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ISSN: 2637-4900

Journal of Community Medicine

Open Access | Review Article

Flavonoid and Stilbene Cytotoxic Phytochemicals Isolated from Genus Macaranga for the Treatment of Cancer Cells: A Review

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Received: Jun 27, 2021
Accepted: Jul 27, 2022
Published Online: Jul 29, 2022
Journal: Journal of Community Medicine
Publisher: MedDocs Publishers LLC
Online edition: http://meddocsonline.org/

Keywords: Cancer cells; Macaranga; Flavonoids; Stilbenes; Cytotoxic; Schweifurthins.

Abstract

Genus Macaranga contains more than 308 species and different species from this genus have variety class of secondary metabolites that are used for different therapeutic purposes. Flavonoids and stilbenes are the major compounds which are isolated from different species of Macaranga. These compounds are cytotoxic to different cancer cell lines like human breast adenocarcinoma (MCF-7), Human Hepatocellular (HepG2), Human Cervical Carcinoma (Hela) and mouse leukemia (P388) cell lines with high to low cytotoxic activities. Schweifurthins are some stilbenes that are isolated from various Macaranga species and have different cytotoxic activity to ward many cancer cells. The synthetic analogues of schweifurthins have also similar cytotoxicity as naturally occurring ones.

Introduction

Natural product chemistry has been a topic of great interest since ancient times, being relevant to the preparation of food stuff, coloring matters, fibers, toxins, medicine etc. Separation methods for the study of natural products have been developed and, without doubt, have greatly stimulated the development of the refined techniques used today, such as the various analytical and preparative chromatographic methods. These methods have made it possible for the isolation of extremely small quantities of compounds. Instruments used for the structural determination of compounds such as UV, IR, NMR and MS have been developed and refined rapidly [1,2].

The Plant Kingdom is an important source of chemical compounds. Compounds such as carbohydrates, amino acids and proteins are classified as primary metabolites, while alkaloids, terpenoides, saponins, steroids, flavonoids, and phenolic and like are classified as secondary metabolites. Such metabolites are essential to plant life, many of them providing a defense mechanism against bacterial, viral and fungal attack and are also analogous to the immune system of animals. Genus Macaranga is the source of variety of natural products that are used as therapeutic purpose [1-3].

Cite this article: Zeleke ZZ. Flavonoid and Stilbene Cytotoxic Phytochemicals Isolated from Genus Macaranga for the Treatment of Cancer Cells: A Review. J Community Med. 2022; 5(2): 1045.

The genus Macaranga belongs to the family Euphorbiaceae that contains more than 308 species [3] and these plants are shrubs or trees that grows up to 15 m tall. Members of this genus are known for their mutual associations with ants which give benefit for them by attacking or feeding on herbivorous insect. In folk medicine, traditional healers use fresh or dried leaves of some Macaranga species to treat swellings, cuts, sores, boils and bruises [4].

A phytochemical review of many literatures indicates that genus Macaranga is rich source of the isoprenylated, geranylated and farnesylated flavonoids and stilbenes [7]. Furthermore, more classes of secondary metabolites like terpenes, tannins, coumarins [4] and other types of compounds are known to be isolated from different species of the genus. Flavonoids and stilbenes are one of the major constituents and are most likely responsible for most of the activities found in the plants of this genus [5]. An increasing number of phytochemical studies are being carried out on plants belonging to the genus due to their various traditional uses. Thus, the isolated natural products from this genus have been reported to display interesting biological activities including antitumor [6,7], cytotoxic, antioxidant, antimicrobial and anti-inflammatory.

In this genus only 26 species including *M Alnifolia, M Barteri, M Bicolour, M Conifer, M Denticulata, M Gigantea, M Gigantifolia, M Hemsleyana, M Indica, M Kurzii, M Lowii, M.Mappa, M Monandra, M.Peltata, M.Pleiostemona, M Pruinosa, M Recurvata, M Rhizinoides, M Ampsonii, M Schweinfurthii, M Sinensis, M Tanarius, M Trichocarpa, M Triloba and M Vedeliana* have been investigated phytochemically [8]. About 190 secondary metabolites have been isolated and identified from this genus. The isolated compounds include flavonoids, stilbenes, tannins, terpenes. coumarins, steroids and other types of compounds. About 90% of the isolated compounds have been reported from the leaves while only 10% is from the other parts [8,9].

Pharmacological studies of genus *Macaranga* indicate the potential of extracts and pure compounds to display specific medical effects. Investigation on the chemistry and pharmacology of this genus showed that its crude extracts and compounds displayed interesting biological activities including anticancer [6,7] and many another biological activities like antifungal, antiviral, antibacterial, antioxidant, antitumor, anti-inflammatory etc [8].

There for the goal of this review paper to assess and evaluates the scientific evidence for the therapeutic claims for Macaranga species in cytotoxicity medical use and summarizes some of species that contains cytotoxic chemical constituents and shows the total synthesis of naturally occuring schweinfurthins anlalogeous.

Cytotoxic phytochemicals isolated from genus macaranga

Materials and methods

Different literature materials are used for references and source of data. Journals, Google scholars, websites, published thesis papers and other literature materials were used for source of information

Introduction to cytotoxic chemicals

Cytotoxic chemicals (drugs) describe a group of medicines that contain chemicals which are toxic to immune cells, preventing their replication or growth, and so are used to treat cancer. They can also be used to treat a number of other disorders such as rheumatoid arthritis and multiple sclerosis. Once inside the body, their action is not generally tightly targeted, and they can produce side effects both to the patients and others who become exposed [11].

Anticancer activity

Cancer is abnormal growth of tissue or cell in which the cell grows spreads and divides in uncontrolled way. Also it is called malignancy. Some cancers may eventually spread into other tissues. Cancer starts when gene changes make one cell or a few cells begin to grow and multiply too much. This may result a growth called a tumor. There are more than 200 types of cancer, including breast cancer, skin cancer, lung cancer, colon cancer, prostate cancer, and lymphoma. Symptoms vary depending on the type.

According [11] based on cell type cancer can group in to five main types as follows;

i. **Carcinoma -** Cancer that begins in the skin or in tissues that line or cover internal organs. There are different subtypes, including adenocarcinoma, basal cell carcinoma, squamous cell carcinoma and transitional cell carcinoma.

ii. **Sarcoma** - Cancer that begins in the connective or supportive tissues such as bone, cartilage, fat, muscle or blood vessels.

iii. **Leukemia** - Cancer that starts in blood forming tissue such as the bone marrow and causes abnormal blood cells to be produced and go into the blood.

iv. **Lymphoma and myeloma** - Cancers that begin in the cells of the immune system open a glossary item

v. **Brain and spinal cord cancers** - These are known as central nervous system cancers.

Cancer treatment may include chemotherapy, radiation, and/or surgery [11]. Many cancers are cured. But in some people cancer can return. Some cancers can't be cured but treatment is often able to control them for some years. Chemotherapy is one of the treatments that use of any drug to treat any disease. But to most people, the word chemotherapy means drugs used for cancer treatment. It's often shortened to "chemo" Surgery and radiation therapy remove, kill, or damage cancer cells in a certain area, but chemo can work throughout the whole body. This means chemo can kill cancer cells that have spread to parts of the body far away from the original (primary) tumor. The main goal of chemotherapy treatment is cure, if possible to destroy, control, if cure is not possible that prevent growth and spread by shrinking tumor and palliation, when the cancer is in advanced condition, meaning it's not under control and has spread from where it started to other parts of the body, the goal may be to improve the quality of life or help the person feel better. Palliative care is used to treatment that's used to reduce symptoms or improve comfort [11-13].

Class of compounds isolated from macaranga genus

Some of cytotoxic chemicals and species that contains cycotoxic chemicals from this genus includes apigenin (**1**) from *M Gigantifolia* [14], flavonoids and flavones most of them are prenylated from *M Triloba* [15], *M Denticulata* [5], *M Indica* [16], *M Adenantha* [17], *M Hispida* [18], *M Lowii* [19], flavonoids and stilbene derivatives from *M Pruinosa, M Recurvata, M Rhizinoides* and *M Trichocarpa* [20], bibenzyls and flavonoids from *M*

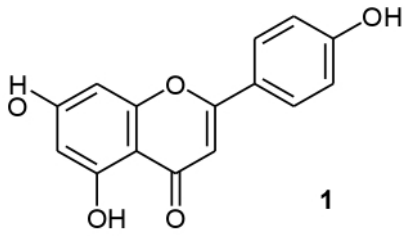
Kurzi, prenylated stilbenes from *M Tanarus* [3], *M Siamensis* and *M Alinofolia* and geranyl (two isoprene unit) stilbenes from *M Schweinfurthii* [21]. Many of the cytotoxic chemicals from the genus are prenylated (one isoprene unit) flavonoids and stilbenes (**2**, **11**, **12**, **13**, **16-18** and **21-23**) and some of them are geranylated (**6**, **10**, **19** and **24-28**) and fransylated (three isoprene unit) (**8**, **9**, 20) [8].

Some cytotoxic chemicals from genus macaranga and their cytotoxicity

Genus Macaranga is the rich source of natural products which have variety of biological active compounds that are used for treat different types of diseases. Among the compounds flavonoids and stilbenes are the major constituents. These flavonoids and stilbenes have different cytotoxic activity for different cancer cell lines [8].

Cytotoxic chemical from macaranga *gigantifolia*

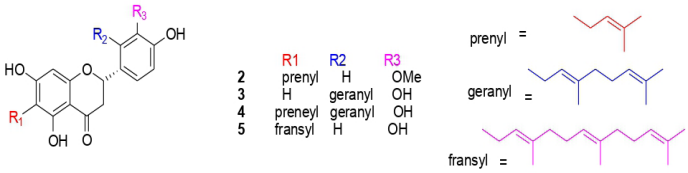
Apigenin (**1**) a flavonoid compound isolated from *Macaranga gigantifolia* leaves and have cytotoxic activity against murine leukimia P-388 cell line with potential activity of IC50 (µg/mL) 14.13 [14].



Scheme 1: Wachemo University Dep.

Cytotoxic chemicals from macaranga trilobi

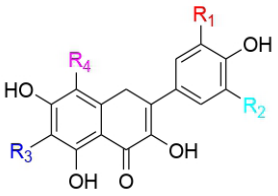
Prenylated, geranylated and farnesylated flavonoids isolated from this plant have been reported to possess several cytotoxic activities. Flavonoids were cytotoxic against three cancer cell lines, namely HL-60 (human leukemia), MCF-7 (human breast cancer), and HeLa (human cervical cancer). The Compounds (**2**), (**3**) and (**4**) showed moderate activity towards HeLa cell lines with IC50 of 12.2, 17.0 and 18.2 respectively and weak activity towards MCF-7 with IC50 22.8, 23.5 and 23.0 respectively. Compound (**5**) exhibited very strong cytotoxic activity against HeLa and HL-60 with IC50 values of 1.3, 3.3 respectively and strong inhibition against MCF-7 cells with IC50 value 5.6. Compounds (**2**) and (**4**) were moderately active against HL-60 cell lines with IC50 value of 15.1 and 11.6, respectively, while (**3**) weakly inhibited the growth of HL-60 cell line with IC50 21.3 [15].



Scheme 2: Structure of some cytotoxic compounds from *M.triboli.*

Cytotoxic chemicals from *Macaranga indica*

Prenylated, geranylated and farnesylated flavonoids isolated from this plant also have anticancer activity for four human cell lines. Compounds (**6-12**) showed cytotoxic activity against human breast adenocarcinoma (MCF-7), Human Hepatocellular (HepG2), Human Cervical Carcinoma (Hela) and mouse leukemia (P388) cell lines. Compounds **12, 7** and **9** inhibit the proliferation of MCF-7 cell line with IC50 values of 15.23, 9.74 and 7.88 respectively. Compounds **(8)** and (**11**) showed cytotoxic activity against HepG2 cell line with IC50 values of 11.84 and 20.35 respectively. Compounds **(8)** and (**11**) exhibit cytotoxicity against Hela cell line with IC50 values of 8.71 and 16.06 respectively. Compounds (**6**) and (**12**) showed cytotoxicity against P388 cell line with IC50 values of 11.82, 18.94 and 3.27 respectively [16]. The compounds are shown in Scheme **3**

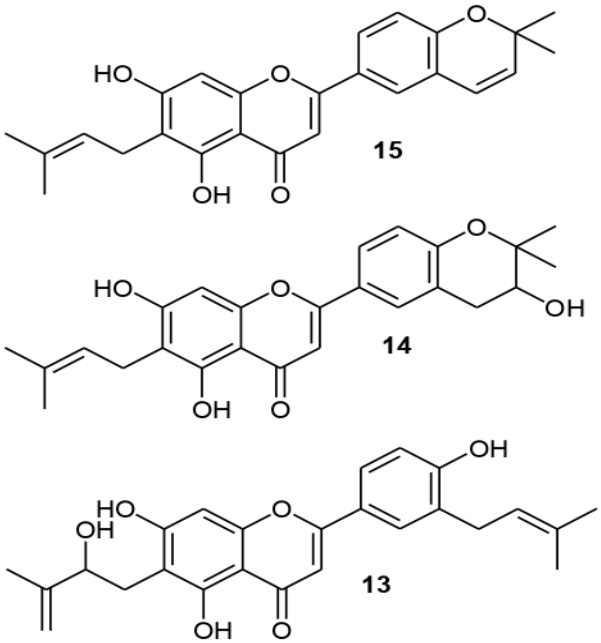


	R1	R2	R3	R4
6	OH	H	fransyl	H
7	H	geranyl	H	H
8	H	prenyl	H	prenyl
9	OH	prenyl	H	prenyl
10	H	prenyl	prenyl	H
11	H	H	geranyl	H
12	OH	prenyl	geranyl	H

Scheme 3: Structure of some cytotoxic compounds from *M.Indica.*

Cytotoxic chemicals from *Macaranga adenantha*

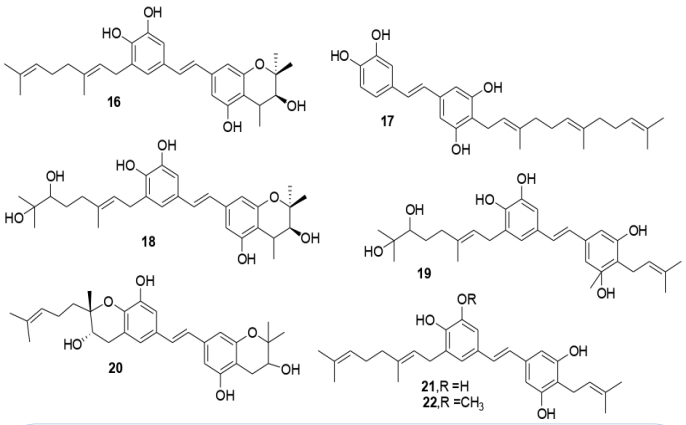
The prenylated compounds isolated from M.adenantha showed cytotoxic activity in human cell lines. The prenyl moieties shows promising biological activities due to further modification by cyclization and hydroxylation resulted in the chemical diversity of the prenylated products. The compounds (**13-15**) are modified prenyl cytotoxic chemicals that are active against two cancer cell lines HepG2 and Hela except (**13**) which have no anticancer activity. The compounds (**14**) and (**15**) exhibits cytotoxic activities against HepG2 cell line with IC50 values of 13.76 and 22.27 respectively. Compound (**15**) exhibit cytotoxic activity against Hela cell line with IC50 value of 16.18 [17].



Scheme 4: Structure of flavonoid compounds from *M Adenantha.*

Cytotoxic chemicals from *Macaranga tanarus*

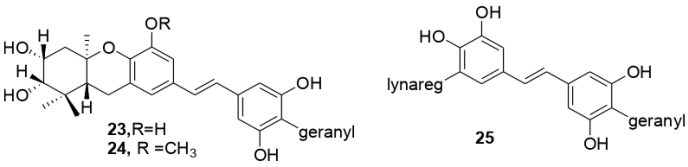
Cytotoxic prenylated, geranylated and fransylated stilbenes of the schweinfurthin series isolated from fruits of *Macaranga tanarius* are schweinfurthins (**16-20**). In addition to these compounds (**21-22**) are also isolated from this species. The compounds (**16-20**) showed cytotoxic activities in the Nano molar to sub-micro molar range on U87 glioblastoma cell line, but only compounds (**16**) and (**20**) were active on the A549 cell line in the sub-micro molar range. While compounds (**21**,**22**) do not show any anticancer activities on these cell lines [3].



Scheme 5: Structure of stilbene compounds (scheweifurthins) from *M Tanarus.*

Cytotoxic chemicals from Macaranga scheweifurthii

Geranylated stilbenes are isolated from *Macaranga scheweifurthii* and this phytochemicals shows different cytotoxicity against many types of human cell cancer lines. For the first time schweifurthins are isolated from this species. Compounds (**23)** and (**24)** are cytotoxic in the 60- cell line human tumor cancer screen. Schweinfurthin A (**23**) showed a mean panel IC50 of 0.36, while schweinfurthin B (**24**) was slightly less potent, giving a mean panel IC50 of 0.81. The brain tumor (CNS) subpanel was the most sensitive to both compounds, while the ovarian cancer cell lines were uniformly resistant. Other sensitive lines to compounds (**23)** and (**24)** are leukemia, lung, CNS, renal and breast cancers lines. But compound **25** (schweifurthin C) is inactive to this cell lines due to lack of hexahydroxanthate ring, which is the pharmacore (reactive part) of the schwiefurthins in addition to stilbene functional group [21].

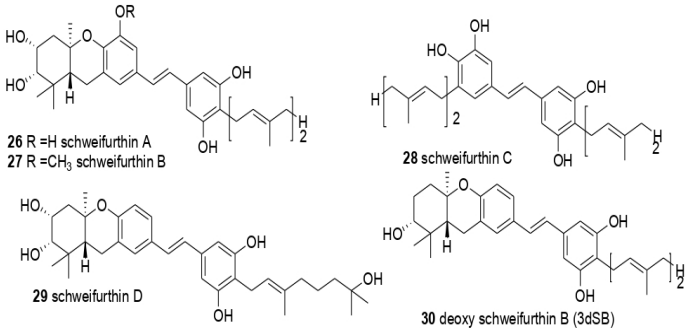


Scheme 6: Structure of schweifurthins from *M Shweifurthii.*

Total synthesis of schweinfurthins

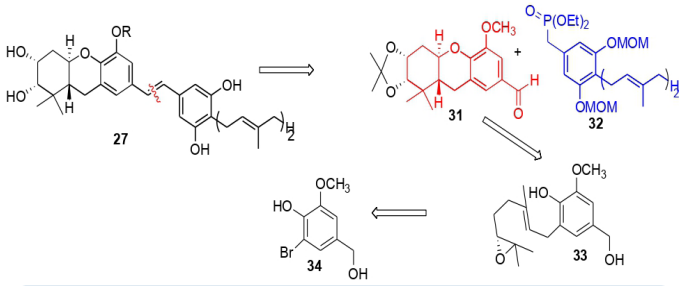
Introductions

Schweifurthins are some stilbene compounds that are isolated from various Macaranga species in small quantities. These compounds showed important and different cytotoxic activity based on the National Cancer Institute's (NCI) 60-cell line assay. Several members of the schweifurthin families are potent and selective inhibitors of cancer cell growth in the NCI 60-cell cancer cell line. This activity encourages development of the schweifurthins as anticancer agents. However, the scarcity of the natural products has hindered biological evaluation leads to synthesis of the natural product schweifurthins and their synthetic analogues [21,22]. While the biosynthesis of the tetracyclic schweinfurthins has not been studied yet, both the structure of the hexahydroxanthene system and the co-occurrence of schweinfurthins [22].



Scheme 7: Some of structure of schweinfurthins.

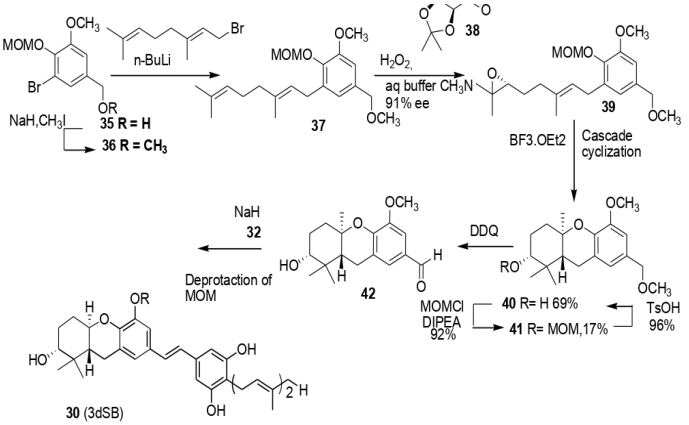
Retro synthesis of Schweinfurthin B



Scheme 8: Retro synthesis of Schweifurthin B.

Forward synthesis of analogues of Schweifurthin B

The new sequence (Scheme 9) began with benzyl alcohol **35**, which itself was available in 3 steps and 94% overall yield from vanillin (sheme 12). The halogen metal exchange reaction in presence of n-BuLi with geranyl bromide provided intermediate **37**.Compound **37** was epoxidized under Shi's conditions with catalyst **38** that epoxide to si-face due to steric hindrance of re-face to produce epoxide **39**. The cascade cyclization of epoxide **39,** which is the protected analogue of an intermediate compound **33,** with $BF_3.OEt_2$ produced a mixture of compounds **40** and **41**. DDQ oxidation of compound **40** proceeded intermediate **42**, now available in much improved yield and in just 8 total steps from commercially available vanillin. Treating compound **42** with NaH and **32** produce compound **30**(3dSB) which is the lead compound or synthetic analogue of compound **27.**

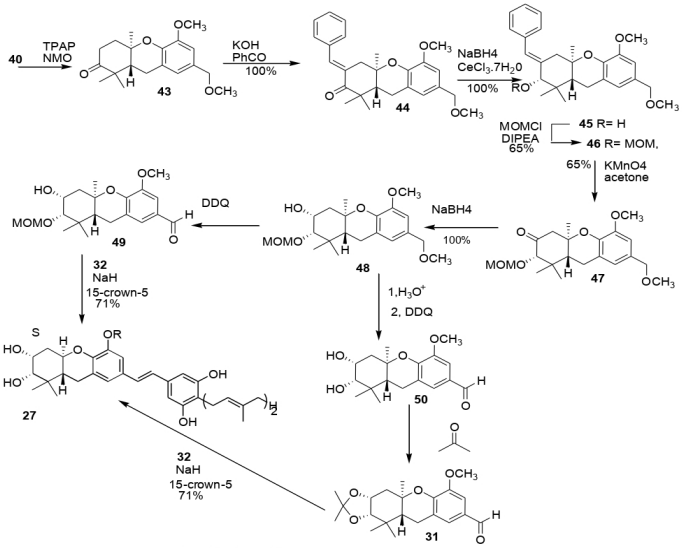


Scheme 9: Synthesis of deoxyschweifurthin B.

Forward synthesis of schweifurthin B starting from intermediate 40

To continue efforts aimed at synthesis of schweinfurthin B, hexahydroxanthene (**40)** was oxidized to afford ketone **(43)** in excellent yield (Scheme 10). Exposing ketone **43** to benzaldehyde and base in ethanol produced enone (**44)** in quantitative yield. The availability of this enone allowed exploration of a vari-

ety of strategies for formation of a 3-keto compound. Reduction of the R, β-unsaturated ketone compound (**44**) produced alcohol (**45**) with the desired configuration at the C-2 position. To prevent potential side reactions, the hindered alcohol (**45**) was protected by MOM to give (**46**). This compound is oxidized with KMnO4 in acetone to produce (**47**). Ketone (**47**) was reduced upon treatment with $NaBH_4$ in quantitative yield to afford alcohol (**48**). Exposing of compound (**48**) to DDQ provided aldehyde (**49**) directly from the methyl ether. Exposing compound (**48**) to acid hydrolysis and DDQ deprotection gives **50** and alcohol groups are protected by acetone to yield intermediate (**31**). Aldehyde (**49**) then was coupled to known phosphonate, which is synthesized from commercially available (**51**) dihydroxylbenzoic acid in 9 steps (**Scheme11**) or aldehyde (**31**) is condensed with (**32**) in the presence of NaH to yield protected stilbene. Finally, acidic hydrolysis of the three MOM acetals or two MOM acetals and hemiacetal under standard conditions provided Schweinfurthin B in moderate yield. Synthetic schweinfurthin B showed to be identical with an authentic sample of the natural material in all respects including specific rotation [21, 22].



Scheme 10: Total synthesis of Schweifurthin B.

Conclusion

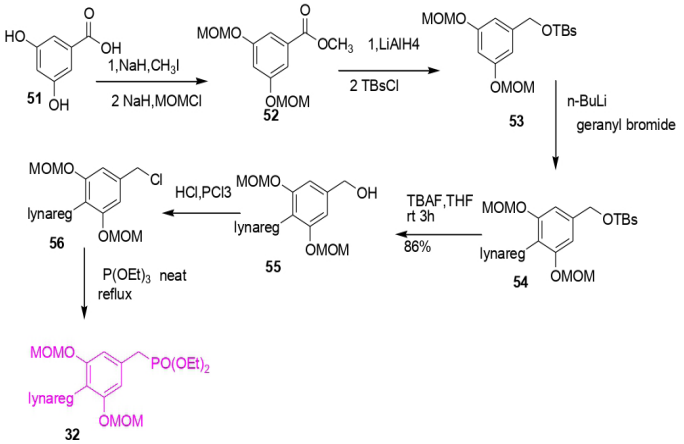
The Plant Kingdom is an important source of chemical compounds that they have pharmacological activities for treating different disease. Genus Macaranga is the largest member of family Euphorbiaceae and different species from this genus have variety class of secondary metabolities that are used for different therapeutic purposes. Flavoinoids and stilbenes are the major compounds which are isolated from different species of Macaranga. These compounds are cytotoxic to different cancer cell lines like human derived lung Adenocarcinoma (A549) Human Breast Adenocarcinoma (MCF-7), Human Hepatocellular (HepG2), Human Cervical Carcinoma (Hela) glioblastoma(U87) and mouse leukemia (P388) cell lines with high to low cytotoxic activities.

Shweinfurthins are stilbenes that are isolated from various Macaranga species in small quantities. These compounds showed different cytotoxic activity based on the National Cancer Institutes (NCI) 60-cell line assay. The scarcity of these natural products has hindered biological evaluation leads to synthesis of the natural product schweifurthins and their synthetic analogues The synthetic schweifurthin B shows almost identical in all respects to naturally obtained schweifurthin B (21-22).

Conflict of interest: the author has no conflict of interest.

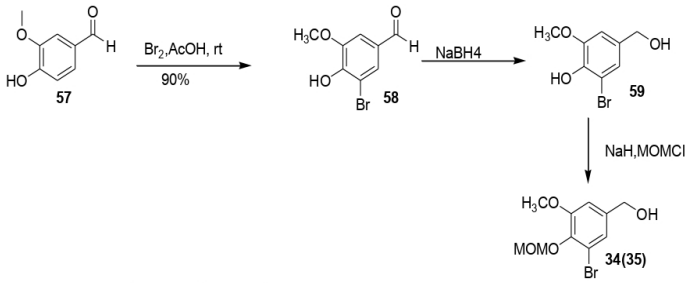
Synthesis of intermediate 32

Compound (**51**) is treated with NaH and CH_3I to methylate OH of acid and again it was treated with NaH and MOMCl to protect alcohol functional group and gives protected alcohol and ester (**52**). Reducing ester functional group with LiAlH4 and protecting the alcohol yields (**53**). This compound undergoes deprotonating by n-BuLi to produce aryl anion and alkylate with geranyl bromide to yield (**54**). Derprotection of TBs by TBAF at room temperature gives (**55**). Substitution reaction on (**55**) with HCl in the presence of PCl_3 gives (**56**). Finally this is refluxed with $P(OEt)_3$ to yield synthetic intermediate (**32**).



Scheme 11: Synthesis of intermediate 32.

Synthesis of intermediate 35 from commercially available vanillin.



Scheme 12: Syntheses of intermediate 34.

References

1. Rasool H. Importance and use of medicinal plants. Journal pharmaceutica Analaytica Acta. 2012; 3: 2153-2435.
2. Pierre MA, Tiphaine P, Jonathan B, Katia G, Laurence M, et al. Integration of Molecular Networking and In-Silico MS MS Fragmentation for Natural Products Dereplication. Journal of analaytical chemistry. 2016; 76: 1686-1699.
3. Péresse T, Jézéquel G, Allard PM, Pham VC, Huong DT, et al. Cytotoxic prenylated stilbenes isolated from Macaranga tanarius. Journal of natural products. 2017; 80: 2684-2691.
4. Darmawan A, Kosela S, Kardono L, Syah YM. Scopoletin, acoumarin derivative compound isolated from Macaranga gigantifolia. Journal of Applied Pharmaceutical Science. 2012; 2: 175-177.
5. Muhammad MU, Mazumdar M, Ariful I, Mohammad TH, Humaira Gulzar Mohammad AS, et al. Evaluation of anti-arthritic, thrombolytic and cytotoxic activities of methanolic and ethanolic extract of Macarangadenticulataleaves. Journal of Medicinal Plants Studies.2016; 4: 08-12.

6. Yoder BJ, orris A, Miller JS, Ratovoson F, Razafitsalama J, et al. (AntiproliferativePrenylatedStilbenes and Flavonoids from Macarangaalnifoliafrom the Madagascar Rainforest. Journal of Natural Product. 2007; 70: 342-346.

7. Zakaria I, Ahmat N, Jaafar FM, Widyawaruyanti A. Flavonoid with antiplasmodial and cytotoxic activities of Macarangatriloba. Fitoterapia (peer-reviewed journal of medical plant research). 2012; 8: 968-972.

8. Joseph JM. Phytochemistry and pharmacology of the genus Macaranga a review. Journal of Medicinal Plant Researches. 2014; 8: 489-503.

9. Ishak Z, Norizan A, Faridahanim M, Jaafar Widyawaruyanti. Flavonoids with antiplasmodial and cytotoxic activities of Macarangatriloba. Journal Elsever. 2012; 8: 968-972.

10. www.hse.gov.uk/healthservices/safe-use- cytotoxicdrugs.htm. at.

11. https://www.webmd.com/cancer/default.htm

12. https://www.cancer.org/treatment/treatments-and-side-effects/treatment-types/chemotherapy/how-is-chemotherapy-used-to-treat-cancer.html

13. http://www.cancerresearchUk.org/what-is-cancer/how-cancer-starts/types-of-cancer

14. Sofa F, Magawati AD. Apigenin an anticancer isolated from Macaranga gigantifolia leaves. Journal of tropical life science. 2016; 6: 7-9.

15. Da-Song Y, Wei-Bing P, Yong-Ping Y, Ke-Chun L, Xiao-Li L, et al . Cytotoxic prenylated flavonoids from macaranga indica. Journal of Fitoterapia. 2015; 10: 187-191.

16. Da-Song Y, Shuang-Mei W, Wei-Bing P, Yong-Ping Y, Ke-Chun L, et al. Minor Prenylated Flavonoids from the Twigs of Macaranga adenantha and their Cytotoxic Activity. Journal of Natural Products and Bio prospecting. 2015; 5: 105-109.

17. Megawati S, Muhammad H, Akhmad D, Puspa DN. Identification and Bioactivity Studies of Flavonoid Compounds from Macaranga hispida (Blume) Mull. Makara Journal of Science. 2015; 19: 96-100.

18. Widiastuti A, Lia DJ, Euis HH, Yana MS. Flavonoids from Macaranga lowii. Journal of Science. 2012; 44: 13-18.

19. Yana M, Syah D M, Juliawaty LD, Euis HH, and Sjamsul AA. Phytochemical of Indonesian Macaranga and their Cytotoxic Properties against P388 Cells. The Open Conference Proceedings Journal. 2013; 4; 1.

20. John AB, Robert HS, Tanya J, and Michael RB. Cytotoxic Geranyl Stilbenes from Macaranga schweinfurthii. Journal of Natural Product. 1998; 6: 1509-1512.

21. Joseph J, Topczewski, JD, Neighbors, and David FW. Total Synthesis of Schweinfurthins B and E. Journal of organic chemistry. 2009; 74: 6965-6972.

22. Kuder, Craig Heath. Schweinfurthins as novel anticancer agents. Thesis PhD (Doctor of Philosophy), University of Iowa. 2009; 19-25.