

SYNTHESIS AND MECHANISM STUDY OF NEW BIVALENT β -CARBOLINE DERIVATIVES

(Kajian Sintesis dan Mekanisma Derivatif Bivalen β -karbolin Baharu)

Nurul Tasnim Noor Aaisa^{1,2}, Karimah Kassim², Nur Azzalia Kamaruzaman³, Mazlin Mohideen^{1*}

¹*Faculty of Pharmacy and Health Sciences,
Universiti Kuala Lumpur Royal College of Medicine Perak, 30450 Ipoh, Perak, Malaysia*

²*Institute of Science,
Universiti Teknologi MARA, 40450 Puncak Alam, Selangor, Malaysia*

³*National Poison Centre,
Universiti Sains Malaysia, 11800 Minden, Pulau Pinang, Malaysia*

*Corresponding author: mazlin.mohideen@unikl.edu.my

Received: 15 September 2021; Accepted: 30 December 2021; Published: 25 February 2022

Abstract

This study reports simple and straightforward methods for synthesizing new bivalent β -carboline compounds using L-tryptophan as a starting material with 1,4-dibromobutane as a dimerization linker. The synthetic route began with coupling L-tryptophan with formaldehyde via Pictet-Spengler condensation to afford tetrahydro- β -carboline, **T1** as the key intermediate. The reaction proceeded with decarboxylation of **T1** using potassium dichromate with acetic acid to afford β -carboline, **T2**. Subsequent alkylation of **T2** using 1,4-dibromobutane as the linker yielded intermediate **T3**, followed by dimerization to furnish the new bivalent β -carboline, **T4**. ¹H and ¹³C NMR confirmed all the synthesized compounds. In addition, this study includes the proposed mechanism for the synthesis of a new bivalent β -carboline compound.

Keywords: synthesis, bivalent β -carboline, L-Tryptophan, Pictet-Spengler condensation, dimerization

Abstrak

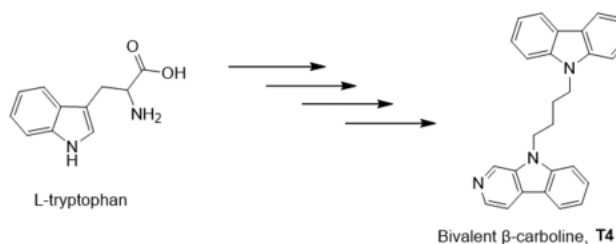
Abstract in Bahasa Malaysia/English Kajian ini melaporkan kaedah mudah dan secara terus untuk mensintesis sebatian baru bivalen β -karbolin menggunakan L-tryptofan sebagai bahan pemulaan dengan 1,4-dibromobutana sebagai penghubung dimerisasi. Laluan sintesis bermula dengan gandingan L-tryptofan dengan formaldehid melalui pemeluwapan Pictet-Spengler untuk mendapatkan tetrahidro- β -karbolin, **T1** sebagai kunci perantaraan. Tindak balas diteruskan dengan pendekarboksilan **T1** menggunakan kalium dikromat dengan asid asetik untuk menghasilkan β -karbolin, **T2**. Seterusnya alkilasi **T2** menggunakan 1,4-dibromobutana sebagai penghubung menghasilkan perantara **T3**, diikuti dengan dimerisasi untuk menghasilkan bivalen β -karbolin baharu, **T4**. Semua sebatian yang disintesis disahkan dengan ¹H NMR dan ¹³C NMR. Sebagai tambahan, kajian ini merangkumi mekanisma yang dicadangkan untuk sintesis sebatian bivalen β -karbolin baharu.

Kata kunci: sintesis, bivalen β -Karbolin, L-Tryptofan, pemeluwapan Pictet-Spengler, dimerisasi

Graphical Abstract

Graphical Abstract

Synthesis of New Bivalent β -Carboline Derivatives



References

1. Chen, X., Guo, L., Ma, Q., Chen, W., Fan, W. and Zhang, J. (2019). Design, synthesis, and biological evaluation of novel n-acylhydrazone bond linked heterobivalent β -carboline as potential anticancer agents. *Molecules*, 24(16): 2950.
2. Ahmad, I., Fakhri, S., Khan, H., Jeandet, P. and Aschner, M. (2020). Targeting cell cycle by β -carboline alkaloids *in vitro*: Novel therapeutic prospects for the treatment of cancer. *Chemico-Biological Interactions*, 330: 109229.
3. Li, S., Yang, B., Zhang, Q., Zhang, J., Wang, J. and Wu, W. (2010). Synthesis and bioactivity of β -carboline derivatives. *Natural Product Communications*, 5(10): 1591-1596.
4. Sharma, S., Yadav, M., Gupta, S. P., Pandav, K. and Kumar, S. (2016). Spectroscopic and structural studies on the interactions of an anticancer β -carboline alkaloid, harmine with GC and AT specific DNA oligonucleotides. *Chemico-Biological Interactions*, 260: 256-262.
5. Du, H., Gu, H., Li, N. and Wang, J. (2016). Synthesis and biological evaluation of bivalent β -carbolines as potential anticancer agents. *Medicinal Chemistry Communications*, 7(4): 636-645.
6. Kumar, S., Singh, A., Kumar, K. and Kumar, V. (2017). Recent insights into synthetic beta-carbolines with anticancer activities. *European Journal of Medicinal Chemistry*, 142: 48-73.
7. Gu, H., Li, N., Dai, J., Xi, Y., Wang, S. and Wang, J. (2018). Synthesis and *in vitro* antitumor activity of novel bivalent beta-carboline-3-carboxylic acid derivatives with DNA as a potential target. *International Journal of Molecule Sciences*, 19(10): 3179.
8. Manasa, K. L., Yadav, S. S. and Nagesh, N. (2020). The β -carboline alkaloids in cancer therapy-recent advancements in this area. *Journal of Pharmacy and Biological Sciences*, 15(3): 1-27.
9. Nenaah, G. (2010). Antibacterial and antifungal activities of (beta)-carboline alkaloids of *Peganum Harmala* (L) seeds and their combinations effects. *Fitoterapia*, 81(7): 779-782.
10. Kuete, V. (2014). Physical, hematological, and histopathological signs of toxicity induced by African medicinal plants. *Toxicological Survey of African Medicinal Plants*, 2014: 635-657.
11. Dai, J., Dan, W., Scheinder, U. and Wang, J. (2018). β -carboline alkaloid monomers and dimers: Occurrence, structural diversity, and biological activities. *European Journal of Medicinal Chemistry*, 157: 622-656.
12. Chen, W., Zhang, G., Guo, L., Fan, W., Ma, Q., Zhang, X., Du, R. and Cao, R. (2016). Synthesis and biological evaluation of novel alkyl diamine linked bivalent β -carbolines as angiogenesis inhibitors. *European Journal of Medicinal Chemistry*, 124: 249-261. Daoud, A., Song, J., Xiao, F. and Shang, J. (2014). B-9-3, a novel beta-carboline derivative exhibits anticancer activity via induction of apoptosis and inhibition of cell migration *in vitro*. *European Journal of Pharmacology*, 724: 219-230.
13. Daoud, A., Song, J., Xiao, F. and Shang, J. (2014). B-9-3, a novel beta-carboline derivative exhibits anticancer activity via induction of apoptosis and inhibition of cell migration *in vitro*. *European Journal of Pharmacology*, 724: 219-230.
14. Shi, B., Cao, R., Fan, W., Guo, L., Ma, Q., Chen, X., Guoxian, Z., Qiu, L. and Song, H. (2013). Design, synthesis and *in vitro* and *in vivo* antitumor activities of novel bivalent β -carbolines. *European Journal of Medicinal Chemistry*, 60: 10-22.
15. Sun, R., Liu, R., Zhou, C., Ren, Z., Guo, L., Ma, Q. and Cao, R. (2015). Synthesis and biological evaluation of piperazine group-linked bivalent β -carbolines as potential antitumor agents. *Medicinal Chemistry Communications*, 6(12): 2170-2174.
16. Luo, B. and Song, X. (2021). A comprehensive overview of β -carboline and its derivatives as anticancer agents. *European Journal of Medicinal Chemistry*, 224: 113688.