Talanta 85 (2011) 2265–2289

Contents lists available at SciVerse ScienceDirect

Talanta

journal homepage: www.elsevier.com/locate/talanta

Review

Analysis of anticancer drugs: A review

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ARTICLE INFO

Article history:
Received 11 May 2011
Received in revised form 15 August 2011
Accepted 16 August 2011
Available online 24 August 2011

Keywords:
Anticancer drug analysis
Cytotoxic agent
Pharmaceutical formulation
Biological sample
Environmental sample
Review

ABSTRACT

In the last decades, the number of patients receiving chemotherapy has considerably increased. Given the toxicity of cytotoxic agents to humans (not only for patients but also for healthcare professionals), the development of reliable analytical methods to analyse these compounds became necessary. From the discovery of new substances to patient administration, all pharmaceutical fields are concerned with the analysis of cytotoxic drugs. In this review, the use of methods to analyse cytotoxic agents in various matrices, such as pharmaceutical formulations and biological and environmental samples, is discussed. Thus, an overview of reported analytical methods for the determination of the most commonly used anticancer drugs is given.

Contents

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doi:10.1016/j.talanta.2011.08.034

1. Introduction

Cancer is a disease in which the control of growth is lost in one or more cells, leading either to a solid mass of cells known as a tumour or to a liquid cancer (i.e. blood or bone marrow-related cancer). It is one of the leading causes of death throughout the world, in which the main treatments involve surgery, chemotherapy, and/or radiotherapy [1]. Chemotherapy involves the use of low-molecular-weight drugs to selectively destroy tumour cells or at least limit their proliferation. Disadvantages of many cytotoxic agents include bone marrow suppression, gastrointestinal tract lesions, hair loss, nausea, and the development of clinical resistance. These side effects occur because cytotoxic agents act on both tumour cells and healthy cells [2]. The use of chemotherapy began in the 1940s with nitrogen mustards, which are extremely powerful alkylating agents, and antimetabolites. Since the early success of these initial treatments, a large number of additional anticancer drugs have been developed [1].

Anticancer drugs can be classified according to their mechanism of action, such as DNA-interactive agents, antimetabolites, antitubulin agents, molecular targeting agents, hormones, monoclonal antibodies and other biological agents [2]. In this review, the most commonly used anticancer drugs (i.e. classical cytotoxic agents) are discussed.

- *Antimetabolites* are one of the oldest families of anticancer drugs whose mechanism of action is based on the interaction with essential biosynthesis pathways. Structural analogues of pyrimidine or purine are incorporated into cell components to disrupt the synthesis of nucleic acids. 5-Fluorouracil and mercaptopurine are typical pyrimidine and purine analogues, respectively. Other antimetabolites, such as methotrexate, interfere with essential enzymatic processes of metabolism.
- *DNA interactive agents* constitute one of the largest and most important anticancer drug families, acting through a variety of mechanisms:
  - Alkylating agents lead to the alkylation of DNA bases in either the minor or major grooves. For example: dacarbazine, procarbazine and temozolomide.
  - Cross-linking agents function by binding to DNA resulting to an intra-strand or inter-strand cross-linking of DNA. Platinum complexes (e.g., cisplatin, carboplatin, oxaliplatin) and nitrogen mustards (e.g., cyclophosphamide, ifosfamide) are the two main groups of this anticancer drug sub-family. Nitrosurea compounds, busulfan and thiotepa are also cross-linking agents.
  - Intercalating agents act by binding between base pairs. The family include anthracyclines (e.g., doxorubicin, epirubicin), mitoxantrone and actinomycin-D.
  - Topoisomerase inhibitors include irinotecan and etoposide compounds. These drugs inhibit the responsible enzymes for the cleavage, annealing, and topological state of DNA.
  - DNA-cleaving agents such as bleomycin interact with DNA and cause strand scission at the binding site.
- *Antitubulin agents* interfere with microtubule dynamics (i.e., spindle formation or disassembly), block division of the nucleus and lead to cell death. The main members of this family include taxanes and vinca alkaloids [2].

Today, with the increase in cancer incidence, treatments containing cytotoxic drugs are widely used. Due to the aging (and increasingly cancer-susceptible) population and the arrival of new treatments, the demand for pharmacy cancer services is expected to more than double over the next 10 years [3]. Even if more selective therapies are developed (e.g., antibodies or molecular targeting agents), treatment schemes will continue to be associated with classical cytotoxic agents.

Consequently, the need for analytical methods to determine anticancer drugs is of outmost importance. The first developed methods for the analysis of cytotoxic compounds are based on the use of liquid chromatography with UV detection (LC-UV). These methods exhibited satisfactory quantitative performance for the analysis of samples containing high concentrations of target drugs (i.e. development of pharmaceutical formulations, stability studies...). However, in the case of samples with low amount of cytotoxics (i.e. biological or environmental analysis), a sample preparation step allowing a pre-concentration of target compounds had to be applied before the LC-UV analysis. In the 1990s, the high selectivity and sensitivity of mass spectrometry revolutionized the whole analytical procedure by simplifying and reducing the sample preparation step. Today, LC–MS is undoubtedly one of the techniques of choice for the analysis of anticancer drugs with very attractive analytical performance. Limit of detection (LOD) in the order of $ng\,mL^{-1}$ are frequently obtained. Other detection systems were coupled to LC such as fluorimetry, evaporative light scattering detector (ELSD) or electrochemical detection (ECD). Furthermore, analytical techniques were also published to determine anticancer drugs such as capillary electrophoresis coupled to UV-detection (CE-UV), amperometric detection or to laser-induced fluorescence (CE-LIF), gas chromatography–mass spectrometry (GC–MS), Raman spectroscopy, infrared spectrometry (IR).

In the first part of this paper, the need for analytical methods allowing the determination of these cytotoxic drugs in various media, such as pharmaceutical formulations, biological matrices and environmental samples, is discussed. In the second part, an overview of the different analytical methods is given according to specific cytotoxic agents.

2. Analysis of cytotoxic drugs: generality

2.1. Analysis of cytotoxic agents in pharmaceutical formulations

From the production of cytotoxic bulk until chemotherapy in a patient, analytical methods are necessary for (i) quality control of bulk and commercialised formulations, (ii) quality control of diluted formulations before patient administration and (iii) studies on formulations regarding compatibility and stability.

2.1.1. Quality control of bulk and formulations

For bulk and pharmaceutical formulations, a valuable method for quality control should be able to simultaneously determine the parent drug and its impurities and degradation products. Quality control, valuable for all pharmaceuticals, must be in agreement with pharmaceutical regulations. Usually, separation techniques offering great selectivity, such as LC or CE, are used. Among the most commonly used detection systems, MS can be considered

the technique of choice. Its high selectivity and sensitivity allows the detection of very low concentrations of impurities or degradation products. For example, Jerremalm et al. studied the stability of oxaliplatin in the presence of chloride and identified a new transformation product (monochloro–monooxalato complex) by LC–MS/MS [4]. However, UV spectrophotometry coupled to a separation technique is used routinely, but the sensitivity of the method must be sufficient for degradation or impurity profile studies. For example, Mallikarjuna Rao et al. developed a stability-indicating LC-UV method for determination of docetaxel in pharmaceutical formulations [5]. LC-UV was also used in studies of the chemical stability of teniposide [6] and etoposide [7] in different formulations.

2.1.2. Quality control of prepared formulation before patient administration

Before administration to the patient, commercialised formulations in the form of freeze-dried powder or high concentrations of drug, are dissolved and/or diluted with sodium chloride (NaCl, 0.9%) or glucose (5%) to obtain the final individualised quantity of drug prescribed by a physician in an appropriate concentration. Stability of these diluted cytotoxic formulations is often limited (or unknown), and they are most often prepared a short time before patient administration by a nurse in the care unit or in a specialised unit at the hospital pharmacy. Even if pharmaceutical regulations do not require a final control of each individualised cytotoxic preparation, analysis can be applied to ensure correct drug concentration and to reduce medication errors and their consequences for patients with increased risk of morbidity and mortality [8].

Different strategies, usually applied by the hospital pharmacy, are used to control the prepared formulation before patient administration. In most cases, these methods allow approximate information on the concentration to be obtained and the cytotoxic substance contained in the reconstituted formulation to be identified. Given the high number of cytotoxic preparations per day and the very short time between prescription, preparation and administration, simple and fast techniques are usually preferred to conventional methods, which are often more expensive and less easy-to-handle. One approach consists of flow injection analysis (FIA) with UV-diode array detection (DAD). As shown by Delmas et al., 80% of cytotoxic preparations (corresponding to 21 different cytotoxic drugs) were successfully determined in a centralised preparation unit in less than 3.5 min [8]. However, due to the absence of separation before detection, the presence of excipients in the formulation can interfere with FIA-UV/DAD analysis, and compounds with similar structures cannot be distinguished.

Quality control of cytotoxic drugs was also performed by coupling Fourier transform infrared (FTIR) spectroscopy and UV spectrophotometry [9,10], which increased the selectivity of the method in comparison to single UV. Identification of the drug compound, excipients and drug concentration was thus achieved in a short analysis time without sample preparation. As for FIA-UV/DAD, additives in cytotoxic formulations or cross-contamination in the analytical system can perturb analyses. Moreover, to the author's knowledge, including quantitative performance with complete validation for quality control of cytotoxic agents has not yet been described with this approach.

Another, more selective technique for quality control of cytotoxic formulations might be Raman spectroscopy. It is a non-destructive and rapid method for identifying and quantifying active drugs and excipients in pharmaceutical formulations [11,12]. Additionally, this analysis is possible without sampling, providing excellent protection for technicians. As for the FTIR and UV/DAD techniques, to the author's knowledge, information on quantitative performance for Raman in cytotoxic formulations has not yet been reported in the literature.

In conclusion, when establishing quality control of cytotoxic drugs in a daily routine before patient administration, generic FIA-UV/DAD assays, FTIR and UV/DAD techniques or Raman spectrometry present interesting approaches in terms of time and simplicity. Nevertheless, the lack of selectivity and quantitative data are the main drawbacks of these techniques.

2.1.3. Formulation studies

Various studies have been performed on the attributes of cytotoxic drugs contained in formulations, including compatibility or stability. The compatibility of cytotoxic drugs with container materials is very important to avoid adsorption or degradation of the active compound, which both have negative consequences for patient treatment [13]. In the 1980s, stability data of antitumor agents in glass and plastic containers [14] or in totally implanted drug delivery systems [15] were established, and a review of stability data for cytotoxic agents was published in 1992 [16]. In these studies, LC-UV was the most commonly used analytical technique.

For new compounds and formulations, stability-indicating methods allowing separation of active compounds and degradation products are required to establish conservation guidelines for each cytotoxic drug in different containers. In the review of Benizri et al., several stability studies were evaluated, antineoplastic agents with sufficient chemical and physical stability were selected for home-based therapy, and a standardisation of anticancer drug stability data was proposed [17].

2.2. Analysis of cytotoxic agents in biological samples

Most of the reported methods were intended for cytotoxic drug quantification in biological matrices, fundamental studies of new drugs, pharmacokinetic (PK) and pharmacodynamic (PD) studies, therapeutic drug monitoring (TDM) or biomonitoring for occupational exposure.

2.2.1. Development of new drugs and formulations

The interaction between drugs and DNA is among the most important aspects of biological studies in drug discovery and pharmaceutical development processes. A review on different techniques used to study anticancer drug–DNA interaction has been published and included the following techniques: DNA-footprinting, nuclear magnetic resonance (NMR), MS, spectrophotometric methods, FTIR and Raman spectroscopy, molecular modelling techniques, and CE [18]. Furthermore, electrochemical approaches can provide new insight into rational drug design and would lead to further understanding of the interaction mechanism between anticancer drugs and DNA [18]. PK and PD studies were frequently the reason for the development of new analytical methods to determine cytotoxic agents in biological samples (e.g., urine, serum, plasma, intracellular matrix, tissues). For example, a recently reported LC–MS/MS method for docetaxel in plasma was found to have better performance than previously reported methods in terms of sensitivity, and it appeared to be a promising method for a large clinical pharmacology study [19].

2.2.2. Therapeutic drug monitoring

TDM for chemotherapy agents is not currently used routinely, mainly due to the lack of established therapeutic concentration ranges. Combinations of different chemotherapies make the identification of a target concentration difficult, as the concentration–effect relationship depends on the different treatments [20]. However, TDM has the potential to improve the clinical use of some drugs and to reduce the severe side effects of chemotherapy. For example, Rousseau et al. reported different possibilities and requirements for TDM [21]. Most commonly, TDM is performed for methotrexate [2]. Reviews on drug monitoring

were already published in 1985 by Eksborg and Ehrsson [22], and hyphenated techniques in anticancer drug monitoring (e.g., GC–MS, LC–MS and CE-MS) were published by Guetens et al. in 2002 [23,24].

2.2.3. Biomonitoring of exposed healthcare professionals

Cytotoxic drugs have been recognised as hazardous for healthcare professionals since the 1970s [25], and different studies have shown how occupational exposure to antineoplastic drugs is associated with a potential cancer risk [26–29]. However, a direct relationship between exposure to cytotoxic contamination and harmful effects is difficult to establish, and no maximal acceptable amount for these drugs has been set by regulation offices until now. Biomonitoring requires very sensitive and selective methods for trace analysis of cytotoxic drugs in urine or blood samples. Moreover, validated and standardised methods are lacking for cytotoxic agent monitoring in biological samples of healthcare professionals [30,31]. The concentration of cytotoxic drugs in biological samples from healthcare professionals, which are exposed to these compounds, is usually lower than for biological samples from patients receiving formulations with drug amount in the order of mg. Even if drug levels are usually lower in urine than in blood samples, urine samples are preferred for practical reasons. That is why methods used for the analysis of cytotoxic drug in samples of healthcare professionals have to exhibit a sufficient sensibility to allow reliable quantification of these compounds. GC–MS and LC–MS are the most commonly used [32,33], but according to the analytes, other techniques may also be interesting (for example, inductively coupled plasma-mass spectrometry (ICP-MS) or voltammetry for platinum compounds [34,35]). Most reported studies have found cytotoxic drugs in the urine or blood of healthcare professionals despite safety standards for handling these compounds [36–39]. According to precautionary principles, exposure should therefore be kept to the lowest possible levels [40].

2.3. Analysis of cytotoxic agents in environmental samples

2.3.1. Surface and air contamination

A complete review of analytical methods used for environmental monitoring of antineoplastic agents was published in 2003 by Turci et al. [36]. Analytical methods for the quantification of one or two model cytotoxic agents and generic methods for the determination of several drugs have been developed. When using marker compounds, wipe samples have been obtained by compound-specific wiping procedures followed by adapted analytical techniques (e.g., voltammetry for platinum drugs [41]). Such methods for marker compounds presented very good quantitative performance regarding detection limits and estimated potential surface contamination [41–46]. However, a wide range of chemotherapy formulations with different drugs and different preparation procedures are usually produced in hospital units. Therefore, to get an overview of several contaminants, multi-compound methods are required with generic wiping procedures. For sufficient selectivity and sensitivity, LC–MS/MS is one of the analytical approaches of choice [47–53].

2.3.2. Wastewater

After administration of anticancer drugs to patients, considerable amounts of cytotoxic agents are eliminated in the urine and thereby reach the wastewater system. Due to their potential toxicity to humans and the environment, analysis of cytotoxic drugs and their metabolites is also needed in hospital effluents and wastewater samples. Various analytical techniques can be used for this purpose, including ICP-MS for platinum compounds [54], CE-UV for fluorouracil [55], LC with fluorescence detection for anthracyclines [56] and LC–MS/MS for antimetabolites [57] and other cytotoxic agents [58,59].

3. Overview of analytical methods for specific cytotoxic drugs

In this Section, analytical methods for each cytotoxic drug are discussed. Only the most commonly used cytotoxic agents, i.e., antimetabolites, DNA interactive agents and antitubulin agents, are considered in this paper.

3.1. Antimetabolites

Analysis of pyrimidine analogues, purine analogues and other antimetabolites are described in this section. The chemical structures of antimetabolites are shown in Fig. 1, and published analytical methods for determination of these compounds in pharmaceutical formulations, biological and environmental samples are reported in Table 1.

3.1.1. Pyrimidine analogues

3.1.1.1. 5-Fluorouracil, tegafur, capecitabine. 5-Fluorouracil (5-FU) is a widely used cytotoxic agent for the treatment of breast tumours and cancers of the gastrointestinal tract, including advanced colorectal cancer. It is also effective for certain skin cancers by topical administration. The main side effects include myelosuppression and mucositis [2]. Tegafur and capecitabine are metabolised to 5-FU and are given orally for metastatic colorectal cancer.

Few stability-indicating LC-UV methods for stability studies of 5-FU in pharmaceutical dosage forms containing various additives [60,61] and in rat caecal tissues [62] have been developed with good quantitative performance in terms of accuracy and precision. Simple sample preparation including centrifugation and dilution was performed and an LOQ of 500 ng mL^{-1} was achieved for 5-FU in rat caecal tissues [62]. However, 5-FU was observed to be degraded under alkaline conditions, while only negligible degradation was observed in acidic, neutral, oxidative and photolytic conditions. Drug combinations of 5-FU and doxorubicin were also successfully determined by LC-UV in injection solutions and biological samples [63]. A complete separation between doxorubicin and methyl hydroxybenzoate, used as a preservative, was obtained.

Generally, published methods for the analysis of tegafur and capecitabine allowed a simultaneous separation and quantification of 5-FU [64,65]. Zero-crossing first-derivative spectrometry [64] and CE-UV with large-volume sample stacking (LVSS) were successfully used for the determination of 5-FU and its prodrug (tegafur) in pharmaceutical formulations [65]. This method is characterised by a short analysis time (less than 3 min) and high selectivity and sensitivity. Without the LVSS procedure, limits of detection (LOD) were 600 ng mL^{-1} and 771 ng mL^{-1} for 5-FU and tegafur in standard solutions, respectively. With the LVSS procedure, however, sensitivity was significantly improved (LODs of 5-FU and tegafur were decreased to 7.9 ng mL^{-1} and 6.5 ng mL^{-1}, respectively). Sensitised chemiluminescence based on potassium permanganate oxidation in the presence of formaldehyde has also been used for the determination of 5-FU in pharmaceuticals and biological fluids [66] and presented an LOD of 30.0 ng mL^{-1} and a calibration range from 100 ng mL^{-1} to 80.0 μg mL^{-1}. Serum samples were prepared by protein precipitation with trichloroacetic acid and standard addition method was used to avoid matrix effects. LC-UV methods have also been reported for impurity profile studies [67], and analysis of bulk products, pharmaceutical formulations [68] and capsules [69] of capecitabine. For capecitabine in standard solutions, these methods have shown LODs and LOQs about 80.0 and 300 ng mL^{-1}, respectively.

Table 1
Analytical methods for antimetabolites.

Compound	Matrix	Analytical technique	References
Azacitidine	Pharmaceutical formulation	LC-UV, spectrophotometry	[93,138–141]
	Biological samples	LC-UV	[142]
	Biological samples	LC–MS/MS	[137]
Azathioprine	Pharmaceutical formulation	^{1}H NMR	[144]
	Pharmaceutical formulation	CE-UV	[145]
	Bulk drug	UHPLC-UV	[143]
	Biological samples	Second derivative spectra method	[465]
	Biological samples	LC-UV	[149–152]
	Biological samples	LC–MS/MS	[148]
	Residues for cleaning validation	LC-UV	[155]
	Chemical degradation	LC-UV	[154]
	Environmental samples	LC-UV	[156]
	Sewage Water	LC–MS/MS	[58]
Capecitabine	Pharmaceutical formulation	LC-UV	[67–69]
	Biological samples	CE-UV	[79]
	Biological samples	Review	[24]
	Biological samples	LC-UV	[80–82]
	Biological samples	LC–MS	[83]
	Biological samples	LC–MS/MS	[84–88]
Cladribine	Biological samples	Spectrofluorimetry	[466]
	Biological samples	LC-UV	[157]
	Biological samples	LC–MS/MS	[158]
Clofarabine	Biological samples	LC–MS/MS	[158]
Cytarabine	Pharmaceutical formulation	FIA	[8]
	Pharmaceutical formulation	LC-UV	[63,90–93]
	Pharmaceutical formulation	LC–MS/MS	[51]
	Biological samples	GC–MS or GC with a nitrogen-sensitive detector	[94]
	Biological samples	LC–MS	[467]
	Biological samples	LC-UV	[63,95–99]
	Biological samples	LC with solid-phase scintillation detection	[100]
	Biological samples	LC–MS/MS	[101–105]
	Biological samples	Supercritical fluid chromatography	[106]
	Biological samples	CE-UV, MEKC-UV	[107–109]
	Wipe samples (surface contamination)	LC–MS/MS	[51,52,89]
	Wastewater	LC–MS/MS	[57]
Fludarabine	Pharmaceutical formulation	FIA	[8]
	Biological samples	LC–MS/MS	[159]
5-Fluorouracil	Pharmaceutical formulation	LC-UV	[8,60,61,63,113]
	Pharmaceutical formulation	CE-UV	[65]
	Biological samples	Review	[24]
	Biological samples	LC-UV	[71]
	Biological samples	LC–MS	[71,88,468,469]
	Biological samples	CE-UV	[73–75,77–79]
	Fundamental study	CE-UV	[76]
	Wipe samples (surface contamination)	GC–MS	[41]
	Wipe samples (surface contamination)	LC-UV	[45,274,279]
	Wipe samples (surface contamination)	LC–MS/MS	[49,89]
	Waste water	LC–MS/MS	[57]
	Hospital effluents	CE-UV	[55]
Gemcitabine	Pharmaceutical formulation	CE-UV	[115]
	Pharmaceutical formulation	LC-UV	[113] [8]
	Pharmaceutical formulation	HPTLC	[114]
	Pharmaceutical formulation	LC–MS/MS	[51]
	Biological samples	Zero-and second order derivative spectrophotometry	[135]
	Biological samples	LC-UV	[63,116–125,135]
	Biological samples	LC–MS	[126]
	Biological samples	LC–MS/MS	[53,127–132,134]
	Fundamental study	LC–MS/MS	[133]
	Wastewater	LC–MS/MS	[57]
	Wipe samples (surface contamination)	LC–MS/MS	[51–53,136]
Hydroxycarbamide	Pharmaceutical formulation	Potentiometry, fluorimetry	[192]
	Pharmaceutical formulation	LC	[193]
	Biological samples (plasma, peritoneal fluid)	LC-ECD	[195]
	Biological samples	LC-UV	[194]
	Biological samples	GC–MS	[196,197]
	Air samples	LC-UV	[198]
Mercaptopurine	Pharmaceutical formulation	CZE-UV	[145]
	Biological samples	Review	[23]
	Biological samples	LC-UV	[149,151]
	Biological samples	LC–MS/MS	[148]

Table 1 (*Continued*)

Compound	Matrix	Analytical technique	References
	Wipe samples (surface contamination)	LC-UV	[156]
Methotrexate	Pharmaceutical formulation	CE-UV	[175]
	Pharmaceutical formulation	FIA	[8,177]
	Pharmaceutical formulation	CD-MEKC	[176]
	Biological samples	Review	[160]
	Biological samples	LC-UV combined with pseudo template molecularly imprinted polymer	[161]
	Biological samples	LC-UV-fluorescence	[162]
	Biological samples	LC–MS/MS	[163]
	Biological samples	CE-UV	[75,164–166,168–171]
	Biological samples	MEKC-UV	[167]
	Biological samples	CE-LIF	[172,174]
	Biological samples	MEKC-LIF	[173]
	Biomonitoring	LC–MS/MS	[27]
	Wipe samples (surface contamination)	LC–MS/MS	[47,51,52,89]
	Wastewater	LC–MS/MS	[58,179,180]
	Fundamental study	PACE (pressure assisted CE)	[178]
Pemetrexed	Pharmaceutical formulation	LC-UV	[181–184]
	Pharmaceutical formulation	LC-ELSD	[184]
	Biological samples	LC-UV	[185,186]
	Biological samples	LC–MS	[187]
Pentostatin	Biological samples	LC–MS	[191]
Raltirexed	Pharmaceutical formulation	CD-MEKC	[189]
	Biological samples	LC–MS	[190]
Tegafur	Pharmaceutical formulation	CE-UV	[65]
	Pharmaceutical formulation	Zero-crossing first derivative spectrometry	[64]
	Biological samples	LC-UV	[470–472]
	Biological samples	GC–MS	[472]
	Biological samples	LC–MS/MS	[473]
Thioguanine	Biological samples	CE-UV	[75]
	Fundamental study	LC–MS/MS	[153]

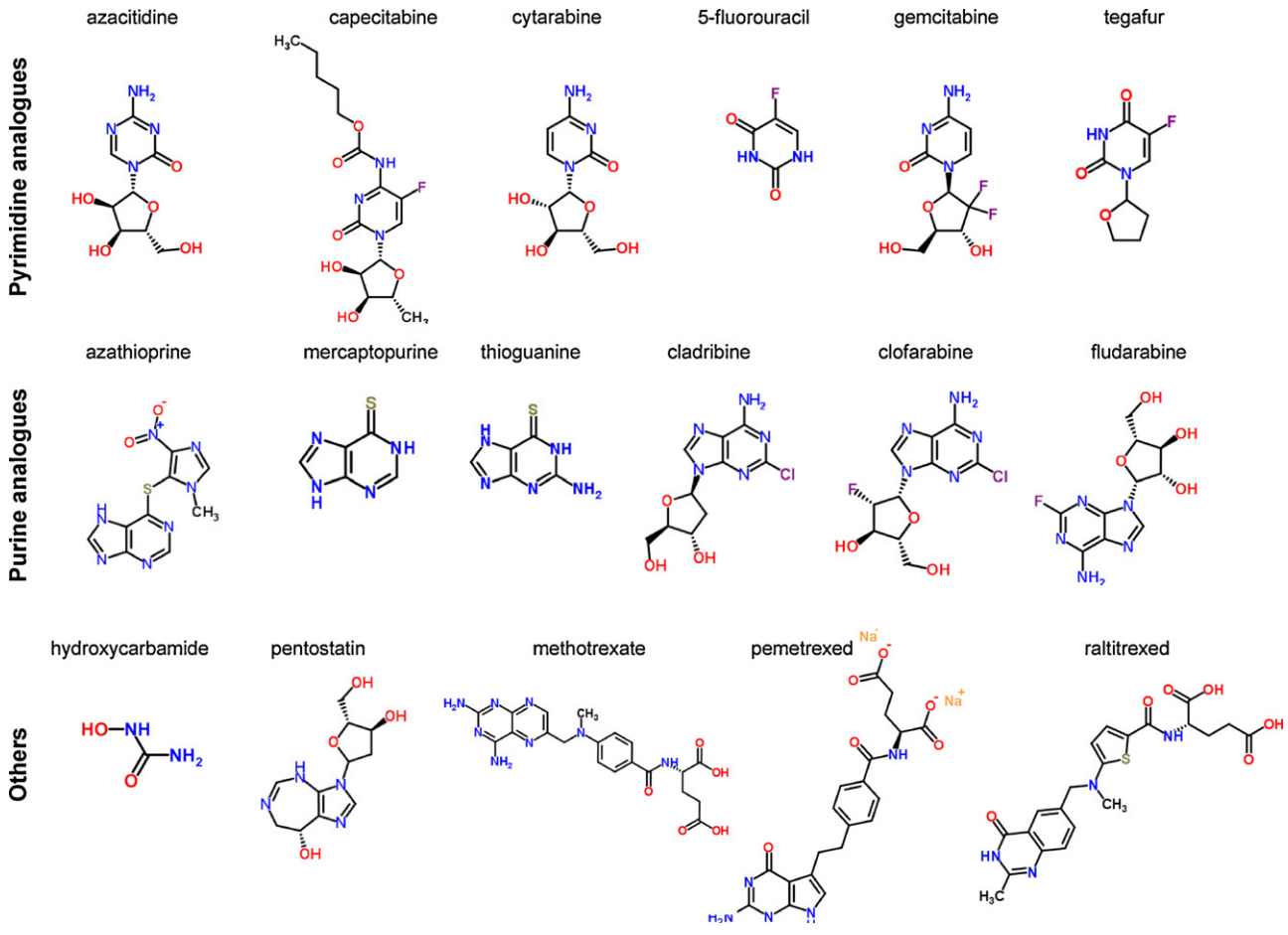

Fig. 1. Chemical structures of antimetabolites.

A large number of analytical methods for the determination of 5-FU, related prodrugs and their metabolites in biological matrices have been developed in the last 30 years. These methods include cell-based culture assays, LC-UV, LC-fluorescence, GC–MS and LC–MS/MS. Advantages and disadvantages of such methods have already been discussed by Breda and Barattè in 2010 [70], including biological sample analysis of tegafur. According to this review, 5-FU monitoring has not yet been widely used, and recent developments with LC–MS/MS and nanoparticle antibody-based immunoassays may facilitate routine monitoring of 5-FU in daily clinical practice. Recently, eight original 5-FU derivatives were synthesized in order to identify new efficient prodrugs of 5-FU and sensitive LC-UV and LC–MS methods were developed to simultaneously quantify 5-FU and its derivatives in human plasma. Sample preparation by centrifugation, filtration and dilution was performed, and MS detection was necessary for characterisation of degradation products [71].

CE methods were not recorded in the review of Breda and Barattè [70], but have also been used for biological samples: CE coupled to amperometric detection for urine and serum samples [72] and CE-UV for plasma [73,74], urine [75], or cell extracts [74,76–79] have been reported. However, the sensitivity was not always sufficient for simultaneous determination of 5-FU and its active metabolites. Indeed, LODs superior to 1 $\mu g\,mL^{-1}$ were achieved for 5-FU and its active metabolite 5-fluoro-29-deoxyuridine-59-monophosphate (FdUMP) and, thus, a preconcentration step (e.g., extraction) and/or the use of more sensitive detection techniques should be investigated [74]. For the determination of capecitabine, LC-UV [80–82] or LC–MS methods [83–88] have been published. With simple protein precipitation followed by LC–MS/MS analysis, very good selectivity and sensitivity values were obtained, with an LOQ of 10 $ng\,mL^{-1}$ for capecitabine in human plasma allowing PK studies [87].

Analysis of 5-FU in environmental samples is particularly interesting because it is one of the most used cytotoxic agents at high doses and therefore an ideal marker compound for other potential contaminants. Surface contamination monitoring using GC–MS [41] or LC [89] was successfully performed. However, due to the high polarity of 5-FU, low retention times were recorded when reversed phase LC columns were used, and separation from different antimetabolites was difficult to obtain. For this reason, the use of hydrophilic interaction liquid chromatography (HILIC) coupled to MS/MS appears to be an attractive approach for the analysis of antimetabolites in wastewater [57]. In the described conditions, baseline separation was obtained for 5-FU, cytarabine, gemcitabine and their metabolites (uracil 1-β-D-arabinofuranoside and 2′,2′-difluorodeoxyuridine) with a resolution superior to 2.4 and an LOQ of 5 $ng\,mL^{-1}$ for 5-FU. In addition, CE-UV allowed the determination of 5-FU in hospital effluents after enrichment by solid-phase extraction (SPE) (concentration factor 500), allowing good quantitative performance with similar quantification limits with an LOQ of 5 $ng\,mL^{-1}$ [55].

3.1.1.2. Cytarabine. Cytarabine is still one of the most effective single agents available for treating acute myeloblastic leukaemia, although myelosuppression is a major side effect [2]. Stability and compatibility data for cytarabine in different containers and admixtures were determined by LC in the 1980s [90–92]. LC methods have also been developed for the analysis of bulk drugs and pharmaceutical formulations containing cytarabine and azacitidine [93]. For biological sample analysis, GC–MS or GC with a nitrogen-sensitive detector was developed for determination of cytarabine in human plasma in 1978 [94]. Different LC-UV methods have also been published for plasma analysis and PK studies within a concentration range in order of $\mu g\,mL^{-1}$ [95–97]. More recently, LC-UV methods were developed and validated for the simultaneous detection of cytarabine and etoposide in pharmaceutical preparations and in spiked human plasma [63]; cytarabine and doxorubicin for TDM [98]; and cytarabine, daunorubicin and etoposide in human plasma for clinical studies [99]. The latter was preceded by SPE with a mixed-mode sorbent and presented LOQs in order of $ng\,mL^{-1}$ [99]. Furthermore, tritium-labelled cytarabine was used to evaluate the intracellular metabolism of cytarabine and was analysed simultaneously with its metabolites by ion-pair LC with solid-phase scintillation detection [100]. Concerning the sample preparation, the incubated cells were lysed by adding a solution containing amphoteric tetrabutylammonium phosphate at pH 3.0, vortexed, centrifuged and filtered before analysis.

Over the last five years, various LC–MS/MS methods for the determination of cytarabine in plasma samples [101–105] or environmental samples [51,52,57] have been reported with good quantitative performance in terms of selectivity and sensitivity. Supercritical fluid chromatography with a simple sample pretreatment procedure showed equivalent accuracy to the analytical results obtained by LC–MS/MS from 50 to 10,000 $ng\,mL^{-1}$ of cytarabine in mouse plasma and have been proven to be reliable for *in vivo* studies [106]. Several CE-UV or micellar electrokinetic chromatography (MEKC)-UV methods also have been found to be suitable for clinical samples and pharmacokinetic studies [107–109]. However, LOQ of cytarabine in human serum was superior by MEKC-UV [109] (3000 $ng\,mL^{-1}$) than by the above mentioned LC–MS/MS methods (i.e.10 $ng\,mL^{-1}$ in rat plasma [104] or 1.0 $ng\,mL^{-1}$ in aqueous solutions [51]).

3.1.1.3. Gemcitabine. Gemcitabine is a more recently introduced compound of the antimetabolites and is used intravenously in association with cisplatin for metastatic non-small cell lung, pancreatic, and bladder cancers. It is generally well tolerated but can cause gastrointestinal disturbances, renal impairment, pulmonary toxicity, and influenza-like symptoms [2].

The first degradation studies were published in 1994 by Lilly Research Laboratories using LC-UV, NMR and MS [110]. Later, physical and chemical stability tests showed good stability for reconstituted solutions up to 35 days at room temperature, but precipitation was observed when stored at 4 °C [111]. Jansen et al. also studied the degradation kinetics of gemcitabine by LC-UV, MS and NMR in acidic solution and identified degradation products [112]. For quality control, preparations of gemcitabine were controlled by LC-UV [113], high performance thin layer chromatography (HPTLC) [114] or LC–MS/MS [51]. A CE-UV method has also been developed for gemcitabine determination in injectable solutions [115]. For biological samples analysis, different LC methods have been published for the determination of gemcitabine and its metabolites in plasma, urine, tissue or cancer cells by LC-UV methods [116–125], LC–MS [126], LC–MS/MS [127–134] and by zero-and second-order derivative spectrophotometric methods [135]. The last method was compared with an LC-UV method for determination of gemcitabine in human plasma and no significant difference was obtained in term of precision with an LOQ of 200 $ng\,mL^{-1}$. Lower LOQs were obtained by LC–MS (i.e. 0.5 $ng\,mL^{-1}$ in human plasma [127]). LC–MS/MS methods were also used for environmental analysis, including surface contamination and wastewater analysis [51–53,57,136] with LOQ values in the order of $ng\,mL^{-1}$ [51,57].

3.1.1.4. Azacitidine. 5-Azacytidine is used for the treatment of myelodysplastic syndromes [137]. LC methods were developed for the determination of cytarabine and azacitidine for bulk drugs and pharmaceutical formulations [93,138,139]. Spectrophotometry and LC-UV were used for degradation studies [140] and for the development of encapsulated drug formulations containing azacitidine [141]. LC-UV [142] and, later, LC–MS/MS [137] were reported for azacitidine determination in plasma. The LC–MS/MS method

was found to be 50 times more sensitive with LOQ of 5 ng mL^{-1} than previously published assays (i.e. LOQ of 250 ng mL^{-1} [142]), and allowed PK and PD studies of azacitidine [137].

3.1.2. Purine analogues

3.1.2.1. Azathioprine, mercaptopurine and thioguanine. Azathioprine, an immunosuppressant agent, is a useful antileukaemic drug and is metabolised to 6-mercaptopurine. Mercaptopurine is also directly used almost exclusively as maintenance therapy for acute leukaemia. Thioguanine is used orally to induce remission in acute myeloid leukaemia [2].

A validated ultra high performance liquid chromatography with UV detection (UHPLC-UV) method was developed for determination of process-related impurities in azathioprine bulk drug. All impurities were well resolved within 5 min and presented LOQs in the range of 490–740 ng mL^{-1} [143]. Quality control for azathioprine in tablets has been performed by ^{1}H NMR spectroscopy [144] and by a stability-indicating CE-UV method, which performed well at separating azathioprine, 6-mercaptopurine and other related substances (including degradation and impurity products) [145]. CE was also useful for determination of 6-thioguanine in urine with an LOQ of 5300 ng mL^{-1} and a simple dilution of urine with water 1:1 [75]. To assess adherence to azathioprine therapy and to identify myelotoxicity and hepatotoxicity, thiopurine metabolite monitoring can be performed by LC-UV [146,147] or LC–MS/MS [147,148]. Additional LC methods for biological samples [149–153], chemical degradation studies [154] or residues after cleaning in production areas [155,156] have been reported. With an LOQ of 290 ng mL^{-1}, the LC-UV method was considered as sensitive enough for routine cleaning validation processes and for quantitative determination of azathioprine in commercial samples [155].

3.1.2.2. Cladribine, clofarabine, fludarabine. Cladribine is given by intravenous infusion for the first-line treatment of hairy cell leukaemia and the second-line treatment of chronic lymphocytic leukaemia in patients who have failed on standard regimens of alkylating agents. Fludarabine is also used for patients with chronic lymphocytic leukaemia after failure of an initial treatment with an alkylating agent. Usefulness is limited by myelosuppression. Clofarabine is approved for treating refractory acute lymphoblastic leukaemia in children after failure of at least two other types of treatment [2].

Yeung et al. developed an LC-UV method preceded by SPE for determination of cladribine in plasma. The described method presented adequate sensitivity and specificity with an LOQ of 50 ng mL^{-1} to study PK of cladribine in rats [157]. Micro-column LC–MS/MS and UHPLC–MS/MS methods were developed for the simultaneous determination of cladribine and clofarabine in mouse plasma samples with a protein precipitation as sample pretreatment [158]. The UHPLC–MS/MS method was sensitive, cost-effective and reliable for high throughput PK screening with a 2 min run time and showed equivalent accuracy (less than 15%) to the analytical results obtained using the micro-column LC–MS/MS method with a one min run time [158]. Simultaneous determination of fludarabine and cyclophosphamide in human plasma has also been successfully performed by a validated LC–MS/MS over a range of 1 to 100 ng mL^{-1} [159].

3.1.3. Other antimetabolites

Methotrexate (MTX) is used as maintenance therapy for childhood acute lymphoblastic leukaemia, in choriocarcinoma, non-Hodgkin's lymphoma, and several solid tumours. It is also administered for the treatment of autoimmune diseases like psoriasis, rheumatoid arthritis, and lupus. Side effects include myelosuppression, mucositis, and gastrointestinal ulceration with potential damage to kidneys and liver that may require careful monitoring. According to the review of Rubino [160], more than 70 papers describing chromatographic assays for MTX and its metabolites have been published in the literature between 1975 and 2000. A wide range of experimental conditions for sample preparation and analyte separation and detection have been employed. Since 2001, LC-UV combined with pseudo template molecularly imprinted polymer [161], LC-UV-fluorimetry [162], and LC–MS/MS [27,163] have been reported for biological samples. LOQ for MTX in human serum was found to be at the level of 10.0 ng mL^{-1} with LC–MS/MS preceded by acetonitrile protein precipitation and filtration [163]. Monitoring of MTX in urine [75,164,165], in whole blood [166,167], plasma [168], serum [169] and tumour samples [170] was also successfully performed by CE-UV. In most of these studies, complete validation for biological samples was achieved. Several sample preparation techniques were used, including simple dilution [75,165], SPE [164,168] and on-line stacking CE [167,168]. CE with high sensitivity cells (Z-cell) showed good precision and accuracy for quantitative analysis of MTX in biological media and led to an approximately 10-fold improvement of the detection limit compared to standard capillaries with LOD in water and urine of 100 ng mL^{-1} [171]. Other improvements to sensitivity were obtained using CE-LIF analysis with detection in the ng mL^{-1} range [172–174].

Another validated CE method allowed chiral separation of racemic MTX in pharmaceutical formulations with precision values below 5% and baseline enantiomers separation within 6 min [175]. Gotti et al. developed and validated (according to ICH guidelines) a cyclodextrin-modified micellar electrokinetic chromatography (CD-MEKC) method to analyse MTX and its most important impurities [176]. Separation was improved by the addition of methanol in the CD-MEKC system and adequate accuracy between 93 and 106% with RSD values lower than 8% was obtained. Additionally, FIA was successfully used for the determination of methotrexate in pharmaceutical formulations [8,177]. The first method used UV detection and was applied for qualitative and quantitative control of cytotoxic preparations in a hospital preparation unit [8]. The second FIA method was coupled with fluorescence detection preceded by oxidation of MTX into a highly fluorescence product (2,4-diaminopteridine-6-carboxylic acid) with acidic potassium permanganate [177]. Under these conditions, intra and interday precision values (RSD) were inferior to 1%. Finally, fundamental studies on the determination of pK values for MTX and other compounds have been performed by pressure-assisted CE-UV [178].

For environmental analysis, LC–MS/MS was employed for MTX determination in water samples [58,179,180] and on several surfaces [47,51,52]. A wiping procedure coupled to LC–MS/MS allowed determination of surface concentration down to 0.1 ng cm^{-2} of MTX and nine other cytotoxic drugs with completely evaluated quantitative performance in terms of accuracy and precision [52].

Pemetrexed is indicated for the treatment of pleural mesothelioma as well as non-small cell lung cancer. Physical and chemical stabilities were established by LC-UV for different pemetrexed formulations (e.g., in PVC bags or plastic syringes) by Zhang and Trissel [181–183]. Recently, an ion-pairing reversed-phase LC method using a double detection analysis (UV and evaporative light scattering detection (ELSD)) was employed to monitor the stability of pemetrexed preparations [184]. UV detection was used to quantify pemetrexed within a concentration range of 0.45 to 0.60 mg mL^{-1} with a total error inferior to 3%. L-Glutamic acid was identified and quantified as a potential degradation product by ELSD with an LOD of 1800 ng mL^{-1}.

A column-switching LC method for pemetrexed determination in human plasma has been developed to support PK studies with an LOQ of 10 ng mL^{-1} [185]. Other LC-UV [186] and LC–MS [187] methods have also been reported for biological samples analysis. Recently, a new ultrafast and high-throughput MS approach for the

therapeutic drug monitoring of pemetrexed in plasma from lung cancer patients was developed by matrix assisted laser desorption/ionisation (MALDI)–MS/MS with an analysis time of only 10 s and good sensitivity and compliance with FDA regulations (within- and between-run accuracy and precision inferior to 15% RSD) [188].

Raltitrexed, a drug approved in Canada, is given intravenously for palliation of advanced colorectal cancer in cases where 5-FU cannot be used. It is generally well tolerated, but can cause myelosuppression and gastrointestinal toxicity [2]. A rapid and effective method was developed for the chiral separation of raltitrexed enantiomers by CD-MEKC to determine the purity of real synthetic drug samples [189]. The enantiomers of raltitrexed could be separated within 13 min with satisfactory resolution and sensitivity (LOD of 1000 ng mL^{-1} for both enantiomers). Determination of raltitrexed in human plasma was successfully performed by LC–MS and achieved good sensitivity and specificity with an LOQ of 2 ng mL^{-1} [190].

Administered intravenously, pentostatin is highly active in hairy cell leukaemia and is able to induce prolonged remissions [2]. However, only a few analytical methods have been reported for this therapy (e.g., determination of pentostatin in culture broth by LC–MS [191]).

Hydroxycarbamide, also called hydroxyurea, is an antineoplastic drug used in myeloid leukaemia, often in combination with other drugs. It can also be used for the treatment of melanoma and to reduce the rate of painful attacks in sickle-cell disease [2]. For quality control, potentiometry and fluorimetry have been described for the determination of hydroxyurea in capsules [192], as well as LC-UV for pharmaceutical formulations and bulk products [193]. LC-UV [194] and LC-ECD [195] allowed quantification of hydroxyurea in plasma and peritoneal fluids. GC–MS methods have also been developed for the analysis of plasma samples containing hydroxycarbamide [196,197]. Both methods were validated: the LOD was 78 ng mL^{-1} and the LOQ was 313 ng mL^{-1} and intra-day and inter-day variations inferior to 10% [196]. In addition, an LC-UV method has been developed for environmental monitoring to reduce exposure through inhalation of drug dusts or droplets by workers involved in the manufacture of this compound [198]. The reported method successfully detected hydroxyurea in the concentration range of 0.001–0.08 mg m^{-3}.

3.2. DNA interactive agents

Analysis of alkylating agents, cross-linking agents, intercalating agents, topoisomerase inhibitors and DNA-cleaving agents are described in this section. The chemical structures of DNA-interactive agents are shown in Figs. 2–6 and the relevant analytical methods for pharmaceutical formulations, biological and environmental samples are reported in Table 2.

3.2.1. Alkylating agents (dacarbazine, temozolomide, procarbazine, ecteinascidin-743)

Dacarbazine is employed as a single agent to treat metastatic melanoma and in combination with other drugs for soft tissue sarcomas. The predominant side effects are myelosuppression and intense nausea and vomiting [2]. Stability and compatibility assays of pharmaceutical formulations of dacarbazine by LC-UV [13,14,199–201] and LC–MS [202] have been described. LC-UV [203,204] and LC–MS/MS [205] methods have also been used for the quantification of dacarbazine and its degradation products in urine and plasma. Due to the extreme hydrophilic and unstable character of dacarbazine and its terminal metabolite (5-amino-4-imidazole-carboxamide), HILIC–MS/MS method with a two-step extraction process was considered as specially adapted for the analysis of these compounds in human plasma [205]. The method was validated and presented good quantitative performance in terms of accuracy, precision and specificity with an LOQ of 0.5 ng mL^{-1} allowing PK studies. With LC-UV method preceded by simple protein precipitation (methanol), PK studies were also possible, however, LOQ in plasma samples of dacarbazine and its metabolites were superior (about 30 ng mL^{-1} for dacarbazine) with a RSD of 20% [204].

Temozolomide is a more-recently introduced compound for the second-line treatment of brain cancers. Structurally similar to dacarbazine, its main advantage is its good oral bioavailability and distribution properties with penetration into the central nervous system [2]. LC-UV methods were used for the development of new drug formulations containing temozolomide, including a dry powder formulation for inhalation [206], liposomes for nasal administration [207] or intravenous injection with solid lipid nanoparticles [208]. Andrasi et al. developed MEKC-UV methods for stability studies of temozolomide and its degradation products in water and serum with short analysis times (1.2 min) [209]. Short analysis time is very important due to the low stability of temozolomide in solution (half-lives inferior to 10 min in physiological conditions). Furthermore, several publications reported the use of LC-UV methods for the quantification of temozolomide and its metabolites in plasma or urine [210–212] and LC–MS/MS [213] methods for 5-(3-N-methyltriazen-1-yl)-imidazole-4-carboxamide), a bioconversion product of temozolomide. In this study, samples were processed and analysed one at a time with an analysis time of 4.5 min, in order to compensate for the inherent instability of the analyte [213]. In addition, an acidic pH (<5) was recommended throughout the collection, sample preparation and analysis to preserve the integrity of the drug [210,212]. Finally, several temozolomide PK studies have been published [214–217].

Procarbazine has significant activity in lymphomas and carcinomas of the bronchus and in brain tumours. Its toxic effects include nausea, myelosuppression, and a hypersensitivity rash that pre-

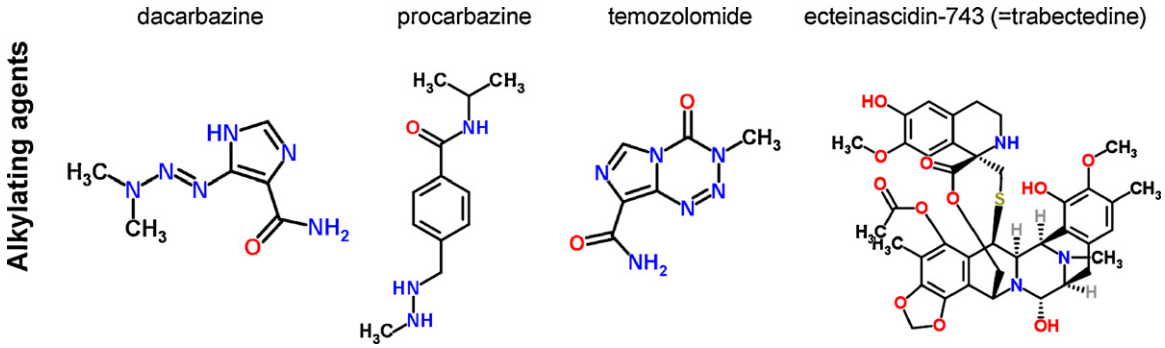

Fig. 2. Chemical structures of DNA-interactive agents: alkylating agents.

Table 2
Analytical methods for DNA interactive agents.

Compound	Matrix	Analytical technique	References
Actinomycin-D	Biological samples	LC–MS/MS	[417–421]
Anthracyclines (aclarubicin, daunorubicin, doxorubicin, idarubicin, epirubicin)	Review	Review	[366–369,423]
	Chemical degradation	LC-UV	[154]
	Pharmaceutical formulation	FIA; LC-UV/Vis	[8,63,370–373]
	Pharmaceutical formulation	LC–MS/MS	[51]
	Biological samples	LC-UV	[63,98,99,393,394]
	Biological samples	LC-chemiluminescence	[385]
	Biological samples	LC-fluorescence	[395–402,413]
	Biomonitoring	LC-fluorescence	[412]
	Biological samples	LC-LIF–MS	[403]
	Biological samples	UHPLC-MS	[409]
	Biological samples	LC–MS/MS	[32,262,263,404–408,411]
	Biological samples	Accelarator mass spectrometry	[410]
	Biological samples	CZE-, MEKC-, MEEKC-UV	[389]
	Biological samples	CE-UV	[374,375]
	Biological samples	CE-LIF	[376–383]
	Biological samples	MEKC-LIF	[386–388]
	Biological samples	CD-MEKC-LIF	[384]
	Biological samples	MALDI-TOF	[383]
	Biological samples	CE-amperometry	[390]
	Fundamental study (pKa)	CE-amperometry	[391]
	Fundamental study	CE-absorption-based wave-mixing detector	[392]
	Wipe samples (surface contamination)	LC-UV	[45,274]
	Hospital effluents	LC-fluorescence	[56]
	Wipe samples (surface contamination)	LC–MS/MS	[49,51,52]
	Wastewater	LC–MS/MS	[58]
Amsacrine	Degradation study	LC-UV	[154]
	Biological sample	Review	[369]
Bleomycin	Pharmaceutical formulation	LC-UV	[439]
	Pharmaceutical formulation	LC–MS	[441]
	Pharmaceutical or biological samples	DNA-based electrochemical strategy	[440]
Busulfan	Review	Review	[22–24]
	Pharmaceutical formulation	HPTLC	[355]
	Pharmaceutical formulation	NIRS	[356]
	Pharmaceutical formulation	LC-UV	[351–353]
	Pharmaceutical formulation	LC-CD	[354]
	Biological samples	LC-UV	[347–349]
	Biological samples	LC-fluorescence	[350]
	Biological samples	LC–MS	[340]
	Biological samples	LC–MS/MS	[341–346]
Camptothecin analogs (irinotecan, topotecan)	Review	Review	[423–427]
	Pharmaceutical formulation	FIA-UV	[8]
	Pharmaceutical formulation	Spectrofluorimetry	[432,474]
	Pharmaceutical formulation	LC-UV	[429–431]
	Pharmaceutical formulation	LC–MS/MS	[51]
	Pharmaceutical formulation	HPTLC	[428]
	Plant extracts	MEKC-UV	[433]
	Biological samples	LC-fluorescence	[475–480]
	Biological samples	Spectrofluorimetry	[474]
	Biological samples	LC–MS/MS	[481]
	Wipe samples (surface contamination)	LC–MS/MS	[51,52]
Chlorambucil	Biological samples	Review	[22,24]
	Biological samples	LC-UV	[296,297]
	Biological samples	LC–MS/MS	[298]
	Biological samples (adducts)	HPLC-MS(n)	[299]
Chlormethine (or nitrogen mustards)	Pharmaceutical formulation, aqueous solution	HPLC-UV	[283–286]
	Biological samples	GC–MS	[288]
	Biological samples	LC-UV	[287]
	Biomonitoring	LC–MS/MS	[292]
	Soil samples	GC–MS	[289,290]
	Aqueous and decontamination solutions	LC–MS	[291]
Cyclophosphamide, ifosfamide	Review	Review	[23,24,255,256]
	Fundamental study (chirality)	Capillary electrochromatography	[282]
	Pharmaceutical formulation	HPTLC	[269]
	Pharmaceutical formulation	LC-UV	[8,268]
	Pharmaceutical formulation	LC–MS/MS	[51]

Table 2 (*Continued*)

Compound	Matrix	Analytical technique	References
	Biological samples	LC–MS	[258–260,467]
	Biological samples	UHPLC-QTOF	[267]
	Biological samples	LC–MS/MS	[159,257,261–265]
	Biomonitoring	LC–MS/MS	[27,32,38,41,53,270–273]
	Wipe samples (surface contamination)	GC–MS	[41,278–280]
	Wipe samples (surface contamination)	LC-UV	[45,274]
	Wipe samples (surface contamination)	LC–MS/MS	[47,49,51–53,136,272,273,275–277]
	Wastewater, surface water	LC–MS/MS	[57,58,179,180,281]
Dacarbazine	Pharmaceutical formulation	FIA-UV	[8]
	Pharmaceutical formulation	LC-UV	[13,14,199–201]
	Pharmaceutical formulation	LC–MS	[202]
	Biological samples	LC-UV	[203,204]
	Biological samples	LC–MS/MS	[205]
Ecteinascidin-743	Biological samples	LC-UV	[224–226]
	Biological samples	LC–MS	[226]
	Biological samples	LC–MS/MS	[226,227]
Estramustine	Biological samples	LC-fluorescence, GC-NPD, GC–MS	[294,295]
	Biological samples	LC–MS/MS	[293]
Etoposide	Review	Review	[369,423]
	Pharmaceutical formulation	LC-UV	[7,8,63]
	Pharmaceutical formulation	LC–MS/MS	[51]
	Biological samples	LC-UV	[63,99]
	Biological samples	LC–MS/MS	[434]
	Biological samples	UHPLC-MS/MS	[435]
	Biological samples	CE-UV	[171]
	Biological samples	CE-LIF	[437]
	Biological samples	MEKC-near-field thermal lens detection	[438]
	Wipe samples (surface contamination)	LC–MS/MS	[51,52]
	Wastewater samples	LC–MS/MS	[58]
Fotemustine	Pharmaceutical formulation	LC-UV	[328]
	Biological samples	LC-UV	[329]
Melphalan	Pharmaceutical formulation	LC-UV	[8,13,316–318]
	Biological samples	Review	[22–24]
	Biological samples	LC-UV	[300–302]
	Biological samples	LC-fluorescence	[304–306]
	Biological samples	LC-ECD	[303]
	Biological samples	LC–MS/MS	[307,308]
	Biological samples (adduct)	LC–MS/MS	[309–314]
	Biological samples (adduct)	LC-ICP-MS	[315]
Mitomycin C	Pharmaceutical formulation	LC-UV	[362,363]
	Biological samples	LC-UV	[358–361]
	Biological samples	LC–MS	[357]
	Biomonitoring	LC-UV	[364,365]
	Ambient air samples	LC-UV	[364,365]
Mitoxantrone	Review	Review	[368,369]
	Biological samples	LC-UV	[414,415]
	Biological samples	LC–MS/MS	[416]
	Aqueous and biological samples	CE-CL	[422]
Nitrosurea (lomustine, carmustine)	Permeability and compatibility studies	LC-UV, LC–MS/MS, spectrophotometry	[13,14,50,321–323]
	Pharmaceutical formulation	LC-UV	[324]
	Biological samples	LC-UV	[319,320,325–327]
Platinum complexes	Review	Review: CE	[228,236–238]
	Pharmaceutical formulation	LC-UV, FIA	[8,229]
	Pharmaceutical formulation	MEKC-UV, MEEKC-UV	[253,254]
	Pharmaceutical formulation	LC–MS/MS	[4]
	Biological samples	Atomic absorption spectra	[482]
	Biological samples	LC-UV	[230]
	Biological samples	LC–MS/MS	[27,231,232]
	Biological samples	LC-ICP-MS	[233,234]
	Biological samples	MEKC, MEEKC	[239–241,243–249]
	Biomonitoring	Voltammetry	[34,35]
	Biomonitoring	ICP-MS	[235]
	Fundamental study	MEEKC-UV	[250,251]
	Fundamental study	MEEKC-ICP-MS	[252]
	Air samples	Voltammetry	[34,35]
	Wipe samples (surface contamination)	Voltammetry	[41]
	Wipe samples (surface contamination)	ICP-MS	[44]
	Wastewater	ICP-MS	[54,233]

Table 2 (*Continued*)

Compound	Matrix	Analytical technique	References
Procarbazine	Pharmaceutical formulation	LC-UV	[199,218,219].
	Pharmaceutical formulation	GC–MS	[199]
	Biological samples	LC-UV	[220]
	Biological samples	LC-amperometry	[221]
	Biological samples	LC–MS	[222,223]
	Sewage water	LC–MS/MS	[58]
Temozolomide	Pharmaceutical formulation	LC-UV	[206–208]
	Pharmaceutical formulation	MEKC-UV	[209]
	Biological samples	LC-UV	[210–212]
	Biological samples	LC–MS/MS	[213]
Teniposide	Review	Review	[369]
	Pharmaceutical formulation	LC-UV	[6]
	Biological samples	UHPLC-MS/MS	[436]
Thiotepa	Review	Review	[23,330]
	Degradation studies	LC-UV	[154,333]
	Pharmaceutical formulation	LC-UV	[334,335]
	Biological samples	GC-NPD	[266,332]
	Biological samples	LC–MS/MS	[264]
	Biological samples	UHPLC-QTOFMS	[331]
Treosulfan	Biological samples	LC-refractometric detection	[336–338]

vents further use of the drug [2]. Procarbazine was determined together with other anticancer drugs in sewage water by selective SPE and UHPLC–MS/MS [58]. In addition, several destruction procedures for toxic compounds including procarbazine were evaluated using LC-UV and GC–MS [199]. Other degradation studies for procarbazine were performed by LC-UV and LC–MS [218,219]. Determination of procarbazine and its metabolites in plasma or urine was achieved by LC-UV [220], LC coupled to amperometric detection [221] and LC–MS [222,223]. With the electrochemical detector, LOD of procarbazine in plasma were obtained in the order of ng mL^{-1}, which was more sensitive than with a typical UV detector [221]. Good sensitivity was also achieved by MS detection with LOQ values of 0.5 ng mL^{-1} for procarbazine in human plasma [223] and 30 ng mL^{-1} for its final metabolite (terephthalic acid isopropylamide) in urine [222].

Ecteinascidin-743 is a novel DNA-binding agent derived from the marine tunicate *Ecteinascidia turbinate*. It has significant activity *in vitro* against melanoma, breast, ovarian, colon, renal, and non-small cell lung and prostate cell lines [2]. For pharmacokinetic or stability studies, LC-UV [224–226], LC–MS [226] and LC–MS/MS [226,227] methods have all been published. Ecteinascidin-743 is administered in $\mu g\,m^{-2}$ dosages, which demands high sensitive analytical method supporting clinical PK studies. Using conventional LC-UV with SPE, an LOQ of 1.0 ng mL^{-1} in plasma was achieved [224], but with SPE followed by LC–MS/MS, an LOQ of 0.01 ng mL^{-1} was obtained [227]. LC–MS/MS was also especially useful in the search for metabolites of ecteinasidin-743 [226].

3.2.2. Cross-linking agents

3.2.2.1. Platinum complexes (cisplatin, carboplatin and oxaliplatin). Platinum complexes belong to the most widely used class of drugs in cancer treatment and possess a pronounced activity in different cancer types. Cisplatin was the first platinum complex used with a pronounced activity in testicular and ovarian cancers. The related analogues carboplatin and oxaliplatin were developed later to reduce the problematic side effects of cisplatin (nephrotoxicity, ototoxicity, and peripheral neuropathy, among others). Carboplatin is used in the treatment of advanced ovarian cancer and lung cancer, while oxaliplatin is licensed for the treatment of metastatic colorectal cancer in combination with fluorouracil and folinic acid [2].

As reported by Espinosa Bosch et al. in 2010 [228], various techniques have been developed for the determination of cisplatin, including derivative spectrophotometry, phosphorescence, atomic absorption spectrometry, GC–MS, CE and LC coupled with different detectors (UV, electrochemical, inductively coupled plasma-atomic emission spectrometry, ICP-MS or electrospray ionisation-mass spectrometry (ESI-MS)). The determination of platinum complexes in biological fluids and tissues presents a particularly interesting challenge because the damage produced in the affected organs is probably due to the association of platinum or the parent drug metabolites with important proteins of the impacted organ [228]. Analytical methods already reported by Espinosa Bosch et al. [228] are not discussed here. In addition, for carboplatin and oxaliplatin in pharmaceutical formulations or biological samples, LC-UV [229,230] LC–MS/MS [4,231,232] and LC-ICP-MS [233,234] have been published. In occupational exposure and environmental studies (air, surfaces, and wastewater), voltammetry [34,35,41] and ICP-MS [44,54,233,235] have been successfully applied with LOD in the order of 0.1 ng mL^{-1}.

According to different authors, CE has emerged as the method of choice for the separation of intact platinum metal complexes and their metabolites due to its high efficiency, versatility and gentle separation conditions for metal complexes [236–238]. Because platinum drugs are non-charged coordination complexes, MEKC or microemulsion electrokinetic chromatography (MEEKC) is often used. The main publications dedicated to the analysis of platinum drugs with MEKC or MEEKC were developed for biological studies, such as clinical sample analysis [239], drug–protein [240–244] and drug–DNA (or nucleotides) binding studies [245–249] and chemical studies [250,251]. Most commonly, UV spectrophotometry was used for the detection of platinum drugs with MEKC or MEEKC, despite ICP-MS also being reported to enhance their selectivity and sensitivity [252]. The LOQs for oxaliplatin samples were slightly lower when ICP-MS detection was used than UV/Vis detection (0.3 mg mL^{-1} instead 0.5 mg mL^{-1}). Few methods of MEEKC and MEKC were also developed for the quality control of diluted formulations of cisplatin, carboplatin, and oxaliplatin [253,254], and the latter was completely validated and successfully applied for cytotoxic preparations at a hospital pharmacy [254].

3.2.2.2. Nitrogen mustards (cyclophosphamide, ifosfamide, melphalan, chlorambucil, chlormethine, estramustine). Cyclophosphamide has a broad spectrum of clinical activity in solid tumours (carcinomas of the bronchus, breast, ovary, and various sarcomas), chronic lymphocytic leukaemia, and lymphomas. Ifosfamide is an analogue

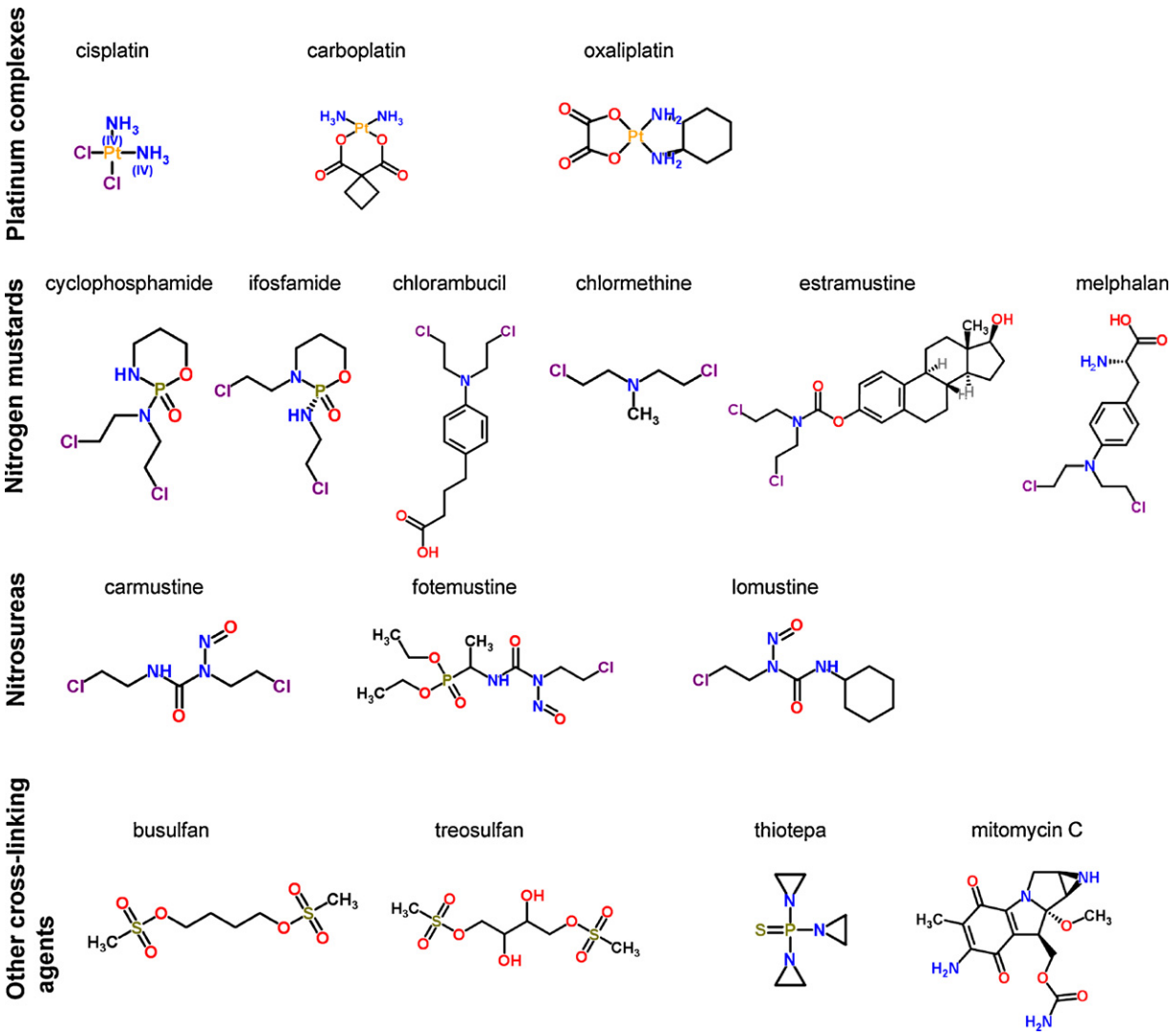

Fig. 3. Chemical structures of DNA-interactive agents: cross-linking agents.

of cyclophosphamide with a similar activity spectrum. Activation of the drugs is obtained after drug metabolism in the liver [2]. Reviews on anticancer drug monitoring, including cyclophosphamide and ifosfamide, using GC–MS [23] and LC–MS [24] were published by Guetens et al. in 2002. Other reviews of the analysis of oxazaphosphorines (cyclophosphamide, ifosfamide, trofosfamide) and their metabolites have given an excellent overview of sensitive and selective analytical methods, but these were published ten years ago [255,256]. GC with nitrogen-phosphorus detection (GC-NPD) was the most used determination technique with and without derivatisation, allowing high selectivity and sensitivity. However, GC–MS, LC-UV and LC–MS for cyclophosphamide and related compounds, and also several analyses of DNA-adducts, were discussed in the review of Baumann and Preiss in 2001 [256]. Moreover, oxazaphosphorines are chiral molecules, administered as a racemic mixture of their two enantiomeric forms, and various assays have been described for studying stereochemical effects [256–258].

Since 2001, LC–MS [258–260] and LC–MS/MS [159,257,261–266] have been characterised by good quantitative performance in terms of sensitivity and selectivity for cyclophosphamide and ifosfamide in biological samples. LOQ in order of ng mL^{-1} were obtained and different sample preparation techniques were used, allowing PK studies. For example, the use of turbulent flow online sample extraction followed by LC–MS/MS analysis decreased sample preparation time and simplified the quantitation of cyclophosphamide and its metabolite carboxyethylphosphoramide mustard (CEPM) in human plasma with sufficient accuracy and precision values (RSD inferior to 3.0%) to allow its application in clinical studies. LOQ of cyclophosphamide and CEPM in human plasma were 500 ng mL^{-1} and 50 ng mL^{-1}, respectively [265]. In another study by LC–MS/MS, sample preparation consisted of dilution of urine with an aqueous solution of the internal standard D4-CP and methanol, and centrifugation. LOD of cyclophosphamide in urine was about 5 ng mL^{-1}, but quantification range was adjusted to the expected concentrations in 24-h urine collections of patients and the urinary concentration of cyclophosphamide was much higher, i.e. in the range of 3000–17,5000 ng mL^{-1} due to the high administrated dosages of this drug [261]. Metabolism profiles of cyclophosphamide and ifosfamide in mice were studied using UHPLC–MS/MS to better understand the selective toxicity of these two compounds [267]. Twenty three urinary metabolites, including five novel drug metabolites, were identified and structurally elucidated. Although cyclophosphamide and ifosfamide went through similar metabolic processes, the amount of metabolites in urine was significantly different between these two drugs.

A stability-indicating LC-UV method allowed the determination of cyclophosphamide in oral suspensions and was used

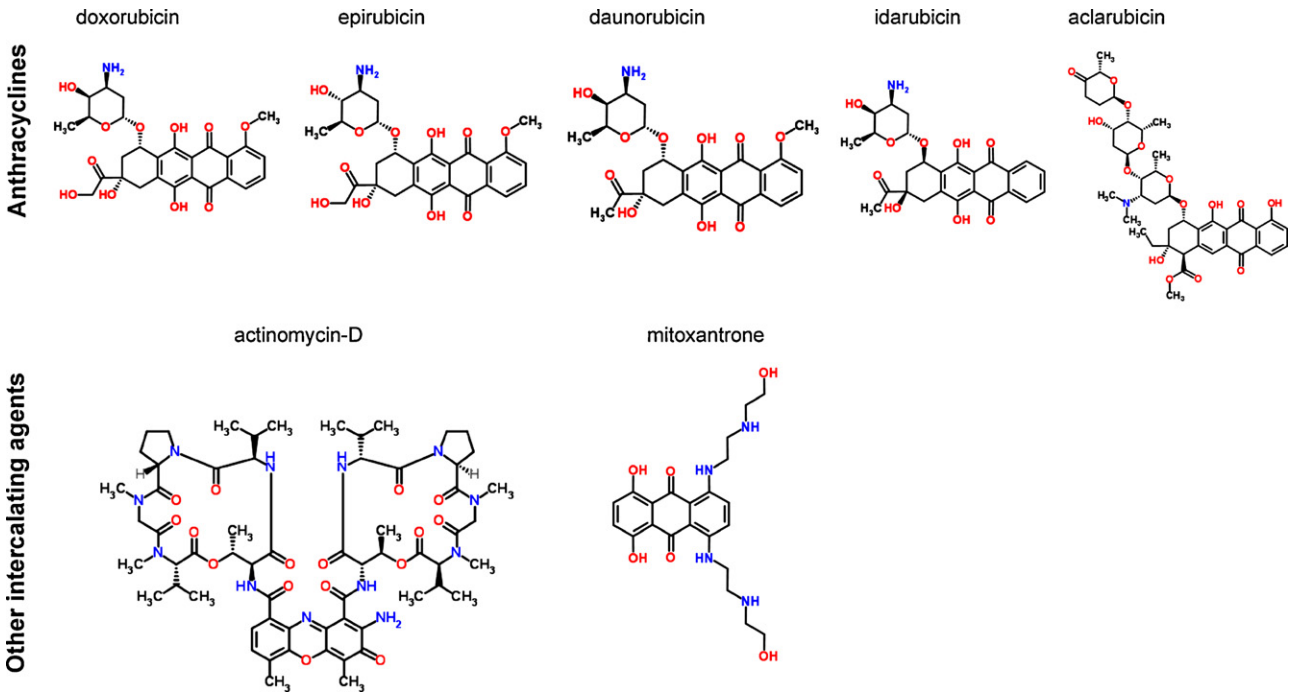

Fig. 4. Chemical structures of DNA-interactive agents: intercalating agents.

to set up storage conditions for simple syrup or suspension [268]. HPTLC [269], LC-UV [8] and LC–MS/MS [51] have been reported for the quality control of hospital formulations. Cyclophosphamide and ifosfamide have also often been analysed in urine samples of healthcare operators for biomonitoring [27,32,38,41,53,270–273], in wipe samples from cytotoxic preparation facilities [41,45,47,49,51–53,57,136,272–280] and in wastewater samples [58,179,180,281]. Cyclophosphamide and

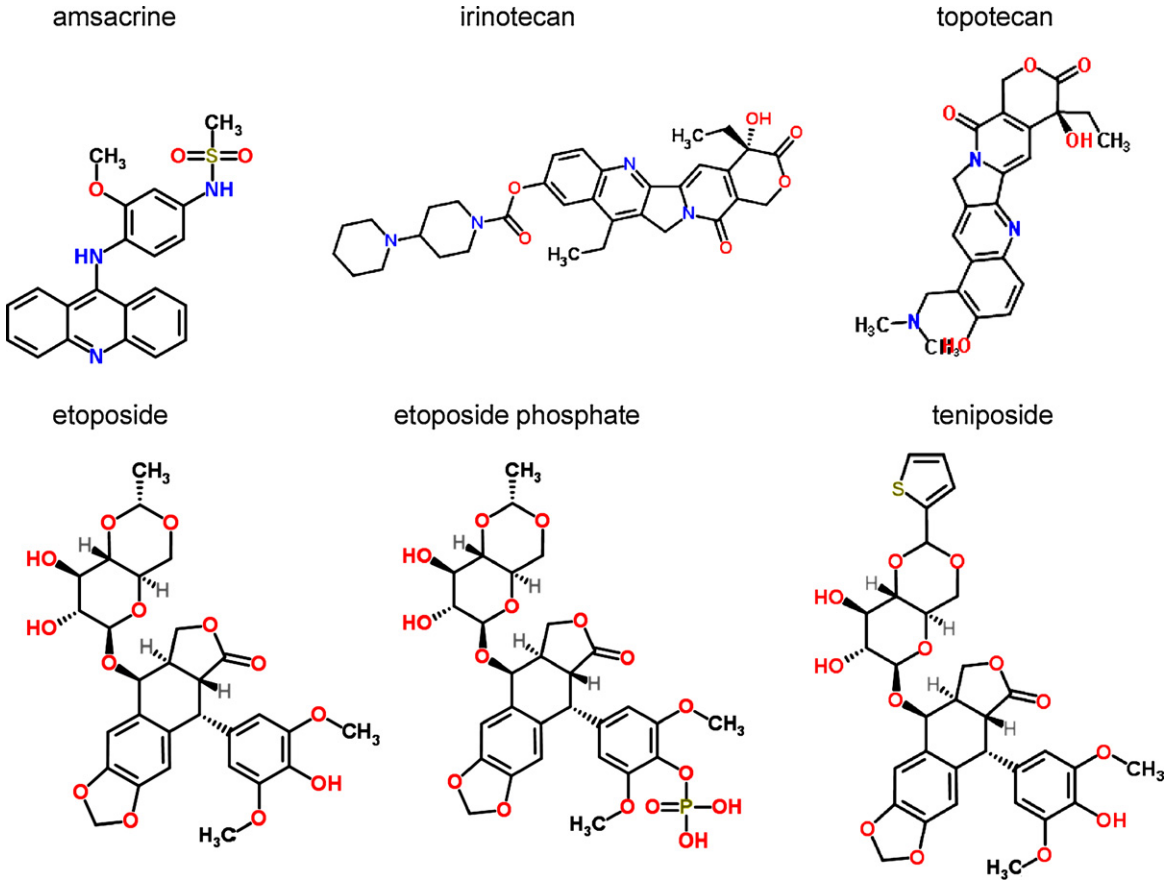

Fig. 5. Chemical structures of DNA-interactive agents: topoisomerase inhibitors.

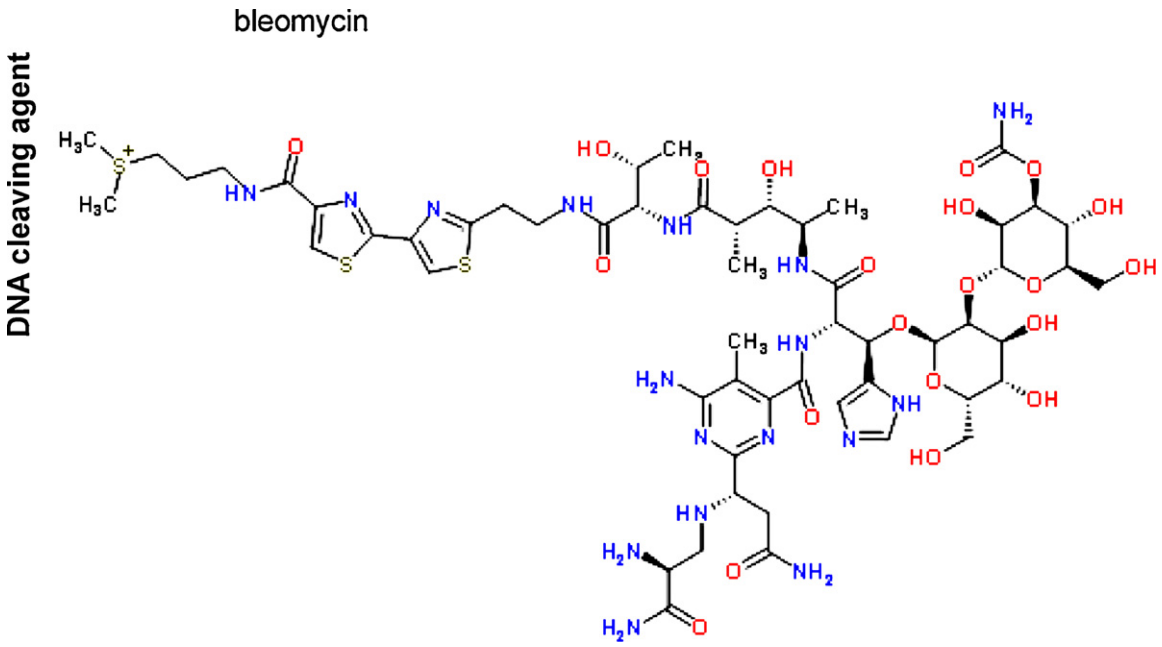

Fig. 6. Chemical structures of DNA-interactive agents: DNA-cleaving agent.

ifosfamide were often used to investigate environmental contamination and LOQs in order of pg to ng mL^{-1} were obtained by LC–MS/MS analysis [51,58,179,180]. Furthermore, Li and Lloyd developed a CE method using capillaries packed with a α1-acid glycoprotein chiral stationary phase for the analysis of enantiomers of cyclophosphamide and ifosfamide [282].

Chlormethine (or mechlorethamine) is used for the treatment of Hodgkin's disease. Due to its chemical reactivity, it must be freshly prepared prior to administration and then delivered via a fast-running intravenous infusion [2]. LC-UV methods, including a pre-derivatisation of mechlorethamine, have been published for the determination of mechlorethamine in aqueous solutions, formulations [283–286] and in plasma [287]. GC–MS methods (with pre-derivatisation) were developed for hydrolysis products of nitrogen mustards in biological samples [288] and for precursors of nitrogen mustards in environmental samples [289,290].

Soil samples were prepared using an on-matrix derivatisation–extraction technique and the method has shown satisfying precision values inferior to 5% within a linearity range from 1 to 12 ng mL^{-1} [289]. Additionally, Chua et al. developed a fast and efficient method of LC–MS for qualitative screening of nitrogen mustards and their degradation products in water and decontamination solutions [291]. Quantification of ultratrace levels (inferior to 1 ng mL^{-1}) of hydrolysis products of nitrogen mustards in human urine was achieved by LC–MS/MS for exposure assessment [292].

Estramustine phosphate is a conjugate consisting of chlormethine chemically linked to an oestrogen moiety. It is usually orally administered to patients with metastatic prostate cancer [2]. A sensitive and selective LC–MS/MS method was developed and validated for the simultaneous determination of estramustine phosphate and its four metabolites (estramustine, estromustine, estrone and estradiol) in human plasma [293]. The assay presented accuracy and precision values inferior to 15% with an LOQ of 10 ng mL^{-1}, and was successfully used for routine analysis of human plasma samples collected in cancer patients with estramustine phosphate treatment. Other studies have used LC with fluorescence detection for estramustine phosphate determination and GC coupled to NPD or MS for metabolite analysis [294,295].

Chlorambucil is useful in the treatment of ovarian cancer, Hodgkin's disease, non-Hodgkin's lymphomas, and chronic lymphocytic leukaemia. Its lower chemical reactivity allows oral dosing [2]. Methods for monitoring anticancer drugs including chlorambucil were published in 1985 by Eksborg and Ehrsson [22] and in 2002 by Guetens et al. [24]. In the last 10 years, LC–UV [296,297] and LC–MS/MS [298] have been used to determine chlorambucil and its metabolite in human serum and plasma. The latter has exhibited specific and sensitive performance for both parent drug and phenyl acetic acid mustard metabolite contained in human serum and plasma with accuracy and precision values inferior to 15%. Moreover, the applied automated SPE procedure was significantly faster than manual sample pre-treatment methods. With LC-UV analysis preceded by acetonitrile protein precipitation, LOQ of chlorambucil in plasma was about 100 ng mL^{-1} [296,297]. In addition, Mohamed et al. reported an LC–MS method for the determination of chlorambucil–DNA adducts [299].

Melphalan is indicated for the treatment of myeloma, solid tumours (e.g., breast and ovarian) and lymphomas [2]. Guetens et al. published a review of hyphenated techniques for anticancer drug monitoring, including GC–MS and LC–MS methods, for melphalan in 2002 [23,24]. LC-UV [300–302], LC-ECD [303] and LC with fluorescence detection [304–306] were also used for the determination of melphalan in biological samples. More recently, LC–MS/MS methods were developed for TDM and pharmacokinetic studies on melphalan [307,308]. Mirkou et al. developed and validated two methods for quantification of melphalan by LC–MS/MS [307]. The first method was adequate for routine use and allowed an accurate determination over a wide range of concentrations (1–500 ng mL^{-1}) with a simple and rapid sample preparation (protein precipitation). The second method using a more selective extraction (i.e. SPE) and HILIC approach allowed quantification of melphalan and its hydrolysis products without matrix effects present with the first one. The hydrolysis products appear rapidly at room temperature and are important to assess a failure during the storage of samples. Several studies on melphalan DNA adducts were published by Van den Driessche et al. [309–313] and Mohamed and Linscheid [314]. Additionally, LC–ICP-MS [315] was also useful for adduct analysis. Furthermore, LC-UV methods were described for the simultaneous determination of melphalan and impurities in

melphalan drug substance [316], for the analysis of pharmaceutical formulations [13,317] and for chemical degradation studies [318]. Chromatographic conditions were able to separate and quantify all impurities found in routine production batches of melphalan at above 0.1% area/area and simple sample preparation by dilution in methanol was used [316].

3.2.2.3. Nitrosurea (lomustine, carmustine, fotemustine). Lomustine is a nitrosurea analogue with a high degree of lipophilicity. Administered orally, it is mainly prescribed for the treatment of certain solid tumours and Hodgkin's disease. Carmustine has a similar activity and toxicity profile to lomustine [2]. Since publications of Hochberg et al. [319] and Yeager et al. [320] reporting LC-UV methods for the analysis of carmustine in biological samples in the 1980s, no further significant developments for this compound have been reported. However, a few papers have been published for the determination of carmustine or lomustine in association with other anticancer drugs. For example, permeability studies on anticancer drugs with different glove materials [50,321,322] and compatibility studies with container materials [13,14,323] were achieved using spectrophotometry, LC-UV and LC–MS/MS techniques. For lomustine, a stability-indicating LC-UV method was recently validated for degradation studies and presented adequate accuracy and precision values with a resolution between impurities and analyte superior to 2.0 [324]. In the case of biological sample analysis and pharmacokinetic studies, few LC-UV methods for lomustine have been developed since 1982 [325–327]. For example, an LC-UV method with a one-step liquid–liquid extraction procedure was used to detect and quantify lomustine and its two monohydroxylated metabolites (trans- and cis-4′-hydroxylomustine) in canine plasma with an LOD of 100 ng mL^{-1} for lomustine [325]. For fotemustine, a chlorethylnitrosourea, LC-UV has been used for both stability [328] and PK studies [329]. In these studies, quantification was performed in the μg mL^{-1} concentration range.

3.2.2.4. Other cross-linking agents. Thiotepa, used as an effective anticancer drug since the 1950s, appears to be one of the most effective anticancer drugs when used in high dose regimens. Its main indications are the treatment of bladder or ovarian cancers, breast cancer and malignant effusions [2]. A review of the chemistry, pharmacology, clinical use, toxicity, pharmacokinetics of thiotepa and analytical methods for its determination was published by Maanen et al. in 2000 [330]. Given that its metabolism is not clearly defined, several studies using UHPLC–MS/MS [331], GC-NPD [266,332] and LC–MS/MS [264] were conducted in the past few years. With the UHPLC–MS/MS method, nine metabolites in urine and five metabolites in serum, including two novel drug metabolites, were elucidated [331]. The LC–MS/MS method was validated for the simultaneous quantification of cyclophosphamide, thiotepa and their respective metabolites in human plasma with an LOQ of 5 ng mL^{-1} and was useful in routine TDM of cancer patients [264]. LC-UV methods were also developed to quantify thiotepa in aqueous solutions [333] and formulations [334,335].

Treosulfan, which is mainly used to treat ovarian cancer, has similar major side effects to nitrogen mustards. LC with refractometric detection methods was developed for pharmacokinetic studies of this compound [336–338]. Centrifugation and microfiltration preceded LC analysis. With this technique, LOQs were 10.0 μg mL^{-1} and 50.0 μg mL^{-1} in plasma and urine, respectively. Since the concentration of treosulfan in plasma and urine after infusion was high, the method was suitable for PK studies of the drug in biological fluids [337,339].

Busulfan is used for the treatment of chronic myeloid leukaemia and as part of conditioning regimens for patients undergoing bone marrow transplantation. Unfortunately, it can cause excessive myelosuppression, resulting in irreversible bone marrow aplasia, and requires careful monitoring [2]. Analytical methods have already been reported in reviews on anticancer drug monitoring in 1985 [22] and 2002 [23,24] and are not discussed in this paper. More recently, the determination of busulfan in serum or plasma was achieved by LC–MS [340] and LC–MS/MS [341–344]. To reduce manual sample preparation, an LC–MS/MS method coupled with turbulent flow on-line sample cleaning technology offered reliable busulfan quantification in serum or plasma and was fully validated for clinical use with an LOQ of 36 ng mL^{-1} [345]. Because of practical limitations in obtaining blood from children, saliva was evaluated as an alternative matrix for therapeutic drug monitoring of busulfan, with subsequent analyses by LC–MS/MS [346]. An online extraction cartridge with column-switching technique was used for sample preparation and LOQs in saliva and plasma were about 10 ng mL^{-1}. In addition, LC-UV [347–349] and LC with fluorescence detection [350] were also used for the determination of busulfan in biological samples. In these studies, precolumn derivatisation was needed for sample preparation and LOQs in plasma about 100 ng mL^{-1} were obtained. Stability studies of several busulfan formulations were performed by LC-UV [351–353] and a method of stability-indicating ion chromatography with conductivity detection was published by Chow et al. [354]. For hospital formulations, an HPTLC method [355] was compared with near infrared spectroscopy [356] for the determination of busulfan in capsules. Similar quantitative performance in terms of accuracy and precision was obtained, but near infrared spectroscopy had the advantage of being a non-invasive technique.

Mitomycin-C is a member of a group of naturally occurring antitumor antibiotics produced by *Streptomyces caespitosus* (*griseovinaceseus*) and was first isolated in 1958. Intravenous mitomycin is used to treat upper gastrointestinal and breast cancers, and administration by bladder instillation allows treating superficial bladder tumours. Adverse events include delayed bone marrow toxicity. It can also be administered in ophthalmology as an adjunctive therapy in trabeculectomy. A simple, fast and reliable LC–MS method was developed for the determination of traces of mitomycin-C in aqueous tumour samples and an LOQ inferior to 0.1 ng mL^{-1} was obtained [357]. LC-UV methods were also reported for the determination of mitomycin C in human ocular tissues [358], in plasma [359–361] and for stability tests of freshly prepared ophthalmic formulation [362] and intravesical instillation solutions [363]. Exposure to mitomycin-C in the operating room during hyperthermic intraperitoneal chemotherapy was monitored in ambient air and in plasma samples from the surgeon by LC-UV [364]. The permeability of the gloves was also investigated using *in vitro* techniques [365].

3.2.3. Intercalating agents

3.2.3.1. Anthracyclines (doxorubicin, epirubicin, daunorubicin, aclarubicin, idarubicin). Anthracyclines are a group of antitumor antibiotics consisting of a planar anthraquinone nucleus attached to an amino-containing sugar. Doxorubicin, daunorubicin, and aclarubicin are natural products extracted from *Streptomyces peucetiusor* or *Streptomyces galilaeus*, while epirubicin and idarubicin are semisynthetic analogues. Doxorubicin is widely used as an anticancer drug because of its broad spectrum of activity (acute leukaemia, lymphomas, and a variety of solid tumours). Adverse events include nausea, vomiting, myelosuppression, mucositis, alopecia and cardiotoxicity by dose accumulation. Daunorubicin is an important agent in the treatment of acute lymphocytic and myelocytic leukaemia, while aclarubicin is used as a second-line treatment for acute nonlymphocytic leukaemia. Epirubicin, a semisynthetic analogue of doxorubicin differing only by its stereochemistry, is similar in terms of efficacy for the treatment of breast cancer. Idarubicin is used in advanced breast cancer after failure of

first-line chemotherapy and in acute nonlymphocytic leukaemia [2].

A review of the physicochemical and analytical properties of anthracycline antitumour agents focused on protolytic equilibria, partition coefficients, self-association, adsorptive properties, metal complexation, spectroscopy and chromatography was published in 1986 [366]. In 2001, various reviews reported analytical methods for anthracyclines and their metabolites [367] or related compounds [368,369]. Generally, separations of these anticancer agents were achieved by LC coupled with various detection techniques including electrochemical or MS. Due to their colour and native fluorescence, UV–Vis or fluorescence detection are particularly adapted.

Quality control of hospital formulations was performed by FIA and LC-UV [8]. Given the similar structure of anthracyclines, FIA-DAD was not able to distinguish all compounds, and a separation by LC was necessary. In addition, pharmaceutical preparations containing a drug mixture of doxorubicin and vincristine [370], doxorubicin and 5-FU [63], or several anthracyclines [371] were successfully analysed by LC-UV. Jelińska and co-workers reported stability studies in the solid state of doxorubicin and daunorubicin [372] and epidoxorubicin [373] by LC-UV.

Due to the cardiotoxicity of the accumulation of anthracyclines, monitoring of plasma or tissue concentrations is of utmost importance. Several studies have reported anthracycline determination in biological samples (plasma, serum, cell extracts) by CE-UV [374,375] and CE-LIF [376–383]. Sweeping preconcentration and electrokinetic injection coupled to CE-UV analysis provided LODs of 1×10^{-9} mol L^{-1} ($\sim$0.5 ng mL^{-1}) for doxorubicin and daunorubicin in plasma samples allowing determination of therapeutic concentrations [374]. LIF detection provided also an extremely sensitive and selective technique for biological samples with LODs in the range of ng mL^{-1}. For example Perez-Ruiz et al. published a CE-LIF method with simple acetonitrile protein precipitation exhibiting LODs inferior to 1.0 ng mL^{-1} for doxorubicin, daunorubicin and idarubicin in serum samples [376]. However, electrophoretic separation between doxorubicin and its metabolite doxorubicinol, which is responsible for the cardiotoxicity, is difficult due to their similar structure and charge. The presence of doxorubicinol was determined separately by matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry [383]. Another approach to overcome this problem was the use of a chiral method (i.e., CD-MEKC-LIF) with a resolution of 2.81 [384] or LC with a photosensitisation reaction followed by chemiluminescence detection with complete baseline separation [385].

Other methods for measurement of intracellular accumulation of anthracyclines in cancer cells were reported, including MEKC-LIF [386–388] with LOD values in order of ng mL^{-1}. MEEKC-UV has also shown good potential for the analysis of anthracyclines in biological samples [389]. However, LOD and LOQ for doxorubicin in plasma were 9.7 μg mL^{-1} and 32.5 μg mL^{-1}, respectivley; which was not sufficient for the application of the method to real clinical samples. Additionally, CE with amperometric detection was used for the analysis of idarubicin in human urine with an LOD of 8.0×10^{-8} mol L^{-1} ($\sim$40 ng mL^{-1}) [390] and for the determination of the dissociation constants of anthracyclines [391]. CE with an absorption-based wave-mixing detector method exhibited high selectivity and sensitivity for anthracycline drugs similar to LIF detection with an LOD of 9.9×10^{-10} mol L^{-1} for daunorubicin (i.e. inferior to 1 ng mL^{-1}) [392].

Since 2001, several methods of LC-UV [63,98,393,394] and LC with fluorimetric detection have been reported for the determination of anthracyclines in biological samples [395–402]. For example, Katzenmeyer et al. reported an LC–LIF-MS method to determine *in vitro* metabolism of doxorubicin [403]. LC-LIF detection allowed quantification of the metabolic compounds while MS detection contributed to the metabolites identification. However, the best selectivities were obtained with LC–MS/MS methods [262,263,404–408] with LOQs inferior or close to 1.0 ng mL^{-1}. Wang et al. used UHPLC–MS to profile urinary metabolites for toxicity-related processes and pathogenesis induced by doxorubicin [409]. An accelerator mass spectrometry method allowed cellular quantification of doxorubicin at femtomolar concentrations with the best sensitivity but without discrimination between parent drug and metabolites [410].

Methods of LC–MS/MS [32,411] and LC-fluorescence [412,413] were used for monitoring anthracyclines in urine samples of healthcare workers or employees of drug manufacturers. Environmental monitoring of anthracyclines together with other anticancer drugs has been achieved in wipe and air samples [49,51,52] and in sewage water [58] using LC–MS/MS or LC with fluorescence detection [56]. Before LC-fluorescence analysis, wastewater samples were pre-concentrated by SPE (concentration factor of 100). The method was reproducible and accurate within a range of 0.1–5 ng mL^{-1} for doxorubicin, epirubicin and daunorubicin (recoveries >80%) and successfully applied for determination of these drugs in hospital effluents. Moreover, an LC-UV method was also developed for surface contamination of 5-FU, ifosfamide, cyclophosphamide, doxorubicin, and paclitaxel with LODs of 500 ng mL^{-1} [45,274] while LODs of 1.0 ng mL^{-1} were obtained by MS detection [51].

3.2.3.2. Mitoxantrone and actinomycin-D. The indications of mitoxantrone are the treatment of metastatic breast cancer, adult nonlymphocytic leukaemia and non-Hodgkin's lymphoma. Actinomycin-D is mainly used to treat paediatric cancers, some testicular sarcomas and AIDS-related Kaposi's sarcoma. The side effects of mitoxantrone and actinomycin-D are similar to those of doxorubicin except that the cardiac toxicity is less prominent. However, cardiac examinations and monitoring are still recommended when a certain cumulative dose has been reached [2]. Chen et al. [369] and Loadman and Calabrese [368] published reviews reporting several LC methods for the determination of mitoxantrone in 2001. Thanks to the presence of chromophores, UV detection is frequently used for the analysis of mitoxantrone, with LOD between 1 and 75 ng mL^{-1}. The sensitivity was improved with ECD with LOD of 0.1 ng mL^{-1} [369]. Recently, other LC-UV [414,415] and LC–MS/MS methods for mitoxantrone [416] and actinomycin-D [417–421] were developed for clinical samples with good quantitative performance in terms of sensitivity and selectivity. LOQs of mitoxantrone in plasma and tissues were in the same concentration order than the above mentioned studies. With simple protein precipitation followed by LC–MS/MS analysis, LOQ of actinomycin-D in plasma was about 0.5 ng mL^{-1} [421]. Finally, CE with chemiluminescence detection was reported for mitoxantrone determination in commercial drugs and in spiked biological samples [422].

3.2.4. Topoisomerase inhibitors

3.2.4.1. Topoisomerase I inhibitors (irinotecan, topotecan). Their lead structure is the natural product camptothecin, a cytotoxic quinoline-based alkaloid with a unique five-ring system extracted from the bark of the Chinese *Camptotheca* and the Asian *Nothapodytes* trees. Clinical use of camptothecin is limited due to poor water solubility and a number of serious side effects. However, several derivatives of camptothecin with improved solubility are now used. Topotecan is administered intravenously for the treatment of metastatic ovarian cancer when first-line or subsequent therapy fails. Irinotecan is licensed for metastatic colorectal cancer in combination with 5-FU and folinic acid or as a monotherapy when 5-FU containing treatments have failed. In addition to dose-limiting myelosuppression, side effects include

gastrointestinal disturbances such as delayed diarrhoea, asthenia, alopecia, and anorexia. The drug is hydrolysed *in vivo* to 7-ethyl-10-hydroxycamptothecin (SN-38), an active metabolite approximately 200–2000-fold more cytotoxic than irinotecan. However, despite its intrinsic potential as an anticancer agent, its poor solubility in most pharmaceutically acceptable solvents limits its clinical use [2].

In 2001, a paper on traditional Chinese medicines and antineoplastic compounds reviewed LC methods for camptothecin, irinotecan, topotecan, and 9-aminocamptothecin in biological samples [423]. LC with fluorescence detection was the most commonly used technique for determination of these compounds in biological samples. Other reviews reporting methods for camptothecin and related compound determination discussed separation efficiency and detection sensitivity and specificity [424–426]. The chemistry, structure–activity relationships and stability of camptothecin analogues were reported with particular attention on the chemical stability. Because the active lactone structure can undergo ring opening under conditions of extraction, pre-treatment and analysis should be studied carefully.

In 2010, a review of bioanalytical methods for irinotecan and its active metabolite SN-38 provided an exhaustive compilation of published assays, with details on validation parameters and applicability [427]. Pharmacokinetic profiling of irinotecan and its metabolites was studied in various species, including cancer patients, by means of LC-UV, LC with fluorescence detection, LC–MS and LC–MS/MS. Concentrations of irinotecan and SN-38 in biological samples in order of ng mL^{-1} were achieved by LC–MS/MS and LC coupled to fluorescence detection analysis [427]. The developed methods continue to find use in the optimisation of newly designed delivery systems with regard to pharmacokinetics for the safe and effective use of irinotecan or SN-38. Studies already reported in these reviews will not be further discussed in this paper and only some references with analytical techniques other than LC or developed for special application areas will be discussed.

HPTLC [428] and LC–MS/MS [51] methods for camptothecin derivatives were developed for quality control of hospital formulations. LC-UV methods were validated for quantitative determination of irinotecan [429] and topotecan [430] in bulk drug samples and formulations. In addition, an LC-UV method was reported for the simultaneous determination of the carboxylate and lactone forms of SN-38 in nanoparticles [431]. Laser-induced fluorescence and photochemical derivatisation was also suitable for irinotecan and topotecan trace analysis [432]. Another example is the determination of camptothecins in extracts of *Nothapodytes foetida* by MEKC-UV [433]. This method was found to be very suitable for monitoring camptothecin concentrations during the cultivation of the medicinal plant. For surface contamination in cytotoxic preparation units, LC–MS/MS analysis allowed the determination of irinotecan and other cytotoxics with well studied quantitative performance in terms of accuracy and precision. LOQ of irinotecan in aqueous solutions was at 1.0 ng mL^{-1} corresponding to a surface contamination of 0.1 ng cm^{-2} [51,52].

3.2.4.2. Topoisomerase II inhibitors (etoposide, teniposide, amsacrine). The lead structure of drugs that inhibit topoisomerase II is podophyllotoxin, a plant alkaloid isolated from the American mandrake rhizome. Etoposide is a semisynthetic glucoside of epipodophyllotoxin and is one of the most effective agents for treating small-cell bronchial carcinoma. It can also be used for testicular cancer and some lymphomas. The toxic effects of this drug include nausea and vomiting, myelosuppression, and alopecia. Teniposide is an etoposide analogue with a similarly broad clinical activity. Amsacrine, another topoisomerase II inhibitor, has an acridine-based structure. Clinically, amsacrine has an activity and toxicity profile similar to doxorubicin. It is administered intravenously for the treatment of advanced ovarian carcinomas, myelogenous leukaemia, and lymphomas. Its side effects include myelosuppression and mucositis [2].

A review of LC methods for the determination of topoisomerase II inhibitors was published by Chen et al. in 2001, including a compilation of LC methods for the analysis of etoposide, teniposide, and amsacrine, as well as anthracyclines, mitoxantrone and others [369]. Methods based on LC coupled to various detectors, such as UV, fluorescence, ECD, MS and ELISA, were reported for etoposide determination in physiological fluids [369,423,434]. In 2010, Sachin et al. developed an UHPLC–MS/MS method with SPE sample pretreatment for the simultaneous determination of etoposide and a piperine analogue in plasma samples with a total run time of 6 min [435]. LOQs for etoposide and the piperine analogue were 2.0 and 1.0 ng mL^{-1}, respectively. Teniposide has been analysed by LC-UV and LC-ECD [369], but recently an UHPLC–MS/MS method was developed for the determination of teniposide in plasma samples with a simple liquid–liquid extraction procedure and using etoposide as internal standard [436]. LOQ of 10 ng mL^{-1} in rat plasma and short analysis time (3.0 min) were obtained and were particularly adequate for a high sample throughout. The intraday and interday precision values (RSD) were less than 15% and the method was considered as suitable for preclinical pharmacokinetic studies of teniposide in rats. Additionally, the chemical stability of teniposide [6] and etoposide [7] in lipid emulsion was monitored by LC-UV. Separation of etoposide phosphate and methotrexate was also achieved by CE-UV with a high-sensitivity cell in a concentration range between 0.1 and 100.0 μg mL^{-1} [171]. CE-LIF [437] and MEKC with near-field thermal lens detection [438] allowed the simultaneous quantification of etoposide and etoposide phosphate in human plasma with similar LODs in order of 100 ng mL^{-1} for etoposide phosphate and 170 ng mL^{-1} for etoposide. For environmental monitoring, sensitive LC–MS/MS methods were reported for etoposide determination in sewage water with LOD in order of ng L^{-1} [58] and for etoposide phosphate quantification on different surfaces [51,52].

3.2.5. DNA cleaving agents (bleomycin)

Bleomycin accumulates in squamous cells and is therefore suitable for the treatment of tumours of the head and neck, Hodgkin's disease and testicular carcinomas. Pharmaceutical preparations containing bleomycin sulphate consist of a mixture of glycopeptide bases obtained from *Streptomyces verticillus* with individual molecular weights in the region of 1300 Da. The analytical and biological inequivalence of two commercial bleomycin formulations was demonstrated using LC-UV [439]. Recently, Yin et al. demonstrated that a sensitive DNA-based electrochemical strategy appeared to be a promising alternative for the determination of trace amounts of bleomycin in pharmaceutical and clinical samples with LOD in the order of picomolar (~0.1 ng mL^{-1}) [440]. Furthermore, an LC–MS method was developed for pharmacokinetic studies of a new formulation of bleomycin in dog plasma after intramuscular injection [441].

3.3. Antitubulin agents

Analysis of taxanes, vinca alkaloids and ixabepilone are described in this section. Chemical structures of antitubulin agents are shown in Fig. 7, and relevant analytical methods for pharmaceutical, biological and environmental samples are reported in Table 3.

3.3.1. Taxanes (paclitaxel, docetaxel)

Paclitaxel is a highly complex tetracyclic diterpene found in the needles and bark of *Taxus brevifolia*, the Pacific yew tree. Pure paclitaxel was isolated in 1966 and its structure published in 1971. However, it did not appear in clinical practice until the 1990s.

Table 3
Analytical methods for antitubulin agents.

Compound	Matrix	Analytical technique	References
Docetaxel	Review	Review	[423]
	Pharmaceutical formulation	LC-UV	[5,442–445]
	Pharmaceutical formulation	FIA	[8]
	Biological samples	CZE, MEKC, MEEKC	[389]
	Biological samples	LC-UV	[393]
	Biological samples	LC–MS	[451]
	Biological samples	LC–MS/MS	[19,452–454]
Paclitaxel	Review	Review	[423]
	Pharmaceutical formulation	FIA	[8]
	Pharmaceutical formulation	LC-UV	[446–448]
	Pharmaceutical formulation	LC–MS	[449]
	Biological samples	MEKC-UV	[455]
	Biological samples	CZE, MEKC, MEEKC	[389]
	Biological samples	LC-UV	[229,393,450]
	Biological samples	LC–MS	[451,483]
	Wipe samples (surface contamination)	LC-UV	[45,274]
	Wipe samples (surface contamination)	LC–MS/MS	[49]
Vinca alkaloides (vincristine, vinblastine, vindesine, vinorelbine)	Review	Review	[423]
	Pharmaceutical formulation	NACE-DAD	[456]
	Pharmaceutical formulation	HPTLC	[457]
	Pharmaceutical formulation	LC-UV	[370]
	Pharmaceutical formulation	LC–MS/MS	[51]
	Plant extracts	LC-UV	[458]
	Plant extracts	CE-MS	[459]
	Biological samples	LC–MS/MS	[417,418,460,461]
	Wipe samples (surface contamination)	LC–MS/MS	[51,52]
	Sewage water	LC–MS/MS	[58]
Ixabepilone	Biological samples	LC–MS/MS	[462–464]

Docetaxel is a more recently introduced semisynthetic analogue with similar therapeutic and toxicological properties. Paclitaxel has relatively poor water solubility and lack of activity in some cancers with resistance, which has prompted ongoing research into new analogues. Given by intravenous infusion, paclitaxel in combination with cisplatin or carboplatin constitutes the treatment of choice for ovarian cancer. Docetaxel is licensed for initial treatment of advanced breast cancer in combination with doxorubicin or alone when adjuvant cytotoxic chemotherapy has failed. The two taxanes are also used for advanced or metastatic non-small-cell lung cancer or for metastatic breast cancer in cases where first-line therapy has failed [2].

For stability testing or quality control of pharmaceutical formulations of docetaxel [5,442–445] and paclitaxel [446–448], LC-UV methods have been developed. Musteata and Pavliszyn used LC–MS for the determination of free concentration of paclitaxel in a

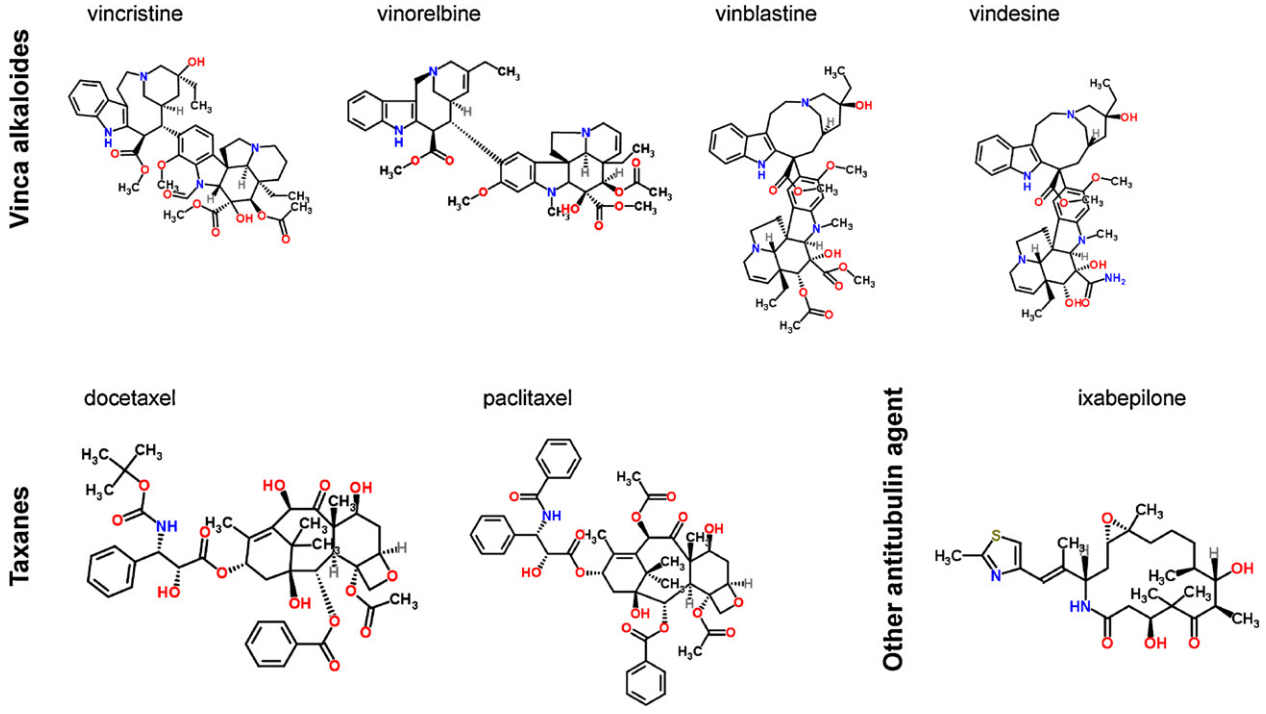

Fig. 7. Chemical structures of antitubulin agents.

liposome formulation [449]. Additionally, control of chemotherapy during preparation was performed by FIA-UV for docetaxel and paclitaxel [8]. In 2001, several methods for the determination of paclitaxel in biological matrices using LC-UV, LC–MS and immunoassays were reported [423].

Since 2001, several LC-UV [229,393,450], LC–MS [451] and LC–MS/MS methods have been developed for taxanes determination in biological samples [19,452–454]. For example, Corona et al. used on-line extraction procedure with LC–MS/MS for high-throughput quantification of docetaxel in plasma. The method was validated and presented LOQ of 0.15 ng mL^{-1} with good accuracy and precision performance and was successfully applied for pharmacokinetics of docetaxel in cancer patients [19]. On-line column-switching was also applied by Bermingham et al. for determination of taxanes and anthracyclines by LC-UV, however the method was not sensitive enough for TDM at low serum concentration because the LOQ was evaluated at 500 ng mL^{-1} [393]. Electrophoretic separation techniques (e.g., CE, MEKC, MEEKC) showed also good potential for taxanes analysis in biological samples [389,455]. For example, a MEEKC-UV method was characterised by a very short separation time and high efficiency and was proven to be flexible for the separation of different combinations of anthracyclines and taxanes [389]. This separation approach could be highly beneficial for biological sample analysis if applied with a sensitive detection system. With UV detection, LOQs were in the order of 84,500 ng mL^{-1} for docetaxel [389].

Contamination and exposure assessment of paclitaxel and other cytotoxic drugs was performed by LC-UV [45,274] and LC–MS/MS [49]. The LC–MS/MS method provided adequate sensitivity for measuring five antineoplastic drugs in air and wipe samples in healthcare environment with LOD of 0.7 ng mL^{-1} for paclitaxel [49].

3.3.2. Vinca alkaloids (vincristine, vinblastine, vinorelbine, vindesine)

The two alkaloids vinblastine and vincristine are constituents of the Madagascar periwinkle (*Vinca rosea*). Isolation and structural identification were reported in the 1960s. Vinblastine synthesis starting from catharanthine and vindoline units was reported in 1979. Because these alkaloids have proven efficacy in therapy to treat certain solid tumours (mainly lung and breast), lymphomas, and acute leukaemia, efforts have been made to design new analogues with reduced toxicity, which resulted in the semisynthetic analogues vindesine and vinorelbine. These agents are given by intravenous administration, and their side effects include neurotoxicity, myelosuppression, and alopecia [2].

A non-aqueous CE-UV method allowed the successful determination of vinorelbine in a commercial pharmaceutical formulation [456]. For quality control of pharmaceutical formulations in hospitals, HPTLC [457], LC-UV [370] and LC–MS/MS [51] have all been used. In 2005, Gupta et al. developed an LC-UV method for the determination of vinca alkaloids in leaf extracts of *Catharanthus roseus* [458]. CE-MS was also successfully used for determination of vinblastine and its precursors vindoline and catharantine in plant samples [459]. As reported in the review on traditional Chinese medicines, analyses of vinblastine, vincristine and vinorelbine in biological samples were achieved by LC-UV, LC with fluorescence detection and LC-ECD [423]. LOQ of these vinca alkaloids in plasma or urine were in order of ng mL^{-1} with LC-fluorescence and LC-ECD. LC–MS/MS methods for vinca alkaloids determination in human plasma [417,418,460,461] and for drug residues in dog urine [262] were also published. For example, Dennison et al. developed a very sensitive LC–MS/MS method with an LOQ of 0.012 ng mL^{-1} for vincristine and its major metabolite in human plasma [460]. For environmental monitoring, an LC–MS/MS method was useful for sewage water analysis [58] and for surface contamination [51,52].

3.3.3. Other antitubulin agents (ixabepilone)

Ixabepilone is a semi-synthetic, microtubule stabilising, epothilone B analogue that displayed activity in taxane-resistant breast cancer patients. A human mass balance study of the novel anticancer agent ixabepilone was performed using accelerator mass spectrometry to investigate elimination pathways [462]. In addition, pharmacokinetics after intravenous and oral administration was established by sensitive and validated LC–MS/MS methods [463,464]. Plasma samples were extracted by acetonitrile protein precipitation and an LOQ of 2 ng mL^{-1} of ixabepilone in human plasma was obtained [464].

4. Conclusion

Over the last thirty years, numerous analytical methods for cytotoxic drug determination in pharmaceutical formulations, biological samples, and environmental samples have been reported in the literature. The first analytical methods, mainly using LC-UV, allowed for the foundations of the use of cytotoxic drugs in treating human cancers to be laid in terms of understanding drug interactions with the organism, developing pharmaceutical formulations and determining the toxicity of these compounds. As with all pharmaceutical substances, more elaborate methods to support pharmacokinetics, pharmacodynamics and therapeutic drug monitoring of cytotoxic drugs have been published thanks to the implementation of detection systems with higher selectivity and sensitivity, such as mass spectrometry. During the last five years, however, particular attention has been focused on the safe handling of cytotoxic drugs and the protection of the environment. Indeed, several papers reporting the analysis of cytotoxic drugs in wastewater, in working environments and in biological samples of healthcare professionals have been published.

Today, with the emergence of new chemotherapy treatments (including biological agents, hormones and molecular targeting agents), the development of useful methods is required for preclinical and clinical studies, but also for the development of formulations containing these compounds, and constitutes the next challenge in the analysis of anticancer drugs.

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