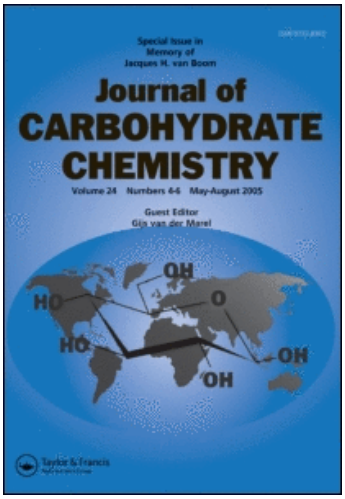

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REVIEW

SUGAR ANALOGUES WITH BASIC NITROGEN IN THE RING AS ANTI-INFECTIVES

Herwig Häusler, R. Pamela Kawakami,[a] Eva Mlaker, Wayne B. Severn,[a] Tanja M. Wrodnigg, and Arnold E. Stütz*

Glycogroup, Institut für Organische Chemie, Technische Universität Graz, Stremayrgasse 16, A-8010 Graz, Austria
[a]AgResearch, Wallaceville Animal Research Centre, P.O. Box 40063, Upper Hutt, New Zealand

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1. INTRODUCTION

Infectious diseases have remained a serious problem for society and concerned government organisations. Due to the dramatic increase of international transport of goods and passengers, dangerous microbial species and infectious diseases can be rapidly distributed over large distances. According to estimations by the World Health

Organisation (WHO), nearly 50,000 people are killed by infectious diseases daily. After having been kept at bay for decades, tuberculosis has returned to claim over three million lives per year. In addition, approximately thirty new infectious diseases such as Legionnaire's disease, HIV, or borreliosis have emerged during the past two decades.[1] Furthermore, long-known species, for example mycobacteria, the causative agents of such diseases as tuberculosis and leprosy, have acquired a high level of resistance to most commonly employed anti-infective agents. Because of the abundance of pathogenic microorganisms, a tremendous fraction of the pharmaceutical market is devoted to anti-infective drugs. Of a $73 billion total global market of chiral drugs, antibiotics are the largest fraction ($20 billion) closely followed only by cardiovascular therapeutics ($17.5 billion).[1]

The concept of anti-infective chemotherapy was introduced by Paul Ehrlich around the turn of the century. This approach is based on the application of "suitable" chemical substances (chemotherapeutic compounds) in the specific inhibition of infectious diseases and tumor cells in the organism. Anti-infective chemotherapy has become a vast and very diverse area due to the many different types of infectious diseases and their corresponding pathogenic microorganisms. Antibiotics (metabolites of microorganisms) and synthetic chemotherapeutic agents are employed to combat

- bacteria (tuberculosis, gangrene, pneumonia, ..),
- viruses (influenza, smallpox, herpes, HIV, ..),
- fungi,
- protozoan parasites (malaria, sleeping sickness, Chagas' disease, ..)
- cancer cells.

The latter are included because malignant cells also behave as intruders into the host's healthy tissue and, consequently, can be treated like an infectious disease.

Molecular targets of anti-infective chemotherapeutics are (amongst others):

- Cell wall biosynthesis and metabolism (β-lactams, Vancomycin,..)
- Cell membrane (ionophore antibiotics)
- Folate metabolism (sulfonamides)
- Nucleotide metabolism (intercalators, nucleoside analogues and mimics)

- Protein biosynthesis (aminocyclitols, tetracyclines, macrolides)
- Tubulin polymerisation

One of the main goals of modern drug research is the fight against microbial resistance towards chemotherapeutic agents. This phenomenon is based on adaptation, mutation and selection principles. Effectively, several means of resistance towards antibiotics can be operational. These can be:

- structural changes in the binding domain
- reduced uptake into the cell and, most importantly,
- deactivation of the therapeutic agent by destruction (for example, β-lactamases cleave the pharmacophoric β-lactam ring in this particular group of antibiotics) or
- derivatisation as is found frequently with important types of antibiotics such as aminocyclitols or chloroamphenicol.

Such derivatisations are typically achieved by enzymes acylating amine or esterifying hydroxyl groups in the respective antibiotic. One important traditional means of overcoming such "detoxifying mechanisms" of microorganisms has been the removal of functional groups prone to enzymatic modification, for example removal of hydroxyl groups as well as alkylation or acylation of select amine moieties.[2]

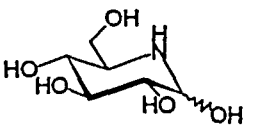
Another viable but time consuming and expensive approach is the search for new chemotherapeutic substances. These approaches include:

- modification of known active compounds
- screening of natural products
- blind screening for a variety of activities
- rational drug design with the aid of computer assisted molecular modeling
- lead extension with combinatorial libraries
- discovery of new biochemical targets and pathways.

The role of carbohydrates as sub-units of a large variety of antibiotic substances is well established. Many antibiotics such as amphotericin,[3] bleomycin,[4] olivomycin,[4] as well as erythromycin contain sugar units or are carbohydrate based compounds like nucleosides,[5] lincomycins[6] or aminocyclitol antibiotics,[7] just to mention a few examples.

2. IMINOSUGARS AND RELATED NATURAL PRODUCTS AS ANTI-INFECTIVE AGENTS

In the 1960s, new classes of carbohydrate related natural products were discovered which have a nitrogen replacing the sugar ring oxygen as the most important structural feature. The first representative of these iminosugars and iminoalditols, 5-amino-5-deoxy-D-glucose (**1**), was isolated from the fermentation broth of *Streptomyces lavaendulae* in 1966 and was coined nojirimycin by the Japanese discoverers.[8] It was found to be an antibiotic with activity against *Shigella*, the causative agent of dysentery. In the same year, Paulsen and Todt reported the synthesis of 1,5-dideoxy-1,5-imino-D-glucitol (**2**), the 1-deoxy derivative of nojirimycin, from 6-aminodeoxy-D-fructose by intramolecular reductive amination.[9] This compound was also obtained by the Japanese group by reduction of nojirimycin and, consequently, coined 1-deoxynojirimycin.[8] Subsequently, a Bayer group isolated compound **2** from fermentation broths of *Bacillus* strains and discovered its strong inhibitory effect on intestinal α-amylases.[10] This interesting feature prompted the Bayer group to investigate the compound's potential as an antidiabetic agent and develop a derivative, miglitol™ (**3**) for the pharmaceutical market.[11]



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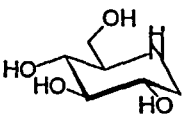

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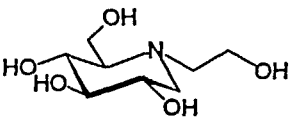

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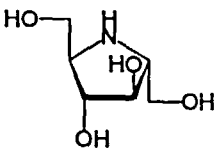

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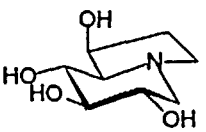

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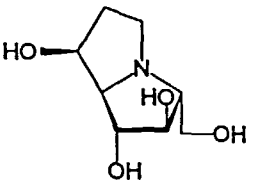

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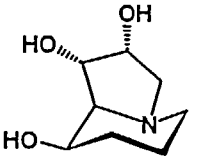
A 5-membered ring isomer of 1-deoxynojirimycin, 2,5-dideoxy-2,5-imino-D-mannitol[12] (**4**), was discovered in 1976 and found to be a potent inhibitor of α- as well as β-glucosidases. Compound **4** has also been coined DMDP (2,5-dihydroxymethyl-3,4-

dihydroxypyrrolidine)[13] and has, like 1-deoxynojirimycin, become the parent compound of a wide range of derivatives with excellent glycosidase inhibitory activities.[14]

In 1981, bicyclic analogues of these iminoalditols were discovered in the seeds of the Australian tree *Castanospermum australe*.[15] The indolizidine castanospermine (**5**) proved to be a highly potent and quite universal α-glucosidase inhibitor, the corresponding pyrrolizidine, australine (**6**),[16] exhibited somewhat less activity against these enzymes. Their close structural relationship could be nicely exploited by a chemical interconversion method devised by Tyler and co-workers.[17]

Another hydroxylated indolizidine alkaloid was first found in *Swainsona canescens*,[18] a wild pea responsible for poisoning of livestock feeding on this plant. Swainsonine (**7**) turned out to be an extremely potent inhibitor of α-mannosidases.[19]



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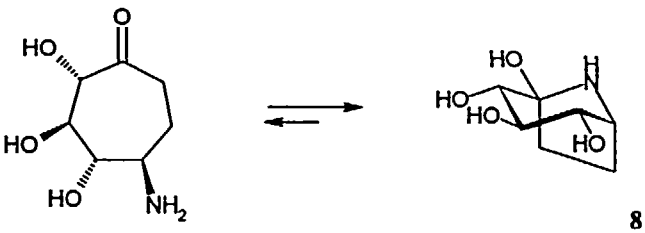
Recently, a new type of iminosugar bearing a *nor*tropane skeleton was discovered in plants such as the common hedge bindweed (*Calystegia sepium*).[20] The calystegins, for example calystegin B_2 (**8**), exhibit a similar alignment of functional groups as the glycosidase inhibitors mentioned above and show good glycosidase inhibitory potencies.[21]



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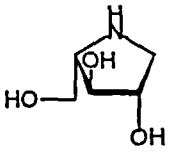
Many iminosugars, iminoalditols as well as related polyhydroxylated indolizidine alkaloids exhibit interesting biological activities, such as insect antifeedant,[22] nematicidal[23] and plant growth regulatory[24] as well as the aforementioned antidiabetic properties.

Due to their pronounced interference with glycosidases of the glycoprotein trimming process,[25] a highly ordered sequential partial degradation of complex oligosaccharides attached to proteins, they also show some exciting antibiotic properties.



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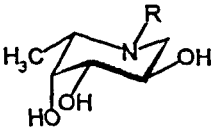
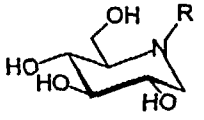
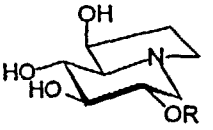


10: R = H
11: R = $(CH_2)_5CO_2Me$



12: R = *n*-Bu



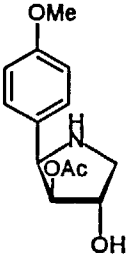
13: R = COC_3H_7

For example, 1,4-dideoxy-1,4-imino-L-arabinitol (**9**) as well as 1,5-dideoxy-1,5-imino-L-fucitol (**10**) and the corresponding *N*-(methoxycarbonylpentyl) derivative (**11**) possess antiretroviral activities.[26] Such properties are even more pronounced in 1-deoxynojirimycin (**2**) and *N*-alkylated derivatives thereof, the *N*-butyl analogue (**12**) being the most efficient.[26] This compound was shown to reduce the HIV titer by five orders of magnitude at non-cytotoxic concentrations. Other examples are castanospermine (**5**) which inhibits HIV syncytium formation and virus replication[27] and the corresponding 6-*O*-butanoyl derivative **13** of castanospermine which exhibits improved activity compared with the parent compound.[28]

Castanospermine was also found to exhibit anti-cancer properties in animal models.[29] Swainsonine was reported to inhibit experimental metastasis of pulmonary cancer[30] in mice and, notably, to activate the immune system.[31] Studies with patients bearing very advanced malignancies have also been conducted.[32]

In addition, both compounds have been found active against protozoal pathogens. Castanospermine protects[33] against cerebral malaria caused by *Plasmodium falciparum*, whereas swainsonine inhibits the association of *Trypanosoma cruzi*, the causative agent of Chagas' disease, with host cells.[34]

Not surprisingly, some, albeit limited, antifungal activities of iminosugar relatives have also been noted. For example, anisomycin (**14**),[35] a simple aryl substituted pyrrolidine, exhibited activity against pathogenic protozoa and fungi.[36] Interestingly, the acetate at C-3 was found to be vital for biological activity. Pramanicin (**15**)[37] was also found active against fungi but, more importantly, was discovered to inhibit *Cryptococcus neoformans* which causes meningitis in AIDS patients, with a minimal inhibitory concentration of 62 nM.



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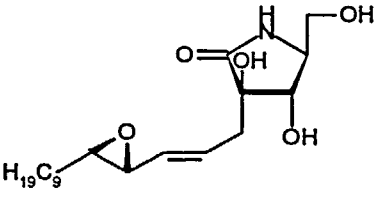

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3. NEW AND EMERGING TARGETS

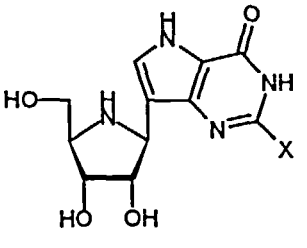
As a consequence of the failure of many classical antibiotic substances to combat contemporary life-threatening infectious diseases, new approaches towards highly potent and selective drugs are deemed necessary. Such routes can be based on employing highly selective agents targeting metabolic pathways unique to micro-organisms. The anti-infective potential of iminosugars and iminoalditols as well as related bicyclic alkaloids has been well investigated and established and, due to the discovery of previously unrecognised metabolic pathways, several new potential targets of iminosugar based anti-infective chemotherapy have emerged in the very recent past. Some notable examples include trypanosomal nucleoside hydrolases[38] as well as a range of bacterial enzymes, for example, aminoacyl-tRNA synthetases,[39] mycobacterial mycothion reductase,[40] NAD synthetase, soluble lytic transglycosylases of peptidoglycan biosynthesis,[41] mycobacterial UDP-galactosyl mutases[42] as well as arabinofuranosyltransferases of mycobacterial cell wall biosynthesis.[43]

Antimycobacterial as well as antiprotozoan agents are very important targets because protozoan parasites infect more than two billion persons worldwide and claim

over two million lives per year. Tuberculosis is the number one killer amongst bacterial infections and new multidrug-resistant strains of *Mycobacterium tuberculosis* have appeared.

3.1 Trypanosomal nucleoside hydrolases

Trypanosomal nucleoside hydrolases are vital purine salvage enzymes for protozoa which have lost the ability to synthesise these important biochemical building blocks.[38] Recently, a New Zealand group in collaboration with Schramm and co-workers have demonstrated that C-1 aryl substituted 1,4-dideoxy-1,4-imino-D-ribitols such as compounds **16** and **17** are highly potent inhibitors of these enzymes with K_i values in the low nM range.[44]



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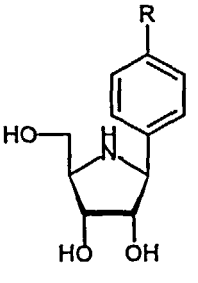

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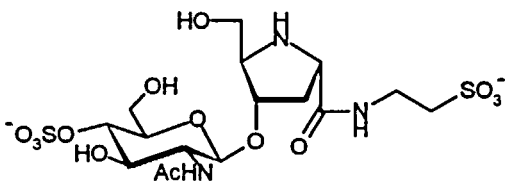
3.2 Bacterial Soluble Lytic Transglycosylases (SLTs)

Bacterial soluble lytic transglycosylases cleave β-1,4-glycosidic bonds of the peptidoglycan network in the murein scaffold of the bacterial cell wall in a quite controlled manner and are necessary for bacterial growth around the cell equator.[45]

Inhibitors of SLTs are potential targets for antibacterial chemotherapy. One such group of compounds, the bulgecins,[46] exhibit bulge inducing and lysis enhancing activities when applied in combination with β-lactam antibiotics, one of the most important types of cell wall active antibacterial agents available. Bulgecin A (**18**) interferes with the formation of disaccharide **19** which contains GlcNAc β-1,4 attached to the 1,6-anhydro derivative of muramic acid oligopeptide.[47]



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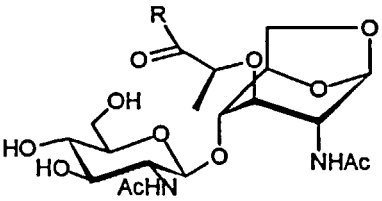

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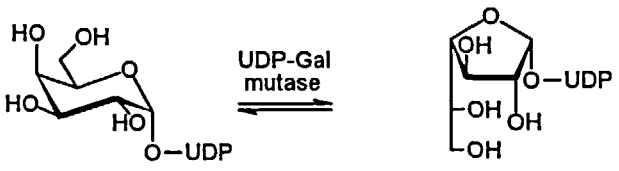
The X-ray structure of SLT from *E. coli* with bulgecin A bound to the active site has been determined[41] allowing the usual approaches to rational drug design on the basis of molecular modeling methodology. So far, this important piece of information does not appear to have been exploited fully.

3.3 Mycobacterial UDP-Gal Mutase

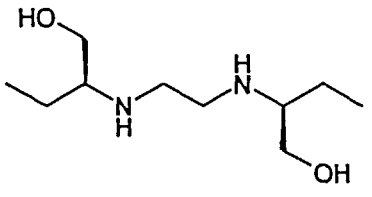


20 21

A major part of the mycobacterial cell wall consists of polymers containing β-galactofuranosyl oligomers.[43] One precursor in their biosynthesis is UDP-galactofuranose, which, in turn, is formed in the equilibrium catalysed by the action of UDP-Gal mutase on UDP-galactopyranose.[42] Recently, Fleet and co-workers have demonstrated that iminoalditols exhibiting the galactofuranosyl motif such as compounds **20** and **21** are good inhibitors of UDP-Gal mutase.[48] This approach could lead to interesting chemotherapeutic agents especially when applied in combination with other cell wall active compounds.

3.4 β-D-Arabinofuranosyltransferases of mycobacterial cell wall biosynthesis

Due to the large proportion of arabinofuranose containing polysaccharides in the cell wall of mycobacteria, suitable and selective inhibitors of the corresponding transferases could emerge as interesting antimycobacterial agents. One of the most important antimycobacterial drugs interfering with the target under consideration, the lipoarabinomannan (LAM) is ethambutol (**22**).[49]



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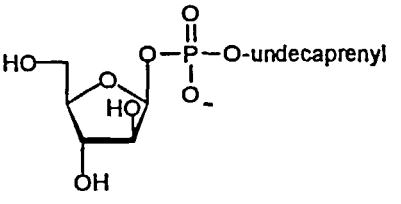

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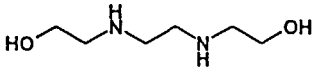
This comparably simple compound has been a frontline agent for about three decades. Nonetheless, its mode of action and important questions as to the nature of its antibacterial activities have remained largely unanswered. Interestingly, various alterations of the ethambutol structure such as, for example, in "isosteric" analogues **22a** to **22j** are deleterious to the antimycobacterial activity in a *Mycobacterium smegmatis* model.[50]

Only recently, the theory that ethambutol inhibits the transfer of arabinofuranosyl units from β-D-arabinofuranosyl undecaprenylphosphate (**23**), the putative substrate of the transferases under consideration, into LAM has been put forward.[43c,51] Recently, hybrid analogues containing iminoalditols exhibiting the D-arabinofuranosyl motif have been synthesised.[52] None of these more complex analogues such as compounds **24** and **25** were found to be nearly as active as ethambutol itself. Conversely, a comparably simple iminoalditol, 2,5-dideoxy-2,5-imino-1-phenylthio-D-glucitol (**26**), has recently been found active against *Mycobacterium avium* complex in an infected macrophage model at a concentration of 4 μg/mL.[53]

In addition, it was demonstrated that this compound leads to increased tumor necrosis factor α (TNFα) production in the infected cells. This interesting finding might be a promising and motivating lead to search for related, possibly even more active compounds.



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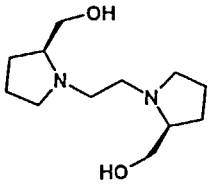

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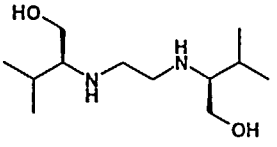

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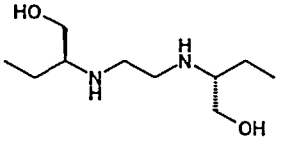

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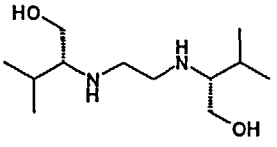

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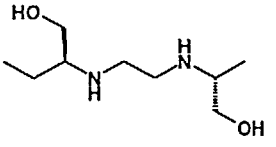

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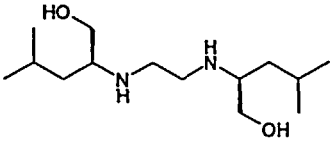

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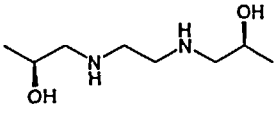

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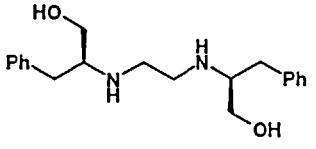
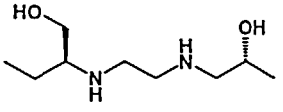
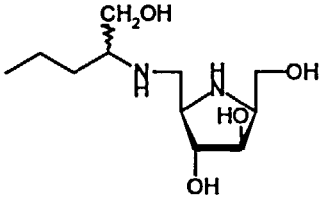


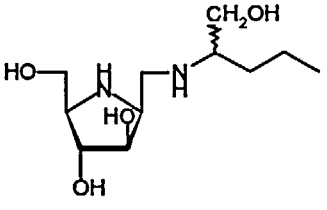
22e



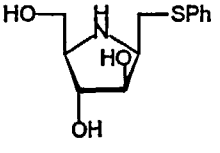
22j



24



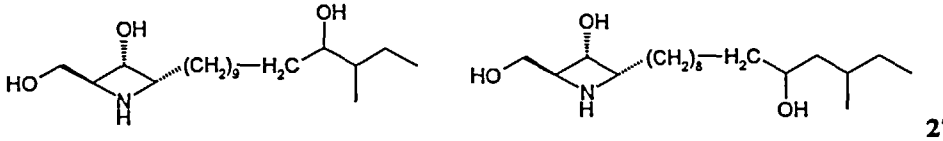
25



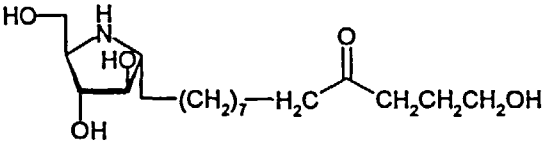
26

4. OUTLOOK

Based on the few examples mentioned, quite a number of different attractive applications of sugar analogues with nitrogen in the ring as probes in the vast field of anti-infective chemotherapy appear to be feasible. In depth investigations into other possible targets unique to the microbial metabolism as well as a steadily increasing number of X-ray structures of microbial enzymes and receptors will augment such development.



27



28

The discovery of new structurally related marine natural products such as penaresidins **27**[54] or novel plant constituents for example broussonetinine C **(28)**[55] combined with the improved techniques of isolation and structure determination will also add impetus to the rapid evolution of the research area under consideration.

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