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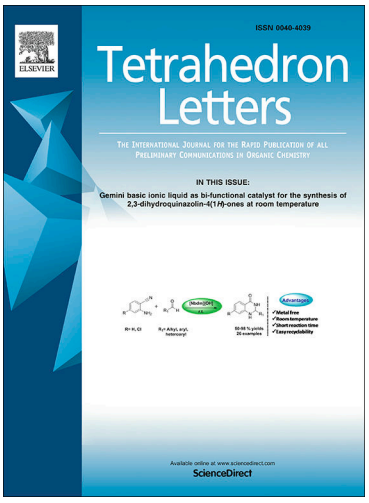

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Cytisine-flavonoid conjugates: synthesis and antitumor structure-activity relationship research

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Abstract: In research of anti-triple negative breast cancer (TNBC) agents, a series of cytisine-flavonoid conjugates (**A-1~G-1**) were designed and synthesized in high yields with (-)-cytisine and flavonoids *via* *N,N*-4-dimethyl-4-aminopyridine (DMAP)-catalyzed synthetic strategy. In addition, the *in vitro* cytotoxicity of the conjugates was tested, and the results showed that some compounds had better cytotoxicity against human breast cancer cells (MDA-MB-231) than the positive control drug Paclitaxel. The studies of structure-activity relationship showed that the conjugates formed by cytisine featuring 5-chloro and flavonoids had better anti-proliferative effect on MDA-MB-231 cells.

Keywords: Cytisine, Flavonoid, Antitumor, Structure-activity relationship

1. Introduction

Natural products have afforded a rich source of compounds and made a huge contribution to human health, especially in the anticancer area, as many anticancer drugs are from natural products and their derivatives[1-3]. Nowadays, the treatment of cancer remains a major challenge, encouraging the sustaining discovery of new lead compounds. Among the research subjects of anticancer drug discovery, the treatment of triple negative breast cancer (TNBC), characterized by tumors that do not express estrogen receptor (ER), progesterone receptor (PR), or human epidermal growth factor receptor 2 (HER2)[4], has been a tough task for breast oncologists for a long time.

(-)-Cytisine is a quinolone alkaloid in the family Leguminosae or Fabaceae, which has been used as respiratory analgesic[5] and smoking cessation drug in Europe for many years[6]. Now, it has been used clinically to treat nicotine addiction[7]. Moreover, recent studies clearly showed that chemically modified cystine showed interesting anti-proliferative activity against human cancer cells[8]. Therefore, the development of rational structural modification of (-)-cytisine[9] for the lead compound discovering for the treatment of TNBC is meaningful.

The combination of pharmacophores is a useful strategy for the rational design of lead compounds. In this context, the natural product tonkinensine B isolated from the roots of *Sophora tonkinensis*, featuring the biologically active (-)-maackiain and (-)-cytisine pharmacophores, was found to having good cytotoxicity against human breast cancer cells (MDA-MB-231) and low cytotoxic effects on the central nervous system in our previous research[10]. Interestingly, tonkinensine B could be synthesized easily by

our biomimetic strategy from (-)-maackiain and (-)-cytisine. However, the small amount of (-)-maackiain in plants greatly limited the synthesis of tonkinensine B in large quantities[11,12], and made the further biological research of tonkinensine B difficult.

As we all know, (-)-maackiain belongs to the flavonoid family, which is the part of polyphenols that widely distributed in natural plants. The structures of flavonoids are consisted of two benzene rings (A and B) and an oxygen-containing heterocyclic ring (C) (**Figure 1**). The subclasses of flavonoids included flavones, isoflavones, flavanones, and others[13,14]. In addition, flavonoids have a wide range of pharmacological properties in terms of antioxidant activity, hepatoprotective activity, antibacterial activity and anticancer activity due to their structure diversity[15,16]. For instance, epicatechin and rutin are strong radical scavengers and inhibitors of lipid peroxidation *in vitro*[17]. Silymarin can be used to treat cirrhosis, ischemic injury, and toxic hepatitis[18]. In recent years, a large number of studies have been carried out on the structural modification of flavonoids, as well as the structure-activity relationship, and the modes of action of the corresponding compounds[19-21]. The results showed that flavonoids were known to be good cytotoxic agents[22-27], and certain anti-proliferative effects on human cancer cells were also determined[28-30].

In this context, we hypothesized that the replacement of (-)-maackiain with readily available natural flavonoids to form a new array of conjugate with (-)-cytisine could circumvent the low yield of tonkinensine B. Herein, a new series of cytisine-flavonoid conjugates and their structure-activity relationship against MDA-MB-231 cells were reported.

2. Results and discussion

2.1. Synthesis

According to previous research, the methylene linker of the conjugates could be installed *via* established aminomethyiation process[31-35]. Thus, with the good nucleophilicity of flavonoids, the cytisine-flavonoid conjugates can be synthesized readily with (-)-cytisine and flavonoids *via N,N*-4-dimethyl-4-aminopyridine (DMAP)-catalyzed aminomethylation under mild conditions. Accordingly, several (-)-cytisine derivatives (**1 ~ 5**) and natural flavonoids (**A ~ E**) were used as substrates (**Figure 1**). To our delight, with the participation of formaldehyde (HCHO), the desired conjugates (**A-1 ~ E-5**) were obtained in good yields (**Scheme 1**) by using *N,N*-4-dimethyl-4-aminopyridine as the catalyst and 1,4-dioxane as the solvent. The result showed that the aminomethylation of 7-hydroxyflavonoids occurred predominantly at 8-position of the chromone core. In the aim of increasing the structure diversity of the conjugates, we assumed that the occupation of 8-position will release the nucleophilicity at 6-position. To prove this hypothesis, a one-pot iodination/Suzuki cross-coupling cascade of flavonoid **A** and **C** was conducted (**Scheme 2**) to block the 8-position. The high regioselectivity of the iodination with *N*-iodosuccinimide (NIS) was facilitated by the good nucleophilicity at 8-position and the fluorinated alcohols[36]. Thus, the 8-phenyl substituted flavonoid derivatives **F** and **G** were obtained in good yields.

With the 8-position blocked flavonoid derivatives **F** and **G** in hand, the aminomethylation process was tested again (**Scheme 3**). Expectingly, the 6-cytisinylmethyl derivatives **F-1** and **G-1** were formed smoothly under the same

conditions. Therefore, a conclusion can be drawn that aminomethylation of 7-hydroxyflavonoids mainly occurred at 8-position of the chromone core. When 8-position was occupied, the reaction occurred at 6-position. The yields of all this new series of conjugates (**A-1 ~ G-1**) were listed in **Table 1**. It's worth noting that all of the synthesized compounds (except **E-1**[33]) are first reported.

2.2. Biological Evaluation

It is known that natural flavonoids and (-)-cytisine have antitumor activities[8, 28-30]. Since the synthesis process completely retains the skeletons of these two natural compounds, it is expected that the newly obtained conjugates will have meliorative biological activities. Thus, the cytotoxicity efficacy of all synthesized compounds (**A-1 ~ G-1**) were tested on MDA-MB-231 cells by using 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. The results obtained were summarized in **Figure 2** (A ~ D), with the drug Paclitaxel (PTX) as the positive control.

The experiment results showed that the newly prepared compounds had better anti-proliferation effects on MDA-MB-231 cells than the starting materials. Some compounds even had better cytotoxicity against MDA-MB-231 cells than PTX (IC_{50} = 25.2 ± 6.3 μM), such as **A-2** (IC_{50} = 22.3 ± 1.6 μM), **A-3** (IC_{50} = 21.9 ± 0.8 μM), **A-4** (IC_{50} = 18.4 ± 0.3 μM), **B-4** (IC_{50} = 24.6 ± 2.2 μM), and **E-4** (IC_{50} = 20.1 ± 0.1 μM). The same set of compounds (**A-1 ~ A-5**) exhibited good anti-proliferative effects on MDA-MB-231 cells.

2.3. Structure-activity relationship

Structure-activity relationship (SAR) studies of the synthesized compounds revealed

the dependence of activity on the type of substitutions presenting both on the cytisine and flavonoids pharmacophores. It should be noted that the cytisine-flavonoid conjugates (**A-4**, **B-4**, **E-4**) formed from 5-chlorocytisine (**4**) and flavonoids (**A**, **B**, **E**) had good performance of anti-proliferative effect on MDA-MB-231 cells. The better potent compound **A-4** (IC_{50} = 18.4 ± 0.3 μM), which exhibited about 1.4 times improvement in activity compared to the positive control drug Paclitaxel (IC_{50} = 25.2 ± 6.3 μM). Therefore, 5-chlorocytisine is of great significance for improving the antitumor activity among cytisine-flavonoid derived compounds. Conversely, the introduction of electron withdrawing groups (such as chloro-, bromo-, and nitro-) at 3-position of (-)-cytisine has no positive effect and may even reduce the activity.

At the same time, we found that the cytisine-flavonoid conjugates synthesized from 7-hydroxyflavonoid (**A**) had better antiproliferative effect than the ones from 7-hydroxyisoflavone and 7-hydroxyflavanone. Interestingly, with the effects of the hydroxyl or methoxy group at 4′-position of 7-hydroxyisoflavones (**D** and **E**), the potency of (-)-cytisine-7-hydroxyisoflavones conjugates against MDA-MB-231 cells can be improved. However, not only the 8-cytisinylmethyl derivatives had a better cytotoxicity against MDA-MB-231 cells, but also the 6-cytisinylmethyl derivatives (**F-1** and **G-1**) exhibited good performance of the anti-proliferative effect. (**Figure 3**)

3. Conclusion

In summary, a novel class of cytisine-flavonoid conjugates were designed and synthesized from readily available flavonoids and (-)-cytisine in order to improve the

inhibitory activity against MDA-MB-231 cells. The results showed that most of the compounds had good cytotoxic activity against MDA-MB-231 cells, and five analogs **A-2**, **A-3**, **A-4**, **B-4**, and **E-4** showed better inhibitory activity. Compound **A-4** containing mono substituted electron-withdrawing chlorine group at 5-position of (-)-cytisine was the better potent inhibitor (IC_{50} = 18.4 ± 0.3 μM), and it was found to have about 1.4 times better activity compared to paclitaxel. Thus, further modification and structure derivatization may lead to the development of selective inhibitors against MDA-MB-231 cells with more potency for the treatment of TNBC patients.

Declaration of Competing Interest

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.

Acknowledegments

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Appendix A. Supplementary data

Supplementary dataassociated with this article can be found, in the online version, at http://

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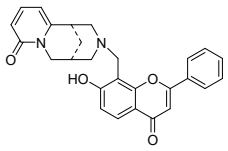
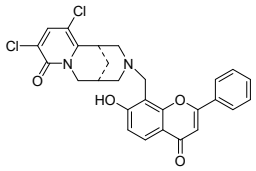
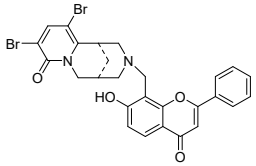
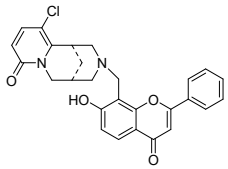
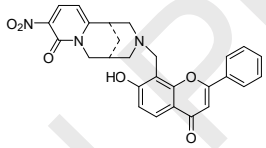
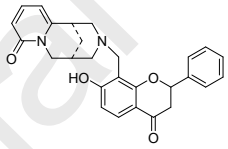
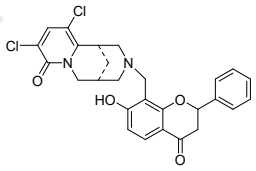
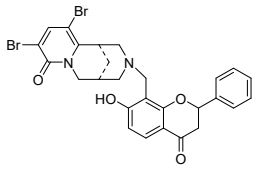
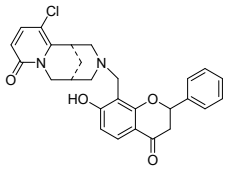
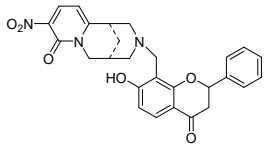
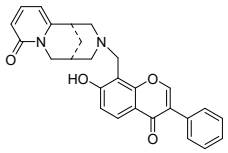
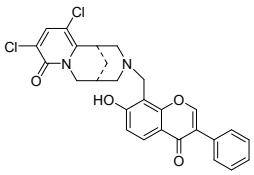
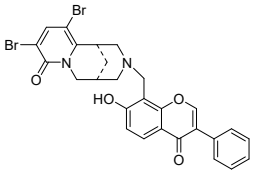
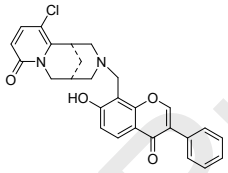
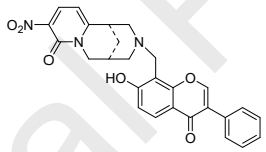
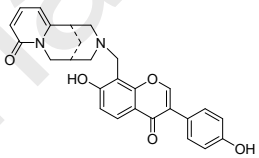
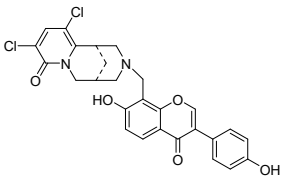
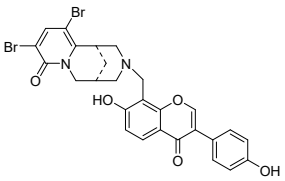
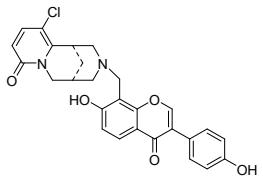
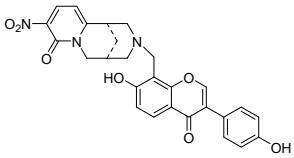
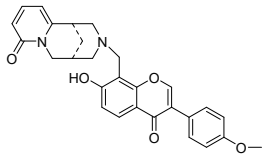
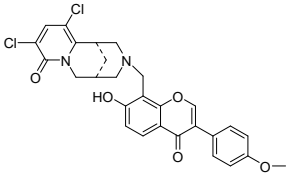
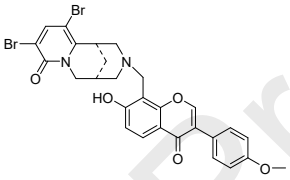
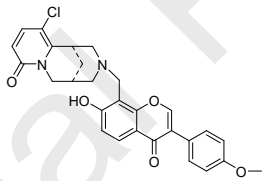
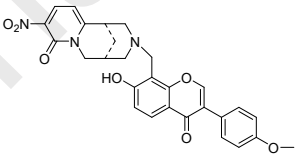
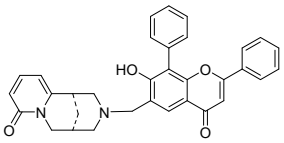
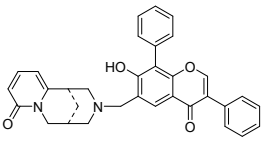
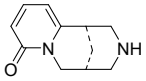
Table 1. Appearance, Yields and IC_{50} values of Compounds

Entry	Compounds	Structure	Appearance	Yields (%)	IC_{50} (μM)
1	**A-1**		White solid	73%	35.0 ± 1.1
2	**A-2**		Yellow solid	61%	22.3 ± 1.6
3	**A-3**		White solid	64%	21.9 ± 0.8
4	**A-4**		White solid	75%	18.4 ± 0.3
5	**A-5**		Yellow solid	85%	58.6 ± 7.9
6	**B-1**		Yellow solid	70%	57.0 ± 1.2
7	**B-2**		Yellow solid	44%	>200
8	**B-3**		Yellow solid	57%	>200
9	**B-4**		White solid	44%	24.6 ± 2.2

10	**B-5**		Yellow solid	70%	>200
11	**C-1**		White solid	82%	93.0 ± 6.4
12	**C-2**		White solid	82%	>200
13	**C-3**		White solid	84%	>200
14	**C-4**		White solid	78%	34.6 ± 6.3
15	**C-5**		Yellow solid	84%	>200
16	**D-1**		White solid	82%	137.6 ± 16.2
17	**D-2**		White solid	63%	74.8 ± 0.2
18	**D-3**		White solid	63%	104.3 ± 0.6

19	**D-4**		White solid	59%	32.0 ± 0.4
20	**D-5**		Yellow solid	55%	156.4 ± 16.8
21	**E-1**		White solid	83%	58.1 ± 2.5
22	**E-2**		White solid	83%	**>** 200
23	**E-3**		White solid	76%	**>** 200
24	**E-4**		White solid	63%	20.1 ± 0.1
25	**E-5**		Yellow solid	82%	107.0 ± 6.9
26	**F-1**		White solid	58%	83.1 ± 4.9
27	**G-1**		White solid	62%	38.7 ± 2.2
28	**Positive Control**	Paclitaxel	White solid	—	25.2 ± 6.3
29	**1**		Yellow solid	—	105.1 ± 2.3

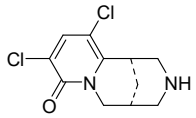
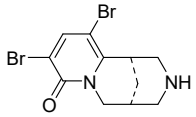
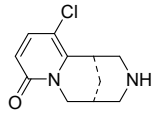
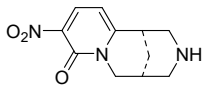
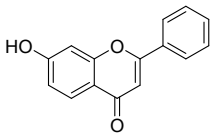
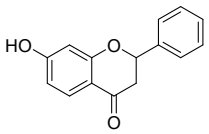
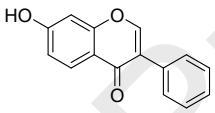
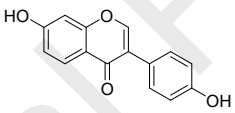
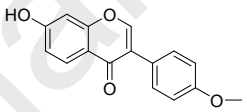
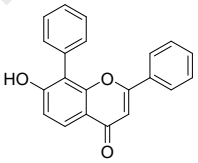
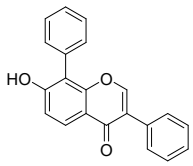
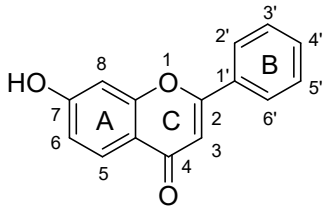
30	**2**		Yellow solid	40%	＞200
31	**3**		Yellow solid	79%	＞200
32	**4**		Yellow solid	45%	＞200
33	**5**		Yellow solid	61%	＞200
34	**A**		Yellow solid	—	＞200
35	**B**		Redsolid	—	＞200
36	**C**		Yellow solid	—	＞200
37	**D**		White solid	—	＞200
38	**E**		White solid	—	＞200
39	**F**		White solid	72%	＞200
40	**G**		White solid	51%	109.26 ± 13.68

Figure Captions

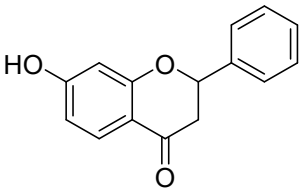
Figure 1. The structures of flavonoids (**A ~ E**) and cytisine derivatives (**1 ~ 5**)

Figure 2. Comparing of the cytotoxicity efficacy of cytisine-flavonoid conjugates (except $IC_{50} > 200$).

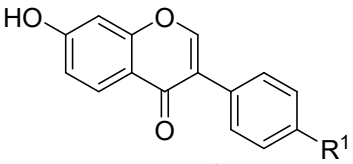
Figure 3. SAR study of cytisine-flavonoid conjugates as potent anti-breast cancer agent.



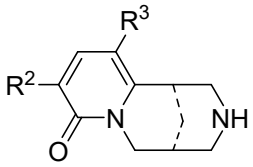
A



B



C: R^1 = H
D: R^1= OH
E: R^1= OCH_3



1: R^2 = R^3 = H;
2: R^2 = R^3 = Cl;
3: R^2 = R^3 = Br;
4: R^2 = H, R^3 = Cl;
5: R^2 = NO_2, R^3 = H

Figure 1.

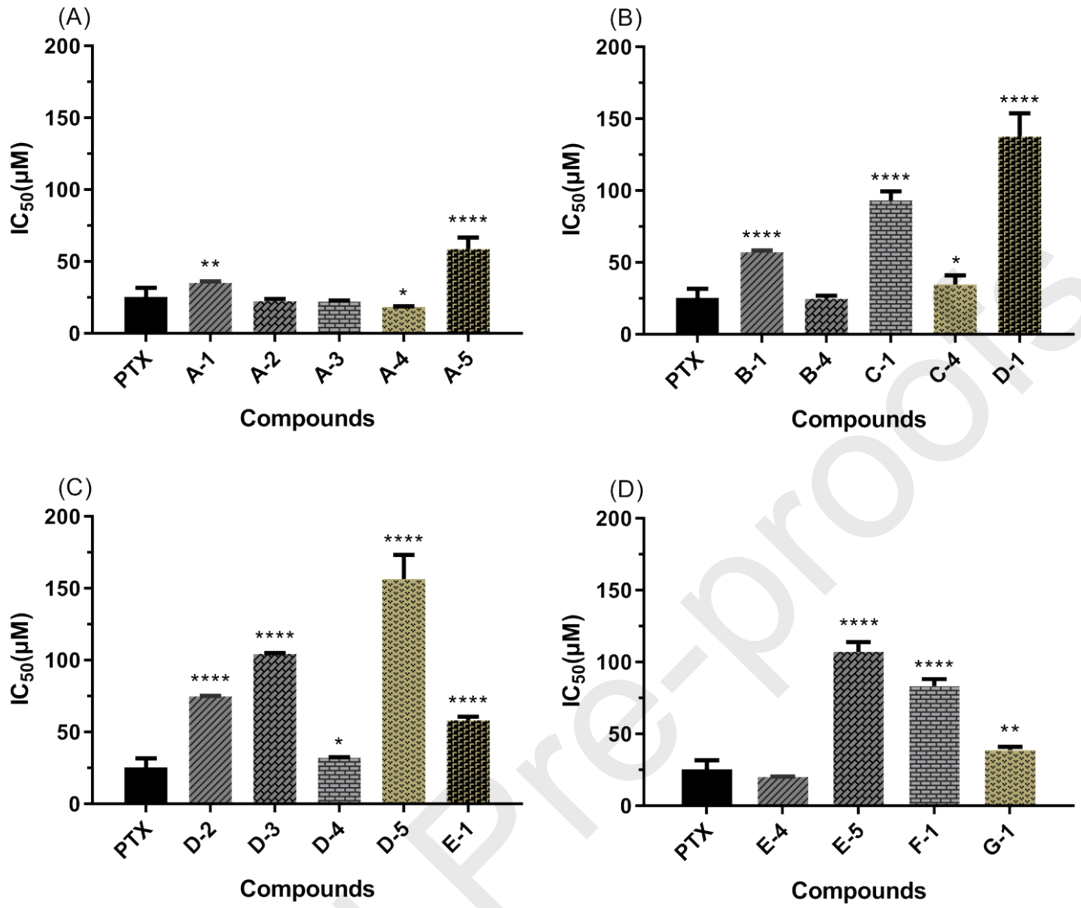


Figure 2.

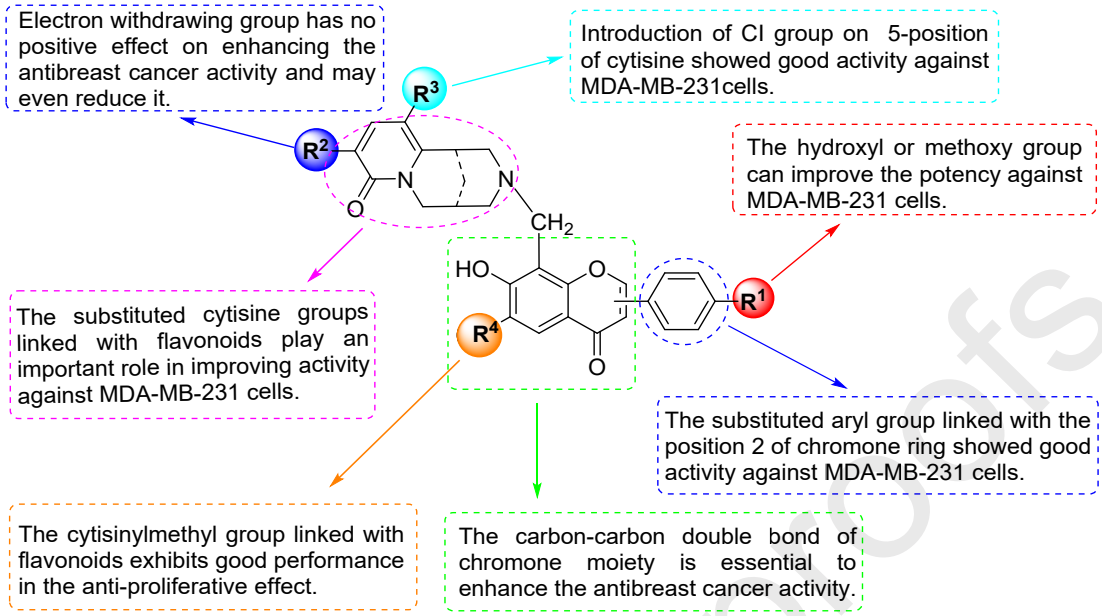


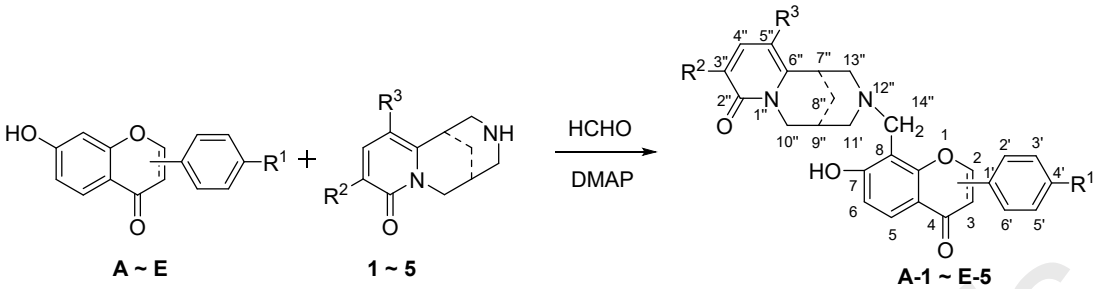
Figure 3.

Scheme Captions

Scheme 1. Synthesis of cytisine-flavonoid conjugates **A-1 ~ E-5**.

Scheme 2. Synthesis of flavonoid derived compounds **F** and **G**.

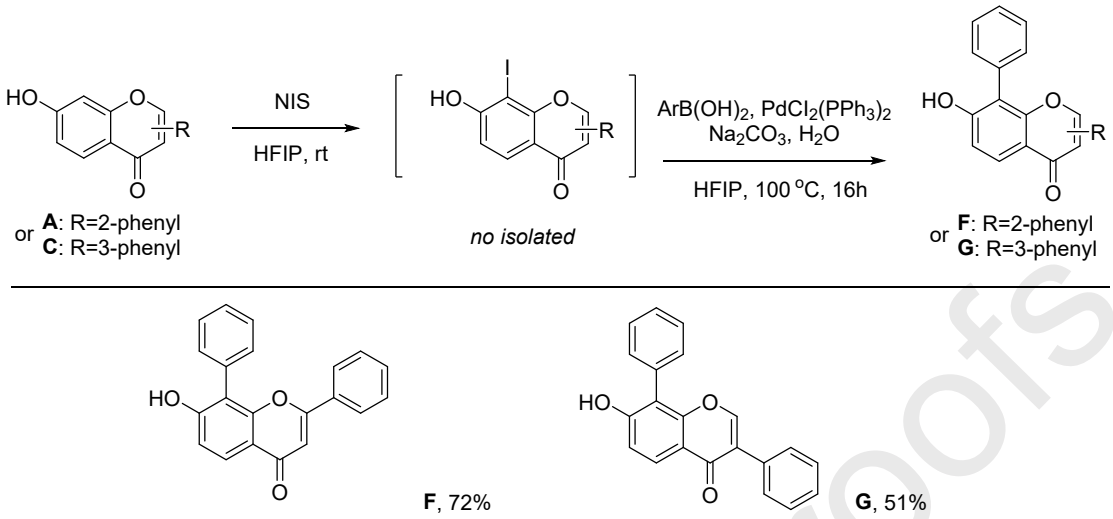
Scheme 3. Synthesis of cytisine-flavonoid conjugates **F-1** and **G-1**.



A, B, C: R^1 = H; **D:** R^1 = OH; **E:** R^1 = OCH_3; **1**: R^2 = R^3 = H; **2**: R^2 = R^3 = Cl; **3**: R^2 = R^3 = Br; **4**: R^2 = H, R^3 = Cl; **5**: R^2 = NO_2, R^3 = H; **A-1, B-1, C-1:** R^1 = R^2 = R^3 = H; **D-1:** R^1 = OH, R^2 = R^3 = H; **E-1:** R^1 = OCH_3, R^2 = R^3 = H; **A-2, B-2, C-2:** R^1 = H, R^2 = R^3 = Cl; **D-2:** R^1 = OH, R^2 = R^3 = Cl; **E-2:** R^1 = OCH_3, R^2 = R^3 = Cl; **A-3, B-3, C-3:** R^1 = H, R^2 = R^3 = Br; **D-3:** R^1 = OH, R^2 = R^3 = Br; **E-3:** R^1 = OCH_3, R^2 = R^3 = Br; **A-4, B-4, C-4:** R^1 = R^2 = H, R^3 = Cl; **D-4:** R^1 = OH, R^2 = H, R^3 = Cl; **E-4:** R^1 = OCH_3, R^2 = H, R^3 = Cl; **A-5, B-5, C-5:** R^1 = R^3 = H, R^2 = NO_2; **D-5:** R^1 = OH, R^2 = NO_2, R^3 = H; **E-5:** R^1 = OCH_3, R^2 = NO_2, R^3 = H

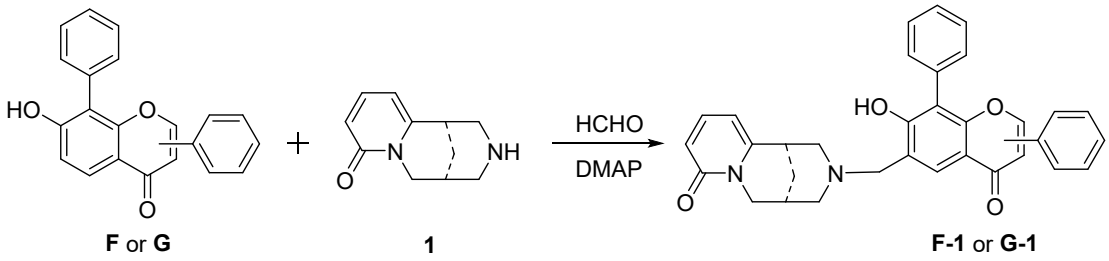
Scheme 1. Synthesis of cytisine-flavonoid conjugates **A-1 ~ E-5**.

[a] Conditions: **A ~ E** (1.0 mmol), **1 ~ 5** (1.2 mmol), 1,4-dioxane (10 mL), DMAP (0.02 mmol, 2.5 mg), HCHO (2.0 mmol, 37 ~ 40%), 110 °C, 2 ~ 3h.



Scheme 2. Synthesis of flavonoid derived compounds **F** and **G**.

[a] Conditions: **A** or **C** (0.5 mmol) and NIS (0.5 mmol) in 2 mL HFIP for the first step. Then $ArB(OH)_2$ (0.75 mmol), Na_2CO_3 (1 mmol), $PdCl_2(PPh_3)_2$ (1.5 mol %) and 2 mL H_2O were added for the second step.



Scheme 3. Synthesis of cytisine-flavonoid conjugates **F-1** and **G-1**.

[a] Conditions: **F** or **G** (0.25 mmol), **1** (0.3 mmol), 1,4-dioxane (2.5 mL), DMAP (0.005 mmol, 0.6 mg), HCHO (0.5 mmol, 37 ~ 40%), 110°C, 2 ~ 3h.

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:

A series of cytisine-flavonoid conjugates were synthesized.
Some of the synthesized compounds showed good antineoplastic activities.
Compound **A-4** showed more potent antitumor activity against MDA-MB-231 cells.
Structure-activity relationship (SAR) of the synthesized compounds were studied.

Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

Cytisine-flavonoid conjugates: synthesis and antitumor structure-activity relationship research

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