Antibacterial Activity of Tetrahydro-β-Carboline-3-Carboxylic Acid and its Derivatives

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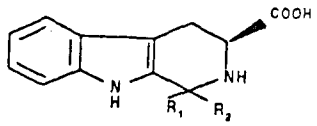
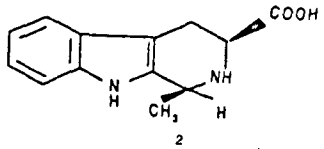
1,2,3,4-Tetrahydro-β-carboline-3-carboxylic acid (THBCC) and three of its derivatives, 1-methyl-THBCC, 1-pyridoxyl-THBCC and 1-methyl-1-carboxyl-THBCC have been synthesised by Pictet-Spengler condensation and their antibacterial activity was evaluated against five bacterial strains by the agar well diffusion method. MIC values were determined by the tube dilution method.

β-Carbolines are distributed widely in plants. These have also been found endogenously in mammalian tissues, including the central nervous system, liver, platelets, plasma and urine[1,2]. These have also been reported to be present in food products and alcoholic beverages[3,4]. β-Carbolines have been reported to inhibit monoamine oxidase, to alter the reuptake of biogenic amines and to interfere with benzodiazepine receptors[5,6]. Their participation in the pathogenesis of alcoholism and psychiatric disorders has been reported[7,10].

1,2,3,4-Tetrahydro-β-carboline-3-carboxylic acid (THBCC) and its derivatives have been synthesised by Pictet-Spengler condensation of tryptophan with various aldehydes and α-oxo acids[11-15]. These compounds have been detected in alcoholic fermentation products such as beer and wine[4,16-19], soya sauce[4,16,20] human milk and sake[21]. β-Carbolines have also been reported to show antiviral[22,23] and antibacterial[24,28] activities. Their photodynamic toxicity to bacteria, fungi and to larvae of *Aedes atropalpus* has also been demonstrated[29]. Where, as such properties for THBCCS have not been reported so for. In this communication we report the antibacterial activity of synthetic THBCC (**1**)[11-14] and its three derivatives, 1-methyl-THBCC (**2**)[11,14] 1-pyridoxyl-THBCC (**3**)[15] and 1-methyl-1-carboxyl-THBCC (**4**)[14,16]. Compound 2 studied was the (-)-(1S,3S isomer (β-methyl and β-COOH) which was the major product. Compounds 3 and 4 are the major products of unknown stereochemistry at position 1, with β-COOH at position 3. The identities of all compounds were confirmed by physical and spectroscopic data reported. The antibacterial activity was determined against five bacterial strains, one gram positive *Staphylococcus aureus* and four gram negative (*Escherichia coli, Salmonella typhi, Proteus mirabilis* and *Klebsiella aerogenes*) bacteria. Agar well diffusion method was used[30]. MIC values were determined by the tube dilution method[31].



Compound	R_1	R_2
1	H	H
3	H	Pyridoxal
4	CH_3	COOH



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The bacteria were grown in nutrient broth and incubated at 37°. The test organisms from overnight cultures were uniformly spread on the nutrient agar. Five millimeter

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TABLE 1 - ANTIBACTERIAL ACTIVITY OF THBCCS 1-4

Bacteria	Zone of inhibition (mm)* compounds				
	1	2	3	4	Tetracycline (30 µg/ml)
S. Typhi	24	22	5	22	20
P. mirabilis	19	19	2	19	20
S. aureus	16	16	2	12	22
E. coli	19	16	2	15	21
K. aerogenes	12	10	1	8	17

*Zone of inhibition after substration of the well dia meter of 5 mm. 200 µl of each compounds at 100 µg/ml concentration was used. The data is mean of three determinations.

Table 2 : MIC OF THBCCs 1-4

Bacteria	MIC (µg/ml) compounds			
	1	2	3	4
S. typhi	40	40	320	40
P. mirabilis	80	80	640	80
S. aureus	80	80	1280	160
E. coli	80	160	1280	160
K. aerogenes	320	320	1280	640

diameter wells were made to which 200 µl of each compound at 100 µg/ml concentration in 50% aqueous methanol were added. The vehicle itself did not show any activity. Tetracycline (30 µg/ml) was used as the standard. The inhibition zone was observed after incubating at 37° for 24 h. The results are given in Table 1. In the tube dilution method for determining MIC values, the concentrations employed were 10, 20, 40, 80, 160, 640 and 1280 µg/ml. The results are given in Table 2.

The sensitivity study of compounds 1 to 4 at 100 µg/ml level, given in Table 1, showed that except for compound 3, all compounds were active against the tested bacteria. The order of sensitivity was *S. typhi, P. mirabilis, E. coli* and *K. aerogenes*. The MIC values given in Table 2 showed the activity to be in the order compound 1> compound 2> compound 4> compound 3. The study shows that in THBCC substitution at position 1 does not enhance the activity, but causes a reduction.

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REFERENCES

1. Airaksinen, M.M. and Kan I., **Med. Biol.**, 1981, 59, 21.
2. Beck, O. and Faull, K.F., **Biochem. Pharmacol.** 1986, 35, 2636.
3. Kinae, N., Yamashita, N., Takahshi, M., Oishi, H., Tomiota, I. and Kanamori, H., **Dev. Food. Sci.**, 1986, 13, 343.
4. Sen, N.P. Stephen, W.O., Seeman, B.P., Lau, Y., Weber, D. and Lewis, D. **Food Chem.**, 1975, 54, 327.
5. Mckenna, D.J. and Towers, G.H.N., **J. Psychoact. Drugs.**, 1984, 16, 347.
6. Rommelspacher, H., May, T. and Salewski, B., **Eur. J. Pharmacol**, 1994, 252, 51.
7. Rommelspacher, H., Damm, H., Strauss, S., and Schmidt, G., **Naunyn-Schmiedbergs-Arch. Pharmacol**. 1984, 32, 107.
8. Spies, C.D., Rommelspacher, H., Schnapper, C., Muller, C., Marks, C., Berger, C., Connard, C., Blum, S., Specht, M. Hannemann, L., Striebel, H.W. and Schaffartzik, W., **Alcoholism Clin. Exp. Res.**, 1995, 19, 969.
9. Myers, R.D., **Experientia,** 1989, 45, 436.
10. Toumisto, L., Airaksinen, M.M., Peura, P. and Erikkson C.J.P., **Pharmacol. Biochem. Behav.**, 1982, 17, 831.

11. Jacobs, W.A and Creig, L.C., **J. Biol. Chem.,** 1936, 113, 759.
12. Harvey, D.G., Miller, E.J., and Robsen, W., **J. Chem. Soc.,** 1941, 153.
13. Brossi, A., Focella, A. and Teitel, S., **J. Med. Chem.,** 1973, 16, 418.
14. Bobbitt, J.M., and Willis, J.P., **J. Org. Chem.,** 1980,45, 1978.
15. Argoudelis, C.J., **J. Agric. Food Chem.,** 1994, 42, 2372.
16. Gutsche, B. and Herderich, M., **J. Agric. Food Chem.,** 1977, 45, 2458.
17. Bosin, T.R., Krogh, S. and Mais, D., **J. Agric. Food Chem.,** 1986, 34, 843.
18. Beck, O. and Holmstedt, B., **Food Cosmet. Toxicol.,** 1981, 19, 173.
19. Herriaz, T., Huang, Z. and Ough, C.S., **J. Agric. Food. Chem.,** 1993, 41, 455.
20. Wakebayashi, K., Ochial, M., Saito, H., Tsuda, M., Sua, Y., Negao, M. and Sugimura, T., **Proc. Natl. Acad. Sci.,** USA, 1983, 80, 2912.
21. Adachi, J., Mizoi, Y., Naito, T., Ogawa, Y., Uetani, Y., and Ninomiya I., **J. Nutr.,** 1991, 121, 646.
22. Hudson, J.B., Graham, E.A. and Towers, G.H.N., **Phytochem. phytobiol.,** 1986, 43, 21.
23. Roshan, I.J., **Fitoterapia** 1990, 61, 153.
24. Poissonnett, G., Potier, P. and Dodd, R.H., **Tetrahedron Lett.,** 1989, 30, 3423.
25. Siddiqui, S., Siddiqui, B.S., Naeed, A., Begum, S., Khan, K.A., Ahmad, A. and Sultana, S., **Fitoterapia,** 1990, 61, 425.
26. Espade, A., Jimenez, C., Debitus, C., and Riguera, R., **Tetrahedron Lett.,** 1993, 34, 7773.
27. Quetin-Leclerc, J., Coucke, P., Delaudec Warin, R., Bassleer, R. and Angenrot, L., **Phytochemistry,** 1991, 30, 1697.
28. Sabira, B., Shahid, U., Siddiqui, B., Shaheenn, B., Arahad, K.S., Mohammad, K.S. and Atiya, Z., **Arzneium Forsch.,** 1996, 46, 1163.
29. MC Kenna, D.J. and Towers, G.H.N., **Phytochemistry,** 1981, 20, 1001.
30. Cruickshank, R., Ed, In; Medical Microbiology, The English Langauage Book Company and E & S Livengstone Ltd., 1965, 893.
31. Kavanagh, F., In; Analytical Microbiology, Academic Press, New york, 1963, 126.
32. Sivropoulow, Kokkini, S., Lanaras, T., Arsenakis, M., **J. Agric. Food. Chem.,** 1995, 43, 2384.
33. Arai, S., Abe, M., Yamashita, M., Kato, H. and Fujimaki, M., **Agric. Biol. Chem.,** 1971, 35, 552.
34. Valin, N., Haybron, D., Groves, L. and Mower, H.F., **Mutation, Res.,** 1985, 158, 159.