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Oncology exploration: charting cancer medicinal chemistry space

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Approaches for the experimental determination of protein–ligand molecular interactions are reliant on the quality of the compounds being tested. The application of large, randomly designed combinatorial libraries has given way to the creation of more-focused 'drug-like' libraries. Prior to synthesis, we wish to screen the potential compounds to remove undesired chemical moieties and to be within a required range of physiochemical properties. We have used a principal-component analysis (PCA) computational approach to analyze the 3D descriptor space of active and non-active (hit-like) cancer medicinal chemistry compounds. We define hit-like those molecules passing the unmodified OpenEye FILTER program. Our analysis indicates that these compounds occupy quite different regions in space. Cancer-active compounds exist in a much greater volume of space than generic hit-like space and most of them fail the commonly applied filters for orally bioavailable drugs. This is of great significance when designing orally bioavailable cancer target drugs.

The successful application of the processes of virtual and physical screening for active ligands is totally reliant on the quality of the molecules being screened. In the simplest terms, if there are no hits in the database or compound library, there is no point in performing the screen. Recent years have seen great advances in our understanding of what makes a molecule drug- or lead-like and cheminformatic treatment of screening collections has focused the attention of discovery research towards drug and lead chemical space. However, when dealing with oncology, the applied and trusted rules of engagement do not always apply.

Partitioning and classifying cancer medicinal chemistry space is not straightforward. A multitude of active cancer ligands, containing different molecular scaffolds, have been identified for the relatively small number of cancer targets. The past two decades have witnessed a tremendous increase in our understanding of the pathology and molecular biology of human cancers [1]. Although enormous progress has been made in the development and identification of new molecular medicines and targets in this area, many of the current clinical treatments for cancers have limitations with respect to efficacy, resistance and toxicity in the patient [2]. There is much scope for the exploitation of the many new molecular targets to develop new cancer treatments with improved specificity, toxicology profiles and efficacy [3].

Cancer chemotherapeutics

The bulk of existing cancer chemotherapeutic drugs causes cell death by several different mechanisms – the majority by non-selectively targeting the cellular processes that cancers utilize to rapidly grow and divide (i.e. the ability to replicate their DNA) [4]. In general, dividing tumor cells have lost the ability to respond to environmental cues, which in normal cells would control physiological functions such as cell division. Normal cells exhibit a higher basal resistance to chemotherapeutic drugs, whereas rapidly dividing cells, such as bone marrow and intestinal mucosa, are highly susceptible to them and severe toxic side effects are common [5]. The discovery of defects in oncogenes has allowed the development of exciting anticancer therapeutics that can selectively target tumor cells and specific tumor biochemical processes,

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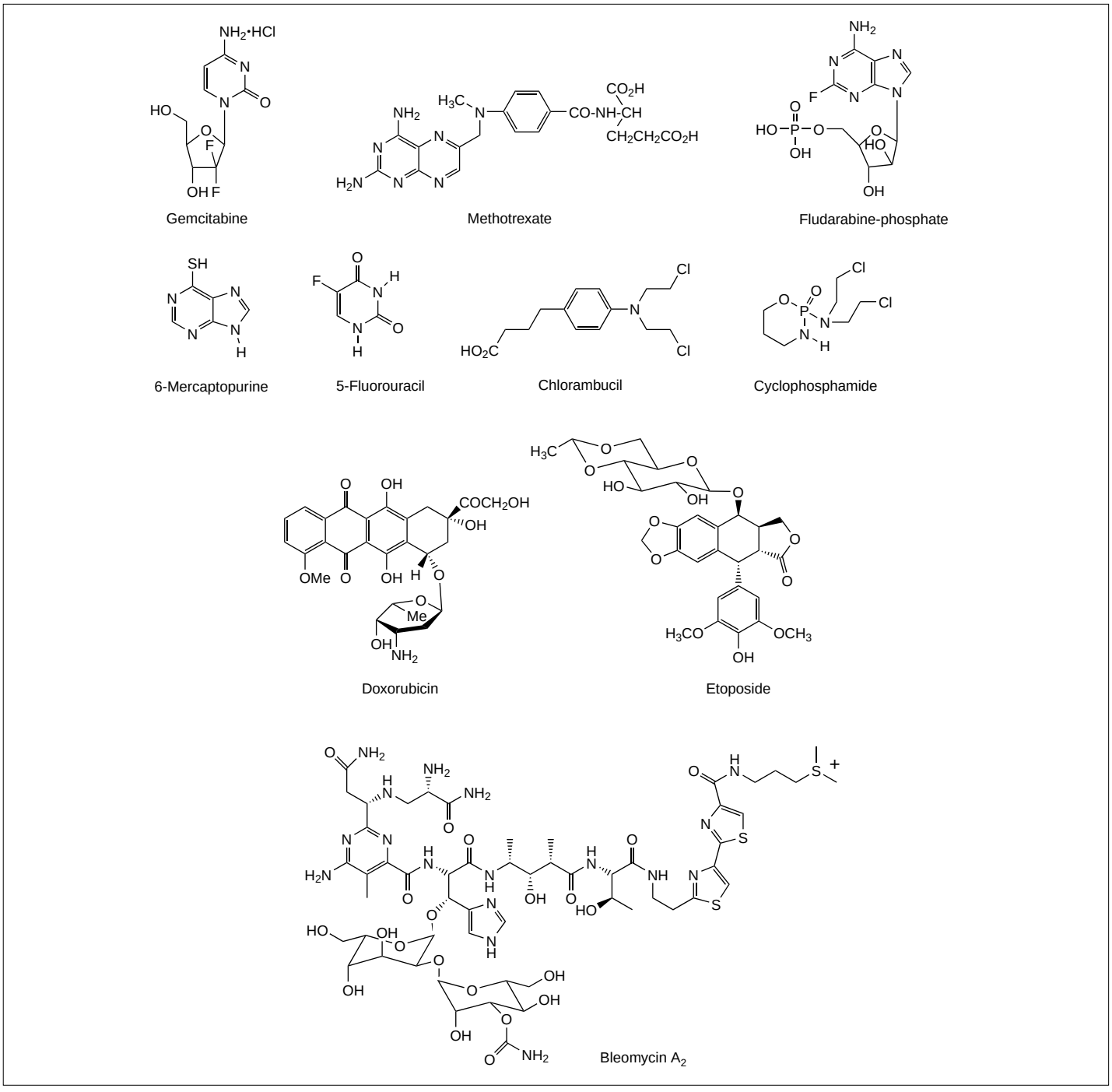

FIGURE 1

Chemical structures of non-selective chemotherapy drugs acting through different mechanisms. A selection of genotoxic and antimetabolic drugs are depicted, illustrating the great variety in structural form of anticancer ligands.

avoiding the cellular toxicity associated with conventional cancer chemotherapeutic drugs [6]. Knowledge of the specific biochemical differences between normal and cancer cells is growing at an exponential rate and this can be potentially exploited for cancer chemotherapy. The recent development of some FDA-approved treatments that target cancer-specific cellular processes demonstrate the utility of these novel approaches [7].

To appreciate the breadth of cancer-related chemical space, we first examine some of the major mechanistic groupings within this space by looking at various classes of oncology therapeutics, with a view to mapping their relative locations in terms of the medicinal chemical space they occupy.

Antimetabolites

Antimetabolites, such as methotrexate, 6-mercaptopurine and gemcitabine (Figure 1), were developed to interfere with specific enzymatic steps in nucleotide biosynthesis in tumor cells. Methotrexate is an inhibitor of dihydrofolate reductase (DHFR) and, as such, limits the formation of nucleotides and thus inhibits DNA replication. It has a significant role in the treatment of breast