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(54) Title: PHARMACEUTICAL PRODUCT COMPRISING A SALICYLATE OF AN ESTERIFIABLE BETA-BLOCKER

(57) Abstract

Salicylates of esterifiable β-blockers, especially Atenolol-O-Aspirinate, Metoprolol-O-Aspirinate, Pindolol-O-Aspirinate and processes for their preparation are described.
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PHARMACEUTICAL PRODUCT COMPRISING A SALICYLATE OF AN ESTERIFIABLE BETA-BLOCKER

The invention relates to pharmaceutical products.

The term "β Blocker" as used in this specification refers to pharmacologically active β Blocker compounds which relieve or act as prophylactic against cardiovascular disease including hypertension, angina pectoris (pain in the heart muscle), cardiac failure, or after a heart attack (post myocardial infarction).

Beta-adrenoceptor blocking agents or antagonists are competitive inhibitors of catecholamines at beta-adrenergic receptor sites. The principal effect of beta blockers is to reduce cardiac activity by diminishing or preventing beta-adrenergic receptor stimulation. Beta blockers inhibit the secretion of renin and alter the sensitivity of the baroreceptor reflex, they also block the sympathetic drive to the heart. This reduces the chronotropic and inotropic responses during exercise and stress thus limiting oxygen requirements.

The beta blockers are effective in reducing the severity and frequency of exertion angina (i.e. pain in the heart brought on by exercise) that is for angina pectoris.

Beta blockers are also important in anti hypertensive therapy (lowering of blood pressure). This is thought to be achieved through the reduction of heart output, and in the inhibition of renin secretion and a change in the sensitivity of the baroreceptor reflex.

Aspirin (acetylsalicylic acid) has been widely used for many years as an analgesic/anti-pyretic and anti-inflammatory agent. As such, it is a most useful drug.
In more recent years, however, it has been discovered that aspirin has a powerful anti-platelet effect. Platelets are microscopic particles within the blood that, under certain circumstances, can stick together to form a thrombus (clot). Aspirin prevents the sticking together of platelets and thus helps prevent the occurrence of heart attack or its complications.

According to the invention there is provided a pharmaceutical product comprising a salicylate of an esterifiable β Blocker.

The term "salicylate" as used in this specification refers to a salicylate or a salt, ester, derivative, complex thereof, or salts of the ester, derivative or complex having anti-platelet activity.

Preferably, the β Blocker is directly esterifiable. In other words, the β Blocker has an hydroxy group which is available for esterification.

In a particularly preferred embodiment of the invention the product is formed by esterification of an esterifiable β Blocker with acetylsalicylic acid.

Preferably the β Blocker is Atenolol.

The invention further provides Atenolol-O-aspirinate and enantiomer(s) thereof.

In another case the β blocker is Metoprolol.

The invention also provides Metoprolol-O-Aspirinate. In a further embodiment the β blocker is Pindalol.

The invention further provides Pindalol-O-Aspirinate.
The invention also provides a process for preparing a pharmaceutical product of the invention by esterifying an esterifiable β blocker with acetylsalicylic acid.

In another embodiment, the process involves esterifying an esterifiable β blocker with salicylic acid.

In one embodiment of the invention the process comprises the steps of:

- protecting the secondary amine group in the β blocker;
- activating the carboxyl group in salicylic acid or derivative thereof;
- direct coupling of the activated carboxyl group of the salicylic acid or derivative thereof; and
- removing protecting groups from the secondary amine group in the β blocker.

In this case, the secondary the secondary amine group in the β blocker is protected by forming an N-BOC derivative of the β blocker secondary amine and, after coupling, the N-BOC protecting group is removed.

In an embodiment of the invention the N-BOC derivative of the β blocker is formed by reaction between the β blocker secondary amine and di-t-butyl in t-BuOH/H2O to form the tert-butyloxycarbamide derivative.

Preferably the N-BOC protecting group is removed using trifluoro-acetic acid to form the trifluoroacetate salt of the Aspirinate. Typically the process includes the step of forming the β blocker Aspirinate base by extraction
from a weakly alkaline medium. Preferably the process includes the steps of acidifying an alcoholic solution of the Aspirinate base in an acid to form a pharmaceutically acceptable salt.

In another embodiment of the invention the carboxyl group in salicylic acid or derivative thereof is activated by one or more of:-

- acid chloride formation;
- pentafluorothioester formation; or
- *in situ* formation of 2,6 dichlorobenzoyl anhydride.

In one case the β is coupled with acetylsalicylic acid derivative having an activated carboxyl group.

In another case the β blocker is coupled with a salicylic acid derivative having a protected hydroxy group. Preferably the hydroxy group is protected by benzyl ether formation. In a preferred embodiment, salicylic acid is converted into O-benzyloxy benzoic acid.

The process also includes removing the salicylic acid hydroxy protection group after coupling. Typically the protected salicylic acid hydroxy group is removed by hydrogenolysis.

In a preferred embodiment of this aspect of the invention, after removal of the protecting group the salicylic acid derivative is acylated.

In one embodiment of the invention the process comprises the steps of:-
forming a protected salicylic acid hydroxy group;

forming an N-BOC derivative of the β blocker secondary amine;

coupling of the protected salicylic acid with the N-BOC β blocker;

removing the protecting group from the salicylic acid hydroxy group;

acylating the salicylic acid; and

removing the N-BOC protecting group.

In another embodiment the process comprises the steps of:

forming an N-BOC derivative of the β blocker secondary amine;

direct coupling of the N-BOC derivative of the β blocker with acetylsalicylic acid;

removing the N-BOC protecting group.

In a further possible embodiment the process comprises the steps of:

forming a pentafluorothiophenol ester of acetylsalicylic acid;

forming an N-BOC derivative of the β blocker secondary amine;
direct coupling of the pentafluorothiophenol ester with N-BOC derivative of the β blocker; and removing the N-BOC protecting group.

In another embodiment the process comprises the steps of forming acetylsalicyloyl chloride;

forming an N-BOC derivative of the β blocker secondary amine;

direct coupling of the N-BOC β blocker with acetylsalicyloyl chloride; and removing the N-BOC protecting group.

In these cases the process preferably include the step, after removal of the protecting group, of forming the β blocker aspirinate base; and, optionally, forming pharmaceutically acceptable salts thereof by acidification of an alcoholic solution of the base using appropriate acids.

The invention further provides a pharmaceutical product whenever prepared by a process of the invention.

The invention also provides a pharmaceutical composition including a pharmaceutical product of the invention. The composition is preferably in the form of a tablet or capsule.

The invention will be more clearly understood from the following description thereof given by way of example only.
β Blockers and their salts, their enantiomers and their salts, derivatives (e.g., esters) and their salts are all 2-ethanolamine derivatives. More specifically, they are compounds of the formula

\[ \text{HO-CH-CH}_2\text{-NH-R} \]

\[ \text{R}^1 \]

in which \( \text{R} = \text{ip, tb or other} \) and \( \text{R}^1 \) represents various substituents.

The following are some examples thereof.

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*ip = iso-Propyl, tb = tert-Butyl, other = various*
EXAMPLE 1
Synthesis of Atenolol-O-aspirinate


Materials:

Acetylsalicylic acid Sigma Ltd MW 180.16
Atenolol MW 266.34
Dicyclohexylcarbodiimide (DCC) Sigma Ltd MW 206.33
10 Dimethylaminopyridine (DMAP) Sigma Ltd MW 122.20

Method
To a stirred solution of acetylsalicylic acid (3.6gms, 0.02 mol) in 30ml dry dichloromethane was added DMAP (0.5 gms) and Atenolol (5.32gms, 0.02mol).

DCC (4.2gms) was added gradually at 0°C and the reaction mixture stirred for 15 minutes. The icebath was removed and the mixture stirred for a further 3 hours. The precipitated urea was removed by filtration and the filtrate evaporated in vacuo. The filtrate was taken up in dichloromethane and then washed with 2 x 25ml portions of 20% citric acid and then by 2 x 25ml portions of saturated sodium bicarbonate solution. The organic layer was dried over anhydrous sodium sulphate and the solvent removed in vacuo to yield the semisolid product Atenolol-O-aspirinate (Yield 30%). The product was characterised as Atenolol-O-aspirinate using FTIR and NMR as shown in Figs. 1 and 2.

FTIR (thin film) νCO: 1747, 1650 cm⁻¹
NMR(CDC\textsubscript{3})300MHz: 1.26, doublet CH(CH\textsubscript{3})\textsubscript{2}: 2.6-2.96 CH\textsubscript{2} and CH: 3.486 singlet
ARCH\textsubscript{2}CO: 2.48 singlet ArOCOCH\textsubscript{3}: 6.9-8.26 aromatics. (8H)

This method is illustrated schematically in Appendix 1 and is an adaptation of the method described by Neises and Steglich, Agnew Chem. Int. Ed. 17 (1978) No. 7, p522-524.

Other appropriate direct esterification methods are given in Larock, R.C., "Comprehensive Organic Transformations" pages 966-972, inclusive, published by VCH 1989.

The product has the following structure.

\[
\text{OCOCH}_3
\]
\[
\text{CH}_2\text{O}\quad\text{CH}_2\text{CONH}_2
\]
\[
\text{COO} \quad \text{CH}_2\text{NHCH(CH}_3\text{)}_2
\]

\begin{center}
\text{Atenolol-O-aspirinate and enantiomer}
\end{center}

\textbf{EXAMPLE 2}

The Product of Example 1 may also be prepared by indirect esterification.

\textbf{2A Esterification via acetylsalicyloyl chloride (Appendix 2A)}

\textbf{Materials:}
Acetylsalicylic acid \quad \text{Sigma}
Thionyl chloride \quad \text{Aldrich Chemicals}
Atenolol
Method

In a 50ml round bottom flask equipped with a reflux condenser with drying tube attached, is placed 36g acetylsalicylic acid. Thionyl chloride 35.2gms is added gradually over 5 minutes. The mixture was heated under gentle reflux for 75 minutes and then cooled. The flask was then transferred to a rotary evaporator in a fume hood and the excess thionyl chloride removed under vacuum. The required acetylsalicyloyl chloride was identified by infra red (vCO 1784cm⁻¹) and NMR(acetyl methyl 3H: 2.46 and aromatics 4H: 8.18 to 7.28).

Dissolve Atenolol (0.5gms, 3.75 mmol) in 25ml chloroform in round bottomed flask fitted with a drying tube. The acetylsalicyloyl chloride (5.5mls, 37.5 mmol) was added gradually and the solution refluxed for 2 hours. The chloroform was evaporated in vacuo and the residue then taken up in ether. The ether was decolorised using charcoal, filtered and the solvent removed in vacuo. The residue was then dissolved in ethanol and the product recovered by precipitation using n-hexane as an oily semisolid. The product (25% yield) was characterised as Atenolol-O-aspirinate using FTIR and NMR as per appended spectra.

This method is an adaptation of the method described by Anspach, R. et al., Ann. Chem., 367, 172-180, 1909.

Esterification of thiols to form esters may also be achieved by treating carboxylic acids such as acetylsalicylic acids, with agents such as:

Phenyldichlorophosphate or the appropriate polyphosphate ester:
Immamoto et al Synthesis 134, 1982
Liu and Sabesan, Can J Chem 58, 2645, 1980
Dellaria et al Synth, Commun. 16, 1043, 1986


Haslam Tetrahedron 36, 2409-2433, 1980
EXAMPLE 3 - Atenolol Aspirinate

Synthesis strategy employed in the coupling of Atenolol to Aspirin.

An alternative route to directly couple Atenolol to acetyl salicylic acid is described in Scheme 1 below. Salicylic acid 1 was dialkylated by forming the benzyl ester as well as the benzyl ether and then hydrolyse the ester functional group of 2 back to the acid under basic conditions. The formation of the benzyl ester of 1 was rapid (Room temperature, 20 min). More vigorous conditions were required to form the benzyl ether (60°C 2 hr, 55%). The hydrolysis of the benzyl ester of 2 was then carried out under standard basic conditions which gave the acid 3 in 95% yield.

One of the more successful methods for the coupling of alcohol units to organic acids is via the lactonisation method described by Yamaguchi and co-workers: Yamaguchi et al Bull. Chem. Soc. Japan, 1979, 52, 1989, Waanders et al Tetrahedron Letters, 1987, 28, 2409. The highest yield of ester 5 was obtained using the following method. The acid 3 and DMAP (4 eq) in toluene were dried by azeotropie distillation and to the dried solution was added a solution of 2,6-dichlorobenzoyl chloride (1 eq) in dry toluene. After refluxing this solution for 5 min, 1.0 equivalent of N-BOC-Atenolol 4 was added. After refluxing for 25 min, analysis of the solution by TLC implied that all of the acid was consumed. After work up (see experimental section), the ester 5 was isolated in 95% after chromatography.

Hydrogenolysis of the benzyl ether 5 was carried out using an equivalent by weight of 10% Pd/C to benzyl ether 5 in ethanol/ethyl acetate. After work-up the phenol was
isolated in quantitative yield. The acetylation of the phenol proceeded cleanly yielding the acetate 6 in 90% yield after work up.

Preparation of ester 5

To a solution of salicylic acid 1 (75 mg, 0.54 mmol) in MeOH-H₂O (30 ml, 10:1) was added aqueous Cs₂CO₃ until the pH of the solution was slightly alkaline (Ph 7.5-8.0). The solvent was then evaporated on a rotary evaporator to leave an oil, to which toluene (30 ml) was added.

Evaporation of the solvent on the rotary evaporator left a white solid of the caesium salt, which was dissolved in DMF (15 ml). To this solution was added benzyl chloride (0.14 g, 1.1 mmol, 2.0 eq). The mixture was left stirring at room temperature for 20 min at which time TLC showed that the formation of the benzyl ester had taken place. The solution was then heated to 60°C and after 2 h, TLC showed that the formation of the benzyl ether 2 had taken place.

After cooling to room temperature, the mixture was partitioned between ether-water (1:1, 120 ml). The organic layer was isolated and the aqueous layer extracted with ether (2 x 50 ml). The combined organic layers were washed with water and dried with MgSO₄.

Filtration followed by evaporation of the solvent left an oil, which was passed through a plug of silica, eluting with hexane-ethyl acetate (30:1), which gave the benzyl ether 2 (95 mg, 55%) as an oil. The benzyl ether 2 (95 mg, 0.3 mmol) was then dissolved in a solution of 2M NaOH in THF-MeOH-H₂O (3:3:2) (16 ml), which was then refluxed. After 2h TLC showed that hydrolysis of the benzyl ester of 2 was complete. Removal of the volatiles on the rotary evaporator left an oil, which was partitioned between
ether (50 ml) and water (50 ml). The aqueous phase was extracted and to it was added a dilute aqueous HCl (1 M, 100 ml) and ether (100 ml). The organic layer was isolated and the aqueous layer extracted with ether (2 x 50 ml). The combined organic extracts were washed with water, dried with MgSO₄, and filtered.

Evaporation, left an acid 3 as a gum, which was dissolved in toluene (50 ml) and to this solution was added DMAP (146 mg, 1.2 mmol). This solution was then dried thoroughly by azeotropic distillation and to the dried solution was added a solution of 2,6-dichlorobenzoyl chloride (62.5 mg, 0.3 mmol) in dry toluene (5 ml). The solution was then refluxed for 5 min and then N-BOC-Atenolol (109 mg, 0.3 mmol, leq) was added. After 10 min of refluxing TLC showed that the formation of ester 5 was complete. Evaporation of the solvent on the rotary evaporator left a gum, which was dissolved in DCM and passed through a plug of silica eluting with ethyl acetate to give the ester 5 as an oil (160 mg, 93%); ¹H (selected peaks only) 1.11 (6H, m, CH(CH₃)₂), 1.45 (9H, s, (CH₃)C-O), 3.46 (2H, s, PhCH₂CONH₂), 3.56 and 4.13 (5H, m, OCH₂CH-CH₂NCH), 5.13 (2H, s, benzylCH₂O), 5.53, 5.60 and 5.99 (3H, br, m, CH-OCO and CONH₂), 6.82-7.9 (13H, m, aromatic proton resonances). ¹³C (selected peaks only) 20.7 (2 x C, CH(CH₃)₂), 28.4 (3 x C, (CH₃)₃C-O), 42.2 (1C, PhCH₂CONH₂), 67.7 and 71.9 (2C, -NCH₂CH₂OAr), 79.8 (1C, (CH₃)₃C-O), 113.5-158.1 (Aromatic carbon resonances), 165.5 and 174.1 (2 x C, COOCH and CONH₂).

Hydrogenolysis of the Benzyl ether of 5 and Acetylation of the resulting Phenol to give acetate 6.

To a solution of 5 (0.1 g, 0.17 mmol) in ethyl acetate (5 ml) and ethanol (5 ml) was added 10% Pd/C (0.1g). Hydrogenolysis of the benzyl ether was carried out at 1
atm pressure under an atmosphere of hydrogen at room temperature. After 24 h TLC indicated that complete removal of the benzyl ester had taken place. The solvent was then removed on the rotary evaporator to leave a black gum. This was then dissolved in DCM, filtered and the filtrate concentrated and passed through a silica gel plug eluting with ethyl acetate. Evaporation of the eluent left the phenol as an oil (79 mg, 95%). $^1$H (selected peak only) 10.69 (1H, s, Phenolic OH). The phenol was then dissolved in anhydrous DCM (5 ml) and to it was added Et$_3$N (65 mg, 0.65 mmol) and DMAP (79 mg, 0.65 mmol). After stirring for 4 h at RT, analysis by TLC showed that all of the phenol had been consumed. Evaporation of the solvent left an oil, which was passed through a plug of silica, eluting with ethyl acetate. Evaporation of the eluent gave acetate 6 as an colourless oil (81 mg, 94%), $^1$H (selected peak only) 2.32 (3H, s, CH$_3$COO).

Removal of the N-BOC protecting group of 6 to give amino trifluoroacetate salt 7

To a stirred solution of TFA (3 ml) in anhydrous DCM (3 ml) at room temperature was added N-BOC carbamate 6 (81 mg, 0.15 mmol). After 3 h of stirring at 0°, the volatiles were removed by evaporation under reduced pressure. DCM (3 x 20 ml) was added to the residue and removed by evaporation under reduced pressure to leave the alkylammonium trifluoroacetate salt 7 as a clear colourless oil. $^1$H (selected peaks only) 1.33 (6H, m, CH(CH$_3$)$_2$), 2.29 (3H, s, CH$_3$COO), 3.44 (2H, s, PhCH$_2$CONH$_2$), 3.49 and 4.23 (5H, m, OCH$_2$CH$_2$NCH$_2$), 5.53, 5.60 and 6.66 (3H, br m, CH-OCO and CONH$_2$), 6.85 and 7.08 (4H, 2d, benzeneacetamide proton resonances), 7.09, 7.28, 7.57 and 7.99 (4H, d, t, t, d, Aspirin aromatic proton resonances). $^1$C (selected peaks only) 19.0 (2 x C, CH(CH$_3$)$_2$), 21.4 (1 x C, CH$_3$CO-O), 42.2 (1C, PhCH$_2$CONH$_2$), 55.0 and 70.1 (2 x C,
\[ \text{CHCH}_2\text{NCH(\text{CH}_3)}_2, 67.7 \text{ and } 71.9 \ (2\text{C, } -\text{NCH}_2-\text{CHCH}_2\text{OAr}), 115 \text{ and } 132 \ (2 \times C, \text{ benzeneacetamide CH resonances}), 124, 128, 134, \text{ and } 136 \ (4 \times C, \text{ Aspirin aromatic CH resonances}), 122, 130, 152 \text{ and } 157 \ (4 \times C, \text{ Quaternary aromatic carbons}), \]

Legend for spectroscopic data Figs. 3 to 14 inclusive.

Fig. 3: \(^1H \text{ nmr}\) Compound 5 \text{ Scheme 1 above}
Fig. 4: \text{ DEPT nmr}\) Compound 5 \text{ Scheme 1 above}
Fig. 5: \(^13C \text{ nmr}\) Compound 5 \text{ Scheme 1 above}
Fig. 6: \(^1H \text{ nmr}\) Compound 5a (phenol) \text{ Scheme 1 above}
Fig. 7: \(^13C \text{ nmr}\) Compound 5a (phenol) \text{ Scheme 1 above}
Fig. 8: \text{ DEPT nmr}\) Compound 5a (phenol) \text{ Scheme 1 above}
Fig. 9: \(^1H \text{ nmr}\) Compound 6 \text{ Scheme 1 above}
Fig. 10: \text{ DEPT nmr}\) Compound 6 \text{ Scheme 1 above}
Fig. 11: \(^13C \text{ nmr}\) Compound 6 \text{ Scheme 1 above}
Fig. 12: \(^1H \text{ nmr}\) Atenolol aspirinate salt form \text{ Scheme 1 above}
Fig. 13: \text{ DEPT nmr}\) Atenolol aspirinate salt form \text{ Compound 7}
Fig. 14: \(^13C \text{ nmr}\) Atenolol aspirinate salt form \text{ Compound 7}

Preparation of Atenolol Aspirinate and conversion to its hydrochloride, fumarate and tartrate salts.

Atenolol Aspirinate Trifluoroacetate (0.2g) was dissolved in 5 ml of methanol and treated with 10% aqueous NaHCO\(_3\) (100 ml). The aqueous solution was extracted with 3 x 30 ml dichloromethane. The organic solution was dried (Na\(_2\)SO\(_4\)) and evaporated yielding Atenolol aspirinate.
Atenolol aspirinate was dissolved in 5% methanolic HCl and stirred for 30 min. The solvent was evaporated to yield the hydrochloric salt.

Treatment of Atenolol aspirinate with 0.5 equivalents of fumaric or tartaric acid in methanol yielded the corresponding fumarate and tartrate salts on evaporation of the solvent.
Scheme 1

1. OH
   (i) C₂H₅CO₂ in MeOH-H₂O (1:1)
   (ii) Benzyl chloride in DMF

2. Ph

3. O
   Ph
   C\text{OH}

4. Ph
   O
   Ph
   HO
   N
   \text{Acetate}

5. O
   Ph
   O
   Ph
   N
   \text{Acetate}

6. O
   Ph
   O
   Ph
   N
   \text{Acetate}

7. O
   Ph
   O
   Ph
   N
   \text{Acetate}

(i) Hydrogenation over 10% Pt/C in ethanolic ethanol
(ii) Acetate, Dimethylamino.pyridine and Et₃N in DCM
(iii) Trifluoroacetic acid in DCM
EXAMPLE 4 - Metoprolol Aspirinate

The title compound was prepared according to the reaction scheme below.

Synthesis of 0-Benzylxoxy benzoic acid 4

\[
\begin{array}{c}
\text{CO}_2\text{H} \\
\text{OCH}_2\text{Ph}
\end{array}
\]

Benzylation of Salicylic acid:
Salicylic acid (1) was dissolved in methanol/water (10:1), treated with 1 molar equivalent of K₂CO₃ and stirred at room temperature for 1 hour. The di-ionic salt 2 obtained by evaporation of the solvent, was treated with two molar equivalents of benzyl bromide in DMF and heated to 60°C for four hours. After workup and silica-gel chromatography the desired product, dibenzyl salicylate 3, was obtained in 61% yield in addition to benzyl salicylate (30%).

Hydrolysis of Dibenzyl salicylate
Dibenzyl salicylate 3 (0.3g) was dissolved in 10 ml of a THF/methanol/water solution (2:1:1) and an equal volume of 2M NaOH was added. The solution was refluxed for 15 min. until the starting material had disappeared as evidenced by TLC. The solution was poured onto 100 ml water and extracted with 3 x 30 ml ether. The aqueous fraction was acidified to pH 3-4 with 2M HCl. The acidic solution was extracted with 3 x 30 ml ether and the combined organic fractions were dried (Na₂SO₄) and evaporated to yield the title compound, 0-benzylxoxy benzoic acid 4 as a solid.
Synthesis of N-BOC Metoprolol 5

Metoprolol (1.0) was dissolved in 5 ml of t-BuOH/H₂O (10:1) and di-t-butyl dicarbonate (0.82g) in 5 ml of t-BuOH/H₂O (10:1) was added. The solution was stirred for 20 hours and then poured onto 100 ml water. The solution was extracted with 3 x 30ml of petroleum-ether (b.p. 40-60C). The combined organic fractions were dried (Na₂SO₄) and concentrated. Flash column chromatography using 3:1 petroleum-ether:ether gave the title compound as a viscous liquid.

Synthesis of N-BOC Metoprolol O-Benzylxy benzoate 6

O-Benzylxy benzoic acid 4 (0.11g) and 4-dimethylamino pyridine (0.24g) 2343 dissolved in 20ml of dry toluene. The solution was heated to reflux and 2,6-dichlorobenzoyl chloride (0.10g) was added. After 10 min. under reflux N-BOC Metoprolol (0.18g) in 5 ml dry toluene was added and reflux was continued for a further 30 min. The mixture
was filtered through silica and the filtrate was evaporated yielding the title compound in quantitative yield.

Debenzylation of N-BOC Metoprolol O-benzlyoxy 6

The above compound was dissolved in 20ml of ethanol/dichloromethane (1:1) and 1 equivalent of Pd-C was added. The mixture was stirred under an atmosphere of hydrogen for 5 hours. The suspension was filtered through silica and the filtrate was evaporated to yield N-BOC Metoprolol Salicylate (7) in quantitative yield as a viscous liquid.

Acetylation of N-BOC Metoprolol Salicylate :  

The above compound was dissolved in 20 ml of dry dichloromethane. Three molar equivalents of acetic anhydride were added with stirring. Two molar equivalents of dry triethylamine and four molar equivalents of DMAP were then added and the solution was stirred for 2 hours at room temperature. The solvent was evaporated and the residue was subjected to slow column chromatography using petroleum-ether:ether (1:1) as eluent. N-BOC Metoprolol Aspirinate (8) was obtained as a viscous liquid. (Yield 80%).

![Chemical Structure](attachment:image.png)

The presence of both aspirin and Metoprolol moieties in the product was confirmed by $^1$H and $^{13}$C nmr.
In the $^1$H nmr the acetate methyl group appeared as a 3H singlet at 2.32 ppm. The aryl hydrogens of aspirin moiety gave rise to 4 multiplets between 6.8 and 8.1 ppm. The latter multiplet was assigned to the aryl hydrogen beta to the ester carbonyl group.

The remaining signals, with the exception of the 9H singlet at 1.47 ppm due to the t-butyl group, are similar to those displayed by metoprolol. The exception is the ester hydrogen which is shifted downfield to 5.6 ppm and appears as a broad multiplet. This in itself is strong evidence that the desired coupling has taken place. The corresponding hydrogen of metoprolol is seen at 4 ppm. The aromatic protons of the metoprolol moiety give rise to two multiplets at 7.28 ppm and 7.54 ppm. The methine proton of the isopropylamine group and the ArOCH$_2$ methylene are present as a broad multiplet between 3.8 and 4.3 ppm. The -CH$_3$OCH$_3$ methylene protons and the amino methylene protons give a multiplet at 3.4-3.65 ppm. The methoxy group gives a singlet at 3.34 ppm. The triplet at 2.81 ppm is assigned to the ArCH$_2$ methylene protons. The acetate protons produce a singlet at 2.32 ppm. The t-butyl group shows up as a singlet at 1.47 ppm. The remaining doublet at 1.14 ppm is due to the isopropylamine methyl protons.

\[ ^{13}C \text{ nmr (ppm)} \]

\[
20.94, \ 28.37, \ 29.6, \ 35.2, \ 58.54, \\
67.63, \ 72.12, \ 73.73, \ 79.87, \ 114.48, \\
123.1, \ 123.69, \ 125.86, \ 129.72, \ 131.47, \\
131.74, \ 133.8, \ 150.66, \ 156.95, \ 163.77, \\
169.48.
\]
Metoprolol Aspirinate Trifluoroacetate 9:

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{CH}_{2}\text{CH}_{2}\text{OCH}_{3} & \\
\text{NH} & \quad \text{CF}_{3}\text{CO}_{2}\text{H}
\end{align*}
\]

N-BOC Metoprolol Aspirinate 8 (0.05g) was dissolved in 10 ml dry dichloromethane and trifluoroacetic acid (3ml) was added. The solution was stirred for 1 hour. The solvent was evaporated yielding the compound as a viscous liquid.

\(^{1}H\) nmr:

The major difference between this spectrum and that of its precursor is the absence of 9H singlet at ~1.4 ppm indicating the t-butoxycarbonyl group has been successfully removed. A broad peak appears at ~8.1 ppm which is probably due to the protons on the quaternary nitrogen. Otherwise there is little difference in the spectra as a visual inspection readily confirms. The isopropylamine methyl groups appear as a doublet at 1.36 ppm. The acetate methyl group appears as a singlet at 2.31 ppm. The ArCH\(_2\)- methylene group is seen as a triplet as 2.83 ppm. The methoxy group appears at 3.36 ppm as a singlet. The methine proton of the isopropylamine group and the -CH\(_2\)OCH\(_3\) methylene give rise to overlapping multiplets at 3.42 to 3.7 ppm. The doublet at 4.24 ppm is assigned to the ArCH\(_2\)- methylene hydrogens. The broad multiplet at 5.6 ppm is assigned to the ester methine proton. The metoprolol aromatic protons are present as two multiplets at 6.83 ppm and 7.12 ppm. The multiplet at 7.12 ppm also contains signals for one of the aspirinate
protons. The three remaining multiplets 7.3 ppm, 7.59 ppm and 7.95 ppm are due to aspirinate protons.

\[
\begin{array}{c}
13\text{C nmr (ppm)} \\
18.55, 18.81, 20.9, 29.6, 34.93, \\
45.74, 51.77, 58.4, 67.11, 69.24, \\
73.61, 114.44, 121.9, 123.48, 126.22, \\
129.94, 131.62, 132.13, 134.74, \\
150.35, 156.16, 159.86, 160.37, \\
160.89, 161.4, 164.16, 170.53.
\end{array}
\]

Legend for spectroscopic data Figs. 15 to 23 inclusive.

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<thead>
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<th>Fig.</th>
<th>NMR Type</th>
<th>Compound</th>
<th>Scheme</th>
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<td>H nmr</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>16</td>
<td>DEPT nmr</td>
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<td>2</td>
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<td>17A</td>
<td>13C nmr</td>
<td>5</td>
<td>2</td>
</tr>
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<td>17B</td>
<td>DEPT nmr</td>
<td>5 (comparison)</td>
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<tr>
<td>18</td>
<td>H nmr</td>
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<td>23</td>
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<td>9</td>
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</table>

Preparation of Metoprolol Aspirinate and conversion to its hydrochloride, fumarate and tartrate salts.

Metoprolol Aspirinate Trifluoroacetate (0.2g) was dissolved in 5 ml of methanol and treated with 10% aqueous NaHCO₃ (100 ml). The aqueous solution was extracted with 3 x 30 ml dichloromethane. The organic solution was dried (Na₂SO₄) and evaporated yielding Metoprolol aspirinate.

Metoprolol aspirinate was dissolved in 5% methanolic HCl and stirred for 30 min. The solvent was evaporated to yield the hydrochloric salt.
Treatment of Metoprolol aspirinate with 0.5 equivalents of fumaric or tartaric acid in methanol yielded the corresponding fumarate and tartrate salts on evaporation of the solvent.
**SCHEME 2**

1. 4-Dimethylamino pyridine (4 eq.) / Toluene / Δ

2. 2,6-Dichlorobenzoyl chloride (1 eq.) / Δ

3. CH$_2$CH$_2$OCH$_3$ (1 eq.) / Δ

4. CH$_3$Ph

5. CH$_2$Ph

6. CH$_3$Ph

7. CH$_2$Ph

8. CH$_2$Ph

9. CH$_2$Ph

Ac$_2$O (3 eq.)

DMAP (4 eq.)

Et$_3$N, CH$_2$Cl$_2$

PhCH$_2$Br (2 eq.)

DMF, 60 °C

NaOH / THF / MeOH / H$_2$O

1. NaOH / THF / MeOH / H$_2$O

2. HCl

H$_2$, Pd–C

EtOH, CH$_2$Cl$_2$

$\text{CF}_3\text{COOH}, \text{CH}_2\text{Cl}_2$

$\text{CF}_3\text{COOH}, \text{CH}_2\text{Cl}_2$
Alternative Synthesis of Metoprolol Aspirinate

To a stirred solution of acetylsalicylic acid (2) (0.05 g, 0.27 mmol) in 20 ml of dry dichloromethane was added DMAP (0.005 g) and N-BOC Metoprolol (1) (0.1g, 0.27 mmol). The solution was cooled to 0°C and DCC (0.06 g, 0.27 mmol) was added. The reaction was stirred at 0°C for 5 min. and at room temperature overnight.

The precipitated dicyclohexylurea was removed by filtration and the filtration was washed with 3x30 ml 1M HCl. The organic layer was washed with 3x30 ml water and the combined organic layers were dried (Na₂SO₄) and evaporated. The residue was purified by slow column chromatography to yield N-BOC Metoprolol Aspirinate (3) as a viscous liquid. This product was converted to Metoprolol Aspirinate Trifluoroacetate (4) in the manner already described.
SCHEME 3

Alternative Synthesis of Metoprolol Aspirinate

1 + 2

\[
\text{CH}_2\text{CH}_2\text{OCH}_3 + \text{DCC, DMAP (cat.)} \rightarrow \text{CH}_2\text{Cl}_2
\]

3

\[
\text{CF}_3\text{COOH, CH}_2\text{Cl}_2
\]

4

Metoprolol aspirinate
EXAMPLE 5 - Pindolol Aspirinate

Schematic for synthesis of pindolol aspirinate - Scheme 4

1. 4-Dimethylaminopyridine (4 eq.)/Toluene/Δ

2. 2,6-Dichlorobenzoyl chloride (1 eq.)/Δ

3. H₂, Pd-C

4. Ac₂O (3 eq.)

5. CF₃COOH, CH₂Cl₂

6. MeOH, 11% eq. NaHCO₃
Synthesis of N-BOC Pindolol (2):

Pindolol (1) (0.93g, 3.74mmol) was dissolved in 5ml of t-BuOH/H2O (10:1) and di-t-butyl dicarbonate (0.82g, 3.74mmol) in 5ml of t-BuOH/H2O (10:1) was added. The solution was stirred for 20 hours and then poured onto 100ml water. The solution was extracted with 3x30ml of petroleum-ether (b.p. 40-60°C). The combined organic fractions were dried (Na2SO4) and concentrated. Flash column chromatography using 3:1 petroleum-ether:ether gave the title compound as a viscous liquid.

The synthesis of O-Benzylxyloxy benzoic acid (3) has been already described (see report on the synthesis of Metoprolol Aspirinate Trifluoroacetate).

Synthesis of N-BOC Pindolol O-Benzylxyloxy benzoate (4):

O-Benzylxyloxy benzoic acid (3) (0.11g) and 4-dimethylamino pyridine (0.24g) were dissolved in 20ml of dry toluene. The solution was heated to reflux and 2,6-dichlorobenzoyl
chloride (0.10g) was added. After 10 minutes under reflux N-BOC Pindolol (0.18g, 0.48mmol) in 5ml dry toluene was added and reflux was continued for a further 30 minutes. The mixture was filtered through silica and the filtrate was evaporated yielding the title compound in quantitative yield.

Debenzylation of N-BOC Pindolol O-benzylxy benzoate (4):

The above compound was dissolved in 20ml of ethanol/dichloromethane (1:1) and 1 equivalent of Pd-C was added. The mixture was stirred under an atmosphere of hydrogen for 5 hours. The suspension was filtered through silica and the filtrate was evaporated to yield N-BOC Pindolol Salicylate (5) in quantitative yield as viscous liquid.

Acetylation of N-BOC Pindolol Salicylate (5):

The above compound was dissolved in 20ml of dry dichloromethane. Three molar equivalents of acetic anhydride were added with stirring. Two molar equivalents of dry triethylamine and four molar equivalents of DMAP were then added and the solution was stirred for 2 hours at room temperature. The solvent was evaporated and the residue was subjected to slow column chromatography using petroleum-ether:ether (1:1) as eluent. N-BOC Pindolol Aspirinate (6) was obtained as a viscous liquid. (Yield 86%).

Pindolol Aspirinate Trifluoroacetate (7):

![Chemical Structure](image-url)
N-BOC Pindolol Aspirinate (6) (0.06g) was dissolved in 10ml dry dichloromethane and trifluoroacetic acid (3ml) was added. The solution was stirred for 1 hour. The solvent was evaporated yielding the title compound as a viscous liquid.

**Pindolol Aspirinate (8):**

Pindolol Aspirinate Trifluoroacetate (0.1g) was dissolved in 5ml of methanol and treated with 10% aqueous NaHCO₃ (100ml). The aqueous solution was extracted with 3x30ml dichloromethane. The organic solution was dried (Na₂SO₄) and evaporated furnishing Pindolol aspirinate.

**Conversion of Pindolol Aspirinate to its hydrochloride, fumarate and tartrate salts:**

Pindolol aspirinate was dissolved in 5% methanolic HCl and stirred for 30 minutes. The solvent was evaporated to yield the hydrochloride salt.

Treatment of Pindolol aspirinate with 0.5 equivalents of fumaric or tartaric acid in methanol yielded the corresponding fumarate and tartrate salts on evaporation of the solvent.
The products of the invention are useful as in a single chemical entity a product which acts both as a β blocker and also has anti-platelet activity as described above is provided.

5 The products may be formulated in any suitable pharmaceutical compositions using conventional excipients or vehicles. Usually the pharmaceutical composition will be provided in a form for oral administration, preferably in a capsule or tablet form.

10 It will be appreciated that the composition may include a diuretic and potassium salts in a single tablet or capsule. The diuretic may be frusemide, amiloride, hydrochlorothiazide or a potassium sparing diuretic such as spironolactone or trimeterene.

15 It will also be appreciated that some of the β blocker aspirinates especially timilol aspirinate may be formulated as an eye drop, i.e. for topical application in the treatment of ocular hypertension and glaucoma.

It will be appreciated that while the invention has been specifically described with reference to an aspirinates of some β blockers it may also be applied to aspirinates of other esterifiable β blockers.

The invention is not limited to the embodiments hereinbefore described which may be varied in detail.
APPENDIX 1

Synthesis of Atenolol-O-aspirinate

\[
\begin{align*}
\text{OCOCH}_3 & + \text{HO} \xrightarrow{\text{DMAP}} \text{C} \xrightarrow{\text{H}} \text{OH} \xrightarrow{\text{DCC}} \text{CH}_2\text{NHCH(CH}_3\text{)}_2 \\
\text{COOH} & \quad \text{CH}_2\text{O} \quad \text{CH}_2\text{CONH}_2
\end{align*}
\]

APPENDIX 2

Esterification via acetylsalicyloyl chloride

\[
\begin{align*}
\text{OCOCH}_3 & \quad \xrightarrow{\text{SOCl}_2} \quad \text{OCOCH}_3 \\
\text{COOH} & \quad \text{CH}_2\text{O} \quad \text{CH}_2\text{CONH}_2 \\
& \quad \text{H} \quad \text{CH}_2\text{NHCH(CH}_3\text{)}_2
\end{align*}
\]

Atenolol-O-aspirinate
CLAIMS

1. A pharmaceutical product comprising a salicylate of an esterifiable \( \beta \) Blocker.

2. A pharmaceutical product as claimed in claim 1 wherein the \( \beta \) Blocker is indirectly esterifiable.

3. A pharmaceutical product as claimed in claim 1 wherein the \( \beta \) Blocker is directly esterifiable.

4. A pharmaceutical product as claimed in claim 3 wherein the \( \beta \) Blocker is atenolol.

5. Atenolol-O-aspirinate.

6. A pharmaceutical product as claimed in claim 3 wherein the \( \beta \) blocker is Metoprolol.


8. A pharmaceutical product as claimed in claim 3 wherein the \( \beta \) blocker is Pindalol.


10. A pharmaceutical product substantially as hereinbefore described with reference to the examples.

11. A process for preparing a pharmaceutical product as claimed in any preceding claim which comprises esterifying an esterifiable \( \beta \) blocker with acetylsalicylic acid.
12. A process for preparing a pharmaceutical product as claimed in any of claims 1 to 10 which comprises esterifying an esterifiable β blocker with salicylic acid.

13. A process for preparing a pharmaceutical product as claimed in any of claims 1 to 11 comprising the steps of:

- protecting the secondary amine group in the β blocker;

- activating the carboxyl group in salicylic acid or derivative thereof;

- direct coupling of the activated carboxyl group of the salicylic acid or derivative thereof with the protected β blocker; and

- removing protecting groups from the secondary amine group in the β blocker.

14. A process as claimed in claim 13 wherein the secondary amine group in the β blocker is protected by forming an N-BOC derivative of the β blocker secondary amine and, after coupling, the N-BOC protecting group is removed.

15. A process as claimed in claim 14 wherein the N-BOC derivative of the β blocker is formed by reaction between the β blocker secondary amine and di-t-butyl in t-BuOH/H₂O to form the tert-butyloxycarbamide derivative.

16. A process as claimed in claim 14 or 15 wherein the N-BOC protecting group is removed using trifluoro-
acetic acid to form the trifluoroacetate salt of the Aspirinate.

17. A process as claimed in claim 16 wherein the process includes the step of forming the β blocker Aspirinate base by extraction from a weakly alkaline medium.

18. A process as claimed in claim 17 wherein the process includes the steps of acidifying an alcoholic solution of the Aspirinate base in an acid to form a pharmaceutically acceptable salt.

19. A process as claimed in any of claims 13 to 18 wherein the carboxyl group in salicylic acid or derivative thereof is activated by one or more of :-

   - acid chloride formation;
   - pentafluorothioester formation; or
   - in situ formation of 2,6 dichlorobenzoyl anhydride.

20. A process as claimed in any of claims 13 to 19 wherein the β blocker is coupled with acetylsalicylic acid derivative having an activated carboxyl group.

21. A process as claimed in any of claims 13 to 19 wherein the β blocker is coupled with a salicylic acid derivative having a protected hydroxy group.

22. A process as claimed in claim 21 wherein the hydroxy group is protected by benzyl ether formation.
23. A process as claimed in claim 21 or 22 wherein salicylic acid is converted into O-benzylxoxy benzoic acid.

24. A process as claimed in any of claims 21 to 23 including the step of removing the salicylic acid hydroxy protection group after coupling.

25. A process as claimed in claim 24 wherein the protected salicylic acid hydroxy group is removed by hydrogenolysis.

26. A process as claimed in claim 24 or 25 wherein, after removal of the protecting group the salicylic acid derivative is acylated.

27. A process for preparing a pharmaceutical product as claimed in any of claims 1 to 10 comprising the steps of:

   forming a protected salicylic acid hydroxy group;

   forming an N-BOC derivative of the β blocker secondary amine;

   coupling of the protected salicylic acid with the N-BOC β blocker;

   removing the protecting group from the salicylic acid hydroxy group;

   acylating the salicylic acid; and

   removing the N-BOC protecting group.
28. A process for preparing a pharmaceutical product as claimed in any of claims 1 to 10 comprising the steps of:

forming an N-BOC derivative of the β blocker secondary amine;

direct coupling of the N-BOC derivative of the β blocker with acetylsalicylic acid; and

removing the N-BOC protecting group.

29. A process for preparing a pharmaceutical product as claimed in any of claims 1 to 10 comprising the steps of:

forming a pentafluorothiophenol ester of acetylsalicylic acid;

forming an N-BOC derivative of the β blocker secondary amine;

direct coupling of the pentafluorothiophenol ester with N-BOC derivative of the β blocker; and

removing the N-BOC protecting group.

30. A process for preparing a pharmaceutical product as claimed in any of claims 1 to 10 comprising the steps:

forming acetylsalicyloyl chloride;

forming an N-BOC derivative of the β blocker secondary amine;
direct coupling of the N-BOC β blocker with acetylsalicyl chloride; and

removing the N-BOC protecting group.

31. A process as claimed in any of claims 27 to 30 including the step, after removal of the protecting group, of forming the β blocker aspirinate base and; optionally, forming pharmaceutically acceptable salts thereof by acidification of an alcoholic solution of the base using appropriate acids.

32. A process substantially as hereinbefore described with reference to the examples.

33. A pharmaceutical product whenever prepared by a process as claimed in any of claims 11 to 31.

34. A pharmaceutical composition including a pharmaceutical product as claimed in any of claims 1 to 10 or 32.

35. A pharmaceutical composition as claimed in claim 34 in the form of a tablet or capsule.

36. A pharmaceutical composition as claimed in claim 34 or 35 wherein the composition includes a diuretic and potassium salts.

37. Timolol aspirinate for topical application in the treatment of ocular hypertension and glaucoma.

38. A pharmaceutical composition substantially as hereinbefore described with reference to the examples.
Fig. 19
### A. CLASSIFICATION OF SUBJECT MATTER

IPC 6  C07C235/34  C07C219/14  C07D209/08  C07D285/10  A61K31/60

According to International Patent Classification (IPC) or to both national classification and IPC

### B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6  C07C  C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database consulted during the international search (name of database and, where practical, search terms used)

### C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>WO, A 88 07044 (INSITE VISION) 22 September 1988</td>
<td>1,3, 11-16, 19-21, 28, 30, 33-35, 37</td>
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<td>see page 7, line 5 - page 8, line 12 see page 3, line 18 - line 20; claims 1,32; examples XVII, XX</td>
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Further documents are listed in the continuation of box C. Patent family members are listed in annex.

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Date of the actual completion of the international search: 15 May 1995

Date of mailing of the international search report: 23/05/95

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