

Supplementary Methods

Synthesis of Flavonoid Derivatives

General procedure of compound 1-4

Hydroxyketones and nitro-substituted benzaldehydes were added to ethanol to give clear solution. To the solution was added 50% (w/w) KOH under ice-bath and the reaction mixture was stirred for 6–12 h at room-temperature. After completion of reaction, the reaction mixture was poured into an ice-water and acidified with 3N HCl. The resulting precipitate was filtered and washed with water. When oil was formed after acidification, it was extracted using appropriate organic solvents. The combined organic layers were dried over MgSO₄. Filtration and evaporation of organic solvent gave a crude solid. The resulting solid was purified with appropriate solvent.

Typical procedures for preparation of chalcone derivatives 4

2-hydroxy-6-methoxyacetophenone (166 mg, 1 mmol) and *m*-nitrobenzaldehyde (151 mg, 1 mmol) were added to 10 ml of ethanol. To the reaction mixture was added 1 ml of 50% (w/w) KOH under ice-bath and the stirred for 12 h at room-temperature. After completion of reaction, the reaction mixture was poured into a 100 ml of ice-water and the resulting solution was acidified with 3N HCl (pH = 3–4) to give a crude precipitate. The resulting solid was filtered and washed with water. The resulting solid was purified with methanol. (Yield: 66%, m.p: 178–180°C, orange)

Typical procedures for preparation of compound 5

According to the procedure of compound 1-4, 2-hydroxynaphthochalcone was synthesized by using 2-hydroxy-1-acetonaphthone (372 mg, 2 mmol) and *m*-nitrobenzaldehyde (302 mg, 2 mmol) as starting materials. Obtained 2-hydroxynaphthochalcone (160 mg, 0.5 mmol) was added to 10 ml of ethanol-water (1:1) mixture solution and catalytic amount of sodium acetate was added to the mixture. The reaction mixture was refluxed at 85°C for 8 h. TLC was applied to check the end-point of the reaction. After completion of reaction, the solvent was evaporated to give a crude precipitation. The crude precipitation was washed with 1:1 mixture of EtOH:H₂O. Purification under EtOH provided pure compound of 5. (Yield: 47%, m.p: 184–186°C, yellow)

General procedure of compound 6-13

To a solution of DMSO was added appropriate chalcones (compound 1-4) and catalytic amount of iodine. The reaction mixture was refluxed at 120°C for 1.5–2 h. The reaction mixture was cooled to room-temperature and poured into ice water to give a precipitate. Under vigorous stirring Na₂S₂O₃ was added to remove iodine. The precipitate was filtered and washed with cold ethanol to give pure compounds.

Typical procedures for preparation of flavone derivative 12

To a solution 1.2 ml of DMSO was added compound 4 (100 mg, 0.3 mmol) and catalytic amount of iodine (20 mol %). The reaction mixture was refluxed at 120°C for 2 h. The reaction mixture was cooled to room temperature and poured into ice water to give a precipitate. The temperature was cooled down under vigorous stirring and Na₂S₂O₃ was added to cold solution to remove iodine. The precipitate was filtered and washed with cold ethanol to give pure compound of 12. (Yield: 62%, m.p:182–184 °C, ivory)

Table S1. The list of flavonoids and derivatives tested in this study.

	Name	MW
	2',3'-DIHYDROXYFLAVONE	254.24
	2',4'-DIHYDROXYFLAVONE	254.24
	3',4'-DIHYDROXYFLAVONE	254.24
	2',3'-DIMETHOXYFLAVONE	282.31
	2',4'-DIMETHOXYFLAVONE	282.31
	3',4'-DIMETHOXYFLAVONE	282.3
	4'-HYDROXY-3'-METHOXYFLAVONE	268.27
	3-HYDROXYFLAVONE	238.24
	3,2'-DIHYDROXYFLAVONE	254.24
	3,3'-DIHYDROXYFLAVONE	254.24
	3,4'-DIHYDROXYFLAVONE	254.24
	3,2'-DIMETHOXYFLAVONE	282.31
	3,3'-DIMETHOXYFLAVONE	282.31
	3,4'-DIMETHOXYFLAVONE	282.31
	3-HYDROXY-2'-METHOXYFLAVONE	268.27
	3-HYDROXY-3'-METHOXYFLAVONE	268.27
	3-HYDROXY-4'-METHOXYFLAVONE	268.27
	3,6-DIHYDROXYFLAVONE	254.24
	3,7-DIHYDROXYFLAVONE	254.24
FLAVONE	3,6-DIMETHOXYFLAVONE	282.31
	3,7-DIMETHOXYFLAVONE	282.31
	3-HYDROXY-6-METHYLFLAVONE	264.29
	3-HYDROXY-6-METHOXYFLAVONE	268.27
	3-HYDROXY-7-METHOXYFLAVONE	268.27
	5,3'-DIHYDROXYFLAVONE	254.24
	5,4'-DIHYDROXYFLAVONE	254.24
	5,4'-DIMETHOXYFLAVONE	282.31
	5,2'-DIMETHOXYFLAVONE	282.31
	4'-HYDROXY-5-METHOXYFLAVONE	254.27
	5,3'-DIMETHOXYFLAVONE	254.24
	5-HYDROXY-7-METHOXYFLAVONE	268.27
	6,2'-DIHYDROXYFLAVONE	254.24
	6,3'-DIHYDROXYFLAVONE	254.24
	6,4'-DIHYDROXYFLAVONE	254.24
	6,2'-DIMETHOXYFLAVONE	282.31
	6,3'-DIMETHOXYFLAVONE	282.31
	6,4'-DIMETHOXYFLAVONE	282.31
	6-HYDROXY-2'-METHOXYFLAVONE	268.27
	6-HYDROXY-3'-METHOXYFLAVONE	268.27
	6-HYDROXY-4'-METHOXYFLAVONE	268.27

Table S1. The list of flavonoids and derivatives tested in this study.

	7-HYDROXYISOFLAVONE	238.25
	7-METHOXYISOFLAVONE	252.27
	7,4'-DIMETHOXY-5-HYDROXYISOFLAVONE	346.33
	7,3',4'-TRIHYDROXYISOFLAVONE	270.24
	3',4'-DIMETHOXY-7-HYDROXYISOFLAVONE	298.3
	6,4'-DIMETHOXY-7-HYDROXYISOFLAVONE	298.3
	7-HYDROXY-6-METHOXYISOFLAVONE	268.27
	5,7,3',4'-TETRAMETHOXYISOFLAVONE	342.35
	7,3',4'-TRIMETHOXYISOFLAVONE	312.33
ISOFLAVONE	2'-CHLORO-5,7-DIMETHOXYISOFLAVONE	316.74
	3'-CHLORO-5,7-DIMETHOXYISOFLAVONE	316.74
	4'-CHLORO-5,7-DIMETHOXYISOFLAVONE	316.74
	6-CHLORO-4',7-DIMETHOXYISOFLAVONE	316.74
	4'-CHLORO-7-HYDROXY-8-METHYLISOFLAVONE	286.72
	4'-CHLORO-7-METHOXY-8-METHYLISOFLAVONE	300.74
	2',6-DICHLORO-7-METHOXYISOFLAVONE	321.16
	4',7-DIMETHOXY-8-METHYLISOFLAVONE	296.33
	4'-BROMO-5,7-DIMETHOXYISOFLAVONE	361.19

Table S1. The list of flavonoids and derivatives tested in this study.

	5,7,4'-TRIHYDROXY-3'-METHOXYFLAVANONE	302.29
	3,7,3',4',5'-PENTAHDROXYFLAVANONE)	304.27
	2,3-DIHDROXYFLAVANONE	224.26
	3,5,7,3',4'-PENTAHDROXYFLAVANONE	304.26
	3,7,3',4'-TETRAHDROXYFLAVANONE	288.26
	2'-HDROXYFLAVANONE	240.26
	3'-HDROXYFLAVANONE	240.26
	4'-HDROXYFLAVANONE	240.26
	6-HDROXYFLAVANONE	240.27
	5-METHOXYFLAVANONE	254.29
	6-METHOXYFLAVANONE	254.29
	2',3'-DIMETHOXYFLAVANONE	284
	3',4'-DIMETHOXYFLAVANONE	283.31
	ERIODICTYOL-7-MTINOSIDE	596.53
	4'-HDROXY-5,7-DIMETHOXYFLAVANONE	300.31
	4'-HDROXY-3'-METHOXYFLAVANONE	270.29
	NARIGENIN-7-NEOHESPERIDOSIDE	580.53
	6,2',3'-TRIMETHOXYFLAVANONE	314.34
	6,2',4'-TRIMETHOXYFLAVANONE	314.34
FLAVANONE	6,3',4'-TRIMETHOXYFLAVANONE	314.34
	7,2',3'-TRIMETHOXYFLAVANONE	314.34
	4'-METHOXYFLAVANONE	254.29
	6,3'-DIMETHOXYFLAVANONE	284.31
	4',5,7'-TRIMETHOXYFLAVANONE	314.34
	5,2',3'-TRIMETHOXYFLAVANONE	314.34
	7,3',4',5'-TETRAMETHOXYFLAVANONE	244.35
	6-CHLORO-3',4'-DIMETHOXYFLAVANONE	318.76
	8-CHLOROFLAVANONE	258.71
	8-CHLORO-4'-FLUOROFLAVANONE	276.7
	6-CHLORO-4'-METHYLFLAVANONE	272.73
	8-CHLORO-4'-METHYLFLAVANONE	272.73
	FLAVANONE AZINE	444.55
	FLAVANONE DIACETYLHYDRAZONE	322.35
	FLAVANONE HYDRAZONE	238.28
	3,7,3',4'-TETRAHDROXYFLAVANONE	288.26
	7,4'-DIHDROXYFLAVANONE	256.26
	4',5,7'-TRIHYDROXY-3'-METHOXYFLAVANONE	302.29
	3,3',4',5,5',7'-HEXAHYDROXYFLAVANONE	320.26
	HESPERETIN-7-O-NEOHESPERIDOSIDE	610.57
	ISOSALCURANETIN-7-O-NEOHESPERIDOSIDE	594.57

The names and molecular weights of all 40 flavones, 40 flavanones and 19 isoflavones tested for the inhibitory effects on the interaction between PIP3-AKT PH domain in this study.

Table S2. The structural information of synthesized flavonoid derivatives.

	R ₁	R ₂	R ₃
1	3,4-phenyl	NO ₂	H
2	3,4-phenyl	OCH ₃	H
3	5,6-phenyl	OCH ₃	H
4	6-OCH ₃	NO ₂	H
5	5,6-phenyl	NO ₂	H
6	3,4-phenyl	OCH ₃	H
7	3,4-phenyl	H	OCH ₃
8	5,6-phenyl	H	OCH ₃
9	5,6-phenyl	OCH ₃	H
10	5,6-phenyl	NO ₂	H
11	5,6-phenyl	H	NO ₂
12	6-OCH ₃	NO ₂	H
13	6-OCH ₃	H	NO ₂

The Rs indicate the positions on flavonoid derivatives shown in Fig. S1.

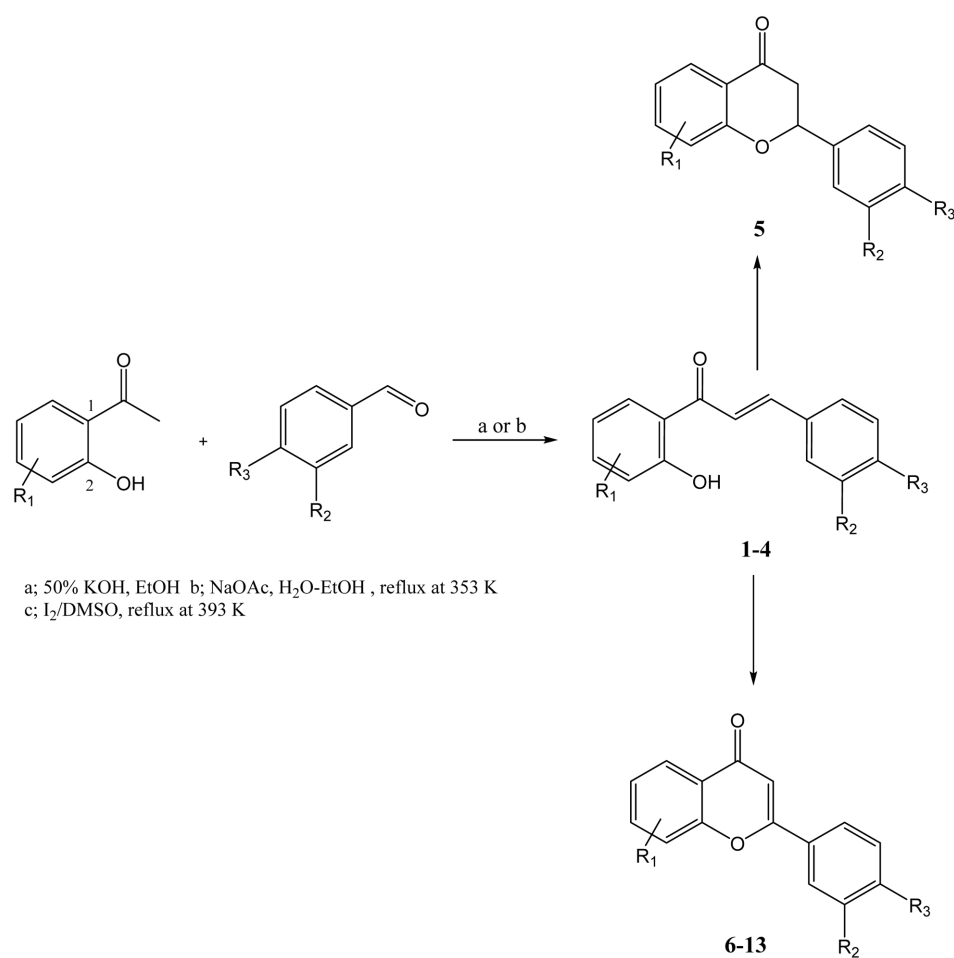


Fig. S1. Scheme to synthesize flavonoid derivatives.