Cyclopropane Derivatives and their Diverse Biological Activities

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Natural and synthetic cyclopropanes bearing simple functionalities are endowed with a large spectrum of biological properties ranging from enzyme inhibitions to insecticidal, antifungal, herbicidal, antimicrobial, antibiotic, antibacterial, antitumor and antiviral activities.

The simple 2-substituted 1-aminocyclopropanecarboxylic acids (ACCs) are currently attracting special attention because of their potential use in conformationally restricted peptides, providing biosynthetic and mechanistic probes. As the immediate biosynthetic precursor of ethylene, the phytohormone that initiates and regulates many aspects of plant growth (germination, inhibition, senescence, fruit ripening, etc.), the parent ACC, structurally related to glycine, is a potent and selective ligand of the glycine modulation site coupled to the *N*-methyl-D-aspartate (NMDA) receptor, one of the four different receptors that mediate the action of the excitatory amino acids (EAA) in the brain transmitter systems; thus, such amino acids have also been proven to be useful in neurochemical studies. The mechanisms responsible for the diverse specific biological activities of compounds containing three-membered carbocyclic moieties are also being discussed.

Keywords: Cyclopropanes, Methanoamino acids, Enzyme inhibition, Drug design, Biomechanisms

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1 Introduction

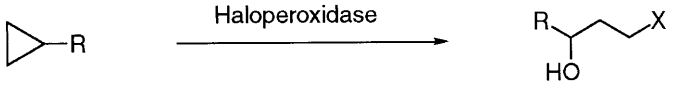
The cyclopropane ring, due to its unusual bonding and inherent ring strain (27.5 kcal/mol) is unique among carbocycles in both its properties and reactions [1]. Therefore, cyclopropane-containing compounds are of great general interest, particularly to synthetic organic chemists and to bioorganic chemists.

Thus, cyclopropane derivatives provide building blocks of unprecedented synthetic potential [2]. Moreover natural and synthetic cyclopropanes bearing simple functionalities are endowed with a large spectrum of biological properties ranging from enzyme inhibitions to antibiotic, antiviral, antitumor and neurochemical properties [3]. Present in animals, plants and microorganisms, or generated transiently in primary and secondary metabolisms, they provide convenient biological probes for mechanistic studies and allow the design of new drugs [4]. The aim of this article is to review the diverse biological activities of compounds containing three-membered carbocyclic moieties, and to indicate when the introduction of a cyclopropane ring will improve the overall biological potency.

2 Mechanisms Responsible for the Bioactivities of Cyclopropane Derivatives

2.1 Addition to the Cyclopropane Bond

Because the reactivity of a cyclopropane closely resembles that of an olefinic double bond [2], haloperoxidases (chloroperoxidase from *Cadariomyces fumago*, bromoperoxidase from *Penicillus capitalus*) add readily to the ring of cyclopropanes **1a,b** in the presence of halide ions and hydrogen peroxide to



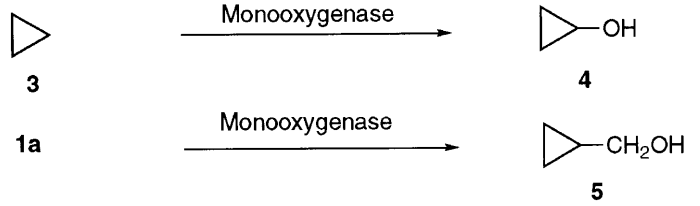
1a R = Me
b Ph

2a, b (X = Cl, Br) (1)

provide α, γ-halohydrins **2 a, b.** The enzyme-mediated cyclopropane ring-opening follows the Markovnikov rule, with the halogen going to the least substituted carbon and the hydroxyl group going to the carbon with substituents best able to stabilize a positive charge, Eq. (1) [5].

2.2 Enzymatic Oxidation

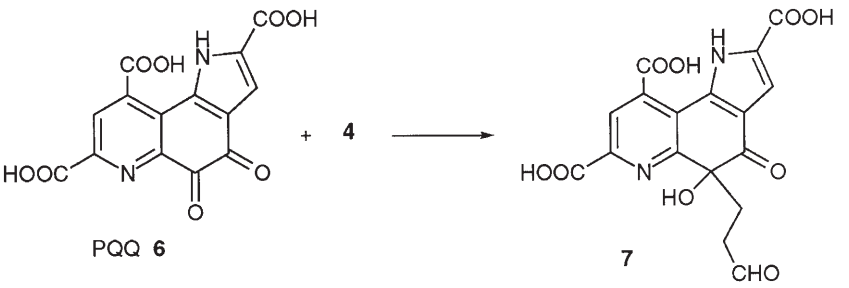
Cyclopropanes have been used to test the reactivity of oxidizing enzymes. Thus, while the monooxygenase enzyme from *Methylococcus capsulatus* oxidizes cyclopropane **3** to cyclopropanol **4**, on the other hand methylcyclopropane **1 a** is oxidized to cyclopropylmethanol **5**, also without ring opening, Eq. (2) [6].



(2)

2.3 One-Electron Oxidation Processes

Pyrroloquinoline quinone (PQQ) (or methoxatin) **6** is a coenzyme, responsible for the oxidation of methanol [7]. It has been found that cyclopropanol **4** inactivates the enzyme from *M. methanica* [8], the dimeric methanol dehydrogenase and the monomeric enzyme from a *Pseudomonas* PQQ-dependent methanol dehydrogenase [9] by forming adducts such as **7**, through a one-electron oxidation process and the ready ring opening of a *cyclopropyloxonium radical*, Eq. (3) [8, 9].

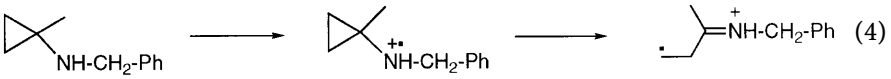


(3)

A flavoprotein oxidase, which is also a methanol oxidizing enzyme, was inhibited by cyclopropanol **4** through the formation of a *N*-5 flavin adduct with a ring opened cyclopropyloxy radical [10].

The *N*-benzyl-1-methylcyclopropylamine **7** is an irreversible inhibitor of the mitochondrial flavoenzyme monoamine oxidase (MAO). It was suggested that

MAO oxidizes amine substrates also by a one-electron route via the *cyclopropylamine radical cation* **8** which undergoes ready ring opening to the iminium radical cation **9** [11]. Then capture by a flavin radical, may cause the enzyme inactivation [12]. This mechanism was established by labeling experiments, Eq. (4) [13].

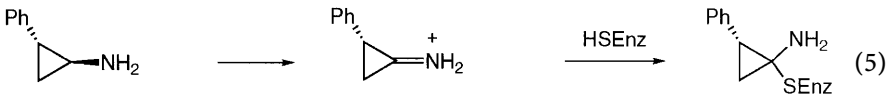


(4)

7 **8** **9**

2.4
Two-Electron Oxidation Processes

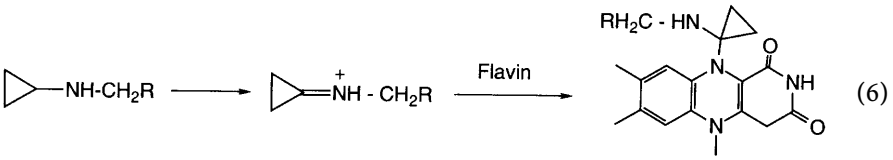
The bioactivity of the *trans*-2-phenylcyclopropylamine **10** (*tranylcypromine*) which is also a potent inhibitor of MAO and an efficient, albeit dangerous tranquillizing drug, would result of a net two-electron oxidation process leading to the *cyclopropyliminium ion* **11**, which then undergoes nucleophilic substitution by a thiol group of cysteine yielding **12**, Eq. (5) [14].



(5)

10 **11** **12**

Likewise, inactivation of MAO by *N*-cyclopropyl-*N*-(arylakyl)amines **13a, b** has been shown to involve the iminium ions **14a, b** which could accumulate to form the flavin adducts **15a, b** Eq. (6) [15].



(6)

13a R = Phenyl
b Indolylmethyl

14a,b

15a,b

2.5
Nucleophilic Substitutions

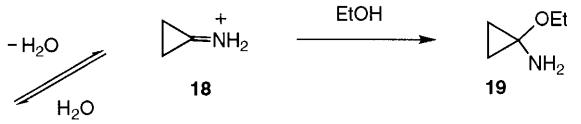
The fruiting body of the inky cap mushroom *Coprinus atramentarius*, Bull. (Basidiomycetes) is apparently non-toxic when eaten alone, but induces in humans and in experimental animals an over-sensitivity to ethanol [16].

The effect is mainly due to the inhibition of NAD^+-dependent aldehyde dehydrogenase (ALDH) which causes an accumulation of acetaldehyde in the body after ethanol ingestion [17]. The compound responsible for the physiological activity of *C. atramentarius* is coprine **16**, a N^5-(1-hydroxycyclopropyl)-L-glutamic acid amide which has been isolated and synthesized, [16a, b]. Thus, when fed

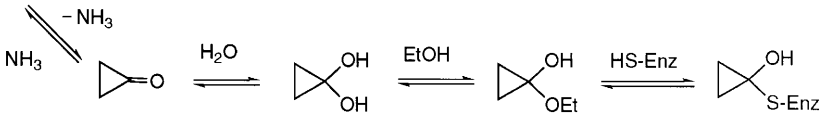
with a combination of mushroom and ethanol, rabbits exhibit a drop in blood pressure [18] and mice show a significant increase in their blood acetaldehyde level [19], while ethanol alone has a negligible effect. 1-Aminocyclopropanol ACP-**17**, the hydrolysis product of coprine **16** formed under acidic conditions or by glutaminase enzymes in mammals and in bacteria, is in fact the actual inhibitor in vivo and in vitro of ALDH, Eq. (7) [17].

16 ACP **17** (7)

However, the hemiaminal **17** is unstable as a free base and readily undergoes exchange reactions. Since the hydroxy moiety of **17** is more easily displaced than the amine moiety, a highly reactive *cyclopropyliminium salt* **18** is formed, which then reacts with weak nucleophiles such as ethanol, to give e. g., **19**. Otherwise in water solution **17** can also probably eliminate ammonia to form the highly reactive cyclopropanone **20**, which is in equilibrium with its hydrate **21** and hemiacetal **22**, Eq. (8) [20]. It has been reported that hydrate **21** is also a potent inhibitor of ALDH [20,21].



ACP **17** **18** **19** (8)



20 **21** **22** **23**

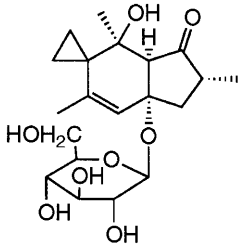
It has been suggested that the inhibition of ALDH by ACP **17** starts with an interaction between the amino group of **17** and the cysteinyl thiolate side chain of the enzyme to form a modified holoenzyme, or that the enzymic reaction may either proceed through the cyclopropanone **20** yielding **24a** or through the iminium ion **18**, yielding the modified enzyme **24b** [17]. Thus, the covalent hemithioacetal **24a** or hemithioaminal enzyme derivatives **24b** rapidly accumulate in the enzyme microenvironment and lead to the observed activity loss, Eq. (9) [21].

24a **24b** (9)

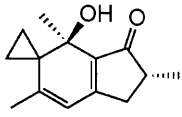
Other enzymes may also be similarly inactivated by such cyclopropanone adducts generated in situ by catalytic unravelling of some latent precursors. NAD^+ as coenzyme favours the electrophilic attack of ACP **17** on the enzymic thiol group, and considerably increases the rate of inhibition [17]. ALDH in brain was also inhibited in rats pretreated with coprine, and aldehyde reductase was slightly inhibited by ACP 17, in vitro [22].

2.6 Electrophilic Ring Opening

The bracken fern, *Pteridium aquilinum* is widely distributed throughout the world and is consumed as a human food in Japan and some other countries. Its toxic effects on livestock have been known since the end of the 19th century; cattle which consume bracken fern exhibit the syndrome known as "*cattle bracken poisoning*". The features include hemorrhage, anorexia, extensive intestine damage, ulceration, pyrexia and bladder carcinomas in animals [23], and enhance esophagal cancer risk in humans [24]. After intensive investigation, ptaquiloside **25** was isolated as the carcinogenic principle of bracken fern [25]. Under weakly alkaline conditions ptaquiloside **25** was converted, with D-(+)-glucose liberation, into the unstable dienone **26** which is responsible for the bracken fern carcinogenicity, Eq. (10) [25].



Ptaquiloside **25**

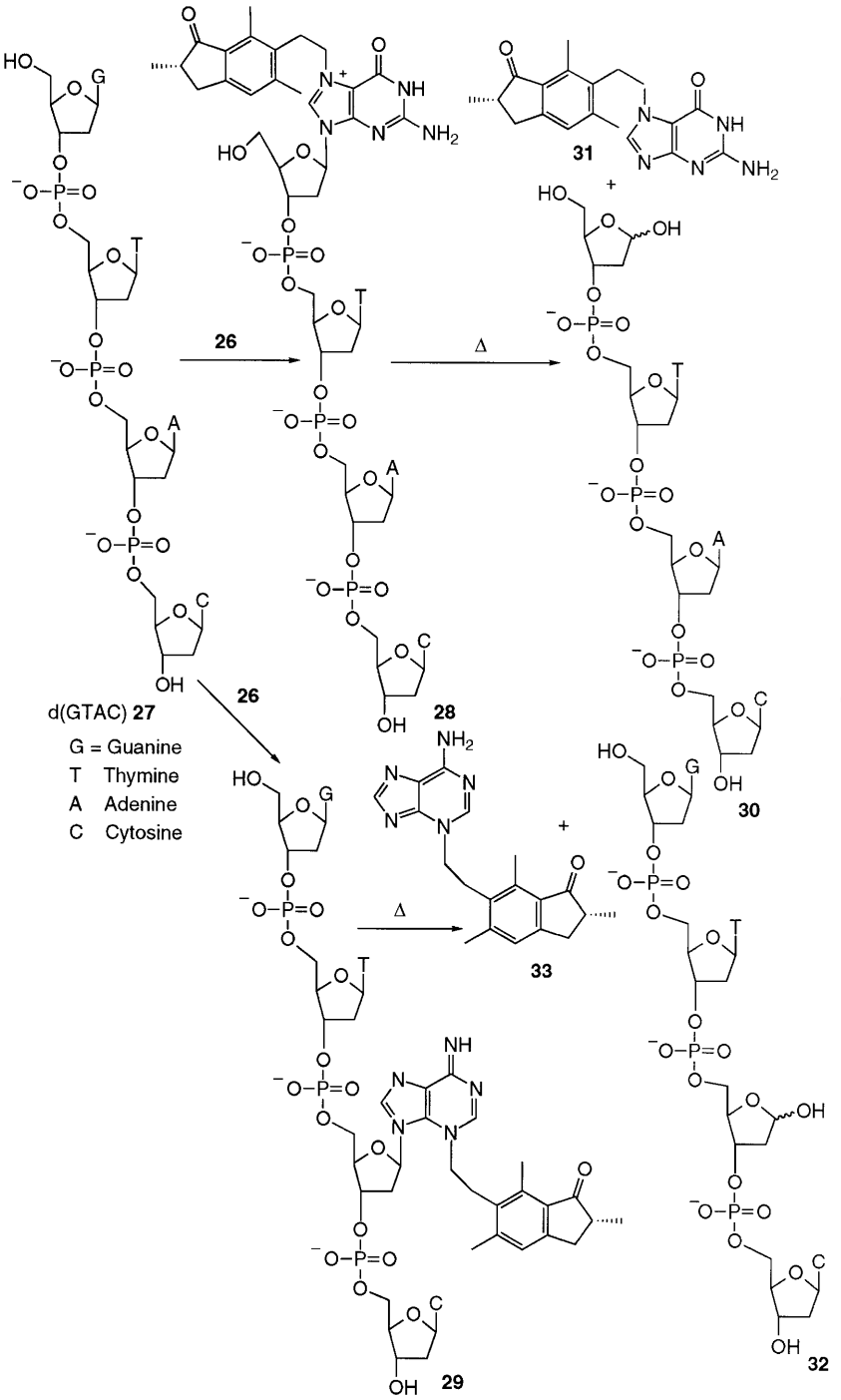


26

(10)

In fact, the cyclopropyl group of **26** is strongly electrophilic and reacts readily with amino acids, nucleosides and nucleotides under mild conditions [25d]. Thus dienone **26** forms covalent adducts with DNA and causes DNA strand breaks; DNA is the principal biological target of ptaquiloside **25** [26].

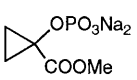
It has been recently shown that the selective alkylation and strand scission of deoxytetranucleotide d(GTAC)-**27** chosen as DNA model, results from the formation of covalent adducts **28** and **29** on the *N*-7 of guanine and *N*-3 of adenine with opening of the cyclopropane ring, respectively. Thermal treatment of **28** (90 °C, 5 min) afforded the d(deoxyribose-TAC) **30** with liberation of *N*-7 alkylguanine **31**, while treatment of **29** provided the d(GT-deoxyribose-C) **32** and the *N*-3 alkyladenine **33** [27]. The stabilities of adducts **28** and **29** were $t_{1/2}$ = 31 h and 3.2 h, respectively; therefore, the cleavage reaction of adduct **29** proceeds much faster than that of **28**, Eq. (11) [27].


d(GTAC) 27
G = Guanine
T Thymine
A Adenine
C Cytosine
26
26
Δ
Δ
28
29
30
31
32
33

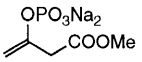
(11)

2.7
Geometric and Electronic Potency

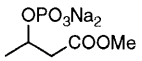
1-Hydroxycyclopropanecarboxylic acid phosphate HCP **34** is an analogue of phosphoenolpyruvate (PEP) **35** which is metabolized by various enzymes. HCP **34** is a potent competitive inhibitor of enzymes utilizing PEP **35**, such as PEP carboxylase, enolase, pyruvate kinase, and probably other enzymes. It is a substantially better inhibitor than phospholactate **36** or phosphoglycolate **37**, presumably because of the similarity of its geometric and electronic structures with phosphoenol pyruvate, Eq. 12 [28].



HCP **34**



35



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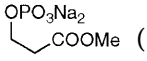
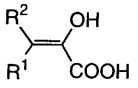
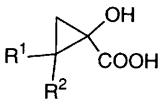


37 (12)

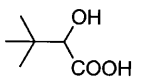
Microorganisms and plants, unlike mammals and other higher organisms, have the ability to biosynthesize amino acids from structurally simple precursors [29], so inhibitors of amino acid biosynthesis may be useful as selectively toxic herbicides and antimicrobial agents [29]. The enzyme dehydratase (2,3-dihydroxy acid hydrolase EC 4.2.1.9) catalyses the metal ion dependent conversion of 2,3-dihydroxy acids to the corresponding α-keto acids, which are the immediate precursors of the amino acids such as valine and isoleucine [30]. Enzymatic dehydration has been shown to proceed through enzyme bound enol intermediates **38a–d** [31]. As stable compounds that resemble the transition state for dehydration should be potent inhibitors of the enzyme [32], the 1-hydroxycyclopropanecarboxylic acids **39a–d**, whose electronic properties of the C-C bond closely resemble that of an olefinic double bond [2] have been tested as inhibitors of this enol producing enzyme. Effectively, the three-membered hydroxy acids **39b–d**, which contain alkyl substituents analogous to the substrates **38b–d** are all more potent competitive inhibitors for the dehydratase from yeast. The 2,2-dimethyl-1-hydroxycyclopropanecarboxylic acid **39b**, is a moderately effective inhibitor of dihydroxy acid dehydratase from yeast and *Escherichia Coli,* but its ring-opened analogue **40** does not inhibit enzymatic dehydration, indicating that the cyclopropane ring does contribute significantly to inhibitory potency, Eq. (13) [33].



38a $R^1, R^2 = H$
b Me
c $R^1 = Et, R^2 = Me$
d $R^1 = Me, R^2 = Et$



39a - d

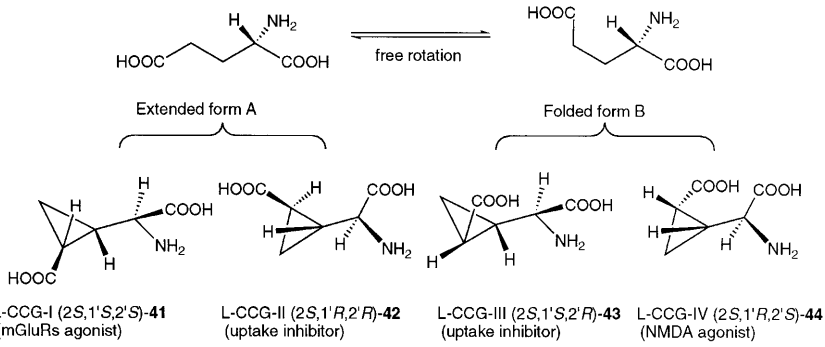


40 (13)

2.8
Conformational Affinity and Potency

The biological activity can be correlated with the conformation of molecules and partial constraint can be obtained by incorporation of a cyclopropane ring. L-Glutamic acid functions at many synapses in the mammalian central nervous system (CNS) as an excitatory neurotransmitter [34] and is implicated in the construction of memory and early learning [35] as well as in the pathogenesis of neuron damage to cause various neuronal diseases [36–38]. It is suggested that glutamate neurotransmission in different synapses is mediated through distinct receptors and combinations of different receptors. Therefore, development of selective and powerful agonists and antagonists appears to be essential for the investigation of molecular mechanisms of glutamate receptors and their physiological functions.

Glutamate receptors have been classified into two types: the ionotropic (iGluRs) and metabotropic (mGluRs) types. The former are further subdivided into *N*-methyl-D-aspartic acid (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA), and kainic acid (KA) receptors according to their selective action as agonists [34]. Starting from the hypothesis that each receptor subtype would require a particular conformation of glutamate for its selective activation, i.e. conformational requirements for activating receptors, the four diastereomers of L-2-(carboxycyclopropyl)glycine CCGs **41**–**44** have been synthesized [39]. They restrict the conformation of glutamate to an extended A or folded form B, Eq. (14).



(14)

L-CCG-I (2*S*,1'*S*,2'*S*)-**41** (mGluRs agonist)
L-CCG-II (2*S*,1'*R*,2'*R*)-**42** (uptake inhibitor)
L-CCG-III (2*S*,1'*S*,2'*R*)-**43** (uptake inhibitor)
L-CCG-IV (2*S*,1'*R*,2'*S*)-**44** (NMDA agonist)

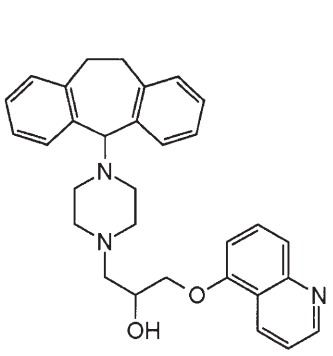
Among the four diastereomers of CCG **41**–**44**, one of the extented types CCG **41** was identified as a selective and powerful agonist of mGluRs. On the other hand, CCG **44**, one of the folded types, exhibited potent affinity to NMDA receptors. These results strongly suggested that the conformational requirement of mGluRs was an extended conformation of glutamate, while that of NMDA receptors was a folded conformation. The other isomers, CCG **42** and **43**, were not potent agonists but were inhibitors of glutamate transport systems at the excitatory synapses. Thus, CCGs are not only applied as a useful pharmacological tool in the neuroscience field but also provide proof that a specific conformation of glutamate is one of the most important factors for activation of distinct types of receptors [40].

L-2-[2-Carboxy-3-(methoxymethyl)cyclopropyl]glycines (MCGs) and other related amino acids have been newly synthetized also in a stereoselective manner [41]. Some of them were found not only to be selective and powerful agonists for the receptors but also to provide useful information with regard to the conformational requirements of glutamate receptors. These amino acids are useful as leading compounds for further conformational studies of glutamate receptors as well as for developing effective drugs for various brain diseases [41].

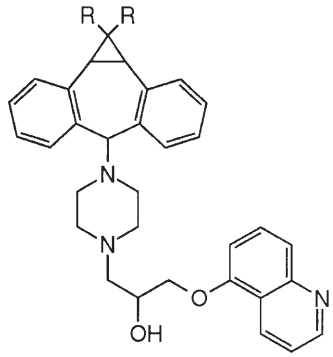
2.9 Conformational Flexibility

Recent efforts have focused on minimizing unwanted biological activities in existing series, while attempting to boost multiple drug resistance (MDR) reversal potency [42]. Due to the lack of understanding of the interaction of MDR reversal agents rational drug design stratagems have so far not led to more potent compounds [43]. MS-073 **45** is a prototypical agent with noteworthy MDR reversal properties containing a dibenzosuberylpiperazine group attached to the 5-position of quinoline *via* a 2-hydroxypropyloxy spacer. The relatively low oral bioavailability reported for this compound is presumably a consequence of its acid lability ($t_{1/2}$ = 15 min at pH 2.0 and 37 °C).

Extensive structural modifications of MS-073 **45** invariably resulted in a loss of potency, usually at least by a factor of ten. However, annelation of a cyclopropyl group to the dibenzosuberane improved or maintained activity ($t_{1/2}$ = 3 h at pH 2.0 and 37 °C). In addition, difluoro or dichloro substitution of the cyclopropane (R=F, Cl) in **46** conferred excellent acid stability to these compounds ($t_{1/2} \geqslant$ 72 h at pH 2.0 and 37 °C), Eq. (15) [44].



MS 073 **45**



46 (R = F, Cl)

(15)

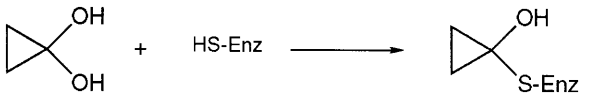
The dibenzosuberyl group has in fact been used as an amine protecting group which can be removed under mildly acidic conditions [45]. The *syn* and *anti* diastereomers of methanodibenzosuberylpiperazine **46** have been synthesized and tested on the proliferation and viability of multidrug resistant CH^RCs chinese hamster cells [44]. The superior potency of the *anti* derivatives of **46** with an axial piperazine over their *syn* counterparts with an equatorial piperizine, has

been interpreted as the result of more efficient π-stacking of the rigid *anti* methanodibenzosuberyl group with overlapping phenylalanine side chains extending outwards form the α-helical backbone of glycoprotein p 170 (P-gp), an energy dependent pump. Such phenylalanine repeat motifs are present in several transmembrane regions of human and murine P-gp [46].

3 Enzyme Inhibitory Activities

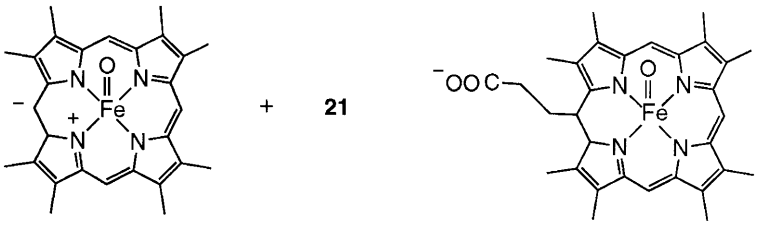
In the preceding paragraph, the mechanisms by which cyclopropyl moieties can induce inactivation of specific target enzymes have been described explicitly. The inactivation is not only related to the inherent chemical reactivity of the three-membered ring resulting from its intrinsic ring strain (enzymatic cleavage, oxidation, etc.) but also from heteroatomic (oxygen, nitrogen, etc.) or electron-withdrawing substituents (aldehydes, ketones, esters, hydroxymethyl esters, etc.) which through the formation of *cyclopropyloxy radical*, *cyclopropylamine radical cation*, *cyclopyliminium cation*, or *cyclopropylcarbinyl radical* or *cation* provide suicide substrates for specific enzymes. On the other hand, cyclopropanone equivalents such as the hemiaminal **17** generated in situ by catalytic unraveling of some latent precursors [17], inactivate enzymes such as aldehyde dehydrogenase for instance, by trapping an essential cysteinyl thiolate side chain in its active site [21].

Thus the cyclopropanone hydrate **21** is an inhibitor of yeast aldehyde dehydrogenase (ALDH) through the nucleophilic substitution of a hydroxyl group by an enzymic thiol **47** leading to the cyclopropanone hemithioacetal **24a**, Eq. (16) [21].



21 **47** **24a** (16)

Horse radish peroxidase on the other hand, is a hemoprotein which is inhibited by alkylation of the porphyrin ring **48** by a β-propionic acid radical resulting from the ring cleavage of the cyclopropanone hydrate **21**, providing the carboxylate **49**, Eq. (17).



48 **49** (17)

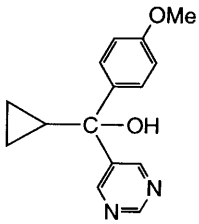
Cytoplasmic and mitochondrial aldehyde dehydrogenases (from beef liver) have also been inactivated by the hydrate **21** [21].

The enzyme chemistry of cyclopropylmethanols has been studied both as inhibitors and mechanistic probes [4, 47]. Thus, a series of alkylcyclopropylmethanol derivatives have been proved as being inhibitors of horse liver alcohol dehydrogenase. There are two sites in the cyclopropylmethanol inhibitors able of reacting with nucleophiles:

- the methylene carbon bearing the hydroxyl group
- the carbons of the cyclopropane ring

However, mechanistic experiments have involved the apices of the cyclopropane ring as targets for the nucleophilic group of the enzyme. Only the *pro*-R hydrogen was usually removed by the enzyme and transferred to NAD^+, and the stereochemical course of the nucleophilic ring opening of the cyclopropanes was consistent with predictions on the basis of frontier orbital theory prediction [48].

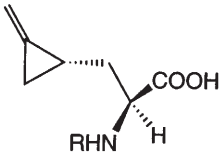
The cyclopropylmethanol ancymidol **50**, applied as soil drench or as a foliar spray, shortened the internodes of ornamental plants. Trials with cultivation of *Chrysanthenum morifolium*, *Euphorbia pulcherrina* and *Tulipa gesneriana* have been described, Eq. (18) [49].



(18)

Ancymidol **50**

(2*S* 4*S*)-3-(2-Methylenecyclopropyl)alanines, so-called hypoglycine A **51** (R = H) and B **52** (R = γ-glutamyl) are the toxic principle of the *isin* (Nigeria) and *ackee* (Jamaica) fruit, *Blighia sapida*, Eq. (19) [50, 51].



(19)

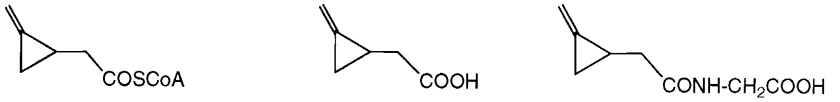
Hypoglycine A (2*S*,4*S*)-**51** R = H

Hypoglycine B (2*S*,4*S*)-**52** $CO(CH_2)_2CH(NH_2)$-COOH

Eating unripe ackee fruits or seeds causes hypoglycaemia and an organic-acidaemia and may have caused 5000 deaths in Jamaica [51–53]. Effectively, administration of hypoglycine A **51** (20–200 mg per kg body-weight) to animals causes the onset of severe hypoglycaemia after a few hours [54]. Gluconeogene-

sis is strongly inhibited so that animals run out of glucose when their glycogen reserves are exhausted [55].

The metabolism of **51** generates methylenecyclopropylacetyl-Co A (MCPA-CoA) **53** in the mitochondrial matrix through oxidative deamination by branched-chain oxo acid decarboxylase [56]. This impairs the oxidation of fatty acids of all chain lengths by inactivating the general acyl-CoA and butyryl-CoA dehydrogenases [56] and forming adducts with their FAD prosthetic group, Eq. (20) [57].

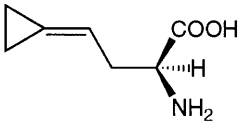


(20)

MCPA-CoA **53** MCPA **54** MCPA-glycine **55**

The rate of oxidation is slowed down and allowed to proceed only as far as butyryl-CoA. There is a marked organicacidaemia in rats and people poisoned with hypoglycine with high plasma concentrations of isovalerate and 2-methylbutyrate, together with lower concentrations of butyrate [54b, 58]. Isovaleryl-CoA and 2-methylbutyryl-CoA are metabolites of leucine and isoleucine, respectively, and isovaleryl-CoA and 2-methylbutyryl-CoA dehydrogenases are also inhibited by (MCPA-CoA) **53**. This is then hydrolyzed to give the (2-methylenecyclopropyl) acetic acid **54**, or conjugated with glycine to form MCPA-glycine **55** catalyzed by glycine *N*-acylase, with CoASH release. A massive excretion of dicarboxylic acids: *cis*-dec-4-ene-1,10-dioic, *cis*,*cis*-dec-4,7-diene-1,10-dioic, *cis*-oct-4-ene-1,8-dioic, glutamic and adipic acids, M-CPA-glycine **55**, *N*-isovalerylglycine has been found in urine from rats treated with hypoglycine A **51** [59]. Concerning the inactivation of acyl-CoA dehydrogenase from pig kidney by a metabolite of hypoglycin A see, Ref. 57 and for the antagonism of hypoglycin toxicity by glycine, see Ref. 60.

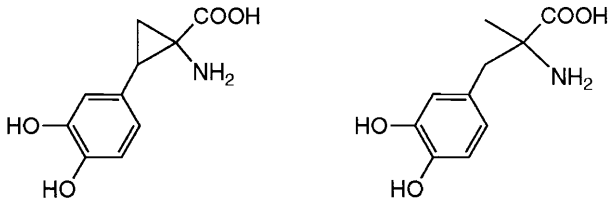
2-Amino-4-cyclopropylidenebutanoic acid (2*S*)-**56**, is a methylenecyclopropane substituted alanine which can be considered as a non-natural isomer of hypoglycine A **51**. It has recently been synthesized racemic [61] and enantiomerically pure [62]. Biological assays have shown that at relatively high concentration the 5,6-methanoamino acid **56** inhibits the metabolism of pyruvate into glucose, but **56** is not active in inducing the mitochondrial oxidation of fatty acids, Eq. (21) [63].



(21)

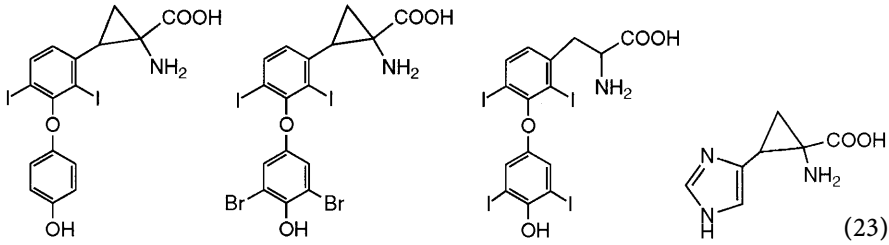
(2*S*)-**56**

A number of 2,3-methanophenylalanine derivatives are efficient inhibitors of DOPA carboxylase [64]. For instance, 2-(3,4-dihydroxyphenyl) ACC **57**, due to its structural analogy with α-methyl DOPA **58**, is a reversible time-dependent inhibitor of DOPA carboxylase and of tyrosine amino transferase, Eq. (22) [65].



57 α-Methyl DOPA **58** (22)

(*Z*)-2,3-Methanothyronine **59** and its dibromo derivative **60** have comparable activity with the thyroxine **61**, a thyroid hormone [66], which exhibited thyromimetic activities in basal metabolism and antigoiter tests (comparison of oxygen consumption and heart rate in normal and thyroidectomized rats) but did not have an inhibitory action on the metabolism developed by triiodothyronine [66]. (*Z*)-2,3-Methanohistidine **62**, tested on rat liver, is an effective inhibitor of histidine decarboxylase, Eq. (23) [67].

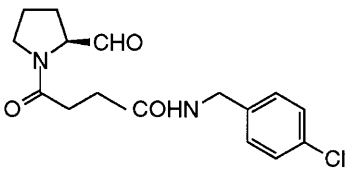


59 **60** Thyroxine **61** **62** (23)

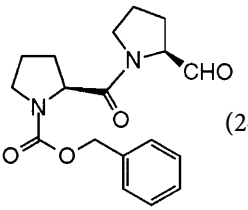
Prolyl endopeptidase (PEP, EC 3.4.21.26) is the only serine protease which is known to cleave a peptide substrate in the C terminal side of a proline residue [68]. This enzyme was first isolated from the human uterus, then purified from lamb kidney, and subsequently named post proline cleaving enzyme (PPCE) [69]. It is widely distributed in various mammalian tissues such as the brain, liver, and kidney [70]. In the central nervous system, PEP degrades proline-containing neuropeptides involved in the processes of learning and memory such as vasopressin, substance P (SP), and thyrotropin-releasing hormone (TRH) [71]. Moreover, cognitive deficits in Alzheimer's disease patients is reported to show improvement with TRH, and one can postulate that PEP inhibitors could prevent memory loss and increase attention span in patients suffering from senilic dementia.

Among numerous low molecular weight inhibitors of PEP described, two prolinal derivatives have been reported as PEP inhibitors: ONO 1603 **63** [72] and *Z* Pro-prolinal **64** [73], in which the formyl group is able to react with the active site of the enzyme, Eq. (24) [74].

Also a new family of inhibitors exemplified by SUAM 1221 **65** [75] has been described in which a pyrrolidinylcarbonyl function at the P1 site is the crucial entity for enzyme recognition, giving rise to the transition state analog of the enzyme-substrate interaction.

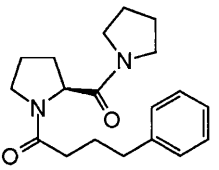


ONO 1603 **63**

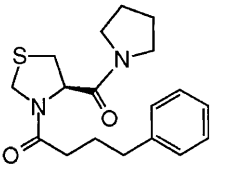


(24)

Z Pro-prolinal **64**



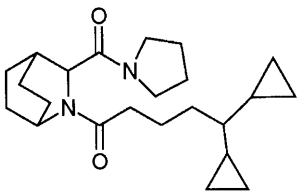
SUAM 1221 **65**



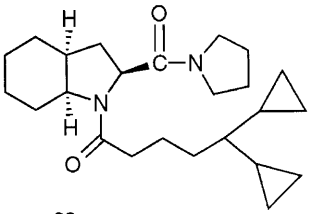
(25)

66

Important improvement in the in vitro activity was obtained when the central proline was replaced by thiaproline (thiaPRO) to give compound **66**, suggesting that modification of the central amino acid (of the proline type) could be of importance in modulating the PEP inhibitory activity, Eq. (25) [76]. In fact, replacement of the proline moiety of **63 – 66** by non-natural amino acids derived from 2-perhydroindole or from 2-azabicyclo[2.2.2]octane and modulation of the side chain by replacement of the terminal phenyl ring by a dicyclopropylcarbinyl moiety afforded derivatives such as **67** and **68** with improved activities (IC_{50} between 10 and 20 nM), Eq. (26).



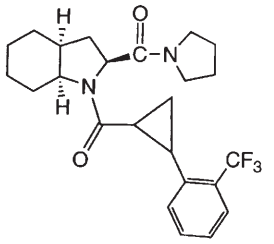
67



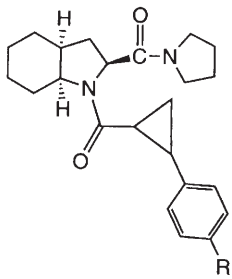
(26)

68

Furthermore, replacing the linear 4-phenylbutanoyl side chain by the (2-phenylcyclopropyl)carbonyl entity as in compound **69**, provided potent inhibitors with IC_{50} culminating at 0.9 nM on a rat cortex enzymatic preparation [77]. Moreover, the configuration on the cyclopropane ring is of prime importance in order to obtain a strong enzymatic inhibitor capacity; it has to be *R*,*R* in order to obtain not only a strong PEP inhibitor in vitro but also a good activity in vivo, as exemplified by inhibitor **70a**, which gives IC_{50} ip and po of 0.3 and 1 mg per kg, respectively. Most important, this original side chain seems to confer a potent and long lasting in vivo PEP inhibitory activity to the central amino acid it is appended to, as exemplified by compounds **69**, **70a**, **b**, Eq. (27) [77].



69



70a R=F
b Me

(27)

Some of these compounds are currently undergoing pharmacological studies on models of attention, learning and memory, as well as extensive preclinical evaluation [77].

4
Phytohormones, Phytotoxicity, Plant Growth Regulatory Activities

1-Amino-1-cyclopropanecarboxylic acid ACC **71** and its derivatives are currently attracting special attention because of their outstanding biological activity and potential use in conformationally restricted peptides, providing biosynthetic and mechanistic probes [64]. In fact, they constitute a unique form of constrained amino acids, naturally occurring either unbound or simply linked in dipeptides [53]. However the structure of BZR-cotoxin, the major component of BZR-toxin, which causes leaf spot disease in corn and induced high pathogenicity in rice plants, has been recently determined to be a cyclic nondepsipeptide involving the ACC moiety, Eq. (28) [78].

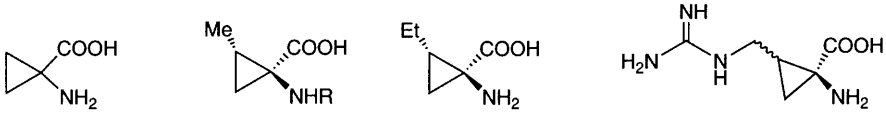
Present in the tissue of many plants [79], ACC **71** is biosynthesized from (*S*)-adenosylmethionine under the catalytic influence of a pyridoxal 5′-phosphate linked enzyme (ACC synthase) [80]. It is the immediate biosynthetic precursor of ethylene, the phytohormone that initiates and regulates many aspects of plant growth, including germination, inhibition, senescence, ripening of fruits, and is engaged in the metabolism of plants [81]. Rigorous demonstrations of this biosynthetic pathway have been established by ACC formation upon incubation of (*S*)-adenosylmethionine with the crude synthase obtained from ripe tomatoes [82] and by ethylene production on addition of ACC to soybean leaves [83] or to apple slices [84]. Another biological transformation of ACC is its cleavage into α-ketobutyrate and ammonia carried out by certain bacteria [85]; thus, ACC deaminase has been isolated from *Pseudomonas* growing on ACC as their sole nitrogen source [86]. Due to its physiological importance ACC **71** and its derivatives have motivated the initiation of several research programmes aimed at the synthesis of these challenging three-membered ring amino acids [87].

(1*S*,2*S*)-2-Methyl-1-aminocyclopropanecarboxylic acid (*norcoronamic acid*) **72a** was isolated from norcoronatine, a component of the phytotoxic fraction of *Pseudomonas syringae* pv *glycinea* [88]. Its *N*-methyl derivative (1*S*,2*S*)-**72b**, isolated from streptomyces *braegensis* subsp. *japonicus*, has been found to be a

constituent of the cyclic peptide portion of the recently discovered DNA-intercalating antibiotics of the quinomycin family, Eq. (28) [89].

(1*S*,2*S*)-2-Ethyl-1-aminocyclopropanecarboxylic acid (*coronamic acid*) **73** was obtained from the hydrolysis of coronatine, a phytotoxin isolated from liquid cultures of plant pathogens *Pseudomonas syringae* pv *atropurpurea*, *Pseudomonas syringae* pv *glycinea*, and *Pseudomonas caronafacience* var. *atropurpurea* [90]. Infection of host plants by these bacteria induces chlorosis on the leaves due to the production of coronatine [90]; this plant toxin also induces hypertrophy of potato cells and inhibition of corn root growth [91]. Plant defense against herbivores involves the release of volatile substances which act as SOS signals, attracting predators that prey on herbivores. It has been shown that coronatine is superior to jasmonic acid in inducing the biosynthesis and emission of volatiles [92]. The biosynthesis of **73** has been demonstrated to occur from isoleucine [93]. Its (1*S*,2*R*) non-natural diastereomer, known as *allo-coronamic acid* is converted into 1-butene by plant tissues; it promises the control of enzymatic processes for plant growth and fruit ripening Eq. (28) [94].

The two other naturally occurring ACC derivatives, (1*S*,2*S*)- and (1*R*,2*S*)-2-(guanidinomethyl)ACC (*carnosadine*) **74**, were isolated from a red alga, *grateloupia carnosa*, Eq. (28) [95].



ACC **71** (1*S*,2*S*)-**72a** R = H **b** Me (1*S*,2*S*)-**73** (1*S*,2*S*)- and (1*R*,2*S*)-**74** (28)

Due to their physiological importance, considerable efforts are currently devoted towards the total synthesis of 2,3-methanoamino acids (ACCs). The parent compound ACC **71** has been readily prepared from acrolein, through the base-induced (K_2CO_3) cyclization of 2-amino-4-chlorobutyronitrile [96] or from one-pot Strecker reaction of cyclopropanone hemiacetal [97].

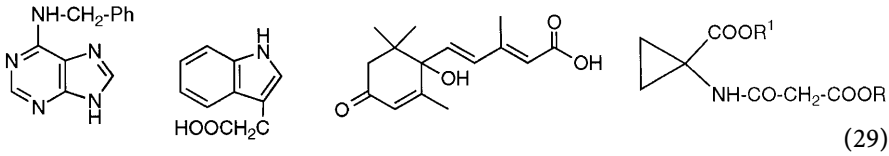
The total asymmetric syntheses of natural (1*S*,2*S*)-norcoronamic **72a** and of (1*S*,2*S*)-coronamic acid **73** have been obtained from the diastereoselective cyclization of chiral non-racemic 2-(*N*-benzylideneamino)-4-chlorobutyronitriles [98]; but one of the shortest syntheses of these attractive amino acids was based on the diastereoselective palladium(0)-catalyzed alkylation and $S_{N'}$ cyclization of 1,4-dichlorobut-2-ene by the anion of 2-aminoacetonitrile derivatives [99]. On the other hand, diastereoselective palladium(0)-catalyzed azidation of chiral non-racemic 1-alkenylcyclopropyl esters provide non-natural (1*R*,2*S*)-norcoronamic acid, enantiomerically pure [100].

The asymmetric syntheses of carnosadine (1*S*,2*S*)-**74** [101] and of its protected derivatives as conformationally constrained surrogates for arginine have also been reported [102]. Different 2-substituted 1-aminocyclopropanecarboxylic acids have also been prepared by azidation of optically active 2-chloro-2-cyclopropylideneacetates [103] and from the cyclopropanation of chiral bicyclic lactams [104].

Selectively deuterated 1-aminocyclopropanecarboxylic acid ACC **71** was prepared to investigate the biosynthesis of ethylene in plants [105a] and of ammonia and 2-ketobutyrate in *Pseudomonas* [105b].

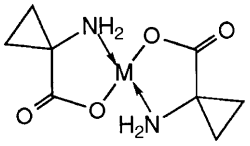
When subjected to drought stress, excised wheat (*Triticum aestivum L.*) leaves increase ethylene production as a result of an increased synthesis of ACC **71** and an increased activity of the ethylene-forming enzyme (EFE) which catalyzes the conversion of ACC **71** to ethylene. Rehydratation to relieve water stress reduces EFE activity to levels similar to those in non-stressed tissue. Pretreatment of the leaves with *N*-benzyladenine (BA) **75** or indole-3-acetic acid IAA **76** prior to drought stress caused further increase in ethylene production. Conversely, pretreatment of wheat leaves with abscisic acid ABA **77** reduced ethylene production to levels of non-stressed leaves, accompanied by a decrease in ACC **71** content, Eq. (29).

ACC **71** was also found to be converted into a non-volatile product, i.e., into 1-(malonylamino)cyclopropanecarboxylic acid **78** (R, R^1 = H) in both nonstressed and water-stressed tissues [106]. The formation of this major metabolite of ACC **71** has also been identified in etiolated buckwheat leaves fed with exogenous ACC or in etiolated soybean (*Glycine soja*) seedlings treated with IAA **76** [107]. Derivatives of **78** (R, R^1 = H, NH_4, alkali or alkali earth metals, Mn) were prepared as plant growth regulators. Thus amino diacid **78** (R, R^1 = H) was a more effective soybean growth regulator than 1-formamidocyclopropanecarboxylic acid [108]. Analogously, treating etiolated cotton seedlings with IAA **76** increased ACC synthase activity, ACC **71** content and the rate of ethylene formation [109]. A direct relationship between the content of IAA **76** in the hypocotyl tissue and the rates of ACC **71** and ethylene formation was observed, Eq. (29) [109].



BA **75** IAA **76** ABA **77** **78** (29)

1-Aminocyclopropanecarboxylic acid-metal complexes **79** (M = transition metal with tetracoordination) also provide useful plant growth regulators, Eq. (30) [110].

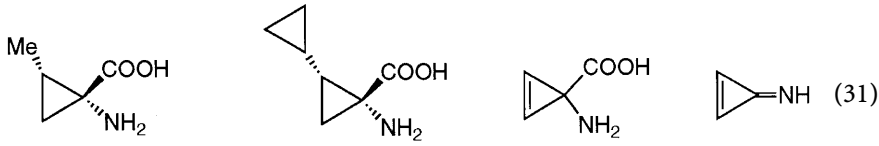


(30)

79

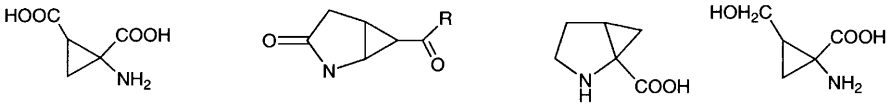
Non-natural ACC derivatives have been synthesized in order to test their eventual biological activity. Thus, in alkyl-ACC derivatives the alkyl and carboxyl groups must be in *trans* positions to be metabolized by plant tissue [111a]. For instance, the *trans*-methyl-ACC **80** serves as a good inhibitor of ethylene

production and is a substrate for propylene production in mungbean hypocotyl segments [111a]. 1-Amino-2-cyclopropylcyclopropanecarboxylic acid **81**, is also a good inhibitor of ethylene biosynthesis probably due to the bulky cyclopropyl group which makes it difficult for **81** to penetrate into the bioactive center; incubation of mungbean hypocotyl segments with various concentrations of **81** provided instead, 1,4-pentadiene by a mechanism involving a 1,2-hydrogen migration in a diradical intermediate, and this is responsible for the suicide inactivation [111b–d]. 1-Aminocyclopropenecarboxylic acid **82** has been shown to be an inhibitor of the ethylene-forming enzyme, an extremely poor substrate for acetylene production and an inhibitor of senescence (carnation antisenescence assay of flowers). The inactivation was postulated to result from the ready formation of the stabilized cyclopropenone imine **83** (aromatic stabilization) which can then undergo nucleophilic attack by an enzymic residue, (vide supra, Sect. 2.5) Eq. (31) [112].



80 **81** **82** **83** (31)

Racemic (*Z*)-2,3-methanoglutamic acid **84** and racemic 2,3-methanopyroglutamic acid derivatives **85a–d** have been prepared by cyclopropanation of a (*Z*)-dehydroglutamic acid derivative [95b,113]. The *β*-naphthylamide **85d** was shown to be stable to enzymatic hydrolysis by pyroglutamate aminopeptidase in vitro [113b]. Racemic 2,3-methanoproline **86** was found to be a weak inhibitor of ethylene-forming enzyme in cucumber cotyledons strips and germinating squash seeds [114]; however 2,3-methanohomoserine **87**, which has a strong ability to inhibit ethylene production from ACC in mungbean hypocotyl segments, will provide a useful tool to deliver reagents to ACC-binding proteins and to remove them from protein mixtures (affinity purification techniques) or elicit an immune response (generation of antibiotics), Eq. (32) [115].



84 **85a** R = OMe; **b** OH; **d** NH-β-Naphth; **c** NHMe **86** **87** (32)

ACC **71** synthase, i.e. (*S*)-adenosylmethionine methylthioadenosine lyase (EC 4.4.1.14), has been purified from several plant tissues [116]. Recently, ACC synthase cDNA clones have been isolated and sequenced from wounded fruit tissues of tomato, winter squash, zucchini, ripening apple and tomato fruit. Using the polymerase chain reaction (PCR), four different ACC synthase gene fragments were obtained by amplification of cDNA derived from mRNA of tomato

fruit and tomato cell culture and used to examine the expression of different ACC synthase transcripts of enhanced ethylene production. It has been proven that tomato ACC synthase is encoded by a multigene family and that the expression of each gene is differentially activated by different developmental, environmental and hormonal factors [117].

Auxin-induced ACC **71** synthase (*acc A*) was purified from slices of immature cucumber fruits and partial amino acid sequences were determined. By using oligonucleotides a cDNA for auxin-induced ACC **71** synthase from winter squash (*Cucurbita maxima* Duch. cv Ebisu) was cloned and its sequence determined. This sequence was markedly different from that for the wound-induced enzyme (*acc W*) from the same plant. The results showed that the gene for *acc A* is different from that for *acc W*; therefore ACC **71** synthase is encoded in two different genes differentially expressed by auxin and wounding. The biological significance of the presence of two different genes for the enzyme has been discussed [118].

Three divergent members (OS-ACS_1, OS-ACS_2 and OS-ACS_3) of a multigene family encoding ACC **71** synthase in rice, which grows in the deepwater regions of South-East Asia, have been cloned. It has been shown that OS-ACS_1 is induced in the shoots whereas OS-ACS_3 is induced in the roots. The protein contains all eleven invariant amino acid residues that are conserved between aminotransferases and ACC synthases cloned from various dicotyledonons plants. The amino acid sequence shares significant identity to other ACC synthases. The extraordinary degree of divergence among ACC synthase isoenzymes within each species arose early in plant evolution and before the divergence of monocotyledonons and dicotyledonons plants [119].

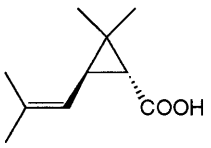
Polymeric forms of ACC **71** were synthesized and their biological activities evaluated. Synergistic interactions between ACC polymers and the cytokinin 6-*N*-benzylaminopurine have been indicated [120].

Germination of witchweed (*S. asiatica*), an important parasitic weed on several poaceous crops, is stimulated by several synthetic compounds. The role of ethylene biosynthesis and action in cytokinin-induced germination was investigated. Whereas conditioned striga seeds treated with ACC **71** produced little ethylene, on the other hand treatments with cytokinin-ACC combinations enhanced ethylene production. Seeds treated with cytokinin-ACC combinations have displayed higher rates of germination. Addition of ACC **71** overcame the effect of aminoethoxyvinylglycine (AVG), which is a potent ACC-synthase inhibitor. A model in which striga germination and embryo growth are limited by low capacity of the seeds to oxidize ACC **71** were consistent with the results. The cytokinin promotes ACC **71** conversion into ethylene and consequent striga germination by enhancing ACC oxidase activity and/or synthesis [121].

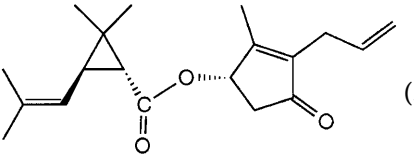
5
Insecticidal, Antifungal and Herbicidal Activities

The *trans*-chrysanthemic acid **88** is an essential component of naturally occurring pyrethrin esters which are present in the flower of *Chrysanthenum cinerariaefolium* and has a defense function in these plants [122]. Very effective as an antifeedant for herbivores, it presents a broad spectrum as an insect repellent.

Synthetic derivatives such as the (*S*)-bioallethrin **89** or bioresmethrin **90** are known for their high insecticidal activity with low mammalian toxicity, Eq. (33, 34) [123].



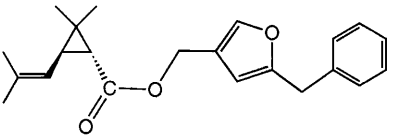
trans-Chrysanthemic acid **88**



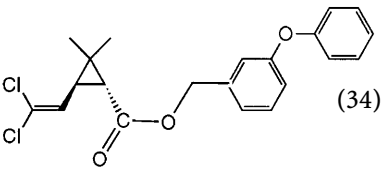
(*S*)-Bioallethrin **89**

(33)

Various structural modifications particularly involving the chrysanthemic acid moiety led to compounds with enhanced stability and insecticidal activity for a wide range of insect pests. It has been reported that plant growth was also stimulated by the photostable insecticidal biopermethrin **91**, Eq. (34) [123c].



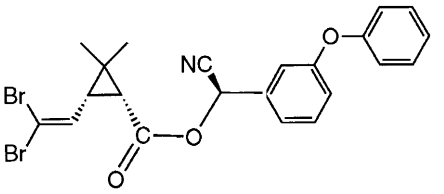
Bioresmethrin **90**



Biopermethrin **91**

(34)

The highest insecticidal activity was reached with the deltamethrin **92**, by introduction of a benzylic cyano group and of a dibromovinyl substituent with the *cis* configuration, Eq. (35) [123c].

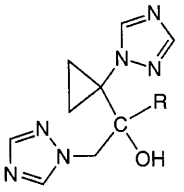


Deltamethrin **92**

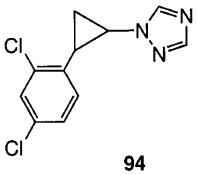
(35)

The mechanism of insecticidal action has been attributed to blocking of the sodium channel in target cell membranes and consequent blocking of ion transport [124]. Following these observations a considerable effort was developed for the preparation of synthetic pyrethroids as commercial insecticides.

Triazolylcyclopropane derivatives are endowed with antimycotic properties [125]. They are also prepared as plant growth regulators and fungicides; for instance **93** (R = unsubstituted and substituted aryl, heteroaryl) markedly inhibited the growth of rice, cotton and soybeans in hot tests [126]. 1-(1,2,4-Triazolyl)-2-(2,4-dichlorophenyl)cyclopropane **94**, is a more effective fungicide against *Podosphaera leucotricha* and a better growth retardant in rice and soybeans than the (1,2,4-triazolyl)pentenone **95**, Eq. (36) [127].



93



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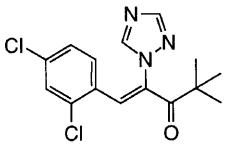
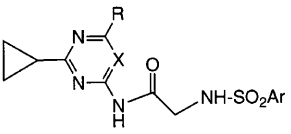


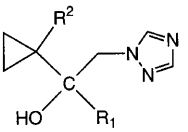
95 (36)

The *N*-(3-cyclopropyl-2,4-pyrimidyl)- **96a** and *N*-(3-cyclopropyl-2,4,6-triazinyl)-*N*-aryl sulfonyl ureas **96b** (R = halo-, amino-, alkoxyalkyl and cycloalkyl: X = CH, N) are useful as plant growth regulators and herbicides. At 500 g per ha the cyclopropyltriazine derivative **96b** (R = OMe, Ar = 2-carbomethoxyphenyl) killed *Abutilon* species and *Sivapis alba* or prevented germination without affecting wheat, Eq. (37) [128].

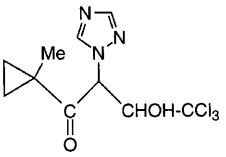
Unsubstituted and substituted aryl- and heteroarylcyclopropyl (methyl-1,2,4-triazolyl)-carbinols have been prepared and used as fungicides and plant growth regulators. Thus the cyclopropylcarbinol **97** ($R^1 = p\text{-}ClC_6H_4$, R^2 = SEt) inhibited the growth of rice, cotton and soybean, and protected apple against *Venturia* infection [129]. The 3-(1,2,4-triazolyl)-3-(1-methylcyclopropylketone)-1-trichloromethylethanol **98** was as effective against *Venturia inaequalis* on apples, Eq. (37) [130].



96a X = CH
b N

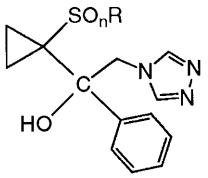


97

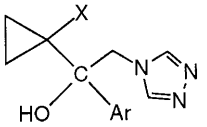


98 (37)

The acid salts and metal complexes of **99** (e.g. R = CCl_3, CCl_2F, $CClF_2$, C_{1-4} perfluoroalkyl) and of **100** (e.g. X = F, Cl, Br, CN, SCN, alkylcarbonyloxy, alkyl carbonylthio, amines) were used as agrochemical fungicides and plant growth regulators, Eq. (38) [131].



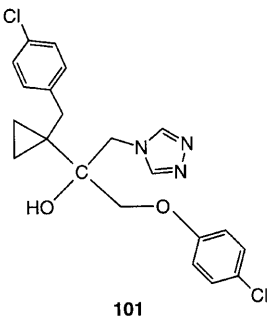
99 (n = 0–2)



100 (38)

Several derivatives of **101** were effective against *Pyrenophorateres, Vertusia indequolis* and *Pyricularia oryzae*; while derivatives of **102** (X = CH_2CH_2, CH = CH, OCH_2, SCH_2) were superior to known similar compounds as plant growth

regulators in soybeans, rye, wheat and cotton, and as fungicides against *Pyricularia oryzae*, *Leptosphaeria rodorum* and *Sphaerotheca fuliginece*. In a post-emergence test, the 1-(2,4-dichlorophenyl)-2-(triazolylethyl)cyclopropane **103** (0.05 wt. %) showed 95% control of *Botrysis cinerea* on paprika, compared to 40% control by a similar triazolylcyclopropane; **103** was also an effective plant growth regulator for barley, Eq. (39) [131].



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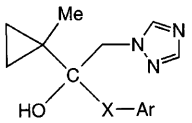

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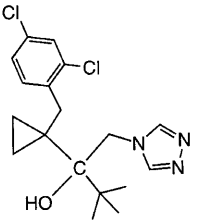
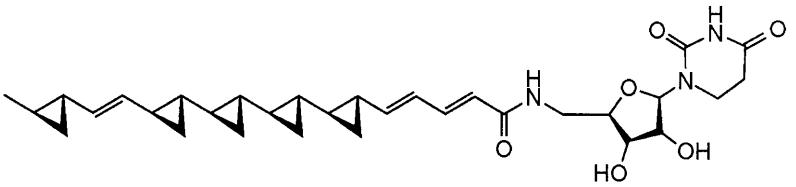


103

(39)

FR 900848 **104** is a natural product isolated from the fermentation broth of *Streptoverticillium fervens*. It shows potent, in vitro selective activity against filamentous fungi such as *Aspergilus niger* and *Mucor rouxianus* with MIC values of 0.05 mg/ml, but is essentially inactive against non-filamentous fungi such as *Candida albicans*, yeasts and gram-positive and gram-negative bacteria [132]. Structurally the molecule is remarkable since it is endowed with five cyclopropanes, four of which are contiguous Eq. (40).



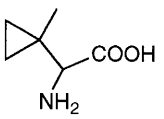
(40)

FR 900848 **104**

The full structure and absolute configuration of FR 900848 **104** has been determined to be (6*R*,8*S*,9*R*,11*S*,12*S*,14*R*,15*S*,17*R*) from X-ray crystallographic study [133]. Strategies for its enantioselective total synthesis are based on an iterative cyclopropanation [134], and on the use of chiral auxiliaries [135]. It has also been prepared by fermentation and isolated from cultures of *Streptoverticillium fervens* to be considered as an agrochemical microbicide [136].

6
Antibiotic, Antimicrobial and Antitumoral Activities

L-2-(1-Methylcyclopropyl)glycine **105** was isolated from the culture broth of *M. miyakanonensis*, and this 3,4-methanoamino acid exhibits an antimicrobial activity against *E. coli* on a synthetic medium, Eq. (41) [137].



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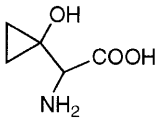
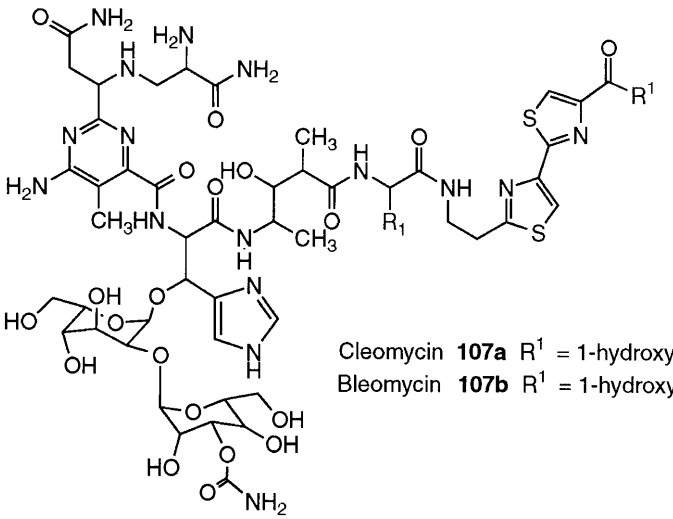


106

(41)

3,4-Methanoserine or cleonine **106** has been isolated from cleomycin **107a**, an antibiotic from the bleomycin-phleomycin group, which is different from bleomycin **107b** only in its threonine moiety [38]. This amino-(1-hydroxycyclopropyl)acetic acid is located in the place of the threonine, Eq. (42).



(42)

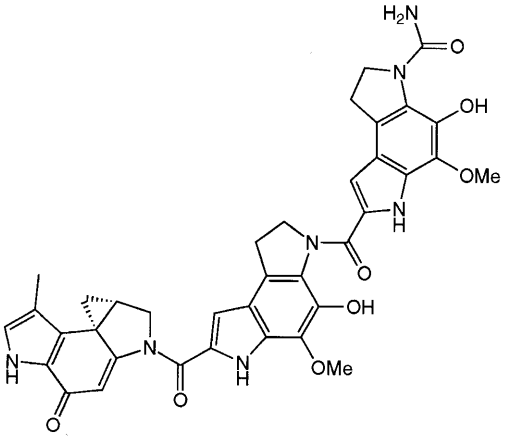
The configuration of cleonine **106** appears to be *S* from a biosynthetic viewpoint [139]; its synthesis from the readily available cyclopropanone cyanohydrine has been reported [140, 141].

CC 1065 **108** is a highly toxic antibiotic isolated from *Streptomyces zelensis* containing a reactive spirocyclopropane ring. It cleaves DNA through a mechanism similar to the cleavage which occurs upon treatment of DNA with the carcinogenic ptaquiloside **25** (vide supra, Sect. 2.6), namely by depurination of alkyladenine adducts, Eq. (43) [142].

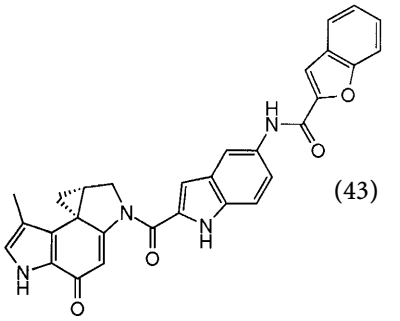
However, significant differences have been observed:

a) The dienone **26**, arising from alkaline hydrolysis of **25**, forms adducts at both guanine and adenine residues
b) The dienone **26** induces the spontaneous cleavage at adenine base sites under physiological conditions, whereas CC 1065 **108** causes cleavage at higher temperature (> 70 °C) [143]. The covalent adenine-adduct of CC 1065 **108** has been reported to undergo at 37 °C a retrohomologous Michael reaction to regenerate the initial cyclopropylpyrroloindole structure and likely intact DNA; in contrast, the *N*-3 adenine adduct of dienone **26** depurinate spontaneously at 37 °C [144]. For these reasons ptaquiloside **25** is a typical carcinogen, whereas CC 1065 **108** is an antitumor agent [27].

Adozelesin **109**, a synthetic analogue of CC 1065 **108**, is also a potent antitumoral agent, Eq. (44) [145]. Both the natural and synthetic compounds containing a cyclopropyl pyrroloindole (CPI) unit were also shown to alkylate the *N*-3 atom of adenine in a certain sequence of DNA, a reaction which mediates the potent biological effects of these drugs [146]. They differ from traditional chemotherapeutic alkylating agents, such as the nitrogen mustards and nitrosoureas [147] by their selectivity for target nucleophilic sites in DNA and their lack of reactivity with other biological nucleophiles [146].



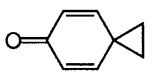
CC 1065 **108**



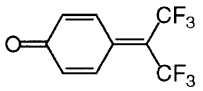
Adozelesin **109**

(43)

Comparison with the reported reactivity of the spiro[2.5]octa-1,4-dien-3-one **110** and 4-(hexafluoroisopropylidene)cyclohexa-2,4-dien-1-one **111** have suggested that the conjugated cyclopropane ring of compounds **108** and **109** imparts a strong acid dependence to its reactivity with nucleophiles, Eq. (45). This property is likely to be relevant for the exceptional reactivity of these antibiotics toward DNA [148].



110



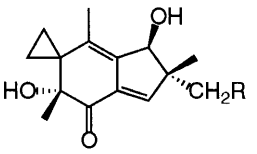
111

(44)

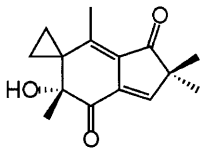
Illudins M **112** and S **113** are sesquiterpenes produced by *Omphalotus illudens*, the jack-o′-lantern mushroom [149]. These compounds demonstrated in vitro selective toxicity for a wide range of tumor cells compared to normal cells, but poor therapeutic indices were found when tested in vivo [150]. The spirocyclopropane and α,β-unsaturated ketone moities present in the illudin skeleton constitute a bis-electrophile that is responsible for the DNA damage (vide supra Sect. 2.6) [150, 151]. Illudin derivatives with greatly improved therapeutic indices have been prepared; first of all dehydroilludin M **114** has shown better

activity against metastatic MV 522 lung carcinoma xenografts than nine known anticancer agents including cisplatin, cytoxan and paclitaxel and comparable efficacy to that of mitomycin C [152]. Then the analogue acylfulvene **115** exceeded the efficacy of dehydroilludin M **114** and that of mitomycin C [150]. The third generation hydroxymethylacylfulvene (HMAF) **116**, caused complete tumour regression in all animals at the maximum tolerated dose of 10 mg kg^{-1} and has been found to exhibit outstanding activity against breast, colon and skin cancer cell lines derived from human tumours [153]. HMAF **116** can be prepared readily from illudin S **113** or from acylfulvene **115**; its total synthesis has been performed from 4-hydroxy-5-methyl-2-cyclopenten-1-one and 1-acetyl-1-(diazoacetyl)cyclopropane in 14 steps and 15% overall yield [154]. Two recent approaches towards the illudin sesquiterpenes have been based on the 1,3-dipolar cycloaddition reaction of a rhodium(II) carbenoid on 2-cyclopentenones [155].

Mycelial cultures of *Mycena leaiana* produce a bright orange pigment, leaianafulvene **117** which exhibits weak antibacterial activities but pronounced cytotoxic activities; a 50% lysis of Ehrlich ascitic tumour (ECA) cells was observed at 2.5 μg ml^{-1} [156].

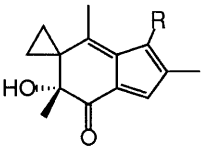


Illudin M **112** (R=H)
Illudin S **113** (R=OH)

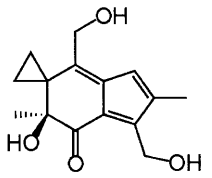


Dehydroilludin M **114**

(45)



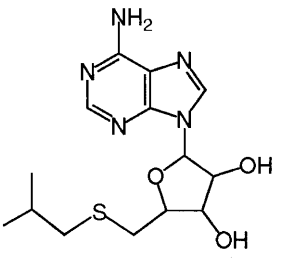
Acylfulvene **115** (R=H)
Hydroxymethylfulvene (HMAF) **116**



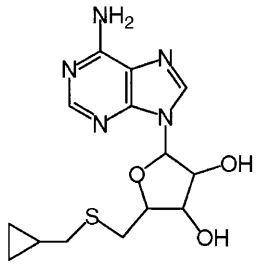
Leaianafulvene **117**

The development of compounds that interfere with the biosynthesis and/or metabolism of (*S*)-adenosylmethionine (AdoMet) (vide supra) as potential chemotherapeutic agents is an area of active investigation [157]. Biological methylation reactions and polyamine biosynthesis, both of which utilize AdoMet, are critically involved in cellular growth and function. Therefore, chemotherapeutic strategies have been based on the antibacterial, antitumor, antiviral and antiparasitic potential of AdoMet derivatives. Among them, has emerged 5′-deoxy-5′-(isobutylthio)adenosine (SIBA) **118** a nucleoside analogue, structurally related to biologically active AdoMet metabolites: (*S*)-adenosylhomocysteine (AdoHcy) (product of AdoMet-mediated methylation reactions) and 5′-deoxy-5′-(methylthio)adenosine (product of spermidine (Spd) and spermine (Spm) biosyn-

thesis, and of ethylene biosynthesis in plants). SIBA **118**, which has potent effects on a number of AdoMet metabolic enzymes (Spd and Spm synthases, MTA phosphorylase, AdoHcy hydrolase) is also an inhibitor of cyclic AMP phosphodiesterase and of cellular nucleoside and sugar transport [158]. 5′-Deoxy-5′-(cyclopropylmethylthio)adenosine (CMPTA) **119**, is a sterically constrained analogue of SIBA **118**, the in vitro and in vivo antitumor activity of which in two murine leukemia cell lines: L1210 (MTA phosphorylase-containing) and L5178Y (MTA phosphorylase-deficient) have been found to be comparable to that of SIBA **118**. These agents are being developed as inhibitors of methylation and/or polyamine synthesis, Eq. (46) [159].



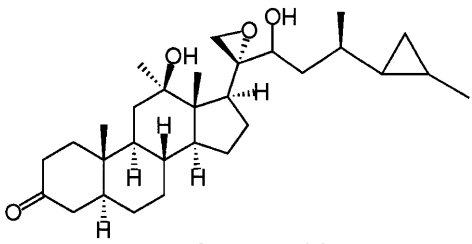
SIBA **118**



CMPTA **119**

(46)

Marine sponges provide a rich source of uncommon sterols the biogenetic origin of which still rises intriguing questions; indeed steroids with a 26-methyl-26,27-cycloergostane skeleton are very rare [160]. Thus, aragusterol A **120**, isolated from the sponge of the genus *Xestospongia* on the coral reef of Aragusuku Island (Okinawa, Japan), possesses potent antitumor activity [161]. This marine cyclopropyl steroid strongly inhibits the cell proliferation of KB, HeLaS3, P388 and LoVo cells in vitro at IC_{50} 0.042, 0.16, 0.022 and 0.0079 µg/ml, respectively. It also shows potent in vivo antitumor activity toward P388 in mice (T/C 172% at 6.25 mg/kg) and L1210 in mice (T/C 220% at 1.6 mg/kg), Eq. (47) [160].

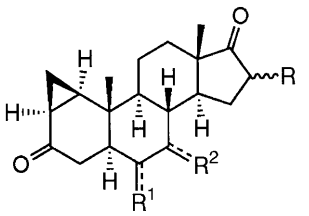


Aragusterol A **120**

(47)

The synthetic cyclopropylandrostenediones **121** (R = H, F; R^1 or $R^2 = CH_2$) provide useful anticancer agents, Eq. (48) [162].

Several bis(dioxopiperazines) exhibit antitumor activity. Thus, ICRF 159 **122** is an inhibitor of DNA synthesis, blocks the cell cycle in G_2-M phase and inhibits metastases in the Lewis lung tumor (3LL) animal model without impeding the

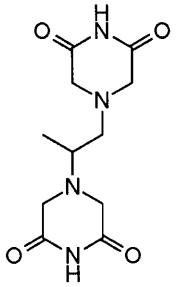


(48)

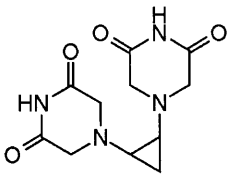
121 (R = H, F; R^1 or R^2 = CH_2)

growth of the primary implant [163]. Stereoselective effects of *cis*-**123** and *trans*-bis(dioxopiperazinyl)cyclopropane **124** on metastases of a hamster lung adenocarcinoma have been investigated in comparison with conformationally mobile ICRF 159 **122** using a Syrian hamster lung adenocarcinoma (LG 1002). Whereas ICRF 159 **122** and **123** significantly inhibited lung metastases, the *trans*-isomer **124** significantly increased the number of metastatic nodules in the lung. It has been concluded that, at least in one tumor model, antimetastatic activity can be separated from metastatic potentiating activity by controlling the drug geometry [164].

The potentiating effects of **124** may be related to an effect on cell volume and glycosaminoglycan biosynthesis, as previously proposed for the effects of **122** on B16 melanoma cells, whereas the *cis*-isomer **123** may selectively cause normalization of developing blood vessels in the primary tumor and thus inhibits metastases, Eq. (49) [165].



ICRF 159 **122**



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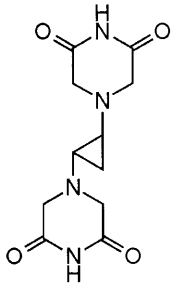


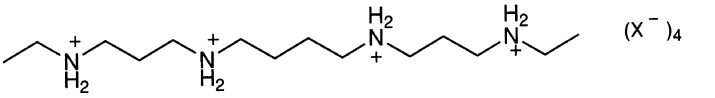
124

(49)

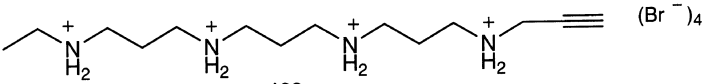
The enzymes involved in the polyamine metabolic pathway have been the subject of intensive study, and a number of specific inhibitors for these enzymes have been designed as potential antitumor or antiparasitic agents [166]. Thus, α-difluoromethylornithine, has become a clinically useful agent [167]. Most of the studies involving inhibitors of polyamine metabolism have focused on enzymes involved in the biosynthetic pathway. Recently, there has been considerable interest generated in the enzyme spermidine/spermine-N^1-acetyltransferase enzyme (SSAT), the rate-limiting step in the back conversion of polyamines. SSAT, in conjunction with polyamine oxidase (PAO), allows for reversal of the biosynthetic pathway and attenuation of the levels of individual polyamines.

The induction level of SSAT in two human lung cancer cell lines which respond differently to treatment with inhibitors of polyamine biosynthesis appears to correlate inversely with the degree of resistance to cytotoxicity following treatment with the polyamine analogue, N^1,N^{12}-bis(ethyl)spermine (BESpm) **125** [168]. Rate of growth and cellular polyamine content in the human small cell lung carcinoma (SCLC) line NCI H82 are minimally affected by BESpm **125**, which appears to down regulate polyamine biosynthesis by the same mechanism as the natural polyamines [161]. By contrast, BESpm **125** was found to be markedly cytotoxic at a concentration of 10 mM in the large cell lung carcinoma (LCC) line NCI H157, accompanied by nearly complete depletion of all intracellular polyamines and a decrease in ornithine decarboxylase (ODC) activity to undetectable levels [170].

In light of the potential value of terminally alkylated polyamines as therapeutic agents, the unsymmetrically substituted polyamine analogues N^1-ethyl, N^{11}-propargyl-4,8-diazaundecane **126** and N^1-ethyl-N^{11}-(cyclopropylmethyl)-4,8-diazaundecane **127** have been synthesized and tested as inhibitors of human SSAT using a crude lysate from H157 cells [168]. Both compounds **126** and **127** were found to be effective inhibitors in this assay system, exhibiting similar potency to the known inhibitor BESpm **125**, and produce a differential superinduction of SSAT in situ which appeared to be associated with a cell-specific cytotoxic response in two human lung cancer cell lines. These BESpm **125** analogues exhibit promising antitumor activity against cultured human lung cancer cells, and should provide additional tools to facilitate the understanding of the regulation of SSAT gene expression, Eq. (50) [1171].



N^1, N^{12}- Bis(ethyl)spermine (BESpm) **125**



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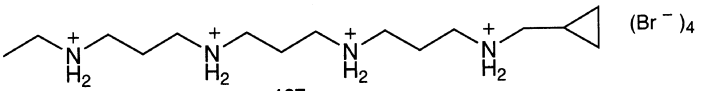


127

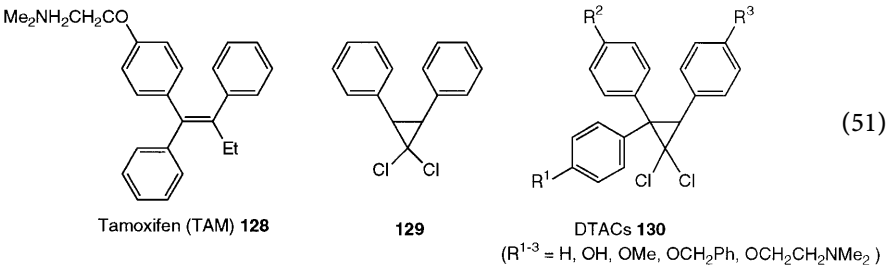
(50)

Antiestrogens block uterine growth and the growth of estrogen-dependent mammary tumors and are effective in the control of other diverse neoplastic diseases, as well as controlling and correcting various endocrine disorders. Their mode of action, although not completely understood, is, however, known to include competitive inhibition at the estrogen receptor (ER) [172], as well as having an estrogen irreversible cytotoxic action linked to their antagonism of calmodulin-activated cellular processes [173]. Tamoxifen (TAM) **128**, a clinically useful triarylethylene (TAE) antiestrogen, elicits varied estrogenic effects, including an increase in the incidence of hepatocellular carcinoma in rats at high doses

[166] and a possible increased risk of endometrial carcinoma [175]. Besides TAM **128**, other TAE antiestrogens also elicit mixed estrogen agonist-antagonist responses [176]. Incomplete remission of estrogen-dependent mammary tumors during treatment with the TAEs appears to be associated, at least in part, with the uterotrophic activity of these compounds [177].

Inhibition of estrogen is a potentially useful strategy for the treatment of hormone-dependent breast tumors in postmenopausal females and possible tumor prevention in premenopausal women. It has been reported that the introduction of a cyclopropyl or dichlorocyclopropyl moiety in place of the olefinic link in estrogenic stilbenes greatly reduces or abolishes their estrogenic activity. Thus, the 1,1-dichloro-*cis*–2,3-diphenylcyclopropane **129**, has antiestrogenic properties with no estrogen agonist activity in the mouse, and is comparable to TAM **128** against the hormone-dependent 7,12-dimethylbenz[a]anthracene-induced rat mammary tumor model [178].

A series of 1,1-dichloro-2,2,3-triarylcyclopropanes (DTACs) **130** (R = H, OH, OMe, OCH_2Ph, $OCH_2CH_2NMe_2$) have been synthesized and tested as antiestrogens, Eq. (51) [179].



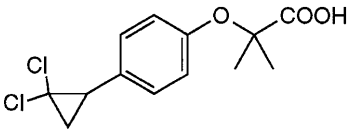
Tamoxifen (TAM) **128** **129** DTACs **130** (R^{1-3} = H, OH, OMe, OCH_2Ph, $OCH_2CH_2NMe_2$) (51)

All DTACs **130** were competitive inhibitors of [^{3}H]-estradiol binding in the immature rat uterine cytosol receptor assay, with relative binding affinities of 0.1–3.6% of estradiol. None of these compounds were estrogenic in the 3-day immature mouse uterotrophic assay at doses up to 750 µg; moreover DTACs **130** with either a methoxy-, benzyloxy- or (dimethylamino)ethoxy- side chain on the ring produced significant decreases in uterine weight. One compound, (*Z*)-1,1-dichloro-2-[4-[2-(dimethylamino)ethoxy]-phenyl]-2-(4-methoxyphenyl) 3-phenylcyclopropane **130** ($R^1 = OCH_2CH_2NMe_2$, R^2 = OMe, R^3 = H), elicited a dose-dependent decrease in vivo comparable to MER 25 (a triphenylethanol derivative with pure antiestrogen property but precluded for use in humans due to its clinical side effects [180]). These compounds, as well as the parent compound **122**, were active in vitro against the estrogen-dependent MCF-7 human breast tumor cell line in a dose-dependent fashion.

Twenty-four cyclopropyl compounds were screened for their antiproliferative activities, eighteen were found to be active and five appeared to be promising pure antiestrogens, superior to tamoxifen **128** not only in the treatment of the estrogen-dependent tamoxifen-responsive breast cancer patients, but also in the treatment of the estrogen-independent, tamoxifen non-responsive, breast cancer patients.

The studies were conducted in the absence or presence of exogenous estradiol to reveal the estrogen-dependent nature of the cyclopropyl compounds [179, 181].

Ciprofibrate **131** is a potent, long-acting hypolipidemic agent. It is effective in type IIa, IIb, III and IV hyperlipoproteinemias and produces a beneficial elevation of the anti-atherogenic high density lipoprotein, Eq. (52) [182].

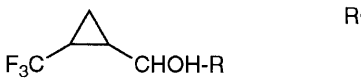


(52)

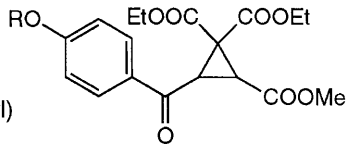
Ciprofibrate **131**

Enantiomerically pure trifluoromethyl- and trifluoroethylcyclopropylcarbinols **132** and derivatives (R = C_{1-2} fluoroalkyl, alkyl, aryl) appeared useful as intermediates for enzyme inhibitors, physiological active substances and antitumoral agents, Eq. (53), [183].

Esters of 1-(4-pentyloxybenzoyl)cyclopropane-2,2,3-tricarboxylic acid **133** have antineoplastic activity. Thus oral application of 100 mg/kg per day to mice for eight days suppressed the growth of transplanted S 37 tumor by 26%, Eq. (53) [184].



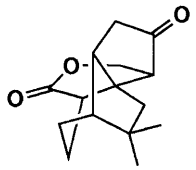
132 (R = C_{1-2} fluoroalkyl, alkyl, aryl)



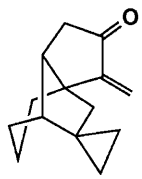
133

(53)

New types of biologically active substances having a spirocyclopropane ring and related to the antibiotic quadrone **134** [185], have been synthesized [186]. The bioassay of 2-methylenetricyclo[4.3.2.$0^{1,5}$]undecan-3-ones **135** and **136** was undertaken against tumor cells of mice in vitro; their cytotoxicity has been observed at almost the same level as that of **134**. Interestingly, **135** has exhibited antimicrobial activity against *Staphylococcus aureus*, *Candida albicans*, *Trichoyhyton foetus* (minimum inhibitory concentration: MIC, 2.5 – 5 µg/ml) and the activity of **136** was somewhat lower (MIC, 20 µg/ml), while quadrone **134** has no antibacterial or antifungal activity at level of 100 µg/ml, Eq. (54) [187].



Quadrone **134**



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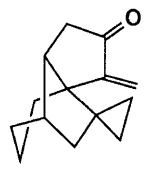


136

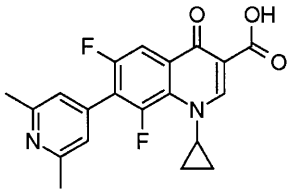
(54)

The mammalian topoisomerase II enzyme catalyzes the double-strand breakage of DNA to allow the second strand passage and thereby control the topology

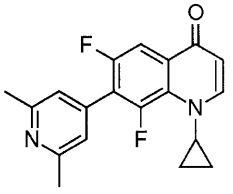
and conformation of DNA [188]. There are many topoisomerase II inhibitors that demonstrate useful antitumor activity (e.g. *m*-AMSA, VP-16 and VM-26) [189], and it has been suggested that enhanced topo-II-mediated DNA cleavage is an important mechanism for these antitumor agents [190]. While quinolone-based inhibitors of bacterial topo-II (DNA gyrase) have long been used successfully as antibacterial agents [191] (vide infra), recent studies have identified some quinolones which also inhibit mammalian topoisomerase II and thus may have a potential as antitumor agents [192].

WIN 57294 **137** is a potent inhibitor of DNA gyrase; it is both clastogenic and mutagenic, which precluded its development as a human anti-infective agent [193]. This compound was subsequently found to possess moderate topo II inhibitory activity (EC_{50}=7.6 μM). Structure activity relationship studies of WIN 57294 **137** resulted in the discovery that the 3-CO_2H group was not a requisite for topo II potency for **138**, (EC_{50}=17 μM) [194]. A conformationally rigid quinolone derivative **139** has been reported to display better topo II potency (EC_{50}=2.77 μM) [195].

A series of novel 4-substituted-1,4-dihydroquinolines **140** were prepared and found to exhibit moderate to excellent mammalian topo II inhibitory activity. Among the compounds prepared, in general, the nitrogen analogues are the most active compounds and the sulfur analogue is the least active one. The most potent analogue **140** (X=NH-2-pyridinyl), had a topo II potency nearly equivalent to VP-16, a clinically useful topo II interactive antitumor agent, Eq. (55) [197].



WIN 57294 **137**



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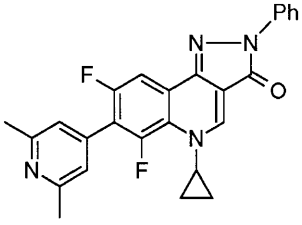

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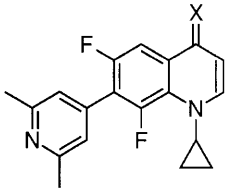


140

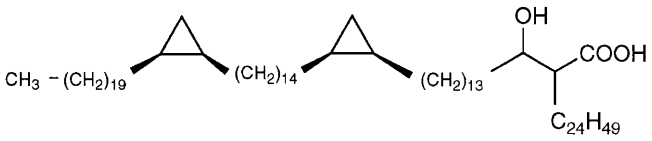
7 Antibacterial Activities

Cyclopropane containing fatty acids are found in bacterial membranes; thus lactobacillic acid **141** has been isolated from *Lactobacillus arabinosus*, *Brucella abortus* and *B. melitensis*, Eq. (56) [188].

(56)

141

Cyclopropyl fatty acids with C_{12}, C_{19} and C_{21} have been formed in many gram-negative and gram-positive bacteria [198]. The mycolic acid **142** (C_{80}) is a major component of the mycobacterial cell wall of the human strain of *M. tuberculosis*, Eq. (57) [199].



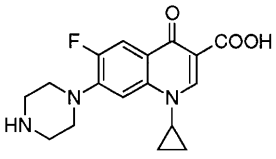
(57)

142

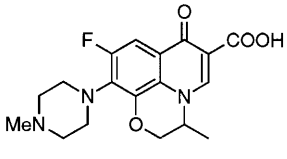
The re-emergence of tuberculosis infections by strains which are resistant to conventional drug therapy has demonstrated the need for alternative chemotherapy against *Mycobacterium tuberculosis.* The fluoroquinolones represent a major class of antibacterials with great therapeutic potential specially against *M. tuberculosis*. Over the years, several structure-activity and side-effect relationships have been developed, covering thousands of analogues, in an effort to improve overall antimicrobial activity while reducing undesirable side effects. The various structural features of the quinolones which govern antibacterial activity and influence the side-effect profile have been reviewed [200]. Those features which most remarkably enhance antimicrobial effectiveness are:

- a halogen (F or Cl) at the 8-position which improves oral absorption and activity against anaerobes
- an alkylated pyrrolidine or piperazine at C^7 which increases serum half-life and potency versus gram-positive bacteria
- and a cyclopropyl group at N^1 and an amino substituent at C^5, both of which improve overall potency [200].

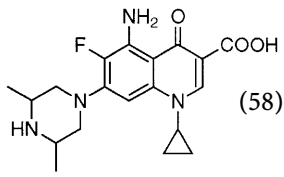
Thus quinolone antibacterial agents, such as ciprofloxacin CPFX **143** [201], ofloxacin OFLX **144** [202], sparfloxacin SPFX **145** [203] and trovaflaxin **146** [204] are members of a major class of antibacterial drugs. These fluoroquinolones show broad-spectrum antibacterial activity and are widely used to treat patients with infections, Eq. (58).



Ciprofloxacin **143**



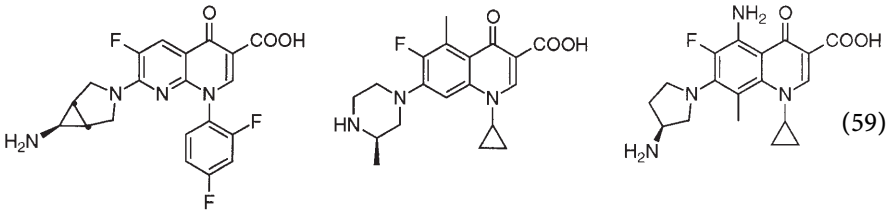
Ofloxacin **144**



Sparfloxacin **145**

(58)

A series of substituted 1-cyclopropyl-6-fluoro-1,4-dihydro-5-methyl-4-oxo-3-quinoline carboxylic acids was synthesized and tested for their in vitro and in vivo antibacterial activity [205a–c]. Among them, 1-cyclopropyl-6-fluoro-1,4-dihydro-5-methyl-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinoline carboxylic acid **147** (grepafloxacin) exhibited potent in vitro antibacterial activity gram-positive bacteria such as *Streptococcus pneumoniae* and high in vivo activity on the experimental systemic infections caused by the gram-positive and -negative bacteria tested. It also showed a high distribution to the lung and bronchoalveolar lavage fluid in comparison to reference drugs and is now undergoing clinical evaluation, Eq. (59) [205b].



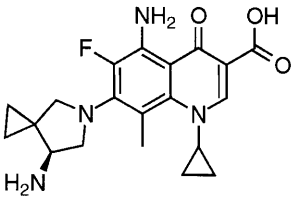
(59)

Trovafloxacin **146** Grepafloxacin **147** **148**

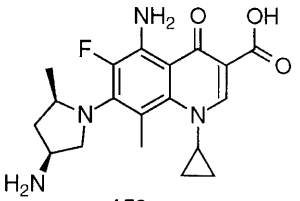
It has been recently found that the 5-amino-8-methyl compound **148** showed strong antibacterial activity (in vitro antibacterial activity of **148** is four times more potent than that of CPFX **149** against both gram-positive and gram-negative bacteria), reduced injury to the chromosome, and reduced quinolone-type toxicity (free from both phototoxicity at a dosage of 30 mg/kg in guinea pigs (i.v.) and convulsion-inducing activity when coadministered with fenbufen at a dosage of 100 mg/kg in mice (i.p.)).

Optimization of the 3-aminopyrrolidine moiety of **148** Eq. (59) [206] was obtained by introduction of C-alkyl (Me, Et, Pr, di-Me, cyclopropyl) and *N*-alkyl groups (Me, di-Me). C-alkylation at the 4-position of the 3-aminopyrrolidine moiety enhanced in vitro and in vivo antibacterial activity. (*S*)-5-Amino-7-(7-amino-5-azaspiro[2.4]hept-5-yl)-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxyclic acid **149** and (3*S*,4*S*)-5-amino-7-(3-amino-4-methyl-1-pyrrolidinyl)-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylic acid **150** showed strong antibacterial activity (in vitro antibacterial activity including quinoline-resistant bacteria is four times more potent than that of ciprofloxacin CPFX **143**; in vivo antibacterial activity is 1.5 to 20 times more potent than that of CPFX **143** and quinolone toxicity is reduced (free from both phototoxicity at a dosage of 30 mg/kg in guinea pigs (i.v.) and convulsion when coadministered with 4-biphenylacetic acid at a dosage of 20 mg in rats (i.c.v.)). Their selectivity between DNA topoisomerase II (derived from eukaryotic cells) and DNA gyrase (derived from bacterial cells) was about 3000-fold, Eq. (60) [207].

For quantitative structure-activity relationship (QSAR) studies a three-dimensional model of a DNA-quinolone complex was built using molecular modeling techniques. It was based on the intercalation of quinolone into the double helix of DNA. It was concluded that the intercalation model is consistent with most available data on the structure of the quinolone complex. This predicted



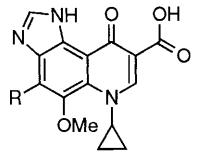
149



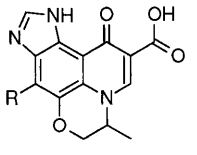
150 (60)

structure is stabilized by the binding of magnesium ion with the sp^2 oxygens present in quinolone, a phosphate and a purine base of the DNA. Substituents of **143–144** are predicted to make hydrophobic interactions in the major and minor groove of DNA, respectively. The piperazinyl substituent could also form hydrogen bonds with amino groups of guanines and the aspartic acid residue at position 87 in DNA gyrase subunit A [208].

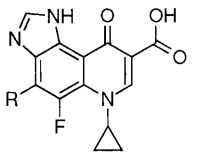
The 5-methoxyimidazoquinolones **151** have been synthetized and have been shown to be superior to the corresponding ofloxacin type analogues **152** in in vitro antibacterial activity. The activity of **151** was equipotent against *S. aureus*, but 2 to 16 times less potent againtst *E. coli* and *P. aeruginosa* compared to that of the 5-fluoro analogues **153a, b**, Eq. (61) [209].



151 R = cyclic amino group



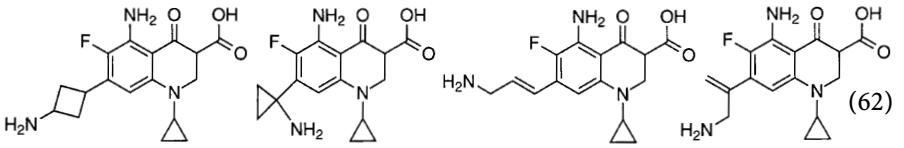
152 R = cyclic amino group



(61)

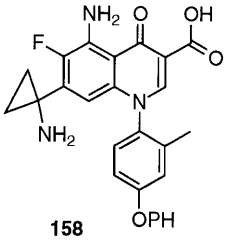
153a R = 4-N-methylpiperazinyl
b 3-methylpyrrolidinyl

Novel C^7-derivatives of 1-cyclopropyl-6-fluoro-4-quinolonecarboxylic acid have been synthesized and evaluated for in vitro antibacterial activity. Compounds **154** (3-aminocyclobutyl), **155** (1-aminocyclopropyl), **156** ((2-aminomethyl)vinyl), and **157** (1-aminomethyl)vinyl) showed significant inhibitory activity, comparable to that of cyprofloxacin **143**, against gram-negative bacteria including *P. aeruginosa*. A good pharmacokinetic profile (serum and brain concentrations and urinary recovery) was obtained for the two cyclic compounds (**154** and **155**), but that of the vinylic compounds (**156** and **157**) was less favorable. Compound **156** was less toxic than **155**, ciprofloxacin **143** or or ofloxacin **144** in terms of acute toxicity and convulsion-induction, Eq. (62) [210].



154 **155** **156** **157** (62)

The three quinolones **158–160** exhibited potent antibacterial activities against both gram-positive and gram-negative bacteria, which are comparable to those of ciprofloxacin CPFX **143** and ofloxacin OFLX **144.** Among the three compounds, the best pharmacological and pharmacokinetic profile was obtained with **160**, an OFLX analogue, which was considerably less toxic than the three reference quinolones **155**, CPFX **143** and OFLX **144**, Eq. (63) [211].



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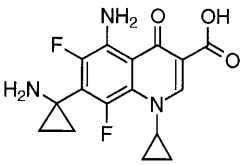

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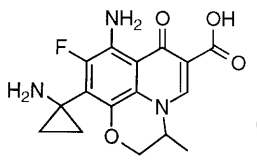
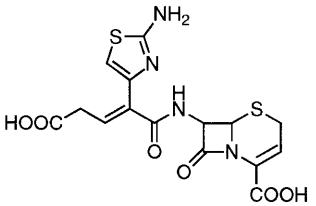


160

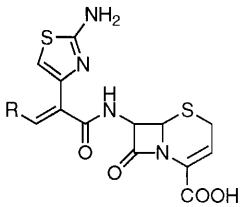
(63)

For other structure-activity relationship of the quinolone antibacterials improved by the presence of cyclopropyl substituents see Ref. [212].

Intensive efforts to expand the antibacterial spectra of existing oral β-lactams [213] have led to a new type of an orally absorbable cephalosporin, ceftibuten **161**, which shows a broad and potent antibacterial activity against most gram-negative bacteria with limited activity against gram-positive ones [214]. Antibacterial activity against gram-positive bacteria was potentiated by increasing the alkyl moiety in the 7β-side chain with decreasing the activity against gram-negative ones. Compounds **162a–c** carrying alkyl groups such as isopropyl, cyclopropyl and cyclopentyl connected directly to the vinyl carbon were slightly less active against gram-positive bacteria and more active against gram-negative bacteria than **162d–e** substituted *via* a methylene group such as propyl, cyclopropylmethyl and cyclopentylmethyl, Eq. (64) [215].



Ceftibuten **161**



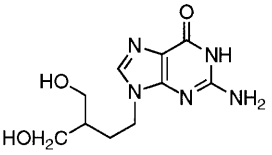
(64)

162a R = iPr **d** cyclopropylmethyl
b cyclopropyl **e** cyclopentylmethyl
c cyclopentyl

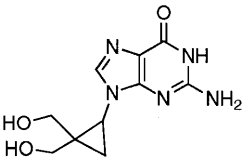
8 Antiviral Activities

More than 60 per cent of all diseases in Europe, North America and Japan are caused by the action of viruses, amongst them bronchitis, hepatitis, influenza, infections by several strains of herpes as well as by human immunodeficiency viruses (HIV) [216]. Modified nucleosides that inhibit the replication of the

viruses have been used in the chemotherapy of these infections [217]. These analogues, which act through similar mechanisms, can be divided into three categories: 1) phosphate modified, 2) base modified, and 3) sugar modified. Most of the known active compounds belong to the two latter groups [218]. Of main interest are compounds the ribose unit of which has been subject to major changes, either by replacement by a cyclopentane or cyclopentene (carbasugars), oxetane or cyclobutane ring, or by an acyclic chain. Thus Penciclovir **163** had emerged as a potent and selective anti herpes-virus agent, particularly active against herpes simplex types 1 and 2 (HSV-1 and HSV-2) and varicella zoster virus (VZV) [219]. In order to clarify the relationship of side chain conformation and flexibility to biological activity, cyclopropane-containing guanine, purine and pyrimidine nucleosides, such as the 9-[2,2-bis(hydroxymethyl)cyclopropyl]guanine **164** for instance, have been synthesized in order to test their potential anti-retroviral activity. The approach overlaps the area of carbocyclic nucleoside analogues, such as the isomeric compound SQ 32,829 **165** [220], which have recently received considerable attention due to their potent antiviral activity, Eq. (65) [221].



Penciclovir **163**



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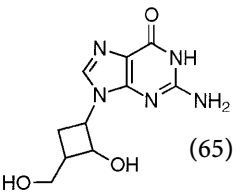
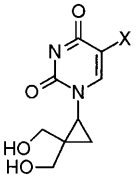


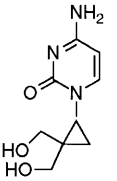
(65)

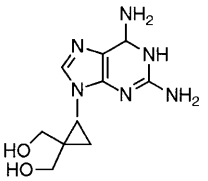
SQ 32,829 **165**

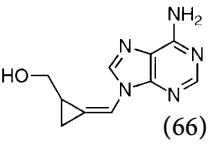
However, the nucleoside analogue **164** was found to be devoid of activity against HSV-1, HSV-2, VZV and the cytomegalovirus (CMV) in human fibroblast (MRC-5) cells. In this case the decreased conformational flexibility resulting from the introduction of the cyclopropyl group into **164** appeared to be unfavourable for interaction with the enzymes involved (vide supra, Sect. 2.9) [222]. Likewise, the cyclopropylpyrimidine **166c–f** and **167**, the cyclopropylpurine nucleosides **168** showed no antiviral activity against HSV-1, HSV-2, HCMV and HIV-1 in cell culture, Eq. (66) [223].

A new class of purine nucleoside analogs such as **169** comprising a methylenecyclopropane moiety has recently been reported to exhibit potent in vitro activity against a number of herpes viruses including human and murine cytomegalovirus (HCMV and MC-MV), Epstein-Barr virus (EBV), varicella-zoster virus (VZV), human herpes virus 6 (HHV 6), herpes simplex virus type 1 and 2 (HSV-1 and HSV-2). They also inhibit the replication of hepatitis B virus and human immunodeficiency virus type 1 (HIV-1) [214]. The (*Z*)-isomer revealed higher biological activity (EC_{50}=26 μM for **169** and comparatively >100 μM for its trans isomer); and (–)-(*Z*)-**169** was highly effective against HIV-1 with EC_{50}=13 μM [215]. Efficient syntheses of these purine nucleoside analogs have been recently reported from the coupling reaction of vicinal dibromocyclopropane derivatives with adenine [225, 226].





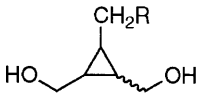




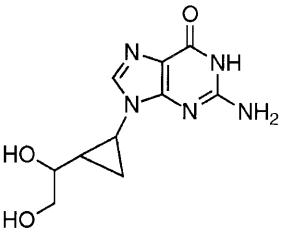
(66)

166a X = H **d** I **167** **168** **169**
b Cl **e** Me
c Br **f** (E)-CH =CHBr

Although the methano homologues of oxetanocin, i. e. the (*Z*) and (*E*) nucleosides **170** (R = adenine, thymine, 5-fluorouracil) were devoid of anti-HSV-1 activity [227], the guanine derivative **170** (R = guanine) showed activity against herpes simplex HSV-1 strain KOS in cell cultures (ID_{50} of 0.023–120 µg/ml) [228]. In vitro, the 9-[2-(1,2-dihydroxyethyl) cyclopropyl]guanine **171** produced an inhibition of virus-induced cytopathogenic effects in E-377 cells challenged with herpes simplex virus (virus rating of 1.8 at 101 mg/ml), Eq. (67) [229].



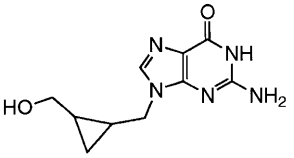
(*E*)- and (*Z*)-**170**
(R = adenine, thymine, 5-fluorouracil, guanine)



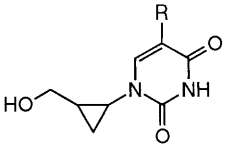
171

(67)

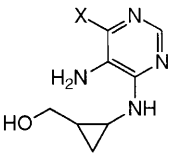
The cyclopropylcarbinol nucleosides **172**–**177** have also been prepared and tested as antiviral, antitumoral, antibacterial agents and neoplasm inhibitors, Eq. 68) [230–232].



172

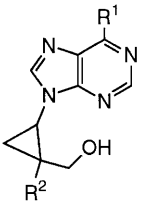


173 (R = Alkyl)

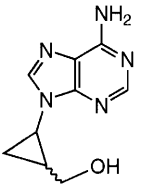


174

(68)



175a R^1 = halo, amino
b R^1 = Cl, R^2 = CH_2OH



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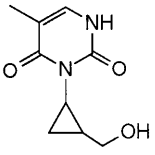
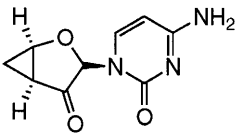


177

Nucleosides such as **178** and **179** containing a cyclopropane ring fused to the sugar portion have shown antiviral activity; their stereocontrolled syntheses have recently been achieved, Eq. (69) [233].



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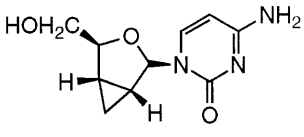
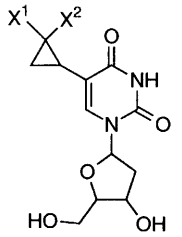
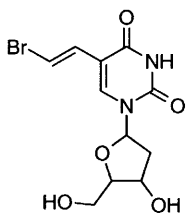


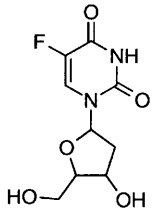
179

(69)

The two diastereomers of 5-(2,2-dichlorocyclopropyl)-**180a** (X^1, X^2=Cl) and the four diastereomers of 5-(2-chlorocyclopropyl)-2′-deoxyuridine **180b** (X^1=Cl, X^2=H), as well as the corresponding brominated **180c, d** and fluorinated derivatives **180e, f** have been prepared and examined for antiviral and cytotoxic activity, in comparison with (*E*)-5-(2-bromovinyl)-2′-deoxyuridine BVDU **181** and 5-fluoro-2′-deoxyuridine FDU **182.** The (1*R*,2*R*)-5-(2-chlorocyclopropyl)-2′-deoxyuridine **180b** was the most active antiviral agent against herpes simplex HSV-1, relatively to BVDU **181** (ED=0.082 μg/ml). Compounds having the *R* configuration at the C-1 and/or C-2 positions of **180a, b** exhibited the most potent antiviral activity. The (1*R*)-difluoro compound **180e** was also more active than BVDU **181** against HSV-1 and a cytotoxic agent in the CCRF-CEM (IC_{50}=230 μM) screen relative to FDU **182**; the (1*S*)-**180e** diastereomer was inactive in both screens. Moreover (1*R*)-**180e** was more resistant to glycosidic bond cleavage by thymidine phosphorylase than its (1*S*) diastereomer, Eq. (70) [234].







(70)

180a X^1, X^2 = Cl
b X^1 = Cl, X^2 = H
c X^1, X^2 = Br
d X_1 =Br, X_2 = H
e X_1, X_2 = F
f X_1 =F, X_2 = H

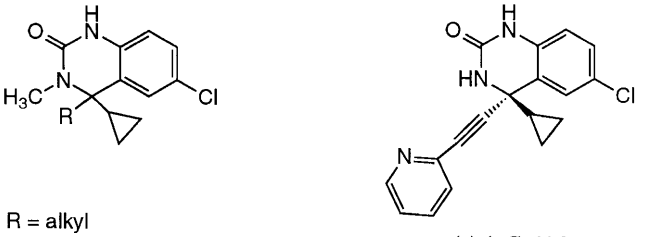
BVDU **181**

FDU **182**

The rapid spread of acquired immune deficiency syndrome (AIDS) has prompted numerous efforts to develop therapeutic agents against the human immunodeficiency virus type 1 (HIV-1) [235]. Efforts have focused on inhibition of the virally encoded reverse transcriptase (RT) enzyme, which is responsible for the conversion of retroviral RNA to proviral DNA. The nucleoside RT inhibitors 3′-azidothymidine (AZT) and dideoxyinosine (ddI) have proven to be clinically useful anti HIV-1 agents [236], but due to their lack of selectivity versus other DNA polymerases, these compounds are flawed by their inherent toxi-

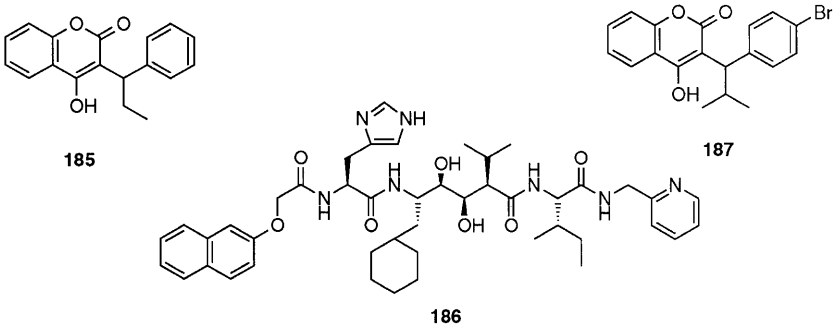
cities [235]. Therefore a considerable number of potent non-nucleoside HIV-1 RT inhibitors which act at an allosteric site unique to HIV-1 RT, providing selectivity versus other DNA polymerases, have been reported [238].

Among them, the cyclopropyldihydroquinazolinones **183a, b** were shown to be potent inhibitors of HIV-1 RT; however their potential therapeutic utility was hampered by metabolic liability. Thus, the 3-methyl group is susceptible to oxidative metabolism, resulting in loss of this substituent; removal of this methyl group results in large losses in inhibitory potency and severe limits in oral bioavailability [239]. The (–)-(4*S*)-enantiomer of compound **184**, where the 3-methyl of **183a** was replaced by a 3-(2-pyridinoethynyl), had exhibited the most favorable overall biological profile to overcome these problems; effectively (4*S*)-**184** was a potent antiviral agent in cultured MT-4 cells infected with HIV-IIIb, possessing a CI C_{95} value of 25 nM (n > 10); its (+)-(4*R*) enantiomer was essentially inactive, Eq. (71).



(71)

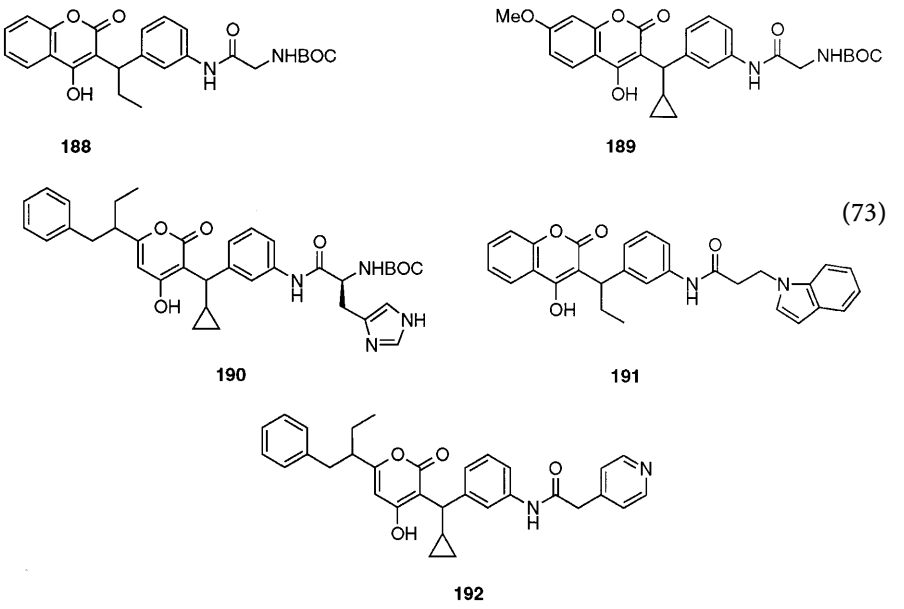
Oral administration of (4*S*)-**184** to rhesus monkeys at 10 µg/kg provided peak levels of 12 mM at 2–4 h, while levels of parent drug remaining above 4 mM after 24 h. In view of this, (4*S*)-**184** was chosen as a candidate for further preclinical investigations; its potential to induce resistance and its activity against a number of known HIV-1 RT mutants are under current investigation [239]. The low oral bioavailability and rapid biliary excretion of peptide-derived HIV protease inhibitors have limited their utility as potential therapeutic agents. From a broad screening program to discover nonpeptidic HIV protease inhibitors, phenprocoumon (compound 185, K_i = 1 mM) was previously identified as a lead template. Overlay of the crystal structures of HIV protease complexes contain-



(72)

ing the peptide-derived inhibitor **186** and the nonpeptidic inhibitor **187** provided the basis for a molecular-modeling study that suggested the incorporation of a carboxamide functionality at the *meta* position of the benzyl side chain at C-3, Eq. (72) [240].

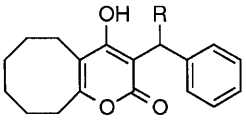
Compound **188** was prepared and shown to have improved inhibitory activity over the reference compound **185**. A crystal structure of the inhibitor **188** HIV protease complex was then determined, and the conformation of the inhibitor **188** in the enzyme active site was compared to that of the conformation expected from the modeling study. On the basis of this structure-based design of compound **188**, additional sets of analogues in the 4-hydroxy coumarin and the 4-hydroxy-2-pyrone series were prepared to evaluate the structure-activity relationship and to discover inhibitors with improved inhibitory potency. The inhibitor **189**, in the 4-hydroxycoumarin series, exhibited high HIV protease inhibitory activity with a K_i value of 1.4 nM. This finding of a specifically added carboxamide functionality to the inhibitory template, which resulted in inhibitors with improved enzyme-binding affinity, provides a new direction for the preparation of new promising series of potent and nonpeptidic HIV protease inhibitors. Although the inhibitors **189** and **190**, contain amino acid residues, compounds **191** and **192**, without amino acids, also showed high inhibitory activity. These latter two compounds provided a basis for the further exploration of more structure-based design experiments with non-amino acid-containing 4-hydroxycoumarin and 4-hydroxy-2-pyrone analogues which are expected to result in potent HIV protease inhibitors, Eq. (73) [240].

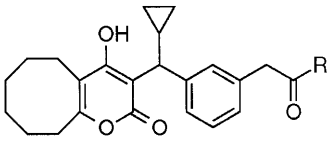


(73)

Recently, the novel cyclooctylpyranone HIV protease inhibitor **193a** was identified and an X-ray structure analysis of this inhibitor complexed with HIV-2 protease was obtained. This crystal structure was used to develop two strategies

for creating derivatives of **193a** with enhanced enzyme inhibitory activity. The first strategy, substitution on the cyclooctyl ring, met with limited success, but provided some interesting information about the conformationally flexible cyclooctyl ring on the inhibitors. The second strategy, substitution at the *meta* postion of the aromatic ring, was far more successful and generated compounds, such as the carboxamide derivatives **194a** (K_i = 3.0 ± 0.4 nM) and **194b** (K_i = 4.0 ± 0.8 nM), which were significantly more active than the corresponding unsubstituted cyclooctylpyranone **193b** (K_i = 11.7 ± 4.7 nM). An X-ray crystal structure of **194b** complexed with HIV-1 protease indicated the increase in binding affinity is most likely due to the additional interactions between the amide substituent and the S3 region of the protease, Eq. (74) [241].





(74)

193a R = Et
b cyclopropyl

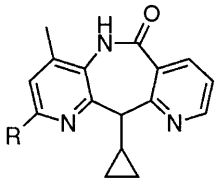
194a R = N-BOC- 2-(3-imidazol)ethylamine
b N-BOC -ethylamine

The only agents currently approved for the treatment of the acquired immune deficiency syndrome (AIDS) exert their therapeutic effects at the level of the human immunodeficiency virus type 1 (HIV-1) reverse transcriptase (RT) enzyme. These therapeutics, the nucleoside analogs AZT [241], DDI [242], DDC [243] and D4T [244], after intracellular transformation to the triphosphates, are incorporated by RT into the nascent proviral DNA and thereby terminate its synthesis. In addition to the nucleoside analogs, there is a second class of RT inhibitors, the non-nucleosides, exemplified by the dipyridodiazepinone nevirapine **195a** [245]. The non-nucleoside RT inhibitors [246–250] bind close to the active site [251–254] inducing conformational changes that affect the catalytic efficiency of the enzyme [255, 256]. Notwithstanding the differing mechanisms of action, the emergence of resistant viruses is a major limitation associated with the use of either nucleoside or non-nucleoside inhibitors of RT [257–259].

The primary cause of viral resistance to nevirapine **195a** is the mutation which substitutes cysteine for tyrosine-181 in RT (Y181 RT) [258]. This Y181C RT is less sensitive to nevirapine **196a** than the wild-type enzyme and also less sensitive to other non-nucleoside inhibitors [259]. Besides improving potency against the wild-type enzyme, a major focus was to achieve significant activity against the Y181C RT. Of the previously reported dipyridodiazepinones [260], only the 2-chloro derivative **195b** displayed significant inhibition of the Y181C RT (IC_{50} = 0.21 mM).

The potency of the dipyridodiazepinone class against the wild-type RT has been enhanced, and inhibition has been extended to the Y181C RT and other mutant RT enzymes by substitution at the 2-position of the dipyridodiazepinone ring system. Excellent activity against wild-type RT can be achieved with methyl or methoxy substituents **195c, d**, although in these cases there is only moderate activity against the Y181C mutant enzyme. Potency against both wild-

type RT and the Y181C RT can be achieved with chloro **195b**, pyrrolyl **195e**, pyrazolyl **195f**, substituted phenyl **195g**, and substituted pyridyl groups **195h**. In addition, some of these substitutions confer activity against mutant RT enzymes resistant to other classes of non-nucleoside RT inhibitors. It remains to be seen whether or not new mutations in the RT enzyme can confer resistance to these more potent analogs of nevirapine, Eq. (75) [261].



(75)

Nevirapine **195a**	R = H	**e**	pyrrolyl
b	Cl	**f**	pyrazolyl
c	Me	**g**	4-NH2Ph
d	OMe	**h**	4-NH_2Pyridyl

Following the discovery of the antiviral activity of the azidothymidine analog, and the activity of the 3′-azido-2′-dideoxyguanosine analog [262], the synthesis of a series of 2-amino-6-substituted-(3′azido-2′,3′-dideoxy-*b*-D-*erythro*-pento-furanosyl)purine analogs **196** was undertaken to explore the structure-activity relationships.

Among the various substituents at the 6-position of the purine ring, only the *trans*-(2-phenylcyclopropyl)amino derivative **196b** consistently demonstrated inhibition of MT4 cell growth (vide supra **10** in Eq. (5), Sect. 2.4), Eq. (76) [263].

(76)

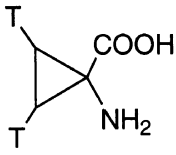
196a R = OH, OR, NH_2, NR_2, SH, SR, Me, CN
b *trans*-2-phenylcyclopropylamino

9 Neurochemical Activities

Anatomical and pharmacological studies have both indicated that the two major transmitter systems within the brain are the inhibitory GABA ergic and the excitatory amino acid (EAA) pathways [264]. At least four different receptors mediate the action of EAA, they are named according to the most selective li-

gand used to characterize them: *N*-methyl-D-aspartate (NMDA), quisqualate, kainate and L-2-amino-4-phosphonobutanoic acid (AP4) receptors. The NMDA receptor has received the most investigation based upon recent advances in the availability of pharmacological tools to study this receptor. It rapidly became clear that the NMDA receptor is a macromolecular complex possessing negative modulatory sites which bind phencyclidine (PCP), Zn^{2+} and Mg^{2+} [265]. Electrophysiological and neurochemical investigations have demonstrated that glycine can modulate the activity of NMDA-operated cation channels [266]. The glycine B site was characterized as a modulatory site of the NMDA receptor complex [267] which can influence the binding of PCP ligands [268]. Various types of antagonists [269], partial agonists [270] and agonists have been identified. Among them ACC **71**, which is structurally related to glycine, is a potent and selective ligand of the glycine modulatory site coupled to NMDA receptors, and appeared to be an even more specific ligand for the glycine B receptor than glycine itself. Therefore, ACC **71** (vide supra, Eq. (28)), may prove useful in neurochemical, pharmacological and electrophysiological studies of the NMDA receptor complex [271].

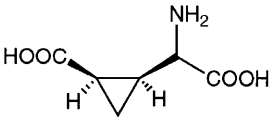
2,3-Di[^{3}H]-ACC **197** has been synthesized as a specific ligand for the glycine-B binding site [272]. The hypothesis of NMDA-mediated cell death in stroke, and the possible involvement of this receptor in neurodegenerative diseases such as Alzheimer's disease and Huntington's chorea have been suggested [273]. Although, the role of the Gly-B site in convulsions (epilepsy) has not been clearly defined, glycine has been shown to be active as an anticonvulsant, Eq. (77) [266].



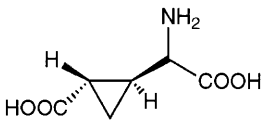
(77)

Both the Gly-B agonist D-cycloserine [275], a positive modulator of the NMDA receptor which enhances performances of learning tasks in rats, and the glycine prodrug, milacernide [276] have demonstrated memory enhancing actions (memory disorders). Therefore, such glycine-B agonists allow the characterization of the possible receptor subtypes and the understanding of the molecular biology of the receptor complex, which are crucial in the design of optimal pharmacological modulators [277].

The syntheses of the four diastereomers of α-(carboxycyclopropyl)glycines (*Z*)-**198a** and (*E*)-**198b** isolated from *Aesculus parviflora* [276], have been reported [277]. Neurobiological assays using a β-hydroxy-L-glutamate (L-BHGA) sensitive neuron from an african giant snail (*Achatina fulica Ferrusae*) [278] have indicated clearly a conformation-activity relationship; thus the diastereomer of **198** with erythro configuration and extended conformation, i.e. with the active conformation of L-BHGA when its interacts with the receptor, was markedly recognized by the neuron receptor, Eq. (78).

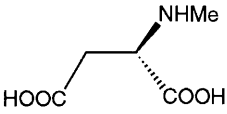


(*Z*)-(2*S*,3*S*,4*R*)-**198a**

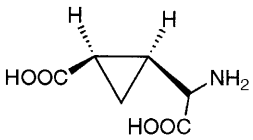


(*E*)-(2*S*,3*S*,4*S*)-**198b** (78)

As it is now clear that excitatory amino acids (EAA) play a critical role as neurotransmitters in the brain [279], in addition to the putative endogenous agonists, synthetic agonists such as NMDA **199** and (2*R*,3*S*,4*R*)-a-(carboxycyclopropyl)glycine **198c** have been identified, Eq. 79 [280].



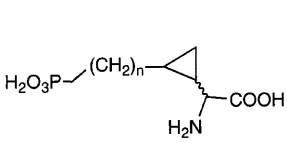
NMDA **199**



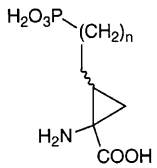
(*Z*)-(2*R*,3*S*,4*R*)-**198c** (79)

They have provided clues about the conformation of agonists at the receptor site. The cyclopropane ring was used to prepare conformationally restricted glutamic acid analogues which have exhibited affinity and potency at the NMDA receptor similar to those of glutamic acid itself and more selectively, they showed decreased affinity at other EAA receptors. These results, led to the consideration of the synthesis of hybrid molecules such as the (*E*)- and (*Z*)-phosphonomethanoamino acids **200**–**202**, in which the basic framework of the related 2-amino-5-phosphonopentanoic acid AP5-**203a**, has been rigidified by a cyclopropane ring, as competitive antagonists for the NMDA receptors.

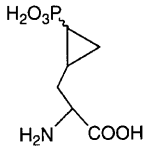
Biological evaluation using [^{3}H]-L-glutamate as radioligand, has shown that among the AP5 analogues, the position of the methano bridge becomes less and less favorable when it moves from the 4,5-position to the 2,3-position. Thus the 4,5-methanol-AP5 compound **202** has a higher affinity for the receptor than its 3,4-isomer **201** (n = 1), and the most favored configuration for the 3,4-methano AP5 **201** is *trans* (*E*). A surprising agonist-like efficacy was manifested by the AP7 analogue **201b** (n = 2), Eq. (80) [281].



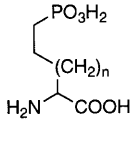
(*E*)/(*Z*) **-200**



(*E*)/(*Z*) **201a** n = 1
b 2



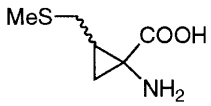
202



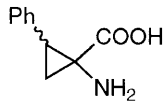
203a n = 1
b 2 (80)

Peptidomimetics of the anti-opiate neuropeptide Phe-Met-Arg-Phe-NH_2 have been synthesized by exchanging the Met with each of the four isomers of 2,3-methanomethionine **204**. All these peptides entailed more morphine absti-

nence in morphine addicted rats, although receptor binding studies in vitro have shown that the methanologues were less strongly bound than the parent peptide [282]. CCK methanologues containing (*Z*) or (*E*)-methanophenylalanine **205** showed different selectivities for the CCK-A or CCK-B receptors, although they were less highly bound than CCK itself, Eq. (81) [283].



204



205

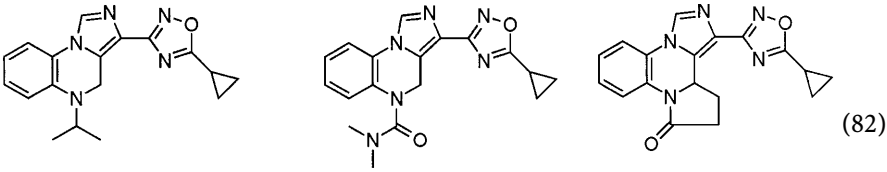
(81)

The development of the benzodiazepine class of drugs for the treatment of a variety of neurological indications has proven to be an outstanting success story in the field of chemotherapy. However, these compounds often produce undesirable side effects when used as anti-anxiety or hypnotic agents. These side effects include sedation, physical dependence, amnesia, muscle relaxation, and ethanol potentiation. The development of a benzodiazepine receptor-based anxiolytic agent devoid of these side effects would constitute a major advance in the field and has been the focus of significant research efforts [284].

Benzodiazepines exert their influence by interacting with the benzodiazepine receptor (BzR) located on the α-aminobutyric acid ($GABA_A$) chloride ion channel complex. Associated with the $GABA_A$ ion channel are a variety of recognition sites for small molecules, which can directly influence the ability of this channel to transport chloride ion across neuronal membranes. In addition to the benzodiazepine receptor, there exist binding sites for γ-aminobutyric acid (GABA), barbiturates, picrotoxin (and other convulsant agents), and neurosteroids [285]. When GABA, the major inhibitory neutrotransmitter in the central nervous system (CNS), binds to its receptor, the flow of chloride ion through the channel is increased and the excitability of the neuron is reduced [286]. Of the many types of receptor-ligand interactions that influence this GABA-induced chloride flux, the benzodiazepine receptor and its ligands have been the most widely studied, with many structural classes discovered which span the entire activity spectrum. Full agonists potentiate the GABA-induced chloride flux to further decrease the excitability of the neuron and have found wide-spread use as anxiolytic, hypnotic and anticonvulsant agents. In contrast, inverse agonists which decrease the flow of chloride ion are proconvulsant and anxiogenic in nature. Antagonists which have minimal or no effect on the chloride flux have neutral activity. Presumably, partial agonists lie within this activity continuum [287]. This is especially intriguing in that partial agonists may display anti-anxiety properties but, due to their lowered intrinsic activity, lack the undesirable side effects often associated with full agonists [288].

The search for viable partial agonists or subtype selective ligands has led to the development of a variety of compounds representing diverse structural types including imidazoquinoxalines, benzodiazepines, imidazopyridines and β-carbolines. In an effort to identify replacement candidates for the partial agonist pandiplon U 78875 **206** [289], which was removed from clinical trials due to

liver enzyme induction, a variety of analogs were prepared and evaluated. One class of compounds studied consisted of imidazo[1,5-*a*]quinoxaline amides, carbamates, thiocarbamates, and ureas of which U-91571 **207** is representative [290]. Analogs within this series had varying activity; however, like **207**, most were partial agonists. Another related class of compounds that was explored involved a series of tetracycles as represented by U-89267 **208**, in which the carbonyl group was constrained to point toward the arene ring by incorporating a *C*(4)-*N*(5) tether (imidazo[1,5-a]-quinoxaline numbering [291]. Interestingly, derivatives from this subseries were full agonists by in vitro measurement (TBPS shift ratio) and were extremely potent in in vivo assays such as the metrazole antagonism assay. Furthermore, compounds such as **208** had unusually high affinity (13 nM) for the $\alpha_6\beta_2\delta_2$ subtype, whereas most derivatives from the "uncyclized" series (e.g. **208**) did not bind to this subtype, Eq. (82) [290–292].



(82)

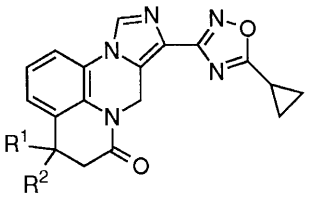
U 78875 **206** (Pandiplon)

U 91571 **207**

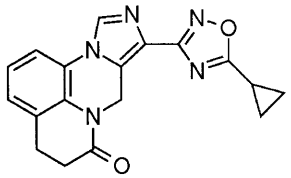
U 89267 **208**

Constraining the appended substituent of U-91571 **207** into a tetracyclic imidazo[1,5-*a*]quinoxaline ring system provided a series of high-affinity ligands for the $GABA_A$/benzodiazepine receptor complex. In addition, this constraint, which forces the carbonyl group into a relatively planar ring system, provided analogs with an antagonist to partial agonist intrinsic activity profile as indicated by TBPS shift and Cl^- current measurement. Only **209a**, **b**, which contain out-of-plane substituents at the 4-position, were nearly full agonists (in vitro). Most analogs were active in a metrazole antagonism assay consistent with ani-convulsant and possible anxiolytic activity. While the most effective analogs in this assay contained out-of-plane 4-substituents, several of the planar derivatives, including **210**, were surprisingly effective, especially considering their intrinsic activity. In contrast to **209**, none of the analogs reported herein had reasonable affinity for the diazepam insensitive $\alpha_6\beta_2\delta_2$ subtype. Clearly, the orientation of the carbonyl group (and added steric bulk) in **210** and related analogs prevents effective interaction with the $\alpha_6\beta_2\delta_2$ subtype in contrast to the nonplanar lactam ring of **208**. In addition, orientating the carbonyl group away from the aryl ring in a planar configuration provides analogs with partial agonist (or antagonist) properties which can, however be overridden by bulky out-of-plane substituents to provide full agonists, Eq. (83) [293].

A series of imidazo[1,5-*a*]quinoxaline amides, carbamates, and ureas which have high affinity for the γ-aminobutyric acid A/benzodiazepine receptor complex was developed. Compounds within this class have varying activities ranging from antagonists to full agonists. However, most analogs were found to be partial agonists as indicated by [^{35}S]TBPS and Cl^- current ratios. Many of these



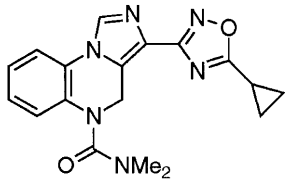
209a R^1, R^2 = Me
b R^1 = H, R^2 = Ph



210

(83)

compounds were also effective in antagonizing metrazole-induced seizures in accordance with anticonvulsant and possible anxiolytic activity. Selected quinoxalines displayed limited benzodiazepine-type side effects such as ethanol potentiation and physical dependence in animal models. *N*,*N*-Dimethyl urea **211** emerged as the most interesting analog, having a partial agonist profile in vitro while possessing useful activity in animal models of anxiety such as the Vogel and Geller assays. In accordance with its partial agonist profile, **211** was devoid of typical benzodiazepine side effects, Eq. (84) [294].



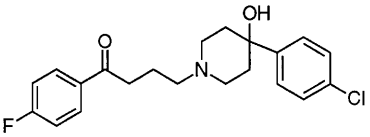
211

(84)

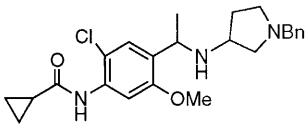
Schizophrenia is one of the most severe phychiatric illnesses and is characterized by hallucinations, delusions, and disorganized thought and behavior which result in major impairment of the patient's social and occupational function. Current medications utilizing typical neuroleptic antipsychotics such as haloperidol **212** show some promising activity in controlling the positive symptoms of schizophrenia. However, their effects are only partial, and they induce a substantial incidence of extrapyramidal symptoms (EPS) as neurological side effects [295]. Traditionally, two dopamine receptor subtypes have been classified on the basis of pharmacological evaluation, namely, the D_1 and D_2 receptors. Existing anti-psychotics are considered to act via the blockade of the classical "D_2 receptor" [296]. Recently, however, molecular biological approaches have led to the discovery of the novel dopamine D_3 and D_4 receptor isoforms [297], which are classified as the D_2-like (D_2, D_3 and D_4) receptor subfamily, and the D_5 receptor [298], which is classified as the D_1-like (D_1 and D_5) subfamily. The D_2-like receptor subfamily isoforms correspond to the classical D_2 receptors. D_3 and D_4 receptors are particularly concentrated in the mesolimbic and mesolimbocortical regions of the central nervous system, respectively [299]; areas which are thought to control emotional and cognitive functions and to be implicated in the pathology of schizophrenia [298]. In contrast, few D_3 and D_4 receptors are found

in the nigrostriatal region, which is rich in D_2 receptors and of which blockade of the dopamine system has been suggested to be associated with EPS [299].

A series of *N*-(3-pyrrolidinyl)benzamide derivatives have been synthesized and evaluated for their binding affinity for dopamine D_2-like receptor subtypes. The SAR studies indicate that the 4-substituent on the benzamide nuclei and the *N*-substituent on the pyrrolidine ring play a critical role in improving D_3 and D_4 selectivity over D_2 receptors. Some preferential D_3 and D_4 antagonists also exhibited potent inhibitory activity against apomorphine-induced climbing behavior in mice. Among them the novel [(cyclopropylcarbonyl)amino]benzamide **214** possesses high affinity for D_3 and D_4 receptors (K_i values of 21 and 2.1 nM respectively) and selectivity for D_4 and D_3 receptors (K_{iD2}/K_{iD4} = 110, K_{iD2}/K_{iD4} = 10) with weak or negligible affinity for other neurotransmitter receptors. In vivo, **213** exhibited inhibitory activity against apomorphine-induced climbing behavior with an ED_{50} value of 0.32 mg/Kc (sc), this biological profile is markedly different from those of known antipsychotics [299]. Thus compound **213** may produce unique pharmacological effects, including atypical antipsychotic effects. Further, it is believed that **213** would contribute to the understanding of the physiological and pharmacological functions of D_2-like receptor isoforms, Eq. (85) [301].



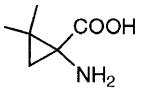
Haloperidol **212**



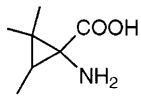
213 (85)

10 Miscellaneous

During work on a series of aspartyl dipeptides containing ACC **71** (vide supra, Eq. (28), Sect. 4) at the carboxyl terminus, it was reported that dispartame Asp-ACC-OMe had a distinct sweet taste [302] and that the corresponding *n*-propyl ester had 250–300 times the sweetness of sucrose [303]. However, replacement of phenylalanine by 2,3-methanophenylalanine gave tasteless analogues of aspartame [293, 304], and some dimethyl-ACC **214** (methanovaline) and trimethyl-ACC **215** aspartame analogues [Asp-$(Me)_n$-ACC-OMe] have a bitter taste. These taste properties, which depend on the number and position of the methyl substituents, have been explained on the basis of topochemical models; thus, a L-shaped conformation of the dipeptide is necessary for sweet taste, Eq. (86) [305].



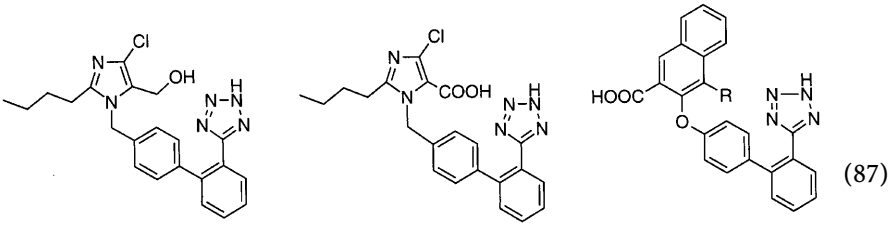
214



215 (86)

The renin-angiotensin system plays an important role in the pathophysiology of cardiovascular disease and agents such as angiotension converting enzyme (ACE) inhibitors are effective for the treatment of hypertension [306]. Antagonism of angiotension II (AII) AT_1 receptors may also be a useful strategy for the treatment of hypertension and seveal groups have disclosed non-peptidic AII antagonists [307].

Many reported AII antagonists, such as losartan **216** and its more pharmacologically active metabolite EXP 3174 **217**, share structural features believed to be important for activity. These include a heterocycle with one or more basic nitrogen atoms, an alkyl substituent in the 2-position relative to the basic nitrogen, an aryl susbtituent with an acidic group in the 3-position and an acid or its metabolic equivalent in the 4-position. Quinolin-4-carboxylic acids **218** appeared to accomodate all these structural features, Eq. (87). An initial study was the modification of the alkyl group R at the 2-position of the quinoline. The activity of the compound where R is *n*-propyl **218a**, confirmed the hypothesis that the quinoline-4-carboxylic acids can be high affinity ligands for the AII receptor. Reducing the size of the substituent to ethyl **218b** had little effect on binding affinity or functional potency but substitution of a methyl group **218c** reduced functional potency by 10 fold. The most interesting compound in this study was the 2-cyclopropyl compound BMS 183920 **218d** which showed very potent and insurmountable antagonism in the functional assays, Eq. (87) [308].



(87)

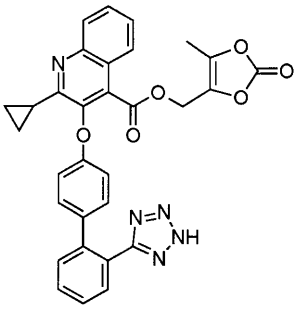
Losartan **216** EXP 3174 **217**

218a R = *n*Pr
b Et
c Me
d cyclopropyl

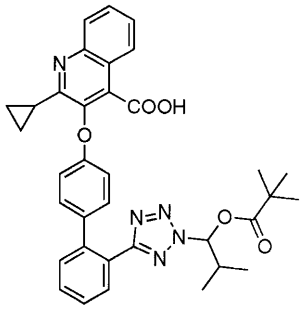
Despite excellent intrinsic potency, weak oral activity limited the in vivo activity of **218d**. Efforts to improve its oral bioavailability by a prodrug approach led to the preparation of two compounds with improved oral activity and bioavailability, the dioxolenonylmethanol ester BMS 184698 **219** and the *N*-alkyl tetrazole prodrug **220**, Eq. (88).

This prodrug modification more than doubled the oral bioavailability of the parent compound. Furthermore, BMS 184698 **219** was shown to be an effective, orally active antihypertensive agent in the sodium-replete spontaneously hypertensive rat. Compared to losartan **216** at 30 mmol/kg *p. o.* once-daily doses, BMS 184698 **219** was the better antihypertensive agent [309].

Retinoids are small molecule hormones that elicit pleiotropic biological responses by activating two families of nuclear receptors which are structurally



BMS 184698 **219**



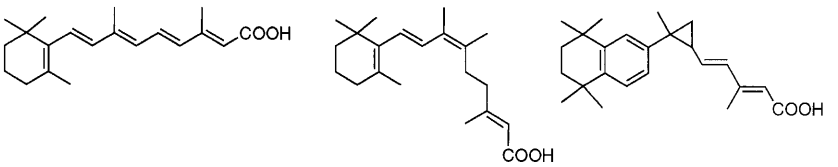
220

(88)

and evolutionarilly related to the steroid/thyroid hormone receptor superfamily [310]. The two families are the retinoic acid receptors (RARs) [311] and the retinoid X receptors (RXRs) [312] and each family consists of three subtypes (α, β, and γ) which are encoded by distinct genes. Physiologically, retinoid hormones regulate a variety of very basic biological functions both in development and in the adult [313]. Disruption of the normal pathways of retinoid homeostasis either by vitamin A deficiency [314] or by alteration of retinoid receptors [315] can lead to disease conditions. Consistent with their broad physiological effects, retinoids are of potential clinical use in a variety of areas including dermatology [316], oncology [317], opthalmology [318] and cardiovascular disease [319].

The physiological hormone for the RARs is all-*trans*-retinoic acid RA **221** and that for the RXRs is its geometric isomer, 9-*cis*-retinoic acid (9-*cis*-RA **222**) [320]. However, these polyolefinic hormones are of only limited use in elucidating the precise biological roles of each receptor family. Synthetic ligands that specifically activate only the RXR or RAR hormonal pathway and which cannot be converted into forms that activate the other pathway would be of much greater use in this regard.

The cyclopropane ring has been used as an isostere for the C9-C10 double bond to obtain locked-9-*cis* and 9-*trans* retinoid analogs. The 9-*cis*-locked analog **223** is the most potent RXR analog described to date. Because of its intrinsic pharmacologic selectivity and because it cannot be converted to an RAR active form, compound **223** is the highest affinity and most potent RXR agonist described to date and would be a very useful tool in defining the biology associated with the RXR hormonal pathways, in vivo (Eq. 89) [321].

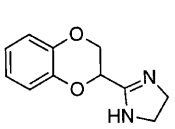


RA **221** 9-*cis*-RA **222** **223**

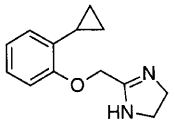
(89)

Imidazolines are one of the most studied classes of α-adrenergic drugs. Discrete structural modifications of these ligands reveal agonist or antagonist properties with varying degrees of selectivity for α-adrenergic receptor subtypes. In addition, several of these ligands also exhibit high affinity for a family of membrane proteins termed imidazoline receptors or imidazoline/guanidinium receptive sites (IGRS). Idaxozan-**224**, for example, a selective α_2-adrenergic receptor antagonist [322] belonging to the imidazoline class, has been shown to recognize these sites in a wide range of tissues, with an affinity comparable with that determined at α_2-adrenergic receptors [323]. Cirazoline **225**, a potent α_1-adrenergic receptor agonist and α_2-adrenergic receptor antagonist [324], exhibits high affinity for IGRS in a variety of tissues [323]. Thus, this molecule can serve as a useful starting point to characterize the structure-activity restrictions of this diverse group of ligand-binding pockets.

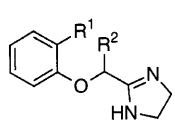
Removal of the cyclopropyl group to give the unsubstituted compound **226a** results in a 10-fold decrease in potency which parallels the decrease in affinity, while efficacy is virtually unaffected. It is worth noting that, if compound **226a** is considered as the reference, substitution at *ortho* position either with an alkyl or alkoxy group increases both potency, with exception of compound **226b**, and affinity. On the other hand, activity is negatively affected, with the exception of cirazoline **225** and compound **226c**, in which the presence of the cyclopropyl group or of the two methyl groups appears to favor retention of activity. This latter finding supports the hypothesis [324] concerning the role played by the cyclopropyl group in increasing activity, Eq. (90) [325].



Idazoxan **224**



Cirazoline **225**

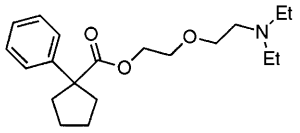


226a R^1, R^2 = H
b R^1 = *s*-Bu, R^2 = H
c R^1, R^2 = Me

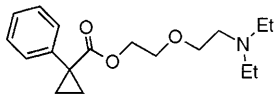
(90)

Carbetapentane (2-[2-(diethylamino)ethoxy]ethyl-1-phenyl-1-cyclopentane carboxylate) **227** binds with high affinity to σ sites [^{3}H]-(+)-3-PPP ((+)-3-(3-hydroxyphenyl)-*N*-propyl piperidine; $K_i = 11$ nM), [^{3}H]dextromethorphan ($K_i = 11$ nM), [^{3}H)-(+)-pentazocine ($K_i = 32$ nM) [326] and demonstrates anticonvulsant [327], antitussive [328], and spasmolytic [329] actions. In an attempt to determine whether these psychoactivities can be attributed to interaction at σ sites, a series of carbetapentane analogs were prepared. Phenyl ring substitution; contraction, expansion, and replacement of the cyclopentyl ring by a methyl group; replacement of the carboxylate function with an amide, methyl ether, and methylamine; and replacement of the *N*,*N*-diethylamino substituent with a morpholinyl or piperidinyl moiety were investigated. All of these novel analogs were evaluated for binding, the most selective ligands were found to be compounds **228–230**. The chemical modifications including replacing the cyclopentyl ring with a smaller ring system, i.e. cyclopropyl **228** or a methyl group

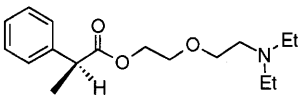
229, replacing the ester function by an amide function **230** or replacing the diethylamino moiety with a morpholino group resulted in >220 fold selectivity over muscarinic receptor binding. Therefore, several of these novel compounds are potent σ selective ligands which can be investigated as potential antitussive, anticonvulsant, and antiischemic agents Eq. (91) [330].



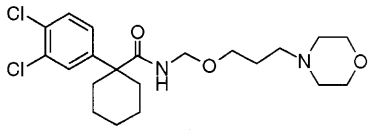
227



228 (91)

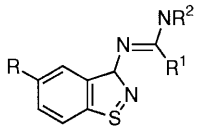


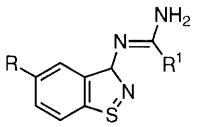
229



230

Amidinobenzisothiazoles **231** displayed remarkable analgesic action and an interesting antiphlogistic action, which is often dissociated from antipyretic action. New derivatives **232a–e** (R=H, Me) have been synthesized in order to evaluate their antiinflammatory, antipyretic and analgesic activities in vivo as well as their in vitro spasmolytic activity and to improve the understanding of structure-activity relationships. Within this series only the compounds **232c** (R=H and Me), and **232d** (R=Me) display a significant analgesis/antipyretic activity devoided of undesirable side effects. Therefore, the introduction of alicyclic structures, i.e. cyclopropane or cyclopentane rings, in the amidinobenzoisothiazole derivatives afforded effective compounds with improved activity, Eq. (92) [331].





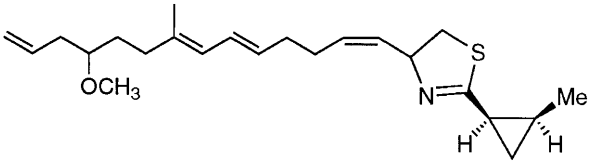
(92)

231 R = H, Me
R^1 = H, Me, Ph
R^2 = H, Me

232a R^1 = CH_2Cl **d** cyclopentyl
b CH_2-CH=CH_2 **e** 2-pyridinyl
c cyclopropyl

Curacin A **233** is a novel antimitotic agent recently isolated from a Caribbean cyanobacterium *Lingbya majuscula* (blue-green algae). It was reported that curacin A inhibited tubulin assembly by binding to the colchicine-binding site [332], which is one of the two distinct drug-binding sites on tubulin. The result is intriguing because curacin A has little structural similarity to known natural and synthetic colchicine-site ligands. Thus, elucidation of the nature of curacin A-binding to tubulin should afford further insight into the molecular mechanism of tubulin-ligand interaction at this site, and could lead to the development

of new bioactive agents, Eq. (93) [333]. The relative configuration of the *cis*-disubstituted cyclopropyl ring [332] and its (2*R*,13*R*,19*R*,21*S*) absolute configuration have been determined [333]; its four stereoisomers have been recently synthesized, Eq. (93) [334].



(93)

Curacin **233**

Recently, was reported the isolation of the unusual metabolite U 106305 **234** from the fermentation broth of *Streptomyces sp*. UC 11136 [335]. The compound is structurally remarkable being graced with six cyclopropane rings, five of which are contiguous. U 106305 **234** shows a striking similarity to the potent antifungal agent FR 900848 **104** (vide supra, Sect. 5) which was isolated from the fermentation broth of *Streptoverticillium fervens* [330]. U 106305 **234** is a potent in vitro inhibitor of the cholestery ester transfer protein (CETP) reaction, thus could be of potential application in the prevention of arteriosclerosis [337]. Its enantioselective total synthesis and stereochemical assignment similar to FR 900848 **104** have been reported, Eq. (94) [338].

(94)

U 106305 **234**

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