HELLENIC REPUBLIC
National and Kapodistrian University of Athens
EST. 1837

SCHOOL OF HEALTH SCIENCES
DEPARTMENT OF PHARMACY
SECTION OF PHARMACOGNOSY AND CHEMISTRY OF NATURAL PRODUCTS

Isolation And Structure Elucidation Of Secondary Metabolites From Marine Organisms Of The Red Sea

DOCTORAL THESIS

MOHAMED TAMMAM

ATHENS
DECEMBER 2020

ABSTRACT

Despite the continuous efforts of many research groups to develop new therapeutic treatments for various health problems, current medicines yield low cure rates and undesirable side effects. In the ongoing search for more effective anticancer and antibiotic agents, marine organisms have emerged as a promising new resource yielding unusual chemical structures with potent biological activities. The vast diversity and relatively unexplored nature of these unique sources of chemodiversity is expected to open a new era to drug discovery. Natural products have been the predominant source of new pharmaceuticals in the last fifty years. Between 1981 and 2002, 60% of the anticancer drugs and 75% of the anti-infectious disease drugs could be traced to or were inspired by natural products. Humankind has explored and exploited the terrestrial environment for more than 3,000 years, but only relatively recently turned its attention to the oceans as a possible source for natural medicines. From the early investigations in the 1970s until now marine organisms have yielded more than 32,000 natural products. Already a number of them are available in the pharmaceutical market, such as ziconotide (strong analgesic for severe pain relief by the brand name Prialt®) and ecteinascidin 743 (potent antitumor for the treatment of soft tissue sarcoma by the brand name Yondelis®), while many compounds are in advanced clinical trials for the treatment of numerous diseases.

In the framework of the present PhD thesis, the chemical composition of organic extracts obtained after the exhaustive extraction of three marine organisms, namely the red alga *Laurencia majuscula*, a sponge of the genus *Lamellodysidea* and the soft coral *Sinulariapolydactyla*, collected from Hurghada and Thuwal, in the Red Sea (Egypt and Saudi Arabia) was investigated. To isolate the secondary metabolites of these marine organisms, the extracts were submitted to a series of chromatographic separations with various solvents and different types of chromatography. The isolated metabolites were identified on the basis of their spectroscopic data (NMR, MS, IR, UV-Vis) and comparison with literature data. In total 64 secondary metabolites have been isolated from these marine organisms, among which 59 have been structurally characterized, including 18 new natural products and one previously reported as a synthetic derivative.

Twenty-two secondary metabolites (1-22) were isolated and identified on the basis of their spectroscopic characteristics from the red alga *L. majuscula* collected from Hurghada, Egypt. These included seven laurane sesquiterpenes (1-7), one cuparane sesquiterpene (8), one seco-laurane derivative (9), one snyderane derivative (10), two chamigranes (11 and 12) and two rearranged chamigranes (13 and 14), one aristolane sesquiterpene (15), one tricyclic diterpene (16), one five-membered C15 acetogenin (17), four tricyclic C15 acetogenins of the maneonene type (18-21) and a chlorinated fatty acid derivative (22). Compounds 2, 3, 5, 6, 9, 17 and 19-21 are new natural products.

From the marine sponge *Lamellodysidea* sp. collected from the coral reef off Thuwal in Saudi Arabia, 11 sesquiterpenes (23-31), mostly containing furan or γ-lactone in their structures, were isolated, three of which are new natural products (25, 30 and 31) and one (33) is reported for the first time from a natural source.

Twenty-six steroids (34-59) have been isolated and structurally characterized from the soft coral *S. polydactyla* collected from Hurghada, Egypt, including 15 4α-methylated derivatives. Compounds 34, 35, 39, 41, 46 and 53 are new natural products. Among them, metabolites 34 and 35 feature the rare 4-methyl-8,9-seco-cholastane steroidal nucleus.

The cytotoxic, anti-inflammatory, anti-angiogenic, and neuroprotective activity of compounds 36–40, 42–45, 47–53 and 55–59, as well as their effect on androgen receptor-regulated transcription was evaluated in vitro in human tumor and non-cancerous cell