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Synthesis and evaluation of a series of quinolinyl *trans*-cyanostilbene analogs as anticancer agents

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A series of novel *trans*- 2-quinolyl-, 3-quinolyl- and 4-quinolyl cyanostilbene derivatives were synthesized as analogs of combretastatin A-4 (CA-4), and evaluated for anticancer activity against a panel of 60 human cancer cell lines. The quinolin-2-yl and quinolin-3-yl analogs containing trimethoxyphenyl (**10** and **16**, respectively) or dimethoxyphenyl (**12** and **18**, respectively) moieties showed growth inhibition against all the cancer cell lines in the panel, with GI_{50} values generally < 1 μM. Quinolin-2-yl-analog **10** exhibited potent growth inhibition against MDA-MB-435 melanoma and NCI-H522 non-small cell lung cancer lines with GI_{50} values of 33 nM and 37 nM respectively. Quinolin-2-yl-analog **12** showed potent growth inhibition against NCI-H522 non-small cell lung cancer lines with a GI_{50} value of 94 nM. Quinolin-3-yl-analog **18** exhibited potent growth inhibition against MDA-MB-435 melanoma and NCI-H522 non-small cell lung cancer lines with GI_{50} values of 53 nM and 69 nM, respectively. Thus, structural modification of the CA-4 molecule has afforded compounds with potential clinical utility in the treatment a variety of different solid tumors.

Introduction

Different fundamental cellular processes, such as cell division, formation and maintenance of cell shape, regulation of motility, cell signaling, secretion, and intracellular transport are regulated by the microtubule system of eukaryotic cells.[1] In anticancer therapy, the inhibition of microtubule function as a therapeutic outcome has been validated utilizing the *cis*-stilbene analog, combretastatin A-4 (CA-4; Fig. 1, **I**). CA-4 is an antimitotic agent isolated from the bark of the South African tree *Combretum caffrum*.[2] The potent cytotoxicity of CA-4 against a wide variety of human cancer cell lines, including multidrug resistant cells, is believed to be due to its effect on microtubule dynamics and its affinity for the colchicine binding site.[3] SAR studies have revealed that the trimethoxyphenyl ring system is essential for the cytotoxic effect of CA-4.[4] Inspite of the potent cytotoxicity of CA-4 the molecule possesses some disadvantageous properties, such as low water-solubility, vascular disruption, and isomerization to the less active *trans*-stilbene isomer (Fig. 1, **II**) in solution.[5] In this respect, the *Z*-isomer of CA-4 represents the *cis*-stilbene geometry, and *Z*-CA-4 analogs are generally 1000-fold more cytotoxic than the corresponding *E*-isomer (*trans*-stilbene geometry). Efforts to overcome the limitations of CA-4 analogs have focused on incorporating different aromatic heterocyclic ring systems into the molecule to improve water-solubility[6], and on designing *cis*-analogs that are incapable of *cis* to *trans* isomerization in solution.

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Recently, Jalily *et al.* and Ohsumi *et al.* have reported on some novel *trans*-cyanocombretastatin analogs (Fig. 1, **III**) as potent inhibitors of tubulin polymerization with activities comparable to that of CA-4; these investigators have demonstrated that a *trans* double bond bearing a nitrile moiety would be an effective replacement for the *cis*-olefinic moiety in CA-4 and its analogues.[7]

In CA-4 analogs, the *Z*-isomer incorporates *cis*-aryl rings about the double bond (i.e. *cis*-stilbene geometry) whereas the isomeric *E*-CA-4 analogs incorporate aryl rings that are *transoid*. It should be noted that according to Cahn–Ingold–Prelog priority rules[8], the addition of a cyano group onto either of the carbons of the *trans*-stilbene double bond will change the *E* configuration to the *Z* configuration. Thus, *trans* cyanocombretastatin analogs are designated as *Z*-configuration, and CA-4 and its non-cyano *cis*-analogs are also designated as *Z*-configuration.

Many reports in the literature have focused on incorporating heterocycles such as benzothiophene,[9] indole,[10] pyrazole,[11] imidazole,[12] isoxazole,[13] 1,2,3-thiadiazole,[14] triazoles,[11,15,16] and 1,2,3,4-tetrazole[11] into the CA-4 structure. Such compounds have been shown to be potent anti-cancer agents. In an earlier communication we have reported on the anti-cancer and antitubulin activity of a series of *Z*- and *E*-benzothiophene combretastatin derivatives (Fig. 1, **IV** and **V**, respectively)[9b] and have demonstrated that *Z*-benzothiophene cyanocombretastatin analogs can overcome cell-associated P-glycoprotein (P-gp)-mediated resistance, since such compounds were equipotent in inhibiting both OVCAR8 and NCI/ADR-RES cell growth.[9b] *Z*-Quinolinyl CA-4 analogs (Fig. 1, **VI**) have also been reported as

potent inhibitors of tubulin polymerization and have improved water-solubility comparable to that of other CA-4 analogs[17]. However, there have been no reported studies on *Z*-quinolinyl cyanocombretastatins, which encouraged us to synthesize a series of novel 2-, 3-, and 4-quinolyl analogs of *Z*-cyanocombretatstatin and to evaluate these novel compounds as potent anti-cancer agents.

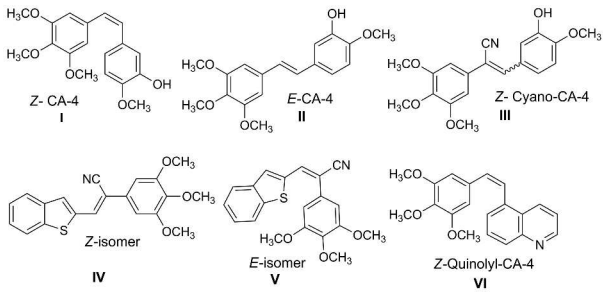


Fig. 1 Chemical structures of *Z*-CA-4 and other structurally related antitubulin agents

In the present communication, we describe the synthesis of a variety of *Z*-2-quinolinyl, *Z*-3-quinolyl and *Z*-4-quinolyl cyanocombretastatin analogs that incorporate trimethoxyphenyl, dimethoxyphenyl, monomethoxyphenyl, hydroxyphenyl or hydroxydimethoxyphenyl moieties, and the evaluation of these analogs as anti-cancer agents against an extensive panel of human cancer cell lines.

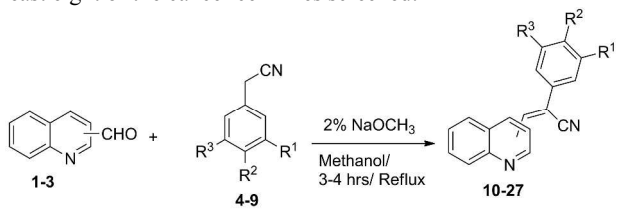
Chemistry

The 2-quinolinyl, 3-quinolyl and 4-quinolyl cyanocombretastatin analogs **10-27** were synthesized by refluxing quinoline-2-carbaldehyde (**1**), quinoline-3-carbaldehyde (**2**) or quinoline-4-carbaldehyde (**3**) with 3,4,5-trimethoxyphenyl-acetonitrile (**4**), 3,4-dimethoxy phenylacetonitrile (**5**), 3,5-dimethoxyphenylacetonitrile (**6**), 4-hydroxyphenylacetonitrile (**7**), 4-methoxyphenylacetonitrile (**8**), and 4-hydroxy-3,5-dimethoxyphenylacetonitrile (**9**) in methanolic 2% sodium methoxide solution (Scheme 1). The desired products were obtained in yields ranging from 85-93%.[18] Confirmation of the structure, geometry and purity of these analogs was obtained from ^{1}H- and ^{13}C-NMR spectrometric, and high resolution MS analysis. Carbon-proton coupling experiments showed that the magnitude of the coupling constant (J_{CH}) of the CN carbon doublet at ~118 *ppm*, arising from coupling with the olefinic proton was > 12 Hz for the above products, which established the *Z*-geometry for these compounds.[7a]

Biological Evaluation

In vitro growth inhibition and cytotoxicity against human cancer cell lines

Compounds **10-27** were evaluated for anti-proliferative activity in a preliminary screen at 10^{-5} M concentration against a panel of 60 human cancer cell lines (NCI-60 panel). The NCI 60 cell panel was divided into subpanels of leukemia, non-small cell lung, colon, central nervous system, melanoma, ovary, renal, prostate, and breast cancer cell lines. From the single dose screen, successful compounds progressed to five concentration-cytotoxicity assays if they exhibited ≥60% growth inhibition in at least eight of the cancer cell lines screened.



S. No	Quinoline	R^1	R^2	R^3
10	Quinolin-2-yl	OCH_3	OCH_3	OCH_3
11	Quinolin-2-yl	H	OCH_3	OCH_3
12	Quinolin-2-yl	OCH_3	H	OCH_3
13	Quinolin-2-yl	H	OH	H
14	Quinolin-2-yl	H	OCH_3	H
15	Quinolin-2-yl	OCH_3	OH	OCH_3
16	Quinolin-3-yl	OCH_3	OCH_3	OCH_3
17	Quinolin-3-yl	H	OCH_3	OCH_3
18	Quinolin-3-yl	OCH_3	H	OCH_3
19	Quinolin-3-yl	H	OH	H
20	Quinolin-3-yl	H	OCH_3	H
21	Quinolin-3-yl	OCH_3	OH	OCH_3
22	Quinolin-4-yl	OCH_3	OCH_3	OCH_3
23	Quinolin-4-yl	H	OCH_3	OCH_3
24	Quinolin-4-yl	OCH_3	H	OCH_3
25	Quinolin-4-yl	H	OH	H
26	Quinolin-4-yl	H	OCH_3	H
27	Quinolin-4-yl	OCH_3	OH	OCH_3

Scheme 1 Synthesis of *Z*-cyanoquinolinyl combretastatins (**10-27**).

From the preliminary screening data, the quinolinyl cyanocombretastatin analogs incorporating a 3,4,5-trimethoxyphenyl moiety (**10** and **16**) and a 3,5-dimethoxyphenyl group (**12** and **18**) showed significant potency and were selected as leads for five dose studies. These studies were designed to determine GI_{50}, TGI and LC_{50} values, which represent the molar drug concentration required to cause 50% growth inhibition, total growth inhibition, and the concentration that kills 50% of the cells, respectively. These compounds were studied at five different concentrations by 10-fold dilutions at 10^{-4}M, 10^{-5} M, 10^{-6} M, 10^{-7} M and 10^{-8} M by dissolving each compound in dimethyl sulfoxide (DMSO)/water and evaluating the effect of the drug over 48 h of incubation.

Compounds **10**, **12**, **16** and **18** exhibited growth inhibition against all 60 human cancer cell lines in the five dose screens. The growth inhibition results of these four molecules are presented in Table 1.

The 2-quinolyl analog **10** [(*Z*)-3-(quinolin-2-yl)-2-(3,4,5-trimethoxyphenyl)acrylonitrile] exhibited potent growth inhibition against 91% of the cancer cell lines in the panel, with GI_{50} values ranging from 0.033 to 0.943 μM; the average GI_{50} value for this compound against all the cancer cell lines in the panel was 0.40 μM. Compound **10** exhibited potent growth inhibition against MDA-MB-435 melanoma cancer cell lines with

a GI_{50} value of 0.033 μM (Table 1).

Table 1 Antitumor activity (GI_{50}/μM)[a] data for the of *Z*-quinolyl cyanocombretastatin analogs on various human tumour cell lines

	10	**12**	**16**	**18**
Panel/cell line	GI_{50} (μM)	GI_{50} (μM)	GI_{50} (μM)	GI_{50} (μM)
Leukemia				
CCRF-CEM	0.248	0.332	1.38	0.332
HL-60(TB)	0.223	0.27	0.329	0.234
K-562	0.080	0.353	0.444	0.243
MOLT-4	0.488	0.419	3.20	0.378
RPMI-8226	0.297	0.433	2.06	0.332
SR	NA	NA	0.569	NA
Lung Cancer				
A549/ATCC	0.375	0.649	0.680	0.556
EKVX	na	na	na	na
HOP-62	0.567	0.959	10.3	0.793
HOP-92	0.736	0.542	0.403	3.09
NCI-H226	4.78	10.8	>100	62.2
NCI-H23	0.751	0.983	2.93	0.747
NCI-H322M	0.718	3.02	27.4	0.903
NCI-H460	0.361	0.339	2.05	0.362
NCI-H522	0.0372	0.094	0.299	0.069
Colon Cancer				
COLO 205	0.198	0.374	0.374	0.398
HCC-2998	0.61	1.42	2.01	1.45
HCT-116	0.234	0.416	0.464	0.420
HCT-15	0.319	0.409	1.08	0.455
HT29	0.24	0.367	0.421	0.362
KM12	0.35	0.425	0.436	0.409
SW-620	0.164	0.357	na	0.352
CNS Cancer				
SF-268	0.835	0.476	9.17	0.654
SF-295	0.277	0.341	0.556	0.243
SF-539	0.197	0.286	0.361	0.289
SNB-19	0.578	0.728	5.23	0.614
SNB-75	0.182	0.311	1.49	0.224
U251	0.355	0.425	1.70	0.374
Melanoma				
LOX IMVI	0.766	0.61	0.645	0.672
MALME-3M	na	0.348	0.691	0.635
M14	0.173	0.36	0.540	0.310
MDA-MB-435	0.033	0.147	0.227	0.053
SK-MEL-2	0.483	0.522	1.05	0.709
SK-MEL-28	0.518	0.896	3.27	1.40
SK-MEL-5	0.243	0.406	0.410	0.249
UACC-257	0.761	nd	nd	12.8
UACC-62	0.092	0.449	0.478	0.357
Ovarian Cancer				
IGROV1	0.846	0.958	3.15	3.50
OVCAR-3	0.163	0.309	0.263	0.279
OVCAR-4	1.43	0.788	13.8	1.73
OVCAR-5	0.580	0.716	3.94	0.587
OVCAR-8	0.446	0.659	3.41	0.584
NCI/ADR-RES	0.112	0.283	0.343	0.224
SK-OV-3	0.524	0.804	1.34	0.576
Renal Cancer				
786-0	0.445	0.501	6.29	0.484
A498	0.295	0.275		0.333
ACHN	1.04	0.773	0.911	1.19
CAKI-1	0.068	0.318	0.346	0.223
RXF 393	0.271	0.334	0.579	0.297
SN12C	0.627	0.661	1.94	0.661
TK-10	4.69	3.28	2.55	17.7
UO-31	0.762	0.573	0.580	nd
Prostate Cancer				
PC-3	0.348	0.584	1.08	0.506
DU-145	0.446	0.801	1.51	0.505
Breast Cancer				
MCF7	0.275	0.537	0.429	0.333
MDA-MB-231/ATCC	0.943	1.02	2.83	1.15
HS 578T	0.689	0.70	1.31	0.715
BT-549	0.315	0.342	1.43	0.388
T-47D	4.76	1.23	9.54	0.628
MDA-MB-468	0.243	1.50	0.870	0.217

na: Not analyzed, nd: not determined [a]GI_{50}: 50% Growth inhibition, concentration of drug resulting in a 50% reduction in net cell growth as compared to cell numbers on day 0.

Substitution of a 3,5-dimethoxyphenyl moiety in place of the 3,4,5-trimethoxyphenyl group in **10** afforded compound **12 [**(*Z*)-3-(quinolin-2-yl)-2-(3,5-dimethoxyphenyl)acrylonitrile], which exhibited potent growth inhibition against 86% of the cells in the human cancer cell panel, with GI_{50} ranging from 0.094 to 0.983 μM; the average GI_{50} value for this compound against all the cancer cell lines in the panel was 0.49 μM. This compound exhibited potent growth inhibition against NCI-H522 lung cancer cell lines with a GI_{50} value of 0.094 μM (Table 1).

The 3-quinolyl isomer of **10,** compound **16** [(*Z*)-3-(quinolin-3-yl)-2-(3,4,5-trimethoxyphenyl) acrylonitrile] exhibited potent growth inhibition against 47% of the cell lines in the human cancer cell panel, with GI_{50} values ranging from 0.227 to 0.911 μM; the average GI_{50} value of this compound against all the human cancer cell lines in the panel was 2.49 μM. Compound **16** exhibited potent growth inhibition against MDA-MB-435 melanoma cancer cell lines with a GI_{50} value of 0.227 μM (Table 1).

The 3-quinolyl isomer of **12,** compound **18 [**(*Z*)-3-(quinolin-3-yl)-2-(3,5-dimethoxyphenyl)acrylonitrile] exhibited potent growth inhibition against 81% of the cell lines in the human cancer cell panel with GI_{50} values ranging from 0.053 to 0.903 μM; the average GI_{50} value of this compound against all the human cancer cell line in the panel is 2.21 μM. Compound **18** exhibited potent growth inhibition against MDA-MB-435 melanoma cancer cell lines with a GI_{50} value of 0.053 μM (Table 1).

Conclusion

A series of novel *Z*-quinolinyl cyanocombretastatin analogs were synthesized and evaluated for anticancer activity against a panel of 60 human cancer cell lines. 2- and 3-quinolyl analogs containing a 3,4,5-trimethoxyphenyl moiety (**10** and **16)**, or a 3,5-dimethoxyphenyl (**12** and **18)** moiety exhibited the most potent growth inhibition with GI_{50} values generally <1 μM against most of the human cancer cell lines in the panel. The 4-quinolyl 3,4,5-trimethoxyphenyl and 4-quinolyl 3,5-dimethoxyphenyl analogs were found to be inactive. Compound **10** exhibited potent growth inhibition against MDA-MB-435 melanoma and NCI-H522 non-small cell lung cancer lines with GI_{50} values of 33 nM and 37 nM, respectively. Compounds **12** and **18** exhibited potent growth inhibition against NCI-H522 non-small cell lung cancer lines with GI_{50} values of 94 nM and 69 nM, respectively. Thus, structural modification of the CA-4 molecule to afford 2-quinolyl and 3-quinolyl analogs of *Z*-cyanocombretatstatin have produced

compounds with potential clinical utility in the treatment a variety of different solid tumors.

General synthetic procedure: ***Synthesis of (Z)-quinolinyl-2-alkoxyphenylacrylonitriles*** **(10-27):** The 2-, 3-, or 4-quinolylcarbaldehyde (1 mole) and the appropriate substituted phenylacetonitrile (1.1 mole equivalent) were added to 2% sodium methoxide in methanol and the mixture heated under reflux for 3 to 6 h. The resulting solution was then cooled to room temperature and poured into ice-cold water to afford a crude yellow solid. The solid was filtered off, washed with water, and finally washed with cold methanol. The obtained crude solid was recrystallized from methanol to afford the desired condensation product as a pure crystalline solid.

Analytical data for the most potent compounds:

(Z)-3-(quinolin-2-yl)-2-(3,4,5-trimethoxyphenyl) acrylonitrile **(10):** Yellow fluffy solid. mp:106-108 ^{0}C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.91 (s, 3H), 3.96 (s, 6H), 7.02 (s, 2H), 7.61 (t, 1H, J_1 = 7.6 Hz, J_2 = 14.8 Hz), 7.78-7.79 (d, 1H, J = 7.2 Hz), 7.86 (s, 1H), 7.86-7.88 (d, 1H, J = 8.40 Hz), 8.14-8.20 (m, 2H), 8.27-8.29 (d, 1H, J = 8.8 Hz) *ppm*; ^{13}C NMR (100 MHz, $CDCl_3$): δ 56.29, 60.96, 103.74, 115.91, 117.44, 120.54, 127.55, 127.64, 127.73, 127.86, 129.43, 129.60, 130.35, 137.00, 139.73, 140.74, 140.87, 148.10, 152.21, 153.59 *ppm*. HRMS calcd for $C_{21}H_{18}N_2O_3$, (M^+): 346.1317. Found 346.1309.

(Z)-2-(3,5-dimethoxyphenyl)-3-(quinolin-2-yl)acrylonitrile **(12):** Yellow crystalline solid, mp:110-112 ^{0}C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.84 (s, 6H), 6.52 (s, 1H), 6.92 (s, 2H), 7.56-7.60 (t, 1H, J_1 = 7.2Hz, J_2 = 15.2 Hz), 7.73-7.77 (t, 1H, J_1 = 8.0 Hz, J_2 = 15.2 Hz), 7.81 (s, 1H), 7.83-7.85 (d, 1H, J = 8.8 Hz), 8.11-8.15 (t, 2H, J_1 = 9.6 Hz, J_2 = 18 Hz), 8.26 (d, 1H, J = 8.8 Hz) *ppm*; ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.52, 101.63, 104.33, 113.92, 117.59, 126.69, 127.37, 127.49, 127.62, 128.78, 129.29, 129.36, 131.16, 135.23, 135.84, 138.33, 148.40, 151.26, 161.31 *ppm*. HRMS calcd for $C_{20}H_{16}N_2O_2$, (M^+): 316.1212. Found 346.1204.

(Z)-3-(quinolin-3-yl)-2-(3,4,5-trimethoxyphenyl)acrylonitrile **(16):** Yellow crystalline solid, mp:155-157 ^{0}C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.90 (s, 3H), 3.95 (s, 6H), 6.92 (s, 2H), 7.60-7.63 (m, 2H), 7.76-7.80 (t, J_1 = 7.2 Hz, J_2 = 15.6 HZ, 1H), 7.92-7.94 (d, J = 8Hz, 1H), 8.10-8.12 (d, J = 8.4 Hz, 1H), 8.9 (s, 1H), 9.1 (s, 1H) *ppm*. ^{13}C NMR (100 MHz, $CDCl_3$): δ 56.36, 61.02, 103.48, 113.92, 117.66, 126.78, 127.38, 127.56, 128.77, 129.32, 129.46, 131.09, 135.06, 137.39, 139.62, 148.34, 151.21, 153.67 *ppm.* HRMS calcd for $C_{21}H_{18}N_2O_3$, (M^+): 346.1317. Found 346.1311.

(Z)-2-(3,5-dimethoxyphenyl)-3-(quinolin-3-yl)acrylonitrile **(18):** Light yellow crystalline solid, mp: 150-152 ^{0}C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.85 (s, 6H), 6.52 (s, 1H), 6.85 (s, 2H), 7.58-7.62 (t, 1H, J_1 = 8.0 Hz, J_2 = 15.2 HZ), 7.66 (s, 1H), 7.76- 7.80 (t, 1H, J_1 = 8.0 Hz, J_2 = 15.6 Hz), 7.92-7.94 (d, 1H, J = 8.0 Hz), 8.10-8.12 (d, 1H, J = 8.8 Hz), 8.93 (s, 1H), 9.09 (d, 1H, J = 1.6 Hz) *ppm*; ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.52, 101.63, 104.33, 113.92, 117.59, 126.69, 127.37, 127.49, 127.62, 128.78, 129.29, 129.36, 131.16, 135.23, 135.84, 138.33, 148.40, 151.26, 161.31 *ppm*. HRMS calcd for $C_{20}H_{16}N_2O_2$, (M^+): 316.1212. Found 346.1208.

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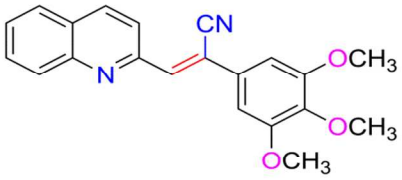
Graphical Abstract

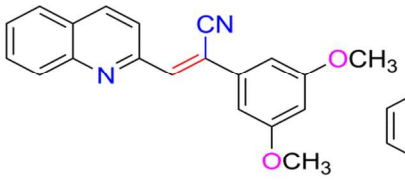
Synthesis and evaluation of a series of quinolinyl *trans*-cyanostilbene analogs as anticancer agents

Narsimha Reddy Penthala, Venumadhav Janganati, Shobanbabu Bommagani and Peter A. Crooks

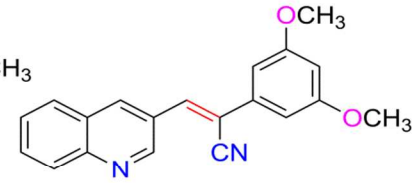
2-Quinolyl- and 3-quinolyl-cyanocombretastatin analogs exhibit potent growth inhibition against a panel of 60 human cancer cell lines.



GI_{50}=33 nM, MDA-MB-435 melanoma cancer
GI_{50}=37 nm, NCI-H522 lung cancer cell lines



GI_{50}=94 nm, NCI-H522 lung cancer lines



GI_{50}=53 nM, MDA-MB-435 melanoma cancer
GI_{50}=69 nm, NCI-H522 lung cancer cell lines