SYNTHESIS OF ANGIOTENSIN-CONVERTING ENZYME (ACE) INHIBITORS: AN IMPORTANT CLASS OF ANTIHYPERTENSIVE DRUGS

Dênis Pires de Lima
Departamento de Química - Universidade Federal de Mato Grosso do Sul - CP 549 - 79070-900 - Campo Grande - MS

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ACE inhibitors are one of the most active classes of molecules that lower blood pressure. This report outlines the discovery, the design and development of new compounds, and, structure-activity relationships for this drug category. Updated approaches to planned syntheses of new worthy ACE-inhibitors are also exploited.

Keywords: ACE inhibitors; antihypertensive; angiotensin.

INTRODUCTION

Angiotensin-converting enzyme plays an important role in the control of arterial blood pressure, and the following discussion has been the background to the synthesis of inhibitors of the enzyme and lead substances for the design of other inhibitors.

In 1898 saline extracts of kidney were shown to contain a pressor substance (*i.e.* a material that increases blood pressure), which was named *renin*. Many years later (1940) renin was shown to be an enzyme that acts on a plasma protein to catalyse the formation of the actual pressor substance. Nomenclature was eventually agreed upon as follows: the pressor substance is called *angiotensin* and the plasma protein, *angiotensinogen.* Several forms of angiotensin have been found, the most important being *angiotensin I* (a decapeptide) and *angiotensin II* (an octapeptide). The latter, that is the more active as a pressor agent, is produced from the former by an enzyme called *angiotensin-converting enzyme* (ACE)[1,2].

The renin-angiotensin system plays an important role in an interrelated set of mechanism for the control of the volume, pressure, and electrolyte composition of blood. Angiotensin II is the main active component, but angiotensin III also has pressor activity (25-50% of that of angiotensin II). Most of the activity of angiotensin II resides in the C-terminal octapeptide[1].

Figures 1 and 2 depict the enzymatically controlled peptide cascade, the renin-angiotensin system (RAS)[3].

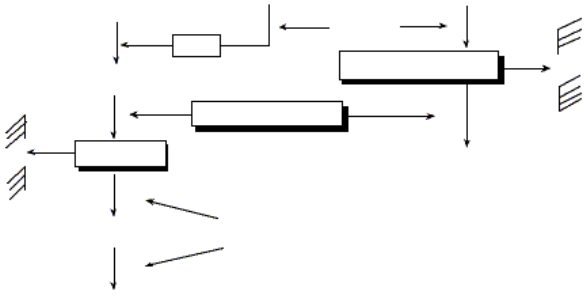


Figure 1. *Processing of angiotensionogen and kininogen (RAS).*

E-mail: dlima@nin.ufms.br

Figure 2. *Sites of stepwise enzymatic cleavage of human angiotensionogen.*

PHARMACOLOGICAL ACTIVITIES OF ANGIOTENSINS

The best-studied effects of angiotensin II are vasoconstriction (constriction of the blood vessels) and stimulation of the synthesis of aldosterone by the adrenal cortex. However, the peptide has numerously other effects, some of which also contribute to the increase in blood pressure[2].

The effects of angiotensin II are exerted through cell surface receptors, which can be blocked selectively by certain analogues of the peptide. Just how action at the receptor level is translated into cellular responses has not yet been elucidated.

Angiotensin converting enzyme (also known as ACE, kininase II, or dipeptidyl carboxypeptidase) is the enzyme responsible for conversion of the decapeptide prohormone angiotensin I into the pressor agent, angiotensin II. It is a zinc-containing enzyme that cleaves dipeptide units from peptide substrates. It is known that proline must not be the penultimate amino acid and this restriction ensures that the enzyme does not degrade angiotensin II. The complexity of the mechanisms for controlling blood pressure are hinted at by the fact that besides catalysing the synthesis of angiotensin II, the most potent pressor substance known, the enzyme also catalyses the destruction of bradykinin (Figure 1), the most potent vasodilator[3].

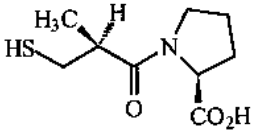
Factors that lower blood pressure or volume tend to stimulate renin secretion, while factors that raise blood pressure or volume have the opposite effect. The relationship between elevated plasma levels of renin to high blood pressure is complex, but agents that block the renin-angiotensin system have been found to lower in many patients with high blood pressure[2].

INHIBITORS OF ANGIOTENSIN CONVERTING ENZYME

In the 1970s, following the brilliant work performed by Ferreira and colleagues[4], Ferreira in collaboration with Greene[5,6] and, finally by Erdos and others investigators[7], two classes of inhibitors of the renin-angiotensin system were identified: angiotensin II antagonists, which block receptors for the natural peptide (without leading to the natural response), and converting enzyme inhibitors, which slow the rate of formation of angiotensin II from its inactive precursor[2].

Examples of the former (angiotensin II antagonists) are either modified peptides in which some of the amino acids of the natural material have been changed as saralasin[8] or, non-peptide antagonists as DUP 753[9].

An important competitive inhibitor of ACE is captopril **1**[1], which inhibits conversion of the relatively inactive angiotensin I to the angiotensin II.

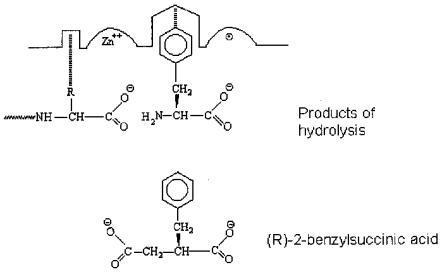


1

RATIONAL SYNTHESIS DESIGN OF ACE INHIBITORS

A brief discussion of the manner in which the compound **1** was designed[1] suggested of some modifications that were incorporated into other new drugs and is therefore given here:

By analogy with bovine pancreatic carboxypeptidase _– also a zinc-containing enzyme —, which hydrolyses a carboxyl terminal peptide[10], it was assumed that a positively charged residue at the active site (analogous to Arginine-145 of carboxypeptidase) binds with the negatively charged C-terminal carboxyl group of the peptide substrate. The enzyme-bond cleavage, is taken to be separated from the positively charged residue by a distance corresponding to a dipeptide unit, as opposed to the distance of a single amino acid unit, since ACE cleaves the terminal dipeptide while carboxypeptidase cleaves the terminal amino acid. It has been found[11] that 2-R-benzylsuccinic acid is a potent competitive inhibitor of carboxypeptidase A, and, it was proposed that the compound was a bi-product analogue that was bound to the active site of the enzyme in a manner that combines the modes of binding of the two products of the enzyme's action (Schemes 1 and 2)[11].

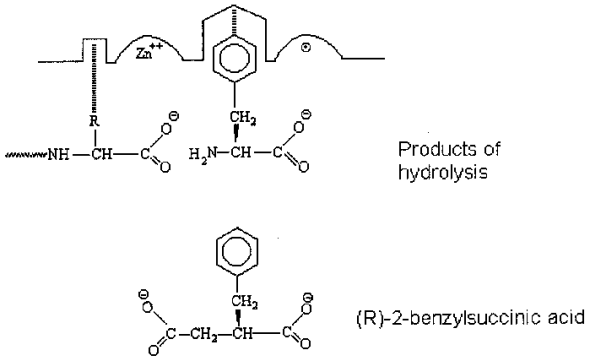


Scheme 1. *Hypothetical active site of carboxypetidase A.*

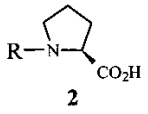
In the case of ACE a *dipeptide* is cleaved and so compounds, of the general type **2**, were examined[11].

Proline was chosen as the carboxyl terminus because of its presence (as the carboxyl terminus) of previously reported ACE inhibitors, ant it was found to provide the most powerful inhibitor of structure **2** among 11 other amino acids.

The length of the chain was varied in an attempt to improve the alignment of the terminal carboxyl with the zinc ion; compounds with succinoyl and glutaroyl chains were the most potent inhibitors. Substitution of both of these chains was examined next and **3** and **4** were found to be especially powerful inhibitors.



Scheme 2. *The collected products hypothesis of enzymes inibitors.*



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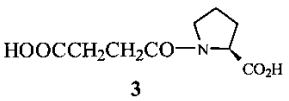

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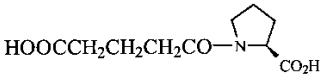

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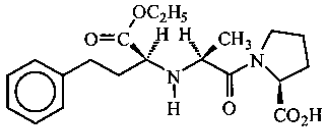
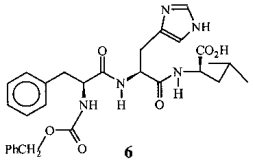
Among a large number of structural modifications that were studied[11], the most important proved to be replacement of the succinoyl COOH by SH, which has a greater affinity with zinc ions. Eventually, studies of the above type led to introduction of captopril **1**- the most potent inhibitor up to the end of 1970s[1]. Various other inhibitors of converting enzyme have since been synthesised. One such is enalaprilic acid. It resembles captopril in containing a "proline surrogate," but it differs in that it is an analogue of tripeptide rather than a dipeptide. Enalaprilic acid itself is poorly absorbed orally; it is administered orally as the monoethyl enalaprilat **5**, which serves as a prodrug.



5

New sophisticated approaches to the synthesis of ACE inhibitors were developed from mid 1980s. Among these, there is a very interesting design of a drug that mimics closely angiotensin I planned by Flynn and co-workers[12]. The tripeptide fragment (*N*-benzyloxycarbonyl Phe-His-Leu-OH; **6**) itself has modest affinity for ACE. Appropriate analyses led to the design of the tricyclic compound (**7**) as a lipophilic, conformationally restricted mimic of tripetide **6**.



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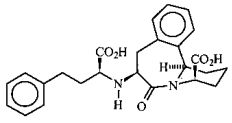

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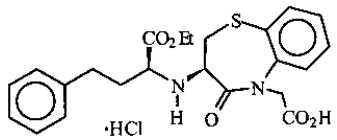
Based on the structure of enalaprilat esters, Gante and Witzel[13], after several conformation-activity and computer-graphic studies, designed a new drug **8** that showed ACE-inhibitory effect.



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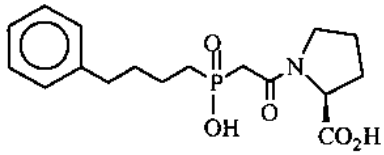
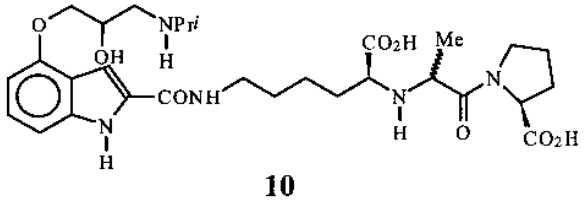
A similar investigation was performed by Petrillo and co-workers[14], that culminated to the synthesis of several phosphinic acid inhibitors incorporating 4-substituted prolines; using as the prototype the phosphinic acid [[hydroxy(4-phenylbutyl) phosphinyl] acetyl]-L-proline **9**. Some of those compounds showed longer duration of action after oral administration.



9

In 1988 Hardy and colleagues synthesised A575C[10,15] a compound which has both ACE inhibitor and beta-blocking activities.



10

A compound that express both of these activities would has an improved therapeutic profile, considering that β-blocker effect causes decrease in heart rate and contractility.[16] In the *in vitro* assays, A575C **10** was found to exhibit both effects and hence it is potentially a novel type of antihypertensive agent.

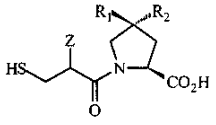
The year of 1988 was fruitful when one focalises the advances occurred into the discussed field. Almquist and colleagues[17] came up with the synthesis of ketomethylene-containing nonapeptide analogues, **11** and **12**. These compounds were potent inhibitors of rabbit lung ACE with more activity than captopril

Cbc-Tyr-Proψ($COCH_2$)Gly-Pro-X-Pheψ($COCH_2$)Gly-Pro

11: X= Lys

12: X= Nle

Smith and co-workers[18] synthesised *N*-(mercaptoacyl)-4-substituted-(*S*)-prolines. Among those compounds, **13** to **18** were the most potent in vivo intravenously.



13: R_1= OCH_3; R_2= H; Z= (*RS*)CH_3

14: R_1=R_2= OCH_2CH_2O; Z= (*RS*)CH_3

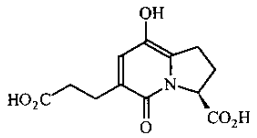
15: R_1=R_2= SCH_2CH_2S; Z= (*RS*)CH_3

16: R_1=R_2= $SCH_2CH_2CH_2S$; Z= (*RS*)CH_3

17: R_1=R_2= SCH_2CH_2S; Z= H

18: R_1=R_2= $SCH_2CH_2CH_2S$; Z= H

It is also very important to mention the article published by researchers from the Eli Lilly laboratories regarding the elucidation of A58365A **19** and A58365B **20**[19]. These compounds are produced by *Streptomyces chromofuscus*, a micro-organism resident in the Brazilian soil[20] and exhibit very important ACE inhibition.



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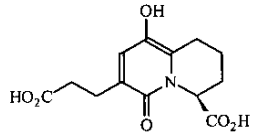
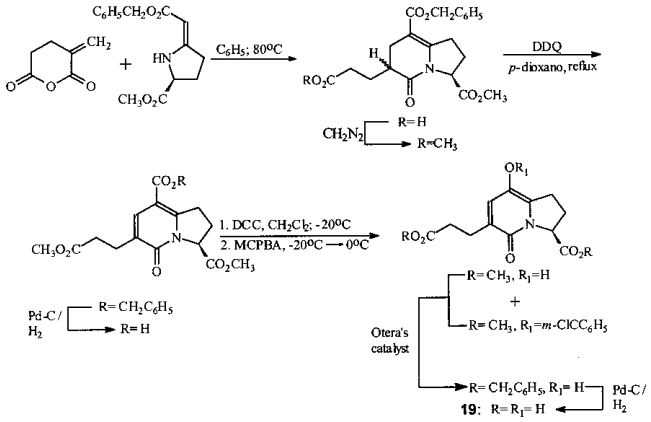
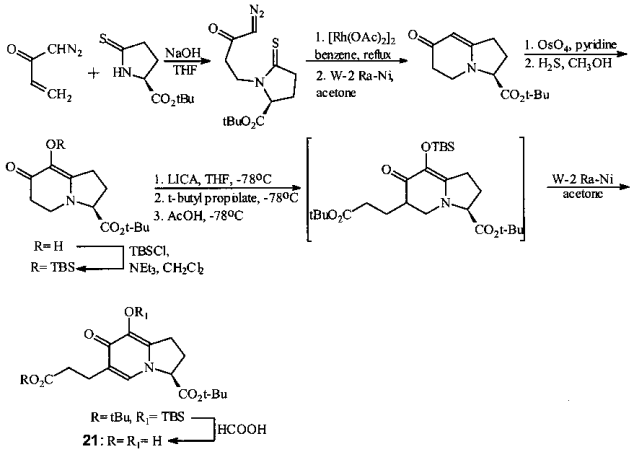


20

The work previously described was the motive to the elegant synthesis of **19** and iso-A58365A **21**, performed by Danishefsky and Fang,[21]

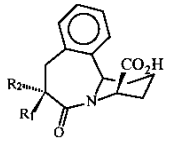


Scheme 3. *Synthesis of A58365A,* ***19****.*



Scheme 4. *Syntheses of* iso-*A58365A,* ***21****.*

In the nineties, studies aimed to the synthesis of conformationally restricted inhibitors of ACE continued, and, Flynn and co-workers[22], prepared the potent thiol containing inhibitors **22** e **23** that are useful probes for studying the active sites of metalloproteases.

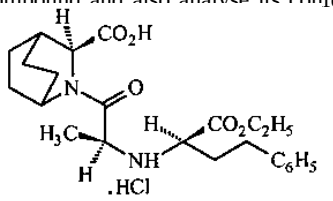


22: R_1= CH_2SH; R_2= H

23: R_1=H; R_2= CH_2SH

As a result of the clinical studies on Zabicipril, **24**, proving

that the substance is a well tolerated, powerful and long acting inhibitor of ACE, researchers from Institut de Recherches Servier and Institut de Chimie des Substances Naturelles in France, decided to prepare the compound and also analyse its conformation[23].



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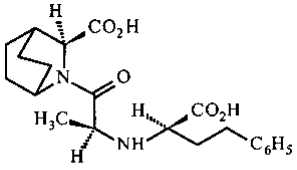
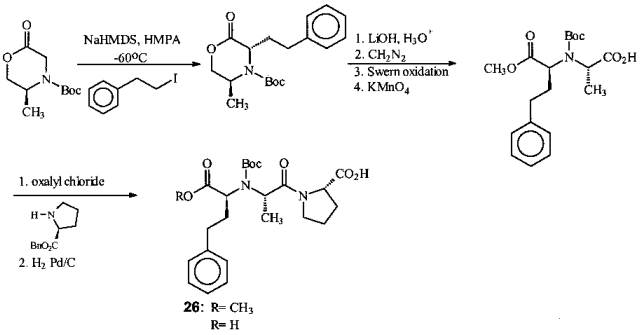
Zabicipril is a prodrug, devoid of action *per se*, which is transformed by liver esterases into its active diacid form Zapiciprilate **25**.



t-Bu-NH2 salt

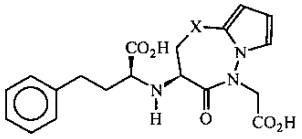
25

After identification of a novel series of renin inhibitory compounds, Baker and Condon[24] prepared the methyl enalaprilat **26** from (5S)-2,3,5,6-tetrahydro-5-alkyl-N-(*tert*-butyloxycarbonyl-4H-1,4-oxazine-2-one as shown in the following Scheme 5.



Scheme 5. *Synthesis of methyl enalaprilat,* ***26****.*

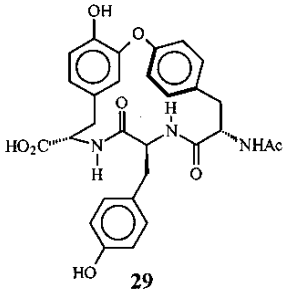
Through a highly regioselective reaction between 4-hydroxy-2-butynoates and (S)-amino-acids esters, Arcadi and co-workers[25] synthesised ACE-inhibitors and carried out a very interesting NMR and crystal X-ray analyses on the products. In this same year, Bolós and co-workers[26] performed the asymmetric synthesis of pyrrolo[2,1-*b*][1,3,4]thiadiazepine derivative **27**. The synthesis was very innovative on account of a novel heterocyclic nucleus was introduced as a part of the molecule of the ACE-inhibitor. The design of the synthesis of **27** was based on an isosteric modification of a previous known compound **28**[27].



27: X= S

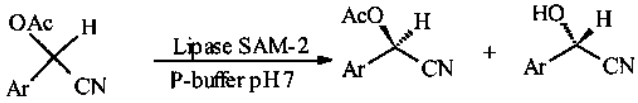
28: X= CH_2

A very ingenious process of SNAr reaction, employing arene-ruthenium chemistry, allowed Pearson and Lee[28] to achieve the synthesis of K-13, **29**. This is a L, L-isodityrosine-derived cyclic tripeptide, isolated from the culture broth of *Micromonospora halophytica* subsp. *exilisia*, that has been shown to be a novel, non-competitive inhibitor of angiotensin I-converting enzyme and a weak inhibitor of aminopeptidase B.



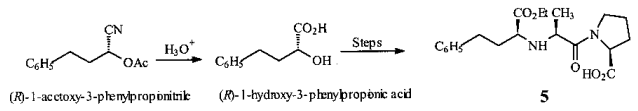
29

A microbiologic proceeding, putting in service hydrolases, granted the preparation of enantiomerically pure compounds. Schneider and colleagues[29] accessed the synthesis of α-hydroxycarboxylic acids *via* esterhydrolase catalysed resolution of the corresponding cyanohydrin acetates (Scheme 6).



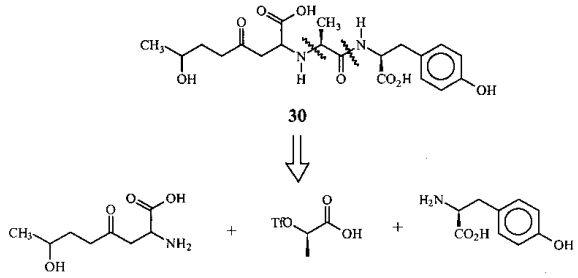
Scheme 6. *Resolution of cyanohydrin acetates.*

Acid catalysed hydrolysis of 1-acetoxy-3-phenylpropionitrile proceeds without racemisation and leads to (R)-1-hydroxy-3-phenylpropionic acid, valuable building block for numerous ACE inhibitors, *e.g.* monoethyl enalaprilat, **5** (Scheme 7).



Scheme 7. *Hydrolysis of α-hydroxycyanohydrin acetates.*

More recently, Baldwin and co-workers[30] examined the preparation of γ-keto α-amino acids *via* carbon based nucleophillic ring opening of activated monocyclic β-lactams and applied the method to the synthesis and stereochemical assignment of the dipeptide ACE inhibitor, WF-10129, **30** based on the following retrosynthetic analysis (Scheme 8).



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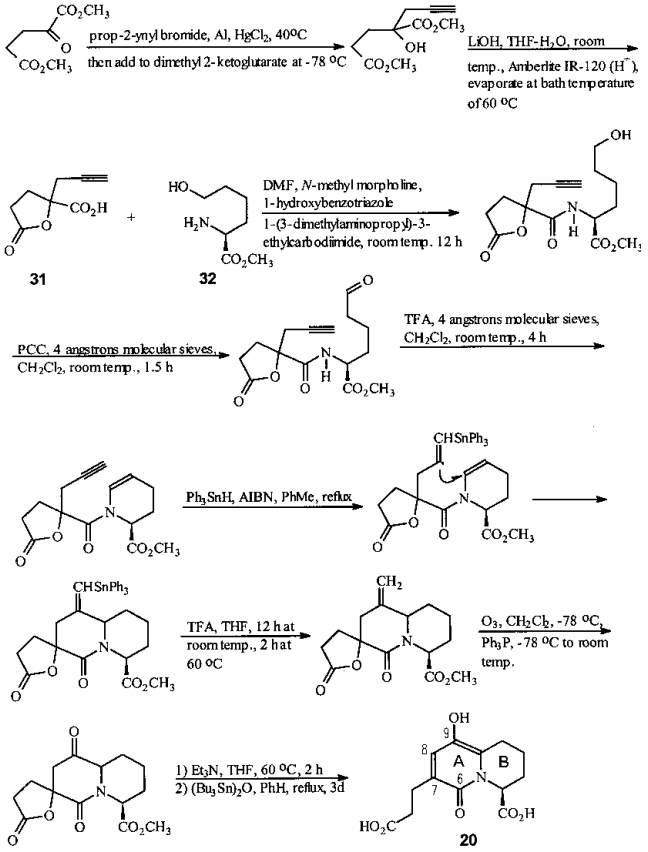
Scheme 8. *Retrosynthetic analysis for preparation of WF-10129,* ***30****.*

It is momentous to account for the synthesis of crystalline (±)-A58365B, **20**, accomplished by Clive's research group[31]. The structure does not appear to be especially complicated, but synthetic work revealed a number of unexpected difficulties. In particular, generation of the C(7)-C(8) double bond is not at all straightforward[32], because ring B is also susceptible to

desaturation. The C(7)-C(8) unsaturation was introduced early- but in the disguised form of a spirolactone **31**. This compound, which was prepared as shown in Scheme 9, represents all the carbons that make up the C(6)-C(9) segment of the natural product, including the propionic side chain.

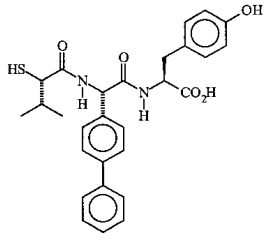
The ring B portion of **20** was constructed[31] (Scheme 9) from ε-hydroxynorleucine methyl ester **32**, which not only has all of the required atoms, but also, could be used without prior hydroxy protection. The key step of coupling ring A **31** and ring B **32** subunits was made by a process based on enyne radical cyclization. This strategy overcome the difficulties revealed in the previous work carried out by Wong and Moeller[32], and Danishefsky and Fang[21].



Scheme 9. *Synthesis of A58365B,* ***20****.*

The development of a single agent which possesses the ability to inhibit both of the membrane-bound zinc metalloproteases, angiotensin-converting enzyme, and neutral endopeptidase (NEP), has been the focus of recent drug discovery[33]. Both of these ectoenzymes are intimately involved in regulatory systems which modulate blood pressure and fluid volume homeostasis. ACE functions as described before[1,2], and, NEP is the major enzyme involved in the metabolic inactivation of atrial natriuretic factor (ANF)[34]- 28-aminoacid polypeptide- that works by eliciting a number of biological responses including diuresis, natriuresis, vasodilation, and, reduction of plasma aldosterone levels. Studies have shown that coadministration of selective ACE and NEP inhibitors in animal models of hypertension has a more beneficial effect than the administration of the single agents separately[35]. It has also been demonstrated that single molecules which possess dual ACE and NEP inhibitory activity also exhibit these synergistic properties[36]. These compounds represent a new class of cardiovascular agents that should be more effective in a broaden range of hypertensive patients. Compounds from the series of a-mercapto dipeptides are ACE and NEP inhibitors, and, one of the best is the biphenyl analog **33**.

Further modification of this compound was undertaken by Fink and collaborators[33], in order to improve its duration of action leading to the cycloleucine **34**.



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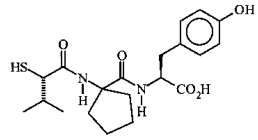
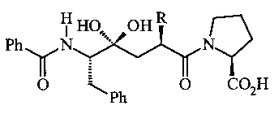


34

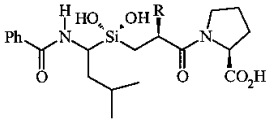
With the advent of Combinatorial Chemistry[37] and its use as a powerful tool in drug discovery[38], libraries of ACE inhibitors were prepared. Blackburn and co-workers[39] described the preparation of such libraries using solid-phase synthesis and affinity selection. The method involved reductive alkylation of resin-bound dipeptides; H-X-Pro-DHPP-PEG-PS or H-X-X-PAL-PEG-PS. Affinity selection of the library compounds identified hydrophilic N-alkylated dipeptides as potential ACE inhibitors.

Another interesting work performed by Sieburth and colleagues[40] reports the use of the ACE inhibitor model **35** for the design of the silanediol inhibitor **36**. The diasteromeric mixture of **36** was tested as ACE inhibitor showing hopeful results.



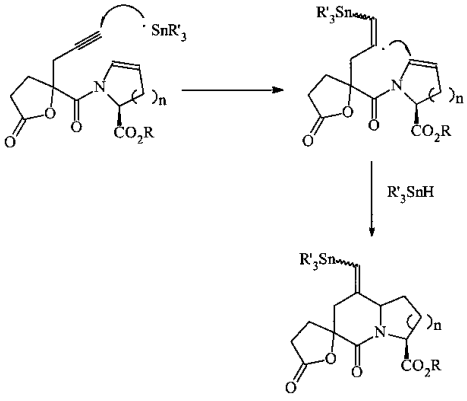
35

R = H or -CH_3



36

The general Clive's approach to compounds of the bicyclic pyridone class[41], involving as the key step, a radical cyclisation, recently allowed the synthesis of racemic A58365A **19** (Scheme 10).



Scheme 10. *General approach to compounds of the bicyclic pyridone class.*

Clive and co-workers[42] have recently achieved the sysnthesis of the optically active forms of A58365A **19** and A58365B **20**.

CONCLUSION

Most of the syntheses shown previously in this review are based on the "*ab initio* drug design." The structure of receptor guided the design of potent and specific inhibitors. In this regard, several new compounds are still to be prepared. The development of agents that possess dual enzyme inhibitor is fruitful field to be exploited as these compounds function as ACE inhibitor and can be used for treating congestive heart failure (CHF).[43]

Lately, important and useful methologies came up to aid of drug design. This is the case of Combinatorial Chemistry,[37] and, microbiological or enzymatic conversion of biological active compounds.[44] Surely these tools will also contribute to plan new ACE inhibitors.

Since the pharmaceutical laboratories have focused hypertension very closely, alternative methods for the blockade of the renin-angiotensin system (RAS) have also been developed. The competitive angiotensin II (AII) antagonists are drugs that have currently being investigated[45] for the treatment of various cardiovascular disorders, including hypertension[46], and the orally active ones have gained undoubted room as potent lowers of blood pressure. Recent valuable works have been published dealing with synthesis of this drug category[47].

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