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Synthesis and antitumor activity of novel alkenyl derivatives of pyridoxine containing a curcumin moiety

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Abstract

A convenient synthetic route to novel alkenyl derivatives of pyridoxine containing a fragment of natural compound curcumin was developed. At the first stage, oxidation of primary hydroxyl group of pyridoxine acetals (ketals) led to a series of novel aldehydes. Wittig reaction of the aldehydes with (4-ethoxy-2,4-dioxybutyl)triphenylphosphonuim chloride resulted in a series of 5- and 6-alkenyl substituted pyridoxine derivatives. The reaction was carried in methylene chloride in a tightly closed reaction vessel under pressure at 70 °C. The desired products were isolated using column chromatography on silica gel. Varying the reaction conditions, such as the reaction temperature, the nature of the base and solvent, did not increase the reaction yield. The obtained compounds were characterized using HRMS in combination with HPLC, NMR spectroscopy (^{1}H, ^{13}C, NOESY, COSY, HSQC), and X-ray crystallography (for crystalline samples). It was demonstrated that the synthesized compounds exist in solution as equilibrium mixtures of two tautomeric forms, β-diketone and keto-enol, in comparable amounts. The keto-enol form was slightly favored, and this effect was more pronounced for 5-substituted as compared to 6-substituted derivatives. The solvent nature did not influence the tautomeric equilibrium. Some of the obtained compounds showed a moderate cytotoxicity *in vitro* against the human embryonic kidney HEK-293 cells and the human breast carcinoma MCF-7 cells with IC_{50} in the range of 30-60 μM and 17-30 μM, respectively, thus demonstrating a selectivity of antitumor action.

References

[1] W. Korytnyk, N. Angelino, B. Lachmann, P.G. Potti. Substrate specificity of pyridoxine dehydrogenase from yeast, and the synthesis and biological activities of 5-vinyl and 5-ethynyl analogs of pyridoxo1. *J. Med. Chem*. **1972**. Vol.15. No.12. P.1262-1265.

[2] W. Korytnyk, S.C. Srivastava, N. Angelino, P.G. Potti, B. Paul. A general method for modifying the 2-methyl group of pyridoxol. Synthesis and biological activity of 2-vinyl- and 2-ethynylpyridoxols and related compounds. *J. Paul, Med. Chem*. **1973**. Vol.16. P.1096-1101.

[3] M.V. Pugachev, R.S. Pavelyev, T.N.T. Nguyen, A.G. Iksanova, O.A. Lodochnikova, Yu.G. Shtyrlin. Synthesis and antitumor activity of pyridoxine monoalkenyl derivatives. *Russ Chem Bull.* **2016**. Vol.65. P.532-536.

[4] M.V. Pugachev, T.M. Bulatov, T.N.T. Nguyen, R.S. Pavelyev, O.I. Gnezdilov, O.A. Lodochnikova, D.R. Islamov, O.N. Kataeva, K.V. Balakin, Yu.G. Shtyrlin. Wittig reactions of a bis-triphenylphosphonium pyridoxine derivative. *Tetrahedron Letters.* **2017**. Vol.58. P.766-769.

[5] M.N. Kathryn, L.D. Jayme, B. Jonathan, G. James, F.P. Guido, A.W. Michael. The Essential Medicinal Chemistry of Curcumin. *J. Med. Chem*. **2017**. Vol.60. P.1620-1637.

[6] N. Luca, M. Angelo, P. Andrea, P. Giovanni, F. Erika, S. Monica. Excited state dynamics of bisdehydroxycurcumin *tert*-butyl ester, a diketoshifted derivative of the photosensitizer curcumin. *PLoS One.* **2017**. Vol.12. P.1-19.

[7] A. Wiseberger, E. Proskauer, J. Riddik, E. Tups. Organic solvents. *Moscow: IL.* **1958**. P.519. (russian)

[8] Chemist's desk book (in 6 vol.). *Leningrad: Chemistry.* **1971**. Vol.2. P.889. (russian)

[9] A. Cohen, E.G. Huges. Synthetical experiments in the B group of vitamins. Part V. Novel derivatives of pyridoxine. *J. Chem. Soc*. **1952**. P.4384-4386.
[10] Y.G. Shtyrlin, R.R. Khairullina, A.A. Rizvanov, R.S. Pavelyev, E.V. Martynova. Antirethroviral compounds based on azidothymidine derivatives. *Pat. Russian Federation 2561501. Kazan State University*. **2015**. *Bul.* No.24. (russian)
[11] A.R. Kayumov, N.V. Shtyrlin, Y.G. Shtyrlin, S.V. Sapozhnikov, E.V. Nikitina. Quaternary ammonium salts based on vitamin B_6 derivatives. *Pat. Russian Federation 2607522. Kazan State University*. **2017**. Bul. No.1. (russian)
[12] A.S. Petukhov. Synthesis, spatial structure and properties of seven-membered pyridoxine acetals. *PhD thesis, Kazan State University.* **2004**. 178p. (russian)
[13] Y.G. Shtyrlin, A.D. Strelnik, A.S. Petukhov, M.R. Garipov, N.V. Shtyrlin, O.A. Lodochnikova, I.A. Litvinov, O.A. Morozov, A.V. Lovchev. Derivatives of pyridoxine with nonlinear optical properties. *Pat. 2501801 Russian Federation. Kazan State University*. **2013**. Bul. No.35. (russian)
[14] L.R. Hoffmann. Procédé pour la préparation de dérivés de pyridine. Pat. FR1384099 (A). **1965**.
[15] W. Korytnyk, E.J. Kris, R.P. Singh. Pyridoxine chemistry. V. synthesis of isopyridoxal, 5-pyridoxic acid lactone, and their derivatives. *J. Org. Chem.* **1964**. Vol.29. P.574-579.
[16] N.V. Shtyrlin, O.A. Lodochnikova, Yu.G. Shtyrlin. Regioisomericoximes and thiosemicarbazones derived from 6-substituted pyridoxines. *Mendeleev Communications*. **2012**. Vol.22. P.169-170.
[17] G.M. Sheldrick. SADABS Version 2007/2. *University of Göttingen, Göttingen*. **2004**.
[18] M.C. Burla, R. Caliandro, B. Carrozzini. Crystal structure determination and refinement via SIR2014. *J. Appl. Cryst*. **2015**. Vol.48. P.306-309.
[19] G.M. Sheldrick. Crystal structure refinement with SHELXL. *Acta. Crystall. Ogr. C. Struct Chem*. **2015**. Vol.71. P.3-8.
[20] L.J. Farrugia. WinGX suite for small-molecule single-crystal crystallography. *J. Appl. Crystallogr*. **1999**. Vol.32. P.837-838.
[21] User manual. APEX (Version 2.1), SAINTPlus-BrukerAdvansed-X-Ray Solutsions. *BrukerXS Inc., Madison, Wisconsin, USA*. **2006**.
[22] A.D. Strelnik. Synthesis and biological activity of some pyridoxine derivatives. *PhD thesis, Kazan State University.* **2010**. P.43-77. (russian)
[23] N.V. Shtyrlin. Synthesis and biological activity of some 6-substituted pyridoxine derivatives. *PhD thesis, Kazan State University.* **2010**. P.4-98. (russian)