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NEWLY FDA-APPROVED DRUGS AND BIOLOGICS (JANUARY-DECEMBER 2005) PART 2

The aim of this review is to survey the new "molecular entities" (NME) drugs and new biological license applications (BLA) approved by the Food and Drug Administration (FDA) in the year 2005 (i.e., those not previously marketed in the United States of America).

In Part 2 only some of the drugs subjected to "Priority Review" (i.e., those representing significant improvements compared with marketed products [1]) will be considered (7 NME, 52 references) [2]. This review follows the others about NME approved by the FDA in the years 1998-2003, NME and BLA approved in 2004 and Part 1 of NME and BLA approved by FDA in 2005 [3].

New Molecular Entities and Biological License Applications Approved in 2005 with Priority Review. Part 2

In order to offer an overview of the subject, the drugs have been divided into therapeutic classes, as can be seen in Fig. 1. Antiviral (as in 1998-2002) and antitumor drugs are present (as in 1998-2004), because of the great interest in the related diseases. In addition enzymes (as in 2004), growth factors, immunomodulatories, an antifungin (as in 2001), an antibiotic (as in 1999, 2000), a chelanting (as in 2004) and an anti-inflammatory (as in 1998-2000) are included in the FDA-approved NME and BLA. In Part 2 antiviral, antineoplastic, antifungin, antibiotic and chelating drugs are reported.

Antiviral drugs

Aptivus® (Boehringer Ingelheim)
Tipranavir, 250 mg, capsules [4]
Indication: non-peptide protease inhibitor (PI) for combination antiretroviral treatment with Abbott's *Norvir* (ritonavir) of human immunodeficency virus (HIV)-1 infected adults with evidence of viral replication, who are highly treatment-experienced or have HIV-1 strains resistant to multiple PIs.
Date approved: 22-06-2005 (available also in Italy [5])

Part 1 of this review has been published on June issue (2007, n. 5), pag. 138.

Highly active antiretroviral therapy (HAART) involves the use of at least three agents from two distinct classes of antivirals: a PI in combination with two nucleoside/nucleotide reverse transcriptase inhibitor [N(t)RTIs]; or a non-nucleoside reverse transcriptase inhibitor (NNRTI) in combination with NRTIs [6]. This therapy has undoubtedly led to a decline in the morbidity and mortality associated with HIV infection. In spite of this, in many HIV-infected patients, particularly in those that initiated antiretroviral monotherapy regimens prior to the HAART era, the strategy is not very efficient [4c]. In addition, the massive viral replication and the high error rate of the reverse transciptase lead to the emergence of drug-resistant strains and the stringent need for new therapeutic approaches [6]. Presently, the main goals of research in the field of antiretroviral drugs, including the PIs class, are the design of better pharmacological agents devoid of severe side effects and resistance problems, and achieving eradication of the virus, possibly with a definitive cure of the disease [6]. The first generation of PIs are all peptidic compounds that mimic the transition state of peptide-cleavage reactions catalyzed by HIV-1 protease [7]. Because of this situation, involving a similarity in their structures which increases the possibility that strains resis-

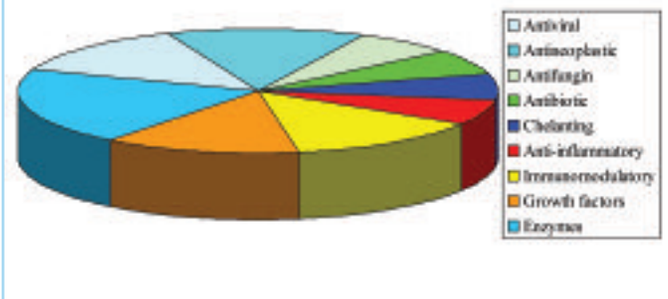

Fig. 1 - Therapeutic classes of NME and BLA approved by "priority review"

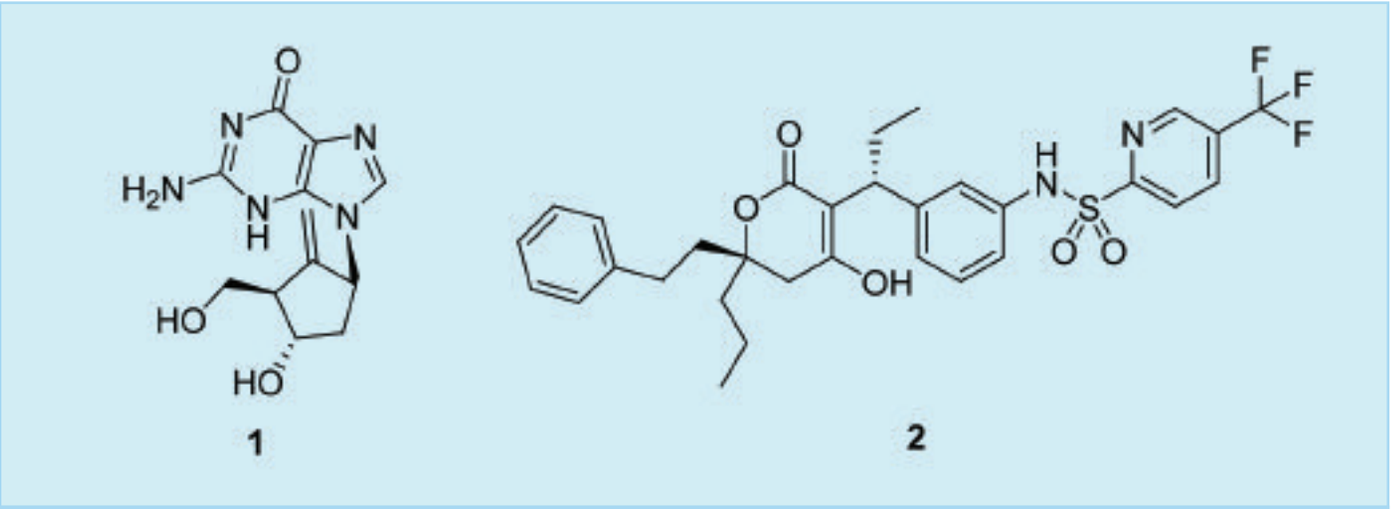

Fig. 2 - Antiviral drugs

tant to one drug will also be resistant to others, one possible strategy is to develop non-peptidic PIs [7].

Tipranavir (**1**, Fig. 2), a sulfonamide-containing dihydropyrone derivative synthesized as described in [8], is the first compound of the new class of non-peptidic HIV-1 PIs launched in the market. **1** was discovered through a structure-based design derived from a broad screening program identifying phenprocoumon as lead nonpeptide HIV PI [9]. **1** inhibits the processing of the viral Gag and Gag-Pol polyproteins in HIV-1 infected cells, thus preventing formation of mature virion [4c]. It has been suggested that **1** binds to the active site of the protease enzyme with fever hydrogen bonds than peptidic PIs, resulting in increased flexibility that allows **1** to adjust to amino acid changes in the active site [4c, 10]. Other studies propose that the strong hydrogen bonding interaction with the amide backbone of the protease active site Asp30 is rsponsible for the favorable antiviral activity of **1** against isolates with multiple PI-associated mutations [4c, 11]. Due to its short half-life, **1** soft gel capsules must be administered along with ritonavir [3d] which is used as a pharmacokinetic booster to decrease metabolism and increase the half-life of **1** [12]. Based on phase III RESIST (Randomized Evaluation of Strategic Intervention in multidrug reSistant patients with Tripanavir) studies the best virologic outcomes were attained when **1**/ritonavir were used in combination with enfuvirtide, an antiretroviral fusion inhibitor, and/or at least two drugs to which the virus has genotypic sensitivity [4c, 13].

Baraclude™ (Bristol-Myers Squibb)

Entecavir, 0.5 or 1 mg & 0.05 mg/mL, tablet & oral solution [14]

Indication: guanosine nucleoside analogue for treatment of chronic hepatitis B (CHB) virus infection in adults with evidence of active viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease.

Date approved: 29-3-2005 (available also in Italy [5])

CHB can be divided into two major categories depending on the presence of the hepatitis B e antigen (HBeAg) and its antibody (anti-HBe): the HBeAg-positive and the HBeAg-negative forms, the first characterized by an extremely high rate of hepatitis B virus (HBV) replication and persistent or intermittently increasing aminotransferase levels, the second that may occur almost immediately after the acute phase of HBV infection or develop after several years of maintaining an immunotolerant state [15]. Patients with CHB carry a significant risk to eventually develop cirrhotic liver disease [16]. Few agents are currently in use for the treatment of CHB: interferon-α, lamivudine and adefovir dipivoxil [3f], but each of these molecules has limitations [15]. Drug resistance limits their efficacy and new drugs are necessary for patients presenting CHB immunocompromised and decompensated, those with normal ALT levels, or resistant to lamivudine or to adefovir dipivoxil, and those who do not respond to the approved therapies [15, 17]. The goals of treatment of CHB are the initiation and maintenance of HBV suppression resulting in an improved clinical outcome [16].

Entecavir (**2**, Fig. 2) is a guanosine nucleoside analog synthesized as described in [18]. **2** is very potent against HBV virus and, differing from lamivudine and adefovir, it is selective, having little activity against HIV and other DNA viruses [19]. **2** can be regarded as prodrugs, as it needs activation for antiviral efficacy

through a phosphorylation process to the nucleoside triphosphate [19a]. By competing with the natural substrate deoxyguanosine triphosphate, **2** triphosphate functionally inhibits all three activities of the HBV polymerase: base priming, reverse transcription of the negative strand from the pregenomic messenger RNA and synthesis of the positive strand of HBV DNA [14c]. Structure-activity relationship studies of **2** analogs are reported in [19a]. In head-to-head studies comparing lamivudine to **2**, the latter was superior in normalization of ALT and in improvement of histology and suppression of HBV DNA in both HBeAg-positive and HBeAg-negative patients with CHB [16, 20].

Antineoplastic drugs

Arranon® (GlaxoSmithKline) (orphan drug)
Nelarabine, 5 mg/mL, injection IV [21]
Indication: nucleoside analogue for the treatment of patients with T-cell acute lymphoblastic leukemia (T-ALL) and T-cell lymphoblastic lymphoma (T-LBL) whose disease has not responded to or has relapsed following treatment with at least two chemotherapy regimens.
Date approved: 28-10-2005

Lymphoid malignancies involving T cell, such as T-ALL and T-LBL, are a relatively rare but often aggressive, subset of blood cancers [22] and are considered the same disease with different clinical presentations [21b]. T-ALL and T-LBL are both usually treated with aggressive combination therapy that can include vincristine, prednisone, an anthracycline, asparaginase, cyclophosphamide and cytarabine [21b] and, in case of T-ALL, also clofarabine [3h]. Although treatment of these cancers has advanced considerably in recent decades, with cure rates of ~80% being achieved in children, patients who do not respond to standard treatments or who relapse have a particularly poor prognosis, and so there is still a need for novel drugs [22].
Nelarabine (**3**, Fig. 3), synthesized as described in [23], is a prodrug of the cytotoxic deoxyguanosine analogue 9-β-D-arabinofuranosylguanine (ara-G), a molecule that cannot be used clinically because of its poor solubility [24]. **3** is 10 times more soluble than ara-G, the product in which it is transformed by an adenosine deaminase and that succesively is phosphorylated to give the active species, the active 5'-triphosphate (ara-GTP) [21b, 22, 24, 25]. The ara-GTP competes with native deoxynucleotides as a substrate for incorporation into DNA by DNA polymerase and it results in inhibition of DNA synthesis and the initiation of apoptosis [24, 26]. **3** monotherapy can be produce a complete response in patients with relapsed T-ALL and T-LBL, permitting some to go on to stem-cell transplantation. The drug's effectiveness as initial therapy or in combination with other drugs remains to be determined. Neurologic adverse effects can be severe [21b].

Nexavar® (Bayer/Onyx) (orphan drug)
Sorafenib tosylate, 200 mg, tablet [27]
Indication: dual Raf kinase/vascular endothelial growth factor (VEGF) receptor inhibitor for treatment of advanced renal cell carcinoma (RCC).
Date approved: 20-12-2005 (available also in Italy [5])

Angiogenesis and proliferation are important processes in blood vessel tumors involving VEGF, the primary mediator of angiogen-

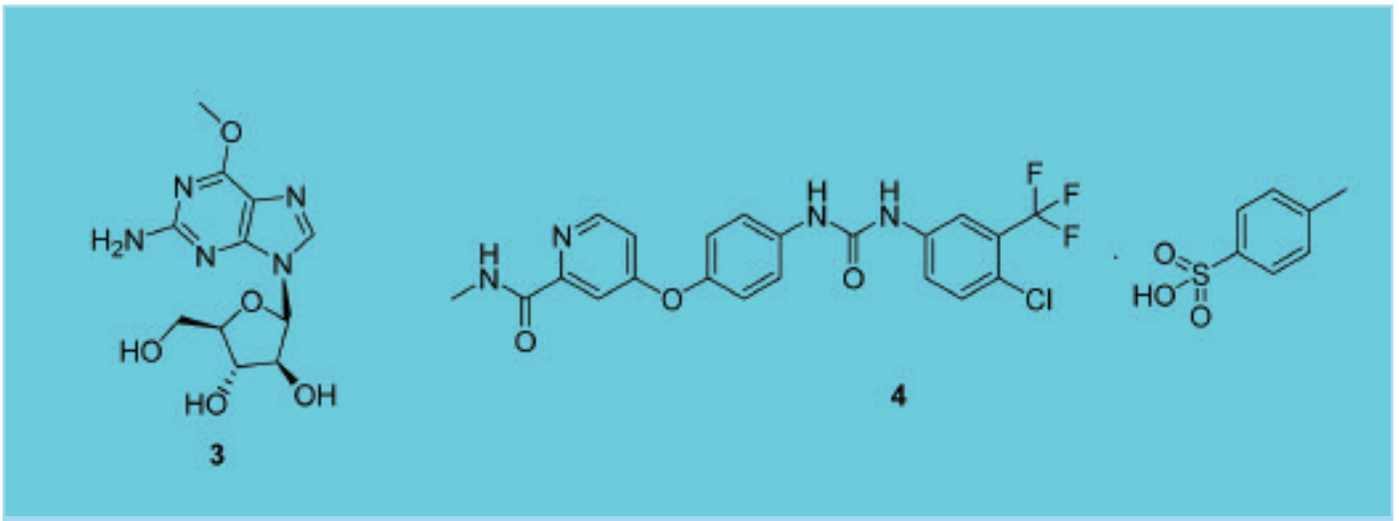

Fig. 3 - Antineoplastic drugs

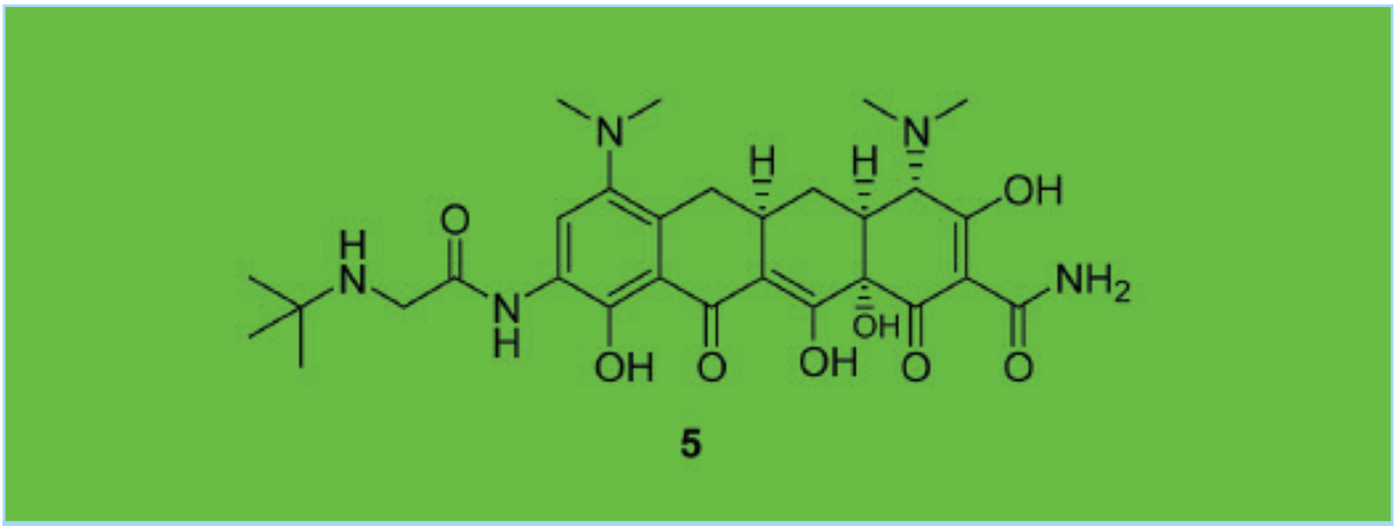

Fig. 4 - Antibiotic drugs

esis, and Ras-mediated signal transduction pathways, which include the key mediator Raf kinase, which controls cell growth and survival [27]. VEGF exerts its biological effect through interaction with receptors present on the endothelial cell surface: upon binding to the extracellular domain of its receptor, dimerization and autophosphorylation of the intracellular receptor tyrosine kinase occurs and a cascade of downstream proteins is activated [27a]. Activation of the Ras pathway results in a cascade of events from the cell surface to the nucleus, ultimately affecting cellular proliferation, apoptosis, differentiation and transformation. This crucial signaling pathway is frequently found to be altered in human cancers, directly controlling formation and progression of tumors [27b]. Raf kinase isoforms (wild-type Raf-1 or the b-raf V600E oncogene) are overactivated in a variety of solid tumor types, including RCC [28], a disease that in metastatic form is historically unresponsive to conventional treatment strategies, with a limited subset of patients experiencing clinically meaningful benefit from IL-2 and/or IFN-α therapy [27a].

Sorafenib tosylate (**4**, Fig. 3) is a biaryl ureidic derivative synthesized as reported in [29]. **4** was identified by high-throughput screening of a combinatorial chemistry library and optimization process of the lead compound discovered, in a medicinal chemistry program aimed to potent and selective Raf kinase inhibitors [29b, 30, 31]. **4**, like imatinib [3e, 32], is a type II kinase inhibitor that, contrary to the majority of kinase inhibitors which are known as type I and target the ATP binding site in its active conformation, preferentially acts with a new binding mode that exploits an additional binding site immediately adjacent to the region occupied by ATP, establishing hydrogen bonding and hydrophobic interactions in the allosteric site [32]. An overview of **4** and related small molecules is outlined in [30, 33]. Approval of **4** came before that of sunitinib, a molecule approved by the FDA in 2006 [34].

Antifungin drugs

Mycamine® (Astellas, formerly Fujisawa)
Micafungin sodium, 50 & 100 mg, injection [35]
Indication: echinocandin antifungal for prophylaxis of Candida infections in patients undergoing hematopoietic stem cell transplantation and the treatment of esophageal candidiasis.
Date approved: 16-03-2005

Invasive fungal infections (IFIs) are being encountered with increasing frequency, especially in those patient populations at high risk (i.e., HIV patients, those undergoing cancer chemotherapy, select surgical intensive care unit patients, and both haematological and solid-organ transplant recipients) [36]. Advances in medicine in recent decades have resulted in an increased incidence of IFIs [35c]. In addition to the growing incidence of IFIs, other concerns have been raised regarding the epidemiology of such infections [36]. Numerous challenges exist to providing safe, effective, timely and affordable therapy for IFIs, such as diagnostic problems including the lack of sensitive, specific and timely diagnostic serologies, as well as the lack of clinically meaningful in vitro antifungal drug susceptibility testing criteria for many fungal pathogens [36]. Thus, there is a need for alternative agents that are effective against a broad range of Candida species, alongside traditional systemic agents such as azole derivatives (e.g. fluconazole, itraconazole) or amphotericin B [35c]. In recent years a new class of molecules, that is the echinocandins, including caspofungin has been developed [3e].

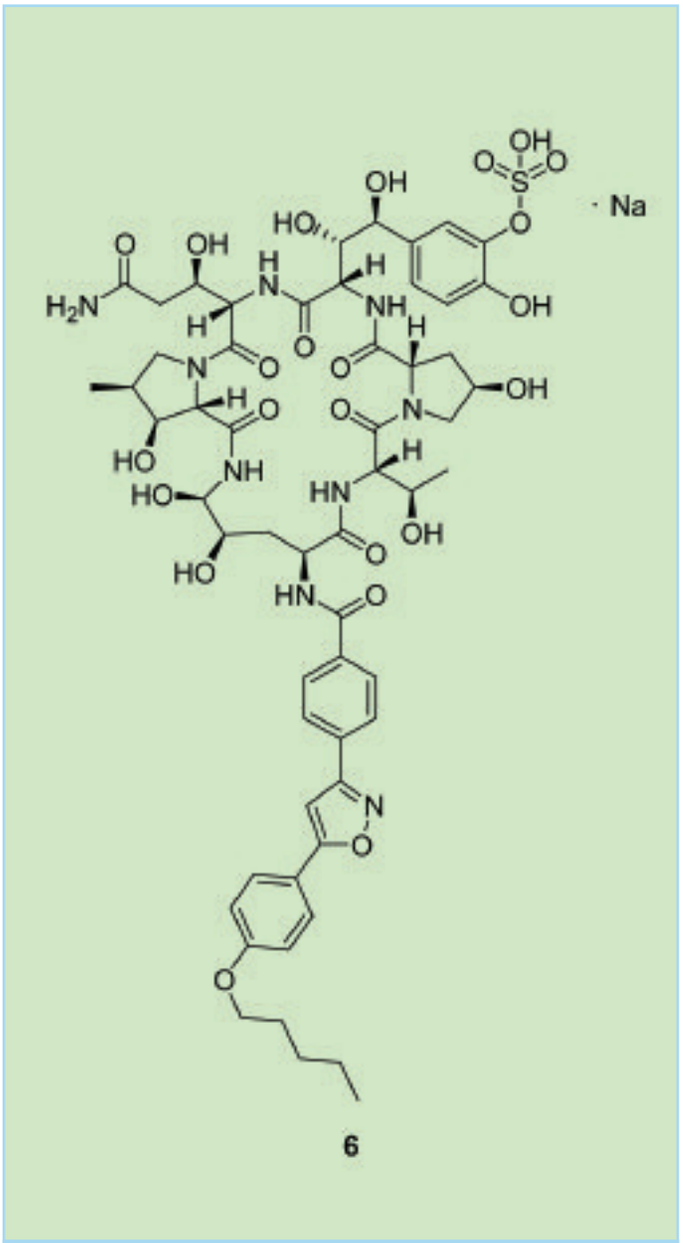

Fig. 5 - Antifungin drugs

Micafungin sodium (**5**, Fig. 4) is a water-soluble echinocandin-like lipopeptide possessing a sulfate ester moiety in the cyclic hexapeptide nucleus. **5** is synthesized from a naturally occurring compound isolated from the culture broth of the fungus *Coleophoma empetri*, as reported in [37]. **5** inhibits in a concentration dependent, non-competitive manner 1,3-β-D-glucan synthase, an enzyme complex specific to fungi and essential for cell wall synthesis of many pathogen fungi, resulting in morphological changes to the cell wall [35, 36]. **5** has pharmacological properties similar to caspofungin and anidulafungin [35], another recently approved echinocandin derivative [36]: an extended spectrum of antifungal activity, no cross-resistance to existing antifungal agents, and lack of mechanism-based toxicity [35a].

Antibiotic drugs

Tygacil® (Wyeth)
Tigecycline, 50 mg, injection [38]
Indication: glycylglycine antibiotic for use as monotherapy to treat complicated intra-abdominal infections (cIAI) and complicated skin and skin structure infections (cSSSI) in patients 18 years of age and older.
Date approved: 15-06-2005 (available also in Italy [5])

In higher risk patients antimicrobial therapy of cIAI should include a regimen containing broader spectrum antimicrobials active against Gram-negative aerobic/facultative anaerobic organisms, including single agents such as extended range beta-lactam/betalactamase agents and carbapenems, and combinations such as an aminoglycoside plus an antianaerobic agent, a third or fourth generation cephalosporin plus an anti-anaerobic agent, aztreonam plus clindamycin, or ciprofloxacin plus metronidazole [39, 40]. When multiply resistant bacteria are suspected, a complex multi-drug regimen is recommended [39]. Risk factors for cSSSI are increasing, notably diabetes and intravenous drug abuse. The increasing prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) in particular, in both healthcare and community settings, similarly complicates the choice of empirical therapy for cSSSI [39]. The glycylcyclines [41] are a new class of broad-spectrum antibacterials structurally related to tetracyclines specifically developed to circumvent the two major mechanisms of resistance to tetracyclines (ribosomal protection and efflux), which have substantially decreased the effectiveness of these agents [38a]. Comparative studies between glycylcyclines and tetracyclines are reviewed in [41].
Tigecycline (**6**, Fig. 5) is a *t*-butylglycylcycline analogue of the tetracycline minocycline synthesized as reported in [42]. **6** is a bacteriostatic agent acting by binding to a single high-affinity intracellular site on the bacterial 30S-ribosome, blocking entry of aminoacyl transfer molecules and, thus, preventing further protein synthesis [38b]. Of the two distinct transfer RNA binding sites (A and P) within the large ribosomal subunit, **6** interacts with a helical region (H34) of the A-site, in a unique mechanism of action relative to other class A-site binding antibacterials [38b, 43]. **6**, like the glycylglycines, possesses the characteristic nucleus consisting of four linear fused tetracyclic rings typical of classic tetracycline, but substitution of an *N*-alkylglycy-

lamido group on the D ring at the position 9 facilitates a broader spectrum of activity, and additionally, creates the ability to overcome most tetracycline resistance mechanisms [38e]. In addition, the steric hindrance due to the large 9-t-butylglycylamido side chain is thought to be important in avoiding resistance [44]. **6** maintains the broad spectrum of activity against Gram-negative and Gram-positive pathogens, anaerobes and atypical bacteria seen with other glycylglycines but showed a good profile against important clinical pathogens, including MRSA, glycopeptide intermediate-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci, penicillin-resistant *Streptococcus pneumoniae* and resistant Gram-negative organisms expressing extended-spectrum β-lactames [38c]. Clinical trials upon cIAI and cSSSI with **6** are included in [39]. An overview of pharmacokinetics, pharmacodynamics, safety and tolerability of **6** is reported in [45].

Chelating drugs

Exjade® (Novartis) (orphan drug)
Deferasirox, 125, 250 & 500 mg, tablet [46]
Indication: iron chelating agent for treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in patients two years of age and older.
Date approved: 02-11-2005

Iron is essential for life as it plays an important role, in many cellular processes, including energy generation, oxygen transport, and DNA synthesis, because it acts as a cofactor within the active site of key enzymes involved in these critical biochemical pathways [47]. Despite this crucial rolean excess of iron is toxic due to the deleterious effects of oxygen species, such as the hydroxyl radical that are highly reactive and able to induce cell death through initiating a series of chemical reactions with many significant biomolecules, resulting in DNA oxidation, mitochondrial damage, and the peroxidation of membrane lipids [47]. Iron overload is a serious and potentially life-threatening complication of rare, chronic blood disorders, including thalassemia and sickle cell disease as well as other rare anemias and myelodysplastic syndromes, which require multiple transfusions over long periods of time [13, 46a]. The maintenance of iron and other essential metal ion balance in humans is based on the presence of homeostatic mechanisms of regulatory absorption, storage, re-utilization and excretion [48] but chronic iron overload occurs as a result of the body's inability to actively eliminate iron [46b]. Iron-chelating agents consist of a range of bidentate, tridentate, and hexadentate ligands in which two, three, or six atoms, respectively, are able to coordinate with iron, forming octahedral complexes [47]. As iron exists in the environment in an insoluble form, microbes have overcome this accessibility problem by excreting low molecular weight ligands, known as siderophores, to specifically sequester iron in a useable form [47]. Many of these siderophores have been used as lead compounds in the search for more efficient and orally active iron chelators [47]. The first-line iron chelator is the deferoxamine, a drug requiring intravenous or slow subcutaneous infusion over a period of 8-12 h, 5-7 times per week and a result, it has low patient acceptance [46b].
Deferasirox (**7**, Fig. 6) is a tridentate chelator using a triazolyl nitrogen and two phenolic oxygens as donor group [47] synthesized as described in [49]. **7** emerged by a combination of rational design, intuition and experience as an entity which best combined high oral potency and tolerability in animals [50]. By using hard donor atoms such as oxygen, **7** can bind Fe(III) specifically, avoiding disturbances to other significant transition metals [47, 51]. Due to its relatively small size, **7** is well absorbed through the gastrointestinal tract and has demonstrated a two- to fivefold increased potency over deferoxamine for the mobilization of iron from tissue both in vitro and in vivo [46a]. A phase 3 study of **7** is described in [52].

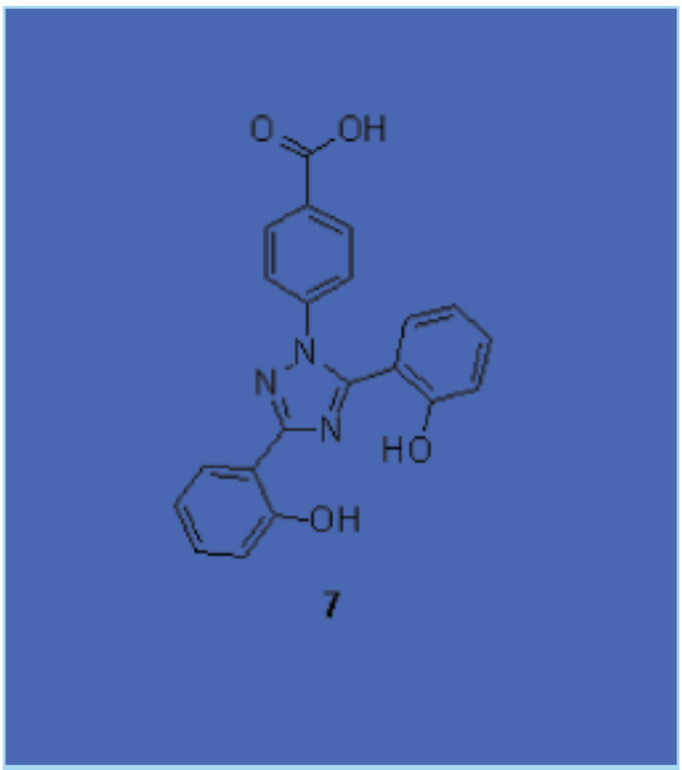

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Fig. 6 - Chelating drugs

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