Synthesis of Resveratrol Acrylamides Derivatives and Biological Evaluation of their Anti-Proliferative Effect on Cancer Cell Lines

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Abstract: A new series of resveratrol acrylamides amine derivatives was designed, synthesized, and evaluated for their anti-proliferative activity against three cancer cell lines including human chronic myelocytic leukemia cell K562, human hepatoma HuH-7 and human lung carcinoma A549. Most of the compounds showed superior activity against three cell lines when compared to parent resveratrol. **C13** had the best anti-tumor activity against the HuH-7 cell line and its IC_{50} was 4.5 μmol/L; **C16** had the best anti-tumor activity against the K562 cell line and its IC_{50} was 2.9 μmol/L; **C18** had the best anti-tumor activity against the A549 cell line and its IC_{50} was 3.8 μmol/L. It could be seen that the activity of the aromatic amine derivatives was better than the fatty amine derivatives by analyzing the experimental data.

Keyword: Resveratrol, Acrylamides amine, Anti-proliferative effect, Synthesis.

1. INTRODUCTION

Resveratrol, a naturally occurring phytoalexin (3,5,4'-trans-trihydr-oxystilbene, Fig. **1**), present in medicinal plants, grape skin, peanuts, and red wine [1], has been extensively investigated as a cardioprotective, anti-inflammatory, and antiaging agent [2]. Recent studies have shown that resveratrol has potent anticancer effects. This was evidenced by its *in vitro* and *in vivo* inhibitory effects on the growth of a number of tumor cell lines including lymphoma, myeloma, melanoma, breast, pancreatic, colorectal, hepatocellular, and prostate carcinoma [3]. Resveratrol was also found to sensitize resistant tumor cell lines to a variety of chemotherapeutic agents, such as paclitaxel, thalidomide, and bortezomib [5, 6].

In view of the great potential of resveratrol as a potent chemotherapeutic agent against a wide variety of cancers, the scaffold of resveratrol has been the subject of synthetic manipulations with improved anticancer activity [7, 8]. Since resveratrol has three hydroxyl groups which are very unstable and easily oxidized, the protection of the hydroxyl groups is the primary consideration in the design in order to improve the stability of the derivatives [9, 10]. Compounds having a substituent at C2 of resveratrol have been reported as proapoptotic anticancer agents. These compounds have been described as inhibitors of tubulin, which has been recognized as an established target of many anticancer drugs [11]. The structure of acrylamides amine side chain attached to the aromatic ring has been proven as core pharmacophore for inhibitors of the Dengue and West Nile virus serine proteases (NS2B-NS3). It turned out that the electron density of the aryl moiety and the central double bond have a crucial influence on the activity of the compounds, whereas the influence of substituents of the amide residue is less relevant [12, 13].

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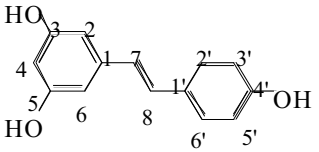

Fig. (1). Resveratrol.

Based on the above considerations, we report the synthesis and anti-tumor evaluation of acrylamides amine derivatives that are resveratrol analogues in the present study.

2. RESULTS AND DISCUSSION

2.1. Synthesis

The synthesis of compounds **C1-C20** is outlined in Scheme **1**.The synthesis of these compounds started from resveratrol. The key intermediate, (*E*)-2, 4-dimethoxy-6-(4-methoxystyryl)benzaldehyde (**B**), was prepared in two steps as previously reported with some modification [14, 15]. First, (*E*)-2, 4-dihydroxy-6-(4-hydroxystyryl)benzaldehyde (**A**) was prepared by the Vilsmeier reaction in CH_3CN from resveratrol in a high yield (98%). The desired intermediate (B) was obtained by reaction of (A) with CH_3I in acetone/K_2CO_3 under refluxing. Then introduction of the aldehyde was to C2 of the resveratrol molecule. Introduced different structure of aryl cyano acrylamide in the molecule using Knoevenagel condensation reaction was to synthesize **C1-C20**. All the synthetic compounds were characterized by ^1H NMR, which was in full accordance with their depicted structures.

2.2. Biological Activity

The anti-proliferative activity of **C1–C20** against HuH-7, K562 and A549 cell lines was evaluated by using the MTT assay. The results were summarized in Table **1**. All the compounds exhibited fairly good anti-proliferative activity with the IC_{50} values within 2.9-12.6 μmol/L, which were much

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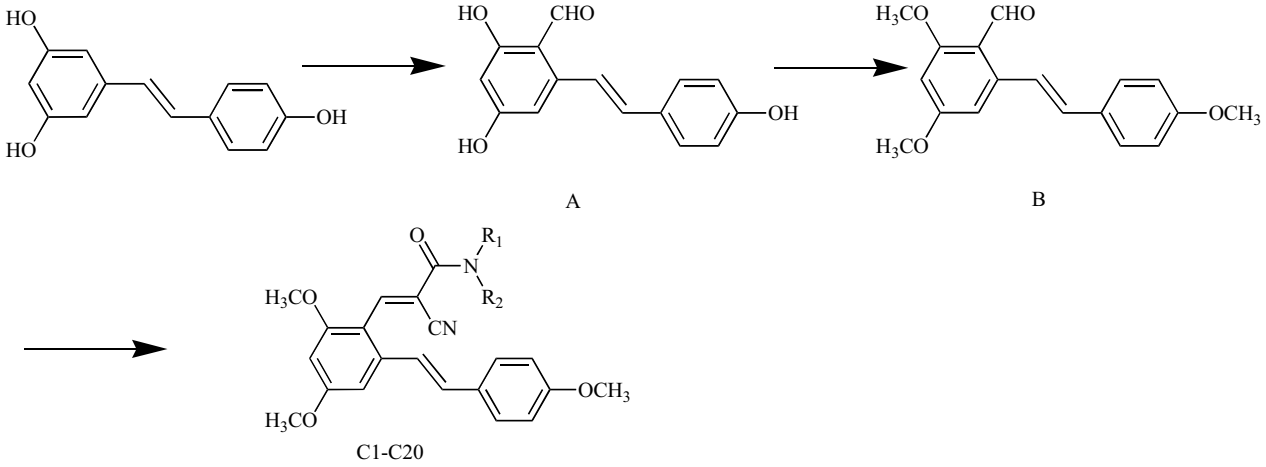
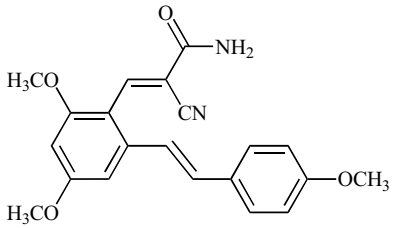
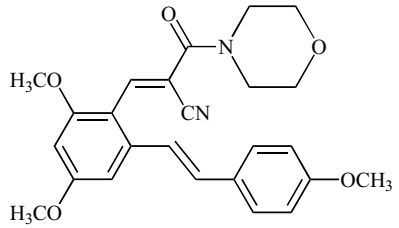
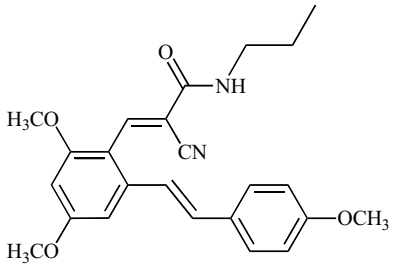
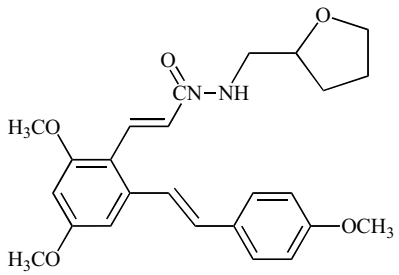
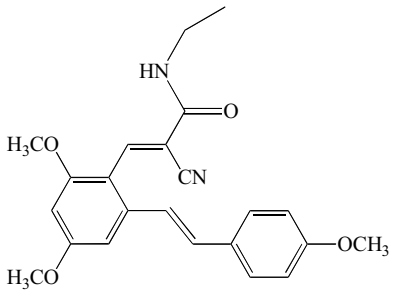
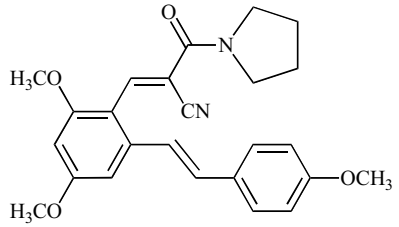
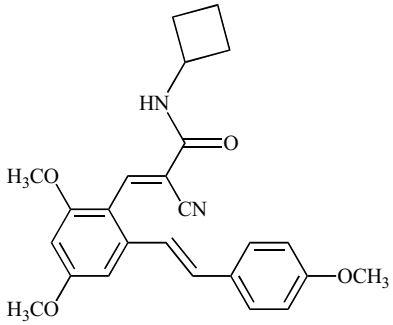
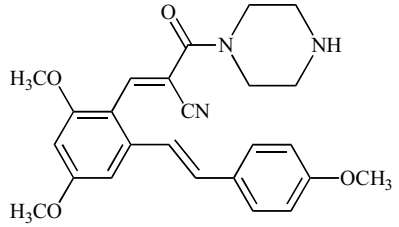
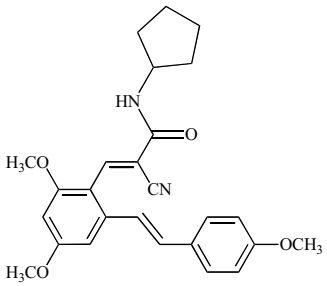
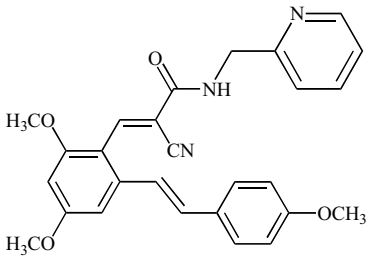
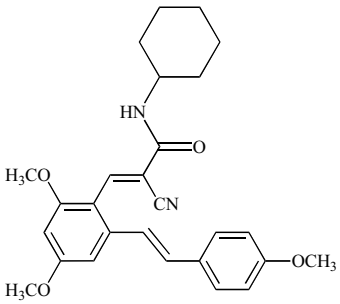
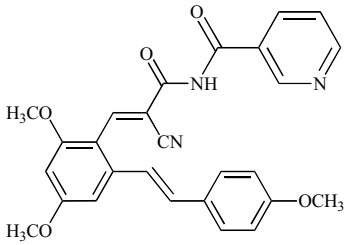
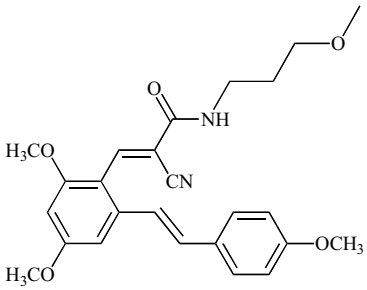
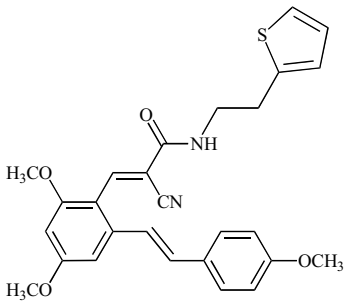
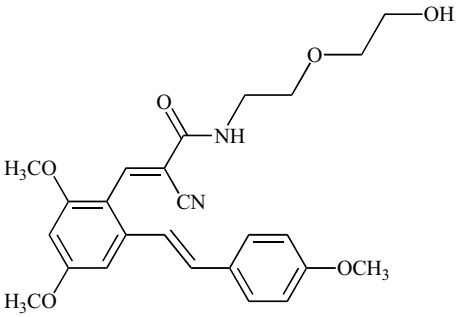
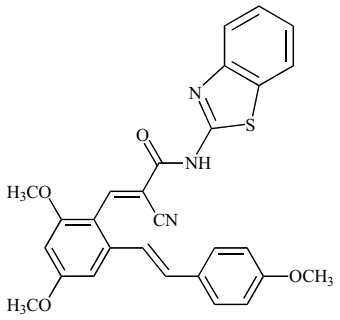
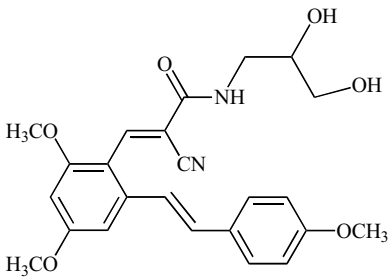
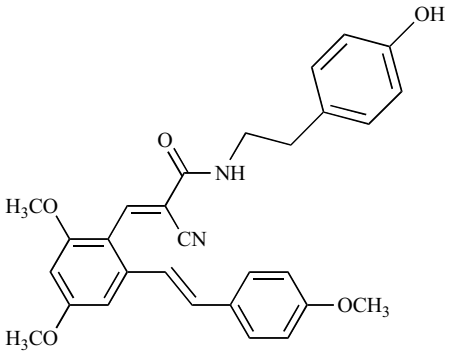


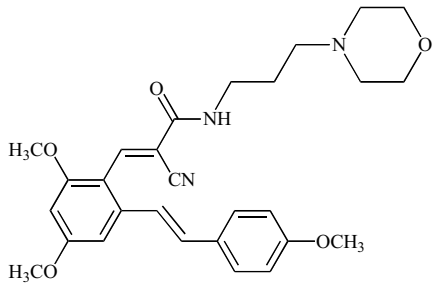
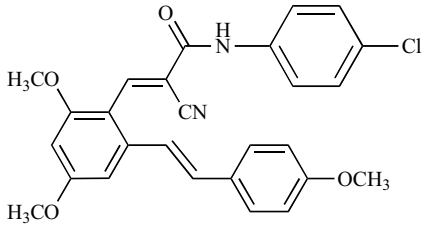
A B C1-C20

Compounds	R1	R2	Compounds	R1	R2
C1	H		C11		
C2	H		C12	H	
C3	H		C13		
C4	H		C14	H	

Scheme 1. Contd…

Compounds	R1	R2	Compounds	R1	R2
C5	H		C15	H	
C6	H		C16	H	
C7	H		C17	H	
C8	H		C18	H	
C9	H		C19	H	

Scheme 1. Contd…

Compounds	R1	R2	Compounds	R1	R2
C10	H		C20	H	

Scheme (1). Synthesis of resveratrol acrylamides amine derivatives **C1-C20**.

Table 1. Antiproliferative Activity (IC_{50}) Against HuH-7, K562 and A549 Cell Lines of Compounds C1–C20.

Compounds	IC_{50} ± SD (μmol/L)		
	HuH-7	K562	A549
C1	9.0±1.8	8.6±1.2	6.8±3.6
C2	12.3±2.4	6.8±2.5	6.7±3.8
C3	12.6±3.4	7.4±1.9	7.1±1.7
C4	7.6±1.1	7.2±3.1	6.9±2.8
C5	9.3±2.8	3.5±2.6	4.2±3.4
C6	6.2±2.1	4.4±2.4	3.9±2.7
C7	6.8±2.4	5.4±1.3	6.4±1.9
C8	9.8±2.5	5.7±2.8	6.8±3.4
C9	6.1±1.3	5.3±2.4	7.2±2.4
C10	8.8±1.8	4.9±2.0	4.1±1.7
C11	9.5±1.6	3.5±1.3	4.8±1.8
C12	9.8±2.1	3.5±2.5	4.8±2.6
C13	4.5±1.6	7.1±3.4	6.5±2.5
C14	6.1±2.6	5.1±2.4	6.7±2.4
C15	6.4±2.5	5.9±1.8	5.9±2.1
C16	5.8±1.7	2.9±2.6	4.9±2.0
C17	5.9±1.5	3.9±1.6	4.5±2.4
C18	5.4±1.4	4.2±1.9	3.8±1.5
C19	4.9±2.6	4.4±2.5	4.6±2.1
C20	6.4±3.7	7.7±3.8	4.3±1.6
Resveratrol	27.1±1.5	24.1±1.6	29.4±2.5

better than resveratrol. Among them, **C13** has the best anti-proliferative activity against the HuH-7 cell line and its IC_{50} is 4.5 μmol/L; **C16** has the best anti-proliferative activity against the K562 cell line and its IC_{50} is 2.9 μmol/L; **C18** has the best anti-proliferative activity against the A549 cell line and its IC_{50} is 3.8 μmol/L.

The anti-proliferative activity of the twenty compounds cells showed with regularity. The (*E*)-2,4-dimethoxy-6-(4-methoxystyryl)benzaldehyde was functionalized with three different groups, i.e. aliphatic amines, heterocyclic amines and aromatic amines.

The obtained results support the findings that the compounds have the anti-proliferative activity in the order: aliphatic amines < heterocyclic amines < aromatic amines. The anti-proliferative effect of aliphatic series derivatives also increased with the increase of carbon atoms of fat ring enhancement. The compounds with the oxygen atom in the aliphatic chain amines have better anti-proliferative activity than those with no oxygen atom.

3. EXPERIMENTAL

3.1. Materials and Methods

All the chemicals used were commercial products employed without further purification. The ^{1}H NMR spectra were recorded on a Bruker DRX 600 model spectrometer in $CDCl_3$, DMSO-d_6 solutions at room temperature with TMS as an internal standard. Chemical shifts (d) for ^{1}H NMR spectra were reported in parts per million to residual solvent protons. Chemical shifts given in parts per million (d, ppm) and the residuals of non-deuterated solvents were use as internal standard (^{1}H NMR: $CDCl_3$: d = 7.25 ppm, DMSO-d_6: d = 2.49 ppm). Coupling constants (*J*) are given in hertz (Hz). Multiplicity is reported as s (singlet), d (doublet), t (triplet), quart (quartet), sept (septet), dd (doublet-doublet), ddd (doublet-doublet-doublet), dt (doublet-triplet), td (tripletdoublet), m (multiplet) and br (broad), respectively. Melting points were measured on a Boetius micro melting point apparatus. Microwave synthesis was performed using a Monowave 300 synthesis reactor from Anton Paar.

3.2. Biological Assay

The test compounds **C1-C20**, in measured quantities, were dissolved in dimethyl sulphoxide (DMSO) to get the final concentrations 10 μg/L, 5 μg/L, 2.5 μg/L, and 1.25 μg/L. The synthesized compounds **C1-C20** were evaluated for anti-tumor activities by MTT. A549, HuH-7, K562 cultures of exponential phase from culture fluid were diluted with sterile water and mixed thoroughly to prepare a clear homogeneous suspension. These suspensions were inoculated in 96-well plates and placed in incubator for 48 h. The 96-well plates added only DMSO (as a negative control) and 20μL different concentrations of test compounds **C1-C20** as well as standard compounds (resveratrol as positive control) were incubated at 37 °C for 72 h. After the incubation period, the plates were added 0.5 g /L MTT serum-free medium, and then placed in incubator for 8 h. After the incubation period, the plates were examined to get optical density (OD) with enzymes labeling instrument at 492 nm.

Synthesis method for (E)-2, 4-dihydroxy-6-(4-hydroxystyryl) benzaldehyde (A)

To a solution of resveratrol (2.28 g, 0.01 mol) in 50 mL of CH_3CN and DMF (0.73 g, 0.01 mol), $POCl_3$ (2.30 g, 0.015 mol) was added dropwise while cooling with an ice/water bath for 0.5 h. The reaction mixture was stirred for another 2 h at room temperature. Then, the solution was added to cold water (300 mL). The yellow solution was stirred under 50 °C for 3 h, and extracted with EtOAc (100 mL × 3). The combined organic layers were washed with water, dried over anhydrous sodium sulfate, filtered and evaporated. Purification by silica gel afforded (A) as yellow powder in 96% yield. Mp: 210–212 °C. 1H NMR (DMSO-d_6): 6.21 (s, 1H),6.62 (s, 1H), 6.78 (d, 2H, *J* = 8.4 Hz), 7.02 (d, 1H, *J* = 16.0 Hz), 7.49(d, 2H, *J* = 8.4 Hz), 7.70 (d, 1H, *J* = 16.2 Hz), 9.71 (s, 1H), 10.27(s, 1H), 10.76 (s, 1H), 12.12 (s, 1H). MS (ESI): 257.3 ($C_{15}H_{12}O_4$, $[M+H]^+$). Anal. Calcd for $C_{15}H_{12}O_4$: C, 51.05; H, 3.86. Found: C, 50.17; H, 3.86%.

Synthesis Method for (E)-2, 4-dimethoxy-6-(4-methoxystyryl)benzaldehyde (B)

To a solution of A (1.28 g, 0.005 mol) and anhydrous K_2CO_3 (2.07 g, 0.015 mol) in 10 mL of CH_3COCH_3, CH_3I (2.84 g, 0.02 mol) was added drop wise. The reaction mixture was refluxed for 24 h. After cooling to room temperature, the reaction mixture was filtrated and the filtrate was dried and evaporated. Purification by silica gel afforded (B) in 84% yield. Mp: 108–109 °C. ^{1}H NMR (DMSO-d_6):3.78 (s, 3H), 3.90 (s, 3H), 3.92 (s, 3H), 6.63 (s, 1H), 6.91 (s, 1H),6.97 (d, 2H, *J* = 7.9 Hz), 7.21 (d, 1H, *J* = 16.2 Hz), 7.50 (d, 2H, *J* = 7.9 Hz), 7.95 (d, 1H, *J* = 16.2 Hz), 10.41 (s, 1H). MS (ESI): 299.3($C_{18}H_{18}O_4$, $[M+H]^+$). Anal. Calcd for $C_{18}H_{18}O_4$: C, 72.47; H, 6.08. Found: C, 72.59; H, 6.07%.

General Method of Synthesis of Compounds C1–C9

A solution of 2-cyanoacetamide (1 equiv), amine (1.0–1.5 equiv) was stirred at room temperature for 4 h. The precipitate was collected by filtration and washed with water/methanol (1:1). Then was dissolve in methanol, addition compound B (0.5 equiv) and N-methylpiperazine (0.05–1.05 equiv), then stirred at reflux overnight. Then, the reaction is cooled to ambient temperature and extracted with dichloromethane (3 × 20 mL). The organic phase is dried with anhydrous sodium sulfate. After removal of the solvent on vacuum, the crude product is purified with silica gel chromatography (75% ethyl acetate in hexanes) to give the title compound.

C1: (E)-2-cyano-3-(2,4-dimethoxy-6-(4-methoxystyryl)phenyl)acrylamide

Yellow solid (75% yield). Mp 153-155 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.50 (s, 1H), 7.43 (d, 2H, J = 8.6 Hz), 7.25 (s, 1H), 6.98 (s, 1H), 6.94 (d, 1H, J = 9.1 Hz), 6.88 (d, 2H, J = 8.6 Hz), 6.73 (d, 1H, J = 1.8 Hz), 6.41 (d, 1H, J = 1.7 Hz), 3.89 (s, 6H), 3.82 (d, 3H, J = 3.2 Hz). MS (ESI): 365.4($C_{21}H_{20}N_2O_4$, $[M+H]^+$). Anal. Calcd for $C_{21}H_{20}N_2O_4$: C, 69.22; H, 5.53; N, 7.69.Found: C, 69.33; H, 5.53; N, 7.69%.

C2: (E)-2-cyano-3-(2,4-dimethoxy-6-(4-methoxystyryl)phenyl)-N-propylacrylamide

Yellow solid (70% yield). Mp 94-96 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.49 (s, 1H), 7.43 (d, 2H, *J* = 8.5 Hz), 7.24 (s, 1H), 6.97 (d, 2H, *J* = 6.7 Hz), 6.87 (d, 2H, *J* = 8.5 Hz), 6.74 (s, 1H), 3.88 (d, 6H, *J* = 5.5 Hz), 3.81 (s, 3H), 3.37 (dd, 2H, *J* = 13.4, 6.6 Hz), 1.64 – 1.61 (m, 2H), 0.97 (t, 3H, *J* = 7.4 Hz). MS (ESI): 407.5($C_{24}H_{26}N_2O_4$, $[M+H]^+$). Anal. Calcd for $C_{24}H_{26}N_2O_4$: C, 70.92; H, 6.45; N, 6.89.Found: C, 70.87; H, 6.45; N, 6.89%.

C3: (E)-2-cyano-N-cyclopropyl-3-(2,4-dimethoxy-6-(4-methoxystyryl)phenyl)acrylamide

Yellow solid (60% yield). Mp 70-72 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.48 (d, 1H, *J* = 4.0 Hz), 8.15 (s, 1H), 7.54 (d, 2H, *J* = 8.7 Hz), 7.23 (d, 1H, *J* = 16.1 Hz), 6.97 (dd,

4H, *J* = 5.6, 3.0 Hz), 6.61 (d, 1H, *J* = 2.0 Hz), 3.89 (s, 3H), 3.84 (s, 3H), 3.78 (s, 3H), 2.80 (ddd, 1H, *J* = 11.2, 7.6, 3.9 Hz), 0.73 – 0.67 (m, 2H), 0.64 – 0.59 (m, 2H). MS (ESI): 405.5($C_{24}H_{24}N_2O_4$, $[M+H]^+$). Anal. Calcd for $C_{24}H_{24}N_2O_4$: C, 71.27; H, 5.98; N, 6.93.Found: C, 71.33; H, 5.98; N, 6.93%.

C4: (E)-2-cyano-N-cyclobutyl-3-(2,4-dimethoxy-6-(4-methoxystyryl)phenyl)acrylamide

Yellow solid (59% yield). Mp 104-106 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.85 (d, 1H, *J* = 7.2 Hz), 7.70 (s, 1H), 7.08 (d, 2H, *J* = 8.7 Hz), 6.77 (d, 1H, *J* = 16.1 Hz), 6.57 – 6.51 (m, 4H), 6.17 (d, 1H, *J* = 1.9 Hz), 3.69 (dd, 1H, *J* = 14.1, 7.0 Hz), 3.45 (s, 3H), 3.40 (s, 3H), 3.33 (s, 3H), 1.45 (t, 2H, *J* = 8.5 Hz), 1.23 (d, 2H, *J* = 8.7 Hz), 1.08 (s, 2H). MS (ESI): 419.5($C_{25}H_{26}N_2O_4$, $[M+H]^+$). Anal. Calcd for $C_{25}H_{26}N_2O_4$: C, 71.75; H, 6.26; N, 6.69.Found: C, 71.78; H, 6.27; N, 6.68%.

C5: (E)-2-cyano-N-cyclopentyl-3-(2,4-dimethoxy-6-(4-methoxystyryl)phenyl)acrylamide

Yellow solid (55% yield). Mp 84-85 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.16 (d, 1H, *J* = 7.4 Hz), 7.72 (s, 1H), 7.09 (d, 2H, *J* = 8.7 Hz), 6.78 (d, 1H, *J* = 16.1 Hz), 6.55 – 6.49 (m, 4H), 6.17 (d, 1H, *J* = 2.0 Hz), 3.88 (dd, 1H, *J* = 16.2, 8.1 Hz), 3.45 (s, 3H), 3.40 (s, 3H), 3.33 (s, 3H), 1.78 – 1.71 (m, 2H), 1.69 – 1.60 (m, 2H), 1.22 (ddd, 2H, *J* = 14.5, 8.5, 3.2 Hz), 0.44 – 0.35 (m, 2H). MS (ESI): 433.5($C_{26}H_{28}N_2O_4$, $[M+H]^+$). Anal. Calcd for $C_{26}H_{28}N_2O_4$: C, 72.20; H, 6.53; N, 6.48.Found: C, 72.28; H, 6.53; N, 6.48%.

C6: (E)-2-cyano-N-cyclohexyl-3-(2,4-dimethoxy-6-(4-methoxystyryl)phenyl)acrylamide

Yellow solid (61% yield). Mp 70-72 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.19 – 8.14 (m, 2H), 7.52 (d, 2H, *J* = 8.7 Hz), 7.21 (d, 1H, *J* = 16.1 Hz), 7.00 – 6.88 (m, 4H), 6.61 (d, 1H, *J* = 2.1 Hz), 3.89 (s, 3H), 3.84 (s, 3H), 3.78 (s, 3H), 3.73 – 3.67 (m, 1H), 1.81 (d, 2H, *J* = 9.6 Hz), 1.72 (d, 2H, *J* = 12.5 Hz), 1.58 (t, 2H, *J* = 12.6 Hz), 1.14 (dd, 2H, *J* = 20.4, 8.7 Hz). MS (ESI): 467.5($C_{27}H_{30}N_2O_4$, $[M+H]^+$). Anal. Calcd for $C_{27}H_{30}N_2O_4$: C, 72.62; H, 6.77; N, 6.27.Found: C, 72.69; H, 6.77; N, 6.28%.

C7: (E)-2-cyano-3-(2,4-dimethoxy-6-(4-methoxystyryl)phenyl)-N-(3-methoxypropyl)acrylamide

Yellow solid (77% yield). Mp 48-50 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.46 (s, 1H), 7.43 (d, 2H, *J* = 8.7 Hz), 6.96 (dd, 2H, *J* = 14.3, 6.1 Hz), 6.91 – 6.88 (m, 1H), 6.88 – 6.86 (m, 2H), 6.74 (t, 1H, *J* = 2.8 Hz), 6.40 (d, 1H, *J* = 2.1 Hz), 3.88 (s, 3H), 3.87 (d, 3H, *J* = 2.1 Hz), 3.81 (s, 3H), 3.53 (dd, 4H, *J* = 10.8, 5.3 Hz), 3.27 (t, 1H, *J* = 5.7 Hz), 3.21 (dt, 1H, *J* = 11.7, 5.7 Hz), 1.88 – 1.84 (m, 2H), 1.57 (dt, 1H, *J* = 12.2, 5.9 Hz). MS (ESI): 437.5($C_{25}H_{28}N_2O_5$, $[M+H]^+$). Anal. Calcd for $C_{25}H_{28}N_2O_5$: C, 68.79; H, 6.47; N, 6.42. Found: C, 68.84; H, 6.47; N, 6.42%.

C8: (E)-2-cyano-3-(2,4-dimethoxy-6-(4-methoxystyryl)phenyl)-N-(2-(2-hydroxyethoxy)ethyl)acrylamide

Yellow solid (77% yield). Mp 55-56 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.49 (s, 1H), 7.43 (d, 2H, *J* = 8.7 Hz), 7.25 (s, 1H), 6.97 (d, 2H, *J* = 12.3 Hz), 6.88 (d, 2H, *J* = 8.7 Hz), 6.74 (d, 1H, *J* = 2.2 Hz), 6.41 (d, 1H, *J* = 2.2 Hz), 3.88 (d, 6H, *J* = 4.4 Hz), 3.81 (s, 3H), 3.76 – 3.74 (m, 2H), 3.67 – 3.65 (m, 2H), 3.61 (dd, 4H, *J* = 10.5, 5.9 Hz). MS (ESI): 453.5($C_{25}H_{28}N_2O_6$, $[M+H]^+$). Anal. Calcd for $C_{25}H_{28}N_2O_6$: C, 66.36; H, 6.24; N, 6.19. Found: C, 66.41; H, 6.24; N, 6.19%.

C9: (E)-2-cyano-N-(2,3-dihydroxypropyl)-3-(2,4-dimethoxy-6-(4-methoxystyryl)phenyl)acrylamide

Yellow solid (49% yield). Mp 165-166 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.24 – 8.18 (m, 2H), 7.52 (d, 2H, *J* = 8.7 Hz), 7.20 (d, 1H, *J* = 16.1 Hz), 7.00 (d, 1H, *J* = 16.1 Hz), 6.95 – 6.93 (m, 3H), 6.59 (d, 1H, *J* = 2.1 Hz), 4.88 (d, 1H, *J* = 5.0 Hz), 4.63 (t, 1H, *J* = 5.7 Hz), 3.87 (s, 3H), 3.82 (s, 3H), 3.75 (s, 3H), 3.66 – 3.60 (m, 1H), 3.40 – 3.35 (m, 2H), 3.16 – 3.13 (m, 1H). MS (ESI): 439.5($C_{24}H_{26}N_2O_6$, $[M+H]^+$). Anal. Calcd for $C_{24}H_{26}N_2O_6$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.81; H, 5.99; N, 6.37%.

General method of Synthesis of Compounds C10–C14

A solution of 2-cyanoacetamide (1 equiv), amine, (1.0–1.5 equiv) was stirred at room temperature for 4 h. The precipitate was collected by filtration and washed with water/methanol (1:1). Then was dissolve in methanol, addition compound B (0.5 equiv) and N-methylpiperazine (0.05–1.05 equiv). The compound was synthesized by the microwave irradiation in microwave reaction instrument . Reaction conditions set for the 800 w, 70 °C and 5 min. Then, the reaction is cooled to ambient temperature and extracted with dichloromethane (3 × 20 mL). The organic phase is dried with anhydrous sodium sulfate. After removal of the solvent on vacuum, the crude product is purified with silica gel chromatography (75% ethyl acetate in hexanes) to give the title compound.

C10: (E)-2-cyano-3-(2,4-dimethoxy-6-(4-methoxystyryl)phenyl)-N-(3-morpholinopropyl)acrylamide

Yellow solid (68% yield). Mp 170-71 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.30 (s, 1H), 8.20 (s, 1H), 7.58 – 7.50 (m, 2H), 7.22 (d, 1H, *J* = 15.9 Hz), 6.98 (t, 4H, *J* = 12.4 Hz), 6.62 (s, 1H), 3.87 (d, 6H, *J* = 19.3 Hz), 3.78 (s, 3H), 3.35 (s, 4H), 2.52 – 2.39 (m, 8H). MS (ESI): 492.6($C_{28}H_{33}N_3O_5$, $[M+H]^+$). Anal. Calcd for $C_{28}H_{33}N_3O_5$: C, 68.41; H, 6.77; N, 8.55. Found: C, 68.61; H, 6.73; N, 8.55%.

C11: (E)-3-(2,4-dimethoxy-6-(4-methoxystyryl)phenyl)-2-(morpholine-4-carbonyl)acrylonitrile

Yellow solid (53% yield). Mp 170-71 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.60 (s, 1H), 7.48 (d, 2H, *J* = 8.7 Hz), 6.95 (dd, 4H, *J* = 9.1, 4.4 Hz), 6.74 (t, 1H, *J* = 3.2 Hz), 6.37 (d, 1H, *J* = 2.2 Hz), 3.89 (s, 6H), 3.80 (s, 3H), 3.56 – 3.51 (m, 2H), 3.46 – 3.40 (m, 2H), 3.32 – 3.25 (m, 2H), 3.24 – 3.17 (m, 2H). MS (ESI): 435.5($C_{25}H_{20}N_2O_5$, $[M+H]^+$). Anal. Calcd for $C_{25}H_{20}N_2O_5$: C, 69.11; H, 6.03; N, 6.45. Found: C, 69.23; H, 6.02; N, 6.44%.

C12: (E)-2-cyano-3-(2,4-dimethoxy-6-(4-methoxystyryl)phenyl)-N-((tetrahydrofuran-2-yl)methyl)acrylamide

Yellow solid (49% yield). Mp 48-49 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.48 (s, 1H), 7.41 (d, 2H, *J* = 4.0 Hz), 6.97 (d, 2H, *J* = 9.5 Hz), 6.87 (d, 2H, *J* = 8.7 Hz), 6.73 (d, 1H, *J* = 1.9 Hz), 6.70 (t, 1H, *J* = 5.1 Hz), 6.40 (d, 1H, *J* = 1.9 Hz),

4.05 (ddd, 1H, *J* = 10.5, 7.0, 3.6 Hz), 3.88 (d, 6H, *J* = 4.0 Hz), 3.81 (s, 3H), 3.78 (d, 1H, *J* = 5.7 Hz), 3.76 (d, 1H, *J* = 7.7 Hz), 3.68 – 3.65 (m, 1H), 3.37 – 3.32 (m, 1H), 2.03 – 1.98 (m, 1H), 1.91 (dt, 2H, *J* = 9.8, 5.3 Hz), 1.61 – 1.57 (m, 1H). MS (ESI): 449.5($C_{26}H_{28}N_2O_5$, $[M+H]^+$). Anal. Calcd for $C_{26}H_{28}N_2O_5$: C, 69.63; H, 6.29; N, 6.25. Found: C, 69.73; H, 6.29; N, 6.25%.

C13: (E)-3-(2,4-dimethoxy-6-(4-methoxystyryl)phenyl)-2-(pyrrolidine-1-carbonyl)acrylonitrile

Yellow solid (72% yield). Mp 173-175 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.67 (s, 1H), 12.25 (d, 2H, *J* = 8.6 Hz), 11.93 (d, 1H, *J* = 16.1 Hz), 11.74 (d, 1H, *J* = 16.1 Hz), 11.68 (s, 1H), 11.67 (s, 2H), 11.32 (d, 1H, *J* = 1.6 Hz), 8.60 (s, 3H), 8.56 (s, 3H), 8.50 (s, 3H), 8.35 (t, 2H, *J* = 6.3 Hz), 8.15 (t, 2H, *J* = 6.6 Hz), 6.63 – 6.56 (m, 4H). MS (ESI): 419.5($C_{25}H_{26}N_2O_4$, $[M+H]^+$). Anal. Calcd for $C_{25}H_{26}N_2O_4$: C, 71.75; H, 6.26; N, 6.69. Found: C, 71.73; H, 6.26; N, 6.68%.

C14: (E)-2-cyano-3-(2,4-dimethoxy-6-(4-methoxystyryl)phenyl)-N-(piperazin-1-yl)acrylamide

Yellow solid (69% yield). Mp 76-78 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.67 (s, 1H), 12.25 (d, 2H, *J* = 8.6 Hz), 11.93 (d, 1H, *J* = 16.1 Hz), 11.74 (d, 1H, *J* = 16.1 Hz), 11.68 (s, 1H), 11.67 (s, 2H), 11.32 (d, 1H, *J* = 1.6 Hz), 8.60 (s, 3H), 8.56 (s, 3H), 8.50 (s, 3H), 8.35 (t, 2H, *J* = 6.3 Hz), 8.15 (t, 2H, *J* = 6.6 Hz), 6.63 – 6.56 (m, 6H). MS (ESI): 434.5($C_{25}H_{27}N_3O_4$, $[M+H]^+$). Anal. Calcd for $C_{25}H_{27}N_3O_4$: C, 69.27; H, 6.28; N, 9.69. Found: C, 69.25; H, 6.28; N, 9.69%.

General method of synthesis of compounds C15–C20

A solution of 2-cyanoacetamide (1 equiv), compound B (1.0–1.5 equiv) was dissolve in methanol, then addition N-methylpiperazine (0.05–1.05 equiv) and warm up to refluex overnight. Then, the reaction is cooled to ambient temperature and extracted with dichloromethane (3 × 20 mL). The organic phase is dried with anhydrous sodium sulfate. After removal of the solvent on vacuum, white solid was obtained. The solid was dissolved in methylene chloride, then add EDCI (1.6 equiv) and (1.6 equiv) HOBt was added after 5 min. The reaction was stirred for 30 min and added (2.0 equiv) aromatic amine , heated to reflux for 10 h. Then, the reaction is cooled to ambient temperature and extracted with dichloromethane (3 × 20 mL). The organic phase is dried with anhydrous sodium sulfate. After removal of the solvent on vacuum, the crude product is purified with silica gel chromatography (75% ethyl acetate in hexanes) to give the title compound.

C15: (E)-2-cyano-3-(2,4-dimethoxy-6-(4-methoxystyryl)phenyl)-N-(pyridin-2-ylmethyl)acrylamide

Yellow solid (52% yield). Mp 182-183 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.57 (d, 1H, *J* = 4.4 Hz), 8.51 (s, 1H), 7.73 (s, 1H), 7.69 (t, 1H, *J* = 7.1 Hz), 7.43 (d, 2H, *J* = 8.6 Hz), 7.31 (d, 1H, *J* = 7.8 Hz), 7.23 (dd, 1H, *J* = 11.7, 6.1 Hz), 7.01 (d, 1H, *J* = 16.0 Hz), 6.95 (d, 1H, *J* = 16.0 Hz), 6.87 (d, 2H, *J* = 8.6 Hz), 6.74 (d, 1H, *J* = 1.8 Hz), 6.41 (d, 1H, *J* = 1.7 Hz), 4.72 (d, 2H, *J* = 4.8 Hz), 3.88 (d, 6H, *J* = 1.2 Hz), 3.81 (s, 3H). MS (ESI): 456.5($C_{27}H_{25}N_3O_4$, $[M+H]^+$). Anal. Calcd for $C_{27}H_{25}N_3O_4$: C, 71.19; H, 5.53; N, 9.22. Found: C, 71.19; H, 5.53; N, 9.22%.

C16: N-((E)-2-cyano-3-(2,4-dimethoxy-6-(4-methoxystyryl)phenyl)acryloyl)nicotinamide

Yellow solid (38% yield). Mp 174-176 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.39 (s, 1H), 8.05 (s, 1H), 7.67 (d, 1H, *J* = 23.8 Hz), 7.57 – 7.52 (m, 3H), 7.16 (d, 1H, *J* = 16.1 Hz), 7.11 (d, 1H, *J* = 3.4 Hz), 7.03 (d, 1H, *J* = 16.1 Hz), 6.94 (d, 4H, *J* = 7.6 Hz), 6.61 (s, 1H), 3.76 (s, 6H), 3.72 (s, 3H). MS (ESI): 470.5($C_{27}H_{23}N_3O_5$, $[M+H]^+$). Anal. Calcd for $C_{27}H_{23}N_3O_5$: C, 69.07; H, 4.94; N, 8.95. Found: C, 69.07; H, 4.94; N, 8.95%.

C17: (E)-2-cyano-3-(2,4-dimethoxy-6-(4-methoxystyryl)phenyl)-N-(2-(thiophen-2-yl)ethyl)acrylamide

Yellow solid (76% yield). Mp 56-67 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 13.29 (t, 1H, *J* = 5.5 Hz), 12.91 (s, 1H), 12.25 (d, 2H, *J* = 8.6 Hz), 12.03 (dd, 1H, *J* = 13.3, 4.6 Hz), 11.95 (d, 1H, *J* = 16.1 Hz), 11.76 – 11.70 (m, 1H), 11.69 – 11.67 (m, 3H), 11.67 (d, 1H, *J* = 5.1 Hz), 11.64 (d, 1H, *J* = 2.5 Hz), 11.33 (d, 1H, *J* = 1.7 Hz), 8.61 (s, 3H), 8.56 (s, 3H), 8.50 (s, 3H), 8.18 (dd, 2H, *J* = 12.9, 6.9 Hz), 7.78 (t, 2H, *J* = 7.1 Hz). MS (ESI): 475.6($C_{27}H_{26}N_2O_4S$, $[M+H]^+$). Anal. Calcd for $C_{27}H_{26}N_2O_4S$: C, 68.33; H, 5.52; N, 5.90; S, 6.76. Found: C, 68.33; H, 5.52; N, 5.90; S, 6.76%.

C18: (E)-N-(benzo[d]thiazol-2-yl)-2-cyano-3-(2,4-dimethoxy-6-(4-methoxystyryl)phenyl)acrylamide

Yellow solid (76% yield). Mp 56-67 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.78 (s, 1H), 7.50 (d, 2H, *J* = 8.7 Hz), 7.10 (d, 1H, *J* = 16.1 Hz), 7.02 – 6.96 (m, 1H), 6.94 (d, 2H, *J* = 8.7 Hz), 6.84 (d, 1H, *J* = 2.1 Hz), 6.50 (d, 1H, *J* = 2.1 Hz), 5.73 (s, 1H), 3.84 (s, 3H), 3.75 (d, 6H, *J* = 9.0 Hz), 3.72 (s, 3H). MS (ESI): 498.6($C_{28}H_{23}N_3O_4S$, $[M+H]^+$). Anal. Calcd for $C_{28}H_{23}N_3O_4S$: C, 67.59; H, 4.66; N, 8.45; S, 6.44. Found: C, 67.56; H, 4.66; N, 8.45; S, 6.44%.

C19: (E)-2-cyano-3-(2,4-dimethoxy-6-(4-methoxystyryl)phenyl)-N-(4-hydroxyphenethyl)acrylamide

Yellow solid (61% yield). Mp 80-81 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.49 (s, 1H), 7.42 (t, 2H, *J* = 8.2 Hz), 7.25 (s, 1H), 7.04 (t, 2H, *J* = 15.4 Hz), 7.00 – 6.92 (m, 2H), 6.90 – 6.85 (m, 2H), 6.76 (d, 2H, *J* = 8.4 Hz), 6.73 (d, 1H, *J* = 2.1 Hz), 6.42 (t, 1H, *J* = 5.6 Hz), 6.40 (d, 1H, *J* = 2.1 Hz), 3.86 (t, 6H, *J* = 10.1 Hz), 3.81 (s, 3H), 3.60 (dd, 2H, *J* = 13.1, 6.9 Hz), 2.81 (t, 2H, *J* = 7.1 Hz). MS (ESI): 485.5($C_{29}H_{28}N_2O_5$, $[M+H]^+$). Anal. Calcd for $C_{29}H_{28}N_2O_5$: C, 71.88; H, 5.82; N, 5.78. Found: C, 71.87; H, 5.82; N, 5.78%.

C20: (E)-N-(4-chlorophenyl)-2-cyano-3-(2,4-dimethoxy-6-(4-methoxystyryl)phenyl)acrylamide

Yellow solid (79% yield). Mp 202-203 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.45 (s, 1H), 10.21 (s, 1H), 8.31 (s, 1H), 7.88 (s, 1H), 7.73 (d, 1H, *J* = 8.7 Hz), 7.27 (d, 2H, *J* = 8.6 Hz), 7.17 (d, 1H, *J* = 16.1 Hz), 7.10 (dd, 2H, *J* = 15.9, 9.9 Hz), 6.99 (s, 1H), 6.85 (s, 1H), 6.62 (s, 1H), 6.42 (s, 1H), 3.82 (s, 3H), 3.77 (s, 3H), 3.58 (s, 3H). MS (ESI): 475.9 ($C_{27}H_{23}ClN_2O_4$, [M+H]+). Anal. Calcd for $C_{27}H_{23}ClN_2O_4$: C, 68.28; H, 4.88; Cl, 7.46; N, 5.90. Found: C, 68.25; H, 4.88; Cl, 7.46; N, 5.90%.

4. CONCLUSION

The present study describes the synthesis of resveratrol acrylamides amine derivatives **C1-C20** from commercially available resveratrol as starting material. The antiproliferative activity of these compounds was evaluated against three cancer cell lines including human chronic myelocytic leukemia cell K562, human hepatoma HuH-7 and human lung carcinoma A549. Most of the compounds showed superior activity against three cell lines when compared to parent resveratrol. Therefore, the present study is valuable for finding the new drugs against cancer cell lines.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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