KINGSTON
UNIVERSITY

SYNTHESIS OF POTENTIAL ENZYME INHIBITORS IN THE TREATMENT OF HORMONE-DEPENDENT PROSTATE CANCER

A THESIS SUBMITTED IN ACCORDANCE WITH THE CONDITIONS GOVERNING CANDIDATES FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

BY

HURIA ABDULKADIR

DEPARTMENT OF PHARMACY
SCHOOL OF PHARMACY AND CHEMISTRY
PENRHYN ROAD
KINGSTON-UPON-THAMES
SURREY
KT1 2EE

September 2006

ACKNOWLEDGEMENTS

I would like to give special thanks to my project supervisor Prof. Sabbir Ahmed without whom this project would have been impossible to complete and my second supervisor Dr. Caroline Owen, for her assistance, guidance, and encouragement throughout this project.

I also would like to thank the research team, especially Rupi for all her support, during our writing up processes. I would also like to take this opportunity to thank Dr. Michael Tsang for his help and encouragement throughout this project and Sachin for the biological evolution of my compounds.

I would like to thank my friends Rina, Moniola and Kwabina. Finally a special thank you to my family especially my mum for the encouragement, patience and support, without which life could have become unbearable.

ABSTRACT

A high proportion of prostate cancer has been shown to be hormone-dependent, in particular, dependent on testosterone (T) and dihydrotestosterone (DHT). The biosynthesis of the androgens is catalysed by the cytochrome P-450 enzyme 17α-hydroxylase/17,20-lyase ($P450_{17\alpha}$) which is responsible for the conversion of pregnanes (for example progesterone) to the androgens (for example androstenedione). However, the biosynthesis of DHT, the more potent androgen is catalysed by 5α-reductase (5αR). The inhibition of these two enzymes would therefore lead to the overall reduction in the level of T and DHT. Thereby leading to a decrease in the stimulation of androgen-dependent cancer cells.

Within the current study, the synthesis of a series of potential inhibitors is described. The compounds synthesised against $P450_{17\alpha}$ were based upon the ability of the compounds to donate a lone pair of electrons to the iron atom within the haem group of the active site of $P450_{17\alpha}$. As such, compounds based on the Evan's chiral auxiliary were synthesised containing a phenylamine moiety. In the synthesis of the compounds, the initial *R* and *S* forms of the chiral auxiliary were initially alkylated (using sodium hydride and alkyl bromide), followed by the nitration (with dilute fuming nitric acid) of the phenyl ring which was subsequently reduced (using palladium on charcoal and hydrogen gas) to give the phenylamine moiety. The reactions proceeded in moderate to good yield without many problems. The reactions were repeated with an alternative chiral auxiliary, namely, 4-methyl-5-phenyl–2-oxazolidinone, however, due to lack of time, only the initial alkylation step was undertaken and was found to proceed in good yield. The biochemical evaluation of the phenylamine based compounds using a literature based assay showed these compounds to be weak inhibitors of $P450_{17\alpha}$, with two compounds (of the range evaluated) showing close to 40% inhibition at 1mM.

The compounds targeted against 5αR, were based upon the ability of the inhibitors to mimic the substrate and thereby allow themselves to be reduced by NADPH, as such, they were based upon pyrrolidine-2,5-dione structure with a C=O moiety to mimic the Δ^5 functionality in T. The *N*-substituted pyrrolidine-2,5-dione was therefore reacted with the appropriate ester in the presence of sodium hydride. In general, the reactions proceeded well, however, the products were obtained in poor yield (ranging from 30% to 12%). Attempts to use an activated carbonyl group (e.g. the use of acyl chloride derivative of the esters) did not result in increased yield. The compounds synthesised were not evaluated against 5αR due to the lack of an assay system.

Abbreviations

AD	Androstenedione
5αR	5-α Reductase
BPH	Benign Prostate Hyperplasia
$CDCl_3$	Deuterated Chloroform
d	Doublet
DCM	Dichloromethane
dd	Doublet of Doublets
DES	Diethylstilbestrol
DHEA	Dehydroepiandrosterone
DHT	Dihydrotesterone
DNA	Deoxyribonucleic Acid
DRE	Digital Rectal Examination
FSH	Follicle Stimulating Hormone
FTIR	Fourier Transform Infrared
g	Gram
GCMS	Gas Chromatography Mass Spectorometry
h	Hour(s)
IC_{50}	Inhibitor Concentration that gives 50% inhibition
K_i	Inhibiton Constant
LH	Leutenising Hormone
LHRH	Leutenising Hormone Releasing Hormone
m	Multiplet
m.p.	Melting Point
mg	Milligram
MHz	Mega Hertz
MS	Mass Spectrometry
NADP	Nicotinamide Adenine Dinucleotide Phosphate
$NADP^+$	Oxidised Nicotinamide Adenine Dinucleotide Phosphate
NADPH	Reduced Nicotinamide Adenine Dinucleotide Phosphate
nM	Nanomolar

NMR	Nuclear Magnetic Resonance
$P450_{17\alpha}$	17α-Hydroxylase/17,20-Lyase
Pd/C	Palladium of Carbon
PSA	Prostate Specific Antigen
R_f	Retention Factor
RT	Room-Temperature
s	Singlet
SAR	Structure Activity Relationship
T	Tetosterone
t	Triplet
TEBG	Testosterone Binding Globulin
TLC	Thin Layer Chromatography
tPSA	Total Prostate Specific Antigen
t_R	Retention Time
TRUS	Transrectal Ultra Sound
TZ	Transitional Zone
UV/Vis	Ultraviolet/Visible
µM	Micromolar
λ	Wavelength
ν	Wavenumber

Contents

Chapter One: Introduction

Chapter Two: Experimental

Synthesis of potential inhibitors of $P450_{17\alpha}$.

Chapter Three: Experimental
Synthesis of derivatives of pyrrolidine-2,5-dione as potential inhibitors of 5AR

Chapter Four: Biochemical evaluation

Chapter Five: References

Chapter One:

Introduction

1.0 INTRODUCTION

1.1 CANCER

The term cancer is used to describe a wide range of disease states involving nearly every type of tissue in the body. Cancer cells lose the functional and phenotypic characteristics of the tissue from which they originate. They undergo malignant transformations. As the malignancy progresses, the cancer cells compete with normal cells for physical space and nutrients. Some malignancies are able to spread via the circulatory or lymphatic systems to remote sites of the body, resulting in the formation of a new foci of malignant cell growth (metastases) far from the original tissue in which the cancer developed (Eales et al, 1997).

1.2 PROSTATE CANCER

The prostate is a small gland located below the bladder and in front of the rectum. It surrounds the upper part of the urethra, and is composed of four zones: anterior fibromuscular stroma, posterior peripheral zone, periurethural transition zone, and posterosuperior central zone (Papatheodorou et al, 2005).

Prostatic carcinoma are the most common malignant diseases among men in the Western World, and the second leading cause of death in the United State (Matsunaga et al, 2004). In 2005 it was estimated that 232,090 men developed prostate cancer in the United States and 30,350 died from this disease (Jemal et al, 2005). During 2004 in Europe there were some 237,800 cases diagnosed and 85,200 deaths (Boyle et al, 2004).

1.3 AETIOLOGY OF PROSTATE CANCER

The aetiology of prostate cancer is not clearly understood, however, it has been suggested that a number of factors may be involved: family history, racial and ethnic factors, diet and hormones (Hillman et al., 2006; Reilly, 1999). Some of these will be briefly discussed subsequently.

1.3.1 DIET

High animal fat intake is associated with prostate cancer. Studies have also shown that several agents found in the diet may prevent the effects of carcinogenic agents or suppress the promotional activity in already induced neoplastic prostatic cells. For example, the flavanoid genistein has been shown to suppress proliferation of prostate cancer cells *in vitro* (Hillman et al, 2006). Lycopene which is found in high concentrations in cooked or crushed tomatoes is thought to reduce the risk of prostate cancer by two or three fold (Reilly, 1999).

1.3.2 FAMILY HISTORY

Studies have identified family history as a risk factor for prostate cancer, typically associated with a two- to four-fold increase in risk (Cerhan et al, 1999). Family history may, however, reflect both genetic and environmental factors. Approximately 10-15% of all cases of prostate cancer are classified as familial and are considered to be different from cases classified as hereditary - the latter category is for men with a clear-cut inherited predisposition. The diagnosis of hereditary cancer cannot be confirmed because there are no prostate cancer genes yet identified, (Narod, 1998).

1.3.3 RACIAL AND ETHNIC FACTORS

Prostate cancer incidence rates vary markedly between ethnic groups. it was estimated that, 27,130,000 black American men developed prostate cancer in the United States, compared to 16,440,000 white American men between 1997 and 2001 (Jemal et al, 2005).

1.4 ENDOCRINOLOGY OF THE PROSTATE

Androgens are necessary for the metabolic processes of normal prostatic epithelial cells and their biosynthetic pathway is shown in Figure 1.1 (Jarman et al., 1998a).

It was demonstrated by Bruchovsky and Wilson (1968) and Anderson and Liao (1968) that the biological activity of androgens in the prostate was directly linked with their conversion to dihydrotestosterone (DHT) within prostatic cells.

Testosterone (T) is synthesised in the testes and the adrenal glands and regulation of the production of androgens is regulated by the hypothalamic pituitary axis through two separate feedback mechanisms. Luteinizing hormone (LH), which is released from the anterior pituitary on stimulation by hypothalamic luteinizing hormone releasing hormone (LHRH), controls the regulation of testicular secretion of T. T is the mediator of negative feedback for LH production, whilst oestrogens are potent inhibitors of pituitary LH release. Androstenedione (AD) and dehydroepiandrosterone (DHEA), which are weak androgens produced by the adrenals and are almost exclusively bound to albumin, do not significantly stimulate the growth and function of the human prostate (Walsh, 1975; Oesterling et al., 1986).

T, produced by the testes, is transported in the blood, bound to sex hormone-binding globulin. It enters the prostate cells and is converted to DHT, by the enzyme 5α-reductase (5αR) (Figure 1.2). This conversion promotes further passive diffusion of T into the cell.

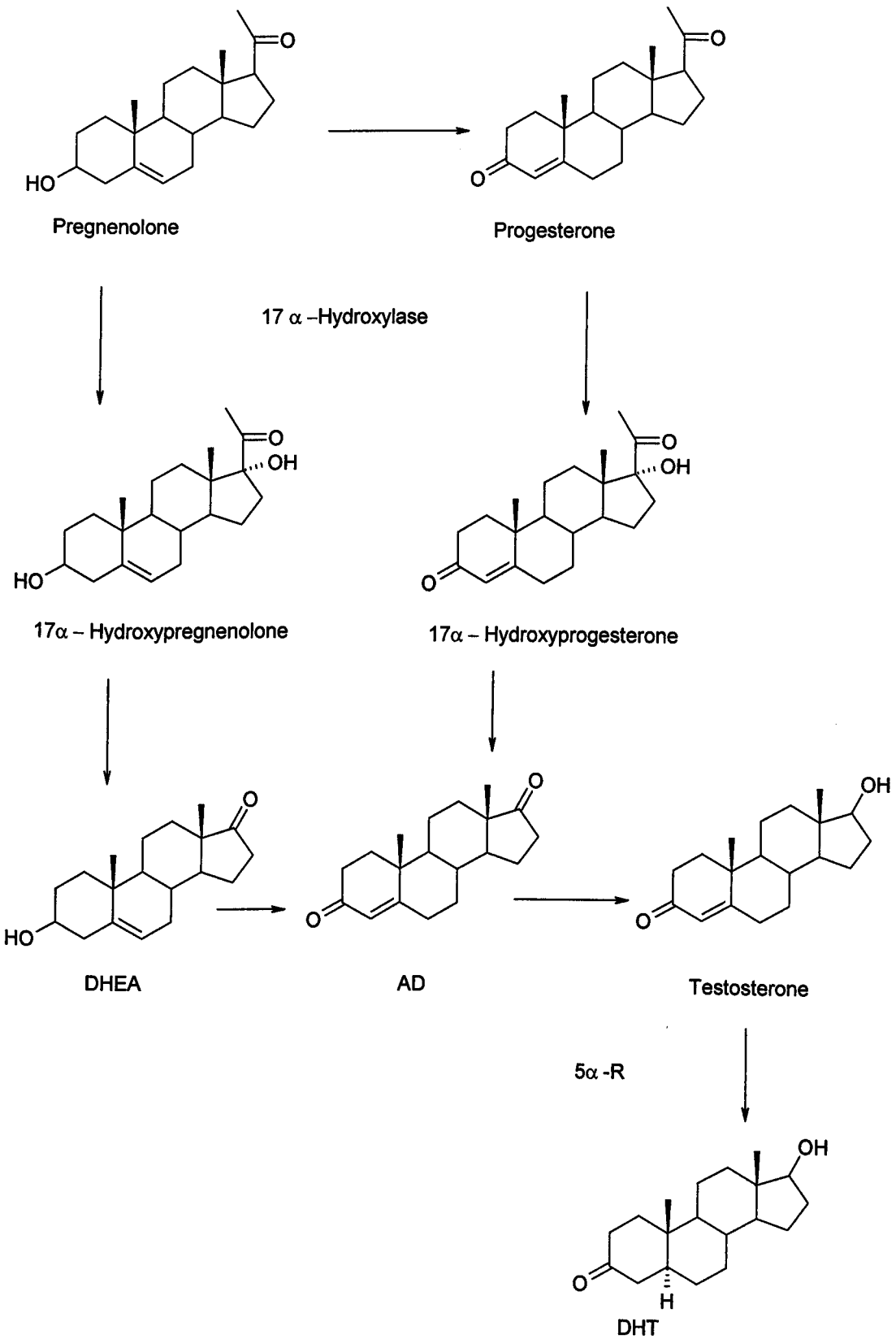
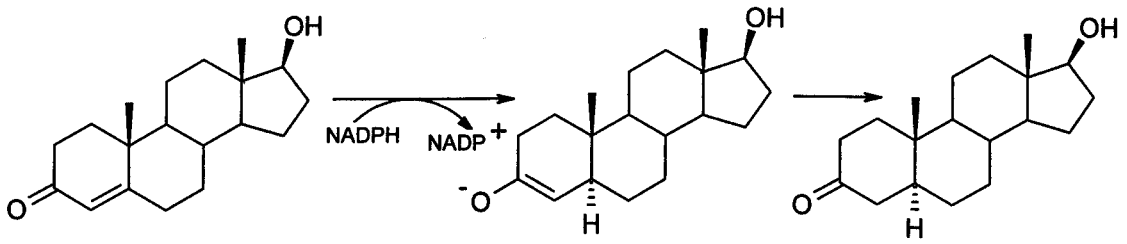


Figure 1.1 Pathway of steroidal biosynthesis



T Enolate intermediate DHT

Figure 1.2 5αR catalysed conversion of T to DHT

These synthesised proteins promote further cellular division, as well as the synthesis of 5αR (Figure 1.2) (Occhiato, 2004). T binds to the same androgen receptor as DHT, but with less affinity. T is thought to be responsible for the differentiation of the wolfian duct into seminal vesicles and the epididymis during embryonic development. In the embryo DHT is believed to be the determinant for the sexual differentiation of the male foetus organs with formation of external genitalia, urethra and prostate. It is thought that at puberty, T induces the maturity of male genitalia whilst DHT is responsible for a full male body hair growth and the enlargement of prostate (Occhiato, 2004).

1.5 PROSTATE CANCER THERAPY

There are a number of treatments for prostate cancer, however, the optimal management of local cancer has yet to be defined. A multimodal approach is currently needed including surgery, cryotherapy, radiation and hormonal therapy (Vicini et al., 1999). The choice of treatment is dependent upon the stage of progression of the disease. Surgery and external radiation are the treatment for organ-confined disease, whereas hormonal manipulation or chemotherapy are the main options in the case of metastatic cancer. Radiotherapy is preferred when patients, because of their advanced age, would not be expected to survive surgery (Krane and Fitzpatrick, 1989).

1.5.1 SURGERY

Radical prostatectomy consists of the removal of the prostate and its surrounding tissues. It is an effective treatment if the cancer has not spread outside the prostatic capsule. However, impotence and loss of libido are the main side-effects of this method.

1.5.2 CRYOTHERAPY

Liquid nitrogen is applied directly in contact with the tumour, sparing nearby tissues. Cryotherapy consists of a cycle of treatment where the tumour is frozen, allowed to warm up and refrozen. However, this method is not considered to be efficient when the cancer has spread to other parts of the body.

1.5.3 INTERSTITIAL IRRADIATION (OR BRACHYTHERAPY)

This type of radiation therapy consists of the implantation of radioactive "seeds" directly in the prostate gland. The radiation emitted by the seeds destroys the cancer cells whilst minimising exposure to surrounding tissues or organs (Vicini et al., 1999). This type of treatment is only effective in cases of organ-defined prostate cancer.

1.5.4 ENDOCRINE THERAPY (SURGICAL CASTRATION)

Endocrine therapy involves the manipulation of hormone levels in the body, either surgically or chemically. It is used to reduce the amount of circulating androgens and thus removes the stimulation for prostatic cancer growth. Methods available include:

1.5.5 ORCHIDECTOMY

This treatment consists of the removal of the testes, the main organ responsible for androgen production. It is useful when the cancer has spread outside the prostatic capsule as it reduces the levels of circulating T. This method of

treatment has been found to give an average reduction of the prostate volume of 30-50% (Sneller et al, 1992). The main side-effects of this treatment are loss of libido, impotence and hot flushes. However, the major side-effect is the emotional aspect of having the testes removed.

1.5.6 OESTROGEN THERAPY

When oestrogens are administered, they reduce the pituitary release of LH by exerting a negative feedback on the hypothalamus and therefore inhibit the production of androgens by the testes. At an oral dose of 3 mg/day, diethylstilboestrol (DES) (Figure 1.3), a synthetic oestrogen achieved castrate levels of plasma T after twenty one days (Shearer et al., 1973). Oestrogen therapy also raises T binding globulin (TEBG) levels, therefore decreasing the amount of free or active plasma T (Ahmed, 1990). However, the side-effects are a major drawback of this method of therapy and include nausea, vomiting, headache and fluid-retention, as short term side-effects, and gynaecomastia, impotence and serious cardiovascular complications as the long term side-effects (Glashan and Robinson, 1981).

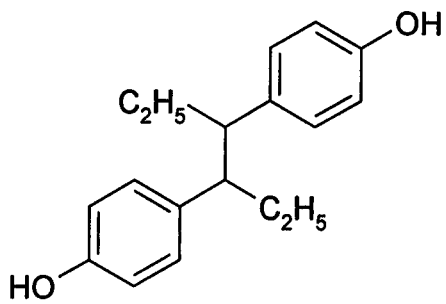


Figure 1.3 Diethylstilboestrol (DES).

1.5.7 LHRH AGONISTS

LHRH was first isolated and then synthesised by Schally and Kastin in 1971. They then synthesised LHRH agonists which proved to be much more active than LHRH with prolonged activity (Schally and Coy, 1980). They cause a down regulation of receptor sites in the anterior pituitary, causing a fall in LHRH production and thus LH, leading to the cessation of testicular stereogenesis. The main analogues studied are leuprolide, goserelin, buserelin and nafarelin.

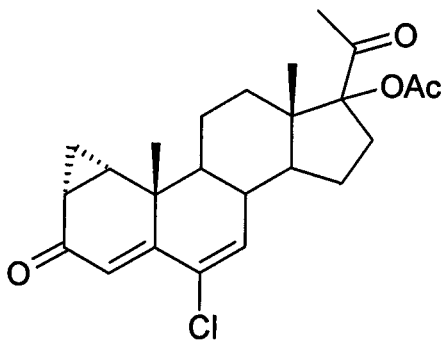
Leuprolide, in a comparative study, was found to suppress T by 86% at an oral dose of 1 mg/day, compared to DES, which suppressed T by 85% at a dose of 3mg/day (Huben and Perrapato, 1991). The side effects of LHRH-agonist therapy has been addressed by few trials and the results have been variable. A recent prospective study in 32 patients with localized PC who received 3 to 5 months of LHRH agonist treatment before radical radiotherapy showed modest short-term effects on cognitive functioning. 129 Significant cognitive decline was observed at 3 months in 47% of the patients with PC, compared with 17% of the control group, who did not have PC or receive LHRH-agonist therapy (Moreau et al, 2006)

1.5.8 ANTIANDROGENS

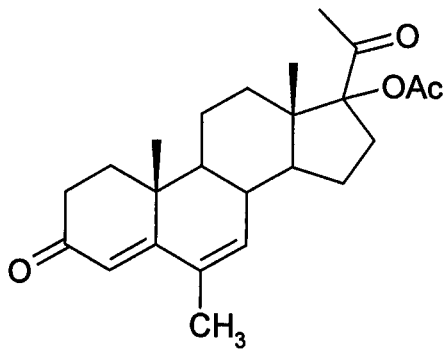
Antiandrogens inhibit the action of T and DHT by binding to their prostatic receptor sites and hence are referred to as androgen-receptor antagonists (Reid et al., 1999). There are two classes of antiandrogens: steroidal and non-steroidal. Cyproterone acetate (Figure 1.4) and megestrol acetate are the two main steroidal antiandrogens.

Cyproterone acetate binds to the receptor of DHT, therefore blocking the formation of the DHT–AR complex and inhibits the production of T in the testes (Wein and Murphy, 1973). It was found to give a 32% five year survival rate in patients with untreated advanced prostate cancer (Devoogt et al., 1986). The side-effects such as gynaecomastia and cardiovascular events, were much lower with cyproterone acetate than with DES (Jacobi et al., 1980), however, it has been found that it does not suppress androgen production as much as orchidectomy, DES or LHRH (McLeod, 1995). Megestrol acetate blocks the release of follicle stimulating hormone (FSH) and LH from the pituitary and inhibits the enzyme 5αR (Geller et al., 1978). In general, the main side-effect of steroidal antiandrogens is breast tenderness, whereas potency and libido are usually maintained.

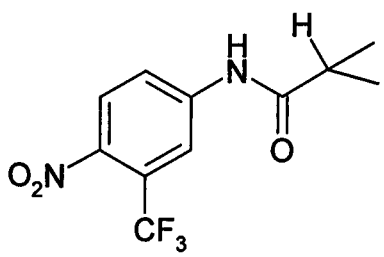
Flutamide and bicalutamide are both non-steroidal antiandrogens (Figure 1.4). Flutamide shows potent antagonistic effects on peripheral, as well as central, androgen receptors. It is a prodrug and interferes with cytoplasmic receptor binding and nuclear transformation (Reid et al., 1999). Libido and potency are preserved with flutamide as the plasma levels of T do not decrease. However, its side-effects are diarrhoea, flushing and breast tenderness (Burton and Trachtenberg, 1986). Bicalutamide, if administered alone, is not as effective as castration (McLeod et al, 1995) and has the same side-effects as flutamide.



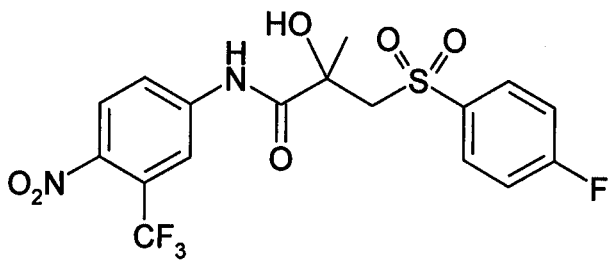
Cyproterone acetate



Megestrol acetate



Flutamide



Bicalutamide

Figure 1.4 Examples of antiandrogens.

1.6 THE ENZYME STEROID 5αR

The enzyme 5αR is a microsomal NADPH-dependent enzyme responsible for the conversion of 4-ene-3-oxosteroids into their corresponding 5α-reducd 3-oxosteroids (Occhiato, 2004), for example, the reduction of T to DHT (Figure 1.5) shows the mechanism of 5αR proposed involving direct hydride transfer from NADPH to C-5 of T with stabilisation of the resulting 3,4-enolate by an electrophile. Initial activation of the enone substrate (T) by coordination to this

electrophilic centre, forms a steroidal species with cationic character at the C-5 position which can therefore undergo hydride transfer. DHT is then formed upon subsequent protonation at the C-4 position of the enolate intermediate (Occhiato, 2004).

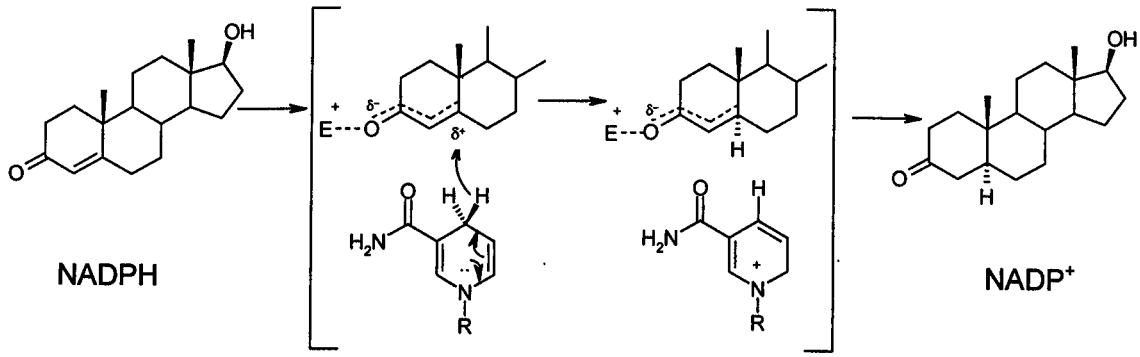


Figure 1.5 Postulated mechanism of action of 5αR (Occhiato, 2004).

Two distinct isozymes of 5αR have been cloned, expressed and characterized (type 1 and type 2). The two isozymes of 5αR have different chromosomal localization, tissue expression patterns and enzyme kinetic parameters. The type 1 isozyme is primarily located in the skin and liver, whereas the type 2 isozyme is expressed mainly in genital tissues, prostate, skin and seminal vesicles R (Occhiato, 2004).

1.7 INHIBITORS OF THE ENZYME 5αR

It was the discovery of the genetic deficiency of 5αR that initially led to the development of inhibitors of this enzyme for the treatment of benign prostate hyperplasia (BPH) since it was discovered that males suffering from the lack of 5αR did not develop the disease. As a result of the underdeveloped gland, it was concluded that inhibitors of 5αR would mimic the inherited defect and could therefore be uitilised in the treatment for BPH and prostate cancer. Thus far, two classes of inhibitors have been considered, namely: steroidal and non-steroidal inhibitors.

1.7.1 STEROIDAL INHIBITORS

This class is divided into three categories; the non-heterocyclic steroidal inhibitors, the 4-azasteroids and the 6-azasteroids.

1.7.2 NON-HETEROCYCLIC STEROIDAL COMPOUNDS

Hsai and Voight (1973) first investigated the required structural features of steroids for maximum inhibition of human foreskin 5αR and their conclusions form the basis for understanding the structure-activity relationship of this class of inhibitors. They concluded that a 3-oxo-$\Delta^{4,5}$ structure is preferred, as well as a 17β but not 17α substituent (Bartsch, et al 2002).

Progesterone was found to be a potent competitive inhibitor of 5αR and derivatives were synthesised which had various substituents at the C17-position, e.g., **(1)** (Figure 1.6). It was concluded that substituents with a hydrophilic character were preferred and large lipophilic groups well tolerated (Hsai and Voight, 1973).

A series of secosteroids, for example **(2)**, have been produced and were found to be non-competitive inhibitors of rat epididymis 5αR (IC_{50}=0.68 μM) and of human foreskin fibroblasts (K_i=0.53 μM). Studies demonstrated that secosteroids are irreversible and act as Michael acceptors at the active site (Abell and Henderson, 1995). A series of 6-methylene derivatives, for example, LY 207320, have shown potent time-dependent irreversible inhibition of rat 5αR (IC_{50}=60 nM), however, LY 207320 has also been shown to have cytotoxic effects in tumour cell-lines (Frye, 1996). Compounds based on LY 207320 are also believed to act as Michael acceptors for an active site nucleophilic residue (Abell and Henderson, 1995). As well as C6-substituted compounds, a number of C4-substituted $\Delta^{4,5}$ steroids have been outlined as competitive inhibitors of human prostatic 5αR. Singh and co-workers (1995) investigated the effects of different C4-substituents in the context of a C-17-*t*-butylamide group. It was concluded

from this study that small polar substituents are preferred for potent type 2 inhibition (e.g. CN, NH_2, OH), whereas larger lipophilic groups are preferred for type 1 inhibitory activity (e.g. SH, Br). Indeed, the most potent compound was found to contain a cyano group at the 4-position and a C17-*t*-butylamide substituent, as in compound **(3)** and which was found to possess an IC_{50} value of 2.9 nM against human 5αR type 2 isozyme. The mechanism of action of **(3)** is believed to be as a transition state mimic. Reduction by the enzyme would give a stable 5α-3-enol which would remain tightly bound to the active site.

Work has also been carried out involving the synthesis of compounds possessing a carboxylate group at the C3-position of the steroid backbone (Figure 1.6). This is believed to result in a stable mimic of the enolate-like transition state by having sp^2 centres at the C3 and C4 positions. It also offers an anionic group at the C3-position as a charged replacement for the enolate (Singh et al. 1995; Kenny et al., 1997).

The presence of $\Delta^{3,5}$ unsaturation has been shown to be required for optimal potency against human prostatic 5αR with compound **(5)** (K_i=30 nM) being more active than compound **(4)** (K_i=7-18 nM). Replacement of the C17-*diiso*-propylamide group in **(5)** by a *t*-butylamide increases the potency (K_i=110 nM) for this particular compound (Holt et al., 1991). The latter compound, SKF 105657 (epristeride), has shown to be a very potent selective uncompetitive inhibitor of human type 2 5αR (IC_{50}=0.18 nM) and weak inhibitor of human type 1 5αR (IC_{50}=1600 nM). *In vivo*, it was found to reduce plasma levels of DHT by 25% to 54% at dose ranging from 0.4 mg to 160 mg after 8 days of treatment. However, epristeride did not appear to suppress DHT to sufficient levels for full clinical benefit.

3-Nitrosteroid inhibitors have been produced and found to be competitive inhibitors (K_i=50 nM, human prostate) which bind to the enzyme-NADPH complex - the 3-carboxylate inhibitors which were found to be uncompetitive and bind to the enzyme-$NADP^+$ complex. This observation appeared to support the hypothesis that the presence of a permenant negative charge (at physiological

pH) within the binding moiety plays an important role in determining the mechanism of inhibition of these compounds. As such, the nitro group inhibits the enzyme via a different mechanism of action to the carboxylate since the negative charge on the carboxylate ion may be neutralised in the presence of strong acids, unlike the O^- present in NO_2 group.

Furthermore, unlike the 3-carboxylate-based inhibitors, addition of Δ^5 unsaturation, as in compound **(7)**, was found to greatly reduce the inhibitory activity (K_i=590 nM) against 5αR whilst the use of phenyl moiety in A-ring, such as compound **(8)**, resulted in an inhibitor with poor inhibitory activity (Ki>5 μM) (Frye et al., 1995).

Phosphinic, phosphonic and sulfuric acid derivatives are also active C3 oxyanion mimics (Figure 1.6). However, removal of the negative charge, for example by replacement of the C_3-SO_3H with C_3-SO_2NH_2, results in loss of inhibitory activity (K_i>5 μM).

The phosphinic acid derivative **(9)** is a more potent selective inhibitor of human prostatic 5αR (K_i=7 nM) than the phosphonic derivative **(10)**. Aromatisation of the A-ring, retains the inhibitory activity (K_i=13 nM) for the phosphinic derivative **(11)** but decreases the activity for the phosphonic derivative **(12)** (K_i=50 nM). The aromatic C3-sulfonic acid-based inhibitor, e.g. compound **(13)**, is equipotent to the phosphonic acid analogue **(11)** (K_i=20-40 nM) (Frye et al., 1995).

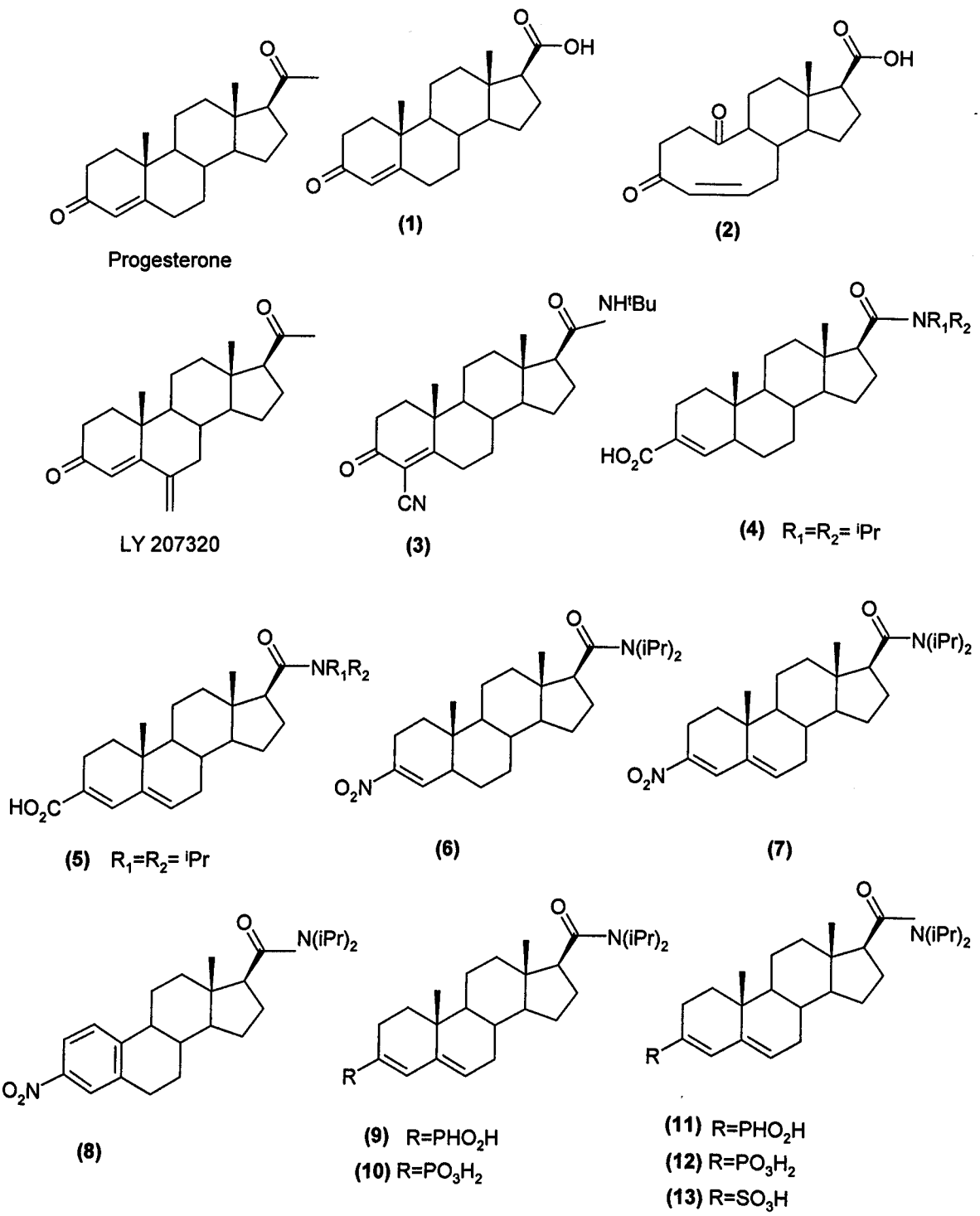


Figure 1.6 Non-heterocyclic steroidal inhibitors of the enzyme 5αR.

1.7.3 4-AZASTEROID INHIBITORS OF 5αR

The potency of this series is presumed to be based upon the ability of the A-ring lactam to interact favourably with the active site residues of 5αR which have

evolved to stabilise an enolate-like transition state (Rasmusson et al, 1984; Rasmusson et al, 1986).

The main structural requirements for optimal potency in the 4-azasteroid series are shown in (Figure 1.7) (Kenny et al., 1997). It was demonstrated that: a $\Delta^{1,2}$ unsaturation does not appear to affect the inhibitory activity; 6- and 7-membered rings result in good inhibitory activity whilst a 5-membered ring results in weak inhibitory inhibitors.

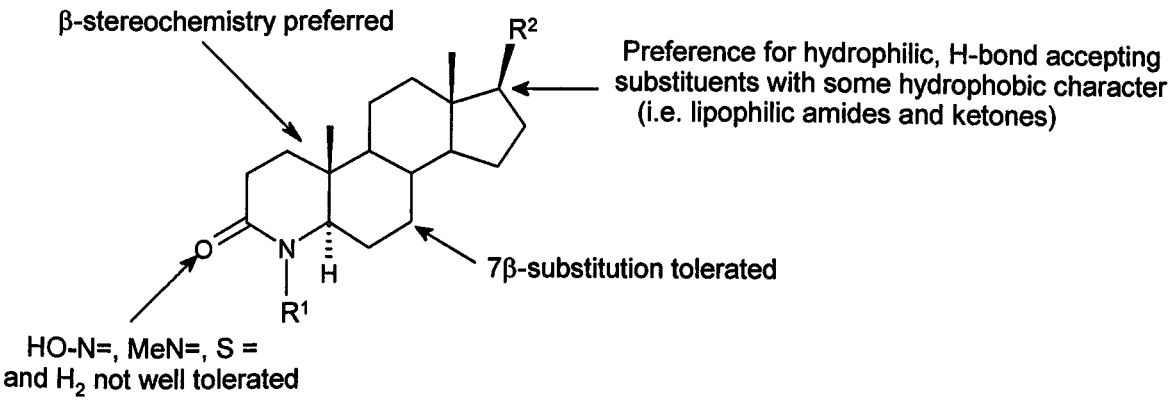


Figure 1.7 Structural requirements for 4-azasteroids (Kenny et al., 1997).

4-Azasteroids have proved to be potent inhibitors of human 5αR with *in vivo* activity (Rasmusson et al., 1984; Rasmusson et al., 1986). Some examples of 4-azasteroids are shown in Figure 1.8.

4-MA is a potent competitive reversible inhibitor of human 5αR type 1 and 2 isozymes (K_i=5 nM, 0.23 nM and 5 nM respectively) as well as possessing good inhibitory activity against rat prostatic 5αR. However, it was found to possess hepatotoxicity resulting in the withdrawal of the drug from clinical development (Liang and Heiss, 1981; Liang et al., 1984). In 1992, finasteride was developed and chosen for its *in vitro* and *in vivo* efficacy. It is a competitive inhibitor and possesses greater potency than 4-MA (IC_{50}=150 nM for type 1 human 5αR and IC_{50}=0.18 nM for type 2 human 5αR) (Frye, 1996). At doses of 0.04 mg to 0.4 g, finasteride was found to induce a reduction in plasma DHT level by 70% to 80% with a return to DHT baseline levels within 7 days.

The mode of action of finasteride was first described as being reversible, however, recent studies have shown that finasteride possesses irreversible inhibitory activity against type 2 human 5αR and a reversible inhibitory activity against the rat type 1 isozyme. Indeed, it has been shown to be a slow-binding, time-dependent irreversible inhibitor of the human type 1 5αR. It is believed to act as a Michael acceptor and a possible mechanism of inhibition is proposed below in (Figure 1.9) (Bull et al., 1996).

MK-434 (Figure 1.8) has been shown to be a potent irreversible inhibitor of prostatic 5αR in humans (IC_{50}=12.5 nM) and to be more effective than finasteride at lowering DHT levels and in reducing the prostate size in a dog model of BPH (Frye et al., 1995).

Structure-activity relationship studies involving derivatives of finasteride have shown that *N*-methylation and the absence of $\Delta^{1,2}$ unsaturation results in potent inhibitory activity against the type 1 isozyme (Frye et al., 1996; Mellin et al., 1993; Kenny et al., 1997). As such, compounds **(14)** (IC_{50}=0.9 nM for type 1 and IC_{50}=2.0 nM for type 2) and **(15)** (IC_{50}=154 nM for type 1 and IC_{50}=125 nM for type 2) are both selective towards the human type 1 isozyme with some activity against the type 2 isozyme. In the series of compounds containing $\Delta^{1,2}$ moiety, optimisation of the C17-substituent was found to improve the inhibitory activity as observed in compounds **(16)**, **(17)** and GS 745.

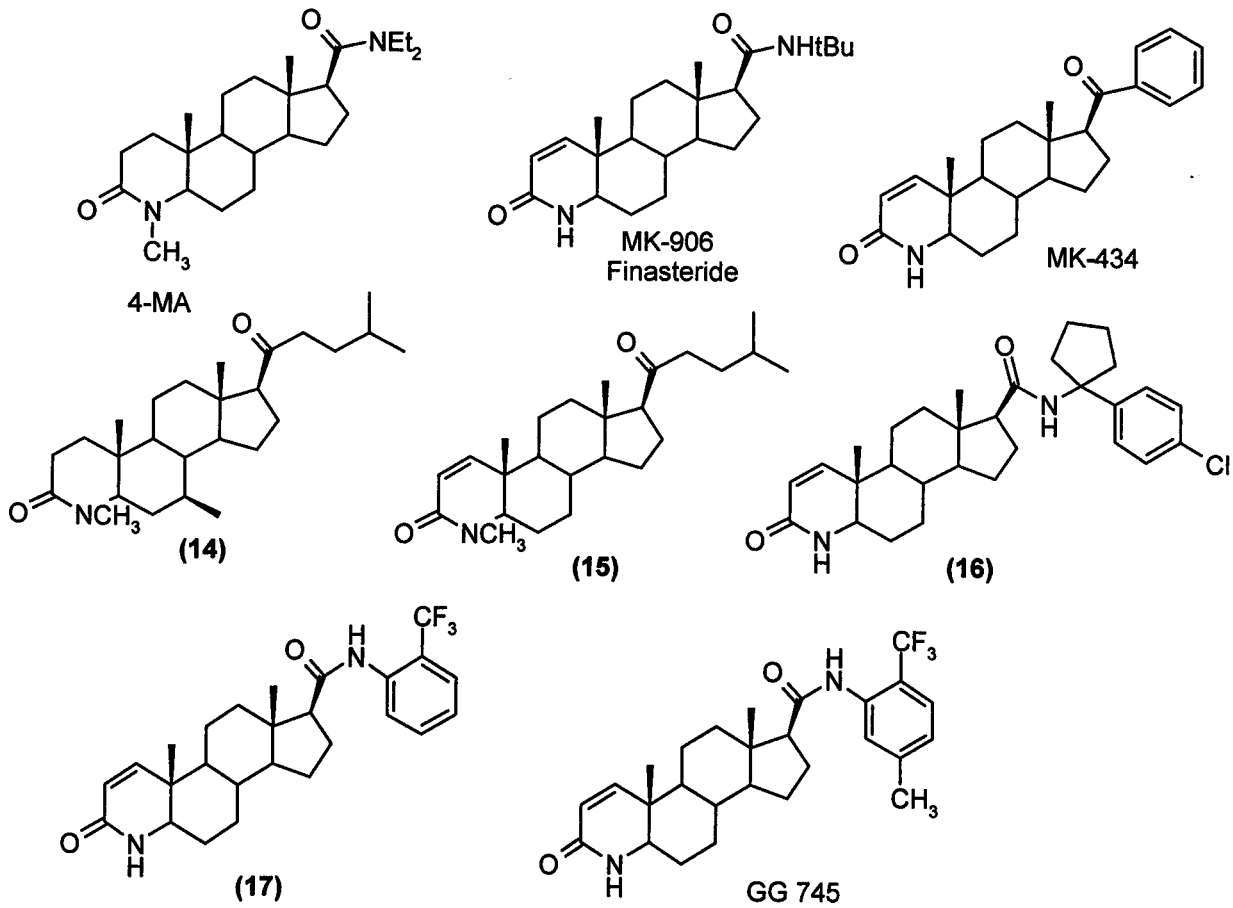


Figure 1.8 4-Azasteroid inhibitors of 5αR.

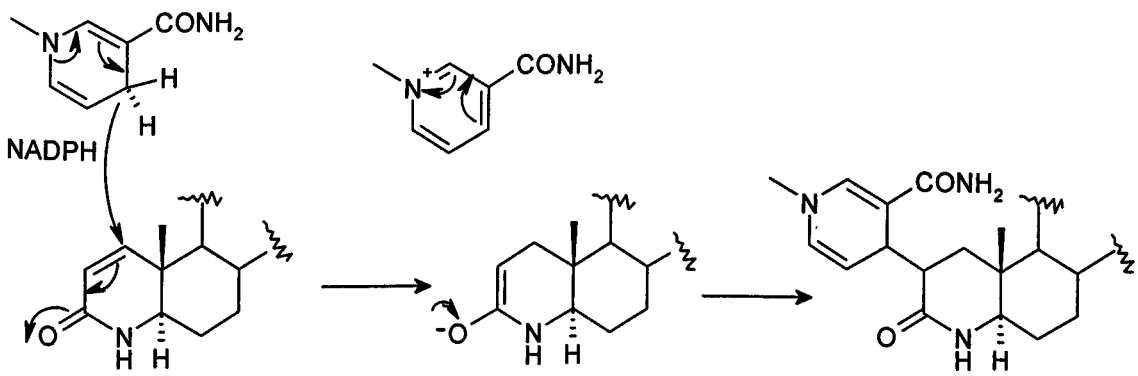


Figure 1.9 Mechanism of inhibition by finasteride (Bull et al., 1996).

Compound **(16)** was shown to be a potent inhibitor of both human isozymes (K_i=6 nM for type 1 and K_i=7 nM for type 2) (Frye et al., 1995), whereas, compound **(17)** was shown to be selective towards the type 2 isozyme (K_i=12 nM and 1.3 nM for type 1 and 2 respectively) (Bakshi et al., 1995). GG 745 was

found to be a more potent dual inhibitor than finasteride with K_i=2.4 nM for the type 1 isozyme and Ki=0.5 nM for the type 2 isozyme and has also been shown to be approximately 5-times more rapid in inactivating the enzyme compared to finasteride. After a single dose of 40mg, a suppression of more than 90% in plasma DHT levels was observed (Bakshi et al., 1995).

1.7.4 6-AZASTEROID INHIBITORS OF THE ENZYME 5αR

The 6-azasteroids contain a ketoanamine function, and are a more potent substrate-like mimic of the transition state than the 4-azasteroids (Rasmusson et al., 1984). They are not substrates for 5αR as the 6-nitrogen donates its electron density through the enone to the crucial interaction, raising the reduction potential of the enone. Most of the 6-azasteroids have been shown to be time-dependent for the inhibition of the type 2 isozyme. The structural requirements for this series of inhibitors are shown below (Figure 1.10) (Kenny et al., 1997).

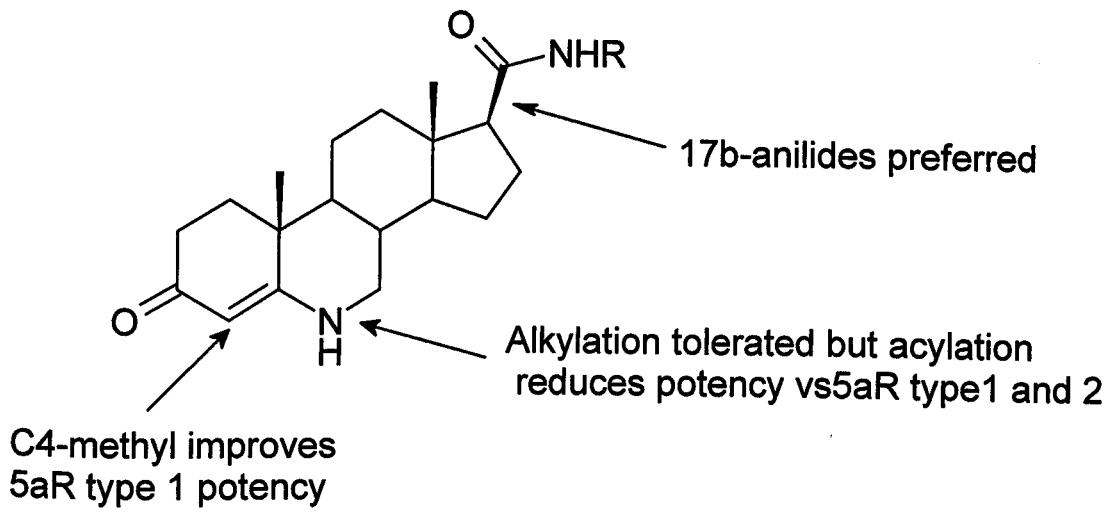


Figure 1.10 Structural requirements for 6-azasteroids.

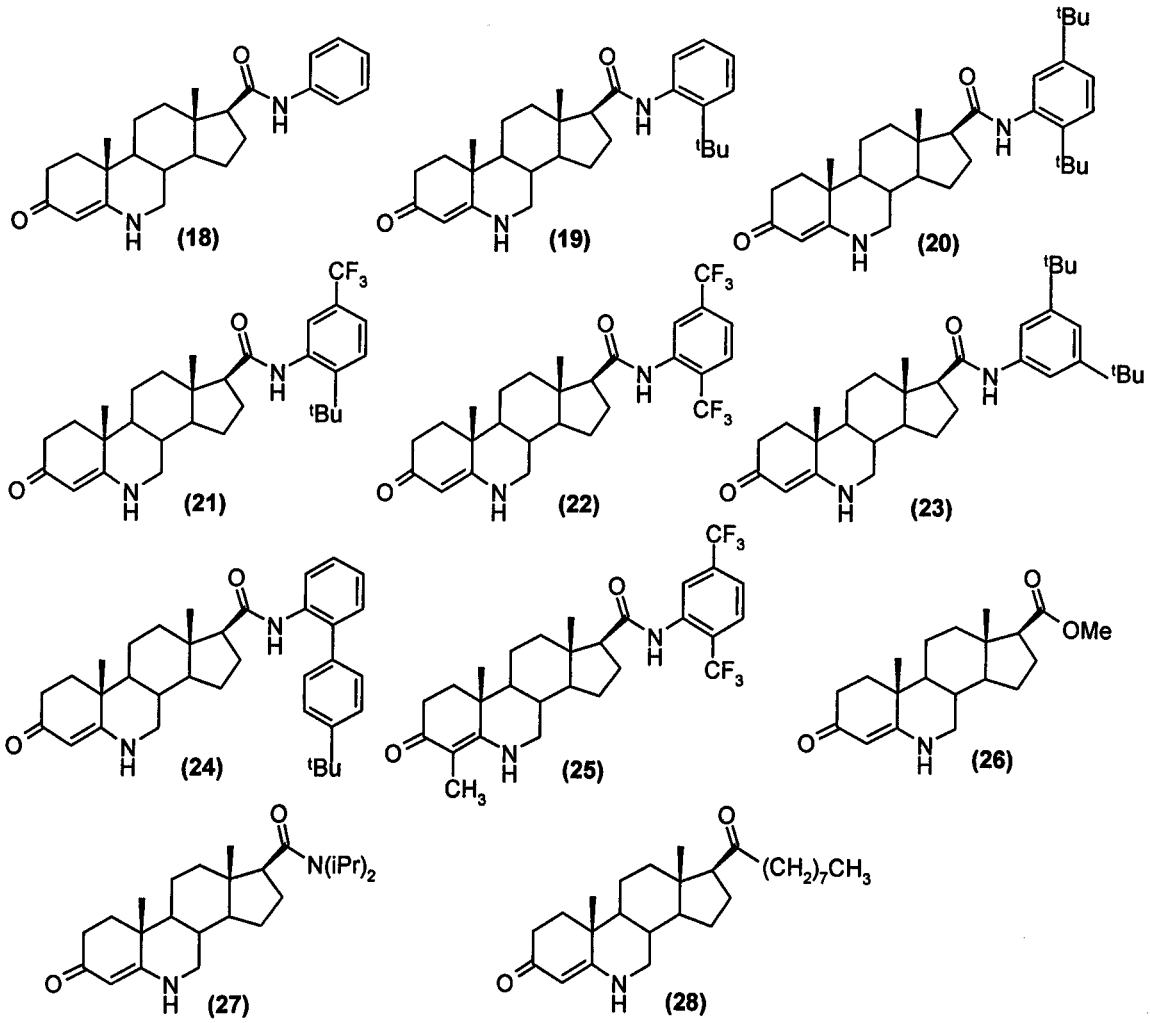


Figure 1.11 6-Azasteroid inhibitors of 5αR.

Optimisation of the C17-substituent was investigated and it was concluded that anilides were preferred at this position (Frye et al., 1993; Frye et al., 1995). Compound **(18)** was investigated as the parent compound and showed potent inhibitory activity towards the 5αR type 2 isozyme, but proved to be a very weak inhibitor of the 5αR type 1 isozyme (K_i=240 nM). Addition of a *t*-butyl group at the 2-position of the phenyl ring **(19)** resulted in an increase in the inhibitory activity towards type 1 and 2 of 5αR (K_i=27 nM and IC_{50}=0.2 nM respectively). Addition of a further substituent on the phenyl ring [e.g. compounds **(20)**, **(21)**, and **(22)**] resulted in further increases in inhibitory potency against both type 1 and 2 isozymes.

Derivatives of **(20)**, where both of the *t*-butyl groups were substituted at the meta-position to the amine moiety, e.g. in compound **(23)**, did not appear to affect potency. However, the introduction of a substituent at the 2-position , as in compound **(24)**, resulted in a sever decrease in potency against type 1 5αR. The combination of a favourable C4-substituent with the best C17-group therefore resulted in compounds which were found to possess picomolar level of inhibition. The C4-methyl compound **(25)** was therefore found to be an extremely potent inhibitor against both human isoenzymes (K_i=0.2 nM against type 1 5αR whilst IC_{50}<0.1 nM for type 2 5αR). Ester **(26)** and amide **(27)** substituents at the C17-position also resulted in compounds possessing potent inhibitors of the human type 2 5αR [K_i= 3.2nM for **(26)** and K_i= 0.36 nM for **(27)** respectively] but poor inhibitors of the type 1 5αR [K_i= 150 nM for **(26)** and K_i= 190 nM for **(27)** respectively] (Frye, 1996). The use of ketone functionality at the C17-position also resulted in potent inhibition, for example compound **(28)** possess Ki= 1.0 nM against type 1 5αR whilst possessing an IC_{50}<0.1 nM against type 2 5αR.

1.7.5 NON-STEROIDAL INHIBITORS

Steroidal inhibitors, by the nature of their structure, have the possibility to act as hormonal agonists, thereby increasing the possibility of side-effects. Therefore research for new 5αR inhibitors has been directed towards cheaper, readily available, non-steroidal compounds. Amide-containing heterocycles and lipophilic carboxylic acids (Frye, 1996), as well as some compounds extracted from natural products (Figure 1.12) have been found to inhibit 5αR. The latter compounds, for example, retinoic acid, γ-linoleic acid and phenazine have, however, been found to possess only weak inhibitory activity.

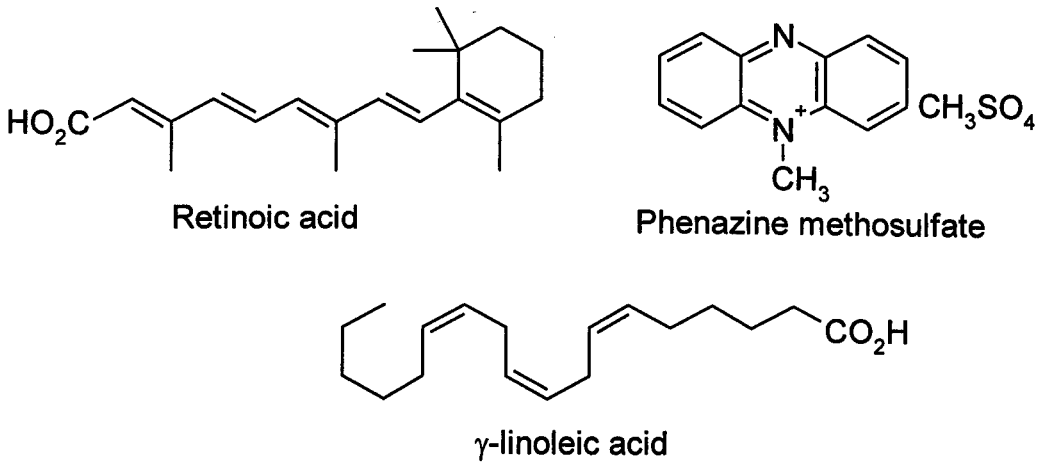


Figure 1.12 Natural non-steroidal inhibitors of 5αR.

Benzoquinolinones (Figure 1.13) are the most widely studied class of non-steroidal inhibitors of 5αR and have been shown to be non-competitive. The parent compound **(29)** was shown to be a weak inhibitor of cultured human foreskin fibroblasts (IC_{50}=6 μg) but introduction of a chlorine moiety at the C8-position, together with *N*-methylation and saturation of the central olefin (*cis*) gave a potent type 1 inhibitor **(30)** with an IC_{50} value of 41 nM (Jones et al, 1993).

Trans isomer derivative of **(30)** (namely, LY191704) was found to be more potent against type 1 (IC_{50}= 8 nM) but possessed weak inhibitor activity against the type 2 isozyme (IC_{50}= 1750 nM). It was demonstrated that the inhibitory potency against the type 1 5αR isozyme was enhanced in compounds with an electron-withdrawing or an electron-donating group at the 8-position on the benzoquinolinones (Jones et al., 1993). Indeed, substitution of the 8-chloro group of LY1704 with other substituents, it was found that the potency decreased following the order: Cl (IC_{50}=8 nM) > Me (IC_{50}=11 nM) > F (IC_{50}=35 nM) > H (IC_{50}= 560 nM) (Jarman et al., 1998a). Compound **(31)** was, however, found to be the most potent inhibitor against human type 1 5αR with weak potency towards the type 2 isozyme (IC_{50}=3.4 and 320 nM respectively).

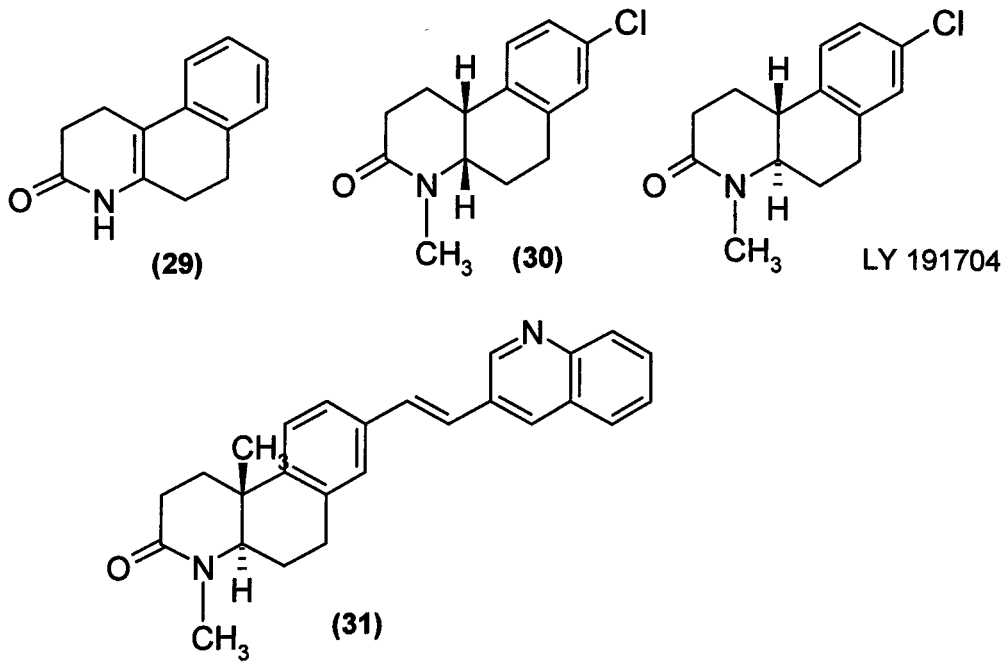


Figure 1.13 Non-steroidal benzoquinolinone inhibitors of 5αR.

Benzophenones have been found to be potent, uncompetitive inhibitors of type 2 human 5αR. The structural requirements for this series are shown below in Figure 1.14 (Kenny et al., 1997).

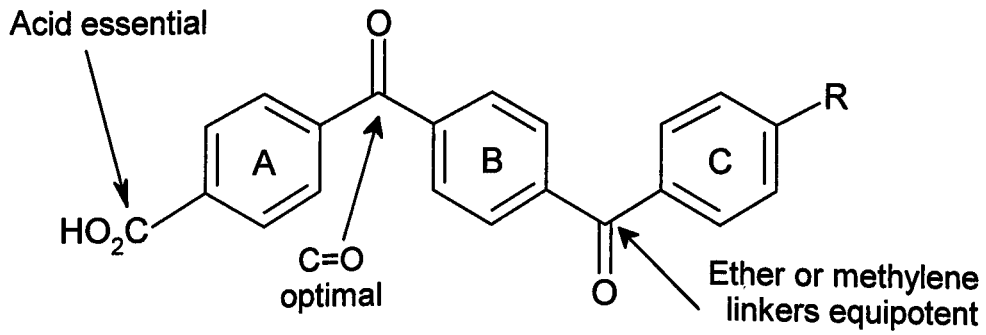


Figure 1.14 Structural requirements for benzophenones

The parent compound **(32)** (Figure 1.14) was found to be a potent selective inhibitor of the human type 2 isozyme (K_i=10 nM) with poor activity towards type 1 5αR (K_i>>10 μM). Substitution with electron-donating groups or with small lipophilic substituents was found to increase the inhibitory potency. Analogues with modified spacers were also shown to be potent and selective type 2 5αR

inhibitors. The mode of action of benzophenones was postulated to be similar to that of the steroidal 5αR inhibitors [such as **(4)**] containing the 3-carboxylic acid moiety (Holt et al., 1995).

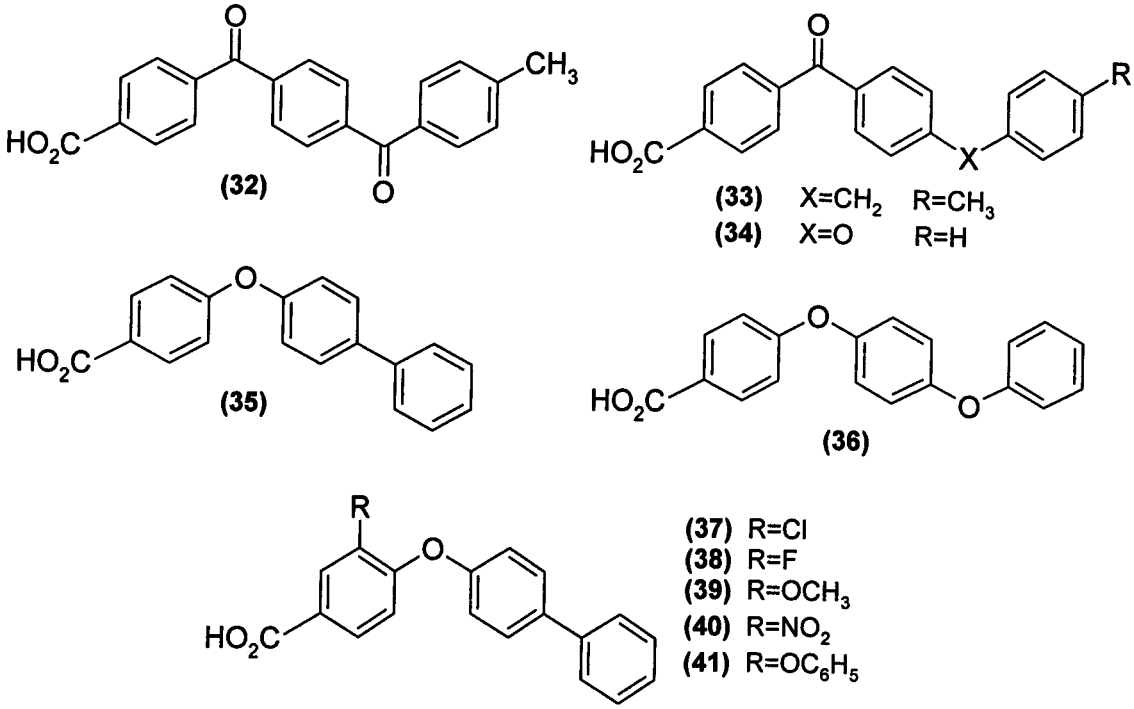


Figure 1.15 Benzophenone and ether derivative inhibitors of 5αR.

Derivatisation of the C=O moiety attached to the 4-methylphenyl functionality to a methylene linkage gave compound **(33)** which was found to be less potent than **(32)** towards the type 2 isozyme and possessed a K_i value of 15 nM. However, the potency was found to increase upon derivatising the methylene linkage to an ether linkage with the C-ring devoid of any substituents, as such, compound **(34)** was found to be a highly potent and selective type 2 5αR inhibitor, with a K_i value of 5 nM. These compounds were however poor inhibitors of the type 1 isozyme (Ki>>10μM) (Holt et al., 1995).

A series of phenoxybenzoic acid derivatives have been synthesised and evaluated *in vitro* against human foreskin fibroblast cells and against human prostate cells at pH 5.5 which were reported to possess optimal inhibitory activity against type 2 5αR (Igarashi et al., 1999). The parent compound **(35)** was found to possess an IC_{50} value of 1.1 nM against rat 5αR and an IC_{50} value of 7.8 nM against human 5αR. The inhibitory activity was found to decrease, however,

against the human prostatic enzyme (IC_{50}=4.1 nM) when an ether linkage was introduced between the B and the C-ring [compound **(36)**], with no inhibitory activity was observed against human foreskin fibroblast cells.

Introduction of a substituent at the 3-position of the A-ring [compounds **(37)–(41)**] gave degrees of potency of the order of OCH_3 > F > Cl > NO_2 > OC_6H_5 when evaluated against human prostatic 5αR enzyme. Igarashi et al. (1999) concluded that hydrophobic substituents at the 3-position were favourable for inhibitory activity, whereas bulky groups were not favoured. These potent inhibitors were then tested against the rat enzyme and showed very poor activity (IC_{50}>1000 nM) suggesting that these compounds are selective towards human prostatic 5αR.

Indole carboxylic acid based compounds have also been studied and have proved to be potent inhibitors of type 2 isozyme. The structural requirements for these compounds are shown in Figure 1.16 (Kenny et al., 1997).

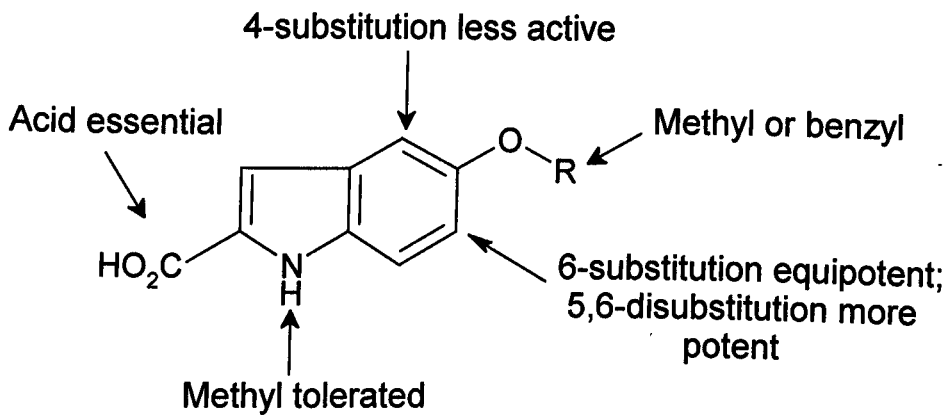
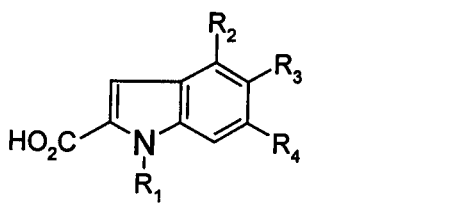


Figure 1.16 Structural requirements for indole carboxylic acids (Kenny et al., 1997).

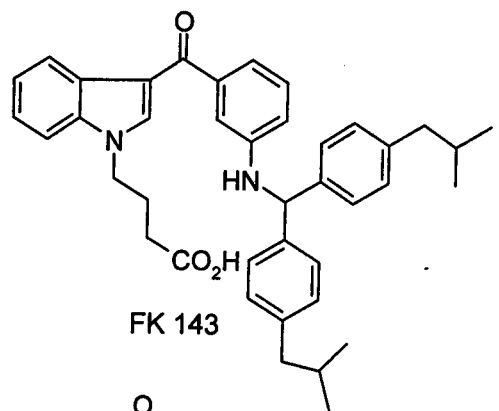
In a structure-activity relationship determination study of indole carbxylic acid based compounds, it was observed that when the phenyl ring was subsituted with a single benzyloxy group [e.g. compound **(42)**] (Figure 1.17), the type 2 5αR potency was found to decrease with *N*-methylation. That is, compound **(42)** was found to possess a K_i value of 40 nM, whereas the N-CH_3 derivative was found to possess a K_i value of 310 nM. However, when the phenyl ring was

disubstituted, as in compounds **(43)** and **(44)**, *N*-methylation was found to enhance inhibitory activity against type 2 5αR [K_i= 20 nM for **(43)** and K_i= 10 nM for **(44)**]. All three compounds [**(42)**, **(43)** and **(44)**], however, were found to possess weak inhibitory activity against the type 1 isozyme (K_i>2500 nM, K_i=460 and 500 nM respectively) (Abell and Henderson, 1995).

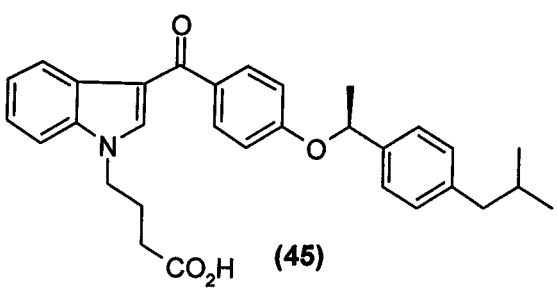
The indole-based compounds were also investigated and were found to be potent inhibitors of the human prostatic enzyme , e.g. FK 143 was found to possess an IC_{50} value of 1.9 nM. Oral administration of this compound in a castrated, as well as an intact rat model, showed a decrease in the prostate weight whilst in dog and rat models, a decrease in prostatic DHT levels was observed (Frye, 1996). Indeed, compound **(45)**, was found to be a potent selective type 2 inhibitor with an IC_{50} value of 40nM against 5αR type 1 and an IC_{50} value of 4 nM for 5αR type 2. In an *in vivo* rat model, doses of 1 mg/kg for ten days resulted in a 35% reduction in prostatic weight.



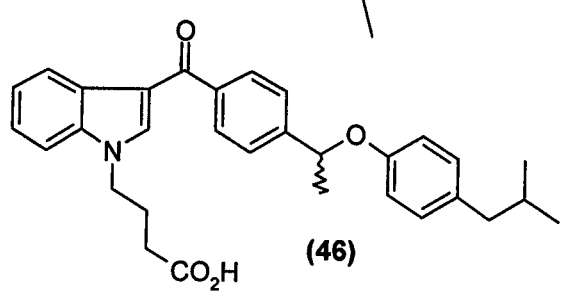
(42) R^1=H R^2=H R^3=OBz R^4=H
(43) R^1=H R^2=H R^3=OCH_3 R^4=OBz
(44) R^1=CH_3 R^2=H R^3=OCH_3 R^4=OBz



FK 143



(45)



(46)

Figure 1.17 Indole based inhibitors of 5αR.

Derivatisation of compound **(45)** involving the reversal of the ether link to give **(46)**, resulted in a highly potent inhibitor which was found to possess an IC_{50}

value of 8 nM against type 1 5αR and an IC_{50} value 10 nM against type 2 5αR (Kenny et al.,1997).

Recently, a series of 2-phenylbenzofuran derivatives were synthesised and evaluated *in vitro* against rat and human 5αR (Nishi et al., 1999) (Figure 1.18). These compounds, in general, were found to possess potent inhibitory activity against the type 1 than the type 2 isozyme.

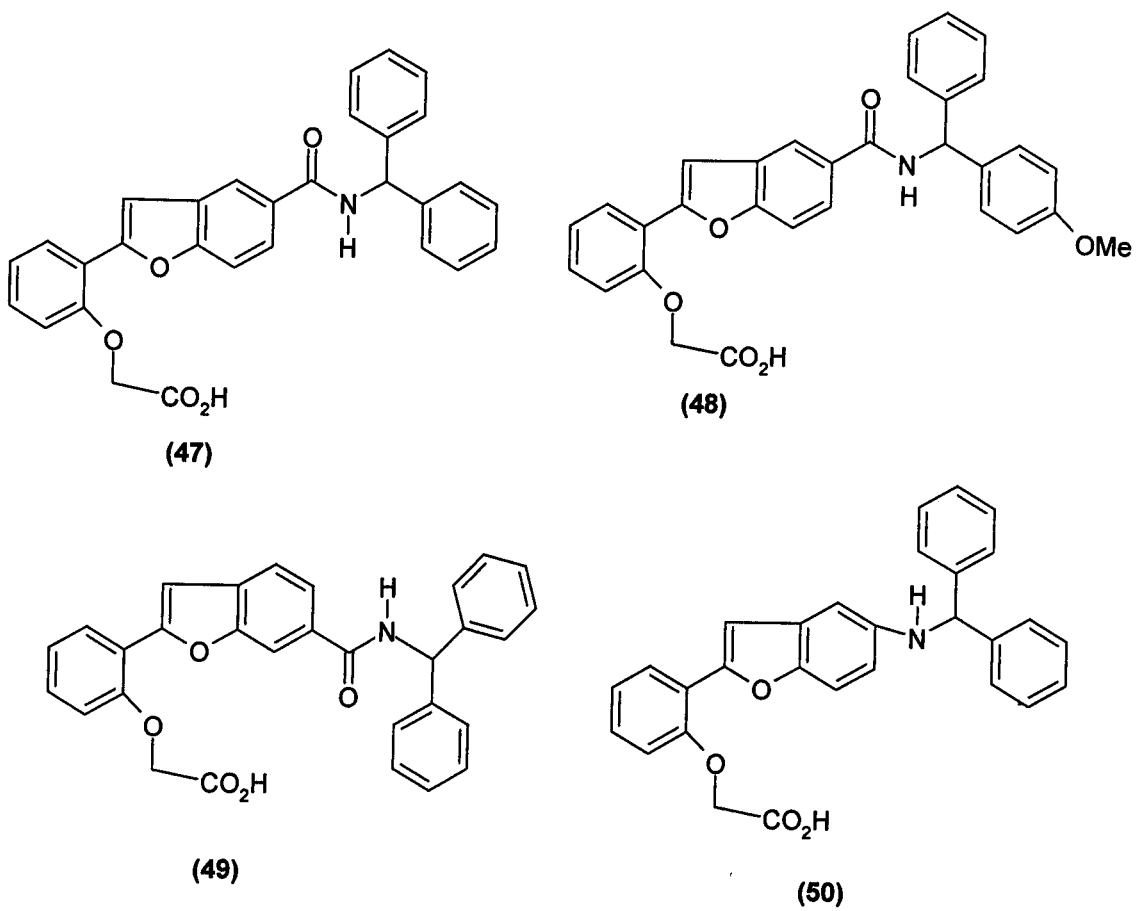


Figure 1.18 2-Phenylbenzofuran derivative inhibitors of 5αR.

The parent compound **(47)** was a weak inhibitor of both isoenzymes possessing an IC_{50} value of 310 nM against human type 1 5αR and an IC_{50} value greater than 105 nM against human type 2 5αR. Derivatisation of the *para*-methoxy group **(48)** was found to greatly increase the potency against the rat enzyme, whilst maintaining the potency versus both the human 5αR isozymes. However, switching the carbamoyl group from the 5-position to the 6-position **(49)** did not change the potency versus the rat enzyme but greatly increased the human 5αR

potency. Replacing the amide functionality with an amine greatly diminished the rat enzyme potency (IC_{50}=1120 nM), whilst greatly increasing the potency versus both human 5αR isozymes (IC_{50}=32 and 30 nM for type 1 and 2 isozymes respectively).

1.7.6 INHIBITION OF CYTOCHROME $P450_{17\alpha}$

Orchidectomy and its medical equivalent, LHRH therapy, are the main treatments for prostate cancer but show considerable side-effects. Another major drawback is that these treatment options only eliminate T produced from the testes and not from the adrenals (Brodie and Njar, 1999). The residual T synthesis by the adrenal route is an important factor in the maintenance of the growth of the tumour. It was thus postulated that inhibition of the production of residual T of adrenal origin by inhibiting the $P450_{17\alpha}$ enzyme within the steroid pathway would achieve an overall lowering of androgen levels (Brodie and Njar, 1999). It has been proposed that the enzyme carries to two distinct activity within the same active site: an initial 17α-hydroxylation followed by the C-C bond cleavage of the C17 side-chain within the progestins and pregnanes.

Numerous inhibitors of $P450_{17\alpha}$ have been reported and a brief summary of these inhibitors will be given here. In general, however, the reported inhibitors can be divided into two categories as with 5αR inhinitors, namely: steroidal and non-steroidal.

1.7.7 NON-STEROIDAL INHIBITORS

Ketoconazole, a broad-spectrum antifungal drug, was found to be useful in the treatment of prostate cancer. It belongs to the imidazole group of compounds and is used as a racemic mixture of the *cis* isomer [(2S,4R) +(2R,4S)] (Rotstein et al., 1992). It is a potent inhibitor of testicular and adrenal T production, and has been shown to be a highly potent and reversible inhibitor of $P450_{17\alpha}$ (possessing K_i=160 nM and 84 nM for 17α-hydroxylase and 17,20-lyase respectively) (Jarman et al., 1998). However, ketoconazole is also found to

inhibit the enzyme corticoid 11β-hydroxylase, thereby blocking adrenal steroidogenesis (Figure 1.1). Furthermore, as a result of its short half-life and the required regular high daily dosing its use was therefore found to be limited and numerous side-effects were observed. As a result, ketoconazole was initially withdrawn from use in the treatment of prostate cancer (Jarman et al., 1998), however, in a recent study, it was found that low doses of ketaconazole may be used with greatly reduced side-effects.

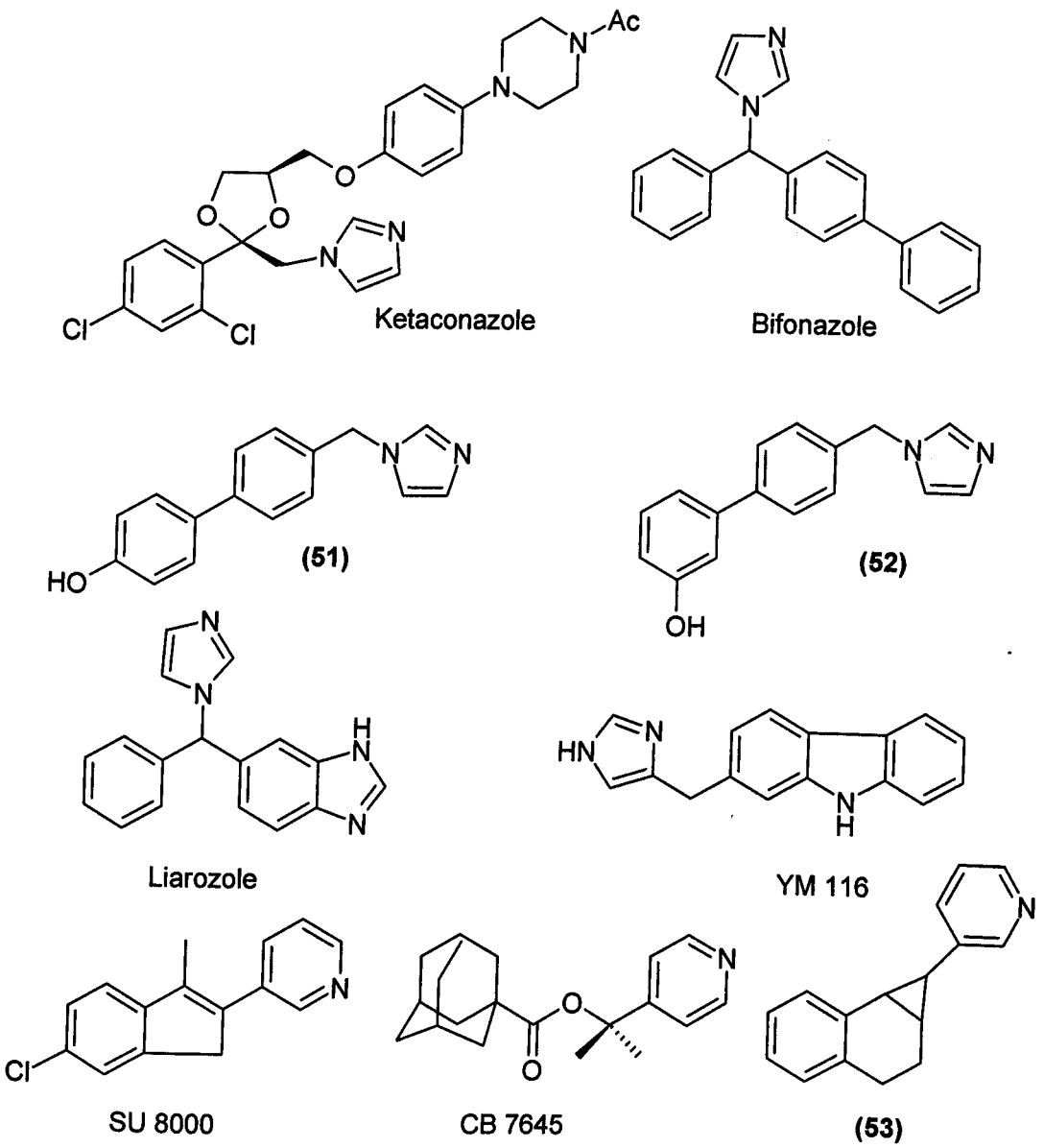


Figure 1.19 Non-steroidal inhibitors of cytochrome $P450_{17\alpha}$.

Another antifungal imidazole compound which was investigated was bifonazole (Figure 1.18), which has been found to be more a potent inhibitor of $P450_{17\alpha}$ than ketoconazole, with K_i values of 86 nM and 56.5 nM for hydroxylase and 17,20-lyase respectively (Jarman et al., 1998). The inhibitory potency of imidazole derivatives is believed to be due to the ability of the imidazole nitrogen to coordinate with the haem iron at the active site. Other potent inhibitors based on the imidazole structure are compounds **(51)** (IC_{50}= 0.31 μM) and **(52)** (IC_{50}= 0.13μM) (Figure 1.19) (Hartmann et al., 1999b). Compound **(51)** has been evaluated *in vivo* in male Sprague-Dawley rats and has been shown to completely block androgen biosynthesis two hours after administration. After six hours, a 50% reduction of T concentration was observed. Compound **(52)** showed limited enhanced inhibitory activity after two hours with a further moderate reduction after six hours.

Benzimidazoles, such as liarozole and triazole derivatives were also found to be potent inhibitors of $P450_{17\alpha}$. Liarozole was found to possess an IC_{50} value of 260 nM for the 17,20-lyase enzyme. It was found to suppress the circulating levels of T in males to castrate levels six hours after intake of a single oral dose of 300 mg. It is now in phase III clinical trials in patients with metastatic prostatic cancer (Brodie and Njar, 1999). An imidazole derivative, YM 116, exhibited high potency with an IC_{50} value of 0.38 nM for 17,20-lyase (Yoden et al., 1996; Ideyama et al., 1998).

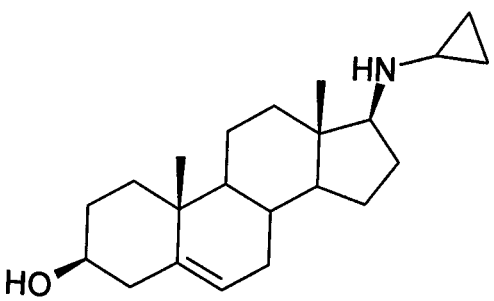
3-Pyridyl derivatives were also found to be potent inhibitors of the enzyme. Compound SU 8000, was the first pyridyl derivative discovered to have good inhibitory potency (K_i=0.04 μM). It was shown to cause a large decrease in weights of the prostate and seminal vesicles but not of the adrenals (Chart et al., 1962).

CB 7645 also proved to be a selective and potent inhibitor of 17,20-lyase (K_i=80 nM), and showed no effects on androgen-sensitive organs. It was tested *in vivo* in mice and it resulted in minimal suppression of the levels of T (Jarman et al., 1998). Potent inhibitors were found in the tetrahydronaphthalene series, such as

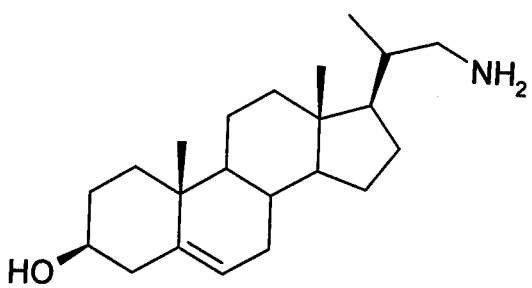
compound **(53)**, which has been shown to be more potent than ketoconazole versus the rat testicular enzyme (K_i=80 nM for 17,20-lyase). However, it is not selective and inhibits the enzymes aromatase and 18-hydroxylase (Jarman et al., 1998).

1.7.8 STEROIDAL INHIBITORS

Mechanism-based inhibitors (Figure 1.20) are thought to compete with the natural substrate and therefore interact with the active site of the enzyme. Following activation by the enzyme via its normal catalytic mechanism, these inhibitors have been found to bind either very tightly or irreversibly to the enzyme, bringing about its inactivation. They proved to be selective and to have lasting *in vivo* effects, therefore reducing toxic side-effects as continued administration of the drug is not necessary.



MDL 27,302



22-ABC

Figure 1.20 Examples of mechanism-based steroidal inhibitors of $P450_{17\alpha}$.

Compound MDL 27,302, synthesised by Angelastro and co-workers (1989), has been found to be a selective competitive irreversible inhibitor of the cynomolgus monkey $P450_{17\alpha}$ enzyme (K_i=90 nM). The inactivation of the enzyme by MLD 27,302 was believed to be dependent upon NADPH and to occur at the active site. A proposed mechanism-based inactivation by MLD 27,302 is shown below in Figure 1.21.

The first step of the inactivation is believed to be an enzymatic one-electron oxidation of the cyclopropylamino nitrogen. This is then followed by ring opening

to form a β-imminium radical which can react with the enzyme whilst the inhibitor is tightly bound to the active site. 22-ABC, has also been described as a potent inhibitor of $P450_{17\alpha}$ with a K_i of 29 nM.

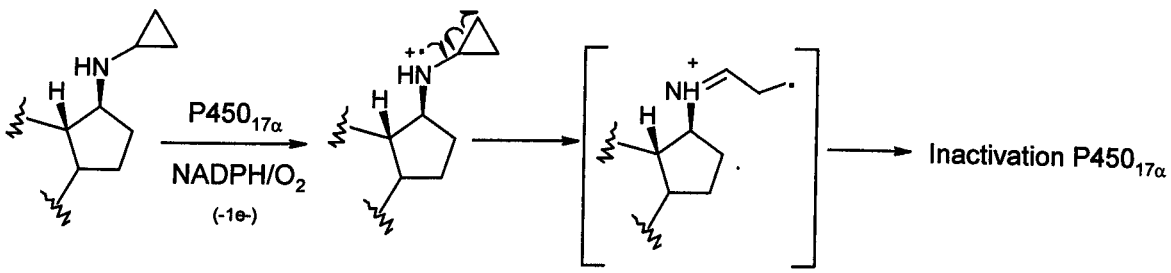
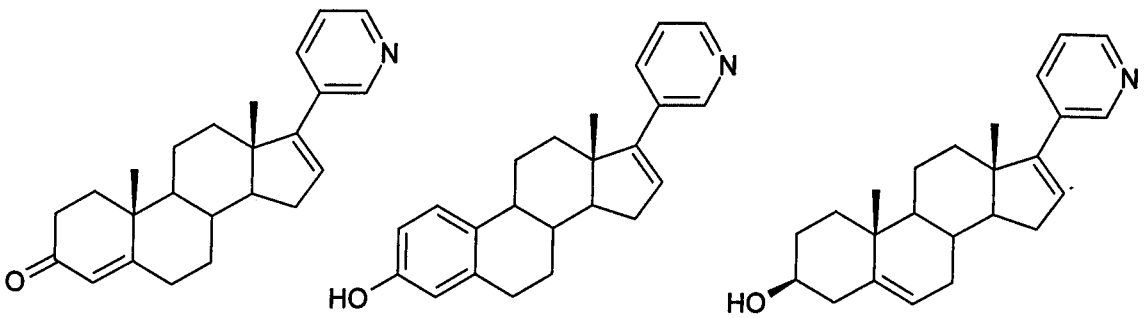


Figure 1.21 Proposed mechanism-based inactivation of $P450_{17\alpha}$ by MLD 27,302.

Another category of inhibitors is the steroid compounds with a heteroaryl substituent at the C17-position (Figures 1.22 and 1.23)



(54) **(55)** Abiraterone

Figure 1.22 Examples of 17-pyridyl derivative inhibitors of $P450_{17\alpha}$.

Of the 17-pyridyl series, compounds **(54)** and **(55)** have been shown to be more potent than ketoconazole with IC_{50} values of 2.8 and 2.6 μM respectively for 17α-hydroxylase and IC_{50} values of 2.1 and 1.8 μM respectively for 17,20-lyase. The most potent inhibitor of this series was found to be abiraterone, which was shown to have a K_i of 1 nM for human 17α-hydroxylase. It was described as competitive and selective. A dose of 0.5 mmol/kg/day for fourteen days resulted

in a suppression of circulating T levels to undetectable levels and also in a reduction in weight of androgen-sensitive organs. However, it was found that 2-pyridyl and 4-pyridyl analogs were weaker than their 3-pyridyl parent structures. This led to the conclusion that the structural requirements for the C17-pyridyl steroids series were a 3-pyridyl group and $\Delta^{16,17}$ unsaturation. It was concluded that these features resulted in the pyridyl residue being placed in the correct orientation for optimal binding to the haem iron.

The 17-azolyl series was found to consist of very potent inhibitors of both human and rat testicular $P450_{17\alpha}$ (Fig 1.23). Compound **(56)**, which has a pyrazole group at the C17-position, proved to be a very potent inhibitor of 17,20-lyase with a K_i of 4 nM. L-39, with an isoxazole group, was found to be a potent dual inhibitor of 17,20-lyase (K_i=22 nM) and 5αR (K_i=28 nM). Administration to mice at doses of 50 mg/kg/day for twenty eight days resulted in a slowed growth and in reduction in weight of human prostate cancer cells, and it was shown to be as effective as castration.

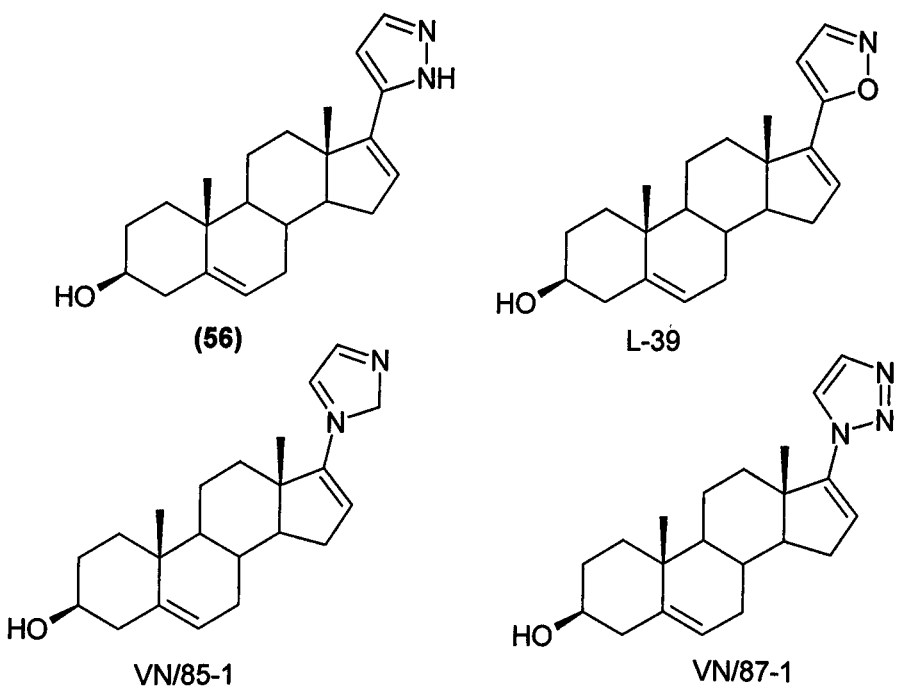


Figure 1.23 Examples of 17-azolyl derivative inhibitors of $P450_{17\alpha}$.

1.8 BASIS OF PRESENT INVESTIGATION

We have observed that the inhibition of enzymes within the steroidal cascade (Figure 1.1) can lead to potential treatments of hormone-dependent disease. As such, the inhibition of 5αR and/or $P450_{17\alpha}$. would be expected to lead to the ablation of T and therefore DHT thereby resulting in the loss of stimulation of androgen-dependent tumour growth. In this study, we aim to synthesise a series of inhibitors targetted towards 5αR and $P450_{17\alpha}$.. The latter enzyme is of particular interest since it is the enzyme which is directly responsible for the biosynthesis of the androgens. In an effort to investigate the use of phenylamine based compounds as potential inhibitors of $P450_{17\alpha}$., compounds based upon the Evan's chiral auxilliary will be investigated (Figure 1.23) these possess an amine group which would be expected to form dative co-valent bond with the Fe at the centre of the haem. The synthesised compounds will then undergo biochemical evaluation to determine thier inhibitory activity.

Against 5αR, we have previously shown using molecular modelling (Ahmed and Denison, 1998a) that the pyrrolidin-2,5-dione compounds possessing a moiety (e.g. a C=O functionality) are able to undergo reduction by NADPH present within the 5αR active site and this may result in inhibitory activity (Figure 1.24).

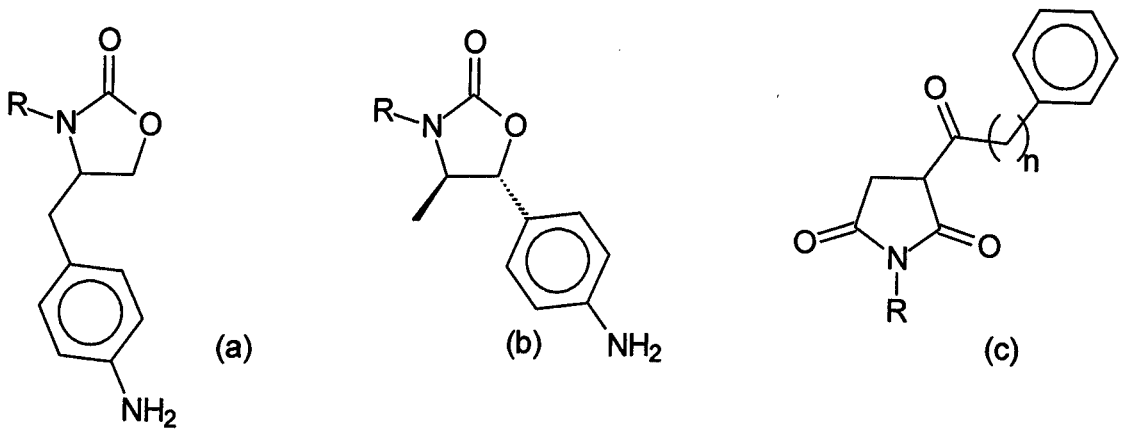


Figure1.24. Compounds as potential inhibitors of both $P450_{17\alpha}$. and 5αR [where (a) and (b) are potential $P450_{17\alpha}$ inhibitors and (c) is a range of 5αR inhibitors].

Chapter Two:

Experimental

Synthesis of potential inhibitors of $P450_{17\alpha}$.

2.0 SYNTHESIS OF POTENTIAL INHIBITORS OF $P450_{17\alpha}$.

2.1 Discussion

The Evans' chiral auxiliary has been extensively used in organic synthesis, in particular, it has been used widely in asymmetric synthesis, in both liquid and solid phases (Evans et al, 1994; Evans et al, 2002; Evans et al, 1988; Evans and Weber, 1987; Evans and Dow, 1986) and is available in both the *R* and *S* forms. A number of derivatives of oxazolidinone now exist and within the current study, we consider the synthesis of the derivatives of both 4-benzyl–2-oxazolidinone and 4-methyl-5-phenyl–2-oxazolidinone.

In the compounds designed as potential inhibitors of the cytochrome P-450 enzyme 17α-hydroxylase/17,20-lyase ($P450_{17\alpha}$), it was hypothesised that the incorporation of an amine group within the phenyl moiety would allow the nitrogen lone pair of electrons to ligate with the haem Fe atom (Figure 2.1), thereby resulting in the inhibition of the enzyme and thus resulting in the subsquent loss of stimulation of prostate cancer cells. Our hypothesis has previously been utilised in the synthesis of inhibitors (based on 4-benzyl–2-oxazolidinone) of the cytochrome P-450 enzyme responsible for oestrogen biosynthesis, namely aromatase (Ahmedt, 2002b), however, the remaining chiral auxiliaries have not been considered as chiral starting material in the synthesis of potential enzyme inhibitors.

In the synthesis of 4-substituted derivatives of 4-benzyl–2-oxazolidinone, we discovered that in most cases the synthetic routes involved the synthesis of the oxazolidinone ring from the enantiomerically pure starting alcohol of the corresponding amino acid. For example, Burgess and Lim (1997) started their synthesis of the 4-hydroxy derivative (such as OH so as to allow binding to solid support) of the Evans' chiral auxiliary with Boc *tert*-butyloxycarbonyl tyrosine benzonitrile [Boc-Tyr-(Bn)], which was reduced to the corresponding alcohol. The *N*-protecting group was removed and the resulting amino acid reacted with phosgene to give the oxazolidinone ring (Scheme 2.1). However, this synthetic route is limited: firstly, if alternative linkages (other than OH) to the solid phase

are required; they are not readily attainable due to the lack of appropriate starting material; secondly, the use of phosgene is not desirable due to the toxic nature of the compound and therefore the environmental impact of this toxic compound.

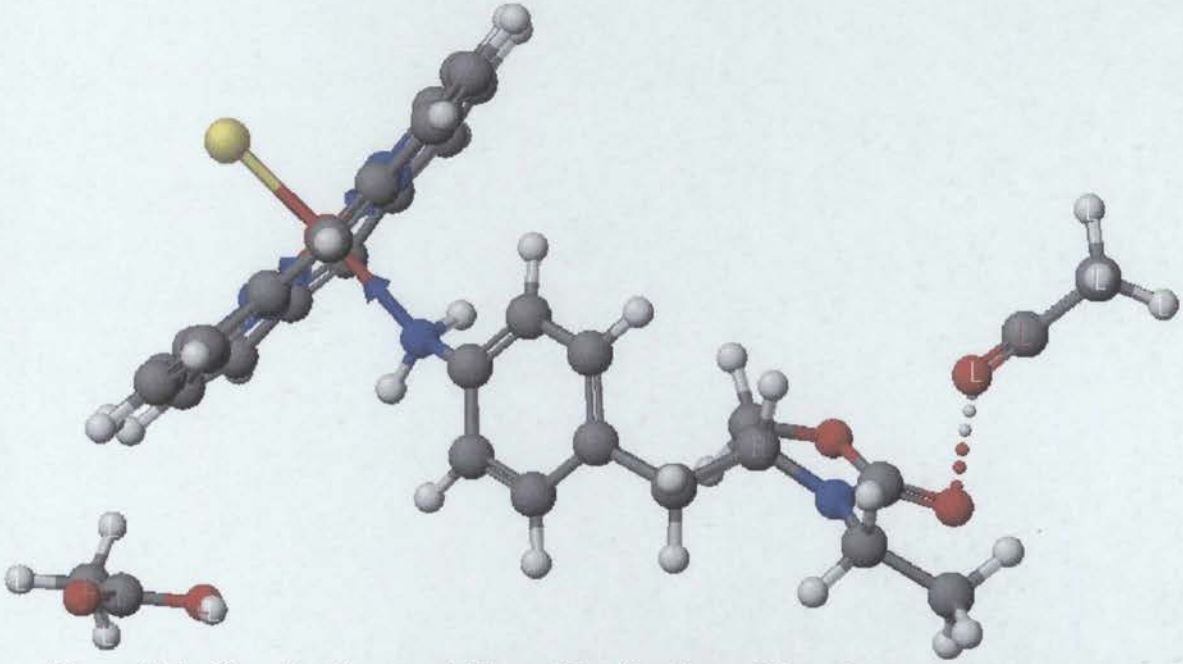
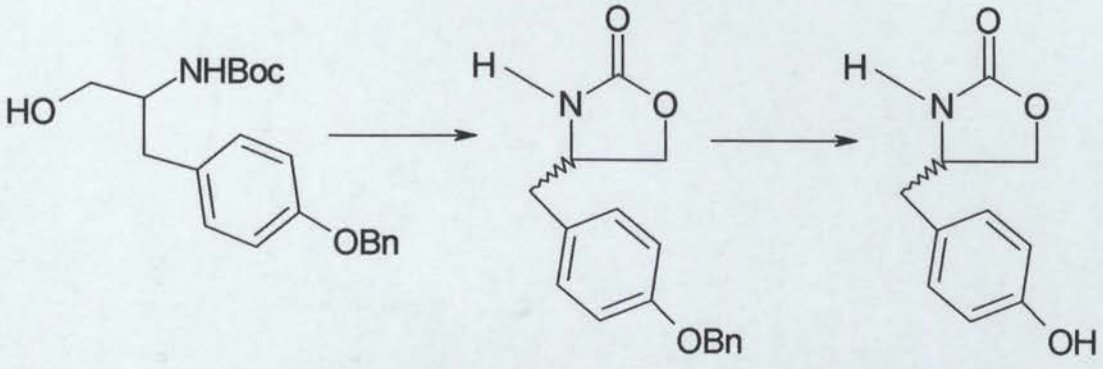


Figure 2.1. Showing the modelling of the ligation of the nitrogen atom to the haem within aromatase.



Scheme 2.1 Route utilised by Burgess and Lim in the synthesis of 4-hydroxy derivative of the Evans' chiral auxiliary (Burgess and Lim, 1997).

Although used extensively in asymmetric synthesis, the Evans' chiral auxiliary has not, in general, been considered as a building block in the synthesis of enzyme inhibitors. In an effort to discover more detailed information regarding the active site of aromatase, Ahmed (2002) has previously considered the 4-

benzyl–2-oxazolidinone based chiral auxiliary on the basis that two enantiomers are readily available, thereby allowing the investigation of the structure activity relationships between the two enantiomers with regard to the inhibition of this enzyme (Ahmed et al, 2002a; Ahmed et al, 2002b). Furthermore, in the modelling of the Evans' chiral auxiliary with respect to the two components of $P450_{17\alpha}$ (namely 17α-hydroxylase and 17,20-lyase), it was postulated that the structure of the oxazolidinone ring may be able to mimic the mode of binding of known inhibitors of 17α-hydroxylase and 17,20-lyase such as those based on the 3-(4-aminophenyl)-alkyl pyrrolidine-2,5-dione (Figure 2.1), which have been reported previously to be weak inhibitors of 17α-hydroxylase/17,20-lyase (Ahmed, 1990; Ahmed et al 1995b).

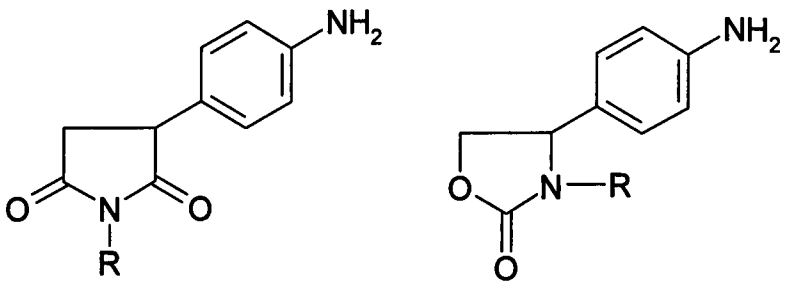
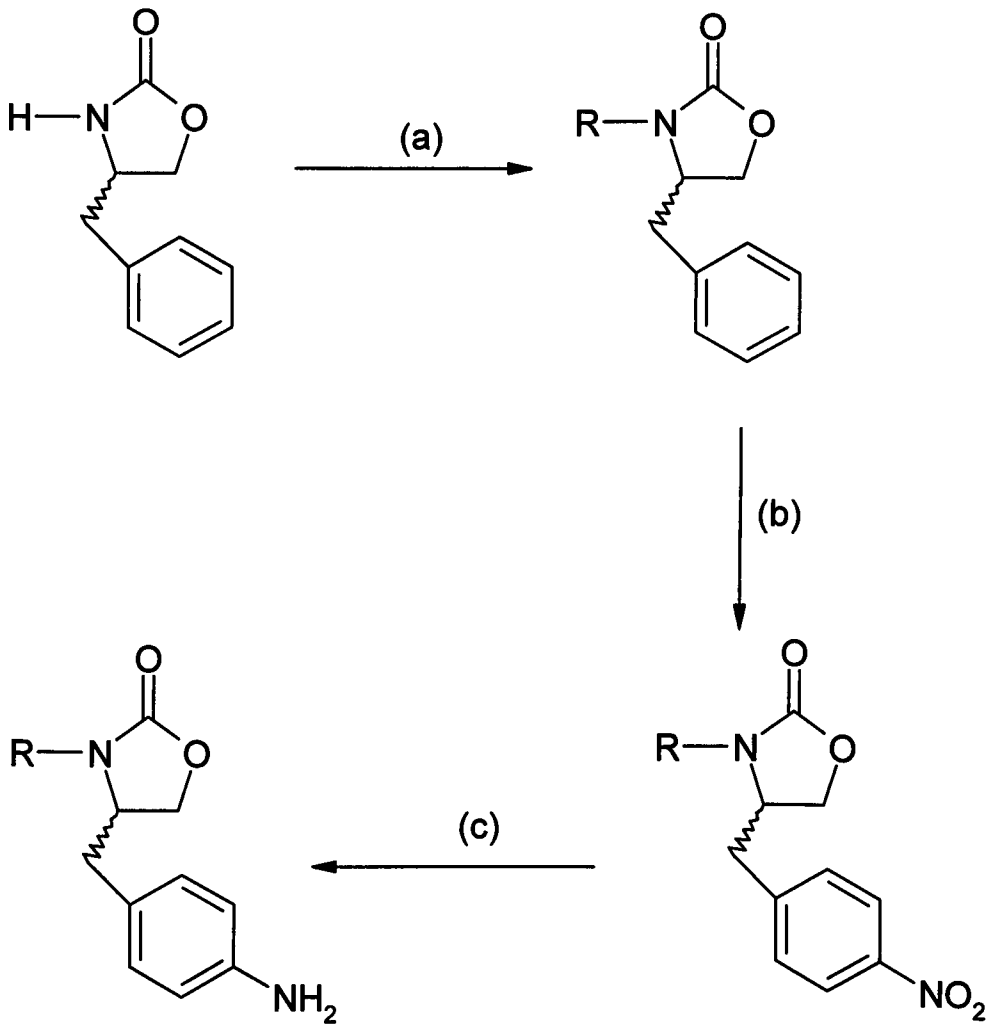


Figure 2.2 To show the similarities between the ring structures of: (a) pyrrolidine-2, 5-dione (Ahmed, 1990); (b) 4-benzyl–2-oxazolidinone- based chiral auxiliary, and; (c) 4-methyl-5-phenyl–2-oxazolidinone based chiral auxiliary.

Furthermore, it was postulated that the derivatisation of the R group may allow us to study the effect of potential steric hindrance on the inhibitory activity, thereby allowing us to explore the area about the active site as well as to observe the optimum alkyl chain length for inhibitory activity.

In the synthesis of the *N*-alkylated 4-benzyl–2-oxazolidinone based compounds we considered the reactions outlined in Scheme 2.2. This series of reactions has been considered previously by Adat (Ahmed, 2002b) in her study into the synthesis of potential aromatase inhibitors. As such, only a brief discussion associated with the present investigation will be given.



Scheme 2.2. Synthesis of potential inhibitors of $P450_{17\alpha}$ using the *R* and *S* enantiomers of the 4-benzyl–2-oxazolidinone (a = NaH/DMF/Δ/R-X; b = HNO_3/DCM/-10°C; c = H_2/Pd/C; R = CH_3 to $C_{10}H_{21}$).

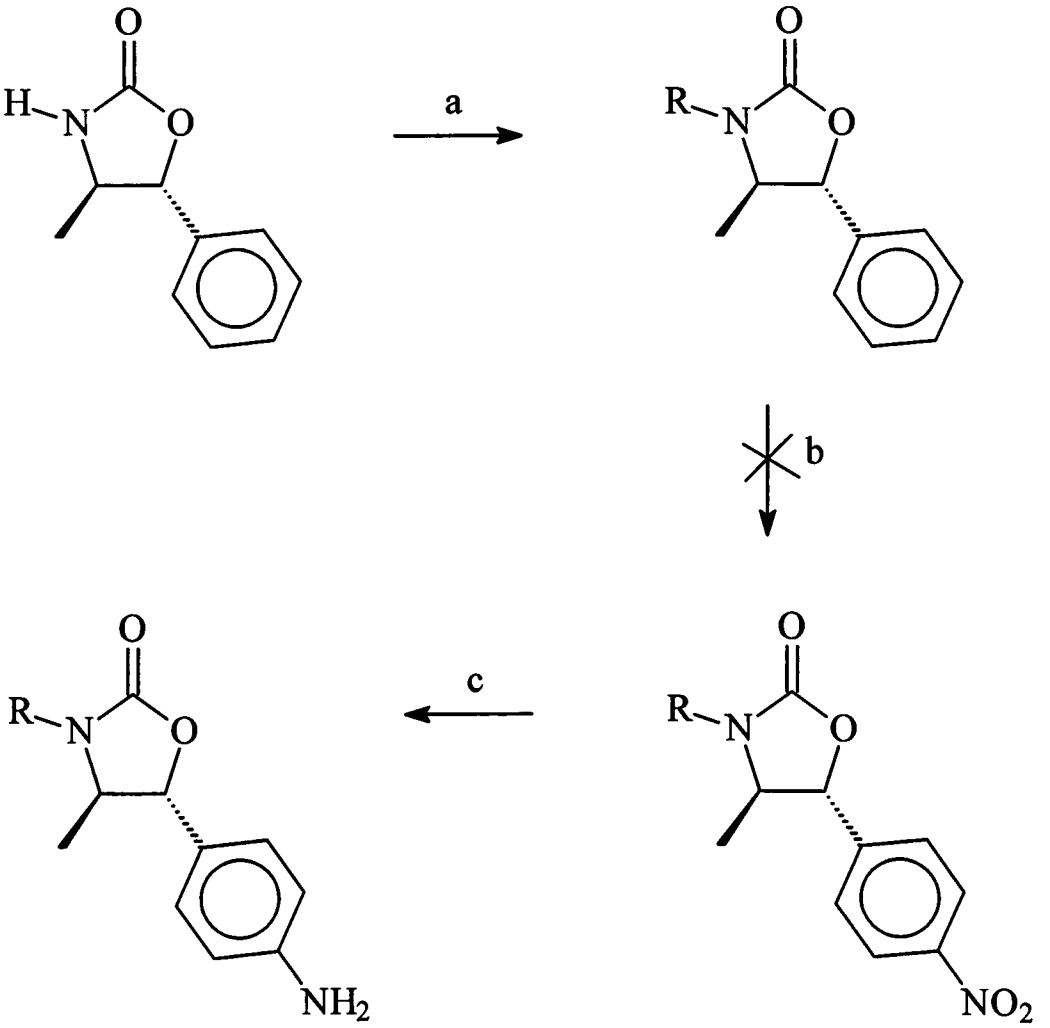
The *N*-alkylation reaction (step a, Scheme 2.2) was attempted using similar reaction conditions to (Ahmed, 2002b) (that is, NaH was used as the deprotonating base in anhydrous DMF as the reaction solvent) and which afforded us the desired range of *N*-alkylated compounds and in high yield (80% to 90%). As previously mentioned, the 4-amino compounds were targeted as potential cytochrome P-450 inhibitors since the amine moiety is able to ligate to the iron atom of the haem. In the synthesis of phenylamine based compounds, (Ahmed, 2002b) undertook an initial nitration of the phenyl ring system followed by the reduction of the nitro group to the corresponding amine. As such, in the nitration of the phenyl ring moiety, we utilised a modified method of Hylands and

Moodie (1997) and which involved the use of dilute (5M) nitric acid and DCM as a solvent at -10°C. This resulted in the target nitrated *N*-alkylated compounds in good yield (70% to 80%), however, it was found that in the synthesis of the longer alkyl chain derivatives (that is, the heptyl, octyl, nonyl and decyl derivatives) the time of reaction was required to be increased so as to optimise the yield, presumably due to the highly hydrophobic nature of these compounds.

The reduction of the nitro derivative to the corresponding amino compound was undertaken using catalytic hydrogenation, using hydrogen gas under pressure and palladium (adsorbed onto charcoal) as a catalyst in 95% ethanol. The reaction proved satisfactory and afforded us the target compounds in high yields (exceeding 90%).

In an effort to ensure that the chiral centre had not undergone any kind of alteration under the reaction conditions used, the specific rotation for all compounds were measured. These were found to be consistent with the parent compound.

In the attempted synthesis of further novel and potential inhibitors of $P450_{17\alpha}$ based on the 4-methyl-5-phenyl–2-oxazolidinone, the reactions outlined in Scheme 2.3 were considered. As can be observed, in general, the scheme is similar to that outlined for the synthesis of 4-(4-aminobenzyl)-2-oxazolidinone (Scheme 2.3). However, due to lack of time, only the initial alkylation step (step a) was undertaken and was found to proceed in good yield (ranging from 80% for the *N*-methyl to 96% for the *N*-decyl derivative). The remaining steps in the synthesis of the 4-methyl-5-(4-aminophenyl)-2-oxazolidinone are currently under investigation within our laboratories.



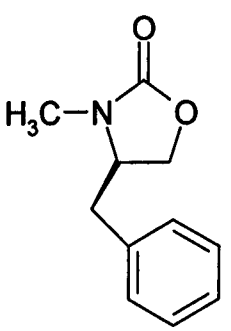
Scheme 2.3. Attempted synthesis of a series of compounds based upon the 4-methyl-5-phenyl–2-oxazolidinone (a = NaH/DMF/Δ/R-X; b = HNO_3/DCM/-10°C; c = H_2/Pd/C; R= CH_3 to $C_{10}H_{21}$).

2.2 Materials and methods

The reagents used were obtained from either Aldrich Chemical Co Ltd or Lancaster Synthesis Ltd. Purity was checked by ^{1}H and ^{13}C NMR (Bucker 300Mhz and 75.5MHz or JEOL 400MHz and 100MHz). Infrared spectrometry was obtained on a Perkin Elmer Fourier transform-paragon 1000 infrared spectrometer. Analytical thin layer chromatography (TLC) was carried out silica gel on PET polyester and visualised by short – wave ultraviolet. Flash chromatography was performed on silica according using 230-400 mesh ASTM silica, the solvent light petroleum, ether and Hexane and diethyl ether. Gas chromatography-mass spectrometry was carried out on a Hewlett 5890 Packard series II GC-MS at a flow rate of 0.58Ml/min, and a temperature range increasing from 120-270 °C at the rate of 10 °C/min. Elemental analysis was undertaken at the school of pharmacy, London.

2.3 EXPERIMENTAL

4-*(R)*-Benzyl-3-methyl-2-oxazolidinone (57)

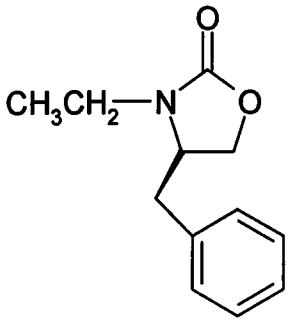


To a solution of *(R)*-4-benzyl-2-oxazolidinone (2.00g, 11.29mmol) in DMF (50mL), NaH (0.45g, 11.29mmol, 60% dispersion in mineral oil) was added in one portion at room temperature. After 15min, iodomethane (1.76g, 12.42mmol) was added in a dropwise fashion. The reaction was left to stir for 48h at 50°C. The reaction mixture was then poured into ice (20mL) and the solvent was removed under reduced pressure leaving a solid yellow compound. The compound was dissolved in DCM (50mL). The DCM layer was washed with water (3 x 100mL) and dried over anhydrous $MgSO_4$. The solvent was removed

under reduced pressure to give **57** (2.01g, 93%) as a pale yellow solid (m.p. 64-65°C); R_f 0.61 [75/25 diethyl ether/petroleum ether (40-60°C)].

$\nu_{(max)}$(Film)/cm^{-1}: 2928.7 (C-H), 1774.9 (C=O); δ_H (400MHz, $CDCl_3$): 7.32 (5H, m, Ph-H), 4.17 (1H, m, NCH), 3.97 (2H, m, OCH_2), 3.10 (1H, d, J=5Hz, Ph-CH_2), 2.87 (3H, s, CH_3), 2.69 (1H, d, J=9Hz, Ph-CH_2); δ_C (100MHz, $CDCl_3$): 159.00 (C=O), 135.39, 129.00, 128.90, 127.17 (ArC), 66.58 (O-CH_2), 58.35 (NCH), 38.39 (Ph-CH_2), 29.50 (CH_3); LRMS (EI): 191 (M^+, 3%), 100 (M^+-C_7H_7 ,100%); GC t_R 8.99 min.

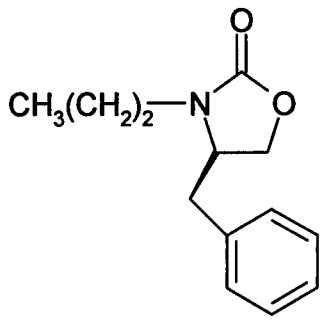
4-(*R*)-Benzyl-3-ethyl-2-oxazolidinone (58)



Compound **(58)** was synthesised following the same procedure as for compound **(57)**, except that iodoethane (1.94g, 12.42mmol) was added to *(R)*-4-benzyl-2-oxazolidinone (2.00g, 11.29mmol) to give **58** (2.02g, 87%) as a clear yellow oil; R_f 0.70 [70/30 diethyl ether/petroleum ether (40-60°C).

$\nu_{(max)}$(Film)/cm^{-1}: 2977.9 (CH-aliphatic), 1751.9 (C=O); δ_H (400MHz, $CDCl_3$): 7.30 (5H, m, Ph-H), 4.14 (1H, m, NCH), 3.98 (2H, m, OCH_2), 3.59 (1H, d, J=7Hz, Ph-CH_2), 3.12 (2H, m, NCH_2), 2.67 (1H, d, J=9Hz, Ph-CH_2), 1.18 (3H, t, J=7Hz, CH_3); δ_C (100MHz, $CDCl_3$): 157.80 (C=O), 135.42, 128.90, 128.83, 127.07 (ArC), 66.60 (O-CH_2), 55.49 (NCH), 38.40 (NCH_2), 36.76 (Ph-CH_2), 12.59 (CH_3); LRMS (EI): 205 (M^+, 3%), 114 (M^+ - C_7H_7 ,100%); GC t_R 9.22 min.

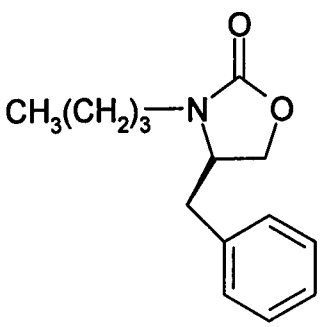
4-*(R)*-Benzyl-3-propyl-2-oxazolidinone (59)



Compound **(59)** was synthesised following the same procedure as for compound **(57)**, except that iodopropane (2.11g, 12.42mmol) was added to *(R)*-4-benzyl-2-oxazolidinone (2.00g, 11.29mmol) to give **59** (2.30g, 93%) as a clear oil; R_f 0.73 [70/30 diethyl ether/petroleum ether (40-60°C)].

$\nu_{(max)}$ (Film)/cm^{-1}: 2965.2 (CH-aliphatic), 1751.6 (C=O); δ_H (400MHz, $CDCl_3$): 7.30 (5H, m, Ph-H), 4.13 (1H, m, NCH), 3.98 (2H, m, OCH_2), 3.47 (1H, d, J=7Hz, Ph-CH_2), 3.07 (2H, m, NCH_2), 2.67 (1H, d, J=9Hz, Ph-CH_2), 1.57 (2H, m, NCH_2CH_2), 0.93 (3H, t, J=7Hz, CH_3); δ_C (100MHz, $CDCl_3$): 158.07 (C=O), 135.47, 128.92, 128.86, 127.11 (ArC), 66.58 (O-CH_2), 55.90 (NCH), 43.63 (NCH_2), 38.35 (Ph-CH_2), 20.62 (CH_2), 11.07 (CH_3); LRMS (EI): 219 (M^+, 3%), 128 (M^+ - C_7H_7 ,100%); GC t_R 9.68 min.

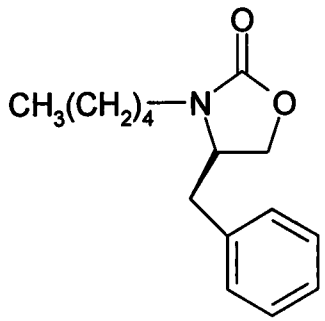
4-*(R)*-Benzyl-3-butyl-2-oxazolidinone (60)



Compound **(60)** was synthesised following the same procedure as for compound **(57)**, except that iodobutane (2.28g, 12.42mmol) was added to *(R)*-4-benzyl-2-oxazolidinone (2.00g, 11.29mmol) to give **60** (2.25g, 85%) as a clear oil; R_f 0.65 [50/50 diethyl ether/petroleum ether (40-60°C)].

$\nu_{(max)}$(Film)/cm^{-1}: 2958.6 (CH-aliphatic), 1752.2 (C=O); δ_H (400MHz, $CDCl_3$): 7.25 (5H, m, Ph-H), 4.13 (1H, m, NCH), 3.99 (2H, m, OCH_2), 3.52 (1H, d, J=7Hz, Ph-CH_2), 3.08 (2H, m, NCH_2), 2.67 (1H, d, J=9Hz, Ph-CH_2), 1.52 (2H, m, $N(CH_2)_2CH_2$), 1.31 (2H, m, $N(CH_2)_3CH_2$), 0.94 (3H, t, J=7Hz, CH_3); δ_C (100MHz, $CDCl_3$): 158.01 (C=O), 135.49, 128.94, 128.86, 127.11 (ArC), 66.58 (O-CH_2), 55.87 (NCH), 41.74 (NCH_2), 38.37 (Ph-CH_2), 29.39 (CH_2), 19.84 (CH_2), 13.65 (CH_3); LRMS (EI): 233 (M^+, 2%), 142 (M^+ - C_7H_7 ,100%); GC t_R 10.22 min.

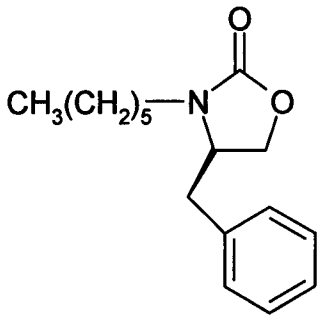
4-*(R)*-Benzyl-3-pentyl-2-oxazolidinone (61)



Compound **(61)** was synthesised following the same procedure as for compound **(57)**, except that iodopentane (2.46g, 12.42mmol) was added to *(R)*-4-benzyl-2-oxazolidinone (2.00g, 11.29mmol) to give **61** (2.40g, 86%) as a clear oil; R_f 0.79 [50/50 diethyl ether/petroleum ether (40-60°C)].

$\nu_{(max)}$(Film)/cm^{-1}: 2930.0 (CH-aliphatic), 1751.6 (C=O); δ_H (400MHz, $CDCl_3$): 7.32 (5H, m, Ph-H), 4.14 (1H, m, NCH), 3.98 (2H, m, OCH_2), 3.54 (1H, d, J=7Hz, Ph-CH_2), 3.09 (2H, m, NCH_2), 2.67 (1H, d, J=9Hz, Ph-CH_2), 1.56 (2H, m, NCH_2CH_2), 1.30 [4H, m, $N(CH_2)_2(CH_2)_2$], 0.91 (3H, t, J=7Hz, CH_3); δ_C (100MHz, $CDCl_3$): 158.04 (C=O), 135.54, 128.98, 128.92, 127.17 (ArC), 66.63 (O-CH_2), 55.93 (NCH), 42.03 (NCH_2), 38.43 (Ph-CH_2), 28.80 (CH_2), 27.05 (CH_2), 22.30 (CH_2), 13.95 (CH_3); LRMS (EI): 247 (M^+, 2%), 156 (M^+ - C_7H_7 ,100%); GC t_R 10.61 min.

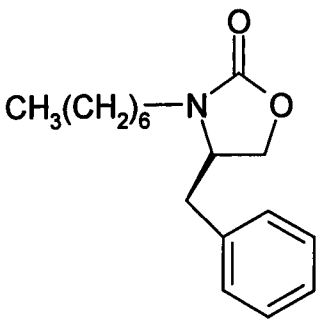
4-*(R)*-Benzyl-3-hexyl-2-oxazolidinone (62)



Compound **(62)** was synthesised following the same procedure as for compound **(57)**, except that iodohexane (2.63g, 12.42mmol) was added to *(R)*-4-benzyl-2-oxazolidinone (2.00g, 11.29mmol) to give **62** (2.60g, 88%) as a clear oil; R_f 0.68 [50/50 diethyl ether/petroleum ether (40-60°C)].

$\nu_{(max)}$(Film)/cm^{-1}: 2928.6 (CH-aliphatic), 1748.3 (C=O); δ_H (400MHz, $CDCl_3$): 7.05 (5H, m, Ph-H), 3.80 (1H, m, NCH), 3.68 (2H, m, OCH_2), 3.26 (1H, d, J=8Hz, Ph-CH_2), 2.82 (2H, m, NCH_2), 2.42 (1H, d, J=8Hz, Ph-CH_2), 1.30 (2H, m, $N(CH_2)_2CH_2$), 1.06 [6H, m, $N(CH_2)_2(CH_2)_3$], 0.68 (3H, t, J=6Hz, CH_3); δ_C (100MHz, $CDCl_3$): 157.08 (C=O), 135.01, 128.21, 127.85, 126.05 (ArC), 65.63 (O-CH_2), 54.85 (NCH), 41.13 (NCH_2), 37.39 (Ph-CH_2), 30.51 (CH_2), 26.42 (CH_2), 25.43 (CH_2), 21.65 (CH_2), 13.14 (CH_3); LRMS (EI): 261 (M^+ , 2%), 170 (M^+ - C_7H_7 ,100%); GC t_R 11.23 min.

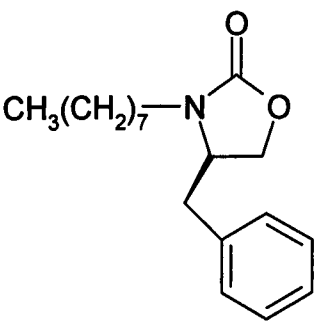
4-*(R)*-Benzyl-3-heptyl-2-oxazolidinone (63)



Compound **(63)** was synthesised following the same procedure as for compound **(57)**, except that iodoheptane (2.81g, 12.42mmol) was added to *(R)*-4-benzyl-2-oxazolidinone (2.00g, 11.29mmol) to give **63** (2.40g, 77%) as a clear oil; R_f 0.79 [50/50 diethyl ether/petroleum ether (40-60°C)].

$\nu_{(max)}$(Film)/cm^{-1}: 2927.9 (CH-aliphatic), 1753.3 (C=O); δ_H (400MHz, $CDCl_3$): 7.18 (5H, m, Ph-H), 4.02 (1H, m, NCH), 3.93 (2H, m, OCH_2), 3.41 (1H, d, J=7Hz, Ph-CH_2), 2.96 (2H, m, NCH_2), 2.56 (1H, d, J=8Hz, Ph-CH_2), 1.45 (2H, m, NCH_2CH_2), 1.17 [8H, m, $N(CH_2)_2(CH_2)_4$], 0.80 (3H, t, J=7Hz, CH_3); δ_C (100MHz, $CDCl_3$): 157.55 (C=O), 135.23, 128.56, 128.34, 126.57 (ArC), 66.11 (O-CH_2), 55.37 (NCH), 41.58 (NCH_2), 37.90 (Ph-CH_2), 31.40 (CH_2), 29.05 (CH_2), 26.89 (CH_2), 26.21 (CH_2), 22.19 (CH_2), 13.64 (CH_3); LRMS (EI): 275 (M^+, 2%), 184 (M^+ - C_7H_7 ,100%); GC t_R 11.83 min.

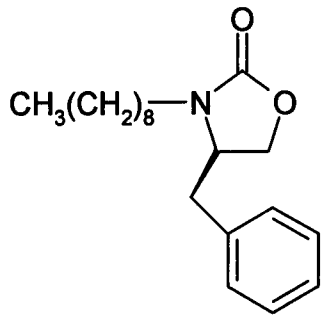
4-*(R)*-Benzyl-3-octyl-2-oxazolidinone (64)



Compound **(64)** was synthesised following the same procedure as for compound **(57)**, except that iodooctane (2.98g, 12.42mmol) was added to *(R)*-4-benzyl-2-oxazolidinone (2.00g, 11.29mmol) to give **64** (2.90g, 89%) as a clear oil; R_f 0.81 [50/50 diethyl ether/petroleum ether (40-60°C)].

$\nu_{(max)}$(Film)/cm^{-1}: 2926.5 (CH-aliphatic), 1753.6 (C=O); δ_H (400MHz, $CDCl_3$): 7.24 (5H, m, Ph-H), 4.07 (1H, m, NCH), 3.95 (2H, m, OCH_2), 3.88 (1H, d, J=7Hz, Ph-CH_2), 3.00 (2H, m, NCH_2), 2.61 (1H, d, J=8Hz, Ph-CH_2), 1.49 (2H, m, NCH_2CH_2), 1.21 [10H, m, $N(CH_2)_2(CH_2)_5$)], 0.84 (3H, t, J=7Hz, CH_3); δ_C (100MHz, $CDCl_3$): 157.68 (C=O), 135.28, 128.65, 128.47, 126.70 (ArC), 66.23 (O-CH_2), 55.48 (NCH), 41.68 (NCH_2), 38.00 (Ph-CH_2), 31.37 (CH_2), 28.80 (CH_2), 26.98 (CH_2), 26.51 (CH_2), 26.30 (CH_2), 22.24 (CH_2), 13.72 (CH_3); LRMS (EI): 289 (M^+, 2%), 198 (M^+ - C_7H_7 ,100%); GC t_R 12.82 min

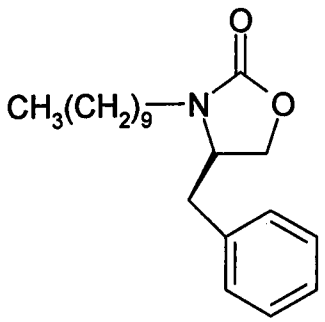
4-*(R)*-Benzyl-3-nonyl-2-oxazolidinone (65)



Compound **(65)** was synthesised following the same procedure as for compound **(57)**, except that iodononane (3.16g, 12.42mmol) was added to *(R)*-4-benzyl-2-oxazolidinone (2.00g, 11.29mmol) to give **65** (3.29g, 96%) as a clear oil; R_f 0.86 [50/50 diethyl ether/petroleum ether (40-60°C)].

$\nu_{(max)}$(Film)/cm^{-1}: 2925.6 (CH-aliphatic), 1755.5 (C=O); δ_H (400MHz, $CDCl_3$): 7.13 (5H, m, Ph-H), 3.93 (1H, m, NCH), 3.85 (2H, m, OCH_2), 3.34 (1H, d, J=9Hz, Ph-CH_2), 2.91 (2H, m, NCH_2), 2.50 (1H, d, J=8Hz, Ph-CH_2), 1.38 (2H, m, NCH_2CH_2), 1.12 [12H, m, $N(CH_2)_2(CH_2)_6$], 0.75 (3H, t, J=7Hz, CH_3); δ_C (100MHz, $CDCl_3$): 157.55 (C=O), 135.23, 128.56, 128.34, 126.57 (ArC), 66.11 (O-CH_2), 55.37 (NCH), 41.58 (NCH_2), 37.90 (Ph-CH_2), 31.40 (CH_2), 28.05 (CH_2), 28.82 (CH_2), 28.77 (CH_2), 26.89 (CH_2), 26.21 (CH_2), 22.19 (CH_2), 13.64 (CH_3); LRMS (EI): 302 (M^+, 2%), 212 (M^+ - C_7H_7 ,100%); GC t_R 13.56 min.

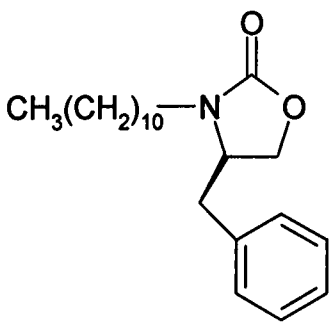
4-*(R)*-Benzyl-3-decyl-2-oxazolidinone (66)



Compound **(66)** was synthesised following the same procedure as for compound **(57)**, except that iododecane (3.33g, 12.42mmol) was added to *(R)*-4-benzyl-2-oxazolidinone (2.00g, 11.29mmol) to give **66** (3.40g, 95%) as a clear oil; R_f 0.88 [60/40 diethyl ether/petroleum ether (40-60°C)].

$\nu_{(max)}$(Film)/cm^{-1}: 2925.4 (CH-aliphatic), 1754.9 (C=O); δ_H (400MHz, $CDCl_3$): 7.20 (5H, m, Ph-H), 4.00 (1H, m, NCH), 3.91 (2H, m, OCH_2), 3.41 (1H, d, J=7Hz, Ph-CH_2), 2.95 (2H, m, NCH_2), 2.56 (1H, d, J=8Hz, Ph-CH_2), 1.45 (2H, m, NCH_2CH_2), 1.17 [14H, m, $N(CH_2)_2(CH_2)_7$], 0.80 (3H, t, J=6Hz, CH_3); δ_C (100MHz, $CDCl_3$): 158.81 (C=O), 135.42, 128.77, 128.57, 126.81 (ArC), 66.35 (O-CH_2), 55.61 (NCH), 41.82 (NCH_2), 38.14 (Ph-CH_2), 31.64 (CH_2), 29.31 (CH_2), 29.28 (CH_2), 29.07 (CH_2), 28.99 (CH_2), 27.12 (CH_2), 26.43 (CH_2), 22.42 (CH_2), 13.86 (CH_3); LRMS (EI): 317 (M^+, 2%), 86 (M^+-CH_3NO_2 ,100%); GC t_R 14.34 min

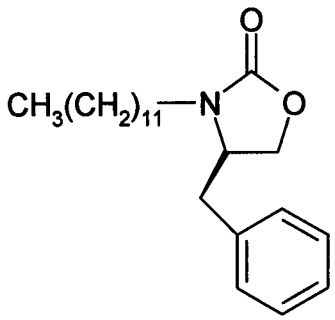
4-*(R)*-Benzyl-3-undecyl-oxazolidin-2-one (67)



Compound **(67)** was synthesised following the same procedure as for compound **(57)**, except that iodoundecane (3.50g, 12.42mmol) was added to *(R)*-4-benzyl-2-oxazolidinone (2.00g, 11.29mmol) to give **67** (3.54g, 95%) as a clear oil; R_f 0.78 [60/40 diethyl ether/petroleum ether (40-60°C)].

$\nu_{(max)}$(Film)/cm^{-1}: 2925.4 (CH-aliphatic), 1754.7 (C=O); δ_H (400MHz, $CDCl_3$): 7.23 (5H, m, Ph-H), 4.03 (1H, m, NCH), 3.93 (2H, m, OCH_2), 3.89 (1H, d, J=7Hz, Ph-CH_2), 2.99 (2H, m, NCH_2), 2.59 (1H, d, J=8Hz, Ph-CH_2), 1.48 (2H, m, NCH_2CH_2), 1.20 [16H, m, $N(CH_2)_2(CH_2)_8$)], 0.83 (3H, t, J=7Hz, CH_3); δ_C (100MHz, $CDCl_3$): 157.65 (C=O), 135.26, 128.94, 128.41, 126.65 (ArC), 66.19 (O-CH_2), 55.45 (NCH), 41.66 (NCH_2), 37.98 (Ph-CH_2), 31.48 (CH_2), 29.17 (CH_2), 29.16 (CH_2), 29.12 (CH_2), 28.91 (CH_2), 28.84 (CH_2), 26.96 (CH_2), 26.27 (CH_2), 22.26 (CH_2), 13.70 (CH_3); LRMS (EI): 331 (M^+, 100%); GC t_R 21.76 min.

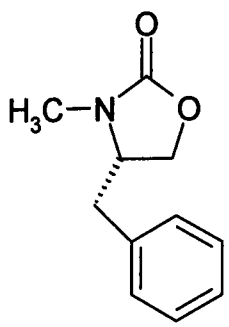
4-*(R)*-Benzyl-3-dodecyl-oxazolidin-2-one (68)



Compound **(68)** was synthesised following the same procedure as for compound **(57)**, except that iododododecane (3.68g, 12.42mmol) was added to *(R)*-4-benzyl-2-oxazolidinone (2.00g, 11.29mmol) to give **68** (3.49g, 89%) as a clear oil; R_f 0.80 [60/40 diethyl ether/petroleum ether (40-60°C)].

$\nu_{(max)}$(Film)/cm^{-1}: 2925.5 (CH-aliphatic), 1755.5 (C=O); δ_H (400MHz, $CDCl_3$): 7.14 (5H, m, Ph-H), 3.94 (1H, m, NCH), 3.86 (2H, m, OCH_2), 3.36 (1H, d, J=7Hz, Ph-CH_2), 2.90 (2H, m, NCH_2), 2.51 (1H, d, J=8Hz, Ph-CH_2), 1.40 (2H, m, NCH_2CH_2), 1.13 [18H, m, $N(CH_2)_2(CH_2)_9$)], 0.76 (3H, t, J=7Hz, CH_3); δ_C (100MHz, $CDCl_3$): 157.49 (C=O), 135.20, 128.50, 128.25, 126.48 (ArC), 66.04 (O-CH_2), 55.30 (NCH), 41.52 (NCH_2), 37.84 (Ph-CH_2), 31.38 (CH_2), 29.11 (CH_2), 29.08 (CH_2), 29.05 (CH_2), 29.02 (CH_2), 28.82 (CH_2), 28.72 (CH_2), 26.84 (CH_2), 26.16 (CH_2), 22.14 (CH_2), 13.58 (CH_3); LRMS (EI): 345 (M^+, 100%); GC t_R 24.59min.

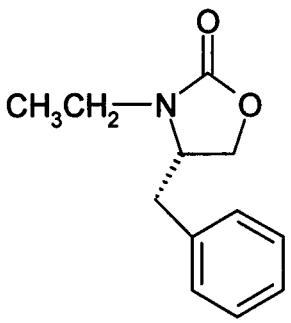
4-*(S)*-Benzyl-3-methyl-2-oxazolidinone (69)



Compound **(69)** was synthesised following the same procedure as for compound **(57)**, except that iodomethane (1.76g, 12.42mmol) was added to *(S)*-4-benzyl-2-oxazolidinone (2.00g, 11.29mmol) to give **69** (1.75g, 81%) as a white solid (mp 78-80°C) R_f 0.70 [70/30 diethyl ether/petroleum ether (40-60°C)].

$\nu_{(max)}$(Film)/cm^{-1}: 2928.8 (CH-aliphatic), 1738.7 (C=O); δ_H (400MHz, $CDCl_3$): 7.32 (5H, m, Ph-H), 4.19 (1H, m, NCH), 3.99 (2H, m, OCH_2), 3.13 (1H, d, J=5Hz, Ph-CH_2), 2.88 (3H, s, CH_3), 2.69 (1H, d, J=9Hz, Ph-CH_2); δ_C (100MHz, $CDCl_3$): 135.38, 129.00, 128.91, 127.17 (ArC), 66.59 (O-CH_2), 58.35 (NCH), 38.39 (Ph-CH_2), 29.51 (CH_3); LRMS (EI): 191 (M^+, 2%), 100 (M^+ - C_7H_7 ,100%); GC t_R 8.87 min.

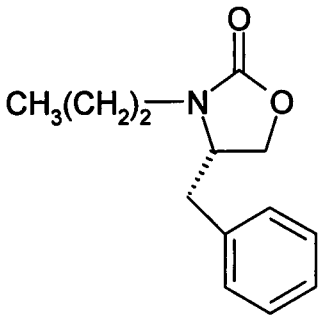
4-*(S)*-Benzyl-3-ethyl-2-oxazolidinone (70)



Compound **(70)** was synthesised following the same procedure as for compound **(57)**, except that iodoethane (1.94g, 12.42mmol) was added to *(S)*-4-benzyl-2-oxazolidinone (2.00g, 11.29mmol) to give **70** (1.92g, 83%) as a clear pale yellow oil; R_f 0.78 [70/30 diethyl ether/petroleum ether (40-60°C)].

$\nu_{(max)}$(Film)/cm^{-1}: 2977.5 (CH-aliphatic), 1750.6 (C=O); δ_H (400MHz, $CDCl_3$): 7.32 (5H, m, Ph-H), 4.14 (1H, m, NCH), 4.00 (2H, m, OCH_2), 3.61 (1H, d, J=7Hz, Ph-CH_2), 3.13 (2H, m, NCH_2), 2.68 (1H, d, J=9Hz, Ph-CH_2), 1.20 (3H, t, J=7Hz, CH_3); δ_C (100MHz, $CDCl_3$): 135.47, 128.96, 128.92, 127.17 (ArC), 66.67 (O-CH_2), 55.58 (NCH), 38.49 (Ph-CH_2), 36.83 (CH_2), 12.68 (CH_3); LRMS (EI): 205 (M^+, 3%), 114 (M^+ - C_7H_7 ,100%); GC t_R 9.13 min.

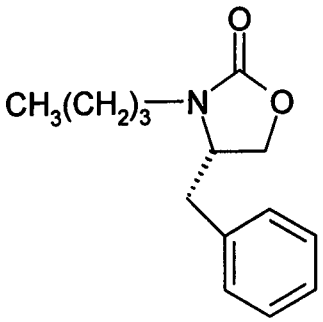
4-*(S)*-Benzyl-3-propyl-2-oxazolidinone (71)



Compound **(71)** was synthesised following the same procedure as for compound **(57)**, except that iodopropane (2.11g, 12.42mmol) was added to *(S)*-4-benzyl-2-oxazolidinone (2.00g, 11.29mmol) to give **71** (1.99g, 80%) as a clear oil; R_f 0.73 [60/40 diethyl ether/petroleum ether (40-60°C)].

$\nu_{(max)}$(Film)/cm^{-1}: 2965.4 (CH-aliphatic), 1752.0 (C=O); δ_H (400MHz, $CDCl_3$): 7.31 (5H, m, Ph-H), 4.14 (1H, m, NCH), 3.98 (2H, m, OCH_2), 3.50 (1H, d, J=7Hz, Ph-CH_2), 3.09 (2H, m, NCH_2), 2.67 (1H, d, J=9Hz, Ph-CH_2), 1.66 (2H, m, NCH_2CH_2), 0.94 (3H, t, J=8Hz, CH_3); δ_C (100MHz, $CDCl_3$): 158.12 (C=O), 135.50, 128.97, 128.91, 127.17 (ArC), 66.63 (O-CH_2), 55.95 (NCH), 43.68 (NCH_2), 38.40 (Ph-CH_2), 20.68 (CH_2), 11.12 (CH_3); LRMS (EI): 219 (M^+, 3%), 128 (M^+ - C_7H_7 ,100%); GC t_R 9.57 min.

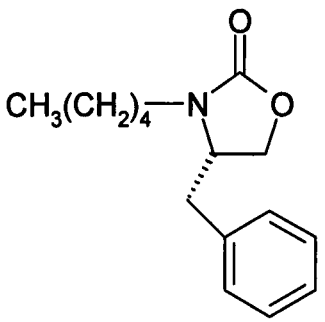
4-*(S)*-Benzyl-3-butyl-2-oxazolidinone (72)



Compound **(72)** was synthesised following the same procedure as for compound **(57)**, except that iodobutane (2.28g, 12.42mmol) was added to *(S)*-4-benzyl-2-oxazolidinone (2.00g, 11.29mmol) to give **72** (2.20g, 84%) as a clear oil; R_f 0.78 [60/40 diethyl ether/petroleum ether (40-60°C)].

$\nu_{(max)}$(Film)/cm^{-1}: 2964.7 (CH-aliphatic), 1752.3 (C=O); δ_H (400MHz, $CDCl_3$): 7.31 (5H, m, Ph-H), 4.14 (1H, m, NCH), 3.97 (2H, m, OCH_2), 3.55 (1H, d, J=7Hz, Ph-CH_2), 3.08 (2H, m, NCH_2), 2.67 (1H, d, J=9Hz, Ph-CH_2), 1.53 (2H, m, NCH_2CH_2), 1.33 (2H, m, $N(CH_2)_2CH_2$), 0.94 (3H, t, J=7Hz, CH_3); δ_C (100MHz, $CDCl_3$): 158.04 (C=O), 135.51, 128.96, 128.89, 127.15 (ArC), 66.60 (O-CH_2), 55.90 (NCH), 41.75 (NCH_2), 38.40 (Ph-CH_2), 29.42 (CH_2), 19.87 (CH_2), 13.68 (CH_3); LRMS (EI): 233 (M^+, 3%), 142 (M^+ - C_7H_7 ,100%); GC t_R 10.09 min.

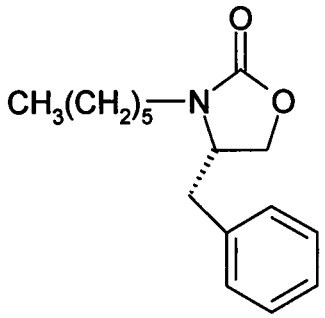
4-*(S)*-Benzyl-3-pentyl-2-oxazolidinone (73)



Compound **(73)** was synthesised following the same procedure as for compound **(57)**, except that iodopentane (2.46g, 12.42mmol) was added to *(S)*-4-benzyl--oxazolidinone (2.00g, 11.29mmol) to give **73** (2.55g, 91%) as a clear oil; R_f 0.75 [50/50 diethyl ether/petroleum ether (40-60°C)].

$\nu_{(max)}$(Film)/cm^{-1}: 2929.5 (CH-aliphatic), 1751.3 (C=O); δ_H (400MHz, $CDCl_3$): 7.32 (5H, m, Ph-H), 4.14 (1H, m, NCH), 3.98 (2H, m, OCH_2), 3.53 (1H, d, J=7Hz, Ph-CH_2), 3.09 (2H, m, NCH_2), 2.68 (1H, d, J=9Hz, Ph-CH_2), 1.56 (2H, m, NCH_2CH_2), 1.29 [4H, m, $N(CH_2)_2(CH_2)_2$)], 0.91 (3H, t, J=7Hz, CH_3); δ_C (100MHz, $CDCl_3$): 135.54, 128.98, 128.92, 127.17 (ArC), 66.63 (O-CH_2), 55.93 (NCH), 42.03 (NCH_2), 38.43 (Ph-CH_2), 28.80 (CH_2), 27.05 (CH_2), 22.30 (CH_2), 13.95 (CH_3); LRMS (EI): 247 (M^+, 3%), 156 (M^+ - C_7H_7 ,100%); GC t_R 10.61 min.

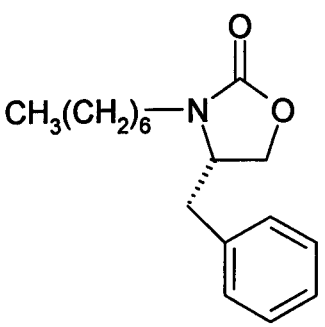
4-*(S)*-Benzyl-3-hexyl-2-oxazolidinone (74)



Compound **(74)** was synthesised following the same procedure as for compound **(57)**, except that iodohexane (2.63g, 12.42mmol) was added to *(S)*-4-benzyl-2-oxazolidinone (2.00g, 11.29mmol) to give **74** (2.51g, 85%) as a clear oil; R_f 0.72 [50/50 diethyl ether/petroleum ether (40-60°C)].

$\nu_{(max)}$(Film)/cm^{-1}: 2929.0 (CH-aliphatic), 1748.1 (C=O); δ_H (400MHz, $CDCl_3$): 7.20 (5H, m, Ph-H), 4.01 (1H, m, NCH), 3.92 (2H, m, OCH_2), 3.40 (1H, d, J=7Hz, Ph-CH_2), 2.97 (2H, m, NCH_2), 2.58 (1H, d, J=8Hz, Ph-CH_2), 1.46 (2H, m, NCH_2CH_2), 1.20 [6H, m, $N(CH_2)_2(CH_2)_3$], 0.80 (3H, t, J=7Hz, CH_3); δ_C (100MHz, $CDCl_3$): 157.56 (C=O), 135.23, 128.57, 128.34, 126.57 (ArC), 66.11 (O-CH_2), 55.36 (NCH), 41.59 (NCH_2), 37.90 (Ph-CH_2), 30.91 (CH_2), 26.84 (CH_2), 25.85 (CH_2), 22.04 (CH_2), 13.53 (CH_3); LRMS (EI): 261 (M^+ , 2%), 170 (M^+ - C_7H_7 ,100%); GC t_R 11.37 min.

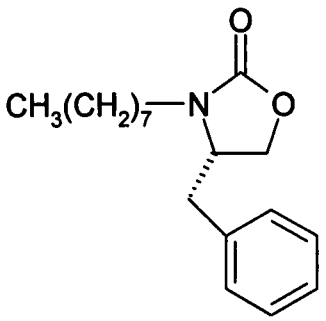
4-*(S)*-Benzyl-3-heptyl-2-oxazolidinone (75)



Compound **(75)** was synthesised following the same procedure as for compound **(57)**, except that iodoheptane (2.81g, 12.42mmol) was added to *(S)*-4-benzyl-2-oxazolidinone (2.00g, 11.29mmol) to give **75** (2.67g, 86%) as a clear oil; R_f 0.78 [50/50 diethyl ether/petroleum ether (40-60°C)].

$\nu_{(max)}$(Film)/cm^{-1}: 2928.0 (CH-aliphatic), 1753.6 (C=O); δ_H (400MHz, $CDCl_3$): 7.24 (5H, m, Ph-H), 4.03 (1H, m, NCH), 3.94 (2H, m, OCH_2), 3.44 (1H, d, J=8Hz, Ph-CH_2), 2.97 (2H, m, NCH_2), 2.59 (1H, d, J=9Hz, Ph-CH_2), 1.47 (2H, m, NCH_2CH_2), 1.21 [8H, m, $N(CH_2)_2(CH_2)_4$)], 0.82 (3H, t, J=7Hz, CH_3); δ_C (100MHz, $CDCl_3$): 157.64 (C=O), 135.24, 128.60, 128.40, 126.64 (ArC), 66.17 (O-CH_2), 55.42 (NCH), 41.62 (NCH_2), 37.94 (Ph-CH_2), 31.27 (CH_2), 28.45 (CH_2), 26.93 (CH_2), 26.20 (CH_2), 22.12 (CH_2), 13.63 (CH_3); LRMS (EI) 276 (M^+, 100%); GC t_R 11.82 min.

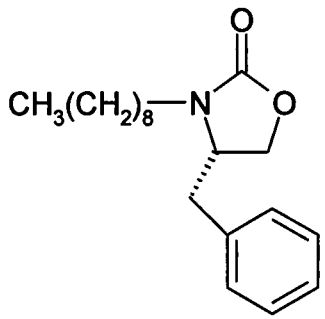
4-*(S)*-Benzyl-3-octyl-2-oxazolidinone (76)



Compound **(76)** was synthesised following the same procedure as for compound **(57)**, except that iodooctane (2.98g, 12.42mmol) was added to *(S)*-4-benzyl-2-oxazolidinone (2.00g, 11.29mmol) to give **76** (2.90g, 89%) as a clear oil; R_f 0.90 [50/50 diethyl ether/petroleum ether (40-60°C)].

$\nu_{(max)}$(Film)/cm^{-1}: 2926.7 (CH-aliphatic), 1753.8 (C=O); δ_H (400MHz, $CDCl_3$): 7.32 (5H, m, Ph-H), 4.14 (1H, m, NCH), 3.99 (2H, m, OCH_2), 3.52 (1H, d, J=7Hz, Ph-CH_2), 3.08 (2H, m, NCH_2), 2.68 (1H, d, J=9Hz, Ph-CH_2), 1.55 (2H, m, NCH_2CH_2), 1.27 [10H, m, $N(CH_2)_2(CH_2)_5$], 0.87 (3H, t, J=7Hz, CH_3); δ_C (100MHz, $CDCl_3$): 158.04 (C=O), 135.57, 128.98, 128.92, 127.17 (ArC), 66.64 (O-CH_2), 55.94 (NCH), 42.09 (NCH_2), 38.46 (Ph-CH_2), 31.73 (CH_2), 29.19 (CH_2), 29.15 (CH_2), 27.38 (CH_2), 26.69 (CH_2), 22.59 (CH_2), 14.04 (CH_3); LRMS (EI) 290 (M^+, 100%); GC t_R 12.75 min.

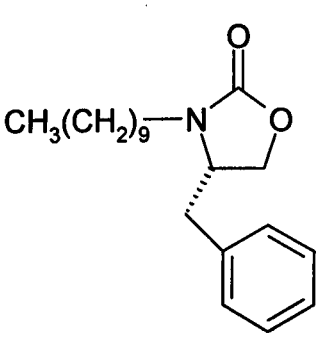
4-*(S)*-Benzyl-3-nonyl-2-oxazolidinone (77)



Compound **(77)** was synthesised following the same procedure as for compound **(57)**, except that iodononane (3.16g, 12.42mmol) was added to *(S)*-4-benzyl-2-oxazolidinone (2.00g, 11.29mmol) to give **77** (3.10g, 91%) as a clear oil; R_f 0.73 [40/60 diethyl ether/petroleum ether (40-60°C)].

$\nu_{(max)}$(Film)/cm^{-1}: 2926.0 (CH-aliphatic), 1755.4 (C=O); δ_H (400MHz, $CDCl_3$): 7.17 (5H, m, Ph-H), 3.97 (1H, m, NCH), 3.81 (2H, m, OCH_2), 3.37 (1H, d, J=7Hz, Ph-CH_2), 2.94 (2H, m, NCH_2), 2.54 (1H, d, J=8Hz, Ph-CH_2), 1.43 (2H, m, NCH_2CH_2), 1.16 [12H, m, $N(CH_2)_2(CH_2)_6$], 0.77 (3H, t, J=7Hz, CH_3); δ_C (100MHz, $CDCl_3$): 157.44 (C=O), 135.20, 128.47, 128.22, 126.44 (ArC), 66.01 (O-CH_2), 55.27 (NCH), 41.50 (NCH_2), 37.81 (Ph-CH_2), 31.26 (CH_2), 28.91 (CH_2), 28.65 (CH_2), 28.65 (CH_2), 26.80 (CH_2), 26.11 (CH_2), 22.05 (CH_2), 13.53 (CH_3); LRMS (EI): 303 (M^+, 3%), 212 (M^+ - C_7H_7 ,100%); GC t_R 13.59 min.

4-*(S)*-Benzyl-3-decyl-2-oxazolidinone (78)

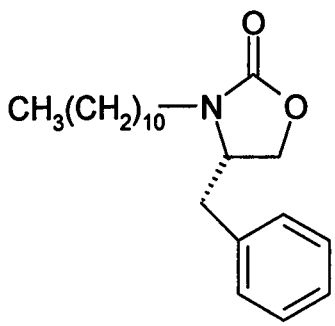


Compound **(78)** was synthesised following the same procedure as for compound **(57)**, except that iododecane (3.33g, 12.42mmol) was added to *(S)*-4-benzyl-2-

oxazolidinone (2.00g, 11.29mmol) to give **78** (3.15g, 88%) as a clear oil; R_f 0.78 [40/60 diethyl ether/petroleum ether (40-60°C)].

$\nu_{(max)}$(Film)/cm^{-1}: 2925.5 (CH-aliphatic), 1753.6 (C=O); δ_H (400MHz, $CDCl_3$): 7.31 (5H, m, Ph-H), 4.14 (1H, m, NCH), 3.98 (2H, m, OCH_2), 3.53 (1H, d, J=7Hz, Ph-CH_2), 3.09 (2H, m, NCH_2), 2.67 (1H, d, J=9Hz, Ph-CH_2), 1.55 (2H, m, NCH_2CH_2), 1.25 [14H, m, $N(CH_2)_2(CH_2)_7$], 0.88 (3H, t, J=7Hz, CH_3); δ_C (100MHz, $CDCl_3$): 158.02 (C=O), 135.52, 128.95, 128.88, 127.14 (ArC), 66.60 (O-CH_2), 55.89 (NCH), 42.04 (NCH_2), 38.40 (Ph-CH_2), 31.82 (CH_2), 29.46 (CH_2), 29.43 (CH_2), 29.23 (CH_2), 29.20 (CH_2), 27.34 (CH_2), 26.65 (CH_2), 22.61 (CH_2), 14.05 (CH_3); LRMS (EI) 317 (M^+, 100%); GC t_R 19.21 min.

4-*(S)*-Benzyl-3-undecyl-oxazolidin-2-one (79)

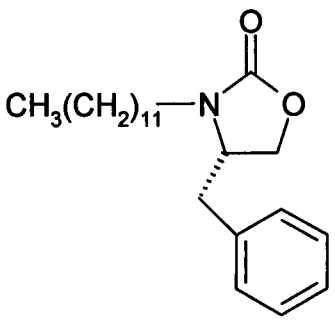


Compound **(79)** was synthesised following the same procedure as for compound **(57)**, except that iodoundecane (3.50g, 12.42mmol) was added to *(S)*-4-benzyl-2-oxazolidinone (2.00g, 11.29mmol) to give **79** (3.31g, 88%) as a clear oil; R_f 0.80 [40/60 diethyl ether/petroleum ether (40-60°C)].

$\nu_{(max)}$(Film)/cm^{-1}: 2925.8 (CH-aliphatic), 1756.0 (C=O); δ_H (400MHz, $CDCl_3$): 7.19 (5H, m, Ph-H), 3.98 (1H, m, NCH), 3.91 (2H, m, OCH_2), 3.40 (1H, d, J=7Hz, Ph-CH_2), 2.94 (2H, m, NCH_2), 2.55 (1H, d, J=8Hz, Ph-CH_2), 1.44 (2H, m, NCH_2CH_2), 1.17 [16H, m, $N(CH_2)_2(CH_2)_8$)], 0.80 (3H, t, J=7Hz, CH_3); δ_C (100MHz, $CDCl_3$): 157.53 (C=O), 135.20, 128.53, 128.30, 126.52 (ArC), 66.08 (O-CH_2), 55.33 (NCH), 41.54 (NCH_2), 37.86 (Ph-CH_2), 31.40 (CH_2), 29.10 (CH_2), 29.07 (CH_2), 29.03 (CH_2), 28.83 (CH_2), 28.74 (CH_2), 26.86 (CH_2), 26.18 (CH_2),

22.17 (<u>C</u>H_2), 13.62 (<u>C</u>H_3); LRMS (EI): 330 (M^+, 3%), 240 (M^+ - C_7H_7 ,100%); GC t_R 15.65 min.

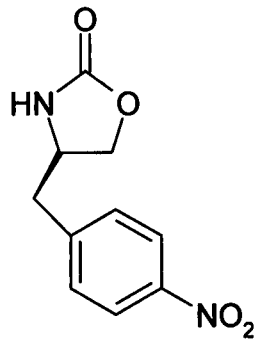
4-*(S)*-Benzyl-3-dodecyl-oxazolidin-2-one (80)



Compound **(80)** was synthesised following the same procedure as for compound **(57)**, except that iododododecane (3.68g, 12.42mmol) was added to *(S)*-4-benzyl-2-oxazolidinone (2.00g, 11.29mmol) to give **80** (3.51g, 90%) as a clear oil; R_f 0.78 [40/60 diethyl ether/petroleum ether (40-60°C)].

$\nu_{(max)}$(Film)/cm^{-1}: 2924.0 (CH-aliphatic), 1755.6 (C=O); δ_H (400MHz, $CDCl_3$): 7.19 (5H, m, Ph-<u>H</u>), 3.99 (1H, m, NC<u>H</u>), 3.90 (2H, m, OC<u>H_2</u>), 3.41 (1H, d, J=7Hz, Ph-C<u>H_2</u>), 2.95 (2H, m, NC<u>H_2</u>), 2.56 (1H, d, J=9Hz, Ph-C<u>H_2</u>), 1.45 (2H, m, NCH_2C<u>H_2</u>), 1.17 [18H, m, $N(CH_2)_2(C$<u>H_2</u>$)_9$)], 0.80 (3H, t, J=7Hz, C<u>H_3</u>); δ_C (100MHz, $CDCl_3$): 157.55 (<u>C</u>=O), 135.23, 128.55, 128.33, 126.55 (Ar<u>C</u>), 66.10 (O-<u>C</u>H_2), 55.36 (N<u>C</u>H), 41.57 (N<u>C</u>H_2), 37.90 (Ph-<u>C</u>H_2), 31.43 (<u>C</u>H_2), 29.16 (<u>C</u>H_2), 29.10 (<u>C</u>H_2), 29.07 (<u>C</u>H_2), 22.24 (<u>C</u>H_2), 28.88 (<u>C</u>H_2), 28.78 (<u>C</u>H_2), 26.90 (<u>C</u>H_2), 26.21 (<u>C</u>H_2), 22.21 (<u>C</u>H_2), 13.65 (<u>C</u>H_3); LRMS (EI): 344 (M^+, 3%), 254 (M^+ - C_7H_7 ,100%); GC t_R 17.11 min.

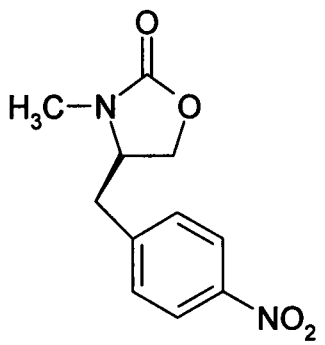
4-*(R)*-(4-nitrobenzyl)-2-oxazolidinone (81)



(R)-4-Benzyl-2-oxazolidinone (1.00g, 5.64mmol) was dissolved in DCM (10mL). Fuming HNO_3 (6mL, 5M) was added drop wise to the reaction mixture and left to stir at -10°C for 3h. The reaction mixture was then quenched in an excess of ice and cold saturated $NaHCO_3$ (50mL). The organic layer was separated and the aqueous layer further extracted with DCM (3 x 25mL). The organic layers were combined and dried over anhydrous $MgSO_4$. Removal of the solvent gave a dark yellow oil which was purified using flash chromatography to give **81** (0.67g, 53%) as a yellow oil. R_f 0.40 (50/50 DCM/EtOAc).

$\nu_{(max)}$(Film)/cm^{-1}: 3298.1 (NH), 1749.8 (C=O), 1518.1, 1346.8 (NO_2); δ_H (400MHz, $CDCl_3$): 8.20 (2H, d, J=9Hz, Ph-H), 7.37 (2H, d, J=9Hz, Ph-H), 5.83 (1H, s, NH), 4.50 (1H, m, OCH_2), 4.13 (2H, m, OCH_2, NCH), 2.94 (2H, d, J=7Hz, Ph-CH_2); δ_C (100MHz, $CDCl_3$): 159.20 (C=O), 147.44 (C-NO_2), 143.35, 129.98, 124.21 (ArC), 69.34 (O-CH_2), 53.19 (NCH), 41.25 (Ph-CH_2); GC t_R. LRMS (EI) 223 (M^+, 100%).

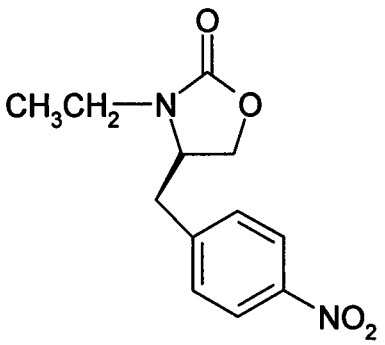
4-*(R)*-3-Methyl-(4-nitrobenzyl)-2-oxazolidinone (82)



Compound **(82)** was synthesised following the same procedure as for compound **(81)**, except that compound **57** (1.00g, 5.23mmol) was used instead of compound *(R)*-4-benzyl-2-oxazolidinone. The organic layer was separated and the aqueous layer further extracted with DCM (3 x 25mL). The organic layers were combined and dried over anhydrous $MgSO_4$. Removal of the solvent gave a yellow oil which was purified using flash chromatography to give **82** (0.49g, 40%) as a yellow oil; R_f 0.58 (80:20 DCM:EtOAc).

$\nu_{(max)}$(Film)/cm^{-1}: 2926.7 (CH-aliphatic), 1738.6 (C=O), 1525.6, 1360.0 (NO_2); δ_H (400MHz, $CDCl_3$): 8.12 (2H, d, J=9Hz, Ph-H), 7.35 (2H, d, J=9Hz, Ph-H), 4.21 (1H, t, J=8Hz, OCH_2), 3.98 (1H, m, NCH), 3.92 (1H, dd, J=6Hz, 9Hz, OCH_2), 3.19 (1H, dd, J=5Hz, 14Hz, Ph-CH_2), 2.85 (4H, m, CH_3, Ph-CH_2); δ_C (100MHz, $CDCl_3$): 157.91 (C=O), 146.90 (C-NO_2), 143.17, 129.91, 123.80 (ArC), 66.01 (O-CH_2), 57.56 (NCH), 37.84 (Ph-CH_2), 29.41 (CH_3); LRMS: (EI) 237 (M^+, 100%); GC t_R 12.02 min

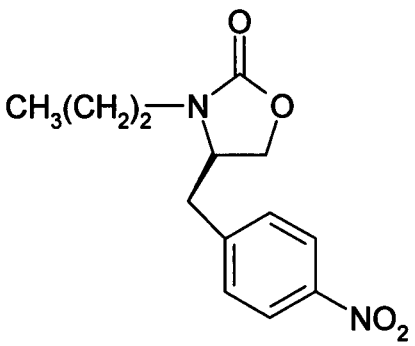
4-*(R)*-3-Ethyl-(4-nitrobenzyl)-2-oxazolidinone (83)



Compound **(83)** was synthesised following the same procedure as for compound **(81)**, except that compound **58** (1.00g, 4.87mmol) was used instead of *(R)*–4-benzyl–2-oxazolidinone. The organic layer was separated and the aqueous layer further extracted with DCM (3 x 25mL). The organic layers were combined and dried over anhydrous $MgSO_4$. Removal of the solvent gave a yellow oil which was purified using flash chromatography to give **83** (0.73g, 60%) as a yellow oil; R_f 0.50 (80/20 DCM/EtOAc).

$\nu_{(max)}$(Film)/cm^{-1}: 2982.9 (CH-aliphatic), 1755.4 (C=O), 1515.1, 1343.2 (NO_2); δ_H (400MHz, $CDCl_3$): 8.11 (2H, d, J=6Hz, Ph-H), 7.33 (2H, d, J=7Hz, Ph-H), 4.07 (2H, m, OCH_2, NCH), 3.91 (1H, m, OCH_2), 3.55 (1H, m, NCH_2), 3.16 (2H; m, NCH_2, Ph-CH_2), 2.83 (1H, dd, J=8Hz, 14Hz, Ph-CH_2), 1.14 (3H, t, J=7Hz, CH_3); δ_C (100MHz, $CDCl_3$): 157.45 (C=O), 146.93 (C-NO_2), 143.18, 129.89, 123.84 (ArC), 66.11 (O-CH_2), 54.80 (NCH), 37.99 (Ph-CH_2), 36.78 (CH_2), 12.51 (CH_3); LRMS (EI) 251 (M^+, 100%); GC t_R 12.30 min.

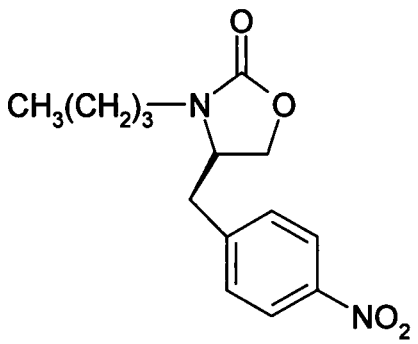
4-*(R)*-3-Propyl-(4-nitrobenzyl)-2-oxazolidinone (84)



Compound **(84)** was synthesised following the same procedure as for compound **(81)**, except that compound **59** (1.00g, 4.56mmol) was used instead of *(R)*-4-benzyl-2-oxazolidinone. The organic layer was separated and the aqueous layer further extracted with DCM (3 x 25mL). The organic layers were combined and dried over anhydrous $MgSO_4$. Removal of the solvent gave a yellow oil which was purified using flash chromatography to give **84** (0.64g, 53%) as a yellow oil; R_f 0.55 (80/20 DCM/EtOAc).

$\nu_{(max)}$(Film)/cm^{-1}: 2968.9 (CH-aliphatic), 1751.7 (C=O), 1518.7, 1348.0 (NO_2); δ_H (400MHz, $CDCl_3$): 8.12 (2H, d, J=9Hz, Ph-H), 7.33 (2H, d, J=9Hz, Ph-H), 4.17 (1H, t, J=8Hz, OCH_2), 4.05 (1H, m, NCH), 3.93 (1H, dd, J=5Hz, 9Hz, OCH_2), 3.42 (1H, m, NCH_2), 3.17 (1H, dd, J=4Hz, 14Hz, Ph-CH_2), 3.00 (1H, m, NCH_2), 2.82 (1H, dd, J=9Hz, 14Hz, Ph-CH_2), 1.54 (2H, m, NCH_2CH_2), 0.88 (3H, t, J=8Hz, CH_3); δ_C (100MHz, $CDCl_3$): 157.68 (C=O), 146.96 (C-NO_2), 143.17, 129.91, 123.87 (ArC), 66.06 (O-CH_2), 55.20 (NCH), 43.59 (NCH_2), 37.90 (Ph-CH_2), 20.55 (CH_2), 10.95 (CH_3); LRMS (EI) 265 (M^+, 100%).

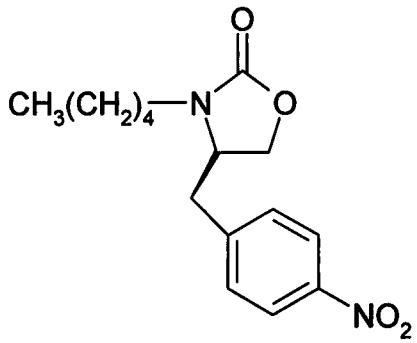
4-*(R)*-3-Butyl-(4-nitrobenzyl)-2-oxazolidinone (85)



Compound **(85)** was synthesised following the same procedure as for compound **(81)**, except that compound **60** (1.00g, 4.29mmol) was used instead of *(R)*-4-benzyl-2-oxazolidinone. The organic layer was separated and the aqueous layer further extracted with DCM (3 x 25mL). The organic layers were combined and dried over anhydrous $MgSO_4$. Removal of the solvent gave a yellow oil which was purified using flash chromatography to give **85** (0.49g, 41%) as a yellow oil; R_f 0.70 (80/20 DCM/EtOAc).

$\nu_{(max)}$(Film)/cm^{-1}: 2932.3 (CH-aliphatic), 1740.0 (C=O), 1518.6, 1346.7 (NO_2); δ_H (400MHz, $CDCl_3$): 8.18 (2H, d, J=9Hz, Ph-H), 7.35 (2H, d, J=9Hz, Ph-H), 4.19 (1H, t, J=8Hz, OCH_2), 4.06 (1H, m, NCH), 3.96 (1H, dd, J=5Hz, 9Hz, OCH_2), 3.52 (1H, m, NCH_2), 3.20 (1H, dd, J=4Hz, 14Hz, Ph-CH_2), 3.04 (1H, m, NCH_2), 2.85 (1H, dd, J=8Hz, 14Hz, Ph-CH_2), 1.54 (2H, m, NCH_2CH_2), 1.32 (2H, m, $N(CH_2)_2CH_2$), 0.93 (3H, t, J=6Hz, CH_3); δ_C (100MHz, $CDCl_3$): 157.68 (C=O), 147.13 (C-NO_2), 143.15, 129.94, 124.03 (ArC), 66.13 (O-CH_2), 55.29 (NCH), 41.80 (Ph-CH_2), 38.07 (CH_2), 29.39 (CH_2), 19.80 (CH_2), 13.61 (CH_3); LRMS (EI) 279 (M^+, 100%); GC t_R 13.50 min.

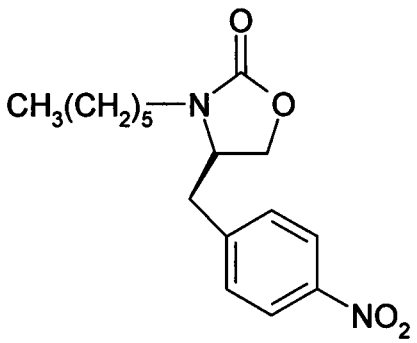
4-*(R)*-3-Pentyl-(4-nitrobenzyl)-2-oxazolidinone (86)



Compound **(86)** was synthesised following the same procedure as for compound **(81)**, except that compound **61** (1.00g, 4.04mmol) was used instead of compound *(R)*-4-benzyl-2-oxazolidinone. The organic layer was separated and the aqueous layer further extracted with DCM (3 x 25mL). The organic layers were combined and dried over anhydrous $MgSO_4$. Removal of the solvent gave a yellow oil which was purified using flash chromatography to give **86** (0.66g, 56%) as a yellow oil; R_f 0.63 [35/35/30 petroleum spirit (40-60°C)/diethylether/DCM].

$\nu_{(max)}$(Film)/cm^{-1}: 2931.9 (CH-aliphatic), 1748.6 (C=O), 1520.0, 1346.9 (NO_2); δ_H (400MHz, $CDCl_3$): 8.17 (2H, d, J=9Hz, Ph-H), 7.34 (2H, d, J=9Hz, Ph-H), 4.17 (1H, t, J=9Hz, OCH_2), 4.05 (1H, m, NCH), 3.95 (1H, dd, J=5Hz, 9Hz, OCH_2), 3.51 (1H, m, NCH_2), 3.19 (1H, dd, J=4Hz, 14Hz, Ph-CH_2), 3.02 (1H, m, NCH_2), 2.84 (1H, dd, J=9Hz, 14Hz, Ph-CH_2), 1.55 (2H, m, NCH_2CH_2), 1.28 (4H, m, $N(CH_2)_2(CH_2)_2$), 0.88 (3H, t, J=7Hz, CH_3); δ_C (100MHz, $CDCl_3$): 157.68 (C=O), 147.19 (C-NO_2), 143.16, 129.94, 124.07 (ArC), 66.14 (O-CH_2), 55.33 (NCH), 42.09 (NCH_2), 38.13 (Ph-CH_2), 28.72 (CH_2), 27.05 (CH_2), 22.24 (CH_2), 13.89 (CH_3); LRMS (EI) 293 (M^+, 100%); GC t_R 14.42 min.

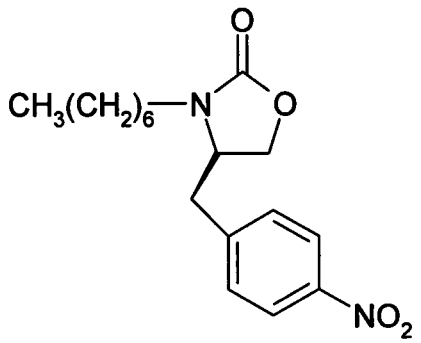
4-*(R)*-3-Hexyl-(4-nitrobenzyl)-2-oxazolidinone (87)



Compound **(87)** was synthesised following the same procedure as for compound **(81)**, except that compound **62** (1.00g, 3.83mmol) was used instead of *(R)*-4-benzyl-2-oxazolidinone. The organic layer was separated and the aqueous layer further extracted with DCM (3 x 25mL). The organic layers were combined and dried over anhydrous $MgSO_4$. Removal of the solvent gave a yellow oil which was purified using flash chromatography to give **87** (0.57g, 49%) as a yellow oil; R_f 0.62 [35/35/30 petroleum spirit (40-60°C)/diethylether/DCM].

$\nu_{(max)}$(Film)/cm^{-1}: 2930.5 (CH-aliphatic), 1750.2 (C=O), 1520.5, 1346.6 (NO_2); δ_H (400MHz, $CDCl_3$): 8.15 (2H, d, J=9Hz, Ph-H), 7.34 (2H, d, J=9Hz, Ph-H), 4.16 (1H, t, J=8Hz, OCH_2), 4.05 (1H, m, NCH), 3.94 (1H, dd, J=5Hz, 9Hz, OCH_2), 3.49 (1H, m, NCH_2), 3.18 (1H, dd, J=4Hz, 13Hz, Ph-CH_2), 3.01 (1H, m, NCH_2), 2.84 (1H, dd, J=8Hz, 14Hz, Ph-CH_2), 1.52 (2H, m, NCH_2CH_2), 1.24 (6H, m, $N(CH_2)_2(CH_2)_3$), 0.84 (3H, t, J=7Hz, CH_3); δ_C (100MHz, $CDCl_3$): 157.65 (C=O), 147.09 (C-NO_2), 143.20, 129.93, 123.99 (ArC), 66.12 (O-CH_2), 55.27 (NCH), 42.07 (NCH_2), 38.07 (Ph-CH_2), 31.28 (CH_2), 27.28 (CH_2), 26.23 (CH_2), 22.41 (CH_2), 13.87 (CH_3); LRMS (EI) 329 (M^++Na, 100%); GC t_R 15.59 min.

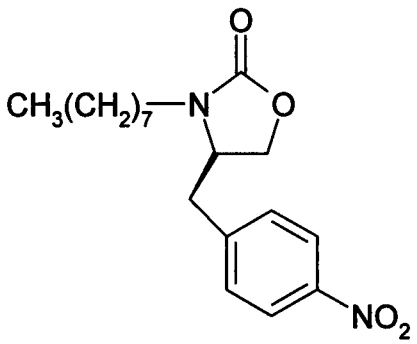
4-*(R)*-3-Heptyl-(4-nitrobenzyl)-2-oxazolidinone (88)



Compound **(88)** was synthesised following the same procedure as for compound **(81)**, except that compound **63** (1.00g, 3.63mmol) was used instead of *(R)*-4-benzyl-2-oxazolidinone. The organic layer was separated and the aqueous layer further extracted with DCM (3 x 25mL). The organic layers were combined and dried over anhydrous $MgSO_4$. Removal of the solvent gave a yellow oil which was purified using flash chromatography to give **88** (0.66g, 57%) as a yellow oil; R_f 0.65 [35/35/30 petroleum spirit (40-60°C)/diethylether/DCM].

$\nu_{(max)}$(Film)/cm^{-1}: 2929.0 (CH-aliphatic), 1750.6 (C=O), 1520.4, 1346.6 (NO_2); δ_H (400MHz, $CDCl_3$): 8.17 (2H, d, J=9Hz, Ph-H), 7.34 (2H, d, J=9Hz, Ph-H), 4.16 (1H, t, J=8Hz, OCH_2), 4.05 (1H, m, NCH), 3.95 (1H, dd, J=5Hz, 9Hz, OCH_2), 3.49 (1H, m, NCH_2), 3.18 (1H, dd, J=4Hz, 14Hz, Ph-CH_2), 3.02 (1H, m, NCH_2), 2.84 (1H, dd, J=8Hz, 14Hz, Ph-CH_2), 1.53 (2H, m, NCH_2CH_2), 1.25 (8H, m, $N(CH_2)_2(CH_2)_4$), 0.85 (3H, t, J=7Hz, CH_3); δ_C (100MHz, $CDCl_3$): 157.66 (C=O), 147.15 (C-NO_2), 143.17, 129.93, 124.04 (ArC), 66.14 (O-CH_2), 55.32 (NCH), 42.11 (NCH_2), 38.13 (Ph-CH_2), 31.61 (CH_2), 28.81 (CH_2), 27.37 (CH_2), 26.56 (CH_2), 22.46 (CH_2), 13.95 (CH_3); LRMS (EI) 321 (M^+, 100%); GC t_R 17.04 min.

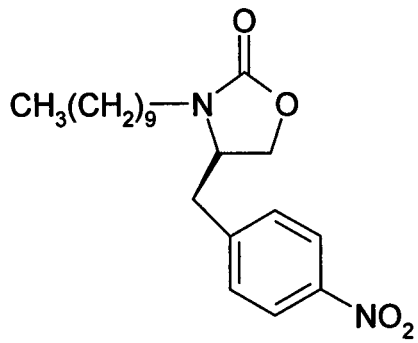
4-*(R)*-3-Octyl-(4-nitrobenzyl)-2-oxazolidinone (89)



Compound **(89)** was synthesised following the same procedure as for compound **(81)**, except that compound **64** (1.00g, 3.45mmol) was used instead of *(R)*-4-benzyl-2-oxazolidinone. The organic layer was separated and the aqueous layer further extracted with DCM (3 x 25mL). The organic layers were combined and dried over anhydrous $MgSO_4$. Removal of the solvent gave a yellow oil which was purified using flash chromatography to give **89** (0.50g, 43%) as a yellow oil; R_f 0.70 [35/35/30 petroleum spirit (40-60°C) diethylether/DCM].

$\nu_{(max)}$(Film)/cm^{-1}: 2928.7 (CH-aliphatic), 1752.2 (C=O), 1521.4, 1346.9 (NO_2); δ_H (400MHz, $CDCl_3$): 8.12 (1H, d, J=9Hz, Ph-H), 7.33 (1H, d, J=9Hz, Ph-H), 4.14 (1H, t, J=8Hz, OCH_2), 4.04 (1H, m, NCH), 3.92 (1H, dd, J=5Hz, 8Hz, OCH_2), 3.46 (1H, m, NCH_2), 3.16 (1H, dd, J=4Hz, 14Hz, Ph-CH_2), 2.99 (1H, m, NCH_2), 2.82 (1H, dd, J=8Hz, 14Hz, Ph-CH_2), 1.50 (2H, m, NCH_2CH_2), 1.21 (10H, m, $N(CH_2)_2(CH_2)_5$), 0.81 (3H, t, J=7Hz, CH_3); δ_C (100MHz, $CDCl_3$): 157.59 (C=O), 146.91 (C-NO_2), 143.21, 129.88, 123.82 (ArC), 66.03 (O-CH_2), 55.13 (NCH), 41.95 (Ph-CH_2), 37.90 (CH_2), 31.50 (CH_2), 28.96 (CH_2), 28.92 (CH_2), 27.20 (CH_2), 26.45 (CH_2), 22.39 (CH_2), 13.85 (CH_3);

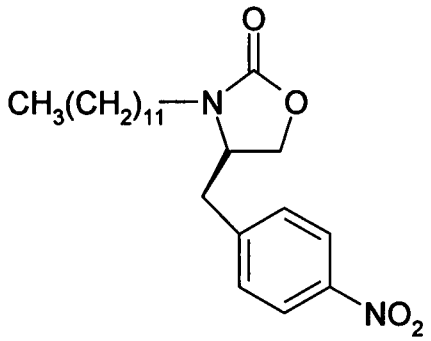
4-*(R)*-3-Decyl-(4-nitrobenzyl)-2-oxazolidinone (90)



Compound **(90)** was synthesised following the same procedure as for compound **(81)**, except that compound **66** (1.00g, 3.15mmol) was used instead of *(R)*-4-benzyl-2-oxazolidinone. The organic layer was separated and the aqueous layer further extracted with DCM (3 x 25mL). The organic layers were combined and dried over anhydrous $MgSO_4$. Removal of the solvent gave a yellow oil which was purified using flash chromatography to give **90** (0.64g, 56%) as a yellow oil; R_f 0.77 [35/35/30 petroleum spirit (40-60°C)/diethylether/DCM].

$\nu_{(max)}$(Film)/cm^{-1}: 2926.5 (CH-aliphatic), 1753.8 (C=O), 1524.1, 1347.0 (NO_2); δ_H (400MHz, $CDCl_3$): 8.20 (2H, d, J=9Hz, Ph-H), 7.34 (2H, d, J=9Hz, Ph-H), 4.17 (1H, t, J=8Hz, OCH_2), 4.04 (1H, m, NCH), 3.96 (1H, dd, J=5Hz, 9Hz, OCH_2), 3.52 (1H, m, NCH_2), 3.19 (1H, dd, J=4Hz, 14Hz, Ph-CH_2), 3.02 (1H, m, NCH_2), 2.84 (1H, dd, J=8Hz, 14Hz, Ph-CH_2), 1.54 (2H, m, NCH_2CH_2), 1.23 (14H, m, $N(CH_2)_2(CH_2)_7$), 0.87 (3H, t, J=7Hz, CH_3); δ_C (100MHz, $CDCl_3$): 157.68 (C=O), 147.27 (C-NO_2), 143.13, 129.93, 124.15 (ArC), 66.17 (O-CH_2), 55.39 (NCH), 42.19 (NCH_2), 38.23 (Ph-CH_2), 31.83 (CH_2), 29.53 (CH_2), 29.49 (CH_2), 29.23 (CH_2), 29.13 (CH_2), 27.44 (CH_2), 26.67 (CH_2), 22.63 (CH_2), 14.08 (CH_3); LRMS (EI) 385 (M^++Na, 100%).

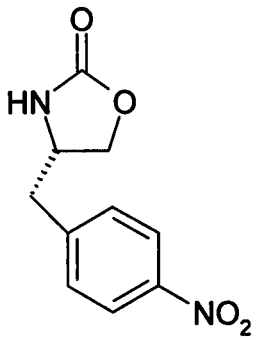
4-*(R)*-3-Dodecyl-(4-nitrobenzyl)-2-oxazolidinone (91)



Compound **(91)** was synthesised following the same procedure as for compound **(81)**, except that **67** (1.00g, 2.89mmol) was used instead of *(R)*-4-benzyl-2-oxazolidinone. The organic layer was separated and the aqueous layer further extracted with DCM (3 x 25mL). The organic layers were combined and dried over anhydrous $MgSO_4$. Removal of the solvent gave a yellow oil which was purified using flash chromatography to give **91** (0.62g, 55%) as a yellow oil; R_f 0.79 [35/35/30 petroleum spirit (40-60°C)/diethylether/DCM].

$\nu_{(max)}$(Film)/cm^{-1}: 2927.7 (CH-aliphatic), 1751.8 (C=O), 1522.1, 1346.8 (NO_2); δ_H (400MHz, $CDCl_3$): 8.20 (2H, d, J=9Hz, Ph-H), 7.34 (2H, d, J=9Hz, Ph-H), 4.17 (1H, t, J=8Hz, OCH_2), 4.04 (1H, m, NCH), 3.96 (1H, dd, J=5Hz, 9Hz, OCH_2), 3.52 (1H, m, NCH_2), 3.19 (1H, dd, J=4Hz, 14Hz, Ph-CH_2), 3.02 (1H, m, NCH_2), 2.84 (1H, dd, J=8Hz, 14Hz, Ph-CH_2), 1.53 (2H, m, NCH_2CH_2), 1.23 (18H, m, $N(CH_2)_2(CH_2)_9$), 0.87 (3H, t, J=7Hz, CH_3); δ_C (100MHz, $CDCl_3$): 157.68 (C=O), 147.29 (C-NO_2), 143.13, 129.94, 124.15 (ArC), 66.17 (O-CH_2), 55.41 (NCH), 42.19 (NCH_2), 38.23 (Ph-CH_2), 31.88 (CH_2), 29.67 (CH_2), 29.60 (CH_2), 29.51 (CH_2), 29.42 (CH_2), 29.32 (CH_2), 29.24 (CH_2), 27.45 (CH_2), 26.69 (CH_2), 22.66 (CH_2), 14.10 (CH_3); LRMS (EI) 413 (M^++Na, 100%)

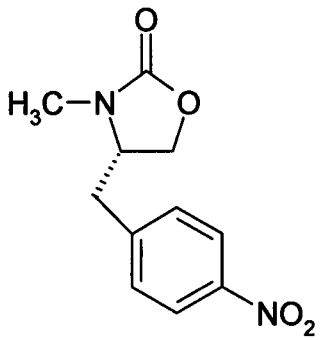
4-*(S)*-(4-nitrobenzyl)-2-oxazolidinone (92)



Compound **(92)** was synthesised following the same procedure as for compound **(81)**, except that compound *(S)*-4-benzyl-2-oxazolidinone (1.00g, 5.64mmol) was used instead of *(R)*-4-benzyl-2-oxazolidinone. The organic layer was separated and the aqueous layer further extracted with DCM (3 x 25mL). The organic layers were combined and dried over anhydrous $MgSO_4$. Removal of the solvent gave a yellow oil which was purified using flash chromatography to give **92** (0.56g, 45%) as a yellow oil; R_f 0.42 (50/50 DCM/EtOAc).

$\nu_{(max)}$(Film)/cm^{-1}: 3290.3 (NH), 1789.1 (C=O), 1519.2, 1359.9 (NO_2); δ_H (400MHz, $CDCl_3$): 8.14 (2H, d, J=9Hz, Ph-H), 7.32 (2H, d, J=9Hz, Ph-H), 6.27 (1H, s, NH), 4.41 (1H, m, OCH_2), 4.08 (2H, m, OCH_2, NCH), 2.94 (2H, m, Ph-CH_2); δ_C (100MHz, $CDCl_3$): 159.40 (C=O), 147.22 (C-NO_2), 143.43, 130.01, 124.10 (ArC), 69.29 (O-CH_2), 53.19 (NCH), 41.12 (Ph-CH_2); LRMS (EI) 223 (M^+, 100%); GC t_R 12.50 min.

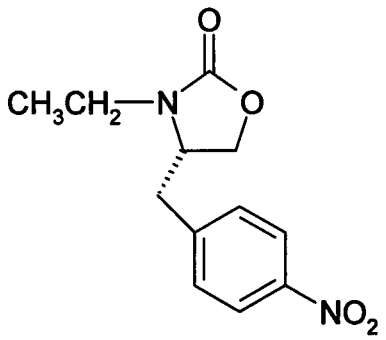
4-*(S)*-3-Methyl-(4-nitrobenzyl)-2-oxazolidinone (93)



Compound **(93)** was synthesised following the same procedure as for compound **(81)**, except that compound **(69)** (1.00g, 5.23mmol) was used instead of *(R)*-4-benzyl-2-oxazolidinone. The organic layer was separated and the aqueous layer further extracted with DCM (3 x 25mL). The organic layers were combined and dried over anhydrous $MgSO_4$. Removal of the solvent gave a yellow oil which was purified using flash chromatography to give **93** (0.57g, 46%) as a yellow oil; R_f 0.44 (70/30 DCM/EtOAc).

$\nu_{(max)}$(Film)/cm^{-1}: 2912.2 (CH-aliphatic), 1751.8 (C=O), 1514.6, 1342.4 (NO_2); δ_H (400MHz, $CDCl_3$): 8.20 (2H, d, J=9Hz, Ph-H), 7.35 (2H, d, J=9Hz, Ph-H), 4.22 (1H, t, J=8Hz, OCH_2), 3.99 (1H, m, NCH), 3.97 (1H, dd, J=8Hz, 14Hz, OCH_2), 3.22 (1H, dd, J=4Hz, 14Hz, Ph-CH_2), 2.90 (4H, m, Ph-CH_2, NCH_3); δ_C (100MHz, $CDCl_3$): 158.04 (C=O), 147.29 (C-NO_2), 143.03, 129.96 124.15 (ArC), 66.16 (O-CH_2), 57.89 (NCH), 38.23 (Ph-CH_2), 29.68 (CH_3); LRMS (EI) 236 (M^+, 100%); GC t_R 12.06 min.

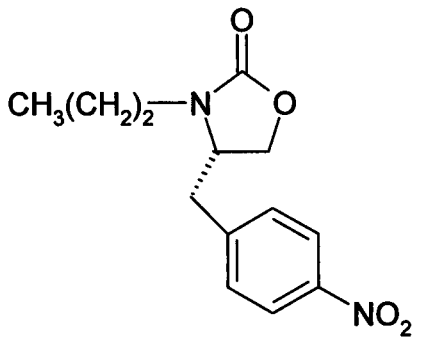
4-*(S)*-3-Ethyl-(4-nitrobenzyl)-2-oxazolidinone (94)



Compound **(94)** was synthesised following the same procedure as for compound **(81)**, except that compound **70** (1.00g, 4.87mmol) was used instead of *(R)*-4-benzyl-2-oxazolidinone. The organic layer was separated and the aqueous layer further extracted with DCM (3 x 25mL). The organic layers were combined and dried over anhydrous $MgSO_4$. Removal of the solvent gave a yellow oil which was purified using flash chromatography to give **94** (0.68g, 53%) as a yellow oil; R_f 0.56 (80/20 DCM/EtOAc).

$\nu_{(max)}$(Film)/cm^{-1}: 2983.0 (CH-aliphatic), 1754.7 (C=O), 1514.7, 1342.7 (NO_2); δ_H (400MHz, $CDCl_3$): 8.12 (2H, d, J=9Hz, Ph-H), 7.34 (2H, d, J=9Hz, Ph-H), 4.17 (1H, t, J=8Hz, OCH_2), 4.09 (1H, m, NC Ph-H), 3.93 (1H, dd, J=5Hz, 8Hz, OCH_2), 3.56 (1H, m, NCH_2), 3.18 (1H, dd, J=4Hz, 14Hz, Ph-CH_2), 3.09 (1H, m, NCH_2), 2.84 (1H, dd, J=8Hz, 14Hz, Ph-CH_2), 1.15 (3H, t, J=7Hz, CH_3); δ_C (100MHz, $CDCl_3$): 157.42 (C=O), 146.92 (C-NO_2), 143.19, 129.89, 123.83 (ArC), 66.10 (O-CH_2), 54.80 (NCH), 37.99 (Ph-CH_2), 36.76 (CH_2), 12.51 (CH_3); LRMS (EI) 251 (M^+, 100%); GC t_R 12.25 min.

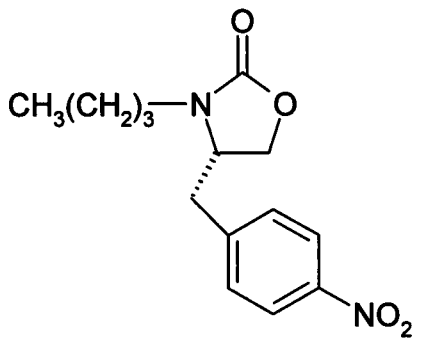
4-*(S)*-3-Propyl-(4-nitrobenzyl)-2-oxazolidinone (95)



Compound **(95)** was synthesised following the same procedure as for compound **(81)**, except that compound **71** (1.00g, 4.56mmol) was used instead of *(R)*-4-benzyl-2-oxazolidinone. The organic layer was separated and the aqueous layer further extracted with DCM (3 x 25mL). The organic layers were combined and dried over anhydrous $MgSO_4$. Removal of the solvent gave a yellow oil which was purified using flash chromatography to give **95** (0.62g, 51%) as a yellow oil; R_f 0.64 (80/20 DCM/EtOAc).

$\nu_{(max)}$(Film)/cm^{-1}: 2934.4 (CH-aliphatic), 1747.4 (C=O), 1518.9, 1346.0 (NO_2); δ_H (400MHz, $CDCl_3$): 8.07 (2H, d, J=9Hz, Ph-H), 7.32 (2H, d, J=9Hz, Ph-H), 4.12 (1H, t, J=8Hz, OCH_2), 4.04 (1H, m, NCH), 3.91 (1H, dd, J=4Hz, 8Hz, OCH_2), 3.99 (1H, m, NCH_2), 3.15 (1H, dd, J=4Hz, 13Hz, Ph-CH_2), 2.98 (1H, m, NCH_2), 2.81 (2H, dd, J=8Hz, 17Hz, Ph-CH_2), 1.48 (2H, m, NCH_2CH_2), 0.84 (3H, t, J=7Hz, CH_3); δ_C (100MHz, $CDCl_3$): 157.55 (C=O), 146.71 (C-NO_2), 143.19, 129.83, 123.62 (ArC), 65.92 (O-CH_2), 54.99 (NCH), 43.39 (Ph-CH_2), 37.66 (CH_2), 20.35 (CH_2), 10.77 (CH_3); LRMS (EI) 265 (M^+, 100%); GC t_R 12.83 min.

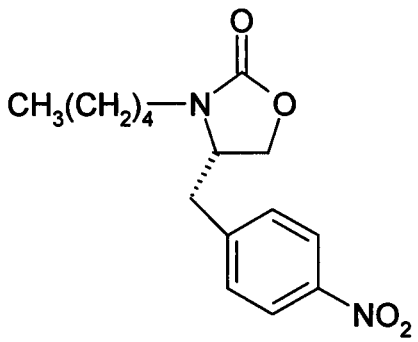
4-*(S)*-3-Butyl-(4-nitrobenzyl)-2-oxazolidinone (96)



Compound **(96)** was synthesised following the same procedure as for compound **(81)**, except that compound **72** (1.00g, 4.29mmol) was used instead of *(R)*-4-benzyl-2-oxazolidinone. The organic layer was separated and the aqueous layer further extracted with DCM (3 x 25mL). The organic layers were combined and dried over anhydrous $MgSO_4$. Removal of the solvent gave a yellow oil which was purified using flash chromatography to give **96** (0.67g, 56%) as a yellow oil; R_f 0.76 (80/20 DCM/EtOAc).

$\nu_{(max)}$(Film)/cm^{-1}: 2960.3 (CH-aliphatic), 1747.8 (C=O), 1519.5, 1346.7 (NO_2); δ_H (400MHz, $CDCl_3$): 8.17 (2H, d, J=9Hz, Ph-H), 7.34 (2H, d, J=9Hz, Ph-H), 4.18 (1H, t, J=8Hz, OCH_2), 4.06 (1H, m, NCH), 3.95 (1H, dd, J=5Hz, 8Hz, OCH_2), 3.55 (1H, m, NCH_2), 3.19 (1H, dd, J=4Hz, 13Hz, Ph-CH_2), 3.03 (1H, m, NCH_2), 2.84 (1H, dd, J=8Hz, 13Hz, Ph-CH_2), 1.52 (2H, m, NCH_2CH_2), 1.31 (2H, m, $N(CH_2)_2CH_2$), 0.92 (3H, t, J=7Hz, CH_3); δ_C (100MHz, $CDCl_3$): 157.68 (C=O), 147.15 (C-NO_2), 143.15, 129.93, 124.04 (ArC), 66.13 (O-CH_2), 55.30 (NCH), 41.81 (Ph-CH_2), 38.08 (CH_2), 29.41 (CH_2), 19.80 (CH_2), 13.62 (CH_3); LRMS (EI) 279 (M^+, 100%); GC t_R 13.40 min.

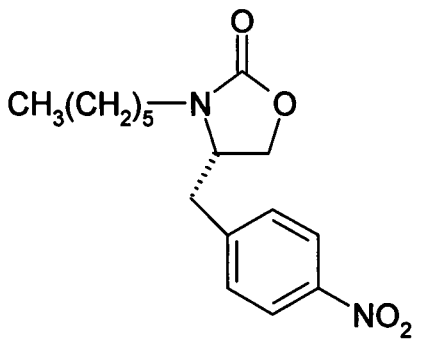
4-*(S)*-3-Pentyl-(4-nitrobenzyl)-2-oxazolidinone (97)



Compound **(97)** was synthesised following the same procedure as for compound **(81)**, except that compound **73** (1.00g, 4.04mmol) was used instead of *(R)*-4-benzyl-2-oxazolidinone. The organic layer was separated and the aqueous layer further extracted with DCM (3 x 25mL). The organic layers were combined and dried over anhydrous $MgSO_4$. Removal of the solvent gave a yellow oil which was purified using flash chromatography to give **97** (0.63g, 53%) as a yellow oil; R_f 0.43 [35/35/30 petroleum spirit (40-60°C)/diethylether/DCM].

$\nu_{(max)}$(Film)/cm^{-1}: 2934.7 (CH-aliphatic), 1749.3 (C=O), 1519.6, 1347.1 (NO_2); δ_H (400MHz, $CDCl_3$): 8.16 (2H, d, J=9Hz, Ph-H), 7.34 (2H, d, J=9Hz, Ph-H), 4.19 (1H, t, J=8Hz, OCH_2), 4.05 (1H, m, NCH), 3.95 (1H, dd, J=5Hz, 9Hz, OCH_2), 3.52 (1H, m, NCH_2), 3.18 (1H, dd, J=4Hz, 13Hz, OCH), 3.02 (1H, m, NCH_2), 2.84 (1H, dd, J=8Hz, 13Hz, Ph-CH_2), 1.54 (2H, m, NCH_2CH_2), 1.27 (4H, m, $N(CH_2)_2(CH_2)_2$), 0.87 (3H, t, J=7Hz, CH_3); δ_C (100MHz, $CDCl_3$): 157.66 (C=O), 147.12 (C-NO_2), 143.17, 129.93, 124.02 (ArC), 66.12 (O-CH_2), 55.29 (NCH), 42.05 (Ph-CH_2), 38.08 (CH_2), 28.68 (CH_2), 27.02 (CH_2), 22.20 (CH_2), 13.86 (CH_3); LRMS (EI) 293 (M^+, 100%); GC t_R 14.47 min.

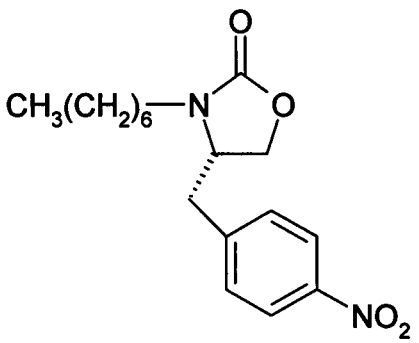
4-*(S)*-3-Hexyl-(4-nitrobenzyl)-2-oxazolidinone (98)



Compound **(98)** was synthesised following the same procedure as for compound **(81)**, except that compound **74** (1.00g, 3.83mmol) were used instead of *(R)*-4-benzyl-2-oxazolidinone. The organic layer was separated and the aqueous layer further extracted with DCM (3 x 25mL). The organic layers were combined and dried over anhydrous $MgSO_4$. Removal of the solvent gave a yellow oil which was purified using flash chromatography to give **98** (0.70g, 60%) as a yellow oil; R_f 0.51 [35/35/30 petroleum spirit (40-60°C)/diethylether/DCM].

$\nu_{(max)}$(Film)/cm^{-1}: 2966.7 (CH-aliphatic), 1749.3 (C=O), 1519.6, 1347.1 (NO_2); δ_H (400MHz, $CDCl_3$): 8.20 (2H, d, J=9Hz, Ph-H), 7.35 (2H, d, J=9Hz, Ph-H), 4.21 (1H, t, J=8Hz, OCH_2), 4.06 (1H, m, NCH), 3.97 (1H, dd, J=5Hz, 9Hz, OCH_2), 3.53 (1H, m, NCH_2), 3.20 (1H, dd, J=4Hz, 13Hz, Ph-CH_2), 3.04 (1H, m, NCH_2), 2.85 (2H, dd, J=8Hz, 13Hz, Ph-CH_2), 1.55 (2H, m, NCH_2CH_2), 1.28 (6H, m, $N(CH_2)_2(CH_2)_3$), 0.89 (3H, t, J=7Hz, CH_3); δ_C (100MHz, $CDCl_3$): 157.69 (C=O), 147.27 (C-NO_2), 143.13, 129.94, 124.13 (ArC), 66.17 (O-CH_2), 55.38 (NCH), 42.18 (Ph-CH_2), 38.23 (CH_2), 31.38 (CH_2), 27.39 (CH_2), 26.33 (CH_2), 22.50 (CH_2), 13.95 (CH_3);. LRMS (EI) 329 (M^++Na, 100%).

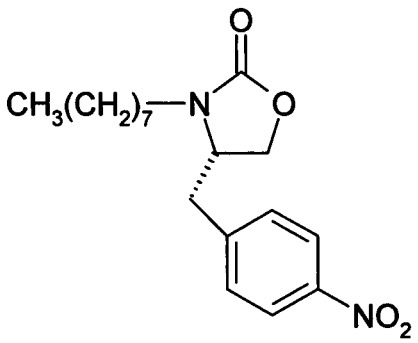
4-*(S)*-3-Heptyl-(4-nitrobenzyl)-2-oxazolidinone (99)



Compound **(99)** was synthesised following the same procedure as for compound **(81)**, except that compound **75** (1.00g, 3.63mmol) was used instead of *(R)*-4-benzyl-2-oxazolidinone. The organic layer was separated and the aqueous layer further extracted with DCM (3 x 25mL). The organic layers were combined and dried over anhydrous $MgSO_4$. Removal of the solvent gave a yellow oil which was purified using flash chromatography to give **99** (63g, 54%) as a yellow oil; R_f 0.61 [35/35/30 petroleum spirit (40-60°C)/diethylether/DCM].

$\nu_{(max)}$(Film)/cm^{-1}: 2931.6 (CH-aliphatic), 1751.5 (C=O), 1521.4, 1347.0 (NO_2); δ_H (400MHz, $CDCl_3$): 8.19 (2H, d, J=9Hz, Ph-H), 7.34 (2H, d, J=9Hz, Ph-H), 4.19 (1H, t, J=8Hz, OCH_2), 4.05 (1H, dd, J=5Hz, 9Hz, NCH), 3.96 (1H, m, OCH_2), 3.50 (1H, m, NCH_2), 3.19 (1H, dd, J=4Hz, 13Hz, Ph-CH_2), 3.02 (1H, m, NCH_2), 2.84 (2H, dd, J=8Hz, 13Hz, Ph-CH_2), 1.54 (2H, m, NCH_2CH_2), 1.27 (8H, m, $N(CH_2)_2(CH_2)_4$), 0.87 (3H, t, J=7Hz, CH_3); δ_C (100MHz, $CDCl_3$): 157.68 (C=O), 147.25 (C-NO_2), 143.15, 129.94, 124.12 (ArC), 66.17 (O-CH_2), 55.38 (NCH), 42.17 (Ph-CH_2), 38.21 (CH_2), 31.66 (CH_2), 28.87 (CH_2), 27.42 (CH_2), 26.61 (CH_2), 22.51 (CH_2), 14.01 (CH_3); LRMS (EI) 321 (M^+, 100%); GC t_R 16.87 min.

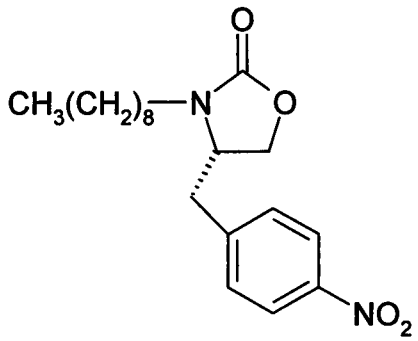
4-*(S)*-3-Octyl-(4-nitrobenzyl)-2-oxazolidinone (100)



Compound **(100)** was synthesised following the same procedure as for compound **(81)**, except that compound **76** (1.00g, 3.45mmol) was used instead of *(R)*-4-benzyl-2-oxazolidinone. The organic layer was separated and the aqueous layer further extracted with DCM (3 x 25mL). The organic layers were combined and dried over anhydrous $MgSO_4$. Removal of the solvent gave a yellow oil which was purified using flash chromatography to give **100** (0.55g, 48%) as a yellow oil; R_f 0.72 [35/35/30 petroleum spirit (40-60°C)/diethylether/DCM].

$\nu_{(max)}$(Film)/cm^{-1}: 2927.7 (CH-aliphatic), 1751.9 (C=O), 1520.9, 1346.6 (NO_2); δ_H (400MHz, $CDCl_3$): 8.13 (1H, d, J=9Hz, Ph-H), 7.35 (1H, d, J=9Hz, Ph-H), 4.16 (1H, t, J=8Hz, OCH_2), 4.07 (1H, m, NCH), 3.94 (1H, dd, J=5Hz, 8Hz, OCH_2), 3.46 (1H, m, NCH_2), 3.18 (1H, dd, J=4Hz, 14Hz, Ph-CH_2), 3.01 (1H, m, NCH_2), 2.85 (1H, dd, J=8Hz, 14Hz, Ph-CH_2), 1.52 (2H, m, NCH_2CH_2), 1.23 (10H, m, $N(CH_2)_2(CH_2)_5$), 0.81 (3H, t, J=7Hz, CH_3); δ_C (100MHz, $CDCl_3$): 157.55 (C=O), 146.92 (C-NO_2), 143.24, 129.97, 123.77 (ArC), 66.03 (O-CH_2), 55.14 (NCH), 41.96 (Ph-CH_2), 37.90 (CH_2), 31.47 (CH_2), 28.93 (CH_2), 28.90 (CH_2), 27.18 (CH_2), 26.43 (CH_2), 22.34 (CH_2), 13.80 (CH_3); LRMS (EI) 357 (M^++Na, 100%).

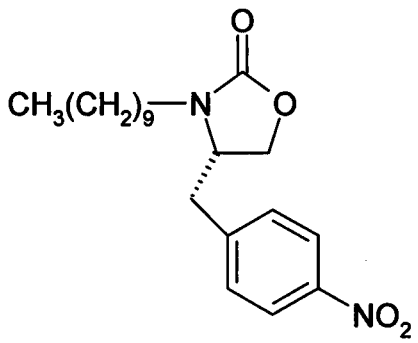
4-*(S)*-3-Nonyl-(4-nitrobenzyl)-2-oxazolidinone (101)



Compound **(101)** was synthesised following the same procedure as for compound **(81)**, except that compound **77** (1.00g, 3.30mmol) was used instead of *(R)*-4-benzyl-2-oxazolidinone. The organic layer was separated and the aqueous layer further extracted with DCM (3 x 25mL). The organic layers were combined and dried over anhydrous $MgSO_4$. Removal of the solvent gave a yellow oil which was purified using flash chromatography to give **101** (0.52g, 45%) as a yellow oil; R_f 0.77 [35/35/30 petroleum spirit (40-60°C)/diethylether/DCM].

$\nu_{(max)}$ (Film)/cm^{-1}: 2927.0 (CH-aliphatic), 1751.9 (C=O), 1521.3, 1346.6 (NO_2); δ_H (400MHz, $CDCl_3$): 8.16 (2H, d, J=8Hz, Ph-H), 7.34 (2H, d, J=8Hz, Ph-H), 4.16 (1H, t, J=8Hz, OCH_2), 4.05 (1H, m, NCH), 3.95 (1H, dd, J=5Hz, 8Hz, OCH_2), 3.48 (1H, m, NCH_2), 3.18 (1H, dd, J=4Hz, 14Hz, Ph-CH_2), 3.01 (1H, m, NCH_2), 2.84 (1H, dd, J=8Hz, 14Hz, Ph-CH_2), 1.53 (2H, m, NCH_2CH_2), 1.22 (12H, m, $N(CH_2)_2(CH_2)_6$), 0.83 (3H, t, J=7Hz, CH_3); δ_C (100MHz, $CDCl_3$): 157.66 (C=O), 147.17 (C-NO_2), 143.19, 129.93, 124.02 (ArC), 66.14 (O-CH_2), 55.33 (NCH), 42.13 (Ph-CH_2), 38.13 (CH_2), 31.72 (CH_2), 29.37 (CH_2), 29.15 (CH_2), 29.10 (CH_2), 27.37 (CH_2), 26.60 (CH_2), 22.53 (CH_2), 13.98 (CH_3); LRMS (EI) 371 (M^++Na, 100%).

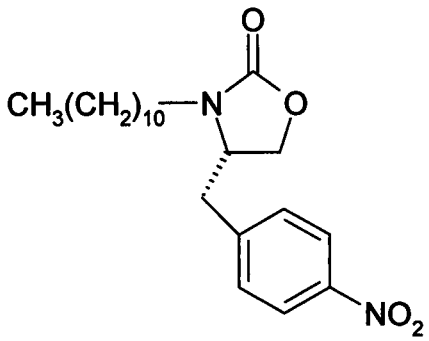
4-*(S)*-3-Decyl-(4-nitrobenzyl)-2-oxazolidinone (102)



Compound **(102)** was synthesised following the same procedure as for compound **(81)**, except that compound **78** (1.00g, 3.15mmol) was used instead of *(R)*-4-benzyl-2-oxazolidinone. The organic layer was separated and the aqueous layer further extracted with DCM (3 x 25mL). The organic layers were combined and dried over anhydrous $MgSO_4$. Removal of the solvent gave a yellow oil which was purified using flash chromatography to give **102** (0.59g, 52%) as a yellow oil; R_f 0.79 [35/35/30 petroleum spirit (40-60°C)/diethylether/DCM].

$\nu_{(max)}$(Film)/cm^{-1}: 2927.6 (CH-aliphatic), 1752.2 (C=O), 1522.0, 1346.9 (NO_2); δ_H (400MHz, $CDCl_3$): 8.22 (2H, d, J=9Hz, Ph-H), 7.36 (2H, d, J=9Hz, Ph-H), 4.21 (1H, t, J=9Hz, OCH_2), 4.06 (1H, m, NCH), 3.98 (1H, dd, J=5Hz, 9Hz, OCH_2), 3.54 (1H, m, NCH_2), 3.21 (1H, dd, J=4Hz, 13Hz, Ph-CH_2), 3.04 (1H, m, NCH_2), 2.86 (1H, dd, J=8Hz, 13Hz, Ph-CH_2), 1.58 (2H, m, NCH_2CH_2), 1.25 (14H, m, $N(CH_2)_2(CH_2)_7$), 0.89 (3H, t, J=7Hz, CH_3); δ_C (100MHz, $CDCl_3$): 155.63 (C=O), 143.13 (C-NO_2), 129.93, 124.15, 113.07, (ArC), 66.17 (O-CH_2), 55.41 (NCH), 42.19 (Ph-CH_2), 38.24 (CH_2), 31.85 (CH_2), 29.49 (CH_2), 29.41 (CH_2), 29.25 (CH_2), 29.13 (CH_2), 27.45 (CH_2), 26.68 (CH_2), 22.65 (CH_2), 14.08 (CH_3); LRMS (EI) 385 (M^++Na, 100%).

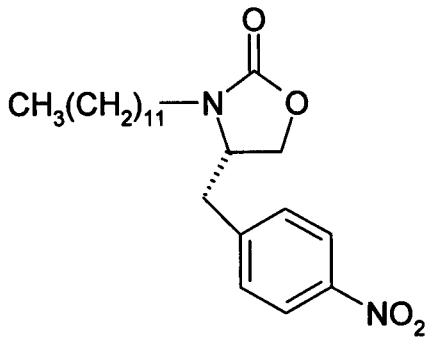
4-*(S)*-3-Undecyl-(4-nitrobenzyl)-2-oxazolidinone (103)



Compound **(103)** was synthesised following the same procedure as for compound **(81)**, except that compound **79** (1.00g, 3.02mmol) was used instead of *(R)*-4-benzyl-2-oxazolidinone. The organic layer was separated and the aqueous layer further extracted with DCM (3 x 25mL). The organic layers were combined and dried over anhydrous $MgSO_4$. Removal of the solvent gave a yellow oil which was purified using flash chromatography to give **103** (0.53g, 47%) as a yellow oil; R_f 0.80 [35/35/30 petroleum spirit (40-60°C)/diethylether/DCM].

$\nu_{(max)}$(Film)/cm^{-1}: 2926.9 (CH-aliphatic), 1752.6 (C=O), 1523.5, 1347.0 (NO_2); δ_H (400MHz, $CDCl_3$): 8.20 (2H, d, J=9Hz, Ph-H), 7.34 (2H, d, J=9Hz, Ph-H), 4.20 (1H, t, J=9Hz, OCH_2), 4.04 (1H, m, NCH), 3.96 (1H, dd, J=5Hz, 9Hz, OCH_2), 3.53 (1H, m, NCH_2), 3.19 (1H, dd, J=4Hz, 13Hz, Ph-CH_2), 3.03 (1H, m, NCH_2), 2.84 (1H, dd, J=8Hz, 13Hz, Ph-CH_2), 1.55 (2H, m, NCH_2CH_2), 1.23 (16H, m, $N(CH_2)_2(CH_2)_8$), 0.87 (3H, t, J=7Hz, CH_3); δ_C (100MHz, $CDCl_3$): 157.68 (C=O), 143.12 (C-NO_2), 140.99, 129.93, 124.16 (ArC), 66.17 (O-CH_2), 61.85 (NCH), 42.19 (Ph-CH_2), 38.24 (CH_2), 31.88 (CH_2), 29.54 (CH_2), 29.28 (CH_2), 29.23 (CH_2), 27.45 (CH_2), 26.68 (CH_2), 22.66 (CH_2), 22.65 (CH_2), 14.10 (CH_3); LRMS (EI) 399 (M^++Na, 100%).

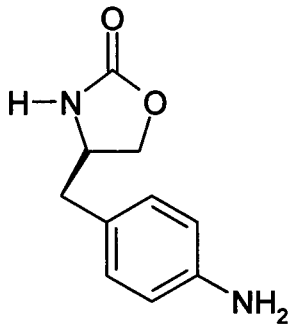
4-*(S)*-3-Dodecyl-(4-nitrobenzyl)-2-oxazolidinone (104)



Compound **(104)** was synthesised following the same procedure as for compound **(81)**, except that compound **80** (1.00g, 2.89mmol) was used instead of *(R)*-4-benzyl-2-oxazolidinone. The organic layer was separated and the aqueous layer further extracted with DCM (3 x 25mL). The organic layers were combined and dried over anhydrous $MgSO_4$. Removal of the solvent gave a yellow oil which was purified using flash chromatography to give **104** (0.58g, 51%) as a yellow oil; R_f 0.84 [35/35/30 petroleum spirit (40-60°C)/diethylether/DCM].

$\nu_{(max)}$(Film)/cm^{-1}: 2927.2 (CH-aliphatic), 1752.5 (C=O), 1523.4, 1346.9 (NO_2); δ_H (400MHz, $CDCl_3$): 8.20 (2H, d, J=9Hz, Ph-H), 7.34 (2H, d, J=9Hz, Ph-H), 4.19 (1H, t, J=9Hz, OCH_2), 4.04 (1H, m, NCH), 3.96 (1H, dd, J=5Hz, 9Hz, OCH_2), 3.52 (1H, m, NCH_2), 3.19 (1H, dd, J=4Hz, 13Hz, Ph-CH_2), 3.02 (1H, m, NCH_2), 2.84 (1H, dd, J=8Hz, 13Hz, Ph-CH_2), 1.58 (2H, m, NCH_2CH_2), 1.23 (18H, m, $N(CH_2)_2(CH_2)_9$), 0.87 (3H, t, J=7Hz, CH_3); δ_C (100MHz, $CDCl_3$): 147.28 (C=O), 143.13 (C-NO_2), 129.93, 124.15, 124.16 (ArC), 66.17 (O-CH_2), 55.41 (NCH), 42.19 (Ph-CH_2), 38.23 (CH_2), 31.89 (CH_2), 29.59 (CH_2), 29.51 (CH_2), 29.32 (CH_2), 29.24 (CH_2), 27.45 (CH_2), 26.68 (CH_2), 22.66 (CH_2), 14.09 (CH_3); LRMS (EI) 413 (M^++Na, 100%).

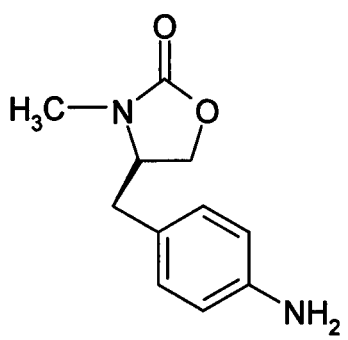
4-*(R)*-(4-Amino-benzyl)-oxazolidin-2-one (105)



Compound **(81)** (0.50g, 2.25mmol) was dissolved in ethanol (20mL) and placed in a hydrogenator. Palladium charcoal (0.1g) was added and left to shake for 4h under pressure at room temperature (RT). The reaction mixture was removed and the catalyst filtered through celite to give **105** (0.38g, 88%) as a dark yellow oil; R_f 0.35 (80:20 DCM:EtOAc).

$\nu_{(max)}$(Film)/cm^{-1}: 3350.9 (NH_2), 2915.4 (CH-aliphatic), 1744.3 (C=O); δ_H (400MHz, $CDCl_3$): 6.86 (2H, d, J=8Hz, Ph-H), 6.55 (2H, d, J=8Hz, Ph-H), 6.16 (1H, s, NH), 4.29 (1H, t, J=9Hz, OCH_2), 4.01 (1H, dd, J=5Hz, 9Hz, OCH_2), 3.91 (1H, m, NCH), 3.65 (2H, s, NH_2), 2.64 (2H, m, Ph-CH_2); δ_C (100MHz, $CDCl_3$): 159.65 (C=O), 145.37 (C-NH_2), 129.76, 125.40, 115.34 (ArC), 69.39 (O-CH_2), 53.82 (NCH), 40.27 (Ph-CH_2); LRMS (EI): 193 (M^+ , 3%), 106 (M^+ -$C_3NH_4O_2$,100%); GC t_R 11.43 min.

4-*(R)*-3-Methyl-(4-aminobenzyl)-2-oxazolidinone (106)

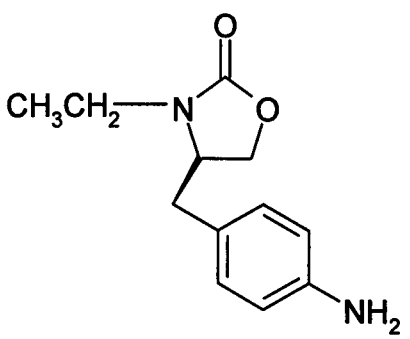


Compound **(106)** was synthesised following the same procedure as for compound **(105)**, except that compound **82** (0.50g, 2.12mmol) were used instead of compound **(81)**. The reaction mixture was removed from the

hydrogenator and the catalyst was filtered through celite to give **106** (0.41g, 94%) as a yellow oil; R_f 0.30 (80/20 DCM/EtOAc).

$\nu_{(max)}$(Film)/cm^{-1}: 3358.2 (NH_2), 2924.7 (CH-aliphatic), 1740.0 (C=O); δ_H (400MHz, $CDCl_3$): 6.87 (2H, d, J=9Hz, Ph-H), 6.58 (2H, d, J=8Hz, Ph-H), 4.13 (1H, t, J=9Hz, OCH_2), 3.92 (1H, dd, J=6Hz, 9Hz, OCH_2), 3.77 (1H, m, NCH), 3.60 (2H, s, NH_2), 2.96 (1H, dd, J=4Hz, 14Hz, Ph-CH_2), 2.82 (4H, m, NCH_2, CH_3), 2.54 (1H, dd, J=9Hz, 14Hz, Ph-CH_2); δ_C (100MHz, $CDCl_3$): 158.54 (C=O), 145.45 (C-NH_2), 129.89, 124.90, 115.48 (ArC), 66.68 (O-CH_2), 58.54 (NCH), 37.50 (Ph-CH_2), 29.49 (CH_3); LRMS (EI): 206 (M^+, 12%), 106 (M^+ - $C_4NH_5O_2$,100%); GC t_R 12.17 min.

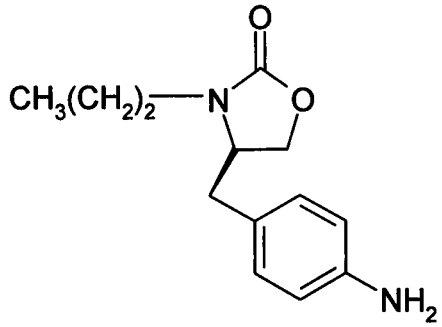
4-*(R)*-3-Ethyl-(4-aminobenzyl)-2-oxazolidinone (107)



Compound **(107)** was synthesised following the same procedure as for compound **(105)**, except that compound **83** (0.50g, 2.00mmol) was used instead of compound **(81)**. The reaction mixture was removed from the hydrogenator and the catalyst was filtered through celite to give **107** (0.40g, 91%) as a yellow oil; R_f 0.33 (80/20 DCM/EtOAc).

$\nu_{(max)}$(Film)/cm^{-1}: 3356.7 (NH_2), 2934.1 (CH-aliphatic), 1739.3 (C=O); δ_H (400MHz, $CDCl_3$): 6.84 (2H, d, J=8Hz, Ph-H), 6.56 (2H, d, J=8Hz, Ph-H), 4.06 (1H, t, J=10Hz, OCH_2), 3.88 (1H, m, OCH_2), 3.59 (2H, s, NH_2), 3.45 (1H, m, NCH_2), 3.06 (1H, m, NCH_2), 2.91 (1H, dd, J=4Hz, 14Hz, Ph-CH_2), 2.47 (1H, dd, J=4Hz, 14Hz, Ph-CH_2), 1.10 (3H, t, J=7Hz, CH_3); δ_C (100MHz, $CDCl_3$): 157.74 (C=O), 145.32 (C-NH_2), 129.46, 124.37, 115.11 (ArC), 66.44 (O-CH_2), 55.35 (NCH), 37.16 (Ph-CH_2), 36.46 (CH_2), 12.36 (CH_3); LRMS (EI): 220 (M^+, 3%), 106 (M^+ - $C_5NH_6O_2$,100%); GC t_R 11.30 min.

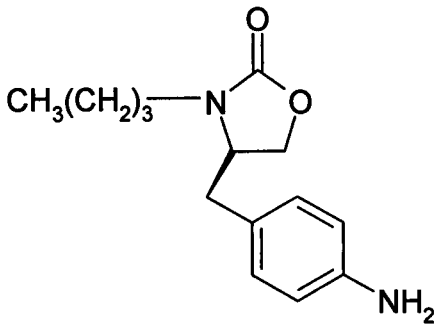
4-*(R)*-3-Propyl-(4-aminobenzyl)-2-oxazolidinone (108)



Compound **(108)** was synthesised following the same procedure as for compound **(105)**, except that compound **84** (0.50g, 1.89mmol) was used instead of compound **(81)**. The reaction mixture was removed from the hydrogenator and the catalyst was filtered through celite to give **108** (0.39g, 88%) as a yellow oil; R_f 0.35 (80/20 DCM/EtOAc).

$\nu_{(max)}$(Film)/cm^{-1}: 3358.3 (NH_2), 2965.6 (CH-aliphatic), 1743.6 (C=O); δ_H (400MHz, $CDCl_3$): 6.90 (2H, d, J=8Hz, Ph-H), 6.61 (2H, d, J=8Hz, Ph-H), 4.10 (1H, t, J=8Hz, OCH_2), 3.97 (1H, m, OCH_2), 3.88 (1H, m, NCH), 3.63 (2H, s, NH_2), 3.42 (1H, m, NCH_2), 3.03 (1H, m, NCH_2), 2.98 (1H, dd, J=4Hz, 14Hz, Ph-CH_2), 2.53 (1H, dd, J=9Hz, 14Hz, Ph-CH_2), 1.56 (2H, m, NCH_2CH_2), 0.91 (3H, t, J=7Hz, CH_3); δ_C (100MHz, $CDCl_3$): 160.18, (C=O), 147.44, (C-NH_2), 131.75, 126.84, 117.37 (ArC), 66.63 (O-CH_2), 58.11 (NCH), 45.56 (Ph-CH_2), 39.37 (CH_2), 22.60 (CH_2), 13.07 (CH_3); LRMS (EI): 234 (M^+, 3%), (M^+, - $C_5NH_6O_2$, 100%); GC t_R 11.76 min.

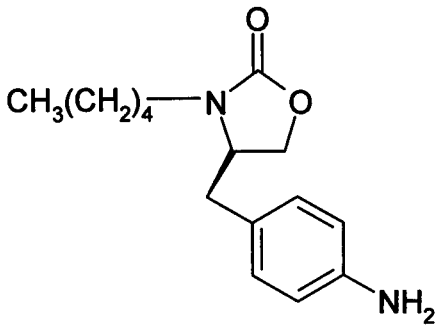
4-*(R)*-3-Butyl-(4-aminobenzyl)-2-oxazolidinone (109)



Compound **(109)** was synthesised following the same procedure as for compound **(105)**, except that compound **85** (0.50g, 1.80mmol) was used instead of compound **(81)**. The reaction mixture was removed from the hydrogenator and the catalyst was filtered through celite to give **109** (0.40g, 90%) as a yellow oil; R_f 0.35 (80/20 DCM/EtOAc).

$\nu_{(max)}$(Film)/cm^{-1}: 3358.4 (NH_2), 2930.4 (CH-aliphatic), 1741.5 (C=O); δ_H (400MHz, $CDCl_3$): 6.86 (2H, d, J=8Hz, Ph-H), 6.57 (2H, d, J=8Hz, Ph-H), 4.06 (1H, m, J=8Hz, OCH_2), 3.91 (1H, dd, J=6Hz, 8Hz, OCH_2), 3.86 (1H, m, NCH), 3.60 (2H, s, NH_2), 3.43 (1H, m, NCH_2), 3.00 (1H, m, NCH_2), 2.94 (1H, dd, J=4Hz, 14Hz, Ph-CH_2), 2.49 (2H, dd, J=9Hz, 14Hz, Ph-CH_2), 1.48 (2H, m, NCH_2CH_2), 1.28 (2H, m, $N(CH_2)_2CH_2$), 0.89 (3H, t, J=7Hz, CH_3); δ_C (100MHz, $CDCl_3$): 158.14 (C=O), 145.45 (C-NH_2), 129.80, 124.95, 115.42 (ArC), 66.66 (O-CH_2), 56.06 (NCH), 41.70 (Ph-CH_2), 37.45 (CH_2), 29.42 (CH_2), 19.87 (CH_2), 13.66 (CH_3); LRMS (EI): 249 (M^+, 3%), 106 (M^+ - $C_7NH_{12}O_2$,100%); GC t_R 12.27 min.

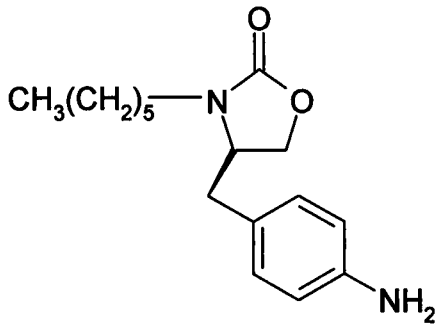
4-*(R)*-3-Pentyl-(4-aminobenzyl)-2-oxazolidinone (110)



Compound **(110)** was synthesised following the same procedure as for compound **(105)**, except that compound **86** (0.50g, 1.71mmol) was used instead of compound **(81)**. The reaction mixture was removed from the hydrogenator and the catalyst was filtered through celite to give **110** (0.41g, 91%) as a yellow oil; R_f 0.40 (80/20 DCM/EtOAc).

$\nu_{(max)}$(Film)/cm^{-1}: 3358.9 (NH_2), 2929.7 (CH-aliphatic), 1743.1 (C=O); δ_H (400MHz, $CDCl_3$): 6.87 (2H, d, J=8Hz, Ph-H), 6.58 (2H, d, J=8Hz, Ph-H), 4.09 (1H, t, J=8Hz, OCH_2), 3.90 (1H, dd, J=6Hz, 8Hz, OCH_2), 3.87 (1H, m, NCH), 3.63 (2H, s, NH_2), 3.42 (1H, m, NCH_2), 3.02 (1H, m, NCH_2), 2.95 (1H, dd, J=4Hz, 14Hz, Ph-CH_2), 2.50 (2H, dd, J=9Hz, 14Hz, Ph-CH_2), 1.49 (2H, m, NCH_2CH_2), 1.26 (4H, m, $N(CH_2)_2(CH_2)_2$), 0.86 (3H, t, J=7Hz, CH_3); δ_C (100MHz, $CDCl_3$): 158.01 (C=O), 145.45 (C-NH_2), 129.61, 124.57, 115.22 (ArC), 66.51 (O-CH_2), 56.85 (NCH), 41.75 (Ph-CH_2), 37.22 (CH_2), 28.60 (CH_2), 26.84 (CH_2), 22.10 (CH_2), 13.78 (CH_3); LRMS (EI): 263 (M^+, 3%), 106 (M^+ - $C_8NH_{14}O_2$,100%); GC t_R 13.37 min.

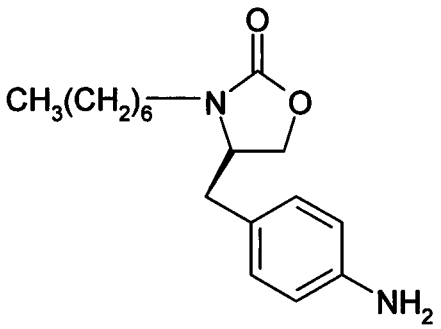
4-*(R)*-3-Hexyl- (4-aminobenzyl 2-oxazolidinone (111)



Compound **(111)** was synthesised following the same procedure as for compound **(105)**, except that compound **87** (0.50g, 1.63mmol) was used instead of compound **(81)**. The reaction mixture was removed from the hydrogenator and the catalyst was filtered through celite to give **111** (0.40g, 89%) as a yellow oil; R_f 0.45 (80/20 DCM/EtOAc).

$\nu_{(max)}$(Film)/cm^{-1}: 3361.0 (NH_2), 2929.7 (CH-aliphatic), 1742.4 (C=O); δ_H (400MHz, $CDCl_3$): 6.92 (2H, d, J=8Hz, Ph-H), 6.63 (2H, d, J=8Hz, Ph-H), 4.12 (1H, m, OCH_2), 3.98 (1H, m, OCH_2), 3.89 (1H, m, NCH), 3.62 (2H, s, NH_2), 3.47 (1H, m, NCH_2), 3.05 (1H, m, NCH_2), 2.99 (1H, dd, J=4Hz, 14Hz, Ph-CH_2), 2.54 (1H, dd, J=9Hz, 14Hz, Ph-CH_2), 1.57 (2H, m, NCH_2CH_2), 1.27 (6H, m, $N(CH_2)_2(CH_2)_3$), 0.87 (3H, t J=7Hz, CH_3); δ_C (100MHz, $CDCl_3$): 145.63, 129.87, 122.13, 115.47 (ArC), 66.70 (O-CH_2), 56.10 (NCH), 42.03 (Ph-CH_2), 37.50 (CH_2), 31.44 (CH_2), 27.37 (CH_2), 26.37 (CH_2), 22.54 (CH_2), 13.98 (CH_3); LRMS (EI): 276 (M^+, 3%), 106 (M^+ - $C_9NH_{16}O_2$,100%); GC t_R 16.26 min.

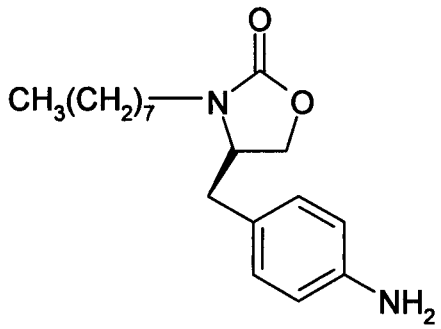
4-*(R)*-3-Heptyl-(4-aminobenzyl)-2-oxazolidinone (112)



Compound **(112)** was synthesised following the same procedure as for compound **(105)**, except that compound **88** (0.50g, 1.56mmol) was used instead of compound **(81)**. The reaction mixture was removed from the hydrogenator and the catalyst was filtered through celite to give **112** (0.42g, 93%) as a yellow oil; R_f 0.44 (80/20 DCM/EtOAc).

$\nu_{(max)}$(Film)/cm^{-1}: 3359.6 (NH_2), 2926.5 (CH-aliphatic), 1743.7 (C=O); δ_H (400MHz, $CDCl_3$): 6.91 (2H, d, J=8Hz, Ph-H), 6.62 (2H, d, J=8Hz, Ph-H), 4.13 (1H, m, OCH_2), 3.97 (1H, m, OCH_2), 3.90 (1H, m, NCH), 3.62 (2H, s, NH_2), 3.46 (1H, m, NCH_2), 3.04 (1H, m, NCH_2), 2.99 (1H, dd, J=4Hz, 14Hz, Ph-CH_2), 2.54 (2H, dd, J=9Hz, 14Hz, Ph-CH_2), 1.50 (2H, m, NCH_2CH_2), 1.25 (8H, m, $N(CH_2)_2(CH_2)_4$), 0.86 (3H, t, J=7Hz, CH_3); δ_C (100MHz, $CDCl_3$): 158.15 (C=O), 145.44 (C-NH_2), 129.85, 125.06, 115.47 (ArC), 66.69 (O-CH_2), 56.10 (NCH), 42.03 (CH_2), 37.50 (Ph-CH_2), 31.70 (CH_2), 28.92 (CH_2), 27.41 (CH_2), 26.66 (CH_2), 22.54 (CH_2), 14.03 (CH_3); LRMS (EI): 290 (M^+ , 3%), 106 (M^+ - $C_{10}NH_{18}O_2$,100%); GC t_R 14.87 min.

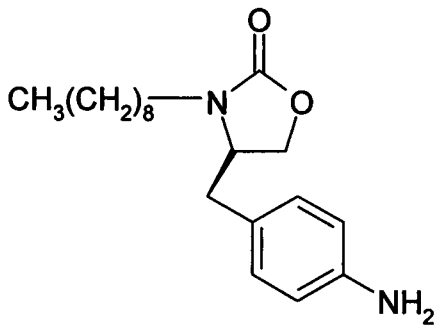
4-*(R)*-3-Octyl-(4-aminobenzyl)-2-oxazolidinone (113)



Compound **(113)** was synthesised following the same procedure as for compound **(105)**, except that compound **(89)** (0.50g, 1.50mmol) was used instead of compound **(81)**. The reaction mixture was removed from the hydrogenator and the catalyst was filtered through celite to give **113** (0.41g, 90%) as a yellow oil; R_f 0.45 (80/20 DCM/EtOAc).

$\nu_{(max)}$(Film)/cm^{-1}: 3360.1 (NH_2), 2926.8 (CH-aliphatic), 1746.3 (C=O); δ_H (400MHz, $CDCl_3$): 6.85 (2H, d, J=8Hz, Ph-H), 6.57 (2H, d, J=8Hz, Ph-H), 4.07 (1H, t, J=8Hz, OCH_2), 3.87 (1H, m, OCH_2), 3.85 (1H, m, NCH), 3.47 (2H, m, NH_2), 3.43 (1H, m, NCH_2), 2.99 (1H, m, NCH_2), 2.92 (1H, dd, J=4Hz, 14Hz, Ph-CH_2), 2.47 (2H, dd, J=9Hz, 14Hz, Ph-CH_2), 1.55 (2H, m, NCH_2CH_2), 1.22 (10H, m, $N(CH_2)_2(CH_2)_5$), 0.85 (3H, t, J=7Hz, CH_3); δ_C (100MHz, $CDCl_3$): 158.05 (C=O), 145.42 (C-NH_2), 129.68, 124.72, 115.31 (ArC), 66.55 (O-CH_2), 55.93 (NCH), 41.86 (Ph-CH_2), 37.30 (CH_2), 31.60 (CH_2), 29.06 (CH_2), 29.03 (CH_2), 27.24 (CH_2), 26.54 (CH_2), 22.46 (CH_2), 13.98 (CH_3); LRMS (EI): 304 (M^+, 3%), 106 (M^+ - $C_{11}NH_{20}O_2$,100%); GC t_R 16.35 min.

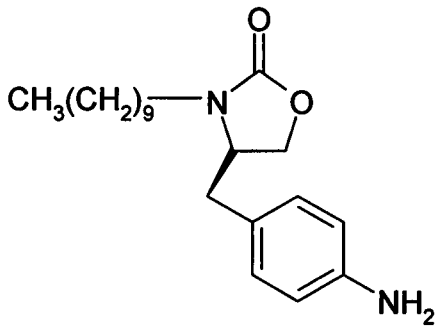
4-*(R)*-3-Nonyl-(4-aminobenzyl)-2-oxazolidinone (114)



Compound **(114)** was synthesised following the same procedure as for compound **(105)**, except that compound 4-*(R)*-3-nonyl-(4-nitro-benzyl)-2-oxazolidinone (0.50g, 1.43mmol) was used instead of compound **(81)**. The reaction mixture was removed from the hydrogenator and the catalyst was filtered through celite to give **114** (0.43g, 94%) as a clear oil; R_f 0.50 (80/20 DCM/EtOAc).

$\nu_{(max)}$(Film)/cm^{-1}: 3359.8 (NH_2), 2925.9 (CH-aliphatic), 1744.7 (C=O); δ_H (400MHz, $CDCl_3$): 6.85 (2H, d, J=8Hz, Ph-H), 6.56 (2H, d, J=8Hz, Ph-H), 4.07 (1H, t, J=8Hz, OCH_2), 3.88 (1H, m, OCH_2), 3.84 (1H, m, NCH_2), 3.61 (2H, m, NH_2), 3.41 (1H, m, NCH_2), 2.99 (1H, m, NCH_2), 2.93 (1H, dd, J=4Hz, 14Hz, Ph-CH_2), 2.48 (1H, dd, J=9Hz, 14Hz, Ph-CH_2), 1.50 (2H, m, NCH_2CH_2), 1.19 (12H, m, $N(CH_2)_2(CH_2)_6$), 0.82 (3H, t, J=7Hz, CH_3); δ_C (100MHz, $CDCl_3$): 158.04 (C=O), 145.44 (C-NH_2), 129.67 124.67, 115.28 (ArC), 66.55 (OCH_2), 55.91 (NCH), 41.85 (Ph-CH_2), 37.28 (CH_2), 31.66 (CH_2), 29.31 (CH_2), 29.10 (CH_2), 29.05 (CH_2), 27.24 (CH_2), 26.54 (CH_2), 22.48 (CH_2), 13.95 (CH_3); LRMS (EI): 276 (M^+, 3%), 106 (M^+ - $C_{12}NH_{22}O_2$,100%); GC t_R 13.91 min.

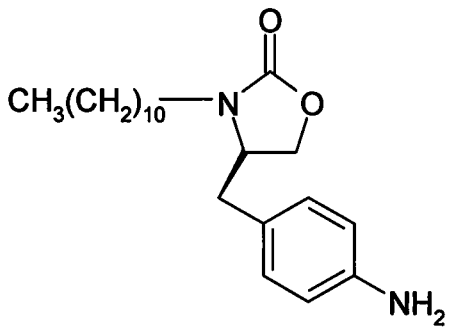
4-*(R)*-3-Decyl-(4-aminobenzyl)-2-oxazolidinone (115)



Compound **(115)** was synthesised following the same procedure as for compound **(105)**, except that compound **90** (0.50g, 1.38mmol) was used instead of compound **(81)**. The reaction mixture was removed from the hydrogenator and the catalyst was filtered through celite to give **115** (0.41g, 89%) as a yellow oil; R_f 0.47 (80/20 DCM/EtOAc).

$\nu_{(max)}$(Film)/cm^{-1}: 3360.8 (NH_2), 2925.1 (CH-aliphatic), 1746.6 (C=O); δ_H (400MHz, $CDCl_3$): 6.86 (2H, d, J=8Hz, Ph-H), 6.57 (2H, d, J=8Hz, Ph-H), 4.08 (1H, m, J=8Hz, OCH_2), 3.91 (1H, m, OCH_2), 3.85 (1H, m, NCH), 3.40 (1H, m, NCH_2), 3.00 (1H, m, NCH_2), 2.94 (1H, dd, J=4Hz, 14Hz, Ph-CH_2), 2.48 (1H, dd, J=9Hz, 14Hz Ph-CH_2), 1.48 (2H, m, NCH_2CH_2), 1.19 (14H, m, $N(CH_2)_2(CH_2)_7$), 0.82 (3H, t, J=6Hz, CH_3); δ_C (100MHz, $CDCl_3$): 158.11 (C=O), 145.43 (C-NH_2), 129.77, 124.86, 115.38 (ArC), 66.63 (O-CH_2), 56.00 (NCH), 41.94 (Ph-CH_2), 37.38 (CH_2), 31.78 (CH_2), 29.52 (CH_2), 29.43 (CH_2), 29.19 (CH_2), 27.33 (CH_2), 26.69 (CH_2), 22.58 (CH_2), 14.03 (CH_3).

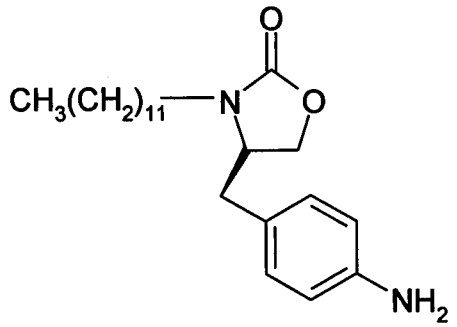
4-*(R)*-3-Undecyl-(4-aminobenzyl)-2-oxazolidinone (116)



Compound **(116)** was synthesised following the same procedure as for compound **(105)**, except that compound 4-*(R)*-3-undecyl-(4-nitro-benzyl)-2-oxazolidinone (0.50g, 1.33mmol) was used instead of compound **(81)**. The reaction mixture was removed from the hydrogenator and the catalyst was filtered through celite to give **116** (0.43g, 93%) as a yellow oil; R_f 0.58 (80/20 DCM/EtOAc).

$\nu_{(max)}$(Film)/cm^{-1}: 3359.2 (NH_2), 2924.5 (CH-aliphatic), 1744.6 (C=O); δ_H (400MHz, $CDCl_3$): 6.86 (2H, d, J=8Hz, Ph-H), 6.57 (2H, d, J=8Hz, Ph-H), 4.08 (1H, m, OCH_2), 3.92 (1H, m, OCH_2), 3.87 (1H, m, NCH), 3.69 (2H, s, NH_2), 3.42 (1H, m, NCH_2), 3.01 (1H, m, NCH_2), 2.94 (1H, dd, J=4Hz, 14Hz, Ph-CH_2), 2.49 (1H, dd, J=9Hz, 14Hz, Ph-CH_2), 1.49 (2H, m, NCH_2CH_2), 1.20 (16H, m, $N(CH_2)_2(CH_2)_8$), 0.84 (3H, t, J=7Hz, CH_3); δ_C (100MHz, $CDCl_3$): 157.95 (C=O), 145.46 (C-NH_2), 129.55, 124.44, 115.15 (ArC), 66.45 (O-CH_2), 55.81 (NCH), 41.75 (Ph-CH_2), 37.17 (CH_2), 31.63 (CH_2), 29.32 (CH_2), 29.31 (CH_2), 29.27 (CH_2), 29.06 (CH_2), 29.01 (CH_2), 27.15 (CH_2), 26.45 (CH_2), 22.41 (CH_2), 13.88 (CH_3); LRMS (EI): 346 (M^+, 3%), 106 (M^+ - $C_{14}NH_{26}O_2$,100%); GC t_R 13.75min.

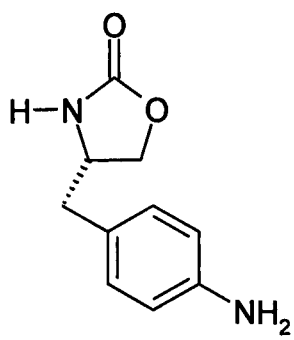
4-*(R)*-3-Dodecyl-(4-aminobenzyl)-2-oxazolidinone (117)



Compound **(117)** was synthesised following the same procedure as for compound **(105)**, except that compound **91** (0.50g, 1.28mmol) was used instead of compound **(81)**. The reaction mixture was removed from the hydrogenator and the catalyst was filtered through celite to give **117** (0.42g, 91%) as a yellow oil; R_f 0.65 (80/20 DCM/EtOAc).

$\nu_{(max)}$(Film)/cm^{-1}: 3359.9 (NH_2), 2924.4 (CH-aliphatic), 1746.7 (C=O); δ_H (400MHz, $CDCl_3$): 6.94 (2H, d, J=9Hz, Ph-H), 6.65 (2H, d, J=9Hz, Ph-H), 4.13 (1H, m, OCH_2), 4.00 (1H, m, OCH_2), 3.92 (1H, m, NCH), 3.64 (2H, s, NH_2), 3.49 (1H, m, NCH_2), 3.06 (1H, m, NCH_2), 3.01 (1H, dd, J=4Hz, 14Hz, Ph-CH_2), 2.56 (1H, dd, J=8Hz, 14Hz, Ph-CH_2), 1.58 (2H, m, NCH_2CH_2), 1.25 (18H, m, $N(CH_2)_2(CH_2)_9$), 0.87 (3H, t, J=7Hz, CH_3); δ_C (100MHz, $CDCl_3$): 145.42 (C-NH_2), 129.87, 125.06, 115.47 (ArC), 66.69 (O-CH_2), 56.10 (NCH), 42.03 (Ph-CH_2), 37.48 (CH_2), 31.89 (CH_2), 29.61 (CH_2), 29.55 (CH_2), 29.52 (CH_2), 29.32 (CH_2), 29.28 (CH_2), 27.41 (CH_2), 26.71 (CH_2), 22.66 (CH_2), 14.10 (CH_3).

4-*(S)*-(4-Amino-benzyl)-oxazolidin-2-one (118)

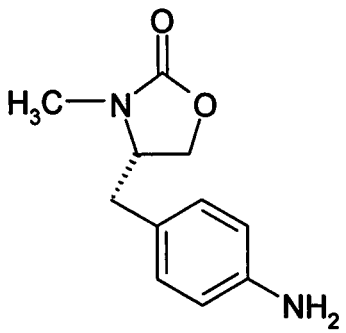


Compound **(118)** was synthesised following the same procedure as for compound **(105)**, except that compound **92** (0.50g, 2.25mmol) was used instead

of compound **(81)**. The reaction mixture was removed from the hydrogenator and the catalyst was filtered through celite to give **118** (0.39g, 90%) as a dark yellow oil; R_f 0.32 (80:20 DCM:EtOAc).

$\nu_{(max)}$(Film)/cm^{-1}: 3350.6 (NH_2), 2914.7 (CH-aliphatic), 1746.8 (C=O); δ_H (400MHz, $CDCl_3$): 6.87 (2H, d, J=8Hz, Ph-H), 6.56 (2H, d, J=8Hz, Ph-H), 6.05 (1H, s, NH), 4.32 (1H, t, J=9Hz, OCH_2), 4.04 (1H, dd, J=5Hz, 9Hz, OCH_2), 3.93 (1H, m, NCH), 3.63 (2H, s, NH_2), 2.65 (2H, m, Ph-CH_2); δ_C (100MHz, $CDCl_3$): 159.63 (C=O), 145.40 (C-NH_2), 129.79, 125.48, 115.41 (ArC), 69.47 (O-CH_2), 53.87 (NCH), 40.35 (Ph-CH_2); LRMS (EI): 192 (M^+, 3%), 106 (M^+ - $C_3NH_4O_2$,100%); GC t_R 11.43 min.

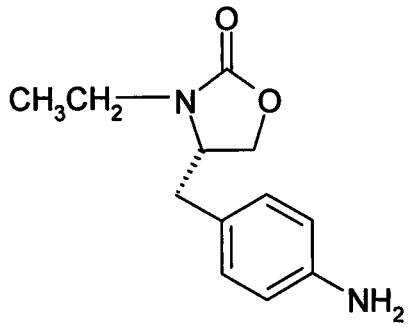
4-*(S)*-3-Methyl-(4-aminobenzyl)-2-oxazolidinone (119)



Compound **(119)** was synthesised following the same procedure as for compound **(105)**, except that compound **93** (0.50g, 2.12mmol) was used instead of compound **(81)**. The reaction mixture was removed from the hydrogenator and the catalyst was filtered through celite to give **119** (0.40g, 92%) as a yellow oil; R_f 0.34 (80/20 DCM/EtOAc).

$\nu_{(max)}$(Film)/cm^{-1}: 3355.6 (NH_2), 2924.7 (CH-aliphatic), 1745.0 (C=O); δ_H (400MHz, $CDCl_3$): 6.92 (2H, d, J=9Hz, Ph-H), 6.62 (2H, d, J=8Hz, Ph-H), 4.15 (1H, t, J=9Hz, OCH_2), 3.97 (1H, dd, J=6Hz, 9Hz, OCH_2), 3.81 (1H, m, NCH), 3.63 (2H, s, NH_2), 3.00 (1H, dd, J=4Hz, 14Hz, Ph-CH_2), 2.85 (3H, s, CH_3), 2.59 (1H, dd, J=9Hz, 14Hz, Ph-CH_2); δ_C (100MHz, $CDCl_3$): 158.53 (C=O), 145.46 (C-NH_2), 129.89, 124.90, 115.47 (ArC), 66.66 (O-CH_2), 58.54 (NCH), 37.51 (Ph-CH_2), 29.49 (CH_3); LRMS (EI): 206 (M^+, 3%), 106 (M^+ - $C_4NH_6O_2$,100%); GC t_R 10.89 min.

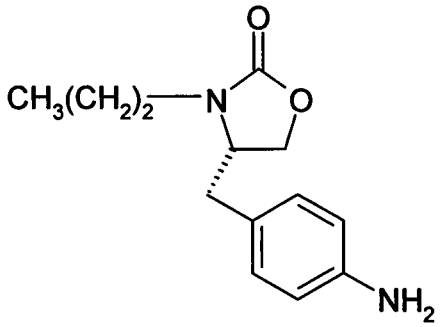
4-*(S)*-3-Ethyl-(4-aminobenzyl)-2-oxazolidinone (120)



Compound **(120)** was synthesised following the same procedure as for compound (105), except that compound **94** (0.50g, 2.00mmol) was used instead of compound **(81)**. The reaction mixture was removed from the hydrogenator and the catalyst was filtered through celite to give **120** (0.41g, 93%) as a yellow oil; R_f 0.35 (80/20 DCM/EtOAc).

$\nu_{(max)}$(Film)/cm^{-1}: 3357.4 (NH_2), 2932.2 (CH-aliphatic), 1739.0 (C=O); δ_H (400MHz, $CDCl_3$): 6.82 (2H, d, J=8Hz, Ph-H), 6.54 (2H, d, J=8Hz, Ph-H), 4.01 (1H, t, J=11Hz, OCH_2), 3.87 (1H, dd, J=5Hz, 11Hz, OCH_2), 3.63 (2H, s, NH_2), 3.43 (1H, m, NCH_2), 3.05 (1H, m, NCH_2), 2.88 (1H, dd, J=4Hz, 14Hz, Ph-CH_2), 2.45 (1H, dd, J=4Hz, 14Hz, Ph-CH_2), 1.08 (3H, t, J=7Hz, CH_3); δ_C (100MHz, $CDCl_3$): 157.65 (C=O), 145.31 (C-NH_2), 129.37, 124.25, 115.02 (ArC), 66.37 (O-CH_2), 55.31 (NCH), 37.09 (Ph-CH_2), 36.41 (CH_2), 12.26 (CH_3); LRMS (EI): 220 (M^+, 3%), 106 (M^+ - $C_5NH_8O_2$,100%); GC t_R 11.30min.

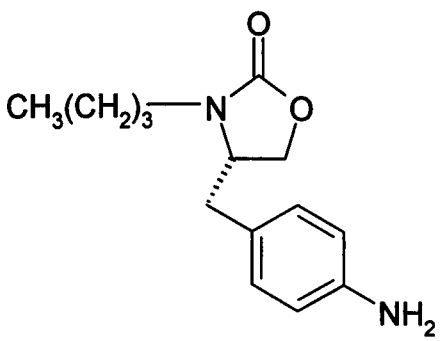
4-*(S)*-3-Propyl-(4-aminobenzyl)-2-oxazolidinone (121)



Compound **(121)** was synthesised following the same procedure as for compound **(105)**, except that compound **95** (0.50g, 1.89mmol) was used instead of compound **(81)**. The reaction mixture was removed from the hydrogenator and the catalyst was filtered through celite to give **121** (0.40g, 90%) as a yellow oil; R_f 0.34 (80/20 DCM/EtOAc).

$\nu_{(max)}$(Film)/cm^{-1}: 3352.2 (NH_2), 2964.1 (CH-aliphatic), 1739.7 (C=O); δ_H (400MHz, $CDCl_3$): 6.90 (2H, d, J=8Hz, Ph-H), 6.67 (2H, d, J=8Hz, Ph-H), 4.09 (1H, t, J=8Hz, OCH_2), 3.93 (1H, dd, J=5Hz, 9Hz, OCH_2), 3.90 (1H, m, NCH), 3.39 (1H, m, NCH_2), 3.00 (1H, m, OCH_2), 2.95 (1H, dd, J=4Hz, 14Hz, Ph-CH_2), 2.52 (1H, dd, J=9Hz, 14Hz, Ph-CH_2), 1.53 (2H, m, NCH_2CH_2), 0.88 (3H, t, J=7Hz, CH_3); δ_C (100MHz, $CDCl_3$): 129.94, 116.37, (ArC), 66.40 (O-CH_2), 56.07 (NCH), 44.13 (Ph-CH_2), 37.47 (CH_2), 20.71 (CH_2), 11.16 (CH_3); LRMS (EI): 235 (M^+, 3%), 106 (M^+ - $C_6NH_{10}O_2$,100%); GC t_R 11.78 min.

4-*(S)*-3-Butyl-(4-aminobenzyl)-2-oxazolidinone (122)

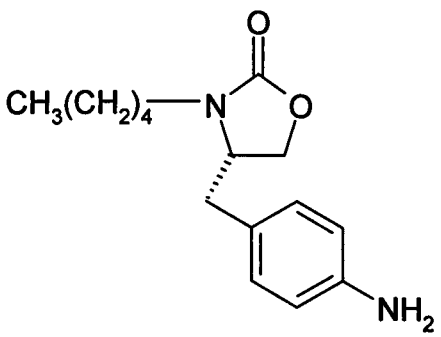


Compound **(122)** was synthesised following the same procedure as for compound **(105)**, except that compound **96** (0.50g, 1.80mmol) was used instead of compound **(81)**. The reaction mixture was removed from the hydrogenator and

the catalyst was filtered through celite to give **122** (0.39g, 87%) as a yellow oil; R_f 0.36 (80/20 DCM/EtOAc).

$\nu_{(max)}$(Film)/cm^{-1}: 3358.0 (NH_2), 2930.4 (CH-aliphatic), 1742.9 (C=O); δ_H (400MHz, $CDCl_3$): 6.87 (2H, d, J=8Hz, Ph-H), 6.58 (2H, d, J=8Hz, Ph-H), 4.09 (1H, m, J=8Hz, OCH_2), 3.93 (1H, dd, J=6Hz, 8Hz, OCH_2), 3.90 (1H, m, NCH), 3.58 (2H, s, NH_2), 3.44 (1H, m, NCH_2), 3.04 (1H, m, NCH_2), 2.95 (1H, dd, J=4Hz, 14Hz, Ph-CH_2), 2.49 (2H, dd, J=9Hz, 14Hz, Ph-CH_2), 1.52 (2H, m, NCH_2CH_2), 1.30 (2H, m, $N(CH_2)_2CH_2$), 0.89 (3H, t, J=7Hz, CH_3); δ_C (100MHz, $CDCl_3$): 158.17 (C=O), 145.44 (C-NH_2), 129.85, 125.03, 115.47 (ArC), 66.69 (O-CH_2), 56.09 (NCH), 41.74 (Ph-CH_2), 37.48 (CH_2), 29.46 (CH_2), 19.92 (CH_2), 13.71 (CH_3); LRMS (EI): 249 (M^+, 3%), 106 (M^+ - $C_7NH_{12}O_2$,100%); GC t_R 12.27min.

4-*(S)*-3-Pentyl-(4-aminobenzyl)-2-oxazolidinone (123)

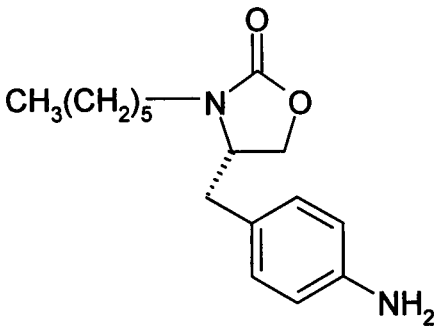


Compound **(123)** was synthesised following the same procedure as for compound **(105)**, except that compound **97** (0.50g, 1.71mmol) was used instead of compound **(81)**. The reaction mixture was removed from the hydrogenator and the catalyst was filtered through celite to give **123** (0.38g, 85%) as a yellow oil; R_f 0.40 (80/20 DCM/EtOAc).

$\nu_{(max)}$(Film)/cm^{-1}: 3358.7 (NH_2), 2929.5 (CH-aliphatic), 1742.8 (C=O); δ_H (400MHz, $CDCl_3$): 6.91 (2H, d, J=8Hz, Ph-H), 6.62 (2H, d, J=8Hz, Ph-H), 4.13 (1H, t, J=8Hz, OCH_2), 3.97 (1H, dd, J=6Hz, 8Hz, OCH_2), 3.94 (1H, m, NCH), 3.63 (2H, s, NH_2), 3.46 (1H, m, NCH_2), 3.05 (1H, m, NCH_2), 2.99 (1H, dd, J=4Hz, 14Hz, Ph-CH_2), 2.54 (2H, dd, J=9Hz, 14Hz, Ph-CH_2), 1.52 (2H, m, NCH_2CH_2), 1.29 (4H, m, $N(CH_2)_2(CH_2)_2$), 0.89 (3H, t, J=7Hz, CH_3); δ_C (100MHz, $CDCl_3$): 158.16 (C=O), 145.44 (C-NH_2), 129.83, 125.02, 115.44 (ArC), 66.67 (O-CH_2),

56.08 (N<u>C</u>H), 41.97 (Ph-<u>C</u>H_2), 37.48 (<u>C</u>H_2), 28.80 (<u>C</u>H_2), 27.05 (<u>C</u>H_2), 22.30 (<u>C</u>H_2), 13.95 (<u>C</u>H_3); LRMS (EI): 263 (M^+, 3%), 106 (M^+ - $C_8NH_{14}O_2$,100%); GC t_R 13.38 min.

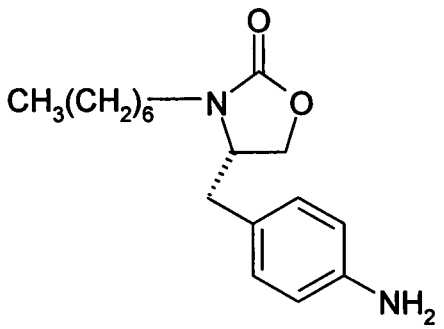
4-*(S)*-3-Hexyl- (4-aminobenzyl)-2-oxazolidinone (124)



Compound **(124)** was synthesised following the same procedure as for compound **(105)**, except that compound **98** (0.50g, 1.63mmol) was used instead of compound **(81)**. The reaction mixture was removed from the hydrogenator and the catalyst was filtered through celite to give **124** (0.41g, 91%) as a yellow oil; R_f 0.43 (80/20 DCM/EtOAc).

$\nu_{(max)}$(Film)/cm^{-1}: 3361.4 (NH_2), 2929.0 (CH-aliphatic), 1743.6 (C=O); δ_H (400MHz, $CDCl_3$): 6.92 (2H, d, J=8Hz, Ph-<u>H</u>), 6.63 (2H, d, J=8Hz, Ph-<u>H</u>), 4.14 (1H, m, OC<u>H</u>$_2$), 3.98 (1H, m, OC<u>H</u>$_2$), 3.90 (1H, m, NC<u>H</u>), 3.62 (2H, s, N<u>H</u>$_2$), 3.41 (1H, m, NC<u>H</u>$_2$), 3.05 (1H, m, NC<u>H</u>$_2$), 2.99 (1H, dd, J=4Hz, 14Hz, Ph-C<u>H</u>$_2$), 2.54 (1H, dd, J=9Hz, 14Hz, Ph-C<u>H</u>$_2$), 1.57 (2H, m, NCH$_2$C<u>H</u>$_2$), 1.28 (6H, m, N(CH$_2$)$_2$(C<u>H</u>$_2$)$_3$), 0.88 (3H, t J=7Hz, C<u>H</u>$_3$); δ_C (100MHz, $CDCl_3$): 158.19 (<u>C</u>=O), 145.43 (<u>C</u>-NH_2), 129.87, 125.09, 115.48 (Ar<u>C</u>), 66.69 (O-<u>C</u>H_2), 56.10 (N<u>C</u>H), 42.03 (Ph-<u>C</u>H_2), 37.51 (<u>C</u>H_2), 31.45 (<u>C</u>H_2), 27.37 (<u>C</u>H_2), 26.37 (<u>C</u>H_2), 22.54 (<u>C</u>H_2), 13.99 (<u>C</u>H_3); LRMS (EI): 276 (M^+, 3%), 106 (M^+ - $C_9NH_{16}O_2$,100%); GC t_R 13.91 min.

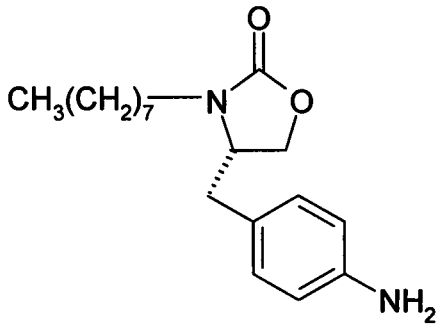
4-*(S)*-3-Heptyl-(4-aminobenzyl)-2-oxazolidinone (125)



Compound **(125)** was synthesised following the same procedure as for compound **(105)**, except that compound **(99)** (0.50g, 1.56mmol) was used instead of compound **(81)**. The reaction mixture was removed from the hydrogenator and the catalyst was filtered through celite to give **(125)** (0.40g, 88%) as a yellow oil; R_f 0.46 (80/20 DCM/EtOAc).

$\nu_{(max)}$(Film)/cm^{-1}: 3361.1 (NH_2), 2927.0 (CH-aliphatic), 1742.9 (C=O); δ_H (400MHz, $CDCl_3$): 6.92 (2H, d, J=8Hz, Ph-H), 6.63 (2H, d, J=8Hz, Ph-H), 4.14 (1H, m, OCH_2), 3.96 (1H, m, OCH_2), 3.89 (1H, m, NCH), 3.63 (2H, s, NH_2), 3.47 (1H, m, NCH_2), 3.05 (1H, m, NCH_2), 2.99 (1H, dd, J=4Hz, 14Hz, Ph-CH_2), 2.54 (2H, dd, J=9Hz, 14Hz, Ph-CH_2), 1.56 (2H, m, NCH_2CH_2), 1.27 (8H, m, $N(CH_2)_2(CH_2)_4$), 0.86 (3H, t, J=7Hz, CH_3); δ_C (100MHz, $CDCl_3$): 157.67 (C=O), 143.09 (C-NH_2), 129.94, 124.15, 115.73 (ArC), 66.17 (O-CH_2), 55.39 (NCH), 53.89 (Ph-CH_2), 42.19 (CH_2), 38.24 (CH_2), 31.68 (CH_2), 27.44 (CH_2), 26.63 (CH_2), 22.53 (CH_2), 14.02 (CH_3); LRMS (EI): 290 (M^+ , 3%), 106 (M^+ - $C_{10}NH_{18}O_2$,100%); GC t_R 14.96 min.

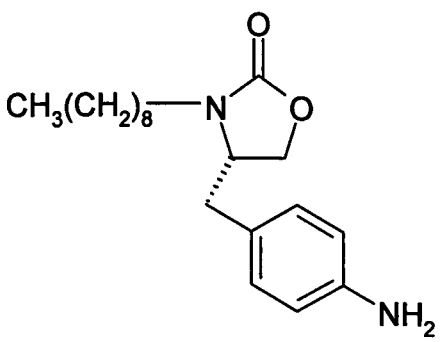
4-*(S)*-3-Octyl-(4-aminobenzyl)-2-oxazolidinone (126)



Compound **(126)** was synthesised following the same procedure as for compound **(105)**, except that compound **100** (0.50g, 1.50mmol) was used instead of compound **(81)**. The reaction mixture was removed from the hydrogenator and the catalyst was filtered through celite to give **126** (0.41g, 90%) as a yellow oil; R_f 0.47 (80/20 DCM/EtOAc).

$\nu_{(max)}$(Film)/cm^{-1}: 3360.8 (NH_2), 2926.0 (CH-aliphatic), 1742.3 (C=O); δ_H (400MHz, $CDCl_3$): 6.91 (2H, d, J=8Hz, Ph-H), 6.62 (2H, d, J=8Hz, Ph-H), 4.11 (1H, t, J=8Hz, OCH_2), 3.97 (1H, dd, J=5Hz, 8Hz, OCH_2), 3.90 (1H, m, NCH), 3.62 (2H, s, NH_2), 3.46 (1H, m, NCH_2), 3.04 (1H, m, NCH_2), 2.99 (1H, dd, J=4Hz, 14Hz, Ph-CH_2), 2.54 (2H, dd, J=9Hz, 14Hz, Ph-CH_2), 1.53 (2H, m, NCH_2CH_2), 1.26 (10H, m, $N(CH_2)_2(CH_2)_5$), 0.85 (3H, t, J=7Hz, CH_3); δ_C (100MHz, $CDCl_3$): 158.16 (C=O), 145.44 (C-NH_2), 129.84, 125.04, 115.47 (ArC), 66.69 (O-CH_2), 56.09 (NCH), 42.02 (Ph-CH_2), 37.48 (CH_2), 31.73 (CH_2), 29.20 (CH_2), 29.17 (CH_2), 27.40 (CH_2), 26.70 (CH_2), 22.60 (CH_2), 14.05 (CH_3); LRMS (EI): 305 (M^+, 3%), 106 (M^+ - $C_{11}NH_{20}O_2$,100%); GC t_R 16.38 min.

4-*(S)*-3-Nonyl-(4-aminobenzyl)-2-oxazolidinone (127)

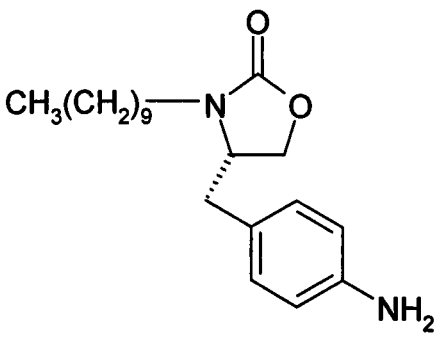


Compound **(127)** was synthesised following the same procedure as for compound **(105)**, except that compound 101 (0.50g, 1.43mmol) was used

instead of compound **(81)**. The reaction mixture was removed from the hydrogenator and the catalyst was filtered through celite to give **127** (0.42g, 92%) as a clear oil; R_f 0.52 (80/20 DCM/EtOAc).

$\nu_{(max)}$(Film)/cm^{-1}: 3362.1 (NH_2), 2925.3 (CH-aliphatic), 1743.5 (C=O); δ_H (400MHz, $CDCl_3$): 6.92 (2H, d, J=8Hz, Ph-H), 6.63 (2H, d, J=8Hz, Ph-H), 4.14 (1H, t, J=8Hz, OCH_2), 3.98 (1H, dd, J=6Hz, 8Hz, OCH_2), 3.89 (1H, m, NCH), 3.47 (1H, m, NCH_2), 3.05 (1H, m, NCH_2), 3.00 (1H, dd, J=4Hz, 14Hz, Ph-CH_2), 2.54 (1H, dd, J=9Hz, 14Hz, Ph-CH_2), 1.54 (2H, m, NCH_2CH_2), 1.24 (12H, m, $N(CH_2)_2(CH_2)_6$), 0.84 (3H, t, J=7Hz, CH_3); δ_C (100MHz, $CDCl_3$): 158.19 (C=O), 145.40 (C-NH_2), 129.87 125.10, 115.50 (ArC), 66.69 (OCH_2), 56.10 (NCH), 42.04 (Ph-CH_2), 37.50 (CH_2), 31.82 (CH_2), 29.48 (CH_2), 29.27 (CH_2), 29.21 (CH_2), 27.41 (CH_2), 26.71 (CH_2), 22.64 (CH_2), 14.09 (CH_3); LRMS (EI): 318 (M^+, 3%), 106 (M^+ - $C_{12}NH_{22}O_2$,100%); GC t_R 17.95 min.

4-*(S)*-3-Decyl-(4-aminobenzyl)-2-oxazolidinone (128)

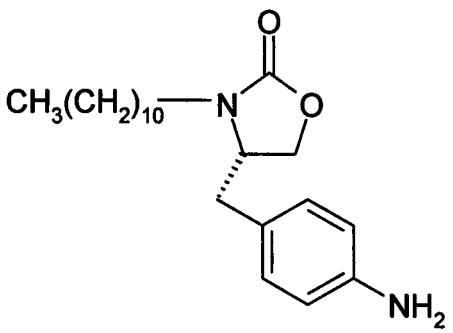


Compound **(128)** was synthesised following the same procedure as for compound **(105)**, except that compound **102** (0.50g, 1.38mmol) was used instead of compound **(81)**. The reaction mixture was removed from the hydrogenator and the catalyst was filtered through celite to give **128** (0.40g, 87%) as a yellow oil; R_f 0.50 (80/20 DCM/EtOAc).

$\nu_{(max)}$(Film)/cm^{-1}: 2924.1 (CH-aliphatic), 1743.4 (C=O); δ_H (400MHz, $CDCl_3$): 6.87 (2H, d, J=8Hz, Ph-H), 6.58 (2H, d, J=8Hz, Ph-H), 4.08 (1H, m, J=9Hz, OCH_2), 3.92 (1H, m, OCH_2), 3.85 (1H, m, NCH), 3.41 (1H, m, NCH_2), 3.08 (2H, s, NH_2), 2.99 (1H, m, NCH_2), 2.94 (1H, dd, J=4Hz, 14Hz, Ph-CH_2), 2.49 (1H, dd, J=9Hz, 14Hz, Ph-CH_2), 1.48 (2H, m, NCH_2CH_2), 1.19 (14H, m, $N(CH_2)_2(CH_2)_7$), 0.82

(3H, t, J=6Hz, C$\underline{H}_3$); δ_C (100MHz, $CDCl_3$): 158.14 ($\underline{C}$=O), 145.28 ($\underline{C}$-NH_2), 129.80, 125.07, 115.53 (Ar$\underline{C}$), 66.66 (O-$\underline{C}H_2$), 56.07 (N$\underline{C}$H), 42.01 (Ph-$\underline{C}H_2$), 37.45 ($\underline{C}H_2$), 31.79 ($\underline{C}H_2$), 29.66 ($\underline{C}H_2$), 29.45 ($\underline{C}H_2$), 29.20 ($\underline{C}H_2$), 29.06 ($\underline{C}H_2$), 27.37 ($\underline{C}H_2$), 26.66 ($\underline{C}H_2$), 22.59 ($\underline{C}H_2$), 14.02 ($\underline{C}H_3$); LRMS (EI): 332 (M^+, 3%), 106 (M^+ - $C_{13}NH_{24}O_2$,100%); GC t_R 20.19 min.

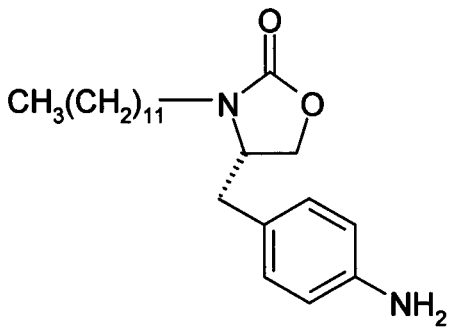
4-*(S)*-3-Undecyl-(4-aminobenzyl)-2-oxazolidinone (129)



Compound **(129)** was synthesised following the same procedure as for compound **(105)**, except that compound **103** (0.50g, 1.33mmol) was used instead of compound **(81)**. The reaction mixture was removed from the hydrogenator and the catalyst was filtered through celite to give **129** (0.41g, 89%) as a yellow oil; R_f 0.56 (80/20 DCM/EtOAc).

$\nu_{(max)}$(Film)/cm^{-1}: 3358.4 (NH_2), 2924.0 (CH-aliphatic), 1743.4 (C=O); δ_H (400MHz, $CDCl_3$): 6.87 (2H, d, J=8Hz, Ph-$\underline{H}$), 6.58 (2H, d, J=8Hz, Ph-$\underline{H}$), 4.07 (1H, m, OCH_2), 3.93 (1H, m, O$\underline{C}H_2$), 3.84 (1H, m, N$\underline{C}$H), 3.58 (2H, s, N$\underline{H}_2$), 3.42 (1H, m, N$\underline{C}H_2$), 3.02 (1H, m, N$\underline{C}H_2$), 2.95 (1H, dd, J=4Hz, 14Hz, Ph-C$\underline{H}_2$), 2.49 (1H, dd, J=9Hz, 14Hz, Ph-C$\underline{H}_2$), 1.52 (2H, m, $NCH_2C\underline{H}_2$), 1.20 (16H, m, $N(CH_2)_2(C\underline{H}_2)_8$), 0.81 (3H, t, J=7Hz, C$\underline{H}_3$); δ_C (100MHz, $CDCl_3$): 158.15 ($\underline{C}$=O), 145.43 ($\underline{C}$-NH_2), 129.86, 125.06, 115.47 (Ar$\underline{C}$), 66.69 (O-$\underline{C}H_2$), 56.10 (N$\underline{C}$H), 42.03 (Ph-$\underline{C}H_2$), 37.48 ($\underline{C}H_2$), 31.88 ($\underline{C}H_2$), 29.64 ($\underline{C}H_2$), 29.55 ($\underline{C}H_2$), 29.52 ($\underline{C}H_2$), 29.31 ($\underline{C}H_2$), 29.27 ($\underline{C}H_2$), 27.42 ($\underline{C}H_2$), 26.72 ($\underline{C}H_2$), 22.66 ($\underline{C}H_2$), 14.09 (CH_3); LRMS (EI): 347 (M^+, 3%), 106 (M^+ - $C_{14}NH_{26}O_2$,100%); GC t_R 11.82min.

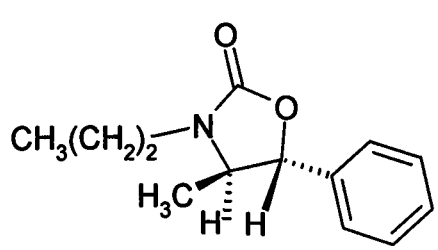
4-*(S)*-3-Dodecyl-(4-aminobenzyl)-2-oxazolidinone (130)



Compound **(130)** was synthesised following the same procedure as for compound **(105)**, except that compound **104** (0.50g, 1.28mmol) was used instead of compound (81). The reaction mixture was removed from the hydrogenator and the catalyst was filtered through celite to give **130** (0.43g, 93%) as a yellow oil; R_f 0.60 (80/20 DCM/EtOAc).

$\nu_{(max)}$(Film)/cm^{-1}: 3360.6 (NH_2), 2925.5 (CH-aliphatic), 1745.5 (C=O); δ_H (400MHz, $CDCl_3$): 6.93 (2H, d, J=9Hz, Ph-H), 6.64 (2H, d, J=9Hz, Ph-H), 4.15 (1H, m, OCH_2), 3.99 (1H, dd, J=6Hz, 9Hz, OCH_2), 3.91 (1H, m, NCH), 3.64 (2H, s, NH_2), 3.48 (1H, m, NCH_2), 3.06 (1H, m, NCH_2), 3.01 (1H, dd, J=4Hz, 14Hz, Ph-CH_2), 2.55 (1H, dd, J=8Hz, 14Hz, Ph-CH_2), 1.55 (2H, m, NCH_2CH_2), 1.25 (18H, m, $N(CH_2)_2(CH_2)_9$), 0.87 (3H, t, J=7Hz, CH_3); δ_C (100MHz, $CDCl_3$): 158.16 (C=O), 145.53 (C-NH_2), 129.86, 125.06, 115.47 (ArC), 66.69 (O-CH_2), 56.10 (NCH), 42.03 (Ph-CH_2), 37.48 (CH_2), 31.89 (CH_2), 29.60 (CH_2), 29.58 (CH_2), 29.54 (CH_2), 29.52 (CH_2), 29.32 (CH_2), 29.27 (CH_2), 27.41 (CH_2), 26.71 (CH_2), 14.09 (CH_3); LRMS (EI^+) 361 (M^++1); GC t_R 25.64 min.

5-Methy-5-phenyl-3-propyl-oxazolidin-2-one (131)

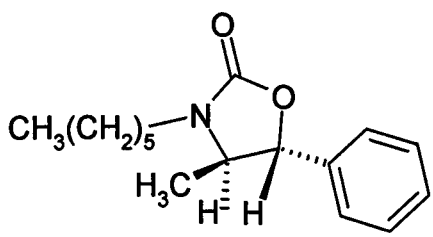


Compound **(131)** was synthesised following the same procedure as for compound **(57)**, except that iodopropane (2.11g, 12.42mmol) was added to *(4S,*

5R)-(-)4-Methyl-5-phenyl-2-oxazolidinone (2.00g, 11.29mmol) to give **131** (2.30g, 93%) as a clear oil; R_f 0.72 [70/30 diethyl ether/petroleum ether (40-60°C)].

$\nu_{(max)}$(Film)/cm^{-1}: 2925.5 (CH-aliphatic), 1753.6 (C=O); δ_H (400MHz, $CDCl_3$): 7.12 (5H,m, Ph-H), 5.38 (1H, d, J=12Hz, NCH), 3.94 (1H, m, OCH), 3.26 (1H, m, NCH_2), 2.81 (1H, m, NCH_2), 1.42 (2H, m, NCH_2CH_2), 0.76 (3H, t, J=7Hz, CH_2CH_3), 0.55 (3H, d, J=6Hz, NCH_3); δ_C (100MHz, $CDCl_3$): 157.79 (C=O), 135.38, 128.38, 128.25, 126.15 (ArC), 54.72 (OCH), 43.44 (NCH), 20.85 (NCH_2), 14.34 (NCH_2CH_2), 11.89 (CH_3); LRMS (EI): 219 (M^+, 40%), 70 [M^+-100%] GC t_R 9.42 min.

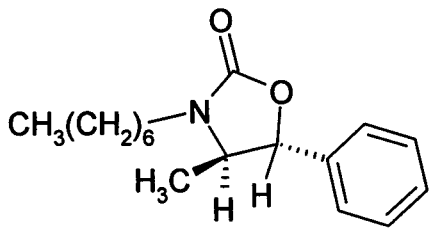
3-Hexyl-4-methyl-5-phenyl- oxazolidin-2-one (132)



Compound **(132)** was synthesised following the same procedure as for compound **(57)**, except that iodohexane (2.63g, 12.42mmol) was added to *(4S, 5R*)-(-)4-Methyl-5-phenyl-2-oxazolidinone (2.00g, 11.29mmol) to give **132** (2.40g, 81%) as a clear oil; R_f 0.72 [50/50 diethyl ether/petroleum ether (40-60°C)].

$\nu_{(max)}$(Film)/cm^{-1}: 2925.8 (CH-aliphatic), 1756.0 (C=O); δ_H (400MHz, $CDCl_3$): 7.08 (5H,m, Ph-H), 5.34 (1H, d, J=8Hz, NCH), 3.91 (1H, m, OCH), 3.27 (1H, m, NCH_2), 2.77 (1H, m, NCH_2), 1.35 (2H, m, NCH_2CH_2), 1.08 (3H, t, J=7Hz, CH_2CH_3),0.68 [6H, m, $N(CH_2)_2(CH_2)_3$], 0.50 (3H, d, J=6Hz, NCH_3); δ_C (100MHz, $CDCl_3$): 157.77 (C=O), 135.35, 128.30, 128.24, 128.01, 126.07 (ArC), 54.66 (OCH), 41.76 (NCH), 31.33 (NCH_2), 27.46 (CH_2), 26.31 (CH_2), 22.49 (CH_2), 22.46 (CH_2), 14.29 ($NCCH_3$) 13.94 (CH_3); LRMS (EI): 261 (M^+, 2%), 170 (M^+-C_7H_7 ,100%); GC t_R 15.47 min.

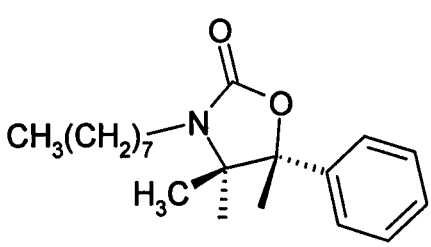
3-Heptyl-4-methyl-5-phenyl-oxazolidin-2-one (133)



Compound **(133)** was synthesised following the same procedure as for compound **(57)**, except that iodoheptane (2.81g, 12.42mmol) was added to *(R)*-4-benzyl-2-oxazolidinone (2.00g, 11.29mmol) to give **133** (2.50g, 80%) as a clear oil; R_f 0.75 [50/50 diethyl ether/petroleum ether (40-60°C)].

δ_H (400MHz, $CDCl_3$): 7.16 (5H,m, Ph-H), 5.41 (1H, d, J=12Hz, NCH), 3.97 (1H, m, OCH), 3.34 (1H, m, NCH_2), 2.84 (1H, m, NCH_2), 1.42 (2H, m, NCH_2CH_2), 1.16 [8H, m, $N(CH_2)_2(CH_2)_4$)], 0.73 (3H, t, J=7Hz, CH_2CH_3), 0.58 (3H, d, J=6Hz, NCH_3); δ_C (100MHz, $CDCl_3$): 157.53 (C=O), 135.29, 128.63, 128.38, 126.33 (ArC), 54.49 (OCH), 41.70 (NCH), 32.24 (NCH_2), 28.29 (CH_2), 27.64 (CH_2), 27.13 (CH_2), 26.88 (CH_2), 22.68 (CH_2), 22.59 (CH_2), 14.35 ($NCCH_3$), 13.58 (CH_3); LRMS (EI): 275 (M^+, 33%), 126 (M^+ - C_7H_7 ,100%); GC t_R 11.78 min.

4-Methyl-3-octyl-5-phenyl-oxazolidin-2-one (134)



Compound **(134)** was synthesised following the same procedure as for compound **(57)**, except that iodooctane (2.98g, 12.42mmol) was added to *(S)*-4-benzyl-2-oxazolidinone (2.00g, 11.29mmol) to give **134** (2.70g, 83%) as a clear oil; R_f 0.85 [50/50 diethyl ether/petroleum ether (40-60°C)].

$\nu_{(max)}$(Film)/cm^{-1}: (CH-aliphatic), (C=O); δ_H (400MHz, $CDCl_3$): 7.27 (5H,m, Ph-H), 5.49 (1H, d, J=8Hz, NCH), 4.04 (1H, m, OCH), 3.44 (1H, m, NCH_2), 2.92 (1H, m, NCH_2), 1.51 (2H, m, NCH_2CH_2), 0.81 (3H, t, J=7Hz, CH_2CH_3), 0.68 [10H, m, $N(CH_2)_2(CH_2)_5$], 0.68 (3H, d, J=6Hz, NCH_3); δ_C (100MHz, $CDCl_3$): 157.79 (C=O), 135.35, 128.49, 128.42, 126.16 (ArC), 54.85 (OCH), 41.91 (NCH), 31.82 (NCH_2), 29.28 (CH_2), 29.25 (CH_2), 27.66 (CH_2), 26.81 (CH_2), 22.68 (CH_2), 14.41 ($NCCH_3$), 14.15 (CH_3).

Chapter Three:

Experimental

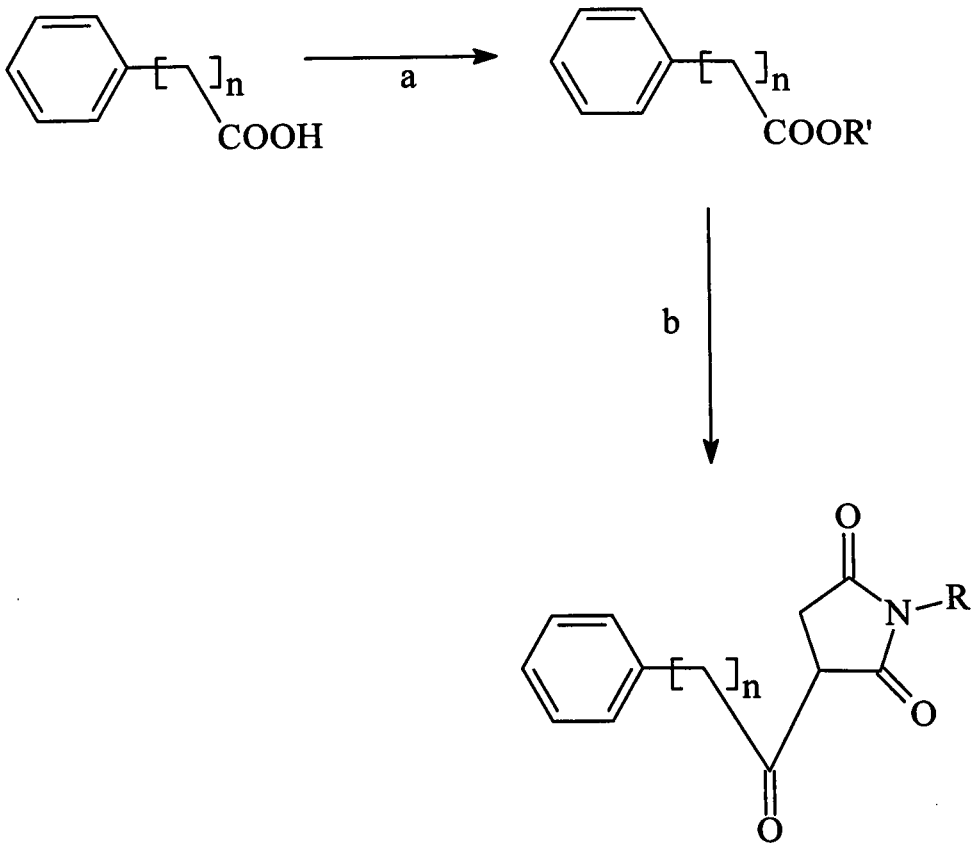
Synthesis of derivatives of pyrrolidine-2,5-dione as potential inhibitors of 5AR

3.0 SYNTHESIS OF DERIVATIVES OF PYRROLIDINE-2,5-DIONE AS POTENTIAL INHIBITORS OF 5AR

3.1 Discussion

A number of methods for the synthesis of pyrrolidine-2,5-dione derivatives involving the formation of the succinimide ring system have been described (Ahmed et al, 1995; Battersby and Westwood, 1987). The methods previously described utilised diacid containing compounds which underwent ring closure to give the pyrrolididn-2,5-dione structure (Scheme 3.1). However, in the synthesis of the target compounds which contained a C=O moiety, the synthesis of the pyrrolidine-2,5-dione ring system in the presence of the additional carbonyl functionality was thought to pose a number of problems and the potential synthesis of numerous side-products.

An alternative route which avoids the formation of the pyrrolidine-2,5-dione moiety is the direct acylation of the succinimide ring (Scheme 3.2) – it was postulated that the use of an appropriate base and an activated carboxyl functionality may allow a potential route to the target compounds with fewer synthetic problems. Within the research group, Denison (2001) has previously described the synthesis of a small range of compounds based upon the 1-methyl-3-(4'-substituted-phenylethanoyl)-pyrrolidine-2,5-dione based compounds using the scheme similar to Scheme 3.2. We therefore adopted a similar synthetic strategy in the synthesis of a wider range of the target compounds. It is interesting to note that whilst an activated C=O functionality would be expected to increase lead to the target compounds, it was found that only the use of an ester functionality lead to the target compounds in moderate to good yeild. Indeed, the use of an acyl chloride, lead to the target compound in <5% yeild – it was postulated that the poor yeild was due to a combination of rapid hydrolysis and reduction (by NaH) of the acyl chloride to give the COOH and CH_2OH derivatives respectively. As such, the reactions were undertaken using the weakly activated ester functionality.



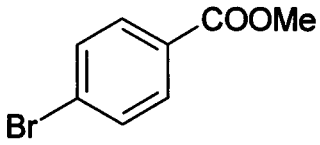
Scheme 3.2 Synthesis of the target compounds involving the acylation of n-substituted pyrrolidine-2,5-dione (a=R'OH/H_2SO_4/ b=NaH/*N*-substituted succinimide; n=1 to 7).

The esters of numerous carboxylic acids were used in the synthesis of the target compounds were the methyl esters. The esterification of the carboxylic acids were therefore undertaken using an acid catalyst [namely concentrated sulfuric acid (H_2SO_4)] which was added to the appropriate carboxylic acid in anhydrous methanol. The esterification reactions proceeded well and in high yield (85%) to give the required products.

The second step in the synthesis of the target compounds involved the acylation of the *N*-substituted-pyrrolidine-2,5-dione with the esters so as to give the desired product (Scheme 3.2). In general, the reactions proceeded well, however, the products were obtained in poor yield (ranging from 30% to 12%). Attempts to increase the yield (involving, for example, increasing the reaction

time) proved unsuccessful, however, sufficient compound was obtained for spectral analysis which showed that the final compound had indeed been synthesised. For example, the elemental analysis shows that compound was synthesised in a highly pure state and this was supported by the appropriate NMR (^{1}H and ^{13}C) and IR data.

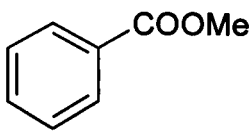
Methyl 4-bromobenzoate (135)



4-Bromobenzoic acid (1.0g, 4.97mmol) was added to methanol (MeOH) (50ml) and conc sulfuric acid (H_2SO_4) (10M, 1ml) and the solution refluxed for 4h. After cooling to room temperature, the methanol was removed under vacuum to leave an oil. The oil was dissolved in dichloromethane (DCM) (50ml) and washed with sodium hydroxide (NaOH) (2M, 10mL), water (3 x 30 mL), dried over anhydrous magnesium sulfate ($MgSO_4$) and filtered. Removal of DCM under vacuum gave a solid which was purified using flash chromatography to give **135** as a white solid (0.92g, 85%) [m.p 78.5-79.2°C R_f 0.81 Petroleum ether: diethyl ether (30: 70); lit. m.p. 78-79°C (Frank ,et al, 1996)].

$\nu_{(max)}$(Film)/cm^{-1}: 2998.0 (CH), 1716.2 (C=O), 1592.0 (Ar C=C); δ_H (300MHz, $CDCl_3$): 7.85 (2H, d, J=8Hz, Ph-H), 7.52 (2H, d, J=8Hz, Ph-H), 3.86 (3H, s, CH_3); δ_C (75MHz, $CDCl_3$): 166.25 (C=O), 131.66,128.97,127.99 (ArC), 52.26 (CH_3); LRMS (EI): 214 (M^+, 30%), 183 [M^+-OCH_3,100%] GC t_R 5.74 min.

Methyl benzoate (136)

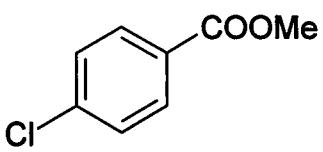


Compound **(136)** was synthesised following the same procedure as for compound **(135)** except that benzoic acid (1g, 8.19mmol) was used instead of 4-Bromobenzoic acid. The oil was purified using flash chromatography [R_f 0.84 petroleum ether: diethyl ether (70: 30)] to give **136** as clear oil (0.95g, 85%).

$\nu_{(max)}$(Film)/cm^{-1}: 2953.3 (CH), 1724.3 (C=O), 1601.6 (Ar C=C); δ_H (300MHz, $CDCl_3$): 7.93 (2H, d, J=8Hz, Ph-H), 7.35 (2H, t, J=8Hz, Ph-H), 3.76 (3H, s, CH_3);

δ_C (75 MHz, $CDCl_3$): 166.77 (C=O), 132.75, 130.09, 129.44, 128.23 (ArC), 51.80 (CH_3).

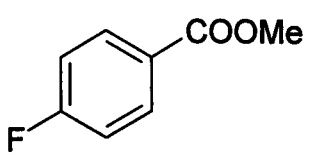
Methyl 4-chlorobenzoate (137)



Compound **(137)** was synthesised following the same procedure as for compound **(135)** except that 4-chlorobenzoic acid (1g, 6.38mmol) was used instead of 4-Bromobenzoic acid. The oil was purified using flash chromatography [R_f 0.81 petroleum ether: diethyl ether (70: 30)], to give **137** as clear colourless oil (0.82g, 75%).

$\nu_{(max)}$(Film)/cm^{-1}: 2953.9 (CH), 1726.0 (C=O), 1597.4 (Ar C=C); δ_H (300MHz, $CDCl_3$): 7.86 (2H, d, J=10Hz, Ph-H), 7.29 (2H, d, J=10Hz, Ph-H), 3.81 (3H, s, CH_3); δ_C (75 MHz, $CDCl_3$): 165.96 (C=O), 139.20, 130.86, 128.57, 128.49 (ArC), 51.11 (CH_3); LRMS (EI): 170 (M^+, 40%), 139 (M^+ -CH_3O, 100%); GC t_R 5.01 min.

Methyl 4-fluorobenzoate (138)

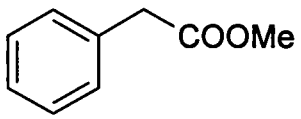


Compound **(138)** was synthesised following the same procedure as for compound **(135)** except that 4-fluorobenzoic acid (1g, 7.14mmol) was used instead of 4-Bromobenzoic acid. The oil was purified using flash chromatography [R_f 0.93 petroleum ether: diethyl ether (70: 30)] to give **138** as clear colourless oil (0.70g, 71%).

$\nu_{(max)}$(Film)/cm^{-1}: 2961.3 (CH), 1716.1 (C=O), 1596.6 (Ar C=C); δ_H (300MHz, $CDCl_3$): 7.90 (2H, d, J=8Hz Ph-H), 6.96 (2H, d, J=8Hz Ph-H), 3.77 (3H, s, CH_3);

δ_C (75 MHz, $CDCl_3$): 167.25, 165.79, 163.89 (C=O), 132.00, 131.88, 126.31, 126.27, 115.41, 115.12 (Ar-C), 51.87 (CH_3).

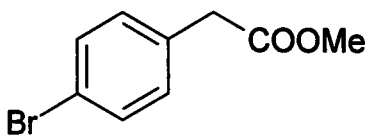
Methyl phenylacetate (139)



Compound **(139)** was synthesised following the same procedure as for compound **(135)** except that phenylacetic acid (1g, 7.35mmol) was used instead of 4-Bromobenzoic acid. The oil was purified using flash chromatography [R_f 0.64 petroleum ether: diethyl ether (70: 30)], to give **139** as clear colourless oil (0.89g, 81%).

$\nu_{(max)}$(Film)/cm^{-1}: 2953.2 (CH), 1739.9, (C=O), 1693.8, 1603.4 (Ar C=C); δ_H (300MHz, $CDCl_3$): 7.33 (5H, m, Ph-H), 3.65 (5H, s, CH_3 and CH_2); δ_C (75 MHz, $CDCl_3$): 172.01 (C=O), 134.07, 129.13, 128.0, 127.1 (ArC), 52.01 (CH_3), 41.19 (CH_2); LRMS (EI): 150 (M^+, 43%), 91 (M^+-$C_2H_3O_2$, 100%); GC t_R 4.05 min.

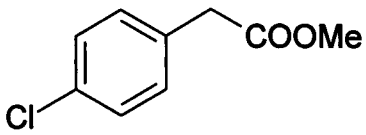
Methyl 4-bromophenylacetate (140)



Compound **(140)** was synthesised following the same procedure as for compound **(135)** except that 4-bromophenylacetic acid (1g, 4.65mmol) was used instead of 4-Bromobenzoic acid. The solid was purified using flash chromatography [R_f 0.83 petroleum ether: diethyl ether (30: 70)] to give **140** as white solid (0.82g, 78%).

$\nu_{(max)}$(Film)/cm^{-1}: 2952.3 (CH), 1738.4 (C=O), 1592.0 (C=C); δ_H (300 MHz, $CDCl_3$): 7.40 (2H, d, J=8Hz, Ph-H), 7.14 (2H, d, J=8Hz, Ph-H), 3.66 (2H, s, CH_2), 3.0 (2H, s, CH_3); δ_C (75 MHz, $CDCl_3$): 171.33 (C=O), 132.8, 131.5, 130.98, 121.0 (ArC), 52.03 (CH_2), 40.35 (CH_3); LRMS (EI): 228 (M^+, 20%), 169 (M^+-$C_2H_3O_2$, 100%); GC t_R 6.96 min.

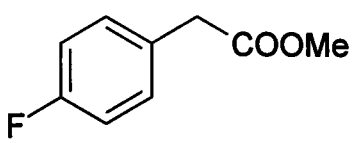
Methyl 4-chlorophenylacetate (141)



Compound **(141)** was synthesised following the same procedure as for compound **(135)** except that 4-chlorophenylacetic acid (1g, 5.86mmol) was used instead of 4-Bromobenzoic acid. The oil was purified using flash chromatography [R_f 0.86 petroleum ether: diethyl ether (30: 70)] to give **141** as yellow oil (0.92g, 86%).

$\nu_{(max)}$(Film)/cm^{-1}: 2953.3 (CH), 1727.3 (C=O), 1597.4, (Ar C=C); δ_H (300MHz, $CDCl_3$): 7.24 (2H, d, J=8Hz, Ph-H), 6.95 (2H, d, J=8Hz, Ph-H), 3.68 (3H, s, CH_3), 3.52 (2H, s, CH_2); δ_C (75 MHz; $CDCl_3$): 171.57 (C=O), 133.04, 132.44, 130.68 (ArC), 40.30 (CH_2), 52.11 (CH_3); LRMS (EI): 184 (M^+, 30%), 125 (M^+-$C_2H_3O_2$, 100%); GC t_R 6.96 min

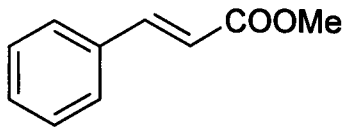
Methyl 4-fluorophenylacetate (142)



Compound **(142)** was synthesised following the same procedure as for compound **(135)** except that 4-fluorophenylacetic acid (1g, 6.48mmol) was used instead of 4-Bromobenzoic acid. The oil was purified using flash chromatography [R_f 0.84 petroleum ether: diethyl ether (30: 70)] to give **142** as clear colourless oil (0.90g, 83%).

$\nu_{(max)}$(Film)/cm^{-1}: 2964.3 (CH), 1720.3 (C=O), 1590.7 (C=C); δ_H (300MHz, $CDCl_3$): 7.21 (2H, dd, J=6Hz, Ph-H), 6.98 (2H, t, J=10Hz, Ph-H), 3.66 (2H, s, CH_2), 3.51 (3H, s, CH_3); δ_C (75 MHz, $CDCl_3$): 160.36 (C=O), 130.90, 130.79, 129.82, 129.78,115.47, 115.18 (ArC), 40.09 (CH_2), 51.91 (CH_3); LRMS (EI): 168 (M^+, 29%), 109 (M^+ - $C_2H_3O_2$%); GC t_R 3.62 min.

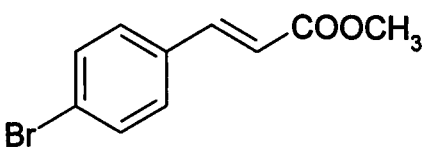
Methyl cinnamate (143)



Compound **(143)** was synthesised following the same procedure as for compound **(135)** except that Cinnamic acid (1.00g, 6.75mmol) was used instead of 4-Bromobenzoic acid. The solid was purified using flash chromatography [R_f 0.55 petroleum ether: diethyl ether (50: 50)] to give **143** as white solid (0.80g, 73%), mp (35.6-37.3^{0}C).

$\nu_{(max)}$(Film)/cm^{-1}: 2961.4 (CH), 1697.0, 1599.3 (C=O); δ_H (300 MHz, $CDCl_3$): 7.53 (1H, d, J=16Hz, , CH-C<u>H</u>), 7.27 (2H, m, Ph-<u>H</u>), 7.12 (3H, m, Ph-<u>H</u>), 6.22 (1H, d, J=16Hz C<u>H</u>-CH) 3.55 (3H, s, C<u>H</u>$_3$); δ_c (75 MHz, $CDCl_3$): 166.88 (<u>C</u>=O), 144.50, 134.23, 130.07, 128.68 (ArC), 127.97 (CH=CH), 117.68 (<u>C</u>HCO$_2$), 51.24 (<u>C</u>H$_3$); LRMS (EI): 162 (M^+, 43%), 103 (M^+ - $C_2H_3O_2$, 100%); GC t_R 6.33 min.

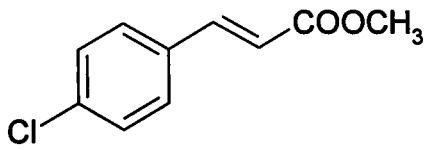
Methyl 4-bromocinnamate (144)



Compound **(144)** was synthesised following the same procedure as for compound **(135)** except that 4-bromocinnamic acid (2.06g, 9.03mmol) was used instead of 4-Bromobenzoic acid. The solid was purified using flash chromatography [R_f 0.58 petroleum ether: diethyl ether (30: 70)] to give **144** as white solid (1.94g, 91%), mp (93.2-94.4^{0}C),

$\nu_{(max)}$(Film)/cm^{-1}: 2960.2 (CH), 1692.0, 1597.3 (C=O); δ_H (300 MHz; $CDCl_3$): 7.51 (1H, d, J=16Hz, CH=C<u>H</u>), 7.42 (2H, d, J=8Hz, Ph-<u>H</u>), 7.31 (3H, d, J=8Hz, Ph-<u>H</u>), 6.33 (1H, d, J=16Hz, C<u>H</u>=CH) 3.7 (3H, s, CH_3); δ_C (75MHz, $CDCl_3$): 167.04 (<u>C</u>=O), 143.39, 133.22, 132.08, 129.42 (ArC), 124.51 (CH=CH), 118.43 (Ph-<u>C</u>H), 51.77(<u>C</u>H$_3$); LRMS (EI): 237 (M^+, 14%), 51 (M^+ - C_8H_7Br, 100%) GC t_R 8.26 min.

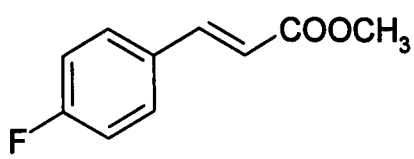
Methyl 4-chlorocinnamate (145)



Compound **(145)** was synthesised following the same procedure as for compound **(135)** except that 4-chlorophenylacetic acid (1g, 5.44mmol) was used instead of 4-Bromobenzoic acid. The solid was purified using flash chromatography [R_f 0.53 petroleum ether: diethyl ether (30: 70)] to give **145** as white solid (0.82g, 76%), mp (76.7-77.6^{0}C).

$\nu_{(max)}$(Film)/cm^{-1}: 2949 (CH),1633.8 (C=O); δ_H (300 MHz, $CDCl_3$): 7.65 (1H, d, J=16Hz, CH=C<u>H</u>), 7.42 (2H, d, J=8Hz, Ph-<u>H</u>), 7.33 (2H, d, J=8Hz, Ph-<u>H</u>), 6.37 (1H, d, J=16Hz, C<u>H</u>=CH) 3.73 (3H, s, CH_3); δ_C (75MHz, $CDCl_3$): δ_C (75MHz, $CDCl_3$): 167.18 (<u>C</u>=O), 143.42, 136.20, 132.83, 129.23,129.1 (ArC), 118.34 (<u>C</u>H=CH), 51.83 (CH=<u>C</u>H), 51.79 (<u>C</u>H$_3$); LRMS (EI): 196 (M^+, 57%), 75 (M^+ - C_7H_5Cl, 100%) GC t_R 7.86 min.

Methyl 4-fluorocinnamate (146)

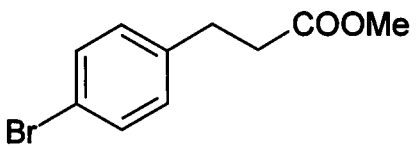


Compound **(146)** was synthesised following the same procedure as for compound **(135)** except that 4-fluorophenylacetic acid (1g, 6.02mmol) was used instead of 4-Bromobenzoic acid. The compound was purified by column chromatography [R_f 0.40 petroleum ether: diethyl ether (30: 70)] to give **146** as white solid (0.85g, 78%), mp (45.6-46.9^{0}C).

$\nu_{(max)}$(Film)/cm^{-1}: 3274.2 (CH),1682.4 (C=O); δ_H (300 MHz, $CDCl_3$): 7.67 (1H, d, J=14Hz, CH=C<u>H</u>), 7.48 (2H, m, Ph-<u>H</u>), 7.04 (2H, t, J=7Hz, Ph-<u>H</u>), 6.33 (1H, d, J=14Hz, C<u>H</u>=CH) 3.79 (3H, s, CH_3); δ_C (75MHz, $CDCl_3$): δ_C (75MHz, $CDCl_3$):

189.05 (C=O), 143.58, 136.00, 12983, 129.89, 117.51, 116.20, (ArC), 115.91 (CH=CH), 51.78 (CH_3).

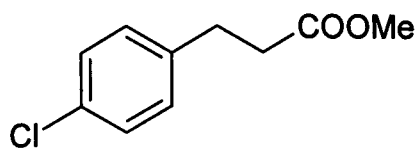
Methyl 3-bromophenylpropionate (147)



Palladium charcoal (0.1g) was added to the metal insert which contained a solution of **(144)** (1g, 4.15mmol) in chloroform (10 ml). The insert was placed inside the hydrogenation reaction vessel and flushed with hydrogen. The reaction was left shaking for four hours. After 4 hours the solvent was filtered using selite and rotary evaporated to yield **147** as clear colourless oil (0.75g, 74%), [R_f = 0.80 Petroleum ether: Diethyl ether (30: 70)].

$\nu\nu_{(max)}$(Film)/cm^{-1}: 2952.0 (CH), 1739.8 (C=O); δ_H (300 MHz, $CDCl_3$): 7.34 (2H, m, Ph-H), 7.31 (2H, m, Ph-H), 3.68 (3H, s, CH_3), 2.99 (2H, t, J=8Hz, Ph-CH_2), 2.65 (2H, t, J=8Hz CH_2-CH_2); δ_C (75MHz, $CDCl_3$): 173.26 (C=O), 140.58, 128.54, 128.32, 126.31 (ArC), 51.54 (CH_3), 35.69 (Ph-CH_2), 30.97 (CH_2-CH_2).

Methyl 3-chlorophenylpropionate (148)

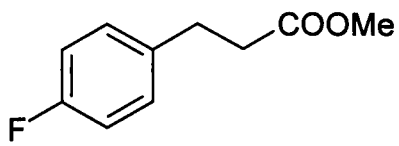


Palladium charcoal (0.1g) was added to the metal insert which contained a solution of **(145)** (1g, 5.08mmol) in chloroform (10 ml). The insert was placed inside the hydrogenation reaction vessel and flushed with hydrogen. The reaction was left shaking for four hours. After 4 hours the solvent was filtered using selite and rotary evaporated to yield **148** as clear oil (0.80g, 79%), [R_f = 0.80 Petroleum ether: Diethyl ether (30: 70)].

$\nu_{(max)}$(Film)/cm^{-1}: 2952.3 (CH), 1738.8 (C=O); δ_H (300 MHz, $CDCl_3$): 7.18 (2H, m, Ph-H), 7.09 (2H, m, Ph-H), 3.60 (3H, s, CH_3), 2.86 (2H, t, J=8Hz, Ph-CH_2), 2.47

(2H, t, J=8Hz CH_2-$C\underline{H}_2$); δ_C (75MHz, $CDCl_3$): 17.92 ($\underline{C}$=O), 138.99, 1131.94, 129.67, 128.54 (ArC), 51.55 ($\underline{C}H_3$), 35.37 (Ph-$\underline{C}H_2$), 30.16 (CH_2-$\underline{C}H_2$); LRMS (EI): 198 (M^+, 33%), 138 (M^+-$C_2H_3O_2$, 100%); GC t_R 6.36 min.

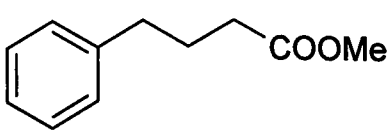
Methyl 3-fluorophenylpropionate (149)



Palladium charcoal (0.1g) was added to the metal insert which contained a solution of **(146)** (1g, 5.55mmol) in chloroform (10 ml). The insert was placed inside the hydrogenation reaction vessel and flushed with hydrogen. The reaction was left shaking for four hours. After 4 hours the solvent was filtered using selite and rotary evaporated to yield **149** as clear colourless oil (0.78g, 77%), [R_f = 0.83 Petroleum ether: Diethyl ether (30: 70)].

$\nu_{(max)}$(Film)/cm^{-1}: 2932.0 (CH), 1739.7 (C=O); δ_H (300 MHz, $CDCl_3$): 7.08 (2H, m, Ph-$\underline{H}$), 6.92 (2H, t, J=8Hz, Ph-$\underline{H}$), 3.61 (3H, s, CH_3), 2.88 (2H, t, J=7Hz, Ph-$C\underline{H}_2$), 2.65 (2H, d, J=8Hz CH_2-$C\underline{H}_2$); δ_C (75MHz, $CDCl_3$): 173.02, 163.06, 159.82 ($\underline{C}$=O), 136.21, 136.17, 129.75, 129.64 (ArC), 115.31, 115.03 (Ar$\underline{C}$-F), 51.46 ($\underline{C}H_3$), 35.64 (Ph-$\underline{C}H_2$), 30.03 ($\underline{C}H_2$); LRMS (EI): 182 (M^+, 43%), 109 (M^+ - $C_3H_5O_2$, 100%); GC t_R 7.84 min.

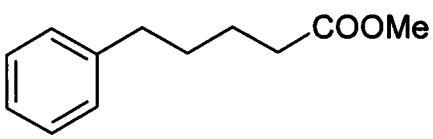
Methyl 4-phenylbutyrate (150)



Compound **(150)** was synthesised following the same procedure as for compound **(135)** except that 4-phenylbutyric acid (1g, 6.09mmol) was used instead of compound 4-Bromobenzoic acid. Compound was purified by column chromatography [R_f 0.95 Petroleum ether: Diethyl ether (30: 70)] to give **150** as clear colourless oil (0.92g, 86%).

$\nu_{(max)}$(Film)/cm^{-1}: 2952.1 (Ar–CH), 1738.4 (C=O), 1453.2, 1437.5 (CH bending); δ_H (300 MHz, $CDCl_3$): 7.31 (2H, m, Ph-H), 7.22 (3H, m, Ph-H) 3.68 (3H, s, CH_3), 2.68 (2H, t, J= 18Hz, Ph-CH_2), 2.36 (2H, t, J=8Hz, Ph-CH_2-CH_2), 1.96 (2H, t, J=8Hz, Ph-CH_2-CH_2-CH_2); δ_C (75MHz, $CDCl_3$): 173.94 (C=O), 141.40, 128.52, 128.42, 126.02 (ArC) 51.51 (CH_3), 35.14 (Ph-CH_2), 33.37 (CH_2), 26.54 (CH_2); LRMS (EI): 178 (M^+, 36%), 104 (M^+-$C_3H_5O_2$, 100%); GC t_R 6.12 min.

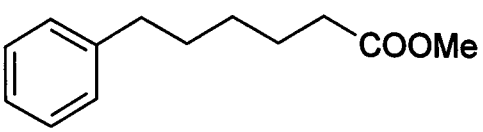
Methyl 5-phenylpentenoate (151)



Compound **(151)** was synthesised following the same procedure as for compound **(135)** except that 5-phenylpentanoic acid (1g, 5.61mmol) was used instead of 4-Bromobenzoic acid. Compound was purified by column chromatography [R_f 0.94 Petroleum ether: Diethyl ether (30: 70)] to give **151** as clear colourless oil (0.89g, 82%).

$\nu_{(max)}$(Film)/cm^{-1}: 2963.1 (Ph-CH), 1728.6 (C=O); δ_H (300 MHz, $CDCl_3$): 7.31 (2H, m, Ph-H), 7.21 (H, m, Ph-H) 3.68 (3H, s, CH_3), 2.67 (2H, t, J=8Hz, Ph-CH_2-CH_2), 2.37 (2H, t, J=8Hz, Ph-CH_2-CH_2), 1.69 (4H, m, CH_2-CH_2COO); δ_C (75MHz, $CDCl_3$): 173.99 (C=O), 142.13, 128.42, 128.36, 125.82 (Ar-C) 51.44 (CH_3), 35.61 (CH_2), 33.92 (CH_2), 30.95 (CH_2), 24.61 (CH_2), ; LRMS (EI): 192 (M^+, 10%), 91 (M^+-$C_5H_9O_2$, 100%); GC t_R 7.013 min.

Methyl 6-phenylhexanoate (152)

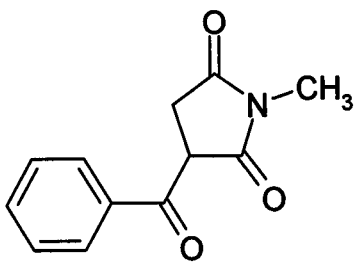


Compound **(152)** was synthesised following the same procedure as for compound **(135)** except that 6-phenylhexanoic acid (1g, 5.20mmol) was used instead of compound 4-Bromobenzoic acid. Compound was purified by column

chromatography [R_f 0.92 Petroleum ether: Diethyl ether (30: 70)] to give **152** as clear colourless oil (0.85g, 79%).

$\nu_{(max)}$(Film)/cm^{-1}: 2932.0 (Ph-CH), 1739.7 (C=O); δ_H (300 MHz, $CDCl_3$): 7.2 (5H, m, Ph-H), 3.7 (3H, s, CH_3), 2.7 (2H, m, Ph-CH_2), 1.6 (4H, m, Ph-CH_2-CH_2), 1.3 (4H, m, CH_2-CH_2-COO); δ_C (75MHz, $CDCl_3$): 174.34 (C=O), 142.69, 128.41, 128.27, 125.62 (ArC) 51.50 (CH_3), 35.90 (Ph-CH_2), 33.98 (CH_2), 31.32 (CH_2), 28.93, (CH_2), 24.64 (CH_3); LRMS (EI): 207 (M^+, 17%), 91 (M^+-$C_6H_{11}O_2$, 100%); GC t_R 7.84 min.

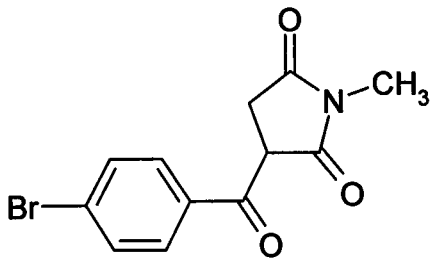
1-Methyl-3-(benzoyl)-pyrrolidine-2,5-dione (153)



Sodium hydride (NaH) (0.29g, 12.25mmol) was added to a solution of *N*-methyl succinimide (0.83g, 7.35mmol) in anhydrous THF (30 ml). methyl benzoate (1g, 7.35mmol) was added to the solution and refluxed for 20hr. After cooling, the solvent was removed under vacuum to leave an oil. The oil was neutralised with aqueous hydrochloric acid (2M, 1ml). Diethyl ether (50ml) was added to the oil and the organic layer was washed with water (3 x 30ml) and dried over anhydrous $MgSO_4$ and filtered. Removal of the solvent under vacuum gave an oil which was purified using flash chromatography to give **153** as yellow oil (0.25g, 22%). [R_f 0.54 Petroleum ether: Diethyl ether (30: 70)]

$\nu_{(max)}$(Film)/cm^{-1}: 2924.0 (Ph–CH), 1755.6 (C=O); δ_H (400 MHz, $CDCl_3$): 8.05 (2H, d, J= 8Hz, Ph-H), 7.48 (3H, t, J=7Hz, Ph-H) 4.80 (1H, dd, J=4Hz, 16Hz, CH-CO), 3.32 (1H, dd, J=4Hz, 8Hz, CHH-CO), 2.93 (3H, s, CH_3), 2.82 (1H, dd, J=8Hz, 16Hz, CHH-CO); δ_C (100MHz, $CDCl_3$): 192.04, 176.19, 172.87 (C=O), 135.54, 134.26, 129.91, 1128.89 (ArC), 47.84 (CO-CH), 31.48 (CH_2), 24.8 (CH_3); LRMS (EI): 216 (M^+,14%), 105 (M^+ - $C_5H_5O_2N$,100%); GC t_R 10.07 min.

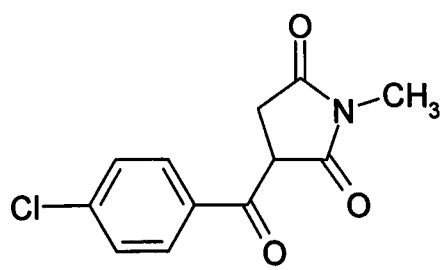
1-Methyl-3-(4'-bromobenzoyl)-pyrrolidine-2,5-dione (154)



Compound **(154)** was synthesised following the same procedure as for compound **(153)** except that methyl 4-bromobenzoate (1g, 4.65mmol) was used instead of compound methyl benzoate. The crude oil was purified by flash chromatography [R_f 0.53 Petroleum ether: Diethyl ether (30: 70)] to give **154** as yellow oil (0.19g, 12%).

$\nu_{(max)}$(Film)/cm^{-1}: 2948.4 (Ph–CH), 1776.9, 1702.7, 1685.5 (C=O),1437.8 (CH aliphatic); δ_H (300 MHz, $CDCl_3$): 7.97 (2H, d, J= 8Hz, Ph-H), 7.66 (2H, d, J= 8Hz, Ph-H) 4.77 (1H, d, J= 4Hz, CH-CO), 3.43 (1H, dd, J= 4Hz, 16Hz, CHH-CO), 2.98 (3H, s, CH_3), 2.86 (1H, dd, J=8Hz, CHH-CO); δ_C (75MHz, $CDCl_3$): 191.44, 175.59, 172.49 (C=O), 134.13, 132.00, 129.83, 129.05 (ArC), 48.62 (CO-CH), 31.36 (CH_2), 24.49 (CH_3); LRMS (EI): 295 (M^+ , 17%), 183 (M^+ - $C_5H_6O_2N$, 100%); GC t_R 11.70 min.

1-Methyl-3-(4'-chlorobenzoyl)-pyrrolidine-2,5-dione (155)

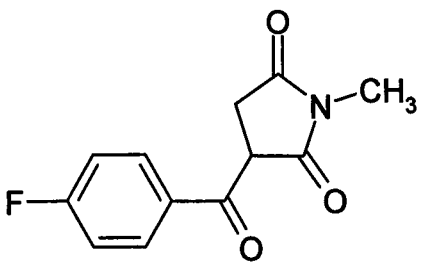


Compound **(155)** was synthesised following the same procedure as for compound **(153)** except that methyl 4-chlorobenzoate (1g, 0.58mmol) was used instead of compound methyl benzoate. The crude oil was purified by flash

chromatography [R_f 0.54 Petroleum ether: Diethyl ether (30: 70)] to give **155** as yellow oil (0.29g, 18%).

$\nu_{(max)}$(Film)/cm^{-1}: 2949.0 (Ph–CH), 1778.4, 1703.2 (C=O), 1437.8 (CH aliphatic); δ_H (300 MHz, $CDCl_3$): 7.93 (2H, d, J= 8Hz, Ph-H), 7.38 (2H, d, J= 8Hz, Ph-H) 4.73 (1H, m, CH-CO), 3.28 (1H, dd, J= 4Hz, 16Hz, CHH-CO), 2.86 (3H, s, CH_3), 2.75 (1H, dd, J=8Hz, CHH-CO); δ_C (75MHz, $CDCl_3$): 191.27, 175.68, 172.64 (C=O), 140.81, 131.17, 129.05, 128.86 (ArC), 48.60 (CO-CH), 31.35 (CH_2), 24.37 (CH_3); LRMS (EI): 251 (M^+ , 17%), 139 (M^+ - $C_5H_6O_2N$,100%); GC t_R 11.10 min.

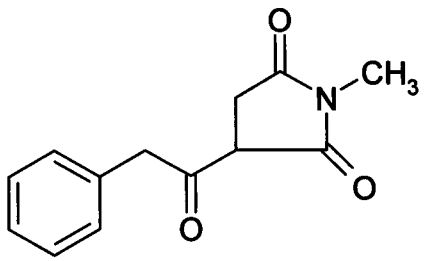
1-Methyl-3-(4'-fluorobenzoyl)-pyrrolidine-2,5-dione (156)



Compound **(156)** was synthesised following the same procedure as for compound **(153)** except that methyl 4-fluorobenzoate (1g, 0.65mmol) was used instead of compound methyl benzoate. The crude oil was purified by flash chromatography [R_f 0.54 Petroleum ether: Diethyl ether (30: 70)] to give **156** as yellow oil (0.23g, 13%).

$\nu_{(max)}$(Film)/cm^{-1}: 2950.0 (Ph–CH), 1779.5, 1703.3 (C=O), 1436.8 (CH_2-CO); δ_H (300 MHz, $CDCl_3$): 8.13 (2H, m, Ph-H), 7.15 (2H, t, J= 7Hz, Ph-H) 4.78 (1H, dd, = 6Hz, 12Hz, CH-CO), 3.41 (1H, d, J= 6Hz, CHH-CO), 2.96 (3H, s, CH_3), 2.84 (1H, dd, J=8Hz, CHH-CO); δ_C (75MHz, $CDCl_3$): 191.27, 175.68, 172.64 (C=O), 133.74, 132.61, 129.90, 129.79 (ArC), 48.57 (CH-CO), 31.42 (CH_2), 25.37 (CH_3); LRMS (EI): 235 (M^+, 17%), 123 ((M^+ - $C_5H_6O_2N$,100%); GC t_R 10.08 min.

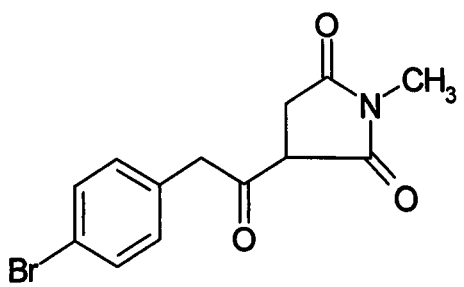
1-Methyl-3-(4'-phenylethanoyl)-pyrrolidine-2,5-dione (157)



Compound **(157)** was synthesised following the same procedure as for compound **(153)** except that methyl phenylacetate (1g, 0.65mmol) was used instead of methyl benzoate. The crude oil was purified by flash chromatography [R_f 0.53 Petroleum ether: Diethyl ether (30: 70)] to give **157** as yellow oil (0.32g, 18%).

$\nu_{(max)}$(Film)/cm^{-1}: 2946.7 (Ph–CH), 1771.9, 1698.5 (C=O); δ_H (300 MHz, $CDCl_3$): 7.27 (2H, m, Ph-H), 7.25 (3H, d, J=8Hz Ph-H), 4.11 (2H, d, J=8Hz Ph-CH_2), 4.01 (1H, dd, J= 6Hz, 14Hz, CH-CO), 3.17 (1H, dd, J= 6Hz, 12 Hz, CHH-CO), 3.11 (3H, s, CH_3), 2.51 (1H, dd, J=8Hz, 18Hz, CHH-CO); δ_C (75MHz, $CDCl_3$): 190.28, 175.58, 172.70 (C=O), 132.90, 129.76, 128.90, 127.32 (ArC), 51.71 (Ph-CH_2), 49.51 (CH-CH_2), 39.37 (CH-CH_2), 24.23 (CH_3); LRMS (EI): 231 (M^+, 55%), 91 (M^+ - $C_6H_6O_3N$,100%); GC t_R 10.28 min; Elemental analysis: Found C, 67.36%; H, 5.67%; N, 6.13%; $C_{13}H_{13}O_3N$ requires C, 67.52%; H, 5.67; N, 6.06%.

1-Methyl-3-(4'-bromophenylethanoyl)-pyrrolidine-2,5-dione (158)

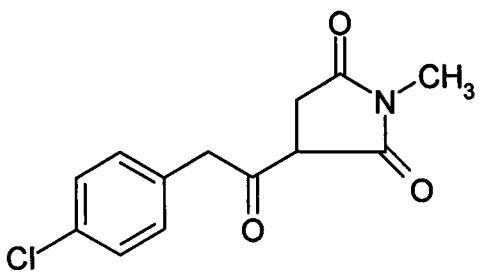


Compound **(158)** was synthesised following the same procedure as for compound **(153)** except that methyl 4-bromophenylacetate (1g, 4.36mmol) was used instead of Methyl benzoate. The crude oil was purified by flash

chromatography [R_f 0.54 Petroleum ether: Diethyl ether (30: 70)] to give **158** as yellow oil (0.40g, 27%).

$\nu_{(max)}$(Film)/cm^{-1}: 1778.1, 1701.2 (C=O); δ_H (300MHz, $CDCl_3$): δ_H (300 MHz, $CDCl_3$): 7.42 (2H, d, J=8Hz, Ph-H), 7.10 (2H, d, J=8Hz, Ph-H), 4.17 (2H, d, J= 16Hz, Ph-CH_2), 3.23 (1H, dd, J=6Hz, CH), 3.23 (1H, d, J= 6Hz, CHH-CO), 2.96 (3H, s, CH_3), 2.58 (1H, dd, J=8Hz, 18Hz, CHH-CO); δ_C (75 MHz, $CDCl_3$): 190.37, 175.34, 172.49 (C=O), 131.95, 131.79, 131.48, 130.58 (ArC), 51.97 (CH), 48.78 (CH_3), 31.40 (CH-CH_2), 25.33 (Ph-CH_2); LRMS (EI): 311 ($M^{+\cdot}$ 11%), 113 (M^+ - $C_6H_6O_3N$,100%); GC t_R 11.137 min; Elemental analysis: Found C, 51.83%; H, 4.30%; N, 3.82%; $C_{14}H_{14}BrO_3N$ requires C, 51.87%; H, 4.36; N, 4.32%.

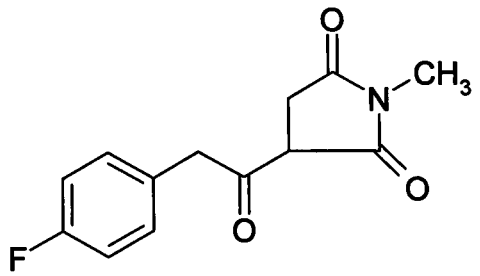
1-Methyl-3-(4'-chlorophenylethanoyl)-pyrrolidine-2,5-dione (159)



Compound **(159)** was synthesised following the same procedure as for compound **(153)** except that methyl 4-chlorophenylacetate (1g, 5.42mmol) was used instead of methyl benzoate. The crude oil was purified by flash chromatography [R_f 0.56 Petroleum ether: Diethyl ether (30: 70)] to give **159** as yellow oil (0.35g, 22%).

$\nu_{(max)}$(Film)/cm^{-1}: 2947.4 (Ph–CH), 1779.7, 1700.5 (C=O), δ_H (300 MHz, $CDCl_3$): 7.26 (2H, m, Ph-H), 7.18 (2H, d, J=18Hz, Ph-H), 4.18 (2H, d, J=18Hz Ph-CH_2), 3.99 (1H, dd, J=6Hz, 14Hz, CH-CO), 3.23 (1H, dd, J=6Hz, 12 Hz, CHH-CO), 2.93 (3H, s, CH_3), 2.55 (1H, dd, J=8Hz, 18Hz, CHH-CO); δ_C (75MHz, $CDCl_3$): 190.58, 175.34, 172.50 (C=O), 133.45, 131.28, 130.23, 128.99 (ArC), 51.95 (Ph-CH_2), 48.71 (CH-CH_2), 31.39 (CH-CH_2), 25.31 (CH_3); LRMS (EI): 265 (M^+, 12%), 125 (M^+ - $C_6H_6O_3N$,100%); GC t_R 11.56 min

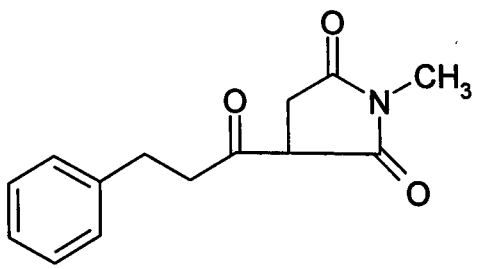
1-Methyl-3-(4'-fluorophenylethanoyl)-pyrrolidine-2,5-dione (160)



Compound **(160)** was synthesised following the same procedure as for compound **(153)** except that methyl 4-fluorophenylacetate (1g, 5.95mmol) was used instead of methyl benzoate. The crude oil was purified by flash chromatography [R_f 0.55 Petroleum ether: Diethyl ether (30: 70)] to give **160** as yellow oil (0.32g, 22%).

$\nu_{(max)}$(Film)/cm^{-1}: 2949.8 (Ph–CH), 1777.9, 1698.2 (C=O), δ_H (300 MHz, $CDCl_3$): 7.17 (2H, m, Ph-H), 7.01 (2H, t, J=8Hz, Ph-H), 4.21 (2H, d, J=8Hz Ph-CH_2), 4.00 (1H, dd, J=6Hz, 14Hz, CH-CO), 3.20 (1H, dd, J=6Hz, 12 Hz, CHH-CO), 2.93 (3H, s, CH_3), 2.59 (1H, dd, J=8Hz, 18Hz, CHH-CO); δ_C (75MHz, $CDCl_3$): 175.42, 172.59, 163.74 (C=O), 131.41, 130.49, 128.63, 115.84 (ArC), 51.89 (Ph-CH_2), 48.51 (CH-CH_2), 31.36 (CH-CH_2), 25.25 (CH_3); LRMS (EI): 249 (M^+, 17%), 109 (M^+ - $C_6H_6O_3N$,100%); GC t_R 9.89 min

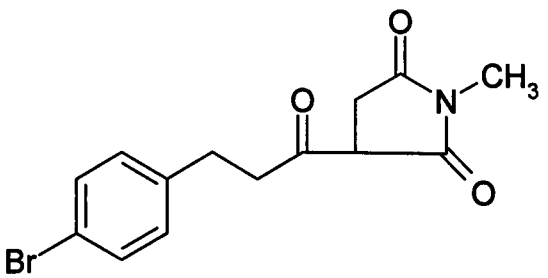
1-Methyl-3-(3-phenyl-propionyl)-pyrrolidine-2,5-dione (161)



Compound **(161)** was synthesised following the same procedure as for compound **(153)** except that methyl 3-phenylpropionate (1g, 6.09mmol) was used instead of methyl benzoate. The crude oil was purified by flash chromatography [R_f 0.55 Petroleum ether: Diethyl ether (30: 70)] to give **161** as yellow oil (0.35g, 23%).

$\nu_{(max)}$(Film)/cm^{-1}: 2937.95 (Ph-CH), 1704.06 (C=O); δ_H (300 MHz, $CDCl_3$): 7.26 (2H, d, J=8Hz, Ph-H), 7.18 (3H, d, J=8Hz, Ph-H), 3.8 (1H, dd, J=4Hz, 8Hz, CHH-CO), 3.32 (2H, m, CH-CH_2), 3.13 (1H, dd, J=6Hz, 12Hz, CHH-CO), 2.8 (3H, t, J=8Hz, CH_3); δ_C (75 MHz, $CDCl_3$): 180.08, 175.59, 172.60, (C=O), 140.31, 128.56, 128.36, 126.30 (ArC), 53.18 (CH), 53.15 (CH-CH_2-CO), 44.13 (CH_2), 31.23 (CH_3); Elemental analysis: Found C, 67.29%; H, 5.27%; N, 5.16%; $C_{14}H_{15}O_3N$ requires C, 68.60%; H, 6.12; N, 5.71%.

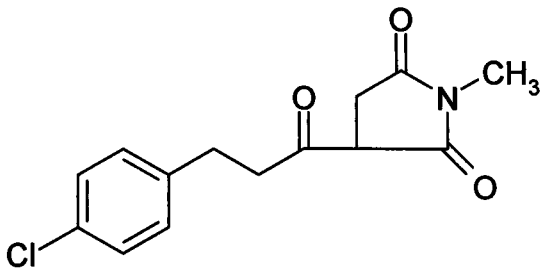
3-[3-(4-Bromo-phenyl)-propionyl]-1-methyl-pyrrolidine-2,5-dione (162)



Compound **(162)** was synthesised following the same procedure as for compound **(153)** except that methyl 3-bromophenylpropionate (1g, 4.15mmol) was used instead of methyl benzoate. The crude oil was purified by flash chromatography [R_f 0.55 Petroleum ether: Diethyl ether (30: 70)] to give **162** as yellow oil (0.22g, 21%).

$\nu_{(max)}$(Film)/cm^{-1}: 2946.65 (Ph–CH), 1776.27 (C=O); δ_H (300 MHz, $CDCl_3$): 7.33 (2H, d, J=8Hz Ph-H), 6.99 (2H, d, J=8Hz Ph-H), 3.85 (2H, d, J=4Hz, CH-CH_2), 3.23 (1H, d, J=4Hz, CH), 2.84 (3H, s, CH_3), 2.42 (2H, m, Ph-CH_2), 2.35 (2H, m, Ph-CH_2-CH_2); δ_C (75 MHz, $CDCl_3$): 175.49, 172.50 (C=O), 139.31, 132.02, 130.11, 128.75, (ArC), 53.18 (CH), 44.18 (CH_3), 29.69 (CH-CH_2), 28.66 (CH_2COOCH), 28.21 (Ph-CH_2), 28.18 (Ph-CH_2-CH_2); Elemental analysis: Found C, 51.83%; H, 4.30%; N, 3.82%; $C_{14}H_{14}BrO_3N$ requires C, 51.87%; H, 4.36; N, 4.32%.

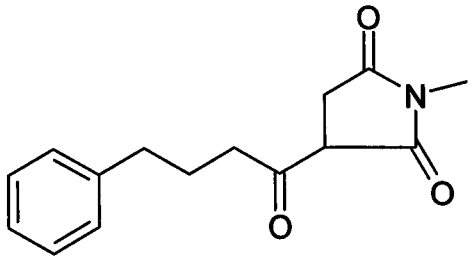
3-[3-(4-chloro-phenyl)-propionyl]-1-methyl-pyrrolidine-2,5-dione (163)



Compound **(163)** was synthesised following the same procedure as for compound **(153)** except that Methyl 3-chlorophenylpropionate (1g, 5.08mmol) was used instead of Methyl benzoate. The crude oil was purified by flash chromatography [R_f 0.54 Petroleum ether: Diethyl ether (30: 70)] to give **163** as yellow oil (0.25g, 19%).

$\nu_{(max)}$(Film)/cm^{-1}: 2947.4 (Ph–CH), 1779.7, 1700.5 (C=O); δ_H (300 MHz, $CDCl_3$): 7.11 (2H, d, J= 8Hz, Ph-H), 7.03 (2H, d, J=8Hz, Ph-H), 3.82 (1H, dd, J=6Hz, 14Hz, CH), 3.32 (2H, m, Ph-CH_2), 3.12 (2H, dd, J=6Hz, 14Hz, CO-CH-CH_2), 2.83 (3H, s, CH_3), 2.54 (2H, d, J=8Hz, CH_2-CH_2); δ_C (75 MHz, $CDCl_3$): 180.73, 175.57, 175.56, (C=O), 138.87, 131.88, 129.77, 128.56 (ArC), 53.15 (Ph-CH_2), 44.13 (CH-CH_2), 31.23 (CH-CH_2), 29.70 (CH_2-CH_2), 25.25 (CH_3); LRMS (EI): 279 (M^+ , 44%), 112 (M^+ - $C_8H_9O_3N$,100%); GC t_R 11.91 min; Elemental analysis: Found C, 60.16%; H, 5.07; N, 4.86%; $C_{14}H_{14}ClO_3N$ requires C, 60.10%; H, 5.05; N, 5.00%.

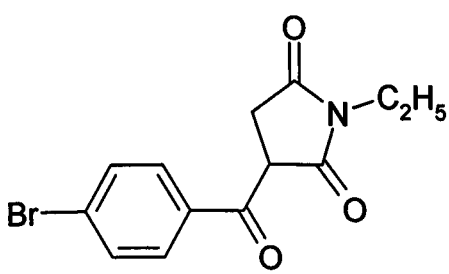
1- Methyl-3-(4-phenyl-butyryl)-pyrrolidine-2,5-dione (164)



Compound **(164)** was synthesised following the same procedure as for compound **(153)** except that Methyl 4-phenylbutyrate (1g, 5.61mmol) was used instead of Methyl benzoate. The crude oil was purified by flash chromatography [R_f 0.52 Petroleum ether: Diethyl ether (30: 70)] to give **164** as yellow oil (0.43g, 30%).

$\nu_{(max)}$(Film)/cm^{-1}: 2924.1 (Ph–CH), 1753.5 (C=O); δ_H (300 MHz, $CDCl_3$): 7.26 (2H, m, Ph-H), 7.18 (3H,m, Ph-H), 3.85 (1H, dd, J=4Hz, CH), 3.65 (3H, s, CH_3), 2.93 (2H, m, CH-CH_2), 2.64 (2H, m, CH_2COOCH), 2.20 (2H, m, Ph-CH_2), 1.92 (2H, m, Ph-CH_2-CH_2); δ_C (75 MHz, $CDCl_3$): 177.60 (C=O), 141.26, 128.48, 128.41, 126.02 (ArC), 42.39 (CH), 34.98 (CH_3), 33.31 (CH-CH_2), 28.19 (CH_2COOCH), 26.26 (Ph-CH_2), 24.72 (Ph-CH_2 CH_2); LRMS (EI): 259 (M^+, 29%), 104 (M^+ - $C_7H_9O_3N$,100%); GC t_R 11.137 min.

3-(4-Bromo-Benzoyl)-1-ethyl-pyrrolidine-2.5-dione (165)

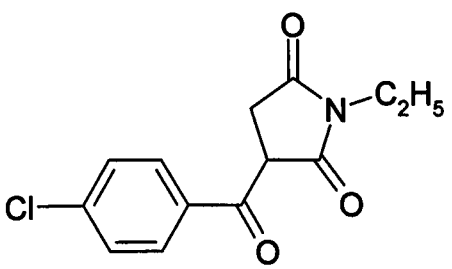


Compound **(165)** was synthesised following the same procedure as for compound **(153)** except that Methyl 4- bromobenzoate (1g, 4.65mmol) was used instead of methyl benzoate and and 1-Ethyl-pyrrolidine-2,5-dione (0.59g,

4.65mmol) was used instead of a solution of *N*-methyl succinimide. The crude oil was purified by flash chromatography [R_f 0.36 Petroleum ether: Diethyl ether (50: 50)] to give **165** as yellow oil (0.38g, 26%).

$\nu_{(max)}$(Film)/cm^{-1}: 2937.60 (Ph–CH), 1775.37, 1704.21 (C=O), δ_H (400 MHz, $CDCl_3$): 8.04 (2H, d, J=8Hz, Ph-H), 7.48 (2H, d, J=8Hz, Ph-H), 4.76 (1H, dd, J=4Hz, 4Hz, CH), 3.52 (2H, d, J=7Hz, CH_2-CH_3), 3.36 (1H, dd, J=4Hz, 4Hz, CHH-CO), 2.89 (1H, dd, J=8Hz, 8Hz, CHH-CO), 1.12 (3H, t, J=7Hz CH_3); δ_C (100MHz, $CDCl_3$): 191.35, 175.30, 172.24 (C=O), 134.11, 132.08, 131.95, 131.23 (ArC), 48.50 (CH-CH_2), 34.36 (CH-CH_2), 33.47, 31.33, 29.64 (CH_2-CH_3) 12.81 (CH_3); LRMS (EI): 311 (M^+ , 11%), 183 (M^+ - $C_6H_8O_2N$,100%); GC t_R 11.25 min;

3-(4-Chloro-Benzoyl)-1-ethyl-pyrrolidine-2.5-dione (166)

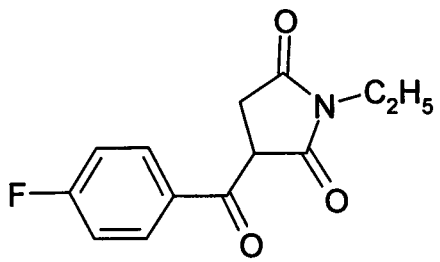


Compound **(166)** was synthesised following the same procedure as for compound **(153)** except that methyl 4-chlorobenzoate (1g, 5.86mmol) was used instead of methyl benzoate and and 1-Ethyl-pyrrolidine-2,5-dione (0.74g, 5.86mmol) was used instead of a solution of *N*-methyl succinimide. The crude oil was purified by flash chromatography [R_f 0.50 Petroleum ether: Diethyl ether (30: 70)] to give **166** as yellow oil (0.32g, 21%).

$\nu_{(max)}$(Film)/cm^{-1}: 2923.8 (Ph–CH), 1777.4, 1705.2 (C=O); δ_H (400 MHz, $CDCl_3$): 8.03 (2H, d, J=8Hz, Ph-H), 7.47 (2H, d, J=8Hz, Ph-H), 4.74 (1H, dd, J=4Hz, 4Hz, CH-CO), 3.52 (2H, d, J=7Hz, CH_2-CH_3), 3.38 (1H, dd, J=4Hz, 4Hz, CHH-CO), 2.78 (1H, dd, J=8Hz, 8Hz, CHH-CO), 1.21 (3H, t, J=7Hz CH_3); δ_C (100MHz, $CDCl_3$): 192.04, 175.94, 173.12 (C=O), 141.42, 134.77, 131.71, 129.66 (ArC), 48.86 (CH-CH_2), 33.78 (CH-CH_2), 31.22 (CH_2-CH_3) 12.81 (CH_3); LRMS (EI): 265

(M^+, 20%), 139 (M^+ - $C_6H_8O_2N$,100%); GC t_R 10.98 min; Elemental analysis: Found C, 58.80%; H, 4.56%; N, 5.18%; $C_{13}H_{12}ClO_3N$ requires C, 58.77%; H, 4.55%; N, 5.27%.

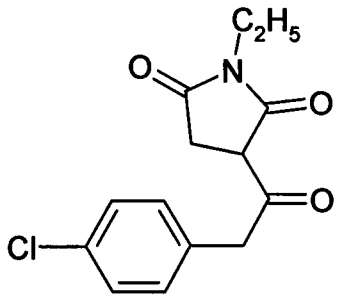
3-(4-Fluro-Benzoyl)-1-ethyl-pyrrolidine-2.5-dione (167)



Compound **(167)** was synthesised following the same procedure as for compound **(153)** except that methyl 4-flurobenzoate (1g, 6.49mmol) was used instead of methyl benzoate and and 1-Ethyl-pyrrolidine-2,5-dione (0.82g, 6.49mmol) was used instead of a solution of *N*-methyl succinimide. The crude oil was purified by flash chromatography [R_f 0.50 Petroleum ether: Diethyl ether (30: 70)] to give **167** as yellow oil (0.47g, 29%).

$\nu_{(max)}$(Film)/cm^{-1}: 2931.9 (Ph–CH), 1715.5 (C=O) δ_H (400 MHz, $CDCl_3$): 8.03 (2H, d, J=8Hz, Ph-H), 7.47 (2H, d, J=8Hz, Ph-H), 4.75 (1H, dd, J=4Hz, 4Hz, CH-CO), 3.52 (2H, d, J=7Hz, CH_2-CH_3), 3.33 (1H, dd, J=4Hz, 4Hz, CHH-CO), 2.78 (1H, dd, J=8Hz, 8Hz, CHH-CO), 1.12 (3H, t, J=7Hz CH_3); δ_C (100MHz, $CDCl_3$): 190.69, 175.40, 172.42 (C=O), 132.68, 132.58, 131.85, 116.09, 115.86 (ArC), 48.46 (CH-CH_2), 34.36 (CH-CH_2), 31.47 (CH_2-CH_3) 12.81 (CH_3); LRMS (EI): 249 (M^+, 20%), (M^+ - $C_6H_8O_2N$,100%); GC t_R 9.81 min.

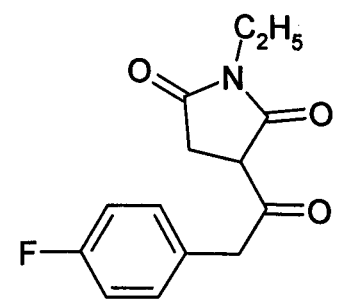
3-[2-(4-Chloro-phenyl)-acetyl]-1-ethyl-pyrrolidine-2,5-dione (168)



Compound **(168)** was synthesised following the same procedure as for compound **(153)** except that 4-chlorophenylacetate (1g, 5.42mmol) was used instead of methyl benzoate and 1-Ethyl-pyrrolidine-2,5-dione (0.68g, 5.42mmol) was used instead of a solution of *N*-methyl succinimide. The crude oil was purified by flash chromatography [R_f 0.50 Petroleum ether: Diethyl ether (30: 70)] to give **168** as yellow oil (0.37g, 25%).

$\nu_{(max)}$(Film)/cm^{-1}: 2941.1 (Ph–CH), 1681.7 (C=O); δ_H (400 MHz, $CDCl_3$): 7.23 (2H, m, Ph-H), 7.11 (2H, d, m, Ph-H), 4.17 (2H, d, J= 16Hz Ph-CH_2), 3.96 (1H, m, CH), 3.45 (2H, m, N-CH_2), 3.14 (1H, dd, J=4Hz, 4Hz, CHH-CO), 2.54 (1H, m, CHH-CO), 1.07 (3H, t, J=7Hz, CH_3); δ_C (100 MHz, $CDCl_3$): 198.80, 175.01, 172.15 (C=O), 133.08, 131.18, 130.91, 128.67 (ArC), 51.70 (CH), 48.42 (CH-CH_2), 34.03 (N-CH_2), 29.49 (Ph-CH_2), 12.91 (CH_3).

3-[2-(4-Fluoro-phenyl)-acetyl]-1-ethyl-pyrrolidine-2,5-dione (169)

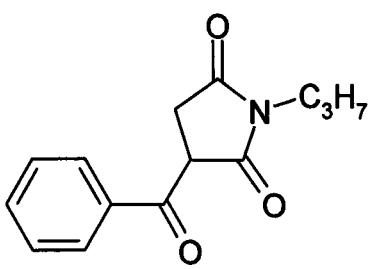


Compound **(169)** was synthesised following the same procedure as for compound **(153)** except that 4–fluorophenylacetic acid (1g, 5.95mmol) was used

instead of methyl benzoate and 1-Ethyl-pyrrolidine-2,5-dione (0.75g, 5.95mmol) was used instead of a solution of *N*-methyl succinimide. The crude oil was purified by flash chromatography [R_f 0.50 Petroleum ether: Diethyl ether (30: 70)] to give **169** as yellow oil (0.32g, 21%).

$\nu_{(max)}$(Film)/cm^{-1}: 2929.5 (Ph–CH), 1742.8 (C=O); δ_H (400 MHz, $CDCl_3$): 7.14 (2H, m, Ph-H), 6.96 (2H, d, m, Ph-H), 4.17 (2H, d, J= 16Hz Ph-CH_2), 3.95 (1H, m, CH), 3.48 (2H, m, N-CH_2), 3.22 (1H, dd, J=4Hz, CHH-CO), 2.54 (1H, dd, J=4Hz, 4Hz, CHH-CO), 1.08 (3H, t, J=7Hz, CH_3); δ_C (100 MHz, $CDCl_3$): 199.13, 175.10, 171.99 (C=O), 131.36, 131.28, 115.89, 115.67 (ArC), 51.72 (CH), 48.63 (CH-CH_2), 34.30 (N-CH_2), 29.71 (Ph-CH_2), 12.86 (CH_3).

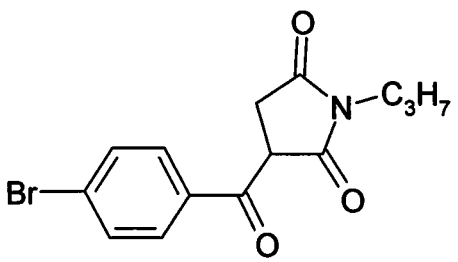
3-Benzoyl-1-propyl-pyrrolidine-2,5-dione (170)



Compound **(170)** was synthesised following the same procedure as for compound **(153)** except that 1-propyl-pyrrolidine-2,5-dione (1g, 7.35mmol) was used instead of a solution of *N*-methyl succinimide. The crude oil was purified by flash chromatography [R_f 0.55 Petroleum ether: Diethyl ether (30: 70)] to give **170** as yellow oil (0.39g, 21%).

$\nu_{(max)}$(Film)/cm^{-1}: 2930.4 (Ph–CH), 1742.9 (C=O); δ_H (400 MHz, $CDCl_3$): 7.65 (2H, m, Ph-H), 7.50 (3H, m, Ph-H), 4.81 (2H, m, N-CH_2), 3.46 (1H, m, CH), 3.63 (1H, dd, J=4Hz, 4Hz, CHH-CO), 2.82 (1H, m, CHH-CO), 1.57 (2H, m, CH_2-CH_3), 1.07 (3H, t, J=7Hz, CH_3); δ_C (100 MHz, $CDCl_3$): 193.02, 175.03, 172.11 (C=O), 134.25, 129.72, 128.76, 128.44 (ArC), 48.36 (CH), 40.90 (CH-CH_2), 31.66 (N-CH_2), 20.84 (CH_2-CH_3), 11.10 (CH_3); LRMS (EI): 245 (M^+, 12%), 105 (M^+ - $C_7H_{10}O_2N$,100%); GC t_R 10.38 min

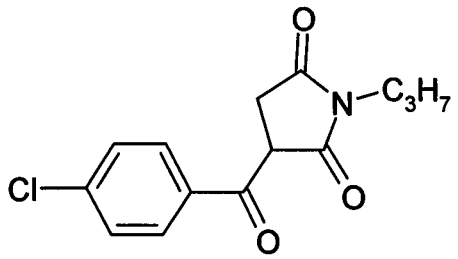
3-(4-Bromo-benzoyl-1-propyl-pyrrolidine-2,5-dione (171)



Compound **(171)** was synthesised following the same procedure as for compound **(153)** except that methyl 4-bromobenzoate (1g, 4.65mmol) was used instead of methyl benzoate and 1-propyl-pyrrolidine-2,5-dione (0.65g, 4.65mmol) was used instead of a solution of *N*-methyl succinimide.. The crude oil was purified by flash chromatography [R_f 0.55 Petroleum ether: Diethyl ether (30: 70)] to give **171** as yellow oil (0.38g, 25%).

$\nu_{(max)}$(Film)/cm^{-1}: 2927.6 (Ph–CH), 1752.2 (C=O); δ_H (400 MHz, $CDCl_3$): 7.96 (2H, d, J=4Hz, Ph-H), 7.65 (2H, d, J=4Hz, Ph-H), 4.76 (2H, m, N-CH_2), 3.47 (1H, m, CH), 3.34 (1H, dd, J=4Hz, 4Hz, CHH-CO), 2.83 (1H, dd, J=8Hz, CHH-CO), 1.57 (2H, m, CH_2-CH_3), 0.93 (3H, t, J=7Hz, CH_3); δ_C (100 MHz, $CDCl_3$): 191.48, 175.53, 172.50 (C=O), 132.09, 131.97, 131.22, 128.96 (ArC), 48.48 (CH), 40.94 (CH-CH_2), 31.34 (N-CH_2), 20.83 (CH_2-CH_3), 11.09 (CH_3); LRMS (EI): 324 (M^+, 28%), 185 (M^+ - $C_7H_{10}O_2N$,100%); GC t_R 10.13 min. Elemental analysis: Found C, 51.96%; H, 4.38%; N, 4.37%; $C_{14}H_{14}O_3NBr$ requires C, 51.87%; H, 4.35; N, 4.32%.

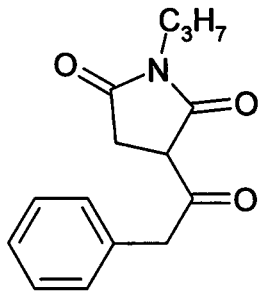
3-(4-Chloro-benzoyl-1-propyl-pyrrolidine-2,5-dione (172)



Compound **(172)** was synthesised following the same procedure as for compound **(153)** except that methyl 4-chlorobenzoate (1g, 5.86mmol) was used instead of methyl benzoate and 1-propyl-pyrrolidine-2,5-dione (0.82g, 5.86mmol) was used instead of a solution of *N*-methyl succinimide. The crude oil was purified by flash chromatography [R_f 0.55 Petroleum ether: Diethyl ether (30: 70)] to give **172** as yellow oil (0.39g, 24%).

$\nu_{(max)}$(Film)/cm^{-1}: 2966.8 (Ph–CH), 1777.6, 1750.3 (C=O); δ_H (400 MHz, $CDCl_3$): 7.99 (2H, d, J=4Hz, Ph-H), 7.43 (2H, d, J=4Hz, Ph-H), 4.74 (1H, dd, J=4Hz, CH), 3.38 (N-CH_2), 3.27 (1H, dd, J=4Hz, CHH-CO), 2.76 (1H, dd, J=8Hz, CHH-CO), 1.49 (2H, m, CH_2-CH_3), 0.86 (3H, t, J=7Hz, CH_3); δ_C (100 MHz, $CDCl_3$): 191.23, 175.45, 172.46 (C=O), 133.59, 131.03, 128.83, 128.68 (ArC), 48.36 (CH), 40.74 (CH-CH_2), 31.24 (N-CH_2), 20.69 (CH_2-CH_3), 10.95 (CH_3); LRMS (EI): 279 (M^+, 25%), 139 (M^+ - $C_7H_{10}O_2N$,100%); GC t_R 11.39 min. Elemental analysis: Found C, 60.39%; H, 5.19%; N, 5.02%; $C_{14}H_{14}NO_3Cl$ requires C, 60.11%; H, 5.04; N, 5.01%.

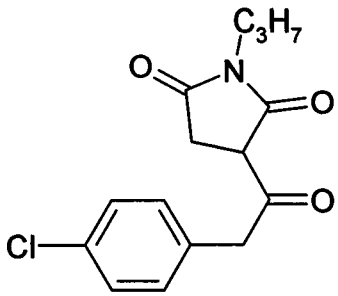
3-Phenylacetyl-1-propyl-pyrrolidine-2,5-dione (173)



Compound **(173)** was synthesised following the same procedure as for compound **(153)** except that methyl phenylacetate (1g, 6.66mmol) was used instead of methyl benzoate and 1-propyl-pyrrolidine-2,5-dione (0.94g, 6.66mmol) was used instead of a solution of *N*-methyl succinimide. The crude oil was purified by flash chromatography [R_f 0.55 Petroleum ether: Diethyl ether (30: 70)] to give **173** as yellow oil (0.42g, 24%).

$\nu_{(max)}$(Film)/cm^{-1}: 3442.5 (Ph–CH), 1738.7 (C=O); δ_H (400 MHz, $CDCl_3$): 7.20 (2H, m, Ph-H), 7.12 (3H, m, Ph-H), 4.74 (2H, d, J=16Hz, Ph-CH_2), 3.89 (1H, m, CH), 3.31 (2H, t, J=7Hz, N-CH_2) 3.06 (1H, dd, J=4Hz, CHH-CO), 2.38 (1H, dd, J=8Hz, CHH-CO), 1.45 (2H, m, CH_2-CH_3), 0.76 (3H, t, J=7Hz, CH_3); δ_C (100 MHz, $CDCl_3$): 199.39, 17.32, 172.53 (C=O), 132.77, 129.85, 128.75, 127.30 (ArC), 51.43 (Ph-CH_2), 40.67 (CH), 31.27 (CH-CH_2), 29.68 (N-CH_2), 21.06 (CH_2-CH_3), 20.74 (CH_2-CH_2) 10.99 (CH_3); LRMS (EI): 259 (M^+, 38%), 91 (M^+ - $C_8H_{10}O_3N$,100%); GC t_R 10.13 min.

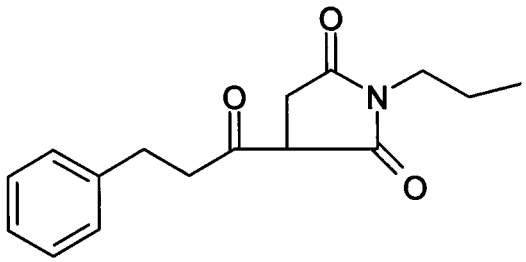
3-[2-(4-Chloro-pheyl)-acetyl]-1-propyl-pyrrolidine-2,5-dione (174)



Compound **(174)** was synthesised following the same procedure as for compound **(153)** except that methyl 4-chlorophenylacetate (1g, 5.42mmol) was used instead of methyl benzoate and 1-propyl-pyrrolidine-2,5-dione (0.76g, 5.42mmol) was used instead of a solution of *N*-methyl succinimide. The crude oil was purified by flash chromatography [R_f 0.54 Petroleum ether: Diethyl ether (30: 70)] to give **174** as yellow oil (0.47g, 30%).

$\nu_{(max)}$(Film)/cm^{-1}: 2966.76 (Ph–CH), 1775.70, 1702.10 (C=O); δ_H (400 MHz, $CDCl_3$): 7.26 (2H, m, Ph-H), 7.13 (2H, m, Ph-H), 4.18 (2H, d, J=16Hz, Ph-CH_2), 4.01 (1H, m, CH), 3.41 (2H, t, J=7Hz, N-CH_2) 3.19 (1H, dd, J=4Hz, CHH-CO), 2.54 (1H, dd, J=8Hz, CHH-CO), 1.45 (2H, m, CH_2-CH_3), 0.84 (3H, t, J=7Hz, CH_3); δ_C (100 MHz, $CDCl_3$): 198.91, 17.25, 172.42 (C=O), 133.28, 131.21, 130.13, 128.73 (ArC), 51.76 (Ph-CH_2), 48.59 (CH), 40.76 (CH-CH_2), 39.84 (N-CH_2), 29.56 (CH_2-CH_3), 20.76 (CH_2-CH_2), 11.03 (CH_3); LRMS (EI): 293 (M^+, 33%), 141 (M^+ - $C_8H_{10}O_2N$,100%); GC t_R 11.36 min.

3-(3-Phenyl-propionly)-1-propyl-pyrrolidine-2,5-dione (175)



Compound **(175)** was synthesised following the same procedure as for compound **(153)** except that 3-phenylpropionate (1g, 6.09mmol) was used instead of methyl benzoate and 1-propyl-pyrrolidine-2,5-dione (0.85g, 6.09mmol) was used instead of a solution of *N*-methyl succinimide. The crude oil was purified by flash chromatography [R_f 0.50 Petroleum ether: Diethyl ether (30: 70)] to give **175** as yellow oil (0.42g, 25%).

δ_H (400 MHz, $CDCl_3$): 7.20 (2H, m, Ph-H), 7.07 (3H, m, Ph-H), 4.74 (2H, d, J=16Hz, Ph-CH_2), 4.69 (1H, s, CH), 3.31 (2H, t, J=8Hz, N-CH_2) 2.83 (2H, m, Ph-CH_2-CH_2), 2.59 (2H, d, J=16Hz, CH_2-CON), 1.48 (2H, m, CH_2-CH_3), 0.78 (3H, t, J=7Hz, CH_3); δ_C (100 MHz, $CDCl_3$): 175.10, 173.43 (C=O), 139.81, 128.55, 128.15, 126.42 (ArC), 40.93 (Ph-CH_2), 40.09 (CH), 38.55 (CH-CH_2), 29.09 (N-CH_2), 20.68 (CH_2-CH_3), 11.02 (CH_3); LRMS (EI): 273 (M^+, 4%), 105 (M^+ - $C_8H_{10}O_3N$,100%); GC t_R 10.98 min.

Chapter Four:

Biochemical evaluation

4.0 BIOCHEMICAL EVALUATION OF PHENYLAMINE BASED COMPOUNDS AGAINST CYTOCHROME $P450_{17\alpha}$.

The Evan's auxilliary based compounds were evaluated (by Mr. Sachin Dhanani) against $P450_{17\alpha}$ using a literature based assay where the conversion of the radiolabelled progesterone and 17α-hydroxyprogesterone (in the presence of the potential inhibitors) to 17α-hydroxyprogesterone and androstenedione respectively were considered. The compounds were found to possess extremely weak inhibitory actvity (Tables 4.1 and 4.2), as a result, no IC_{50} values were determined. Phenylamine based compounds have previously been reported by Ahmed et al (1995a) as possessing weak inhibitory activity against similar cytochrome P450 enzymes such as aromatase. In their study, the authors proposed that the weak inhibitory activity was due to the poor electron donating ability of the phenylamine moiety, leading to weak Fe to inhibitor N bond. This was supported by the observation of potent inhibitory activity against aromatase within a series of azole-based compounds (Ahmed et al, 1995b) possessing a substituted phenyl alkyl imidazoles backbone. Indeed, in a recent study, the biochemical evaluation of substituted phenyl alkyl imidazoles against $P450_{17\alpha}$ resulted in the discoverey of highly potent inhibitors of this enzyme (Patel et al, 2006). It should be noted, however, that the evaluation of these compounds against aromatase (Adat, 2004) showed these compounds to be good inhibitors of aromatase.

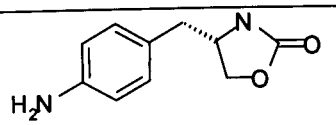
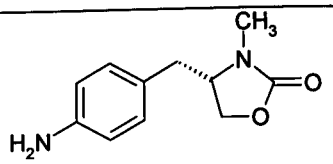
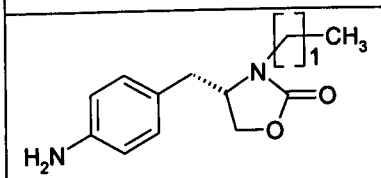
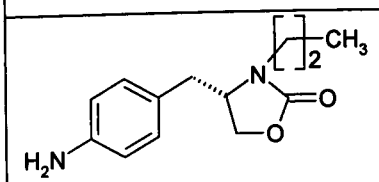
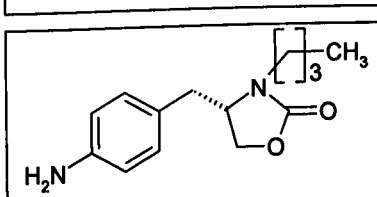
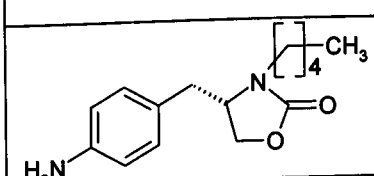
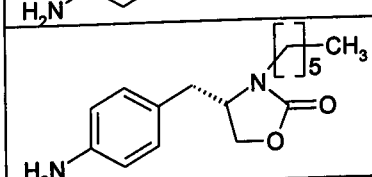
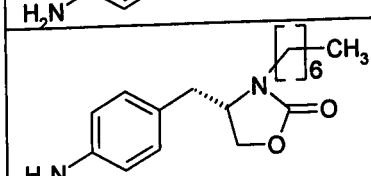
Structure	17α-hydroxylase % Inhibition	17,20-lyase % Inhibition
	3.80 ± 0.91[b]	15.06 ± 2.59[b]
	8.18 ± 2.51[b]	16.14 ± 1.97[b]
	4.82 ± 1.60[a] 16.35 ± 3.32[b]	30.00 ± 1.44[b]
	4.87 ± 4.11[b]	32.94 ± 4.44[b]
	12.83 ± 0.01[b]	31.63 ± 3.49[b]
	5.93 ± 1.45[b]	24.12 ± 1.63[b]
	15.72 ± 3.87[b]	24.27 ± 1.36[b]
	12.76 ± 7.40[b]	7.84 ± 0.79[a]

Table 4.1 Results from preliminary screening and IC_{50} data of some *para*-substituted 4-*(S)*-(4-amino-benzyl)-oxazolidin-2-one for 17α-hydroxylase/17,20-lyase activity. (Where [a] [I] = 500μM, [b] [I] = 1000μM).

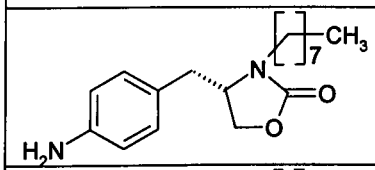
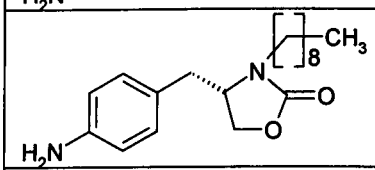
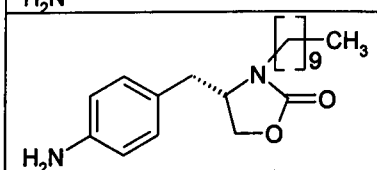
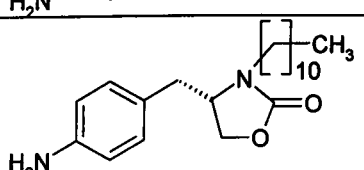
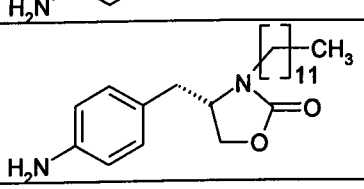
Structure	17α-hydroxylase % Inhibition	17,20-lyase % Inhibition
	10.24 ± 7.28[b]	13.26 ± 1.04[a] 40.97 ± 0.66[b]
	11.30 ± 0.27[b]	9.80 ± 0.14[a] 39.73 ± 0.50[b]
	14.98 ± 0.54[b]	0[b]
	7.11 ± 1.15[b]	0[b]
	0[b]	15.13 ± 4.64[b]

Table 4.2 Results from preliminary screening and IC_{50} data of some *para*-substituted 4-*(S)*-(4-amino-benzyl)-oxazolidin-2-one for 17α-hydroxylase/17,20-lyase activity. (Where [a] [I] = 500μM, [b] [I] = 1000μM).

4.1 SUMMARY

In summary, some 47 number of compounds have been synthesised within the current study and which were targeted towards two major enzymes, namely, 5α-reductase and 17α-hydroxylase/17,20-lyase.

The compounds targeted towards 5α-reductase were based upon the substituted phenyl alkoxy pyrrolidine-2,5-dione backbone such that the compounds mimicked the natural substrate, namely testosterone (Figure 4.1). That is, the rationale for the design of these compounds was that the compounds would mimic the natural substrate and thus block the active site, thereby resulting in an overall reduction in the DHT levels – as result of which the stimulation of the androgen-dependent disease (such as BPH or indeed, prostate cancer) would be significantly reduced resulting in a subsequent reduction in tumour mass.

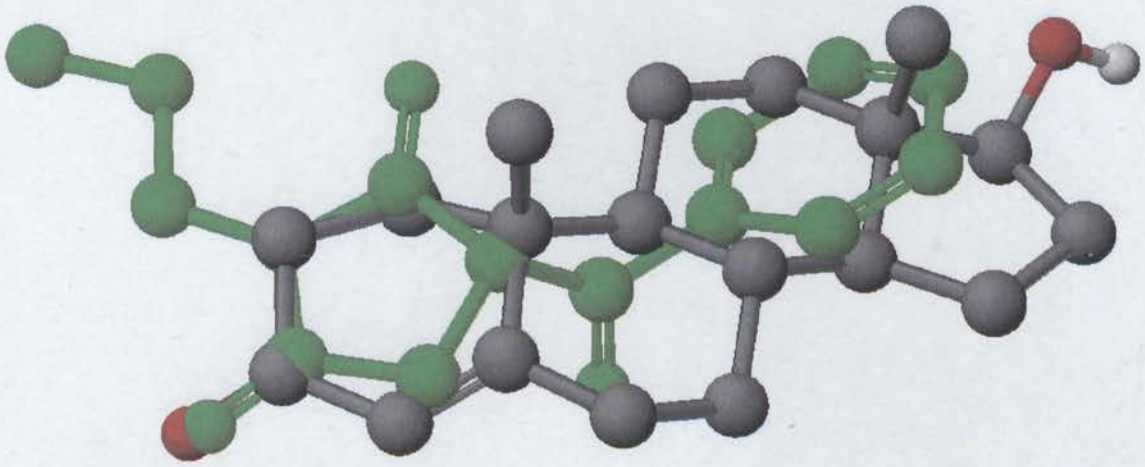


Figure 4.1 Superimpositioning of compound **170** onto the steroid backbone so as to show the potential mimicking of the substrate.

The overall results of the current study is however, inconclusive since the compounds have not been fully evaluated against the 5α-reductase family of enzymes (namely the two isozymes of this enzyme), however, initial results have shown that the compounds may possess IC_{50} values in the low micro molar range – compound **170** has recently been shown to possess some 60% inhibitory activity at an inhibitor concentration of 30μM.

The compounds targeted towards 17α-hydroxylase/17,20-lyase were designed such that the compounds would undergo reversible interaction with the Fe atom at the centre of the haem. That is, the rationale for the design of these compounds was that the compounds would block the active site through the formation of a dative co-valent bond with the haem whilst undergoing interaction with potential hydrogen bonding groups within the enzyme active site (Figure 4.2).

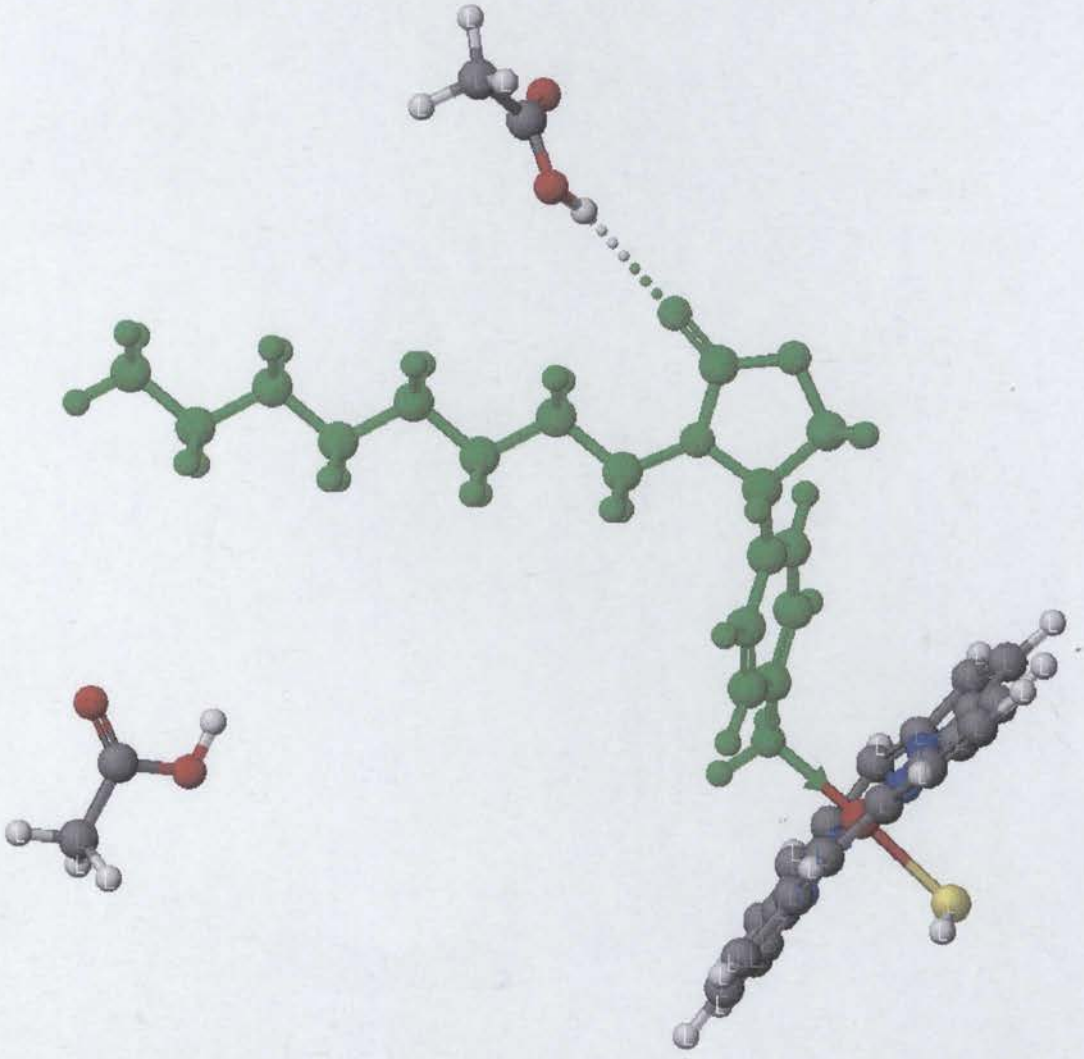


Figure 4.2 To show the postulated mode of action of the phenylamine based compounds against the enzyme complex 17α-hydroxylase/17,20-lyase, in particular, the inhibitor is shown to undergo interaction with one of the hydrogen bonding group hypothesised to exist at the active site as well as dative covalent bond formation.

As such, this would result in the reduction in the biosynthesis of the initial androgens (androstenedione from progesterone and dehydroepiandrosterone from pregnenolone) as a result of which the biosynthesis of the family of androgens would be greatly limited, thereby resulting in the overall reduction of androgen level within both plasma, and more importantly, within the diseased androgen dependent cells. However, all of the compounds proved to be extremely weak inhibitors of 17α-hydroxylase/17,20-lyase. Whilst initially the result of the biochemical evaluation of the phenylamine based compounds would appear to be a major set back in the further design of potential inhibitors of 17α-hydroxylase/17,20-lyase, the lack of any inhibitory activity within these compounds (even up to an inhibitor concentration of 1mM) is however, extremely useful as it shows that these compounds are selective inhibitors of the general cytochrome P-450 family of enzymes. That is, these compounds have previously been reported as good inhibitors of the cytochrome P-450 enzyme aromatase - Table 4.3 shows the IC_{50} values (and therefore the relative potency) obtained for a small range of compounds evaluated against aromatase in comparison to the standard compound aminoglutethimide (AG).

Substituent on the oxazolidinone ring	IC_{50}/μM	Relative potency
Pr	4.2 ± 0.2	22.67
Bu	1.5 ± 0.2	63.45
Pe	0.83 ± 0.05	114.70
Hex	1.2 ± 0.1	79.33
Hept	3.6 ± 0.06	26.44
AG	95.2 ± 0.5	1

Table 4.3 IC_{50} values and relative potencies of the compounds (w.r.t. AG) for a small range of the *R*-enantiomer based compounds (values are average of triplicate determinations) (Ahmed et al, 2002).

As can be observed from the Table above, the compounds proved to be potent inhibitors of aromatase with the pentyl derivative possessing approximately 114 fold potency when compared to AG. In comparison, when the S-enantiomer

based derivatives were evaluated against 17α-hydroxylase/17,20-lyase, the compounds was found to possess less than 50% inhibition at an inhibitor concentration of 1000μM. As such, the inability of these compounds to inhibit 17α-hydroxylase/17,20-lyase shows that these compounds are good lead compounds in the further design of specific aromatase inhibitors and which should possess greatly reduced side-effects due to their specificity.

In conclusion therefore, the compounds design as potential inhibitors of 5α-reductase have shown some good inhibition which supports the rationale for the design of the inhibitors whilst the poor inhibitory activity possessed by the oxazolidineone based compounds targeted against 17α-hydroxylase/17,20-lyase shows that these compounds are specific inhibitors of aromatase, as such, both sets of compounds are good lead compounds for their respective target enzyme.

Chapter Five:

References

REFERENCES

- A -

Abell A.D., and Henderson B.R., 1995, Steroidal and nonsteroidal inhibitors of steroid 5-alpha-reductase, Curr Med Chem , **2**, pp 583–597.

Ahmed S, Adat S, Murrells A and Owen C.P., 2002a, Novel oxazolidinone based compounds as inhibitors of aromatase and the use of the substrate–heme complex approach in the rationalisation of these compounds, Biochem Bioph Res Co, **294**,2, 7, pp 380-383.

Ahmed S, Adat S, Murrells A, Owen C.P., 2002b, Yonas A., 2002, Design, synthesis, and evaluation of 4-(40-aminobenzyl)-2-oxazolidinones as novel inhibitors of the cytochrome P-450 enzyme aromatase, Bioorg. Chem, **30**, pp 315-331.

Ahmed, S. and Patel, C. H., 2001, Molecular modelling and a quantitative study of inhibitors of 5α-reductase (5AR) - an insight into the available space for the side chains of steroidal inhibitors of 5AR, J Pharm Pharmacol, **53S**, pp208-208.

Ahmed, S. and Denison, S., 1998a, Structure activity relationship study of known inhibitors of the enzyme 5α-Reductase (5AR), Bioorg Med Chem Lett, **8**, pp 409-414.

Ahmed, S., 5α-Reductase and Denison, S., 1998b, Derivation of a representation of the 5 enzyme (5AR) active site from the consideration of the reaction mechanism, Bioorg Med Chem Lett, **8**, pp 2615-2621.

Ahmed, S. and Denison, S., 1997, Derivation of a representation of the 5α-Reductase enzyme (5AR) active site from the consideration of the reaction mechanism, J Pharm Pharmacol, **49**, S4, pp 104-104.

Ahmed, S., 1996, Molecular modelling of 5α-reductase inhibitors, Pharmaceutical Sciences, **2**, pp 251-253.

Ahmed S, 1995a, Molecular Molecular modelling of inhibitors of aromatase- a novel approach , Bioorg Med Chem Lett, **5**, 15, pp 1673-1678.

Ahmed S, 1995b, Molecular modelling of inhibitors of 17α-Hydroxylase-a novel approach, Bioorg Med Chem Lett, **5**, 23, pp 2795-2800.

Ahmed S, Design synthesis and biochemical evaluation of 17α- Hydroxylase and 17,20-Lyase inhibitors, PhD thesis 1990.

Albertsen P.C., 1996, Screening for prostate cancer is neither appropriate nor cost effective, Urol. Clin. North Am., **26**, pp 521–530.

Anderson K.M., and Liao S., 1968, Selective retention of dihydrotestosterone by prostatic nuclei, Nature, **219**, pp 277–9.

- B -

Bakshi R.K., Rasmusson G.H., Patel G.F., Mosley R.T., Chang B., Ellsworth K., Harris G.S., Tolman R.L., 1995, 4-Aza-3-oxo-5 alpha-androst-1-ene-17 beta-N-aryl-carboxamides as dual inhibitors of human type 1 and type 2 steroid 5 alpha-reductases. Dramatic effect of N-aryl substituents on type 1 and type 2 5 alpha-reductase inhibitory potency, J. Med. Chem., **38**, pp 3189–92.

Bartsch G, R. Rittmaster, H. Klocker, 2002, Dihydrotestosterone and the concept of 5a-reductase inhibition in human benign prostatic hyperplasia World J Urol **19** pp413-425.

Battersby AR, Westwood SW., 1987, Journal of the Chemical Society Perkins Transaction, pp 1679.

Berry S.J., Coffey D.S., Walsh P.C., Ewing L.L., 1984, The development of human benign prostatic hyperplasia with age, J. Urol., **132**, pp 474–479.

Bittner S., Barneis Z., Felix S., 1975, A convenient method of transesterification under neutral conditions, Tetrahedron Lett., **16**, pp 3871–3874.

Bosland M., 1988, The etiopathogenesis of prostate cancer with special reference to environmental factors. Adv. Cancer Res., **51**, pp 1–106.

Boyle P and Ferlay J, 2004, Cancer incidence and mortality in Europe, International Agency for Research on Cancer, Lyon, France.

Bull H.G., Garcia-Calvo M., Andersson S., Baginsky W.F., Chan H.K., Ellsworth D.E., Miller R.R., Stearns R. A., Bakshi R.K., Rasmusson G.H., Tolman R.L., Myers R.W., Kozarich J.W., Harris G.S., 1996, Mechanism-Based Inhibition of Human Steroid 5-Reductase by Finasteride: Enzyme-Catalyzed Formation of NADP-Dihydrofinasteride, a Potent Bisubstrate Analog Inhibitor, J. Am. Chem. Soc., **118**, pp 2359–2365.

Burton S, Trachtenberg J., 1986, Effectiveness of antiandrogens in the rat, J Urol, **136**, pp 932-935.

Buttyan R., Shabsigh A., Perlman H., Colombel M., 1999, Regulation of apoptosis in the prostate gland by androgenic steroids, TEM., **10**, pp 4 –54.

- C -

Carter B.S., Carter H.B., Isaacs J.T., 1990, Epidemiologic evidence regarding predisposing factors to prostate cancer, Prostate, **16**, pp 187–97.

Cerhan J R, Parker A S, Putnam S D, Chiu B C-H, Lynch C F, Cohen M B, Torner J C,1999, Family history and prostate cancer risk in a population-based cohort of Iowa men, Cancer Epidem Biomar , **8**, 53–60.

Clayden J., Greeves N., Warren S., Wothers P., 2001, Organic chemistry, first edition, pp 282, 289.

- D -

Dai W,J., Gutai J.P., Kuller L.H., Cauley J.A., 1988, For the MRFIT Research Group: Cigarette smoking and serum sex hormones in men, Am J Epidemiol, **128**, pp 796–805.

deVere White R.W., Deitch A.D., Jackson A.G., Gandour-Edwards R., Marshalleck J., Soares S.E., Toscano S.N., Lunetta J.M., Stewart S.L., 1998, Racial differences in clinically localised prostate cancers in black ad white men, J Urol, **159**, pp 1979 – 1982.

Devgan S.A., Henderson B.E., Yu M.C., Shi C.Y., Pike M.C., Ross R.K., Reichardt J.K., 1997, Genetic variation of 3 beta- hydroxy-steriod dehydrogenase type II in three racial/ethnic groups: implications for prostate cancer risk, Prostate, **33**, pp 9–12.

De Voogt HJ, Smith PH, Pavone-Macaluso M, de Pauw M &Suciu S., 1986, Side effects of diethylstilbestrol, cyproterone acetate, medroxyprogesterone acetate andestramustine phosphate used for the treatment of advancedprostatic cancer: results from European Organization for Research on Treatment of Cancer trials 30761 and 30762 Cardiovascular, J. Urol, **135,** PP 303-307.

E

Eales L.J, 1997, Immunology for life scientists A basic introduction.pp215-216. John Wiley And Sons, Chichester.

- F -

Feneley M.R., Jan H., Granowska M., Mather S.J., Ellison D., Glass J., Coptcoat M, Kirby R.S., Ogden C., Oliver R.T.D., Badenoch D.F., Chinegwundoh F.I., Nargund V.H., Paris A.M.I., Britton K.E., 2000, Imaging with prostate-specific membrane antigen (PSMA) in prostate cancer, Prostate cancer and prostatic diseases, **3**, pp 47.

Fessenden R.J., Fessenden J.S., Logue M., 1998, Organic chemistry, sixth edition, pp 613–614, 640–642, 649–651.

Fleischmann J., Perinetti E.P., Catalona W.J., 1981, J Urol, **126**, pp 389–392.

Frank W, Monatsh. Chem., 1996, 127, pp 895.

Fry S., 1996 Inhibitors of 5α-Reductase, Curr. Pharm. Des, **2**, pp 59-84.

Fry S, Curt D, Patrick R, Roger N, George F, Robert A, Raymoand J, Kenneth W, Batchelor H, Neal Bramson J, Darren S, Stephanie L, Arnold D, Mark B, Marcia L, Gaochoa T, Frank W, Timothy K, Michael K, Mary G, James E, Dallas K.., 1995, Structure- activity relathionships for inhibition of type1 and 2 human 5α- Reductase and human adrenal 3β- Hydroxy-Δ^5 steroid dehydrogenase/ 3-keto -Δ^5 steroid_isomerase by 6- azandrost-4-en-3-ones: Optimization of the c17 substituent, J. Med. Chem, **38**, pp 2621-2627.

- G -

G.A., 1993, A retrospective cohort study of vasectomy and prostate cancer in US men, JAMA, **269**, pp 878–882.

Geller J, Albert J and Samuel S. C. Yen., 1978, Treatment of advanced cancer of prostate with megestrol acetate, Urol, **12**, 5, pp 537-541.

Giovanucci E., Tosteson T.D., Speizer F.E., Ascherio A., Vessey M.P., Colditz Glashan R.W and Robinson M.R, 1981, Cardiovascular complications in the treatment of prostatic carcinoma, Br J Urol, **6** pp624–627.

Glode LM, Smith JA., 1987, Long-term suppression of luteinizing hormone, follicle-stimulating hormone and testosterone by daily administration of leuprolide, J Urol, **137**, 1, pp 57-60.

Graham S, Haughey B, Marshall J, et al., 1983, Diet in the epidemiology of carcinoma of the prostate gland, J Natl Cancer Inst, **70**, pp 687–692.

Gronberg H., Isaacs S.D., Smith J.R., Carpten J.D., Bova G.S., Freije D., Xu J., Meyers D.A., Collins F.S., Trent J.M., Walsh P.C., Isaacs W.B., 1997, Journal of American Medical Association, 278, **pp** 125 –1255.

- H -

Hanchette C.L. and Schwartz G.G, 1992, Geographic patterns of prostate cancer mortality, cancer, **70**, pp 2861–2869.

Hartmann, R. W, Reichert, M.; Goehring, S., 1999 Novel 5-alpha-reductase inhibitors. Synthesis and structure-activity studies of 5-substituted 1-methyl-2-pyridones and 1-methyl-2-piperidones. Eur. J. Med. Chem, **29**, pp 807-817.

Hartwell L.H., Weinert T.A., 1989, Checkpoints: Controls that ensure the order of the cell cycle events, Science, **246**, pp 629–634.

Hasia, S, Voight W, J., 1973, The Antiandrogenic Action of 4-Androsten-3-one-17beta-Carboxylic Acid and its Methyl Ester on Hamster Flank, Organ Endo, 92 pp.1216.

Hasimoto S., Furukawa I., Kuroda T., 1980, A facile method of transesterification using phosphorus ylid, Tetrahedron Lett, **21**, pp 285 –2860.

Haslam E, 1980, Recent development in methods for the esterification and protection of the carbonyl group, tetrahedron, **36**, pp 2409–2433.

Hayes R.B., Pottern L.M., Greenberg R., et al., 1993, Vasectomy and prostate cancer in US blacks and whites, Am J Epidemiol, **137**, pp 263–269.

Hiatt R.A., Armstrong M.A., Klatsky A.L., Sidney S., 1994, Alcohol consumption, smoking and other risk factors and prostate cancer in a large health plan cohort in California (united States), Cancer Causes Control, **5**, pp 66–72.

Holt D, A, Yamashita D.S, Konialian-Beck A, Luengo J.I, Abell A.D, Bergsma D.J, Brandit M, Levy M.A., 1995, Benzophenone and indolecarboxylic acids: Potent Type-2-Specific inhibitors of human steroid 5α-Reductase, J. Med.Chem, **38**, pp 13-15.

Holt D, Levy M, Yen H, Metcalf B, Weir P., 1991, Inhibition of steroid 5α-Reductase by nitro steroids, Med. Chem. Lett, **1**, pp 27-32.

Howie B.J and Schultz T.D., 1985, Dietary and hormonal interrelationships among vegetarian Seventh Day Adventists and nonvegetarian men, Am J Clin Nutr, **42**, pp 127–134.

Hsing A.W., McLaughlin J.K., Zheng W., Gao Y., Blot W.J., 1994, Occupation, physical activity, and risk of prostate cancer in Shanghai, Peoples Republic of China, Cancer Causes Control, **5**, pp 136–140.

Huben RP, Perrapato SD., 1991, Drug therapy of prostatic cancer, Drugs. **5**, 1, pp 353-63.

Hylands and Roy B. Moodie., 1998, Reactions of 3-phenyloxetane and 7-oxabicyclo[2.2.1] heptane with dinitrogen pentoxide in dichloromethane, J. Chem. Soc., Perkin Trans, **2**.

Ideyama Y, Kudoh M, Tanimoto K, Susaki Y, Nanya T, Nakahara T, Ishikawa H, Yoden T, Okada M, Fujikura T, Akaza H, Shikama H., 1998, Novel nonsteroidal inhibitor of cytochrome P450(17alpha) (17alpha-hydroxylase/C17-20 lyase), YM116, decreased prostatic weights by reducing serum concentrations of testosterone and adrenal androgens in rats, prostate, **1**, 15;37, pp 8-10.

Igarashi S, Kimura T, Naito R, Hara H, Fujii M., 1999, A novel class of inhibitors for human steroid 5-alpha-reductase: phenoxybenzoic acid derivatives. I. Chem Pharm Bull Tokyo, **47**, pp 1073-1080.

Ingles S.A, et al, 1998, Association of prostate cancer with vitamin D receptor haplotypes in African Americans, Cancer Res , **58**, pp 1620–1623.

Jacobi GH, Altwein JE, Kurth KH, Basting R & Hohenfellner R., 1980, Treatment of advanced prostatic cancer with parenteralcyproterone acetate: a phase III randomised trial, Br. J. *Urol,* **52**, pp 208-215.

Jarman M, Smith H.J, Nicholls P.J, Simons C., 1998, Inhibitors of enzymes of androgen biosynthesis: Cytochrome P45017a and 5a-steroid reductase, Nat. Prod. Rep, pp 495.

Jemal A., Thomas A., Murray T., Thun M., 2005, Cancer statistics 2005, CA: A cancer journal for clinicians, **55**, pp 10- 30.

John E.M., Whittemore A.S., Wu A.H., et al., 1995, Vasectomy and prostate cancer: results from a multiethnic case-control study, J Natl cancer Inst, **87**, pp 662–669.

Jones, C. D, Audia, J. E, Lawhorn, D. E, McQuaid, L. A, Neubauer B, 1993, Nonsteroidal inhibitors of human type I steroid 5-alpha-reductase. J Med Chem, 36, pp 421-423.

Joseph A., Smith J.R., Soloway M.S., Young M.J., 1999, Complication of advanced prostate cancer, Urol, **54**, pp 8–14.

- K -

Kenny, B.; Ballard, S.; Blagg, J.; Fox, D., 1997, Pharmacological Options in the Treatment of Benign Prostatic Hyperplasia. *J. Med. Chem,* **40**, 1293-1315.

Kolonel L.N., Yoshizawa C.N., Hankin J.H., 1988, Diet and prostatic cancer: A case-control study in Hawaii, Am J Epidemiol, **61**, pp 999–1012.

Krane R, Fitzpatrick J.M., 1989, Treatment options for prostatic carcinoma, The prostate. New York, Churchill Livingston pp 433-439.

Kuban D.A., El-Mahdi A.M., Sigfred S.V., et al, 1986, Characteristics of spinal cord compression in adenocarcinoma of prostate, Urol, **28**, pp 364–369.

- L -

Lee I., Paffenbarger R.S. jr., Hsieh C., 1992, Physical activity and risk of prostatic cancer among college alumni, Am J Epidemiol, **135**, pp 169–179.

Liang T and Heiss C.E., 1981, Inhibition of 5α-reductase, receptor binding, and nuclear uptake of androgens in the prostate by a 4-methyl-4-aza-steroid, J. Biol. Chem. **256** pp 7998–8005.

Liang T, Brooks J.R, Cheung A, Reynolds G.F, G.H. Rasmusson., 1984, 4-Azasteroids as inhibitors of 5α-reductase. In: F. Brescian, J.B.K. King, M.E. Lippman, M. Namer and J.P. Raynaud, Editors, *Hormones and Cancer* **2**, Raven Press, New York, pp 497–505.

March J., 1992, Advanced organic chemistry – reactions, mechanisms, and structure, fourth edition, pp 392 – 396.

Matsunaga N, Kaku T, Akio Ojida, Tanaka T, Hara T, Yamaoka M, Kusaka M and Tassaka A., 2004, C17,20-Lyase inhibitors. Part 2: Design, synthesis and structure-activity relationships of (2-naphthylmethyl)-1 H-imidazoles as novel C17,20-lyase inhibitors, bioorgan med chem., **12**, pp 4313-4336

McConnell J.D., 1991, Physiologic basis of endocrine therapy for prostatic cancer, Urology Clin North America, **18**, pp 1–13.

McLeod D. G., 1995, Prostate Cancer Diagnosis, J.Urol, 153, 5, PP 1570-1571.

McMurry J., 1996, organic chemistry, fourth edition, pp 815–818.

Mellin, R. D. Busch and Gary H. Rasmusson, Theodore N., 1993, Azasteroids as inhibitors of testosterone 5α-reductase in mammalian skin, J. Steroid Biochem. Mol. Biol, **44**, 2, pp 121-131.

Mettlin C., 1997, Clinical oncology update: Prostate cancer: Recent developments in the epidemiology of prostate cancer, European Journal of Cancer, **33**, no 3, pp 340–347.

Mettlin C., Natarajan N., Huben R., 1990, Vasectomy and prostate cancer risk, Am J Epidemiol, **132**, pp 1056–1061.

Milsted RAV., 1989, Initiation of LHRH monotherapy for prostate cancer. In: Therapeutic progress in urological cancer. New YorkAlan R. Liss, pp 69-74.

Mirosevich J., Bentel J.M., Zeps N., Redmond S.L., Antuono M.F.D'., Dawkins H.J.S., 1999, Androgen receptor expression of proliferating basal and luminal cells in adult murine ventral prostate, J endo, **162**, pp 341–350.

Montironi R, Mazzucchelli R, Marshall J.R., et al., 1999, Prostate cancer prevention: review of target populations, pathological biomarkers, and chemopreventive agents, J Clin Pathol, **52**, pp 793–803.

- N -

Narod S, 1998, Genettic epidemiology of prostate cancer, **1423:** 1-13

Nishi T, Fukazawa T, Ishibashi K, Nakajima K, Sugioka Y, Iio Y, i Kurata, Itoh K, Mukaiyama O, Satoh Y., 1999, Combined NK1 and NK2 tachykinin receptor antagonists: Synthesis and structure-activity relationships of novel oxazolidine analogues, Bioorg. Med. Chem. Lett, 9, 6, PP 875-880.

Njar and Brodie A.M.H., 1999, Inhibitors of 17α-hydroxylase/17,20-lyase (CYP17) potential agents for the treatment of prostate cancer, Curr Pharm Des **5**, pp. 163–180.

Nomura A.M.Y., Kolonel L.N., 1991, Prostate cancer: A current perspective, Am J Epidemiol, **13**, 200–227.

- O -

Occhiato E.G, Guarna A, Danza G and Serio M., 2004, Selective non-steroidal inhibitors of 5α-reductase type1, J steroid biochem, **88**, pp 1-16.

Oesterling JE, Epstein JI, Walsh PC (1986) The inability of adrenal androgens to stimulate the adult human prostate: an autopsy evaluation of men with hypogonadotropic hypogonadism and panhypopituitarism. J Urol pp134-1030

Ornstien D.K., Dahut W.L., Lance A., Liotta., Emmert-Buck M.R., 1999, Review of AACR meeting: New research approaches in the prevention and cure of prostate cancer, 2–6 December 1998, Indian Wells, CA, Biochimica et Biophysica Acta, **1424**, pp R11–R19.

- P -

Papatheodorou A, Ellinas P, Tandeles S, Takis F, Poulias H, Nikolaou I, and batakis N, 2005, Transrectal ultrasonography and ultrasound-guided bioposies of the prostate gland: how, when and where. Curr probl diagn radiol.

Parkin D.M., Muir C.A., Whelan S.L., 1992, Cancer incidence in five continents, **6**, IARC Press, Lyon.

Pentyala S.N., Lee J., Hsieh K., Waltzer W.C., Trocchia A., Musacchia L., Rebecchi M.J., Khan S.A., 2000, Prostate cancer: A comprehensive review, Medical oncology, **17**, pp 85–105.

Pergament M.L., Swaim W.R., Blackard C.E., 1976, Disseminated intravascular coagulation in the urologic patient, J urol, **116**, pp 1–6.

- R -

Rasmusson G, Reynolds G, Utne T, Jobson R, Primka R, Berman C, Brooks J., 1984, Azasteroids as Inhibitors of rat Prostate 5-alpha reductase, J. Med. Chem, **27**, pp1690-1701.

Rasmusson G, Reynolds G, Utne T, Jobson R, Primka R, Berman C, Brooks J., 1986., Azasteroids: Structure-activity relationships for inhibition of 5alpha-reductase and of androgen receptor binding, J. Med Chem, **29**, 11, pp. 2298-2315.

Rang H.P., Dale M.M., Ritter J.M., 1999, Pharmacology, Fourth Edition, pp 664–668.

Reid P, Kantoff P, William OH., 1999 Antiandrogens in prostate cancer, Invest. New Drugs, **17**, pp. 271–284.

Reilly O.P.H., 1999, Aetiology and pathology of prostate cancer, **6**, pp 65–67.

Rosenberg L., Palmer J.R., Zauber A.G., et al., 1994, The relation of vasectomy to the risk of cancer, Am J Epidemiol, **140**, pp 431–438.

Ross R.K., Bernstein L., Lobo R.A., et al, 1992, 5-alpha-reductase activity and risk of prostate cancer among Japanese and US white and black males, Lancet, **339**, pp 887–889.

Ross R.K., Shimizu H., Paganini-Hill A., et al., case control of prostate cancer in blacks and whites in Southern California, J Natl Cancer Inst, **78**, pp 869–874.

Rotstein DM, Kertesz DJ, Walker KA, Swinney DC., 1992, Stereoisomers of ketoconazole: preparation and biological activity, J Med Chem, **15**, 35, pp 2818-25.

Rubin H., Lome L.G., Presman D., 1974, Neurological manifestation of metastatic prostatic carcinoma, J urol, **111**, pp 799–802.

Ruijter E., Van DE KAAC., Miller G., Ruijter D., Debruyne F., Schalken J., 1999, Molecular genetics and epidemiology of prostate carcinoma, Endocrinology review, **20**, pp 22–45.

Ruoslahti E., 1996, How cancer spreads, Scientific American, **275**, no 3, pp 72–7.

- S -

Schally A V and Coy D H, 1980, LH-RH agonists and antagonists, Int J Gynaecol Obstet, **18**, 5, pp 318-324

Schwartz G.G., Hulka B.S., 1990, Is vitamin D deficiency a risk factor for prostate cancer? (Hypothesis), Anticancer Research, **10**, 1307–12.

Shearer R J, Hendry W F, Sommerville I F, **1973,** Plasma testosterone an accurate monitor of hormone treatment in prostatic cancer, Br J Urol, **45**, 668-77.

Singh X, Cote J, Laplante S, Vielleux R, Labrie F., 1995, Synthesis and in vitro evaluation of 4-substituted N-(1, 1-Dimethylethyl)-3- oxo-4- androstene-17β-carboxamides as 5α- Reductase inhibitors and antiandrogens, J Med. Chem, **38**, pp 1456-1461.

Slattery M.L. and West D.W., 1993, Smoking, alcohol, coffee, tea, caffeine, and theobromine: risk of prostate cancer in Utah (United States), Cancer causes control, **4**, pp 559–563.

Sneller Z.W, Hop W.C, Carpentier P.J, Schroder F.H., 1992 Prognosis and prostatic volume changes during endocrine management of prostate cancer: a longitudinal study, J Urol, **147**, pp962-966.

Spitz M.R., Currier R.D., Fueger J.J., Babaian R.J., Newell G.R., 1991, Familial patterns of prostate cancer: a case-control analysis, J Urol, **146**, pp 1305–1304.

- T -

Talamini R., Franceschi S., La Vecchia C., Guanmeri S., Negri E., Smoking habits and prostate cancer: a case-control study in Northern Italy, Prev Med, **22**, pp 400–408.

Tavani A., Negri E., Franceschi S., Talamani R., La Vecchia C., 1994, Alcohol consumption and risk of prostate cancer, Nutr Cancer, **21**, pp 25–31.

Trichopoulos D., Li F.P., Hunter D.J., 1996, What causes cancer, Scientific American, **275**, no 3, pp 80–7.

- V -

Ventura S., Pennefather J.N., Frederick M., 2002, Cholinergic innervation and function in the prostate gland, Pharmacol Therapeut, **94**, pp 1–20.

Vicini, F.A., Kini, V.J, Diokno, A, Spencer, W, 1999, The Role of Androgen Deprivation in the Definitive Management of Clinically Localized Prostate Cancer Treated with Radiation Therapy, Int J Radiat Oncol, **43**(4): pp 707-713.

- W -

Walsh P.C and Siiteri P.K, 1975, Suppression of plasma androgens by spironolacetone in castrated men with carcinoma of the prostate. J Urol pp114-254.

Wang Y., Corr J.G., Thaler H.T., Tao Y., Fair W.R., Heston W.D., 1995, Decreased growth of established human prostate LNCaP tumours in nude mice fed a low fat diet. J Natl Cancer Inst, **87**, pp 1458–1462.

Wein AJ, Murphy JJ, 1973, Experience in the treatment of prostatic carcinoma with cyproterone acetate, Urol, **7**, 109, pp68-70.

Weinburg R.A., 1996, How cancer rises, Scientific American, **275**, no 3, pp 62–70.

West D.W., Slattery M.L., French T.K., Mahoney A.W., 1991, Adult dietary intake and prostate cancer risk in Utah: A case control study with special emphasis on aggressive tumours. Cancer Causes Control, **2**, pp 8 – 4.

Whittemore A.S., Wu A.H., Kolonel L.N., et al, 1995,Family history and prostate cancer risk in blacks, white, and Asian men in the United states and Canada, Am J Epidemiol, **14**, pp 732–740.

Willet W.C., and Hunter D.J., 1994, Vitamin a and cancers of the breast, large bowel, and prostate: epideniologic evidence. Nutr Rev, **52**, pp S553–S59.

Wingo P.A., Tong T., Bolden S., 1995, Cancer Statistics, CA: A cancer journal for clinicians, **45**, pp 8–30.

- X -

Xue L., Li Kiu M., Newmark H., et al., 1999, Influence of dietary calcium and vitamin D on diet-induced epithelial cell hyper-proliferation in mice, J Natl Cancer Inst, **91**, pp 176–181.

- Y -

Yoden T, Okada M, , Kawaminami E, Shimada Y, Kudoh M, Isomura Y, Shikama H, Fujikura T., 1996, Studies on aromatase inhibitors. I. Synthesis and biological evaluation of 4-amino-4H-1,2,4-triazole derivatives. Chem Pharm Bull, Tokyo, **44**, pp 1871-1879.

- Z -

Zhao X.Y., Feldman D., 2001, The role of vitamin D in prostate cancer, Steroids, **66**, pp 293 –300.

Zock P.L and Katan M.B, 1998, Linoleic acid intake and cancer risk: a review and meta-analysis, Am J Clin Nutr, **68**, pp 14 –153.