1. Natural products in drug discovery: Clinical evaluations and investigations

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Abstract. Natural products (NPs) have provided the source for the majority of FDA-approved agents and continue to be one of the major sources of inspiration for future drug discovery. The R&D thrust in the pharmaceutical sector today is focused on development of new drugs, innovative/indigenous processes for known drugs, development of NP-based drugs through investigation of leads obtained from the traditional systems of medicine as well as other resources. Present review describes natural products (NPs), semi-synthetic NPs and NP-derived compounds that have been registered, undergoing registration or in clinical development since 1998 till June 2010 by disease area i.e. infectious (bacterial, fungal, parasitic and viral), immunological, cardiovascular, neurological, inflammatory and related diseases and Oncology. This review also highlights the recently launched natural product-derived drugs, new natural product templates and late-stage development candidates.

1. Introduction

The interesting chemicals identified as NPs are derived from the phenomenon of biodiversity in which the interactions among organisms and their environment formulate the diverse complex chemical entities within the
organisms that enhance their survival and competitiveness. Today, R&D thrust in the pharmaceutical sector is focused on development of new drugs, innovative/indigenous processes for known drugs and development of plant-based drugs through investigation of leads obtained from the traditional systems of medicine as well other resources [1,2].

History of medicine dates back practically to the existence of human civilization and use of NPs by human have been traced from ancient records such as the use of Artemisia annua in China, opium poppy (active principle morphine) in Egypt, snakerooot plant (active principle reserpine) in India, willow tree (salicin) & foxglove (active principle digitalis - a mixture of compounds such as digitoxin, digitonin, digitalin) in England and ipecacuanha root (active principle emetine), coca bush (active principle cocaine) and cinchona bark (active principle quinine) in Mesoamerica. The current accepted modern medicine or allopathy has gradually developed over the years by scientific and observational efforts of scientists. However, the basis of its development remains rooted in traditional medicine and therapies.

Plants have always been a rich source of NP leads e.g. morphine, cocaine, digitalis, quinine, tubocurarine, nicotine, muscarine, paclitaxel (Taxol™) and artemisinin. The success of penicillin encouraged the discovery of new antibiotics from microorganisms. Mining of the bacterial genome and identification of crucial targets followed by study of new bacterial or fungal strains have resulted in discovery of significant antibacterial agents such as the cephalosporins, tetracyclines, aminoglycosides, rifamycins and chloramphenicol. Since past five decades, marine sources e.g. coral, sponges, fish and marine microorganisms have attracted scientists from different disciplines leading to the discovery of several marine NPs with promising biological activity such as curacin A, eleutherobin, discodermolide, bryostatins, dolostatins, and cephalostatins. Venoms and toxins (peptides and non-peptides) occurring in snakes, spiders, scorpions, insects, and other microorganisms are also significant in drug discovery due to their specific interactions with macromolecular targets in the body, and have been proved crucial while studying receptors, ion channels, and enzymes. Toxins like $\alpha$-bungarotoxin (from cobras), tetrodotoxin (from puffer fish) and teprotide (from Brazilian viper) etc. are in clinical trials for drug development. Similarly, the neurotoxins obtained from Clostridium botulinum (responsible for botulism, a serious food poisoning), has been found significant to prevent muscle spasm.

The review summarizes the 3 groups of compounds classified as NPs, semi-synthetic NPs and NP-derived compounds that have been registred, undergoing registration or in clinical development since 1998 to June 2010 by disease area i.e. infectious (bacterial, fungal, parasitic and viral),
immunological, cardiovascular, neurological, inflammatory and related
diseases and oncology. The compounds which have biological activities
and are derived from natural sources, \textit{e.g.}, plants, animals and
microorganisms have been grouped as NPs. The compounds that
are derived from a NP template using semi-synthesis have been
grouped in semi-synthetic NPs while the compounds that were synthetically
derived or in some cases inspired from a NP template have been
classified as NP-derived compounds [3-5]. The review also presents
an update of previous reviews published in relevance to present context
[6-10].

\textbf{Table 1.} NP-derived drugs launched during 1998-2004; lead compounds and
therapeutic area.

<table>
<thead>
<tr>
<th>Year</th>
<th>Trade name</th>
<th>Lead compound</th>
<th>Disease area</th>
</tr>
</thead>
<tbody>
<tr>
<td>1998</td>
<td>orlistat (Xenical\textsuperscript{®})</td>
<td>lipstatin</td>
<td>Antiobesity</td>
</tr>
<tr>
<td>1998</td>
<td>cefoselis (Wincef\textsuperscript{®})</td>
<td>cephalosporin</td>
<td>Antibacterial</td>
</tr>
<tr>
<td>1999</td>
<td>dalfopristin and quinupristin (70 :30 mixture) (Synercid\textsuperscript{®})</td>
<td>streptogramin B 44 &amp; streptogramin A 45</td>
<td>Antibacterial</td>
</tr>
<tr>
<td>1999</td>
<td>valrubicin (Valstar\textsuperscript{®})</td>
<td>doxorubicin $164$</td>
<td>Oncology</td>
</tr>
<tr>
<td>1999</td>
<td>colforsin daropate (Adele, Adehl\textsuperscript{®})</td>
<td>forskolin</td>
<td>Cardiotonic</td>
</tr>
<tr>
<td>2000</td>
<td>arteether (Artemotil\textsuperscript{®})</td>
<td>artemisinin $65$</td>
<td>Antimalarial</td>
</tr>
<tr>
<td>2001</td>
<td>ertapenem (Invanz\textsuperscript{TM})</td>
<td>thienamycin $5$</td>
<td>Antibacterial</td>
</tr>
<tr>
<td>2001</td>
<td>caspofungin (Cancidas\textsuperscript{®})</td>
<td>pneumocandin B</td>
<td>Antifungal</td>
</tr>
<tr>
<td>2001</td>
<td>telithromycin (Ketek\textsuperscript{®})</td>
<td>erythromycin $51$</td>
<td>Antibacterial</td>
</tr>
<tr>
<td>2001</td>
<td>pimecrolimus (Elidel\textsuperscript{®})</td>
<td>ascomycin</td>
<td>Atopic dermatitis</td>
</tr>
<tr>
<td>2002</td>
<td>galantamine (Reminyl\textsuperscript{®})</td>
<td>galantamine</td>
<td>Alzheimer’s disease</td>
</tr>
<tr>
<td>2002</td>
<td>micafungin (Funguard\textsuperscript{®})</td>
<td>FR901379</td>
<td>Antifungal</td>
</tr>
<tr>
<td>2002</td>
<td>amrubcin hydrochloride (Calsed\textsuperscript{®})</td>
<td>doxorubicin $164$</td>
<td>Oncology</td>
</tr>
<tr>
<td>2002</td>
<td>biapenem (Omegacin\textsuperscript{®})</td>
<td>thienamycin $5$</td>
<td>Antibacterial</td>
</tr>
<tr>
<td>2002</td>
<td>nitisineone (Orfàdin\textsuperscript{®})</td>
<td>leoptospermone</td>
<td>Antityrosinaemia</td>
</tr>
<tr>
<td>2003</td>
<td>miglustat (Zavesca\textsuperscript{®})</td>
<td>1-deoxynojirimycin</td>
<td>Type 1 Gaucher disease</td>
</tr>
<tr>
<td>2003</td>
<td>mycophenolate sodium (Myfortic\textsuperscript{®})</td>
<td>mycophenolic acid</td>
<td>Immunosuppression</td>
</tr>
<tr>
<td>2003</td>
<td>rosvustatin (Crestor\textsuperscript{®})</td>
<td>mevastatin</td>
<td>Dyslipidemia</td>
</tr>
<tr>
<td>2003</td>
<td>pitavastatin (Livalo\textsuperscript{®})</td>
<td>mevastatin</td>
<td>Dyslipidemia</td>
</tr>
<tr>
<td>2003</td>
<td>daptomycin (Cubicin\textsuperscript{TM})</td>
<td>daptomycin</td>
<td>Antibacterial</td>
</tr>
<tr>
<td>2004</td>
<td>everolimus (Certican\textsuperscript{TM})</td>
<td>sirolimus $10$</td>
<td>Immuno-suppression</td>
</tr>
</tbody>
</table>
2. Drug approval processes

The Investigational New Drug (IND) application is submitted to the FDA or EMA before commencement of clinical trials. Once clinical trials are successfully completed, the applicant files New Drug Application (NDA) in the US or Marketing Authorization Application (MAA) in Europe seeking drug’s approval for marketing, to which the agency replies in the form of “approval letter”, “non-approval letter” or “approvable letter”. An “approval letter” allows the applicant to begin marketing of product, while a “non-approval letter” rejects the application. An “approvable letter” informs the applicants that the agency have completed their scientific review and determined that the application can be approved pending resolution of minor deficiencies identified in the letter or during an inspection of the manufacturing facilities.

Table 2. NP-deived drugs launched during 2005-2010; lead compounds, and therapeutic area.

<table>
<thead>
<tr>
<th>Year</th>
<th>Trade name</th>
<th>Lead compound</th>
<th>Disease area</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005</td>
<td>Dronabinol 1/Cannabidol 2 (Sativex®)</td>
<td>Dronabinol 1/cannabidol 2</td>
<td>Pain</td>
</tr>
<tr>
<td>2005</td>
<td>Fumagillin 3 (Flisint®)</td>
<td>Fumagillin 3</td>
<td>Antiparasitic</td>
</tr>
<tr>
<td>2005</td>
<td>Doripenem 4 (Finibax®/Doribax™)</td>
<td>Thienamycin 5</td>
<td>Antibacterial</td>
</tr>
<tr>
<td>2005</td>
<td>Tigecycline 6 (Tygacil®)</td>
<td>Tetracycline 7</td>
<td>Antibacterial</td>
</tr>
<tr>
<td>2005</td>
<td>Ziconotide 8 (Prialt®)</td>
<td>Ziconotide 8</td>
<td>Pain</td>
</tr>
<tr>
<td>2005</td>
<td>Zotarolimus 9 (Endeavor™ stent)</td>
<td>Sirolimus 10</td>
<td>Cardiovascular surgery</td>
</tr>
<tr>
<td>2006</td>
<td>Anidulafungin 11 (Eraxis™/Ecalta™)</td>
<td>Echinocandin B 12</td>
<td>Antifungal</td>
</tr>
<tr>
<td>2006</td>
<td>Exenatide 13 (Byetta®)</td>
<td>Exenatide-4 13</td>
<td>Diabetes</td>
</tr>
<tr>
<td>2007</td>
<td>Lisdexamfetamine 14 (Vyvanse™)</td>
<td>Amphetamine 15</td>
<td>ADHD</td>
</tr>
<tr>
<td>2007</td>
<td>Retapamulin 16 (Altabax™/Altargo™)</td>
<td>Pleuromutilin 17</td>
<td>Antibacterial</td>
</tr>
<tr>
<td>2007</td>
<td>Temsirolimus 18 (Torisel™)</td>
<td>Sirolimus 10</td>
<td>Oncology</td>
</tr>
<tr>
<td>2007</td>
<td>Trabectedin 19 (Yondelis™)</td>
<td>Trabectedin 19</td>
<td>Oncology</td>
</tr>
<tr>
<td>2007</td>
<td>Ixabepilone 20 (Ixempra™)</td>
<td>Epothilone B 21</td>
<td>Oncology</td>
</tr>
<tr>
<td>2008</td>
<td>Methylnaltrexone 22 (Relistor®)</td>
<td>Naltrexone 23</td>
<td>Pain</td>
</tr>
<tr>
<td>2009</td>
<td>Everolimus 24 (Afinitor®)</td>
<td>Sirolimus 10</td>
<td>Oncology</td>
</tr>
<tr>
<td>2009</td>
<td>Telavancin 25 (Vibativ™)</td>
<td>Vancomycin 26</td>
<td>Antibacterial</td>
</tr>
<tr>
<td>2009</td>
<td>Romidepsin 27 (Istodax®)</td>
<td>Romidepsin 27</td>
<td>Oncology</td>
</tr>
<tr>
<td>2009</td>
<td>Capsaicin 28 (Qutenza®)</td>
<td>Capsaicin 28</td>
<td>Pain</td>
</tr>
<tr>
<td>2010</td>
<td>Monobactam aztreonam 29 (Cayston™)</td>
<td>Aztreonam 29</td>
<td>Antibacterial</td>
</tr>
</tbody>
</table>
3. NP based drugs approved during 1998-2004

A total of 21 NP and NP-derived drugs were launched in the United States, Europe or Japan during 1998-2004 that can be classified as 3 NPs, 10 semi-synthetic NPs and 8 NP-derived drugs (Table 1).

3.1. NP based drugs approved during 2005-2010

A total of 19 NP based drugs were approved for marketing worldwide in between the year 2005 to April 2010, among which 7 being classified as NPs, 10 semi-synthetic NPs and 2 NP-derived drugs (Table 2).

Veregen™ (Polyphenon® E ointment), a defined mixture of catechins obtained from green tea, is the first ever herbal medicine to receive FDA approval in 2006. Veregen™ was developed by MediGene AG and launched in the US by Bradley Pharmaceuticals in December 2007 for topical use against genital warts. In March 2010, Solvay launched Veregen® (10 % ointment) in Germany.

Sativex®, a mixture of dronabinol 1 and cannabidiol 2 obtained from the cannabis plant, is the world's first pharmaceutical prescription medicine that was launched in Canada (April 2005) and was later approved by Health Canada (August 2007) as adjunctive analgesic for severe pain in advanced cancer patients [11]. Sativex® has been recommended by FDA to enter directly in Phase III trials and as of November 2009, GW Pharmaceuticals have completed the recruitment for Phase II/III trial against cancer pain. In March 2010, GW Pharmaceuticals provided an update on the progress of regulatory submission for Sativex® oromucosal spray for the treatment of the symptoms of spasticity due to multiple sclerosis.

Fumagillin (Flisint®, Sanofi-Aventis) 3, an endothelial cell proliferation inhibitor isolated from Aspergillus fumigatus [12], was approved in France in September 2005 for the treatment of intestinal microsporidiosis. Fumagillin 3 can also block the blood vessel formation through binding to methionine aminopeptidase II and is under clinical investigations as an angiogenesis inhibitor for the treatment of cancer.

Among carbapenem-type β-lactams, doripenem (Finibax®, Doribax™) 4 is an ultra-broad spectrum injectable antibiotic launched in Japan (2005) by Shionogi & Co. while ertapenem, a NP derived compound based on structure of thienamycin 5 is being marketed by Merck as Invanz™. In October 2007, Johnson & Johnson (J&J) obtained formal FDA approval for use of 4 in intra-abdominal and urinary tract infections.

Tigecycline (Tygacil®) 6, a glycyclycline antibiotic structurally similar to teracycline 7, was approved by FDA in June 2005 against intra-abdominal
and complicated skin and skin structure infections (SSSIs). Tigecycline 6 was developed by Francis Tally and contains a centralised four-ring carbocyclic skeleton substituted at the D-9 position conferring broad spectrum activity. Tigecycline 6 inhibits protein translation by connecting with 30S ribosome and hinders amino-acyl tRNA molecules coming to A site ribosomal subunit [13]. As of May 2006, the 6 has been approved in Europe and later a supplementary NDA for community-acquired pneumonia (CAP) was submitted to the FDA in October 2007.

Ziconotide (Prialt®) 8, a synthetic-conotoxin and calcium channel blocker, isolated from *Conus magus* [14], causes pain relief by inhibiting pro-nociceptive neurochemical releases in the brain and spinal cord [15]. In December 2004, the FDA approved 8 when delivered as infusions into the cerebrospinal fluid using intrathecal pump system. In 2005, Elan launched 8 in US and Europe while rights for marketing 8 in Europe were obtained by Eisai in March 2006.
Zotarolimus 9, a derivative of sirolimus 10, is an active principle of Endeavor™ stent that is being used as anti-proliferative agent by Medtronic [16,17]. In July 2005 Endeavor™ was approved by European commission for the sale while FDA approved it in February 2008 for the treatment of coronary artery disease.

Anidulafungin 11 (Eraxis™ in US, Ecalta™ in Europe), a semi-synthetic derivative of echinocandin B 12, was originally developed by Eli Lilly against invasive and oesophageal candidiasis and candidemia. Anidulafungin 11 was later licensed to Vicuron Pharmaceuticals, which was purchased by Pfizer in June 2005. Pfizer gained FDA approval for Eraxis™ in the US (February 2006) and Ecalta™ in Europe (July 2007).

Exenatide 13 (Byetta®), a 39 amino acid peptide isolated from the oral secretions of Heloderma suspectum (Gila monster) [18], mimics the antidiabetic or glucose-lowering properties of incretins. In April 2005, Eli Lilly obtained FDA approval for 13 while EMEA in November 2006 approved it to Amylin Pharmaceuticals for use in type 2 diabetes mellitus [19]. Amylin Pharmaceuticals, Eli Lilly and Alkermes submitted a NDA in May 2009 for subcutaneous dosing of 13 once weekly that was accepted in July 2009 by the FDA.

Attention-Deficit Hyperactivity Disorder (ADHD), a neurodevelopmental disorder in which dopaminergic and noradrenergic neurotransmission are supposed to be dysregulated, is primarily characterized by the co-existence of attentional problems and hyperactivity. Despite abuse potentials methylphenidate and amphetamines were used for Attention-Deficit Hyperactivity Disorder (ADHD) management since many years. Lisdexamfetamine (Vyvanse™, NRP104) 14 consisting of dextroamphetamine coupled with L-lysine was designed by New River Pharmaceuticals produces effects similar to placebo on intravenous administration, however on oral administration it converts into D-amphetamine 15 in the gastrointestinal (GI) tract [20]. In February 2007, FDA approved 14 to treat ADHD.

Pleuromutilin 16, a fungal metabolite inhibiting protein synthesis in bacteria [21], is the lead compound of retapamulin (SB-275833) 17 developed by GlaxoSmithKline. In June 2007, EMEA approved an ointment containing 1% retapamulin 17 called Altabax™ in the US and Altargo™ in Europe for topical treatment of impetigo caused by Staphylococcus aureus or Streptococcus pyogenes.

Temsirolimus (Torisel®, CCI-779) 18, a derivative of 10 and mTOR inhibitor [22] developed by Wyeth in various Phase III trials was approved in May 2007 by the FDA and November 2007 by the EMEA for the treatment of renal cell carcinoma (RCC) [23].
Trabectedin (Yondelis®, ecteinascidin-743, ET-743) \(19\), an alkaloid obtained from *Ecteinascidia turbinate* [24], is a DNA minor groove binder that inhibits cell proliferation by disrupting the cell cycle. Trabectedin \(19\) is sold by Zeltia and J&J against advanced soft tissue sarcoma (STS). In September 2007, the EMEA has approved \(19\) for use against ovarian cancer and STS. In November 2009, Yondelis® received its second marketing authorisation from the European Commission against relapsed platinum-sensitive ovarian cancer when administered in combination with DOXIL®/Caelyx®.
Ixabepilone (Ixempra™, BMS-247550) 20, a semi-synthetic derivative of epothilone B 21 produced by *Sorangium cellulosum* [25], was developed by Bristol-Myers Squibb (BMS) as an anticancer drug that binds to β-tubulin and suppresses the dynamics of microtubule. In October 2007, BMS gained FDA approval for 20 as a monotherapy and in combination with Xeloda® for the treatment of breast cancer, resisting standard therapy [26].

Methylnaltrexone (MOA-728, Relistor® by Wyeth) 22, a derivative of naltrexone 23 that blocks peripheral opioid receptors activated by opioids and
thus is significant in management of alcohol and opioid dependence [27]. Wyeth and Progenics in May 2007 filed an NDA for subcutaneous doses of 22 against opioid induced constipation (OIC) and other pain indications that was approved in April 2008 by Health Canada and the FDA. As of May 2009 an oral formulation of 22 is under Phase II trials against OIC in chronic pain.

Everolimus (Luveniq™ or LX211) 24, an mTOR inhibiting derivative of 10 is marketed as immunosuppressant by Novartis under Zortress™ (USA) and Certican™ (Europe and other countries) in transplantation medicine, and Afinitor® for use in advanced renal cell carcinoma (RCC). Certican™ was approved in 2004 as immunosuppressant while in March 2009 the FDA has approved 24 against advanced RCC after failure of Sutent® (sunitinib) or Nexavar® (sorafenib).
Natural products in drug discovery

Telavancin (Vibativ™, TD-6424) 25, a semisynthetic derivative of vancomycin 26 that inhibits bacterial growth through binding to D-Ala-D-Ala [28], was developed by Theravance in partnership with Astellas for use against Gram-positive cSSSIs and MRSA that was approved in September 2009 by the FDA. Theravance has also submitted telavancin 25 to the FDA in a second indication against nosocomial pneumonia or hospital acquired pneumonia (HAP). In November 2009, the FDA released a complete response letter to Theravance for telavancin 25 NDA against nosocomial pneumonia.

Romidepsin (depsipeptide, FK228, FR901228, Istodax®) 27 extracted from the bacteria Chromobacterium violaceum, is a histone deacetylase (HDAC) inhibitor [29] developed by Gloucester Pharmaceuticals under National Cancer Institute (NCI) sponsorship for treatment of cutaneous and peripheral T-cell lymphoma (TCL). In November 2009, the FDA approved 27 to use in the treatment of selective cutaneous TCL patients previously treated with minimum of one prior systemic therapy. In January 2010, Celgene completed the acquisition of Gloucester Pharmaceuticals.

Capsaicin (Qutenza®) 28, isolated from chili peppers of genus Capsicum [30], produces burning sensation on contact to tissues though binding to vanilloid receptor subtype 1 (VR 1) [31]. In November 2009, the FDA approved Qutenza® (a transdermal 8% patch of 28) to use in treatment of neuropathic pain combined with postherpetic neuralgia. In April 2010, NeurogesX launched Qutenza® in US. Aztreonam lysine (CaystonTM) 29 is an inhaled lysine salt formulation [32] that was evaluated by Gilead in various Phase III trials against cystic fibrosis (CF) patients infected with the Gram-negative bacteria Pseudomonas aeruginosa. In February 2010, the FDA approved 29 against CF patients.
4. Infectious diseases

4.1. Antibacterial

NP-derived drugs have played their crucial role in anti-infective drug discovery and the majorities of antibacterial drugs currently in clinical use are NPs or were designed using NP templates. Despite having complex structure the development of a NP to an antibacterial drug entirely depends on its ability to penetrate bacterial cell membranes. The success of penicillin encouraged the discovery of other compounds from natural sources against bacterial infections and as a result nearly all novel classes of antibiotics belong to NP sourced scaffolds [33].

Ceftobiprole medocaril (BAL-5788) 30, a cephalosporin antibiotic with excellent activity against methicillin-resistant *Staphylococcus aureus*, penicillin-resistant *Streptococcus pneumoniae, Pseudomonas aeruginosa*, and *Enterococci* [34], was filed for regulatory approval in the US and Europe in July 2007 by Basilea Pharmaceutica and J&J affiliated Cilag GmbH International to use in the treatment of cSSSIs. In November 2008, the approval of 30 was declined by the FDA with recommendation of two new studies to access safety and efficacy in treatment of cSSSIs. Additionly, various Phase III trials are underway for HAP/CAP. Ceftaroline acetate (PPI-0903, TAK-599) 31, discovered by Takeda and licensed to Cerexa, shows efficacy against the penicillin-resistant *S. pneumoniae* and is under Phase II development by Forest Laboratories to use in the treatment of cSSSIs and CAP [35].

Tebipenem pivoxil (ME-1211, L-084) 32, an oral carbapenem antibiotic is under Phase III clinical development by Meiji Seika in Japan for treatment of otolaryngological/respiratory infections. Tomopenem (CS-023, RO4908463, R1558) 33 [36], by Daiichi Sankyo for treatment of common nosocomial infections and PZ601 (SM-216601, Protez) 34 [37], against MRSA and *Pseudomonas aeruginosa*, are currently in Phase II trials. ME1036 (CP5609) 35, a DHP-1-stable parenteral carbapenem having excellent *in vitro* activity against multidrug-resistant (MDR) *staphylococci* and *Enterococcus faecalis* was licensed by Cerexa and Forest Laboratories from Meiji Seika Kaisha. ME1036 35 is currently under Phase I evaluation. Likewise, sulopenem (CP-70429) 36, is being evaluated by Pfizer in various Phase I trials [38].

Faropenem daloxate (SUN-208, BAY-56-6824) 37 is a penem-type β-lactam licensed to Replidyne by Daiichi Suntory Pharma for marketing in conjunction with Forest Pharmaceuticals [39]. In December 2005, Replidyne submitted an NDA to the FDA for use of 37 in the treatment of bacterial...
sinusitis (BS), chronic bronchitis (CB), CAP and uncomplicated (SSSIs). In response to Replidyne’s NDA, the FDA in March 2007 agreed for Phase III placebo-controlled trials of 37, one each in BS and CB along with two non-inferiority CAP trials. However, these additional trials have certainly delayed the launch of drug.

\[ R = \text{OH} \]

\[ R = \text{CH}_3 \]
Dalbavancin (Zeven®, BI-397) 38, a semi-synthetic derivative of the teicoplanin analogue A40926 39, was discovered by Biosearch Italia and being developed by Pfizer for the treatment of cSSSIs [40]. In February 2005, Vicuron Pharmaceutical (now a part of Pfizer) filed an NDA for 38 to use in the treatment of patients suffering from cSSSIs. In response, the FDA released an approval letter in December 2007, however, as of September 2008 Pfizer have withdrawn all the marketing applications of 38 for running another Phase III trial.

Oritavancin (Nuvocid™, LY-333328) 40, a chloroeremomycin 41 derivative inhibiting cell-wall synthesis, was discovered and developed by Eli Lilly and acquired by InterMune in 2001 and later transferred to Targanta Therapeutics in 2005. In February 2008, Targanta submitted an NDA for 40 to the FDA that was not approved due to insufficient data. Additionally, a MAA was submitted by Targanta for 40 to EMEA that was accepted for review in June 2008. TD-1792 42, a vancomycin-cephalosporin heterodimer successfully evaluated by Theravance in Phase II trials against cSSSIs including MRSA, has been designed to target 2 key targets in bacterial cell wall synthesis. In July 2007, Theravance disclosed to meet primary and secondary endpoints of non-inferiority trial compared to vancomycin 26.

Ramoplanin factor A2 (known as “ramoplanin”) 43, the major component of the lipopeptide antibiotic drugs obtained from Actinoplanes ATCC 33076 [41], inhibits cell wall synthesis in bacteria by forming U-shaped structures that are able to bind and capture Lipid II (C35-MurNAc-peptide-GlcNAc), a specific intermediate in membrane formation [42]. Oscient Pharmaceuticals hold the North American right and are evaluating orally active doses of 43 in Phase II trials against Clostridium difficile associated GI tract infections [43].

NXL-103 (XRP2868), an orally available mixture (70:30) of flopristin (RPR132552A, streptogramin A-type) 44 and linopristin (RPR202698, streptogramin B-type) 45 that inhibit bacterial protein synthesis through the synergistic binding to different sites on the peptidyltransferase domain of the 50S ribosomal subunit [44], was discovered by Sanofi-Aventis [45]. Novexel in October 2008 announced for positive Phase II trials of NXL-103 against CAP and cSSSIs including MRSA.

Friulimicin B 46, a lipopeptide antibiotic produced by Actinoplanes friuliensis HAG 010964 [46], exerts activity through complex formation with bactoprenol-phosphate, resulting in inhibition of peptidoglycan and teichoic acid biosynthesis in bacteria [47], is under Phase I clinical development (July 2007) by MerLion Pharmaceuticals. Structure of friulimicin B 46 was confirmed after the crystal structure of amphomycin tsushimaycin (A-1437 B) 47, an aspartic acid analogue of 46 was published in late 2005.
Moli1901 (duramycin, 2262U90) 48, obtained from *Streptomyces cinnamoneum* [48], enhances the chloride transport and increases fluid secretion *in vitro*, thus finds significance for the treatment of CF [49]. Moli1901 48 is currently under clinical development by AOP Orphan in collaboration with Lantibio in Europe. In March 2007, Lantibio announced the positive results of Phase II trial of aerosolized 48 in adolescents and adults suffering from CF. An ophthalmic solution of 48 for treatment of dry eye syndrome is also under Phase II trials by Lantibio.

Omiganan 49, originally purified from neutrophils of bovine, is an indolicidin 50 derivative that can interact with the bacterial cytoplasmic membrane and has been found significant against antibiotic-resistant and sensitive bacterial infections [50]. Omiganan 49 was developed by MIGENIX and later licensed to Cadence Pharmaceuticals and Cutanea Life Sciences for catheter-related infections (coded Omigard™, CPI-226, MBI-226) and dermatological diseases (coded as CLS001, MX-594AN), respectively. Cadence Pharmaceuticals are currently evaluating a gel-based formulation of 49 in Phase III trials while another phase III trials for treatment of rosacea, a chronic inflammatory skin disorder are underway.
Erythromycin \(51\), macrolide antibiotic produced by actinomycetes, exerts antibacterial activity through inhibition of protein synthesis by binding to peptidyltransferase site of 50S subunit \([51]\). Among other derivatives, cethromycin \(52\), EP-420 \(53\) and BAL-19403 \(54\) are currently in clinical development. Cethromycin (ABT-773) \(52\) was discovered by Abbott Laboratories and later acquired by Advanced Life Sciences to use in the treatment of CAP and anthrax \([52]\). Advanced Life Sciences in October 2008 submitted a NDA to use \(52\) in the treatment of mild-to-moderate CAP which was accepted by FDA in December 2008. The cethromycin \(52\) (Restanza\textsuperscript{TM}) has demonstrated clinically and statistically significant survival rate in placebo-controlled non-human primate studies with anthrax, plague and tularemia. In September 2009, the FDA has given orphan drug designation to \(52\) for the treatment of plague and tularemia. Likewise, EP-420 (EP-013420) \(53\), a bridged bicyclic derivative of \(51\) is currently under Phase II clinical development by Enanta and Shionogi for treatment of CAP \([53]\). BAL19403 \(54\), a macrolide antibiotic significant against clinical isolates of \textit{Propionibacterium acnes} with mutations in the 2057 to 2059 region of 23S rRNA conferring resistance to \(51\), is under clinical development by Basilea for the treatment of acne \([54]\). Telithromycin (Ketek\textsuperscript{®}) \(55\) is the first approved ketolide developed by Sanofi-Aventis that received approval from the European Commission (July 2001) and the FDA (in 2004) for treatment of respiratory infections. Telithromycin \(55\) displays bactericidal activity by blocking the progression of the growing polypeptide chain through binding with the 50S subunit of ribosome. Tiacumicin B (OPT-80, PAR-101) \(56\), a macrolactone isolated by Abbott \([55]\) from actinomycetes, inhibits RNA synthesis and is under phase III clinical development by Optimer Pharmaceuticals for the treatment of \textit{Clostridium difficile}-associated diarrhea (CDAD) \([56]\).

PTK-0796 (MK-2764) \(57\) is an aminomethylcycline inhibiting protein synthesis in bacteria, was discovered and evaluated by Paratek in Phase II trials for the treatment of common hospital infections. PTK-0796 \(57\) was in-licensed
by Novartis form Paratek for collaborative Phase III clinical development. In October 2009, Novartis gained exclusive marketing rights of 57 to use in the treatment of MRSA, MDR Streptococcus pneumoniae and vancomycin-resistant enterococci.

Eritoran (E5564) 58, a second-generation lipid A antagonist [57] designed by Eisai from Rs-DPLA 59 isolated from Rhodopseudomonas sphaeroides [58], inhibits endotoxin response through antagonism of the Toll-like receptor 4 (TLR4) [59,60].
CBR-2092 60, a hybrid antibiotic inhibiting RNA and DNA synthesis is being developed by Cumbre Pharmaceuticals for treatment of gram-positive cocci infections. CBR-2092 60 is supposed to exert antimicrobial activity through combined effects on RNA polymerase, DNA topoisomerase IV and DNA gyrase. Currently, CBR-2092 60 is in Phase IIa trial by Cumbre for treatment of infections caused by gram-positive cocci [61].

### 4.2. Antifungal

Invasive fungal infections – infections of the bloodstream and organs within the body (e.g. meningitis, pneumonia, peritonitis) – are important causes of morbidity and mortality in liver, pancreas, heart, kidney and lung (i.e. solid organ) transplant recipients [62]. Fungi are eukaryotes and, despite
the presence of a cell wall, fungi are more similar to mammalian cells on a cellular level than to bacteria, making the treatment of mycotic infections difficult [63]. Only 2 NP-derived compounds, aminocandin 61 and SPK-843 62 are undergoing clinical evaluation. Due to lack of biological target, 1,3-β-D-glucan synthesis in human, echinocandin derivatives have been considered significant against refractory aspergillosis and invasive infections by Candida species [64]. Among other semi-synthetic echinocandins, caspofungin (launch 2001, Cancidas®, Merck), micafungin (launch 2002, Mycamine®/Funguard®, Astellas) and anidulafungin 11 (launch 2006, Eraxis™/Ecalta™, Pfizer) have been approved. Deoxymulundocandin 63, isolated from Aspergillus sydowii [65], is the lead compound of aminocandin (NXL-201, IP960, HMR-3270) 61 and exhibit excellent activity against Candida albicans and C. tropicalis by destabilizing the fungal cell membrane. SPK-843 62, a semi-synthetic derivative of patrician-A 64, is under clinical development by Dutch company APARTS BV [66] that has acquired world wide rights for the development of 62.

4.3. Antiparasitic

The use of medicinal plants against parasitic diseases has been traced to ancient times i.e. bark of Cinchona calisaya and Strychnos pseudoquina, root and leaves of Deianira erubescens, bark of Remijia ferruginea [67].

Artemisinin (Artemotil®) 65, obtained from traditional Chinese medicine Artemisia annua, was approved in the year 2000 for the treatment of chloroquine-resistant Plasmodium falciparum malaria and cerebral malaria. The World Health Organization has strongly discouraged the use of 65 as a monotherapy since malarial parasites are developing resistance to the drug. However, combination therapies that include 65 are the preferred treatment for malaria and are both effective and well tolerated in patients. Artemotil® is currently used only as a second line drug in severe cases of malaria and is also increasingly being used against vivax malaria. As of May 2009, arterolane (RBx11160, OZ-277) 66, a trioxolane modelled on artemisinin 65 pharmacophore, is under Phase III clinical development for the treatment of malaria by Ranbaxy in combination with piperaquine [68].

Paromomycin 67 (Humatin™, King Pharmaceuticals), an orphan drug extracted from Streptomyces krestomuceticus [69], was approved in September 2006 by Drug-Controller General of India for the treatment of patients suffering from visceral leishmaniasis (VL). Paromomycin 67 was developed by the Institute for OneWorld Health [70] and is an off-patent antibiotic marketed in the US to treat intestinal parasites.
4.4. Antiviral

Virus is a small infectious agent that can replicate only inside the living cells of organisms bringing most common (i.e. cold, influenza, chickenpox and cold sores) to greatest human health risk (i.e. ebola, AIDS, avian influenza and SARS). Researches over last 25 years have resulted in the identification of many natural product templates significant to antiviral drug discovery, however fewer are in clinical investigation.
Betulinic acid 68, a topoisomerase I inhibitor isolated from bark of Betula pubescens [71], is currently in Phase I clinical development. Bevirimat (PA-457) 69, obtained from Syzygium claviflorum, was evaluated by Panacos in Phase Iib trial for development as combination therapy with other standard antiviral drugs. Bevirimat 69 inhibits the final step of the HIV Gag protein processing and thus blocks HIV maturation [72]. In January 2009, Myriad Genetics announced for the acquisition of all rights from Panacos for 69. Ribavarin 70, a NP-derived compound structurally similar to pyrazomycin and showdomycin, was marketed as ‘Rebetol’ until 2005 by Schering Plough with Valeant Pharmaceuticals in the US. Valeant Pharmaceuticals are developing taribavirin (Viramidine®, ribamidine) 71, a liver-targeting prodrug of ribavarin 70 [73], is in various Phase II/III trials for the treatment of chronic hepatitis C virus (HCV). In 2006, 71 failed to meet the non-inferiority efficacy endpoints in Phase III trials by Valeant. In 2007, Valeant initiated another Phase Iib trial for 71 with higher doses and reported the final results in June 2009 against HCV.

MBI-3253 (celgosivir, 6-O-butanoylcastanospermine) 72, a glucosidase inhibitor and semi-synthetic derivative of indolizine alkaloid castanospermine 73 isolated from Castanospermum australe seeds [74], is an investigational antiviral drug under clinical development by MIGENIX. As of January 2009, MIGENIX has completed Phase II clinical studies of 72 as a “triple combination” (with peginterferon α-2b and ribavarin 70) and a “double combination” (with peginterferon α-2b) in HCV patients. After discontinuation of exclusive option agreement with United Therapeutics Corporation (UTC) in April 2009, MIGENIX are seeking other strategic options for further development of 72.

Cyclosporin 74, a cyclophilin inhibitor obtained from Beauveria nivea, exerts significant antiviral activity. However, due to calcineurin-related and immunosuppressive side effects development of 74 as antiviral drug is not possible [75]. NIM 811 (SDZ NIM 811, cyclosporin 29, MeIle4-cyclosporin) 75, discovered by Sandoz (now Novartis) with 1700 times less immunosuppressive activity than cyclosporin 74 [76], was evaluated in Phase I trial for anti-HIV and HCV activity. Likewise, debio-025 (UNIL025, MeAla3EtVal4-cyclosporin) 76, a cyclophilin inhibitor with 7000 times less immunosuppressive activity than 74, is being evaluated by Debiopharm in various phase Iib trials for the treatment of HCV [77,78]. In February 2010, Novartis in-licensed the exclusive rights to develop and market 76, as potential first-in-class antiviral agent except in Japan.

4-Methylumbelliferone (Heparvit®) 77 is a naturally occurring coumarin that is in Phase II development by MTmedical Institute of Health and BioMonde for the treatment of HBV and HCV. 1,5-DCQA (1,5-di-O-
caffeoylquinic acid) \( \text{78} \), a HIV-1 integrase inhibitor extracted from *Inula Britannic*, is under human clinical trials by Chinese Academy of Military Medical Sciences for treatment of HIV/AIDS and hepatitis B \[\text{79}\].

WAP-8294A\(_2\) (JA-002) \( \text{79} \), produced by the Gram-negative *Lysobacter* species exerts antibacterial activity by interacting selectively to membrane phospholipids and causes severe damage to bacterial membrane \[\text{80}\]. The aRigen Pharmaceuticals are evaluating injectible, gel and cream of \( \text{79} \) in various Phase I/II trials to treat MRSA and acne. In August 2009, New Energy and Industrial Technology Development Organization (NEDO), Japan has decided for funding two-thirds R&D costs to aRigen Pharmaceuticals until February 2011 for development of \( \text{79} \) as first-line anti-MRSA product candidate.
5. Neurological diseases

Historically, the alkaloids like morphine 80 isolated from *Papaver somniferum* and physostigmine 81 extracted from *Physostigma venenosum*, were used to treat severe pain and diseases of central nervous system (CNS). (+)-huperzine A 82, a sesquiterpene alkaloid and acetylcholinesterase (AChE) inhibitor extracted from *Huperzia serrata* [81], is being evaluated by Chinese scientists against Alzheimer’s disease. The National Institute on Aging (NIA) is evaluating orally administered formulation of 82 in Phase II trials against Alzheimer's disease [82]. Morphine-6-glucuronide (M6G) 83, produced by metabolism of artemisone (BAY 44-9585) 84 (obtained through semi-synthesis from artemisinin 63) in human body, was evaluated successfully by CeNeS Pharmaceuticals as significant analgesic in Phase III trials in Europe. PAION in June 2008 acquired CeNeS Pharmaceuticals and later in November 2008 disclosed for completion of two Phase III trials. A spicamycin derivative KRN-5500 85, obtained from *Streptomyces alanosinicus* [83], was evaluated by DARA BioSciences in Phase I trials against neuropathic pain. DARA BioSciences are currently running Phase IIa trials of 85 given intravenously (IV) to cancer patients suffering from neuropathic pain [84].

Debio 9902 (ZT-1) 86, synthesized by Shanghai Institute of Material Medica, is a prodrug of 82 licensed to Debiopharm. Debiopharm in June 2007 announced the positive results of a Phase IIa trial of 86 against mild Alzheimer’s disease. As of October 2008, Debiopharm have started tablet
formulation bridging study of 86 as Investigational New Drug (IND) to treat Alzheimer’s patients. Lobeline 87, a VMAT2 ligand [85] reducing the methamphetamine induced dopamine release, is a significant tobacco smoking cessation agent occurring in Hippobroma longiflora [86]. Lobeline 87 is being evaluated by Yaupon Therapeutics and NIH as a dopamine modulating agent under Phase II trials against ADHD and methamphetamine addiction.

Anabaseine 88, isolated from marine worms of the phylum Rhynchocoela [87], stimulates the neuronal nicotinic receptors thus has been considered significant in the treatment of Alzheimer’s disease as Alzheimer’s brain loses many of its nicotinic receptors by the time of death [88]. The 3-(2,4-dimethoxybenzylidene)-anabaseine (DMXBA; also called GTS-21) 89, a synthetic derivative of 88, was evaluated against Alzheimer’s disease in a sponsored research by Taiho Pharmaceutical to Kem’s University of Florida.
The University of Florida licensed 89 to Osprey Pharmaceuticals whose assets were purchased by CoMentis (previously Athenagen) in April 2006. CoMentis are currently assessing 89 in various Phase I/II trials for safety assessment and cognitive improvement in ADHD patients.

Tetrodotoxin (Tectin™, Wex Pharmaceuticals) 90, extracted from the puffer fish [89], blocks the action potentials in nerves through binding to sodium channels in cell membrane [90]. Wex are evaluating 90 in collaboration with Chinese medical institute against cancer pain and management of opiate withdrawal symptoms in Phase III and I trials, respectively. Also a Phase IIa trial of 90 against neuropathic pain caused by cancer chemotherapy is underway by Wex Pharmaceuticals.

Capsaicin 28 and related compounds (called as capsaicinoids) are produced by chili peppers as irritants against certain herbivores and fungi. Among capsaicinoids, Xen-2174 91, obtained from venom of Conus marmoreus targeting norepinephrine transporter (NET) was discovered by researchers at the University of Queensland. Xenome are associated with Phase II development of 91 against acute post-operative and chronic pain in cancer patients resistant to morphine and hydromorphone. Anesiva are evaluating capsaicin 28 (coded 4975, ALGRX 4975, Adlea™) in various clinical trials against pain indications such as severe post-surgical pain, post-traumatic neuropathic pain and musculoskeletal diseases [91]. Anesiva in December 2008, disclosed to meet primary end point in a phase III trial of 28 against acute pain following orthopedic surgery. Winston Laboratories are associated with Phase III trials of civamide (cis-capsaicin, zucapsaicin, WL-1001) to treat episodic cluster headache and knee osteoarthritis. Winston in October 2008 filed a NDS to Canada for Civanex® (civamide 0.075%) to use against osteoarthritis pain. In February 2009, an orphan drug designation to Civanex® was given by FDA with NON release to Winston Pharmaceuticals in October 2009.
Phlorizin 92, a flavonoid that belongs to the group of dihydrochalcones obtained from bark of pear \((Pyrus communis)\), apple, cherry and other fruit trees (family-Rosaceae), is a sodium glucose co-transporters (SGLTs) inhibitor that lowers glucose plasma level and improves insulin resistance [92] but has poor intestinal absorption and become inactive by lactase-phlorizin hydrolase. Dapagliflozin (BMS-512148) 93, a 92 derivative that selectively inhibits SGLT2, is under clinical development by Bristol-Myers Squibb (BMS) in collaboration with AstraZeneca for the treatment of 2 diabetes. In October 2009, the BMS announced the positive results of Phase III placebo controlled trial of 93.

Resveratrol 94, a triphenolic stilbene occurring in many plants is significant against clinical indications such as cancer, ischemic injuries and cardiovascular disease [93]. Resveratrol 94 is an agonist of Saccharomyces cerevisiae silent information regulator (Sir2) protein, a class III histone deactylase whose presence causes extension of lifespan in S. cerevisiae, Caenorhabditis elegans and Drosophila melanogaster [94]. Italian scientists in 2006 observed 56% increase in median life span of Nothobranchius furzeri [95], a fish when supplemented with 94. SRT-501, a formulation of 94 by Sirtris Pharmaceuticals, acts by increasing mitochondrial activity and is under clinical investigations against diabetes and obesity. Sirtris has announced the positive results of Phase IIa trial in which oral doses of 1.25 or 2.5 grams of SRT501 was found safe at twice daily dosing for 28 days in type 2 diabetes. A similar Phase IIa cancer trial with SRT501 is under way.

Cannabinoids are a group of secondary metabolites responsible for pharmacological properties of Cannabis sativa (cannabis plant) [96]. CP 7075 (IP 751, ajulemic acid, CT-3) 95, a synthetic cannabinoid, suppressing IL-1β and matrix metalloproteinases (MMPs) through a peroxisome proliferator-activated receptor (PPAR) γ-mediated mechanism [97], was investigated by Indevus Pharmaceuticals in pre-clinical studies. In October 2007, the drug was licensed by Cervelo Pharmaceuticals for Phase I trials in neuropathic pain.
6. Cardiovascular and metabolic diseases

Natural products have played an important role in development of drugs against cardiovascular and metabolic diseases. Simvastatin (Zocor®, Merck), a lipid-lowering statin obtained from fermentation product of *Aspergillus terreus*, inhibits 5-hydroxy-3-methylglutarylcoenzyme A (HMG-CoA) reductase. Orlistat (Xenical®), a lipstatin derivative isolated from *Streptomyces toxytricini* [98], inhibits pancreatic lipases and used for the treatment of obesity. Captopril, ramipril and quinapril are the examples of some antihypertensive angiotensin-converting enzyme (ACE) inhibitors derived from the snake venom. An endopeptidase (NEP) inhibitor, ilepatrial (AVE-7688) 96, is being developed by Sanofi-Aventis in various Phase IIb/III trials to treat hypertension while phase II trial for diabetic nephropathy. (+)-1-Deoxygalactonojirimycin 97 and (+)-galactonojirimycin 98 obtained from *Streptomyces* species [99] display strong inhibitory activity toward several β-galactosidases. Miglustat (Zavesca®) was used earlier to treat Type 1 Gaucher disease (GD1) by Actelion. Migalstat (Amigal™, AT1001, 1-deoxygalactonojirimycin, 1-deoxygalactostatin) 97, a semi-synthetic derivative of 98, stabilizes protein structures and restores correct folding through binding with them. (+)-1-Deoxygalactonojirimycin 97 is an orphan designated drug by European Commission in May 2006 to use in treatment of Fabry disease. As of January 2010, the 97 is being evaluated under Phase III trials by Amicus Therapeutics in collaboration with Shire
Pharmaceuticals against Fabry disease. Isofagomine (Plicera™, AT2101) 99, an aza-sugar that mimics the carbocation transition state used by glycosidases [100], is under clinical development by Amicus Pharmaceuticals to treat Gaucher’s disease [101]. Amicus in October 2009 announced the positive results of a Phase II trial for two dose regimens consisting of 225 mg of 99 given three days on/four days off and seven days on/seven days off.

Ruboxistaurin (LY333531) 100, inhibiting protein kinase C (PKC), is being developed by Eli Lilly to use in the treatment of microvascular complications in diabetes mellitus [102]. In February 2006, Lilly submitted a NDA for use of 100 in diabetic peripheral retinopathy. In August 2006, the FDA issued an “approvable” letter to Lilly while suggesting another Phase III trial for additional efficacy. SCH 530348 (TRA) 101, a PAR-1 antagonist [103] similar to himbacine 102 obtained from Galbulimima baccata, is in Phase III clinical trials by Schering-Plough for the treatment of cardiovascular diseases such as atherosclerosis, ischemia, myocardial infarction and stroke.
Genaera Corporation are associated with clinical development of trodusquemine (MSI-1436) 103 and squalamine 104 extracted from *Squalus acanthias* [104]. MSI-1436 103 is a protein tyrosine phosphatase 1B inhibitor [105] that is being evaluated by Genaera in a second Phase I trial using an ascending single dose in overweight type 2 diabetics under the obesity IND.

Ouabain (g-strophanthin) 105, a cardiac glycoside occurring in ripe seeds of *Strophanthus gratus* and bark of *Acokanthera ouabaio*, involves binding to and inhibition of the plasma membrane Na$^+$/K$^+$-ATPase attainable *in vitro* or with intravenous dosage [106]. Likewise, digoxin 106, isolated from *Digitalis lanata* (foxglove plant) [107], also exists in the human adrenal gland and is significant in atrial fibrillation and atrial flutter. Rostafuroxin (PST 2238) 107, an ouabain antagonist, is under Phase II development by Sigma-Tau to use in the treatment of chronic arterial hypertension.
Mitemcinal (GM-611) \textbf{108}, an agonist of motilin that lacks the antibiotic properties of \textbf{51} and increases the amplitude & frequency of antral contractions and initiates gastric contractions, was discovered by Chugai Pharma. Phase I trials of \textbf{108} in Japan has been completed by Chugai while Phase II trials in US are still running against diabetic reflux oesophagitis and idiopathic gastroparesis \cite{108}. Chugai are also conducting Phase II trials of \textbf{108} against irritable bowel syndrome (IBS).

Pyridoxamine (Pyridorin\textsuperscript{TM}) \textbf{109}, consisting of a pyridine ring bearing hydroxyl, methyl, aminomethyl, and hydroxymethyl substituents, is a vitamin B\textsubscript{6} analogue \cite{109} that was evaluated by BioStratum in two phase II trials demonstrating retardation of diabetic nephropathy. In October 2006, BioStratum licensed \textbf{109} to NephroGenex, which has initiated a new Phase IIb trial in patients with type 2 diabetes. Taisho Pharmaceutical is evaluating \textbf{109} (coded as K-163) in Phase II trials against diabetic nephropathy. In January 2009, the FDA ruled for regulation of \textbf{109} as a pharmaceutical drug and awarded a fast track drug designation.

7. Immunological, inflammatory and related diseases

Autoimmune and inflammatory disease condition arises through aberrant reactions of the human adaptive or innate immune systems. Aspirin, discovered in the late 1890s, is still a significant analgesic and anti-inflammatory drug. Salbutamol, a $\beta_2$-adrenergic receptor agonist, is marketed by GlaxoSmithKlinen to treat asthma and chronic obstructive pulmonary disease. Cyclosporin \textbf{74} (1983), tacrolimus (1993), sirolimus \textbf{10} (1999), mycophenolate sodium (2003) and mycophenolate mofetil (1995) are among some important immunosuppressive drugs sourced from natural products. Everolimus (Luveniq\textsuperscript{TM} or LX211) \textbf{110}, a derivative of \textbf{10} inhibiting mTOR, is marketed by Novartis as immunosuppressant Certican\textsuperscript{®} in organ transplantation.

Voclosporin (ISA-247, R1524, LX211) \textbf{111}, a derivative of \textbf{74} inhibiting calcineurin \cite{110}, is under Phase IIb trial to prevent kidney graft rejection and Phase III trial against psoriasis. Voclosporin \textbf{111} was licensed by Lux Biosciences from Isotechnika for ophthalmic indications. As of March 2009, Lux Biosciences have completed Phase III trials of \textbf{111} oral capsules against uveitis. In February 2010, Lux Biosciences filed a NDA to the FDA and MAA to the EMA for \textbf{111} under Luveniq\textsuperscript{TM} against non-infectious uveitis, which were accepted by respective agencies in March 2010. Eupatilin \textbf{112}, a flavone isolated from Korean traditional medicine Artemisia argyi possess efficacy against chronic diarrhea \cite{111}. DA-6034 \textbf{113}, a synthetic \textbf{112} derivative, is being developed by Dong-A Pharmaceuticals in Phase I and II trials against dry eye and gastritis, respectively.
8. Oncological diseases

8.1. Small-molecule anticancer agents

8.1.1. Plant-derived compounds

Camptothecin 114, a topoisomerase I inhibitor isolated from *Camptotheca acuminata* [112], exhibits significant anticancer activity. Among other camptothecin class of drugs, belotecan (Camptobell, CDK-602) was developed and launched in 2004 by Chung Kun Dong in Korea [113]. BNP-1350 (Karenitecin®) 115 is an investigational drug under clinical
development by BioNumerik Pharmaceuticals for cancer chemotherapy. As of February 2008, BioNumerik are running the Phase III trial of 115 against ovarian cancer [114]. Difromotecan (BN80915) 116, a 115 analogue [115], is being developed by Ipsen under Phase II trials to treat advance metastatic cancers. Gimatecan (ST-1481) 117, an oral topoisomerase I inhibitor, is currently in Phase II development by Novartis against solid tumors [116]. Elomotecan (BN-80927, LBQ707, R-1559) 118, inhibiting topoisomerase I and II, is a promising Phase I pipeline by Ipsen in oncology (e.g. colon, breast and prostate cancer) [117]. DRF 1042 105 is a 114 derivative evaluated by Dr. Reddy’s Laboratories in Phase I trials to use in the treatment of various cancers [118]. Dr. Reddy’s Laboratories in September 2006 collaborated with ClinTec International for joint Phase II/III development of 119. In September 2006, Sonus Pharmaceuticals initiated a Phase I study of SN2310 120, a prodrug of SN-38 121 to address cancer is presently ongoing. In May 2008, Sonus merged with OncoGenex Technologies and the new company, OncoGenex Pharmaceuticals has included 120 as a strong oncology pipeline.
Combretastatin A-4 phosphate (Zybrestat™, CA4P) 121, a prodrug of combretastatin A-4 122 obtained from South African Bush Willow Combretum caffrum [119], is a reversible tubulin depolymerizing agent that causes tumour-associated endothelial cells to change from a flat to a round shape, thus by plugging the blood vessels deprives the tumour from oxygen and nutrients. Oxigene are evaluating 121 as a vascular disrupting agent (VDA) [120] and as on September 2008, Phase III trial against anaplastic thyroid cancer (ATC) is underway. Oxigene in November 2009 disclosed the positive results of a Phase II trial of 121 in non-small cell lung cancer (NSCLC). Ombrabulin (AVE8062) 123, another 122 derivative licensed to Sanofi-Aventis from Ajinomoto, is under Phase III trials in advanced STS patients. Combretastatin A-1 diphosphate (OXi4503) 124, a pro-drug of combretastatin A-1 125 that is capable of binding to proteins and nucleic acids [121], is under various Phase I trials by OXGENE to use in the treatment of advanced-stage solid tumors. Noscapine (CB3304, noscapine) 126, a benzylisoquinoline alkaloid occurring in the plants of family Papaveraceae, is a microtubule targeting antitussive currently in Phase I/II trials by Cougar Biotechnology for the treatment of multiple myeloma [122].

Vinblastine (Alkaban-AQ®, Velban®) 127, a microtubule inhibitor isolated from Catharanthus roseus [123], has been found significant when given intravenously to patients suffering from Hodgkin's disease, non-Hodgkin's lymphoma, Kaposi's sarcoma, choriocarcinoma, TCL, breast, testicular, lung, neck and head cancers. Vinflunine (Javlor®) 128, a fluorinated vinca alkaloid [124] discovered by Laboratoires Pierre Fabre, was submitted for registration with the EMEA in June 2008, after positive Phase III trial for metastatic treatment of bladder cancer. In June 2009, Pierre Fabre received a positive opinion with recommendation for marketing authorization of 128 in the metastatic treatment of bladder cancer.

Paclitaxel (Taxol™, Abraxane™) 129, isolated from Taxus brevifolia [125], is a mitotic inhibitor that stabilizes microtubules and interferes with the normal breakdown of microtubules during cell division. Bristol-Myers Squibb (BMS) are associated with commercial development of 129. Cabazitaxel (XRP6258) 130 and larotaxel (XRP9881) 131 have been designed by Sanofi-Aventis as poor substrates for membrane-associated P-glycoprotein (P-gp), overexpressed in taxane resisting cells [126] and are in Phase III trials against pancreatic and hormone-refractory prostate cancers [127]. Luitpold Pharmaceuticals are developing DHA-paclitaxel (Taxoprexin®) 132, a fatty acid conjugate of 129, in Phase III trials against metastatic melanoma [128]. Spectrum are associated with Phase I/II development of intravenous/oral ortataxel (IDN-5109, BAY-59-8862) 133, a third generation taxane with toxicity/tolerance profile similar to 129. As of
June 2009, the 133 is under Phase II trials in taxane-refractory solid tumors [129]. Milataxel (MAC-321, TL-00139) 134, a poor substrate for P-gp, is under Phase II clinical development by Wyeth Pharmaceuticals to use in the treatment of colorectal neoplasms [130]. Tesetaxel (DJ-927) 135, an orally administered semi-synthetic taxane, was evaluated by Genta in various Phase I/II trials against advanced gastric and breast cancer [131]. The Phase II clinical trials of 135 are running for the treatment of patients with advanced melanoma having a normal serum lactate dehydrogenase (LDH) and have progressed after one chemotherapy regimen. Other taxanes that are in Phase II clinical development, i.e. TPI-287 136 by Tapestry Pharmaceuticals and BMS-188797 137 by Bristol-Myers Squibb, to treat patients suffering from pancreatic and advanced malignancies, respectively are currently in Phase II clinical development [132].
Acrony cine 138, an alkaloid isolated from *Acronychia baueri*, exhibits activity against various solid tumors such as S-180 and AKR sarcomas, X-5563 myeloma, S-115 carcinoma and S-91 melanoma. S23906-1 139, a benzoacronycine derivative inhibiting DNA synthesis and S-phase cell cycle arrest, is currently in Phase I trials for the treatment of solid tumors [133].

Homoharringtonine (omacetaxine mepesuccinate, Ceflatonin®) 140, a myelosuppressive alkaloid isolated from *Cephalotuxus fortuneii*, inhibits Mcl-1 protein synthesis and induces apoptosis [134]. The European Commission in October 2004 granted orphan designation to Stragen France SAS for 140 against acute myeloid leukemia (AML) that was later transferred to ChemGenex Europe SAS in January 2009. The FDA in January 2009 designated 140 as orphan drug against myelodysplastic syndromes (MDS). In September 2009, a NDA for 140 under Omapro™ (omacetaxine mepesuccinate) was submitted by ChemGenex to the FDA for use in the treatment of chronic myelogeneous leukemia (CML) patients having T315I
mutation or failed in imatinib therapy. ChemGenex are also running Phase II trial of 140 for treatment of refractory or relapsed AML patients failed to intensive chemotherapy.

3′-O-methyl-nordihydroguaiaretic acid (NDGA) 141, a lignan isolated from Larrea divaricatta exhibits significant anticancer activity by retardation of tumor cell proliferation through inhibition of insulin-like growth factor receptor (IGF-1R) and the c-erbB2/HER2/neu receptor. Terameprocol 142, a synthetic 141 derivative that induces apoptosis in cancer cells through inactivation of maturation promoting factor, was licensed by Erimos from The Johns Hopkins University. Terameprocol 142 is currently in various Phase I/II trials by Erimos against solid tumors, glioma and leukemia [135]. Epipodophyllotoxin (F11782) 143, a non-intercalating dual inhibitor of both topoisomerases I and II, was originally isolated from root of Podophyllum peltatum [136]. Tafluposide 144, a 143 derivative, is being developed by Pierre Fabre under Phase I/II trials for various tumor types [137]. Ingenol 145, isolated from the sap of Euphorbia peplus, is under clinical development by Peplin Biotech for topical treatment of basal cell carcinomas and squamous cell carcinomas [138]. After merger of Peplin with LEO Pharma in November 2009, ingenol mebutate (PEP005) 146, a 145 derivative that
activates PKC, is currently in Phase III trials against actinic keratosis (AK). In December 2009, LEO Pharma disclosed the positive results of 146 in two Phase III trials against AK lesions on head (including the face and scalp) while announced to meet the primary endpoint in February 2010 with disappearance of AK lesions in non-head locations.

Daidzein 147, an isoflavone occurring in *Pueraria Mirifica*, soybeans and soy products, exhibits clinical indication against tumors [139]. Phenoxodiol 148 is a synthetic 147 derivative that was licensed by Marshall Edwards from Novogen for development as combination therapy against ovarian cancer and as mono-therapeutic agent for the treatment of prostate and cervical cancers, resistant to standard chemotherapy [140]. Phenoxodiol 148 is supposed to inhibit sphingosine-1-phosphate and is under Phase III development by Marshall Edwards to restore chemosensitivity in patients with ovarian cancer resisting platinum drugs. A phase II trial of 148 against castrate and noncastrate prostate cancer is also under way. Triphendiol (NV-196), an orally-delivered chemosensitizing derivative of 148 that was licensed to Marshall Edwards by Novogen, is under Phase I trials for use in combination therapy against cholangiocarcinoma, advanced prostate cancer and melanoma. An orphan drug status was granted to 148 by the FDA for cholangiocarcinoma, prostate cancer and stage IIb-IV malignant melanoma. In January 2009, FDA granted IND approval to 148. Genistein 149, a soy-derived antineoplastic phytoestrogen, inhibits protein-tyrosine kinase and induces cell differentiation, is under Phase I/II trials by Astellas, Bausch & Lomb for treatment of tumors. Genistein 149 is also supposed to inhibit topoisomerase-II, resulting in DNA fragmentation and apoptosis. (-)-Gossypol (AT-101) 150, a pan-Bcl-2 inhibitor isolated from the cottonseed plant of genus *Gossypium* [141], is under Phase I/II clinical development by Ascenta Therapeutics to address prostate, brain and lung cancers. In October 2009 Ascenta announced the results of Phase I trial for two combination regimens containing 150 for the treatment of malignant brain tumor.
ASA 404 (vadimezan, AS1404 and DMXAA) 151, a tumor-VDA and derivative of flavone-8-acetic acid 152, was discovered at Auckland Cancer Society Research and later in-licensed by Antisoma. Novartis AG in April 2007 signed an agreement with Antisoma for worldwide rights and co-selling of 151 in the US. As of April 2008, the 151 is currently in Phase III clinical trials by Novartis as a second line treatment for NSCLC. The β-Lapachone (ARQ-501) 153, isolated from Tabebuia avellanedae, induces expression of cyclin dependent kinase inhibitor 1A (CDKN1A or p21) and exerts anti-tumor effect by sustained increase of the pro-apoptotic protein E2F-1 [142]. The β-Lapachone 153 is currently in Phase II trials by ArQule as a combination therapy against pancreatic and ovarian cancer.

Alvocidib (Flavopiridol, HMR 1275) 154, a CDK inhibitor and synthetic derivative of rohitukine 155 isolated from Dysoxylum binectariferum [143], is being developed by Sanofi-Aventis in collaboration with NCI. As on May 2009, the 154 is under late Phase III clinical development by Sanofi-Aventis against NSCLC while Phase IIb trial for the treatment of chronic lymphocytic leukemia (CLL).

Curcumin 156, isolated from Curcuma longa roots, can interfere with the p53 tumor suppressor pathway and is under various Phase I/II trials worldwide while a Phase III trial for the treatment of metastatic colon cancer (MCC) is underway [144]. RTA 402 (CDDO-Me, Bardoxolone methyl) 157,
an IkB alpha kinase activation inhibitor and synthetic derivative of oleanolic acid 158 [145], is being evaluated by Reata Pharmaceuticals under Phase I/II trials against prostate cancer and Phase II trials for the treatment of type 2 diabetes with chronic kidney disease (CKD). RTA 402 157 is an orphan drug by the FDA against prostate cancer. In January 2010, Kyowa Hakko Kirin gained exclusive rights from Reata Pharmaceuticals to develop and commercialize 157 in Japan and other selected Asian regions to treat type 2 diabetes with CKD.

Betulinic acid (ALS-357) 68, a topoisomerase I inhibitor isolated from *Betula pubescens* [146], is an orphan drug (by the FDA) in Phase I trial by Advanced Life Sciences for the treatment of malignant melanoma. Silybin 159, a flavonolignan isolated from *Silybum marianum*, is the active constituent of IdB 1060 (silybin-phosphatidylcholine complex, Siliphos®). Silybin 159 is currently in Phase II trials by American college of gastroenterology for chemoprevention of cancer [147].
8.1.2. Microorganism-derived compounds

8.1.2.1. Actinomycetes

Pladienolide D 160, obtained from fermentation broth of Streptomyces platensis Mer-11107, exerts significant antiproliferative activities against variety of cancer cell lines. E7107 161, a synthetic 160 derivative that binds with spliceosome-associated protein 130 (SAP130) and inhibits the splicing of pre-mRNA, is in various Phase I trials by Eisai against solid tumors [148]. Chartreusin (U-7257) 162 isolated from Streptomyces chartreusis and elsamicin A (BMY-28090, elsamitrucin) 163 isolated from actinomycete strain J907-21, are the antibiotics that inhibit RNA synthesis and result in single-strand scission of DNA [149]. Elsamicin A 163 is also a topoisomerase I/II inhibitor being developed by Spectrum Pharmaceuticals in Phase II trials to use in the treatment of advanced solid tumors.

Doxorubicin 164, an anthracycline antibiotic capable of intercalating with DNA, was isolated from bacteria occurring in soil samples taken from Castel del Monte, an Italian castle. Doxorubicin 164 is an orphan drug by the FDA against acute lymphocytic leukemia (ALL) and AML. Valrubicin (Valstar®), a semi-synthetic 164 derivative was approved in 1999 for the treatment of bladder cancer but was withdrawn in 2002 due to some manufacturing issues and has been relaunched in September 2009. L-annamycin 165, a topoisomerase II inhibitor that was developed at the MD Anderson Cancer Center, is currently in Phase I/IIa trials by Callisto
Pharmaceuticals for the treatment of younger and adults with refractory or relapsed ALL or AML. Berubicin (RTA744, WP744) 166, a DNA intercalator capable of crossing the BBB, hence is significant for the treatment of primary brain tumor. Reata Pharmaceuticals are associated with Phase II development of 166 against malignant gliomas. Likewise, sabarubicin (MEN-10755) 167 [150], a topoisomerase II inhibitor and disaccharide analogue of 164, is currently in Phase II clinical trials by Menarini Pharmaceuticals against solid tumors [151]. Nemorubicin (MMDX, PNU-152243A) 168, a 3′-deamino-3′[2-(S)-methoxy-4-morpholinyl] derivative of 164, is a topoisomerase I inhibitor exhibiting activity against selected tumors resistant to current treatment. Nerviano Medical Sciences are evaluating 168 in Phase I/II trials.

Distamycin A 169, a DNA minor groove binder (MGB) and lead compound of brostallicin (PNU-166196) 170, was originally developed by Nerviano [152]. Nerviano had transferred the exclusive world right of 170 to Systems Medicine Inc (SMI) which was taken over by the Cell Therapeutics. Currently, the 170 is in phase II trials by Cell Therapeutics as monotherapy against metastatic or advanced stage STS.
Geldanamycin 171 is an antineoplastic benzoquinone ansamycin antibiotic and was discovered from broth and mycelium of *Streptomyces* species [153]. Tanespimycin (17-AAG, KOS-953, NSC-330507) 172, a comparatively less toxic antibiotic derived from 171, can bind to HSP90 and interrupts the MAPK pathway. As on November 2009, Kosan have completed a Phase II/III trial of 172 in combination with Velcade® against relapsed-refractory multiple myeloma. Alvespimycin (17-DMAG, KOS-1022, NSC-707545) 173, a second generation HSP90 inhibitor [154] is in clinical development by Kosan to use in the treatment of solid tumors. As on January 2008, 173 is in Phase I trials in combination with trastuzumab & paclitaxel (Taxol®) against solid tumors, Phase II monotherapeutic trials against HER2-positive metastatic breast cancer and Phase I trials for the treatment of solid tumors. Retaspimycin (IPI-504, 17-AAG hydroquinone salt) 174, a HSP90 inhibitor, is being developed byInfinity Pharmaceuticals in Phase I/II clinical trials to address certain cancers. Currently, the Infinity are evaluating 174 in a Phase II trial against NSCLC while enrolling patients for another Phase II trial in combination with Herceptin® against breast cancer.

Deforolimus (AP23573, MK-8669) 175, is an mTOR inhibitor co-developed by Merck and ARIAD Pharmaceuticals to address several tumor types including sarcoma. The name of 175 was changed to ‘ridaforolimus’ by ARIAD in May 2009 and as on December 2009, the enrollment for a Phase III study in patients with metastatic STS and bone sarcomas has been completed by ARIAD. Besides, ARIAD are also running several Phase I/II trials of 175 as a single agent and in combination therapies. Salinosporamide A (NPI-0052) 176, a proteasome inhibitor produced by a marine bacterium
Salinispora tropica [155], exerts activity by modifying the threonine residues of the 20S proteasome. Nereus are associated with Phase I clinical development of 176 to use in the treatment of solid tumors and lymphomas. As on April 2008, Nereus Pharmaceuticals are enrolling patients for a Phase Ib trial of 176 in combination with vorinostat (Zolinza®, Merck & Co.) against selected solid tumor malignancies.

Staurosporine 177, isolated from bacterium Streptomyces staurosporeus [156], a precursor of protein kinase inhibitors like enzastaurin (LY317615) 178 and midostaurin (PKC-412, CGP 41251, 4'-N-Benzoyl-staurosporine) 179, has significant anticancer potentiels. Enzastaurin (LY317615) 178 is a serine/threonine kinase inhibitor [157] that was evaluated in Phase II trials by Eli Lilly to use in the treatment of NSCLC patients. As of April 2010, the 178 is under Phase III trials for the treatment of diffuse large B-cell lymphoma. Midostaurin (PKC-412) 179 inhibits protein kinases including FLT3 [158] and is in Phase II trials by Novartis to treat AML patients carrying FLT3 mutations. K252a 180, an alkaloid isolated from Nocardiosis species, is the lead compound of lestaurtinib (CEP-701, KT-5555) 181 that inhibits FLT3 and tyrosine phosphorylation of Trk A. As of 2008, the 181 is in Phase II trials against myeloproliferative disorders and Phase III trials for the treatment of AML. Likewise, KRX-0601 (UCN-01, KW-2401) 182, inhibiting a broad spectrum of kinases including CDKs, is being developed by Keryx (Kyowa Hakko) in Phase II clinical trials under sponsorship of NCI against melanoma, TCL and SCLC.

Diazepinomicin (ECO-4601, TLN-4601) 183, a dibenzodiazepine alkaloid isolated from the culture of a marine actinomycete of the genus Micromonomospora [159], can bind to peripheral benzodiazepine receptor (PBR) and inhibits the Ras/MAP kinase signaling pathway involved in cellular proliferation and migration [160]. ECO-4601 183 was found safe and well-tolerated in Phase I/II trials conducted by the NCI and Thallion. ECO-4601 183 can cross the BBB and as on September 2008, Thallion are enrolling patients for Phase II trial of 183 as a second line treatment for GBM.
8.1.2.2. Eubacteria

Prodigiosin (Streptorubin B) 184, a Bcl-2 inhibitor and lead compound of obatoclax (GX15-070) 185, is produced by strains of the bacterium Serratia marcescens [161]. Gemin X are developing intravenous infusion of 185 in multiple Phase I/II trials as a monotherapy in hematological and solid tumors while in combination with carboplatin & etoposide to treat SCLC and with bortezomib (Velcade®) against mantle cell lymphoma (MCL). In March 2009, Gemin X launched a Phase II study of 185 as first-line treatment for SCLC while disclosed the results of a Phase Ib trial in May 2009 against extensive-stage SCLC.

8.1.2.3. Myxobacteria

Patupilone (epothilone B, EPO-906) 21, produced by the myxobacterium Sorangium cellulosum, is a microtubule-stabilizing agent currently in Phase III trials by Novartis against ovarian cancer [162]. Sagopilone (ZK-EPO, ZK-219477) 186, a synthetic 21 derivative, can retain activity in MDR cancer cells overexpressing the P-gp [163]. As of February 2010, Schering AG is evaluating 186 in Phase II trials for the treatment of lung, ovarian and prostate cancers. Epothilone D (desoxyepothilone B) 187, a natural polyketide inhibits the disassembly of microtubules by binding to tubulin. 9,10-Didehydroepothilone D (KOS-1584) 188 [164], a 187 derivative, being evaluated by Kosan Pharmaceuticals to use in the treatment of multiple solid tumors. In Phase I dose escalation trials by Kosan, 188 has demonstrated efficacy and tolerability against patients with ovarian cancer and NSCLC. As of February 2007, Kosan were planning to initiate Phase II clinical development of 188 against multiple solid tumors in collaboration with Roche.
8.1.2.4. Fungi

NPI-2350 (halimide, phenylahistin) \textsuperscript{189} is a tubulin-depolymerizing agent isolated from a marine fungi \textit{Aspergillus ustus} \textsuperscript{[165]}. Nereus are developing plinabulin (NPI-2358) \textsuperscript{190}, a synthetic \textsuperscript{189} analog in various clinical trials for the treatment of NSCLC \textsuperscript{[166]}. In November 2009, Nereus announced the positive results of a Phase II trial in NSCLC patients. Irofulven (MGI-114, HMAF) \textsuperscript{191} is a DNA synthesis inhibitor and analog of illudin S \textsuperscript{192}, a sesquiterpene toxin found in mushrooms of the genus \textit{Omphalotus} \textsuperscript{[167]}. Eisai (MGI Pharma) are currently evaluating \textsuperscript{191} in various Phase II/III trials in patients with advanced-stage prostate cancer and GI solid tumors.

8.1.3. Marine-derived compounds

Plitidepsin (Aplidin\textsuperscript{®}) \textsuperscript{193}, extracted from \textit{Aplidium albicans} \textsuperscript{[168]}, is being evaluated by PharmaMar in Phase II trials to use in the treatment of hematological and solid tumors. Plitidepsin \textsuperscript{193} inhibits the vascular endothelial growth factor (VEGF) and is currently in Phase II trials by PharmaMar as a first-line monotherapy treatment and in combination with dacarbazine for advanced unresectable melanoma \textsuperscript{[169]}. Halichondrin B \textsuperscript{194}, isolated from \textit{Halichondria okadai} sponge \textsuperscript{[170]}, was identified as a significant anticancer agent by NCI. Eribulin mesylate (E7389, ER-086526, NSC-707389) \textsuperscript{195}, a \textsuperscript{194} analog, is being developed by Eisai against advanced breast cancer patients. Eribulin \textsuperscript{195} is a microtubule dynamics inhibitor and in March 2010, Eisai has submitted regulatory applications to agencies in Japan, US and EU for approval of \textsuperscript{195} to use in the treatment of locally advanced or metastatic breast cancer. Hemiasterlin \textsuperscript{196}, derived from marine sponges \textsuperscript{[171]}, is capable of inhibiting tubulin assembly and disrupts normal microtubule dynamics by depolymerizing the microtubules. E7974 \textsuperscript{197}, a synthetic analogue of \textsuperscript{196}, can bind to $\alpha$- and $\beta$-tubulin and is under Phase I clinical development by Eisai against a variety of human tumor xenografts.

Psammaplin A \textsuperscript{198}, an inhibitor of key several enzymes that control gene expression, DNA replication and angiogenesis, was originally isolated from the marine sponge \textit{Psammaplinaplysilla}. Panobinostat (LBH-589) \textsuperscript{199}, a synthetic \textsuperscript{198} analog and pan-deacetylase inhibitor that induces death of tumor cell lines but not the normal cells, is in Phase Ib/II clinical trials by Novartis to use as monotherapy and in combination with chemotherapy and/or targeted therapy against Hodgkins lymphoma, malignant melanoma, AML/MDS and other hematological malignancies \textsuperscript{[172]}. Currently, Novartis are enrolling patients for Phase III trial in relapsed malignant melanoma.
Bryostatin 1 \textit{200}, a macrolide lactone isolated from \textit{Bugula neritina} collected from the Gulf of California and Mexico, inhibits PKC [173] and was granted with orphan drug status by the FDA (2001) and a similar designation by the EU (2002) for use as combination therapy with Taxol\textsuperscript{TM} against esophageal cancer. In 2001, Arizona State University licensed \textit{200} to GPC Biotech, which are associated with current Phase I/II trials under the guidance of the NCI. Jorumycin \textit{201}, isolated from \textit{Jorunna funebris} produces cytotoxic effects through binding to DNA [174] and is the lead compound of Zalypsis\textsuperscript{®} (PM00104/50) \textit{202} being developed by PharmaMar in Phase I trials for the treatment of solid tumors or lymphoma. As on November 2009, the \textit{202} is in Phase II trials for treating cervical and endometrial cancer patients previously treated with standard chemotherapy.

Dolastatin 15 \textit{203}, is an antimitotic agent structurally related to dolastatin 10 \textit{205}, a five-subunit peptide obtained from \textit{Dolabella auricularia} [175]. Tasidotin (synthadotin, ILX-651) \textit{204}, an analog \textit{203}, induces G\textsubscript{2}/M phase cell cycle arrest by inhibiting tubulin polymerization was evaluated by Genzyme in Phase I/II trials against solid tumors. In May 2009, Genzyme signed an agreement with Ergomed for the co-development of \textit{204} as an antineoplastic agent. Soblidotin (YHI-501, TZT-1027, auristatin PE) \textit{206}, a derivative of \textit{205}, inhibits tubulin polymerization and is under Phase II trials by Yakult Honsha for treatment of solid tumors. Kahalalide F \textit{207}, obtained from the Hawaiian sea slug \textit{Elysia rufescens}, can alter lysosomal membrane function [176] and is in Phase II trials since October 2008 for the treatment of severe psoriasis. In June 2009, the \textit{207} was licensed by Medimetriks Pharmaceuticals from PharmaMar for uses outside of oncology and neurology. PM02734 (Irvalec\textsuperscript{®}) \textit{208}, another \textit{207} derivative, is in Phase II trials against solid tumors by PharmaMar. As on February 2010, PharmaMar are recruiting patients for Phase I trial of \textit{207} in combination with erlotinib against advanced malignant solid tumors.

8.2. NP-antibody anticancer conjugates

Anticancer agents conjugated with various supports (antibodies, polymers, liposomes and nanoparticles etc.) have been extensively explored during the last few decades [177]. Zinostatin stimalamer (ZSS), conjugated with a molecule of neocarzinostatin (NCS) chromoprotein and two molecules of polystyrene-co-maleic acid [178], was launched by Yamanouchi (now Astellas) in Japan against hepatocellular carcinoma.

Gemtuzumab ozogamicin (Mylotarg\textsuperscript{®}) \textit{209} linked to calicheamicin \textit{210} (obtained from \textit{Micromonospora echinospora}), was co-developed by Wyeth and
UCB Pharma. Likewise, inotuzumab ozogamicin (CMC-544), a calicheamicinin-antibody conjugated with CalichDMH and hydrazone linker attached to humanized IgG4 anti-CD22 [179], is being developed by Wyeth and UCB Pharma in Phase II/III trials against non-Hodgkin’s lymphoma in combination with rituximab, a chimeric human IgG1 antibody that targets another B-lymphoid lineage-specific molecule, CD20 [180].

Maytansine 211, isolated from plants of the genus *Maytenus*, is a microtubule inhibitor that failed to show significant activity at non-toxic concentrations in Phase I/II trials. ImmunoGen are associated with clinical development of IMGN-242 (HuC242-DM4) 212, a maytansinoid DM4 and huC242 conjugate, currently in Phase II trials for CanAg-expressing cancers. In June 2009, ImmunoGen discontinued the development of 212 and are seeking for out-licensing. ImmunoGen are also evaluating IMGN-901 (HuN901-DM1) 213, a maytansinoid DM1 and huN901 conjugate targeting CD56 expressing tumors, is under Phase I trials against multiple myeloma while Phase II trial for the treatment of SCLC. The FDA in March 2010 awarded orphan drug designation to 213 for use against merkel cell carcinoma (MCC).

9. Conclusion

Natural products have been the major sources of chemical diversity for starting materials while driving pharmaceutical discovery over the past century.
Today, NPs are finding increasing use as probes to interrogate biological systems as part of chemical genomics and related researches. The modification of natural products in an effort to alter their biochemical capacity is a common technique utilized by synthetic and medicinal chemists. There have been remarkable achievements in the field of ‘natural products drug discovery’ during last three decades and several compounds having profound biological activities have been searched out with the help of modern and sophisticated techniques. The quality of leads arising from NP discovery is better and often more bio-friendly, due to their co-evolution with the target sites in biological systems.
The large number of NP-derived compounds in various stages of clinical development indicates that the use of NP templates is still a viable source of new drug candidates. In future, the ‘natural products drug discovery’ will be more holistic, personalized and involve wise use of ancient and modern therapeutic skills in a complementary manner so that maximum benefits can be accrued to the patients and the community.

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References


