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Synthesis and Bioactivity of Natural Occurring Petasin-Like Derivatives as Antitumor Agents

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Abstract

Petasin is a potential antitumor against human neuroblastoma cell SK-N-SH by inhibiting the ERK1/2 phosphorylation. In view of its great activity and new antiproliferative mechanisms, a series of petasin derivatives were designed and synthesized, which showed great antiproliferative activity. Among them compounds 1h and 1f were more effective against SK-N-SH cells than petasin with the IC_{50} values of 0.87 and 2.63 μM, respectively.

Keywords

Petasin, SK-N-SH, Mechanism, Derivative, Antiproliferative Activity

1. Introduction

Neuroblastoma (neuroblastoma, NB) [1] is the most common extracranial tumor in infants and young children. Recent clinical statistics show that the neuroblastoma has become the third most common cause of death after renal tumor and leukemia during the childhood [2] [3]. Due to the diversity of clinical manifestations, its treatment varies accordingly. In general, neuroblastoma needs surgery and radioactive therapy, chemotherapy and other treatments are also used for the residual tumors.

Petasin (**Figure 1**) is the active component of *Petasites hybridus* L. (Petasites Tricholobus, Compositae), which has been reported to possess many bioactivities including analgesic, anti-inflammation, and inhibition of ileum

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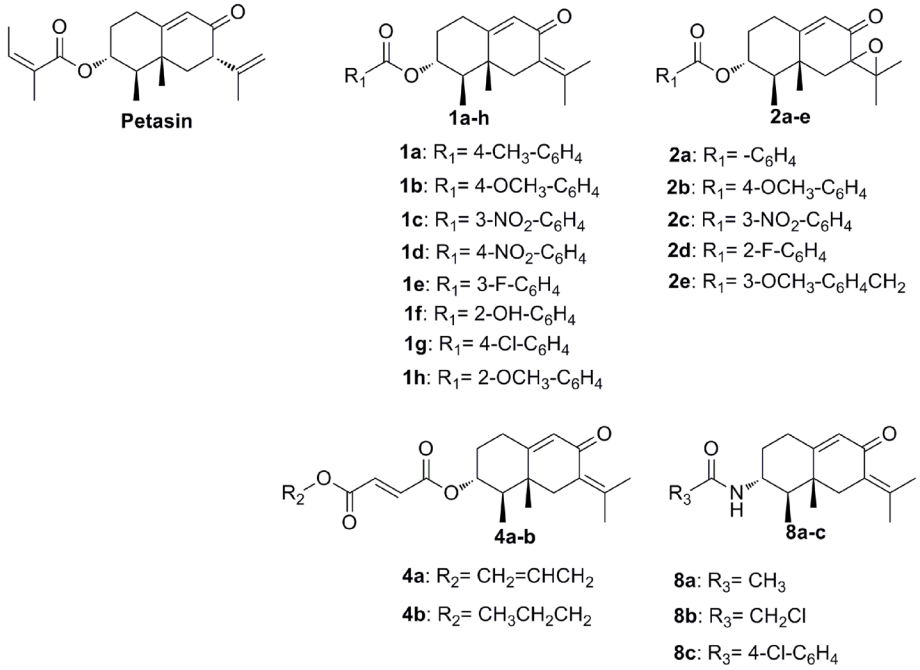


Figure 1. The structures of petasin and petasin derivatives (R_1, R_2, R_3 = alkyl group).

contraction. In our group, the great antitumor activity against Sk-N-SH was reported for the first time [4]. Petasin successfully inhibited the proliferation but not induced the apoptosis. The inhibition of ERK1/2 phosphorylation might be involved in the antiproliferation.

Based on the above results, a series of petasin derivatives were designed and synthesized (**Figure 1**) for investigating the structure-activity relationship and discovering new antiproliferative agents.

2. Chemistry

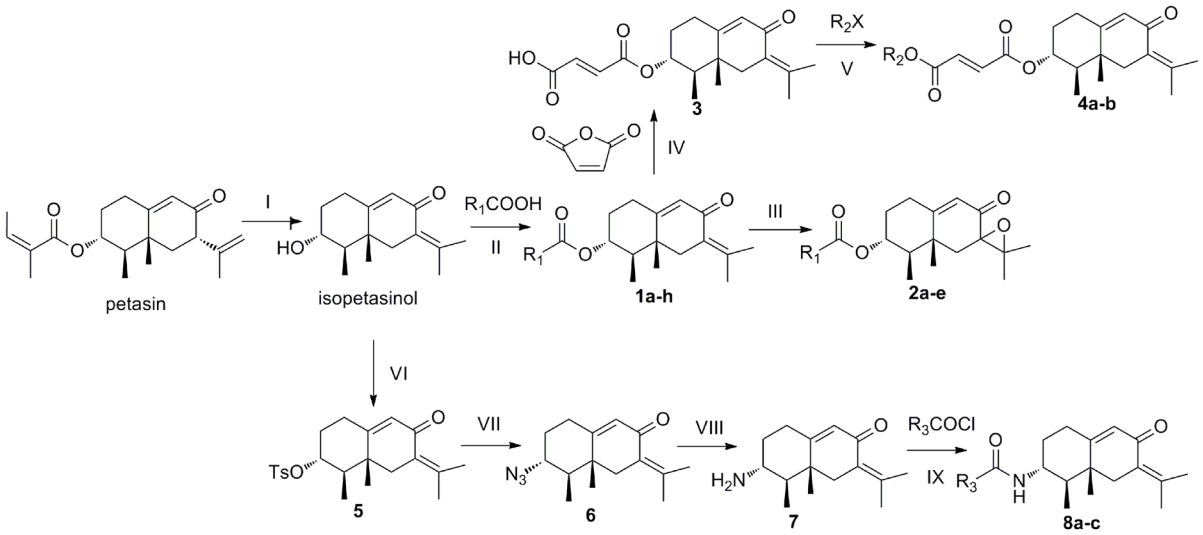
Petasin derivatives were efficiently synthesized as described in **Scheme 1**. Compounds **1a-h** and **3** were obtained from the isopetasinol by acylation reactions with carboxylic acids or maleic anhydride [5] [6]. Isopetasinol was prepared by the hydrolysis [7] of petasin in the presence of NaOH. Compounds **2** were prepared by an epoxidation [8]-[10] of compounds **1**. Compounds **4a-b** with an unsaturated side chain were synthesized by the reaction of compound **3** and different alkyl halides.

To further investigate SARs, compounds **8a-c** with an amide functional group were designed and synthesized [11]-[17]. Tosylation of isopetasinol resulted in compound **5**, followed by nucleophilic substitution with NaN_3 giving the corresponding azide **6**. Zn-mediated reduction of compound **6** produced compound **7**, which was then subjected to prepare compounds **8a-c** by acylation reactions.

3. Results and Discussion

The IC_{50} values for all obtained petasin analogues against three human cancer cell lines including SK-N-SH, MGC-803 and HepG-2 were determined using MTT assay [18]-[22]. Natural occurring petasin, isopetasinol and cisplatin were used as positive controls. The results were demonstrated in **Table 1**. The cell-based investigation demonstrated that some synthetic compounds showed much more potent or comparable antiproliferative activity compared to the petasin. Especially they showed selective antiproliferative activities toward SK-N-SH cells with weak inhibition against other tumor cells.

Compared to petasin, the antiproliferative activities of isopetasinol against the tested cancer cell lines was decreased significantly (IC_{50} > 100 μM), which indicated that an additional unsaturated ester group is beneficial for the activity. Therefore, substituted benzoic ester group was introduced as represented in compounds **1a-h**. Interestingly, some of these compounds showed great cytotoxicity against SK-N-SH and were much more potent than petasin and cisplatin. Compounds with electron-donating groups attached to the phenyl ring were much



Scheme 1. Reagents and conditions: 1) NaOH, CH_3OH, 62˚C, 4 - 6 h; 2) DMAP, DCC, CH_2Cl_2, 0˚C, 6 h; 3) m-ClC_6H_5COOOH, CH_2Cl_2, rt, 3 h; 4) $(C_2H_5)_3N$, CH_2Cl_2, 0˚C, 2 h; 5) Na_2CO_3, DMF, 65˚C, 2 h; 6) m-$CH_3C_6H_5SO_2Cl$, $(C_2H_5)_3N$, CH_2Cl_2, 0˚C, 6 h; 7) NaN_3, DMF, 95˚C, 8 h; 8) Zn, NH_4Cl, THF/H_2O, 2 h, rt; 9) $(C_2H_5)_3N$, CH_2Cl_2, 0˚C, 2 h.

Table 1. *In vitro* inhibitory activity of petasin derivatives against SK-N-SH, MGC-803 and HepG-2 cell lines.

Compd	IC_{50} (μmol/L)		
	SK-N-SH	MGC-803	HepG-2
1a	12.01 ± 1.27	>100	38.02 ± 1.87
1b	5.98 ± 1.06	12.99 ±2.62	64.17 ± 2.06
1c	14.91 ± 1.85	12.84 ± 1.87	34.55 ± 3.51
1d	>100	13.73 ± 2.46	30.30 ± 2.43
1e	31.36 ± 2.01	33.84 ± 2.85	33.82 ± 2.01
1f	2.63 ± 0.76	24.83 ± 1.97	57.33 ± 2,53
1g	61.25 ± 3.21	40.40 ± 3.41	32.02 ± 1.98
1h	0.87 ± 0.28	>100	27.46 ± 1.63
2a	34.78 ± 3.56	43.75 ± 3.78	>100
2b	76.23 ± 2.18	>100	>100
2c	26.87 ± 1.87	>100	49.34 ± 1.76
2d	48.95 ± 2.14	>100	>100
2e	>100	>100	>100
4a	14.54 ± 1.43	43.19 ± 2.86	58.17 ± 3.01
4b	12.76 ± 1.52	>100	>100
8a	>100	>100	>100
8b	31.80 ± 2.07	36.86 ± 3.41	27.63 ± 2.43
8c	64.31 ± 2.65	78.37 ± 4.01	43.98 ± 3.01
Isopetasinol	>100	>100	>100
Petasin	5.76 ± 0.98	34.41 ± 2.75	26.84 ± 1.65
Cisplatin	12.32 ± 1.06	10.88 ± 1.86	8.14 ± 0.89

more potent than those with electron-withdrawing groups. Among them, compound **1h** and **1f** showed the best cytotoxicity with the IC_{50} values of 0.87 and 2.63 μM, respectively, which were about 14 or 15 fold more potent than cisplatin (IC_{50} = 12.32 μM).

Compounds **2a-e** with epoxy ring showed bad antiproliferative activity against SK-N-SH with the IC_{50} values more than 26 μM and were less potent than cisplatin and petasin (IC_{50} = 5.76 μM), which indicated that exo-double bond were important for the antiproliferative activity. Besides, the antiproliferative activity of compounds **4a-b** and compounds **8a-c** also become to be worse than that of compounds **1a-1h** and the positive control.

In conclusion, SAR of new petasin derivatives against SK-N-SH showed that an additional ester group and the exo-double bond were important for the antiproliferative activity. Furthermore the isomerization of the double bond and unsaturated ester unaffected the antiproliferative activity. But if the ester group was substituted with amide group, the antiproliferative activity against Sk-N-SH showed a certain extent effects. And compounds **1h** and **1f** were discovered, which showed selective and great antiproliferative activity with IC_{50} values of 0.87 and 2.63 μM against SK-N-SH cells. The result in this study is valuable for the design and optimization of petasin derivative and the discovery of new antiproliferative agent.

4. Experimental Section

4.1. Chemistry

Petasin, extracted from Ligularia fischeri with traditional ethanol reflux. Reagents and solvents were purchased from commercial sources and were used without further purification. Thin-layer chromatography (TLC) was performed on silica gel GF_{254} plates. Silicagel GF_{254} and H (200 - 300 mesh) from Qingdao Haiyang Chemical Company was used for TLC, preparative TLC, and column chromatography respectively. Melting points were determined on an X-5 micromelting apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 400 MHz and 100 MHz spectrometer respectively. High resolution mass spectra (HRMS) were recorded on a Waters Micromass Q-T of Micromass spectrometer by electrospray ionization (ESI).

4.1.1. General Procedure for the Synthesis of Compounds 1a-h

A mixture of isopetasinol (1 equiv) and Carboxylic acid (1.5 equiv) in CH_2Cl_2 in the presence of DMAP (1 equiv) and DCC (1 equiv) was stirred at 0˚C for 6 h. The disappearance of compound isopetasinol was monitored by TLC. Upon completion, the solvent was removed and water was added, the reaction mixture was extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$ and concentrated under vacuum to afford the crude product. The crude product was purified by a flash column to yield the pure product **1a-h**.

1,8a-dimethyl-6-oxo-7-(propan-2-ylidene)-1,2,3,4,6,7,8,8a-octahydronaphthalen-2-yl-4-methylbenzoate (1a). Yellow solid, yield 75%, mp: 71.2˚C - 72.1˚C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 - 7.25 (m, 4H, ArH), 5.81 (s, 1H, HC = C), 5.14 - 5.01 (m, 1H, CH), 2.96 (d, J = 13.7 Hz, 1H, CH_2), 2.52 (d, J = 13.6, 1H, CH_2), 2.42 (s, 3H, CH_3), 2.39 - 2.26 (m, 2H, CH_2), 2.23 (d, J = 11.0 Hz, 1H, CH_2), 2.11 (s, 3H, CH_3), 1.87 (s, 3H, CH_3), 1.81 (d, J = 11.0, 1H, CH_2), 1.63 - 1.54 (m, 1H, CH), 1.08 (s, 3H, CH_3), 1.04 (d, J = 6.7 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.94, 191.66, 166.23, 165.15, 143.73, 143.43, 129.60, 129.11, 127.59, 127.14, 126.76, 74.01, 46.34, 42.27, 41.17, 31.65, 30.91, 30.13, 22.61, 22.13, 21.65, 17.19, 10.83. HR-MS (ESI): Calcd. $C_{23}H_{28}O_3$, $[M+H]^+$ *m/z*: 352.2126, found: 352.2128.

1,8a-dimethyl-6-oxo-7-(propan-2-ylidene)-1,2,3,4,6,7,8,8a-octahydronaphthalen-2-yl-4-methoxybenzoate (1b). Yellow solid, yield 70%, mp: 107.7˚C - 110.4˚C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 - 6.95 (m, 4H, ArH), 5.83 (s, 1H, HC=C), 5.13 - 5.04 (m, 1H, CH), 3.89 (s, 3H, CH_3), 2.98 (d, J = 13.7 Hz, 1H, CH_2), 2.56 (d, J = 13.7, 1H, CH_2), 2.46 - 2.29 (m, 2H, CH_2), 2.25 (d, J = 11.0 Hz, 1H, CH_2), 2.13 (s, 3H, CH_3), 1.89 (s, 3H, CH_3), 1.82 (d, J = 11.0, 1H, CH_2), 1.63 - 1.57 (m, 1H, CH), 1.10 (s, 3H, CH_3), 1.06 (d, J = 6.7 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.99, 191.71, 165.93, 165.26, 163.45, 143.46, 131.59, 127.14, 126.72, 122.71, 113.65, 73.85, 55.46, 46.38, 42.28, 41.17, 31.70, 30.91, 30.15, 22.62, 22.14, 17.19, 10.83. HR-MS (ESI): Calcd. $C_{23}H_{28}O_4$, $[M+H]^+$ *m/z*: 368.2047, found: 368.2049.

1,8a-dimethyl-6-oxo-7-(propan-2-ylidene)-1,2,3,4,6,7,8,8a-octahydronaphthalen-2-yl-3-nitrobenzoate (1c). White solid, yield 74%, mp: 128.9˚C - 132.8˚C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 - 7.64 (m, 4H, ArH), 5.82 (s, 1H HC = C), 5.12 - 5.01 (m, 1H, CH), 2.95 (d, J = 13.7 Hz, 1H, CH_2), 2.56 (d, J = 13.7 Hz, 1H, CH_2), 2.47 - 2.39 (m, 2H, CH_2), 2.21 (d, J = 11.1 Hz, 1H, CH_2), 2.12 (s, 3H, CH_3), 1.88 (s, 3H, CH_3), 1.78 - 1.70 (m, 1H, CH), 1.59 (d, J = 11.0 Hz, 1H, CH_2), 1.09 (s, 3H, CH_3), 1.06 (d, J = 6.7 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.02, 191.53, 165.14, 164.52, 147.95, 143.63, 132.98, 131.74, 129.65, 127.88, 126.99, 123.96,

76.40, 45.85, 42.28, 41.04, 30.95, 29.94, 22.63, 22.16, 17.17, 10.79. HR-MS (ESI): Calcd. $C_{22}H_{25}NO_5$, $[M+H]^+$ *m/z*: 383.1807, found: 383.1809.

1,8a-dimethyl-6-oxo-7-(propan-2-ylidene)-1,2,3,4,6,7,8,8a-octahydronaphthalen-2-yl-4-nitrobenzoate (1d). White solid yield 75%, mp: 88.1˚C - 91.4˚C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 - 8.21 (m, 4H, ArH), 5.84 (s, 1H, HC = C), 5.17 - 5.09 (m, 1H, CH), 2.99 (d, J = 13.7 Hz, 1H, CH_2), 2.58 (d, J = 13.7 Hz, 1H, CH_2), 2.48 - 2.31 (m, 2H), 2.26 (d, J = 11.0 Hz, 1H, CH_2), 2.14 (s, 3H, CH_3), 1.89 (s, 3H, CH_3), 1.86 (d, J = 11.2, 1H, CH_2), 1.72 - 1.64 (m, 1H, CH), 1.11 (s, 3H, CH_3), 1.08 (d, J = 6.7 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.86, 191.48, 164.32, 164.29, 150.61, 143.79, 135.67, 130.71, 126.99, 126.92, 123.60, 75.66, 46.16, 42.25, 41.13, 31.52, 30.93, 29.99, 22.65, 22.17, 17.17, 10.93. HR-MS (ESI): Calcd. $C_{22}H_{25}NO_5$, $[M+H]^+$ *m/z*: 383.1807, found: 383.1813.

1,8a-dimethyl-6-oxo-7-(propan-2-ylidene)-1,2,3,4,6,7,8,8a-octahydronaphthalen-2-yl-3-fluorobenzoate (1e). White solid, yield 73%, mp: 115.1˚C - 116.7˚C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 - 7.27 (m, 4H, ArH), 5.82 (s, 1H, HC = C), 5.11 - 5.03 (m, 1H, CH), 2.98 (d, J = 13.7 Hz, 1H, CH_2), 2.57 (d, J = 13.7 Hz, 1H, CH_2), 2.46 - 2.29 (m, 2H, CH_2), 2.26 (d, J = 11.2 Hz, 1H, CH_2), 2.12 (s, 3H, CH_3), 1.87 (s, 3H, CH_3), 1.82 (d, J = 11.4, 1H, CH_2), 1.61 - 1.53 (m, 1H, CH), 1.09 (s, 3H, CH_3), 1.05 (d, J = 6.7 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.99, 191.60, 164.90, 143.60, 127.04, 126.87, 125.31, 120.23, 120.01, 116.58, 116.35, 74.83, 46.21, 42.25, 41.13, 31.55, 30.94, 30.05, 22.64, 22.15, 17.17, 10.87. HR-MS (ESI): Calcd. $C_{22}H_{25}FO_3$, $[M+H]^+$ *m/z*: 356.1863, found: 356.1865.

1,8a-dimethyl-6-oxo-7-(propan-2-ylidene)-1,2,3,4,6,7,8,8a-octahydronaphthalen-2-yl-2-hydroxybenzoate (1f). White solid, yield 73%, mp: 128.8˚C - 134.6˚C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.81 (s, 1H, OH), 7.84 - 6.89 (m, 4H, ArH), 5.82 (s, 1H, HC = C), 5.14 - 5.06 (m, 1H, CH), 2.99 (d, J = 13.7 Hz, 1H, CH_2), 2.56 (d, J = 13.7 Hz, 1H, CH_2), 2.48 - 2.30 (m, 2H, CH_2), 2.26 (d, J = 11.2 Hz, 1H, CH_2), 2.12 (s, 3H, CH_3), 1.87 (s, 3H, CH_3), 1.83 (d, J = 11.2, 5.5 Hz, 1H, CH_2), 1.72 – 1.62 (m, 1H, CH), 1.09 (s, 3H, CH_3), 1.06 (d, J = 6.7 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.91, 191.53, 164.42, 161.86, 143.72, 135.89, 129.75, 126.96, 119.23, 117.68, 112.47, 75.08, 46.18, 42.24, 41.15, 31.58, 30.96, 30.08, 22.66, 22.41, 17.61, 10.97. HR-MS (ESI): Calcd. $C_{22}H_{26}O_4$, $[M+H]^+$ *m/z*: 354.1906, found: 354.1907.

1,8a-dimethyl-6-oxo-7-(propan-2-ylidene)-1,2,3,4,6,7,8,8a-octahydronaphthalen-2-yl-4-chlorobenzoate (1g). Yellow solid, yield 63%, mp: 69.2˚C - 72.8˚C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 - 7.43 (m, 4H, ArH), 5.81 (s, 1H, HC = C), 5.10 - 5.02 (m, 1H, CH), 2.98 (d, J = 13.7 Hz, 1H, CH_2), 2.56 (d, J = 13.7, 1H, CH_2), 2.44 - 2.30 (m, 2H, CH_2), 2.25 (d, J = 11.1 Hz, 1H, CH_2), 2.11 (s, 3H, CH_3), 1.86 (s, 3H, CH_3), 1.84 - 1.76 (m, 1H, CH), 1.58 (d, J = 11.2 Hz, 1H, CH_2), 1.08 (s, 3H, CH_3), 1.04 (d, J = 6.7 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.99, 191.61, 165.32, 164.83, 143.62, 139.52, 130.97, 128.77, 128.74, 127.04, 126.84, 74.65, 46.26, 42.26, 41.14, 31.59, 30.92, 30.07, 22.63, 22.15, 17.17, 10.86. HR-MS (ESI): Calcd. $C_{22}H_{25}ClO_3$, $[M+H]^+$ *m/z*: 372.1570, found: 372.1571.

1,8a-dimethyl-6-oxo-7-(propan-2-ylidene)-1,2,3,4,6,7,8,8a-octahydronaphthalen-2-yl-2-methoxybenzoate (1h). White solid, yield 73%, mp: 102.1˚C - 103.7˚C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 - 6.96 (m, 4H, ArH), 5.80 (s, 1H HC = C), 5.11 - 5.01 (m, 1H, CH), 3.91 (s, 3H, CH_3), 2.97 (d, J = 13.7 Hz, 1H, CH_2), 2.56 (d, J = 13.7, 1H, CH_2), 2.45 - 2.31 (m, 2H, CH_2), 2.24 (d, J = 11.0 Hz, 1H, CH_2), 2.11 (s, 3H, CH_3), 1.87 (s, 3H, CH_3), 1.78 (d, J = 11.0 Hz, 1H, CH_2), 1.62 - 1.51 (m, 1H, CH), 1.10 (s, 3H, CH_3), 1.08 (d, J = 6.7 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.89, 191.67, 165.95, 165.27, 159.13, 143.36, 133.47, 131.31, 127.18, 126.70, 120.13, 112.09, 74.07, 55.90, 46.27, 42.29, 41.17, 31.61, 30.16, 22.59, 22.12, 17.19, 10.74. HR-MS (ESI): Calcd. $C_{23}H_{28}O_4$, $[M+H]^+$ *m/z*: 368.2071, found: 368.2072.

4.1.2. General Procedure for the Synthesis of Compounds 2a-e

A mixture of petasin derivatives (1 equiv) which were synthesized as the route II and m-ClC_6H_5COOOH (1.5 equiv) in CH_2Cl_2 was stirred at room temperature for 3 h. The disappearance of petasin derivatives was monitored by TLC. Upon completion, the solvent was removed and water was added, the reaction mixture was extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$ and concentrated under vacuum to afford the crude product. The crude product was purified by a flash column to yield the pure product **2a-e**.

3',3',8,8a-tetramethyl-3-oxo-3,5,6,7,8,8a-hexahydro-1H-spiro[naphthalene-2,2'-oxiran]-7-ylbenzoate (2a). White solid, 90%, mp: 136.1˚C - 137.6˚C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 - 7.48 (m, 5H, ArH), 5.97 (s, 1H, HC = C), 5.14 (m, 1H, CH), 2.66 (d, J = 14.5 Hz, 1H, CH_2), 2.54 - 2.45 (d, J = 14.5 Hz, 1H, CH_2), 2.38 (d, J =

11.2 Hz, 1H, CH_2), 2.28 - 2.15 (m, 2H, CH_2), 1.89 (d, *J* = 11.2, 1H, CH_2), 1.72 - 1.64 (m, 1H, CH), 1.48 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.05 (d, *J* = 6.7 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.74, 167.29, 166.14, 133.17, 130.13, 129.59, 129.59, 128.46, 128.46, 125.42, 73.47, 65.79, 65.15, 47.00, 42.12, 40.48, 31.47, 30.48, 21.20, 19.31, 18.93, 10.68. HR-MS (ESI): Calcd. $C_{22}H_{26}O_4$, $[M+H]^+$ *m/z*: 354.1925, found: 354.1924.

3',3',8,8a-tetramethyl-3-oxo-3,5,6,7,8,8a-hexahydro-1H-spiro[naphthalene-2,2'-oxiran]-7-yl-4-methoxybenzoate (2b). White solid, yield 92%, mp: 206.4˚C - 208.8˚C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 - 6.95 (m, 4H, ArH), 5.96 (s, 1H, HC = C), 5.10 (m, 1H, CH), 3.89 (s, 3H, CH_3), 2.66 (d, *J* = 14.5 Hz, 1H, CH_2), 2.49 (d, *J* = 14.5 Hz, 1H, CH_2), 2.40 - 2.33 (d, *J* = 11.2 Hz, 1H, CH_2), 2.27 - 2.08 (m, 2H, CH_2), 1.87 (d, *J* = 11.2 Hz, 1H, CH_2), 1.76 - 1.68 (m, 1H, CH), 1.48 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), 1.03 (d, *J* = 6.7 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.76, 167.47, 165.89, 163.55, 131.63, 131.63, 125.36, 122.50, 113.70, 113.70, 73.04, 65.81, 65.14, 55.48, 47.07, 42.13, 40.49, 31.55, 30.51, 21.19, 19.31, 18.93, 10.66. HR-MS (ESI): Calcd. $C_{23}H_{28}O_5$, $[M+H]^+$ *m/z*: 384.1995, found: 384.1996.

3',3',8,8a-tetramethyl-3-oxo-3,5,6,7,8,8a-hexahydro-1H-spiro[naphthalene-2,2'-oxiran]-7-yl-2-nitrobenzoate (2c). White solid, yield 91%, mp: 169.8˚C - 171.7˚C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 - 7.68 (m, 4H, ArH), 5.96 (s, 1H, HC=C), 5.15 (m, 1H, CH), 2.63 (d, *J* = 14.8 Hz, 1H, CH_2), 2.52 (d, *J* = 14.7 Hz, 1H, CH_2), 2.47 (d, *J* = 11.2 Hz, 1H, CH_2), 2.13 (m, 2H, CH_2), 1.78 (d, *J* = 11.2 Hz, 1H, CH_2), 1.70 - 1.63 (m, 1H, CH), 1.48 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), 1.04 (d, *J* = 6.7 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.62, 166.79, 165.14, 147.90, 133.03, 131.82, 129.58, 127.77, 125.49, 124.01, 75.51, 65.72, 65.13, 46.56, 42.13, 40.36, 30.65, 30.30, 21.19, 19.27, 18.92, 10.59. HR-MS (ESI): Calcd. $C_{22}H_{25}NO_6$ $[M+H]^+$ *m/z*: 399.2785, found: 399.2783.

3',3',8,8a-tetramethyl-3-oxo-3,5,6,7,8,8a-hexahydro-1H-spiro[naphthalene-2,2'-oxiran]-7-yl-2-fluorobenzoate (2d). White solid, yield 87%, mp: 136.4˚C - 137.8˚C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 - 7.32 (m, 4H, ArH), 5.97 (s, 1H HC = C), 5.16 - 5.05 (m, 1H, CH), 2.66 (d, *J* = 14.4 Hz, 1H, CH_2), 2.46 (d, *J* = 14.4 Hz, 1H, CH_2), 2.41 - 2.33 (d, *J* = 11.1 Hz, 1H, CH_2), 2.26 - 2.11 (m, 2H, CH_2), 1.89 (d, *J* = 11.2 Hz, 1H, CH_2), 1.72 - 1.63 (m, 1H, CH), 1.48 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.04 (d, *J* = 6.7 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.68, 167.0, 164.99, 163.73, 161.27, 132.31, 130.17, 125.34, 120.14, 116.61, 74.01, 65.76, 65.16, 46.91, 42.11, 40.46, 31.39, 30.41, 21.19, 19.29, 18.93, 10.69. HR-MS (ESI): Calcd. $C_{22}H_{25}FO_4$, $[M+H]^+$ *m/z*: 372.1805, found: 372.1806.

3',3',8,8a-tetramethyl-3-oxo-3,5,6,7,8,8a-hexahydro-1H-spiro[naphthalene-2,2'-oxiran]-7-yl-2-fluorobenzoate (2e). White solid, yield 87%, mp: 123.8˚C - 124.1˚C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 - 6.87 (m, 4H, ArH), 5.92 (s, 1H HC=C), 4.86 (m, 1H, CH), 3.82 (s, 3H, CH_3), 3.58 (s, 2H, CH_2), 2.53 (d, *J* = 14.4 Hz, 1H, CH_2), 2.46 (d, *J* = 14.4 Hz, 1H, CH_2), 2.23 - 2.11 (d, *J* = 11.2 Hz, 1H, CH_2), 2.04 (m, 2H, CH_2), 1.68 (d, *J* = 11.2 Hz, 1H, CH_2), 1.54 - 1.47 (m, 1H, CH), 1.45 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.21 (s, 3H, CH_3), 0.86 (d, *J* = 6.7 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.68, 171.53, 167.21, 158.76, 130.19, 130.19, 125.95, 125.35, 114.03, 114.03, 73.20, 65.74, 65.08, 55.26, 46.73, 42.02, 40.82, 40.39, 31.28, 30.37, 21.16, 19.21, 18.91, 10.37. HR-MS (ESI): Calcd. $C_{24}H_{30}O_5$, $[M+H]^+$ *m/z*: 398.2160, found: 398.2161.

4.1.3. General Procedure for the Synthesis of Compounds 4a-b

A mixture of petsasinol (1 equiv) and Maleic anhydride (0.9 equiv) in CH_2Cl_2 in the presence of $(C_2H_5)_3N$ (1 equiv) was stirred at 0˚C for 2 h. The disappearance of compound petsasinol was monitored by TLC. Upon completion, the solvent was removed and water containing HCl was added, the reaction mixture was extracted with CH_2Cl_2. The combined organic layer was dried over anhydrous $MgSO_4$ and concentrated under vacuum to afford the crude product. The crude product was added to a stirred solution of Excessive halids in the presence of $NaCO_3$ in DMF at 65˚C. The disappearance of the crude product was monitored by TLC. Upon completion, the solvent was removed and water containing NaCl was added, the reaction mixture was extracted with EA. The combined organic layer was dried over anhydrous $MgSO_4$ and concentrated under vacuum to afford the crude product. The crude product was purified by a flash column to yield the pure product **4a-b**.

allyl (1,8a-dimethyl-6-oxo-7-(propan-2-ylidene)-1,2,3,4,6,7,8,8a-octahydronaphthalen-2-yl)-fumarate (4a). Yellow oil, yield 68%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.31 (d, *J* = 12.2 Hz, 1H, HC = C), 6.28 (d, *J* = 12.1 Hz, 1H, HC = C), 5.97 (m, 1H, HC = C), 5.80 (s, 1H, HC = C), 5.38 (d, *J* = 17.2 Hz, 1H, HC = C), 5.30 (d, *J* = 10.4 Hz, 1H, HC = C), 4.96 (m, 1H, CH), 4.71 (d, *J* = 5.8 Hz, 2H, CH_2), 2.94 (d, *J* = 13.7 Hz, 1H, CH_2), 2.49 (d, *J* = 13.6, 4.4 Hz, 1H, CH_2), 2.34 (m, 2H, CH_2), 2.21 (d, *J* = 11.2 Hz, 1H, CH_2), 2.11 (s, 3H, CH_3), 1.87 (s, 3H, CH_3),

1.74 - 1.67 (d, J = 11.2 Hz, 1H, CH_2), 1.51 (m, 1H, CH), 1.05 (s, 3H, CH_3), 1.02 (d, J = 6.7 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.64, 164.89, 164.84, 163.42, 143.65, 131.53, 130.02, 129.58, 127.01, 126.76, 118.97, 75.03, 65.92, 45.99, 42.23, 41.10, 31.23, 29.99, 22.63, 22.14, 17.17, 10.70. HR-MS (ESI): Calcd. $C_{22}H_{28}O_5$, $[M+H]^+$ *m/z*: 372.2015, found: 372.2013.

1,8a-dimethyl-6-oxo-7-(propan-2-ylidene)-1,2,3,4,6,7,8,8a-octahydronaphthalen-2-yl-propylfumarate (4b). Yellow oil, yield 69%, ^1H NMR (400 MHz, $CDCl_3$) δ 6.29 (d, J = 12.3 Hz, 1H, HC = C), 6.25 (d, J = 12.3 Hz, 1H, HC = C), 5.80 (s, 1H, HC = C), 4.95 (m, 1H, CH), 4.16 (t, J = 6.8 Hz, 2H, CH_2), 2.94 (d, J = 13.7 Hz, 1H, CH_2), 2.50 (d, J = 13.7 Hz, 1H, CH_2), 2.41 - 2.27 (m, 2H, CH_2), 2.21 (d, J = 11.1 Hz, 1H, CH_2), 2.11 (s, 3H, CH_3), 1.87 (s, 3H, CH_3), 1.74 (dd, J = 14.3, 7.1 Hz, 2H, CH_2), 1.69 - 1.64 (d, J = 11.1 Hz, 1H, CH_2), 1.56 - 1.48 (m, 1H, CH), 1.05 (s, 3H, CH_3), 1.02 (d, J = 6.7 Hz, 3H, CH_3), 0.98 (t, J = 7.4 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.66, 171.60, 165.32, 164.88, 143.55, 130.10, 129.54, 127.04, 126.76, 74.91, 66.92, 51.64, 45.99, 42.22, 41.09, 31.23, 30.00, 22.62, 21.81, 20.72, 17.15, 10.70. HR-MS (ESI): Calcd. $C_{22}H_{30}O_5$, $[M+H]^+$ *m/z*: 374.2174, found: 374.2172.

4.1.4. General Procedure for the Synthesis of Compounds 8a-c

A mixture of petasinol (1 equiv) and TsOCl (1.5 equiv) in CH_2Cl_2 in the presence of $(C_2H_5)_3N$ (1 equiv) was stirred at 0˚C for 6 h. Then the mixture was filtered and concentrated in vacuum. The residue was purified by flash column to yield the pure product **5**. The NaN_3 was added to a stirred solution of product **5** in DMF at 95˚C for 8 h. The disappearance of product 5 was monitored by TLC. After purification, the product **6** was afforded and was reduced with Zn power (1 equiv) in the presence of NH_4Cl (2 equiv) to produce **7**. Condensation of product **7** with different kinds of acyl chloride (2 equiv) in CH_2Cl_2 in the presence of $(C_2H_5)_3N$ (1 equiv) resulted in acyl derivatives. Upon completion, the solvent was removed and water was added, the reaction mixture was extracted with CH_2Cl_2. The combined organic layer was dried over anhydrous $MgSO_4$ and concentrated under vacuum to afford the crude product. The crude product was purified by a flash column to yield the pure product **8a-c**.

N-(1,8a-dimethyl-6-oxo-7-(propan-2-ylidene)-1,2,3,4,6,7,8,8a-octahydronaphthalen-2-yl)acetamide (8a). Yellow oil, yield 66%, ^1H NMR (400 MHz, $CDCl_3$) δ 5.96 (s, 1H, NH), 5.75 (s, 1H, HC = C), 4.21 (m, 1H, CH), 2.87 (d, J = 14.4 Hz, 1H, CH_2), 2.44 (d, J = 14.6, Hz, 1H, CH_2), 2.24 - 2.18 (d, J = 11.1 Hz, 1H, CH_2), 2.15 - 2.04 (m, 2H, CH_2), 2.09 (s, 3H, CH_3), 2.02 (s, 3H, CH_3), 1.82 (s, 3H, CH_3), 1.75 - 1.67 (d, J = 11.1 Hz, 1H, CH_2), 1.24 (m, 1H, CH), 1.03 (s, 3H, CH_3), 1.01 (d, J = 6.7 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.44, 169.98, 165.75, 144.53, 127.17, 127.11, 49.39, 43.82, 41.67, 41.03, 30.95, 27.18, 23.77, 22.80, 22.31, 18.18, 12.02. HR-MS (ESI): Calcd. $C_{17}H_{25}NO_2$, $[M+H]^+$ *m/z*: 275.1972, found: 275.1975.

2-chloro-N-(1,8a-dimethyl-6-oxo-7-(propan-2-ylidene)-1,2,3,4,6,7,8,8a-octahydronaphthalen-2-yl)acetamide (8b). Yellow oil, yield 66%, ^1H NMR (400 MHz, $CDCl_3$) δ 6.98 (s, 1H, NH), 5.83 (s, 1H, HC = C), 4.20 (m, 1H, CH), 4.13 (s, 2H, CH_2), 2.93 (d, J = 14.2 Hz, 1H, CH_2), 2.47 (d, J = 14.2 Hz, 1H, CH_2), 2.32 - 2.23 (d, J = 11.1 Hz, 1H, CH_2), 2.18 - 2.03 (m, 2H, CH_2),2.13 (s, 3H, CH_3), 1.85 (s, 3H, CH_3), 1.75 (d, J = 11.1 Hz, 1H, CH_2), 1.26 (m, 1H, CH), 1.11 (s, 3H, CH_3), 1.07 (d, J = 6.7 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.40, 165.75, 165.17, 144.61, 127.17, 127.06, 50.17, 43.76, 43.01, 41.58, 40.89, 30.75, 27.03, 22.78, 22.26, 17.88, 12.09. HR-MS (ESI): Calcd. $C_{17}H_{24}ClNO_2$, $[M+H]^+$ *m/z*: 309.1579, found: 309.1580.

4-chloro-N-(1,8a-dimethyl-6-oxo-7-(propan-2-yli-dene)-1,2,3,4,6,7,8,8a-octahydronaphthalen-2-yl)benzamide (8c). Yellow oil, yield 66%, ^1H NMR (400 MHz, $CDCl_3$) δ 7.71 - 7.45 (m, 4H, ArH), 6.33 (s, 1H, NH), 5.86 (s, 1H, HC = C), 4.43 (m, 1H, CH), 2.95 (d, J = 14.2 Hz, 1H, CH_2), 2.49 (d, J = 14.2 Hz, 1H, CH_2), 2.33 - 2.28 (d, J = 11.1 Hz,), 2.22 - 2.19 (m, 2H, CH_2), 2.15 (s, 3H, CH_3), 1.92 (d, J = 11.3 Hz,), 1.87 (s, 3H, CH_3), 1.31 - 1.25 (m, 1H, CH), 1.17 (s, 3H, CH_3), 1.13 (d, J = 6.7 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.37, 166.38, 165.29, 144.75, 137.92, 133.09, 131.46, 129.05, 128.77, 128.13, 127.24, 127.06, 50.12, 44.03, 41.59, 41.05, 30.89, 27.20, 22.83, 22.32, 18.29, 12.18. HR-MS (ESI): Calcd. $C_{22}H_{26}ClNO_2$, $[M+H]^+$ *m/z*: 371.1710, found: 371.1708.

4.2. Bioassays

4.2.1. Grow Inhibition Assay

The petasin derivatives were assayed for *in vitro* anticancer activity by using MTT method. Cells were seeded in 96-well plates at a density of 4.6×10^3 cells/well for 24 h. The cancer cell lines included SK-N-SH, MGC-803

and HepG-2. The seeded cells were treated with various concentrations of the test derivatives for 48 h. After 20 ml of MTT (3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide) solution (5 mg/mL) was added to each well and incubated for 4 h at 37˚C. The medium containing MTT was discarded; then 150 mL of dimethyl sulfoxide (DMSO) was added to each well. And the plates were agitated until the dark blue crystals (formazan) had completely dissolved. The absorbance was measured using a microplate reader at a wavelength of 490 nm. The average 50% inhibitory concentration (IC_{50}) was determined from the concentration response curves according to the inhibition ratio for each concentration.

4.2.2. Statistical Analysis

Cell activity data were analysed by the SPSS 17.0 software and were expressed as means ± standard error (SE).

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