferative, antioxidant [10a-c], anti-inflammatory, and anticancer properties[11-13] widely described. New stilbene derivatives are created, manufactured, and evaluated on different cellular targets in order to increase cancer chemopreventive and/or therapeutic activity, as well as bioavailability in comparison to the parent medication. The medicinal chemistry community has paid close attention to these potentially novel c hemotherapeutic drugs. Many analogues of resveratrol have one or both aromatic rings that have been replaced differently. There are medications in clinical use that have a stilbenecenter, and numerous cross derivatives have been explored on various biological targets [18a-b]. Combretastatin A-4, a stilbene derivative, has emerged as a promising candidate for powerful in vitro and in vivo anticancer bioactivities throughout the process of discovering chemicals active in the prevention and treatment of cancer [19].

CA-4 and other combretastatins have significant anticancer/antivascular activity, which prompted us to manufacture several novel analogues mimicking structural features of CA-4 and to test them for antiangiogenic and anticancer activity in order to uncover new anticancer drugs with potent activity. It has been found that several analogues with a furan ring in their structure show substantial antitubulin action.To assess the effect of such change on activity, the 3, 4, 5-trimethoxyphenyl ring of CA-4 is substituted by substituted-furan in the produced analogues. The ethylene bridge of CA-4 is substituted with various groups in some of the produced analogues to test the influence of such change on activity.

MATERIALS AND METHOD

Chemistry

In the presence of triethylamine, carboxylic acid (8) was produced by base catalysed condensation of o-nitrophenyl acetic acid (2) with corresponding 5-chloro-2-formyl furan (7). Carboxylic acid (8) was esterified with methanol using a catalytic quantity of H_2SO_4 to produce matching ester derivatives (9). In refluxing benzene, thionyl chloride was reacted with carboxylic acid (8) to provide the corresponding acid chlorides (10), which were then reacted with suitable amine to give the amide derivatives (11a-k).

Recrystallization/column chromatography was used to purify all of the chemicals. TLC was used to assess the purity of the compounds. Infrared, 1H NMR, and mass spectroscopy were used to confirm the structure of the produced compounds. (Table 1 lists the physical characteristics of the produced compounds, whereas figure 1 shows the synthesis procedure).

Silica gel was used for column chromatography (Qualigens, particle size 60-120 mm). All melting points were calculated using a DECIBEL digital melting point instrument and are displayed as-is. To validate the quality of commercial reagents utilised, compounds generated, and to observe the reactions, silica gel G'sthin layer

chromatography (TLC) plates were employed. Table 1 lists the solvent systems used to perform the TLC to check the purity of the compounds produced. Iodine vapours and UV light were used to find the spots. FT-IR spectrophotometers 8400S (SHIMADZU) and SPECTRUM RX1 (PERKIN ELMER) were used to collect IR spectra (KBr Pellets). ^{1}H NMR spectras were recorded on 300 MHz dpx300 and av300 spectrometers using TMS as internal standard in DMSO. Mass spectra were recorded on an API 3000 LC/MS/MS Q3 (SHIMADZU) spectrometer.

GENERAL PROCEDURE OF PREPARATION OF COMPOUNDS

Procedure of preparation of compounds 8

A combination of 5-chloro-2-formyl furan (7), p-nitrophenyl acetic acid (2 mmol), and triethylamine (0.5 ml) in acetic anhydride (5 ml) was heated at reflux for 12 hours, then transferred into a warm saturated sodium carbonate mixture (50 ml) and left for 12 hours. The ether extracts (2x50 ml) were used to extract the combination, and the ether extracts were cast-off. The acidified aqueous solution was filtered and dried, and the precipitated product was acidified with dilute HCl. Column chromatography was used to purify the product.

Procedure of preparation of compounds 9

A 0.5 mmolstirred solution of carboxylic acid 8 in absolute methanol (20 ml) was added to the combination, which was then heated in reflux for 6 hours. Evaporation removed around 90% of the surplus methanol, and the rest was placed into freezed water (300 ml). The product was excavated using ether (2x40 ml), and the collective extracts were washed with a 2 percent aqueous NaOH solution (2x50 ml) before being rinsed with water (200 ml). The required product was obtained by evaporating ether.

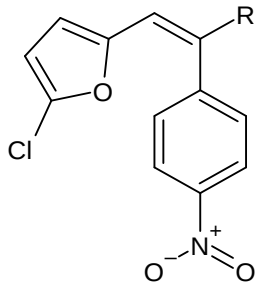
Procedure of preparation of compounds 10

Refluxed for 6 hours was a combination of carboxylic acid 8 (0.5 mmol) and thionyl chloride (1 ml) in benzene (10 ml). Additionalbenzeneand thionyl chloride were separated at decreased pressure, and the remainder was vaccum dried for 30 minutes to get the required product. Recrystallization of EtOAc-hexane purified the product.

Procedure of preparation of compounds 11a-k

A solution of acid chlorides 10 (prepared from 8 in 0.5 mmol scale, as stated above) in THF (5 ml) was poured to a solution of suitable amine (0.5 mmol) in THF (5 ml) (10 ml). For 3 hours, the mixture was mixed. The residue was put onto ice after the solvents were removed at decreased pressure (200 g). The ether (2x20 ml) was used to extract the product, which was then washed and dried. The unfinished product was obtained by evaporating ether. Recrystallization of EtOAc-hexane purified the product.

Table 1 Physical parameters of synthesized compounds



Compound No.	R	M.P.^{o}C	$R_f$value[a]	Recrystallization solvent	Molecular Formula
8	Carboxyl	175-177	0.623	EtOAc-Hexane (1:1)	$C_{13}H_9ClNO_5$
9	methoxycarbonyl	207-209	0.826	EtOAc-Hexane (1:1)	$C_{14}H_{11}ClNO_5$
10	chlorocarbonyl	128-130	0.923	EtOAc-Hexane (1:1)	$C_{13}H_8Cl_2NO_4$
11a	ethylcarbamoyl	140-142	0.585	EtOAc-Hexane (1:1)	$C_{15}H_{14}ClN_2O4$
11b	carbamothioylcarbamoyl	145-148	0.731	EtOAc-Hexane (1:1)	$C_{14}H_{11}ClN_3O_4S$
11c	4-fluorophenylcarbamoyl	133-136	0.690	EtOAc-Hexane (1:1)	$C_{19}H_{13}ClFN_2O_4$
11d	2-methylphenylcarbamoyl	122-124	0.751	EtOAc-Hexane (1:1)	$C_{20}H_{16}ClN_2O_4$
11e	2-chlorophenylcarbamoyl	112-114	0.702	EtOAc-Hexane (1:1)	$C_{19}H_{13}Cl_2N_2O_4$
11f	pyridine-4-ylcarbamoyl	185-187	0.575	EtOAc-Hexane (1:1)	$C_{18}H_{13}ClN_3O_4$
11g	naphthalene-1-ylcarbamoyl	119-121	0.722	EtOAc-Hexane (1:1)	$C_{23}H_{16}ClN_2O_4$
11h	Piperidin-1-ylcarbonyl	161-164	0.437	EtOAc-Hexane (1:1)	$C_{18}H_{18}ClN_2O_4$
11i	Piperazin-1-ylcarbonyl	182-184	0.592	EtOAc-Hexane (1:1)	$C_{17}H_{17}ClN_3O_4$
11j	2-methoxyphenylcarbamoyl	121-123	0.563	EtOAc-Hexane (1:1)	$C_{20}H_{16}ClN_2O_5$
11k	aminoantipyrinylcarbonyl	142-144	0.758	EtOAc-Hexane (1:1)	$C_{24}H_{20}ClN_4O_5$

[a]Mobile phase consists of dichloromethane:carbontetrachloride:methanol in ratio 10:10:1.

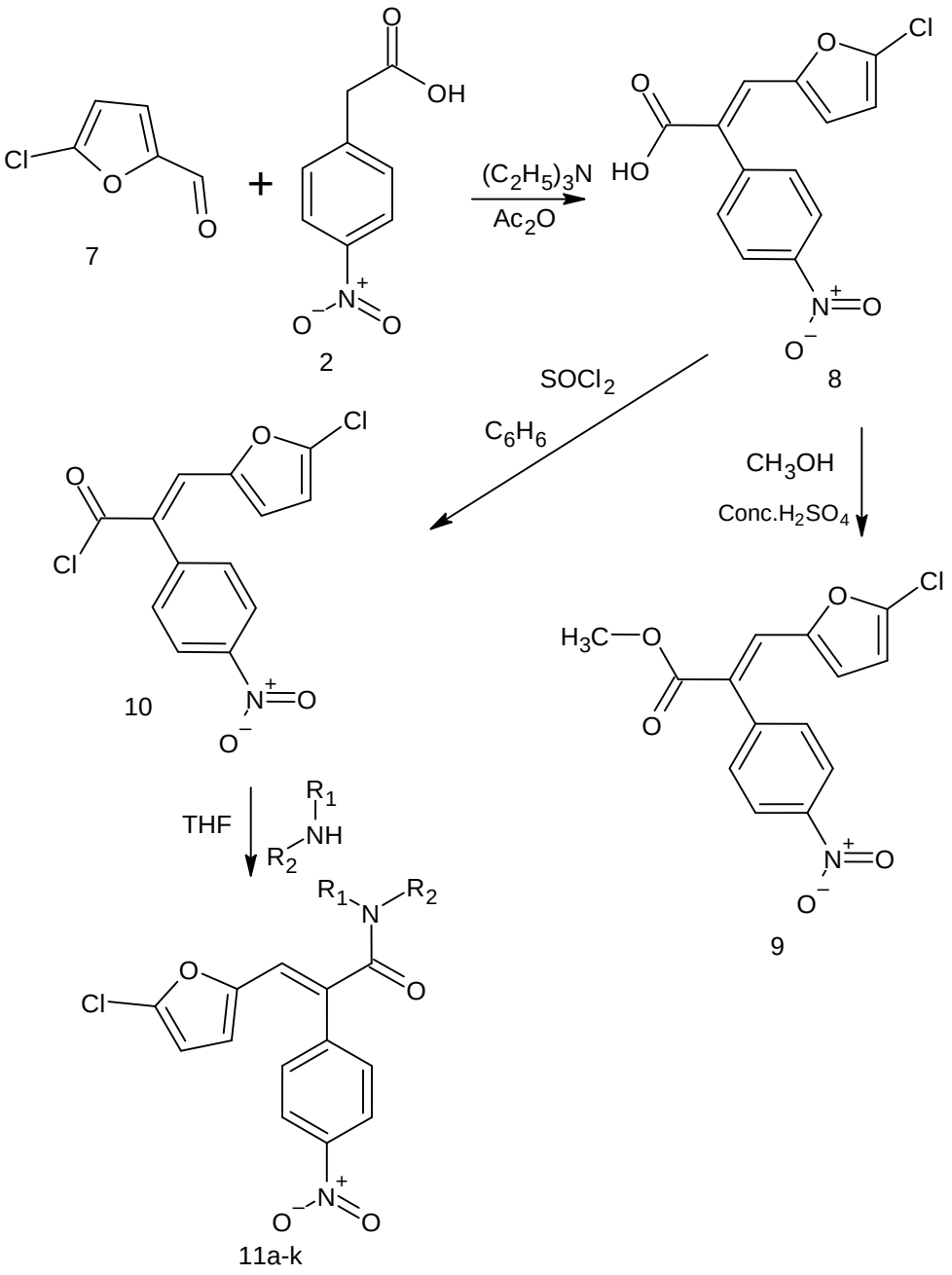


Figure 1 Scheme of synthesis of compounds

Antiangiogenesis study by chorioallantoin membrane (CAM) assay

CAM assays are often used as the primary approach to evaluate the effect of antigenic compounds. The basis of this experiment is the formation of a placental membrane, in which at a certain stage of fetal development the formation of new blood vessels in a fertilized egg takes place. The effect of test-impregnated agarose beads on the vascular membrane of open eggs on angiogenesis is evaluated. Fertilized eggs were obtained for testing from Kelchina incubators in Ghaziabad.

Procedure

Twelve eggs were used in each experiment to test one drug at a certain dose. The eggs were fertilised under ideal circumstances of 370°C and 80% relative humidity. The shells of eggs were cleaned with 70% EtOH to avoid infection. After 72 hours, a syringe was used to retrieve 8-10 ml of albumin from the lower side of the egg, and the hole was bandaged. After the upper half of the shell was removed, the eggs were covered in a plastic sheet and incubated for another 72 hours. When the diameter of the CAM was between 1.8 and 2.6 cm, the pellets containing the test chemicals were placed on it.In a 2.5 percent agarose solution, test compounds were dissolved or suspended. Following gel formation, a micropipette for viscous solutions was used to extract the bulk of agarose gel appropriate to the dosage of the test chemical to be administered to the CAM. As a result, the agarose pellets are not consistent in size. Because the half-cone-shaped agarose pellets sink somewhat into the CAM, they are stuck. The antiangiogenic impact was assessed after 24 hours, either with a stereomicroscope and observation of the avascular zone around the pellet, or with naked eye observation of the avascular zone surrounding the pellet (if clear). Antiangiogenic activity is graded on a scale of 0 to 2, with 0 indicating no impact, 1 suggesting a moderate effect, and 2 indicating a significant effect (capillary free zone is at least twice as large as the pellet). Membrane irritation and embryotoxicity can also be assessed. B-1, 4-galactan sulphate (LuPS S5), with an average molecular weight of 20000, was used as a positive control, and an agarose pellet was used as a blank [20].

Anticancer activity

Compounds showing potent antiangiogenic activity were further subjected for anticancer activity against HCT-116 (colon cancer) and MCF-7 (breast cancer) cell lines by using modified MTT assay method.

Procedure of the *in vitro* cancer activity

Human tumour cell lines from the cancer screening panel were grown in RPMI-1640 medium with 5% foetal bovine serum and 2 mM L-glutamine. For a typical screening experiment, cells were injected onto 96 well microtiter plates in 100 L at plating densities ranging from 5,000 to 40,000 cells/well, depending on the doubling period of certain cell lines. Before introducing experimental medications, the microtiter plates were incubated for 24 hours at 37°C, 5% CO2, 95% air, and 100% relative humidity after cell inoculation. After 24 hours, two plates of each cell line were fixed in situ with trichloroacetic acid (TCA) to represent a measurement of the cell population at the moment of drug delivery (Tz). Experimental medications were solubilized in 400 times the needed final maximum test concentration in dimethyl sulfoxide (DMSO) and kept refrigerated before to use. At the moment of medication administration, an aliquot of frozen concentrate was thawed and diluted to twice the specified final maximum test concentration with complete medium containing 50 g/ml gentamicin. Additional four, 10-fold, or 12-log serial dilutions were made to provide a total of five drug concentrations plus control. By adding aliquots of 100 l of these varied drug dilutions to appropriate microtiter wells already holding 100 l of medium, the required final drug concentrations were attained.

The plates were then incubated for another 48 hours at 37°C, 5% CO2, 95 percent air, and 100 percent relative humidity after the drug was administered. The test was completed by adding cold TCA to the adhering cells. The cells were fixed in place by gently adding 50 l of cold 50% (w/v) TCA (final concentration, 10% TCA) and incubated for 60 minutes at 4°C. The supernatant was discarded, and the plates were washed five times with tap water and air dried. Sulforhodamine B (SRB) solution (100 l) in 0.4 percent (w/v) acetic acid was added to each well, and plates were incubated for 10 minutes at room temperature. After staining, the plates were washed five times with 1 percent acetic vinegar and air dried to eliminate any unbound colour. After solubilizing the bound dye with 10 mMtrizma base, the absorbance was measured using an automated plate reader at 515 nm. The procedure was the same for suspension cells, with the difference that the test was finished by gently pouring 50 l of 80 percent TCA into the wells to settle the cells in the bottom (final concentration, 16 percent TCA).The percentage growth was calculated using the seven absorbance measurements of time zero (Tz), control growth (C), and test growth in the presence of drug at the five concentration levels for each of the drug concentration levels (Ti). The percentage of growth inhibition was calculated using the following formula:

[(Ti-Tz)/(C-Tz)] x 100 for concentrations for which Ti>/=Tz

[(Ti-Tz)/Tz] x 100 for concentrations for which Ti<Tz.

For each experimental drug, three dosage response parameters were computed. The drug concentration resulting in a 50% reduction in the net protein increase (as measured by SRB staining) in control cells during the drug incubation was calculated as (Ti-Tz)/(C-Tz) x 100 = 50, which is the drug concentration resulting in a 50% reduction in the net protein increase (as measured by SRB staining) in control cells during the drug incubation. Ti = Tz was used to calculate the medication concentration that resulted in total growth inhibition (TGI).[(Ti-Tz)/Tz] x 100 = -50 was used to compute the drug concentration that resulted in a 50% reduction in measured protein at the conclusion of the drug treatment compared to the beginning (LC50), suggesting a net loss of cells following treatment. If the level of activity was attained, values were computed for each of these three parameters; however, if the effect was not reached or surpassed, the value was stated as higher or less than the maximum or lowest concentration tested [21].

Results and Discussion

In the presence of triethylamine, base catalysed condensation of p-nitrophenyl acetic acid with substituted furan, followed by esterification, or reaction with thionyl chloride followed by reaction with suitable amine yielded analogues of (Z)-1-(5-chloro-furan-2-yl)-2-(4-nitrophenyl) ethene.

Infrared, 1H NMR, and mass spectroscopy were used to confirm the structure of the produced compounds. All of the synthesised compounds' spectral data (1H NMR, IR, and Mass) were found to be in perfect agreement with the hypothesised structures.

Data of spectral studies

8: (2E)-3-(5-chloro-2-furyl)-2-(4-nitrophenyl)acrylic acid:FTIR (KBr) cm^{-1} 3039 and 860 (C-H), 3019 and 750 (Ar-H), 1705 (C=O), 1670 (C=C), 1597 and 1409 (COO^-), 1520 and 1340 (C-NO_2), 1233 and 1001 (C-O), 672 (C-

Cl); ^{1}H NMR (DMSO) δ 10.10 (s, 1H), 8.26 (d, 2H), 8.20 (d, 1H), 7.87 (s, 1H), 7.68 (d, 1H), 7.48 (d, 2H), 6.84 (t, 1H); MS (TISI) 293.5 (M^+).

9: Methyl (2E)-3-(5-chloro-2-furyl)-2-(4-nitrophenyl)acrylate:FTIR (KBr) cm^{-1} 3040 and 858 (C-H), 2925 and 1460 (CH_3), 1735 (C=O), 1690 (C=C), 1599 (C=C of Ar), 1521 and 1346 (C-NO_2), 1218, 1129 and 1020 (C-O), 750 (Ar-H), 683 (C-Cl); ^{1}H NMR (DMSO) δ 8.27 (d, 2H), 7.91 (d, 1H), 7.69 (s, 1H), 7.39-7.69 (m, 3H), 6.88 (t, 1H), 3.51 (s, 3H); MS (TISI) 307.6 (M^+).

10: (2E)-3-(5-chloro-2-furyl)-2-(4-nitrophenyl)acryloyl chloride:FTIR (KBr) cm^{-1} 3039 and 860 (C-H), 3021 and 760 (Ar-H), 1800 (C=O), 1688 (C=C), 1606 (C=C of Ar), 1526 and 1346 (C-NO_2), 1260 and 1020 (C-O), 718 (C-Cl); ^{1}H NMR (DMSO) δ 8.29 (s, 1H), 8.27 (d, 2H), 8.10 (d, 1H), 7.71 (d, 1H), 7.44 (d, 2H), 6.89 (t, 1H); MS (TISI) 311.5 (M^+).

11a: (2E)-N-ethyl-3-(5-chloro-2-furyl)-2-(4-nitrophenyl)acrylamide:FTIR (KBr) cm^{-1} 3427 and 1560 (N-H), 3044 and 858 (C-H), 2892 (CH_3), 1680 (C=O), 1659 (C=C), 1599 (C=C of Ar), 1520 and 1341 (C-NO_2), 1466 (CH_2), 1240 and 1000 (C-O), 750 (Ar-H), 697 (C-Cl); ^{1}H NMR (DMSO) δ 9.19 (s, 1H), 8.25-8.35 (m, 3H), 7.94 (s, 1H), 7.60 (d, 1H), 7.51 (d, 2H), 6.90 (t, 1H), 2.90 (q, 2H), 1.16 (t, 3H); MS (TISI) 320.7 (M^+).

11b: (2E)-N-carbamothioyl-3-(5-chloro-furan-2-yl)-2-(4-nitrophenyl)prop-2-enamide: FTIR (KBr) cm^{-1} 3469, 3350 and 1599 (NH_2), 3440 (N-H), 3043 and 857 (C-H), 3022 and 749 (Ar-H), 1689 (C=O), 1666 (C=C), 1520 and 1346 (C-NO_2), 1237 and 1000 (C-O), 1120 (C=S), 685 (C-Cl); ^{1}H NMR (DMSO) δ 9.57 (s, 2H), 8.51 (s, 1H), 8.30 (d, 2H), 8.10 (d, 1H), 7.80 (s, 1H), 7.69 (d, 1H), 7.40 (d, 2H), 6.86 (t, 1H); MS (TISI) 337.5 (M^+).

11c: (2E)-N-(4-fluorophenyl)-3-(5-chloro-furan-2-yl)-2-(4-nitrophenyl)prop-2-enamide: FTIR (KBr) cm^{-1} 3433 (N-H), 3048 and 858 (C-H), 3024 and 750 (Ar-H), 1690 (C=O), 1661 (C=C), 1601 (C=C of Ar), 1519 and 1346 (C-NO_2), 1237 and 1001 (C-O), 1124 (C-F), 678 (C-Cl); ^{1}H NMR (DMSO) δ 9.59 (s, 1H), 8.29 (d, 2H), 8.10 (d, 1H), 7.77 (m, 3H), 7.67 (s, 1H), 7.39 (d, 2H), 7.21 (d, 2H), 6.92 (t, 1H); MS (TISI) 386.4 (M^+).

11d: (2E)-3-(5-chloro-furan-2-yl)-N-(2-methylphenyl)-2-(4-nitrophenyl)prop-2-enamide: FTIR (KBr) cm^{-1} 3428 (N-H), 3057 and 876 (C-H), 3030 and 749 (Ar-H), 2946 and 1459 (CH_3), 1685 (C=O), 1670 (C=C), 1599 (C=C of Ar), 1516 and 1339 (C-NO_2), 1245 and 1006 (C-O), 683 (C-Cl); ^{1}H NMR (DMSO) δ 9.44 (s, 1H), 8.30 (d, 2H), 8.10 (d, 1H), 7.80 (s, 1H), 7.70 (d, 1H), 7.05-7.47 (m, 6H), 6.96 (t, 1H), 2.29 (s, 3H); MS (TISI) 382.6 (M^+).

11e: (2E)-N-(2-chlorophenyl)-3-(5-chloro-furan-2-yl)-2-(4-nitrophenyl)prop-2-enamide: FTIR (KBr) cm^{-1} 3437 (N-H), 3066 and 877 (C-H), 3029 and 750 (Ar-H), 1680 (C=O), 1666 (C=C), 1600 (C=C of Ar), 1522 and 1340 (C-NO_2), 1230 and 998 (C-O), 710 (C-Cl); ^{1}H NMR (DMSO) 9.67 (bs, 1H), 8.29 (d, 2H), 8.08 (d, 1H), 7.99 (d, 1H), 7.75 (s, 1H), 7.60-7.70 (m, 2H), 7.46 (d, 2H), δ 7.20-7.29 (m, 2H), 6.86 (t, 1H); MS (TISI) 402.5 (M^+).

11f: (2E)-3-(5-chloro-furan-2-yl)-2-(4-nitrophenyl)-N-(pyridin-4-yl)prop-2-enamide: FTIR (KBr) cm^{-1} 3445 (N-H), 3050 and 854 (C-H), 3029 and 750 (Ar-H), 1688 (C=O), 1659 (C=C), 1641 (C=N-C), 1598 (C=C of Ar), 1518 and 1346 (C-NO_2), 1233 and 1005 (C-O), 680 (C-Cl); ^{1}H NMR (DMSO) δ 9.77 (s, 1H), 8.50 (d, 2H), 8.28 (d, 2H), 8.08 (d, 1H), 7.81 (s, 1H), 7.69 (d, 1H), 7.30-7.47 (m, 4H), 6.99 (t, 1H); MS (TISI) 369.7 (M^+).

11g: (2E)-3-(5-chloro-furan-2-yl)-N-(naphthalen-1-yl)-2-(4-nitrophenyl)prop-2-enamide: FTIR (KBr) cm^{-1} 3426 (N-H), 3068 and 765 (Ar-H), 3029 and 859 (C-H), 1685 (C=O), 1651 (C=C), 1601 (C=C of Ar), 1520 and 1347 (C-NO_2), 1239 and 1005 (C-O), 689 (C-Cl); ^{1}H NMR (DMSO) δ 9.54 (s, 1H), 8.29 (d, 2H), 8.00-8.10 (m, 3H), 7.80 (s, 1H), 7.30-7.69 (m, 7H), 7.01 (d, 1H), 6.90 (t, 1H); MS (TISI) 418.6 (M^+).

11h: (2E)-3-(5-chloro-furan-2-yl)-2-(4-nitrophenyl)-1-(piperidin-1-yl)prop-2-en-1-one: FTIR (KBr) cm^{-1} 3016 and 859 (C-H), 2960 and 1456 (CH_2), 1678 (C=O), 1645 (C=C), 1600 (C=C of Ar), 1527 and 1339 (C-NO_2), 1241 and 1004 (C-O), 1198 (NR_3), 750 (Ar-H), 683 (C-Cl); ^{1}H NMR (DMSO) δ 8.28 (d, 2H), 8.08 (d, 1H), 7.80 (s, 1H), 7.69 (d, 1H), 7.45 (d, 2H), 6.86 (t, 1H), 3.58 (t, 4H), 1.39-1.53 (m, 6H); MS (TISI) 360.6 (M^+).

11i: (2E)-3-(5-chloro-furan-2-yl)-2-(4-nitrophenyl)-1-(piperazin-1-yl)prop-2-en-1-one: FTIR (KBr) cm^{-1} 3445 (N-H), 3038 and 855 (C-H), 3020 and 751 (Ar-H), 2956 and 1455 (CH_2), 1666 (C=O), 1600 (C=C of Ar), 1519 and 1346 (C-NO_2), 1246 and 1000 (C-O), 1196 (NR_3), 686 (C-Cl); ^{1}H NMR (DMSO) δ 8.29 (d, 2H), 8.06 (d, 1H), 7.79 (s, 1H), 7.71 (d, 1H), 7.35 (d, 2H), 6.88 (t, 1H), 3.40 (t, 4H), 2.80 (t, 4H), 1.77 (s, 1H); MS (TISI) 361.7 (M^+).

11j: (2E)-3-(5-chloro-furan-2-yl)-N-(2-methoxyphenyl)-2-(4-nitrophenyl)prop-2-enamide: FTIR (KBr) cm^{-1} 3438 (N-H), 3037 and 856 (C-H), 3022 and 750 (Ar-H), 2946 and 1464 (CH_3), 1689 (C=O), 1659 (C=C), 1599 (C=C of Ar), 1520 and 1341 (C-NO_2), 1239 and 1011 (C-O), 685 (C-Cl); ^{1}H NMR (DMSO) δ 9.82 (s, 1H), 8.30 (d, 2H), 8.10 (d, 1H), 7.79 (d, 1H), 7.70 (s, 1H), 7.64 (d, 1H), 7.39 (d, 2H), 6.98-7.05 (m, 3H), 6.90 (t, 1H), 3.90 (s, 3H); MS (TISI) 398.7 (M^+).

11k:(2E)-N-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-3-(5-chloro-furan-2-yl)-2-(4-nitrophenyl)prop-2-enamide: FTIR (KBr) cm^{-1} 3421 (N-H), 3034 and 855 (C-H), 3020, 750 and 703 (Ar-H), 2923 and 1469 (CH_3), 1711 and 1678 (C=O), 1659 (C=C), 1600 (C=C of Ar), 1520 and 1344 (C-NO_2), 1228 and 1000 (C-O), 1187 (NR_3), 677 (C-Cl); ^{1}H NMR (DMSO) δ 9.60 (s, 1H), 8.27 (d, 2H), 8.10 (d, 1H), 7.81 (s, 1H), 7.67 (d, 1H), 7.26-7.52 (m, 6H), 6.90-6.95 (m, 2H), 3.38 (s, 3H), 2.47 (s, 3H); MS (TISI) 478.6 (M^+).

Antiangiogenic activity

Table 2 shows the effects of the test substances on angiogenesis. Because most compounds demonstrated a hazardous impact at greater doses, all of the compounds were evaluated at a level of 0.01 mg/pellet, i.e. less than 40 nmol/pellet. Compounds 10 and 11h showed an antiangiogenic score of higher than 1. The antiangiogenic score of all other substances was less than one. Compound 11h was determined to be the most powerful among (Z)-1-(5-chloro-furan-2-yl)-2-(4-nitrophenyl) ethene analogues, scoring 1.4±0.1, which is similar to standard.

The findings reveal that compound 10 and 11h have potent antiangiogenic properties. Compound 10 containsCOCl group as bridge substituent whereas compound 11h contains piperidin-1-ylcarbonyl group as bridge substituent. Aromatic substituted compounds (11c-g) were the least active. So, compounds with the piperidin-1-ylcarbonyl andchlorocarbonyl moiety on the (Z)-1-(5-chloro-furan-2-yl)-2-(4-nitrophenyl) ethene skeleton are among the most active in our investigation. The antiangiogenic action of the series investigated is influenced by the size of bridge substituents.

Table 2Antiangiogenic activity of synthesized compounds in the CAM assay

Test compound	Concentration (mg/pellet)	Antiangiogenicscore[b] ± sd (n = no. of experiment)
8	0.01	0.9 ± 0.1 (n =3)
9	0.01	0.8 ± 0.1 (n =2)
10	0.01	1.2 ± 0.1 (n =3)
11a	0.01	0.9 ± 0.1 (n =2)
11b	0.01	0.5 ± 0.2 (n =2)
11c	0.01	0.3 ± 0.3 (n =2)
11d	0.01	0.6 ± 0.1 (n =2)
11e	0.01	0.2 ± 0.1 (n =2)
11f	0.01	0.5 ± 0.1 (n =2)
11g	0.01	0.3 ± 0.1 (n =2)
11h	0.01	1.4 ± 0.1 (n =2)
11i	0.01	0.8 ± 0.1 (n =2)
11j	0.01	0.7 ± 0.1 (n =2)
11k	0.01	0.3 ± 0.1 (n =2)
Agarose pellet		0.1 ± 0.1 (n =10)
β-1,4-galactan sulphate (LuPS S5)	0.05	1.4 ± 0.1 (n =10)

[b]0 = no or weak effect, 1 = medium effect, 2 = strong effect

Anticancer activity

Table 3 shows anticancer activity of screened compounds (10 and 11h) against of HCT-116 (colon cancer) and MCF-7 (breast cancer) cell lines by modified MTT assay method. Compound 11h showed maximum activity with % growth inhibition of 28.78 and 16.28 against HCT-116 and MCF-7 cell lines respectively. Results revealed that ((Z)-1-(5-chloro-furan-2-yl)-2-(4-nitrophenyl) ethene analogueshave anticancer potential against HCT-116 (colon cancer) and MCF-7 (breast cancer) cell lines.

Table 3 Anticancer activity of compounds against of HCT-116 (colon cancer) and MCF-7 (breast cancer) cell lines by modified MTT assay method

Test compound	Concentration (dose)	% Growth Inhibition	
		HCT-116	MCF-7
10	10 µM	22.55	11.22
11h	10 µM	28.78	16.28

CONCLUSION

Antiangiogenic activity testing revealed that compounds 10 and 11h exhibited considerable antiangiogenic activity. Antiangiogenic action was discovered to be affected by the size of the bridge substituent (on the Ethylene Bridge). Compounds with aromatic substituents were least active. The most appropriate groups were determined to be piperidin-1-ylcarbonyland chlorocarbonyl. Compound 11h showed maximum anticancer activity with % growth inhibition of 28.78 and 16.28 against HCT-116 and MCF-7 cell lines respectively. Results revealed that synthesized analogues anticancer potential against HCT-116 (colon cancer) and MCF-7 (Breast cancer) cell lines. Finally, it's possible that further derivatization of these molecules will be pursued in the hopes of obtaining more selective and potent anticancer medicines.

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