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Editorial:

THIOSEMICARBAZONES AS NEW ANTITUMOR COMPOUNDS

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Version en español

The search of new compounds with medicinal applications is promoting important therapeutic advances and generates a new scientific multidisciplinary field where chemistry, pharmacy and biomedicine overlap together with other specialities. Thiosemicarbazones are some of the studied compounds. These sulfur-containing organic substances exhibit an interesting biological activity, which has been studied for more than fifty years[1]. In this sense, it is worth mentioning the efforts carried out in the cancer research. During the middle 1960s some of these derivatives showed high antitumor activity in different assays[2-3]. This fact encouraged to perform the first clinical trials, early stopped due to the unexpected low activity in humans[4].

In addition, cellular targets of these substances were identified, mainly redox cellular processes and several enzymatic systems as topoisomerases, dehydrogenases, polymerases and nucleoside kinases[5-8]. Among the last ones, it is remarkable the inhibition of ribonucleotide reductases (RNRs), enzymes

that transform ribonucleoside diphosphates into deoxyribonucleoside diphospates to give the basic constituents of DNA[9].

The synthesis of new more selective and less toxic compounds led to the attainment of a novel drug (3-aminopyridine-2-carboxaldehyde thiosemicarbazone, ATSC), which is currently involved in phase I and II clinical trials[10-13]. In parallel, other compounds exhibiting even better biological activity than ATSC have been developed[14]. Among them, there are some metal-organic derivatives. Binding of such organic molecules to metal ions gives rise to very stable coordination compounds. It also allows to modify the physicochemical properties of the thiosemicarbazones. Thus, their usually low water solubility drastically increases upon coordination. Moreover, a fine selection of the metal ion leads to a control of the stability of these substances against decomposition reactions.

Finally, the coordination induces changes in the acid-base behavior and the redox properties as in the metal ions as in the thiosemicarbazones. These physicochemical transformations affect the biological activity. For instance, it has recently been suggested that inhibition of RNRs is actually carried out by thiosemicarbazoneiron complexes[15], it has also been demonstrated that copper derivatives activate lysosomal apoptosis pathway[16] and, finally, both ions-containing compounds are responsible for the redox activity shown by thiosemicarbazones inside the cell[17].

On the other hand, thiosemicarbazonecopper compounds are yielding quite promising findings in diagnosis. In this regard, ^{64}Cu-based thiosemicarbazone radiopharmaceuticals are being explored to be used in PET (positron emission tomography) because of the hypoxia-selective tissue uptake, and they have been approved for use in clinical trials in patients with cervical cancer[18].

In summary, the interesting results obtained in therapy and diagnosis become the thiosemicarbazones and their metal complexes into very attractive systems to be studied with a great applicative prospect. However, it is necessary a deeper research of these compounds in order to diminish their toxicity and increase the effectiveness in humans.

To achieve these goals, the preparation of new compounds, studies on structure-properties relationships and the reactivity against biomolecules, which are in an early stage, should be carried out. The advances in this field could be very useful to interpret the biological properties, as the interactions and bonding of thiosemicarbazone compounds to biological targets, and virtually to increase their therapeutic possibilities.

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