COPPER(II) COMPLEXES OF SCHIFF BASE LIGANDS AS PROMISING ANTICANCER AGENTS

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Based on World Health Organization (WHO) report, it was estimated that one in five people before age 75 will suffer from **cancer** during their lifetime, and more than 13 million cancers death will happen in 2030. Although many efforts for treatment of cancer diseases have been carried out and much progress have been eventuated from diagnosis to treatment of cancer, but some of cancer patients do not respond to therapy or recurrence subsequent initial response. Nevertheless, chemotherapy is a basic approach for the treatment of cancer diseases. However, because of drug resistance and considerable side effects drug-induced toxicity, the discovery of new metal analogs with promising activity and high therapeutic index is an urgent need.

Cisplatin was the first FDA-approved metal-containing compound compound for cancer treatment in 1978. The great successes achieved with platinum-based antitumor agents, have promoted the development of metal-based drugs.
However, all these Pt-based drugs are associated with severe side effects and evolution of drug resistance during therapy processes, which has stimulated chemists to seek and develop more effective, less toxic, and target-specific metal-based anticancer drugs [1].
The fundamental role of **copper** and the recognition of its complexes as important bioactive compounds in vitro and in vivo aroused an ever-increasing interest in these agents as potential drugs for therapeutic intervention in various diseases. The vast array of information available for their bioinorganic properties and mode of action in several biological systems is the base for the development of a novel generation of highly active copper complex drugs with minimized side effects which could add significantly to the current clinical research and practice [2].
Schiff bases are versatile ligands synthesized from the condensation of an amino compound with carbonyl compounds and these coordinate to metal ions via azomethine nitrogen Schiff's base. Schiff bases are a critical class of compounds in medical chemistry that have demonstrated significant chemotherapeutic and antibacterial application. Schiff base Cu(II) complexes revealed great potential for antiproliferative, antibacterial, and gastroprotective activity [3].
Coumarins are a wide class of natural and synthetic compounds that showed diverse pharmacological activities including anti-cancer activity. Among the wide variety of coumarins, 7-hydroxycoumarin derivatives have been shown to possess desirable antiproliferative activities. In particular, their antibacterial, antifungal and anticancer activities make the compounds attractive for further derivatization and screening as novel therapeutic agents [4]. Taking these compounds as lead, we have designed and synthesized a series of new copper(II) complexes with coumarin-derived Schiff base ligands.

Two series of Schiff bases were prepared by condensation of 8-formyl-7-hydroxy-4-methylcoumarin and 8-acetyl-7-hydroxy-4-methylcoumarin with *p*-substituted aniline derivatives. These compounds were used as ligands in the synthesis of copper(II) complexes. The obtained Schiff bases as well as copper complexes are mostly novel molecules. Only the products of condensation 8-formyl-7-hydroxy-4-methylcoumarin with *p*-toluidine [5] and 8-acetyl-7-hydroxy-4-methylcoumarin with *p*-toluidine and its copper(II) complex [6] were synthesized, but the anticancer activity of these compounds was not determined.

The assay of their cytotoxic activity is in progress. Preliminary, we have identified two copper(II) coordination compounds of 7-hydroxy-8-[1-(4-methoxyphenyloimino)ethyl]-4-methyl-2H-chromen-2-one and 7-hydroxy-8-[1-(4-hydroxyphenyloimino)ethyl]-4-methyl-2H-chromen-2-one having dose-dependent antiproliferative activity on HeLa cancer cell line.
Additionally, the Schiff bases – derivatives of substituted salicylaldehydes and 2-hydroxyacetophenones condensed with appropriate anilines were prepared. However, such compounds have been reported in scientific papers [7-9], their copper complexes have not been assayed yet, and may serve as an useful tool in structure-reactivity relationship investigation.

References

[1] S. Dasari and P. B. Tchounwou, Eur. J. Pharmacol. 740 (2014) 364–378.
[2] C. Marzano, M. Pellei, F. Tisato and C. Santini, Anti-Cancer Agents in Medicinal Chemistry, 9 (2009), 185-211.
[3] A. M. Abu-Dief , I. M. A. Mohamed, Beni-Suef University Journal of Basic and Applied Sciences, 4 (2015) 119-133.
[4] S. Emami, S. Dadashpour, Eur. J. Med. Chem. 102 (2015) 611-630.
[5] V.F. Traven, I.V. Ivanov, A.V. Panov, O.B. Safronova, and T.A. Chibisova, Russian Chemical Bulletin, International Edition, 57 (9) (2008) 1989-1995.
[6] A. P. Mishra, J. Indian Chem. Soc. 75 (1998) 251-252.
[7] Cronenberger et.al., Chimica Therapeutica (1968), 87-99.
[8] T. B. Nguyen, Q. Wang and F. Guéritte, Synth. Commun, 42 (18) (2012) 2648-2663.
[9] P. Kopel, J. Kamenıcek, V. Petricek, A. Kurecka, B. Kalinska, J. Mrozinski, Polyhedron 26 (2007) 535–542.

Proponowana przez autora forma prezentacji: komunikat (15 min)