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How to cite

GUICHARD, Nicolas et al. Antineoplastic drugs and their analysis: a state of the art review. In: Analyst, 2017, vol. 142, p. 2273–2321. doi: 10.1039/c7an00367f

This publication URL: https://archive-ouverte.unige.ch/unige:96003
Publication DOI: 10.1039/c7an00367f

Analyst

CRITICAL REVIEW

View Article Online
View Journal | View Issue

Cite this: *Analyst*, 2017, **142**, 2273

Antineoplastic drugs and their analysis: a state of the art review

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Received 2nd March 2017,
Accepted 10th May 2017

DOI: 10.1039/c7an00367f

rsc.li/analyst

The number of patients suffering from cancer is constantly increasing and, consequently, the number of different chemotherapy treatments administered is increasing. Given the high reactivity and toxicity of antineoplastic drugs, analytical methods are required in all pharmaceutical fields, from drug development to their elimination in wastewater; including formulation quality control, environment and human exposure and therapeutic drug monitoring. The aim of this paper is to provide an overview of the analytical methods available for the determination of antineoplastic drugs in different matrices such as pharmaceutical formulations, biological and environmental samples. The applicability and performance of the reported methods will be critically discussed, with focus on the most commonly used antineoplastic drugs. Only conventional compounds and small molecules for targeted therapy will be considered in the present review.

1 Introduction

The World Health Organisation stated that the incidence of cancer increased from 12.7 million in 2008 to 14.1 million in 2012.[1] This trend is expected to continue with the number of new cancer cases increasing by 70% over the next two decades. This bleak prognosis leads to a growing prescription for antineoplastic drugs, which constitute, with surgery and/or radiotherapy, the main treatment in oncology. Two classes of antineoplastic drugs from different generations can be distinguished, namely conventional molecules and drugs from targeted therapy. Conventional chemotherapy appeared at the beginning of the 20th century with the development of chemical weapons[2]. One of the first families of antineoplastic drugs still administered today constitutes molecules with a structure related to mustard gas used on the battlefields of World War I. A side effect observed with this gas (that has a myelosuppressive action) initiated the development of the first antineoplas-

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tic drugs against leukemia.[3] Driven by this success, the USA decided to launch several national programs with the main objective of developing new molecules for cancer treatment. Then, an unbridled race towards the discovery of new anticancer drugs, such as antifolate compounds, purine and pyrimidine analogues and also antibiotics, started for a period of 20 years. Most of the conventional antineoplastic drugs administered today were developed during this period. The war against cancer knew a second offensive with the apparition of targeted therapies in the '90s. However, in spite of the promising discovery of these new molecules which act with precision, thus reducing side effects, heavy weapons represented by the conventional antineoplastic drugs remain the first-line molecules for the chemical treatment of a large number of cancers.

The high chemical reactivity of conventional antineoplastic drugs is responsible for their anticancer activity, but also represents their main drawback. Indeed, this high chemical reactivity makes such molecules extremely unstable and strongly toxic. Particular attention has therefore been paid to these compounds in terms of safety and quality. In this context, numerous methods were reported for the analysis of antineoplastic drugs in different fields, from the development of stable pharmaceutical products to wastewater treatment, including quality control of the formulation and therapeutic drug monitoring.

It can be noted that products containing antineoplastic drugs are almost exclusively intermediate pharmaceutical forms available as a lyophilisate or a concentrated solution of the active drug. Under these conditions, the highest compound stability can be obtained, and thus the desired therapeutic effect can be guaranteed. A reconstitution step, usually performed extemporaneously by the hospital staff (nurse or pharmacy operators), converting the intermediate form to a formulation ready to be administered to the patient, has to be performed. The analysis of reconstituted formulations, which are considered as high-risk products, prior to patient administration, is an unavoidable step from a quality control point of view. Given the toxicity of these molecules, in the last ten years focus has been on the determination of antineoplastic drug traces in the environment (hospital pharmacies, care units or effluents) and in biological fluids from the person handling these compounds, to control exposure.

The aim of this paper is to complete a review already published in 2011 by our group.[4] A critical overview of the reported analytical methods for antineoplastic drugs is provided. A significant number of new references are added and the methods used for the analysis of small molecules from targeted therapy are also discussed. Biological agents such as monoclonal antibodies are not considered in the present review.

2 Conventional antineoplastic drugs

Three different families of conventional antineoplastic drugs can be distinguished according to their action on deoxyribonucleic acid (DNA):

- Molecules acting on DNA synthesis (antimetabolites);
- Molecules with a direct action on DNA, called DNA-interactive agents (alkylating agents, intercalating agents and topoisomerase inhibitors);
- Molecules with an action on mitosis (antitubulin agents).

2.1. Antimetabolites

Antimetabolites belong to one of the oldest families of antineoplastic drugs. They include molecules such as methotrexate, and more recent compounds such as gemcitabine (GemC). In all cases, the mechanism of action of these compounds is to prevent DNA replication. Antimetabolites inhibit the synthesis of DNA components by acting as lures. They are structural analogues of purine and pyrimidine bases (similar to nucleobases or nucleosides), and folic analogues (inhibition of nucleic acid synthesis). Table 1 reports analytical methods published for the determination of antimetabolites.

2.1.1. Folic analogues. These compounds target folic coenzymes involved in the synthesis of nitrogenous bases. The first folic acid antagonist, namely aminopterin, was discovered in the late '40s for the treatment of childhood leukemia.[5] It was rapidly replaced by a less active but also less toxic agent,

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Table 1 Analytical methods for the detection of antimetabolite drugs

Antimetabolites	Matrices	Techniques	Ref.
Methotrexate	Molecule/ formulations	LC-UV	13 and 47
		CE-UV	43, 48 and 49
	Biological matrices	LC-UV	11, 12, 45 and 46
		LC-MS	17, 21, 24, 26, 30–34
		CE-UV	35–40, 42, 45 and 133
		CE-LIF	44
	Environment	LC-MS	15, 16, 19, 20, 22, 23, 25, 27–29, 134 and 135
Pemetrexed	Molecule/ formulations	LC-UV	51, 53–56 and 60
	Biological matrices	LC-UV	50 and 52
		LC-MS	57 and 136
Raltitrexed	Molecule/ formulations	CE-UV	61
	Biological matrices	LC-MS	59
5-fluorouracil	Molecule/ formulations	LC-UV	66, 67, 72, 74 and 137
		CE-UV	108
	Biological matrices	LC-UV	67, 85, 89 and 93
		LC-MS	34, 80, 95, 100–102
		LC-FD	97
		CE-UV	39, 105 and 109
	Environment	LC-UV	138
		LC-MS	28, 29, 78 and 103
		CE-UV	106 and 107
		GC-MS	27, 113 and 114
Azacitidine	Biological matrices	LC-MS	82 and 83
Gemcitabine	Molecule/ formulations	LC-UV	66, 73, 74 and 137
	Biological matrices	LC-UV	68–70, 87, 88, 91, 92, 96, 98 and 99
		LC-MS	34, 75–77, 81, 94, 104 and 136
	Environment	LC-UV	114
		LC-MS	19, 29, 103 and 135
Cytarabine	Molecule/ formulations	LC-UV	13, 67, 71 and 74
		CE-UV	111
	Biological matrices	LC-UV	67
		LC-MS	34, 79, 86, 90 and 139
		CE-UV	110–112
	Environment	LC-MS	18, 19, 29 and 103
6-Mercaptopurine	Biological matrices	LC-UV	123
		LC-MS	33
		LC-FD	130
6-Thioguanine	Biological matrices	LC-UV	120
		LC-MS	33, 121 and 131
		LC-AD	129
		CE-UV	39
Azathioprine	Molecule/ formulations	LC-UV	119
		CE-UV	132
	Biological matrices	LC-UV	118 and 125
	Environment	LC-UV	122 and 140
		LC-MS	134
Fludarabine	Biological matrices	LC-MS	127
Cladribine	Biological matrices	LC-UV	128
		LC-MS	126
Clofarabine	Biological matrices	LC-MS	126

amethopterin, also known as methotrexate, which is still extensively used 70 years after its discovery (for the treatment of osteosarcomas, acute lymphoblastic leukemias, Hodgkin's disease, breast, bladder and lung cancers). In the '90s, new folic analogues emerged, including raltitrexed[6] and pemetrexed,[7] with the aim of preventing methotrexate resistance and toxicity. Fig. 1 shows the structure of folic acid and its antagonists.

Molecules with a structure close to that of folic acid are characterised by the presence of two carboxylic acid groups. Their solubility depends on the pH of the solution. Indeed, with pK_a values of the carboxylic acid groups between 3.3 (pemetrexed) and 4.7 (methotrexate), neutral or basic solutions are required for their solubilisation. The presence of an asymmetric carbon is another property of folic analogues. *S*-Methotrexate, *S*-pemetrexed and *S*-raltitrexed are active forms, while *R*-forms are considered as impurities.[8]

Since 1975, more than 100 articles have described different analytical methods for the extraction, separation and detection of methotrexate.[4,9,10] Most of the reported methods are based on the use of liquid chromatography (LC) coupled with UV spectrophotometry (UV)[11,12,13,14] or mass spectrometry (MS), when there was a need for high selectivity and/or sensitivity.[15–22,23,24,25,26,27,28,29,30,31,32,33,34] Limits of detection

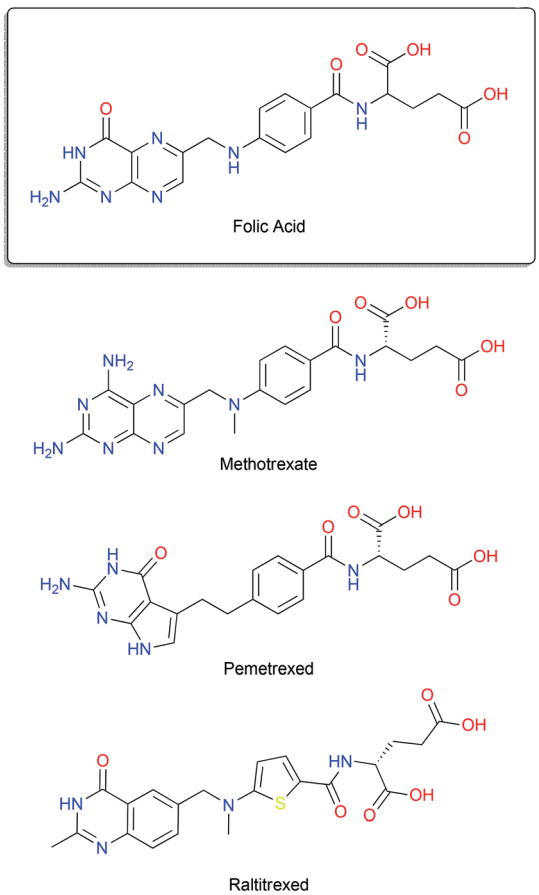


Fig. 1 Structure of folic acid and its analogues.

(LOD) inferior to 1 ng mL^{-1} were usually reached with LC-MS.[24,32] Capillary electrophoresis (CE) coupled with UV detection[35–43] or laser induced fluorescence detection (LIF)[44] was also proposed as a suitable approach for the analysis of methotrexate, since the molecule is ionisable. To improve the sensitivity of CE methods, zeta cell[38] or conventional sample preparation steps were used (LOD in the order of μg mL^{-1}). Solid phase extraction (SPE),[15,16,20,22,35,39,41,32,33,34] liquid–liquid extraction (LLE)[40] and protein precipitation (PP)[24,30,31,11,14,17,36] were among the most widely used sample preparation techniques when analysing methotrexate in complex matrices. Column-switching methods with SPE coupled with the analytical system (column and detection) were also developed for methotrexate analysis.[26] Methotrexate enantiomers separation was carried out by LC-UV[45–47] and CE-UV.[48,49] Contrary to methotrexate, only a few analytical methods have been reported in the literature for the most recent compounds (*i.e.*, raltitrexed and pemetrexed). The analytical methods for pemetrexed were based on LC coupled to UV,[50–55,56] MS[57,58] or evaporative light scattering detector (ELSD).[51] In our opinion, ELSD is not recommended for analysing pemetrexed since this molecule is UV-active and ELSD is often less sensitive and selective than the commonly used UV detectors. A methodology including a PP step followed by LC-MS analysis was also developed for the determination of raltitrexed in human plasma with a limit of quantification (LOQ) of 2 ng mL^{-1}.[59] For impurity profiling of active ingredients, separation of pemetrexed and raltitrexed enantiomers were obtained by LC-UV[60] and CE-UV,[61] respectively. In LC-UV, a polysaccharide chiral stationary phase was employed, while the chiral selector (cyclodextrins) was directly added to the BGE in CE-UV.

2.1.2. Pyrimidine analogues. As the name suggests, these substances have structures close to the endogeneous pyrimidine bases (thymine, cytosine and uracil). Biochemical lures disrupt the synthesis of nucleic acids. The first compound, developed in the '50s,[62] was a uracil molecule with a fluorine atom in the 5-position, named 5-fluorouracil (5FU). This old substance remains the most prescribed molecule in oncology and its main application is the treatment of colorectal cancer. The structures of the most familiar compounds of this subfamily of antineoplastic agents are shown in Fig. 2.

Discovered in the late '50s/early '60s, following research on marine sponges, cytarabine paved the way for a series of cytidine analogues (cytosine nucleoside).[63] In 1964, azacitidine, whose structure differed by the presence of an additional nitrogen atom in the 5-position of the cytosine nucleus, was produced.[64] It was only in the '90s that GemC appeared in the arsenal of antineoplastic drugs, synthesized a decade earlier by Eli Lilly Laboratories.[65]

A wide range of analytical methods have been developed for pyrimidine analogues. Historically, the most commonly used technique was reversed phase LC (RPLC) coupled with UV[66–72,73,74,13] or MS.[18,19,75–82,83,84,29,34] LOD inferior to 1 ng mL^{-1} can be obtained for the analysis of pyrimidine analogues by LC-MS. For example, Marangon *et al.* developed an LC-MS method including a PP step, for the determination of GemC and its metabolite in plasma, achieving a LOD of 0.1 ng mL^{-1}.[77] The main limitation of these methods is the poor retention of pyrimidine analogues on a C18 stationary phase under RPLC conditions. Indeed, pyrimidine analogues are small hydrophilic molecules having log *P* values between −0.9 and −3.5. To have a sufficient retention for these relatively polar molecules, different strategies were applied in LC including the use of ion pairing reagents,[85–88] ion exchange chromatography,[89–92] porous graphitic carbon support,[93] the derivatisation of pyrimidine analogues prior to their analysis by RPLC,[94,95] or the use of normal phase chromatographic supports.[96–99] However, all of these approaches suffer from obvious limitations, including long column equilibration, poor kinetic performance, tedious sample preparation procedures, or incompatibility with MS.

More recently, hydrophilic interaction chromatography (HILIC) has been proposed as an alternative strategy for the analysis of 5FU[100,101,102] and cytidine analogues[103,104] as shown in Fig. 3. In brief, a polar stationary phase is used in HILIC, together with a mobile phase composed of a large proportion of acetonitrile and aqueous buffer. The limitations previously described for ion pairing chromatography, ion exchange chromatography or normal phase LC were all tackled with HILIC, and this is why this analytical technique was successfully applied for the analysis of pyrimidine analogues.

Various CE-UV methods have also been suggested for the analysis of 5FU[39,105–108,109] and cytarabine,[110–112] since CE

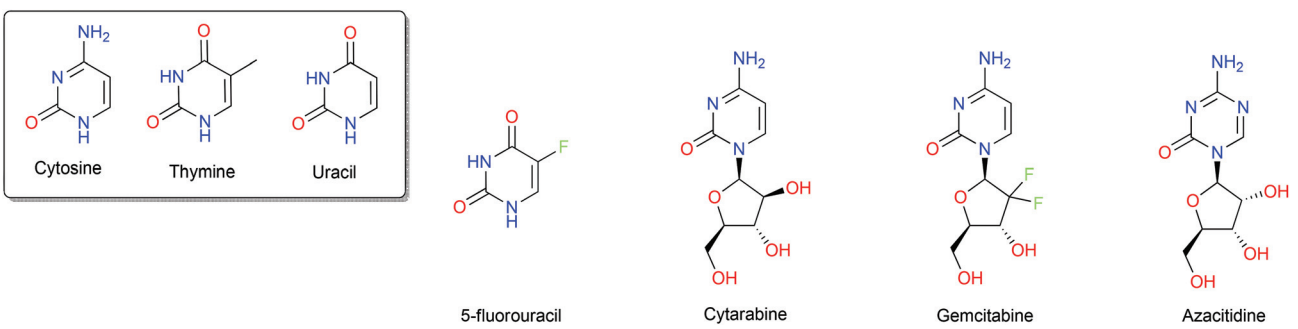


Fig. 2 Structures of pyrimidine bases and their analogues.

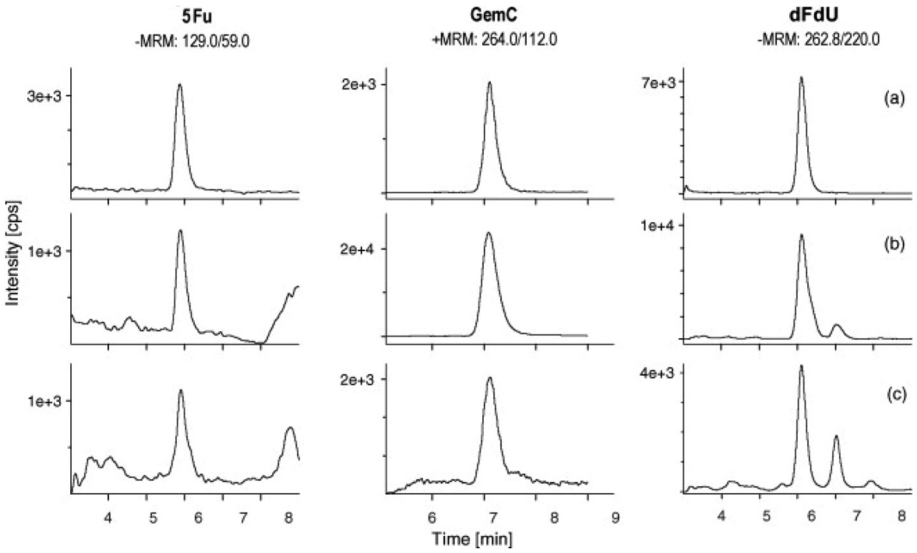


Fig. 3 Multiple reaction monitoring chromatograms of 5FU, GemC and its metabolite (dFdU) obtained for the analysis of calibration standards in (a) spiked hospital wastewater, and (b) hospital wastewater, by hydrophilic interaction chromatography coupled to MS. Adapted from ref. 103, 2009, with permission from Elsevier.

works with any type of ionisable substance, whatever the polarity. LOD of 1.7 ng mL^{-1} was reached for the analysis of 5FU in effluents using an SPE-CE-UV method.[106] Gas chromatography (GC) coupled to MS was also used for the analysis of 5FU,[113,114,27] but the time consuming and tedious derivatisation step means low popularity of GC for the analysis of these non-volatile compounds.

2.1.3. Purine analogues. Like pyrimidine analogues, purine analogues are incorporated into cell components to disrupt the synthesis of nucleic acids. Their structures are inspired by the endogenous purine bases (Fig. 4). Two generations of compounds can be discerned: nitrogenous base analogues (6-mercaptopurine, 6-thioguanine and azathioprine) and nucleoside analogues (fludarabine, cladribine and clofarabine). The first generation appeared in the '50s after a study of more than 100 purine analogues revealed their inhibitory activity on DNA synthesis of guanine and hypoxanthine compounds with a sulfur in the 6-position instead of an oxygen atom.[115,116] 6-Mercaptopurine and 6-thioguanine are mainly used for the treatment of leukemia, while azathioprine (6-mercaptopurine prodrug) is used for its myelosuppressive activity. Despite their significant adverse effects (myelosuppression and digestive disorders) and anticancer activity that is subject to a large inter-individual variation (metabolic pathway by a polymorphic enzyme: thiopurine methyltransferase (TPMT)), these three substances are still present in the chemotherapy arsenal. In the '80s, two additional molecules were discovered (fludarabine and cladribine) and were used ten years later as models for the synthesis of clofarabine, a more stable and active molecule.[117] This second generation of purine analogues are today used against leukemia.

Purine analogues are less hydrophilic than pyrimidine analogues. Thus, RPLC was the main technique employed for the analysis of both the first[118–125] and second generation[126–128] purine analogues. It should be noted that several studies were based on the analysis of the products resulting from the

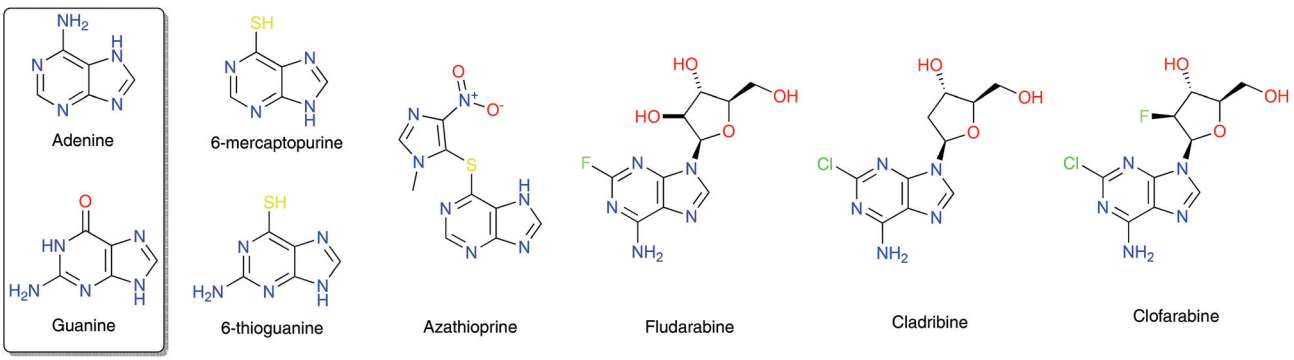


Fig. 4 Structures of purine bases and their analogues.

metabolism of the first generation purine analogues, given their potential toxicity.[120,121,125] 6-Methylmercaptopurine produced by TPMT was frequently sought in globules of patients undergoing treatment to define their phenotyping, since TPMT deficiency led to severe toxicity.[121] In addition to UV detection (which was the most widely used), amperometric detection (AD),[129] fluorescence detection (FD)[130] and MS detection[121,126,127,131] were also coupled to LC for the determination of purine analogues. LOQ of 1 ng mL^{-1} were usually obtained for purine analogues determination by LC-MS.[127,126] Concentrations of 6-mercaptopurine at 0.0615 ng mL^{-1} in urine samples were detected by a LC-FD method using metal palladium to form coordination complexes and enhance the detection signal.[130] A CE-UV method based on the use of borate buffer as background electrolyte (BGE) were also successfully used for the analysis of azathiopurine and its impurities in formulations,[132] or 6-thioguanine in urine[39] with a LOD in the order of 1 μg mL^{-1}.

2.2. DNA interactive agents

2.2.1. Alkylating agents. Alkylating agents represent the oldest family of antineoplastic drugs with the introduction of chlormethine in the late '40s. This family originated from mustard gas, which was used as a chemical weapon during World War I. The observation of an aplastic anemia appearing with severe burns, a few days after exposure, was the starting point for the search for anticancer drugs with reduced side effects. Alkylating agents are organic compounds with one or more electrophilic groups that react with the nucleophilic groups of DNA nucleobases in double helix or proteins, by covalently incorporating alkyl groups (Fig. 5) thereby altering replication and transcription processes. Analytical methods for detecting alkylating agents are reported in Table 2. Today, seven classes of alkylating agents can be distinguished:

- Nitrogen mustard analogues;
- Oxazophosphorines;
- Ethylene imines;
- Nitrosoureas;
- Alkylsulfonates;
- Triazenes and hydrazines;
- Platinum derivatives.

2.2.1.1. Nitrogen mustard analogues. Nitrogen mustard analogues are characterised by the presence of bis(2-chloroethyl)amino groups generating an azyridium ion which binds preferentially to the nitrogen atom at the 7-position of guanine. Given the high reactivity and, consequently, instability in solution, nitrogen mustards are generally orally administered. Only chlormethine and mephalan are administered by injection. To overcome their instability in water, injectable formulations are dry forms that need to be solubilised extemporaneously (patient administration must be carried out within 1 h after solubilisation). This limits the hydrolysis of the molecule in aqueous media (chloride groups are substituted by hydroxy groups in water) which leads to an inactive compound.

The analysis of nitrogen mustard analogues is very difficult because of their instability. Chlormethine was usually analysed by LC-UV after a derivatisation step leading to a stable and UV detectable compound.[141–143] Products resulting from chlor-

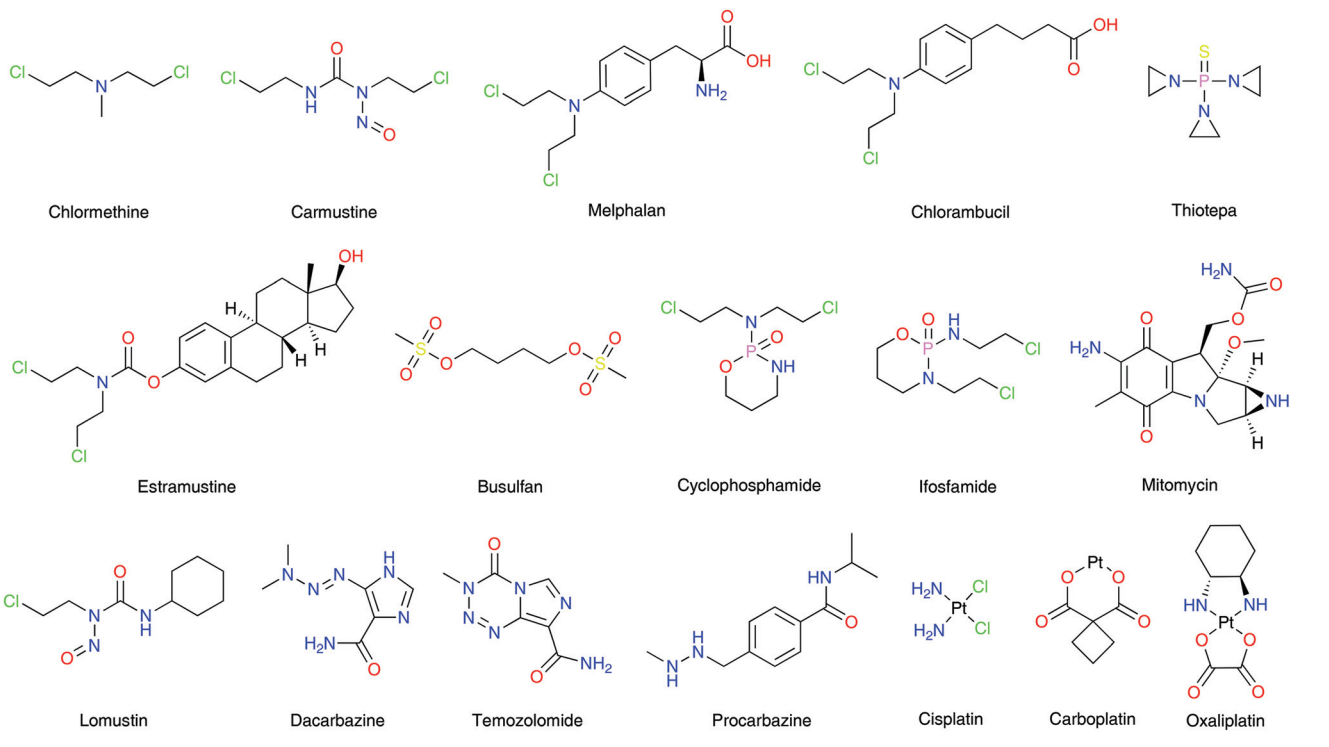


Fig. 5 Structures of alkylating agents.

Table 2 Analytical methods for the detection of alkylating agents

Alkylating agents	Matrices	Techniques	Ref.
Chlorambucil	Biological matrices	LC-UV	45
		LC-MS	162
		CE-UV	45
Chloromethine	Molecule/ formulations	LC-UV	141, 142, 143
Estramustine	Biological matrices	LC-FD	163
		LC-MS	164
		GC-NPD	163
		GC-MS	163
Mephalan	Molecule/ formulations	LC-UV	146, 137
	Biological matrices	LC-UV	147, 148, 149
		LC-MS	153, 154, 155, 156–160 and 161
		LC-FD	150 and 151
		LC-EC	152
Cyclophosphamide	Molecule/ formulations	LC-UV	137 and 186
	Biological matrices	LC-UV	189
		LC-MS	21, 34, 78, 127, 136, 168–180, 193, 194, 305 and 306
	Environment	LC-UV	138
		LC-MS	15, 16, 19, 20, 22, 23, 25, 28, 29, 78, 134, 135 and 307
		GC-MS	27
Ifosfamide	Molecule/ formulations	LC-UV	137
	Biological matrices	LC-UV	188
		LC-MS	21, 34, 136, 170, 176, 179–181, 184, 185, 187 and 191
		GC-NPD	190
		GC-MS	195
	Environment	LC-UV	138
		LC-MS	19, 20, 22, 23, 25, 29, 78, 134, 135, 192 and 307
		GC-MS	27
Mitomycine	Molecule/ formulations	LC-UV	201, 203 and 205
		LC-MS	205
	Biological matrices	LC-UV	208, 209, 211, 212, 214 and 215
		LC-MS	210
	Environment	LC-UV	214 and 215
		LC-MS	29 and 213
Thiotepa	Molecule/ formulations	LC-UV	200, 202 and 204
	Biological matrices	LC-MS	171, 206 and 207
		GC-NPD	207
	Environment	LC-UV	140
Carmustine	Molecule/ formulations	LC-UV	220, 217 and 221
		LC-MS	219
Lomustine	Biological matrices	LC-UV	222 and 223
Busulfan	Molecule/ formulations	LC-UV	238
	Biological matrices	LC-UV	28, 233–237
		LC-FD	239
		LC-MS	178, 183, 240–249
		GC-MS	226–230
		GC-ECD	231 and 232
Procarbazine	Biological matrices	LC-MS	262
	Environment	LC-MS	308
Dacarbazine	Molecule/ formulations	LC-UV	250–252
	Biological matrices	LC-UV	260 and 45
		LC-MS	34 and 266
		CE-UV	45
Temozolomide	Molecule/ formulations	LC-UV	254 and 255
	Biological matrices	LC-UV	253, 256–259 and 261
		LC-MS	263 and 264
		CE-UV	267
	Environment	LC-MS	135
Procarbazine	Biological matrices	LC-MS	265
	Environment	LC-MS	22
Cisplatin	Molecule/ formulations	LC-UV	137
		CE-UV	4, 297, 303 and 304
		CE-MS	302
	Biological matrices	LC-UV	273
		LC-MS	274 and 278
		LC-ICP-MS	280, 283 and 284
		ICP-MS	287 and 21
		CE-UV	295 and 300
		Absorptive voltammetry	288, 289 and 290
	Environment	ICP-MS	286
		LC-ICP-MS	280, 282 and 285
		Absorptive voltammetry	288, 290 and 113
Carboplatin	Molecule/ formulations	LC-UV	269, 271 and 137
		CE-UV	4, 297 and 301
	Biological matrices	LC-UV	270
		LC-MS	275, 136 and 309
		LC-ICP-MS	280 and 283
		ICP-MS	287 and 21
		Absorptive voltammetry	289 and 290
	Environment	LC-MS	29
		ICP-MS	286
		LC-ICP-MS	280 and 282
		Absorptive voltammetry	290 and 113
Oxaliplatin	Molecule/ formulations	LC-UV	291
		CE-UV	4, 298 and 299
		CE-ICP-MS	279
	Biological matrices	LC-MS	276 and 277
		LC-ICP-MS	280, 281 and 283
		ICP-MS	287 and 21
		CE-UV	300
		Absorptive voltammetry	289 and 290
	Environment	LC-MS	310
		ICP-MS	286
		LC-ICP-MS	280
		Absorptive voltammetry	290 and 113

methine hydrolysis were determined either by LC-MS[144] or GC-MS[145] in biological matrices.

LC coupled to a wide range of detectors such as UV,[137,146–149] FD,[150,151] electrochemistry (EC)[152] and MS[153–160] were successfully used for melphalan assay. Based on the chemical structure of the molecule, there is no reason to use fluorescence since the molecule does not possess an extended π conjugation system in its structure. Indeed, similar LOD values (between 5 and 10 ng mL^{-1}) were obtained for LC-UV and LC-FD methods for the analysis of melphalan in plasma. With MS detection, LOQ of 1 ng mL^{-1} was reached for melphalan in biological samples.[154] Chlorambucil was determined by CE-UV and LC-UV in biological matrices with an inferior LOQ of 1 μg mL^{-1}.[45] Studies based on the analysis of DNA/nucleotide adducts with melphalan[155–160,161] and chlorambucil[162] in biological samples by LC-MS have also been published.

Finally, methods based on LC-FD,[163] LC-MS,[164] GC-MS and GC coupled to a nitrogen–phosphorus detector (NPD)[163] were developed for the analysis of estramustine and its main metabolites in biological matrices. With a simple PP step prior to LC-MS analysis, LOQ of 3 ng mL^{-1} was obtained for the estramustine assay in plasma.[164]

2.2.1.2. Oxazophosphorines. Oxazophosphorine compounds appeared in the '50s and are clearly less reactive than nitrogen mustards. They were derived from a concept designed to chemically mask the high reactivity of the active compound up to its target (tumor cell), where specific enzymes were responsible for the conversion to the active form.[165] Indeed, the nitrogen-phosphorus bond does not allow a direct ionisation of the bis(2-chloroethyl) group. The activation, including heterocycle opening resulting from the oxidation of the carbon in the 4-position and formation of chlorethylazirine responsible for the alkylation of DNA, is carried out by P450 cytochromes. The two spearheads of the oxazophosphorines are cyclophosphamide and ifosfamide which have multiple applications (blood cancers, sarcomas, breast cancers...).

Although many methods based on the use of thin layer chromatography (TLC) or GC have been developed for the analysis of oxazophosphorine compounds,[166,167] LC-MS[21,58,127,168–182,23,25,29,183,184,185] and LC-UV[186] remain the techniques of choice. The analysis of the active metabolite of cyclophosphamide (4-hydroxycyclophosphamide) requires an additional derivatisation step immediately after biological sampling, because of its very low stability (half-life of approximately 4 minutes). Various stabilizing agents, such as phenylhydrazine,[174] ansyldrazine,[177] methylhydroxylamine[169] and semicarbazide,[184,171] have been suggested.

Since oxazophosphorines, and more particularly cyclophosphamide, are the most prescribed antineoplastic agents and are administered at high concentrations (mg mL^{-1}), these compounds are often used as markers during studies of exposure to cytotoxic agents. Several LC-MS methods have been developed for the determination of oxazophosphorine traces in environmental and biological matrices, with LOD's lower than 1 ng mL^{-1}. For example, concentrations of 50 pg mL^{-1} oxazophosphorines in urine have been detected by LC-MS including LLE, during biological monitoring of hospital personnel exposed to antineoplastic drugs.[21]

Oxazophosphorine compounds are chiral molecules (asymmetric phosphorus) administered as a racemate mixture to the patient (the *S*-enantiomer has more potent anticancer activity). Protein-based columns[187–192] or polysaccharide-based columns[193,194] allow resolution of oxazophosphorine enantiomers. Ifosfamide enantiomers and their metabolites in urine and serum can be discriminated by a β-cyclodextrine capillary GC column.[195]

2.2.1.3. Ethylene imines. Ethylene imines contain one or more azyridine rings which lead to the formation of aziridinium ions responsible for the alkylating action of the compounds (such as nitrogen mustards). The absence of charge on the aziridine ring makes these molecules less reactive than nitrogen mustards. The first compound of this subfamily, called thiotepa, was discovered in the '50s.[196] Its main indications are ovary, breast and bladder cancers, but it remains scarcely used. The other important molecule belonging to this subfamily is mytomycin C, an antibiotic produced by a bacterium (*Streptomyces caespitosus*) also discovered in the late '50s.[197] It is inactive and requires an enzymatic reduction to induce the opening of the aziridine ring to obtain the alkylating molecule. Mitomycin C is mainly used for the treatment of cancers of the digestive system.

Ethylene imines are unstable in aqueous solution. Indeed, thiotepa degrades rapidly by opening cycles (P–N cleavage) to give the aziridinium ion, polymerising to an insoluble product.[198] In the case of mitomycin C, substitution of an amine group in the 7-position by a hydroxyl group (basic conditions), or loss of a methoxy group and opening of the aziridine ring (acid conditions), can occur.[199] Therefore, pharmaceutical formulations containing ethylene imine molecules are dry forms to be reconstituted and diluted before patient administration.

Due to their low stability in solution, different methods for both thiotepa and mitomycin C were used in degradation studies[140,200] or in stability studies of pharmaceutical formulations.[201–204,205] These methods were mainly based on LC-UV. Since thiotepa metabolism is still uncertain, LC-MS methods were also developed more recently for the identification of potential metabolites.[171,206,207] de Jonge *et al.* have developed an LC-MS method for the determination of thiotepa, cyclophosphosphamide and their main metabolites in plasma, and a LOQ of 5 ng mL^{-1} was achieved for thiotepa.[171] An LOQ of 25 ng mL^{-1} was obtained for the determination of thiotepa in urine by GC-NPD following LLE as the sample preparation step.[207] For mitomycin C, analyses are based on the use of LC-UV and LC-MS and allow the detection of the molecule in biological[208–212] and environmental matrices.[29,213–215] Similar sensitivities are usually obtained for mitomycin (LOD in the order of ng mL^{-1}) with each technique. However, given the high sensitivity and selectivity of MS, it is possible to make the sample preparation step quicker prior to LC analysis, for example a simple dilution of the sample can be included.[210]

2.2.1.4. Nitrosoureas. Nitrosourea compounds have the characteristic of giving, under basic conditions, the diazohydroxide moiety, which generates a highly reactive cation, responsible for the alkylating activity of this subfamily of antineoplastic drugs. The first compound (*N*-methyl-*N*′-nitro-*N*-nitrosoguanidine or MNNG) was developed in the '50s.[216] Studies carried out on MNNG allowed the development of new molecules such as:

- MNU (*N*-methyl-*N*-nitrosourea), in the early '60s, which demonstrated good permeability of the blood–brain barrier (treatment of brain tumors);
- BCNU (carmustine), in the late '60s;
- CCNU (lomustine) in the '70s.[216]

The main applications of these molecules are for the treatment of cerebral tumors and melanomas.

Given their relative lipophilic character (log *P* values between 1.5 and 2.5), nitrosourea compounds, in particular carmustine, are interesting for permeability studies on protective gloves[217–219] and for studies dealing with the interaction of substances with the usual containers of pharmaceutical formulations.[220,221] Reported methods are based on the use of spectrophotometry[218] and LC-UV.[217,219–221] Wallemacq *et al.* obtained an LOD of 59 ng mL^{-1} for carmustine in water using LC-UV.[219] Similar sensitivities were obtained with LC-UV methods for the determination of lomustine[222,223] in plasma.

2.2.1.5 Alkylsulfonates. Discovered in the '50s, busulfan is the only compound in this subfamily of alkylating agents.[224] Originally orally administered for the treatment of chronic myeloid leukemia, busulfan was also injected as part of the conditioning regimens for patients undergoing bone marrow transplants at the end of the 20th century. Busulfan is characterized by very low solubility and stability in water, pharmaceutical formulations contain solubilising agents (dimethylacetamide and polyethylene glycol 400) to limit rapid busulfan hydrolysis into tetrahydrofuran and methanesulfonic acid.[225]

Numerous methods have been developed for the analysis of busulfan in blood matrices. Indeed, due to wide inter-patient variation in the pharmacokinetics and the narrow therapeutic range of busulfan, it was essential to introduce pharmacological therapeutic monitoring during treatment with this antineoplastic drug. For this purpose, different analytical techniques were applied. GC coupled to MS,[226–230] or to an electron capture detector (ECD)[231,232] were published for the analysis of busulfan in blood, with an LOQ between 10 and 150 ng mL^{-1}. However, these methods require an additional derivatisation step prior to separation because busulfan is a non volatile and thermolabile compound. LC-UV is not an interesting approach for the determination of busulfan because it does not contain any chromophoric groups. This explains why all reported LC-UV methods also included a derivatisation step, often inspired by those used in GC with similar sensitivities.[28,233–237] An LC-UV method with a derivation step using diethylthiocarbamate provided a successful study of busulfan stability in injectable solutions contained in different medical devices in the concentration range 0.05–0.5 mg mL^{-1}.[238] A similar strategy was applied to the analysis of this compound in plasma by LC-FD with a LOD and LOQ of 9 ng mL^{-1} and 20 ng mL^{-1}, respectively.[239] The derivatisation step became redundant with LC-MS.[178,240–247,248,183] Busulfan concentrations of 0.2 ng mL^{-1} were quantified by a LC-MS, including PP sample preparation and only 100 μL plasma sample.[248]

To analyse busulfan in complex biological matrices, the use of several sample preparation techniques have been reported: LLE,[243,246] SPE on 96-well plates format[178] and in-line[241], as well as PP.[242,244,245,248,183] Recently, busulfan determination was also achieved by LC-MS in whole blood, using dried blood spots followed by methanol desorption[240] with an LOQ of 50 ng mL^{-1}. Danso *et al.* have developed a very fast SPE method coupled to MS for the analysis of busulfan in plasma with an LOQ of 25 ng mL^{-1}.[249] Selectivity was provided by the sample preparation (PP step prior to the SPE) and by the use of a triple quadrupole mass spectrometer.

2.2.1.6 Triazenes and hydrazines. Triazene compounds are characterised by the presence of 3 adjacent nitrogen atoms and are activated by hepatic cytochromes *via* the formation of a methyldiazonium ion (responsible for alkylating action). The two representative compounds of this subfamily are dacarbazine and temozolomide. Discovered in the '70s, dacarbazine is mainly used in the treatment of melanoma and Hodgkin's lymphoma in an injectable form. The development of temozolomide was more recent (late '80s, early '90s). Given its good stability under acidic conditions, possible oral administration, large distribution in the central nervous system and antitumor activity, temozolomide constitutes the treatment of choice for brain tumors (multiform glioblastomas).

Procarbazine is a hydrazine compound (two adjacent nitrogen atoms) developed first as a monoamine oxydase inhibitor in the '60s. In oncology, it is used for the treatment of Hodgkin's lymphoma. Its activation is also achieved by cytochrome enzymes, leading to the formation of diazonium ions.

LC-UV was mainly used for the determination of dacarbazine[250–252] and temozolomide[253–255] in stability/degradation studies. Few methods based on LC-UV[256–261] and LC-MS[262–266] were reported for the analysis of triazene compounds and procardazine in biological matrices. An LOQ of 0.5 ng mL^{-1} was achieved for the analysis of dacarbazine[266] and procarbazine[265] in plasma samples by LC-MS. Lower sensitivity (LOQ of 50 ng mL^{-1}) was reached with LC-MS for the temozolomide assay in plasma.[264]

A micellar electrokinetic chromatography (MEKC) method has also been reported for the determination of temozolomide and its degradation products in water and serum.[267] The choice of the MEKC method was based on: (i) the absence of charge on temozolomide in neutral and acidic conditions; and (ii) its low stability in solution.

2.2.1.7. Platine derivatives. All the compounds belonging to this subfamily of antineoplastic drugs contain a platinum atom in the oxidation state II, the nature of ligands reflects the history of their development.

Even if the first compound of this subfamily, cisplatin, was synthesised initially in 1844, its anticancer activity was accidentally discovered only in the '60s.[268] Its high toxicity (and

more particularly its nephrotoxicity) and various resistance phenomena led to the development of new molecules. The applied strategy focused on a reduction of toxicity by increasing water solubility and stability. In this perspective, the chlorine atoms were substituted by carboxylate chelating groups. Among all the molecules synthesised and evaluated, carboplatin (developed at the end of the '80s) was particularly interesting, due to its wider therapeutic index and reduced toxicity. The bidentate cyclobutanedicarboxylate ligand gives carboplatin greater stability than the chloride ligands. However, this second generation of compounds suffers, under chlorine-rich conditions, from a substitution of the carboxylate group by chlorine, leading to the formation of cisplatin. Therefore, manipulations of carboplatin should be avoided with solutions containing chlorine, to limit toxicity. In addition, because carboplatin has a close structure to cisplatin, it is also inactive against cisplatin-resistant tumors. Consequently, there was a need to develop a new molecule without these problems of resistance. Thus, the third generation of platinum derivatives appeared in the late '90s, with a 1,2-diaminocyclohexane group, whose anticancer activity against tumors resistant to cisplatin and carboplatin, has been demonstrated. Due to the presence of two bidentate ligands, oxaliplatin was the most stable platinum derivative. However, it can be noted that chloride ions are not recommended in the presence of oxaliplatin to avoid any substitution of the ligands by chlorine atoms, leading to highly reactive products (formation of mono or dichloro platinum complexes). Today, cisplatin is still prescribed in the treatment of solid tumors such as neuroblastomas, while carboplatin is mainly used in the treatment of ovarian cancers. Oxaliplatin is mainly used in the treatment of colorectal cancers.

Different analytical techniques were used for the determination of derivative platinum compounds. Given their low UV-absorbance and high instability, the development of methods for the platinum derivatives assay can be considered as difficult. Few LC-UV methods were reported but all of them suffered from poor sensitivity (limit of quantification (LOQ) in the order of a few μg mL^{-1}).[269–271] The introduction of an additional derivatisation step improved sensitivity (up to a factor of 100) with LC-UV methods.[272,273] Better LOQ's, between 2 and 25 ng mL^{-1}, were reached with LC-MS.[274–278] However, the technique of choice for the detection of platinum derivatives was undoubtedly inductively coupled plasma mass spectrometry (ICP-MS). ICP-MS coupled to a separation technique,[279–284,285] or not,[21,286,287] is characterised by an excellent LOQ, in the range 0.1 to 1 μg mL^{-1}. A chromatogram obtained for the analysis of platinum compounds by LC-ICP-MS is reported in Fig. 6.[280] Without separation prior to ICP-MS, the quantification of total platinum was performed. On the other hand, absorptive voltammetry was also successfully applied for the quantification of total platinum with an LOD in the order of pg mL^{-1} in biological matrices. However, similar to oxazophosphorine compounds, platin derivative agents belong to the most administered antineoplastic drugs (often in high concentrations too) and are often used as markers in exposure studies. Hence, all of these techniques are used even if absorptive voltammetry methods offer better sensitivity. This is because this analytical technique requires a sample degradation step *via* photolysis digestion.[113,288–290]

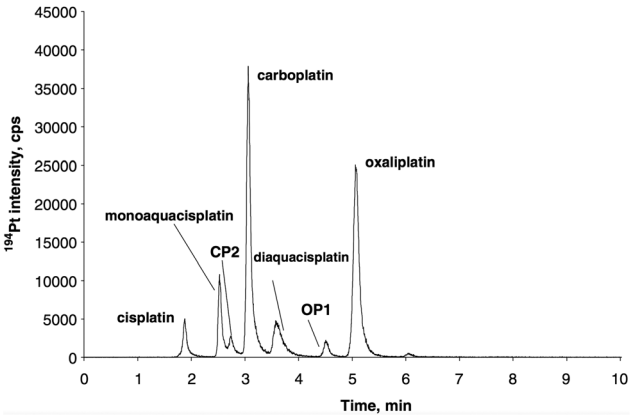


Fig. 6 Chromatogram obtained for the analysis of platinum compounds and degradation products of cisplatin (monoaquacisplatin, diaquacisplatin), carboplatin (CP2) and oxaliplatin (OP1) in water by LC-ICP-MS. Adapted from ref. 280 by permission of Springer, 2005.

For the separation step, different chromatographic supports were used, including reversed phase columns,[269,270,277,281,278] ion exchange columns,[275] HILIC support[285] or cellulose based columns for the enantiomer resolution of oxaliplatin.[291] CE was also reported as a promising technique for the separation of platinum derivatives.[292–294] MEKC methods with UV detection allowed a baseline resolution between cisplatin, carboplatin and oxaliplatin.[295–297] Detection limits in the order of 0.6 μg mL^{-1} were reported for cisplatin in serum after a sample preparation step based on ultrafiltration.[295] Microemulsion electrokinetic chromatography (MEEKC) methods coupled to UV detection were also developed in the context of fundamental studies.[298,299] An MEEKC method coupled to ICP-MS detection was reported for the characterisation of oxaliplatin and other platinum derivatives in drug development.[279] Due to the signal suppression effects of surfactants employed in MEEKC, the sensitivity was only improved by a factor of 1.5 compared to UV detection, to the detriment of the separation (peak broadening due to the interfacing and detector carry-over). More conventional CE methods were also developed in interaction studies (between platinum compounds and blood proteins)[300] and for the analysis of platinum derivatives and nucleoside adducts.[301–304] Under these conditions, the molecule to be analysed was a charged macromolecule.

2.2.2. Intercalating agents. Intercalating agents are planar polycyclic molecules that can be incorporated between contiguous base pairs of DNA. DNA replication and transcription are then inhibited. Direct action on topoisomerase II and I, or formation of free radicals are the two proposed modes of action of these intercalating agents. The structures of the main

intercalating agents and the analytical methods used for their analysis are reported in Fig. 7 and Table 3, respectively.

2.2.2.1 Anthracyclines. Anthracyclines are natural antibiotic molecules derived from pigments produced by *Streptomyces peucetius*.[311,312] They have a common structure composed of an anthracyclinone entity (responsible for their red coloration) and aminoglucoside. The first molecules of this subfamily were discovered in the early '60s and were called daunorubicin and doxorubicin. A slight difference in structure (C9 chain terminated with a primary alcohol for doxorubicin and methyl for daunorubin) resulted in significant changes in the activity spectra of these two molecules. Doxorubicin is used for the treatment of lymphomas, breast, stomach, ovarian and bladder cancers, while daunorubicin is indicated for the treatment of chronic lymphocytic leukemia. Both molecules exhibit high cardiotoxicity. Therefore, the following developments of new anthracyclines focused on molecules with lower side effects. Epirubicin, a semi-synthetic derivative of doxorubicin (an epimer in the hydroxyl group at the carbon in 4-position of aminoglycoside) appeared in the '80s. Although epirubicin has approximately the same indications as doxorubicin, differences in metabolism and pharmacokinetics of the molecule are observed, including an increase in distribution volume, 4-*O*-glucuronidation, an increase of clearance and a decrease of half-life. Thus, high doses of epirubicin can be administered without an increase in cardiotoxicity. At the same time, a semi-synthetic analog of daunorubicin, namely idarubicin, also appeared on the market. Compared to daunorubicin, idarubicin lost the C4 methoxy group, conferring greater lipophilicity. Idarubicin exhibits a wider spectrum of activity and lower cardiotoxicity. Treatment can be orally administered and its main indications are breast cancer and some types of leukemia. Anthracyclines are characterized by stability in solution within a very narrow pH range (between pH 5–7). Indeed under acid pH conditions, the molecules precipitate whereas at basic pH, they degrade rapidly. Liposomal injection solutions of doxorubicin and daunorubicin have been developed to reduce their cardiotoxicity by limiting their distribution to the heart.

Numerous LC and CE methods have been published for the analysis of anthracyclines in the last three decades. For most LC methods, reversed phase chromatographic supports were used. LC-UV methods were applied for the determination of anthracyclines in solution[67,313–317,74] or in biological matrices.[67,318,319] Given the high cardiotoxicity of anthracyclines (due to the accumulation of the drug in myocardium), drug monitoring of patients is generally required. The sensitivity of the developed method was of the utmost importance. For example, an LOD of 5 ng mL^{-1} and LOQ of 30 ng mL^{-1} were obtained for the determination of doxorubicin in different tissues by SPE-LC-UV.[319] Fluorescence spectrophotometry was found to be particularly well suited to the detection of anthracyclines, due to their anthracyclinone ring. Thus, method sensitivity was drastically improved.[320–330] LOD of 0.3–0.75 ng ml^{-1} and LOQ of 1–2.5 ng mL^{-1} were reached for the analysis of doxorubicin, epirubicin, daunorubicin and idarubicin in plasma and saliva (LLE was employed as a sample preparation step prior to LC-FD analysis).[323] The use of MS as a detection system offered even better sensitivity.[172,173,179,331–336,337,338] Indeed, an LOD and LOQ

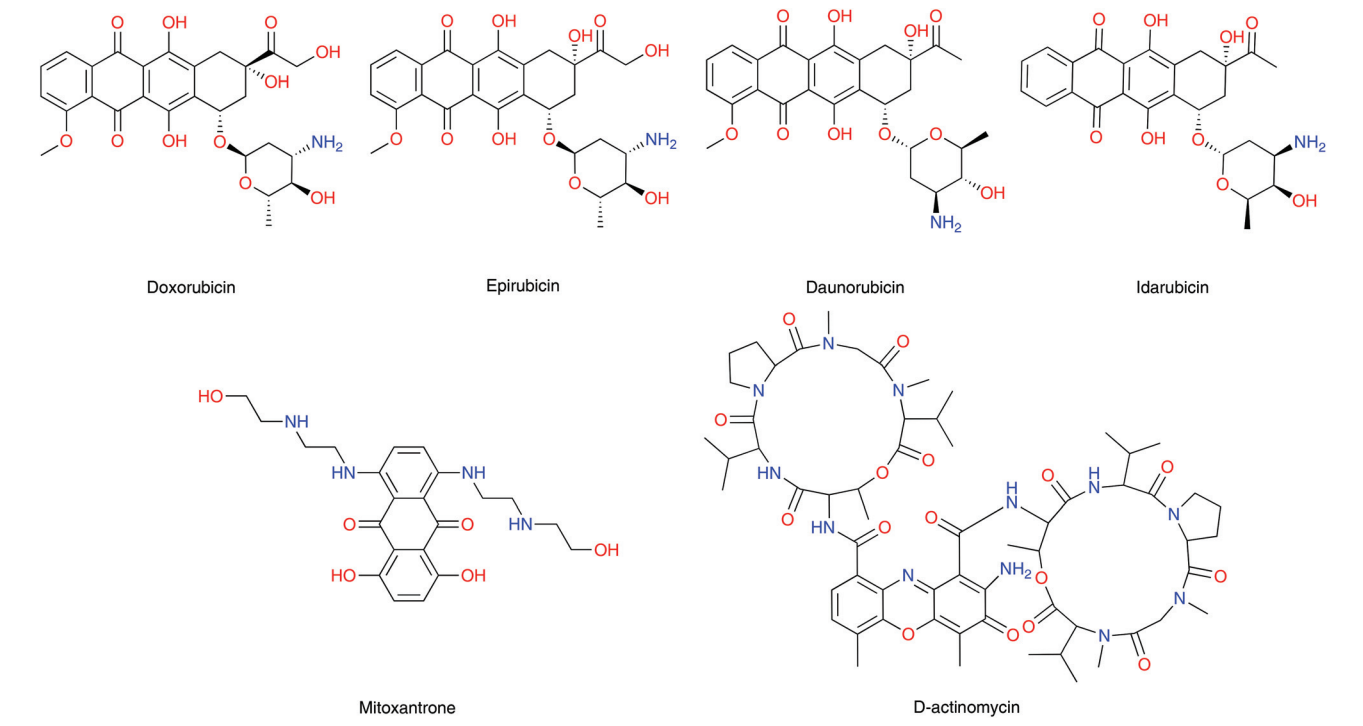


Fig. 7 Structures of intercalating agents.

Table 3 Analytical methods for the detection of intercalating agents

Intercalating agents	Matrices	Techniques	Ref.
Doxorubicin	Molecule/ formulations	LC-UV	313, 314, 67 315 316 and 74
	Biological matrices	LC-UV	67, 318 and 319
		LC-FD	320, 322, 323, 324 325, 326, 327, 328, 329 and 330
		LC-MS	331, 172, 173, 333, 179, 335, 337, 338 and 34
		LC-LIF	339
		CE-LIF	341, 342, 343, 344, 345, 346, 347 and 349
		CE-UV	350 and 363
	Environment	LC-UV	138
		LC-MS	29, 78, 19, 22, 135 and 307
Epirubicin	Molecule/ formulations	LC-UV	313, 317 and 74
	Biological matrices	LC-UV	318
		LC-FD	321, 323, 324 and 325
		LC-MS	334, 179, 335 and 34
		CE-LIF	344, 345, 347 and 349
	Environment	LC-MS	19 and 307
Daunorubicin	Molecule/ formulations	LC-UV	313, 314 and 74
		LC-FD	323 and 324
		LC-ELSD	340
	Biological matrices	LC-UV	318
		LC-FD	364
		LC-MS	179, 335 and 336
		CE-LIF	345, 346, 347, 348 and 349
		CE-UV	350 and 363
Idarubicin	Molecule/ formulations	LC-UV	313 and 137
	Biological matrices	LC-FD	323 and 324
		LC-MS	335
		CE-LIF	345 and 346
Mitoxanthrone	Biological matrices	LC-UV	354 and 355
		LC-MS	361
Actinomycin D	Biological matrices	LC-MS	356–358 and 360

lower than 0.01 ng mL^{-1} and 0.1 ng mL^{-1} were obtained, respectively, for the LC-MS analysis of anthracyclines in urine treated by SPE.[335] LC-LIF-MS was also developed for studying *in vitro* metabolism of doxorubicin: quantification was performed on the results obtained with LIF detection (LOD ~ 1 μg mL^{-1}) and metabolites identification was performed with MS detection.[339] LC-ELSD was also applied for the analysis of daunorubicin and its degradation products for a stability study of injectable solution of anthracycline (0.25 mg mL^{-1} was the lowest concentration of standard solutions tested), but the interest of ELSD for anthracyclines is not obvious since these molecules can be easily detected by UV, FD and MS.[340]

As already mentioned, CE was another separation technique widely used for the determination of anthracyclines. LIF detection[341–349] is usually preferred to UV detection[350] to improve sensitivity. However, the poor UV sensitivity observed in CE (due to the narrow optical path of the capillaries) can be compensated for by a sweeping preconcentration step and an electrokinetic injection. Under such conditions, an LOD of 0.5 μg mL^{-1} was reached for anthracyclines in plasma.[350] LIF detection coupled to conventional CE[343,346,347,349] or MEKC methods[342,344,345] offered better sensitivities (LOD inferior to 1 ng mL^{-1}) without the need for a preconcentration step and using the hydrodynamic injection. The addition of a chiral modifier (hydroxy-propyl-γ-cyclodextrine) to the BGE used in CE provided a resolution baseline between doxorubicin and its metabolite doxorubicinol (slight structural difference: OH group instead of a carbonyl group in 13-carbon), responsible for the cardiotoxicity.[342] Finally, it can be noted that in the majority of the developed CE methods, an organic solvent was added in the BGE to improve the solubility and stability of the anthracyclines and reduce their adsorption on the capillary walls.[351] An electropherogram obtained for the analysis of three anthracycline compounds by CE-LIF and demonstrating the influence of organic solvent in the BGE on the separation efficiency is illustrated in Fig. 8.[349]

2.2.2.2 Mitoxantrone and actinomycin D. Mitoxanthrone and actinomycin D are molecules with a planar tricyclic structure (like anthracyclines). Discovered in the late '80s, mitoxantrone originated from an American program on the development of intercalating molecules.[352] Actinomycin D (or dactinomycin) is a peptide antibiotic isolated from strains of *Streptomyces parvullus* in the early '50s.[353] Mitoxantrone is available as a concentrated acid-buffered solution (because of hydrolysis in a basic medium) and is mainly used for the treatment of prostate cancers. Formulations containing actinomycin D are indicated for the treatment of nephroblastomas, neuroblastomas in children and testicular cancers.

LC was generally used for the determination of mitoxanthrone and actinomycin D. Developed methods were based on C18 stationary phase, coupled to UV[354,355] and MS detection.[356–361] An LOQ of 5 ng mL^{-1} was obtained for the LC-UV analysis of mitoxantrone in plasma.[354,355] For the same compound, a ten-fold increase in sensitivity was observed in LC-MS.[361] Due to the concomitant administration of vincristine and actinomycin D in the treatment of various pediatric cancers, several LC-MS methods have been developed for the simultaneous determination of these two anticancer drugs in biological matrices.[356–359] An LOD of 0.007 ng mL^{-1} and LOQ of 0.05 ng mL^{-1} were reached for the analysis of actinomycin D in plasma using a SPE-LC-MS procedure.[358] A CE method coupled to chemiluminescence detection was also reported for the determination of mitoxantrone in injectable solutions and biological samples.[362]

2.2.3. Topoisomerase inhibitors. Toposiomerases are enzymes responsible for the cleavage, annealing and topological state of DNA. Two categories of topoisomerases can be distinguished: topoisomerase I and topoisomerase II. Topoisomerase I acts on one strand of the DNA, while topoisomerase II acts on both strands of the DNA. Inhibitors of these enzymes are used primarily as anticancer agents (but also as antibacterial and antiparasitic agents). The structures

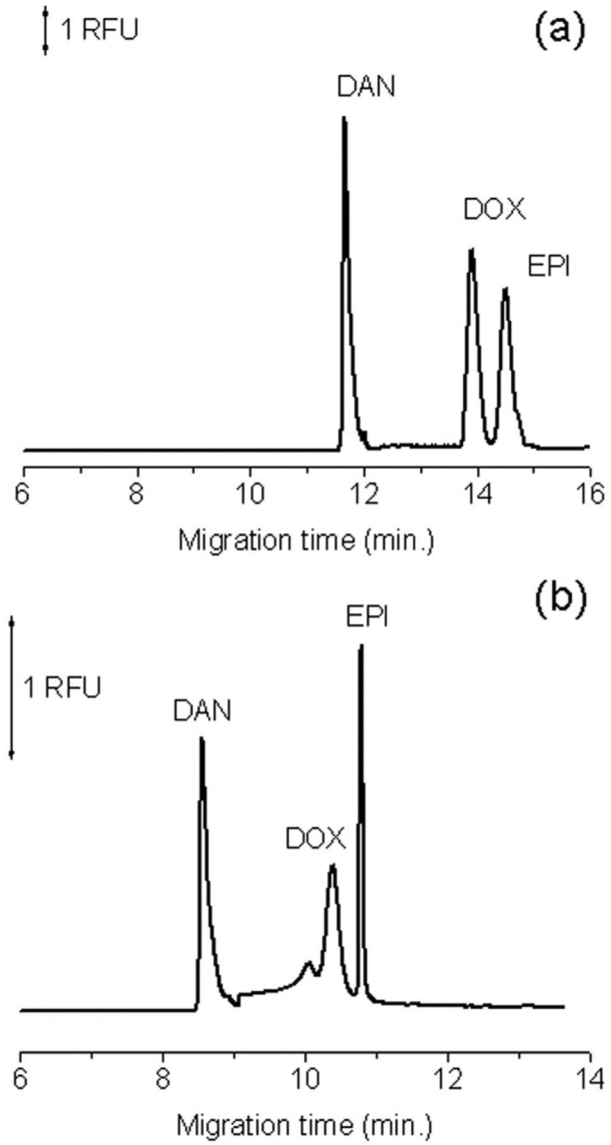


Fig. 8 Electropherograms of daunorubicine (DAN), doxorubicine (DOX) and epirubicine (EPI) obtained by CE-LIF analysis with BGE (105 mM borate pH 9.0) containing 30% methanol (a), and 10% methanol (b). Adapted from ref. 349, 2008, with permission from Wiley.

of the main topoisomerase inhibitors are depicted in Fig. 9. Analytical methods for the analysis of topoisomerase inhibitors are reported in Table 4.

2.2.3.1. Topoisomerase I inhibitors. Topoisomerase I inhibitors are derived from camptothecin first isolated in the '60s from the bark of an Asian tree named *Camptotheca acuminata*. Despite its anticancer activity, camptothecin was rapidly abandoned due to the high toxicity (hemorrhagic cystitis) of the soluble sodium salt. It appeared that the lactone ring of camptothecin is responsible for its anticancer activity. The fact that this cycle opened up in the preparation of sodium salts and could be reformed in the acid environment of the bladder, explained the toxicity of this molecule.[365] The interest in this molecule reappeared in the '80s with the discovery of camptothecin action on topoisomerase I. Thus, camptothecin served

Table 4 Analytical methods for the detection of topoisomerase inhibitors

Topoisomerase inhibitors	Matrices	Techniques	Ref.
Irinotecan	Biological matrices	LC-FD	371, 374, 372, 376, 377, 378 and 380
		LC-MS	370, 375, 373, 381, 375, 385, 387, 388, 389, 390 and 136
		CE-UV-LIF	391
	Environment	LC-MS	19, 135 and 307
Topotecan	Molecule/ formulations	LC-UV	382
	Biological matrices	LC-FD	379, 383 and 384
		LC-MS	386
Etoposide	Molecule/ formulations	LC-UV	67, 393, 394 and 137
		LC-FD	364
	Biological matrices	LC-UV	67
		LC-MS	395, 396, 136 and 34
		CE-LIF	397
		CE-UV	38
	Environment	LC-MS	19, 22, 134 and 135

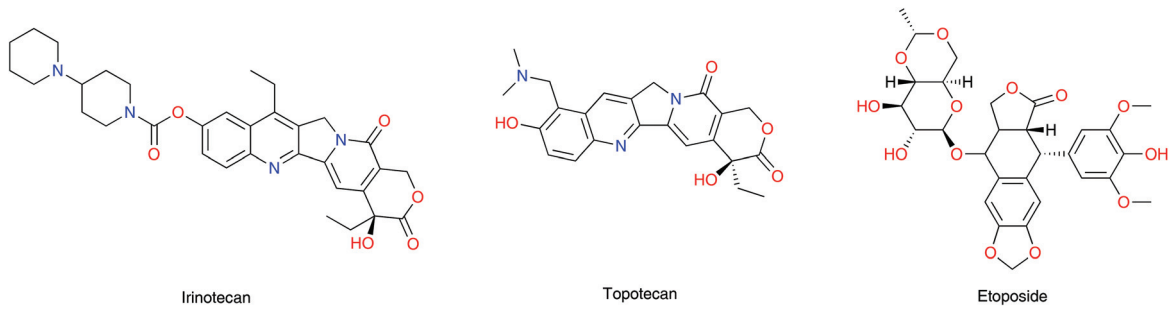


Fig. 9 Structures of topoisomerase inhibitors.

as a model for the development of various water-soluble semi-synthetic compounds, by retaining a lactone ring in which the two main representative compounds were irinotecan and topotecan. Discovered in the '90s, irinotecan is indicated in colorectal cancers and topotecan in certain cancers of the ovary, cervix and lung. Irinotecan is a prodrug that is activated by liver carboxylesterases (active form SN-38: loss of the bipiperidylcarbonyl chain). Both molecules are stable at acid pH (if pH > 4: opening of the lactone ring leads to an inactive carboxylate form).

The methods developed for the analysis of camptothecins are essentially based on LC.[366–369] When developing an analytical method for the determination of camptothecins in biological matrices, several features have to be taken into account. First of all, it should be noted that the lactone and carboxylate forms of camptothecins coexist under biological conditions (equilibrium depending on pH and temperature). In other words, the method must allow the analysis of the desired form (s) (active lactone, inactive or total carboxylate). Then, the lactone (lipophilic) forms are able to diffuse through the cell membranes (and more particularly through the red blood cells) even within the sample. Moreover, the carboxylesterases present in the biological matrices contribute to the conversion of irinotecan into SN-38 within the sample as well. Thus, inactivation of carboxylesterases (in the case of irinotecan) and rapid extraction of the camptothecins contained in biological matrices (and in particular blood fluids) must be carried out rapidly after collection.

LC methods reported the analysis of the lactone form only,[344–346] lactone and carboxylate forms separately[347–351] and all the forms together with an equilibrium shift to the lactone form in acidic conditions. Usually, separations were performed on reversed phase supports. Several studies have succeeded in resolving the lactone forms and carboxylate forms by ion-pair chromatography to increase retention of the carboxylate forms.[377–380] In the case of irinotecan analysis, carboxylesterase inactivation was accomplished by the immediate addition of sodium dodecyl sulfate (SDS)[372] or zinc sulfate[373] to the sample.

Detection using, UV,[382] FD[371,372,377,379,380,383,384] and MS[370,373,375,381,385–390] were the most widespread. LC-UV methods were developed for the analysis of topotecan in pharmaceutical formulations and in blood samples with an LOQ of 0.070 μg mL^{-1}.[382] More sensitive detectors, such as FD or MS, allowed an LOQ in the order of 1 ng mL^{-1} to be reached for camptothecines in biological matrices. Finally, a quantification of SN-38 in plasma concentrations of 50 pg mL^{-1} was achieved thanks to a microfluidic chip-based nano-LC-MS method.[385]

A CE-UV-LIF method including solid-supported liquid extraction (SLE) was developed to quantify irinotecan and SN-38 in urine samples with an LOQ in the order of 30 ng mL^{-1} for both analytes.[391]

2.2.3.2. Topoisomerase II inhibitors. Two antineoplastic drugs act on topoisomerase II: anthracyclines (considered in this paper for their intercalating action) and podophyllotoxins.

Podophyllotoxins extracted from the plant roots of the *podophyllum* family are considered to be highly toxic molecules, even though they were used as medicinal remedies centuries ago thanks to their antimitotic action. In the '50s, a series of podophyllotoxin derivatives were synthesized and studied in the hope of finding a molecule that retained its anticancer action, but with less toxicity.[392] These studies led to etoposide in 1966. Its low solubility in water required the presence of numerous excipients in injectable formulations such as sorbate 80, polyethylene glycol 300 solubilizing agents and buffering agents such as citric acid (to avoid the *cis*-lactone epimerization of molecules occurring in basic conditions). However, precipitation of the molecule can be observed during dilution of the formulation and rapid administration of etoposide is hampered by the high volumes injected to cover the prescribed dose. The etoposide phosphate appeared in the '90s to overcome the solubility problem of the original molecule. This prodrug is rapidly converted in the blood to etoposide, by alkaline phosphatases.

Etoposide was mainly analysed by LC-UV,[67,393,394] LC-FD[364] and LC-MS.[58,395,396,34] UV sensitivity was sufficient to achieve etoposide analysis in pharmaceutical formulations.[393,394] However, more sensitive detectors such as FD (LOQ of 52.5 ng mL^{-1}) and MS (LOQ between 2 and 10 ng mL^{-1}) were required for etoposide assays in plasma samples. CE allowed the determination of etoposide in plasma with an LOQ of 0.1–0.2 μg mL^{-1}, using either a UV zeta-cell[38] or LIF detector.[397]

2.3. Antitubulin agents

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 vinca alkaloids and taxanes.

2.3.1. Vinca alkaloids. The antineoplastic properties of Madagascar periwinkle alkaloids (*Catharanthus roseus*) were discovered during research on its use as an antidiabetic by Malagasy people. The first anticancer alkaloids extracted from the leaves of the plant were vinblastine in 1958 and vincristine three years later. These two molecules consist of a catharanthine nucleus and a vindoline nucleus. The low natural abundance of these compounds (a few ppm in the leaves), the multitude of different alkaloids present in the leaves and their toxicity (neurotoxicity for vincristine and myelosuppression for vinblastine), have encouraged studies on the synthesis of structural analogues. The latter gave rise to two semi-synthetic molecules: vindesine and vinorelbine in the '80s. Recently, a fluorinated derivative also appeared, namely vinflunine, which is a molecule close to vinorelbine, but with two fluorine atoms in 20′-position and a single 3′–4′ bond. The structures of vinca alkaloids are reported in Fig. 10. Today, vinca alkaloids are used in the treatment of leukemias, lymphomas and some solid tumors. Table 5 reports the analytical methods for vinca alcaloids.

The analysis of vinca alkaloids has been carried out on plant extracts,[398–403] pharmaceutical formulations,[316,404] biological samples[358,359,405–420,421] and environmental

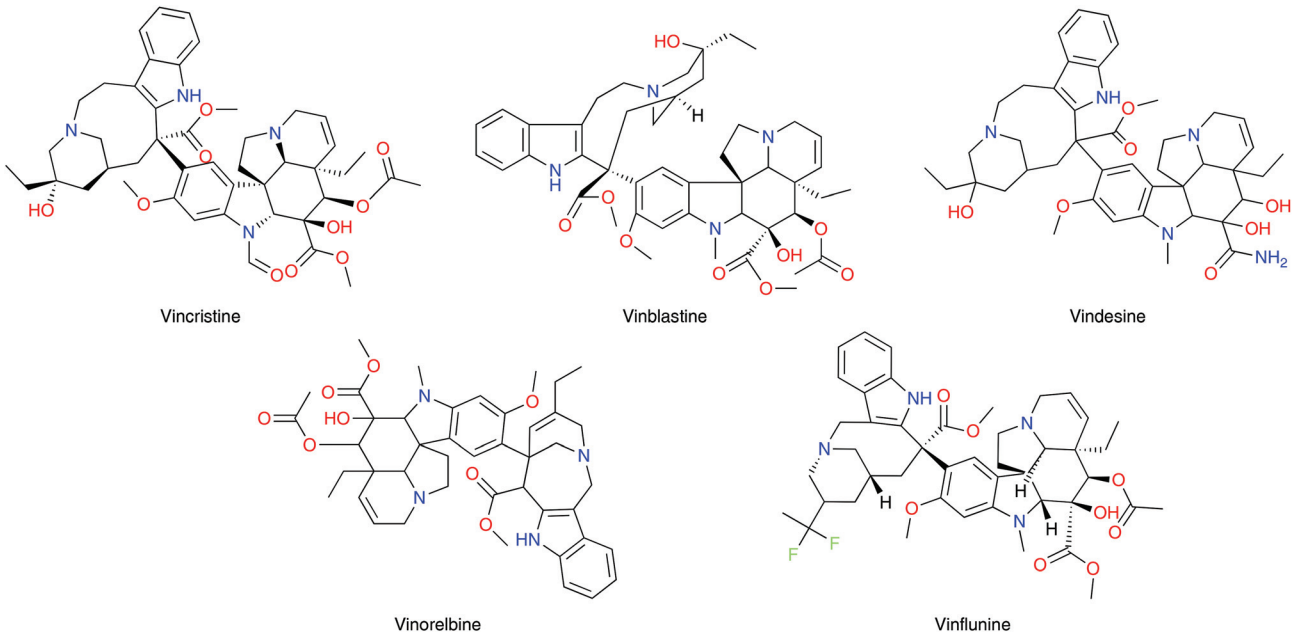


Fig. 10 Structures of vinca alkaloids.

Table 5 Analytical methods for the detection of vinca alcaloids

Vinca alcaloids	Matrices	Techniques	Ref.
Vincristine	Molecule/ formulations	LC-UV	316
		CE-UV	404
	Plant extracts	LC-UV	400, 402 and 403
		LC-MS	401
	Biological matrices	LC-UV	402
		LC-MS	34, 173, 356, 358, 359, 407, 409, 413 and 421
	Environment	LC-MS	19, 22, 28, 134 and 307
Vindesine	Molecule/ formulations	CE-UV	404
	Biological matrices	LC-MS	418
	Environment	LC-MS	307
Vinblastine	Molecule/ formulations	CE-UV	404
	Plant extracts	CE-MS	398
		LC-MS	399 and 401
		LC-UV	400, 402 and 403
	Biological matrices	LC-UV	402
		LC-MS	34, 173, 405, 410 and 411
	Environment	LC-MS	307
Vinorelbine	Molecule/ formulations	CE-UV	404
	Biological matrices	LC-MS	406, 408, 410, 414 and 416
		CE-ECL	423
Vinflunine	Biological matrices	LC-UV	419
		LC-MS	415, 417 and 420

samples.[18,19,134,307,422] Vinca alcaloid extraction from plants was generally performed by ultrasound in acid media followed by LLE.[45,398–401] For the sample preparation of biological samples, SPE,[358,359,405,407,408,411,414,418] LLE[409,410,413,415–417,419,421] and PP[420] were used. Although some methods based on CE have been published, LC was the most widely used separation technique for the analysis of vinca alkaloids.

Most of the LC methods are based on reversed phase C18 supports. Nevertheless, cyano,[419,420] pentafluorophenylpropyl[405] or HILIC[418] columns also allowed vinca alkaloids separation and quantification, with good analytical performance in terms of efficiency and reproducibility.

Detection of the molecules separated by LC was achieved by UV[316,400,402,419,403] or MS.[18,19,134,307,358,359,399,401,405,407–411,413–418,420,422] Acidic conditions were usually applied due to the good stability of vinca alkaloids at these pH values. Thus, MS detection was performed on the $[M + H]^+$ molecular ion or the doubly-charged $[M + 2H]^{2+}$ ion. The LOQ ranged from 1 ng mL^{-1} (or slightly lower) by MS to a few μg mL^{-1} by UV.

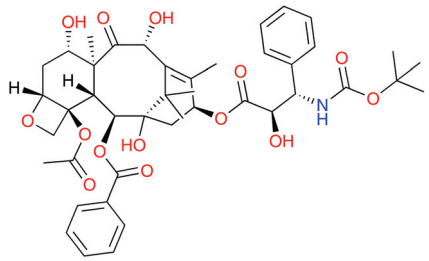
CE methods are scarcely reported for the determination of vinca alkaloids. A CE-UV method in non-aqueous conditions (NACE) allowed the separation of ten different vinca alkaloids in less than 10 min.[404] Extracts from *Catharanthus roseus* containing vinblastine were also successfully analysed by CE-MS.[398] Finally, the analysis of vinorelbine in urine samples was achieved by CE coupled to an electrochemiluminescence detection (ECL) with LOD in the order of 7 ng mL^{-1}.[423]

2.3.2. Taxanes. A compound extracted from the bark of *Taxus Brevifolia* demonstrated anticancer activity in the '60s, namely taxol or paclitaxel.[424] However, it appeared that the first clinical trials conducted on taxol raised toxicity problems linked to the formulation and not to the active molecule. Since taxol is a molecule poorly soluble in water and therapeutically

active at high concentrations, the presence of solubilizing agents is essential in the pharmaceutical formulation. The developed formulation contained a mixture of polyoxyethylated triglycerides (which are toxic and allergenic). In addition, more than 2500 trees needed to be felled to harvest 1 kg of taxol. A solution was introduced in the '80s by Pierre Potier (also author of the discovery of vinorelbine) with the hemi-synthesis of paclitaxel from a precursor (non-cytotoxic) available from a renewable source (*Taxus baccata* needles).[425] This route also gave rise to another taxane with anticancer properties, docetaxel. Slightly soluble in water, docetaxel injectable formulations contain ethanol and polysorbate 80 (a less toxic excipient). The main indication of docetaxel is the treatment of breast and lung cancer. Paclitaxel is also used in ovarian cancer. The structures of the taxanes and their analytical methods are shown in Fig. 11 and Table 6, respectively.

Most methods for taxanes analysis are based on RPLC coupled to MS[305,309,426–442] and UV detection.[138,269,443–453] LODs lower than 0.05 ng mL^{-1} were reached for the analysis of docetaxel in blood using a column-switching method involving a preconcentration step on a trapping column, prior to LC-MS analysis.[435] Paclitaxel in plasma was quantified down to a concentration of 45 ng mL^{-1} using an LLE-LC-UV procedure.[447] Several column-switching methods were proposed to reduce sample handling and/or concentrate paclitaxel[438] or docetaxel[429,434,435,442] as shown in Fig. 12. Given their strong binding to plasma proteins, free or bound fractions of taxanes were evaluated in biological samples. Thus, an ultrafiltration step was included at the start of the whole analytical procedure.[305,436]

CE was also employed for taxanes determination.[363,454] Different CE, MEEKC and MEKC methods coupled to UV



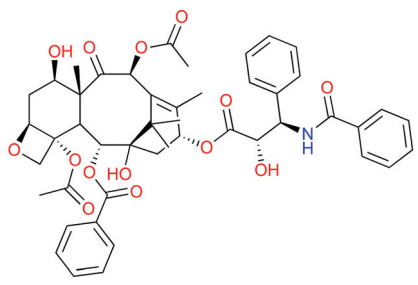


Fig. 11 Structures of taxanes.

Table 6 Analytical methods for the detection of taxanes

Taxanes	Matrices	Techniques	Ref.
Paclitaxel	Molecule/ formulations	LC-UV	269, 443–445, 447–449, 452 and 453
	Biological matrices	LC-UV	446, 447, 451 and 452
		LC-MS	34, 309, 410, 426, 428, 430, 431, 438 and 441
		CE-UV	454
	Environment	LC-UV	138
		LC-MS	28, 134, 135 and 307
Docetaxel	Molecule/ formulations	LC-UV	450
	Biological matrices	LC-MS	305, 410, 427 and 429, 431–437, 439, 440 and 442
		CE-UV	363
	Environment	LC-MS	134 and 307

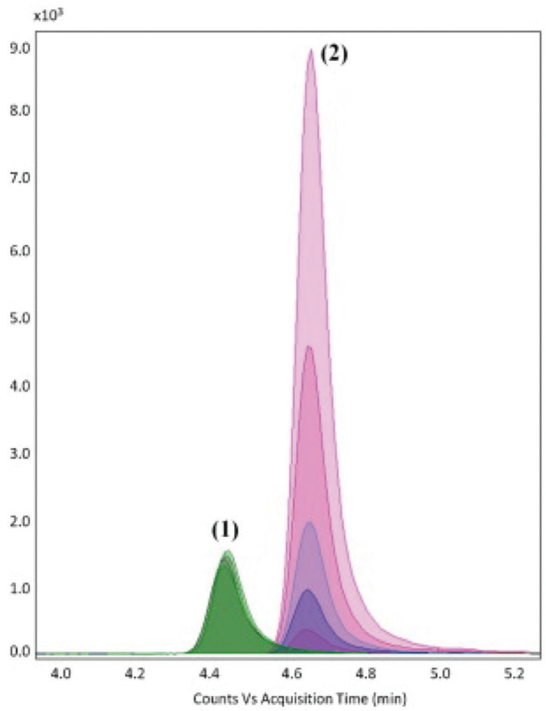


Fig. 12 On-line SPE-LC-MS chromatograms of docetaxel[2] over the concentration range 10–200 μg L^{-1} in plasma with paclitaxel[1] as the internal standard. Adapted from ref. 435, 2013, with permission from Elsevier.

allowed the separation of docetaxel and several anthracyclines in plasma samples.[363] An LOD of 20 ng mL^{-1} was observed for the analysis of placlitaxel in plasma by LLE-MEKC-UV.[454]

3. Small molecules for targeted therapy

Conventional anticancer molecules act without discrimination between normal and tumor cells. This lack of specificity is

responsible for almost all the adverse effects of these anticancer treatments described so far. The apparition of molecules whose action is targeted specifically on tumor cells gave new breath to chemotherapy and new hope in the treatment of certain cancers. These "search-head missiles" are characterized by wider therapeutic indexes and reduced toxicity. Two main classes of molecules constitute targeted therapies: small molecules and monoclonal antibodies. Only small molecules are discussed in this paper.

3.1. Tyrosine kinase inhibitors

Tyrosine kinase inhibitors are low molecular weight compounds whose target is the inhibition of tyrosine kinase enzymes (TK). TK enzymes catalyse the transfer of phosphate to proteins from adenosine triphosphate (ATP) and play a major role in cell regulation such as proliferation, survival, migration and differentiation. TK inhibitors react with membranes (intracellular) or cytoplasmic enzymes, which induce molecule diffusion through the cell membrane. TK inhibitors are used in oncology when targeted TK's are activated by mutations and are responsible for tumor progression.[455]

Imatinib was the first TK inhibitor used as an anticancer agent. Discovered in the '90s, imatinib was derived from drug development efforts to target the bcr-abl protein. It corresponds to 2-phenylaminopyrimidine to which methyl and benzamide groups have been added to improve the interaction with the protein. Imatinib is indicated for the treatment of chronic myeloid leukemia. Two analogues appeared later on the market to tackle the phenomena of resistance and intolerance: dasatinib and nilotinib. Lapatinib and erlotinib, which act on epidermal growth factor receptors (EGFR), were commercialized in the 2000s for the treatment of breast cancer and some lung cancers, respectively. Sunitinib, used in the treatment of gastrointestinal and renal cancers, completes the family of TK inhibitors by targeting vascular endothelial growth factor (VEGFR) receptors. Fig. 13 shows the structures of TK inhibitors.

Different techniques have been used for the determination of TK inhibitors in pharmaceutical formulations, biological and environmental samples (Table 7). LC is the technique of choice as shown in the literature.[456] Indeed, 90% of the published methods are based on LC, while the remaining 10% involve another analytical technique (CE, GC or UV). LC was carried out essentially in the reversed phase mode, although the use of a HILIC column allows the simultaneous determination of imatinib, dasatinib and nilotinib in plasma.[457] An ion pairing LC method also contributed to the improvement of the imatinib peak shape compared to RPLC.[458] It may be noted that sunitinib can exist as two isomers (*cis* and *trans*). Available in the *cis* form in pharmaceutical formulations, sunitinib is converted into a *trans* form in solution under light. Several methods are able to resolve the two isomers using a conventional reversed phase column.[459,460]

Different sample preparations were used to extract TK inhibitors from biological matrices such as PP, LLE and SPE (off-line and on-line). Several methods involving column-switching systems were reported for the purification and concentration of the analytes before analytical separation. For example, Couchman *et al.* developed a method including a large particles support for the extraction of nine TK inhibitors and their metabolites in blood samples before separation on a C18 chromatographic support and MS detection.[461] With a sample volume of 50 μL, an LOQ of 1 ng mL^{-1} was obtained for dasatinib. Using a larger sample volume (100 μL after a PP step), an LOQ of 0.03 ng mL^{-1} was reached for the analysis of imatinib in biological matrices with a column-switching

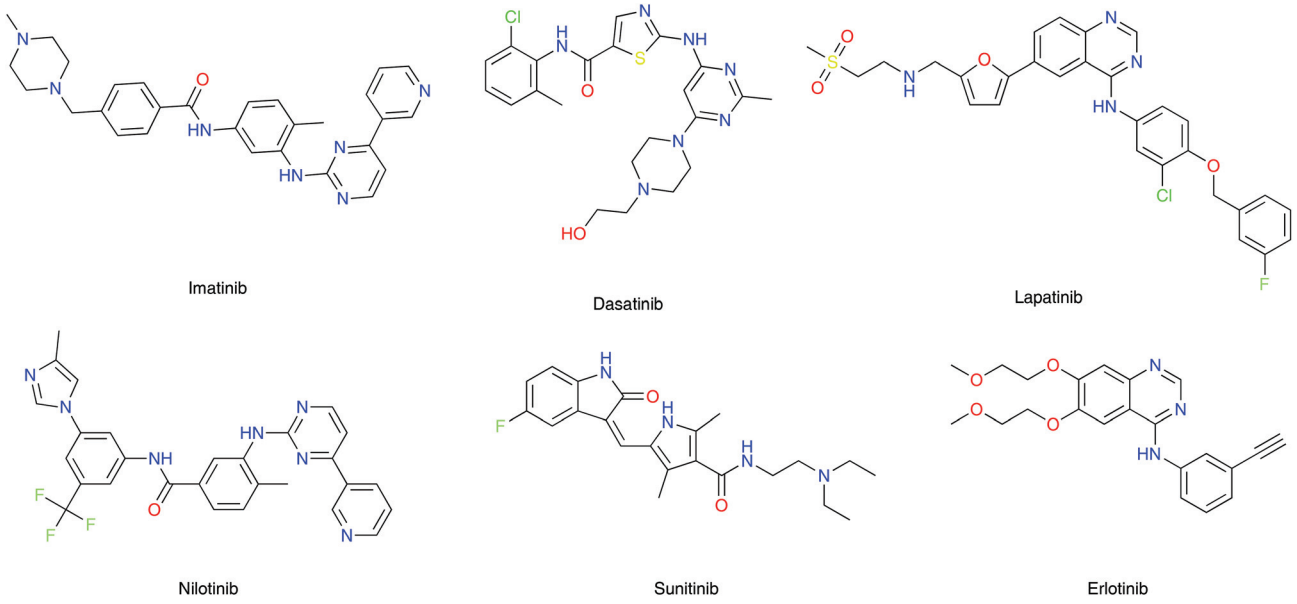


Fig. 13 Structures of tyrosine kinase inhibitors.

Table 7 Analytical methods for the detection of TK inhibitors

TK inhibitors	Matrices	Techniques	Ref.
Imatinib	Molecule/ formulations	LC-UV	466–470
		CE-UV	58 and 471
	Biological matrices	LC-UV	458, 464, 472–485
		LC-MS	457, 461, 462, 472, 486–512
		CE-UV	39, 41 and 513
		CE-MS	514
	Environment	LC-MS	135
Dasatinib	Molecule/ formulations	LC-UV	515
		CE-UV	515
	Biological matrices	LC-UV	479, 474, 441, 516, 517 and 518
		LC-Fluo	465
		LC-MS	457, 461, 486, 491, 493, 494, 497, 500, 507, 510, 519 and 520
Nilotinib	Molecule/ formulations	LC-UV	521
	Biological matrices	LC-UV	463, 475, 479, 522, 523
		LC-MS	457, 461, 486, 491, 493–495, 497, 500, 507, 510, 524 and 525
Lapatinib	Molecule/ formulations	LC-UV	526 and 527
	Biological matrices	LC-UV	464, 528, 529
		LC-MS	461, 486, 491, 493, 495, 497, 500, 510, 520, 530 and 531
Erlotinib	Molecule/ formulations	LC-UV	532
	Biological matrices	LC-UV	464, 516, 533–536 and 529
		LC-MS	461, 486, 491, 492, 495, 500, 510, 537–544, 545, 546 and 547
		CE-UV	548
	Environment	LC-MS	135
Sunitinib	Molecule/ formulations	LC-MS	549
	Biological matrices	LC-UV	464, 550 and 551
		LC-MS	459–461, 486, 491, 495, 497, 500, 507, 510, 537, 552–559
		CE-MS	560

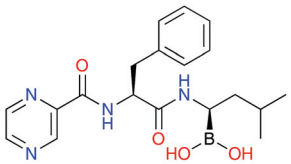
system and LC-MS.[462] A similar approach involving a sample preconcentration step and on-line extraction was applied for the analysis of nilotinib in plasma using UV detection.[463] In this case, an LOQ of 5 ng mL^{-1} was achieved. Garrido-Cano *et al.* developed an LC-UV method using a micellar mobile phase allowing direct injection of filtered plasma for the determination of 4 TK inhibitors.[464] A total analysis time of about 20 min and LOQ of 50 ng mL^{-1} were obtained. Finally, even if most of the TK inhibitors determination was performed with LC-UV and LC-MS, a LC-FD method was also published for the analysis of dasanitib in plasma with sensitivities close to those obtained in LC-UV (*i.e.*, 50 ng mL^{-1}).[465]

CE coupled to UV or MS was also used for the analysis of TK inhibitors. Conventional CE or NACE methods allow the determination of imatinib, erlotinib and sunitinib for drug purity testing or biological samples analysis (Table 1). A CE-UV method involving β-cyclodextrins in the BGE has demonstrated real potential for the quality control of imatinib (drug and impurities).[58] Concentration values of 5–10 ng mL^{-1} were quantified thanks to a stacking injection of large volume sample. Sunitinib and its main metabolites in urine were finally analysed by NACE-MS after a simple one-tenth dilution of the sample at concentrations between 0.5 and 50 μg mL^{-1}.[560]

3.2. Proteasome inhibitor

Synthesized in the '90s, the only representative compound of this anticancer family is bortezomib (Fig. 14). Bortezomib affects the capacity of cancer cells (myeloma cells) to interact with the microenvironment of the bone marrow and thus promotes cell death by its inhibitory action on the proteasome (a proteinaceous complex that degrades proteins). Bortezomib is produced as a trimer of boronic anhydride. The formulations are in the form of lyophilisates (also containing mannitol). Mannitol reacts with boroxine to form a stable monomeric diester which is hydrolysed in the reconstitution step (adding 0.9% NaCl) to bortezomib (active boric acid).[561] Bortezomib is used primarily in the treatment of multiple myelomas. Analytical methods for the analysis of bortezomib are reported in Table 8.

LC remains the main separation technique employed for the analysis of bortezomib in pharmaceutical formulations[562–564] or in biological samples.[486,565,566] A fast LC-MS (less than 2 min) method was developed for the determination of bortezomib within cultured myeloma cells and media. This ultra-fast analysis limits the degradation of bortezomib, which is known to be instable in solution.[565] MS detection was carried out on the dehydrated protonated molecular ion ($[M - H_2O + H]^+$) in positive ESI mode. Shu *et al.* developed an LC-MS method including an off-line SPE step for the quantification of bortezomib and 5 other drugs commonly used in multiple myeloma chemotherapy in biological



Bortezomib

Fig. 14 Bortezomib structure.

Table 8 Analytical methods for the detection proteasome inhibitor

Proteasome inhibitor	Matrices	Techniques	Ref.
Bortezomib	Molecule/ formulations	LC-UV	562, 563 and 564
	Biological matrices	LC-MS	486, 565, 566 and 306

matrices with an LOQ of 2 ng mL^{-1}.[306] Byrn *et al.* propose different methods to compare the contents and impurity profile of two pharmaceutical formulations available on the US market.[563] The presence of an additional impurity as well as a different inactive/active form ratio between the two formulations demonstrated that they were not strictly equivalent.

3.3. mTOR inhibitors

Discovered more than 30 years ago, sirolimus (or rapamycin) is a macrolide produced by *Streptomyces hygroscopicus* and was initially used as an immunosuppressant. It would be necessary to wait until the end of the '90s to witness its use in oncology. Its action is based on an intracellular serine/threonine kinase (mTOR for mammalian target of rapamycin), which is an enzyme involved in several cellular processes such as angiogenesis, metabolic modulation, cell cycle and apoptosis. This protein complex is involved in the tumor progression of certain cancers. In the mid-2000s, a water-soluble sirolimus ester was developed, namely temsirolimus, which is a prodrug whose active form is sirolimus (rapid hydrolysis). A few years later, a second analogue of sirolimus, everolimus, enlarged the family of mTOR inhibitors. Although widely used as immunosuppressants after organ transplantation, mTOR inhibitors can also be used for the treatment of kidney and lymphoma cancers. Fig. 15 shows the structures of the major inhibitors of mTOR and Table 9 lists the reported analytical methods.

Inhibitors of mTOR were mainly analysed in biological matrices even if some methods were published for their determination in solution or in pharmaceutical formulations, as in the case of stability studies or for quality control purposes.[567–570] Their narrow therapeutic window and highly variable blood levels (for the same administered dose) make mTOR inhibitors analysis in whole blood essential (mTOR inhibitors are concentrated in the red blood cells). In recent years, many analytical methods have been reported for the analysis of mTOR inhibitors in biological samples.[571–574,84]

Table 9 Analytical methods for the detection of mTOR inhibitors

mTOR inhibitors	Matrices	Techniques	Ref.
Sirolimus	Molecule/ formulations	LC-UV	567 and 570
	Biological matrices	LC-UV	575, 576, 578, 581, 586, 592, 593, 594, 595, 596 and 597
		LC-MS	577, 580, 582, 584, 585, 598, 599, 602, 603, 605, 606, 607, 609, 617, 618, 619, 600, 601, 604, 608, 610, 620, 621, 624 and 626
		LC-EC	627
		CE-UV	628
		CE-MS	630
Temsirolimus	Molecule/ formulations	LC-UV	569
Everolimus	Molecule/ formulations	LC-UV	568
	Biological matrices	LC-UV	589, 590 and 591
		LC-MS	577, 579, 583, 587, 588, 598, 599, 602, 612, 603, 605, 613, 614, 606, 607, 609, 615, 622, 616, 617, 618, 619, 625 and 626

Two analytical techniques can be discerned: immunoassays and LC. The comparison of these two approaches shows their comparable performances.[575–586,587,588] The main limitation of immunoassays is the cross-reactivity with metabolites. Only separative techniques are considered in this review.

LC-UV is an interesting technique for the analysis of mTOR inhibitors in blood.[575,576,578,581,589–597] Nevertheless, the achieved sensitivity was too limited and an additional extrac-

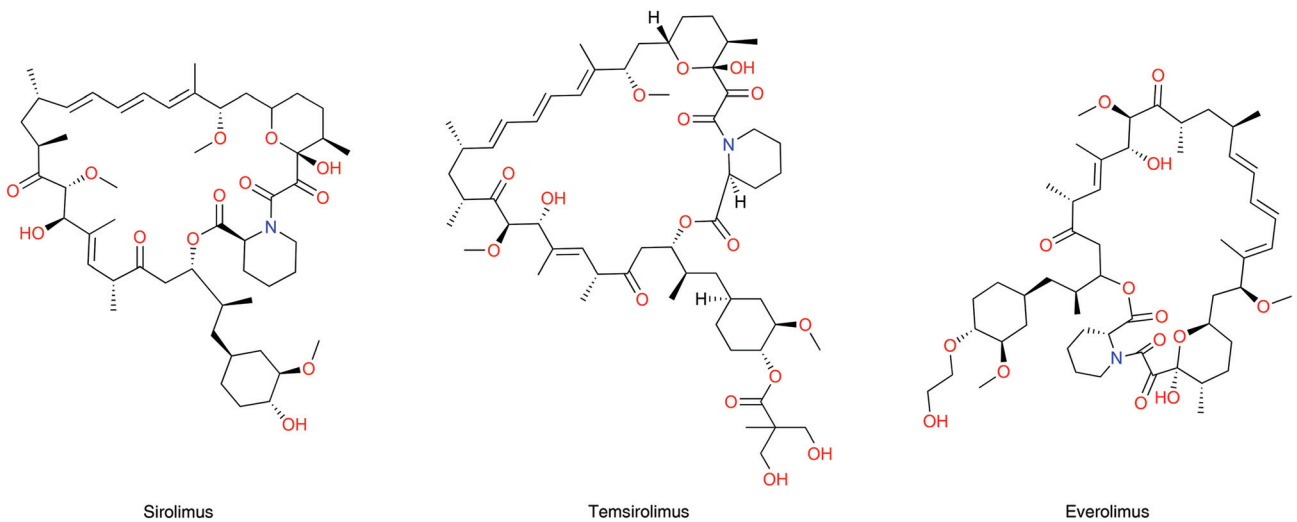


Fig. 15 Structures of mTOR inhibitors.

tion step allowing purification and preconcentration of the analyte was required, such as LLE[575,581,591,592,595–597] or SPE including a prior PP.[580,589,590,593,594,596] As an example, an LLE-LC-UV method allowed the determination of everolimus in whole blood at concentrations between 1 and 200 ng mL^{-1}.[589] The sensitivity and selectivity provided by MS helped to ease sample preparation in clinical chemistry laboratories. Column-switching systems coupling the extraction support to the chromatographic column before MS detection were also used for the analysis of sirolimus[598–611] and everolimus[598,599,602,603,605–607,609,612–614] in whole blood. LLE[615] or SPE[616] on 96-well plates constitutes another approach for sample preparation automatisation. The automatisation of a PP step with a liquid handling platform was also applied for the LC-MS analysis of mTOR inhibitors in blood.[617] Blood sample analysis on blotting paper was particularly useful in the case of mTOR inhibitors by facilitating the collection and processing of the sample prior to LC-MS analysis.[618–622]

Under such conditions, concentrations in the order of ng mL^{-1} were detected. It can be noted that MS detection of mTOR inhibitors was mainly performed *via* adducts formation including sodium adducts[601,602] or ammonia adducts[623,624,625] because of the neutral character of these molecules. An LOQ often inferior to 1 ng mL^{-1} was obtained with MS detection.[626] Electrochemistry detection was also successfully used for sirolimus analysis in blood at concentrations of 1 to 50 ng mL^{-1}.[627]

CE was also used for the determination of mTOR inhibitors. A CE-UV method with a BGE containing SDS and acetonitrile allowed the analysis of sirolimus in blood with an LOQ of 0.2 ng mL^{-1} thanks to a preconcentration factor of 10 obtained with SPE and a large injection volume (focusing technique).[628] Screening for mTOR inhibitors in extracts from natural products was finally performed by CE-LIF.[629]

4 Conclusion

The analytical procedures developed for the analysis of anticancer agents chronologically follow progress in the field of analytical sciences. Two major periods can be distinguished. The first one corresponds more or less to the second half of the 20th century. During this period, the majority of analytical methods developed for the determination of antineoplastic drugs were based on chromatographic techniques such as LC or GC using poorly selective and sensitive detectors. These analytical tools were mostly used in the quality control framework of the anticancer molecule (impurity profiling) and in therapeutic drug monitoring (dose adjustment). Then, there has been increasing interest on the impact of these highly toxic molecules on humans and the environment. To deal with these more complex matrices and attain sufficient limits of detection, the introduction of highly sensitive and selective techniques such as LC-MS opened the era of trace analysis of antineoplastic drugs. Indeed, most analytical methods published since the early 2000s were based on LC-MS. Even if these methods are mainly applied for therapeutic drug monitoring of antineoplastic agents, an increasing numbers of publications concerned exposure studies. The trace detection in humans handling these molecules (other than patients) and in the environment, is becoming more and more powerful thanks to more efficient analytical techniques, which raise discussion on their real impact on health at very low concentrations.

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