The Contribution of Oxazolidinone Frame to The Biological Activity of Pharmaceutical Drugs and Natural Products

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Abstract: The development of resistance by the antibiotics in the Gram-positive pathogenic bacteria over the last twenty years and continuing today has created a need for new antibiotic classes, which may be unaffected by existing bacterial resistance. The oxazolidin-2-ones represent not only a new class with a novel mechanism of action, but also satisfy the requirement for overcoming the resistance mechanisms. Both linezolid and eperozolid, the first chemical candidates, arose from the piperazine subclass, with the first one being chosen further development because of its enhanced pharmacokinetic properties. The main attractive traits of the oxazolidinone series has encouraged further work in the area, and the patent literature reveals that extensive chemical investigation is currently being made. The unexpected early resistance development emphasizes the need for further exploration of features of the oxazolidinone to eliminate these deficiencies. Recently, several changes, involving the C5 side chain as well the N-phenyl heterocyclic ring, give promise for such improvement. Oxazolidinone antibacterial agents comprise also ketolides, derivatives of macrolides, such as erythromycin A, with a newly formed carbamate cycle, with a largely unexplored potential.

The oxazolidinone nucleus does not appear only in the structures of antimicrobial drugs, but a number of biological activities are connected with frameworks including the oxazolidinone ring. A partial list of these activities comprises enzyme inhibitors, agonists and antagonists, with a particular citation for a new generation of selective monoamino oxidase inhibitors (befloxatone).

The oxazolidinone moiety was found in the structure of few biologically active natural products, such as (-)-cytoxazone and streptazolin.

Moreover, in some cases the oxazolidinone ring has been chosen for the preparation of isosteric aza analogues of natural compounds (podophyllotoxin, pilocarpine) that can be more easily synthesised and more hardly inactivated.

Finally, the participation of oxazolidinone chiral auxiliaries to several syntheses of natural products must be acknowledged.

Key Words: Oxazolidinones, antibacterial agents, MAO inhibitors, metalloproteinases inhibitors, (-)-cytoxazone, (+)-streptazolin.

INTRODUCTION

The oxazolidin-2-one nucleus does not appear only in the structures of a huge number of antimicrobial drugs, but also in the framework of molecules endowed with different biological activities, such as selective cyclooxygenase–2 inhibition, non peptidic $\alpha_v\beta_3$ antagonist action till to herbicide properties. This paper will deal with an overview of the multiple activities connected with the oxazolidin-2-one frame. Cyclic carbamate moieties are also present in biologically active natural products or in isosteric aza analogues of natural compounds. The participation as chiral auxiliaries to the synthesis of stereochemically complex molecules, will be also reported.

1. ANTIBACTERIAL AND ANTIMICROBIAL OXAZOLIDIN-2-ONES

1.1. Novel Oxazolidinones After Linezolid

The discovery of a novel classes of antibacterial agents with a novel mechanism of action appeared as a considerable promise for the solution to the problem of bacterial resistance [1].

Starting from the first clinical candidates, Dup-105 and Dup-721 [2], an iterative medicinal chemistry effort culminated in compound PNU-100592, namely eperezolid [3] (Chart **1**). Systematic bioisosteric replacement for the piperazine ring led to the identification of the morpholine derivative PNU-100766, which subsequently became known as linezolid [3].

Linezolid has a spectrum of activity against virtually all important Gram positive pathogens. The unique mechanism of action of linezolid makes cross-resistance with other antimicrobial agents unlikely. The antimicrobial activity of linezolid versus other commonly used agents, the health – economic outcome of the drug *vs* vancomycin and teicoplanin, and safety issues, have been recently reviewed and updated [4]. The many attractive traits of the oxazolidinone series has encouraged further work in the area, and the patent literature reveals that extensive chemical programs exist [5].

To give an idea of the variety of antimicrobial compounds based on the oxazolidinone skeleton, some examples

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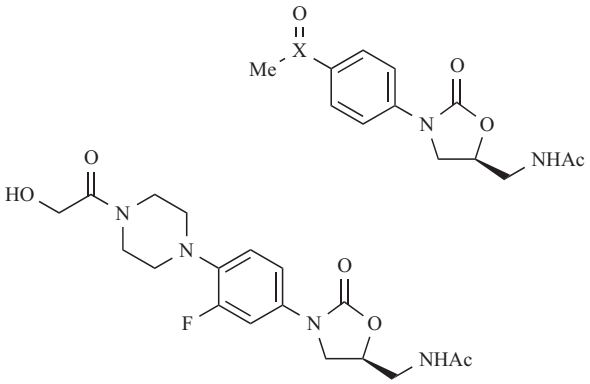
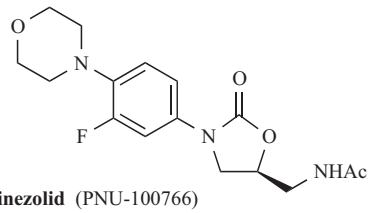


Eperezolid (PNU-100592)

	X
DUP-105	S
DUP-721	C

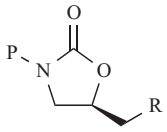


Linezolid (PNU-100766)

Chart (1).

are summarized in Chart **2** [6], where both the N-substituent of C-5-methylamino side chain and the C-4' substituent of the pendant N-3'-fluoroaryl moiety have been changed.

However, some linezolid-resistant enterococci have recently already been isolated after intensive linezolid therapy [7] and the first reports of resistant *Streptococcus aureus*



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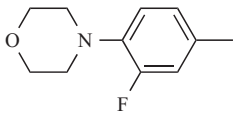
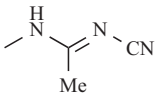
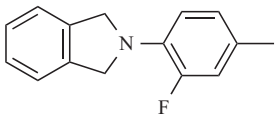
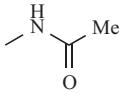
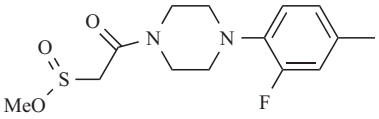
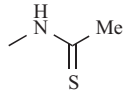
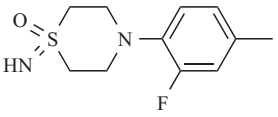
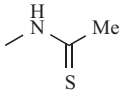
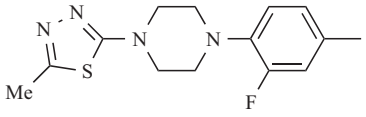
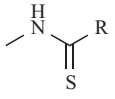
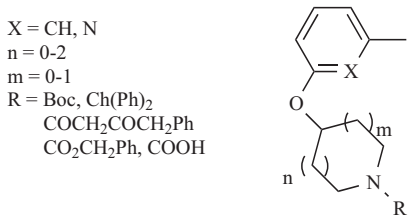
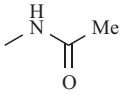
		[6a]
		[6b]
		[6c]
		[6d]
		[6e]
	R = H, NH_2, alkyl cycloalkyl, etc.	
		[6f,g]

X = CH, N
n = 0-2
m = 0-1
R = Boc, $Ch(Ph)_2$
$COCH_2COCH_2Ph$
CO_2CH_2Ph, COOH

Chart (2).

strains have been published [8]. This unexpectedly early resistance (although limited to few examples) emphasizes the need for further exploration of features of the oxazolidinone series to overcome these deficiencies. The first of these changes regarded the acetamidomethyl side chain, which had been relatively unexplored: in a series of papers the introductions of substituents, such as 5-thiourea (**5**), 5-thiocarbamate (**5a**) or 5-dithiocarbamate (**5b**) [9] and N-substituted heterocyclic aryl moieties (**5c**) [10], as potential replacements for the acetamido methyl side chain, have been reported (Chart **3**). Along this line, a series of oazolidin-2-ones bearing at the C-5 position nitrogen heterocyclic (triazol and imidazol) rings (**6**-**6b**) or the hydroxamic acid functionality (**6c**) [11a] was synthesized.

Compound **6b** (**PH-027**) demonstrated potent antibacterial activity, which is comparable to or better than that of linezolid against antibiotic-susceptible standard and clinically isolated resistant strains of gram positive bacteria. The authors claimed that the C-5 triazole substitution, as compared with the C-5 acetamidomethyl functionality, was a new structural alternative for potent antibacterial activity in the oxazolidinone class. The same authors prepared (Chart **4**) more recently a new series of N-linked 5-triazolyl methyl oxazolidin-2-ones **7** with varying substitution at the piperazine nitrogen in 4 position: most of the compounds showed excellent antibacterial activity against susceptible and resistant Gram-positive organisms [11b].

Gravestock *et al.* [12] programmed the synthesis of side chain amide analogues starting from the active 4-(dihydropyranil)-aryl oxazolidinone **8**. The preparation of the cyclic amide **9** also furnished the O-alkylation product **10** (Chart **5**). The target pyridone had poor minimum inhibitory concentrations (MICs) against *S. aureus* strain, but the O-linked pyridine **10** unexpectedly had MICs close to that of linezolid. The preparation of a series of 2-pyridyloxy analogues did not ameliorate the MIC: movement of the pyridyl nitrogen to 3 (**10a**) or 4 (**10b**) position led to decreases in activity, and while the diazines (**10c-e**) were comparable in activity, there was a marked drop for the 2-pyrimidine **10f**. The replacement of the six-membered ring of **10** with a five-membered heterocycle, as in **10g** or **10h**, and the preparation of the more versatile N-acyltetrahydropyridyl-aryl analogues instead of dihydropyranyl-aryl pendants, such as **11a**/**11b** are at the basis of a second series of oxazolidinones, which expressed compound **11c**, as an antibacterial of exceptional potency (average MIC 0.1 μg/mL) [12].

However, being the *in vivo* activity of thiaheterocycles limited, further optimization concentrated on the isoxazoles in the tetrahydro pyridine series (Chart **6**). Introduction of the hydroxyacetyl motif of eperezolid (as in **12a**), and extending the theme to dihydroxypropyl analogues (as in **12b-d**) gave compounds with MICs significantly better than those found for lunezolid. Some items emerged in this phase of study:

a) stereochemistry in the dihydroxypropyl side chain made no difference in activity;

b) difluoro-substituted compounds were not more potent, in spite of some early indications;

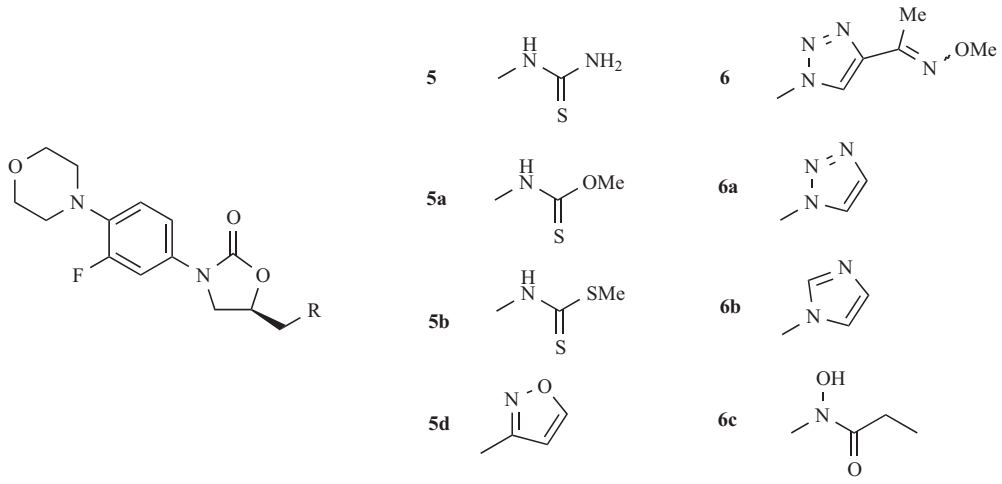


Chart (3).

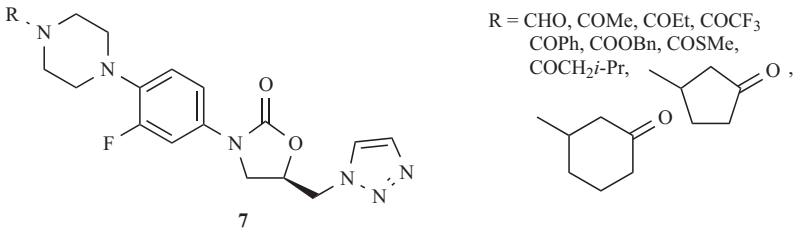


Chart (4).

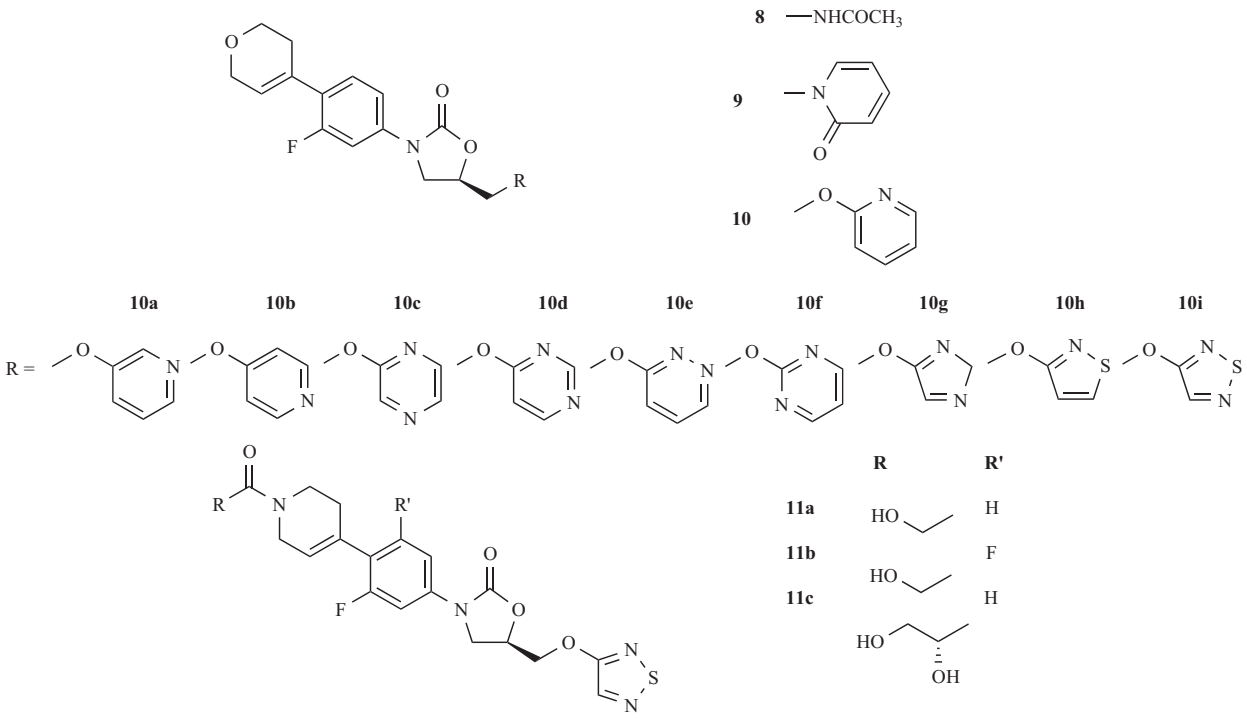


Chart (5).

c) sulphur-containing heterocycles (**12e)** had again superior potency to its oxygen analogs (**12a)**.

Since one of the limiting feature of these compounds for *in vivo* work was their aqueous solubility, compounds with oxidized sulphur, such as **12f-h**, were among the groups selected for further study.

The authors concluded that good activity *in vivo* can be obtained with a correct combination of substituents on C-5 and pendant phenyl rings, but some potent *in vitro* tetrahydroheterocycles may give poor or misleading *in vivo* results as a consequence of their rapid metabolism. Most promising are the compounds bearing aryl tetrahydropyridine units with appropriate acyl functions, such as dihydroxypropanoyl and close relatives. One such compound has been taken forward to early clinical studies as AZD-2563 and will be discussed separately.

On the other border, series of C5-acetamido oxazolidin-2-ones, with varying substituents of the pendant aryl ring, were synthesized. Benzazepine oxazolidines **13** and **13a** dis-

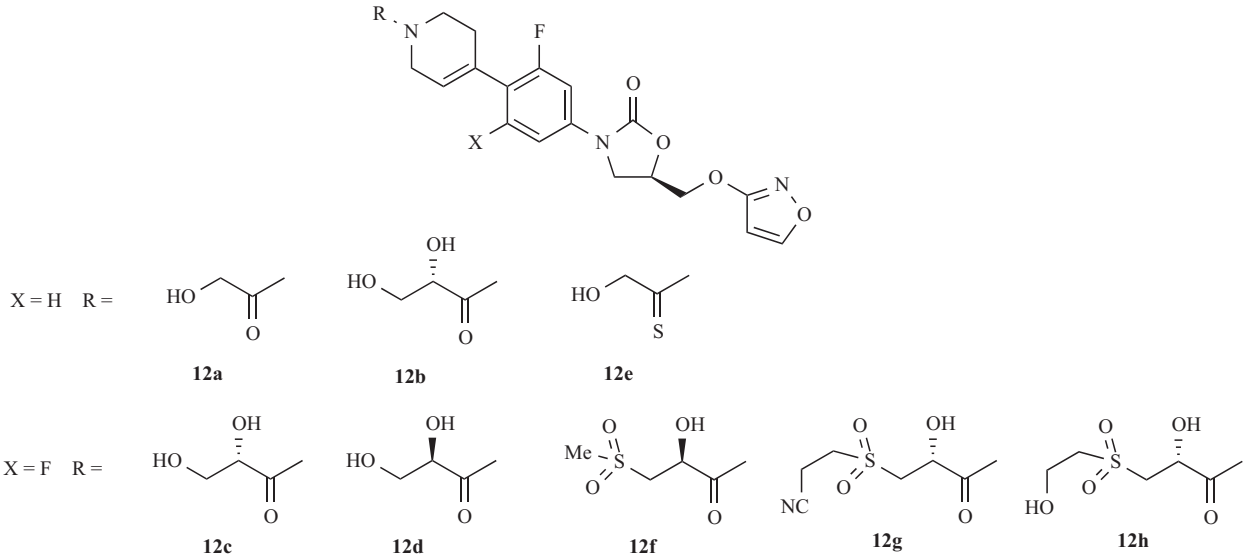
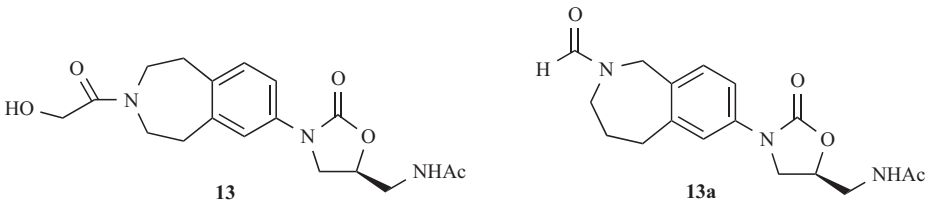


Chart (6).



13 **13a**

Chart (7).

played *in vitro* Gram-positive antibacterial activity comparable to linezolid against clinically relevant organisms [13].

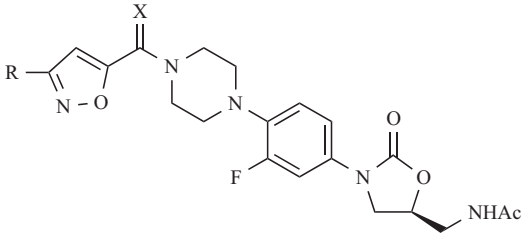
A South Korean group described the synthesis and the effect on the activity of oxazolidinones having a rigid bioisostere of hydroxymethyl group of eperezolid, i.e. the isoxazole moiety (**14a,b)** [14a]. The same group reported on the evaluation of the antibacterial activity of oxazolidinone analogues having methiylenepiperidinyl (**15a**) and methylenepyrrolidinyl (**15b)** groups [14b]. They also synthesized a series of isoxazolyl tetrahydropyridinyl derivatives of the types **16** and **17**. As a result, the carbamoylisoxazol **16f** demonstrated a minimum inhibitory concentration (MIC) values 2-4 fold better than that of linezolid against all of tested organisms [14c].

Some novel oxazolidinone derivatives (**18-24**), which were recently found to be equipotent or more potent than linezolid *in vitro*, are depicted in Chart **9** with the reference literature [15a-h].

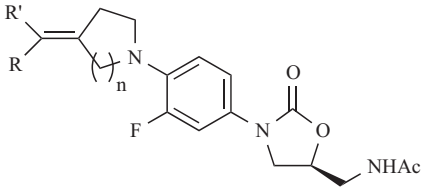
One of the efforts to identify a new and potentially improved antibacterial agents, using the oxazolidinone silhouette as a starting point, involved searching to replace the central heterocyclic ring. Both benzisoxazolinones (**25a**) and pyrroles (**25b**) showed a lack of antibacterial activity (Chart **10**). The isoxazolinone system (**25c**), however, has proven to be an effective bioisostere of the oxazolidinone heterocycle [16]. Substitution at varying positions resulted in analogs with improved potency (4-position), while other substitutions (*e.g.* 3-position or disubstitution) produced drastically reduced antibacterial activity. The pharmacological profiles of the isoxazolinone version of linezolid ad eperozolid are under investigation

1.2. Promising Clinical Candidates

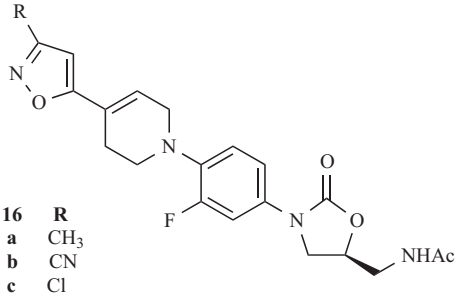
Novel oxazolidinones, containing a number of substituted five-membered heterocycles attached to the piperazinyl–phenyl-oxazolidinone core of eperozolid, have been synthesized. Further modifications led to several compounds with potent activity against a spectrum of resistant and susceptible gram-positive organisms, along with the identification of Ranbezolid (RBX 7644 Chart **11**) as a clinical candidate [17a]. Ranbezolid, tested against 306 anaerobes in compari-



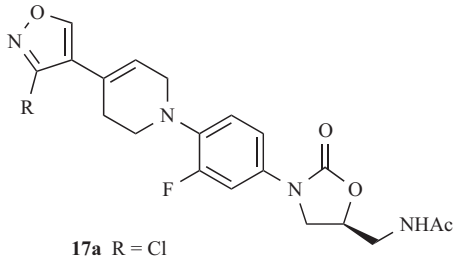
14a X = H_2 R = alkyl, alkoxy, heterocyclyl, halogen
14b X = O R = alkyl, alkoxy, heterocyclyl, halogen



15a n = 2
15b n = 1

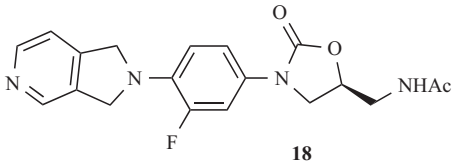


16 **R**
a CH_3
b CN
c Cl
d CF_3
e CO_2Et
f $CONH_2$



17a R = Cl
17b R = CN

Chart (8).



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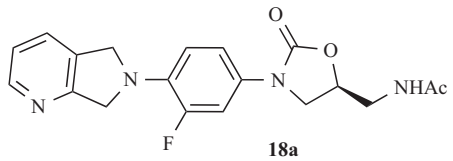
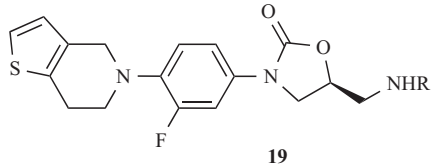


18a

[15a]



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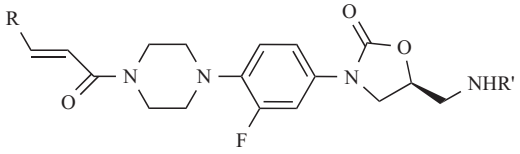
R = COMe, CSMe, $CONH_2$, $CSNH_2$
CSOMe, CSSMe

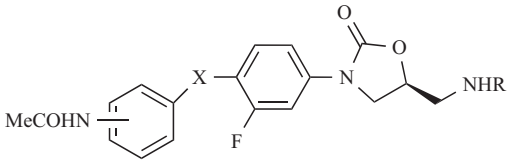
[15b,c]



20

	R	R'
a	Ph	COMe
b	1-naphthyl	COMe
c	4-BrPh	COMe
d	Me	COMe
e	4-MeOPh	CSMe

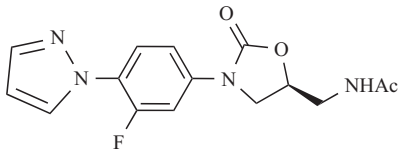
[15d]



21

X = O, S
R = $CSNH_2$, CSOMe,
$CSNMe_2$, $CSNHNH_2$

[15e]



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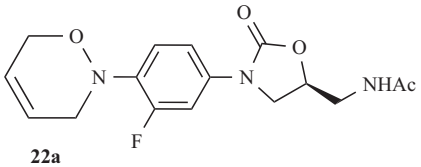
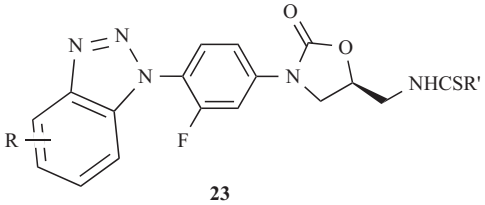


22a

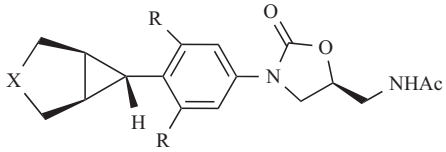
[15f]



23

R = H R' = NH_2, NHR", OMe, OCH_2R"
R = CO_2Me R' = NH_2, OMe

[15g]

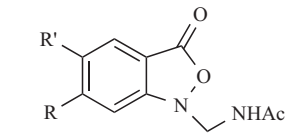


24

X = O, S, SO_2, NR'_2
R = H, F

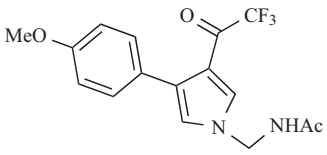
[15h]

Chart (9).

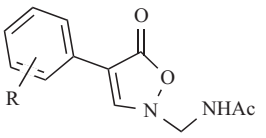


R = H, Me, OMe Cl, F, SMe
R' = H, Cl, CF_3 R = R' = -OCH_2O-

25a



25b

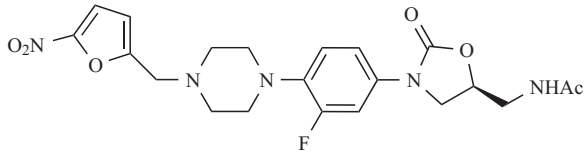


R = H, 3-F, 3-OMe, 3-CF_3, etc.

25c

Chart (10).

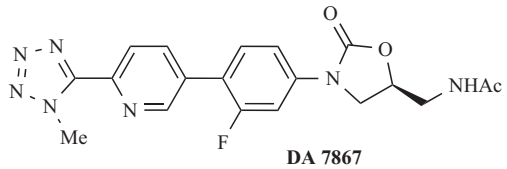
son with 11 other agents exhibited a good activity [17b]; moreover, it proved useful in the prevention and treatment of device-related infections caused by staphylococci, inhibiting biofilm producing bacteria [17c].



RBX 7644

Chart (11).

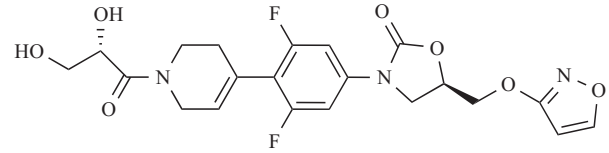
Analogously, DA 7867 (Chart **12**) was selected among several pyridin-phenyl oxazolidinones and evaluated against clinical isolates of aerobic and anaerobic bacteria, to be found more potent than linezolid *in vitro* [18a]. Excretion and metabolism [18b-d], pharmacokinetics [18e,f] and *in vitro* activity [18g,h] of DA 7867 have been studied in several papers.



DA 7867

Chart (12).

By contrast, AZD 2563 (Chart **13**) emerged from a new series of compounds that had a C-5 substitution with O- or N- linked, five- and six-member aromatic heterocycles. Exploration of SAR yielded the new, potent series of the O-linked isoxazoles, leading to the selection of the pre-clinical candidate AZD 2563 [12]. Clinical vancomycin intermediate *Staphylococcus aureus* (VISA), heterogeneous VISA, and laboratory-generated linezolid resistant *S. aureus* strains were all susceptible to AZD 2563 [19a]. The new oxazolidinone, targeted at Gram-positive bacteria, was evaluated and compared with linezolid and other agents against 802 aerobic bacterial isolates for spectrum of activity, bactericidal activity, and the effect of miscellaneous factors upon activity *in vitro*. The last one was essentially unaffected by altering pH, inoculum size, the type of testing medium, or the inclusion of human serum up to 25% v/v [19b]. A huge literature dealt with the activity of AZD 2563[19c-f].



AZD 2563

Chart (13).

Cumulatively, the reported results demonstrate a potential for oxazolidinone analogues with improved potencies and other properties over linezolid and eperezolid, and the scope for further diversification in this important new class of antibacterials.

The new research, addressed toward broadening of the antibacterial spectrum of this class of compounds, re-establishing sensitivity to linezolid resistant strains and lowering the toxicity potential, has yielded new bioisosteres of the oxazolidinone ring and, in another approach, created hybrid structures with existing Gram-negative active drug classes.

New oxazolidinone –based drugs are in early clinical development and indications are that this class of antibacterials will continue to show promise [20].

1.3. N-thiolated Oxazolidin-2-ones

Infection caused by methicillin-resistant *Staphylococcus aureus* (MRSA) are becoming particularly difficult to treat with conventional antibiotics such as penicillin. In the search for new antibacterial agents, a novel family of lipophilic N-thiolated β-lactams **26** (Chart **14**), that are effective growth inhibitor of MRSA, came on the stage. The mode of action and the structure-activity profiles of these compounds suggested that the role of the lactam ring is to provide a structural framework for delivery of the thiol moiety and may not be absolutely required for the activity. To probe this possibility and to expand on the structural diversity of anti-MRSA compounds available for clinical development, oxazolidin-2-ones were taken into consideration, as potential antibacterially active organothiocarriers [21]. Differentially substituted N-thiolated oxazolidin-2-ones **26a-e** were prepared for antimicrobial screening and compared to two reference compounds **26** and penicillin G.

In almost every case, the five oxazolidin-2-ones displayed about equal activity against both *S. aureus* and MRSA as did the corresponding β-lactam **26**, and were uniformly much more effective than penicillin G against the MRSA strains. The bioactivity was not significantly affected by the presence of the substituents at either the C4 or C5 centers, or at both, in contrast to previous observations from studies on β-lactams. Moreover, replacement of the N-methylthio moiety of compound **26d** for N-sec-butylthio (**26e**) leads to no significant improvement in anti MRSA activity [22]. To probe whether absolute stereochemistry was a determinant of activity, enantiomerically paired oxazolidinones (*R*)-**26f**/(*S*)-**26f** and (*R*)-**26g**/(*S*)-**26g** were then evaluated for anti-MRSA activity. The first couple (phenyl substituents) afforded somewhat larger inhibition zones than the second (isopropyl substituents). A small but discernible difference in bioactivities of the two enantiomeric forms was evidenced, but not completely evaluated. The four compounds inhibited also the growth of *Bacillus anthrax* and other six species, but whereas (*R*)-**26f** and (*S*)-**26f** had identical activity, the (*R*)-**26g** derivative possessed much weaker and more sporadic activity compared to the (*S*)-enantiomer **26g**.

1.4. Tricyclic Macrolides

The hypothesis that resistance mechanisms can be overcome by increasing the ribosome binding affinity was addressed by the introduction of ketolides. These modified erythromycin analogues (Chart **15**) possess 3-keto and 11, 12-carbamate functionalities with an aryl group strategically placed to maximize the ribosomal secondary interaction. The two most promising ketolides ABT-733 [23] and telithromycin [24] were shown to effectively address the issue of resistance. Another ketolide displaying a favorable profile against resistance was TE-802 [25], which is characterized by hav-

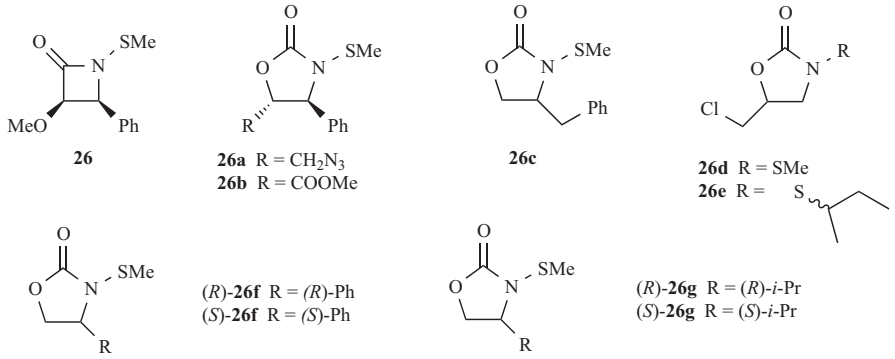


Chart (14).

ing a ketolide framework with an additional iminoethane bridge spanning the carbamate nitrogen and the C-9 position.

More recently the new erythromycin tricycle **27a** was constructed combining the readily available allylic alcohol **27** (a bye product of the synthesis of erythromycin A) with the azidoisocianate **28** [26]. The condensation product (not shown) gave the final product **27a** by cyclization of the carbamate, reduction of the azide group to amine and cyclization to the 9-carbonyl (Scheme **1**). The methodology eliminated the purification and epimerization associated with he original synthesis and provided an interesting scaffold, which could be further elaborated.

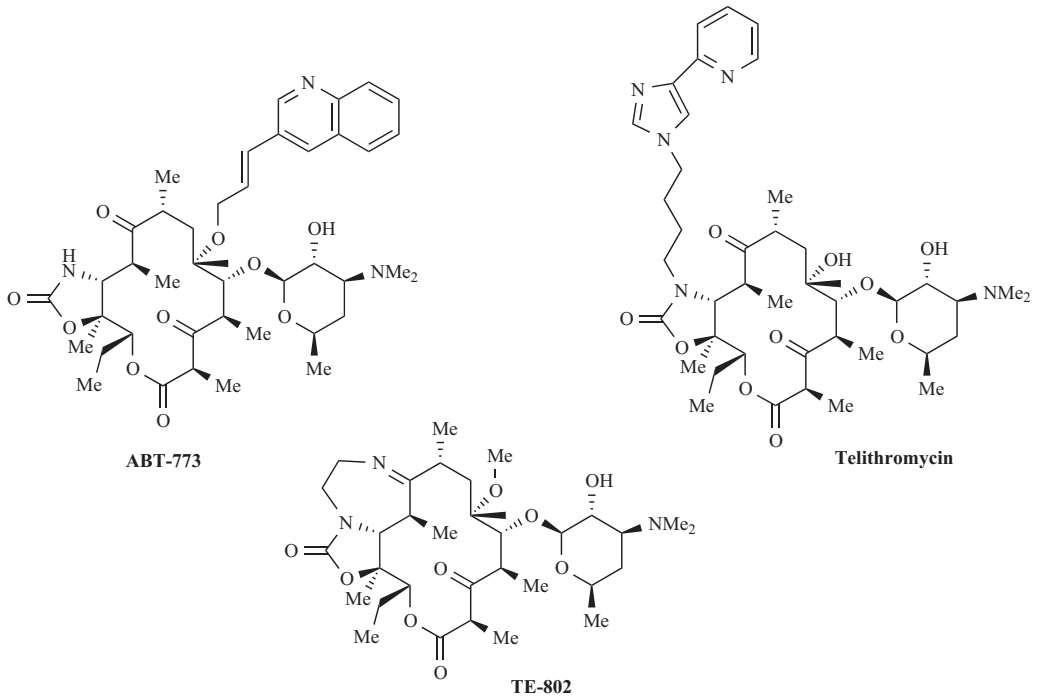
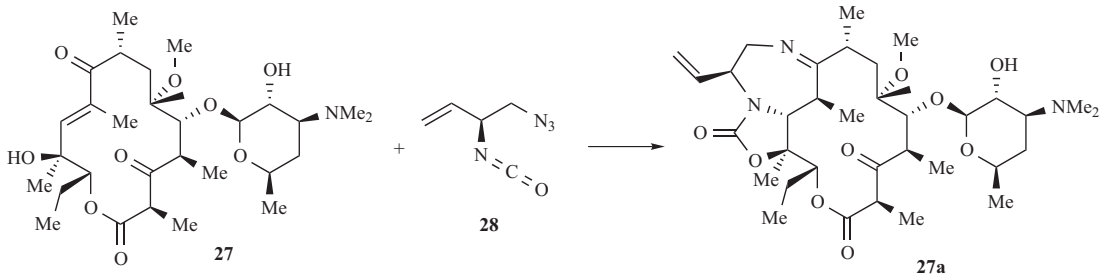


Chart (15).



Scheme 1.

2. MONOAMINE OXIDASE INHIBITORS

Irreversible and unspecific inhibitors of MAO were the first modern antidepressants, but after an initial success they fell into discredit due to adverse side effects. After initial enthusiasm, the use of monoamine oxidase inhibitors (MAOIs) has been limited by the wide range of possible interactions between the drug and tyramine–containing food, resulting in hypertensive reactions. However, at the end of the XX century, interest in MAO inhibitors has been renewed because of progress in basic research, a milestone being the finding that there are two subtypes of monoamine oxidase, MAO-A and MAO-B: these are distinct proteins with high amino acid homology, which showed different substrate specificities *in vitro* and different distributions within the central nervous system and in peripheral organs. MAO-A seems to be mainly involved in the metabolism of 5-hydroxytriptamine and noradrenaline, whereas MAO-B predominantly deaminates 2-phenyl-ethylamine, tiramine and probably dopamine. These characteristic indicate distinct physiological functions of the two MAO subforms and require different modes of enzyme inhibition. The most important pharmacological effects of the new types of MAO inhibitors are observed in neuropsychiatric disorders. The inhibitors of MAO-A show a favorable and relatively fast action in various forms of mental depression, as classical MAO inhibitors. Other possible indications of these drugs include disorders with cognitive impairment, e.g. dementia of the Alzheimer type. Conversely, MAO-B inhibitors (like L-deprenyl) exert a L-dopa-sparing effect, prolong L-dopa action and seem to have a favorable influence regarding on-off disabilities in subject with Parkinson's disease [27]. Discovery of the two main subgroups of monoamine oxidase led to the synthesis of MAOI selective for one or other of these isoenzymes. Agents, such as toloxatone, **29** [28] and befloxatone (**30**) [29], which are not only selective, but reversible in their inhibition of MAO-A (RIMAs), have been synthesized and have proven antidepressant efficacy (Chart **16**).

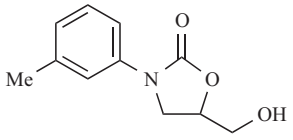
Whilst they are less likely to induce hypertensive reactions with the concomitant administration of sympathomimetic drugs or with tyramine-rich foodstuff, RIMAs also retain a potential for adverse interaction with other drugs.

2.1. Befloxatone

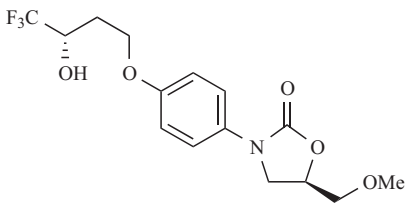
Befloxatone was selected as drug candidate for the treatment of depression after a study of the mechanism of action of MAO-A inhibitors in the phenyloxazolidinone series. The oxazolidinone was shown to be well tolerated in healthy volunteers and was developed in Sinthelabo Recherche laboratories as an antidepressant [29]. *In vitro* and *ex-vivo* studies showed that blefotaxone possessed a marked activity (rom 0.21 to 0.29 mg/Kg po) in anti-depressive-sensitive behavioral models in rats (from 0.03 to 0.15 mk/Kg po) and mice. At these doses beflotaxone does not induce a significant potentiation of oral tyramine. The drug was devoid of sedative, anticholinergic and cardiovascular effects and is rapidly and extensively distributed in rat brain. The neurochemical profile demonstrated that befloxatone was more potent *vs* MAO-A than reference compounds (befloxatone> harmaline> toloxatone) by an inhibition time-dependent and fully reversible after dilution. In the rat brain, befloxatone (0.75 mg/Kg p.o.) increased levels of norepinephrine, dopamine and 5-hydroxytryptamine and decreased the levels of their respective deaminated metabolites. These variations were dose-dependent and reversed 24 hr after administration. The drug did not interact with monoamine uptake mechanism or with a variety of neurotransmitter or drug receptor sites [30].

Identification of the forces responsible for the crystal cohesion of befloxatone revealed functional groups that could interact with monoamine oxidase. Electronic absorption spectroscopy measurements confirmed the hypothesis of a privileged interaction of phenyloxazolidinone-type inhibitors with the flavin cofactor of MAO. Additional sites of interaction with the protein core of MAO-A were also examined with regard to the primary structure of the enzyme. As a result, a model was proposed for the reversible inhibition of MAO-A by befloxatone *via* long distance, reversible interactions with the flavine adenine nucleotide (FAD) cofactor of the enzyme and with specific amino acids of the active site. This model was partially corroborated by experimental evidence and should be helpful in designing new potent inhibitors of monoamine oxidase [31].

[^{11}C]Befloxatone has been synthesized to be used as medical imagery agent for the diagnosis of human normal or pathologic states related to a modification in the distribution of monoamine oxidase by positron emission tomography (PET), a high-resolution, sensitive, non-invasive and quantitative imaging technique [32a]. The results obtained *in vivo* not only confirmed the biochemical and pharmacological profile, but also pointed out that carbon-11 labelled befloxatone as an excellent tool in neurological and/or psychiatric disorders, in chronic neurodegenerative diseases (Alzheimer's, Parkinsons etc) or in tobacco smoking. [32b]. In a recent application, quantification of myocardial binding sites (Bmax) by PET in monkeys, i.v. injected with [11C]befloxatone, revealed that inhalation of tobacco smoke decreases



Toloxatone



Befloxatone

Chart (16).

more than 25% the value of Bmax, whereas nicotine does not [32c].

2.2. Other Oxazolidinone-based MAO-A Inhibitors

Oral administration to dog of MAO-A inhibitor ER-4539 (Chart **17**) produced in the plasma a new metabolite E2011, which was isolated in large scale by HPLC after incubation with dog liver microsomal preparations. The new compound was synthesized and shown to have improved the MAO-A inhibitory action in regard to biopharmaceutical characteristic in rat and dog [33a]. Several studies confirmed the novel E2011 as a selective and reversible inhibitor of MAO-A [33b-d].

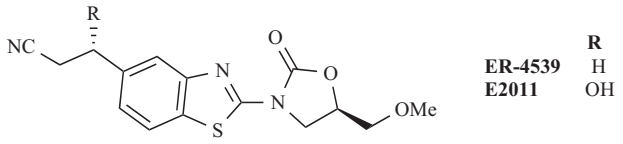


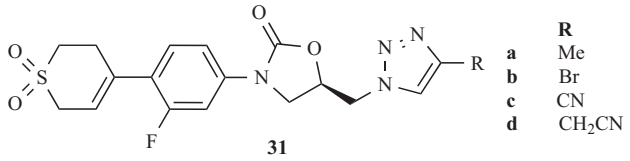
Chart (17).

3-(1H-Pyrrol-1-yl)-2-oxazolidinones (**29**) have been synthesized as pyrrole analogues of toloxatone (Humoryl), and their monoamine oxidase (MAO) type A and B inhibitory activities have been evaluated. The majority of these compounds showed higher inhibitory activity against the A isoform of the enzyme, the sole exception being the (*S*)-5-aminomethyl derivative. (*R*)-5-methoxymethyl-3-(1H-pyrrol-1-yl)-2-oxazolidinone, the most potent among test derivatives, was 78-fold more potent than toloxatone [34a].

The same group prepared 3-(1H-pyrrol-2-and –3yl)-2-oxazolidinones (**30a** and **30b**) isomeric of **29** (Chart **18**) to be evaluated as anti-MAO agents: the most potent was (*R*)-5-methoxy-methyl-3-(1H-pyrrol-1-yl)-oxazolidin-2-one, endowed with very high potency (K_i = 4.9 nM) and A-selectivity (10,200), about 116 fold greater than that of befloxatone [34b]. Oxazolidinone MAO-A inhibitors have been recently reviewed and modifications to avoid undesirable vascular effects were discussed [35].

The research avenues of antibacterial oxazolidinones and MAO-A inhibitor oxazolidinones cross and may overlap in the activity of some derivatives. Novel dimerized derivatives with identical substitution of the two C-5 side chains have been synthesized, to obtain experimental evidence for the orientation of oxazolidinones in the active site of MAO. These substrates reduced the enzyme fully without any trace of semiquinone intermediate. Only oxazolidinone inhibitors with a bromoimidazole substituent increased the yields of semiquinone intermediate obtained during the chemical reduction. Docking experiments confirmed that the binding of the oxazolidinone ring in the aromatic cage was favored [36].

Conversely, compounds **31a-d** (Chart **19**), with a 4-substituted 1,2,3-triazole in place of the conventional acetamide, were found to be good antibacterials with reduced or no activity against MAO-A. The results are especially promising for the development of oxazolidinones with an improved safety profile [37].



31

Chart (19).

3. OTHER BIOLOGICAL ACTIVITIES OF OXAZOLIDINONES

3.1. Inhibition of Proteins or Enzymes

3.1.1. Inhibition of the D-fructose Transporter Protein GLUT5

A major difficulty in analysis of D-fructose interactions with its transporter is its ability to exist in α,β-pyranose or α,β-furanose forms. Conformationally restricting the number of ring conformations was considered to be important in the development of new analogues. On the other hand, L-sorbose, which is predominantly present in solution in the pyranose form, is not well recognized. The possibility that L-sorbose analogues might be good inhibitors if they could be locked into a furanose ring form had not been explored. The inhibition of the glucose transporter 5 (GLUT5) by D-fructose and L-sorbose derived 1,3-oxazolidin-2-thiones (OXT, **32a** and **32b**, respectively) and 1,3-oxazolidin-2-ones (OXO, **33a** and **33b**) has been studied to provide a rational basis for an interaction model [38a]. From these studies, it appears that locked conformation of ketofuranoses provide better interacting molecules (by factor 6) with D-fructose transporter GLUT5 than those previously reported [38b].

3.1.2. Irreversible Inhibition of Carboxypeptidase A

α-Benzyl-1,3-oxazolidin-2-one-4-acetic acid **34** (BOOA) with α,4S and αS,4R configurations were designed and synthesized as inactivator of carboxypeptidase A (CPA) [39a], a zinc-containing proteolytic enzyme that cleaves off the C-terminal amino acid residue of a hydrophobic side chain.

All four possible stereoisomers of BOOA were synthesized and their CPA inhibitory activities were evaluated (Chart **21**). Surprisingly, all of the four stereoisomers inhibit CPA in a time dependent manner [39b]. The inhibited enzyme did not regain its enzymic activity upon dialysis. The

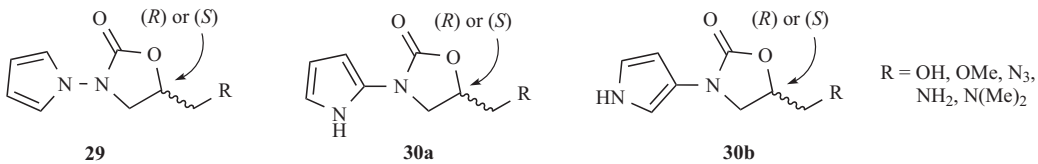


Chart (18).

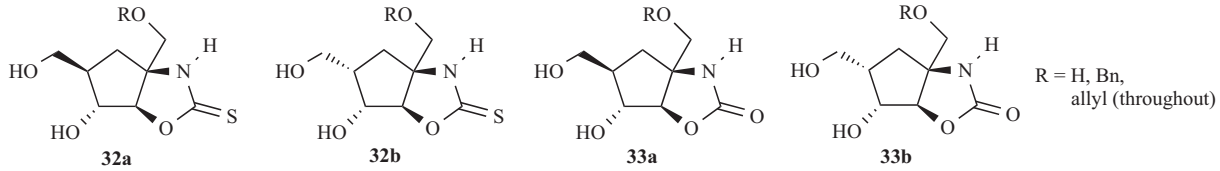


Chart (20).

kinetic results strongly suggested that the inactivators attach covalently to the enzyme at the active site, as confirmed by the analysis of ESI mass spectral data of the inactivated CPA. The lack of stereospecifity and regiospecificity led the authors to propose that the ring cleavage occurs by nucleophilic attack at the 2-position rather than at the 5-position and the ring opening takes place by an addition-elimination mechanism. The 5-substituted derivative 34a, a structural isomer of 34, was also found to inactivate CPA in an irreversible manner, reinforcing the proposed mechanism.

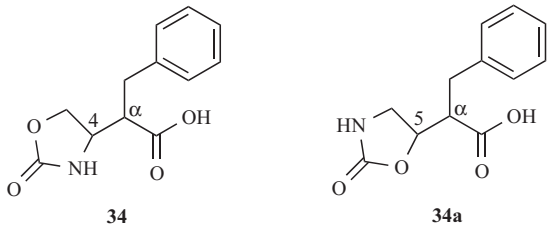


Chart (21).

3.1.3. Selective Cyclooxygenase-2 Inhibition

Selective cyclooxygenase-2 (COX-2) inhibitors could provide anti-inflammatory, analgesic and antipyretic drugs devoid of the unwanted side effects such as ulcers and renal failure associated with the classical nonselective non-steroidal anti-inflammatory drugs [40a]. The indenone **35a** was one of five compounds designed on the basis of a three-dimensional quantitative structure-activity relationship (3D-QSAR) study [40b] and was synthesized starting from chalcone **35** (Scheme **2**). Compound **35a** displayed experimental IC_{50} (0.54 μM) value *vs* COX-2 largely different from the 3D-QSAR predicted value (0.002 μM); moreover, it was not possible to determine accurately its selectivity (COX-1/COX-2 ratio) because of lack of solubility, a feature that could explain the low experimental inhibitory value.

3.1.4. Matrix Metalloproteinases Inhibitors

Matrix metalloproteinases (MMPs) are involved in extracellular degradation and the number of disease states that these enzymes impact on are many. Angiogenesis, wound healing, inflammatory reaction, management of the blood brain barrier, and general maintenance of the joints, all depend on these enzyme, which remodel connection tissues in the extracellular matrix. MMPs, particularly the gelatinises, mediate extracellular matrix and basement-membrane degradation during the early stages of tumor growth. They also activate growth factors by inactivating growth-factor binding proteins and releasing mutagenic compounds from the matrix proteins, thus directly inducing tumor-cell proliferation. The MMps inhibitors are mostly targeted at the right hand (prime) side of the active site, which contains a hydrophobic S1' pocket. Nearly all MMPIs have a functional group which binds the Zn atom in the active site and the so called P1' substituent.

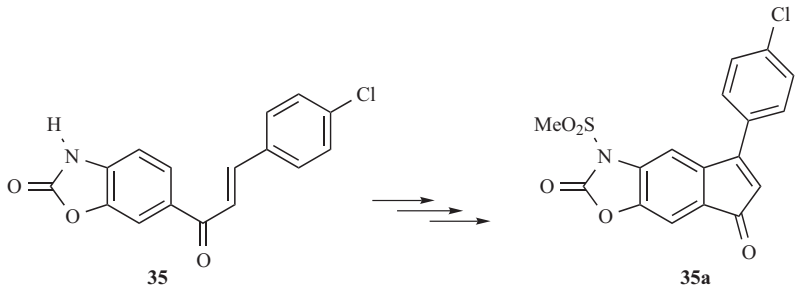
Oxazolidinon-2-ones have been used as starting material for the preparations of MMPs inhibitors (Scheme **3**). The 1,3-oxazolines **37** were synthesized from **36** by Pd-catalyzed ring opening, decarboxylation and cyclization of the amide to form **37a**. Removal of the O-protecting group from **37a** with tetrabutylammonium fluoride provided **37** in quantitative yields. Twenty analogs with variation in the potential P1' group (X) were prepared and evaluated for biological activity against MMPs [41].

Other matrix metalloproteinase inhibitors, such as **39** were prepared from the oxazolidin-2-one intermediate **38,** which in turn was obtained from L-serine methyl ester by cyclization with triphosgene and subsequent reduction [42].

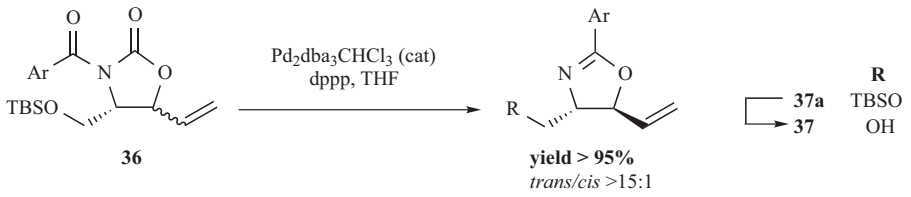
3.1.5. Inhibitors of Cytochrome P-450 Enzyme Aromatase (AR)

On the basis of molecular modelling studies, *S*- and *R*-enantiomers of N-alkyl-4-(4'-aminobenzyl)-oxazolidin-non-2-ones **40** (Chart **23**) were synthesized and tested for human placental aromatase inhibition *in vitro*, using [1β, 2β-3H] androstenedione as a substrate for the AR enzyme.

The compounds were found to be more potent than standard aminoglutethimide (AG) and as such proved to be good lead compounds in the search for more specific AR inhibi-



Scheme 2.



Scheme 3.

tors. In general, the *R*-forms appeared to be more potent than the inhibitors based upon *S*-enantiomers, except for the *S*-methyl as compared with the *R*-decyl derivative. In the *R*-series the inhibition activity increased with the length of the *N*-chain and was observed to reach a maximum with the pentyl and hexyl derivatives. By contrast, in the S-series the activity decreased regularly with the chain length [43].

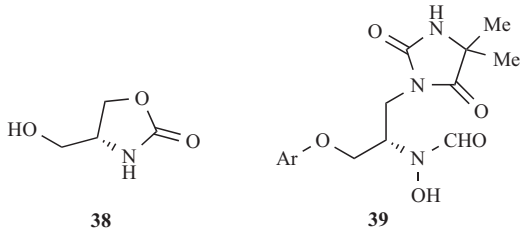


Chart (22).

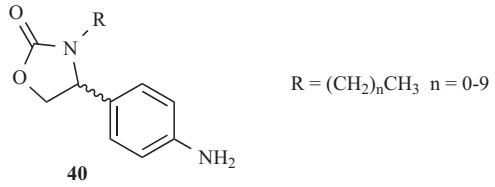


Chart (23).

3.1.6. Inhibitors of Phospholipase A2

All stereoisomers of N-acyl-4,5-disubstituted oxazolidinone phospholipid analogs **41** have been synthesized: the (4*R*,5*S*)-derivatives showed stronger inhibitory activity toward type II phospholipase A2 than the 4-substituted oxazolidinone analog **41a** previously reported [44].

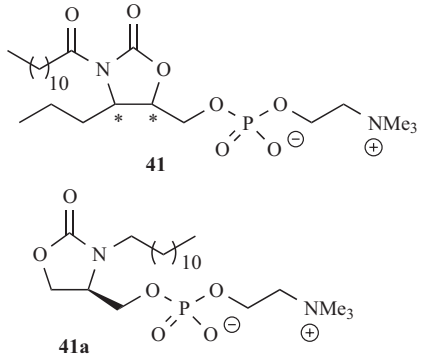


Chart (24).

3.2. Receptors Agonists and Antagonists

Compound **42** (Chart **25**), an intermediate for the synthesis of β-3 agonist, [*R*-(*R**, *R**)]-5-[2-[(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-1,3-benzodioxole-2,2-dicarboxylic acid disodium salt, was prepared by an improved process [45].

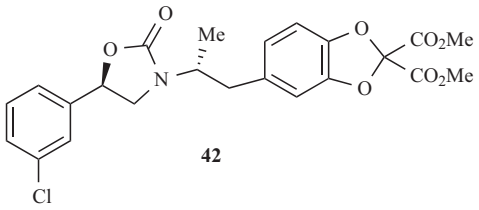


Chart (25).

Compounds such as **43a** in Chart **26** have been patented as selective antagonists for human α1A receptors with the followings claims: lowering of intracellular pressure, inhibition of cholesterol synthesis, relaxation of the lower urinary tract tissue, treatment of benign prostatic hyperplasia, impotency, cardiac arrhythmia *etc.* [46a]. The same group prepared oxazolidine–based and related compounds **43b** with strong binding affinity for human receptors [46b]. Adrenergic α1A receptors antagonists (**43c** and **43d**) were also synthesized and patented by Selnick *et al.* [46c,d].

A benzoxazolidinone group appears among the 3-aryl substituents tested for a series of non-peptide $\alpha_v\beta_3$ antagonists, some of which (e.g. **44a** - **44c** in Chart **27**) displayed a significantly improved oral pharmaco- kinetics in dogs. However, the more polar benzoxazolidinone **44d** was a less potent antagonist and suffered decreased bioavailability and higher clearance relative to **44a** - **44b** [47].

Among the oxazolidin-2-ones of general structure 45 (X = O, S, H_2; X' = O, S, CH_2; R = optionally substituted Ph, NH_2, CH=CHPh, C≡CPh, alkyl, alkoxy; R'=H, alkyl, acyl) compound 45a showed an ED_{50} of 4.2 mg/kg orally in mice in the reserpine antagonism test [48].

The novel 3-[3-dimethylaminocyclobutyl)indole $5HT_{1B/1D}$ receptor partial agonist **4991 W93** (Chart **29**) was synthesized and pharmacologically evaluated, as a potential drug for the treatment and prophylaxis of migraine, a debilitating condition afflicting some 5-10 % of the population. The compound was designed on the basis of a pharmacophoric model of binding the receptor, which suggested the 3-aminocyclobutyl group as potential ethylamine isostere of zolmitripan. The last one was one of the more liphofilic molecules developed by the first antimigraine agent, suma-

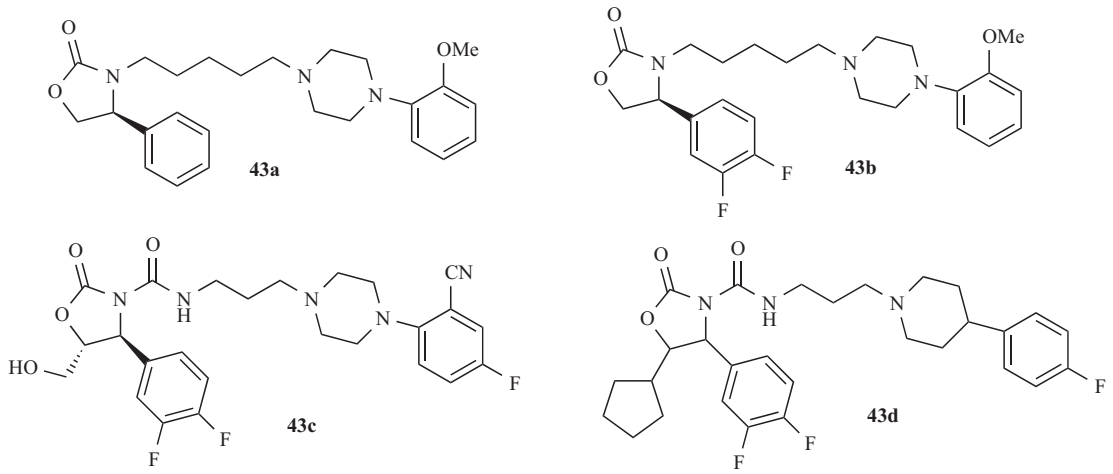


Chart (26).

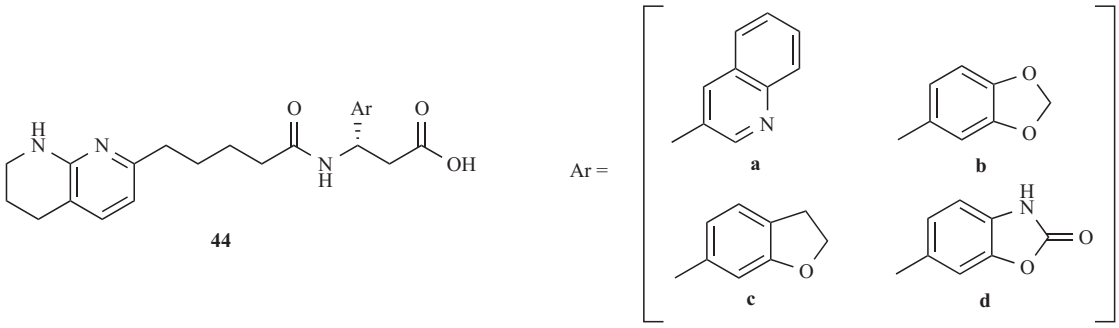


Chart (27).

tripan. **4991W93** was found to be an exceptionally potent inhibitor of electrically induced plasma extravasations [49].

EMD-95885, a selective antagonist for NMDA receptors containing NR2B subunits, has been labeled in the benzoxazolinone moiety. [^{11}C]-**EMD-95885** (Chart **30**) was evaluated pharmacologically *in vivo* as a potential positron emission tomography (PET) radioligand for imaging the NMDS receptor [50].

3.3. Miscellaneous

The β-lactam nucleus of the cholesterol absorption inhibitor ezetimibe was substituted by the oxazolidin-2-one, isoxazoline and pyrazoline rings. The oxazolidinone surro-

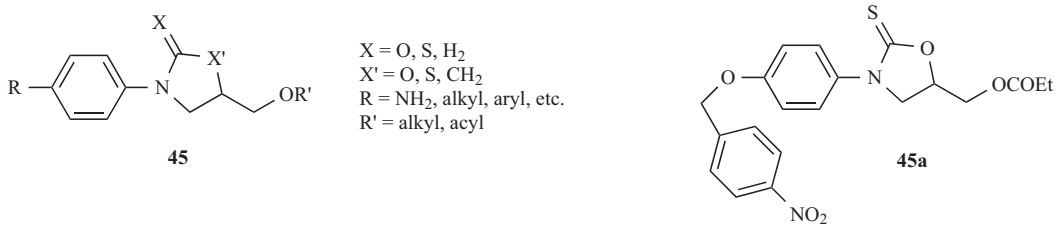


Chart (28).

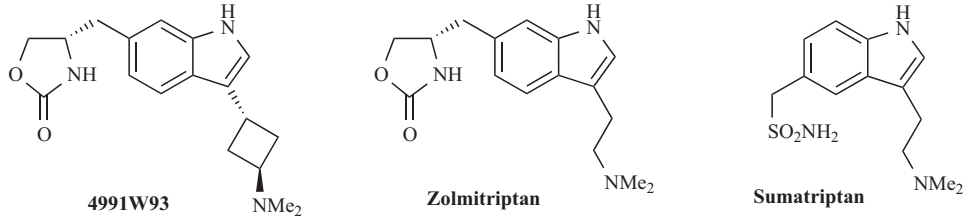
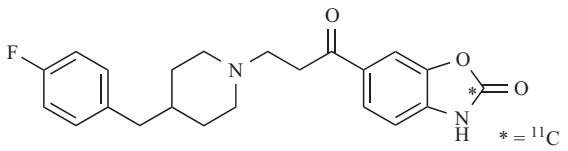


Chart (29).



[^{11}C]EMD-9855

Chart (30).

gate **46** showed *in vitro* inhibitory efficacy in a brush border membrane vesicle assay [51] (Chart **31**).

4. NATURAL PRODUCTS

The oxazolidin-2-one ring is quite rare in the framework of the natural products, but it has been sometimes used to replace other rings or residue for the preparation of analogues of bioactive molecules; the cyclization of carbamate residues has been also employed for this target. Moreover, chiral auxiliaries have been largely used in the synthesis of stereochemically complex fragments of natural compounds.

4.1. Natural Oxazolidin-2-ones

Natural products bearing an oxazolidin-2-one moiety are quite rare in current literature.

(-)-Cytoxazone (**55** in Chart **33**) was isolated by Osada and co-workers (1998) from a soil sample of *Streptomyces* sp. and assigned the structure (4*R*, 5*R*)-5-(hydroxymethyl)-4-(4-methoxyphenyl)-2-oxazolidinone; the absolute configuration was established by comparison of circular dichroism (CD) spectra of the natural product with those of (*R*)- and (*S*)-4-phenyl-oxazolidin-2-one, and was confirmed by X-ray single crystal analysis [60]. The compound showed a cytokine-modulating activity by inhibiting selectively the signaling pathway of Th2 (but not Th1) cells.

Among the several syntheses of **55** and its stereoisomers reported in the last years [61], the chemoenzymatic synthesis of (-)-cytoxazone and its (+)-isomer stands out: kinetic resolution of (+/)-**55** with *Penicillium camambertii* (Pcaml) gave the (+)-alcohol (50.6% yield, *ee* 89.3%), and the acetate (-)-**55a** (*ee* 88.2%) (Scheme **4**). Crystallization increased to 95.2% the *ee* of (+)-**55**, while the natural isomer (-)-**55** was obtained also wit 0h a 95.2 *ee* after acetate hydrolysis of (-)-**55a** and crystallization [62].

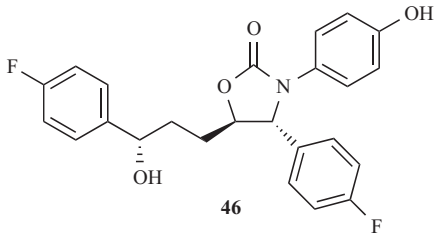
The uninterrupted interest in cytoxazone is testified by the number of papers, dealing with the synthesis, published during 2004 [63].

(+)-Streptazolin (**56** in Chart **34**), a lipophilic neutral tricyclic compound, was first isolated by Drautz *et al.* [64] in 1981 from a culture of *Streptomyces viridochromogenes* and later rediscovered by chemical screening of *Streptomyces luteogriseus* and a high-producing strain of *Streptomyces* sp. [65].

Notably, in spite of the low antimicrobial activity exhibited by streptazolin, some Diels-Alder adducts of the compound with naphthoquinones have been reported to possess antitumor activity comparable to that of adriamycin on leukemia L1210 cells [66].

Although the compound might be kept for several days in diluted solutions at low temperatures, the purification of streptazolin was rather difficult because of its tendency to polymerize in concentrated form; for this reason, the structural investigation, based on NMR spectral data, chemical degradation and X-ray analysis was performed on the more stable O-acetyl dihydrostreptazolin **56a**, obtained by catalytic hydrogenation and acetylation. Puder *et al.* reported the isolation from *Streptomyces sp.* of additional secondary metabolites (Chart **35**), including 13-hydroxystreaptazolin (**56b**), 9-hydro-xystreptazolin (**56c**) and 5-O-(β-D-xylopyranosyl) streptazolin (**56d**) [67].

More recently, oxidized streptazolin-related compounds (Chart **36**), 8α-hydroxy streptazolone (**57a**), 4,12-epoxy-



46

Chart (31).

Other emerged biological activities are summarised in the Chart **32**.

Compound	Biological activity or use	Literature
47	Intermediate for the preparation of antidiabetic and antiobesity agents	[52]
48	Oxazolidinone derivatives (oxazolidienones) for hypoglycemic and hypolipidemic activities	[53]
49	Inhibition of epithelial cell (sheet) migration and growth	[54]
50	Significant activity in neurokinin A receptor-binding	[55]
51	Treatment of bone resorption and osteoporosis	[56]
52	Oral direct Factor Xa inhibitor	[57]
53	Potential psychotropic and antidepressant activity	[58]
54	Useful as photoaffinity probe	[59]

(Chart 32 Contd….)

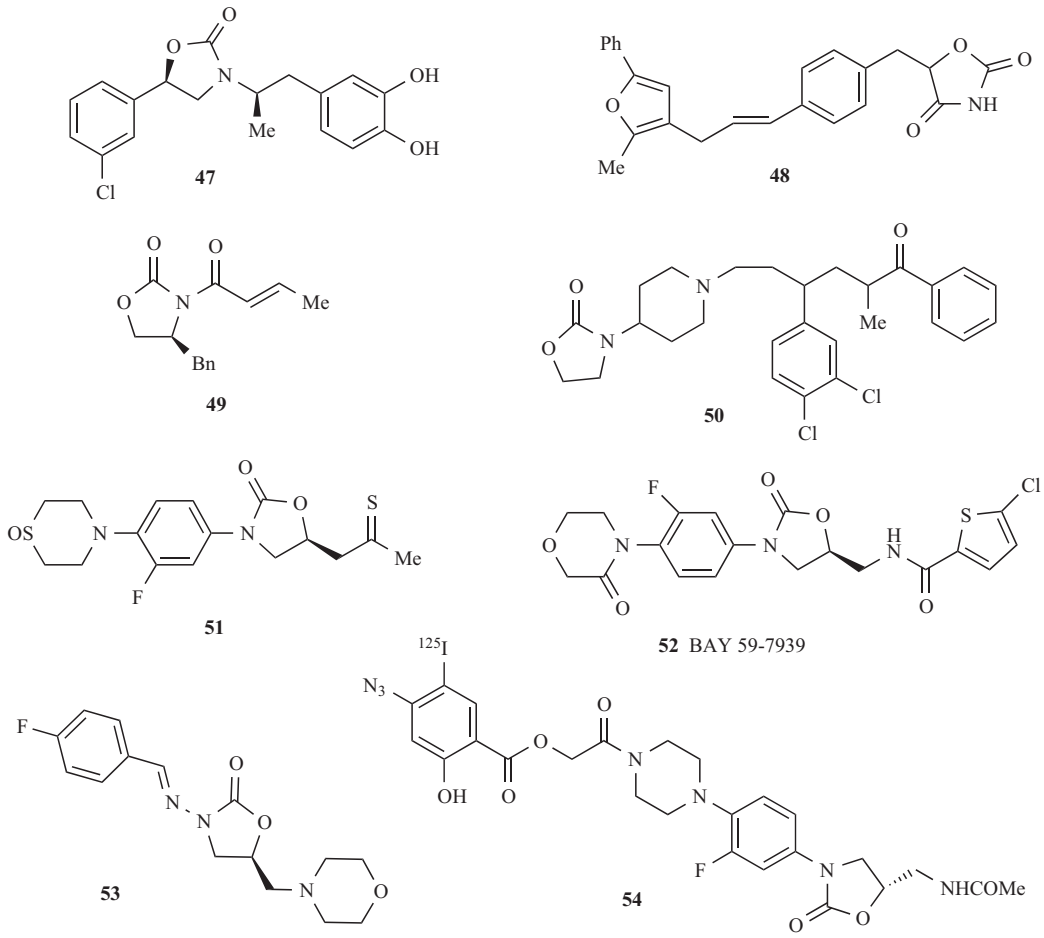


Chart (32).

streptazoline (**57b**), 9β-hydroxystreptazolin (**57c**) and the dimer **57d** have been described [68].

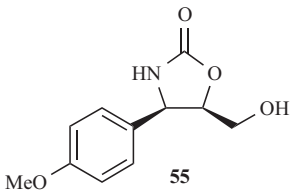
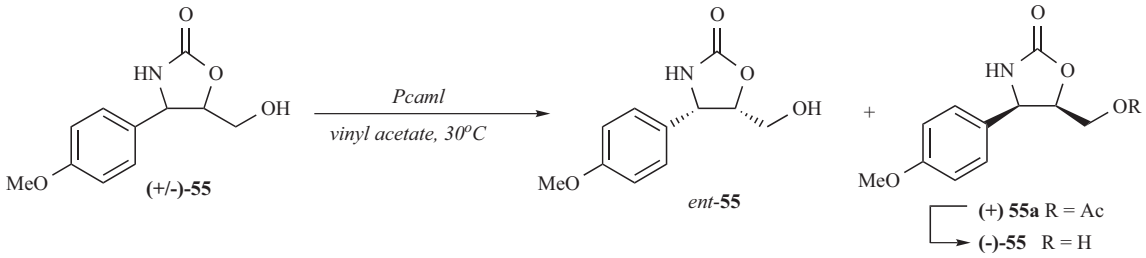
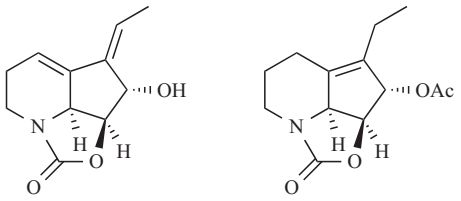


Chart (33).

Biosynthetic studies on streptazolin have been performed by Mayer and Thiericke [69] by feeding *Streptomyces sp.* microorganism (strain FH-S 2184) with sodium [^{13}C]acetate, sodium [^{13}C]formate, [^{13}C]urea, L-[methyl-^{13}C]methionine, [$^{15}N_2$]ammonium sulfate and L-[^{15}N]glutamic acid. The unique tricyclic skeleton was shown to be assessed by a mixed biosynthesis *via* the polyketide pathway, the one-carbon and nitrogen pool, as well as oxygen from air. The first total synthesis of streptazolin in racemic form has been reported by Kozikowski and Park [70]. The synthesis (7% overall yield) confirmed the structure assignment of streptazolin, and, in particular, the stereochemistry of the exocyclic



Scheme 4.



56 **56a**

Chart (34).

olefin, a feature that had not been rigorously assigned in the analytical work.

The *bis*-oxazolidin-2-one **58** w (Chart **37**) as purified from the colonial tunicate *Clavelina oblonga* [71] and the absolute configuration was determined by microscale LC/MS-Marfeys's analysis through the following steps [72]: a) strong acid hydrolysis (12M HCl, 100-110 °C) of **58** to liberate 3-amino-1,2-propanediol, stereochemically stable under these conditions; b) treatment of the hydrolisate with 2,4-dinitrophenyl-5-fluoro-L-alanilamide (Marfey's reagent [73]) to give diastereomeric derivatives; c) resolution by LCMS and identification of the absolute configurations by comparison with standards.

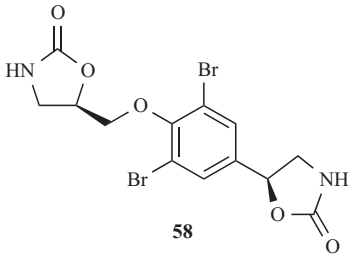
4.2. Analogues of Natural Products

Compounds **59a**/**59b** (Scheme **5**) are the isosteric 2-aza analogues of podophyllotoxin **59c** and *epi*podophyllotoxin **59d**, two natural products of renewed importance in the antitumoral research.

The 1,2-*cis*-2,3-*trans* configuration, a crucial factor for the biological activity, is a severe obstacle for the synthesis of *C* and *D* rings of podophyllotoxins.

The 2-aza-analogues appeared thus more accessible and all the four geometrical isomers were synthesized [74]. The ring D closure was obtained by treatment of the intermediate **59** with $COCl_2$ in the presence of Et_3N in CH_2Cl_2 at 0°C (Scheme **5**).

Pilocarpine (**60a** in Chart **38**), an alkaloid first isolated over 100 years ago, is currently used for the treatment of glaucoma and xerostomia (salivary gland dysfunction), while its thiolactone **60b** was developed as a clinical candidate for the treatment of Alzheimer's disease [75]. A cyclic carbamate analogue (**60c**) of pilocarpine was shown to be equivalent with the natural product using a standard *in vitro* assay and was expected to have a longer duration of biological action, because two sites for inactivation of pilocarpine (epimerization and lactone hydrolysis) have been eliminated. Moreover, carbamate analogues not only are more easily synthesized, being one of the two stereogenic centers eliminated, but also have greater stability [76].



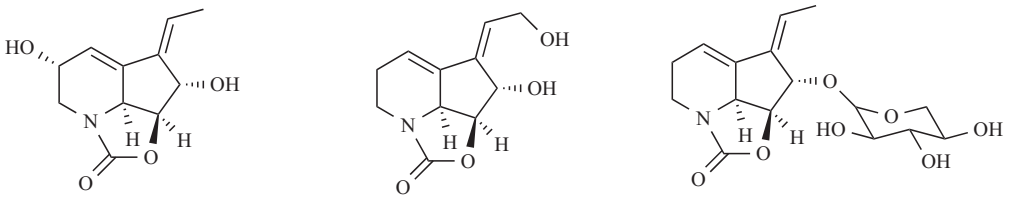
58

Chart (37).

The related chiral intermediate ketone **60d** was prepared from D-serine and 1-methylimidazole [77]. The best approach is resumed in Scheme **6**.

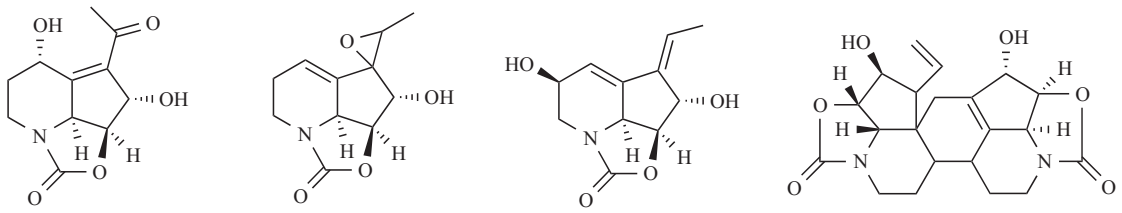
Cyclization of carbamate components of complex molecules to form the oxazolidin-2-one ring has been often performed to vary and study the biological activity of analogues of natural products.

The potent anticancer compound TNP-470 (**61b** in Chart **39**), obtained from a natural antibiotic (fumagillin, **61a**) by replacement of the unsaturated ester chain by an O-(chloroacetyl)carbamoyl moiety, was 50 times more active than the natural product and devoid of its side effects [78].



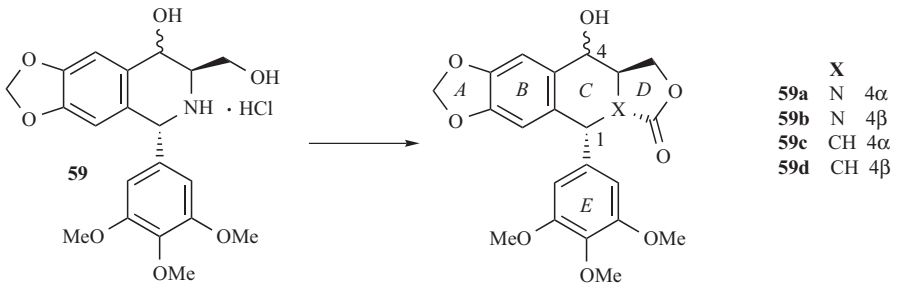
56b **56c** **56d**

Chart (35).



57a **57b** **57c** **57d**

Chart (36).



Scheme 5.

The anti-angiogenic activity of TNP-470 was retained when the methoxy group was replaced by a carbohydrate pyranyl ring and cyclic analogues, such as **62**, were prepared. However, most of the compounds were less active than fumagillin, except **62** with R = -C ≡ C-C_5H_{11}, R' = CH_3, which was equiactive against the human tumor cell line A-431 [79].

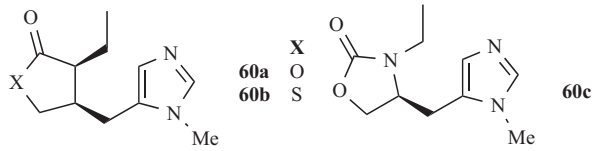


Chart (38).

4.3. Reactions with Chiral Auxiliaries

Chiral oxazolidin-2-ones have been employed as auxiliaries also in the synthesis of biologically active natural product.

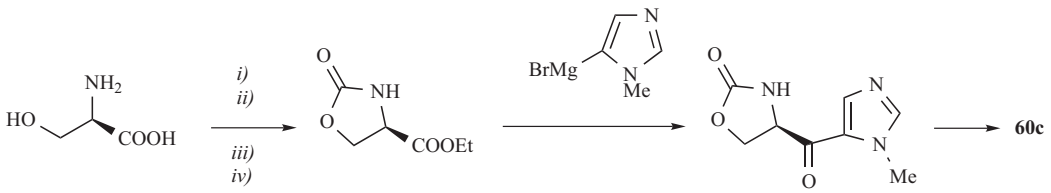
The allylic alcohol **64a**, intermediate for the synthesis of fragment C13-C22 of the potent antitumor polyketide (-)-callystatin A (Scheme **7**), was prepared starting from N-propionyl oxazolidin-2-one **63** [80]. An asymmetric aldol addiction of the boron enolate derived from **63** with 2-(*S*)-methyl butanal gave the alcohol adduct **63a** in 89% yield and ds > 95:5. Exchange of the oxazolidinone auxiliary **63a** with N, O-dimethyl hydroxylamine followed by silylation gave the Weinreb's amide **64**, which was converted into the aldehyde and then to the (*E*)-α,β-unsaturated ester, which finally was reduced to the alcohol **64a**, as a precursor the of the diol **65** (fragment C15-C22).

In the synthesis of fragment **X** of epothilone B, (S)-3-acryloyl-4-benzyl-2-oxazolidinone **66** was converted in the intermediate **67** by a series of reactions characteristic of chiral auxiliaries (Scheme **8**): a) conjugate addition to yield **66a**; b) hydroxylation of the sodium enolate derived from **66a** with Davis' oxaziridine; c) protection of alcohol **66b** as silyl ether **66c**; d) exposure to catalytic potassium thioethoxide in ethanetiol. The thioester **67** was obtained with an overall 55%yield along with recovered oxazolidinone (93%) [81].

The bicyclic oxazolidinone 68 (Chart **40**), intermediate of the synthesis of the antitumor marine sponge alkaloid agelastatin has been prepared by hetero Diels-Alder cycloaddition of cyclopentadiene with N-sulfinylmethyl carbamate. The cycloadduct was converted to the corresponding allylic sulfoxide and then to 68 by a [2,3] sigmatropic rearrangment [82].

CONCLUSIONS

On the small oxazolidinone scaffold many complex molecular frameworks have been built in the search of better



Scheme 6.

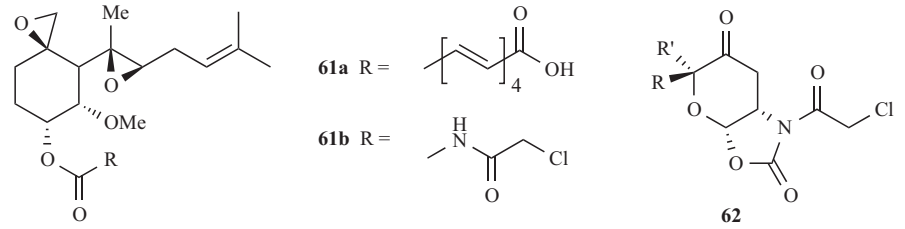
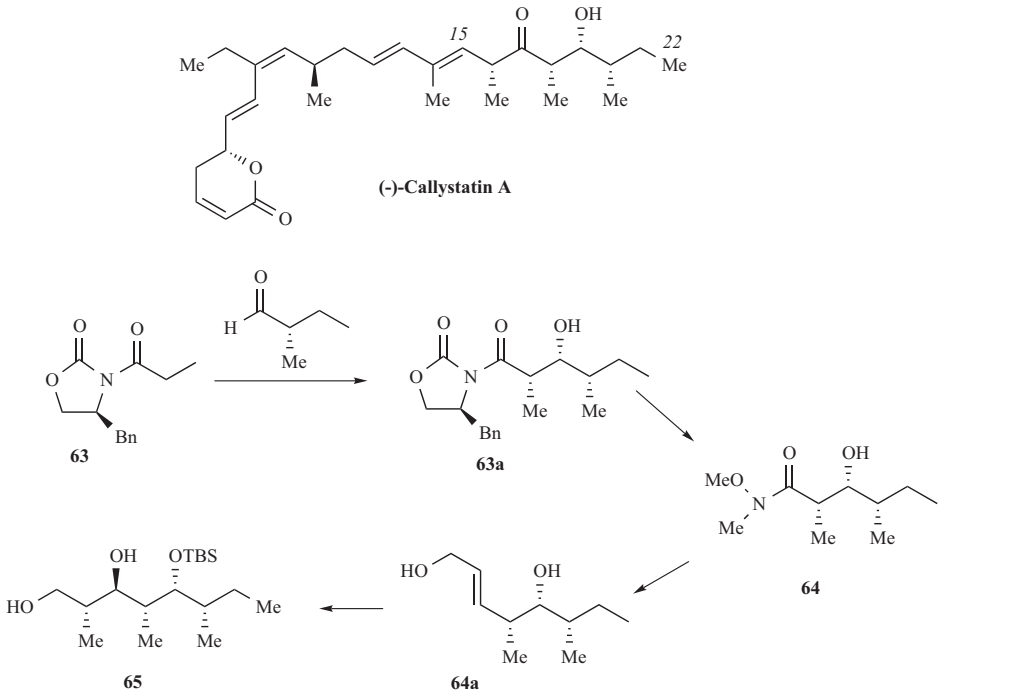
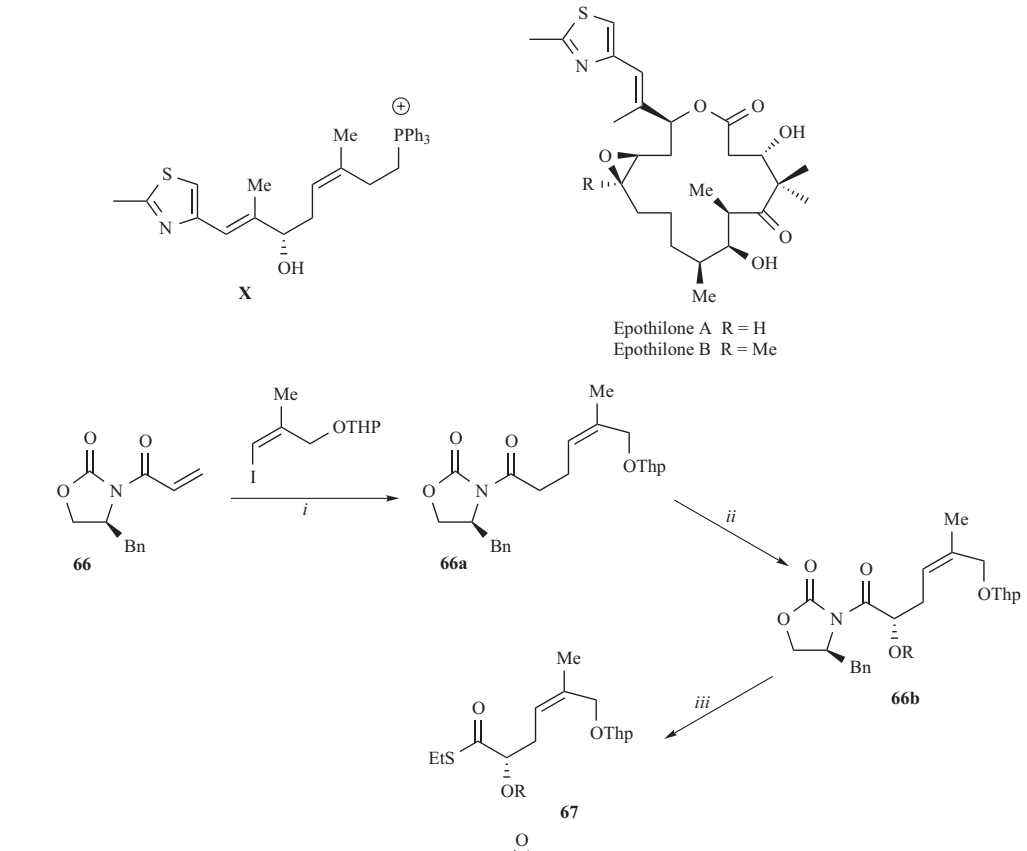


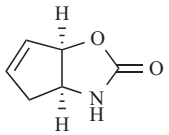
Chart (39).



Scheme 7.



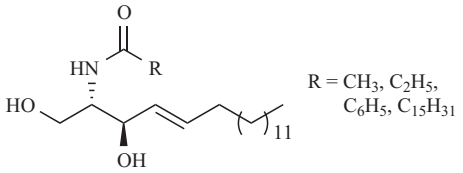
Scheme 8.



68

Chart (40).

and better antimicrobial activity or novel biological properties. The continue extension on the two opposite sides (N-3 and C-5 substitutions) has furthermore been enriched by a continue variation of the constituents, as in a combinatory model (see also the employment of oxazolidinone building blocks in the combinatorial generation of diverse skeletons of small molecules [83].



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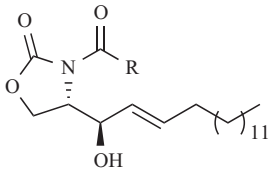

69a

Chart (41).

After several years the research of novel oxazolidinone derivatives has not been yet exhausted.

Many members of a huge number of oxazolidinone potential antibacterial compounds have been investigated for other desired or not biological activities, for instance, the MAO-A inhibition.

Compared to the results of pharmaceutical studies, the contribution from the natural products is relatively modest; however, it should be noticed the simplification introduced in the studies by the substitution with the oxazolidinone frame of more stereochemically complex rings.

The importance of the oxazolidinone nucleus in medicinal chemistry is sometimes hidden as in the case of ketolides (see above) or the use as protective group [84]. Very recently, the oxazolidin-2-one ring has been formed in the preparation of ceramide analogs, as potential anticancer agents.

The primary alcohol in sphingoid backbone of ceramide **69** (Chart **41**) might perturb the metabolic pathway by a possible involvement in various biological reactions. Constrained ceramide analogs **69a** may overcome this drawback without metabolic perturbation [85].

Last but not least, the participation of oxazolidinone chiral auxiliaries to the synthesis of enantiomerically pure biologically active molecules must be acknowledged [86].

ACKNOWLEDGMENTS

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