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AO DE SOUZA[1], DG PEREIRA[2], N DURÁN[1,3]
[1]IQ, UNICAMP, BRAZIL
[2]UNIMEP, BRAZIL
[3]NCA, UMC, BRAZIL

Structure and Activity of Aromatic Propenamine Derivatives

Contents

Abstract

This review reports aspects related to the structure and biological activities of compounds possessing the aminoallyl group in their structures (propenamines). The compounds were classified depending on the pharmacological effect as antihistaminic agents, inhibitors of 5-hydroxytriptamine (5-HT) and noradrenaline (NE) uptake, anti-tripanosomatid, antimycobacterial or as antifungic activity. Cytotoxicity on mammalian cells is also described as well as the importance of some geometric isomers on the biological effect.

Key words: Propenamines, structure, antihistaminic, antimycobacterial, anti-tripanossomatid, cytotoxicity, allylamines.

Invited Review

Correspondence

N Durán
Biological Chemistry Laboratory, Instituto de Química, Universidade Estadual de Campinas, CP 6154, CEP. 13083-970, Campinas, SP, Brasil.
Phone: 55-19-3788-3149 Fax 55-19-3788-3023
E-mail: duran@iqm.unicamp.br

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Introduction

The aminoallyl propenamine moiety (Figure 1) is present in some important clinically available drugs such as antidepressant, antifungal and antihistamic agents. Compounds possessing this structural unit have also been investigated as possible anti-infective agents, particularly in tuberculosis, Chagas disease and Leismaniasis models. This article deals with the main structural aspects related to their biological activities.

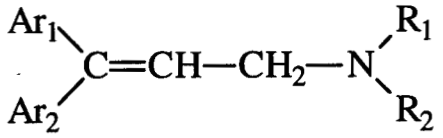


Figure 1. General formulae of the diarylpropenamine moiety. Ar_1 and Ar_2 are usually aromatic rings and the nitrogen is often tertiary linked to methyl groups.

These compounds will be grouped depending on the pharmacological effect they have as antihistaminic agents, inhibitors of 5-HT and noradrenaline uptake, anti tripanosomatid or antimycobacterial activity. Cytotoxicity on mammalian cells is also described as well the importance of some geometric isomers on the biological effect.

It is important to note that there has been no investigation of the antihistaminic properties and also of the antitripanossomatid or antimycobacterial activities of these compounds. This consideration should be taken into account since there is similarity among the structures of these chemicals.

Antihistaminic Agents

Histamine is known to play an important role in different physiological and pathophysiological processes; it increases vasodilatation, vascular permeability, smooth muscle contraction and gastric acid secretion, modulates various immune functions and is involved in neurotransmission. A large quantity of histamine is released from mast cells, basophil granulocytes and histaminergic neurons in the central nervous system (Mitsuhashi & Payan, 1992; Watanabe *et al.*, 1990). Histamine can act not only on cell surface receptors (H1 , H2 and H3 receptors), but may also bind to intracellular binding sites like cytochrome P450 enzymes (LaBella *et al.*, 2000; Brandes *et al.*, 2000; 1992). Acting as an autocrine or intracrine mediator, histamine may have a possible role in cell proliferation, differentiation, hematopoiesis, embryonic development, regeneration and wound healing (Artuc *et al.*, 1999; Dy *et al.*, 1993; Endo *et al.*, 1992).

Histamine is made up of an imidazole ring that can exist in two tautomeric forms (Figure 2). Two-carbon chain with a terminal α-amino group are attached to the imidazole ring. Whenever cell damage occurs, histamine is released and stimulates the dilation and increases the permeability of small blood vessels. The advantage of this to the body is that defensive cells (e.g. white blood cells) are released from the blood supply into an area of tissue damage and are able to combat any potential infection. The release of histamine can also be a problem. When an allergic reaction or irritation is experienced, histamine is release and produces the same effects when they are not really needed.

The early antihistamine drugs were therefore designed to treat conditions such as hay fever, rashes, insect bites or asthma. Two examples of these early antihistamines are Mepyramine and Diphenydramine (Figure 2).

It is known that histamine could also stimulate gastric acid release. However,

conventional antihistaminic failed to have any effect on gastric acid release and also failed to inhibit other actions of histamine. The scientists therefore proposed the existence of two different types of histamine receptors. Conventional antihistaminics known in the early sixties were already selective in that they were able to inhibit the histamine receptors involved in the inflammation process (classified as H1-receptors) and were unable to inhibit the proposed histamine receptors responsible for gastric acid secretion (classified as H2-receptors).

An important unwanted side effect of H1-antagonists is their sedative activity. Until now only a few non-sedative antagonists are known, but it is not clear why some compounds are sedative and others are not. Only two modeling studies dealt with the sedative properties of H1-antagonists (Barbe *et al.*, 1983; Pepe *et al.*, 1989).

Cinnarizine, 1-(diphenylmethyl)-4-(3-phenyl-2-propenyl)-piperazine (Figure 2), is a piperizine derivative that, besides its usefulness as antihistaminic for the symptomatic management of nausea and vertigo in labyrinthine disturbance and for prevention of motion sickness, is used in the treatment of vascular disorders (Reynolds, 1989). Its mode of action seems to involve inhibition of Ca^{2+} entry to the inside of the cell (Godfraind & Kaba, 1969).

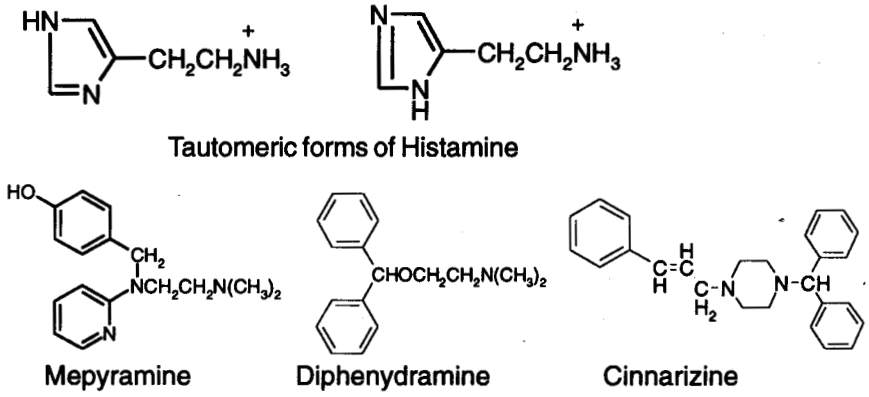


Figure 2. Chemical structures of Histamine, Mepyramine, Diphenydramine and Cinnarizine.

The diarylpropenamine unit is present in both Phenindamine and Mebhydrolin (Figure 3), in which the aminoalkyl side chain becomes part of a heterocyclic system. These drugs are of particular interest because their rigid ring structures with a fixed distance between important pharmacophores help to define structural requirements for H1 antagonistic activity (Di Bella *et al.*, 1995).

Structure-activity studies on antihistaminic agents revealed that the presence of a planar diarylpropenamine ArC=CH-CH_2N unit and a pyrrolidino ring as the side chain tertiary amine is important for antihistaminic activity (Waringa *et al.*, 1975; Riley &

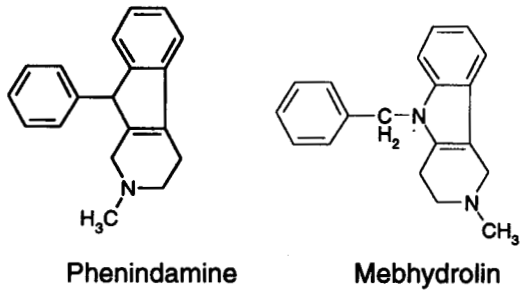


Figure 3. Chemical structures of antihistaminic agents sharing the propenamine unit

DeRuiter, 1998). Triprolidine, Pyrrobutamine and Acrivastine represent such drugs (Figure 4). Giving the important differences in activity of their individual isomers, they are commercialized as the *E* isomers (Riley & DeRuiter, 1998). Triprolidine, as its hydrochloride salt, is the most active as the (*E*)-2-[1-(4-methylphenyl)-3-(1-pyrrolidinyl)-1-propenyl]-pyridine isomer (Di Bella *et al.*, 1995).

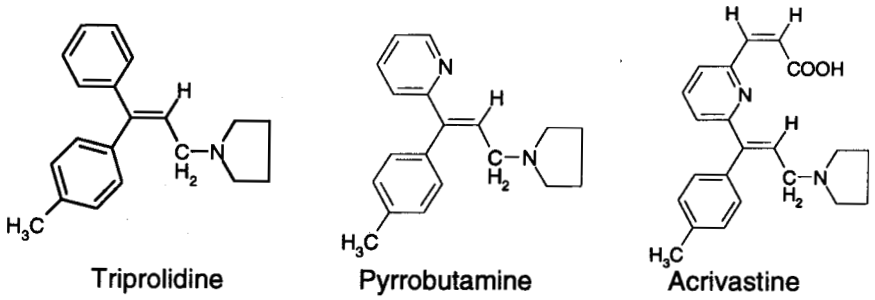


Figure 4. Chemical structures of Triprolidine, Pyrrobutamine and Acrivastine.

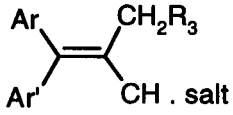
Acrivastine (Figure 4) differs from Triprolidine by the presence of a carboxyethenyl group at the 6-position of the pyridyl ring. The enhanced polarity of this group limits the blood-brain barrier penetration and thus acrivastine produces less central effects than triprolidine (Cohen *et al.*, 1985[a,b]; Mann *et al.*, 2000; Plember van Balen *et al.*, 2001).

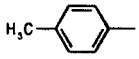
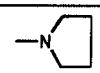
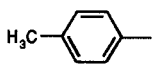
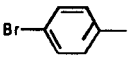
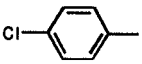
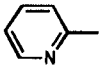
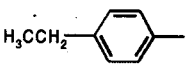
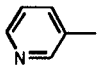
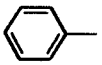
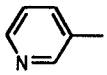
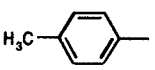
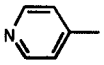
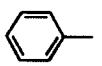
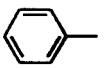
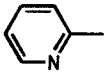
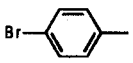
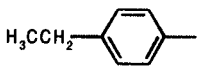
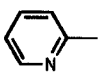
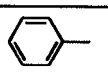
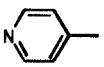
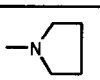
Propenamines of the Triprolidine class are of special value as probes of the histamine H1 receptor because of the rigid nature of much of their molecular framework, that allows investigation of the requirements of the two aromatic binding sites, proximal and distal, to the electrostatic site of the receptor. The antihistaminic, Triprolidine (which has the *E* configuration) and its corresponding *Z*-isomer provide a frequently quoted example of a geometrically isomeric pair whose members differ substantially in their biological potencies (Casy, 1989). Table 1 summarizes the chemical structures of some derivatives of Triprolidine.

Isomers of Triprolidine having the a-pyridylethylene type of structures (*i.e.* E 2-pyridyl/CH_2N isomers) showed high and specific antihistaminic activity and the other isomer of each pair was considerably less active (Adamson *et al.*, 1951). Triprolidine bound strongly to guinea-pig cerebral cortex and its affinity constant (Ka) was about 100 times that of its *Z*-congener. The *E*:*Z* Ka ratio for Triprolidine and its geometrical isomer is one-sixth to one-tenth of the values recorded in the gut-bath experiments, a result which may suggest that H1-receptor sites of guinea-pig ileum and cerebellum are not identical. The Ka ratio of the geometrical isomers, *E*/*Z* of 4-chlorophenyl derivatives (Trip Der 4) was 44, a value inferior to that of the Triprolidine as a result of the relatively greater affinity of the halogenated *Z* isomer. In the *E*-series of the Triprolidine derivatives, replacement of 4-methyl by 4-ethyl had little influence upon affinity, while small decreases were observed following substitution by chlorine or bromine. Replacement of 2-pyridyl of Triprolidine by 3-pyridyl led to a product of a remarkably high affinity, exceeding that of the parent. This result was surprising in view of the low potency of the *E*-analogue of Zimelidine on guinea-pig ileum and rat cerebellum sites (5-6% that of (+)-bromopheniramine (Hall & Ogren, 1984), although the potency-raising influence of pyrrolidino (as in Tripr Der 7) over dimethylamino is well known (Ison & Casy, 1971). The *Z*-4-pyridyl (Trip Der 8) analogue, like other geometrical isomers of this configuration, had a Ka value in the 10^7 M^{-1} range rather than 10^9 as found for *E*-congeners.

In an assay to evaluate the ability of these compounds to protect rats against

Table 1. Chemical structures of Triprolidine and its derivatives (E/Z).



Triprolidine derivatives (Trip Der 1 -18)			
	Ar	Ar'	R_3
Triprolidine			
Trip Der 1			
Trip Der 2			
Trip Der 3			
Trip Der 4			
Trip Der 5			
Trip Der 6			
Trip Der 7			
Trip Der 8			
Trip Der 9			
Trip Der 10			
Trip Der 11			
Trip Der 12			
Trip Der 13			-N(CH3)2
Trip Der 14			
Trip der 16			-N(CH3)2
Trip Der 15			-N(CH3)2
Trip Der 17			
Trip Der 18			

a lethal dose of compound 48/80 (a mixture of oligomers recognized as a potent histaminic-releasing agent) (Niemegeer *et al.*, 1978), Triprolidine stands out as the most effective protecting agent. Trip Der 4, Trip Der 10, Trip Der 11 and 3-pyridyl analogues were all effective at a dose of 10 mg kg^{-1}; of these only the 3-pyridyl derivative (Trip Der 7) was effective at 2.5 mg kg^{-1}. All these derivatives belong to the *E* configuration series; the *Z* analogue (Trip Der 4) was ineffective at 10 mg kg^{-1}. The *Z*-4-pyridyl analogue (Trip Der 6), although of similar (low) affinity to *Z*-Trip Der 4 at central sites, proved the more effective protecting agent. These data are in reasonable accord with the in vitro potency findings (Casy *et al.*, 1992[a]).

Triprolidine was employed to study the presence and the characterization of the role of the endogenously produced histamine during *in vitro* dendritic cell differentiation induced by interleukin-4 and granulocyte-monocyte colony stimulating factor (GM-CSF). During *in vitro* differentiation, parallel culture incubation was performed by adding H1 receptor antagonist Triprolidine and other factors. The results showed simultaneously increase on both histidine decarboxylase level and histamine content during differentiation of elutriated monocytes toward dendritic cells. The H1 blocker Triprolidine decreased the expression of CD45 from day 3 around 60-80% of control value. These results suggest that locally generated histamine is involved in the expression of CD40 and CD45 (Szeberenyi *et al.*, 2001).

The antihistaminic potencies of the 3-amino-1,1-diarylprop-1-enes and related compounds, were measured by their ability to antagonize the histamine-induced contraction of the guinea-pig ileum (Ison & Casy, 1971).

Between the compounds Trip Der 1/13 and Trip Der 14/15, there was a pronounced enhancement of potency followed by replacement of dimethylamino by 1-pyrrolidino in 3-amino-1-aryl-1-(2-pyridyl) propenes. A similar observation was previously observed by White *et al.* (1951). Casy & Ison (1970) reported that 1,2-diaryl-4-(1,pyrrolidino) butenes (Figure 5) also possess significant antihistaminic potencies and there appears to be a diminished stereospecific dependence upon activity amongst 4-(1-pyrrolidino) butenes compared with those found for 4-dimethylamino and 4-piperidino analogues. Both *E* and *Z* but-1-enes are moderately potent while the *E* but-2-ene has a pA2 (referring to their competitive antagonistic activities) approaching 8. Pyrrobutamine, the *Z* analogue of the last compound, which is in clinical use was confirmed as a very potent antihistaminic agent but its pA2 is not known because it had a non-competitive mechanism of action.

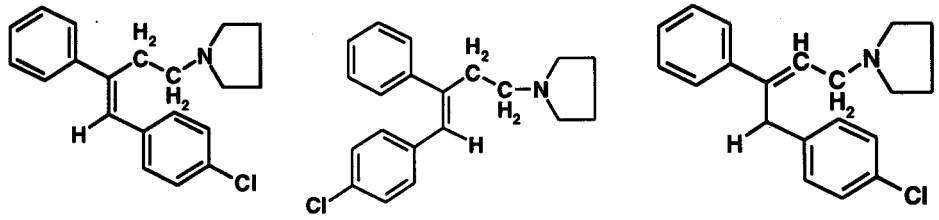


Figure 5. Chemical structures of 1,2-diaryl-4-(1-pyrrolidino)butenes (*E* But-1-ene, *Z* But-1-ene, *E* But-2-ene).

uantitative structure activity relationships (QSAR) analyses indicated that the two aromatics rings and a basic amino group are essential for receptor binding (Borea e*et al.*, 1986) and at least seven classes of classical H1-antagonists bind at the same receptors site (Terlaak *et al.*, 1992).

There is ample evidence of the stereoselective nature of H1 histamine receptors

(Casy, 1989; Casy *et al.*, 1992[a,b]). The configuration of a chiral center close to the diaryl unit of the molecule is very important to the biological activity. Receptor sensibility to the disposition of the two-aryl groups about a benzylic carbon is also apparent in antihistaminics of the aminopropene type.

Isomers derivatives of Triprolidine (configuration *E* for 2-pyridyl, *Z* for phenyl) had higher affinities than corresponding *Z*(2-pyridyl) or *E*(phenyl) isomers, while receptor stereoselective are maintained in the less potent 3-pyridyl analogues.

An essentially coplanar ArC=CCN arrangement has previously been advanced as an important requirement for antihistaminic activity in 1,1-diaryl-prop-1-enes and 1,2-diarylbut-2-enes (Cason & Ison, 1970). Although direct comparison of Trip Der 16 (*E/Z*) and the unsubstituted phenyl analogues - Trip Der 1 (*E/Z*) is not possible because the two sets of isomers were tested on separate occasions, it is clear that (i) both the *E* and *E/Z* mixture [Trip Der 16 (*E/Z*)] are significantly active, (ii) the *E* derivative of Trip Der 16 is more potent than the *Z* isomer of Trip Der 16 and (iii) the *E ortho*-tolyl derivative of Trip Der 16 is more potent than the phenyl congener Trip Der 1. The factors which increase the deviation of the Ar' and C=C planes in antihistaminic of structure I have an advantageous effect upon potency either in terms of association of Ar' at the receptor or because of a concomitant increase in the population of planar ArC=C conformers (Ison & Casy, 1971).

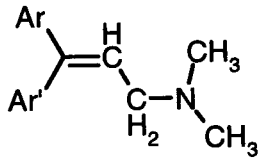
From a pharmacological point of view, the results raise the question of the general superiority of 2-pyridyl over phenyl and substituted phenyl as the aryl group *E* to aminomethyl in antihistaminic drugs of structure I (Figure 1). This appears to be true when the choice is between 2-pyridyl and *p*-chlorophenyl or *p*-tolyl but is less certain in the case of phenyl itself in view of results on 1,1-diphenyl-3-pyrrolidinoprop-1-ene (Trip Der 14). The significant potency of the *E/Z* mixture (Trip Der 18) further demonstrates that non-pyridyl containing analogues of structure I retain pronounced antihistamine properties while the lower activity of Trip Der 17 compared with Trip Der 14 shows that phenyl is preferred to *p*-tolyl as the aromatic group *E* to CH_2N in I.

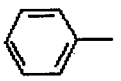
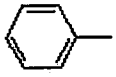
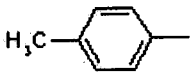
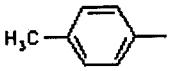
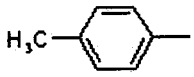
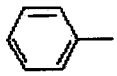
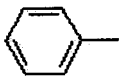
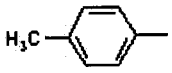
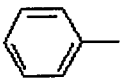
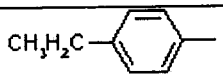
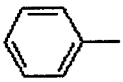
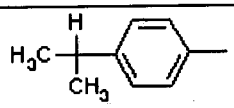
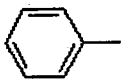
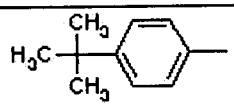
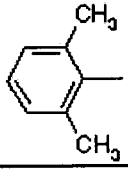
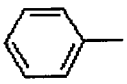
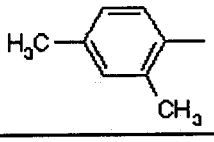
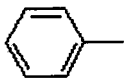
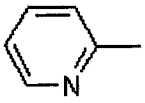
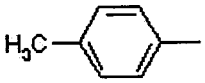
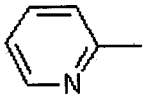
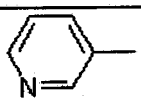
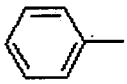
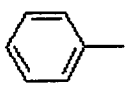
Waringa and Nauta (1975) synthesized several derivatives of structure I (R1 e R2=-CH3) related on Table 2, which were denominated Type B. In these compounds *para* substitution of the phenyl ring occurs at the expense of the anti H1 activity when the corresponding nucleus (the *E*-nucleus) in B-1 is substituted in *para*-position (B-4). A *para*-methyl group in the other nucleus exerts an opposite effect; B-3 has a receptor affinity which is 7 times greater than that of the unsubstituted compound B-1. When both phenyl nuclei are provided with a *para*-methyl group (B-2), an even smaller antagonistic activity results. In Table 2, can observe that activity decreases as the *para*-alkyl group on the *E*-nucleus becomes bulkier. No pA2 could be calculated for the tert butyl compound and activities tabulated refer to compounds separated into their *E/Z*-isomers by means of fractional crystallization.

The determination of the antagonistic activity of mixtures of optical isomers (Type B) by Barlow et al. (1972) indicates that even traces of contamination may have a substantial influence on the pA2 value measured for the least active compound. If the *E*-isomer should completely lack affinity for the receptor, the presence of as little of 1.6% of the *Z*-isomer would account for the observed pA2 value. This may explain why the di-*para*-substituted compound B-2 seems to be less active than B-4, whilst a *para*-methyl group on the *Z*-nucleus is supposed to have a positive effect (B-3 and B-1).

The ability of *ortho* substituents in the *Z*-phenyl ring (B-13 and B-15) to decrease activity might be related to the influence of these groups on the orientation of

Table 2. Chemical structures of Diarylpropenamines.



Type B	Ar	Ar'	PA_2*	PD_2[1]
B-1=Trip Der 15			7.46	5.06
B-2			5.95	5.35
B-3			8.46	6.34
B-4			6.68	5.04
B-6			6.36	5.37
B-8			5.54	5.03
B-10			-	5.25
B-13			6.13	5.42
B-15			7.08	5.38
B-21			7.38	
B-23			8.22	
B-26			5.6	
B-28			5.85	

*values ± 0.3

the ring. In this respect, Waringa *et al.* (1975) are not in agreement with the suggestion of Ison and Casy (1971) that "factors which increase the deviation of the *Z*-phenyl and C=C planes have an advantageous effect on potency". *Ortho*-methyl substitution also lowers activity in the diphenhydramine series (Rekker *et al.*, 1975; 1971). Ison *et al.* (1973) claims that in diphenyl-aminopropenes replacement of the phenyl group *E* to the aminomethyl group by a 2-pyridyl group increases the pA2 (anti H1) by half a unit whilst a similar replacement of the other ring decreases the pA2 by the same factor.

Rekker *et al.* (1972) showed that the anti H1 activities of pyridyl analogues in diphenhydramine derivatives indicated that replacement of a phenyl group by a 3-pyridyl group lowered activity whilst the introduction of a 2- or 4-pyridyl group had virtually no positive effect. However, it is already clear that replacement of a *Z*-phenyl group by a 3- or 4-pyridyl group markedly reduces affinity. Replacement of the *E*-phenyl group appears to have no measurable effect on activity (B-1 and B-21, B-3 and B-23).

Dismissing this discussion, Waringa *et al.* (1975) concluded that for a compound of the diarylpropenamine type to have sufficient anti H1 activity the following requirements should be satisfied: (i) the *E*-aryl ring may be a phenyl or a 2-pyridyl ring, preferably lacking a substitute in the *para*-position; (ii) the *Z*-aryl ring may be a phenyl or a benzyl group; a 3-pyridyl or a 4-pyridyl ring is unfavorable; (iii) the *Z*-aryl ring should preferably have a methyl group or a halogen atom in the *para*-position; (iiii) the *Z*-aryl ring should not be substituted in the *ortho*-positions.

Inhibitors of 5-Hydroxytryptamine (5-HT) and Noradrenaline (NE) Uptake

The hypothesis involving the biogenic amines, especially 5-Hydroxytryptamine (5-HT) and Norepinephrine (NE) (Figure 6), in the etiology of depression (Schildkraut, 1965; Coppen, 1967) has aroused interest in the search for selective inhibitors of neuronal 5-HT and NE reuptake. Almost all tricyclic antidepressants (TCAs) are able to block neuronal reuptake of 5-HT and NE, and accordingly, increase synaptic availability of these neurotransmitters in the central nervous system stimulating the adrenergic activity (Isaacson, 1998). A series of substituted diphenylpropenamines, sharing structural similarities with TCAs, revealed to be also potent inhibitors of 5-HT uptake and had comparable activities with clinically effective tricyclic antidepressants. Particularly the monomethylamino compounds (R_1 = H; R_2 = -CH_3), in which one of the two-phenyl

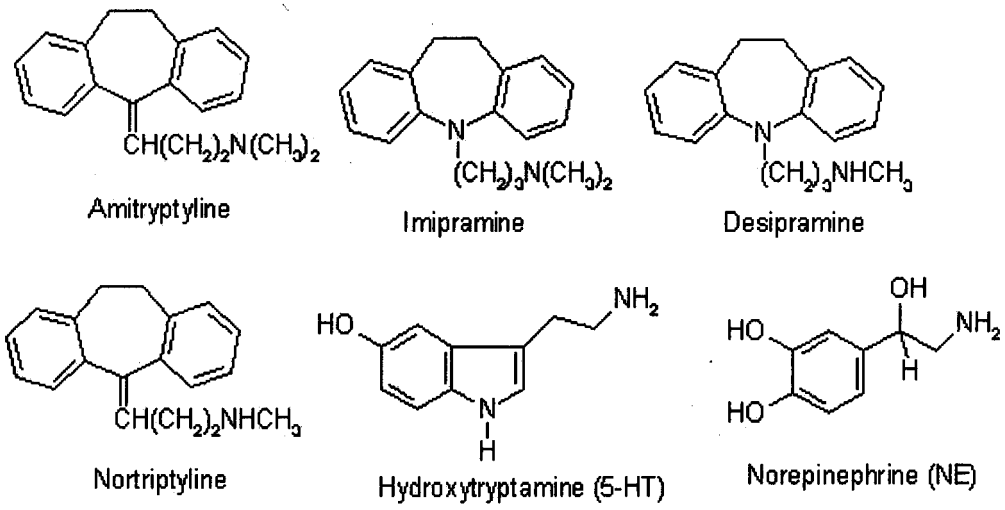
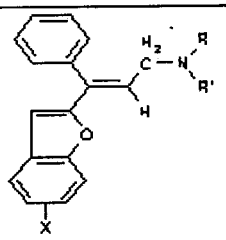
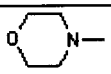
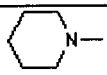
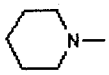
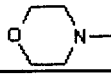
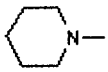


Figure 6. Chemical structures of Amitriptyline, Imipramine, Desmethylimipramine (Desipramine), Nortriptyline, Hydroxytryptamine (5-HT) and Norepinephrine (NE).

groups was substituted by a halogen (F, Cl, Br) at the *para*-position, were the most active members of this series (Jones *et al.*, 1971).

Regarding NE uptake, secondary amines had also markedly superior inhibitory effects over the corresponding tertiary amines; however, Diphenylpropenamines were much less potent than Amitriptyline, Imipramine, Nortriptyline, and Desipramine (Figure 6) (Maxwell *et al.*, 1969). This was observed by Ravina *et al.* (1973), who synthesized a series of 1-Phenyl-1-(substituted 2-benzofuryl)-3-amino-1-propenes and none of those showed antidepressant activity (Table 3).

Table 3. Chemical structures of 1-Phenyl-1-(substituted 2-benzofuryl)-3-amino-1-propenes, hydrochlorides (II).

Compounds  II		
	X	NRR'
IIa	-	$N(CH_3)_2$
IIb	-	
IIc	-	
IId	5-CH_3	$N(CH_3)_2$
IIe	5-CH_3	
IIf	5-CH_3	
IIg	5,7-$(CH_3)_2$	-$(CH_3)_2$
IIh	5,7-$(CH_3)_2$	
IIi	7-O-CH_3	$N(CH_3)_2$

By the other hand, Zimelidine (*Z*)-3-(4-bromophenyl)-N,N-dimethyl-3-(3-pyridyl) allylamine and particularly its primary metabolite, the secondary amine Norzimelidine (Figure 7), revealed to be potent and selective inhibitors of the neuronal uptake of 5-HT (Ross & Renyi, 1977; Ogren *et al.*, 1981). The *Z* configuration observed in both drugs, where the pyridyl and the allylamines moieties are oriented in a *Z* relation, account for this selective action on 5-HT; the *E* isomer of Zimelidine is a non selective inhibitor of 5-HT and Noradrenaline (NA), and the corresponding *E* isomer of Norzimelidine is a potent and selective NA uptake inhibitor (Ross & Renyi, 1977).

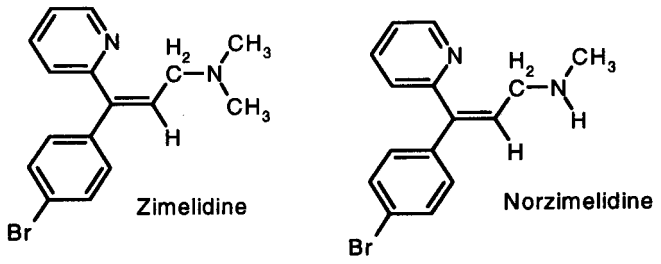


Figure 7. Chemical structures of Zimelidine and Norzimelidine.

Zimelidine was employed in Europe but produced Guillain-Barré syndrome and was withdrawn from use (Isaacson, 1998). However, it is still experimentally used as a pharmacological tool in drug research (Lucki *et al.*, 1994). Superfussion of hippocampal slices obtained from rat chronically administered with the antidepressant drug Zimelidine demonstrated that tumor necrosis factor-alpha (TNF)-mediated inhibition of [H-3] NE release is transformed, such that [H-3]NE release is potentiated in the presence of TNF, an effect that occurs in association with alpha (2)-adrenergic receptor activation. However, chronic Zimelidine administration does not alter stimulation-evoked [H-3] NE release whereas others antidepressant react contrary to this effect (Nickolas *et al.*, 2001).

The endogenous tetrapeptide Achatin-I (Gly-D-Phe-Ala-Asp), isolated from the ganglia of an African giant snail (Achatina fulica Férussae) was proposed as an excitatory neurotransmissor for Achatina neurons (Kamatani *et al.*, 1989; Kim *et al.*, 1991[a,b]). Achatin-I applied by brief pressure can produce an inward current (I*in*) on an Achatina giant neuron type, periodically oscillating neuron (PON). Triprolidine and their analogues, showed a tendency to inhibit the Iin, produced by Achatin-I on PON, suggesting that the effective structures vary to a wide extent (Salunga *et al.*, 1996).

The compounds from Trip Der 1 to Trip Der 8, at 10^{-4} $molL^{-1}$ showed a tendency to inhibit the I*in*. Trip Der 1 having 1-phenyl and 1-(2-pyridyl) in *E*-configuration were slightly less effective than Trip Der 5 having the similar structure in *Z*-configuration. Triprolidine having 4-methyl in 1-phenyl of Trip Der 1 was more effective than Trip Der 1. Trip Der 8 having 3-dimethylamino instead of 3-pyrrolidino of Trip Der 5 was less effective than Trip Der 5.

As to the structure-activity relationships of Triprolidine and its analogues for blocking the Iin produced by Achatin-I on PON, these compounds in *Z*-configuration seemed to be more effective than those in *E*-configuration. The presence of a methyl group in 1-phenyl of Triprolidine, and 1-(4-pyridyl) instead of 1-(2-pyridyl), potentiated the effects. Further, 3-dimethylamino instead of 3-pyrrolidino weakened the effects.

From the dose (pressure duration)-response curves of Achatin-I under the two Triprolidine analogues, Trip Der 3 and Trip Der 6, and on the Lineweaver-Burk plot of these data, these two compounds inhibited no competitively the I*in* caused by Achatin-I. Therefore, Salunga *et al.* (1996) proposed that the inhibition caused by these compounds is not the event in the achatin-I receptor sites, but is caused by affecting the activity of the cyclic AMP-PKA and/or Ca^{2+} - calmodulin systems or the Na^{+} channels.

Anti Trypanossomatid Activity

In 1982, Barrett *et al.* reported the trypanocidal activity of a diarylpropenamine derivative. Following this research, several derivatives of structure

I were synthesized and their trypanocidal activity investigated (De Conti *et al.*, 1996[a,b]; Pereira *et al.*, 1998; De Souza *et al.*, 2001[a]) (Table 3). These derivatives are substituted at the *para*-position on the phenyl moiety and are obtained as a mixture of the *E*/*Z* isomers (nearly 1:1) (Der 1-Der 12). In Der 13 and Der 14 the phenyl ring was substituted by 2-thienyl or furan, respectively. These compounds posses a remarkable trypanocidal activity *in vitro* (De Conti *et al.*, 1996[a,b]; De Souza *et al.*, 2001[a]) and *in vivo* (Barrett *et al.*, 1982; Pereira *et al.*, 1998). Their *in vitro* activities against trypomastigotes, amatigotes and epimastigotes were higher than the standard drugs, crystal violet and nifurtimox (Table 4).

Der 10, Der 11 and Der 12 against *T. cruzi* (amastigote) were 13.2, 4.4 and 18. folds, more active, respectively, than crystal violet at 4°C (ED_{50}/24h= 536.6±3.0 $\mu molL^{-1}$). In the experiments with the proliferative epimastigotes, the activity of Der 12 (ED_{50}/24 h= 8.4±1.2 $\mu molL^{-1}$) was about twice that of the Der 10 (ED_{50}/24 h= 16.5±1.7 $\mu molL^{-1}$). Between the derivatives assayed, the Der 10 was the most active.

The geometric isomers of the Der 3 and Der 1 were also isolated and their biological effect evaluated. *Z* isomers of both tested 2-propen-1-amine derivatives are more active, *in vitro*, against cultured trypomastigotes than their respective *E* counterpart. Although being more active, *Z* isomers are, also, more toxic to mammalian and bacteria *E. coli* (De Conti *et al.*, 1996[a,b]). This stereoselectivity in the action may be due to differences either in the physical-chemical properties of each isomeric form or in the interaction of them with parasite-specific macromolecules, probably enzymes.

Der 3 showed an excellent activity in the murine model of acute Chagas disease. The treatments with Der 3 produced a consistent parasitemia suppression combined with a full protection against natural death caused by the infection. This compound was active even at the relatively lower dose of 5 mg/kg, for 9 consecutive days, which was comparable to the findings with benznidazole at a 20-folds higher dose (100 mg/kg), under similar experimental conditions (Pereira *et al.*, 1998).

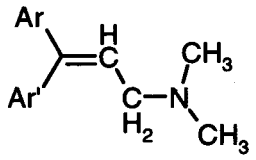
Considering the leishmanicidal activity of these derivatives (Table 4) and the toxicity on V79 cells (as showed on Table 5), the selective index (SI), which corresponds to the ratio between IC_{50} for V79 cells and the ED_{50} for *Leishmania amazonensis*, was calculated. As can be observed in Table 5, the best SI values were found for Der 3 (SI=46.4), Der 8 (SI=38.1) and Der 10 (SI=27.2), which shows that the concentration that lysis 50% of the parasites were respectively, 46.4, 38.1 and 27.2-fold more toxic to *Leishmania* than to mammalian cells, V79 (De Souza *et al.*, 2002; Pereira & De Souza, 2002).

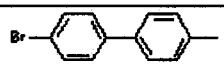
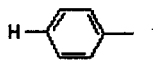
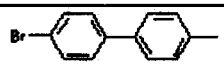
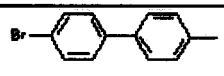
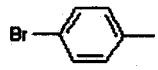
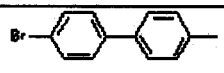
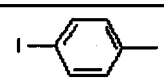
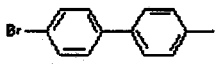
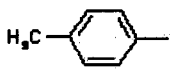
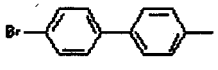
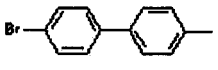
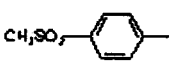
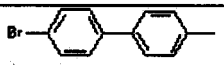
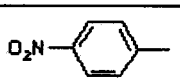
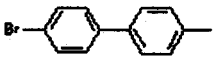
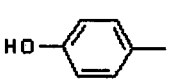
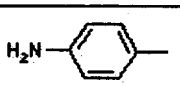
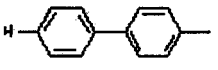
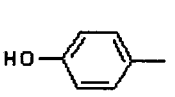
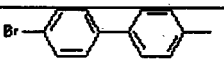
At 100 $\mu molL^{-1}$, Der 13 led to total elimination of promastigotes of *L. amazonensis*, and the ED_{50}/24 h was 3.0 ± 0.3 $\mu molL^{-1}$. *Leishmania* was more susceptible to Der 13 than *T. cruzi*, suggesting different mechanisms for the action of the Der 13 against these parasites. Pentamidine isothionate (Araújo *et al.*, 1998) is 6 folds more effective *in vitro* against *L. amazonensis* (ED_{50}/24h = 0.46 $\mu molL^{-1}$) than Der 13, but its clinical use is associated with severe side effects, including cardiac arrest problems (Marsden *et al.*, 1985).

Cytotoxicity on V79 Cells

The cytotoxicity on V79 cells were measured by reduction of MTT (MTT), nucleic acid content (NAC) and Neutral Red uptake (NRU) techniques. Table 6 presents

Table 4. Structures of some propenamine derivatives and their tripanocidal activity (ED_{50}/24 hours $\mu molL^{-1}$).



	Ar	Ar'	Tripo (4°C)	Ama (24°C)	Epi (28°C)
Der 1			18.8 ± 1.2	6.6 ± 1.2	12.7 ± 0.1
Der 2			50.8 ± 8.1	6.7 ± 0.3	15.8 ± 1.7
Der 3			12.1 ± 1.0	2.3 ± 0.2	13.2 ± 1.6
Der 4			33.0 ± 0.5	8.9 ± 0.3	17.8 ± 2.1
Der 5			22.0 ± 0.5	23.1 ± 1.0	25.1 ± 3.5
Der 6			54.9 ± 2.2	6.1 ± 0.8	27.1 ± 2.2
Der 7			34.4 ± 4.8	6.0 ± 0.6	18.2 ± 3.0
Der 8			35.0 ± 2.7	6.9 ± 0.4	24.3 ± 2.0
Der 10			29,1 ± 2,1	ND	16,5 ± 1,7
Der 11			29.1 ± 2.1	ND	30.4 ± 3.1
Der 12			25.7 ± 1.7	ND	8.4±1.2
Der 13			60.6 ± 6.8	6.8 ± 0.5	11.9 ± 1.4
Der 14			35.1 ± 1.2	9.5 ± 0.8	37.2 ± 4.0
	Crystal violet		536.6 ± 3.0	ND	ND

ED_{50}=concentration that inhibit 50% of the proliferation of the parasites; ND= not determined; Tripo=tripomastigote; Ama=amastigote; Epi=epimastigote.

Table 5. Leishmanicidal Activity of some propenamines derivatives against promastigotes of *L. amazonensis* (ED_{50}/24 hours $\mu molL^{-1}$).

2-propen-1-amine	ED_{50}	IC_{50}[a]	SI
Der 1	0.6283	8.68[c]	13.69
Der 3	0.2332	10.88[c]	46.36
Der 4	3.4	24.40[c]	7.17
Der 8	0.2415	9.2[c]	38.10
Der 5	4.0	7.18[c]	1.78
Der 6	0.5376	7.0[c]	13.02
Der 10	0.2450	6.66[d]	27.18
Der 12	0.4167	9.57[d]	22.97
Der 13	3.0 ± 0.3	28.2	9.4

ED_{50}=concentration that inhibit 50% of the proliferation of the parasites; IC_{50}= concentration that inhibit 50% of the proliferation of the cells; SI=IC_{50} for V79 cells/ED_{50} for *L. amazonensis*; [a] measured by the nucleic content acid assay (NAC).

Table 6. Cytotoxicity of the Der 1-13 on V79 cells.

Derivatives	IC_{50} $\mu molL^{-1}$		
	NAC	NRU	MTT
Der 1	8.6	4.98	10.0
Der 2	10.0	6.32	12.0
Der 3	10.8	11.0	5.7
Der 4	24.39	35.45	> 40
Der 8	9.2/8.2	5.8	7.5
Der 5	> 25	> 20	> 25
Der 6	7.0	5.02	8.30
Der 7	48.0	20.0	40.0
Der 10	6.66	7.55	7.19
Der 11	25.51	28.97	28.03
Der 12	9.57	16.84	18.02
Der 13	28.2	23.9	39.8

the inhibitory concentrations (IC_{50}) of the derivatives of propenamines from our group (De Conti *et al.*, 1996[a,b]; Oliveira *et al.*, 1999; De Souza e*et al.*, 2001[a]). Although the MTT, NRU and NAC tests monitor cellular viability (De Reuck & Cameron, 1963), the parameters

analyzed are different. The reduction of MTT is used to assess the mitochondrial dehydrogenase activity of viable cells. The NAC or protein content evaluates the content of cellular macromolecules, which are indicative of total cell number. The NRU is employed to determine the lysosomal integrity.

Der 10 was the most toxic of the series with lower IC_{50} values. However, Der 4, 7, 11 and 13 are less toxic to V79 cells with higher IC_{50} values than the other ones. In this case, a combination of inductive (σI) and MR effects (Hansh *et al.*, 1995) are probably involved in this toxicity.

Promising studies on encapsulation of propenamine derivatives with cyclodextrin, liposomes, microspheres and nanospheres are actually in progress in our groups in order to reduce the toxicity and increase the solubilization of the compounds (De Souza *et al.*, 2001[b,c]).

Antimycobacterial Activity

The antimycobacterial activities of the Der 1-13 were determined against *Mycobacterium tuberculosis* H37Rv ATCC 27294, *M. tuberculosis* H37Ra ATCC 25177, *M. avium* ATCC 15769, *M. malmoense* ATCC 29571, *M. kansasii* ATCC 12478 and on *M. tuberculosis* strains isolated from clinical specimens (Adolfo Lutz Institute - ALI strains) (De Souza *et al.*, 1998; 2001[a]). Der 1 and Der 3 with their respective geometric isomers showed good antimycobaterial activity against different species of mycobacteria, as compared with Ethambutol, mainly on the clinical specimens of *M. tuberculosis* with MICs values of 5 μmol L^{-1}. For the clinical specimens strains studied, the compounds Der 1-4, Der 8 and Der 10-12 showed MIC between 4 and 49 μmol L^{-1}. Der 5 (79 μmol L^{-1}) and Der 7 (34-68 μmol L^{-1}) exhibited low antimycobacterial activities on standard mycobacteria strains. The geometric isomers (*E*/*Z*) of Der 1 and Der 3 showed activities similar to that of the isomeric mixture of Der 1 and Der 3 showing that there is no advantage in the use of the isolated isomers, at least for the in vitro assays. *M. avium*, *M. malmoense*, *M. celatum* and *M. intracellulare* were less susceptible to the compounds that exhibited higher MIC values than the clinical specimens ones. This result was expected since nontuberculosis mycobacteria are less susceptible to the chemotherapy of tuberculosis.

In the case of *M. tuberculosis* H37Ra and *M. tuberculosis* H37Rv, the halogen at the *p*-position in the phenyl moiety of the Der 2-4 exert a significant effect on their activity at lower IC_{50} values (on V79 cells) than the MIC values. Presumably, in these strains of amino group (Der 11) also exerts an efficient volume effect due to its MR value (molar refractivity) similar to the halogens (Hansh *et al.*, 1995). Similar explanation for the *p*-OH group (Der 10) can be proposed, since the MR value is slightly lower than the other mentioned before. It is interesting to notice that Der 3 (*p*-Br) and Der 4 (*p*-I) are the most widely effective on the different mycobacteria strains and acted efficiently in almost all the tested strains, standard or from clinical specimens. Other comparison can be made between the Der 10 and Der 12. The Der 10 seems to be more effective with lower MIC than Der 12, which does not contain a bromine atom at the *para*-position of the biphenyl ring. Probably, bromine gives a lipophilic character to the molecule increasing the ability of the drug to pass through the membrane and consequently there is an increase of the antimycobacterial activity. The *M. tuberculosis* H37Rv and *M. tuberculosis* H37Ra were more susceptible to Der 13 than *M. avium*, *M. kansasii* or *M. malmoense* with MIC of 20 μmol L^{-1}.

Preliminary results from our laboratory showed that the Der 1 inhibited the growth of the dermatophyte *Trychophyton rubrum* at 10 μmol L^{-1} and presented a reduction

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Swan SH, Elkin EP, Fenster L. The question of declining sperm density revisited: An

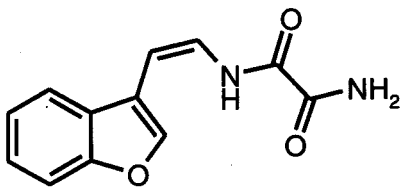

Figure 8. Chemical structure of 3-benzofuryl-3-(oxalamide) amino-1-propene (Igzamide).

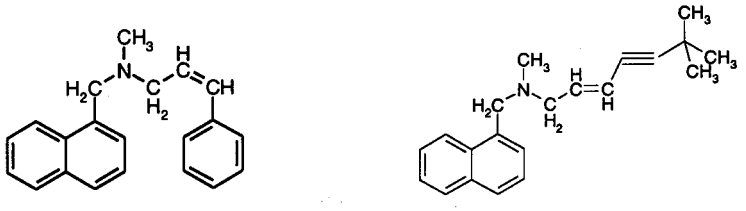

Figure 9. Chemical structures of the allylamines Naftifine and Terbinafine.

discovered based on exploration of structure-activity relationships of Naftifine, and is the first pharmaceutical agent to contain a (*E*)-1,3-enyne structural element (Stütz, 1987).

Naftifine and Terbinafine and other allylamines interfere in the biosynthesis of ergosterol (Figure 10), an essential sterol in the cell membranes of fungi (Stütz, 1987) and recently an antifungal review was published indicating allylamines as important compounds in the actual times (Katz, 2000). They act as potent, selective inhibitors of squelene epoxidase, a key enzyme in the sterol biosynthesis involved in the oxidation of squelene to squalene epoxide (Figure 10). This inhibition results in accumulation of squalene, depletion of ergosterol and, consequently, disruption of the fungal membrane. Accumulation of lipid-like vesicles was observed in electron microscopical studies on fungi treated with Naftifine (Petranyi *et al.*, 1984; Abe *et al.*, 1994). A broadly based routine screening program at Sandoz showed that Naftifine was higly effective against a number

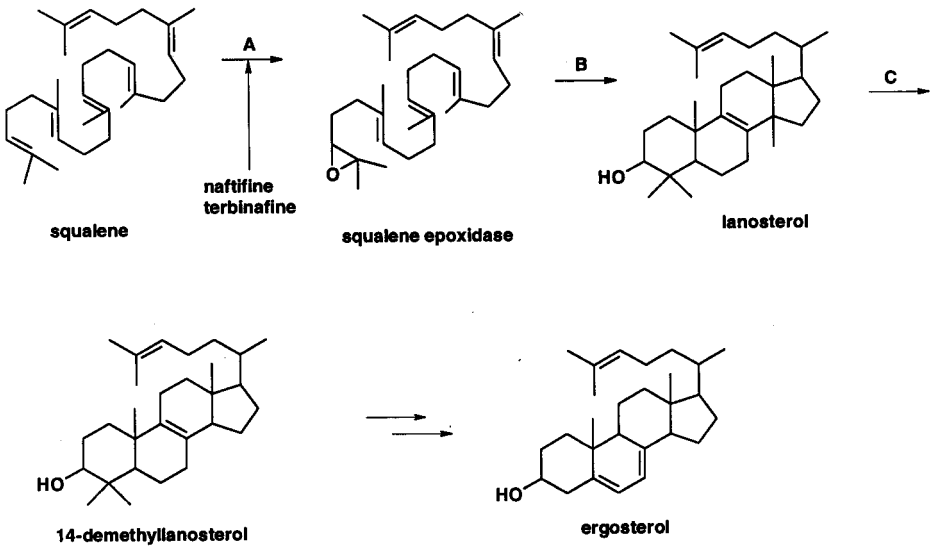

Figure 10. Steps in the biosynthesis of ergosterol from squalene (modified from Martin, 1998). Enzyme systems:
A: squalene epoxidase (squelene monooxygenase E.C. 1.14.99.7); B: squalene epoxide cyclase (lanosterol synthase, E.C. 5.4.99.7); C: lanosterol 14a-demethylase complex.

of human pathogenic fungi (Stutz, 1987; Stutz *et al.*, 1986). After extensive investigation of its pharmaceutical and toxicological properties Naftifine was tested intensively for several years in hospitals and first became commercially available in various countries (Germany, Austria, Malaysia, Singapore) in 1985 under the name of Exoderil. In Brazil it is commercialized as Naftin (Amaral *et al.*, 2001).

Posteriory researches proved that compounds derivatives of Naftifine (III-VII) (Figure 11) were inactive in antimycotic tests *in vitro*. It was therefore concluded that nitrogen atom, the double bond and the 1-substituted naphthalene ring were of importance and also that the aromatic ring system could not be interchanged (Stutz, 1987).

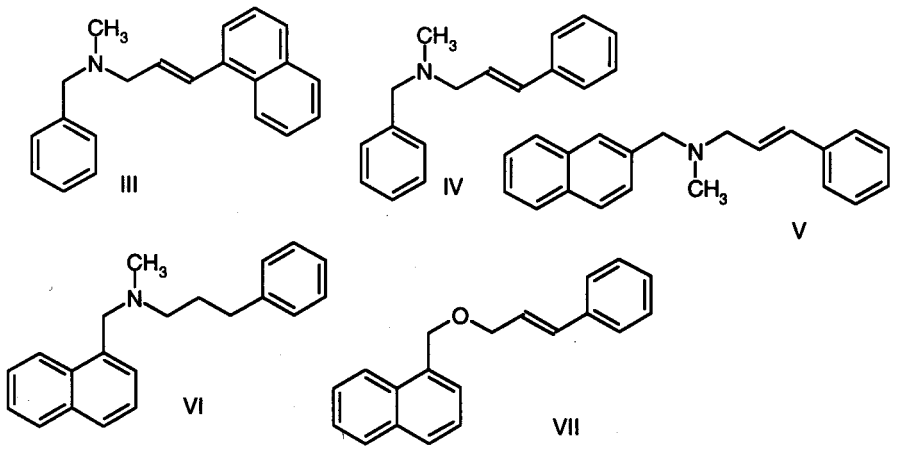

Figure 11. Chemical structures of Naftifine derivatives - III-VII.

Other allylamine congeners were studied to see if whether the distance between the individual functional group and between the aromatic systems could be decreased or increased without affecting the activity. All the compounds showed that Nafitifine activity depends on specific structural requirements (Stutz, 1987). Structural variations of Naftifine leads to the obtention of Terbinafine, a more active antimycotic. The activity (MIC) against *T. mentagrophytes* for naftifine and Terbionafine were 0.05 mgL^{-1} and 0.006 mgL^{-1}, respectively (Stutz, 1987).

A number of Xanthone derivatives bearing the basic Naftitine and Butenafine structure were described. The Butenafine Xanthone analogues show significant activity against *Cryptococcus neformans* (Salmoiraghi *et al.*, 1998). The methyl group of Naftifine and Butenafine were replaced by an azolic nucleus to obtain new compounds which exhibit the characteristic of both allylamine and azole antifugals (Castellano *et al.*, 2000; De Jaham *et al.*, 2000).

A systematic review of topical treatment for fungal infections of the skin and nails of the feet was published (Hart *et al.*, 1999). The final conclusion was that allylamines, azoles and undecenoic acis were effectives in placebo controlled trials. Allylamines cure slightly more infections than azoles but are much more expensive than azoles. The most cost effective strategy is first to treat with azoles or undecenoic acid and to use allylamines only if that fails.

Metabolism of Allylamines

Terbinafine is an allylamine that has *in vitro* activity against dermatophytes and some molds. It diffuses to the keratinocytes from the blood stream because it is lipophilic

and keratinophilic and reaches the stratum corneum and hair follicles (Faergemann *et al.*, 1993). Similar to the action of azoles, Terbinafine inhibits fungal ergosterol synthesis; however, this occurs at a different stage in the synthesis pathway. Terbinafine inhibits squalene epoxydation and avoids many of the drug interactions seen with the azoles because it is not metabolized through cytochrome P-450. Terbinafine is well tolerated, with gastrointestinal upset and skin reactions occurring in only 2% to 7% of patients. Loss of the sense of taste has been reported, but this side effect passes several weeks after therapy has ended. Terbinafine has a long half-life and it is fungicidal (Ryder, 1989). Terbinafine is available in Canada as a 250 mg scored tablet, but a liquid formulation is not available.

Oral Terbinafine has been studied in clinical trials for the treatment of tinea capitis in children (Alvi *et al.*, 1992; Haroon *et al.*, 1992,1996; Nejjam *et al.*, 1995; Kullavanijaya *et al.*, 1997). In one controlled, comparative trial (Ryder, 1989), four weeks of treatment with Terbinafine was as effective as eight weeks of therapy using Griseofulvin (cure rate 93% versus 88%). In two controlled trials that compared one, two and four weeks of Terbinafine, one trial (n=161) did not show a difference among groups and the other (n=82) showed a higher cure rate at 12 weeks in the group treated for four weeks ($P<0.05$). The predominant causative agent in these studies was *Trichophyton* species. The evidence from these studies and from an open clinical trial for the treatment of tinea capitis caused by *M. canis* suggests that four to six weeks of oral Terbinafine may be less effective for tinea capitis due to *M. canis* than for tinea capitis due to *Trichophyton* species (Dragos & Lunder, 1997). Terbinafine does not affect cytochrome P-450 3A and it has few drug interactions.

Synthesis and Separation of the Geometric Isomers

Different methods for preparing these olefins, involving Grignard reagents (Jones *et al.*, 1971), Wittig reactions (Heinisch *et al.*, 1991; De Conti *et al.*, 1996[a]), palladium-catalyzed amination (Bäckvall *et al.*, 1981), dehydration of alcohols (Waringa & Nauta, 1975; Högberg *et al.*, 1981) have been described.

Ison and Casy (1971) reported that for diarylpropenamines compounds, isomers arose in cases where Ar ≠ Ar and in most of these at least one form was isolated in a pure condition whilst the composition of mixtures was known from their nuclear magnetic resonance spectra. The proportion of isomeric alkenes formed was dependent on their equilibration rates since the conditions employed to dehydrate the precursors 1 permitted isomerization. Compound 1 (Figure 12) exposed to hot acid during 2 hours formed significant amounts of the two possible isomers 2a and 2b, while 3 yielded a single aminopropene 3a. Kinetic control of the last reaction was achieved by reducing the heating period to 15 min when approximately equal amounts of the two isomers were formed (Ison & Casy, 1971). The configurational assignment of isomers derived from 1 was initially based on differences in their ultraviolet spectra as described before by Adamson *et al.* (1957, 1958). In Triprolidine and its isomer, the *E* vinylic signal was lower filed in the spectra of both the free bases and the oxalate salts.

For Triprolidine derivatives, there was a good separation of isomeric peaks. The isosbestic point was used as the wavelength for detection to assure equality of isomeric response. The time of retention of an *E*-isomers of Trip Der 1-8 was less that of the corresponding *Z* isomer (Casy *et al.*, 1992[a,b]). UV-absorption experiments had shown that the pyridine ring of Triprolidine is oriented coplanar with the olefinic bond (Adamson *et al.*, 1957).

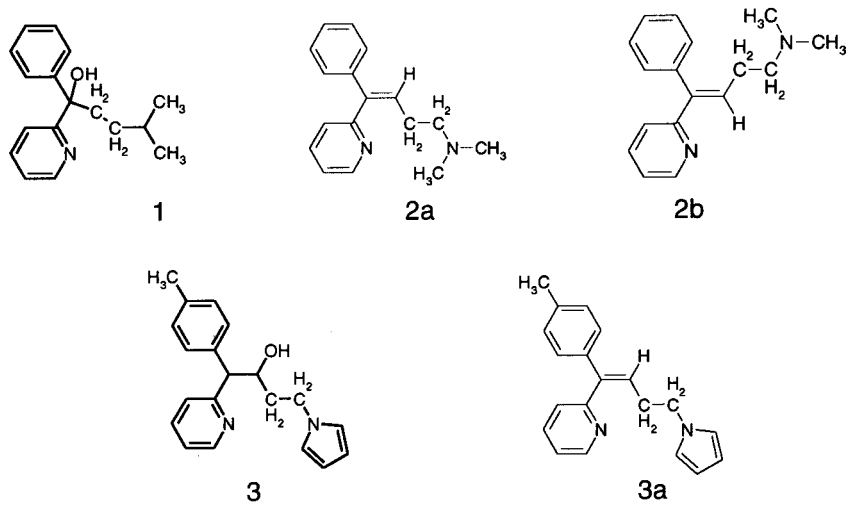

Figure 12. Chemical structures of compounds 1, 2a, 2b, 3 and 3a.

The antihistaminic compounds (B1-B8) were synthesized by dehydrating the corresponding alcohols. When formed, isomeric olefins were separated by fractional crystalization of their hydrochloric salts and their structure elucidated (Waringa & Nauta, 1975).

1-phenyl-1-(4-pyridil)-3-N,N-dimethylpropen-1-amine (*Z*-isomer) (type B) was converted quantitatively into the *E*-isomer. The 3-pyridil compound was not liable to such an isomerization. This indicates that its *E*/*Z* isomers do not differ much in stability as the product distribution is thermodynamically controlled under equilibrating conditions.

Propenamines Der 1-14 were synthesized by a Wittig reaction from their corresponding ketones with good yields. The geometric isomers from Der 1- and Der 3 were separated by thin layer chromatography (TLC) and high performance liquid chromatography (HPLC) as previously described (De Conti *et al.*, 1998).

Concluding Remarks

All compounds described in this review has the aminoallyl group in their structure and their preparation by organic synthesis is relatively simple. Although they have a similar structures, their biological effects are different and basically related with antihistaminic, anti-tripanossomatid, antimycobacterial or antifungic activities. There is no report about the effect of antihistaminic and antidepressant agents on pathogens like mycobacteria or trypanossomatids. It should be interesting to assay these compounds against pathogens and with the results to perform a structure activity relationship (SAR) studies to design new drugs to treat diseases like leishmaniasis or tuberculosis. With respect to the antimycobacterial activity new allylamines and others compounds are being assayed in order to find efficient drugs.

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