Pharmacological Research 209 (2024) 107431

Contents lists available at ScienceDirect

Pharmacological Research

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

Recent developments of topoisomerase inhibitors: Clinical trials, emerging indications, novel molecules and global sales

Andrey D. Bondarev [a], Jörgen Jonsson [a], Vladimir N. Chubarev [b], Vadim V. Tarasov [b], Francisco Alejandro Lagunas-Rangel [a,c,*], Helgi B. Schiöth [a,*]

[a] Department of Surgical Sciences, Functional Pharmacology and Neuroscience, Uppsala University, Uppsala, Sweden
[b] Advanced Molecular Technologies, Limited Liability Company (LLC), Moscow 354340, Russia
[c] Laboratory of Pharmaceutical Pharmacology, Latvian Institute of Organic Synthesis, Riga, Latvia

ARTICLE INFO

Keywords:
Anthracyclines
Quinolones
Novobiocin
Camptothecins
Drug resistance

ABSTRACT

The nucleic acid topoisomerases (TOP) are an evolutionary conserved mechanism to solve topological problems within DNA and RNA that have been historically well-established as a chemotherapeutic target. During investigation of trends within clinical trials, we have identified a very high number of clinical trials involving TOP inhibitors, prompting us to further evaluate the current status of this class of therapeutic agents. In total, we have identified 233 unique molecules with TOP-inhibiting activity. In this review, we provide an overview of the clinical drug development highlighting advances in current clinical uses and discussing novel drugs and indications under development. A wide range of bacterial infections, along with solid and hematologic neoplasms, represent the bulk of clinically approved indications. Negative ADR profile and drug resistance among the antibacterial TOP inhibitors and anthracycline-mediated cardiotoxicity in the antineoplastic TOP inhibitors are major points of concern, subject to continuous research efforts. Ongoing development continues to focus on bacterial infections and cancer; however, there is a degree of diversification in terms of novel drug classes and previously uncovered indications, such as glioblastoma multiforme or *Clostridium difficile* infections. Preclinical studies show potential in viral, protozoal, parasitic and fungal infections as well and suggest the emergence of a novel target, TOP IIIβ. We predict further growth and diversification of the field thanks to the large number of experimental TOP inhibitors emerging.

1. Introduction

Nucleic acids, DNA and RNA, are fundamental molecules of life, responsible for storing genetic information that encodes various instructions to maintain homeostasis. The double helical structure of DNA highlights its particular importance as the primary genetic information store, facilitating both the packaging of the molecule and the regulation of accessibility of the protein-coding information [1]. Such a structure, however, creates topological problems, such as the parental strands of circular DNA forming a link of very high order that is difficult to disentangle prior to cell division [2]. An evolutionary mechanism to solve these problems is the DNA topoisomerase (TOP) enzyme family catalyzing the passage of individual DNA strands through one another [3].

The TOP enzymes, while essential to main vital functions of DNA in proliferating cells, can also exert genotoxic effect when subjected to stress, including TOP poisons; targeting TOP in cancer cells results in their death [4]. Unsurprisingly, this has sparked interest towards exploiting this enzyme family as chemotherapeutics. As early as in 1984, TOP II inhibition was established as the primary molecular mechanism of action for amsacrine, etoposide and doxorubicin, used as antineoplastic agents; TOP I was later on identified as the molecular target for the naturally occurring anticancer drug camptothecin as well [5]. Furthermore, an accidental discovery of nalidixic acid in 1962 eventually emerged in the development of a wide range of quinolone-based antimicrobials targeting DNA gyrase [6]. Recent years have seen a significant overall interest towards TOP inhibitors; the ClinicalTrials.gov records mention as much as 6529 registered trials involving TOP inhibitors as of January, 2024. Furthermore, several TOP inhibitors, daunorubicin, doxorubicin, etoposide and irinotecan, are listed in the

* Correspondence to: Department of Surgical Sciences, Functional Pharmacology and Neuroscience, Uppsala University, BMC Box 593, Husargatan 3, Uppsala 751 24, Sweden.
E-mail addresses: francisco.lagunas@neuro.uu.se (F.A. Lagunas-Rangel), helgi.schioth@neuro.uu.se (H.B. Schiöth).

https://doi.org/10.1016/j.phrs.2024.107431
Received 14 June 2024; Received in revised form 9 September 2024; Accepted 19 September 2024
Available online 20 September 2024

WHO Model List of Essential Medicines [7], highlighting therapeutic importance of this class of drugs.

During our investigation of trends within clinical trials [8–10], we have noticed a large number of studies involving both the investigational and approved agents targeting TOP enzymes, prompting us to conduct our own investigation. The aim of present review is to provide a comprehensive overview of the most recent trends in clinical use and research involving TOP inhibitors and discuss opportunities and challenges for their further development. This review aims to provide a thorough overview of the latest trends in both the clinical application and research of TOP inhibitors, examining the opportunities and challenges for their continued development. We explore the broad range of clinical indications, highlight promising but underexplored areas of research, and address the main issues currently associated with the use of TOP inhibitors. Additionally, we incorporate market analysis data to link emerging research trends with their practical, real-world applications.

2. Search strategy and selection criteria

To gather evidence on antineoplastic TOP inhibitors, we conducted a comprehensive search of the PubMed database using the keywords "topoisomerase" OR "TOP" AND "inhibitor" AND "cancer" OR "neoplasms." For evidence related to antimicrobial TOP inhibitors, we applied the keywords "topoisomerase" OR "TOP" AND "inhibitor" AND "antibacterial" OR "antiviral" OR "antifungal" OR "antiprotozoal." This review is part of a broader series of our recent analyses focused on current trends in targeting proteins for drug development [81–83].

3. TOP enzyme family overview

The TOP enzyme family is divided into classes based on the type of breaks it introduces into the DNA molecule [3]; the TOP I enzymes introduce transient single-stranded breaks into the DNA molecule, while the TOP II introduce double-stranded breaks. The prokaryotic TOP I and TOP III, along with the eukaryotic TOP IIIβ, also possess RNA TOP activity [11]. Based on the nature of protein linkage, the TOP I class is further subdivided into TOP IA and IB subfamilies [12]; the TOP IA enzymes are linked to a 5'-phosphate group, while the TOP IB enzymes get linked to a 3'-phosphate group. The prokaryotic organisms feature TOP I [13], TOP III [14], DNA gyrase [15] and TOP IV [16] proteins. DNA gyrase and TOP IV are heterotetramers, composed of $GyrA_2GyrB_2$, and $ParC_2ParE_2$ subunits, respectively [17]; ParC is homologous to GyrA, while ParE is homologous to GyrB. The eukaryotes feature TOP I [18], TOP II [19] and TOP III [20] proteins; in humans, TOP II and TOP III are present in two isoforms [21–23]. Viral TOP proteins has been

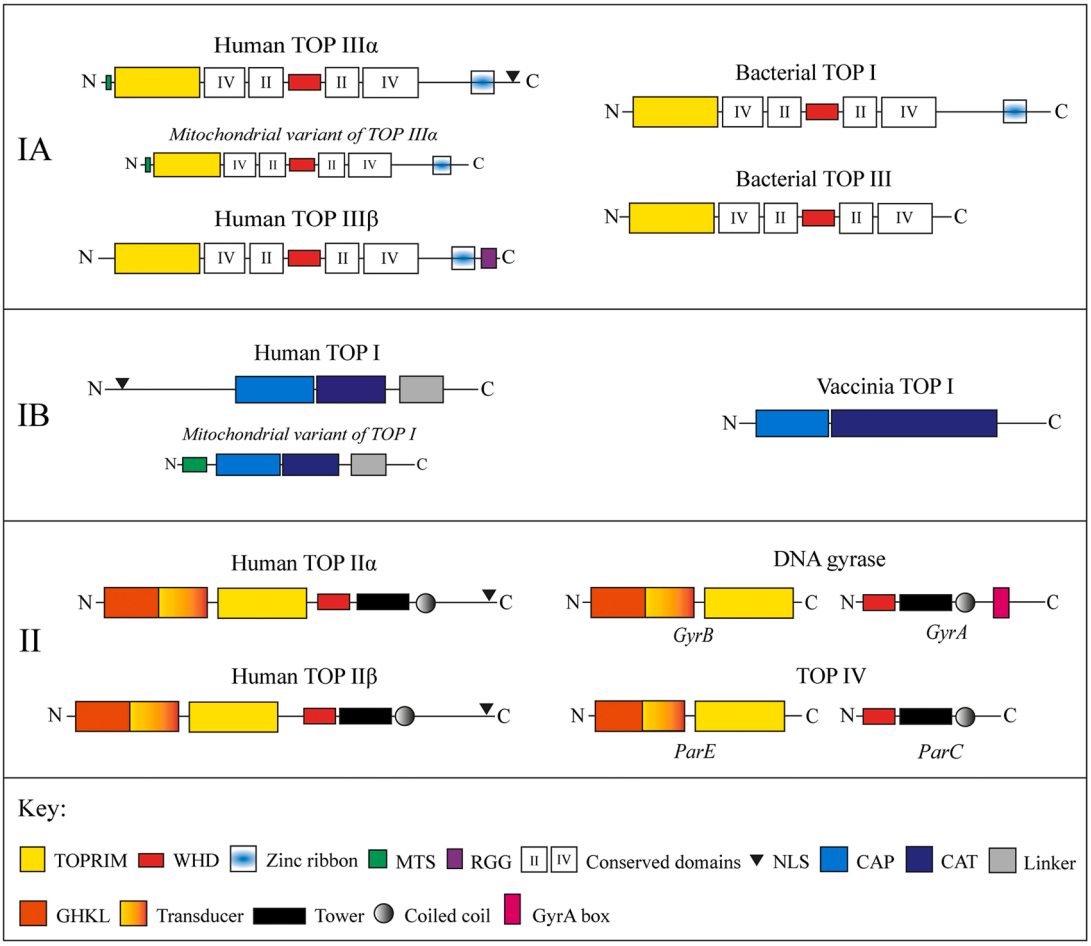

Fig. 1. Key structural features of the eukaryotic and prokaryotic TOP proteins. This figure schematically depicts the key structural features of the eukaryotic and prokaryotic TOP isoforms. Structural features are summarized as per [26]. In the type IA and II proteins, TOPRIM functions as a divalent metal ion binding element, while zinc ribbon domains in the type IA are involved in DNA binding [26]. In TOP IIIβ, RNA-binding activity is dependent on the conserved RGG motif [27]. Mitochondrial variants of TOP IIIα and TOP I are characterized by the MTS sequence for mitochondrial import [28,29]; in TOP IIIα, proteins with predominantly nuclear localization possess both NLS and MTS [28]. In DNA gyrase, the GyrA box is essential for supercoiling activity [26]. Abbreviations: TOPRIM, topoisomerase-primase fold; WHD, winged-helix domain; MTS, mitochondrial targeting sequence; RGG, RNA-binding domain; NLS, nuclear localization signal sequence; CAP, capping module; CAT, catalytic module; GHKL, ATPase domain.

identified as well, such as poxvirus TOP I [24] and African swine fever virus TOP II [25]. Fig. 1 illustrates the domain architecture for some of the therapeutically relevant TOP proteins.

Within cells, eukaryotic TOP proteins are characterized by the predominantly nuclear localization; TOP IIIα [28] and TOP I [29] in the higher eukaryotes are also localized in the mitochondria. In the prokaryotes, subcellular localization varies across species; *Escherichia coli* DNA gyrase is predominantly localized in the cytoplasm [30], while in *Bacillus subtilis* it is characterized by the focal nucleoid localization [31]. A similar pattern can be seen in TOP IV; it is associated with the inner membrane in *E. coli* [32], but has diffuse nucleoid localization in *B. subtilis* [31]. The tissue expression pattern in eukaryotic TOP proteins is broad. For the TOP III isoforms, northern blot analysis showed three transcripts of *TOP3A* and two transcripts of *TOP3B* [23]; the former was detected in testis, heart, skeletal muscle and pancreas, while the latter are prominently expressed in thymus, testis, ovary, small intestine, heart and skeletal muscle. TOP I is characterized by prominent RNA expression in the lymphoid tissue [33] and tissue specificity for endothelial cells [34]; its mitochondrial variant is preferentially expressed in skeletal muscle, heart, brain, and fetal liver [29]. TOP II isoforms are ubiquitously expressed in human tissues with a differential pattern [35,36]; TOP IIα is preferentially expressed in zones of proliferation, while TOP IIβ is present in a broader range of cell populations, including quiescent cells. Northern blot analysis of adult murine tissues showed the most prominent expression of TOP IIα in in the thymus, spleen and bone marrow, while TOP IIβ were detected in the spleen, bone marrow, uterus, ovary, lymph nodes, adrenal gland, eye, bladder and heart [37].

Biologically, TOP enzymes modulate DNA and RNA metabolism by correcting topological problems that arise during transcription, replication, recombination, as well as chromosome condensation [38,39]. To achieve this, TOP enzymes catalyze transesterification reaction between the TOP tyrosyl functional group and a DNA phosphate group, leading to the breakage of a DNA backbone bond and the formation of a covalent TOP-DNA intermediate [38]. The enzymes have been described to play a wide range of functionally critical roles in cells. In higher eukaryotes, they are critical in the early embryonal development as well as somatic cell viability [40]; mouse knockouts on TOP I, TOP IIα, TOP IIβ and TOP IIIα lose viability. Additionally, TOP IIβ plays important roles in tissue development and cell differentiation, specifically in the nervous system [41]; knockout model showed impaired expression of genes involved in neuron migration, cell adhesion, voltage-gated Ca^{2+} channel and synaptic transmission. TOP IIIα is an essential component of the mitochondrial DNA, involved in its separation machinery [42]. TOP IIIβ is involved in neurogenesis, associated with synaptic plasticity [43]; knockout mouse model additionally present with a reduced life-span and autoimmunity. In prokaryotes, TOP I and TOP III are involved in chromosomal segregation and cell division [44]; suppressing *topB* in *topA* deletion *E. coli* strains produced highly filamented cells over time with aberrant nucleoid structures. DNA gyrase is involved in supporting nascent chain elongation during replication of the chromosome, while TOP IV is involved in separating daughter chromosomes during the terminal stage of DNA replication [17]. Both have been shown to partially complement each other [45]; TOP IV can replace DNA gyrase during replication elongation *in vitro* and partially *in vivo*, while overexpression of *gyrA* and *gyrB* partially rescues a *parC* and *parE* mutant.

The potential of TOP enzymes as therapeutic targets has long been recognized, most notably in cancer and bacterial infections. For instance, overexpression of TOP IIα is associated with a poor survival in invasive breast cancer [46], pancreatic adenocarcinoma [47] and glioma [48]. TOP I is implicated in tumorigenesis, associated with autoimmune diseases including systemic sclerosis, and linked with autism spectrum disorders (ASD), such as Angelman syndrome [49]. DNA gyrase and TOP IV are long recognized as major targets for antibacterials [6,17]; the bacterial TOP I and TOP III are suggested as plausible targets as well [50]. The poxvirus DNA TOP I is suggested as a target for antiviral drugs owing to the enzyme's involvement in early infection to increase transcription [51]. TOP IIIβ is another potential antiviral target, involved in replication of positive-sense RNA viruses [52]. Furthermore, TOP IIIβ has been linked to cancer and neurologic disorders; its deletion causes genome instability, as identified in a patient with bilateral renal cancer [53], while pathogenic variants in *TOP3B* were found in patients with schizophrenia and ASD [54]. Biallelic pathogenic variants in *TOP3A* may be implicated in mitochondrial diseases, such as chronic progressive external ophthalmoplegia plus syndrome [42] and Bloom syndrome-like phenotype with prenatal-onset growth restriction and microcephaly [55]. In the next section, we will provide an introduction to the TOP inhibitors as a class of therapeutic agents and discuss a brief methodology of the dataset used in our study.

4. TOP inhibitors overview and dataset

Chemically, TOP inhibitors encompass a diverse group of compounds that can be grouped into nine classes [56]: N-heterocyclic compounds, transition-metal complexes, fatty-acid derivatives and derivatives of naturally-occurring quinones, flavonoids, coumarins, lignans, polyphenols and diterpenes. Based on the mechanism of action, TOP inhibitors can be divided into two main groups, TOP poisons and catalytic inhibitors [57]. TOP poisons act by interfering with the breakage-rejoining reaction of TOP enzymes by trapping the cleavable TOP-DNA complex [58]. Catalytic inhibitors block the ability of TOP proteins to attach to the substrate, subdivided into DNA-binding inhibitors and enzyme-binding inhibitors based on their molecular mechanism [57,59]. DNA-binding inhibitors act by impeding the access of TOP enzymes to DNA sequences, while enzyme-binding agents either "freeze" the protein in one conformation, or inhibit ATP binding [59].

In our dataset, we have included 233 unique TOP inhibitors. The Fig. 2 maps the approved and investigational inhibitors to individual TOP isoforms, as well as provides the phylogenetic relationship between prokaryotic and eukaryotic TOP proteins. The data was extracted from updated versions of our previously published analyses on drug-target interactions of both approved agents as well as agents in clinical development [8–10]. These studies were originally based on information from the Drugs in Clinical Trials Database (discontinued) from CenterWatch [63] and the DrugBank database [64] and spans from 1983 to 2019. The targets, mechanisms of action, and indications were manually assessed using published studies and public databases including Drugs@FDA [65], EMA Medicines [66] and NICE Technology appraisal guidance [67] databases. IUPHAR/BPS Guide to Pharmacology [68] was additionally sourced for information on targets and nomenclature. US clinical trial information was obtained from the National Institute of Health Clinical Trials resource [69]. Where applicable, other regional clinical trial information was additionally included, identified through registries, such as the EMA EU Clinical Trials Register [70], or the NHMRC Australian New Zealand Clinical Trials Registry [71]. In order to ensure comprehensiveness of our analysis, we additionally refer to a number of earlier reviews on the subject published over the past decade (i.e., 2010–2021), including patent reviews [5] and overviews on the development of TOP inhibitors as antineoplastic [57,72–76] and antibacterial drugs [6,72,77–80].

In sections below, we will discuss the current state of the TOP inhibitors' clinical uses and research. For the approved agents, we will discuss the efficacy and safety profiles for selected drugs and comment on the evident trends related to the further development of respective classes. For the investigational agents, we will provide a summary on some of the currently available clinical and/or pre-clinical data, and will attempt to speculate on the opportunities and challenges associated with their future clinical use.

5. TOP inhibitors in clinical practice – overview

As of 2024, there are at least 62 TOP inhibitors that have been explicitly approved by FDA or any other regulatory authority and/or

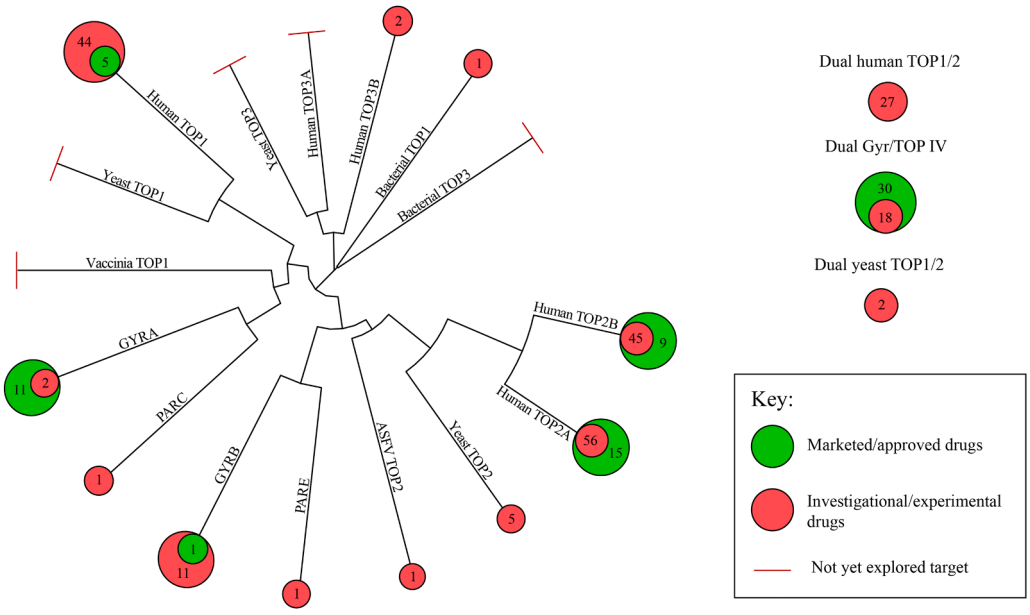

Fig. 2. Marketed and investigational TOP inhibitors mapped to the eukaryotic and prokaryotic TOP proteins. This figure illustrates the phylogenetic relationship between the prokaryotic and eukaryotic TOP proteins and maps the identified marketed and investigational/experimental agents to their targets. The source organism of bacterial proteins' sequences – *E. coli*, the source of yeast proteins' sequences – *Saccharomyces cerevisae*. The amino acid sequences for each protein were obtained from UniProt (UniProtKB database) [60]. Multiple sequence alignment was performed using Clustal Omega (RRID:SCR_001591). The phylogenetic tree was visualized in R Studio using ape 5.0 [61] and ggtree [62] packages and annotated in Adobe Illustrator CC 22.1. Abbreviations: ASFV, African swine fever virus.

have received marketing authorization in any region. The approval statuses and associated trade names were determined through the DrugBank [84], Drugs@FDA [65], EMA Medicines [66], Inxight Drugs [85] and AdisInsight [86] database records, as well as Google search engine. The majority of currently marketed indications are bacterial infections; solid and hematological neoplasms are represented to a lesser

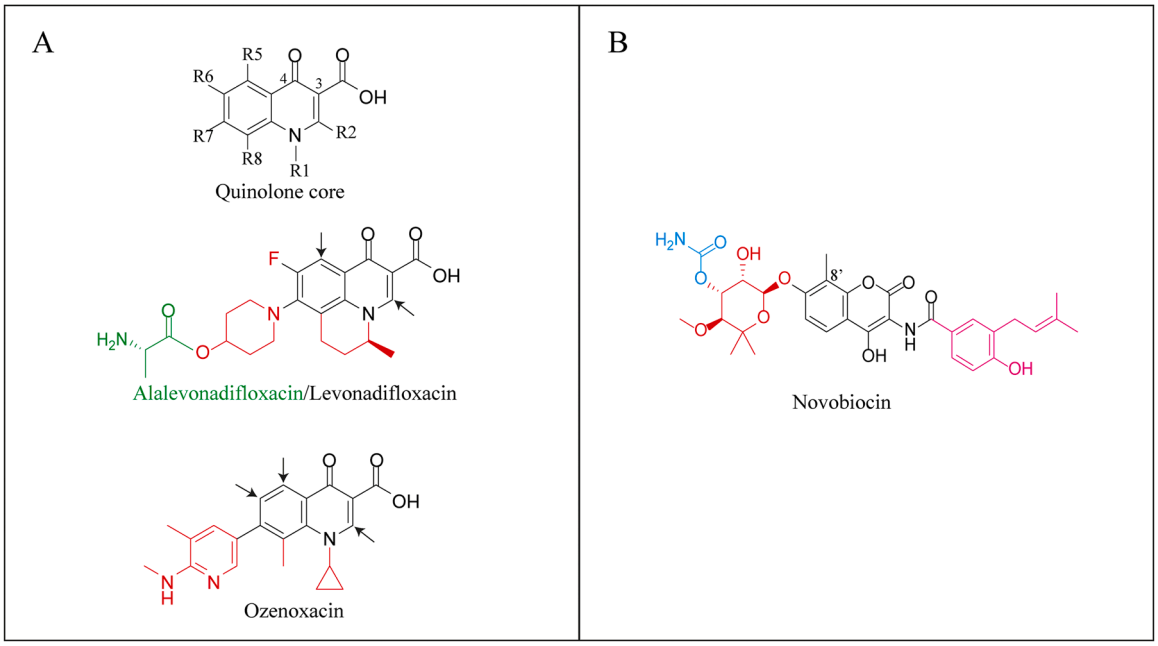

Fig. 3. Pharmacophore features of the antibacterial TOP inhibitors. This figure presents structures for the marketed antibacterial TOP inhibitors included in the analysis and highlights some of their pharmacophoric features. A) In quinolones, modifications of R1 substituent increases the overall potency; importantly, cyclopropyl (see ozenoxacin) confers the highest activity and increases the volume of distribution [87]; modifications of other substituents affect activities against Gram-positive bacteria (R5, R7 and R8), Gram-negative bacteria (R6 and R7) and anaerobes (R8). Green highlights the structural difference between alalevonadifloxacin and levonadifloxacin, red denotes unique functional groups. B) In aminocoumarins, the noviose sugar moiety (red) is critical for activity. Specifically, the carbamoyl group in novobiocin (light blue) forms a hydrogen bond with water molecule in the ATP-binding site [88]; additionally, methyl group in the C-8' position of the aminocoumarin moiety enhances potency. A prenylated 4-hydroxybenzoyl moiety (pink) is the functional group affecting pharmacokinetics [89]. Chemical structures are drawn in ChemDrawJS 18.1 (PerkinElmer Inc., USA), composed in Adobe Illustrator CC 22.1 and based on the data from PubChem database [90]. The chemical structures are: levonadifloxacin (PubChem CID: 9850038), alalevonafloxacin (PubChem CID: 16734914), ozenoxacin (PubChem CID: 9863827) and novobiocin (PubChem CID: 54675769).

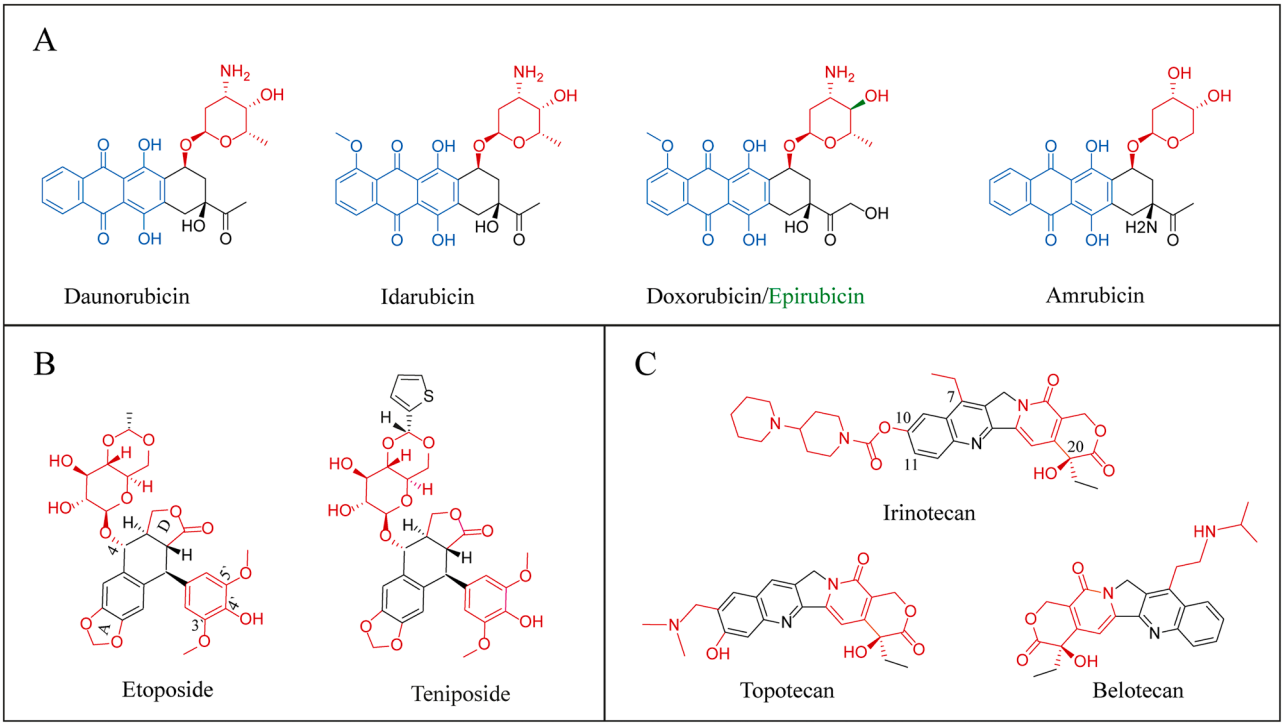

Fig. 4. Pharmacophore features of the antineoplastic TOP inhibitors. This figure presents structures for the marketed antineoplastic TOP inhibitors included in the analysis and highlights their pharmacophoric features. A) In anthracyclines, the aminosugar moiety daunosamine (red) is essential for activity, while the fused ring system (blue) modulates the orientation of the intercalated chromophore, affecting the external interactions of daunosamine [91]. Epirubicin is the 4'-epi-isomer of doxorubicin (green). B) In podophyllotoxin derivatives, the major structural differences from the parent compound are demethylation in the C-4' position, 4-epimerization and a glucose moiety fused to the ring core by a glucoside bond (red) [92]. Modifying A ring results in a decreased potency, replacing D ring by a lactam can slightly increase in potency, while demethylation in either C-3' and C-4', or C-3', C-4' and C-5' positions produce most potent analogues [92]. C) In camptothecins, modifications of the quinoline moiety in positions C-7, C-9 and C-10 contribute to an increase in anticancer activity [93]; additionally, the S-configuration at C-20, pyridone moiety and intact lactone ring are considered essential. Chemical structures are drawn in ChemDrawJS 18.1 (PerkinElmer Inc., USA), composed in Adobe Illustrator CC 22.1 and based on the data from PubChem database [90]. The chemical structures are: daunorubicin (PubChem CID: 30323), idarubicin (PubChem CID: 42890), doxorubicin (PubChem CID: 31703), epirubicin (PubChem CID: 41867), amrubicin (PubChem CID: 3035016), etoposide (PubChem CID: 36462), teniposide (PubChem CID: 452548), irinotecan (PubChem CID: 60838), topotecan (PubChem CID: 60700) and belotecan (PubChem CID: 6456014).

extent. Figs. 3 and 4 present chemical structures of selected TOP inhibitors included in the study and illustrates some of their pharmacophore features.

5.1. TOP inhibitors as antimicrobial drugs

The majority of antimicrobial TOP inhibitors in market belong to the quinolone class. A broad group of drugs targeting DNA gyrase and TOP IV, quinolones encompass four generations, defined based on the spectrum of antibacterial activity [87]. The prototypical agent of the class was nalidixic acid, first reported in 1962 and marketed as early as in 1964 (***NegGram***®, FDA) for the treatment of urinary tract infections (UTI) caused by susceptible Gram-negative bacteria [94]. Nalidixic acid showed effectiveness against a wide range of such bacteria [95]; however, it lacked activity against *Pseudomonas aeruginosa*, an important causative agent of UTIs characterized by poor clinical outcomes and high risks of resistance [96]. A number of derivative compounds were subsequently developed, such as oxolinic acid (***Pradoxol***®, 1974), piromidic acid (***Panacid***®, 1972), cinoxacin (***Cinobac***®, 1979), flumequine (***Apurone***®, 1977), pipemidic acid (***Pipram***®, 1975) and rosoxacin (***Eradacin***®, 1981). Collectively known as the first-generation quinolones, they were all marketed to treat uncomplicated UTIs [97]; rosoxacin was additionally active in some sexually transmitted diseases, particularly gonorrhea [98,99]. Importantly, the addition of piperazine moiety at C-7 in pipemidic acid conferred very limited activity against Gram-positive bacteria and added activity against *P. aeruginosa* [100]. Additionally, flumequine, characterized by a fluorine in C-6, laid the foundation for the new class of fluoroquinolones [97].

Further efforts to improve the pharmacodynamic and pharmacokinetic properties led to the development of novel generations, characterized by the increasingly broader spectrum of antibacterial activity and clinical indications [78,97]. Among the earliest examples of such compounds were norfloxacin, pefloxacin, enoxacin, fleroxacin, ofloxacin, temafloxacin, lomefloxacin, ciprofloxacin, nadifloxacin and rufloxacin. Collectively known as the second-generation quinolones, these drugs are characterized by an enhanced activity against Gram-negative bacteria, including *P. aeruginosa*, limited activity against atypical pathogens and retained a limited activity against Gram-positive bacteria [87,97]. The third generation further expanded the activity against Gram-positive bacteria and atypical pathogens [87,97]; some examples include enrofloxacin, sparfloxacin, grepafloxacin, clinafloxacin, levofloxacin, balofloxacin, gatifloxacin, pazufloxacin, temafloxacin and tosufloxacin. The fourth-generation quinolone antibiotics enhanced activity against anaerobes [87]. The generation includes prulifloxacin, trovafloxacin, moxifloxacin, gemifloxacin, besifloxacin, garenoxacin, sitafloxacin and alatrofloxacin. Approved indications for some of the most commonly prescribed quinolones are summarized in Table 1.

The most recent approvals of fluoroquinolones include finafloxacin, delafloxacin, zabofloxacin, lascufloxacin, levonadifloxacin and alalevonadifloxacin [78]. Finafloxacin is approved by the FDA as ***Xtoro***® (2014) in acute otitis externa. Delafloxacin is approved by the FDA as ***Baxdela***® (2017) and EMA as ***Quofenix***®® (2019) in acute bacterial skin and skin structure infections (ABSSSI) and community-acquired pneumonia (CAP). Zabofloxacin was originally approved in South Korea as ***Zabolante***® (2015) in acute bacterial exacerbations of chronic

Table 1
Selected commonly used quinolone antibiotics. This table summarizes marketed formulations for some of the commonly used quinolone antibiotics, identified as per [97,98]. Indications are listed according to the Drugs@FDA records.

Drug name	Generation	Developer	Trade name(s)	Indication(s)
Ciprofloxacin	Second	Bayer Pharmaceuticals	***Cipro***®	Skin and skin structure infections, bone and joint Infections, complicated intra-abdominal infections, infectious diarrhea, typhoid fever, uncomplicated cervical and urethral gonorrhea, inhalational anthrax post-exposure in adult and pediatric patients, plague in adult and pediatric patients, chronic bacterial prostatitis, acute bacterial exacerbations of chronic bronchitis, urinary tract infection, acute uncomplicated cystitis, complicated urinary tract infection and pyelonephritis in pediatric patients, acute sinusitis
			Ciloxan®	Corneal ulcers, bacterial conjunctivitis
			Cetraxal®	Acute otitis externa
			Ciprodex®	Combination with dexamethasone; acute otitis media in pediatric patients (age 6 months and older) with tympanostomy tubes, acute otitis externa in pediatric (age 6 months and older), adult and elderly patients
			Otovel®	Combination with fluocinolone acetonide; acute otitis media in pediatric patients (age 6 months and older) with tympanostomy tubes
Ofloxacin	Second	Daiichi Seiyaku	***Ocuflox***®	Corneal ulcers, bacterial conjunctivitis
			Floxin®	Acute bacterial exacerbations of chronic bronchitis, community-acquired pneumonia, uncomplicated skin and skin structure infections, acute, uncomplicated urethral and cervical gonorrhea, nongonococcal urethritis and cervicitis, mixed infections of the urethra and cervix, acute pelvic inflammatory disease (including severe infection), uncomplicated cystitis, complicated urinary tract infections, prostatitis
			Floxin® Otic	Chronic suppurative otitis media in patients 12 years old and older with perforated tympanic membranes, acute otitis media in pediatric patients one year and older with tympanostomy tubes, otitis externa in adults and pediatric patients 6 months and older
Norfloxacin	Second	Kyorin	***Noroxin***®	Uncomplicated urinary tract infections (including cystitis), complicated urinary tract infections, uncomplicated urethral and cervical gonorrhea, and prostatitis
			Chibroxin®	Bacterial conjunctivitis
Levofloxacin	Third	Daiichi Seiyaku	***Levaquin***®	Nosocomial and community-acquired pneumonia, acute bacterial sinusitis, acute bacterial exacerbations of chronic bronchitis, complicated and uncomplicated skin and skin structure infections, chronic bacterial prostatitis, complicated and uncomplicated urinary tract infections, acute pyelonephritis, inhalational anthrax post-exposure, plague
			Iquix®	Corneal ulcers
			Quixin®	Bacterial conjunctivitis
Moxifloxacin	Third	Bayer	***Avelox***®	Acute bacterial sinusitis, acute bacterial exacerbations of chronic bronchitis, community-acquired pneumonia of mild-to-moderate severity, uncomplicated skin and skin structure infections
			Vigamox®, ***Moxeza***®	Bacterial conjunctivitis

obstructive pulmonary disease; it has subsequently been marketed in the Middle East and North Africa region (2016) and China (2017). Lascufloxacin is approved for a wide range of respiratory and otorhinolaryngologic infections in Japan as ***Lasvic***® (2019). Levonadifloxacin and alalevonadifloxacin, its orally active prodrug, are approved in India for treating ABSSSI as ***Emrok***® and ***Emrok O***®®, respectively. Additionally, two nonfluorinated quinolones have been approved, nemonoxacin and ozenoxacin. Nemonoxacin is marketed as ***Taigexyn***® in Taiwan (2014) and mainland China (2016) for treating CAP. Ozenoxacin is approved in Japan as ***Zebiax***® (2015) for topical use in acne vulgaris and superficial skin infections and by FDA as ***Xepi***® (2017) for impetigo.

Clinically, quinolones represent some of the most frequently prescribed class of antibiotics. According to a 2016 study in the US [101], the total number of quinolone prescriptions increased by 402 % over the course of 1991–2015 time-frame with ciprofloxacin and levofloxacin being most commonly reimbursed. In the EU and EEA, quinolones' use has been described as one of the fastest growing since 1997 and up to 2001; according to 2017 data [102], there has been an increasing variability in proportion of quinolone use out of all antibiotics for systemic use ranging from 2.46 % in Norway to 21.49 % in Cyprus. However, such an extensive use inevitably contributes to the development of resistance. In the US, fluoroquinolone-resistant *E. coli* was found to be widely prevalent (22.1 %) across the US emergency department patients with UTI (N = 3779 patients) [103]. Furthermore, the overall gonococcal resistance to ciprofloxacin in the EU/EEA over the course of 2009–2016 period was found to be 51.8 % (vs. 7.1 %, 4.3 %, and 0.2 % to azithromycin, cefixime and ceftriaxone, respectively) [104].

While the potency of most quinolone antibiotics is reported to be high, one of the limiting factors of their use is toxicity [97]; the most common adverse drug reactions (ADRs) are gastrointestinal effects, CNS reactions, arthralgia, phototoxicity and QTc interval prolongation. Among the potentially life-threatening ADRs are tendonitis, tendon rupture, aortic rupture and dissection; this prompted both the FDA and EMA to issue a set of regulatory warnings in 2016–2019, recommending that quinolone antibiotics should be generally avoided in self-limiting and/or mild-to-moderate uncomplicated bacterial infections [105,106]. The ruling also included limiting use in certain groups, such as the elderly, patients with kidney disease, aortic aneurysm, peripheral atherosclerotic vascular diseases and hypertension, as well as genetic conditions such as Marfan syndrome and Ehlers-Danlos syndrome [106,107]. The EMA specifically ruled this for nalidixic acid, pipemidic acid, cinoxacin, flumequine, ciprofloxacin, levofloxacin, lomefloxacin, moxifloxacin, norfloxacin, ofloxacin, pefloxacin, prulifloxacin and rufloxacin [106]. Furthermore, FDA reports a significant decrease in blood sugar as another point of concern for the elderly patients and patients with diabetes who are taking hypoglycemic drugs due to a risk of coma [108].

Among the particularly interesting recent approvals are levonadifloxacin and ozenoxacin, characterized by resistance suppression properties. For instance, levonadifloxacin is not a substrate to the NorA efflux transporter and preferentially targets DNA gyrase which contributes to a lower frequency of mutations and a narrow mutation selection window [109]. A retrospective, multicenter, real-world study [110] showed 97.8 % overall clinical success rate (N = 227 patients), with less than 1 % experiencing ADRs; noteworthy, a combination therapy of IV levonadifloxacin followed by oral alalevonadifloxacin produces 100 % clinical success rate (n = 11 patients). Ozenoxacin is also characterized by a sufficiently high antibacterial activity against quinolone-resistant *S. aureus*, as reported in a study involving skin-derived methicillin-susceptible and methicillin-resistant strains isolated in 2019 and 2020 in Japan [111]. Several *in vitro* studies showed significantly lower minimal inhibitory concentrations against strains overexpressing NorA

and MepA, as well as *gyrA*, *grlA* or *gyrA-grlA* mutants, as compared to other quinolones including moxifloxacin, levofloxacin, ciprofloxacin and norfloxacin [112]. Based on the results of a pooled analysis of two Phase 3 clinical trials [113], the clinical improvement was reported to be 88.5 % (n = 357 patients), with 78.2 % responding to placebo (n = 354 patients); <0.1 % patients experienced treatment-related ADRs (N = 875 patients).

Among the non-quinolone antibiotics, only novobiocin, an aminocoumarin antibiotic, had been marketed. Aminocoumarins are biosynthesized by the *Streptomyces* bacteria, primarily targeting the subunit B of DNA gyrase [114]. TOP IV is a secondary target for aminocoumarins; novobiocin is significantly less potent against the ParE subunit, as compared to DNA gyrase [115]. Despite potency, a number of factors, such as poor oral bioavailability, low activity against the Gram-negative bacteria and rapid emergence of resistant strains has long been recognized as negatively impacting the wider clinical use of this class of drugs [116,117]. The only marketed aminocoumarin, novobiocin, was originally marketed as ***Albamycin***® in 1964 for the treatment of serious staphylococcal infections for human use and as ***Albadry Plus***® for the treatment of bovine subclinical mastitis caused by susceptible strains of *Staphylococcus aureus* and *Streptococcus agalactiae*. However, the clinical use of novobiocin in humans had been limited and the drug had not been manufactured in the US since 1999 [77]. Furthermore, it was completely withdrawn from the US market in 2011 due to safety concerns [118]; the drug was reported to cause skin reactions, jaundice, hepatic failure, and hematologic effects (neutropenia, anemia, and thrombocytopenia).

Likely linked to its poor safety profile as an antibacterial agent, novobiocin has also been explored in cancer, targeting TOP II and acting as a catalytic inhibitor [119]. The drug has been described to potentiate the cytotoxic activity of epipodophyllotoxins in human lung and ovarian carcinoma, and leukemia *in vitro* [120,121], as well as to overcome BCRP-mediated multidrug resistance [122]. Clinically, it showed activity in non-small cell lung cancer (NSCLC) when administered prior to a high dose of cisplatin (N = 36 patients) [123]; 9 % of patients responded partially with a median survival of 6.9 months. While there had been no significant clinical developments in recent years, ClinicalTrials.gov records list a dose-escalation Phase 1 study of novobiocin as a DNA polymerase theta (POLθ) inhibitor (NCT05687110), suggesting multiple mechanisms of its antineoplastic activity.

Additionally, there is one antimalarial drug in market that features TOP as one of its targets, a benzo-naphthyridine pyronaridine. The drug is characterized by complex mechanism of action [124]; it is suggested that binding with hematin is the principal mechanism of pyronaridine's action in malaria. However, there is evidence on TOP II involvement as well; pyronaridine was found to inhibit the decatenation activity of *P. falciparum* TOP II at 11 μM [125]. However, it was also reported that pyronaridine doesn't generate protein-DNA complexes within parasite cells, an indicator of TOP II inactivation [126]; importantly, 9-anilinoacridine derivatives containing 3,6-diNH_2 substitutions with 1′-electron donating, and 1′-electron withdrawing groups produced such complexes. Pyronaridine has been approved by the EMA (***Pyramax***®) in 2012 for the treatment of acute, uncomplicated malaria infection caused by *Plasmodium falciparum* and *P. vivax* in combination with artesunate. In *P. falciparum* infection, pyronaridine was considered efficacious with a PCR-adjusted treatment failure rate of less than 5 %, based on a meta-analysis of five clinical trials (n = 5711 patients) [127]. Pyronaridine is currently under consideration for use in cancer; it was shown to act as a TOP II inhibitor in breast cancer cell lines, hindered tumor progression in mice with human breast cancer xenografts and showed synergism when given in combination with gemcitabine and cisplatin [128]. Additionally, the drug showed activity in cystic echinococcosis, a zoonotic disease caused by the larval stage of the dog tapeworm *Echinococcus granulosus*, acting as a TOP I inhibitor [129].

To summarize, quinolones are recognized as a valuable class of antibacterial agents, generally to be used in potentially life-threatening infections, unresponsive to other options. The recent trend concentrates on developing molecules with a better safety profile and resistance suppression; simultaneous activity against DNA gyrase and TOP IV is evident to be effective in minimizing risks of developing resistance, as well as to counteract quinolone-resistant microorganisms. Aminocoumarins provide interesting insights on drug discovery tools for naturally occurring compounds; structural features of aminocoumarins are determined by differences in the corresponding biosynthetic gene cluster, modifiable through genetic engineering [130]. While there is no conclusive evidence on the use of TOP inhibitors in malaria, TOP II inhibition is an interesting strategy; in addition to pyronaridine, TOP II inhibitors amsacrine and etoposide, along with norfloxacin, showed activity against asexual stages of *P. falciparum* [131]. Recent development of an engineered *P. falciparum* TOP II [132] is a particularly important tool for future drug development and optimization efforts here.

5.2. TOP inhibitors as antineoplastic drugs

The majority of marketed antineoplastic TOP inhibitors belong to the class of anthracyclines, selective to TOP II. The original agents of this class to be discovered were doxorubicin and daunorubicin, also isolated from the *Streptomyces* bacteria (*S. peucetius*) [133]; while daunorubicin was the earliest identified compound, doxorubicin showed the highest potency and spectrum of antitumor activity. Doxorubicin was marketed in 1974 as ***Adriamycin***® for treating a broad range of tumors including breast cancer, leukemias, lymphomas, Wilms' tumor, neuroblastoma, sarcomas and carcinomas. Daunorubicin was marketed in 1979 as ***Cerubidine***® for remission induction in acute nonlymphocytic leukemia (ANLL) in adults and acute lymphocytic leukemia (ALL) in adults and children. Recently, a novel formulation of liposomal daunorubicin in combination with cytarabine (***Vyxeos***®, 2017) was additionally approved in for the treatment of newly-diagnosed therapy-related AML or AML with myelodysplasia-related changes in adults and pediatric patients.

Subsequently, a number of derivative synthetic and semi-synthetic compounds were developed, most notably including doxorubicin derivatives pirarubicin [134], valrubicin [135], epirubicin [136] and amrubicin [137], and daunorubicin derivative idarubicin [138]. Pirarubicin is marketed in Japan (1988) and China (1993) as ***Therarubicin***® for breast cancer, hematological malignancies, as well as for uterine, head and neck, bladder and ovarian cancers. Valrubicin is marketed as ***Valstar***® (1998) in bladder cancer; it was withdrawn from market in 2002 due to manufacturing issues and re-introduced in 2009 [139]. Epirubicin is marketed as ***Ellence***® in breast cancer, amrubicin is marketed as ***Calsed***® (Japan, 2002) for treating lung cancer, while idarubicin is used in acute myeloid leukemia (AML) in adults, marketed as ***Idamycin***®. Aclarubicin is a biosynthetic anthracycline with superior therapeutic index compared to doxorubicin and daunorubicin [140]; it is marketed as ***Aclacinon***®® in Japan (1981) and China (1992) for leukemia, lymphoma, breast, lung, ovarian and gastric cancers. A number of structurally related compounds, such as amsacrine and mitoxantrone were developed as well [141]; amsacrine is a rationally synthesized aminoacridine and mitoxantrone is a synthetic amino anthraquinone. Amsacrine is marketed as ***Amsidine***® in acute leukemia in adults, while mitoxantrone is marketed as ***Novantrone***® in ANLL and advanced hormone-refractory prostate cancer. Other formulations of mitoxantrone (ex. ***Onkotrone***®®) are also used in metastatic breast cancer, chronic myeloid leukemia and non-Hodgkin lymphoma.

The other two distinct classes of antineoplastic TOP inhibitors are semi-synthetic derivatives of podophyllotoxin and camptothecin. Podophyllotoxin is an aryltetralin lignan isolated from the roots and rhizomes of *Podophyllum* species of plants [142]. While podophyllotoxin itself lacks any TOP-modulating activity, its semi-synthetic derivatives, collectively known as epipodophyllotoxins, are characterized by the TOP II inhibiting activity [143]. Marketed epipodophyllotoxins are

etoposide and teniposide [142]. Etoposide was approved by the FDA in 1983 as ***Vepesid***® for the treatment of small-lung cancer (SCLC) and testicular cancer; its prodrug, etoposide phosphate, has additionally been developed to improve convenience of use, marketed as ***Etopophos***® in 1996. Teniposide was approved as ***Vumon***® for the treatment of refractory childhood ALL in 1992. Camptothecin, an alkaloid derived from the *Camptotheca acuminata* tree, is a TOP I inhibitor with distinct pharmacological properties, including low affinity for TOP I cleavage complex and reversibility of binding, allowing control over drug exposure and cleavage complex trapping [144]. However, poor water solubility and instability of the parent compound prompted development of several semi-synthetic derivatives, out of which irinotecan, topotecan and belotecan have been approved for clinical use [72]. Irinotecan was originally marketed in 1996 as ***Camptosar***® for use in carcinoma of the colon or rectum; its liposomal formulation is approved in metastatic pancreatic adenocarcinoma (***Onivyde***®, 2015). Topotecan is marketed as ***Hycamtin***® for the treatment of SCLC, metastatic ovarian cancer and recurrent cervical cancer in 1996, while belotecan is marketed as ***Camtobell***® in South Korea (2003) for treating SCLC and ovarian cancer.

Recently, two antibody-drug conjugates linked with camptothecin derivatives were approved as well, trastuzumab deruxtecan and sacituzumab deruxtecan. Trastuzumab deruxtecan consists of a monoclonal HER2-directed antibody linked with a deruxtecan, an exatecan derivative [145]. It is approved as ***Enhertu***® by the FDA (2019) and EMA (2021); the indications include unresectable or metastatic HER2-positive and HER2-low breast cancer, NSCLC with activating HER2 mutation, and HER2-positive advanced gastric cancer. Sacituzumab gavitecan is a Trop2-directed antibody linked with SN-38, a metabolite of irinotecan [146]. It is approved as ***Trodelvy***® in 2020 (FDA) and 2021 (EMA); the FDA-approved indications include metastatic triple-negative and HR-positive/HER2-negative (HR+/HER2-) breast cancer, and locally advanced/metastatic urothelial cancer, while in the EU it is authorized in breast cancer only.

In addition to the major classes above, two uncategorized small molecules have been marketed, sobuzoxane and paclitaxel. Sobuzoxane is a bis(2,6-dioxopiperazine) derivative, targeting TOP II [147]; it is approved in Japan as ***Perazolin***® for adult T-cell leukemia and lymphoma. Paclitaxel is a taxane, derived from *Taxus brevifolia*, marketed as ***Taxol***® for use in advanced carcinoma of the ovaries, resistant/relapsed breast cancer, AIDS-related Kaposi's sarcoma and NSCLC [148]. While the main mechanism of action in paclitaxel is described as microtubule stabilization, it was shown that the drug also exhibits an atypical interaction against TOP IIα [149]; low concentrations in the nanomolar range stimulated its catalytic activity, while concentrations over 5 μM resulted in inhibition.

In the clinical practice, antineoplastic TOP inhibitors occupy a prominent niche in cancer therapy. Among the most commonly prescribed anthracyclines are doxorubicin, epirubicin, daunorubicin and idarubicin [150]; they are reported to have been used in 32 % of breast cancer patients, up to 70 % of elderly lymphoma patients, and in up to 60 % of childhood cancer survivors. Doxorubicin has historically been recognized as the mainstay agent to treat advanced breast cancer with epirubicin showing comparable efficacy. As a single-agent, doxorubicin was reported to produce 47 % overall response rate (ORR; n = 68 patients) with median survival of 12 months, while epirubicin showed 49 % ORR (n = 70 patients) and median survival of 10 months [151]. In both agents, partial responses (PR) comprised the majority (33.82 % vs. 41.42 %, respectively). In newly-diagnosed AML, daunorubicin is characterized by 52 % complete remission rate (CR) and a 9 % 5-year overall survival rate (OS) [152]; idarubicin was shown to have higher CR (62 %) and a higher 5-year OS (13 %).

Cardiotoxicity is widely reported in the literature as one of the significant ADRs that hamper wider application of anthracyclines [150, 153]. The exact pathophysiology is not yet understood [153]; however, the dominant theories involve the generation of reactive oxygen species (ROS), as well as drug-induced inhibition of TOP IIβ. Polymorphisms affecting genes, encoding cytochromes P450 and several other metabolic enzymes are potentially implicated as well [154]. Among the reported strategies to counter this are the use of cardioprotective agents, including cardiovascular drugs and dexrazoxane [153]. Dexrazoxane is a bisdioxopiperazine, approved as ***Zinecard***® by the FDA (1995); the principal mechanism of its cardioprotective activity is considered to be transient depletion of TOP IIβ which leads to a reduction in doxorubicin-induced double strand breaks [155]. According to a 2022 meta-analysis [156], dexrazoxane is deemed effective in reducing anthracycline-associated cardiotoxicity in adults; the risk ratio (RR) of clinical heart failure (CHF) was found to be 0.22 while for combined CHF and subclinical myocardial dysfunction (MD) – 0.37. No significant differences in tumor response rate, OS and progression-free survival were found. Another important strategy is the development of novel formulations, such as liposomal and other nanoformulations [157]. For instance, PEGylated liposomal doxorubicin was the first such formulation to be marketed as ***Doxil***® in the US and Japan, and ***Caelix***® elsewhere; ***Lipodox***® has been additionally approved as a generic in 2013 by the FDA. ***Myocet***® is a non-PEGylated liposomal doxorubicin marketed in the EU and Canada. As compared to conventional doxorubicin, liposomal formulations also contribute to an effective reduction of cardiotoxicity; according to a 2010 meta-analysis [158], RR of CHF and combined CHF/MD are 0.20 and 0.38, respectively. No significant changes were observed in tumor ORR, OS and PFS; however, liposomal doxorubicin was found to improve PFS as compared to epirubicin (7.7 months vs. 5.6 months).

Epipodophyllotoxin etoposide is characterized by a schedule-dependent activity in SCLC, producing ORR as much as 89 % (84 % PR) as a single-agent use in treatment-naïve patients with extensive disease (n = 19 patients) when administered intravenously on a 5-day schedule [159]. Based on the aggregate data [160], etoposide has poorer ORR in previously treated patients (13 %). In testicular cancer, etoposide was found to produce a 35 % ORR in refractory patients (N = 97 patients) [161]; the majority of responses are partial as well (approximately 33 % PR). Teniposide showed a 26.67 % responsiveness as a single agent in patients with advanced refractory childhood ALL (n = 15 patients) [162]. A notable ADR for this class of TOP inhibitors is treatment-related AML, predominantly associated with a weekly or twice-weekly administration schedule [163]. Balanced translocations involving *MLL* and *AML1* are among the most frequent in epipodophyllotoxin-associated AML [164].

Irinotecan is characterized by a 17.7 % ORR in pre-treated patients (n = 130 patients) with advanced colorectal cancer and 18.8 % ORR in the treatment-naïve patients (n = 48 patients) [165]. In pancreatic cancer, it produced a comparable response in both treatment-naïve (8.8 % ORR (N = 34 patients)) [166] and pre-treated (9 % ORR (N = 33 patients)) [167] patients; the median OS values were 5.2 months and 6.6 months, respectively. In SCLC, a Phase 2b comparison study of belotecan vs. topotecan showed a 33 % ORR in belotecan and 21 % in topotecan [168]; the median PFS was 4.8 months and 3.8 months, the median OS - 13.2 months and 8.2 months. Interestingly, while topotecan is the most commonly used chemotherapeutic agent in refractory/relapsed SCLC, an anthracycline amrubicin is suggested to be a preferred option, showing better responsiveness and OS; a pooled analysis (N = 803 patients) showed 39 % ORR and a 69 % six-month OS in amrubicin [169] vs. 5 % ORR and a 36 % six-month OS in topotecan (N = 1347 patients) [170]. In ovarian cancer, belotecan showed a 33.3 % ORR as a single agent (n = 18 patients), compared to 20 % for topotecan (n = 25 patients) [171]. In cervical cancer, topotecan showed a 18.6 % ORR in treatment-naïve patients (n = 43 patients) and 12.5 % in pre-treated patients (n = 41 patients) [172]. PFS and OS were reported to be 2.4 months and 6.4 months for the former group, and 2.1 months and 6.6 months for the latter.

Trastuzumab deruxtecan showed significant improvements in studied tumors. In breast cancer, the DESTINY-Breast01 Phase 2 trial (N =

184 patients) showed a 60.9 % ORR (54.9 % PR) and 16.4 months median PFS [173]. A recently published real-world early access program data from France (N = 459 patients) [174] showed a comparable tumor ORR of 56.7 %. In HER2-low breast cancer, the drug showed 52.3 % ORR (49.1 % PR) in the DESTINY-Breast04 Phase 3 trial (n = 373 patients) with 9.9 months median PFS and 23.4 months median OS [175]. In NSCLC, the DESTINY-Lung01 Phase 2 trial showed 55 % ORR (54 % PR), with 8.2 months median PFS and 17.8 months median OS (N = 91 patients) [176]. In gastric cancer, ORR was reported to be 51 % (42 % PR), 12.5 months median OS and 5.6 months median PFS in the DESTINY-Gastric01 Phase 2 study (n = 125 patients) [177]. Among ADRs, interstitial lung disease and myelosuppression were reported as the most notable across the trials. Sacituzumab govitecan showed 21 % ORR with 13.9 months OS at 12 months and 5.5 months median PFS in the TROPiCS-02 Phase 3 trial involving HR+/HER2- breast cancer patients (n = 272 patients) [178]. In triple-negative breast cancer, the ASCENT Phase 3 study showed comparable results: 35 % ORR with 12.1 months median OS and 5.6 months median PFS (n = 235 patients) [179]. In urothelial carcinoma, the drug showed 27 % ORR, 10.9 months median OS and 5.4 months median PFS in the TROPHY-U-01 Phase 2 trial (n = 113 patients) [180]. The ADR principally included diarrhea and hematological toxicities, such as anemia, leukocytopenia, thrombocytopenia and neutropenia.

To conclude, antineoplastic TOP inhibitors have showed positive antitumor activity as single agents; however, they are typically used in clinical practice as parts of combination regimens (Table 2). The key trend in regards to safety, particularly for anthracyclines, is the development of nanoformulations to improve safety. Among the promising novel approaches are encapsulation in ferritin nanocages and co-delivery within a liposomal system [157]. An interesting recent development here is co-administration of doxorubicin H-ferritin nanocages with trastuzumab, demonstrating protection against mitochondrial cardiotoxicity and lower off-target accumulation in heart as per an *in vivo* study in mice [185]. The recent approvals of trastuzumab deruxtecan and sacituzumab govitecan is a major milestone for personalized therapeutic approaches, producing strong tumor responses.

6. TOP inhibitors in clinical research

In our dataset, we identified 164 unique molecules with TOP inhibiting activity which have either been under pre-clinical or clinical development, or which have been investigated previously but are either discontinued or have an unknown development status as of 2024. The majority of identified molecules, 117 agents, have one or more neoplastic indications; 32 agents have been studied as antimicrobials with antibacterial, antifungal, antiviral and antiprotozoal activities. Fifteen experimental molecules have been shown to have a dual activity acting as both antineoplastic and antimicrobial drugs.

6.1. Novel antineoplastic TOP inhibitors

Among the identified novel antineoplastic TOP inhibitors, 18 agents are currently in an ongoing clinical development (Table 3). Novel camptothecin derivatives include four novel antibody-deruxtecan conjugates, datopotamab deruxtecan (Dato-DXd), patritumab deruxtecan (HER3-DXd), ifinatamab deruxtecan (I-DXd) and raludotatug deruxtecan (R-DXd); novel SN-38 formulations are under development as well. Additionally, three non-camptothecin TOP I inhibitors have been investigated, indenoisoquinolines LMP400 (indotecan), LMP744 and LMP776 (indimitecan). Anthracyclines are represented as well, such as berubicin, aldoxorubicin, camsirubicin, sabarubicin, annamycin and daunomustine. Two unique developments include an antineoplastic quinolone vosaroxin [186] and CX-5461 (pidnarulex), originally derived from a group of fluoroquinolones that were shown to have dual TOP II and G-quadruplex interactions [187].

Two antibody-deruxtecan conjugates, Dato-DXd and HER3-DXd, have reached regulatory stages of its development in NSCLC and breast cancer. Dato-DXd is a TROP2-directed conjugate; it has been mainly investigated in two pivotal Phase 3 TROPION trials, NCT04656652/EudraCT 2020–004643–80 (advanced metastatic NSCLC) and NCT05104866/EudraCT 2020–005620–12 (HR+/HER2- breast cancer). Dato-DXd showed a 26.4 % ORR and a median PFS of 4.4 months in NSCLC (n = 299 patients) [188]; in the subset of patients with non-squamous disease (n = 229 patients), ORR was 31.2 % with 5.6 months median PFS. In breast cancer, it showed 36.4 % ORR and 6.9 months median PFS (n = 365 patients) [189], leading to its Biologics License Application in the US accepted in April, 2024 [190]. HER3-DXd is a HER3-directed conjugate investigated in a pivotal Phase 2 HERTHENA trial in patients with locally advanced or metastatic EGFR-mutated NSCLC (NCT04619004; EudraCT 2020–000730–17). It showed 29.8 % ORR, 5.5 months median PFS and 11.9 months median OS (n = 225 patients) [191]; CNS ORR in patients with nonirradiated brain metastases at baseline (n = 30 patients) is 33.3 %.

I-DXd and R-DXd showed interesting developments as well. I-DXd, a

Table 2
Selected combination regimens of antineoplastic TOP inhibitors. This table presents evidence on the efficacy and safety profiles for selected combination regimens of antineoplastic TOP inhibitors. Combination regimens are: FAC, combination regimen of 5-fluorouracil, doxorubicin and cyclophosphamide; FEC, combination regimen of 5-fluorouracil, epirubicin and cyclophosphamide; PE, combination regimen of cisplatin and etoposide; TP, combination regimen of cisplatin and topotecan; NALIRIFOX, combination regimen of liposomal irinotecan, oxaliplatin, leucovorin and 5-fluorouracil. Abbreviations: ORR, objective response rate; CR, complete remission; OS, overall survival; ALL, acute lymphoblastic leukemia; SCLC, small cell lung cancer; CT, clinical trial.

Combination regimen	Indication	Number of patients	Efficacy profile	Safety profile	CT reference
FAC	Advanced breast cancer	n = 221 patient	56.5 % ORR, 613 days median survival time	Leukopenia (28 %), anemia (14 %), thrombocytopenia (14 %), nausea (47 %), stomatitis (13 %), alopecia (61 %), cardiac toxicity (21 %; mainly ST-T changes)	[181]
FEC	Advanced breast cancer	n = 222 patients	53.6 % ORR, 591 days median survival time	Leukopenia (15 %), anemia (2 %), thrombocytopenia (23 %), nausea (35 %), stomatitis (14 %), alopecia (60 %), cardiac toxicity (12 %; mainly sinus tachycardia)	[181]
Idarubicin + cytarabine	Refractory/relapsed ALL	N = 88 patients	59 % CR, 13 % projected survival at 46 months	Myelosuppression (100 %), nausea and vomiting (51 %), mucositis (40 %), diarrhea (23 %)	[182]
PE	Extensive disease SCLC	n = 348 patients	45.5 % ORR, 32.6 % 1-year survival rate, 41 weeks median OS	Thrombocytopenia (14.07 %), neutropenia (60.77 %), anemia (14.97 %)	[183]
TP	Extensive disease SCLC	n = 358 patients	55.5 % ORR, 36.7 % 1-year survival rate, 44.9 weeks median OS	Thrombocytopenia (43.64 %), neutropenia (61.27 %), anemia (30.92 %)	[183]
NALIRIFOX	Metastatic pancreatic ductal adenocarcinoma	n = 383 patients	42 % ORR, 45.6 % 12-month survival rate, 11.1 months median OS	Diarrhea (20 %), hypokalemia (15 %), neutropenia (14 %), nausea (12 %), anemia (11 %), decreased neutrophil count (10 %)	[184]

Table 3
Antineoplastic TOP inhibitors in an ongoing clinical development. This table summarizes currently available evidence on investigational antineoplastic TOP inhibitors included in our dataset. Targets are listed as per developer websites and InxightDrugs database records. Indications are listed as per developer websites, AdisInsight database records and clinical trial registries. Abbreviations: CT, clinical trial.

Drug name	Developer	TOP selectivity	Indication(s)	Highest CT phase
SN−38	Multiple formulations	TOP I	Solid tumors	Phase 2
Berubicin	CNS Pharmaceuticals	TOP II	Glioblastoma multiforme	Phase 2
Camsirubicin	Monopar Therapeutics	TOP II	Advanced soft tissue sarcoma	Phase 1b
Aldoxorubicin	ImmunityBio	TOP II	Solid tumors	Phase 3
Indimitecan	Gibson Oncology	TOP I	Relapsed solid tumors	Phase 1
LMP−744	Gibson Oncology	TOP I	Relapsed solid tumors and lymphomas; veterinary canine lymphoma	Phase 1
Indotecan	Gibson Oncology	TOP I	Solid tumors	Phase 1
Gimatecan	Lee's Pharmaceuticals	TOP I	Solid tumors	Phase 2
Pidnarulex	Sehnwa Biosciences	TOP II	Breast cancer, ovarian cancer, prostate cancer, hematological cancers	Phase 2
Silatecan	Vivacitas Oncology	TOP I	Glioblastoma multiforme, colorectal cancer, ovarian cancer, pancreatic cancer, non-small cell lung cancer	Phase 2
Sabarubicin	Menarini Pharmaceuticals	TOP II	Small cell lung cancer	Phase 2
Annamycin	Moleculin Biotech	TOP II	Acute myeloid leukemia, soft tissue sarcoma	Phase 1b/2
Datopotamab deruxtecan	Daiichi Sankyo /w AstraZeneca	TOP I	Breast cancer, non-small cell lung cancer, solid tumors	Preregistration
Patritumab deruxtecan	Daiichi Sankyo /w Merck	TOP I	Non-small cell lung cancer, gastric cancer, solid tumors	Preregistration
Ifinatamab deruxtecan	Daiichi Sankyo /w Merck	TOP I	Extensive stage small cell lung cancer, prostate cancer, esophageal squamous cell carcinoma	Phase 2
Raludotatug deruxtecan	Daiichi Sankyo /w Merck	TOP I	Renal cell carcinoma, ovarian cancer	Phase 1
Daunomustine	Paradox Pharmaceuticals	TOP II	Canine lymphoma	Phase 1
Vosaroxin	Denovo Biopharma	TOP II	Acute myeloid leukemia, precursor B-cell lymphoblastic leukemia-lymphoma, myelodysplastic syndrome	Phase 3

B7-H3 directed conjugate, showed 52.4 % ORR in a Phase 1/2 trial in patients with advanced SCLC (n = 21 patients), with 5.6 months median PFS and 12.2 months median OS [192]. Its further development involves a Phase 2 IDeate trial; ClinicalTrials.gov records list NCT05280470, currently in a *Recruiting* stage, while EudraCT 2022–000503–13 is *Ongoing* in Germany. R-DXd, a CDH6-directed conjugate, showed 46 % ORR in patients with advanced platinum-resistant ovarian cancer (n = 50 patients), with 7.9 months median PFS in a Phase 1 study [193]; a continuation Phase 2/3 REJOICE trial (NCT06161025) is currently in a *Recruiting* stage. Preclinical studies involving R-DXd additionally showed efficacy in renal cell carcinoma [194], a Phase 1 trial (NCT04707248) is in a *Recruiting* stage as well.

While the recent approval of sacituzumab gavitecan represents a major milestone for SN-38 development at large, there are several investigational small molecule delivery systems in trials as well. SN-38 is characterized by a number of negative physicochemical properties, such as low water solubility, poor stability in clinically available solvents and rapid inactivation under physiological pH, making it direct delivery difficult [195]. For instance, CEB-01, a poly(lactic-co-glycolic acid) polymeric drug with a delivery system loaded with SN-38, is in an *Ongoing* development in patients with recurrent or locally advanced retroperitoneal soft tissue sarcoma after surgery (Phase 1; NCT04619056). PLX038, a PEGylated form of SN-38, is in a *Recruiting* stage for a Phase 1/2 trial in primary CNS tumors (NCT06161519) and a Phase 2 trial in metastatic, platinum-resistant ovarian, primary peritoneal, and fallopian tube cancers (NCT05465941). Additionally, it has been in an *Ongoing* Phase 1/2 evaluation in SCLC and other solid tumors in combination with a poly (ADP-ribose) polymerase (PARP) inhibitor rucaparib (NCT04209595). Published evidence showed potent activity in *BRCA1* and *ATM* mutant xenografts and a complete and durable tumor response to a combination of PLX038 and rucaparib in a patient with *ATM*-deficient breast cancer [196]. Importantly, an *in vivo* study in rats showed disposition of the drug to be independent of *UGT1A* activity, highlighting its utility in patients with liver dysfunction [197]. TRX-920, formulated as an oral gel, and SNB-101, a nanoparticle formulation, are both investigated in solid tumors; two Phase 1 trials are listed on ClinicalTrials.gov, NCT06143774 and NCT04640480, respectively.

The development of indenoisoquinolines followed a similar rationale to improve stability of the camptothecin derivatives, as well as to improve their efficacy profile [144]. Among the important recent milestones is indotecan receiving the FDA orphan drug designation in malignant glioma [198]. A proof-of-concept study [199] showed PTEN-deficient glioma cells particularly sensitive to the drug; it also showed synergistic cytotoxicity with niraparib, another PARP inhibitor. Additionally, SLFN11 was shown as one of the dominant drug determinants for the three investigational indenoisoquinolines, showing synergism with a PARP inhibitor olaparib [200]. Additionally, LMP744 showed in a recent report a prolonged stabilization in 16.67 % of patients with colorectal cancer with prior disease progression on irinotecan (n = 24 patients) [201]. Indimitecan showed stabilization in 30 % of patients (n = 34 patients) with relapsed solid tumors and lymphomas [202].

Among novel anthracyclines, the key focus is on development of molecules with minimal cardiotoxicity. For instance, camsirubicin, a 5-imino-13-deoxy analogue of doxorubicin, is reported to show preference for TOP IIα over TOP IIβ [203]. To date, it is investigated in soft tissue sarcomas; a Phase 2 study showed 6-months PFS and OS rates of 38 % and 74 %, respectively [204]. Additionally, a recently *Terminated* due to lack of enrolment Phase 1b dose-escalation study (NCT05043649) showed 18–21 % tumor size reduction [205]. Annamycin, a 4-demethoxy analogue of doxorubicin, is characterized by organotropic properties and the ability to overcome multidrug resistance. Its structural features, particularly deamination at the C-3' position, results in an increased cellular uptake and retention, as well as confers a reduced cardiotoxicity and diminished affinity for cardiolipin [206]. Additionally, annamycin is characterized by an equal accumulation pattern in cardiac muscle cells and cardiac non-muscle cells [207]. Ongoing clinical studies include a Phase 1/2 dose-escalation study of the liposomal form in combination with cytarabine in AML (NCT05319587) and two single-agent Phase 1/2 studies in soft tissue sarcomas with pulmonary metastases (NCT05518526, NCT04887298). Published clinical evidence shows CR as much as 80 % (n = 8 patients) with no cardiotoxicity in annamycin as a single agent [208].

Other unique developments include berubicin and aldoxorubicin. Berubicin is characterized by a significant CNS uptake and exhibits a 44 % clinical benefit rate in glioblastoma multiforme with one durable

complete response and 10 patients with stable disease (n = 25 patients) [209]. Aldoxorubicin is an albumin-binding hydrophobic prodrug of doxorubicin with a 6-maleimidocaproic acid hydrazide moiety, showing a superior efficacy over doxorubicin in advanced soft-tissue sarcoma by prolonging median PFS (5.6 % vs. 2.7 %), and improving rates of 6-month PFS (46 % vs. 23 %) and ORR (25 % vs. 0 %) [210]. According to a pharmacokinetic study (n = 18 patients) [211], aldoxorubicin is characterized by very low amounts of doxorubicin and doxorubicinol excreted in the urine after its administration. A major metabolite of doxorubicin, doxorubicinol is also believed to be implicated in anthracycline-mediated cardiotoxicity, compromising both systolic and diastolic cardiac function [212]. It functions as a potent inhibitor of cationic pumps, including the Ca^{2+} pump of sarcoplasmic reticulum, the Na^{+}/K^{+} pump of sarcolemma and the F0F1 proton pump of mitochondria [212,213]. Additionally, most of doxorubicin present in the circulation after aldoxorubicin administration remains bound to albumin via the acid-sensitive linker with little free doxorubicin being released in the bloodstream [211]. A recently reported recombinant protein-based nanodrug carrier is described to further improve bioavailability of aldoxorubicin [214]; the carrier enhanced the antitumor activity in osteosarcoma model, mitigated cardiotoxicity and increased the drug's bioavailability by 17-fold.

The first-in-class antineoplastic quinolone vosaroxin (previously known as voreloxin) had been evaluated in AML both as a single agent and in combination regimens. It acts as a TOP II inhibitor, intercalating DNA and poisoning the enzyme, causing DNA double-strand breaks, G2 arrest, and apoptosis, resembling the mode of action of etoposide and doxorubicin [215,216]. In contrast to etoposide, vosaroxin causes dose-dependent, site-selective DNA fragmentation [215]. Compared to doxorubicin, it doesn't induce detectable replication fork collapse during S phase and induces less overall DNA fragmentation [216]. Importantly, it is not a substrate to the P-gp efflux pump (ABCB1), active in drug-resistant cell lines overexpressing P-glycoprotein [217]. As a single-use agent its efficacy profile has only been published for the elderly patients (NCT00607997); vosaroxin showed 32 % combined remission rate, 6.5 months median leukemia-free survival and 7 months of median OS (n = 113 patients) [218]. The ongoing studies include a Phase 1 trial of vosaroxin in combination with azacitidine in myelodysplastic syndrome (NCT01913951) and a Phase 2 study of vosaroxin in combination with cytarabine in patients with untreated AML (NCT02658487). Pharmacokinetically, vosaroxin is excreted mostly unchanged with N-desmethylvosaroxin being the only circulating metabolite detected in plasma [219]; however, the combined vosaroxin + N-desmethylvosaroxin $AUC_{0-\infty}$ was 21 % lower than the TRA $AUC_{0-\infty}$ in plasma, suggesting possible formation of protein bound metabolites.

Pidnarulex is currently under evaluation in a Phase 1b trial (NCT04890613) in advanced solid tumors, including BRCA1/2, PALB2 or HRD mutant tumors; an exploratory Phase 1 study showed 14 % ORR [220]. Pidnarulex was previously studied in a Phase 1 trial in advanced hematologic malignancies in Australia (ACTRN12613001061729); its main cytotoxic mechanism TOP II poisoning was established in melanoma and lymphoma cell lines [221]. Noteworthy, a recent study further identified TOP IIβ isoform as the primary target for pidnarulex and showed selective cytotoxicity to high-risk neuroblastoma improving survival in orthotopic patient-derived xenograft neuroblastoma mouse models [222]. Additionally, combining pidnarulex with a TOP I inhibitor was shown to reduce clonogenic survival and tumor growth *in vivo* in high-grade serous ovarian cancer [223]. The drug is characterized by low water solubility; encapsulating copper-complexed pidnarulex in liposomes is one strategy to overcome this described in the literature. The complex is stable at pH 7.4 and exhibits increased plasma circulation longevity, increasing the total exposure to the drug [224]. A critical point of concern associated with pidnarulex is an extensive, nonselective, collateral mutagenesis. According to an *in vitro* study [225], pidnarulex exhibits a higher overall mutation burden for mutagenesis of substitutions (SBS) with mutagenesis index (MI) of 6.8, and small insertions and deletions (MI = 2.1) signatures compared to cisplatin (MI = 0.6 and 1, respectively). Furthermore, the odds of causing a stop gain mutation in genes causally implicated in cancer were found to be 1.15 times higher in SBS-pidnarulex than common environmental exposures.

6.2. Novel antimicrobial TOP inhibitors

Among the antimicrobial TOP inhibitors in our dataset, we identified five novel molecules in an ongoing clinical development (Table 4). Two molecules, zoliflodacin and gepotidacin, represent novel first-in-class agents to treat gonococcal infections, also known as the novel bacterial topoisomerase inhibitors (NBTI). Zoliflodacin (ETX0914) is a spiropyrimidinetrione [226], while gepotidacin (GSK2140944) belongs to the class of triazaacenaphthylenes [227]. Two other novel agents, DNV3837 (oxaquin) and TNP-2092, are quinolone-containing hybrid molecules; DNV3837 is a prodrug that consists of an oxazolidinone-quinolone combination [228], TNP-2092 is a conjugate of rifamycin with a fluoroquinolone [229]. OPS-2071 is a novel quinolone antibiotic with a broad spectrum of antibacterial activity.

NBTIs is a novel class of antibacterial TOP inhibitors with the mechanism of action distinct from quinolones, subclassified into Type I and Type II [80]; gepotidacin belongs to the former and zoliflodacin to the latter. The common structural features in Type I NBTIs are the DNA-intercalating heteroaromatic "left-hand side", the enzyme-bound heteroaromatic "right-hand side" and their connection through a cyclic or bicyclic linker moiety [230]. Type I NBTIs target the DNA gyrase/TOP IV complex with the pre-cleaved DNA [231]; the binding site of these molecules is located on the two-fold axis at the GyrA/ParC dimer interface and doesn't overlap the binding site to quinolones. Type II NBTIs are derived from QPT-1 that target GyrB/ParE in mechanisms distinct from both novobiocin and quinolone antibiotics [232]. Zoliflodacin, specifically, is distinct from quinolones in blocking religation of the cleaved DNA after the removal of Mg^{2+} from the DNA-gyrase-inhibitor complex [233]. Zoliflodacin is currently studied in an *Ongoing* Phase 3 non-inferiority trial (NCT03959527) comparing the drug to the combination of ceftriaxone and azithromycin for the

Table 4
Antimicrobial TOP inhibitors in an ongoing clinical development. This table summarizes currently available evidence on investigational antimicrobial TOP inhibitors included in our dataset. Targets are listed as per developer websites and InxightDrugs database records. Indications are listed as per developer websites, AdisInsight database records and clinical trial registries. Abbreviations: CT, clinical trial.

Drug name	Developer	TOP selectivity	Indication(s)	Highest CT phase
Zoliflodacin	Entasis Therapeutics	DNA gyrase (GyrB subunit)	Gonorrhea	Phase 3
Oxaquin	Morphochem	DNA gyrase, TOP IV	*C. difficile* infections	Phase 2
OPS−2071	Otsuka Pharmaceutical	DNA gyrase	Irritable bowel syndrome	Phase 2
TNP−2092	Tennor Therapeutics	DNA gyrase, TOP IV	Prosthetic joint infection, acute bacterial skin and soft tissue infections, hepatic encephalopathy, irritable bowel syndrome, diabetic foot infection	Phase 2
Gepotidacin	GlaxoSmithKline	DNA gyrase, TOP IV	Uncomplicated urinary tract infections, gonorrhea	Phase 3

treatment of uncomplicated gonorrhea, showing the non-inferiority margin of 5.31 % [234]. An earlier Phase 2 study (n = 141 patients) showed zoliflodacin to be particularly effective in rectal (100 %) and urogenital (96 %) gonococcal infections [235]; in pharyngeal infection zoliflodacin produced response in 82 % patients. Gepotidacin similarly showed 96 % efficacy in urogenital gonorrhea (n = 69 patients) [236]. Consequent Phase 3 non-inferiority trials of gepotidacin vs. nitrofurantoin (EAGLE-2 and EAGLE-3) [237] both showed non-inferiority of gepotidacin; EAGLE-3 showed gepotidacin to be superior (14.6 %). Importantly, however, resistance to zoliflodacin was identified to potentially emerge in commensal *Neisseria* spp., that could then be transferred to *N. gonorrhea* via transformation [238].

Oxaquin is currently under evaluation in a Phase 2 exploratory trial in patients with *Clostridium difficile* infections (NCT03988855). While oxaquin itself is inactive, the principal antibacterial activity associated with the drug is due to its active form DNV3837/MCB3681 [239]; the water-soluble prodrug is rapidly converted *in vivo* after the intravenous administration. As a class, oxazolidinone-quinolone hybrids are characterized by a combination of protein synthesis and GyrA/ParC inhibition [240]. An *in vitro* susceptibility study of 199 *C. difficile* PCR ribotypes from 21 European countries showed good activity in oxaquin against the bacteria with no evidence on resistance in isolates showing either moxifloxacin or linezolid resistance, or both [241]. TNP-2092, according to the developer's website [242], is currently studied for the treatment of prosthetic joint infection, acute bacterial skin and skin tissue infection, cirrhotic hepatic encephalopathy, irritable bowel syndrome with diarrhea (IBS-D) and diabetic foot infection. *In vitro* activity studies showed potent activity against *Helicobacter pylori*, including strains resistant to clarithromycin and levofloxacin [243], and periprosthetic joint-associated staphylococci [244]. Additionally, *in vivo* studies in rats showed effectiveness in disrupting of the biofilm formation, as well as alleviating the abnormal bone absorption and reactive bone changes around the prosthesis [245], and significant changes in gut microbiota that are associated with improvements in hepatic encephalopathy symptoms [246]. Its mechanism of action includes RNA polymerase and GyrA/ParC inhibition [247]; it is not a substrate for efflux pumps, including NorA. OPS-2071 is currently in the *Recruiting* stage of a Phase 2 trial on IBS-D (NCT05923892). The drug is characterized by activity against enteropathogenic bacteria, particularly *Clostridioides difficile in vitro* and *in vivo* [248], and *Campylobacter jejuni in vitro* [249]. In addition to the antibacterial activity, it suppresses LPL-induced TNF-α production and T cell responses in a dose-dependent manner [250]. Compared to other major antibiotics, it is characterized by a lower minimal concentration at which there is no emergence of resistant bacteria [248,249]. Furthermore, the drug showed low systemic exposure and high distribution and concentration in the large intestine and caecal contents [248].

6.3. Experimental TOP inhibitors

In addition to the drugs in clinical development above we noted a large number of molecules that have been shown to exhibit TOP-mediated activity in *in vitro* and/or *in vivo* studies. Some of the particularly interesting molecules are discussed below.

The overall trend within experimental antineoplastic molecules is a focus on developing novel classes of molecules, identifying mechanisms of drug resistance, and exploring novel targets. Among the particularly interesting experimental antineoplastic molecules are bisacridine NSC690634 and thiacyanine NSC96932, acting as TOP IIIβ poisons [251]. Both compounds were studied in the colorectal and lung carcinoma cell lines and were shown to trap TOP IIIβ cleavage complex, acting on RNA; NSC690634 was additionally found to increase R-loops in a TOP IIIβ-dependent manner. Structurally, the molecules contain a pair of nitrogen-substituted small aromatic rings joined by a 3-carbon linker; structure-activity studies showed that the length of linker moiety in each compound is critical for activity; for instance, bisacridines with a 6- or 8-carbon linker, or thiacyanines with a 5- or 7-carbon linker were rendered ineffective in trapping TOP IIIβ complex. The other interesting recent developments are loonamycin, an indolocarbazole alkaloid from *Nocardiopsis flavescens* [252], and novel ellipticine derivatives *N*-methyl-5-demethyl ellipticine and 2-methyl--*N*-methyl-5-demethyl ellipticinum iodide [253]. Loonamycin is characterized by potent *in vitro* activity in triple-negative breast cancer via multiple mechanisms, including TOP I [254], while the novel ellipticine derivatives show superior potency as compared to the parent compound. Additionally, a series of *ortho*-carborane-containing 1,3,5 triazines has been synthesized for the development of boron neutron capture therapy, including TAZ-6 and several derivative compounds [255]; 2,4-Bis(*N*,*N*-diethylamino)-6-(*o*-carboran-1-yl)-1,3,5-triazine and 2,4-Bis(*N*,*N*-*n*-propylamino)-6-(*o*-carboran-1-yl)-1,3,5-triazine were found to be the most potent. Novel indenoisoquinoline LMP517 has been recently described as well, showing improved antitumor activity in SCLC xenografts [256]; it is described as a dual TOP I/II inhibitor that targets cells independently of their position in the cell cycle. Furthermore, a derivative copper (II) indenoisoquinoline complex WN197 has been reported, with cytotoxic activity shown in adenocarcinoma cell lines at concentrations below 0.5 μM [257]. At low concentrations, it is characterized by TOP I inhibition, while higher concentrations produce inhibition of both TOP II isoforms. The drug produces cytotoxic effect via autophagy with Beclin-1 accumulation, LC3-II formation, p62 degradation and RAPTOR phosphorylation in the mTOR complex.

Among experimental antimicrobial TOP inhibitors, several molecules highlight potential novel design strategies and indications. In the antibacterial TOP inhibitors, novel simocyclinones D9, D10 and D11, produced by *Kitasatospora* sp. and *Streptomyces* sp., provide important evidence on the structure-activity showing the importance of the A-ring modifications for the overall activity [258]. It additionally gave valuable insights on simocyclinones' biosynthetic pathway, disproving the role of a modular polyketide synthase system and showing the role of the new stand-alone ketosynthase genes. The parent compound of this class, simocyclinone D8, is characterized by an aminocoumarin moiety [259]. However, it doesn't inhibit the DNA-independent ATPase activity and doesn't stimulate cleavage complex formation, antagonizing both Ca^{2+}- and quinolone-induced cleavage complex formation. A recent discovery of isoquinoline sulfonamide derivative LEI-800 represents another important advance in diversifying antibacterial TOP inhibitors, offering a limited cross-resistance between quinolones [260]. A DNA gyrase inhibitor with specificity against GyrA, it binds to a previously unexploited binding site and inhibits the Ca^{2+}- and quinolone-induced cleavage complex formation. A series of triazoloacridinones and imidazoacridones showed antifungal activity, acting as TOP II inhibitors, representing an important advancement in antifungal TOP inhibitors. Particularly, compounds IKE5 and IKE13 were found to be among the most potent ($IC_{50} = 7.7 \pm 1.1$ μM and 6.2 ± 1.2 μM, respectively), IKE5 also was not a substrate for multidrug ABC transporter, while IKE7 showed the ability to overcome fluconazole-resistance in *C. glabrata* [261]. Antiviral TOP inhibitors represent a relatively niche area with few molecules evaluated for such an activity. One example is an isoflavone genistein showing TOP II-mediated activity against African swine fever virus [262]. Its antiviral activity was found to be maximal when added to cells at middle-phase of infection.

6.4. TOP inhibitors with non-chemotherapeutic action

At least two TOP inhibitors showed non-cytotoxic activities, potentially mediated through TOP inhibition. Apigenin, along with camptothecin, have been found to suppress seizure phenotypes in a *Drosophila* model of epilepsy, reducing recovery time from seizures [263]. Ethoxidine, another camptothecin analog, showed paradoxical effects on angiogenesis depending on the concentration used [264]; only low concentration increased expression of vascular endothelial growth factor (VEGF) and endothelial nitric oxide synthase (eNOS), as well as NO

and superoxide anion productions. However, while the involvement of TOP I inhibition in VEGF and eNOS expression modulation was reported previously [264], a recent study in a model of mouse hindlimb ischemia showed lack of TOP inhibition after low-dose ethoxidine [265].

7. Discussion

As of 2024, the bulk of commercially available drugs of this class have chemotherapeutic indications, such as cancer, bacterial infections and malaria. Quinolones are a major class of antibacterial TOP inhibitors tackling a broad range of indications. In neoplastic disorders, TOP inhibitors of the anthracycline class are the mainstay therapy for many types of cancer. The ongoing clinical research continues in this direction, potentially contributing to expanding neoplastic indications, such as glioblastoma multiforme, or bacterial indications, such as *C. difficile* infections or IBS-D. A fairly large number of investigational TOP inhibitors, particularly with antineoplastic indications, have been either discontinued, suspended or otherwise unknown, however; we noted 38 antineoplastic and 7 antimicrobial drugs in this status (Supplementary Tables 1 and 2). The precise cause is unknown for most drugs; however, some are reported to have been discontinued for efficacy and/or safety reasons. For instance, becatecarin, a rebeccamycin analogue, failed to demonstrate superiority in biliary tract tumors compared to existing therapies, such as 5-fluorouracil [266]. Its development was additionally hampered by insufficient supply of rebeccamycin, making the parent compound production process optimisation a major factor [267]. NXL-101 is an example of an investigational TOP inhibitors discontinued for safety issues; its development was discontinued due to prolonged QT signals in the heart observed in healthy subjects [268].

Among the marketed TOP inhibitors, the key points of concern are negative ADR profile and the emergence of drug resistance. Ongoing research focuses on understanding such mechanisms. For instance, the most common mechanism of high-level resistance to quinolones is due to mutations within the quinolone resistance-determining regions of the genes that encode DNA gyrase and TOP IV [269]. Other important mechanisms mentioned in the literature are chromosomal mutations that lead to a reduced drug accumulation and plasmid-mediated mechanisms of resistance mediated by the Qnr proteins [269,270]. Enzymes involved in the quinolone modification, such as an aminoglycoside transferase AAC(6′)Ib-cr and a phosphorylase CrpP have been implicated as well [270]. In cancer, anthracyclines and camptothecins are subjected to a wide range of factors affecting its sensitivity, including drug efflux/influx mechanisms, cancer cell stemness, autophagy or altered metabolic pathways [271,272]. For instance, resistance to doxorubicin can be mediated by the high levels of ATP-binding cassette transporters, particularly ABCB1, ABCC1 and ABCG2 [271]. ABCB1 and ABCG2, along with ABCC2, are involved in resistance to irinotecan [272]. Further characterization of their biological functions would open up opportunities for drug discovery efforts to confer more advanced protection. Another important direction is drug repurposing; however, it can also lead to the emergence of novel targets. For instance, novobiocin was recently identified as a first-in-class POLθ inhibitor, killing HR-deficient breast and ovarian tumors in experimental models [273]. Among the antineoplastic TOP inhibitors in market, anthracycline-associated cardiotoxicity is a notable safety issue and a key trend in the ongoing clinical and pre-clinical research. Several investigational anthracyclines in clinical and pre-clinical research provide valuable insights on structural features affecting safety, which will undoubtedly help the future development efforts. Furthermore, combination regimens and liposomal formulations are proving to be useful tools to improve efficacy and safety.

In regards to countering resistance and general development of clinical TOP inhibitors' candidates, particularly in regards to antineoplastic TOP inhibitors, an important aspect is identification of predictive biomarkers of response. To date, several markers of sensitivity to TOP I and TOP II has been identified. For instance, CHFR-promoter methylation was identified to positively correlate with greater responsiveness to SN38 in advanced colon cancer *in vitro* [274]. It was also positively correlated with clinical response to irinotecan-based systemic chemotherapy and increased PFS for patients treated with irinotecan-containing FLOFIRI in combination with bevacizumab. On the other hand, elevated systemic immune-inflammation (SII) index has been associated with advanced tumor stage in SCLC and lower OS (12 months vs. 17 months in low SII) when treated with etoposide and platinum-based chemotherapy [275]. Other markers are under investigation as well, including TIMP-1 in glioblastoma with SN-38 and epirubicin [276], SLFN11 and HRD in solid and hematological tumors with exatecan [277], and EGFR and BRG1 with etoposide in NSCLC [278]. At least two Phase 2 clinical trials have been conducted designed to include patients with an increased expression of a gene (TOP1) to evaluate the effect on effectiveness of irinotecan (EudraCT 2012–002348–26 and 2012–002347–23). While the studies didn't reach the planned number of patients [279], this effort highlights the need of identifying better fitting common clinically relevant markers. Epigenetic modifiers, including histone deacetylase (HDAC) inhibitors, are recognised as an important approach as well due to HDAC inhibitors being capable to resensitize tumor cells to TOP II [271]. Additionally, development of dual inhibitors is of considerable interest [75]; for instance, series of novel compounds containing pyrimido[5,4-*b*]indole and pyrazolo[3,4-*d*]pyrimidine motifs with dual TOP II/HDAC activity have been synthesized recently [280]. Among antimicrobial TOP inhibitors, zoliflodacin is an important lesson to learn. Novel classes of antibiotics, while therapeutically invaluable, may pose risk of developing resistance, potentially via unique mechanisms; a problem that warrants attention during development.

The future development of this field has a significant potential to diversify in future thanks to the ongoing basic research efforts. TOP I inhibition could become a plausible approach in managing tumor-associated epilepsy, a common comorbidity in CNS cancers [281]. Synergism between TOP I and PARP inhibition is another valuable development, providing novel insights on tumor biology and opening up potential therapeutic strategies. Additionally, there is an interesting trend in diversification of antimicrobial indications associated with TOP inhibitors, such as viral, fungal and parasitic infections. Another important recent advance is characterization of TOP IIIβ as a possible therapeutic target, which will further improve the available armamentarium to treat cancer, as well as potentially provide therapeutic options to treat positive-sense RNA viral infections and neurological disorders. TOPIIIβ is unique as the only TOP enzyme capable of correcting topological problems that arise in both the DNA and RNA metabolism. While functional implications of such problems in RNA metabolism are poorly understood, recent work described a unique TOPIIIβ-RNA interaction. Specifically, the residues D185, R194 and R524 showed hydrogen bond formation with the 2′-OH of the RNA ribose sugar that is part of the nucleotide at the −4 position from the cleavage site [282]. We believe this will provide an important foundation for potential drug design strategies for further development of TOPIIIβ inhibitors. Additionally, the discovery of novel simocyclinones D9, D10 and D11 led to a better understanding of simocyclinone biosynthesis; this could inspire further studies involving other classes of naturally occurring compounds. This is of great importance for the field given a large number of TOP inhibitors being naturally occurring substances and/or their derivatives. Overall, we expect the ongoing trends in TOP inhibitors' basic research to continue.

The global market value of quinolone antibiotics was reported to be USD 48.8 billion in 2022, expected to grow up to 69.4 billion in 2030 with a predicted annual growth rate (CAGR) of 4.5 % [283]. Another report suggests growth from USD 48.31 billion in 2023–50.65 billion in 2024 at CAGR of 4.9 % and 61.51 billion in 2028 at CAGR of 5 % [284]. Among the factors positively impacting quinolones market growth are the rise in incidence of infectious diseases and antibiotic resistance, while patent expiry and lack of access to treatment options hinder it

[285]. In anthracyclines, the global market value was USD 1.39 billion in 2022, expecting to grow up to USD 2.31 billion by 2030 at CAGR of 6.6 % [286]. By 2028, it is projected to reach USD 1.97 billion at CAGR of 6.8 % [287]. Here, the main drivers are the increasing prevalence of cancer, growing R&D efforts and government health expenditure, while the negative ADR profile is seen as a challenge for market growth [286, 287].

8. Conclusion

Here, we provided a comprehensive overview of TOP inhibitors with focus on novel agents, indications and formulations. The current clinical uses of this class of drugs are bacterial infections and a wide range of neoplastic disorders; the key trend is a focus on improving safety and tackling drug resistance. The ongoing clinical and preclinical research contributes to diversification of neoplastic and antimicrobial indications, as well as allows us to better understand mechanisms of toxicities associated with TOP inhibitors. We predict that further efforts to understand the biology of TOP proteins, as well as mechanisms behind drug resistance and toxicities, will contribute to the market growth and will facilitate development of novel molecules and combination regimens.

Ethical approval

Not applicable.

Consent to participate

Not applicable.

Consent for publication

Not applicable.

Funding

HBS is supported by the Swedish Research Council (2019-01066 and 2022-00562) and the Novo Nordisk Foundation.

CRediT authorship contribution statement

Vadim V. Tarasov: Writing – review & editing, Conceptualization. **Vladimir N. Chubarev:** Writing – review & editing, Validation, Formal analysis, Data curation. **Helgi B. Schiöth:** Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition, Conceptualization. **Francisco Alejandro Lagunas-Rangel:** Writing – review & editing, Conceptualization. **Andrey D. Bondarev:** Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Data curation, visualization, Conceptualization. **Jörgen Jonsson:** Writing – review & editing, Supervision, Formal analysis.

Declaration of Competing Interest

The authors declare no conflict of interest.

Data availability

No data was used for the research described in the article.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.phrs.2024.107431.

References

[1] A. Travers, G. Muskhelishvili, DNA structure and function, FEBS J. 282 (12) (2015) 2279–2295, https://doi.org/10.1111/febs.13307.
[2] A. Vologodskii, Disentangling DNA molecules, Phys. Life Rev. 18 (2016) 118–134, https://doi.org/10.1016/j.plrev.2016.05.001.
[3] J.C. Wang, DNA topoisomerases, Annu Rev. Biochem 65 (1996) 635–692, https://doi.org/10.1146/annurev.bi.65.070196.003223.
[4] T.K. Li, L.F. Liu, Tumor cell death induced by topoisomerase-targeting drugs, Annu Rev. Pharm. Toxicol. 41 (2001) 53–77, https://doi.org/10.1146/annurev.pharmtox.41.1.53.
[5] D.B. Khadka, W.J. Cho, Topoisomerase inhibitors as anticancer agents: a patent update, Expert Opin. Ther. Pat. 23 (8) (2013) 1033–1056, https://doi.org/10.1517/13543776.2013.790958.
[6] S.N. Dighe, T.A. Collet, Recent advances in DNA gyrase-targeted antimicrobial agents, Eur. J. Med Chem. 199 (2020) 112326, https://doi.org/10.1016/j.ejmech.2020.112326.
[7] World Health Organization Model List of Essential Medicines – 22nd List, 2021 Geneva , World Health Organization , 2021, Model List of Essential Medicines – 22nd ListWorld Health Organization, 2021.
[8] M. Rask-Andersen, M.S. Almén, H.B. Schiöth, Trends in the exploitation of novel drug targets, Published 2011 Aug 1. Nat. Rev. Drug Discov. 10 (8) (2011) 579–590, https://doi.org/10.1038/nrd3478.
[9] M. Rask-Andersen, S. Masuram, H.B. Schiöth, The druggable genome: evaluation of drug targets in clinical trials suggests major shifts in molecular class and indication, Annu Rev. Pharm. 54 (2014) 9–26, https://doi.org/10.1146/annurev-pharmtox-011613-135943.
[10] M.M. Attwood, M. Rask-Andersen, H.B. Schiöth, Orphan Drugs and Their Impact on Pharmaceutical Development [published correction appears in Trends Pharmacol Sci. 2018 Dec;39(12):1077], Trends Pharm. Sci. 39 (6) (2018) 525–535, https://doi.org/10.1016/j.tips.2018.03.003.
[11] M. Ahmad, D. Xu, W. Wang, Type IA topoisomerases can be "magicians" for both DNA and RNA in all domains of life, RNA Biol. 14 (7) (2017) 854–864, https://doi.org/10.1080/15476286.2017.1330741.
[12] J.J. Champoux, DNA topoisomerases: structure, function, and mechanism, Annu Rev. Biochem 70 (2001) 369–413, https://doi.org/10.1146/annurev.biochem.70.1.369.
[13] C.D. Lima, J.C. Wang, A. Mondragón, Three-dimensional structure of the 67K N-terminal fragment of E. coli DNA topoisomerase I, Nature 367 (6459) (1994) 138–146, https://doi.org/10.1038/367138a0.
[14] A. Mondragón, R. DiGate, The structure of Escherichia coli DNA topoisomerase III, Structure 7 (11) (1999) 1373–1383, https://doi.org/10.1016/s0969-2126(00)80027-1.
[15] M. Gellert, K. Mizuuchi, M.H. O'Dea, H.A. Nash, DNA gyrase: an enzyme that introduces superhelical turns into DNA, Proc. Natl. Acad. Sci. USA 73 (11) (1976) 3872–3876, https://doi.org/10.1073/pnas.73.11.3872.
[16] J. Kato, Y. Nishimura, R. Imamura, H. Niki, S. Hiraga, H. Suzuki, New topoisomerase essential for chromosome segregation in E. coli [published correction appears in Cell 1991 Jun 28;65(7):1289], Cell 63 (2) (1990) 393–404, https://doi.org/10.1016/0092-8674(90)90172-b.
[17] C. Levine, H. Hiasa, K.J. Marians, DNA gyrase and topoisomerase IV: biochemical activities, physiological roles during chromosome replication, and drug sensitivities, Biochim Biophys. Acta 1400 (1-3) (1998) 29–43, https://doi.org/10.1016/s0167-4781(98)00126-2.
[18] L. Stewart, G.C. Ireton, L.H. Parker, K.R. Madden, J.J. Champoux, Biochemical and biophysical analyses of recombinant forms of human topoisomerase I, J. Biol. Chem. 271 (13) (1996) 7593–7601, https://doi.org/10.1074/jbc.271.13.7593.
[19] T. Uemura, K. Morikawa, M. Yanagida, The nucleotide sequence of the fission yeast DNA topoisomerase II gene: structural and functional relationships to other DNA topoisomerases, EMBO J. 5 (9) (1986) 2355–2361, https://doi.org/10.1002/j.1460-2075.1986.tb04504.x.
[20] J.W. Wallis, G. Chrebet, G. Brodsky, M. Rolfe, R. Rothstein, A hyper-recombination mutation in S. cerevisiae identifies a novel eukaryotic topoisomerase, Cell 58 (2) (1989) 409–419, https://doi.org/10.1016/0092-8674(89)90855-6.
[21] F.H. Drake, J.P. Zimmerman, F.L. McCabe, et al., Purification of topoisomerase II from amsacrine-resistant P388 leukemia cells. Evidence for two forms of the enzyme, J. Biol. Chem. 262 (34) (1987) 16739–16747.
[22] R. Hanai, P.R. Caron, J.C. Wang, Human TOP3: a single-copy gene encoding DNA topoisomerase III, Proc. Natl. Acad. Sci. USA 93 (8) (1996 Apr 16) 3653–3657, https://doi.org/10.1073/pnas.93.8.3653. PMID: 8622991; PMCID: PMC39666.
[23] S.W. Ng, Y. Liu, K.T. Hasselblatt, S.C. Mok, R.S. Berkowitz, A new human topoisomerase III that interacts with SGS1 protein, Nucleic Acids Res 27 (4) (1999) 993–1000, https://doi.org/10.1093/nar/27.4.993.
[24] N. Minkah, Y. Hwang, K. Perry, et al., Variola virus topoisomerase: DNA cleavage specificity and distribution of sites in Poxvirus genomes, Virology 365 (1) (2007) 60–69, https://doi.org/10.1016/j.virol.2007.02.037.
[25] R. García-Beato, J.M. Freije, C. López-Otín, R. Blasco, E. Viñuela, M.L. Salas, A gene homologous to topoisomerase II in African swine fever virus, Virology 188 (2) (1992) 938–947, https://doi.org/10.1016/0042-6822(92)90558-7.
[26] A.J. Schoeffler, J.M. Berger, DNA topoisomerases: harnessing and constraining energy to govern chromosome topology, Q Rev. Biophys. 41 (1) (2008) 41–101, https://doi.org/10.1017/S003358350800468X.
[27] D. Xu, W. Shen, R. Guo, et al., Top3β is an RNA topoisomerase that works with fragile X syndrome protein to promote synapse formation, Nat. Neurosci. 16 (9) (2013) 1238–1247, https://doi.org/10.1038/nn.3479.

[28] Y. Wang, Y.L. Lyu, J.C. Wang, Dual localization of human DNA topoisomerase IIIalpha to mitochondria and nucleus, Proc. Natl. Acad. Sci. USA 99 (19) (2002) 12114–12119, https://doi.org/10.1073/pnas.192449499.

[29] H. Zhang, J.M. Barceló, B. Lee, et al., Human mitochondrial topoisomerase I, Proc. Natl. Acad. Sci. USA 98 (19) (2001) 10608–10613, https://doi.org/10.1073/pnas.191321998.

[30] M. Thornton, M. Armitage, A. Maxwell, et al., Immunogold localization of GyrA and GyrB proteins in Escherichia coli, Microbiology 140 (Pt 9) (1994) 2371–2382, https://doi.org/10.1099/13500872-140-9-2371.

[31] S. Tadesse, P.L. Graumann, Differential and dynamic localization of topoisomerases in Bacillus subtilis, J. Bacteriol. 188 (8) (2006) 3002–3011, https://doi.org/10.1128/JB.188.8.3002-3011.2006.

[32] J. Kato, H. Suzuki, H. Ikeda, Purification and characterization of DNA topoisomerase IV in Escherichia coli, J. Biol. Chem. 267 (36) (1992) 25676–25684.

[33] M. Uhlén, L. Fagerberg, B.M. Hallström, et al., Proteomics. Tissue-based map of the human proteome, Science 347 (6220) (2015) 1260419, https://doi.org/10.1126/science.1260419.

[34] A. Eisenreich, V.Y. Bogdanov, A. Zakrzewicz, et al., Cdc2-like kinases and DNA topoisomerase I regulate alternative splicing of tissue factor in human endothelial cells, Circ. Res 104 (5) (2009) 589–599, https://doi.org/10.1161/CIRCRESAHA.108.183905.

[35] D.W. Zandvliet, A.M. Hanby, C.A. Austin, et al., Analysis of foetal expression sites of human type II DNA topoisomerase alpha and beta mRNAs by in situ hybridisation, Biochim Biophys. Acta 1307 (2) (1996) 239–247, https://doi.org/10.1016/0167-4781(96)00063-2.

[36] H. Turley, M. Comley, S. Houlbrook, et al., The distribution and expression of the two isoforms of DNA topoisomerase II in normal and neoplastic human tissues, Br. J. Cancer 75 (9) (1997) 1340–1346, https://doi.org/10.1038/bjc.1997.227.

[37] G. Capranico, S. Tinelli, C.A. Austin, M.L. Fisher, F. Zunino, Different patterns of gene expression of topoisomerase II isoforms in differentiated tissues during murine development, Biochim Biophys. Acta 1132 (1) (1992) 43–48, https://doi.org/10.1016/0167-4781(92)90050-a.

[38] J.C. Wang, Cellular roles of DNA topoisomerases: a molecular perspective, Nat. Rev. Mol. Cell Biol. 3 (6) (2002) 430–440, https://doi.org/10.1038/nrm831.

[39] Y. Pommier, A. Nussenzweig, S. Takeda, C. Austin, Human topoisomerases and their roles in genome stability and organization, Nat. Rev. Mol. Cell Biol. 23 (6) (2022) 407–427, https://doi.org/10.1038/s41580-022-00452-3.

[40] J.L. Nitiss, Investigating the biological functions of DNA topoisomerases in eukaryotic cells, Biochim Biophys. Acta 1400 (1-3) (1998) 63–81, https://doi.org/10.1016/s0167-4781(98)00128-6.

[41] A. Vávrová, T. Šimůnek, DNA topoisomerase IIβ: a player in regulation of gene expression and cell differentiation, Int J. Biochem Cell Biol. 44 (6) (2012) 834–837, https://doi.org/10.1016/j.biocel.2012.03.005.

[42] T.J. Nicholls, C.A. Nadalutti, E. Motori, et al., Topoisomerase 3α Is Required for Decatenation and Segregation of Human mtDNA, Mol. Cell 69 (1) (2018) 9–23. e6, https://doi.org/10.1016/j.molcel.2017.11.033.

[43] Y. Joo, Y. Xue, Y. Wang, et al., Topoisomerase 3β knockout mice show transcriptional and behavioural impairments associated with neurogenesis and synaptic plasticity, Published 2020 Jun 19, Nat. Commun. 11 (1) (2020) 3143, https://doi.org/10.1038/s41467-020-16884-4.

[44] Q. Zhu, P. Pongpech, R.J. DiGate, Type I topoisomerase activity is required for proper chromosomal segregation in Escherichia coli, Proc. Natl. Acad. Sci. USA 98 (17) (2001) 9766–9771, https://doi.org/10.1073/pnas.171579898.

[45] J. Hirsch, D. Klostermeier, What makes a type IIA topoisomerase a gyrase or a Topo IV? Nucleic Acids Res 49 (11) (2021) 6027–6042, https://doi.org/10.1093/nar/gkab270.

[46] J.K. O'Connor, L.J. Hazard, J.M. Avent, R.J. Lee, J. Fischbach, D.K. Gaffney, Topoisomerase II alpha expression correlates with diminished disease-free survival in invasive breast cancer, Int J. Radiat. Oncol. Biol. Phys. 65 (5) (2006) 1411–1415, https://doi.org/10.1016/j.ijrobp.2006.02.045.

[47] Z. Zhou, S. Liu, M. Zhang, et al., Overexpression of topoisomerase 2-alpha confers a poor prognosis in pancreatic adenocarcinoma identified by co-expression analysis, Dig. Dis. Sci. 62 (10) (2017) 2790–2800, https://doi.org/10.1007/s10620-017-4718-4.

[48] Y. Liu, J. Ma, J.S. Song, et al., DNA topoisomerase II alpha promotes the metastatic characteristics of glioma cells by transcriptionally activating β-catenin, Bioengineered 13 (2) (2022) 2207–2216, https://doi.org/10.1080/21655979.2021.2023985.

[49] M. Li, Y. Liu, Topoisomerase I in human disease pathogenesis and treatments, Genom. Proteom. Bioinforma. 14 (3) (2016) 166–171, https://doi.org/10.1016/j.gpb.2016.02.004.

[50] Y.C. Tse-Dinh, Bacterial topoisomerase I as a target for discovery of antibacterial compounds, Nucleic Acids Res 37 (3) (2009) 731–737, https://doi.org/10.1093/nar/gkn936.

[51] F. Da Fonseca, B. Moss, Poxvirus DNA topoisomerase knockout mutant exhibits decreased infectivity associated with reduced early transcription, Proc. Natl. Acad. Sci. USA 100 (20) (2003) 11291–11296, https://doi.org/10.1073/pnas.1534874100.

[52] K.R. Prasanth, M. Hirano, W.S. Fagg, et al., Topoisomerase III-β is required for efficient replication of positive-sense RNA viruses, Antivir. Res 182 (2020) 104874, https://doi.org/10.1016/j.antiviral.2020.104874.

[53] T. Zhang, M. Wallis, V. Petrovic, J. Challis, P. Kalitsis, D.F. Hudson, Loss of TOP3B leads to increased R-loop formation and genome instability, Open Biol. 9 (12) (2019) 190222, https://doi.org/10.1098/rsob.190222.

[54] M. Ahmad, W. Shen, W. Li, et al., Topoisomerase 3β is the major topoisomerase for mRNAs and linked to neurodevelopment and mental dysfunction, Nucleic Acids Res 45 (5) (2017) 2704–2713, https://doi.org/10.1093/nar/gkw1293.

[55] C.A. Martin, K. Sarlós, C.V. Logan, et al., Mutations in TOP3A Cause a Bloom Syndrome-like Disorder [published correction appears in Am J Hum Genet. 2018 Sep 6;103(3):456] [published correction appears in Am J Hum Genet. 2024 May 2;111(5):996], Am. J. Hum. Genet 103 (2) (2018) 221–231, https://doi.org/10.1016/j.ajhg.2018.07.001.

[56] X. Liang, Q. Wu, S. Luan, et al., A comprehensive review of topoisomerase inhibitors as anticancer agents in the past decade, Eur. J. Med Chem. 171 (2019) 129–168, https://doi.org/10.1016/j.ejmech.2019.03.034.

[57] K. Buzun, A. Bielawska, K. Bielawski, A. Gornowicz, DNA topoisomerases as molecular targets for anticancer drugs, J. Enzym. Inhib. Med Chem. 35 (1) (2020) 1781–1799, https://doi.org/10.1080/14756366.2020.1821676.

[58] L.F. Liu, DNA topoisomerase poisons as antitumor drugs, Annu Rev. Biochem 58 (1989) 351–375, https://doi.org/10.1146/annurev.bi.58.070189.002031.

[59] G. Capranico, M. Binaschi, M.E. Borgnetto, F. Zunino, M. Palumbo, A protein-mediated mechanism for the DNA sequence-specific action of topoisomerase II poisons, Trends Pharm. Sci. 18 (9) (1997) 323–329, https://doi.org/10.1016/s0165-6147(97)01095-x.

[60] UniProt Consortium, UniProt: the universal protein knowledgebase in 2023, Nucleic Acids Res 51 (D1) (2023) D523–D531, https://doi.org/10.1093/nar/gkac1052.

[61] E. Paradis, K. Schliep, ape 5.0: an environment for modern phylogenetics and evolutionary analyses in R, Bioinformatics 35 (3) (2019) 526–528, https://doi.org/10.1093/bioinformatics/bty633.

[62] G. Yu, Using ggtree to visualize data on tree-like structures, Curr. Protoc. Bioinforma. 69 (1) (2020) e96, https://doi.org/10.1002/cpbi.96.

[63] Center Watch. Clinical Research and Drug Information. Available at: ⟨https://www.centerwatch.com/⟩, 2018 (Last accessed March 2, 2018).

[64] D.S. Wishart, Y.D. Feunang, A.C. Guo, et al., DrugBank 5.0: a major update to the DrugBank database for 2018, Nucleic Acids Res 46 (D1) (2018) D1074–D1082, https://doi.org/10.1093/nar/gkx1037.

[65] US Food and Drug Administration. Drugs@FDA: FDA Approved Drug Products. Available at: ⟨https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm⟩, 2024 (Last accessed May 3, 2024).

[66] European Medicines Agency. EMA Medicines database. Available at: ⟨https://www.ema.europa.eu/en/medicines⟩, 2024 (Last accessed April 25, 2024).

[67] National Institute for Health and Care Excellence. NICE Guidance and Advice list. Available at: ⟨https://www.nice.org.uk/guidance/published?ngt=Technology%20appraisal%20guidance&ndt=Guidance⟩, 2024 (Last accessed May 22, 2024).

[68] S.D. Harding, J.F. Armstrong, E. Faccenda, et al., The IUPHAR/BPS Guide to PHARMACOLOGY in 2024, Nucleic Acids Res 52 (D1) (2024) D1438–D1449, https://doi.org/10.1093/nar/gkad944.

[69] The National Institute of Health. Clinical Trials database. Available at: ⟨https://clinicaltrials.gov⟩, 2024 (Last accessed April 13, 2024).

[70] European Medicines Agency. EU Clinical Trials Register. Available at: ⟨https://www.clinicaltrialsregister.eu/ctr-search/search⟩, 2024 (Last accessed April 13, 2024).

[71] National Health and Medical Research Council. The Australian New Zealand Clinical Trials Registry. Available at: ⟨https://www.anzctr.org.au/TrialSearch.aspx⟩, 2024 (Last accessed April 13, 2024).

[72] Y. Pommier, E. Leo, H. Zhang, C. Marchand, DNA topoisomerases and their poisoning by anticancer and antibacterial drugs, Chem. Biol. 17 (5) (2010) 421–433, https://doi.org/10.1016/j.chembiol.2010.04.012.

[73] J.L. Delgado, C.M. Hsieh, N.L. Chan, H. Hiasa, Topoisomerases as anticancer targets, Published 2018 Jan 23, Biochem J. 475 (2) (2018) 373–398, https://doi.org/10.1042/BCJ20160583.

[74] A. Thomas, Y. Pommier, Targeting topoisomerase I in the era of precision medicine, Clin. Cancer Res 25 (22) (2019) 6581–6589, https://doi.org/10.1158/1078-0432.CCR-19-1089.

[75] Ž. Skok, N. Zidar, D. Kikelj, J. Ilaš, Dual inhibitors of human DNA topoisomerase II and Other Cancer-Related Targets, J. Med Chem. 63 (3) (2020) 884–904, https://doi.org/10.1021/acs.jmedchem.9b00726.

[76] A. Dehshahri, M. Ashrafizadeh, E. Ghasemipour Afshar, et al., Topoisomerase inhibitors: pharmacology and emerging nanoscale delivery systems, Pharm. Res 151 (2020) 104551, https://doi.org/10.1016/j.phrs.2019.104551.

[77] T. Khan, K. Sankhe, V. Suvarna, A. Sherje, K. Patel, B. Dravyakar, DNA gyrase inhibitors: progress and synthesis of potent compounds as antibacterial agents, Biomed. Pharm. 103 (2018) 923–938, https://doi.org/10.1016/j.biopha.2018.04.021.

[78] A. Rusu, I.A. Lungu, O.L. Moldovan, C. Tanase, G. Hancu, Structural characterization of the millennial antibacterial (fluoro)quinolones-shaping the fifth generation, Published 2021 Aug 18. Pharmaceutics 13 (8) (2021) 1289, https://doi.org/10.3390/pharmaceutics13081289.

[79] G.S. Bisacchi, J.I. Manchester, A new-class antibacterial-almost. lessons in drug discovery and development: a critical analysis of more than 50 years of effort toward ATPase inhibitors of DNA gyrase and topoisomerase IV, ACS Infect. Dis. 1 (1) (2015) 4–41, https://doi.org/10.1021/id500013t.

[80] S.L. Badshah, A. Ullah, New developments in non-quinolone-based antibiotics for the inhibiton of bacterial gyrase and topoisomerase IV, Eur. J. Med Chem. 152 (2018) 393–400, https://doi.org/10.1016/j.ejmech.2018.04.059.

[81] A.D. Bondarev, M.M. Attwood, J. Jonsson, V.N. Chubarev, V.V. Tarasov, H. B. Schiöth, Recent developments of HDAC inhibitors: emerging indications and novel molecules, Br. J. Clin. Pharm. 87 (12) (2021) 4577–4597, https://doi.org/10.1111/bcp.14889.

[82] M.M. Attwood, D. Fabbro, A.V. Sokolov, S. Knapp, H.B. Schiöth, Trends in kinase drug discovery: targets, indications and inhibitor design [published correction appears in Nat Rev Drug Discov. 2021 Oct;20(10):798], Nat. Rev. Drug Discov. 20 (11) (2021) 839–861, https://doi.org/10.1038/s41573-021-00252-y.

[83] A.D. Bondarev, M.M. Attwood, J. Jonsson, et al., Recent developments of phosphodiesterase inhibitors: clinical trials, emerging indications and novel molecules, Published 2022 Nov 24. Front Pharm. 13 (2022) 1057083 https://doi.org/10.3389/fphar.2022.1057083.

[84] C. Knox, M. Wilson, C.M. Klinger, et al., DrugBank 6.0: the DrugBank Knowledgebase for 2024, Nucleic Acids Res 52 (D1) (2024) D1265–D1275, https://doi.org/10.1093/nar/gkad976.

[85] V.B. Siramshetty, I. Grishagin, Đ.T. Nguyễn, et al., NCATS Inxight Drugs: a comprehensive and curated portal for translational research, Nucleic Acids Res 50 (D1) (2022) D1307–D1316, https://doi.org/10.1093/nar/gkab918.

[86] AdisInsight International. AdisInsight database. Available at: ⟨https://adisinsight.springer.com⟩. (Last accessed April 15, 2024).

[87] T.D.M. Pham, Z.M. Ziora, M.A.T. Blaskovich, Quinolone antibiotics, Published 2019 Jun 28. Medchemcomm 10 (10) (2019) 1719–1739, https://doi.org/10.1039/c9md00120d.

[88] R.H. Flatman, A. Eustaquio, S.M. Li, L. Heide, A. Maxwell, Structure-activity relationships of aminocoumarin-type gyrase and topoisomerase IV inhibitors obtained by combinatorial biosynthesis, Antimicrob. Agents Chemother. 50 (4) (2006) 1136–1142, https://doi.org/10.1128/AAC.50.4.1136-1142.2006.

[89] K. Sasaki, H. Takada, C. Hayashi, et al., Synthesis of novobiocin derivatives and evaluation of their antigonococcal activity and pharmacokinetics, Bioorg. Med Chem. 92 (2023) 117381, https://doi.org/10.1016/j.bmc.2023.117381.

[90] S. Kim, J. Chen, T. Cheng, et al., PubChem 2023 update, Nucleic Acids Res 51 (D1) (2023) D1373–D1380, https://doi.org/10.1093/nar/gkac956.

[91] F. Zunino, G. Pratesi, P. Perego, Role of the sugar moiety in the pharmacological activity of anthracyclines: development of a novel series of disaccharide analogs, Biochem Pharm. 61 (8) (2001) 933–938, https://doi.org/10.1016/s0006-2952(01)00522-6.

[92] B.H. Long, A.M. Casazza, Structure-activity relationships of VP-16 analogues, Cancer Chemother. Pharm. 34 (Suppl) (1994) S26–S31, https://doi.org/10.1007/BF00684860.

[93] K.M. Kacprzak, Chemistry and Biology of Camptothecin and its Derivatives, in: K. Ramawat, J.M. Mérillon (Eds.), Natural Products, Springer, Berlin, Heidelberg, 2013, https://doi.org/10.1007/978-3-642-22144-6_26.

[94] G.S. Bisacchi, Origins of the quinolone class of antibacterials: an expanded "discovery story", J. Med Chem. 58 (12) (2015) 4874–4882, https://doi.org/10.1021/jm501881c.

[95] H.H. Zinsser, Nalidixic acid in acute and chronic urinary tract infections, Med Clin. North Am. 54 (5) (1970) 1347–1350, https://doi.org/10.1016/S0025-7125(16)32600-1.

[96] J.N. Newman, R.V. Floyd, J.L. Fothergill, Invasion and diversity in Pseudomonas aeruginosa urinary tract infections, J. Med Microbiol 71 (3) (2022) 001458, https://doi.org/10.1099/jmm.0.001458.

[97] P. Ball, Quinolone generations: natural history or natural selection, J. Antimicrob. Chemother. 46 (Suppl T1) (2000) 17–24, https://doi.org/10.1093/oxfordjournals.jac.a020889.

[98] R.A. Dobson, J.R. O'Connor, S.A. Poulin, R.B. Kundsin, T.F. Smith, P.E. Came, In vitro antimicrobial activity of rosoxacin against Neisseria gonorrhoeae, Chlamydia trachomatis, and Ureaplasma urealyticum, Antimicrob. Agents Chemother. 18 (5) (1980) 738–740, https://doi.org/10.1128/AAC.18.5.738.

[99] B. Romanowski, T.W. Austin, F.L. Pattison, et al., Rosoxacin in the therapy of uncomplicated gonorrhea, Antimicrob. Agents Chemother. 25 (4) (1984) 455–457, https://doi.org/10.1128/AAC.25.4.455.

[100] M. Shimizu, Y. Takase, S. Nakamura, H. Katae, A. Minami, Pipemidic acid, a new antibacterial agent active against Pseudomonas aeruginosa: in vitro properties, Antimicrob. Agents Chemother. 8 (2) (1975) 132–138, https://doi.org/10.1128/AAC.8.2.132.

[101] Z.S. Almalki, X. Yue, Y. Xia, P.R. Wigle, J.J. Guo, Utilization, spending, and price trends for quinolones in the US medicaid programs: 25 years' experience 1991-2015, Pharm. Open 1 (2) (2017) 123–131, https://doi.org/10.1007/s41669-016-0007-y.

[102] N. Adriaenssens, R. Bruyndonckx, A. Versporten, et al., Consumption of quinolones in the community, European Union/European Economic Area, 1997-2017, J. Antimicrob. Chemother. 76 (12 Suppl 2) (2021) ii37–ii44, https://doi.org/10.1093/jac/dkab176.

[103] B.A. Faine, M.A. Rech, P. Vakkalanka, et al., High prevalence of fluoroquinolone-resistant UTI among US emergency department patients diagnosed with urinary tract infection, 2018-2020, Acad. Emerg. Med 29 (9) (2022) 1096–1105, https://doi.org/10.1111/acem.14545.

[104] S. Jacobsson, M.J. Cole, G. Spiteri, M. Day, M. Unemo, Euro-GASP Network. Associations between antimicrobial susceptibility/resistance of Neisseria gonorrhoeae isolates in European Union/European Economic Area and patients' gender, sexual orientation and anatomical site of infection, 2009-2016, Published 2021 Mar 18. BMC Infect. Dis. 21 (1) (2021) 273, https://doi.org/10.1186/s12879-021-05931-0.

[105] U.S. Food and Drug Administration. FDA Drug Safety Communication: FDA updates warnings for oral and injectable fluoroquinolone antibiotics due to disabling side effects. Available at: ⟨https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-updates-warnings-oral-and-injectable-fluoroquinolone-antibiotics⟩.

[106] European Medicines Agency. Quinolone- and fluoroquinolone-containing medicinal products – referral. Available at: ⟨https://www.ema.europa.eu/en/medicines/human/referrals/quinolone-fluoroquinolone-containing-medicinal-products#related-medicines⟩.

[107] U.S. Food and Drug Administration. FDA warns about increased risk of ruptures or tears in the aorta blood vessel with fluoroquinolone antibiotics in certain patients. Available at: ⟨https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-increased-risk-ruptures-or-tears-aorta-blood-vessel-fluoroquinolone-antibiotics⟩.

[108] US Food and Drug Administration. FDA reinforces safety information about serious low blood sugar levels and mental health side effects with fluoroquinolone antibiotics; requires label changes. Available at: ⟨https://www.fda.gov/drugs/drug-safety-and-availability/fda-reinforces-safety-information-about-serious-low-blood-sugar-levels-and-mental-health-side⟩.

[109] S.S. Bhagwat, M. Nandanwar, A. Kansagara, et al., Levonadifloxacin, a novel broad-spectrum anti-MRSA benzoquinolizine quinolone agent: review of current evidence, Published 2019 Dec 24. Drug Des. Devel Ther. 13 (2019) 4351–4365, https://doi.org/10.2147/DDDT.S229882.

[110] K.D. Mehta, J.B. Sharma, A. Anand, et al., Real-world evidence of efficacy and safety of levonadifloxacin (Oral and IV) in the management of acute bacterial skin and skin structure infections (ABSSSI): findings of a retrospective, multi-center study, Published 2022 Apr 20, Cureus 14 (4) (2022) e24299, https://doi.org/10.7759/cureus.24299.

[111] I. Kurokawa, S. Kanayama, O. Yamasaki, Antimicrobial activity of ozenoxacin and other antimicrobials against Staphylococcus aureus strains isolated from clinical skin specimens in Japan in 2019 and 2020, J. Infect. Chemother. 28 (12) (2022) 1693–1696, https://doi.org/10.1016/j.jiac.2022.08.014.

[112] J. Vila, A.A. Hebert, A. Torrelo, et al., Ozenoxacin: a review of preclinical and clinical efficacy, Expert Rev. Anti Infect. Ther. 17 (3) (2019) 159–168, https://doi.org/10.1080/14787210.2019.1573671.

[113] A.A. Hebert, N. Albareda, T. Rosen, et al., Topical antibacterial agent for treatment of adult and pediatric patients with impetigo: pooled analysis of phase 3 clinical trials, J. Drugs Dermatol. 17 (10) (2018) 1051–1057.

[114] L. Heide, The aminocoumarins: biosynthesis and biology, Nat. Prod. Rep. 26 (10) (2009) 1241–1250, https://doi.org/10.1039/b808333a.

[115] S. Bellon, J.D. Parsons, Y. Wei, et al., Crystal structures of Escherichia coli topoisomerase IV ParE subunit (24 and 43 kilodaltons): a single residue dictates differences in novobiocin potency against topoisomerase IV and DNA gyrase, Antimicrob. Agents Chemother. 48 (5) (2004) 1856–1864, https://doi.org/10.1128/AAC.48.5.1856-1864.2004.

[116] P. Laurin, D. Ferroud, M. Klich, et al., Synthesis and in vitro evaluation of novel highly potent coumarin inhibitors of gyrase B, Bioorg. Med Chem. Lett. 9 (14) (1999) 2079–2084, https://doi.org/10.1016/s0960-894x(99)00329-7.

[117] F. Collin, S. Karkare, A. Maxwell, Exploiting bacterial DNA gyrase as a drug target: current state and perspectives, Appl. Microbiol Biotechnol. 92 (3) (2011) 479–497, https://doi.org/10.1007/s00253-011-3557-z.

[118] Determination That ALBAMYCIN (Novobiocin Sodium) Capsule, 250 Milligrams, Was Withdrawn From Sale for Reasons of Safety or Effectiveness. Federal Register/Vol. 76, No. 12/Wednesday, January 19, 2011/Notices. Available at: ⟨https://www.govinfo.gov/content/pkg/FR-2011-01-19/pdf/2011-1000.pdf⟩.

[119] A.K. Larsen, A.E. Escargueil, A. Skladanowski, Catalytic topoisomerase II inhibitors in cancer therapy, Pharm. Ther. 99 (2) (2003) 167–181, https://doi.org/10.1016/s0163-7258(03)00058-5.

[120] G. Rappa, A. Lorico, A.C. Sartorelli, Potentiation by novobiocin of the cytotoxic activity of etoposide (VP-16) and teniposide (VM-26), Int J. Cancer 51 (5) (1992) 780–787, https://doi.org/10.1002/ijc.2910510519.

[121] G. Rappa, J.R. Murren, L.M. Johnson, A. Lorico, A.C. Sartorelli, Novobiocin-induced VP-16 accumulation and MRP expression in human leukemia and ovarian carcinoma cells, Anticancer Drug Des. 15 (2) (2000) 127–134.

[122] K. Shiozawa, M. Oka, H. Soda, et al., Reversal of breast cancer resistance protein (BCRP/ABCG2)-mediated drug resistance by novobiocin, a coumermycin antibiotic, Int J. Cancer 108 (1) (2004) 146–151, https://doi.org/10.1002/ijc.11528.

[123] G.K. Ellis, J. Crowley, R.B. Livingston, J.W. Goodwin, L. Hutchins, A. Allen, Cisplatin and novobiocin in the treatment of non-small cell lung cancer. A Southwest Oncology Group study, Cancer 67 (12) (1991) 2969–2973, https://doi.org/10.1002/1097-0142(19910615)67:12<2969::aid-cncr2820671205>3.0.co;2-m.

[124] C. Bailly, Pyronaridine: An update of its pharmacological activities and mechanisms of action, Biopolymers 112 (4) (2021) e23398, https://doi.org/10.1002/bip.23398.

[125] P. Chavalitshewinkoon, P. Wilairat, S. Gamage, W. Denny, D. Figgitt, R. Ralph, Structure-activity relationships and modes of action of 9-anilinoacridines against chloroquine-resistant Plasmodium falciparum in vitro, Antimicrob. Agents Chemother. 37 (3) (1993) 403–406, https://doi.org/10.1128/AAC.37.3.403.

[126] S. Auparakkitanon, P. Wilairat, Cleavage of DNA induced by 9-anilinoacridine inhibitors of topoisomerase II in the malaria parasite Plasmodium falciparum, Biochem Biophys. Res Commun. 269 (2) (2000) 406–409, https://doi.org/10.1006/bbrc.2000.2305.

[127] J. Pryce, M. Taylor, T. Fox, P. Hine, Pyronaridine-artesunate for treating uncomplicated Plasmodium falciparum malaria, Published 2022 Jun 21, Cochrane Database Syst. Rev. 6 (6) (2022) CD006404, https://doi.org/10.1002/14651858.CD006404.pub4.

[128] P.J. Villanueva, D.A. Gutierrez, L. Contreras, et al., The antimalarial drug pyronaridine inhibits topoisomerase ii in breast cancer cells and hinders tumor progression in vivo, Clin. Cancer Drugs 8 (1) (2021) 50–56, https://doi.org/10.2174/2212697x08666210219101023.

[129] J. Li, W. Wang, J. Yao, et al., Old drug repurposing for neglected disease: Pyronaridine as a promising candidate for the treatment of Echinococcus granulosus infections, EBioMedicine 54 (2020) 102711, https://doi.org/10.1016/j.ebiom.2020.102711.
[130] N.G. Bush, K. Evans-Roberts, A. Maxwell, DNA Topoisomerases, 10.1128/ecosalplus.ESP-0010-2014, EcoSal 6 (2) (2015), https://doi.org/10.1128/ecosalplus.ESP-0010-2014.
[131] P. Chavalitshewinkoon-Petmitr, G. Pongvilairat, S. Auparakkitanon, P. Wilairat, Gametocytocidal activity of pyronaridine and DNA topoisomerase II inhibitors against multidrug-resistant Plasmodium falciparum in vitro, Parasitol. Int 48 (4) (2000) 275–280, https://doi.org/10.1016/s1383-5769(99)00028-8.
[132] D.G. Mudeppa, S. Kumar, S. Kokkonda, J. White, P.K. Rathod, Topoisomerase II from human malaria parasites: expression, purification, and selective inhibition, J. Biol. Chem. 290 (33) (2015) 20313–20324, https://doi.org/10.1074/jbc.M115.639039.
[133] R.B. Weiss, G. Sarosy, K. Clagett-Carr, M. Russo, B. Leyland-Jones, Anthracycline analogs: the past, present, and future, Cancer Chemother. Pharm. 18 (3) (1986) 185–197, https://doi.org/10.1007/BF00273384.
[134] S. Tsukagoshi, Pirarubicin (THP-adriamycin)], Gan Kagaku Ryoho 15 (9) (1988) 2819–2827.
[135] S.V. Onrust, H.M. Lamb, Valrubicin, Drugs Aging 15 (1) (1999) 69–76, https://doi.org/10.2165/00002512-199915010-00006.
[136] F. Ganzina, 4'-epi-doxorubicin, a new analogue of doxorubicin: a preliminary overview of preclinical and clinical data, Cancer Treat. Rev. 10 (1) (1983) 1–22, https://doi.org/10.1016/s0305-7372(83)80029-2.
[137] T. Shimizu, M. Takada, T. Yana, M. Fukuoka, [Amrubicin], Nihon Rinsho 60 (Suppl 5) (2002) 374–377.
[138] R.J. Cersosimo, Idarubicin: an anthracycline antineoplastic agent, Clin. Pharm. 11 (2) (1992) 152–167.
[139] M.S. Cookson, S.S. Chang, C. Lihou, et al., Use of intravesical valrubicin in clinical practice for treatment of nonmuscle-invasive bladder cancer, including carcinoma in situ of the bladder, Ther. Adv. Urol. 6 (5) (2014) 181–191, https://doi.org/10.1177/1756287214541798.
[140] H.J. Röthig, H.P. Kraemer, H.H. Sedlacek, Aclarubicin: experimental and clinical experience, Drugs Exp. Clin. Res 11 (2) (1985) 123–125.
[141] S. Wadler, J.Z. Fuks, P.H. Wiernik, Phase I and II agents in cancer therapy: I. Anthracyclines and related compounds, J. Clin. Pharm. 26 (7) (1986) 491–509, https://doi.org/10.1002/j.1552-4604.1986.tb02942.x.
[142] S. Motyka, K. Jafernik, H. Ekiert, et al., Podophyllotoxin and its derivatives: potential anticancer agents of natural origin in cancer chemotherapy, Biomed. Pharm. 158 (2023) 114145, https://doi.org/10.1016/j.biopha.2022.114145.
[143] S.Y. Liu, B.D. Hwang, M. Haruna, Y. Imakura, K.H. Lee, Y.C. Cheng, Podophyllotoxin analogs: effects on DNA topoisomerase II, tubulin polymerization, human tumor KB cells, and their VP-16-resistant variants, Mol. Pharm. 36 (1) (1989) 78–82.
[144] Y. Pommier, Topoisomerase I inhibitors: camptothecins and beyond, Nat. Rev. Cancer 6 (10) (2006) 789–802, https://doi.org/10.1038/nrc1977.
[145] S.J. Keam, Trastuzumab deruxtecan: first approval, Drugs 80 (5) (2020) 501–508, https://doi.org/10.1007/s40265-020-01281-4.
[146] Y.Y. Syed, Sacituzumab govitecan: first approval, Drugs 80 (10) (2020) 1019–1025, https://doi.org/10.1007/s40265-020-01337-5.
[147] S. Tsukagoshi, [A novel antitumor agent, sobuzoxane (MST-16)], Gan Kagaku Ryoho 21 (7) (1994) 1089–1097.
[148] B.A. Weaver, How Taxol/paclitaxel kills cancer cells, Mol. Biol. Cell 25 (18) (2014) 2677–2681, https://doi.org/10.1091/mbc.E14-04-0916.
[149] V. Dhawan, D.S. Swaffar, A unique paclitaxel-mediated modulation of the catalytic activity of topoisomerase IIalpha, Anticancer Drugs 10 (4) (1999) 397–404, https://doi.org/10.1097/00001813-199904000-00008.
[150] J.V. McGowan, R. Chung, A. Maulik, I. Piotrowska, J.M. Walker, D.M. Yellon, Anthracycline chemotherapy and cardiotoxicity, Cardiovasc Drugs Ther. 31 (1) (2017) 63–75, https://doi.org/10.1007/s10557-016-6711-0.
[151] D.J. Perez, V.J. Harvey, B.A. Robinson, et al., A randomized comparison of single-agent doxorubicin and epirubicin as first-line cytotoxic therapy in advanced breast cancer, J. Clin. Oncol. 9 (12) (1991) 2148–2152, https://doi.org/10.1200/JCO.1991.9.12.2148.
[152] A systematic collaborative overview of randomized trials comparing idarubicin with daunorubicin (or other anthracyclines) as induction therapy for acute myeloid leukaemia. AML Collaborative Group 1 (103 Br. J. Haematol. , 1998, 031100–109.
[153] W.C.M. Dempke, R. Zielinski, C. Winkler, S. Silberman, S. Reuther, W. Priebe, Anthracycline-induced cardiotoxicity - are we about to clear this hurdle, Eur. J. Cancer 185 (2023) 94–104, https://doi.org/10.1016/j.ejca.2023.02.019.
[154] A.A. Bagdasaryan, V.N. Chubarev, E.A. Smolyarchuk, et al., Pharmacogenetics of drug metabolism: the role of gene polymorphism in the regulation of doxorubicin safety and efficacy, Published 2022 Nov 4. Cancers 14 (21) (2022) 5436, https://doi.org/10.3390/cancers14215436.
[155] S. Deng, T. Yan, C. Jendrny, et al., Dexrazoxane may prevent doxorubicin-induced DNA damage via depleting both topoisomerase II isoforms, Published 2014 Nov 18. BMC Cancer 14 (2014) 842, https://doi.org/10.1186/1471-2407-14-842.
[156] E.C. de Baat, R.L. Mulder, S. Armenian, et al., Dexrazoxane for preventing or reducing cardiotoxicity in adults and children with cancer receiving anthracyclines, Published 2022 Sep 27, Cochrane Database Syst. Rev. 9 (9) (2022) CD014638, https://doi.org/10.1002/14651858.CD014638.pub2.
[157] R. Mattioli, A. Ilari, B. Colotti, L. Mosca, F. Fazi, G. Colotti, Doxorubicin and other anthracyclines in cancers: activity, chemoresistance and its overcoming, Mol. Asp. Med 93 (2023) 101205, https://doi.org/10.1016/j.mam.2023.101205.
[158] E.C. van Dalen, E.M. Michiels, H.N. Caron, L.C. Kremer, Different anthracycline derivates for reducing cardiotoxicity in cancer patients, Published 2010 May 12, Cochrane Database Syst. Rev. 2010 (5) (2010) CD005006, https://doi.org/10.1002/14651858.CD005006.pub4.
[159] M.L. Slevin, P.I. Clark, S.P. Joel, et al., A randomized trial to evaluate the effect of schedule on the activity of etoposide in small-cell lung cancer, J. Clin. Oncol. 7 (9) (1989) 1333–1340, https://doi.org/10.1200/JCO.1989.7.9.1333.
[160] D.H. Johnson, J.D. Hainsworth, K.R. Hande, F.A. Greco, Current status of etoposide in the management of small cell lung cancer, Cancer 67 (1 Suppl) (1991) 231–244, https://doi.org/10.1002/1097-0142(19910101)67:1+<231::aid-cncr2820671305>3.0.co;2-e.
[161] P.J.Sr Loehrer, Etoposide therapy for testicular cancer, Cancer 67 (1 Suppl) (1991) 220–224, https://doi.org/10.1002/1097-0142(19910101)67:1+<220::aid-cncr2820671303>3.0.co;2-o.
[162] M. Björkholm, Etoposide and teniposide in the treatment of acute leukemia, Med Oncol. Tumor Pharm. 7 (1) (1990) 3–10, https://doi.org/10.1007/BF03000484.
[163] C.H. Pui, R.C. Ribeiro, M.L. Hancock, et al., Acute myeloid leukemia in children treated with epipodophyllotoxins for acute lymphoblastic leukemia, N. Engl. J. Med 325 (24) (1991) 1682–1687, https://doi.org/10.1056/NEJM199112123252402.
[164] S.A. Strickland, N. Vey, Diagnosis and treatment of therapy-related acute myeloid leukemia, Crit. Rev. Oncol. Hematol. 171 (2022) 103607, https://doi.org/10.1016/j.critrevonc.2022.103607.
[165] P. Rougier, R. Bugat, J.Y. Douillard, et al., Phase II study of irinotecan in the treatment of advanced colorectal cancer in chemotherapy-naive patients and patients pretreated with fluorouracil-based chemotherapy, J. Clin. Oncol. 15 (1) (1997) 251–260, https://doi.org/10.1200/JCO.1997.15.1.251.
[166] D.J. Wagener, H.E. Verdonk, L.Y. Dirix, et al., Phase II trial of CPT-11 in patients with advanced pancreatic cancer, an EORTC early clinical trials group study, Ann. Oncol. 6 (2) (1995) 129–132, https://doi.org/10.1093/oxfordjournals.annonc.a059107.
[167] S.Y. Yi, Y.S. Park, H.S. Kim, et al., Irinotecan monotherapy as second-line treatment in advanced pancreatic cancer, Cancer Chemother. Pharm. 63 (6) (2009) 1141–1145, https://doi.org/10.1007/s00280-008-0839-y.
[168] J.H. Kang, K.H. Lee, D.W. Kim, et al., A randomised phase 2b study comparing the efficacy and safety of belotecan vs. topotecan as monotherapy for sensitive-relapsed small-cell lung cancer, Br. J. Cancer 124 (4) (2021) 713–720, https://doi.org/10.1038/s41416-020-01055-5.
[169] N. Horita, M. Yamamoto, T. Sato, et al., Amrubicin for relapsed small-cell lung cancer: a systematic review and meta-analysis of 803 patients, Published 2016 Jan 11. Sci. Rep. 6 (2016) 18999 https://doi.org/10.1038/srep18999.
[170] N. Horita, M. Yamamoto, T. Sato, et al., Topotecan for relapsed small-cell lung cancer: systematic review and meta-analysis of 1347 patients, Published 2015 Oct 21. Sci. Rep. 5 (2015) 15437 https://doi.org/10.1038/srep15437.
[171] H.S. Kim, N.H. Park, S. Kang, et al., Comparison of the efficacy between topotecan- and belotecan-, a new camptothecin analog, based chemotherapies for recurrent epithelial ovarian cancer: a single institutional experience, J. Obstet. Gynaecol. Res 36 (1) (2010) 86–93, https://doi.org/10.1111/j.1447-0756.2009.01101.x.
[172] S. Ackermann, M.W. Beckmann, F. Thiel, T. Bogenrieder, Topotecan in cervical cancer, Int J. Gynecol. Cancer 17 (6) (2007) 1215–1223, https://doi.org/10.1111/j.1525-1438.2007.01003.x.
[173] S. Modi, C. Saura, T. Yamashita, et al., Trastuzumab deruxtecan in previously treated HER2-positive breast cancer, N. Engl. J. Med 382 (7) (2020) 610–621, https://doi.org/10.1056/NEJMoa1914510.
[174] T. Petit, N. Hajjaji, E.C. Antoine, et al., Trastuzumab deruxtecan in previously treated HER2-positive metastatic or unresectable breast cancer: real-life data from the temporary use authorization program in France, Cancer Med 13 (9) (2024) e7168, https://doi.org/10.1002/cam4.7168.
[175] S. Modi, W. Jacot, T. Yamashita, et al., Trastuzumab deruxtecan in previously treated HER2-low advanced breast cancer, N. Engl. J. Med 387 (1) (2022) 9–20, https://doi.org/10.1056/NEJMoa2203690.
[176] B.T. Li, E.F. Smit, Y. Goto, et al., Trastuzumab deruxtecan in HER2-mutant non-small-cell lung cancer, N. Engl. J. Med 386 (3) (2022) 241–251, https://doi.org/10.1056/NEJMoa2112431.
[177] K. Shitara, Y.J. Bang, S. Iwasa, et al., Trastuzumab deruxtecan in previously treated HER2-positive gastric cancer, N. Engl. J. Med 382 (25) (2020) 2419–2430, https://doi.org/10.1056/NEJMoa2004413.
[178] Hope S. Rugo, et al., Primary results from TROPiCS-02: A randomized phase 3 study of sacituzumab govitecan (SG) versus treatment of physician's choice (TPC) in patients (Pts) with hormone receptor–positive/HER2-negative (HR+/HER2-) advanced breast cancer, -LBA1001, JCO 40 (2022) LBA1001, https://doi.org/10.1200/JCO.2022.40.17_suppl.LBA1001.
[179] A. Bardia, S.A. Hurvitz, S.M. Tolaney, et al., Sacituzumab govitecan in metastatic triple-negative breast cancer, N. Engl. J. Med 384 (16) (2021) 1529–1541, https://doi.org/10.1056/NEJMoa2028485.
[180] S.T. Tagawa, A.V. Balar, D.P. Petrylak, et al., TROPHY-U-01: a phase II open-label study of sacituzumab govitecan in patients with metastatic urothelial carcinoma progressing after platinum-based chemotherapy and checkpoint inhibitors, J. Clin. Oncol. 39 (22) (2021) 2474–2485, https://doi.org/10.1200/JCO.20.03489.
[181] Italian Multicentre Breast Study with Epirubicin, G. Ambrosini, M. Balli, et al., Phase III randomized study of fluorouracil, epirubicin, and cyclophosphamide v fluorouracil, doxorubicin, and cyclophosphamide in advanced breast cancer: an Italian multicentre trial, J. Clin. Oncol. 6 (6) (1988) 976–982, https://doi.org/10.1200/JCO.1988.6.6.976.

[182] F. Giona, A.M. Testi, S. Amadori, et al., Idarubicin and high-dose cytarabine in the treatment of refractory and relapsed acute lymphoblastic leukemia, Ann. Oncol. 1 (1) (1990) 51–55, https://doi.org/10.1093/oxfordjournals.annonc.a057675.
[183] T.H. Fink, R.M. Huber, D.F. Heigener, et al., Topotecan/cisplatin compared with cisplatin/etoposide as first-line treatment for patients with extensive disease small-cell lung cancer: final results of a randomized phase III trial, J. Thorac. Oncol. 7 (9) (2012) 1432–1439, https://doi.org/10.1097/JTO.0b013e318260de75.
[184] Z.A. Wainberg, D. Melisi, T. Macarulla, et al., NALIRIFOX versus nab-paclitaxel and gemcitabine in treatment-naive patients with metastatic pancreatic ductal adenocarcinoma (NAPOLI 3): a randomised, open-label, phase 3 trial, Lancet 402 (10409) (2023) 1272–1281, https://doi.org/10.1016/S0140-6736(23)01366-1.
[185] F. Andreata, A. Bonizzi, M. Sevieri, et al., Co-administration of H-ferritin-doxorubicin and Trastuzumab in neoadjuvant setting improves efficacy and prevents cardiotoxicity in HER2 + murine breast cancer model, Published 2020 Jul 10. Sci. Rep. 10 (1) (2020) 11425 https://doi.org/10.1038/s41598-020-68205-w.
[186] J.A. Abbas, R.K. Stuart, Vosaroxin: a novel antineoplastic quinolone, Expert Opin. Invest. Drugs 21 (8) (2012) 1223–1233, https://doi.org/10.1517/13543784.2012.699038.
[187] H. Xu, L.H. Hurley, A first-in-class clinical G-quadruplex-targeting drug. The bench-to-bedside translation of the fluoroquinolone QQ58 to CX-5461 (Pidnarulex), Bioorg. Med Chem. Lett. 77 (2022) 129016, https://doi.org/10.1016/j.bmcl.2022.129016.
[188] M.-J. Ahn, et al., 509MO Datopotamab deruxtecan (Dato-DXd) vs docetaxel in previously treated advanced/metastatic (adv/met) non-small cell lung cancer (NSCLC): Results of the randomized phase III study TROPION-Lung01, Ann. Oncol. Volume 34 (2023) S1665–S1666, https://doi.org/10.1016/j.annonc.2023.10.588.
[189] A. Bardia, et al., LBA11 Datopotamab deruxtecan (Dato-DXd) vs chemotherapy in previously-treated inoperable or metastatic hormone receptor-positive, HER2-negative (HR+/HER2–) breast cancer (BC): Primary results from the randomised phase III TROPION-Breast01 trial, Ann. Oncol. Volume 34 (2023) S1264–S1265, https://doi.org/10.1016/j.annonc.2023.10.015.
[190] AstraZeneca Press Release. Datopotamab deruxtecan Biologics License Application accepted in the US for patients with previously treated metastatic HR-positive, HER2-negative breast cancer. Available at: ⟨https://www.astrazeneca.com/media-centre/press-releases/2024/fda-accepts-dato-dxd-bla-for-breast-cancer.html#!⟩.
[191] Helena A. Yu, et al., HERTHENA-Lung01, a phase II trial of patritumab deruxtecan (HER3-DXd) in epidermal growth factor receptor–mutated non–small-cell lung cancer after epidermal growth factor receptor tyrosine kinase inhibitor therapy and platinum-based chemotherapy, JCO 41 (2023) 5363–5375, https://doi.org/10.1200/JCO.23.01476.
[192] Daiichi-Sankyo Press Release. Ifinatamab Deruxtecan Continues to Demonstrate Durable Responses in Patients with Advanced Small Cell Lung Cancer in Early Trial. Available at: ⟨https://www.daiichisankyo.com/files/news/pressrelease/pdf/202309/20230910_E1.pdf⟩.
[193] Daiichi-Sankyo Press Release. Raludotatug Deruxtecan Continues to Demonstrate Promising Clinical Activity in Patients with Advanced Ovarian Cancer in Early Trial. Available at: ⟨https://www.daiichisankyo.com/files/news/pressrelease/pdf/202310/20231022_E2.pdf⟩.
[194] H. Suzuki, S. Nagase, C. Saito, et al., Raludotatug deruxtecan, a CDH6-targeting antibody-drug conjugate with a DNA topoisomerase I inhibitor DXd, is efficacious in human ovarian and kidney cancer models, Mol. Cancer Ther. 23 (3) (2024) 257–271, https://doi.org/10.1158/1535-7163.MCT-23-0287.
[195] J. Yang, L. Jia, Z. He, Y. Wang, Recent advances in SN-38 drug delivery system, Int J. Pharm. 637 (2023) 122886, https://doi.org/10.1016/j.ijpharm.2023.122886.
[196] A. Thomas, S.D. Fontaine, M.E. Diolaiti, et al., PLX038: A long-acting topoisomerase I inhibitor with robust antitumor activity in ATM-deficient tumors and potent synergy with PARP inhibitors, Mol. Cancer Ther. 21 (11) (2022) 1722–1728, https://doi.org/10.1158/1535-7163.MCT-22-0217.
[197] S.D. Fontaine, A.D. Santi, R. Reid, P.C. Smith, G.W. Ashley, D.V. Santi, PLX038: a PEGylated prodrug of SN-38 independent of UGT1A1 activity, Cancer Chemother. Pharm. 85 (1) (2020) 225–229, https://doi.org/10.1007/s00280-019-03987-z.
[198] National Cancer Institute. FDA grants orphan drug designation to indotecan for the treatment of glioma. Available at: ⟨https://ccr.cancer.gov/news/article/fda-grants-orphan-drug-designation-to-indotecan-for-the-treatment-of-glioma⟩.
[199] O. Kim, M. Butler, Z. Sergi, et al., Combined inhibition of topoisomerase I and poly(ADP-ribose) polymerase: a synergistic therapeutic strategy for glioblastoma with phosphatase and tensin homolog deficiency, Published 2023 Aug 21. Neurooncol Adv. 5 (1) (2023) vdad102 https://doi.org/10.1093/noajnl/vdad102.
[200] L. Marzi, L. Szabova, M. Gordon, et al., The indenoisoquinoline TOP1 inhibitors selectively target homologous recombination-deficient and schlafen 11-positive cancer cells and synergize with olaparib, Clin. Cancer Res 25 (20) (2019) 6206–6216, https://doi.org/10.1158/1078-0432.CCR-19-0419.
[201] Brian Ko, et al., Phase 1 study of indenoisoquinoline LMP744 in adults with relapsed solid tumors and lymphomas, -3022, JCO 41 (2023) 3022, https://doi.org/10.1200/JCO.2023.41.16_suppl.3022. -3022.
[202] G.H. O'Sullivan Coyne, et al., Phase I study of indenoisoquinolines LMP776 in adults with relapsed solid tumors and lymphomas, -2558, JCO 35 (2017) 2558, https://doi.org/10.1200/JCO.2017.35.15_suppl.2558. -2558.
[203] N.E. Frank, B.J. Cusack, T.T. Talley, G.M. Walsh, R.D. Olson, Comparative effects of doxorubicin and a doxorubicin analog, 13-deoxy, 5-iminodoxorubicin (GPX-150), on human topoisomerase IIβ activity and cardiac function in a chronic rabbit model, Invest N. Drugs 34 (6) (2016) 693–700, https://doi.org/10.1007/s10637-016-0388-x.
[204] B.A. Van Tine, M. Agulnik, R.D. Olson, et al., A phase II clinical study of 13-deoxy, 5-iminodoxorubicin (GPX-150) with metastatic and unresectable soft tissue sarcoma, Cancer Med 8 (6) (2019) 2994–3003, https://doi.org/10.1002/cam4.2136.
[205] Monopar Therapeutics Press Release. Monopar Provides Encouraging Camsirubicin Clinical Data Update. Available at: ⟨https://ir.monopartx.com/press-releases/detail/75/monoparprovides-encouraging-camsirubicin-clinical-data⟩.
[206] U. Consoli, W. Priebe, Y.H. Ling, et al., The novel anthracycline annamycin is not affected by P-glycoprotein- related multidrug resistance: comparison with idarubicin and doxorubicin in HL-60 leukemia cell lines, Blood 88 (2) (1996) 633–644, https://doi.org/10.1182/blood.V88.2.633.bloodjournal882633.
[207] D. Kolonias, T. Podona, N. Savaraj, L. Gate, P. Cossum, T.J. Lampidis, Comparison of annamycin to adriamycin in cardiac and MDR tumor cell systems, Anticancer Res 19 (2A) (1999) 1277–1283.
[208] L. Gil, A. Wierzbowska, T. Wróbel, et al., Results of a phase I Study of Liposomal Annamycin for Treatment of R/R AML Patients, Br. J. Cancer Res 6 (1) (2023) 613–622, https://doi.org/10.31488/bjcr.183.
[209] Z. Muzyczenko, S. Silberman, S. Hsu, D. Picker. A Randomized, Controlled Trial Of Berubicin, A Novel Topoisomerase II Inhibitor, After First-Line Therapy For Glioblastoma Multiforme (GBM): Updated Results. 2023 SNO/ASCO CNS Cancer Conference. Available at: ⟨https://assets.cnspharma.com/production/publications/Berubicin-SNO-ASCO-Poster-2023.pdf?dm=1717154550⟩.
[210] S.P. Chawla, Z. Papai, G. Mukhametshina, et al., First-line aldoxorubicin vs doxorubicin in metastatic or locally advanced unresectable soft-tissue sarcoma: a phase 2b randomized clinical trial, JAMA Oncol. 1 (9) (2015) 1272–1280, https://doi.org/10.1001/jamaoncol.2015.3101.
[211] M.M. Mita, R.B. Natale, E.M. Wolin, et al., Pharmacokinetic study of aldoxorubicin in patients with solid tumors, Invest N. Drugs 33 (2) (2015) 341–348, https://doi.org/10.1007/s10637-014-0183-5.
[212] R.D. Olson, P.S. Mushlin, D.E. Brenner, et al., Doxorubicin cardiotoxicity may be caused by its metabolite, doxorubicinol, Proc. Natl. Acad. Sci. USA 85 (10) (1988) 3585–3589, https://doi.org/10.1073/pnas.85.10.3585.
[213] R.J. Boucek, Jr, R.D. Olson, D.E. Brenner, E.M. Ogunbunmi, M. Inui, S. Fleischer, The major metabolite of doxorubicin is a potent inhibitor of membrane-associated ion pumps. A correlative study of cardiac muscle with isolated membrane fractions, J. Biol. Chem. 262 (33) (1987) 15851–15856.
[214] S. Wang, B. Li, H. Zhang, et al., Improving bioavailability of hydrophobic prodrugs through supramolecular nanocarriers based on recombinant proteins for osteosarcoma treatment, Angew. Chem. Int Ed. Engl. 60 (20) (2021) 11252–11256, https://doi.org/10.1002/anie.202101938.
[215] R.E. Hawtin, D.E. Stockett, J.A. Byl, et al., Voreloxin is an anticancer quinolone derivative that intercalates DNA and poisons topoisomerase II, Published 2010 Apr 15. PLoS One 5 (4) (2010) e10186 https://doi.org/10.1371/journal.pone.0010186.
[216] R.E. Hawtin, D.E. Stockett, O.K. Wong, C. Lundin, T. Helleday, J.A. Fox, Homologous recombination repair is essential for repair of vosaroxin-induced DNA double-strand breaks, Oncotarget 1 (7) (2010) 606–619, https://doi.org/10.18632/oncotarget.195.
[217] U. Hoch, J. Lynch, Y. Sato, et al., Voreloxin, formerly SNS-595, has potent activity against a broad panel of cancer cell lines and in vivo tumor models, Cancer Chemother. Pharm. 64 (1) (2009) 53–65, https://doi.org/10.1007/s00280-008-0850-3.
[218] R.K. Stuart, L.D. Cripe, M.B. Maris, et al., REVEAL-1, a phase 2 dose regimen optimization study of vosaroxin in older poor-risk patients with previously untreated acute myeloid leukaemia, Br. J. Haematol. 168 (6) (2015) 796–805, https://doi.org/10.1111/bjh.13214.
[219] C.M. Nijenhuis, L. Lucas, H. Rosing, et al., Metabolism and disposition of the anticancer quinolone derivative vosaroxin, a novel inhibitor of topoisomerase II, Invest N. Drugs 35 (4) (2017) 478–490, https://doi.org/10.1007/s10637-017-0428-1.
[220] J. Hilton, K. Gelmon, P.L. Bedard, et al., Results of the phase I CCTG IND.231 trial of CX-5461 in patients with advanced solid tumors enriched for DNA-repair deficiencies, Published 2022 Jun 24. Nat. Commun. 13 (1) (2022) 3607, https://doi.org/10.1038/s41467-022-31199-2.
[221] P.M. Bruno, M. Lu, K.A. Dennis, et al., The primary mechanism of cytotoxicity of the chemotherapeutic agent CX-5461 is topoisomerase II poisoning, Proc. Natl. Acad. Sci. USA 117 (8) (2020) 4053–4060, https://doi.org/10.1073/pnas.1921649117.
[222] M. Pan, W.C. Wright, R.H. Chapple, et al., The chemotherapeutic CX-5461 primarily targets TOP2B and exhibits selective activity in high-risk neuroblastoma, Published 2021 Nov 9. Nat. Commun. 12 (1) (2021) 6468, https://doi.org/10.1038/s41467-021-26640-x.
[223] S. Yan, J. Xuan, N. Brajanovski, et al., The RNA polymerase I transcription inhibitor CX-5461 cooperates with topoisomerase 1 inhibition by enhancing the DNA damage response in homologous recombination-proficient high-grade serous ovarian cancer, Br. J. Cancer 124 (3) (2021) 616–627, https://doi.org/10.1038/s41416-020-01158-z.
[224] A.W.Y. Leung, M. Anantha, W.H. Dragowska, M. Wehbe, M.B. Bally, Copper-CX-5461: A novel liposomal formulation for a small molecule rRNA synthesis inhibitor, J. Control Release 286 (2018) 1–9, https://doi.org/10.1016/j.jconrel.2018.07.025.

[225] G.C.C. Koh, S. Boushaki, S.J. Zhao, et al., The chemotherapeutic drug CX-5461 is a potent mutagen in cultured human cells, Nat. Genet 56 (1) (2024) 23–26, https://doi.org/10.1038/s41588-023-01602-9.
[226] P.A. Bradford, A.A. Miller, J. O'Donnell, J.P. Mueller, Zoliflodacin: An Oral Spiropyrimidinetrione Antibiotic for the Treatment of Neisseria gonorrheae, Including Multi-Drug-Resistant Isolates, ACS Infect. Dis. 6 (6) (2020) 1332–1345, https://doi.org/10.1021/acsinfecdis.0c00021.
[227] R.R. Watkins, D. Thapaliya, T.L. Lemonovich, R.A. Bonomo, Gepotidacin: a novel, oral, 'first-in-class' triazaacenaphthylene antibiotic for the treatment of uncomplicated urinary tract infections and urogenital gonorrhoea, J. Antimicrob. Chemother. 78 (5) (2023) 1137–1142, https://doi.org/10.1093/jac/dkad060.
[228] R. Kullar, M.N. Tran, E.J.C. Goldstein, Investigational TReatment Agents for Recurrent Clostridioides Difficile Infection (rCDI), Published 2020 Oct 9. J. Exp. Pharm. 12 (2020) 371–384, https://doi.org/10.2147/JEP.S242959.
[229] A.S. Surur, D. Sun, Macrocycle-antibiotic hybrids: a path to clinical candidates, Published 2021 Apr 30. Front Chem. 9 (2021) 659845 https://doi.org/10.3389/fchem.2021.659845.
[230] A. Kolarič, M. Anderluh, N. Minovski, Two decades of successful SAR-grounded stories of the novel bacterial topoisomerase inhibitors (NBTIs), J. Med Chem. 63 (11) (2020) 5664–5674, https://doi.org/10.1021/acs.jmedchem.9b01738.
[231] B.D. Bax, P.F. Chan, D.S. Eggleston, et al., Type IIA topoisomerase inhibition by a new class of antibacterial agents, Nature 466 (7309) (2010) 935–940, https://doi.org/10.1038/nature09197.
[232] A.A. Miller, G.L. Bundy, J.E. Mott, et al., Discovery and characterization of QPT-1, the progenitor of a new class of bacterial topoisomerase inhibitors, Antimicrob. Agents Chemother. 52 (8) (2008) 2806–2812, https://doi.org/10.1128/AAC.00247-08.
[233] G. Kern, T. Palmer, D.E. Ehmann, et al., Inhibition of Neisseria gonorrhoeae Type II Topoisomerases by the Novel Spiropyrimidinetrione AZD0914, J. Biol. Chem. 290 (34) (2015) 20984–20994, https://doi.org/10.1074/jbc.M115.663534.
[234] The Global Antibiotic Research & Development Partnership. Positive results announced in largest pivotal phase 3 trial of a first-in-class oral antibiotic to treat uncomplicated gonorrhoea. Available at: ⟨https://gardp.org/positive-results-announced-in-largest-pivotal-phase-3-trial-of-a-first-in-class-oral-antibiotic-to-treat-uncomplicated-gonorrhoea/⟩.
[235] S.N. Taylor, J. Marrazzo, B.E. Batteiger, et al., Single-dose zoliflodacin (ETX0914) for treatment of urogenital gonorrhea, N. Engl. J. Med 379 (19) (2018) 1835–1845, https://doi.org/10.1056/NEJMoa1706988.
[236] S.N. Taylor, D.H. Morris, A.K. Avery, et al., Gepotidacin for the treatment of uncomplicated urogenital gonorrhea: a phase 2, randomized, dose-ranging, single-oral dose evaluation, Clin. Infect. Dis. 67 (4) (2018) 504–512, https://doi.org/10.1093/cid/ciy145.
[237] F. Wagenlehner, C.R. Perry, T.M. Hooton, et al., Oral gepotidacin versus nitrofurantoin in patients with uncomplicated urinary tract infection (EAGLE-2 and EAGLE-3): two randomised, controlled, double-blind, double-dummy, phase 3, non-inferiority trials, Lancet 403 (10428) (2024) 741–755, https://doi.org/10.1016/S0140-6736(23)02196-7.
[238] S. Abdellati, J.G.E. Laumen, T. de Block, et al., Gonococcal resistance to zoliflodacin could emerge via transformation from commensal Neisseria species. an in-vitro transformation study, Published 2024 Jan 12. Sci. Rep. 14 (1) (2024) 1179, https://doi.org/10.1038/s41598-023-49943-z.
[239] M.U. Rashid, A. Dalhoff, T. Bäckström, et al., Ecological impact of MCB3837 on the normal human microbiota, Int J. Antimicrob. Agents 44 (2) (2014) 125–130, https://doi.org/10.1016/j.ijantimicag.2014.03.016.
[240] M.F. Gordeev, C. Hackbarth, M.R. Barbachyn, et al., Novel oxazolidinone-quinolone hybrid antimicrobials, Bioorg. Med Chem. Lett. 13 (23) (2003) 4213–4216, https://doi.org/10.1016/j.bmcl.2003.07.021.
[241] J. Freeman, S. Pilling, J. Vernon, M.H. Wilcox, In vitro activities of MCB3681 and eight comparators against clostridium difficile isolates with known ribotypes and diverse geographical spread, -16. Published 2017 Feb 23, Antimicrob. Agents Chemother. 61 (3) (2017) e02077, https://doi.org/10.1128/AAC.02077-16.
[242] Tennor Therapeutics Pipeline. Available at: ⟨https://www.tennorx.com/en/pipeline.html#section01⟩.
[243] B. Wang, Q. Zhao, W. Yin, et al., In-vitro characterisation of a novel antimicrobial agent, TNP-2092, against Helicobacter pylori clinical isolates, Published 2018 Jul 24, Swiss Med Wkly 148 (2018) w14630, https://doi.org/10.4414/smw.2018.14630.
[244] C.R. Fisher, S.M. Schmidt-Malan, Z. Ma, Y. Yuan, S. He, R. Patel, In vitro activity of TNP-2092 against periprosthetic joint infection-associated staphylococci, Diagn. Microbiol Infect. Dis. 97 (3) (2020) 115040, https://doi.org/10.1016/j.diagmicrobio.2020.115040.
[245] T. Dai, C. Ma, F. Zhang, et al., The efficacy and safety of intra-articular dual-acting antibacterial agent (TNP-2092) for implant infection-associated MRSA, Published online December 26, J. Infect. Dis. (2023), https://doi.org/10.1093/infdis/jiad588. Published online December 26.
[246] Y. Yuan, X. Wang, X. Xu, et al., Evaluation of a dual-acting antibacterial agent, TNP-2092, on gut microbiota and potential application in the treatment of gastrointestinal and liver disorders, ACS Infect. Dis. 6 (5) (2020) 820–831, https://doi.org/10.1021/acsinfecdis.9b00374.
[247] A.S. Surur, D. Sun, Macrocycle-antibiotic hybrids: a path to clinical candidates, Published 2021 Apr 30. Front Chem. 9 (2021) 659845 https://doi.org/10.3389/fchem.2021.659845.
[248] D. Oka, N. Yamaya, T. Kuno, et al., In Vitro and In Vivo Antibacterial Activities of a Novel Quinolone Compound, OPS-2071, against Clostridioides difficile [published correction appears in Antimicrob Agents Chemother. 2022 Mar 15;66 (3):e0233821. doi: 10.1128/aac.02338-21], -20. Published 2021 Mar 18, Antimicrob. Agents Chemother. 65 (4) (2021) e01170, https://doi.org/10.1128/AAC.01170-20.
[249] D. Oka, R. Changkwanyeun, T. Yamaguchi, C. Nakajima, Y. Suzuki, M. Matsumoto, In vitro antibacterial activity of OPS-2071 against Gram-positive and Gram-negative enteropathogenic bacteria, J. Antimicrob. Chemother. 77 (12) (2022) 3248–3255, https://doi.org/10.1093/jac/dkac308.
[250] M. Sato, K. Fujii, H. Takagi, et al., Antibacterial and immunosuppressive effects of OPS-2071, a candidate therapy for inflammatory bowel disease, Dig. Dis. Sci. 67 (8) (2022) 3993–4007, https://doi.org/10.1007/s10620-021-07237-2.
[251] W. Wang, S. Saha, X. Yang, Y. Pommier, S.N. Huang, Identification and characterization of topoisomerase III beta poisons, Proc. Natl. Acad. Sci. USA 120 (34) (2023) e2218483120, https://doi.org/10.1073/pnas.2218483120.
[252] C.L. Yang, B. Zhang, W.W. Xue, et al., Discovery, biosynthesis, and heterologous production of loonamycin, a potent anticancer indolocarbazole alkaloid, Org. Lett. 22 (12) (2020) 4665–4669, https://doi.org/10.1021/acs.orglett.0c01456.
[253] K.R. Vann, Y. Ergün, S. Zencir, S. Oncuoglu, N. Osheroff, Z. Topcu, Inhibition of human DNA topoisomerase IIα by two novel ellipticine derivatives, Bioorg. Med Chem. Lett. 26 (7) (2016) 1809–1812, https://doi.org/10.1016/j.bmcl.2016.02.034.
[254] X. Sun, Z. Lu, Z. Liang, et al., Transcriptomics and proteomics characterizing the anticancer mechanisms of natural rebeccamycin analog loonamycin in breast cancer cells, Published 2022 Oct 17. Molecules 27 (20) (2022) 6958, https://doi.org/10.3390/molecules27206958.
[255] H.S. Ban, H. Nakamura, Boron-based drug design, Chem. Rec. 15 (3) (2015) 616–635, https://doi.org/10.1002/tcr.201402100.
[256] L. Marzi, Y. Sun, S.N. Huang, A. James, S. Difilippantonio, Y. Pommier, The Indenoisoquinoline LMP517: a novel antitumor agent targeting both TOP1 and TOP2, Mol. Cancer Ther. 19 (8) (2020) 1589–1597, https://doi.org/10.1158/1535-7163.MCT-19-1064.
[257] C. Molinaro, N. Wambang, T. Bousquet, et al., A Novel Copper(II) Indenoisoquinoline Complex Inhibits Topoisomerase I, Induces G2 Phase Arrest, and Autophagy in Three Adenocarcinomas, Published 2022 Feb 24. Front Oncol. 12 (2022) 837373 https://doi.org/10.3389/fonc.2022.837373.
[258] O. Bilyk, E. Brötz, B. Tokovenko, A. Bechthold, T. Paululat, A. Luzhetskyy, New simocyclinones: surprising evolutionary and biosynthetic insights, ACS Chem. Biol. 11 (1) (2016) 241–250, https://doi.org/10.1021/acschembio.5b00669.
[259] R.H. Flatman, A.J. Howells, L. Heide, H.P. Fiedler, A. Maxwell, Simocyclinone D8, an inhibitor of DNA gyrase with a novel mode of action, Antimicrob. Agents Chemother. 49 (3) (2005) 1093–1100, https://doi.org/10.1128/AAC.49.3.1093-1100.2005.
[260] A.T. Bakker, I. Kotsogianni, M. Avalos, et al., Discovery of isoquinoline sulfonamides as allosteric gyrase inhibitors with activity against fluoroquinolone-resistant bacteria, Nat. Chem. 16 (9) (2024) 1462–1472, https://doi.org/10.1038/s41557-024-01516-x.
[261] K. Rząd, I. Gabriel, E. Paluszkiewicz, et al., Targeting yeast topoisomerase II by imidazo and triazoloacridinone derivatives resulting in their antifungal activity, Published 2024 Feb 13. Sci. Rep. 14 (1) (2024) 3594, https://doi.org/10.1038/s41598-024-54252-0.
[262] E. Arabyan, A. Hakobyan, A. Kotsinyan, et al., Genistein inhibits African swine fever virus replication in vitro by disrupting viral DNA synthesis, Antivir. Res 156 (2018) 128–137, https://doi.org/10.1016/j.antiviral.2018.06.014.
[263] J. Song, L. Parker, L. Hormozi, M.A. Tanouye, DNA topoisomerase I inhibitors ameliorate seizure-like behaviors and paralysis in a Drosophila model of epilepsy, Neuroscience 156 (3) (2008) 722–728, https://doi.org/10.1016/j.neuroscience.2008.07.024.
[264] N. Clere, S. Faure, J.J. Helesbeux, O. Duval, R. Andriantsitohaina, Paradoxical effects of ethoxidine, a topoisomerase I inhibitor, in the cellular processes leading to angiogenesis on endothelial cells, Carcinogenesis 32 (3) (2011) 286–295, https://doi.org/10.1093/carcin/bgq260.
[265] N. Clere, K.H.T. To, S. Legeay, et al., Pro-angiogenic effects of low dose ethoxidine in a murine model of ischemic hindlimb: correlation between ethoxidine levels and increased activation of the nitric oxide pathway, Published 2017 Apr 12. Molecules 22 (4) (2017) 627, https://doi.org/10.3390/molecules22040627.
[266] Exelixis Press Release. Helsinn to Discontinue Becatecarin Trial Program. Available at: ⟨https://ir.exelixis.com/news-releases/news-release-details/helsinn-discontinue-becatecarin-trial-program⟩.
[267] K. Pommerehne, J. Walisko, A. Ebersbach, R. Krull, The antitumor antibiotic rebeccamycin-challenges and advanced approaches in production processes, Appl. Microbiol Biotechnol. 103 (9) (2019) 3627–3636, https://doi.org/10.1007/s00253-019-09741-y.
[268] Biospace. Novexel Discontinues Development of NXL 101. Available at: ⟨https://www.biospace.com/novexel-discontinues-development-of-nxl-101⟩.
[269] S. Correia, P. Poeta, M. Hébraud, J.L. Capelo, G. Igrejas, Mechanisms of quinolone action and resistance: where do we stand, J. Med Microbiol 66 (5) (2017) 551–559, https://doi.org/10.1099/jmm.0.000475.
[270] J. Ruiz, Transferable Mechanisms of Quinolone Resistance from 1998 Onward, -19. Published 2019 Aug 14, Clin. Microbiol Rev. 32 (4) (2019) e00007, https://doi.org/10.1128/CMR.00007-19.
[271] R. Mattioli, A. Ilari, B. Colotti, L. Mosca, F. Fazi, G. Colotti, Doxorubicin and other anthracyclines in cancers: activity, chemoresistance and its overcoming, Mol. Asp. Med 93 (2023) 101205, https://doi.org/10.1016/j.mam.2023.101205.
[272] S. Kumar, M.Y. Sherman, Resistance to TOP-1 inhibitors: good old drugs still can surprise us, Published 2023 Apr 13. Int J. Mol. Sci. 24 (8) (2023) 7233, https://doi.org/10.3390/ijms24087233.

[273] J. Zhou, C. Gelot, C. Pantelidou, et al., A First-in-class Polymerase Theta Inhibitor Selectively Targets Homologous-recombination-deficient Tumors, Nat. Cancer 2 (6) (2021) 598–610, https://doi.org/10.1038/s43018-021-00203-x.
[274] T. Hagiwara, K. Sugimoto, H. Momose, et al., CHFR-promoter-methylation status is predictive of response to irinotecan-based systemic chemotherapy in advanced colorectal cancer, Anticancer Res 42 (2) (2022) 697–707, https://doi.org/10.21873/anticanres.15528.
[275] C. Wang, S. Jin, S. Xu, S. Cao, High Systemic Immune-Inflammation Index (SII) Represents an Unfavorable Prognostic Factor for Small Cell Lung Cancer Treated with Etoposide and Platinum-Based Chemotherapy, Lung 198 (2) (2020) 405–414, https://doi.org/10.1007/s00408-020-00333-6.
[276] C. Aaberg-Jessen, L. Fogh, M.D. Sørensen, B. Halle, N. Brünner, B.W. Kristensen, Overexpression of TIMP-1 and Sensitivity to Topoisomerase Inhibitors in Glioblastoma Cell Lines, Pathol. Oncol. Res 25 (1) (2019) 59–69, https://doi.org/10.1007/s12253-017-0312-5.
[277] U. Jo, Y. Murai, K.K. Agama, et al., TOP1-DNA Trapping by Exatecan and Combination Therapy with ATR Inhibitor, Mol. Cancer Ther. 21 (7) (2022) 1090–1102, https://doi.org/10.1158/1535-7163.MCT-21-1000.
[278] C.M. Fillmore, C. Xu, P.T. Desai, et al., EZH2 inhibition sensitizes BRG1 and EGFR mutant lung tumours to TopoII inhibitors [published correction appears in Nature. 2018 Nov;563(7732):E27. doi: 10.1038/s41586-018-0580-6], Nature 520 (7546) (2015) 239–242, https://doi.org/10.1038/nature14122.
[279] I. Kümler, E. Balslev, J. Stenvang, et al., Two open-label, single arm, non-randomized phase II studies of irinotecan for the treatment of metastatic breast cancer in patients with increased copy number of the topoisomerase I gene, Published 2019 Jun 13. BMC Cancer 19 (1) (2019) 573, https://doi.org/10.1186/s12885-019-5788-9.
[280] M. Zhao, K. Yang, X. Zhu, et al., Design, synthesis and biological evaluation of dual Topo II/HDAC inhibitors bearing pyrimido[5,4-b]indole and pyrazolo[3,4-d] pyrimidine motifs, Eur. J. Med Chem. 252 (2023) 115303, https://doi.org/10.1016/j.ejmech.2023.115303.
[281] D.Y. Chen, C.C. Chen, J.R. Crawford, S.G. Wang, Tumor-related epilepsy: epidemiology, pathogenesis and management, J. Neurooncol 139 (1) (2018) 13–21, https://doi.org/10.1007/s11060-018-2862-0.
[282] Y. Mamun, Y.C. Tse-Dinh, P. Chapagain, Insights into the DNA and RNA Interactions of Human Topoisomerase III Beta Using Molecular Dynamics Simulations, J. Chem. Inf. Model 64 (15) (2024) 6062–6071, https://doi.org/10.1021/acs.jcim.4c00472.
[283] Data Bridge Market Research. Global Quinolones Market – Industry Trends and Forecast to 2030. Available at: ⟨https://www.databridgemarketresearch.com/reports/global-quinolones-market⟩.
[284] The Business Research Company. Quinolones Global Market Report 2024. Available at: ⟨https://www.thebusinessresearchcompany.com/report/quinolones-global-market-report⟩.
[285] Allied Market Research. Quinolones Market Size, Share, Competitive Landscape and Trend Analysis Report by Product Type, by Application and by End User: Global Opportunity Analysis and Industry Forecast, 2023-2032. Available at: ⟨https://www.alliedmarketresearch.com/quinolones-market-A14826⟩.
[286] Data Bridge Market Research. Global Anthracyclines Market – Industry Trends and Forecast to 2030. Available at: ⟨https://www.databridgemarketresearch.com/reports/global-anthracyclines-market⟩.
[287] The Business Research Company. Anthracycline Global Market Report 2024. Available at: ⟨https://www.thebusinessresearchcompany.com/report/anthracycline-global-market-report⟩.