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Heteroaromatic analogs of the resveratrol analog DMU-212 as potent anti-cancer agents

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ABSTRACT

Heteroaromatic analogs of **DMU-212** (**8-15**) have been synthesized and evaluated for their anti-cancer activity against a panel of 60 human cancer cell lines. These novel analogs contain a *trans*-3,4,5-trimethoxystyryl moiety attached to the C2 position of indole, benzofuran, benzothiazole or benzothiophene ring (**8**, **11**, **13** and **14**, respectively) and showed potent growth inhibition in 85% of the cancer cell lines examined, with GI_{50} values <1 μM. Interestingly, *trans*-3,4- and *trans*-3,5-dimethoxystyryl **DMU-212** analogs **9**, **10**, **12** and **15** exhibited significantly less growth inhibition than their 3,4,5-trimethoxystyryl counterparts, suggesting that the *trans*-3,4,5-trimethoxystyryl moiety is an essential structural element for the potent anti-cancer activity of these heterocyclic **DMU-212** analogs. Molecular modeling studies showed that the four most active compounds (**8**, **11**, **13** and **14**) all bind to the colchicine binding site on tubulin, and that their binding modes are similar to that of **DMU-212**.

In anticancer therapy, the inhibition of microtubule function as a therapeutic strategy has been validated by utilizing the natural product resveratrol (*trans*-3,5,4'-trihydroxystilbene) and its derivatives (Fig. 1; structures **I-III**) as tubulin targeting agents.[1, 2] Resveratrol, a well-known natural polyphenolic phytoalexin compound extracted from a variety of medicinal plants and from grapes,[3] is a potent anti-oxidant[4,5] and also inhibits platelet aggregation.[6,7] Resveratrol and its analogs have been shown to exhibit various cancer chemo-preventive properties, due to their modulation of multiple cellular processes, including apoptosis, cell cycle progression, inflammation, and angiogenesis.[8]

A series of methoxy derivatives of resveratrol have been reported as anti-cancer agents against various human cancer cell lines.[2,9] Among these, (*E*)-3,5,4'-trimethoxystilbene (Fig. 1; structure **II**) and (*E*)-3,4,5,4'-tetramethoxystilbene (**DMU-212,** Fig. 1; structure **III**) exhibit potent anti-cancer activity and 30- to 100-fold enhanced cytotoxicity in comparison to resveratrol.[10] These methoxy derivatives have been identified as microtubule-destabilizing agents endowed with anti-angiogenic and vascular-targeting propeties.[1]

The combretastatins, are another potent group of natural products that are inhibitors of microtubule function.[11,12] Combretastatin analogs have been extracted from the bark of the South African tree *Combretum caffrum*, and among these natural products, combretastatin A-4 (Fig. 1; structure **IV**), a *cis*-stilbene analog, is a well-known anti-mitotic agent.[13] The potent cytotoxicity of CA-4 against a wide variety of human cancer cell lines, including multidrug resistant cells, is due to its effect on microtubule dynamics and its affinity for the colchicine binding site on tubulin.[14]

A number of *trans*-CA-4 analogs structurally related to **DMU-212**, e.g. compound **V** (Fig.1), has been found to possess potent anti-cancer activity in cells in culture at cytotoxic concentrations.[15,16] Also, recent studies have shown that *trans*-cyanostilbene analogs that are structurally related to both **DMU-212** and *trans*-CA-4, e.g. compound **VI**, (Fig. 1), are inhibitors of tubulin polymerization with potencies comparable to that of CA-4.[17,18]

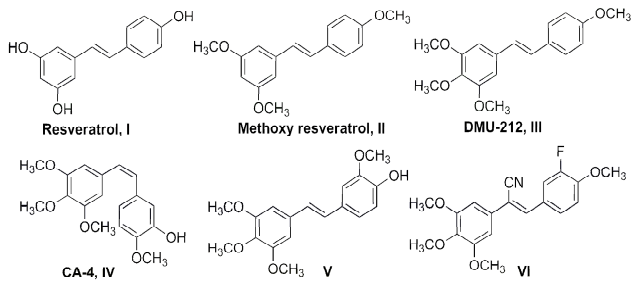

Fig. 1 Chemical structures of potent anti-cancer agents

We have previously reported on the synthesis of a wide variety of *cis*- and *trans*-substituted cyanostilbene analogs as anti-tubulin agents.[17] Also, we have recently described the synthesis and potent anti-cancer activity of some *cis*- and *trans*-cyanostilbene analogs in which one of the phenyl moieties has been replaced with a heteroaromatic moiety such as benzothiophene[19] and quinoline.[20]

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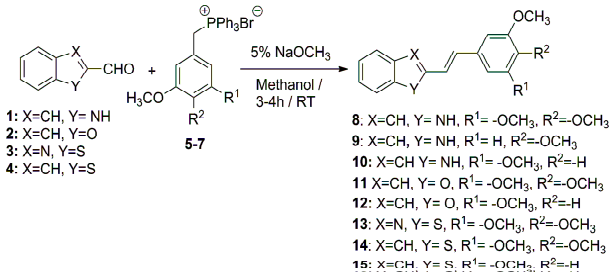
In the present communication, we report on the synthesis and anti-cancer activities of a variety of heteroaromatic **DMU-212** analogs (**8-15**) in which the 4-methoxyphenyl moiety in the **DMU-212** molecule has been replaced with a variety of well-known bio-active heterocyclic ring systems such as indole, benzofuran, benzothiazole and benzothiophene. The methoxy substitution pattern in the *trans*-3,4,5-trimethoxystyryl moiety in these compounds has also been varied.

A series of indole, benzo[*b*]furan, benzo[*b*]thiophen and benzo[*d*]thiazole analogs of **DMU-212** (**8-15**) were synthesized by indole-2-carbaldehyde (**1**), benzo[*b*]furan-2-carbaldehyde (**2**), benzo[*d*]thiazole-2-carbaldehyde (**3**), and benzo[*b*]thiophen-2-carbaldehyde (**4**), with a variety of triphenyl phosphonium bromide salts (**5-7**) in 5% sodium methoxide methanol at room temperature for 3-4 h (Scheme 1).



Scheme 1 Synthesis of heteroaromatic analogs of **DMU-212** (**8-15**)

Confirmation of the structure and purity of these analogs was obtained from ^{1}H- and ^{13}C-NMR, and high resolution mass spectroscopic analysis. The geometry of the double bond in these molecules was established as the *trans*-configuration from ^{1}H-NMR studies [the *trans*-stilbene olefinic proton *J*-values range from 15-16 Hz, while the *cis*-stilbene olefinic protons have *J*-value ranging from 7.4-8.6 Hz].[21]

All the synthesized molecules were evaluated for their anti-cancer activity in a preliminary screen against a panel of 60 human cancer cell lines (NCI-60 panel) at a concentration of 10^{-5} M utilizing the procedure described by Rubinstein et al.[22] In this cellular assay the growth inhibition of the test compounds is measured by determining percentage cell growth (PG) inhibition. Optical density (OD) measurements of sulforhodamine B (SRB)-derived color, just before exposing the cells to the test compound (ODt_{zero}), and after 48 h exposure to the test compound (OD_{test}) or the control vehicle (OD_{ctrl}) is recorded. The growth percentage compared to control is calculated utilizing the reported formulas.[23] The NCI 60 cell panel includes different subpanels representing leukemia, non-small cell lung, colon, central nervous system, melanoma, ovary, renal, prostate, and breast cancer cell lines.

A single dose preliminary screening of the compounds was carried out on all the synthesized compounds (**8-15**) at 10^{-5} M concentration. From the preliminary screening the compounds which showed 60% or more growth inhibition in at least eight of the cell lines were further screened at five different concentrations (10^{-4}M, 10^{-5} M, 10^{-6} M, 10^{-7} M and 10^{-8} M) following 48 h of incubation. From the single dose studies, four (**9**, **10**, **12**, **15**) of the eight compounds evaluated were not considered for subsequent 5-dose studies because they only showed 60% or more growth inhibition in two to six cell lines in the panel. Compounds **8**, **11**, **13** and **14** were each evaluated in 5-dose studies designed to determine growth inhibition (GI_{50}) values, which represent the molar drug concentration required to cause 50% cell growth inhibition.

The four 3,4,5-trimethoxystyryl analogs **8, 11, 13** and **14** exhibited potent cytotoxicity in the 5-dose NCI-60 human cancer cell assay, and because of their structural similarity to **DMU-212**, the cytotoxic activity of these novel heterocyclic analogs likely results from their interaction with the colchicine binding site on tubulin. The growth inhibition results for the above compounds are presented in Table 1, and are summarized below.

The substitution of the *trans*-3,4,5-trimethoxystyryl moiety at the C2 position of an indole ring afforded compound **8**, which exhibited potent growth inhibition against 88% of the cancer cell lines in the panel, affording GI_{50} values ranging from 0.15 to 0.963 µM, with an average GI_{50} value of 0.90 µM for all the cell lines in the panel. This compound exhibited growth inhibition against MDA-MB-435 melanoma and UO-31 renal cancer cell lines with GI_{50} values of 0.15 and 0.17 µM, respectively (Table 1).

Incorporating the *trans*-3,4,5-trimethoxystyryl moiety at the C2 position of a benzofuran ring afforded compound **11.** This compound exhibited potent growth inhibition against 78% of the cancer cell lines in the panel, with GI_{50} values ranging from 0.078 to 0.895 µM, and an average GI_{50} value of 1.42 µM for all the cells in the panel. Compound **11** exhibited growth inhibition against MDA-MB-435 melanoma, SR leukemia, and HOP-92 lung cancer cancer cell lines with GI_{50} values of 0.078, 0.094 and 0.170 µM, respectively (Table 1).

Table 3. Anti-tumor activity (GI_{50}/µM)[a] data for the heteroaromatic **DMU-212**[b] analogs **8**, **11**, **13**, **14** from the 5-dose human cancer cell panel assay

Panel/cell line	**8**	**11**	**13**	**14**
	GI_{50}	GI_{50}	GI_{50}	GI_{50}
Leukemia				
CCRF-CEM	0.368	0.425	0.133	0.262
HL-60(TB)	0.347	0.356	0.037	0.246
K-562	0.393	0.267	0.041	0.088
MOLT-4	0.854	0.852	1.28	0.424
RPMI-8226	0.388	0.700	0.158	0.268
SR	0.241	0.094	0.036	0.120
Lung Cancer				
A549/ATCC	0.624	0.615	0.118	0.310
EKVX	na	na	na	10.3
HOP-62	0.933	0.775	0.393	0.420
HOP-92	0.201	0.170	0.036	0.322
NCI-H226	0.559	1.10	0.245	0.442
NCI-H23	0.677	3.09	0.726	0.324
NCI-H322M	nd	15.9	nd	0.649
NCI-H460	0.374	0.416	0.117	0.351
NCI-H522	0.294	0.436	0.163	0.153
Colon Cancer				
COLO 205	0.343	0.406	0.049	0.209
HCC-2998	2.25	0.334	2.23	0.307
HCT-116	0.534	0.522	0.072	0.246
HCT-15	0.469	0.402	0.063	0.328
HT29	0.335	0.375	0.038	0.234
KM12	0.436	0.508	0.072	0.213
SW-620	0.333	0.444	0.043	0.293
CNS Cancer				
SF-268	0.708	0.861	0.568	0.985
SF-295	0.311	0.356	0.070	0.442
SF-539	0.231	0.273	0.076	0.299
SNB-19	0.461	0.584	0.095	0.362
SNB-75	0.329	0.475	0.162	0.190
U251	0.442	0.668	0.088	0.338
Melanoma				
LOX IMVI	0.664	0.895	1.90	0.382
MALME-3M	0.388	0.413	0.072	0.826
M14	0.332	0.479	0.063	0.169

MDA-MB-435	0.150	0.078	0.024	0.036
SK-MEL-2	0.426	0.767	0.064	0.323
SK-MEL-28	0.944	0.837	0.313	0.346
SK-MEL-5	0.305	0.345	0.047	0.267
UACC-257	nd	16.4	15.0	0.520
UACC-62	0.465	0.507	0.050	0.185
Ovarian Cancer	0.504	0.807	0.249	0.520
IGROV1				
OVCAR-3	0.234	0.429	0.069	0.224
OVCAR-4	0.691	1.15	1.81	0.553
OVCAR-5	0.963	2.94	0.939	0.547
OVCAR-8	0.587	2.05	0.396	0.352
NCI/ADR-RES	0.365	0.511	0.106	0.070
SK-OV-3	0.676	0.656	0.165	0.263
Renal Cancer	0.802	0.850	1.32	0.445
786-0				
A498	0.281	0.408	0.041	0.213
ACHN	0.620	0.863	1.22	0.810
CAKI-1	0.382	0.580	0.143	4.35
RXF 393	0.275	0.329	0.142	0.168
SN12C	1.64	4.09	9.37	0.666
TK-10	21.6	8.46	11.1	0.566
UO-31	0.172	1.15	0.376	0.513
Prostate Cancer	0.381	0.524	0.138	0.276
PC-3				
DU-145	0.384	1.86	0.272	0.402
Breast Cancer	0.395	0.373	0.313	0.285
MCF7				
MDA-MB-231/ATCC	1.30	1.17	0.713	0.450
HS 578T	0.257	0.499	0.171	0.275
BT-549	0.938	1.09	3.72	0.326
T-47D	nd	0.693	0.961	nd
MDA-MB-468	0.285	0.662	0.825	na

na: Not analyzed; nd: not determined; [a]GI_{50}: concentration of drug resulting in a 50% reduction in net cell growth, as compared to cell numbers on day 0. [b]Five dose NCI cancer cell screening data for **DMU-212** has been previously reported.[15]

Placing the *trans*-3,4,5-trimethoxystyryl moiety at the C2 position of a benzothiazole ring afforded compound **13,** which exhibited significant growth inhibition against 81% of the cancer cell lines in the panel with GI_{50} values ranging from 0.024 to 0.961 µM and an average GI_{50} value of 1.02 µM. This compound exhibited growth inhibition against 3 out of 6 of the cell lines in the leukemia sub-panel (GI_{50} values 0.036-0.041 µM); 5 out of 7 of the cell lines in the colon cancer sub-panel (GI_{50} values 0.038-0.072 µM); 4 out of 6 of the cell lines in the CNS cancer sub-panel (GI_{50} values of 0.070-0.095 µM); and 6 out of 9 of the cell lines in the melanoma sub-panel (GI_{50} values 0.024-0.072 µM). Compound **13** also exhibited potent growth inhibition of HOP-92 lung, OVCAR-3 ovarian, and A498 renal cancer cell lines with GI_{50} values of 0.036. 0.069, and 0.041 µM, respectively (Table 1).

The substitution of the *trans*-3,4,5-trimethoxyphenyl moiety at the C2 position of a benzothiophene ring afforded compound **14**, which exhibited potent growth inhibition against 95% of all the cancer cell lines in the panel with GI_{50} values ranging from 0.036 to 0.985 µM and an average GI_{50} value of 0.59 µM. This compound exhibited growth inhibition against MDA-MB-435 melanoma, NCI/ADR-RES ovarian, and K-562 leukemia cancer cell lines with GI_{50} values of 0.036, 0.070 and 0.088 µM, respectively (Table 1).

Molecular modeling studies were performed for **DMU-212** (**II**) and the four heterocyclic analogs **8**, **11**, **13** and **14** utilizing SYBYL-X 2.1 software. Binding interactions of these analogs were studied by docking them at the colchicine-binding site on tubulin. 3-D coordinates for the tubulin-colchicine complex were obtained from the RSCB protein data bank (pdb id: 4O2B). For preparation of tubulin to perform the docking calculations, the geometry of the protein molecule was optimized using energy minimization techniques after the addition of hydrogen atoms. Since no structured water molecule was present in the binding pocket, all the water molecules in the protein were deleted during the preparation of protein structure for docking calculations. Amino acid side chain bumps were fixed and terminal amino acids were charged to mimic the biological environment. Hydrogen atoms were added to the structure. The Kollman force field was applied and the protein was minimized using the Powell method and Pullman charges. Structures of compounds were initially generated in 2-D format in Chem Draw.

For generating energy-minimized structures, the 2-D structures of the molecules were converted to 3-D using Chemdraw3D and the structures saved in Mol2 format. All the structures were imported to Sybyl in the Mol2 format. In SYBYL, the TRIPOS force field was applied and 3-D structure coordinates went through a series of minimization processes. Firstly, all the structures were minimized using the BFGS method. After that, MOPAC charges were calculated for each molecule followed by steepest decadence minimization step. Each molecule was then checked for charges, bond angle, torsion angles and geometry. All the molecules were saved in one directory and prepared for docking via the ligand preparation tool. For the docking analysis using the Surflex program, a protomol was generated at the colchicine-binding site in tubulin. This protomol is the representation of the binding site that simulates the binding environment experienced by the ligand. The docking analysis was performed using the Suflex Dock-Gemox module and lists the C-scores (consolidated scores) for each molecule (Table. 2). C-score is a measure of the goodness of fit. The C-score function combines the binding score obtained from five different scoring algorithms, namely: total score, G-score, PMF score, D-score and Chem Score. In these docking calculations, the flexibilities of the ligands were accounted for by considering 20 different conformational states and scoring each of them. Docking analysis at the cochicine-binding site demonstrated the binding mode of the resveratrol analogs. Among the tested **DMU-212** analogs, compounds **13** and **14** exhibited the strongest binding interaction at the colchicine-binding site on tubulin compared to the other two analogs. All five compounds exhibited hydrogen bonding interactions with ASN 258. Interestingly, compound **8** also exhibited hydrogen bonding with THR 353, and compound **14** exhibited two hydrogen bonding interactions with ASN 258 (Fig. 2).

Compounds **8** and **13** also exhibited hydrophobic interactions with Gln 247, and compound **14** exhibited interactions with Met 325, Gln 247, Leu 248. **DMU-212** had interactions with Lys 352, but no strong hydrophobic interactions were identified for compound **11**.

Table 2. Docking results for **DMU-212**, **8**, **11**, **13**, and **14** at the colchicine-binding site on tubulin

Comp.	No. of H-bonds	Maximum C-score	No. of positions with maximum C-score/20
DMU-212	1	4	1
8	2	4	2
11	1	4	2
13	1	5	1
14	2	5	2

In summary, compounds **DMU-212**, **8**, **11**, **13** and **14** all exhibited similar binding interactions with tubulin at the colchicine-binding site, with compounds **13** and **14** exhibiting the most favorable interactions.

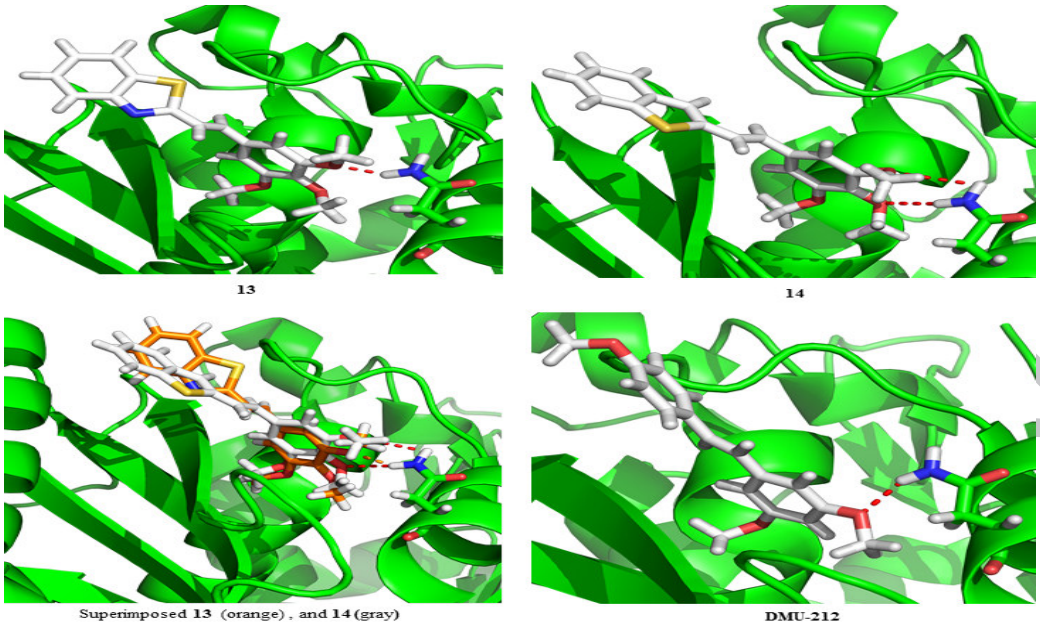


Fig. 2 Molecular docking studies of compounds **13, 14** and **DMU-212** at the colchicine binding site on tubulin

Conclusion

Novel heteroaromatic **DMU-212** analogs (**8-15**) have been synthesized and evaluated for their anti-cancer activity against a panel of 60 human cancer cell lines. Compounds containing a *trans*-3,4,5-trimethoxystyryl moiety (**8**, **11**, **13**, and **14**) showed potent growth inhibition with GI_{50} values generally <1 μM against most of the cancer cell lines in the panel. The removal of just one aromatic methoxy group from these compounds to afford either *trans*-3,4-dimethoxystyryl (**9**) or *trans*-3,5-dimethoxy styryl (**10**, **12**, **15**) analogs results in a decrease in anti-cancer activity, which indicates that the 3,4,5-trimethoxystyryl moiety is an essential structural element for the observed potent anti-cancer activity of these **DMU-212** analogs. Compounds **8**, **11**, **13** and **14** all exhibited significant growth inhibition against most of the human cancer cells in the 60-cell panel, and the results from the molecular modeling studies are consistent with the *in vitro* anti-cancer activities of these molecules being mediated via their binding to the colchicine binding site on tubulin. The above four molecules were considered as important lead compounds for further development as anti-cancer drugs.

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24. ***General procedure for the synthesis of heteroaromatic analogs of DMU-212 (8-15):*** A mixture of carbaldehyde (0.001 mol), alkoxy triphenyl phosphonium bromide (0.001 mol), and sodium methoxide (2.5 gm) in methanol (50 ml) was stirred at room temperature for 3-4 h. Crushed ice was then added to afford a solid product. The crude solid was isolated by filtration and washed several times with cold methanol (3 x 5 ml). The resulting pale yellow solid was then recrystallized from methanol to afford the desired (*E*)-2-(3,4,5-trimethoxystyryl)heteroaromatic product. ***(E)-2-(3,4,5-trimethoxy styryl)-1H-indole (8):*** mp: 228-230^{0}C, ^{1}H NMR ($CDCl_3$); δ 3.87 (s, 3H), 3.92 (s, 6H), 6.61 (s, 1H), 6.72 (s, 2H), 6.82-6.86 (d, *J*=16.4 Hz, 1H), 7.01-7.05 (d, *J*=16 HZ, 1H), 7.079-7.11 (t, *J*=7.2 Hz, 14.8Hz, 1H), 7.17-7.21 (t, *J*=7.2 Hz,

15.2 Hz 1H), 7.33-7.35 (d, *J*=7.6 Hz, 1H), 7.57-7.59 (d, *J*=7.6 Hz, 1H), 8.27 (brs, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 56.22, 60.89, 103.30, 103.69, 110.46, 118.53, 120.23, 120.50, 120.70, 122.85, 127.04, 127.08, 128.96, 132.57, 136.18, 136.91, 138.05, 153.46. HRMS calcd for $C_{19}H_{20}NO_3$, (MH^+): 310.1438. Found 310.1435. ***(E)-2-(3,4-dimethoxystyryl)-1H-indole (9)****:* mp:203-205 ^{0}C; ^{1}H NMR ($CDCl_3$); δ 3.91 (s, 3H), 3.95 (s, 3H), 6.58 (s, 1H), 6.83-6.86 (d, *J*=10.4 Hz, 1H), 6.88 (s, 1H), 6.97 (s, 1H), 7.01- 7.11 (m, 3H), 7.16-7.20 (t, *J*=7.2 and 15.2 Hz, 1H), 7.32-7.34 (d, *J*=8Hz, 1H), 7.56-7.58 (d, *J*=8Hz, 1H), 8.22 (brs, 1H, NH);^{13}C NMR ($CDCl_3$): δ 55.87, 55.95, 103.23, 108.40, 110.48, 111.27, 117.18, 119.82, 120.13, 120.48, 122.65, 127.00, 129.04, 129.92, 136.53, 136.84, 149.06, 149.21 *ppm.* HRMS calcd for $C_{18}H_{18}NO_2$, (MH^+): 280.1332. Found 280.1327. ***(E)-2-(3,5-dimethoxystyryl)-1H-indole (10)****:* mp:134-136 ^{0}C, ^{1}H NMR ($CDCl_3$): δ 3.84 (s, 6H), 6.42 (s, 1H), 6.62 (s, 1H), 6.66 (s, 2H), 6.80-6.84 (d, *J*=16.4 Hz, 1H), 7.07-7.13 (m, 2H), 7.18-7.22 (t, *J*=7.2, 15.2Hz, 1H), 7.33-7.35 (d, *J*=8Hz, 1H), 7.58-7.60 (d, *J*=7.6Hz, 1H), 8.25 (brs, 1H, NH), ^{13}C NMR ($CDCl_3$): δ 55.38, 100.01, 104.10, 104.42, 110.63, 119.53, 120.20, 120.66, 122.94, 127.05, 128.94, 136.10, 136.98, 138.84, 161.03 *ppm.* HRMS calcd for $C_{18}H_{18}NO_2$, (MH^+): 280.1332. Found 280.1341. ***(E)-2-(3,4,5-trimethoxystyryl)benzo[b]furan (11):*** mp:124-126 ^{0}C, ^{1}H NMR ($CDCl_3$): δ 3.87 (s, 3H), 3.91 (s, 6H), 6.66 (s, 1H), 6.75 (s, 2H), 6.88-6.92 (d, *J*=16Hz, 1H), 7.20-7.26 (m, 3H), 7.44-7.46 (d, *J*=8.4 Hz, 1H), 7.51-7.53 (d, *J*=7.6Hz, 1H) *ppm*; ^{13}C NMR ($CDCl_3$): δ 56.11, 60.98, 103.72, 105.04, 110.82, 115.88, 120.79, 122.90, 124.60, 129.11, 130.21, 132.25, 138.36, 153.44, 154.83, 154.94 *ppm.* HRMS calcd for $C_{19}H_{19}O_4$, (MH^+): 311.1278. Found 311.1273. ***(E)-2-(3,5-dimethoxystyryl) benzo[b]furan (12):*** mp: 29-31^{0}C, ^{1}H NMR ($CDCl_3$): δ 3.83 (s, 6H), 6.41-6.42 (d, *J*=1.6Hz, 1H), 6.68 (s, 3H), 6.95-6.99 (d, *J*=16.4Hz, 1H), 7.20-7.26 (m, 3H), 7.45-7.47 (d, *J*=8.0 Hz, 1H) 7.51-7.53 (d, *J*= 7.2Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 55.37, 100.56, 104.71, 105.43, 110.88, 116.92, 120.84, 122.89, 124.68, 129.07, 130.23, 138.53, 154.85, 154.90, 161.01 *ppm.* HRMS calcd for $C_{18}H_{17}O_3$, (MH^+): 281.1172. Found 281.1170. ***(E)-2-(3,4,5-trimethoxy styryl)benzo[d]thiazole (13):*** mp: 125-127 ^{0}C, ^{1}H NMR ($CDCl_3$): δ 3.91 (s, 3H), 3.93 (s, 6H), 6.83 (s, 2H), 7.33-7.48 (m, 4H), 7.87 (s, 1H), 8.0 (s, 1H) *ppm;* ^{13}C NMR ($CDCl_3$): δ 56.12, 60.96, 104.47, 121.48, 122.89, 125.32, 126.33, 130.95, 134.26, 137.47, 153.5, 153.8, 166.78 *ppm.* HRMS calcd for $C_{18}H_{18}NO_3S$, (MH^+): 328.1002. Found 328.1007. ***(E)-2-(3,4,5-trimethoxy styryl)benzo[b]thiophene (14)****:* mp:154-156 ^{0}C, ^{1}H NMR ($CDCl_3$): δ 3.87 (s 3H), 3.92 (s, 6H), 6.73 (s, 2H), 6.89-6.93 (d, *J*=16 Hz, 1H), 7.20 (s, 1H), 7.30 (m, 2H), 7.68-7.77 (dd, *J1*=6.8 Hz, *J2*=31.2 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 56.14, 60.96, 103.67, 110.0, 121.79, 122.18, 123.11, 123.35, 124.51, 124.73, 130.78, 132.29, 138.81, 140.18, 142.74, 153.43 *ppm.* HRMS calcd for $C_{19}H_{19}O_3S$, (MH^+): 327.1049. Found 327.1047. ***(E)-2-(3,5-dimethoxystyryl) benzo[b]thiophene (15):*** mp:103-105 ^{0}C, ^{1}H NMR ($CDCl_3$): δ 3.83 (s, 6H), 6.41 (s, 1H), 6.66 (s, 2H), 6.90-6.94 (d, *J*= 15.6 Hz, 1H), 7.25-7.30 (m, 4H), 7.68-7.78 (dd, *J*=6.4 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 55.73, 100.80, 104.93, 122.56, 123.16, 123.78, 123.85, 124.85, 125.14, 131.15, 138.93, 139.28, 140.50, 143.01, 161.35 *ppm.* HRMS calcd for $C_{18}H_{17}O_2S$, (MH^+): 297.0944. Found 297.0947.

Graphical Abstract

Heteroaromatic analogs of the resveratrol analog DMU-212 as potent anti-cancer agents

Narsimha Reddy Penthala, Shraddha Thakkar and Peter A. Crooks

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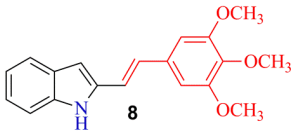
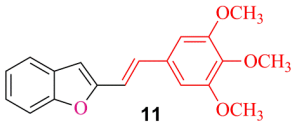


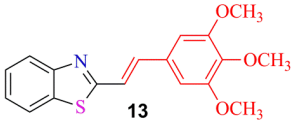
8

MDA-MB-435 melanoma, GI_{50} = 0.15 µM;
UO-31 renal cancer, GI_{50} = 0.17 µM;



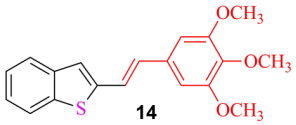
11

MDA-MB-435 melanoma, GI_{50} = 0.078 µM
SR Leukemia, GI_{50} = 0.094 µM



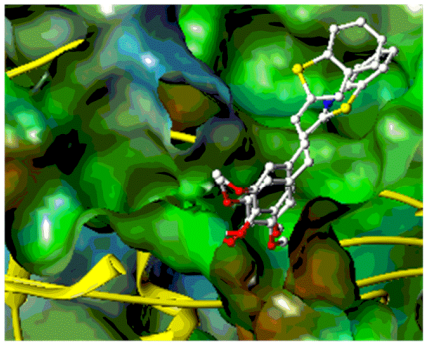
13

MDA-MB-435 melanoma, GI_{50} =0.024 µM;
SR Leukemia, GI_{50} = 0.036 µM;



14

MDA-MB-435 melanoma, GI_{50} = 0.036 µM
NCI/ADR-RES ovarian, GI_{50} = 0.070 µM



Suprimposed **13** and **14**