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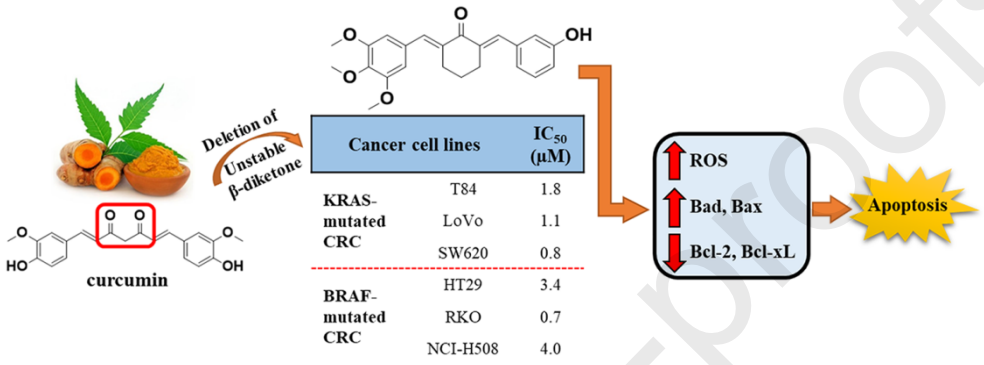

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Synthesis and in-vitro anti-cancer evaluations of multi-methoxylated asymmetrical diarylpentanoids as intrinsic apoptosis inducer against colorectal cancer.

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ABSTRACT

In the present study, a series of nine stable 3,4,5-methoxylphenyl-containing asymmetrical diarylpentanoids, derivatives of curcuminoids, have been synthesized, characterized and evaluated for their in-vitro anti-cancer potential against a panel of BRAF- and KRAS-mutated colorectal cancer cell lines including T84, LoVo and SW620, HT29, RKO and NCI-H508, respectively. Structure-activity relationship study on cytotoxicity of tested compounds suggested that the presence of meta-hydroxyl and adjacent dimethoxyl groups are crucial for enhanced cytotoxicity of diarylpentanoids. Among the evaluated analogs, **8** has been identified as the lead compound due to its highest chemotherapeutic index of 9.9 and nano molar scale cytotoxicity against SW620 and RKO. Colonies formation and cell cycle analyses on **8**-treated RKO cells showed that **8** exhibits strong anti-proliferative activity by inducing G2/M-phase cell arrest. Subsequent flow cytometry based annexin-V and DCFHDA studies suggested that **8** could induce apoptosis through intracellular ROS-dependent pathway. Further Western blot studies confirmed that 8 has induced intrinsic apoptosis in RKO cells through the up-regulations of Bad and Bax pro-apoptotic proteins and down-regulations of Bcl-2 and Bcl-xL pro-survival proteins. In all, the present results suggest that **8** could be a potent lead which deserves further modification and investigation in the development of small molecule-based anti-colorectal cancer agents.

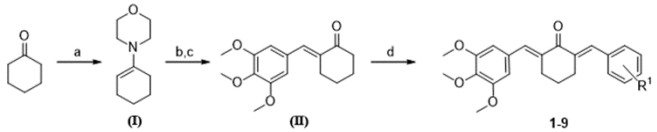
Colorectal cancer (CRC) is the 3rd most common type of cancer and 2nd leading cause of cancer death worldwide. According to Globocan 2018, there were 1.8 million people who were diagnosed with CRC and the death number has exceeded 850,000 cases. Worrying, these numbers are estimated to be escalated to approximately 3.1 and 1.3 million, respectively, by 2040.[1] On top of this, CRC has caused a total economic impact of 99 billion USD globally in 2008 and this number is expected to be increased exponentially along with the rapid rising of CRC patient number.[2] Based upon these, effective treatments with better safety profile and cheaper cost are urgently needed to reduce the impact of cancers on global human and economic health.

To date, available treatments of CRC are solely based on surgery and chemotherapy. Oxaliplatin and 5-fluorouracil (5-FU) are the mainstay in CRC treatments. Oxaliplatin is a platinum metal complex that disrupts DNA replication and transcription by forming intrastrand platinum-DNA crosslinks while 5-FU is a pyrimidine antimetabolite that interrupts DNA synthesis by inhibiting thymidylate synthase that necessary for DNA synthesis.[3,4] Due to their different in mechanism of actions, these chemotherapeutic agents are often used as synergistic combination to treat advanced or metastatic CRC. Unfortunately, although such combination possesses enhanced anti-tumor activity, its therapeutic potential was cushioned off by the associated side effects including nausea, diarrhea, hand-foot syndrome and neuropathy.[5,6] These unpleasant side effects not only restrict the full anti-cancer potential of the respective chemotherapy but also reduce the quality of life of the cancer patients. On this account, safer and more effective drugs are therefore needed.

Among the natural occurring small molecules, curcumin, the major chemical constituent of turmeric, has been suggested as the most potent candidate in the search of alternative cancer therapeutic agents based upon its remarkable anti-cancer properties. In past few decades, curcumin was showed to inhibit various cancer cell lines including lung, bladder, colorectal, breast

and excellent safety profile with extremely mild toxicity *in-vivo*.[5–9] Unfortunately, several studies revealed that curcuminoids are chemically unstable as their unsaturated *β*-diketone fragment tends to be cleaved by aldo-keto reductase of liver cells, which thereby reduce its therapeutic potential.[10–12] Based upon this, monocarbonyl diarylpentanoids, a bioactive family of curcuminoid derivatives without the reactive *β*-diketone moiety has been the focus of curcuminoid-based studies.

Monocarbonyl diarylpentanoids is a 5-carbon spacer bioactive family which derived from curcumin by replacing the unstable diketone moiety with mono ketone fragment. Several studies have proven that the replacement of such moiety has improved their stability chemically and metabolically.[13,14] Monocarbonyl diarylpentanoids were found to exhibit excellent anti-cancer properties based on their anti-proliferative and anti-angiogenetic effects on various cancer cell lines including breast, lung, colon, pancreatic and prostate cancer cells.[15–19] Meanwhile, several mechanistic studies showed that monocarbonyl diarylpentanoids could induce cancer cells' death through Bcl-2 proteins inhibition and caspases activation.[20–23] Based upon these, monocarbonyl diarylpentanoid derivatives are therefore a potent family to replace curcumin in the search of alternative cancer therapeutic agents. Although diarylpentanoids can be isolated from natural products, its respective experimental procedures are less cost effective yet time consuming.[24] Therefore, structural modification through chemical synthesis is currently being pursue. In our previous study, we have demonstrated that 3,4,5-trimethoxyphenyl moiety is superior for the anti-cancer activity of monocarbonyl diarylpentanoid derivatives.[25] Thus, in continuing our efforts in optimizing the monocarbonyl diarylpentanoids, the aim of the present study is to develop a series of 3,4,5-trimethoxyphenyl-containing diarylpentanoids and evaluate for their oncolytic potential.



[x]Reagents and conditions: (a) morpholine, *p*-toluene-sulfonic acid, toluene, reflux (2 h); (b) 3,4,5-trimethoxy benzaldehyde, 80˚C (8 h); (c) H_2O, reflux (0.5 h); (d) benzaldehyde, EtOH, 6M NaOH, RT (overnight).

Scheme 1 represents the synthetic pathway of 3,4,5-trimetoxyphenyl-containing diarylpentanoids. As depicted in scheme 1, compounds **1-9** were prepared in 2-steps manner which involved Stork enamine alkylation and aldol condensation.[26] Stork enamine alkylation was first performed by reacting cyclohexanone with morpholine under reflux condition to achieve intermediate **I**. The crude product of intermediate **I** was then reacted with 3,4,5-trimethoxybenzaldehyde to afford intermediate **II**. Upon purification, intermediate **II** was further reacted with appropriate benzaldehydes to achieve target compounds **1-9**. Since the final compounds are asymmetrical diarylpentanoids, the detection of two singlets at chemical shift of 7.5-8.0 ppm in the proton NMR spectra is therefore the evidence to confirm the presence of desired compounds as these two peaks represent the vinylic protons of two differently substituted bezylidene All synthesized compounds were purified by column chromatography and characterized by ^{1}H-NMR, ^{13}C-NMR, and high-resolution electron impact-mass spectrometry (HRMS). The purity of synthesized compounds was confirmed to be greater than 95% based on their respective HPLC profiles. The synthesized compounds were listed in **Table 1.**

Table 1. Chemical structures of compounds **1-9**

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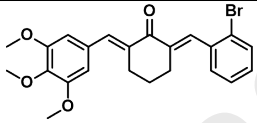
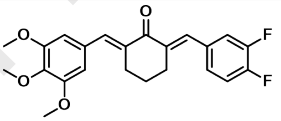
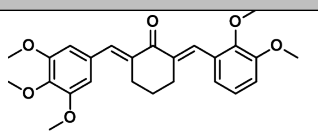
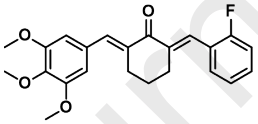
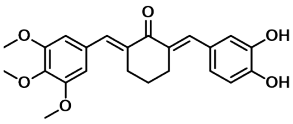
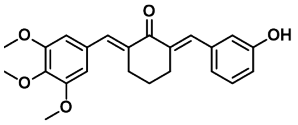
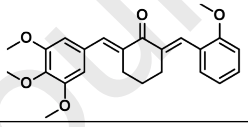
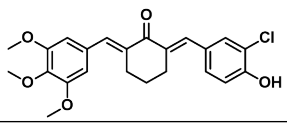
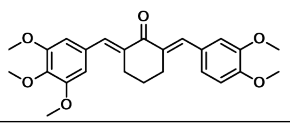
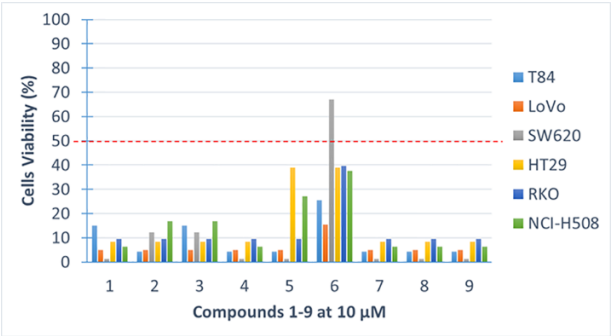
1		4		7	
2		5		8	
3		6		9	

Cmpd = Compound

The *in-vitro* cytotoxic activity of the synthesized diarylpentanoids on KRAS (T84, LoVo and SW620) and BRAF (HT29, RKO and NCI-H508) mutated human colorectal cancer cell lines were determined by MTT assay as previously described.[25] The preliminary screening results obtained are summarized **Figure 1**.



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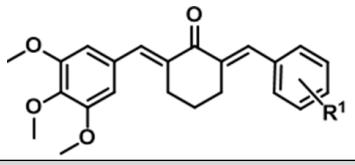
LoVo and SW620) and BRAF (HT29, RKO and NCI-H508) mutated human colorectal cancer cell lines at a testing concentration of 10 µM. The red line across the graph represents the threshold percentage for further IC_{50} determination

As expected, all synthesized diarylpentanoid analogs showed significant cytotoxicity against all tested cancer cell lines at a testing concentration of 10 µM. This has confirmed the superior anti-cancer activity of 3,4,5-trimethoxyphenyl fragment. To further inspect the role of different functional groups on cytotoxic study were performed. **Table 2** has summarized the IC_{50} values of the synthesized compounds on various cell lines, in which 5-FU and normal human dermal fibroblasts (NHDF) were served as controls**.** Meanwhile, since **7** and **9** have been reported as strong anti-cancer agents, they therefore were served as reference compounds to evaluate the successfulness of the present optimization study in improving the anti-cancer potential of diarylpentanoid system.[25]

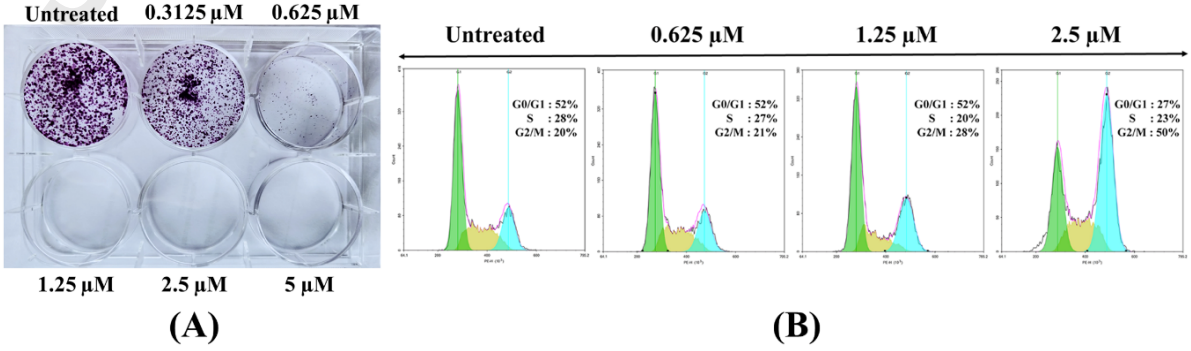
Table 2. Cytotoxicity of **1-9** on T84, LoVo and SW620, HT29, RKO and NCI-H508 and NHDF cell lines



Compound	R^1	IC_{50} (µM) KRAS T84[a]	KRAS LoVo[a]	KRAS SW620[a]	BRAF HT29[a]	BRAF RKO[a]	BRAF NCI-H508[a]	NHDF[b]	Chemotherapeutic index
5-FU	-	>10	2.7	>10	>10	2.9	8.8	>50	-
1	2-Br	4.2	2.8	3.3	2.8	2.5	2.7	12.4	3.0-5.0
2	2-F	3.5	2.3	4.1	1.7	2.2	4.0	11.1	2.7-6.5
3	2-OMe	3.9	2.6	4.5	3.2	3.6	4.8	18.8	3.9-7.2
4	3.4-F	2.2	1.9	2.1	1.6	1.5	2.0	4.0	1.8-2.7
5	3,4-OH	3.6	2.7	3.2	8.5	3.1	7.0	9.0	1.1-3.3
6	3-Cl-4OH	6.5	4.8	>10	7.6	6.5	5.6	25.3	3.3-5.3
7	2,3-OMe	2.1	1.1	2.0	1.2	1.2	2.2	7.9	3.6-7.2
8	3-OH	1.8	1.1	0.8	3.4	0.7	4.0	6.9	1.8-9.9
9	3,4-OMe	1.9	1.7	1.6	1.5	1.3	1.7	5.8	3.1-4.5

[a] **Colorectal cancer cells**
[b] **Normal human dermal fibroblast cells**

As shown in **Table 2**, all synthesized compounds except **5** and **6** have displayed excellent cytotoxicity on all tested cancer cell lines (< 5 µM) in which **8** was found to be the most potent candidate due to its highest chemotherapeutic index of 9.9 and lowest IC_{50} values of 0.8 and 0.7 µM against SW620 and RKO, respectively. Meanwhile, three other compounds (**4**,**7** and **9**) were found to possess strong cytotoxicity based on their IC_{50} values of approximately 2 µM across all tested cancer cell lines. However, among these three strong cytotoxic agents, **4** was having the least potential due to its relatively higher toxicity against human normal cells. It is noteworthy that all synthesized compounds have displayed similar cytotoxicity against both BRAF and KRAS mutated cancer cell lines which suggests that the desired diarylpentanoids system may not be BRAF- or KRAS-specific inhibitors. Further SAR study revealed that *meta*-hydroxyl and adjacent dimethoxyl moieties are crucial for better cytotoxicity of diarylpentanoids as **7, 8** and **9** have displayed improved activities in comparison to that of other analogs. In contrast, *para*-hydroxylphenyl was found to be an undesired fragment as compounds with such substitution (**5** and **6**) have displayed much lower cytotoxicity as compared to the rest of synthesized compounds. These results are in consistent with our previous findings in which the presence of *meta*-hydroxyl and adjacent dimethoxyl moieties improved the cytotoxicity of diarylpentanoids while the insertion of *para*-hydroxyl group reduced their anti-cancer potential.[25] Interestingly, when a comparison was made between the most active compounds (**7**, **8** and **9**), *meta*-hydroxylphenyl was found to be a more desirable substitution pattern than adjacent methoxy groups as **8**, a *meta*-hydroxylated diarylpentanoid has achieved lower IC_{50} values than its dimethoxylated analogs **7** and **9**. Noteworthy, 3,4-difluorophenyl fragment may not be an interesting substitution pattern as compound with such moiety (**4**) has displayed strong toxicity against human normal cells. Thus, based on the promising cytotoxicity and relatively higher chemotherapeutic index of **8**, it was selected for further colony formation and cell cycle analysis.[27,28] The results obtained were compiled in **Figure 2**.



As depicted in **Figure 2A**, the colonies of RKO cells were completely inhibited by **8** at the testing concentrations of 1.25, 2.5 and 5 µM while only very little colonies were observed in cells treated with 0.625 µM of the same compound. This dose-dependent inhibition implies that **8** exhibits strong anti-proliferative activity against RKO cell line. Subsequent cell cycle analysis showed that **8** could induce G2/M arrest in RKO cells as the treatment with 2.5 µM of **8** has drastically increased the G2/M population of RKO cells from 20% to 50%. Thus, based on both anti-proliferative and cell cycle analysis, the present results suggest that **8** inhibits proliferation of RKO cells through G2/M-phase cell arrest. To further investigate the underlying cytotoxic mechanisms of **8** on RKO cell line, flow cytometry and Western blot studies were performed and the results obtained were summarized in **Figure 3**.[29,30]

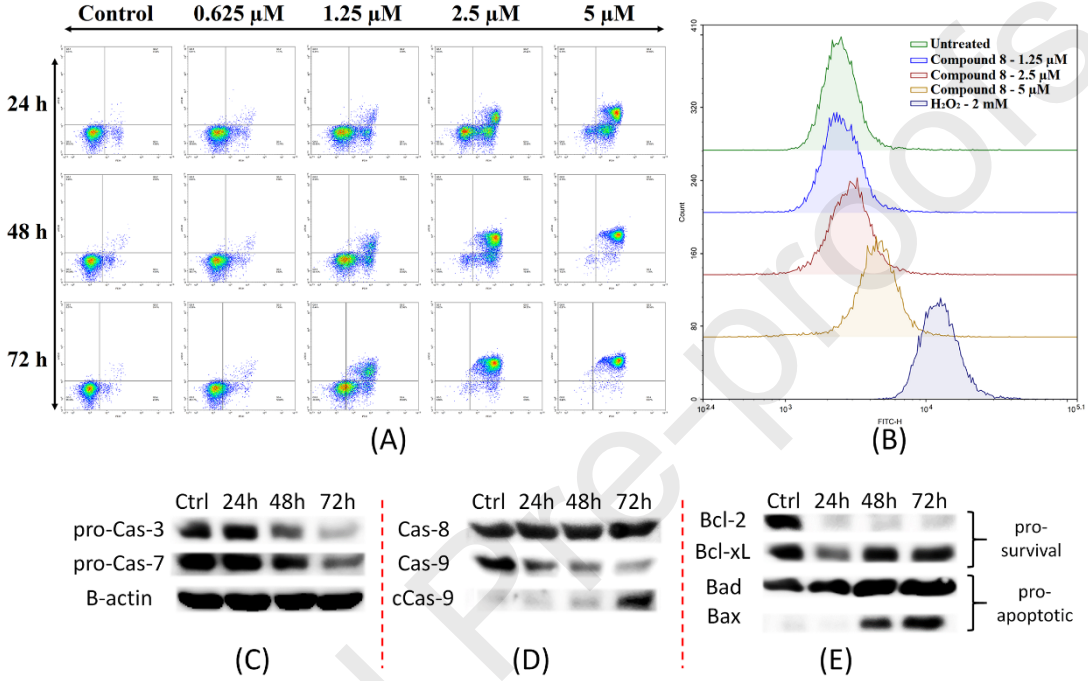


Figure 3. Representative annexin-V-based apoptosis (A) and intracellular ROS profiles (B) of **8**-treated RKO cells at selected time points. Western blot analysis on executioner caspases (C) initiator caspases (D) as well as pro-survival and pro-apoptotic (D) proteins in **8**-treated RKO cells at 24h, 48h and 72h of post-treatments.

As depicted in **Figure 3A**, density plots that represent cell populations were found to shift from left to right and upper right as the treatment concentrations of **8** increased. This observation suggests that **8** is a dose-dependent apoptosis inducer as such shifting pattern indicates the initiation and progression of cell apoptosis. Meanwhile, similar shifting of cell populations was also being observed when the treatment period was prolonged to 48h and 72h. This implies that **8** is also a time-dependent apoptosis inducer. In order to validate the apoptosis inducing ability of **8**, Western blot analysis on procaspases-3 and -7 were performed. As shown in **Figure 3C**, the cellular pools of both procaspases-3 and -7 were found to be depleted upon the treatment with **8**. This observation thus confirmed the presence of apoptosis in **8**-treated RKO cells as procaspases-3 and -7 are the two critical proenzyme which will be cleaved into activated caspases-3 and -7 to initiate cell apoptosis.[31] In order to identify the type of apoptosis induced by **8**, its effects on caspases-8 and -9 were studied.[32] As showed in **Figure 3D,** treatment with **8** has successfully down-regulated and up-regulated the expression of procaspase-9 and caspase-9, respectively. This observation indicates that **8** could induce intrinsic apoptosis in RKO cells. Meanwhile, the expression of caspase-8 was found to be independent to the treatment of **8** which suggests that extrinsic apoptosis is not responsible for the **8**-mediated cell death. Based upon these, **8** is therefore confirmed to be an intrinsic apoptosis inducer.

In order to further elucidate the apoptotic mechanism caused by **8**, its effects on intracellular ROS as well as pro-survival and pro-apoptotic proteins were studied. As depicted in **Figure 3B**, the fluorescence intensities of the treated cells were found to be directly proportional to the concentrations of **8**. This shows that **8** could trigger intracellular ROS production in dose-dependent manners, which in turn implies that ROS is involved in the apoptosis induction of **8** on RKO cells. Meanwhile, as shown in the Western blot analysis on pro-survival proteins (**Figure 3E**), 24h treatment with **8** has successfully reduced the protein expression of Bcl-2 and Bcl-xL which indicates that **8** could inhibits both Bcl-2 and Bcl-xL proteins as early as 24h of post-treatment. Noteworthy, a drastic increment of Bcl-xL expression was observed when the compound treatment was prolonged to 72h. This selective up-regulation of Bcl-xL could be rationalized by the activated defensive and survival machinery of **8**-treated RKO cells as Bcl-xL has been reported to be a more effective anti-apoptotic protein against cell apoptosis.[33] However, the activation of proposed defensive and survival machinery in **8**-treated RKO cells may be overcome by the pro-apoptotic behavior of **8** as

Bad and Bax proteins. Taken all together, the present results confirmed that **8** is a dose- and time-dependent apoptosis inducer which could induce ROS-dependent intrinsic apoptosis through the up-regulations of Bad and Bax as well as down-regulation of Bcl-2 and Bcl-xL proteins. The results are summarized in **Figure 4.**

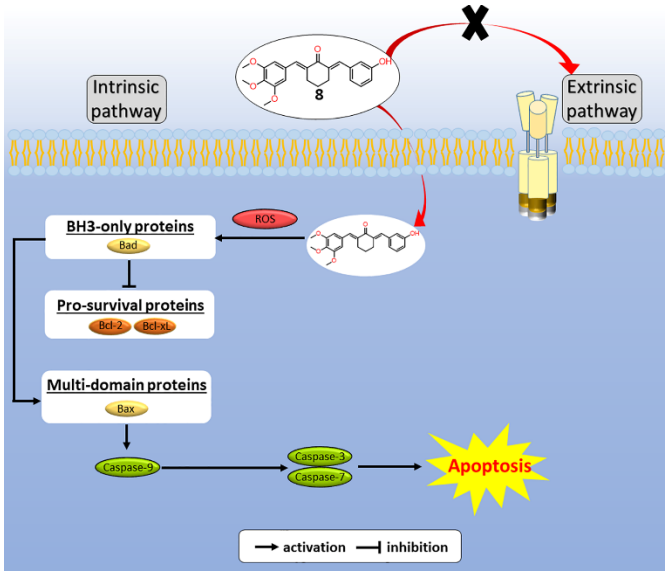


Figure 4. Illustration of intrinsic apoptosis mechanism induced by **8** on RKO cells.

In all, the present study has successfully optimized the anti-cancer potential of diarylpentanoid system as compound **8**, a new diarylpentanoid analog was found to exhibit improved cytotoxicity in comparison to that of previously reported compounds **7** and **9**. Apart from showing nano molar scale cytotoxicity, **8** was found to possess strong anti-proliferative activity through G2/M cell cycle arrest. On top of this, **8** was also found to induce intrinsic apoptosis by altering both pro-apoptotic and pro-survival proteins. Thus, based on present findings, it is plausible to conclude that **8**, a diarylpentanoid system containing both 3,4,5-trimethoxyphenyl and meta-hydoxyphenyl moieties, is a potent anti-cancer candidate which deserves further extensive studies including structural modification on the cyclohexanone bridge as well as in-vivo pharmacokinetic and pharmacodynamic analyses. The present study not only successfully optimized the iarypentanoid structure but also

Acknowledgments

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Supplementary Material

Supplementary data to this article can be found online at

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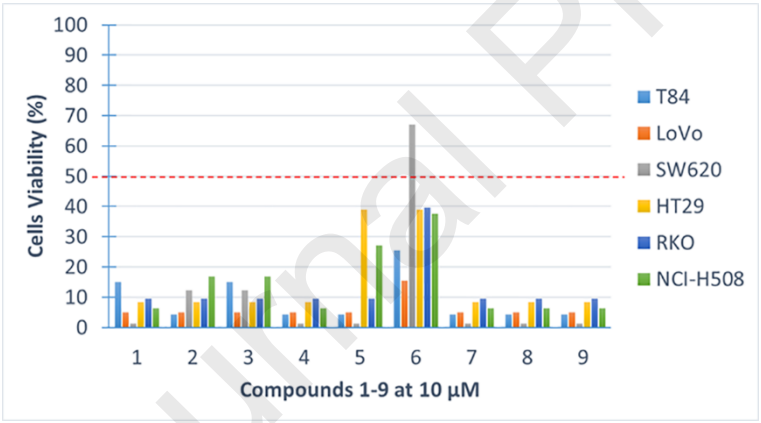
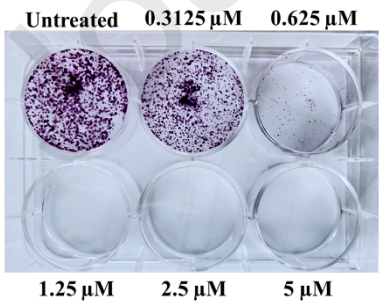
Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:





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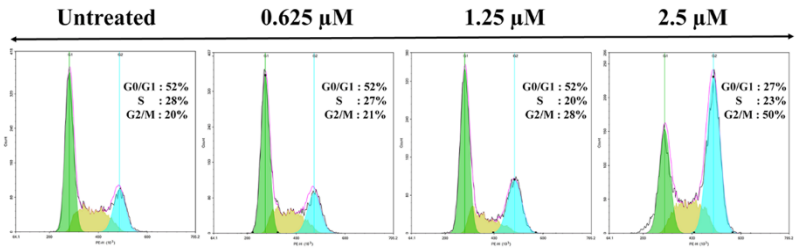

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