Synthesis and evaluation of [18F]fluoroprogestins and [18F]fluorometoprolol

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CHAPTER 1

INTRODUCTION

As a general introduction, in this first Chapter the reader is invited to make a short journey through the disciplines that have had a major influence on the work presented in this thesis: physics, pharmacology and chemistry. The synthesis of relevant radioactive ligands is reviewed.

1.1 About this thesis

The preparation of several receptor binding ligands, labelled with a positron emitting radionuclide, is described in this thesis. The joined development of the imaging technique Positron Emission Tomography[1] (PET) and this type of labelled compounds, provide a unique means to monitor, *in vivo* and in a quantitative way, physiological processes in the human body. Many of these processes are regulated by hormone-receptor interactions. Deviations in this system can give rise to the occurrence of various diseases. In this respect, information on the receptor status is of great interest to the treatment of diseases related to these receptors. Much effort has been invested in the development of methods to quantify receptors, both *in vivo* and *in vitro*. The use of radioactivity has been indispensable in this respect, and is still applied on a routine basis. It started with the use of tritium (^{3}H) and carbon-14 (^{14}C) in *in vitro* studies (which are still in effect today) and it evolved into the modern *in vivo* imaging techniques as PET and SPECT (Single Photon Emission Computed Tomography[2]). PET and SPECT are diagnostic tools in nuclear medicine, and must be distinguished from the therapeutic application of radioactivity, e.g. in the treatment of cancer.

Positive results of *in vivo* PET-studies have been reported in the case of dopamine receptors in relation to mental disorders,[3] ß-adrenergic receptors in the failure of the heart[4] and estrogen receptors in breast cancer.[5] Many other classes of receptors are under investigation, and new ligands are reported continuously. With respect to the fields of interest in our institute, we have chosen to focus our attention on two different classes of receptors to visualise: the progesterone and $ß_1$-adrenergic receptors.

1.2 Positron Emission Tomography

Radionuclides used in PET decay by positron emission (β^+-decay). A positron is a particle with the same mass as an electron, but with an opposite charge. When a positron combines with an electron (its counter particle), both particles will annihilate. Obeying Einstein's law, the mass of the positron and electron (2 x 9.1×10^{-31} g) is converted into two photons of 511 keV each, which are emitted in two diametrically opposed directions.

The gamma quanta are detected by a positron camera consisting of a circular array of detectors. An annihilation event is only then accepted when the two 511 keV photons strike two opposite scintillation detectors within a certain time interval. Scattered photons that reach only one of the detectors are rejected. By measuring the radioactivity from all angles, the distribution of an administered radioactive tracer in the body can be quantitatively determined. The resolution of the images depends on the dimensions of the BGO crystals (BGO = $Bi_4Ge_3O_{12}$, Bismuth Germanium Oxide) used in the detector and the decay energy of the radionuclide. With modern positron cameras, a resolution of 3-5 mm is feasible.[6]

1.2.1 Positron emitting radionuclides

isotope	$t_{½}$ (min)	E_{max} (MeV)	β^+ (%)
^{11}C	20.3	0.96	100
^{13}N	10.0	1.19	100
^{15}O	2.0	1.72	100
^{18}F	109.7	0.63	97
^{75}Br	95.5	1.74	76
^{76}Br	16.1	3.98	57

Table 1.1 Positron emitting isotopes for PET.

The radionuclides ^{11}C, ^{13}N, ^{15}O and ^{18}F are frequently used in PET studies and have found wide application in radiochemistry for the preparation of positron emitting radiopharmaceuticals. The radionuclides ^{11}C, ^{13}N and ^{15}O have the advantage to be introduced in a molecule without altering the pharmacological properties of the radioactive ligand with respect to the unlabelled natural compound. However, the short half-life of these three radionuclides limits the extent of chemical manipulation and makes prolonged scanning studies

impossible. The bromine isotopes $^{75,76}Br$ are rarely used nowadays for clinical application, because these radionuclides have rather unfavourable decay characteristics.[7] The radionuclide fluorine-18 was chosen for the studies described in this thesis, because of its relatively long decay time and the possibility to produce it in high yields and with high specific activity.[@]

1.2.2 Features of fluorine-18

Fluorine-18 decays for 96.9% by the emission of a positively charged electron (positron, β^+) and a neutrino (ν). This emission is the result of a transformation in the nucleus of a proton into a neutron. The nuclide which is formed in this process is oxygen-18. The remaining 3.1% of fluorine-18 decays by electron capture.

$$^{18}F \rightarrow {}^{18}O + \beta^+ + \nu$$

Scheme 1.1 Decay of fluorine-18

During the last decade, the application of fluorine-18 in PET-studies is more and more appreciated. The development of an efficient method to prepare no-carrier-added (n.c.a.) [^{18}F]fluoride with high specific activity has tremendously increased the radiochemical and biomedical potential of this radionuclide.

The atomic radius of fluorine, the smallest element of the periodic table, is comparable to that of hydrogen. This implies that steric effects of a fluorine for hydrogen substitution will hardly interfere with the binding of the ligand to the receptor. The high electronegativity of fluorine is more likely to influence the biochemical properties of a fluorinated ligand compared to the unsubstituted analogue. Indeed, fluorine substitution in pharmacological active compounds can have a (positive) effect on the biological properties.[8]

Fluorine-18 can be produced in an electrophilic ([^{18}F]F_2) or nucleophilic ([$^{18}F^-$]) form.[9] Much effort has been made to convert the extremely reactive [^{18}F]F_2-gas to more selective reagents, such as [^{18}F]acetylhypofluorite[10] (AcO[^{18}F]) or [^{18}F]-diethylaminosulfur trifluoride[11] ([^{18}F]DAST). However, for reasons to be explained in Chapter 2, reagents based on [^{18}F]F_2 are not suitable for the

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[@] The specific activity is the amount of radioactivity (Becquerel, Bq or Curie, Ci) per mass unit (mol), and is usually expressed as GBq/μmol or Ci/mmol (Chapter 2).

synthesis of receptor binding ligands and therefore [$^{18}F^-$] is preferred in the experiments described in this thesis. The radiochemical aspects of [^{18}F]fluoride will be dealt with in more detail in Chapter 2.

1.3 Receptors and PET

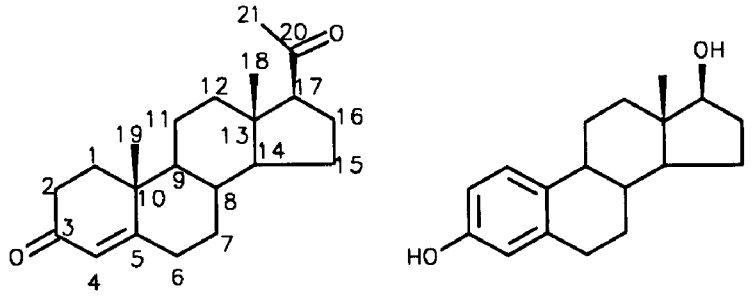
Receptors are proteins which are capable of binding certain compounds (ligands) with high affinity and selectivity.[12] The resulting receptor-ligand complex exerts a biochemical response; e.g. it initiates the synthesis of certain proteins.[13] By these receptor-ligand interactions biochemical processes are regulated. With PET it is possible to monitor *in vivo* the binding of a ligand to a receptor in a quantitative way. Thus, deviations in the regional receptor density of a tissue can be determined and the effect of therapy can be monitored.

The nature of receptors puts some constraints on ligands to be used in a PET study. Firstly, the ligand should have a high **affinity** for the receptor to be studied. In order for a ligand to be successfully used in the visualisation of receptors, it should have a higher affinity for the receptor than the circulating, natural ligand. The affinity of a ligand for a specific receptor is usually expressed in terms of the dissociation constant (K_D) or the Relative Binding Affinity (RBA) and is determined by competition experiments with a high-affinity, radioactive ligand. Secondly, the ligands should exhibit a high **selectivity** towards the receptor which is studied. Thirdly, the relatively low concentration of receptors (in target tissues usually in the order of 10^{-15} mol/mg tissue) imposes a constraint on the **specific activity** of the ligand. To avoid saturation and to assure maximum binding of the radioactive ligand to the receptor, the specific activity should therefore be high. For steroids, a minimum specific activity of 40 GBq/μmol (1000 Ci/mmol) is generally accepted.[14] Fourthly, the ligand must have favourable **metabolic characteristics**. The ligand should be stable or the labelled metabolites should not accumulate in the target tissue, to prevent interference with the quantification of the receptor density.

1.4 Progesterone receptors and breast cancer

Human mammary cancer is one of the major causes of death of women in the Western world today.[15] In The Netherlands, on a population of 15 million people, 7000 cases of breast cancer are discovered each year and 3000 women die because of this disease.[16] Breast cancer occurs rarely in men, the reported frequency is approximately 1% of the rate in women.[17] Variables that have been

associated with an increased risk for breast cancer are among others: a family history of breast cancer, early menarche, late age at first childbirth, late age at meno pause, history of benign breast disease, and exposure to ionizing radiation.[18]



1.1 1.2

*Figure 1.1 Structure of the sex hormones progesterone **1.1** and estradiol **1.2**. The atom designation of steroids is shown for progesterone.*

The biological factors which cause the occurrence of breast cancer are not yet well known,[19] although strong evidence exists that endogenous estrogens are involved in promoting both the formation and growth of breast tumors.[20] Progesterone **1.1** is believed to play a more protecting role. Indeed, breast carcinomas can sometimes be treated by the administration of anti-estrogens, such as tamoxifen,[21] or progestins, as medroxyprogesterone acetate.[22]

A major part of human mammary tumors are found to contain relatively high levels of progesterone and/or estrogen receptors (PR and ER respectively).[23] The success of endocrine therapy is related to the ER and PR density of the tumor.[24] It is assumed that the presence of PR in the tumor indicates an intact hormonal pathway. Patients with a tumor which is rich in ER and PR have therefore the best chance that endocrine therapy will result in regression of the tumor.[25] The chance on a positive result of endocrine therapy ranges from 30 to 40%, but in comparison with alternatives such as chemotherapy, hormone manipulations have the advantage of lower toxicity.[26]

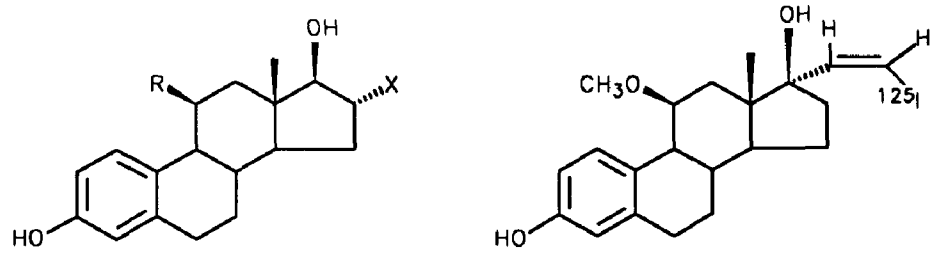
Detection of the tumor is generally achieved by self-evaluation and X-ray techniques. Both methods are able to detect tumors larger than 1 cm^3 in size but they do not provide information on the receptor status of the tumor. Until now, it is clinical practice to remove a sample of the tumor, and determine the receptor density *in vitro*. The development of a method which is capable of assaying the

receptor density *in vivo* would circumvent in some cases the necessity of surgery. Also, it would allow the detection of receptor positive metastases.

1.4.1 SPECT, PET and breast cancer

For a number of years attempts have been made to visualise *in vivo* the receptors of steroid hormones. Most of this effort was directed towards the progesterone and estrogen receptors, but also the androgen[27] and corticoid[28] receptors are studied. In this section, a review is given of a number of labelled steroids that have been prepared for the visualisation of ER and PR in breast carcinomas.

SPECT-tracers.- Radioactive iodinated steroids have been prepared for application in Single Photon Emission Tomograpy (SPECT), e.g. 16α-[^{125}I]iodoestradiol[29] **1.3a**@ (Figure 1.2). A selective uptake of **1.3a** in human ovarian tumor was found, but the tumor/blood ratio was low due to the presence of labelled metabolites in blood.[30] The iodine-131 analogue was also prepared and evaluated as a tracer for ER positive breast tumors.[31] It was not possible to image tumors with both compounds in such a way that an estimation of the ER density was possible.



1.3a R = H; X = ^{125}I or ^{131}I
1.3b R = CH_3O; X = ^{123}I or ^{125}I

1.4

Figure 1.2 Structure of some iodinated estrogens for SPECT.

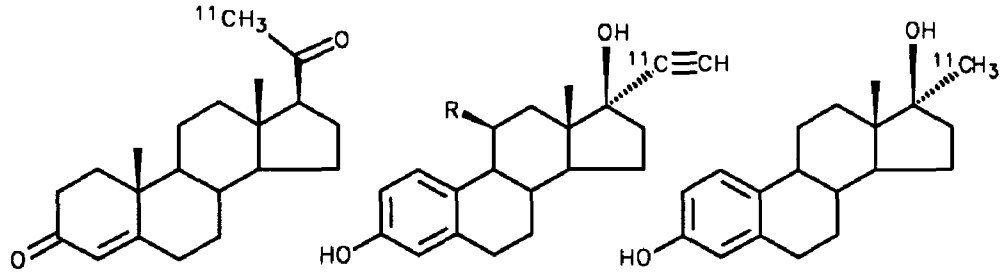
The 11ß-methoxy analogue **1.3b** of 16α-iodoestradiol has much better *in vivo* binding characteristics and is more resistant towards hepatic metabolism, resulting in a lower accumulation of radioactivity in the liver. The compound has been prepared in an [^{125}I]iodinated form by Zielinski and coworkers[32] and, recently,

@ Numbers refering to labelled compounds are underscored.

also labelled with iodine-123 by the same group.[33] The reported specific activity of these [^{123}I]iodinated compounds was very high, and ranged between 1,500-2,000 GBq/μmol (40-50,000 Ci/mmol).

17α-[^{125}I]Iodovinyl-11ß-methoxyestradiol **1.4** has been considered both as an imaging[34] and radiotherapeutic[35] ligand. In an *in vitro* experiment, Epperly *et al.*[35] found **1.4** to be cytotoxic to MCF-7 human breast carcinoma cells. A problem closely related to this type of labelled compounds is the extensive hepatic metabolism, accompanied by a considerable accumulation of radioactivity in the liver. With respect to radiotherapeutic applications, requiring a relatively high dose of radioactivity, this is a serious drawback. I.P. injections could prevent the first uptake by the liver,[35] but a successful application of **1.4** *in vivo* has not yet been reported.

PET-tracers.- In our research group the positron emitting radionuclide carbon-11 was applied for the synthesis of [21-^{11}C]progesterone[36] **1.1** and the estrogens 17α-[^{11}C]ethynylestradiol[37] **1.5a**, 11ß-methoxy-17α-[^{11}C]ethynylestradiol (moxestrol)[37] **1.5b** and 17α-[^{11}C]methylestradiol[38] **1.6** (Figure 1.3).



1.1 **1.5a** R = H **1.6**

1.5b R = CH_3O

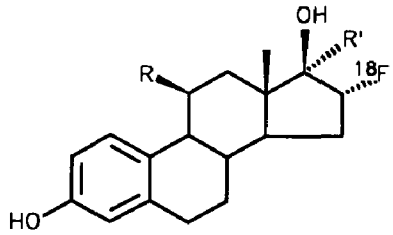
*Figure 1.3 Structure of [21-^{11}C]progesterone (**1.1**), 17α-[^{11}C]ethynylestradiol (**1.5a**), [^{11}C]moxestrol (**1.5b**) and 17α-[^{11}C]methylestradiol (**1.6**).*

The *in vivo* binding of the tritiated analogues of **1.5a**, **1.5b** and **1.6** was investigated in a DMBA-induced@ tumor model.[39] High uterus/blood and tumor/blood ratios were found for **1.5a,b** and **1.6**. However, the specific activity of the corresponding carbon-11 labelled estrogens was too low to result in a high uptake of radioactivity in the tumor. Besides, it can be doubted whether the half-

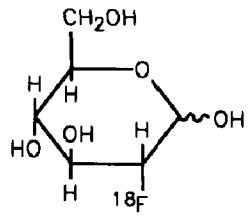
@ DMBA = Dimethylbenz(a)anthracene

life of carbon-11 will permit the scanning of the *in vivo* uptake of a labelled steroid for a long enough period of time, since acceptable target/non-target ratios are most often found 2-3 hours after injection of the tracer.

The half-life of fluorine-18 (110 min) and the attainable high specific activity make fluorine-18 to the radionuclide of choice for the visualisation of ER and PR *in vivo*. Kiesewetter *et al.*[40] prepared a series of [^{18}F]fluorinated estrogens with good *in vivo* characteristics. Especially 16α-[^{18}F]fluoroestradiol **1.7a** exhibited a high target/non-target ratio. This compound has been screened in patient studies[5] with nice results; in 1987 a scan with **1.7a** was chosen as "Image of the Year".[41]



1.7a R = R' = H
1.7b R = CH_3O; R' = C≡CH
1.7c R = C_2H_5; R' = C≡CH



1.8

*Figure 1.4 16α-[^{18}F]fluoroestrogens (**1.7a,b,c**) and [^{18}F]FDG (**1.8**).*

Recent reports[42] by the same group on the synthesis of 11ß-methoxy-, 11ß-ethyl- and 17α-ethynyl-derivatives of 16α-[^{18}F]fluoroestradiol **1.7a** suggested that these compounds are even more potent (**1.7b,c**, Figure 1.4).

The report of Mintun and coworkers[5a] on the visualisation of ER of a breast tumor with **1.7a** is at present the only successful *in vivo* application of a labelled steroid. Breast tumors have also been visualized with 2-[^{18}F]fluoro-2-deoxyglucose ([^{18}F]FDG) **1.8**, a fluorine-18 labelled analogue of glucose.[43] However, with [^{18}F]FDG only the *metabolic* activity of a tumor can be assessed.

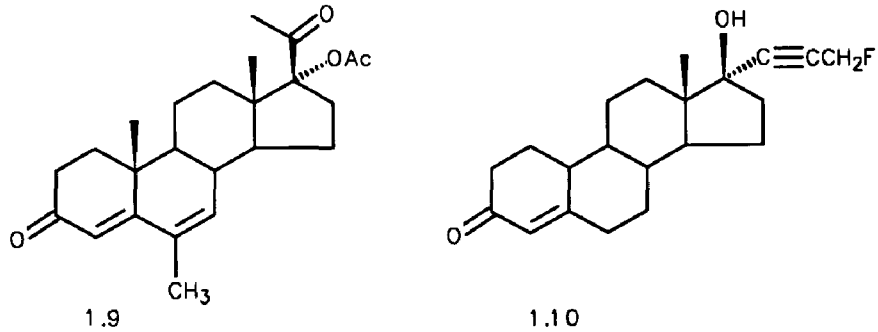
The application of a labelled estrogen has a drawback, since hormonal therapy is generally performed with anti-estrogens (antagonists). These compounds do occupy ER, but do not give the biological effect of estradiol itself (an agonist), thereby interfering with the growth of the tumor. During hormonal therapy ER is occupied with antiestrogens and the ER density cannot be assessed with a labelled ligand. In contrast to ER, PR remains available for quantification. Moreover, the

PR-density is a valuable marker for the hormone responsiveness of the tumor.[23,24] This, and the fact that at the start of our investigations no labelled progesterone derivative was successfully used in PET, prompted us to develop a high affinity positron emitting PR-ligand.

1.4.2 Characteristics of a fluorine-18 labelled progestin

Many studies have been carried out in which the influence of substitution of the progesterone skeleton on the biochemical properties of progestins has been investigated.[44] Taylor and Kent[45] have reviewed a number of fluorinated steroids. Bélanger *et al.*[46] and Heikinheimo *et al.*[47] have evaluated 11ß-alkylated 19-norsteroids which were claimed to have a high affinity for PR. The introduction of an 11ß-substituent in estrogens also has a positive effect on the binding of estrogens to ER.[48]

In the search for long lasting contraceptives there has been interest in the development of metabolically stable progestins.[49] It was found that the metabolic stability is positively influenced by the introduction of a substitutent at the 6-position and/or a 4,6-diene-entity.[50,51] For instance, megestrol acetate, 17α-acetoxy-6-methyl-4,6-pregnadiene-3,20-dione **1.9**, is more resistant towards hepatic metabolism than progesterone **1.1**.[51] Substitution of progesterone at C-16α and C-17α has also been suggested to increase the metabolic stability.[52,53]



1.9 1.10

*Figure 1.5 Structure of megestrol acetate (**1.9**) and 17α-(3-fluoro-1-propynyl)-nortestosterone (**1.10**).*

Brandes and Katzenellenbogen have performed a survey of several fluorinated androgens and progestins.[54] They found that of the steroids studied, 17α-(3-fluoro-1-propynyl)-nortestosterone **1.10** has the highest affinity and selectivity for

PR. However, the relative binding affinity (RBA = 66, relative to progesterone = 100) is too low to compete with progesterone for PR.

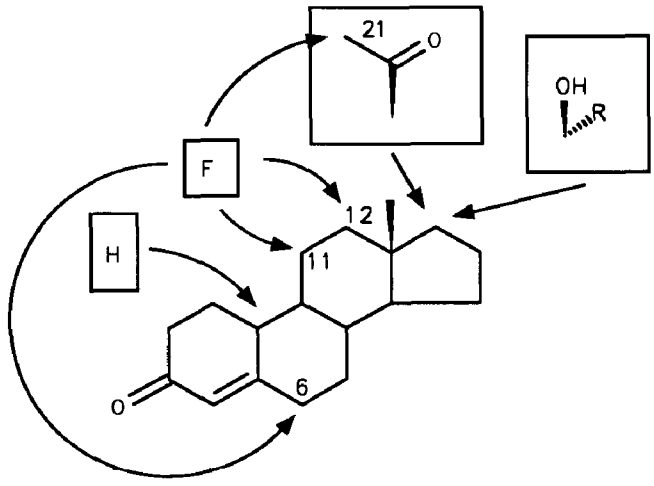


Figure 1.6 Possible labelling sites with fluorine-18 and structural variation of the progestin skeleton.

In 1988 the same authors[55] published a review summarizing some of the essential properties of a ligand necessary for a high affinity for PR (Figure 1.6). The 3-keto-4-ene entity is required for binding PR. The same is valid for the 17ß-acetoxy group, but this group can be replaced by 17ß-hydroxy-17α-alkyl substituents. Furthermore, progestins lacking the angular 10-methyl group (19-norprogestins) exhibit a higher affinity for PR. Substitution of the 6-position with a methyl group, either in α- or ß-position, increases binding. Favourable positions for the introduction of fluorine, with respect to increasing affinity, are the 6α-, 11ß-, 12α- and 21-position.[55,56]

Smith *et al.*[57] confirmed the benificial effect of fluorine substitution in the 6α-position of progesterone and explained it by hydrogen bonding of the electronegative fluorine with a proton donor of the receptor. In contrast to the 6α-position, 6ß-fluorine has a negative effect on the binding affinity of the progestin, due to its inductive effect on the 3-keto group.[58] This effect is stronger when fluorine is in the axial position (6ß), than in the equatorial position (6α). As a result of the inductive effect, the interaction between the C-3 carbonyl and a proton donor on the receptor is weakened and the affinity of the ligand for the receptor is reduced.

We have chosen to investigate two possibilities for the introduction of fluorine-18 into the progesterone molecule. One attempt was directed towards the 21-position in the acetyl side chain of the molecule, the other objective was the introduction of a fluorine-18 substituent at the 6-position. These two positions would allow the screening of two different classes of progestins, either based on progesterone **1.1** or on 17α-alkylated derivatives of androstenedione as **1.10** (e.g. d-norgestrel[59]). The synthesis of the 21-[^{18}F]fluoroprogestins is presented in Chapter 3, the attempts for the preparation of the 6α-[^{18}F]fluoro-labelled steroids are described in Chapter 4.

1.5 ß-Adrenergic receptors and the heart

Beta-adrenergic receptors (ß-adrenoceptors) are involved in the regulation of the rate and contractile force of the heart.[60] In 1967 Lands[61] proposed the existence of two subtypes of these beta-adrenoceptors: the $ß_1$- and $ß_2$-receptors. High densities of the $ß_2$-adrenoceptors are mostly found in periferic parts of the human body and control for example the bronchial muscles. The $ß_1$-adrenergic receptors are found mainly in the heart and are involved in the regulation of the heart function and the coronary flow.

The natural ligands for ß-adrenoceptors, noradrenaline and adrenaline, are neurotransmitters of the sympathetic nervous system. Both compounds show a similar affinity for the $ß_1$-adrenoceptors, whereas for $ß_2$-adrenoceptors the affinity of adrenaline is higher than noradrenaline. (Nor)adrenaline is also produced by the adrenal glands in "stress, fight or flight" situations. The physiological effect of these agonists can be counteracted by the administration of antagonists that bind with high affinity to the ß-adrenoceptors. The use of these antagonists, popularly known as "beta-blockers", results in a decrease of the heart rate and contractility (blood pressure).

Changes in number and/or affinity of these cardiac neurotransmitter receptors have been associated with several cardiac diseases,[62] such as congestive heart failure[63,64] and infarction.[65] In failing human hearts, the $ß_1$-subpopulation has been reported to be always decreased in size, whereas changes in the $ß_2$-subpopulation are more variable.[66] Therefore, the assessment of the $ß_1$-adrenoceptor density is of most interest, and synthetic efforts are directed mainly towards the synthesis of a labelled, selective $ß_1$-ligand.

The alterations of the $ß_1$- and $ß_2$-subpopulations have been demonstrated *in vitro* in samples collected mainly during surgery or post mortem. A general disadvantage of these *in vitro* binding studies is the loss of the natural

environment of the receptors. In addition, no information is gained on the time-course of changes in receptor density during the disease process, the spatial distribution of such changes within the heart, or the influence of therapy. With PET it would be possible to measure the receptor density *in vivo* and to perform dynamic studies.

1.5.1 PET and heart failure

Apart from the quantification of ß-adrenoceptors in the heart, application of PET in cardiology has been reported in the measurement of the glycolysis in the myocardium with [^{18}F]FDG,[67] blood flow with [^{15}O]water[68] and [^{13}N]-ammonia,[69] oxygen consumption with [^{11}C]acetate,[70] fatty acid oxidation with [^{11}C]palmitate[71] and the muscarine receptor density with [^{11}C]MQNB (N-[^{11}C]methyl quinuclidinyl benzylate).[72]

Several ligands have been prepared in a labelled form for the *in vivo* quantification of ß-adrenoceptors, such as practolol,[73] pindolol,[74] propranolol,[75] metoprolol[75] **1.12** and carazolol[76] **1.13.** Thus far, such efforts have not been very successful because the affinity of the tracers for ß-receptors was too low, or a relatively high level of non-specific binding made quantitative imaging impossible.

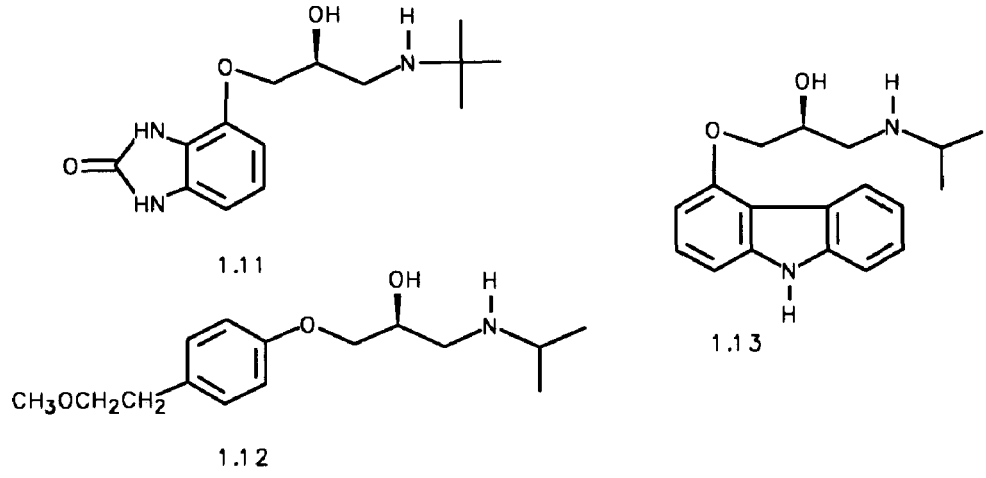


Figure 1.7 CGP 12177 (1.11), metoprolol (1.12) and carazolol (1.13).

Until now, only [^{11}C]CGP 12177 **1.11** has been used successfully for the *in vivo* quantification of the ß-adrenoceptor density in the heart.[4] The S-(-) isomer of

1.11 is a non-selective ß-adrenoceptor antagonist, and has a high affinity for the $ß_1$-adrenoceptors (K_D = 0.2-0.9 nM).[77] CGP 12177 **1.11** was prepared from [^{11}C]phosgene as was described by Bouillas *et al.*[78] Due to its very low lipophilicity, **1.11** binds only to receptors on the cell surface and not to desensitised or internalised receptors.[79] This is an important feature of CGP 12177 and other hydrophilic ß-ligands, since only the ß-adrenoceptors on the membrane surface are available for binding neurotransmitters. Recently, the asymmetric synthesis of **1.11** has been reported.[80,81] CGP 12177 **1.11** is presently also under investigation by our group.[82]

1.5.2 Possibilities for a [^{18}F]fluorinated $ß_1$-ligand

As shown in Figures 1.7 and 1.8, beta-blockers generally possess a phenoxy-propanolamine backbone. The phenyl-ring of the molecule can be substituted with a great variety; the amino functionality is often alkylated with an isopropyl- or *t*-butyl-group, although many other modifications are possible.

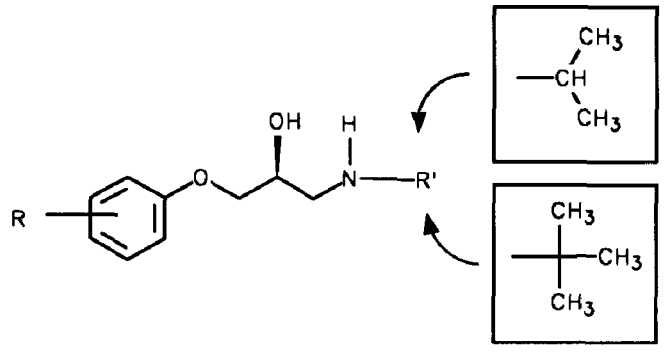


Figure 1.8 Structural variations of high-affinity beta-blockers.

Introduction of a positron emitting radionuclide in the N-alkyl-group would yield a flexible approach towards the labelling of a beta-blocking agent. This approach allows the screening of a large number of $ß_1$-selective ligands for their suitability as a tracer for PET. In the past, this approach has been applied for the synthesis of ß-adrenoceptor ligands labelled with carbon-11,[73-76] and recently also for fluorine-18.[83] We have chosen to investigate the synthesis of a [^{18}F]fluorinated ß-ligand to enable a prolonged dynamic study of the $ß_1$-adrenoceptors.[76] The results of these investigations are described in Chapter 5.

1.6 Aims and scope

The aim of the present investigations was to develop new receptor binding ligands for PET. In this thesis the syntheses of fluorine-18 labelled progestins and β_1-adrenergic ligands are described. Three approaches towards [^{18}F]fluorination are investigated: i) direct S_N2-substitution, ii) opening of an epoxide and iii) [^{18}F]fluoroalkylation. The positron emitting radionuclide fluorine-18 was used because of its relatively long decay time and the possibility to produce it in high yields and with high specific activity. The target systems which were applied for the production of fluorine-18, are described in Chapter 2. Important chemical and physical aspects of [^{18}F]fluoride are reviewed in the same Chapter. In Chapter 3, the synthesis of 21-[^{18}F]fluorinated progestins is discussed. The synthesis of four 21-[^{18}F]fluoroprogesterone derivatives is described and the results of an *in vivo* evaluation of two of these ligands are discussed. Possible routes leading to 6α-[^{18}F]fluoroprogestins are presented in Chapter 4. The radiochemical approaches towards the synthesis of these ligands are discussed. In Chapter 5 the proposed routes to the fluorine-18 labelled β_1-adrenergic ligands are described and evaluated in the synthesis of two model compounds. 1'-[^{18}F]Fluorometoprolol, the [^{18}F]fluorinated analogue of a potent beta-blocker, is prepared using one of the investigated methods. The biological effect of fluorine substitution of a β_1-adrenergic ligand is discussed on the basis of an *in vitro* and *in vivo* evaluation.