Colorectal cancer (CRC) is malignancy located in the low segment of the digestive tract. In 2020 this disease left a total of 1.9 million reported cases and a total of 935,173 deaths across the world. This makes it the third most common type of cancer and the second deadliest one. Currently, the most common treatments to this disease are combinations of the drugs 5-fluorouracil, oxaliplatin, irinotecan and the modulation agent leucovorin. Despite these treatments are effective to fight the CRC, they are also non-selective, that means they kill both cancer cells and normal cells, this carries to a series of adverse effects and to the resistance development of the cancer cells to the medical treatments.

In view of this problematic, we propose the hybrid molecules as a therapeutic alternative in the treatment of CRC. These molecules are the combination of two or more molecular entities which have a biological activity, these entities are combined by a chemical transformation in order to create a single molecule which have structural motifs of all the parent compounds. Therefore, we expect to obtain a compound with an enhanced biological activity, less adverse effects and a better bioavailability.

Melatonin known as the sleep hormone, is a compound present in all the vertebrates which have some remarkable pharmacological properties. It is reported that melatonin has anxiolytic, analgesic, anti-inflammatory, antioxidant and especially cytotoxic activity against several cancer cell lines. With special interest in this work, quinazolinones and monastrol-based compounds have highlighted because their remarkable cytotoxic and antiproliferative potency.

Based on the aforementioned, this research aims for the design and synthesis of two series of new hybrids molecules based on the combination of melatonin with the 2,3-dihydroquinazolinone ring or monastrol derivatives moieties, respectively (Figure 1). These hybrids are functionalized with several aromatic moieties to allow a structural diversity and compare their biological properties to examine the biological properties of the synthetized molecules, the cytotoxicity of the molecules will be tested against a colorectal carcinoma cell line SW480 and against a non-tumoral cell line CHO-K1, as well as their antiproliferative response.
By the date the two series of hybrid molecules are completely synthetized and characterized which represents a total 22 new hybrid molecules which 12 correspond to a series of 2,3-dihydroquinazoline – melatonin hybrids and the other 10 to a monastrol derivatives – melatonin series. The corresponding reactions were carried on conditions such as reflux heating and magnetic stirring. This allows us to obtain the two series of hybrids with global yields ranging between 39 and 59% for the 2,3-dihydroquinazolinoe – melatonin series and between 11 and 28% for the monastrol derivatives – melatonin series. Finally, in silico studies showed that these compounds exhibit good pharmacokinetic properties.

The realization of biological assays which allow us to determinate the cytotoxic and antiproliferative potential of the synthetized molecules is still pending, with this information we expect not only to find the most active compounds but to do a structure – activity relationship (SAR) that allows us to know which are the functionalization patrons that provide the greatest activity against CRC cells and the lesser cytotoxicity in front of non-malignant cells.

![Molecular design of the proposed molecular hybrids](image)

**Fig. 1** Molecular design of the proposed molecular hybrids

**References**