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A REVIEW ON AMENTOFLAVONE

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ABSTRACT

Amentoflavone, is a bioflavonoid constituent of some of flora which includes ginkgo biloba, hypericum perforatum. It can have interaction with many medicinal drugs by using being a potent inhibitor of CYP3A4 and CYP2C9 which are enzymes chargeable for the metabolism of some drugs in the body. Flavonoids exhibit a extensive variety of activities including antioxidant, antiviral, Antibacterial and anticancer pastime. As formerly we showed that amentoflavone is an activator of hPPARγ. Human PPARγ (hPPARγ) regulates the proliferation, apoptosis, and various human most cancers cells. Activated hPPARγ has both tumor suppressor and tumor promoter. To affirm the mechanism of motion of amentoflavone in most cancers cells, we analyzed whether or not amentoflavone remedy affects the appearance of hPPARy the use of opposite transcription polymerase chain response and actual time quantitive PCR. Amentoflavone is synthesized with the aid of way of three techniques i.e natural, semi synthetic and synthetic methods. Among this synthetic method is widely used industrially. Application of the Suzuki-Miyaura response within the synthesis of flavonoids, is of vital magnificence of natural merchandise, is studied. Amentoflavone and three different flavonoids were separated from the ethanol extract of Selaginella sinensis. Amentoflavone show strong antiviral pastime in opposition to respiratory syncytial virus (RSV). The cytotoxic interest of amentoflavone is examined against 5 human most cancers cell strains (MCF-7, A549, HeLa, MDA-MB231, and PC3) treating with tetrazolium-primarily based colorimetric MTT assay. There is not such decided fixed dosage of amentoflavone.

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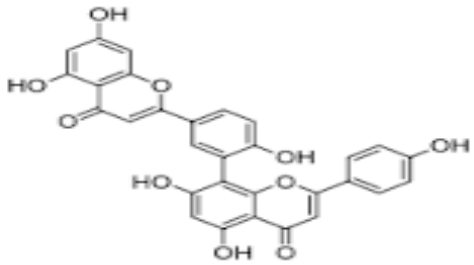
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INTRODUCTION

Amentoflavone, is a bioflavonoid constituent of some of flora which include ginkgo biloba, hypericum perforatum.[1] Amentoflavone extracted from plant Hypericum perforatum modified into evaluated for its topical anti–inflammatory activity. It can have interaction with many medicinal drugs by using being a potent inhibitor of CYP3A4 and CYP2C9 which are enzymes chargeable for the metabolism of some drugs in the body. [1] As it is a member of bioflavone beauty is of youngster constituent anti depressant. And described as high affinity inhibitor of benzodiazepines agonist.[2]

Flavonoids exhibit a extensive variety of activities including antioxidant, antiviral, Antibacterial and anticancer activities[3,]. As formerly we showed that amentoflavone is an activator of hPPARγ. Human PPARγ (hPPARγ) regulates the proliferation, apoptosis, and various human most cancers cells. Activated hPPARγ has both tumor suppressor and tumor promoter. It has moreover been said that activation of hPPARy motives increase in PTEN (phosphate and tensin homologue). Amentoflavone has antagonist interest inside the direction of hPPARγ this mechanism is unsure.[4]



Structure 1: Structure of Amentoflavone.

IUPAC NAME

8-[5-(5,7-Dihydroxy-4-oxo-chromen-2-yl)-2-hydroxyl-phenyl]-5,7-dihydroxy-2-(4-hydroxyphenyl) chromen-4-one.other names are Didemethyl-ginkgetin 3', 8"- Biapigenin[1]

CHEMICAL FORMULA[1]

$C_{30}H_{18}O_{10}$

CLASSIFICATION[5]

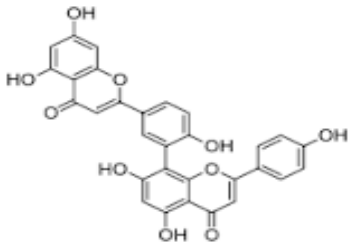
Amentoflavone is a bioflavonoid depending upon their nature they are classified as bioflavonoids.

a) Amentoflavone.
b) 7, 7"-di-O-methylamentoflavone.
c) 7, 4', 7", 4"'-tetra-O-methylamentoflavone.
d) Heveaflavone.

MODE OF ACTION

Jane R.Hanrahan et al shows that flavones is a class of flavonoid that binds to benzodiazepine site at GABAa receptor and apply anxiolytic activity in mice without any unwanted effects similar with the use of benzodiazepines.[6] He analyzed the mechanism of anticancer activity of amentoflavone. To confirm the mechanism of action of amentoflavone in cancer cells, Eunjung Lee et al analyzed whether amentoflavone treatment affects the appearance of hPPARy using reverse transcription polymerase chain reaction and real time quantitive PCR.[7] He first used RT-PCR for observe hPPARγ mRNA appearance and found that amentoflavone concentration dependent increase in hPPARγ mRNA levels in MCF-7and HeLa cells.[8]

STRUCTURAL ACTIVITY RELATIONSHIP [9]



Flavonoids exhibit a broad range of biological activities including antibacterial activity. However, the mechanism of their antibacterial activity has not been fully examined. The antibacterial activity and membrane interaction of 11 flavonoids (including 2 polymethoxyflavones and 4 isoflavonoids) against Escherichia coli were examined in this study. The antibacterial capacity was determined as flavonoids > polymethoxyflavones > isoflavonoids. A quantitative structure-activity relationship (QSAR) study demonstrated that the activity of the flavonoid compounds can be related to molecular hydrophobicity and charges on C atom at

position3 (C3). The QSAR model could be used to identify the antibacterial activity of flavonoids which could lead to natural compounds having important use in food and medical industry.

PREPARATION OF AMENTOFLAVONE

NATURAL METHOD OF PREPARATION [10]

According to Wen-yi Kang et al S. tamariscina is an essential Chinese traditional medicine[7]. Entire plant of was extracted with methanol at room temperature to yield the product. The methanol extract was re suspended in water, dicholoremethane, ethyl acetate and n-butanol. The ethyl acetate was placed in silica gel column and eluted using chloroform/methanol/water. Their TLC pattern were mixed to yield subfractions which were finally purified by repeated column chromatography with silica gel to give amentoflavone.

EXTRACTION AND ISOLATION OF AMENTOFLAVONE [10]

Acidic Extraction of S.tamariscina:

Dried powder of entire plant of S.tamariscina was extracted three times with acetone water at room temperature. After dehydration of the solvent in vacuum, the potent extract was suspended in water and extracted with petroleum ether, ethyl acetate and n–butanol to yield petroleum ether ethyl acetate and butanol extract.

Ethyl Acetate Fraction of S .tamariscina:

Dried powder of entire plant of S .tamariscina was extracted with NaOH solution three times at 50C for about 30 min. After filtration the filtrate was adjusted the PH value to 3.0 and the precipitate was dried in vacuum to yield ethyl acetate fraction of S.tamariscina.

Amentoflavone:

Acidic extraction of S. tamariscina was isolated on silica gel with petroleum ether ethyl acetate and amentoflavone was identified by the method of HPLC compared to amentoflavone standard. Majority of amentoflavone contained by fraction of petroleum ether and ethyl acetate this was further frequently chromatographed on sephadex to yield amentoflavone .

SEMI SYNTHETIC PREPARATION OF AMENTOFLAVONE

Jane R. Hanrahan et al show types for preparation of amentoflavone he used dead autumnal dried leaves of Ginkgo biloba for isolation of amentoflavone. The dried autumnal yellow leaves were grind to fine powder and first extracted twice with hexane to remove non polar components The unpurified bioflavone extract was purified using silica gel and similar chromatography to yield pure bioflavones which was recognized approximately a 1:1 combination of ginkgetin and isoginkgetin

Combination of ginkgetin and isoginkgetin was demthylated using hexadecyltribut- Phoshonium bromide in refluxing hydrogen bromide.The entire hydrolysis of all methoxyls occurs after 60-72 hr. The unpurified product was purified by using silica gel and similar chromatography a recrystalization to provide amentoflavone.[11]

SYNTHETIC PREPARATION OF AMENTOFLAVONE

3'-Iodo-4-Methoxybenzyaldehyde[5]

Lin RC etal shows preparation by using p-Anisaldehyde was dissolved in glacial acetic acid, iodine monochloride/ICl solution turned into dropped to the response combination heated to 60ºC and mixed for 10 h, then saturated NaS_2O_4 (aqueous) changed into dropped to the response combination till the answer was clean, evaporated to cast off CH_2Cl_2 and standed in ice-bathtub for 30 min for the duration of this era a white precipitate fashioned, filtered and got white solid, crystallized from methanol resulted inside the favored product. Yield 55%.

4, 4', 6'-Trimethoxy-3-Iodo-2'-Hydroxychalcone[12]

Saponara R et al shows method as mentioned in synthesis of 4, 4', 6'-trimethoxy- 3'-iodo-2'-hydroxy-chalcone. Yield 90%.

4', 5, 7-Trimethoxy-3'-Iodoflavone[11]

Hanrahan JR et al shows method mentioned in preparing 4', 5, 7-trimethoxy- 8-iodoflavone above. Yield: 98%.

4', 5, 7-Trimethoxy-3'-Pinacolatboronflavone[13]

Sosa S et al shows by using an oven-dried round-bottomed flask equipped with magnetic stir bar and a rubber septum cool at room temperature in a apparatus, the flask was charged with $PdCl_2$, 4',5,7-trimethoxy-3'-iodoflavone and potassium acetate then distilled dimethyl formamide is added to the flask through a syringe, the mixture is then degassed by nitrogen gas for 5 min, raising the temperature to 80ºC, refluxed for overnight, monitored by TLC. The mixture is cooled at room temperature, filtered, and HCL (10%) is added to destroy dimethyl formamide and then extracted by ethyl acetate. The organic layer is washed by brine and water, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuum. The crude material is purified by column ($CHCl_3$-methanol (100:1) to get the target compound. Yield 50%.

2-Hydroxy-4, 6-Dimethoxy-Acetophenone[10]

Yue SM et al shows preparation by using 2,4,6-Trihydroxyacetophenone is dissolved in anhydrous acetone with stirring and potassium carbonate is from methanol to yield 2-hydroxy- 4,6-dimethoxyacetophenone. Yield: 98%.

2-Hydroxy-3-Iodo-4, 6-Dimethoxy-Acetophenone [14]

Kunert O et al shows by using 2-Hydroxy-4,6-dimethoxyacetophenone is dissolved in glacial acetic acid, iodine solution in CHCl3 in ice-tub, HNO3 is dropped stirred in ice-tub for three hr, examine by TLC with solvent system of hexane-acetone .Saturated $Na_2S_2O_4$ aqueous is dropped in mixture till there is no exchange in colour extracted with dichloromethane washed with water(3 times). Natural layer is separated and dried over magnesium sulfate, concentrated in vacuum to yield brown solid. Yield 93%.

4, 4', 6'-Trimethoxy-3'-Iodo -2'-Hydroxy-Chalcone[15]

Mbaveng AT et al shows 2-Hydroxy-3-iodo-4,6-dimethoxy-acetophenone is dissolved in methanol mixed for 5~10 min until the solid dissolved completely, KOH is added and mixed until the solution became solid and 4-methoxybenzaldehyde is added to the reaction mixture, stirred for 20 h, 3% HCL is added to the solution follow by concentrated HCl until the solution was acidic (PH 6.5~7.0), some yellow solid formed and filter, wash with water, recrystallized from methanol to afford the title compound as yellow solid. Yield 90%.

4', 5, 7-Trimethoxy-8-Iodoflavone[16]

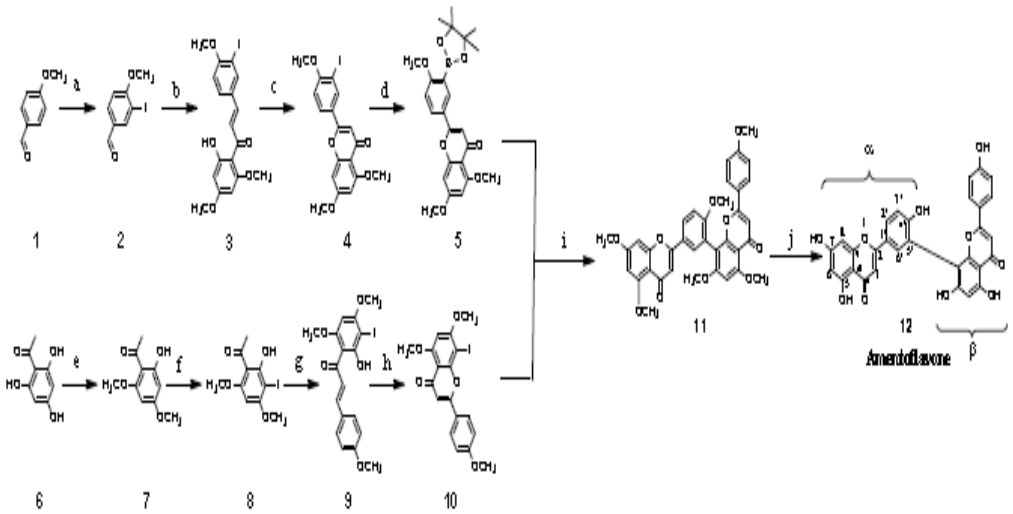
Muller D et al shows by using 4,4',6'-Trimethoxy-3'-iodo-2'-hydroxychalcone dissolved in dimethyl sulfoxide and iodine is added to the resulted solution and heated with stirring to 100ºC overnight, cooled the reaction at room temperature. Saturated $Na_2S_2O_3$ (aqueous) is added to the solution until the color no longer changed, filter and the solid are crystallized from methanol to get the title compound. Yield 95%.

4', 5, 7, 4''', 5'', 7''-Hexamethoxy-Amentoflavone[17]

Selepe MA et al shows by using an oven-dried round-bottomed flask equipped with magnetic stir bar and a rubber septum is allowed to cool at room temperature in a desiccator, the flask was charged with palladium, add 4',5,7-trimethoxy-3'-pinacolatoboron flavone , 4',5,7-trimethoxy-8-iodoflavone, and NaOH , then distilled dimethyl formamide-water (9:1) is added to the flask by syringe, the mixture is then degassed by nitrogen gas for 10 min, raising the temperature to 80ºC, refluxed for overnight. The mixture is cooled at room temperature, filter, and HCL (10%) is added to destroy dimethyl formamide, and then extracted by ethyl acetate, the organic layer is washed by brine and water, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuum, the crude material is purified by crystallization in methanol to get the target compound. Yield 51%.

Amentoflavone[18]

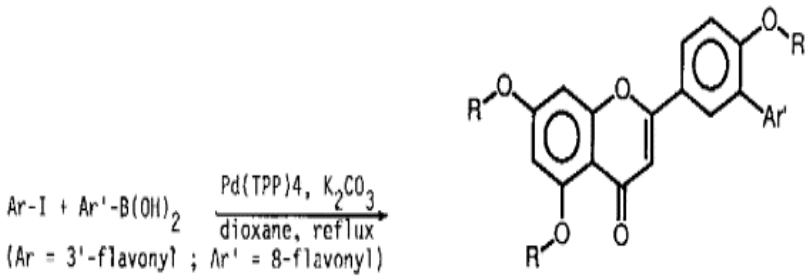
Jang J et al shows the preparation by using 4', 5, 7, 4''', 5'', 7''-Hexamethoxy-amentoflavone dissolved in $CHCl_3$ and BBr_3 is added to the solution and refluxed at 65ºC for 10 h. Reaction is observe by TLC. The reaction mixture is cooled at room temperature and followed by adding methanol to destroy BBr_3, concentrated in vacuum. The crude solid is washed with saturated $NaHCO_3$ (aqueous), filtered and washed by methanol to get the final product as a yellow solid. Yield 86%.



Structure 2: Synthetic preparation of amentoflavone [18]

SYNTHESIS OF AMENTOFLAVONE [18]

Amentoflavone derivatives are prepared by catalytic coupling reaction of 8- flavone- boronic acids with iodoflavones.3-arylflavones, as bioflavonoid are done by this method.



Structure 3: Synthesis of amentoflavone [18]

APPLICATION OF SUZUKI-MIYAURA REACTION [17]:

Selepe MA et al shows the application of Suzuki-miyaura in synthesis of flavonoids which is an important class of natural products. This reaction not only employed to give acces to flavonoid nuclei but also used for the dimeric synthesis of flavonoids.

PHARMACOLOGICAL ACTIVITIES OF AMENTOFLAVONE

Antiviral activity[19]:

Paul Pui-Hay et al shows anti viral activity of amentoflavone and three other flavonoids were separated from the ethanol extract of Selaginella sinensis. Amentoflavone display potent antiviral activity against respiratory syncytial virus (RSV). The contents of amentoflavone in species of Selaginella were confirmed by reversed-phase HPLC. Upper respiratory infection, mostly in infants and children, is a common disease worldwide. The nucleoside analog ribavirin is presently utilized widely for treating RSV infections in healthcare settings such as hospitals and nursing homes.

Anti inflammatory activity [18]:

Numerous quantity of wogonin derivatives were synthesized as identical as of wogonin and evaluated for their inhibitory activities of PGE2 production. Wogonin derivatives are improved at B ring of wogonin have been obtained from 2,4-Dihydroxy-3,6-dimethoxyacetophenone through numerous steps.

Inhibitory activity against phosphorlipase A_2 [20]:

The synthetic biflavones are presented in different inhibitory activities against $sPLA_2$-IIA. Among them, the biflavone having a C–C 4′–4′ linkage shows comparable inhibitory activity with that of natural biflavonoid, ochnaflavone, and 7-fold stronger activity than that of amentoflavone.

CONCLUSION

We have developed an efficient synthesis of amentoflavone from a valuable natural product by using Suzuki coupling. This method is commonly similar but different from the reported procedure. Amentoflavone is confirmed by Mass, NMR Spectroscopy and Melting point. The new developed methods for the synthesis of amentoflavone can be used for the generation of natural and biologically active bioflavonoid. It is commonly known that amentoflavone has many pharmacological activities. In this investigation the pharmaceutical and biological activities of amentoflavone shows the sronger cytotoxicities against MCF-7 and HeLa cancer cell lines.

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