Trop J Nat Prod Res, March 2024; 8(3):6480-6486 ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

Tropical Journal of Natural Product Research

Available online at https://www.tjnpr.org

Review Article

# PTP1B Inhibitors from Indonesian Plants and Its Structure-Activity Relationship: A Review

Magie M. Kapojos[1]*, Mario Walean[1], Delfly B. Abdjul[1,2]

[1]Department of Pharmacy, Faculty of Science and Technology, Prisma University, Manado 95126, Indonesia.
[2]North Sulawesi Research and Development Agency, Manado 95040, Indonesia.

ARTICLE INFO

*Article history:*
Received 19 February 2024
Revised 23 February 2024
Accepted 04 March 2024
Published online 01 April 2024



ABSTRACT

Diabetes is still a world health problem because of the large number of sufferers and from year to year shows a trend of increasing the number. Type 2 diabetes is the most common type found as well as the largest contributor to diabetes cases, with a percentage of more than 90%. To overcome this problem, more potent and efficient type 2 diabetes drugs are urgently needed. Protein tyrosine phosphatase 1B (PTP1B) is one of the enzyme targets in the discovery of new drugs for type 2 diabetes because it has an important contribution as a negative regulator in the blood sugar transport mechanism, especially in the insulin and leptin signaling pathways. Based on this role, compounds that can act as PTP1B inhibitors have great potential to be developed as new drug candidates for type 2 diabetes. Natural products derived from plants with extraordinary structural diversity are expected to provide potential PTP1B inhibitor scaffolds for developing type 2 diabetes drugs. This review focuses on the structure-activity relationship (SAR) of compounds derived from Indonesian plants that have shown PTP1B inhibitory activity to provide information about the correlation between chemical structures and PTP1B activity that can be useful for the selection of potential scaffolds for type 2 diabetes drug development.

***Keywords*:** PTP1B inhibitors; Structure-activity relationship;plants; Indonesia.

## Introduction

Type 2 diabetes is characterized by hyperglycemia and insulin resistance, which cause severe complications including cardiovascular disease, nephropathy, retinopathy, and neuropathy.[1] Type 2 diabetes is the most common type found as well as the largest contributor to diabetes cases, with a percentage of more than 90%, and from year to year shows a trend of increasing the number of sufferers.[2,3]The International Diabetes Federation (IDF) reports that in 2021, around 536.6 million adults aged between 20 and 79 years in the world (around 10.5% of the total population in that age group) will suffer from diabetes. It is estimated that this will increase to 642.7 million (11.3%) in 2030 and 783.2 million (12.2%) in 2045, or an increase of around 73.6 million compared to the number of sufferers in 2019 (463 million).[4]

Protein tyrosine phosphatase 1B (PTP1B) is one of the enzyme targets in the discovery of new drugs for type 2 diabetes because it has an important contribution as a negative regulator in the blood sugar transport mechanism, especially in the insulin and leptin signaling pathways.[5,6] Based on this role, compounds that can act as inhibitors of PTP1B have great potential to be developed as new drug candidates for type 2 diabetes.

Natural products have historically been widely acknowledged as an important part of new drug discovery due to their enormous structural diversity and bioactivity. Related to approval drugs, natural sources account for 70% of the 1562 new drugs that were approved between 1981 and 2014.[7]

*Corresponding author. E mail: magie_kapojos@yahoo.com
Tel: +62 811-431-180

**Citation:** Kapojos MM, Walean M, Abdjul DB. PTP1B Inhibitors from Indonesian Plants and Its Structure-Activity Relationship: A Review. Trop J Nat Prod Res. 2024; 8(3):6480-6486. https://doi.org/10.26538/tjnpr/v8i3.2

Official Journal of Natural Product Research Group, Faculty of Pharmacy, University of Benin, Benin City, Nigeria

Moreover, nine drugs derived from natural products were among the 38 small-molecule drugs approved by the US FDA (Food and Drug Administration) in 2019.[8] The use of natural products is not only limited to final pharmaceutical products but can be a source for the development of new drug discoveries by providing new chemical scaffolds through the guidance of the structure-activity relationship (SAR).[9,10] SAR is an approach for determining connections between a compound's target biological activity and its chemical structure.[11] This method can provide essential structural information to help medicinal chemists synthesize desirable new compounds.[11,12]

Plants are a source of natural medicine that humans have used for thousands of years to overcome their health problems.[13,14] This utilization is closely related to the local wisdom of each region as a result of the trial-and-error exercise to alleviate disease symptoms.[15] The usage of these plants has been increasingly refined through generations, and it is now known as traditional medicine in many contexts.[16] The evolution and development of science in the fields of medicine and chemistry are very helpful in discovering new medicines from plants.[17,18] This development plays an important role in the discovery of medicines from plants such as paclitaxel (ovarian and breast cancer), artemisinin (malaria), and silymarin (heart disease).[19,20] Moreover, even at the beginning of the 21st century, around 11% of the 252 types of medicines categorized by the WHO as basic and essential medicines originated from flowering plants.[21] Over the past few decades, various plants have been examined for novel drugs and bioactive substances.[22]. Regarding the discovery of bioactive compounds for the development of new drugs, plants are still the source that attracts the attention of researchers. Presently, approximately 200,000 secondary metabolites have been discovered and identified,[23] and some of them showed PTP1B activity.[24–27]

Although qualitative SAR involvement can forecast bioactivities and generate an idea about them, its application in the early phases of natural product investigation is still uncommon.[28] The current article focuses on the structure-activity relationship (SAR) of compounds derived from Indonesian plants that have shown PTP1B inhibitory activity. Understanding the SAR of these compounds can provide valuable insights into their mode of action and help identify key structural

features responsible for their PTP1B activity. Additionally, studying the SAR can aid in the design and synthesis of novel derivatives with improved potency and selectivity against PTP1B, potentially leading to the development of new type 2 diabetes drugs.

## Methods

Several databases, including the American Chemical Society, Elsevier, PubMed, MDPI, and Google Scholar, are used to find articles that contained terms such as 'PTP1B', 'protein tyrosine phosphatase 1B', 'plants', and 'Indonesian'.

## Results and Discussion

*Sesquiterpenes*

Chemical investigation to find PTP1B inhibitors on the leaves of *Blumea balsamifera (L.)* led to the isolation of eight sesquiterpenes (1–8) (Figure 1), including a new guaiane sesquiterpene (1).[29] Samboginone (7), a eudesmane sesquiterpene, inhibited the activity of PTP1B by 25.8 µM of $IC_{50}$. On the other hand, compound 8 was inactive despite having a similar structure to 7. Therefore, the activity of the eudesman-type, as shown in 7 and 8, is influenced by the addition of functional groups attached to the rings of these compounds. Unfortunately, the PT1B activity was also absent for the other sesquiterpenes (1–6) isolated from this plant. This finding suggests that the eudesman-type is more favorable for the activity against PTP1B than the guaianes (1–5) or caryophyllene (6).The active compound 7 was evaluated for the TCPTP activity to understand the selectivity. However, compound 7 ($IC_{50}$ 12.5 µM) also exhibited the inhibitory activity of TCPTP.

Another series of sesquiterpenes (Figure 2) were obtained from the aerial parts of *Wedelia prostrata (Hemsl)* with two new rare-type eudesmanolide analogs (9 and 10) together with five known compounds (11–15).[30] Wedelolide D (12) displayed PTP1B activity with 32% inhibition at 20 µM, while the other eudesmanolide compounds (9–11 and 13–15) were inactive at the same concentration. A comparison of 12 with the similar compounds 10 and 11 reveals that the ester moiety attached at C-8 slightly influences the activity, which is that the tigloyloxy group is more favorable than methacryloxy or isobutyryloxy. In addition, substituting the isobutyryloxy unit at C-6 in 11 with methacryloxy as seen in 9 did not enhance the activity.

Five humulane-type sesquiterpenes were isolated from the *Zingiber aromaticum (Val)* rhizome (Figure 3).[31] (5*R*)-2,6,9-humulatrien-5-ol-8-one (19) was the most active compound against PTP1B with 27.7 µM of $IC_{50}$. Other isolated compounds (16–18 and 20) had lower activity, ranging from 15.9 to 62.6% of PTP1B inhibition at 10 µg/mL. Although it has a similar structure, compound 20 (15.9% inhibition at 10 µg/mL) exhibited lower activity than compound 19, indicating that the hydroxyl group at C-5 is essential for PTP1B activity. Moreover, adding an epoxy moiety, as seen in 16–18, was unfavourable to inhibiting PTP1B.

*Diterpenes*

Two diterpenes from the *ent-kaurene* class (21 and 22) were isolated from the aerial parts of *W. prostrata* (Figure 4).[30] Further phytochemical investigation of the residual fractions of this plant afforded ten more *ent-kaurene* diterpene analogs (23–32) (Figure 4).[32] *ent*-3β-cinnamoyloxykaur-16-en-19-oic acid (21) and *ent*-kaur-16-en-19-oic acid (25) are the most potent PTP1B inhibitors among all isolated compounds, with $IC_{50}$ values of 8.3 and 7.7 µM, respectively. Despite having a similar structure, compound 22 showed much reduced PTP1B activity compared with 21, suggesting that the additional functional group in the C-3 position is essential for the activity. This finding is supported by comparing compounds 29 (29% inhibition at 33 µM) and 30 ($IC_{50}$ 13 µM). Furthermore, the other compounds with variations of the C-3 moiety, angeloyloxy (23 and 27), tigloyloxy (24 and 28), and hydroxyl (30), displayed less PTP1B inhibition, indicating the cinnamoyloxy group, as seen in 21 and 25, is more favorable for this activity. In addition, PTP1B activity is more prone to diterpenes with a 9-H framework (21–24*)* than 9-unsaturated bond analogs (29 and 30), a secondary alcohol (31), a lactone (32), and 9-OH analogs (25–28).

*Triterpenes*

The methanol extract of *Melaleuca leucadendron* (*L)* fruits demonstrated good PTP1B inhibitory activity with an $IC_{50}$ of 2.05 µg/mL.[33] Further chemical investigation of this extract led to the isolation of two pentacyclic triterpenes, betulinic acid (33) and ursolic acid (34) (Figure 5). Compounds 33 and 34 showed remarkable PTP1B inhibitory activity, with $IC_{50}$ values of 1.5 and 2.3 µg/mL, respectively. Moreover, compound 33 showed slightly higher activity than 34, indicating that PTP1B activity was more susceptible to pentacyclic triterpenes with a cyclopentane ring in 33 than cyclohexane in 34.

Ursolic acid (34) and a related compound, asiatic acid (35), were also reported from the leaves of *Syzygium polyanthum (Wight)* (Figure 5).[34] Compound 35 ($IC_{50}$ 5.7 µM) had lower activity than 34 ($IC_{50}$ 4.3 µM) in the PTP1B assay. Therefore, the hydroxylation at C-2 and C-24 was unfavorable for the activity. Furthermore, two more ursolic acid analogs (36 and 37) were identified from the aerial parts of the *Lantana camara (L)* (Figure 5).[35] Pomonic acid (36) and pomolic acid (37) inhibit the PTP1B with $IC_{50}$ values of 10.5 and 10.6 µM, respectively. The hydroxylation at the C-19 position in 37 reduced more than two fold the PTP1B activity compared to the parent compound 34.

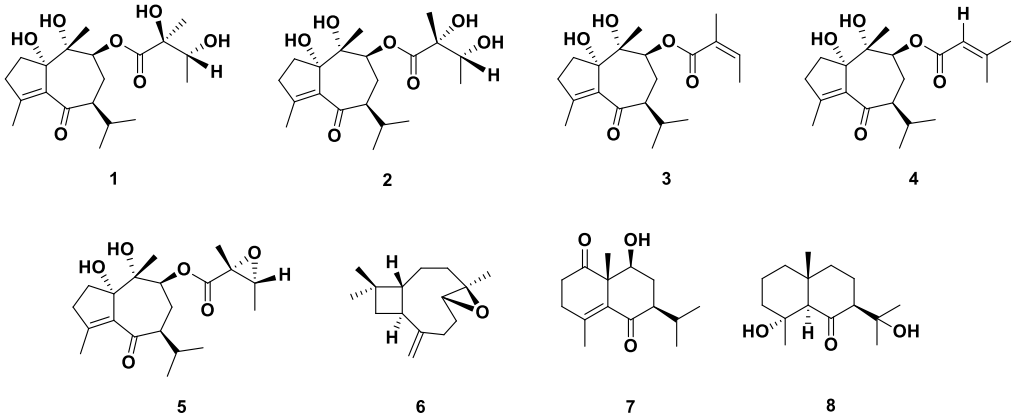


**Figure 1:** Sesquiterpenes isolated from *B. balsamifera*

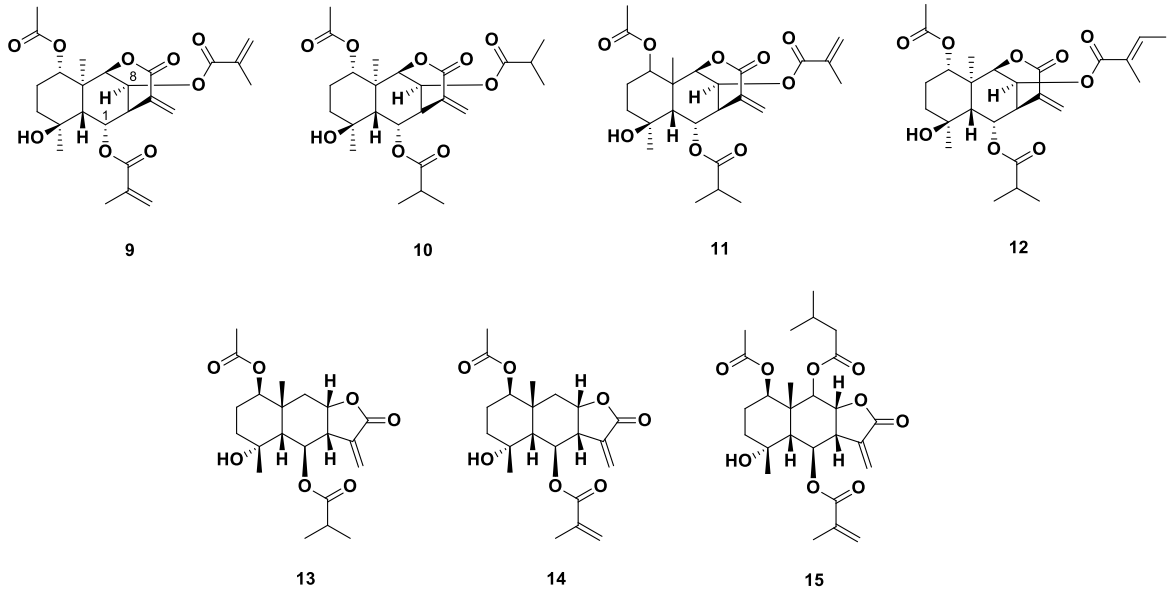


**Figure 2:** Sesquiterpenes isolated from *W. prostrata*

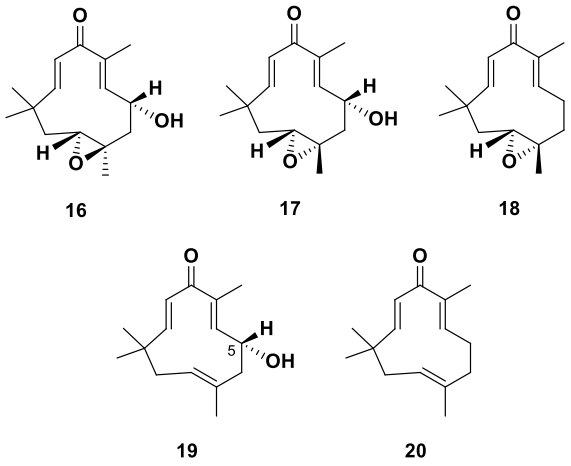


**Figure 3:** Sesquiterpenes isolated from *Z. aromaticum*

Besides two ursolic acid derivatives (36 and 37), separation of the ethanol extract of *L. camara* (aerial part) using bioassay guidance resulted in the isolation of eighteen more oleanane triterpenes (38–55), including four new compounds (38–41) (Figure 6).[35] Among the triterpenes found in this plant, oleanolic acid (45) is the most potent PTP1B inhibitor with a 2.0 µM $IC_{50}$ value. The PTP1B activity of compound 52 ($IC_{50}$ 6.9 µM), a closely related skeleton of 45, exhibited threefold weaker, suggesting that the additional moiety at the C-3 position is important for PTP1B activity and the hydroxyl, as seen in 45, is more suitable than the ketone group in 52. The new compounds (38–41), characterized by hydroxylation at C-24, and the ether linkage type represented by 54 and 55 also showed weaker PTP1B activity compared to the oleanolic acid analogs (44–48). Therefore, pentacyclic triterpenes with C-24 hydroxylation, C-3 oxidation, or ether linkage types are unfavorable for PTP1B activity. Moreover, the other analogs of 45 with an additional group at C-22, such as methylbutanoyloxy (44, $IC_{50}$ 7.3 µM), hydroxyl (46, $IC_{50}$ 7.9 µM), angeloyloxy (47, $IC_{50}$ 7.2 µM), and dimethylacryloyloxy (48, $IC_{50}$ 5.1 µM), had less PTP1B activity, indicating the group type attached at this position enhanced the PTP1B activity. This finding is supported by the similar pattern of activity displayed by the structure comparison of C-3 oxidation groups (49–53), C-24 hydroxylation groups (38–43), or the ether linkage types (54 and 55). Moreover, oleanolic acid was also isolated together with its derivative, arjunolic acid (56) from *S. polyanthum* (Figure 6).[34] However, hydroxylation at C-2 and C-23 in 56 ($IC_{50}$ 3.3 µM) decreased the PTP1B activity compared to compound 45.

*Steroids*

*S. polyanthum* leaves produce three steroid compounds (Figure 7): campest-4-en-3-one (57), campesterol (58), and cycloartenone (59). Compound 57 ($IC_{50}$ 10.4 µM) showed the strongest PTP1B activity.[36] Replacement of the ketone at C-3 with a hydroxyl, as seen in 58, results in a loss of PTP1B activity, indicating that the substituent at the C-3 position is important for the activity. In addition, several functional group variations in the steroid framework, as shown in 59, could not increase PTP1B activity.

*Acylbenzenes*

Four novel acylbenzene compounds (60–63) were isolated from the leaves of *S. polyanthum* collected in Bantul, Jogjakarta, during the investigation to find PTP1B inhibitors from Indonesian medicinal plants (Figure 8).[36] Compound 62 showed the most potent PTP1B activity, with an $IC_{50}$ of 4.0 µM. Although they have a similar framework, compound 61 ($IC_{50}$ 5.8 µM) showed less activity than compound 62. Therefore, a double bond in the acyl chain, as shown in compound 62, enhances PTP1B activity. Moreover, structural comparison between 60 ($IC_{50}$ 13.1 µM) and 61 ($IC_{50}$ 5.8 µM) revealed that the methyl group attached at the tip of the acyl chain, as seen in 61, was more favorable than the carboxylic acid in 61. Furthermore, compound 63 displayed weaker PTP1B activity than compound 60, suggesting that the length of the acyl chain is important for PTP1B activity.

Further phytochemical investigation of this plant collected in Manado, North Sulawesi, yielded five acylbenzene compounds (60–61 and 64–66) (Figure 8).[34] Compound 64 was reported as a new compound. The comparison between 64 ($IC_{50}$ 9.6 µM) and 60 ($IC_{50}$ 13.1 µM) confirmed previous findings that PTP1B activity in acylbenzenes is influenced by acyl chain length; the longer acyl chain exhibited higher activity. This finding is also supported by the results of the structural comparison between 65 ($IC_{50}$14.0 µM) and 66 ($IC_{50}$ 9.5 µM).

*Alkylamide*

A novel alkylamide compound (67) and three known analogs (68–70) were obtained using bioassay-guided purification of the aerial part of *Spilanthes paniculata (DC)* (Figure 9).[37] Compound 68 showed PTP1B activity with 24 µM of $IC_{50}$. In contrast, compounds 67, 69, and 70 were inactive at 38-45 µM. Thus, the presence of endoperoxide in 67, and variations of double bonds as seen in 69 and 70, are not favorable for PTP1B activity.

## Conclusion

Potential PTP1B inhibitor compounds isolated from Indonesian plants with $IC_{50}$ values less than 10 uM are dominated by the triterpene group and followed by the acylbenzene derivatives, which contributed eighteen and four compounds, respectively. Structural comparisons revealed several suggestions that influence PTP1B activity in the triterpene group. The group attached at C-3 is essential for PTP1B activity, and the hydroxyl group in this position is more suitable than the ketone group. Another finding revealed that the pentacyclic triterpenes with a cyclopentane ring as seen in betulinic acid (33) showed stronger PTP1B activity compared to a similar compound without this ring (34). Among all isolated compounds, oleanolic acid (45) is the most potent PTP1B inhibitor with a 2.0 uM $IC_{50}$. In some experiments, this compound is also used as the PTP1B assay's positive control.[38-40] Moreover, there were three important findings affecting the activity of the acylbenzene derivative (60–66**)**, *i.e.*, the presence of a double bond at the acyl chain, the length of the acyl chain, and the functional group at the tip of the acyl chain.

Indonesia, known for its rich biodiversity, has great promise for discovering PTP1B inhibitor compounds as new scaffolds for the development of type 2 diabetes drugs. Regretfully, there hasn't been much study done on PTP1B inhibitors made from Indonesian botanicals. Thus far, in the search for PTP1B inhibitors in Indonesian plants, 70 compounds have been identified, 22 of which have strong PTP1B inhibitory activity ($IC_{50}$< 10 µM). From this point of view, Indonesian plants are still an attractive source for finding new PTP1B inhibitors.

## Conflict of Interest

The authors declare no conflict of interest.

## Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

## Acknowledgments

All authors contributed equally to this work. This work was funded by Direktorat Jenderal Pendidikan Tinggi, Riset, dan Teknologi, Kementerian Pendidikan, Kebudayaan, Riset, dan Teknologi Republik Indonesia in 2023.

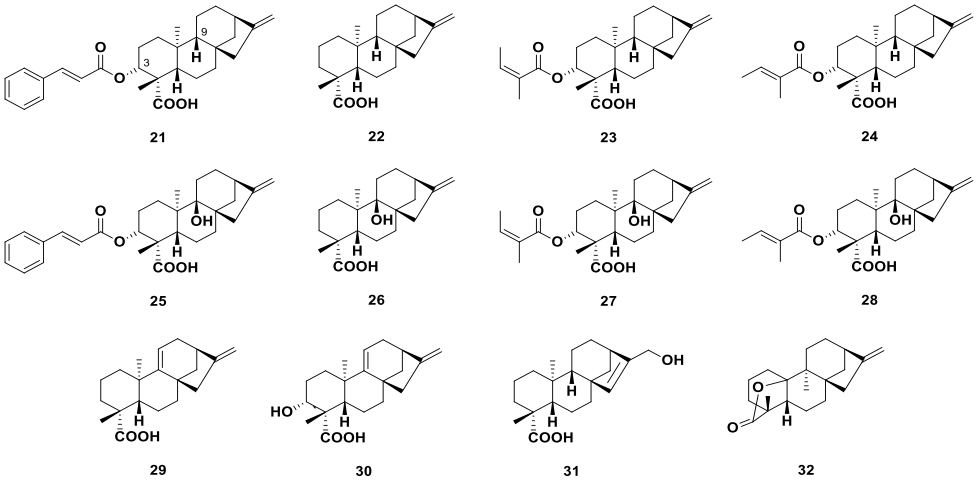


**Figure 4:** Diterpenes isolated from *W. prostrata*

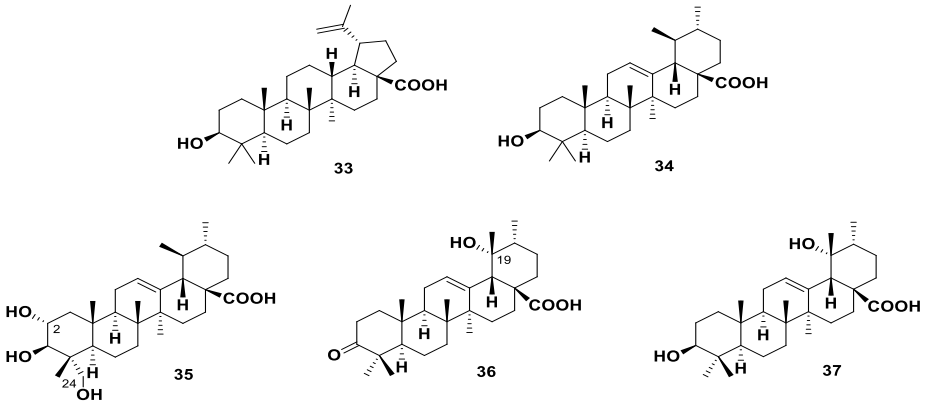


**Figure 5:** Triterpenes isolated from *M. leucadendron, S. polyantum,* and *L. camara*

ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

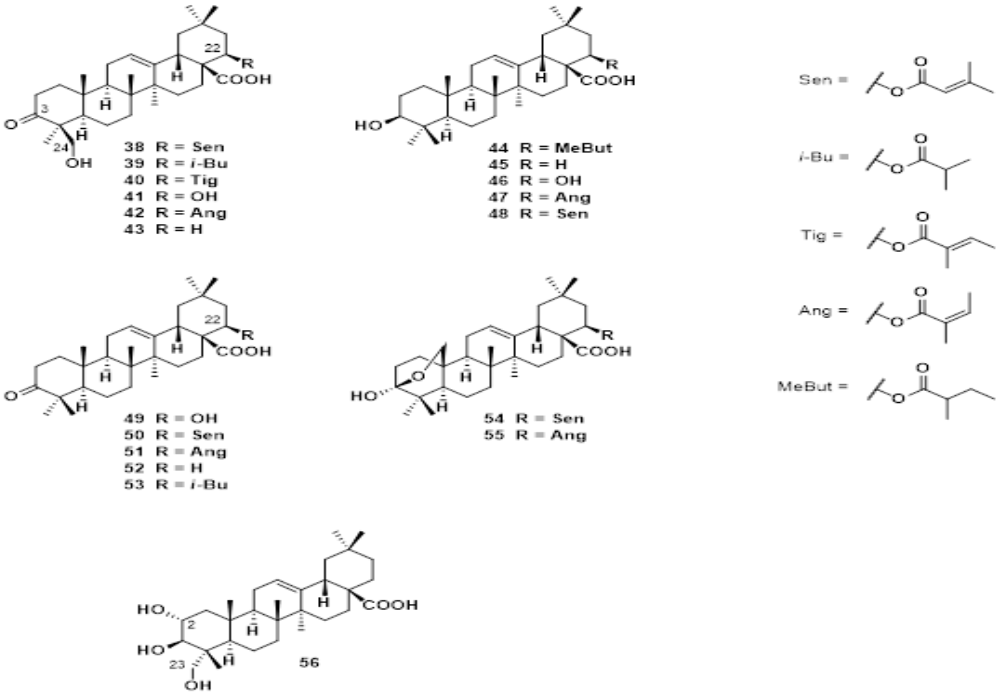


**Figure 6:** Other triterpenes isolated from *L. camara* and *S. polyantum*

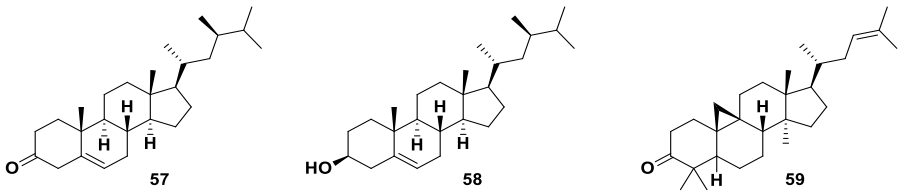


**Figure 7:** Steroids isolated from *S. polyantum*

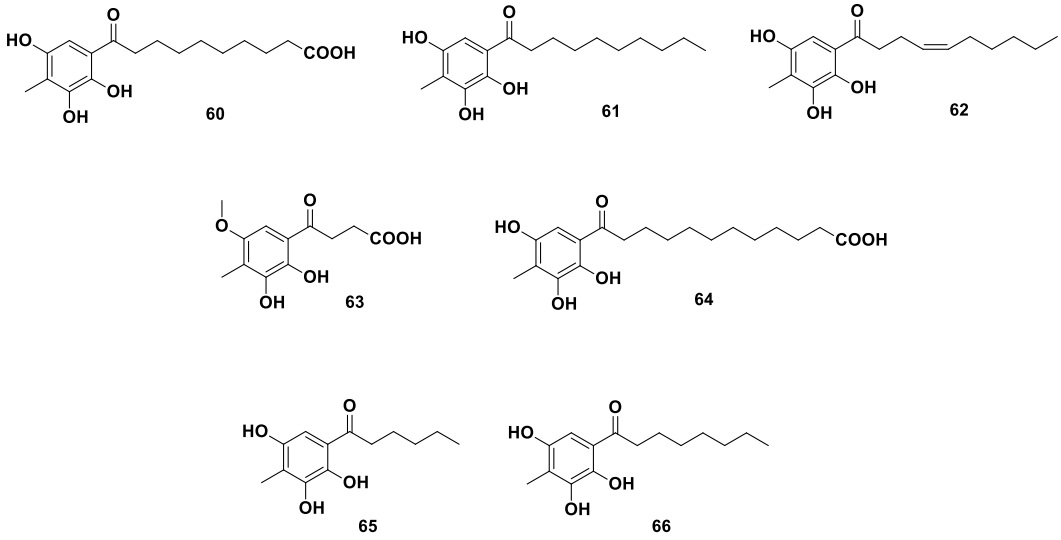


**Figure 8:** Acylbenzenes isolated from *S. polyantum*

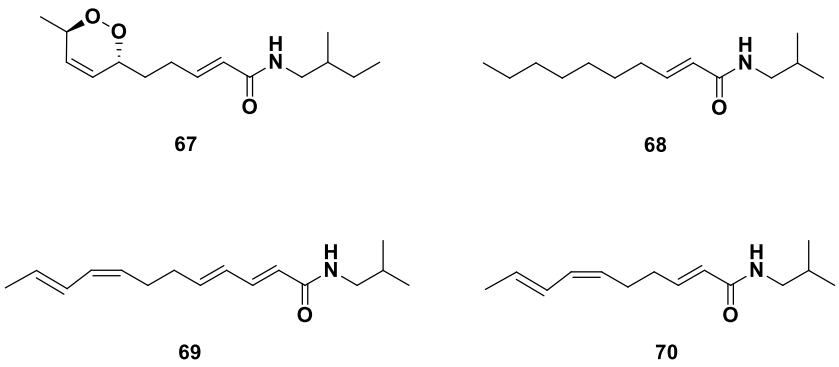


**Figure 9:** Alkylamides isolated from *S. paniculata*

## References


1. Ito Y, Fukui M, Kanda M, Morishita K, Shoji Y, Kitao T, Hinoi E, Shirahase H. Therapeutic effects of the allosteric protein tyrosine phosphatase 1B inhibitor KY-226 on experimental diabetes and obesity via enhancements in insulin and leptin signaling in mice. J Pharmacol Sci. 2018; 137: 38-46.
2. Roden M, Shulman GI. The integrative biology of type 2 diabetes. Nature 2019; 576: 51-60.
3. Artasensi A, Pedretti A, Vistoli G, Fumagalli L. Type 2 diabetes mellitus: A review of multi-target drugs. Molecules 2020; 25: 1987.
4. International Diabetes Federation. IDF diabetes atlas 10th edition. Brussels, Belgium, 2021. https://www.diabetesatlas.org.
5. Singh S, Grewal AS, Grover R, Sharma N, Chopra B,Dhingra AK, Arora S, Redhu S, Lather V. Recent updates on development of protein-tyrosine phosphatase 1B inhibitors for treatment of diabetes, obesity and related disorders. Bioorg Chem. 2022; 121: 105626.
6. Behl T, Gupta A, Sehgal A, Albarrati A, Albratty M, Meraya AM, Najmi A, Bhatia S, Bungau S. Exploring protein tyrosine phosphatases (PTP) and PTP-1B inhibitors in management of diabetes mellitus. Biomed Pharmacother. 2022; 153: 113405.
7. Newman DJ, Cragg GM. Natural products as sources of new drugs from 1981 to 2014. J Nat Prod. 2016; 79: 629-661.
8. De la Torre BG, Albericio F. The pharmaceutical industry in 2019. An analysis of FDA drug approvals from the perspective of molecules. Molecules 2020; 25: 745.
9. Igarashi M, Ishizaki Y, Takahashi Y. New antituberculous drugs derived from natural products: Current perspectives and issues in antituberculous drug development. J Antibiot. 2018; 71: 15-25.
10. Truax NJ, Romo D. Bridging the gap between natural product synthesis and drug discovery. Nat Prod Rep. 2020; 37: 1436-1453.
11. Schetz JA. Structure-activity relationships: Theory, uses and limitations. Ref. Modul Biomed Sci. 2015. doi:10.1016/b978-0-12-801238-3.05329-0.
12. Bandodkar B, Shandil RK, Bhat J, Balganesh TS. Two decades of TB drug discovery efforts-What have we learned? Appl Sci. 2020; 10: 5704.
13. Süntar I. Importance of ethnopharmacological studies in drug discovery: role of medicinal plants. Phytochem Rev. 2020; 19: 1199-1209.
14. Nunes CDR, Arantes MB, Pereira SMDF, Cruz LLD, Passos MDS, Moraes LPD, Vieira IJC, Oliveira DBD. Plants as sources of anti-inflammatory agents. Molecules 2020; 25: 3726.
15. Thomford NE, Senthebane DA, Rowe A, Munro D, Seele P, Maroyi A, Dzobo K. Natural products for drug discovery in the 21st century: Innovations for novel drug discovery. Int J Mol Sci. 2018; 19: 1578.
16. Salmerón-Manzano E, Garrido-Cardenas JA, Manzano-Agugliaro F. Worldwide research trends on medicinal plants. Int J Environ Res Public Health 2020; 17: 3376.
17. Weller MG. A unifying review of bioassay-guided fractionation, effect-directed analysis and related techniques. Sensors 2012; 12: 9181-9209.
18. Gorlenko CL, Kiselev HY, Budanova EV, Zamyatnin AA, Ikryannikova LN. Plant secondary metabolites in the battle of drugs and drug-resistant bacteria: New heroes or worse clones of antibiotics? Antibiotics 2020; 9: 170.
19. Atanasov AG, Waltenberger B, Pferschy-Wenzig EM, Linder T, Wawrosch C, Uhrin P, Temml V, Wang L, Schwaiger S, Heiss EH, Rollinger JM, Schuster D, Breuss JM, Bochkov V, Mihovilovic MD, Kopp B, Bauer R, Dirsch VM, Stuppner H. Discovery and resupply of pharmacologically active plant-derived natural products: A review. Biotechnol Adv. 2015; 33: 1582-1614.
20. Che CT, Zhang H. Plant natural products for human health. Int J Mol Sci. 2019; 20: 2-5.
21. Veeresham C. Natural products derived from plants as a source of drugs. J Adv Pharm Technol Res. 2012; 3: 200-201.
22. Majumder R, Das CK, Mandal M. Lead bioactive compounds of *Aloe vera* as potential anticancer agent. Pharmacol Res. 2019; 148: 104416.
23. Kessler A, Kalske A. Plant secondary metabolite diversity and species interactions. Annu Rev Ecol Evol Syst. 2018; 49: 115-138.
24. Nguyen DT, To DC, Tran TT, Tran MH, Nguyen PH. PTP1B and α-glucosidase inhibitors from *Selaginella rolandi-principis* and their glucose uptake stimulation. J Nat Med. 2021; 75: 186-193.
25. Nguyen PH, Tuan HN, Hoang DT, Vu QT, Pham MQ, Tran MH, To DC. Glucose uptake stimulatory and PTP1B inhibitory activities of pimarane diterpenes from *Orthosiphon stamineus* Benth. Biomolecules 2019; 9: 859.
26. Ren YM, Zhang R, Feng Z, Ke CQ, Yao S, Tang C, Lin L, Ye Y. Macrocephatriolides A and B: Two guaianolide trimers from *Ainsliaea macrocephala* as PTP1B inhibitors and insulin sensitizers. J Org Chem. 2021; 86: 17782-17789.
27. Zhang Z, Shang ZP, Jiang Y, Qu ZX, Yang RY, Zhang J, Lin YX, Zhao F. Selective inhibition of PTP1B by new anthraquinone glycosides from *Knoxia valerianoides*. J Nat Prod. 2022; 85: 2836-2844.
28. Panggabean JA, Adiguna SP, Murniasih T, Rahmawati SI, Bayu A, Putra MY. Structure–activity relationship of cytotoxic natural products from Indonesian marine sponges. Rev Bras Farmacogn. 2022; 32: 12-38.

29. Saifudin A, Tanaka K, Kadota S, Tezuka Y. Chemical constituents of *Blumea balsamifera* of Indonesia and their protein tyrosine phosphatase 1B inhibitory activity. Nat Prod Commun. 2012; 7: 815-818.
30. Abdjul DB, Yamazaki H, Maarisit W, Losung F, Rotinsulu H, Wewengkang DS, Sumilat DA, Namikoshi M. Eudesmanolide sesquiterpenes and protein tyrosine phosphatase 1B inhibitory ent-kaurene diterpenes from aerial parts of Indonesian *Wedelia prostata*. Phytochem Lett. 2017; 20: 191-195.
31. Saifudin A, Kadota S, Tezuka Y. Protein tyrosine phosphatase 1B inhibitory activity of Indonesian herbal medicines and constituents of *Cinnamomum burmannii* and *Zingiber aromaticum*. J Nat Med. 2013; 67: 264-270.
32. Abdjul DB, Yamazaki H, Kanno S, Kirikoshi R, Tomizawa A, Takahashi O, Maarisit W, Losung F, Rotinsulu H, Wewengkang DS, Sumilat DA, Kapojos MM, Namikoshi M. Absolute structures of wedelolide derivatives and structure–activity relationships of protein tyrosine phosphatase 1B inhibitory *ent*-kaurene diterpenes from aerial parts of *Wedelia* spp. collected in Indonesia and Japan. Chem Pharm Bull. 2018; 66: 682-687.
33. Saifudin A, Lallo SA, Tezuka Y. The potent inhibitors of protein tyrosine phosphatase 1B from the fruits of *Melaleuca leucadendron*. Pharmacognosy Res. 2016; 8: 38-41.
34. Kapojos MM, Abdjul DB, Yamazaki H, Yagi A, Uchida R. Screening of Indonesian edible plants for bioactive constituents and a new protein tyrosine phosphatase 1B inhibitory acylbenzene derivative from leaves of Indonesian *Syzygium polyanthum*. Chem Pharm Bull. 2020; 68: 903-906.
35. Abdjul DB, Yamazaki H, Maarisit W, Rotinsulu H, Wewengkang DS, Sumilat DA, Kapojos MM, Losung F, Ukai K, Namikoshi M. Oleanane triterpenes with protein tyrosine phosphatase 1B inhibitory activity from aerial parts of *Lantana camara* collected in Indonesia and Japan. Phytochemistry 2017; 144: 106-112.
36. Saifudin A, Tanaka K, Kadota S, Tezuka Y. Protein tyrosine phosphatase 1B (PTP1B)-inhibiting constituents from the leaves of *Syzygium polyanthum*. Planta Med. 2012; 78: 1378-1381.
37. Abdjul DB, Yamazaki H, Maarisit W, Kirikoshi R, Takahashi O, Losung F, Kapojos MM, Namikoshi M. Protein tyrosine phosphatase 1B inhibitory components and a new unique N-alkylamide derivative with an endoperoxide bridge from aerial parts of Indonesian *Spilanthes paniculata*. Phytochem Lett. 2018; 24: 71-74.
38. Zhang YN, Zhang W, Hong D, Shi L, Shen Q, Li JY, Li J, Hu LH. Oleanolic acid and its derivatives: New inhibitor of protein tyrosine phosphatase 1B with cellular activities. Bioorganic Med Chem. 2008; 16: 8697-8705.
39. Sumilat DA, Yamazaki H, Kanno SI, Saito R, Watanabe Y, Namikoshi M. Biphenyl ether derivatives with protein tyrosine phosphatase 1B inhibitory activity from the freshwater fungus *Phoma* sp. J Antibiot.2017; 70: 331-333.
40. Yamazaki H, Takahashi K, Iwakura N, Abe T, Akaishi M, Chiba S, Namikoshi M, Uchida R. A new protein tyrosine phosphatase 1B inhibitory α-pyrone-type polyketide from Okinawan plant-associated *Aspergillus* sp. TMPU1623. J Antibiot. 2018; 71: 745-748