# THE SYNTHESIS OF PRODRUGS AND NOVEL ANALOGUES OF β-SYMPATHOMIMETIC BRONCHODILATORS

by

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A thesis submitted to the University of the Western Cape in fulfillment of the requirements for the degree of Master of Science.



This research was carried out in the Department of Chemistry at the University of the Western Cape under the supervision of

Dr. F. Ameer, PhD(Natal) and

Prof. I. R. Green, PhD(UCT).

**April 1998**

# DECLARATION

I declare that this thesis is my own work. It is being submitted for the degree of Master of Science at the University of the Western Cape. It has not been submitted before for any degree or examination at any other University.

Mortimer Hilary Adams

# DEDICATION

This thesis is dedicated to my family for their love, support and understanding.

# ACKNOWLEDGEMENTS

I would like to record my sincere appreciation to various individuals without whom this research would not have been possible. To them I wish to extend my gratitude:

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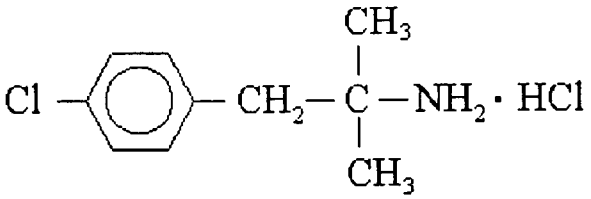
Thanks to all my friends in the Department who provided those many light-hearted moments during the last few years.

Finally I would like to express my sincere gratitude to my parents, brother and sister for their unwavering encouragement, support and enthusiasm during my years of study.

I could not have wished for more.

# ABREVIATIONS USED:



**CP** : 2-Amino-1-(p-chlorophenyl)-2-methylpropane hydrochloride.

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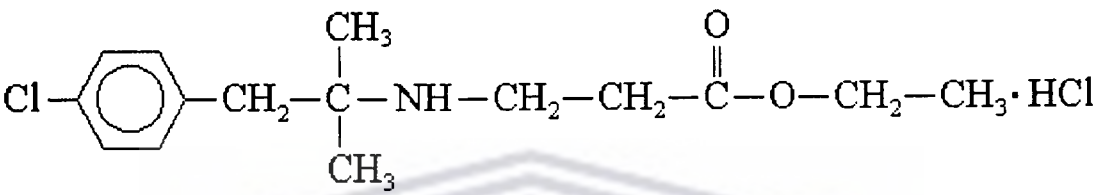

**CPE** : Ethyl 3-[N-1'-(p-chlorophenyl)-2'-methyl-2'-propyl]-aminopropionate hydrochloride.

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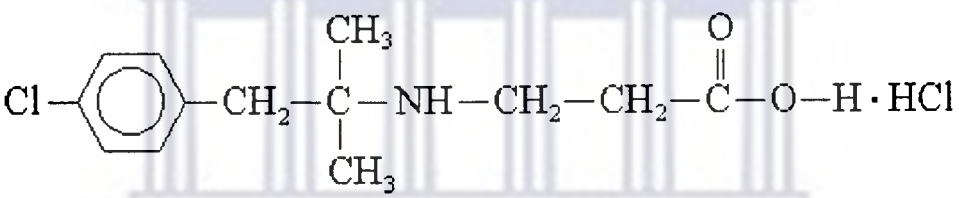

**CPA** : 3-[N-1'-(p-chlorophenyl)-2'-methyl-2'-propyl]-aminopropionic acid hydrochloride.

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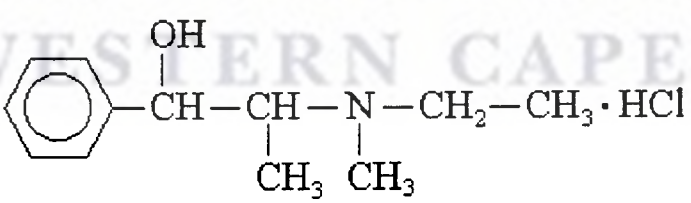

**ET** : 2-N-ethyl-N-methylamino-1-phenylpropan-1-ol hydrochloride.

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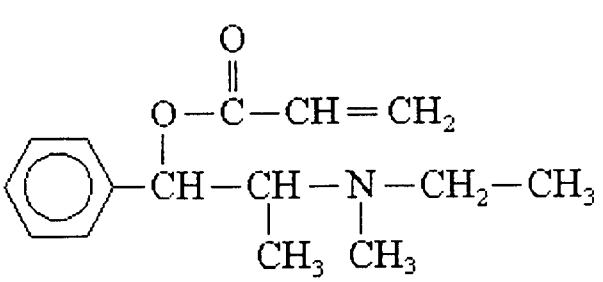

**ETA** : 2-(N-ethyl-N-methylamino-1-phenyl)-propyl propenoate.

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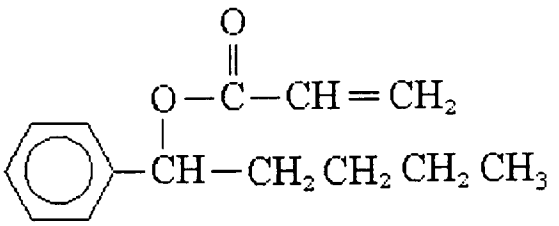

**AP'** : 1-phenylpentyl propenoate

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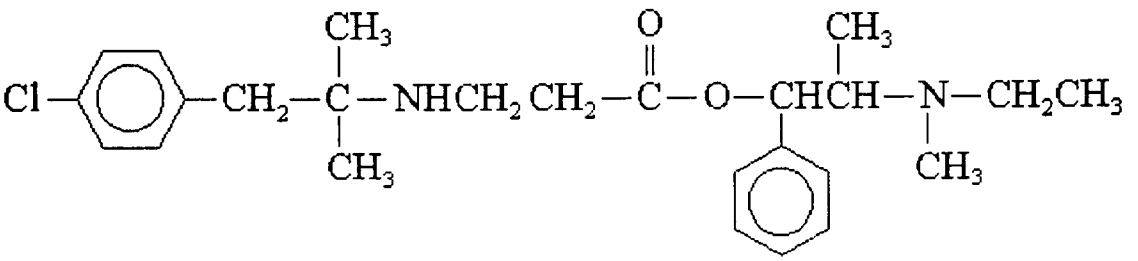

**CPETA** : 2'-N-ethyl-N-methylamino-1'-phenylpropyl 3-(N-1'-p-chlorophenyl-2'-methyl-2'-propyl) aminopropionate.

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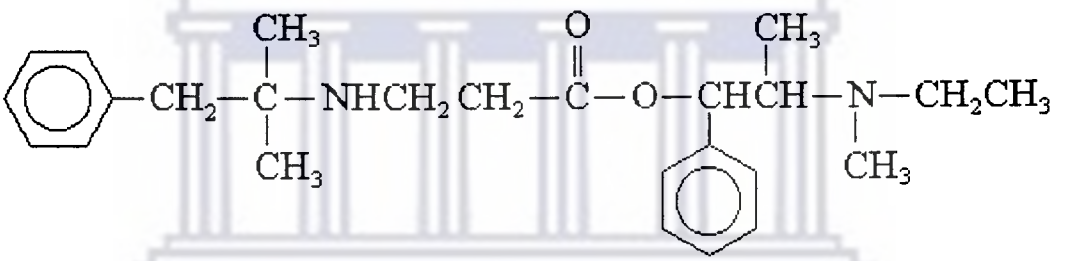

**PETA** : 2'-N-ethyl-N-methylamino-1'-phenylpropyl 3-(N-1'-phenyl-2'-methyl-2'-propyl) aminopropionate.

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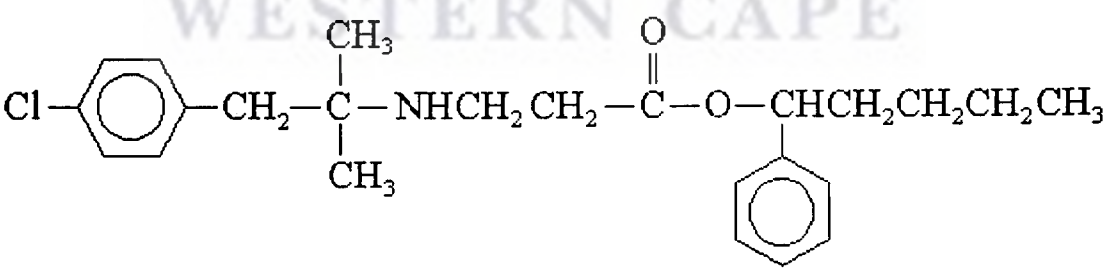

**CPAP'** : 1-phenylpentyl 3-N-(1'-p-chlorophenyl-2'-methyl-2'-propyl) aminopropanoate.

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# ABSTRACT

Prodrugs are reversible derivatives of active drugs destined to undergo chemical or enzymatic transformation to the active drug after administration in order that the active drug may subsequently elicit the desired pharmacological response. In synthesizing a prodrug, the physico chemical properties of a drug are altered by suitable functionalisation of an appropriate appendage of the drug molecule such that some barrier or problem may be circumvented or obviated in totality.

Prodrugs of bronchodilators have been produced with the aim of reducing enzymatic degradation, improving their bio-availability and, displaying a marked separation between their desirable bronchodilator and undesirable cardiovascular activities.

Chlorphentermine (**11**), a lung accumulating amine, was used as a carrier molecule in novel prodrugs which potentially possess these attributes. Model prodrugs viz. CPE (**20**) and CPETA (**14**), consisting of chlorphentermine (**11**) connected through a propionic ester link to ethanol and etafedrine (**13**), respectively, were synthesized by reacting the alcohols with acryloyl chloride and the resultant acrylates subsequently reacted with chlorphentermine (**11**).

CPA (**21**), the prodrug hydrolysis product of CPE (**20**), was also synthesized. Closely related analogues of CPETA (**14**) namely PETA (**15**) and CPAP' (**16**) were then synthesized. PETA (**15**) was synthesized by the condensation of methylamino-1-phenylpropane (phentermine) and etafedrine (**13**).

# CHAPTER ONE

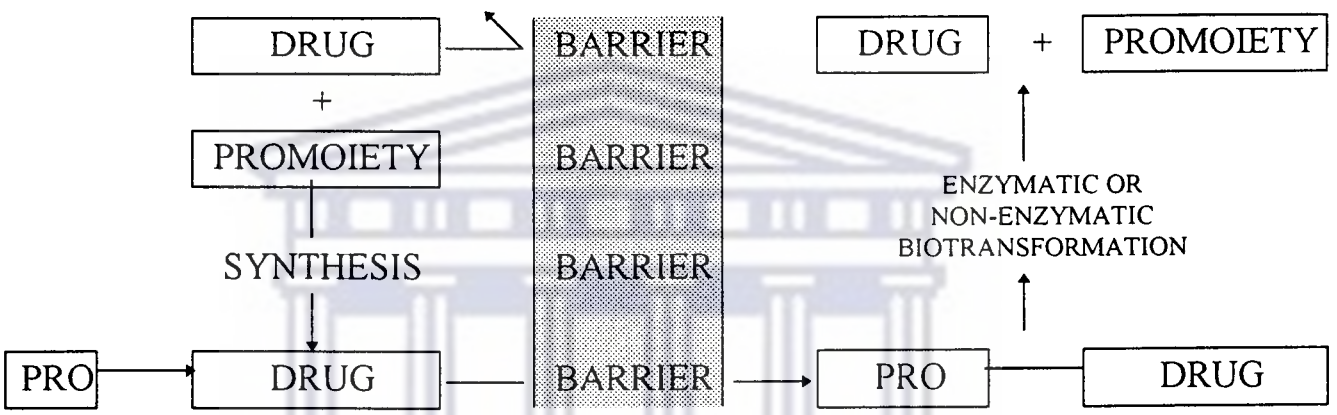
# BACKGROUND, AND AIMS OF THE PROJECT

INTRODUCTION:

During the 1970's a general tendency started to develop in which it became apparent that the commonly used processes of delivering therapeutic agents to the sites of their action within the body were somewhat inefficient and unreliable. Optimization of drug delivery and consequently, improving the drug efficacy implied an efficient and selective delivery and transport of a drug substance to its site of action. The subsequent recognition of this importance led to a large scale increase in research activities in this area, and much attention has been focused on approaches which aim at enhancing the efficacy and reducing the toxicity and undesirable side effects[1].

Prodrug design[1] comprises an area of drug research that is concerned with the optimization of drug delivery. A prodrug is a pharmacologically inactive derivative of a parent drug molecule that requires spontaneous or enzymatic transformation within the body in order to release the active drug, and which has improved delivery properties over the parent drug molecule. In producing a prodrug, the physicochemical properties of a drug are altered so that some barrier or problem may be circumvented or obviated in totality. A molecule with optimal structural configuration and physicochemical properties for eliciting the desired therapeutic response at its target site, does not necessarily possess the best molecular form and properties for its point of ultimate action. Usually, only a minor fraction of the doses administered reaches the target area. Additionally

since most agents interact with non-target sites as well, an inefficient delivery may result, further compounded by undesirable side effects. These facts of differences in transport and delivery are common characteristics for many drug molecules and are the basic reasons why bioreversible chemical derivatization of drugs, i.e. prodrug formation, is a means by which a substantial improvement in the overall efficacy of drugs can often be achieved[2]. The prodrug approach to problem solving is illustrated in Scheme I.



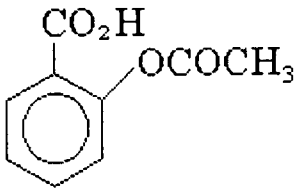

Scheme 1

As seen in Scheme 1 the physicochemical properties of the drug are altered by the attachment of a pro-moiety. This allows the prodrug to pass through the barrier and, once past the barrier, revert back to the parent drug by a postbarrier enzyme or nonenzymatic process[3].

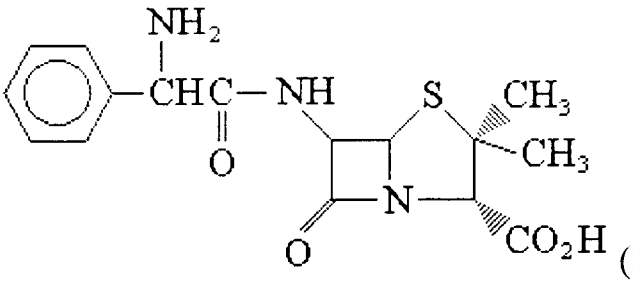
Prodrug research[1] matured as a branch of pharmaceutical research during the 1970's. Over the years this chemical approach to optimization of drug delivery has undergone considerable expansion, largely as a result of an increased awareness and understanding of the physicochemical factors that affect the efficacy of drug delivery and action. Nearly all therapeutic agents possess various physicochemical and biological properties, some desirable and others undesirable.

The pharmaceutical world is concerned with minimizing the number and magnitude of undesirable properties of a drug, while retaining the desirable therapeutic activity. Several drugs are now used clinically in the form of prodrugs for example aspirin (**1**) and ampicillin (**2**)[4], and, as the prodrug approach is becoming an integral part of the new drug design process, one may expect that newly designed drugs in many cases will appear as prodrugs.

The β-sympathomimetic broncodilators[5] are extremely popular in the treatment of patients suffering from obstructive respiratory disease. Traditionally, shortcomings such as low onset and short duration of action, lack of selectivity for bronchial smooth muscle, low oral availability as well as the stimulatory effects on the cardiovascular system were associated with the clinical use of these compounds[6]. Many of these shortcomings have, however, been overcome by newer β-adrenergic agents which exhibit prolonged duration of action and can be conveniently administered. The most serious remaining problem associated with the current use of β-sympathomimetic bronchodilators is the frequently accompanying cardiovascular and muscle tremor side effects. Based on currently available information, all effective bronchodilators in clinical use seem to have cardiovascular side effects when administered orally or by intravenous injection[5].

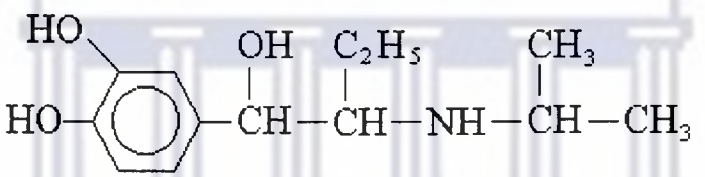



(**1**)



(2)

Alquist and Lands[7, 8] have distinguished several types of adrenergic receptors in an attempt to eliminate the cardiovascular side effects of bronchodilators, particularly the β-sympathomimetic bronchodilators. Their attempts primarily centered on efforts to make these drugs more lung selective in action by the development of $\beta_2$-agonists, such as isoetharine (**3**), terbutaline (**4**), salbutamol (**5**) and pirbuterol (**6**), and employment of the inhalation route of administration[5].



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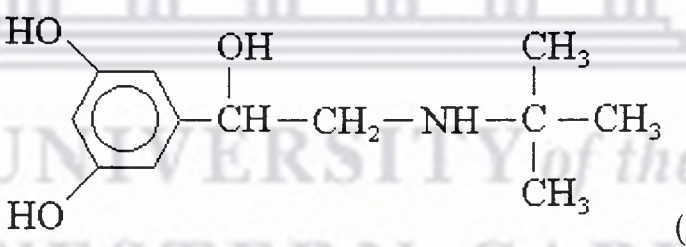

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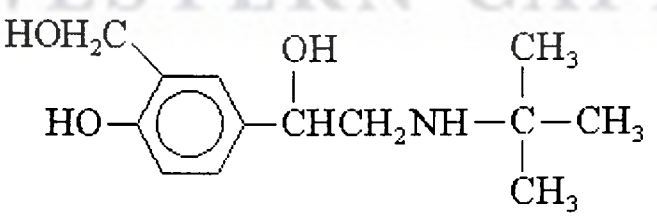

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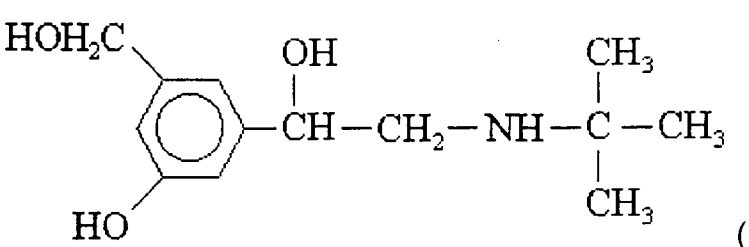
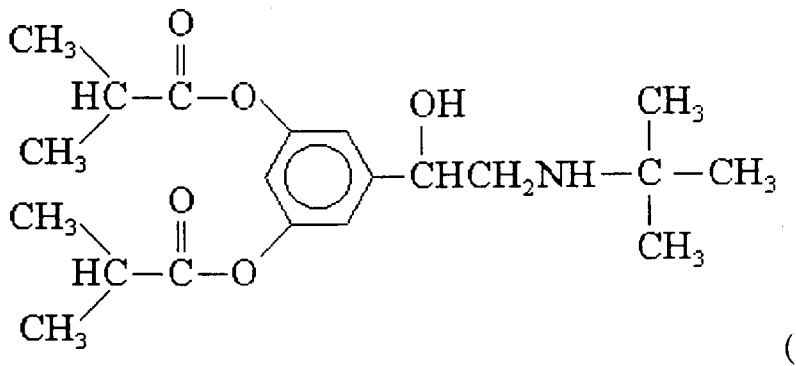


(6)

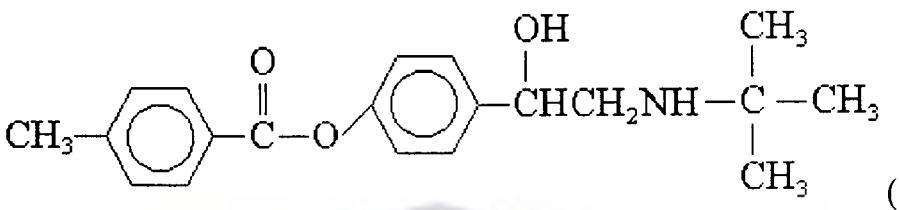
Although the introduction of these agents considerably improved therapy with sympathomimetic bronchodilators, they did not entirely solve the problem of cardiovascular side effects, chiefly because none of the presently used agents are specific $\beta_2$-receptor stimulants[8]. This may be illustrated by considering the long acting relatively selective $\beta_2$-agonist terbutaline (**4**), which still produces significant arrythogenic effects when administered subcutaneously[7] or orally[9] in high bronchodilator doses. High oral doses of pirbuterol (**6**) and salbutamol (**5**) also cause an increase in heart rate [10]. Since $\beta_2$-receptors are involved in the facilitation of skeletal nerve transmission the problem of muscle tremor was not even addressed during the development of these $\beta_2$-agonists.

Improvement in the lung selectivity of the $\beta_2$-agonists may elleviate both the cardiovascular and muscle tremor side effects. The selectivity of $\beta_2$-sympathomimetics may be improved if they are administered via the inhalation route. However, absorption and the subsequent response is often erratic and unpredictable. Furthermore, the potential still exists for $\beta_2$-agonists administered via this route to reach the circulation system and cause undesired side effects. The best solution to improve lung selectivity of the $\beta_2$-bronchodilators therefore appears to lie within the use of prodrugs of these bronchodilators[5, 8].

Prodrugs of bronchodilators have been synthesized with the aim of reducing enzymatic degradation, improving their oral bioavialability and producing a greater differentiation between the bronchodilator and cardiovascular effects. Ibuterol (**7**), bitolterol (**8**) and the di-p-toluate ester of isoproterenol (**9**) are examples of bronchodilator prodrugs synthesized with these aims in mind[11, 12].



(7)



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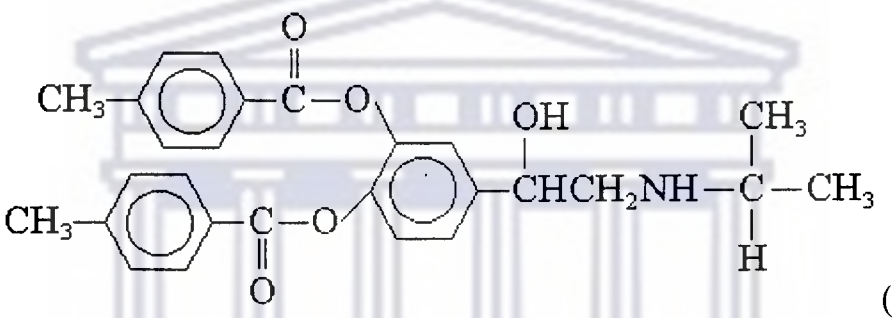
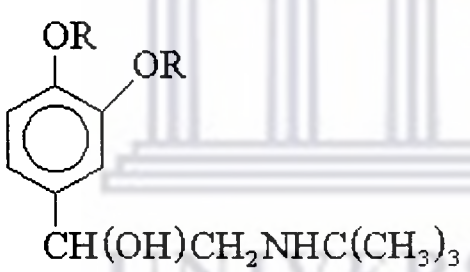


(9)

Ibuterol (7) is the di-isobutyric acid ester of terbutaline (4), which being a resorcinol derivative, is resistant to inactivation by catechol-o-methyltransferase. However it is readily metabolized, mainly via a sulphate conjunction, after oral administration[13]. In addition the lung uptake of terbutaline (4) from the blood is low[14]. The use of ibuterol (7) does however, improve the lung bioavailability of terbutaline (4). Ibuterol (7) is inactive as such as a bronchodilator, but it is rapidly hydrolyzed in the lung and blood to active terbutaline (4) which may however, redistribute from the lung[14]. Thus, unfortunately, sufficient terbutaline (4) may be released after administration of high doses of ibuterol (7) so that tremor and cardiovascular side effects might still be evident with the use of this prodrug. A similar pattern of lung uptake and rapid bronchodilator release has been observed

with another prodrug, viz. the di-p-toluate ester of isoproterenol (**9**)[12]. Hence, cardiovascular side effects are also anticipated with this prodrug.

With bitolterol (**10a**), the di-p-toluate ester of tertbutylarterenol (**10b**), an improved oral bioavailability as well as a longer duration of action and significant bronchodilator – cardiovascular activity differentiation were obtained[11, 15, 16]. The slower onset and prolonged duration of the bronchodilator effect of bitolterol (**10a**) was consequently attributed to the high affinity and possible binding of the ester in the lung tissue and its subsequent gradual release and slow hydrolysis to the active catecholamine (**10b**). The improved bronchodilator – cardiovascular activity differentiation may, however, also be due to the presence of higher esterase activity in the lung compared to the heart[16, 17].




10a : R = p—$CH_3C_6H_4CO$—

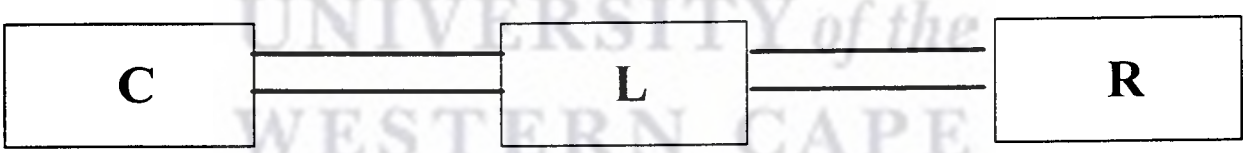
10b : R = H

In general, studies so far conducted on presently available prodrugs of bronchodilators reveal that improved penetration of the lung by the prodrug is insufficient to produce a significant improvement in site – specific delivery unless the delivered parent drug is retained in the lung. In their critical review of the general topic of prodrugs and site – specific delivery, Stella and Himmelstein[3] made the same observation. It may, however, be extremely difficult or even impossible to obtain lung retention of the $\beta_2$-agonist as such without risking loss of activity. Further, it is also obvious that the enhanced uptake of the present

bronchodilator prodrugs is mainly as a result of their increased lipophilicity, a property which governs the diffusive transport of compounds across most biological membranes. Better results may be obtained with bronchodilator prodrugs which have more specific lung uptake characteristics.

A basic fundamental criterion for the prodrug approach to be useful in solving drug delivery and retention problems is the ready availability of chemical derivatives satisfying the prodrug requirements, the most prominent of these being interconversion of the prodrug to the active drug[2, 12].

The realization of this objective required the design and synthesis of new and different model compounds containing a lung accumulation property as well as serving as a carrier. For structural design purposes three distinct parts of a model system were identified, viz., the carrier section (C), an enzyme link (**L**) and a side chain which could be altered in both composition and length (**R**), illustrated in Scheme 2.




Where C = carrier section

L = enzyme link

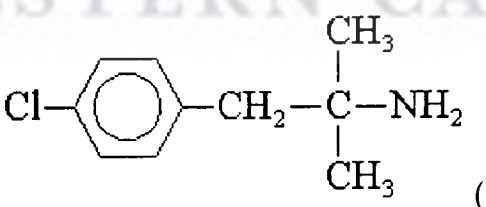
R = side chain

Scheme 2

Chlorphenternine (**11**) was selected as the carrier section of the prodrug. The preferential distribution of chlorphenternine (**11**) in the lung tissue has been

noted by several workers[18, 19, 20]. Chronic administration of this drug to patients results in lung concentration of more than 100 times the concentration in plasma[18]. The accumulated chlorphentermine exhibits wide spread localization in the pulmonary tissue where it has been found to concentrate in lung macrophages of type I and II alveolar epithelial cells, endothelial cells, pulmonary smooth muscle cells and in bronchial epithelium[21]. Chlorphentermine (**11**) is clearly a compound which appears to have the correct minimal structural requirements needed for selective uptake and persistence in the lung. It should be an ideal choice as carrier in the initial investigation of the potential use of lung accumulating compounds to deliver drugs specifically to the lung. Its pharmacological activity and toxic effects may restrict its usefulness to the initial explorative investigation of this hypothesis, but its wide localization in lung tissue should enhance the chances of delivery of the active drug at its exact site of action in the lung.
In addition this compound contains essentially only one reactive centre, viz. a primary amine. Use of this can be made since by suitable chemical means, the chain extension can be effected by employing the nucleophilicity of the nitrogen atom.





(**11**)

A propionic acid ester was considered as the link moiety in the prodrug. The ester group was chosen as the labile link because it has been stated that the lung possess high esterase activity which should ensure that hydrolysis of the prodrug occurs in that organ[12, 14, 16]. Since the inductive effect of the ester group would

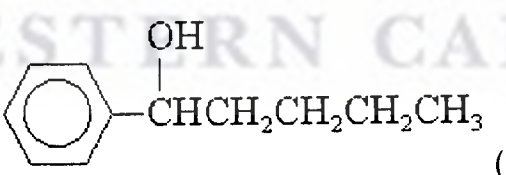
influence the basicity of the nitrogen atom of the carrier, it has to be separated from the nitrogen. At the same time, though, the overall molecular size of the prodrug has to be restricted, since an increase in prodrug size might adversely affect the influence of the carrier in such a prodrug[17]. The two carbon separation obtained by employing the propionic acid ester link was considered to be an ideal compromise.

The following criteria were set up for the model agents to be delivered to the lung via the prodrug:

(a) the agent had to be chemically as simple as possible;

(b) have some chemical features in common with the sympathomimetic bronchodilators; and (c) be quantifiable. These requirements are in large met by 1-phenyl-1-pentanol (**12**). In common with most of the sympathomimetic bronchodilators it possesses a secondary benzylic alcohol group and its use also presented the opportunity to ascertain whether aliphatic esters derived from this group would behave differently to the phenolic esters previously employed in $\beta_2$-agonist prodrugs.

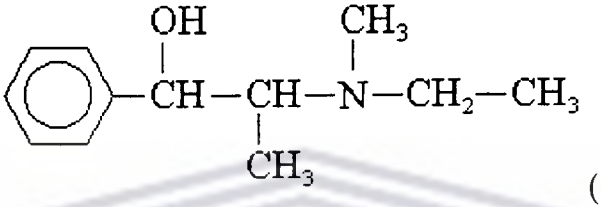




(**12**)

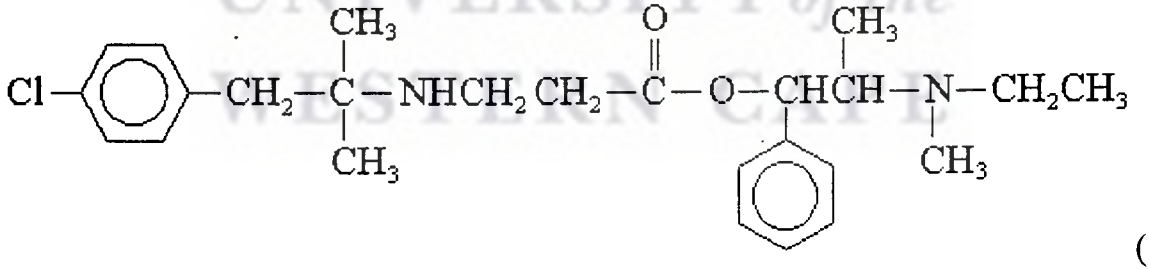
Etafedrine (**13**), a 5-atom analogue, with similar bronchodilator and cardiovascular properties as the parent drug, was another model agent used as the R group in the prodrug. It was considered since it would allow us to determine whether active bronchodilator could be delivered via this prodrug approach. There are some similarities between etafedrine (**13**) and 1-phenyl-1-pentanol (**12**)

in that both have the benzylic hydroxyl group and both have a maximum chain length of five atoms. Differences between (**12**) and (**13**) are obvious in that the latter has two branches in the chain as well as the presence of the tertiary nitrogen which could at best incorporate some nucleophillic character. This aspect was considered to be important to test, in view of the fact that similar bronchodilation properties have been observed as indicated above.

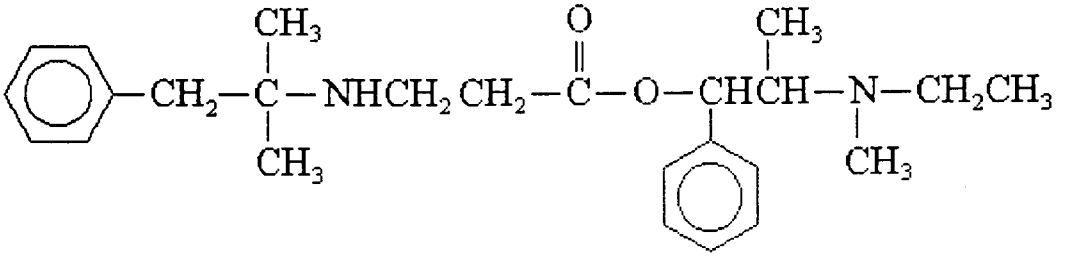


(**13**)

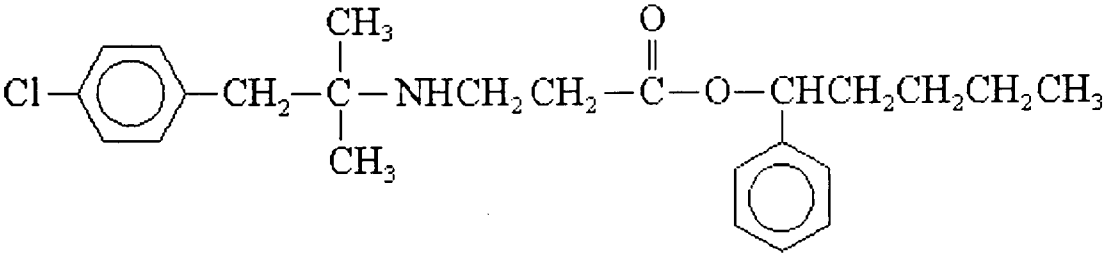
Additionally, it was envisaged that similar synthetic procedures could be employed in the prodrugs 2'-N-ethyl-N-methylamino-1-phenylpropyl 3-(N-1'-p-chlorophenyl-2'-methyl-2'-propyl) aminopropionate (**CPETA**)(**14**), 2'-N-ethyl-N-methylamino-1'-phenylpropyl 3-(N-1'-phenyl-2'-methyl-2'-propyl) aminopropionate (**PETA**)(**15**) and 1-phenylpropyl 3-N-(1'-p-chlorophenyl-2'-methyl-2'-propyl) aminopropanoate (**CPAP'**)(**16**).



(**14**)



(**15**)



**(16)**

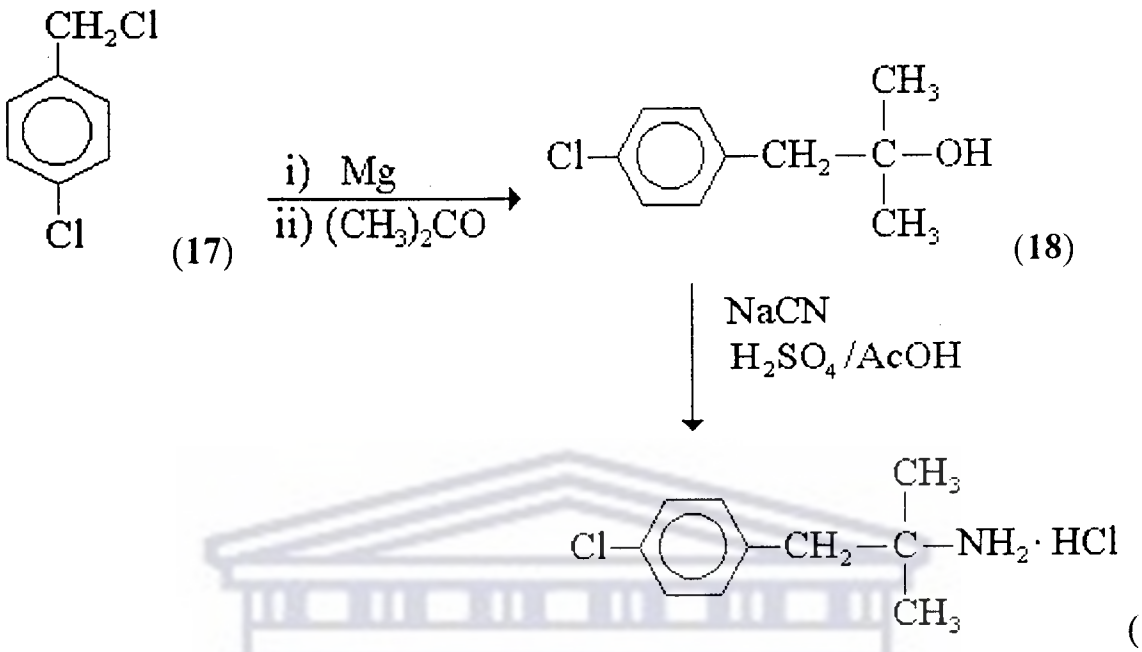
The objective of this research program was to employ chlorphentermine (**11**) as the carrier sector of the prodrug due to its known ability to accumulate in the lung and to develop a synthetic route for the synthesis of three model produgs two of which incorporate chlorphentermine (**11**) viz. **CPETA** (**14**) and **CPAP'** (**16**) and one not incorporating chlorphentermine (11) but rather phentermine viz. **PETA** (**15**) and to evaluate them for lung accumulation characteristics as well as pharmacological activity. From the results it would be established whether this prodrug approach achieved better site - specific delivery and whether there was enhanced retention of the drugs in the lungs.

# CHAPTER TWO

# RESULTS AND DISCUSSION

2.1 β–sympathomimetic bronchodilators are extremely popular in the treatment of obstructive respiratory disease. A problem associated with the use of these in the treatment of obstructive airways disease is the lack of sufficient lung selectivity of the available agents. When these agents are used, cardiovascular and muscle tremor side effects are unavoidable. Prodrugs of bronchodilators have been produced, for example ibuterol (**7**) and bitolterol (**8**), to improve the bioavailability and to produce a greater separation between cardiovascular and bronchodilator activities. There is very little evidence that these prodrugs also produce a significant improvement in lung selectivity. Thus the utilisation of another prodrug design which displays improved lung uptake and retention might prove more successful. Hence model prodrugs employing chlorphentermine (**11**) as a carrier were designed and synthesised.

Synthesis of chlorphentermine hydrochloride (**19**) is depicted in Scheme 3 below. This represents the carrier part of the prodrug molecule.

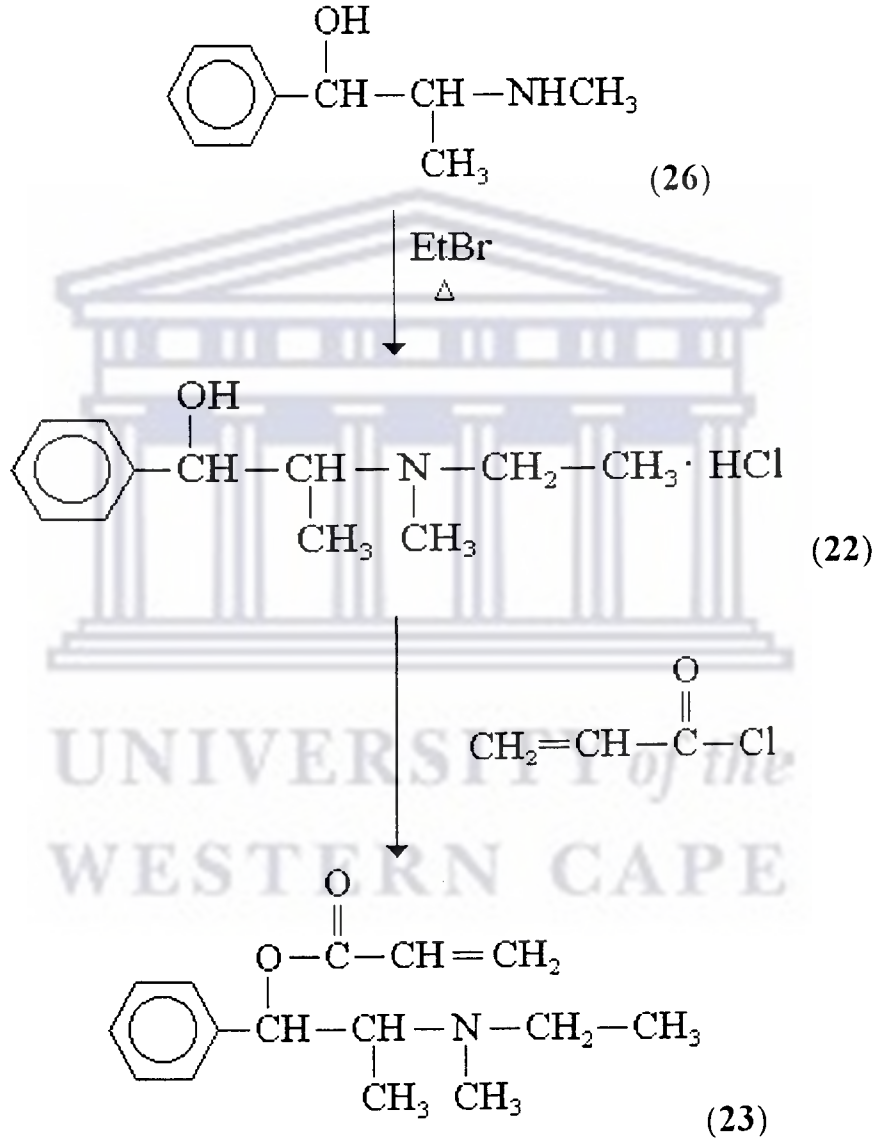



SCHEME 3

Alcohol (**18**) was obtained via the Grignard reagent formed from the commercially available precursor p-chloro-benzylchloride (**17**) and acetone in a 60 % yield. This reaction was scaled up to 20 gram amounts without any problem. Conversion of alcohol (**18**) into the ammoniumchloride (**19**) was achieved by treatment with sodium cyanide in a 49 % yield. During the reaction great care had to be taken to keep the temperature below 20°C when addition of the mixture of sulphuric acid and glacial acetic acid was made to the aqueous sodium cyanide. During the addition of the alcohol (**18**) to this mixture, moderately fast stirring had to be maintained to maximise the biphasic reaction.

2.3 The next objective was to synthesise a model compound which is a) chemically as simple as possible, b) have some chemical features in common with sympathomimetic bronchodilators and c) is quantifiable to be delivered to the lung via the prodrug.

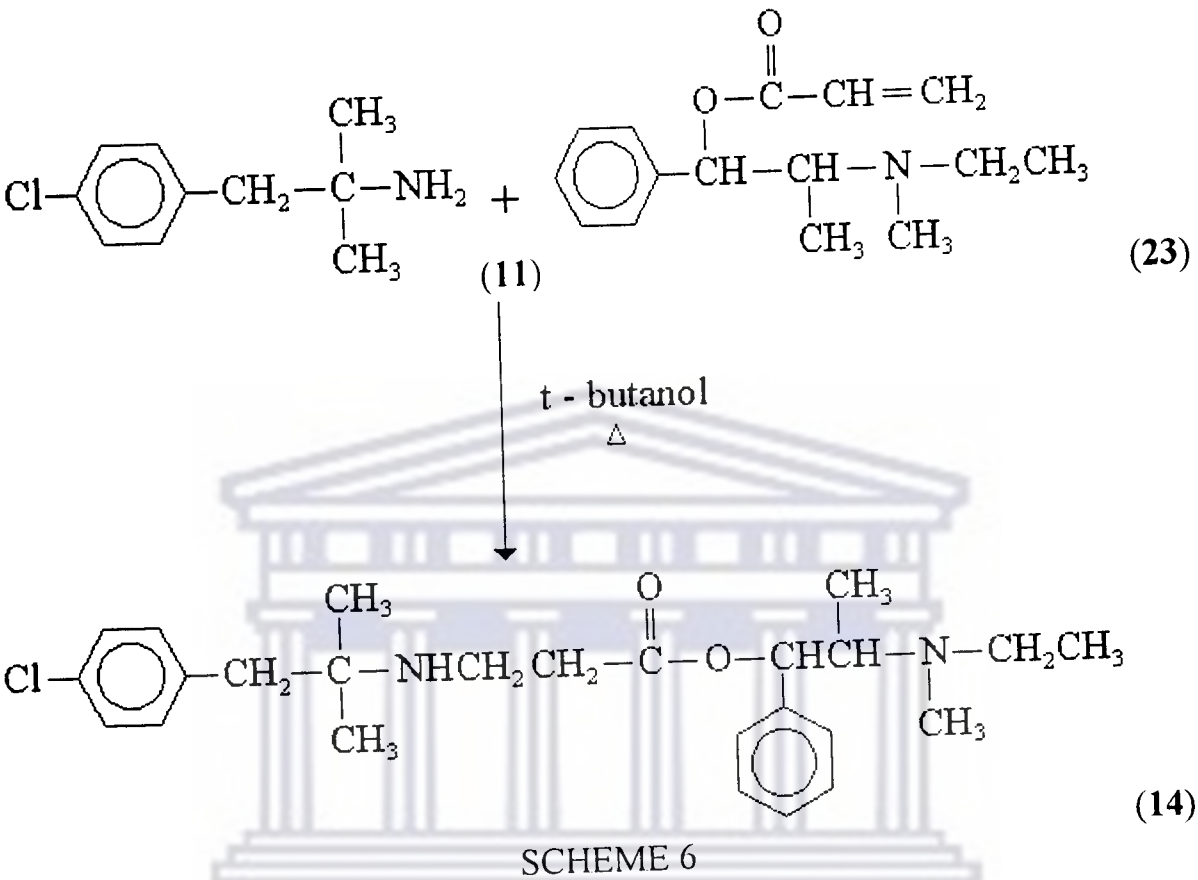
Synthesis of 2-(N-ethyl-N-methylamino-1-phenyl)-propyl propenoate (**23**)(ETA).




SCHEME 5

Chemoselective differentiation between the N and O nucleophilic centres of alcohol (**26**) was achieved by using neat ethylbromide and stirring for 24 hours at 25°C followed by heating on a water-bath for 5 hours. The product isolated was identified as being alcohol (**22**) by the disappearance of the N-H signal in the infrared spectrum and the presence of a quartet at δ3.39 (***J*** 7Hz) in the $^{1}$H n.m.r spectrum for the C***H***$_2$-N system. The alcohol group was identified by a broad $D_2O$ exchangeable singlet at δ3.16. Condensation between the free base of (**22**) and acryloyl chloride proceeded smoothly and rapidly at low temperatures. Temperatures higher then 25°C were avoided in this step, since the application of heat resulted in the polymerisation of the acrylate unless an inhibitor such as cuprous chloride was used[22]. The product isolated was identified as the ester (**23**) by the presence of the carbonyl group stretching frequency at 1738cm$^{-1}$ in the infrared spectrum and the disappearance of the OH signal at δ3.16 in the $^{1}$H n.m.r spectrum. Both the alcohol (**22**) and ester (**23**) were obtained in low yields due to losses incurred during preparative layer chromatography isolation of these final products.

2.4 The aim of this section is to describe the convergent synthetic steps in the synthesis of target molecules CPETA (**14**) and PETA (**15**) and are depicted in Schemes **6** and **7** respectively.




SCHEME 6

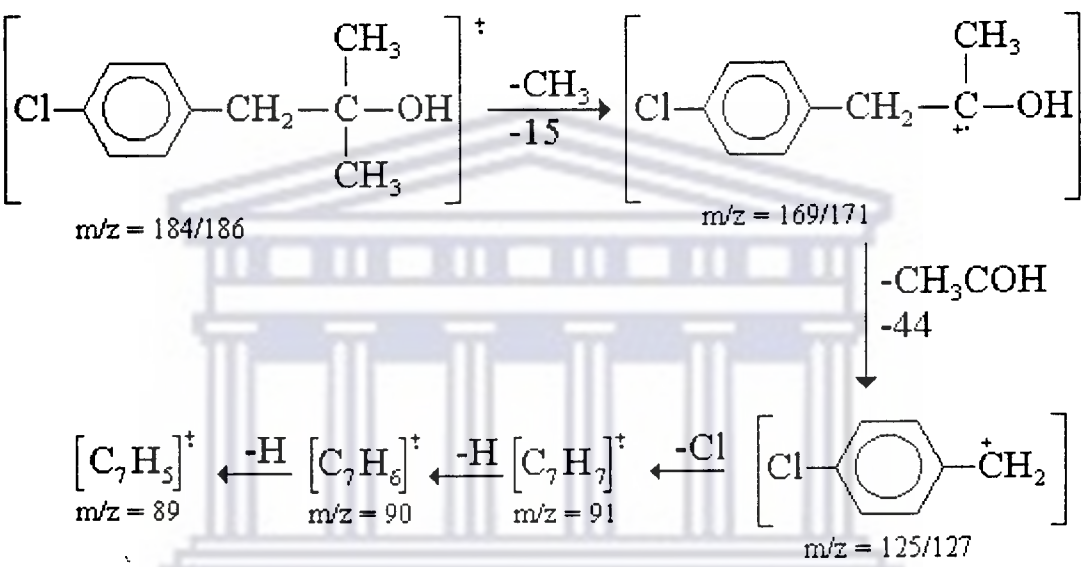
Condensation between chlorphentermine (**11**) and etafedrine acrylate (**23**) was best achieved in anhydrous tertiary butanol at reflux temperature for 24 hours. The crude product was plated and thus the first model prodrug CPETA (**14**) was achieved but in low overall yield. In order to handle the thick oily product it was converted into the hydrochloride which in itself also proved problematic due to its hygroscopic nature. Attempts to convert the initial oily product (**14**) into a sulphate salt proved to be unsuccessful as well. Confirmation of the structure of CPETA (**14**) was demonstrated by an ester carbonyl stretching band at 1725cm$^{-1}$ in the

# CHAPTER 3

# DISCUSSION OF MASS SPECTRA

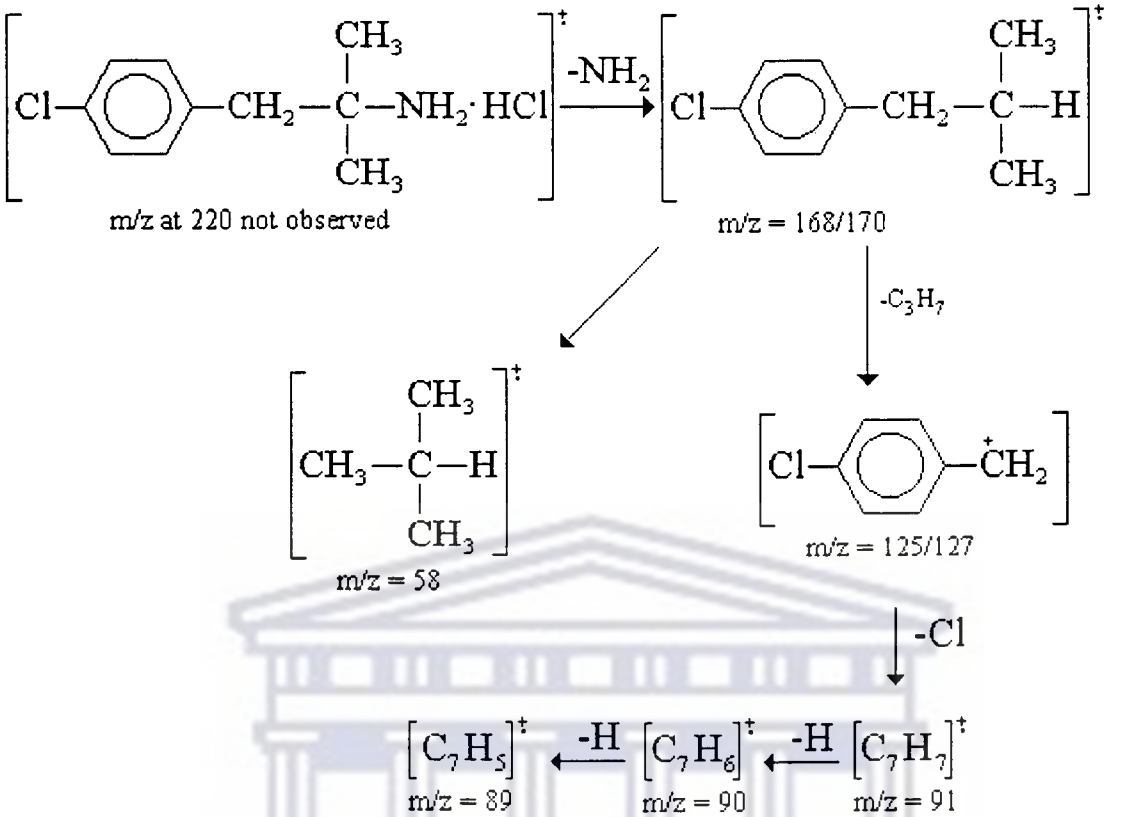
In this chapter the Mass Spectra of the intermediates and target molecules will be briefly illustrated in terms of their fragmentation patterns.

1-(p-chlorophenyl)-2-methyl-propanol (**18**)



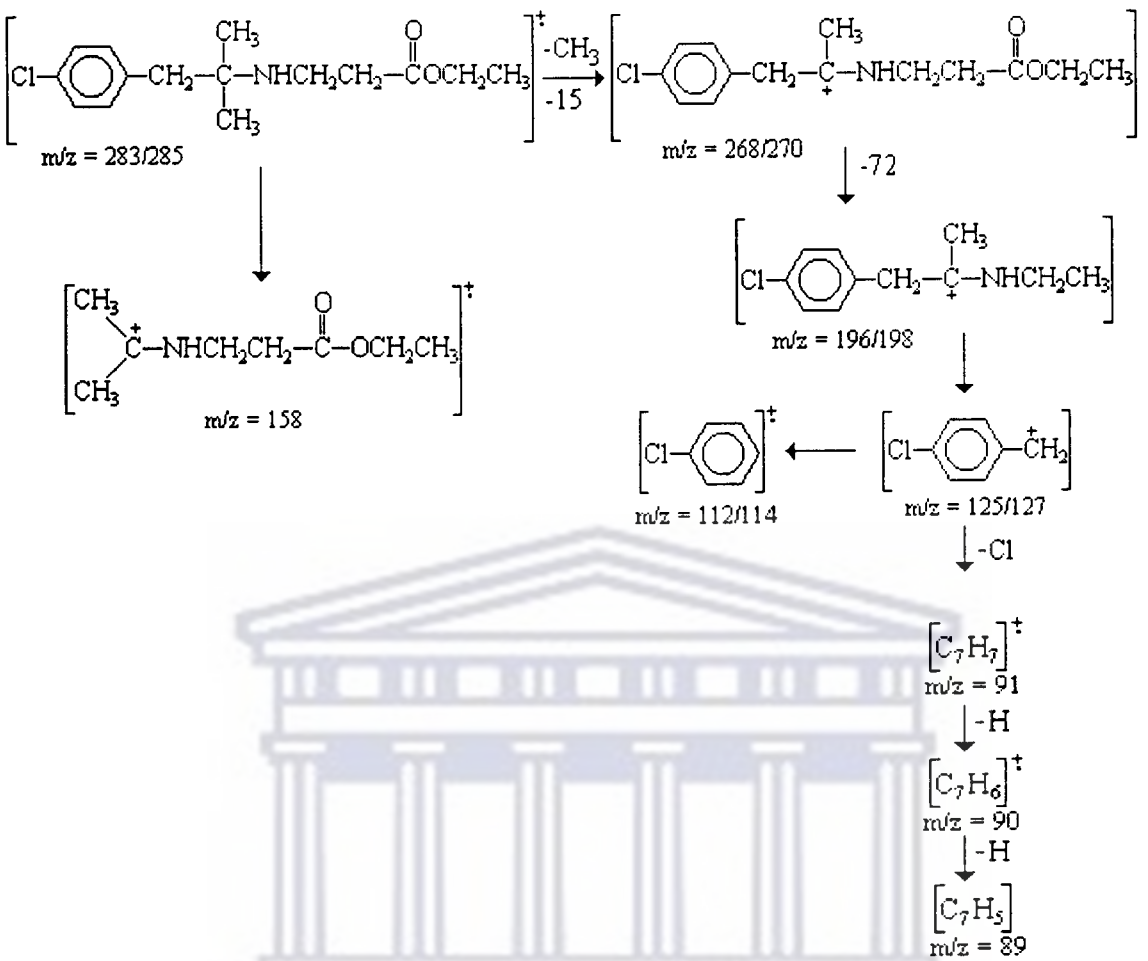

It is interesting to note that the expected loss of water was not observed, i.e. no peaks of $M^+$-18 at m/z = 162/164 were observed but rather loss of a methyl group occurred initially, followed by loss of acetaldehyde. The fragment ions at m/z = 125/127 are common in all the fragmentation patterns having his group present in the parent compound.

2-amino-1-(p-chlorophenyl)-2-methylpropane hydrochloride (**19**)




The molecular ion at m/z = 220 was not observed. The first ion observed involved fission between the C-N band to give the ion pair at m/z = 168/169. Further fragmentations are shown above.

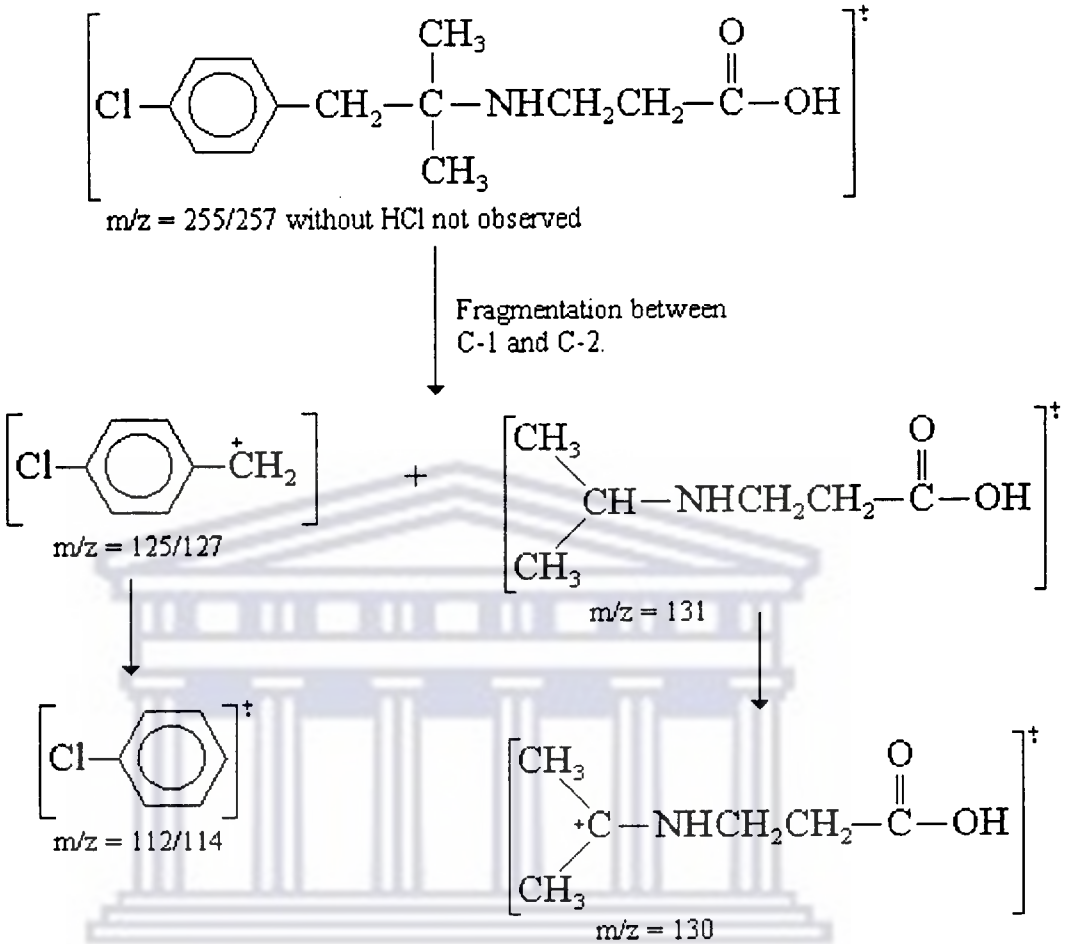
Ethyl 3-[N-1'-(p-chlorophenyl)-2'-propyl]-aminopropionate hydrochloride **(20)**




Again the molecular ion at m/z = 283/285 was not observed but rather a loss of methyl to produce the ion pair at m/z = 268/270. Cleavage of the ester then yields the ion pair at m/z = 196/198 and thereafter fragmentation to the familiar ion pair at m/z = 125/127. In an alternative fragmentation, cleavage between C-1' and C-2' leads to a molecular ion at m/z = 158 and the ion pair at m/z = 125/127.

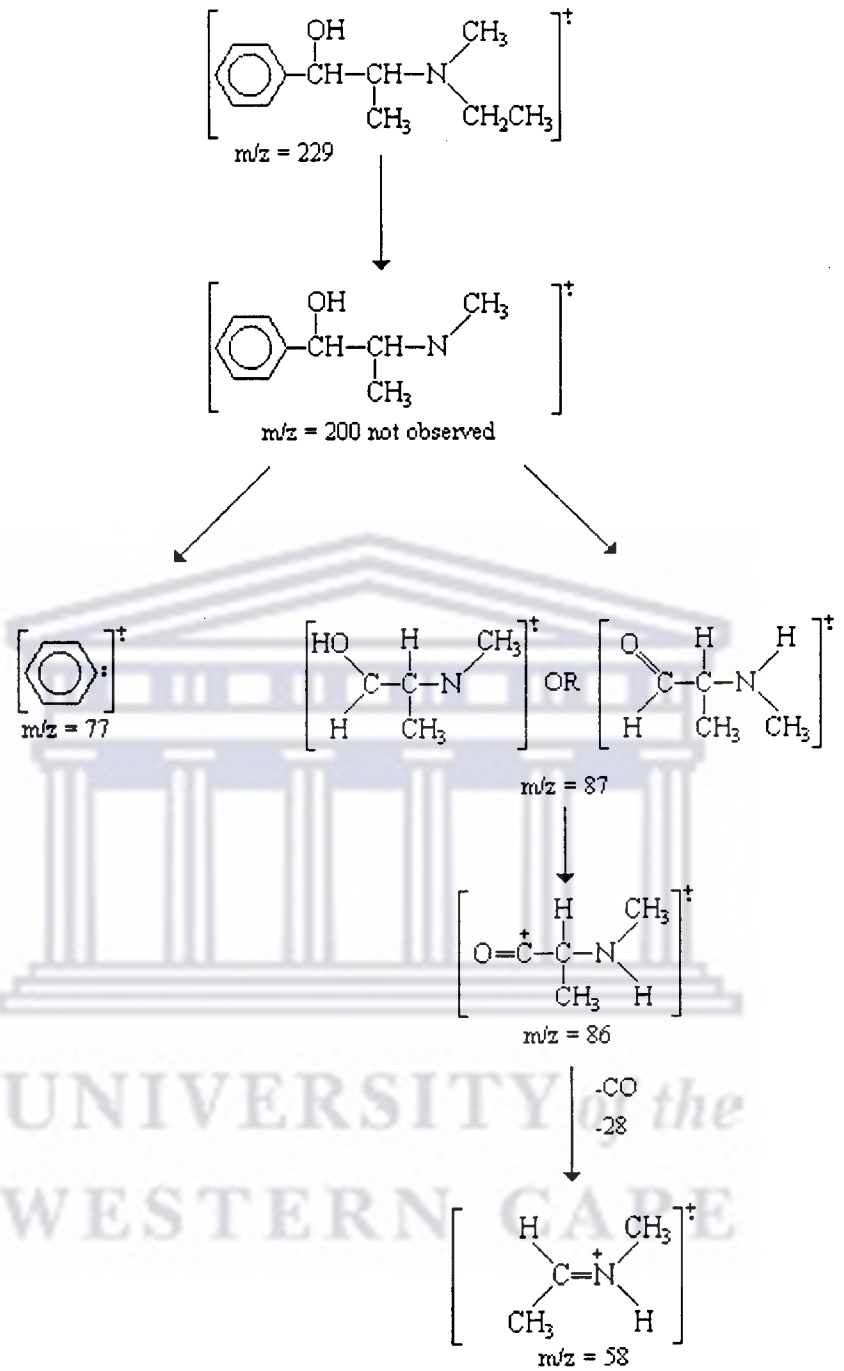
3-[N-1'-(p-chlorophenyl)-2'-methyl-2'propyl]aminopropionic acid hydrochloride

**(21)**



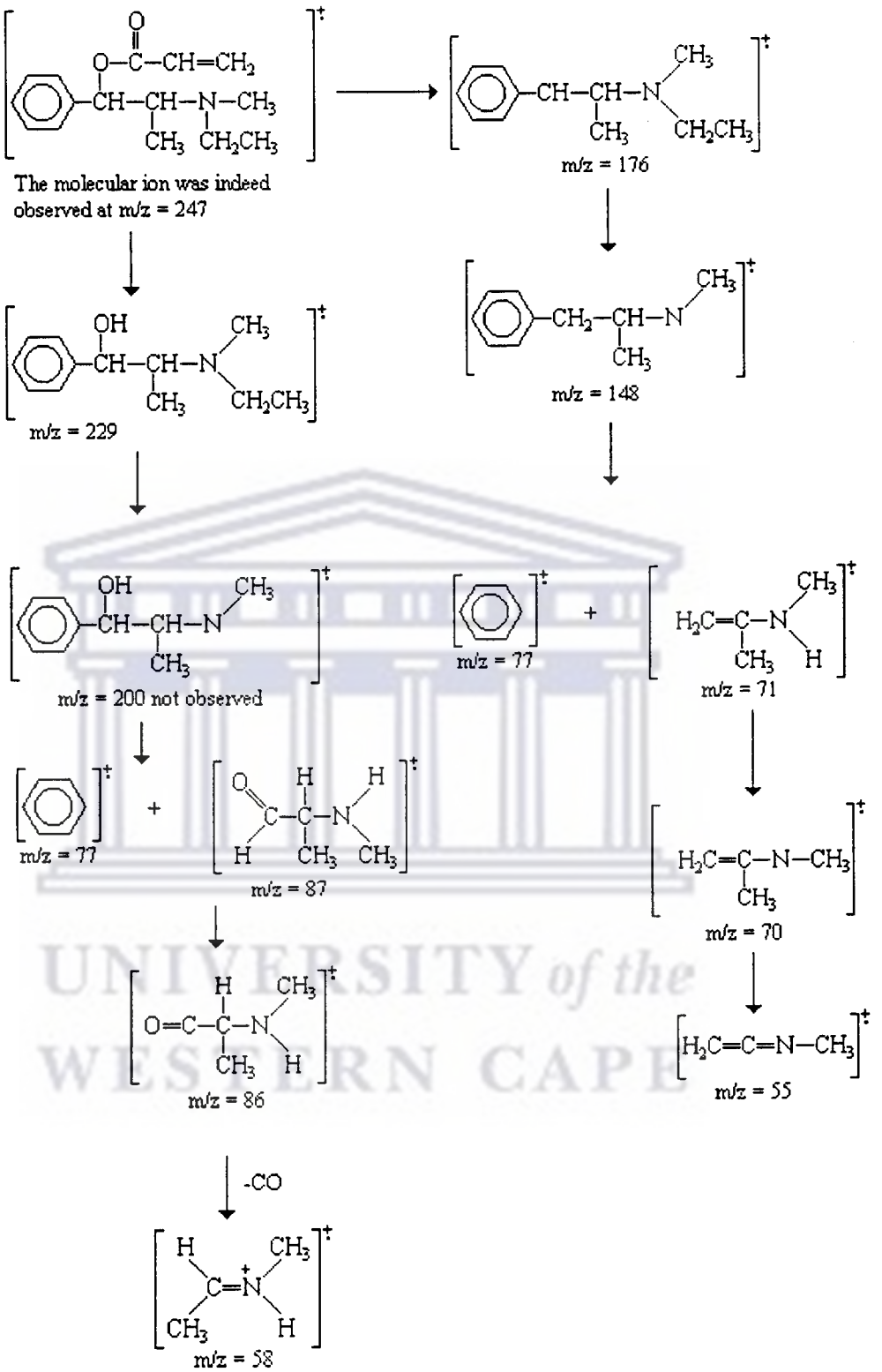

Again the molecular ion at m/z = 255/257 was not observed. Cleavage between C-1' and C-2' leads to a molecular ion at m/z = 131 and again the ion pair at m/z = 125/127.

2-N-ethyl-N-methylamino-1-phenylpropan-1-ol hydrochloride (**22**)




The molecular ion was observed at m/z = 229. Loss of the ethyl group from N-C fission produced an unstable fragment of m/z = 200 which was not observed. However further fragments thereof were observed at m/z = 87 showing concomminant loss of the benzene ring. Loss of a CO molecule from the ion at m/z = 86 yielded the imine at m/z = 58.

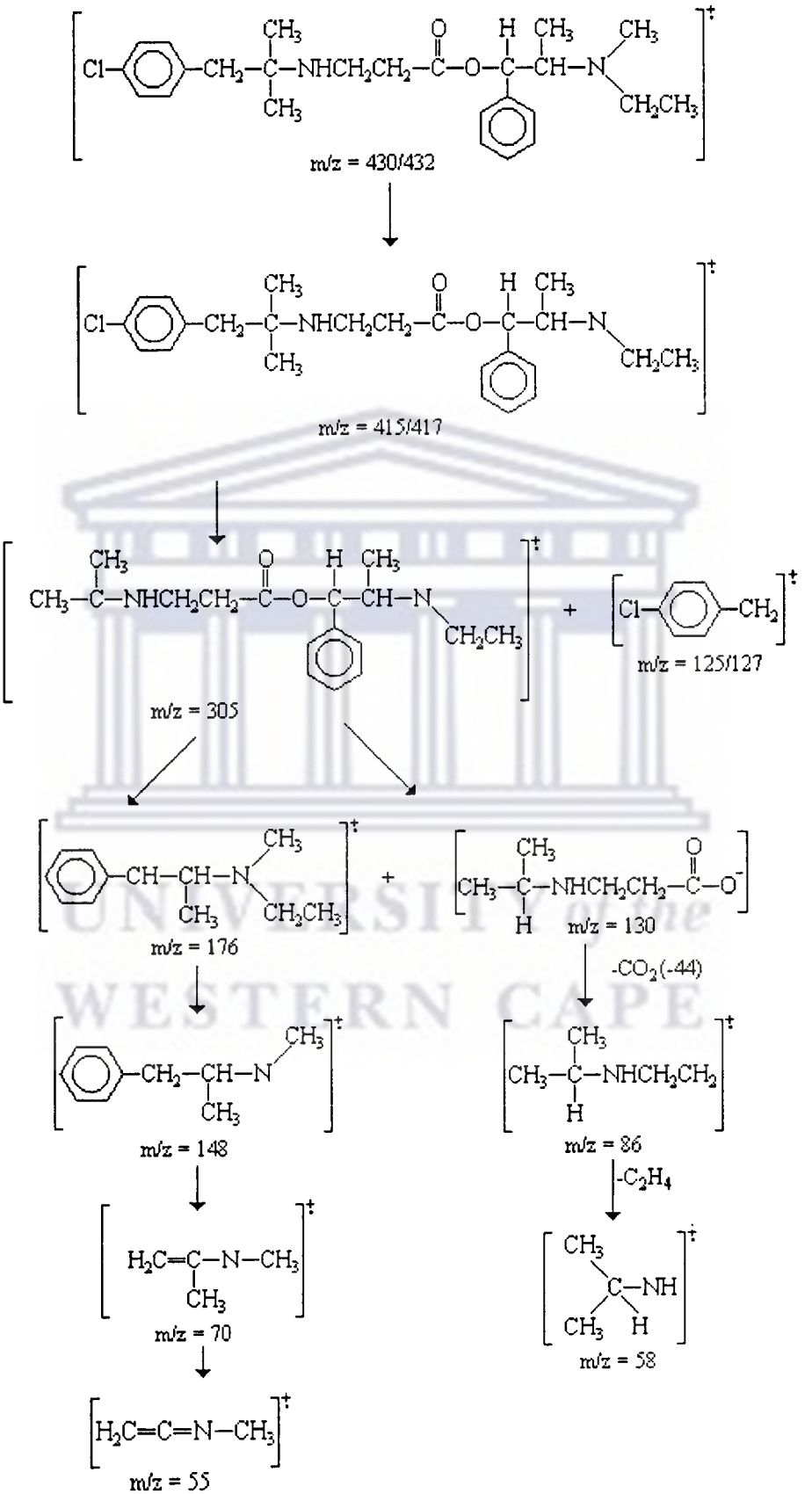
2-(N-ethyl-N-methylamino-1- phenyl)-propyl propenoate (**23**)




The molecular ion was observed at m/z = 247. We believe that two different fragmentation patterns operate in this case. In the one case the ester cleaves at the C-O bond of the alcoholic moiety to produce the ion at m/z = 176.

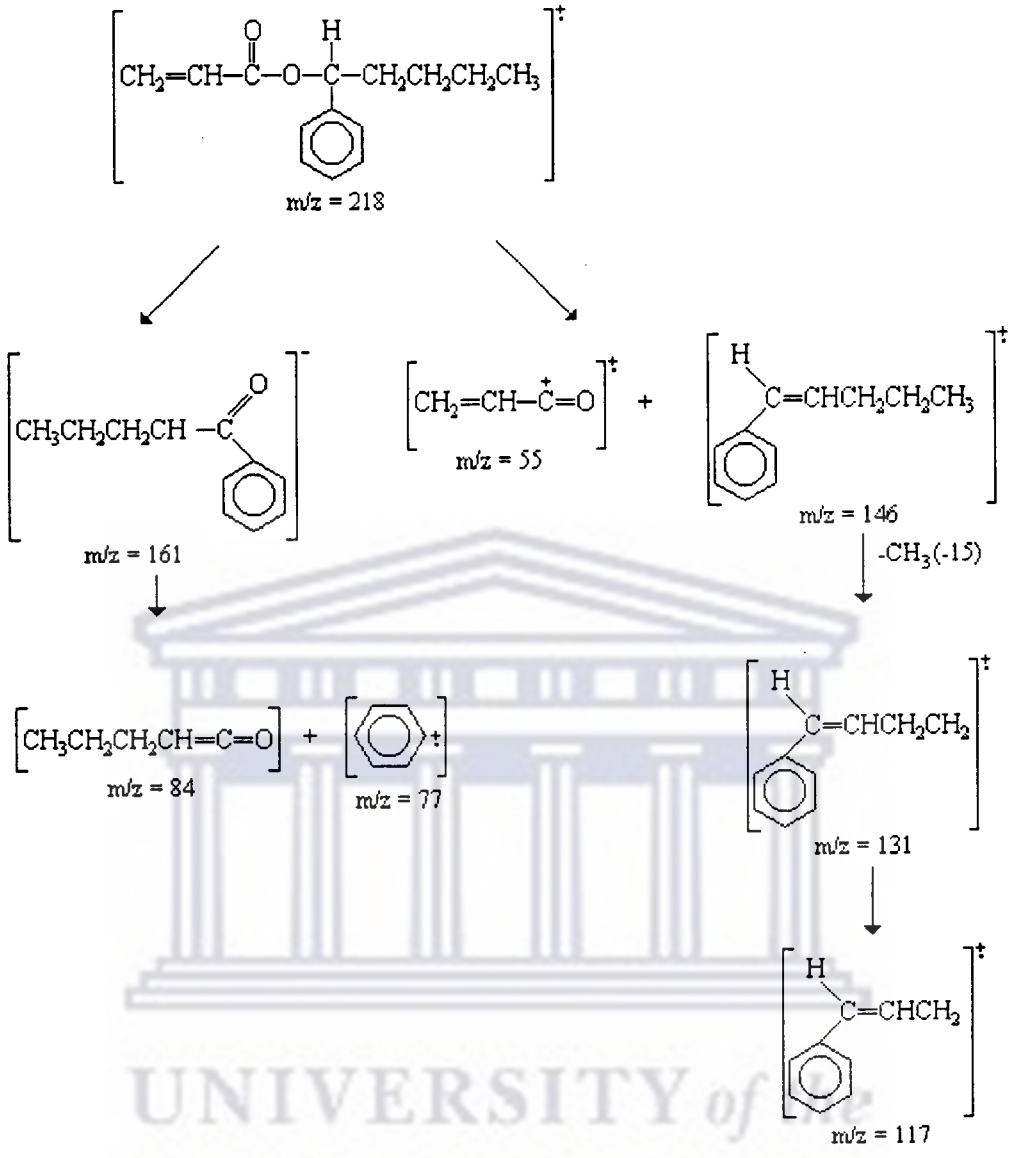
Loss of an ethyl group yields the ion at m/z = 148. Further fragmentation results from the cleavage of the C-aryl ring bond. In the alternative fragmentation pattern, the ester group must cleave at the C-O single bond adjacent to the carbonyl group to give the ion at m/z = 229. Peaks observed are similar to the fragmentation pattern described previously for compound (**22**).

2'-N-ethyl-N-methylamino-1'-phenylpropyl 3-(N-1'-p-chlorophenyl-2'-methyl-2'-propyl) aminopropionate (**14**)



The molecular ion was observed at m/z = 430/432. Again we speculate that the pathway that is apparent for the fragmentation pattern involves loss of an N-methyl group to yield the ion pair at m/z = 415/417. This is followed by the usual C-1' - C-2' cleavage to produce the ion at m/z = 305 and the aromatic moiety at m/z = 125/127. Breakdown of the fragment at m/z = 305 then occurs at the ester C-O band of the alcohol to form fragments at m/z = 130 and m/z = 176. Further fragmentation of each is as depicted above.

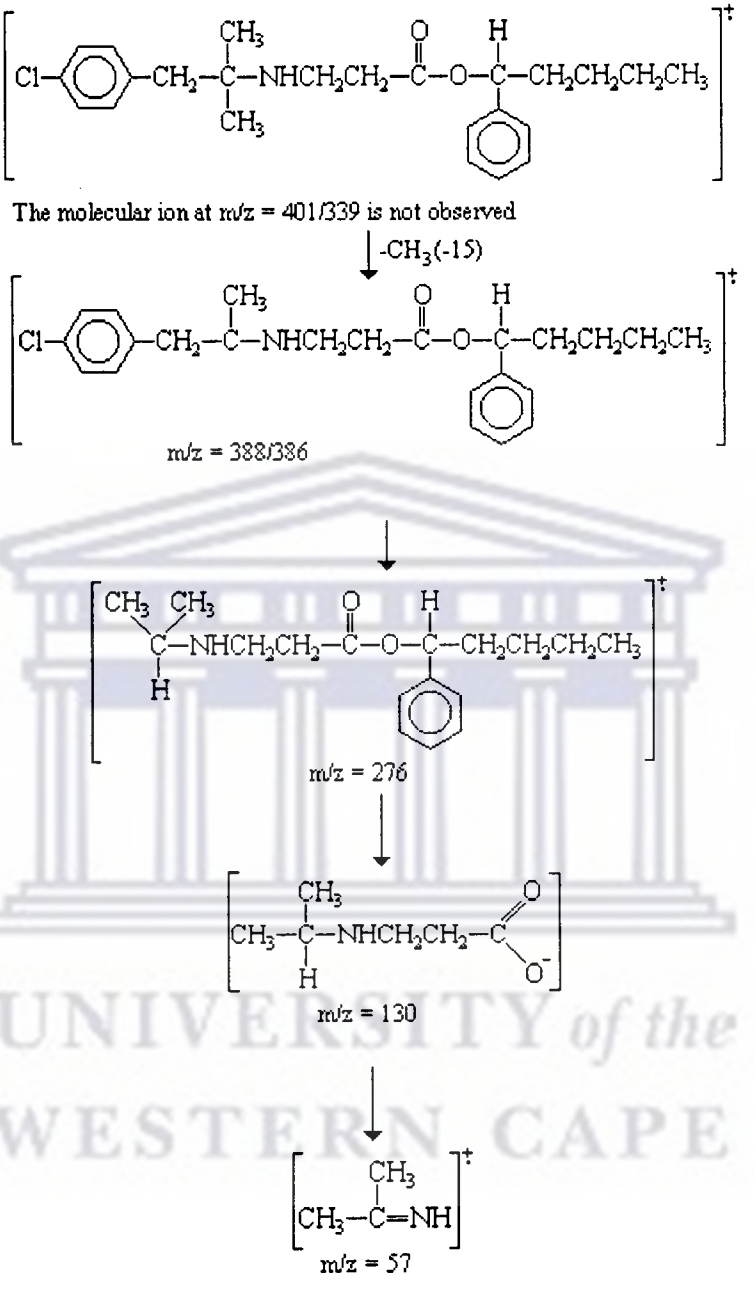
1-phenylpentyl propenoate (25)




The molecular ion was observed at m/z = 218. Again we speculate that the pathway that is apparent for the fragmentation pattern involves the cleavage of the ester alcohol followed by loss of water to yield the ion m/z = 146 whereas on the other hand oxidation lead to the ketone at m/z = 161. Further fragmentation of each is as depicted above.

1-phenylpropyl 3-N-(1'-p-chlorophenyl-2'-methyl-2'-propyl) aminopropanoate

**(16)**




The molecular ion was not observed at m/z = 401/399 but rather a loss of methyl to produce the ion pair at m/z = 388/386. The usual C-1' - C-2' cleavage produced the ion at m/z = 276. This is followed by an ester cleavage to yield the familiar ion at m/z = 130 followed by decarboxylation and loss of ethyl to yield the ion at m/z = 57.

# CONCLUSION

The main objective of this study was to develop synthetic methods for the efficient synthesis of prodrugs having chlorphentermine and phentermine as carrier molecules. An aliphatic ester was used as an enzyme link and etafedrine and 1-phenyl-1-pentanol as model agents. This objective was reached and all model products were isolated as oils.

The bronchodilator effects are currently under investigation and once these results are known one may proceed to try and increase the yields or to produce prodrugs with different carrier and or different linkages.

Future work could focus on other methods to isolate these prodrugs as salts and to improve on the yields of final products.

Infrared (IR) spectra were recorded on Pye-Unican SP300 Spectrophotometer as nujol mulls.

Hexane refers to that fraction of boiling point 65-70°C. The term "residue obtained after extraction" refers to the organic fraction remaining after the aqueous solution is extracted, the organic fraction dried over Magnesium sulphate and then filtered and stripped of solvent on a rotary evaporator.

3-[N-1'-(p-chlorophenyl)-2'-methyl-2'-propyl]-aminopropionic acid hydrochloride (CPA) (21)

Chlorphentermine base (**11**) (10.12g; 55.15mmol), ethylacrylate (20ml; 20mmol) and t-butanol (10ml) were heated under reflux at 70-80°C for 24 hours. The ester was isolated as described previously by PLC using ethylacetate as eluent and directly treated with 3M NaOH (30ml) and heated under reflux for 5h. The reaction mixture was cooled and the pH carefully adjusted to pH 6-7 with concentrated hydrochloric acid. At this stage the solution was heated to redissolve the precipitate formed. Upon cooling, white crystals formed which were filtered and washed with anhydrous ether. The filtrate was cooled in ice to provide a further crop of product. In this way the acid (CPA) (**21**) was obtained as the hydrochloride (8.37g; 52 %), as colourless crystals, m.p. 191-194°C (from ethanol-ether); $V_{max}$ 1665cm$^{-1}$; $\delta_H$ 1.21(6H, s, 2xC***H***$_3$), 2.50(1H, s, $D_2O$ exchangeable N***H***), 2.81(2H, t, ***J*** 7Hz , - $NCH_2CH_2$ CO), 3.03(2H, s, Ar C***H***$_2$-), 3.16(2H, t, ***J*** 7Hz-NC***H***$_2$ $CH_2$ C = O), 7.28(2H, d, ***J*** 7Hz , 2' - and 6'-H), 7.39 (2H, d, ***J*** 7Hz, 3'- and 5'-H), 9.28(1H, bs, $D_2O$ exchangeable, COO***H***); $\delta_c$ 22.3, 30.8, 36.6, 39.1, 39.5, 39.9, 42.0, 58.9, 128.2, 131.8, 132.5, 134.3 171.5.

Found: C, 53.20 % H, 6.65 %; N, 4.72 %; $M^+$132/130 .

Calc. for $C_{13}H_{19}Cl_2NO_2$: C, 53.44 %; H, 6.55 %; N, 4.79 % $M^+$ 295/293.

Mass Spec: 132 (100), 130 (100), 127(10), 125 (10), 112 (13).

2-N-ethyl-N-methylamino-1-phenylpropan-1-ol hydrochloride (ET) (**22**)

A mixture of anhydrous α-ephedrine (**26**)(50.0g; 0.30mol) and ethylbromide (40.0g; 0.37mol) was stirred at room temperature for 24 hours and then heated on a water-bath for 5 h. The cooled reaction mixture was diluted with water (100ml), acidified with 10 % hydrochloric acid and the aqueous solution was washed with diethyl ether (3x50ml). The aqueous phase was carefully basified with solid sodium hydroxide and the liberated amine was extracted with diethyl ether (3x70ml). The ethereal phase was evaporated under reduced pressure, and 5M sodium hydroxide (50ml) and benzenesulphonylchloride (40ml) were added to the viscous colourless residue (36.g) in a 500ml erlenmeyer flask. The flask was tightly stoppered and shaken carefully for 5 minutes. During shaking the flask was cooled by periodic dipping in a cold water-bath and the pressure build-up was released. When the reaction subsided, the flask was warmed on a water-bath for 30 minutes. Thereafter the flask was cooled and the contents acidified with 10 % hydrochloric acid (100ml). The aqueous phase was washed with diethyl ether (3x20ml) and then carefully basified with solid sodium hydroxide and heated for 2 h. The liberated etafedrine base (**13**) was extracted into ether (3x70ml). The combined ethereal phases were washed with 1M sodium hydroxide (2x20ml), dried with anhydrous magnesium sulphate and, after filtration, the ethereal phase was saturated with dry hydrogen chloride gas to produce the hydrochloride salt (ET) (**22**) (20.64g; 30 %), m.p. 218°C-221°C as long needles (from ethanol-ether); $\delta_H$ 1.05(3H, d, ***J*** 7Hz, CH-C***H***$_3$), 1.29(3H, t, ***J*** 6.8 Hz, $CH_2$-C***H***$_3$), 2.80(3H, s, N-C***H***$_3$), 3.16(1H, bs, $D_2O$ exchangeable O***H***), 3.39(2H, q, ***J*** 7Hz, C***H***$_2$$CH_3$), 5.49(1H, m, $CH_3$C***H***), 6.10(1H, d, ***J*** 7Hz, ArC***H***),

7.33(5H, m, Ar***H***), $\delta_c$ 5.0, 9.4, 35.2, 49.0, 64.8, 69.7, 125.5. 126.1, 128.1, 142.6.

Found: C, 62.86 %; H, 8.91 %; N, 6.15 %, $M^+$229.

Calc. for $C_{12}H_{20}ClNO$: C, 62.73 %; H, 8.77 %; N,6.11 %; $M^+$229.

Mass Spec: 229 (1), 87 (10), 86 (100), 77 (1), 58 (22).

2-(N-ethyl-N-methylamino-1-phenyl)-propyl propenoate (ETA) (**23**)

Etafedrine hydrochloride (**22**) (2.01g; 8.76mmol) was dissolved in distilled water (10ml). The solution was made basic with 5M sodium hydroxide and the liberated base was extracted with diethyl ether. The residue obtained upon work-up was dissolved in dry ether (60ml) and treated with acryloyl chloride (0.9ml; 0.12mmol) drop-wise over a period of 20 minutes at 25°C. The reaction mixture was stirred for 6 h at 25°C after which distilled water (10ml) was added, the two phases separated and the ethereal phase was extracted with cold 0.1M hydrochloric acid (2x5ml) and then made basic with 5M aqueous sodium hydroxide. The resulting solution was extracted with diethyl ether (3x15ml) to afford a residue that was purified by chromatography using ethylacetate-hexane (1:4) as eluent. In this way the pure ester (**23**) (1.23g; 44 %) was obtained as a colourless viscous oil; $V_{max}$ 1738cm$^{-1}$; $\delta_H$ 0.96-1.10(6H, m, -CHC***H***$_3$ and -$CH_2C$***H***$_3$), 2.28(3H, s, N-C***H***$_3$), 2.53(2H, q, ***J*** 7 Hz, -C***H***$_2$$CH_3$), 3.11(1H, m, -C***H***$CH_3$), 5.82-6.49(4H, m, ArC***H*** and vinyl ***H***'s),7.29(5H, m, Ar***H***); $\delta_C$ 9.8, 13.3, 37.1, 47.7, 61.9, 76.4, 77.7, 126.3, 127.3, 128.0, 128.6, 130.7, 140.1, 165.1.

Found: C, 72.52 %; H, 8.71 %; N, 5.41 % $M^+$247.

Calc. for $C_{15}H_{21}NO_2$: C, 72.84 %; H, 8.56 %; N, 5.66; $M^+$247.

Mass Spec: 247 (1), 176 (2), 148 91), 87 (43), 86 (100), 77 (3), 58 (50), 55 (52).

2'-N-ethyl-N-methylamino-1'-phenylpropyl 3-(N-1'-p-chlorophenyl-2'-methyl-2'-methyl-2'-propyl) aminopropionate. (CPETA) (**14**)

Etafedrine acrylate (ETA) (**23**) (1.06g; 4.29mmol) and chlorphentermine base (**11**) (1.10g; 5.99mmol) were added to t-butanol (5.0ml) and heated under reflux at 70-80°C for 24 h. The reaction was monitored by TLC. Thereafter the t-butanol was evaporated off on a rotary evaporator and the residue was purified by PLC using triethylamine-ethylacetate (1:9) as eluent. In this way the product (**14**) was obtained as a thick yellow oil (546mg; 21.20 %) with $R_f$ = 0.8; $V_{max}$ 1735 $cm^{-1}$; $\delta_H$ 0.84-1.13(12H, m, 2x$CH_3$, -CH$CH_3$ and $CH_2CH_3$), 2.25(3H, s, - N-$CH_3$), 2.43-2.62(7H, m, N-***H***, $CH_2CH_2$ CO and Ar$CH_2$), 2.85-3.03(3H, m, -$CH_3CH$-N and -$CH_3$N-$CH_2$-$CH_3$), 5.89(1H, d, ***J*** 7Hz, PhC***H***-CH), 7.07-7.33 (9H, m, Ar***H***); $\delta_C$ 9.6, 11.8, 13.3, 26.6, 35.9, 37.2, 37.7, 46.5, 47.7, 61.7, 76.4, 126.4, 127.4, 128.0, 131.9, 136.8, 140.2, 171.8.

Found: C, 69.26 %; H, 8.37 %; N, 6.39 %; $M^+$430.2371.

Calc. for $C_{25}H_{35}ClN_2O_2$: C, 69.67 %; H, 8.18 %; N, 6.50 %; $M^+$430.2377.

Mass Spec: 430 (1), 415 (1), 305 (4), 176 (72), 148 (22), 130 (15), 86 (100), 70 (22), 58 (17), 55 (10).

2'-N-ethyl-N-methylamino-1'-phenylpropyl 3-(N-1'-phenyl-2'-methyl-2'-propyl) aminopropionate (PETA) (**15**)

Etafedrine acrylate (ETA) (**23**) (1.02g; 4.13mmol) and phentermine (**24**) (0.89g; 6.00mmol) were added to t-butanol (5ml) and heated under reflux at 70-80°C for 24 h. The reaction was monitored by TLC. Thereafter the t-butanol was evaporated off on a rotary evaporator and the residue was purified by PLC using triethylamine-ethylacetate (1:9) as eluent to afford the product (**15**) (480mg, 20.20 %) as a light yellow oil with $R_f = 0.8$; $V_{max}$ 1737 $cm^{-1}$; $\delta_H$ 0.82-1.09 (12H, m, 2x$CH_3$, C-$CH_3$ and $CH_2CH_3$), 2.24(3H, s, -N-$CH_3$), 2.44-2.58(5H, m, -$CH_2$-$CH_2$-C and -N*H*), 2.67(2H, s, Ar$CH_2$), 2.89-3.08(3H, m, $CH_3CH$ and -N-$CH_2CH_3$), 5.91(1H, d, *J* 7 Hz, Ar-C*H*-O), 7.12-7.36(10H, m, Ar*H*), $\delta_C$ 9.9, 13.3, 26.7, 36.1, 37.2, 37.8, 47.3, 47.7, 53.3, 61.8, 76.0, 76.4, 77.0, 77.6, 126.0, 126.1, 130.4, 138.4 140.3, 171.9.

Found: $M^+$ 396.2763.

Calc. for $C_{25}H_{36}N_2O_2$: $M^+$ 396.2776.

Mass Spec: 396 (1), 305 (1), 176 (1), 148 (2), 130 (1), 86 (100), 70 (21), 58 (30), 55 (10).

1-phenylpentyl propenoate (AP') (**25**)

1-Phenyl-1-pentanol (**12**) (3.63g; 22mmol), triethylamine (1.5ml) and diethyl ether (100ml) were stirred together at 25°C. Acryloyl chloride (4.02g; 44mmol) was slowly added over 20 minutes. The reaction mixture was stirred at 25°C for a further 24 h. Distilled water (30ml) was added to the reaction mixture and the ethereal phase was washed with distilled water (2x20ml). All the aqueous phases were made basic and extracted with ether (3x30ml). The combined ethereal extracts were washed with 0.1M hydrochloric acid (2x20ml) and the residue obtained upon work-up was chromatographed using ethylacetate-hexane (1:9) as eluent to afford the ester (**25**) (2.86g; 59.63 %) as a thick white oil with $R_f$ 0.8; $V_{max}$ 1737cm$^{-1}$; $\delta_H$ 0.90 (3H, t, ***J*** 6.8 Hz, 5-H), 1.20-1.40 (4H,m, 3- and 4-H), 1.90 (2H, m, 2-H), 5.80-5.85 (2H, m, 1-H and ***cis*** -CH=C***H***$_2$), 6.15 (1H, dd, ***J*** 17.4 and 8.2 Hz, C***H***=CH$_2$), 6.45 (1H, dd, ***J*** 17.4 and 1.6 Hz, ***trans*** -CH=C***H***$_2$) and 7.36 (5H, m, Aryl ***H***); $\delta_C$ 13.9, 20.4, 27.6, 36.1, 76.4, 126.6, 127.9, 128.5, 128.8, 130.8, 140.9, 165.7.

Found: $M^+$ 218.1316.

Calculated for $C_{14}H_{18}O_2$: $M^+$ 218.1307

Mass Spec: (218 (18), 161 (26), 146 (14), 117 (25), 77 (10), 55 (100).

1-phenylpropyl 3-N-($1^1$-p-chlorophenyl-$2^1$-propyl) aminopropanoate (CPAP') (**16**)

AP' (**25**) (0.89g; 4.1mmol) and chlorphentermine base (**11**) (1.11g; 6mmol) were added to t-butanol (5.0ml) and heated under reflux at 70-80°C for 24 h. The reaction was monitored by TLC. Thereafter the t-butanol was evaporated off by vacuum distillation. The residue obtained was purified by PLC using hexane-ethylacetate-triethylamine (5:4:1) as eluent to afford the ester (**16**) (648mg; 26.93 %) as a thick light yellow oil with $R_f = 0.8$; $V_{max}$ 1738cm$^{-1}$; $\delta_H$ 0.90 (3H, t, ***J*** 7Hz, -$CH_2CH_2CH_3$), 1.01(6H, s, 2x$CH_3$), 1.34(4H, m, -$CH_2CH_2CH_2CH_3$), 1.84(2H, m, CH(Ar)$CH_2CH_2$), 2.55(2H, t, ***J*** 7Hz, -N-$CH_2$-$CH_2$-C), 2.61(2H, s, Ar$CH_2$),2.89(2H, t, ***J*** 7Hz, -N-$CH_2$-$CH_2$), 5.75(1H, t, ***J*** 7Hz, Ar-CHO), 7.05-7.28(9H, m, Ar***H***), $\delta_C$ 13.9, 22.4, 26.7, 27.7, 36.0, 37.8, 46.6, 53.2, 76.5, 77.1, 77.7, 126.6, 127.9, 128.1, 128.5, 131.8, 132.1, 137.0, 141.0, 172.3.

Found: $M^+$ 401.2111.

Calc. for $C_{24}H_{32}NO_2Cl$: $M^+$ 401.2119.

Mass Spec: 401, 399, 388 (2), 386 (2), 276 (97), 130 (100), 57 (10).

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