International Journal of
Molecular Sciences

MDPI

Editorial

Special Issue "Development and Synthesis of Biologically Active Compounds"

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The intention of this Special Issue is to focus on new achievements in the design, preparation, and in vitro and in vivo biological evaluation of bioactive molecules that can result in the development of natural or artificial potent compounds looking for promising pharmaceuticals and agrochemicals. The relevance of the search for biologically active molecules for the creation of original drugs is due to the widespread occurrence of socially significant diseases such as cardiovascular, oncological, infectious, and neurodegenerative ones.

Cancer is an extremely prevalent disorder responsible for a large number of deaths year by year worldwide [1]. Most of the articles in this Special Issue are devoted to the search for new compounds with antiproliferative and cytotoxic activities and overcoming related problems. Thus, Sodano et al. [2] designed and synthesized a cyclopentadienone conjugated to an inactive dienophile as a new non-metal CO-releasing molecule (CORM), capable of generating CO upon the influence of enzymes. New CORM is toxic to a number of human tumor cell lines including drug-resistant ones. It was efficiently taken up by drug-resistant tumor cells and it was capable of restoring their sensitivity to chemotherapeutic agents by inducing a CO-dependent mitochondrial oxidative stress that resulted in mitochondrial-dependent apoptosis. This work follows on from the authors' previous works [3–7] showing that certain compounds releasing gaseous signaling molecules, namely nitrogen monoxide (NO) and hydrogen sulfide (H_2S), can facilitate overcoming the resistance of tumor cells to doxorubicin. These results highlight the significance of small signaling molecule donors in cases of traditional chemotherapy ineffectiveness and thus offer the prospects for novel combination strategies to succeed in chemosensitization and overcoming multidrug resistance.

In screening for bioactivity, there is a problem of the precipitation of a lipophilic compound in an aqueous environment [8]. To overcome the issue, Semenova et al. [9] examined the employment of Pluronics as cosolvents in the in vivo evaluation of some potent microtubule destabilizers. These destabilizers included albendazole, diarylisoxazole [10], and two chalcones [11,12], which were found to be cytotoxic against human cancer cells. The phenotypic sea urchin embryo model was used to provide a rapid and reliable assessment of antiproliferative activity. Phenotypic screening using sea urchin embryo assay demonstrated that all tested compounds preserved antimitotic activity in a water-containing medium when their DMSO or 2-pyrrolidone stock solutions were diluted with Pluronic P123 or Pluronic F127. These results allow one to suggest Pluronics as cosolvents for improving the solubility of lipophilic compounds in water-containing media.

Despite the significant progress of science and technology in the production of synthetic pharmaceuticals, medicines of natural origin play an essential role in cancer therapy. It was evaluated that from 1981 to 2019, about a quarter of all newly approved antitumor drugs were associated with natural compounds. Nevertheless, the development of bioactive compounds of natural origin into drugs has remained challenging due to the difficulties

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Citation: Gazieva, G.A.; Chegaev, K. Special Issue "Development and Synthesis of Biologically Active Compounds". *Int. J. Mol. Sci.* **2024**, *25*, 4015. https://doi.org/10.3390/ijms25074015

Received: 26 February 2024
Revised: 28 March 2024
Accepted: 1 April 2024
Published: 4 April 2024

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in product isolation and laborious synthesis [13]. These problems are reflected in the Special Issue. Two articles consider cytotoxic naturally occurring compounds and their analogues. Grudzień et al. [14] described the toxicity of xanthohumol and its natural and semisynthetic derivatives using three canine lymphoma and leukemia cell lines. Xanthohumol derivatives induced apoptosis in the studied cell lines. A decrease in Bcl-2 level in cells treated with xanthohumol was revealed by Western blotting. Gettler et al. [15] elaborated a universal synthetic methodology for the enantioselective formation of a benzo[c]oxepine framework found in natural compounds. This approach was successfully applied to the first total synthesis of heterocornol D, earlier extracted from the fungus *Pestalotiopsis heterocornis*. The absolute configurations of the natural heterocornol D stereocenters were determined. In total, synthesis of four stereoisomers of this natural polyketide was realized. The presented synthetic strategy was also extended synthesizing heterocornol C that possessed cytotoxic activity [16].

In addition, Cybulski et al. [17] synthesized five new amide conjugates of hydroxycinnamic acids with the known analog of the naturally occurring alkaloid neocryptolepine, i.e., antitumor 5,11-dimethyl-5*H*-indolo[2,3-*b*]quinoline [18,19]. Three conjugates demonstrated significant antiproliferative effect on pancreatic cancer (BxPC-3 and metastatic AsPC-1), breast cancer (MCF-7), and cervical cancer cells (HeLa). One of them showed dose-dependent efficiency towards both BxPC-3 and metastatic AsPC-1 pancreatic cancer cells with a reasonable selectivity index for both tumor cell lines in comparison with normal dermal fibroblasts.

Several publications concern the study of the cytotoxic and antibacterial, antiaggregation, or antiphytopathogenic activities of synthesized compounds. In the investigation by Shybanov et al. [20], the regio- and stereoselective synthesis of novel hydantoin and thiohydantoin-based spiro-compounds was developed. The obtained compounds showed moderate cytotoxicity to MCF7, A549, HEK293T, and VA13 cell lines. Several tested substances had noticeable antibacterial properties against the *Escherichia coli* BW25113 DTC-pDualrep2 strain that has a normal cell wall, but the substances were practically inactive against the *Escherichia coli* BW25113 LPTD-pDualrep2 strain that has corrupted cell walls.

Castaño et al. [21] prepared several novel series of chalcone–sulfonamide hybrid compounds which were applied for the subsequent construction of the heterocyclic pyrazoline derivatives. The antiproliferative and antituberculosis effects of the obtained compounds were tested. Several compounds exhibited potent antiproliferative effect towards the LOX IMVI (melanoma) cell line and towards the entire group of leukemia cell lines with IC_{50} values ranging from 0.34 to 2.52 μM. Two substances inhibited the growth of *Mycobacterium tuberculosis* H37Rv at concentrations below 10 μM.

Napiórkowska et al. [22–24] devoted several years to the study of the biological properties of benzofuran derivatives, resulting in the identification of bromosubstituted benzofurans possessing high antitumor activity. Among the series of novel 2-acetyl-3-(bromo)methyl benzofurans, two bromomethyl derivatives exhibited selective cytotoxic effect to leukemia cancer cells (K562) compared to that against normal cells (HaCaT) with a favorable therapeutic index. These derivatives induced apoptosis in the explored cancer cells through enhancing the activity of executioner caspases 3/7, had pro-oxidative effect, increased reactive oxygen species, and inhibited the excretion of pro-inflammatory interleukin 6 in K562 cells. The screening for antibacterial activity of benzofurans using standard and clinical strains showed that one compound exhibited a modest effect against Gram-positive strains.

Bogdanov et al. [25] prepared two series of new fluorinated N-benzylisatins and water-soluble isatin-3-hydrazones. Fluorinated N-benzylisatins possessed cytotoxic action against M-HeLa and HuTu 80 cancer-derived cells, inducing apoptosis through mitochondrial membrane dissipation and reactive oxygen species generation in cancer cells. In addition, two compounds exhibited antiplatelet effect at the reference compound, acetylsalicylic acid, level. Among the new water-soluble pyridinium isatin-3-acylhydrazones, three compounds

exhibited the most potent activity towards fungal and bacterial phytopathogens and can be employed for developing agrochemicals to control plant diseases.

To continue a previous investigation [26], Vinogradova et al. [27] evaluated fungicidal activity of new S-alkyl substituted thioglycolurils against six phytopathogenic fungi and two pathogenic yeasts. Several S-alkyl thioglycolurils inhibited the growth of *Venturia inaequalis* and *Rhizoctonia solani* mycelium by 85–100% with somewhat lower activity towards other phytopathogens. Ethylsulfanyl-substituted compounds demonstrated significant activity towards yeast *Candida albicans*. For these compounds, their hemolytic effect and cytotoxicity were assessed in relation to human red blood cells and human embryonic kidney cells, respectively. Two ethylsulfanyl derivatives demonstrated low hemolytic and cytotoxic activities in connection with normal human cells along with strong antifungal effect towards *Candida albicans*.

Aksenov et al. [28] synthesized diverse 3,5-di-(hetero)aryl-4-benzyl-substituted α,β-unsaturated γ-hydroxy butyrolactams. These compounds are in great demand in synthetic organic and medicinal chemistry [29].

Human lactate dehydrogenase (hLDH), in particular isoform hLDHA, has been identified as a therapeutic target for treating various diseases such as cancer [30], vascular diseases [31,32], inflammatory diseases [33], and primary hyperoxaluria [34]. Salido et al. [35] synthesized the analogues of naturally occurring A-type proanthocyanidin containing a 2,8-dioxabicyclo[3.3.1]nonane core. Nine 2,8-dioxabicyclo[3.3.1]nonane derivatives were characterized by IC_{50} values of less than 10 μM towards hLDHA. The enantiomers of the most effective and selective substances were separated using chiral HPLC. The study of inhibitory activity of pure enantiomers derived from 2,8-dioxabicyclo[3.3.1]nonane showed that the absolute configuration had little effect on hLDHA inhibition. The authors ascertained that dextrorotatory enantiomers are preferable because the kinetic investigation of hLDHA inhibition by enantiomers manifested a noncompetitive inhibition behavior for both enantiomers, with the dextrorotatory enantiomer being 2–4 times more effective in inhibiting the hLDHA enzyme.

Catalytic antibodies possess numerous functions compared to monoclonal antibodies due to their specific ability to decompose antigens enzymatically. Hence, a plethora of such antibodies and their subunits have been prepared since 1989 [36–40]. Nonaka et al. [41] performed methodical research on two catalytic antibody light chains, #7TR and H34, by modifying the purification techniques, pH values, and reagents used. In the peptidase activity tests and kinetic studies, high catalytic activity of the light chains took place when the chains were obtained under basic conditions. These results indicate that a slight structure adjustment of the catalytic antibodies occurs during the purification procedure to improve the catalytic activity whereas the antigen recognition capability remains unchanged. When the #7TR and H34 chains were produced under the reported conditions, they highly increased the degradability of Amyloid-beta and PD-1 peptides, respectively. These results offer exciting prospects of using catalytic antibodies to alter the course of Alzheimer's disease and cancer.

Human immunodeficiency virus (HIV) causes one of the deadliest disorders, acquired immunodeficiency syndrome (AIDS) [42,43]. At present, one of the intensively evolving fields of organic and medicinal chemistry is the design and discovery of new substances that can inhibit one of the HIV enzymes, particularly HIV-1 integrase [44,45]. One review [46] presented an assay of the publications concerning the synthetic approaches to obtain pyridine-comprising HIV-1 integrase inhibitors from 2003 to the present. The review emphasizes that the area of chemistry related to the preparation of new HIV-1 integrase inhibitors comprising pyridine core remains in demand and is needed for the development and search for new medicines against HIV.

Conflicts of Interest: The authors declare no conflicts of interest.

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