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European Journal of Pharmaceutical Sciences 24 (2005) 315–323
EUROPEAN JOURNAL OF PHARMACEUTICAL SCIENCES
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A new amino-masking group capable of pH-triggered amino-drug release

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Received 9 September 2004; received in revised form 11 November 2004; accepted 18 November 2004

Abstract

The prodrug approach is potentially useful for mitigating pharmaceutical problems—such as poor membrane permeability or stability—which commonly occur with amino drugs. On the other hand there persists a dearth of useful systems for masking amines that satisfy the prodrug requirements of good in vitro stability coupled with predictable and rapid drug release in response to a local tissue condition. This study describes an evaluation of aminoindanes as bioreversibly masked amines poised to undergo elimination to the parent amine. Several model amine and amino drug indanone derivatives were synthesised. pK_a values were determined by capillary electrophoresis and pH rate profiles for elimination and amine liberation were measured. The aminoindanone system appears to have particular applicability to secondary amino substrates whose indanone derivatives are stable at low pH but undergo drug release at rates corresponding to first-order half-lives of <5 min at pH 7.4.

Keywords: Amine; Prodrug; pH-sensitive release; Indanone; Indenone

1. Introduction

The prodrug strategy involves the temporary masking of a drug functional group, usually in an effort to improve a candidate drug's stability (Gershonov et al., 2000), safety (Shanbhag et al., 1992) or passive oral drug delivery (Aungst et al., 1995). In general, the success of the approach hinges upon a marked contrast between the stability of the prodrug form in vitro, and its vulnerability to attack and drug release in response to an enzymatic or local tissue pH condition following administration. The prodrug approach has been particularly effective in addressing pharmaceutical problems with carboxyl- or hydroxyl-bearing drugs, mainly due to the very wide possibilities for ester prodrug design. Progress in the area of amino prodrug design has been somewhat slower. The major differences between amino derivatives such as amides or carbamates and carboxylic esters from a prodrug point of view, is the greater susceptibility of esters to undergo hydrolysis by esterases, and the general chemical and enzymatic stability of amides and other amine derivatives. Among the numerous attempts to build chemical or enzymatic vulnerability into amino derivatives are the Mannich bases (Bundgaard and Johansen, 1980), imines (Krause et al., 1995), carbamates (Gogate and Repta, 1987), enaminones (Naringrekar and Stella, 1990), tetrahydrothiadizine-2-tiones (Aboul-Fadl and El-Shorbagi, 1996), as well as coumarin-based systems that are poised to undergo spontaneous cyclisation (Wang et al., 2000) and analogous 'trimethyl lock' designs (Amsberry and Borchardt, 1991). Notwithstanding these endeavours, there remains a dearth of amine-masking systems with suitable release kinetics to be useful in prodrug design.

We have recently reported on the behaviour of certain 3-aminoindanones (Fig. 1, **1**) which are stable at low pH values but undergo unexpectedly rapid elimination approaching neutrality, generating in the process, the highly conjugated indenone **3** (Simplício et al., 2004). The objective of the present study was to determine if this behaviour could be exploited in the design of prodrug systems where the amine **2** could be

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doi:10.1016/j.ejps.2004.11.006

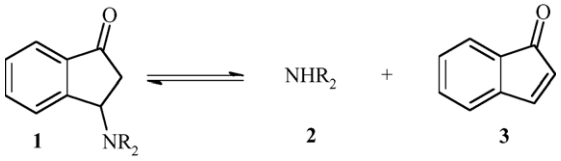

Fig. 1. Scheme showing the elimination/addition equilibrium of aminoindanones at 37 °C.

Table 1
Amines used for the preparation of the indenone derivatives **1a**–**1k**

Compound	RR′NH (amine)
1a	Dimethylamine
1b	Ethylamine
1c	Piperidine
1d	Ephedrin
1e	Tryptophan methyl ester
1f	Alanine methyl ester
1g	Phenylethyl amine
1h	Atenolol
1i	Desloratadine
1j	Dopamine
1k	L-Dopa ethyl ester

a candidate drug molecule. Such systems might be employed in the temporary masking of amines in order to increase drug stability or lipophilicity, for example, in the protection of peptides and protein from protease-mediated decomposition by reversibly protecting basic amino acid residues. This paper describes the synthesis and physicochemical evaluation of eleven model aminoindanone derivatives as potential prodrugs of the parent amine (Table 1).

2. Materials and methods

2.1. Materials

Atenolol was obtained from Societá Italiana Medicinali Scandicci. Desloratadine (micronised USP) was donated by Schering-Plough (Avondale). Ephedrine, D,L-tryptophan ethyl ester hydrochloride and alanine ethyl ester hydrochloride were obtained from Sigma. L-3,4-Dihydroxyphenylalanine 99%, dimethylamine hydrochloride, piperidine, 2-phenylethylamine 99%, 1-indanone 99%, 2-methyl-1-indanone 99%, *N*-bromosuccinimide, benzoyl peroxide (70% remainder water) and triethylamine were purchased from Aldrich. Merck silica gel 60 (particle size 0.040–0.063 mm) was used for flash column chromatography. Carbon tetrachloride was from Riedel-de Haën. Phosphoric acid (+99%, Fluka), sodium dihydrogen orthophosphate (BDH) and tetrabutylammonium dihydrogenphosphate (97%, Aldrich) were used for the preparation of running buffers for capillary electrophoresis. Citric acid monohydrate (99% ACS, Aldrich), boric acid (M&B) and tripotassium orthophosphate (BDH) were used for the preparation of buffers for kinetic studies. Acetonitrile (Riedel-de Haën) for HPLC was used for the preparation of stock solutions. Aqueous solutions were prepared with distilled and deionised water (Milli-Q Water System, Millipore).

2.2. Synthesis

The synthetic approach to the candidate aminoindanones is outlined in Fig. 2. Indanone (**4**) was brominated at the benzylic position using the Wohl-Ziegler bromination (Huang and Williams, 1958) employing *N*-bromosuccinimide (NBS) in carbon tetrachloride and a catalytic quantity of dibenzoylperoxide at reflux for 45 min. The 3-bromoindanone product (53%) was obtained following evaporation and separation by flash chromatography from its 2-bromoindanone isomer (24%). The aminoindanones were generated by treating the 3-bromoindanone with the amine in dry dichloromethane in the presence of a tertiary base. The compounds were obtained in 25–87% yield following evaporation and flash chromatography. A general synthetic method is given below under Section 2.3. D,L-Tryptophan and D,L-alanine methyl esters were used because the indanone derivatives of these were more easily synthesised and purified than the corresponding amino acid derivatives. Similarly, L-dopa ethyl ester was used in preference to L-dopa. Where the amine was achiral, the product 3-aminoindanone was obtained as a mixture of isomers. The other chiral amines (alanine, tryptophan, ephedrine, L-dopa ethyl ester) gave more complex product mixtures and the approach to dealing with each of these cases is described in the synthetic section. Generally, it was found that mixtures of diastereomers could be collectively analysed without any difficulty. The aminoindanones were characterised by ^{1}H and ^{13}C NMR, IR and high resolution mass spectroscopy (HRMS) and shown to be pure (>99% by area normalisation) by capillary electrophoresis, TLC and HPLC. IR spectra were obtained using a Perkin-Elmer Paragon 1000 FT infrared spectrometer. Liquid or oil samples were analysed as neat films from dichloromethane on NaCl plates; solid samples were analysed using KBr tablets. Wave numbers (IR ν_{max}) are presented for characteristic functional groups and are expressed in cm^{-1}. ^{1}H and ^{13}C NMR were recorded at 20 °C on a Brucker DPX 400 spectrophotometer (400.13 MHz ^{1}H, 100.61 MHz ^{13}C) at the

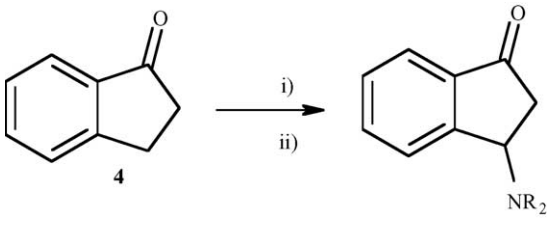

Fig. 2. Scheme showing the synthesis of aminoindanones: (i) *N*-bromosuccinimide, CCl_4; (ii) R_2NH, Et_3N, DCM.

Department of Chemistry, Trinity College Dublin. Samples were dissolved in deuterated chloroform ($CDCl_3$) or deuterated dimethyl sulfoxide ($(CD_3)_2SO$). Chemical shifts are in ppm. Coupling constants are in Hz. ^1H shifts were assigned relative to the tetramethylsilane (TMS) peak at 0.00 ppm and ^{13}C shifts were assigned relative to the central peak of the $CDCl_3$ triplet at 77.0 ppm or relative to the middle peak of the $(CD_3)_2SO$ septet at 39.7 ppm. ^1H NMR assignments are reported in the following form: shift values (number of protons, multiplicity and shape, coupling constant (when applicable), proton assignment). ^{13}C NMR assignments are reported in the following form: shift values (number of carbons (if more than one), carbon assignment). HRMS were acquired on a Micromass spectrometer (TOF, EI mode) at the Department of Chemistry, Trinity College, Dublin.

2.3. General synthesis of amino-indanone analogues

A solution of 3-bromoindanone (0.21 g) in dry dichloromethane (20 ml) was cooled to 0 °C when triethylamine (1.9 eq) was added, followed by the amine (1 eq). The reaction was stirred for 3–12 h at 0 °C and monitored by TLC. The desired aminoindanones were obtained following evaporation of the solvent and flash chromatography (25–87%) **1a**–**1k** (Table 1). When the hydrochloride form of the amine was used, the quantity of triethylamine was doubled. Each reaction was stirred at 0 °C for 3–12 h and the reactions monitored by TLC. The solvent was removed by evaporation and the residue purified by flash column chromatography.

3-Dimethylaminoindan-1-one **1a** was prepared from dimethylamine hydrochloride (0.08 g, 1 mmol) and 3-bromoindanone (0.21 g, 1 mmol). The reaction mixture was separated by flash chromatography (hexane/ethyl acetate, 8:2) and the title compound isolated as an amber oil (75 mg, 43%). IR ν_{max} (NaCl plate) 1715 (C=O) cm^{-1}. δ_H ($CDCl_3$) 2.06 (6H, s, C$\underline{H}_3$NC$\underline{H}_3$), 2.61 (1H, dd, J_{gem} = 19.0, J_{vic} = 7.0, CHC$\underline{H}_2$C=O), 2.74 (1H, dd, J_{gem} = 19.0, J_{vic} = 3.0, CHC$\underline{H}_2$C=O), 4.61 (1H, dd, J = 3.0, 7.0, C$\underline{H}$CH$_2$C=O), 7.47 (1H, t, J = 7.5 C$\underline{H}$CHCHCC=O), 7.67 (1H, t, J = 7.5, C$\underline{H}$CHCC=O), 7.73 (1H, d, J = 7.5, C$\underline{H}$CHCHCHCC=O), 7.78 (1H, d, J = 7.5, C$\underline{H}$CC=O). δ_C ($CDCl_3$) 35.1 (CH$\underline{C}_2$C=O), 40.5 (2C, $\underline{C}$H$_3$), 62.7 ($\underline{C}$HCH$_2$C=O), 123.2 ($\underline{C}$HCC=O), 126.7 ($\underline{C}$HCHCHCHCC=O), 128.8 ($\underline{C}$HCHCHCC=O), 134.8 ($\underline{C}$HCHCC=O), n.d. ($\underline{C}$CHCHCHCH$\underline{C}$C=O), 206.7 ($\underline{C}$C=O), *m/z* 176.1066 (MH^+, expected: 176.1075).

3-Ethylamino-indan-1-one **1b** was prepared as described, from ethylamine hydrochloride (0.16 g, 2 mmol) and 3-bromoindanone (0.42 g, 2 mmol). The solvent was removed and the residue subjected to flash chromatography (dichloromethane/methanol, 95:5) and the title compound obtained as a brown oil (0.14 g, 41%). IR ν_{max} (NaCl plate) 1713 (C=O) cm^{-1}. δ_H ($CDCl_3$) 1.16 (3H, d, J = 7.0, C$\underline{H}_3$), 1.68 (1H, br, S, N$\underline{H}$), 2.52 (1H, dd, J_{gem} = 18.6, J_{vic} = 3.0, CHC$\underline{H}_2$C=O), 2.76 (2H, m, C$\underline{H}_2$CH$_3$), 2.96 (1H, dd, J_{gem} = 18.6, J_{vic} = 6.5, CHC$\underline{H}_2$C=O), 4.47 (1H, dd, J = 3.0, 6.5, NHC$\underline{H}$CH$_2$C=O), 7.42 (1H, t, J = 7.5, C$\underline{H}$CHCC=O), 7.61–7.68 (2H, m, C$\underline{H}$C$\underline{H}$CCHNH) 7.73 (1H, d, J = 7.5, C$\underline{H}$CC=O). δ_C ($CDCl_3$) 15.3 ($\underline{C}$H$_3$), 41.8 ($\underline{C}$H$_2$CH$_3$), 44.7 (CH$\underline{C}$H$_2$C=O), 56.0 (NH$\underline{C}$HCH$_2$), 123.2 ($\underline{C}$HCHCC=O), 125.8 ($\underline{C}$HCCHNH), 128.5 ($\underline{C}$HCC=O), 134.7 ($\underline{C}$HCHCCHNH), 136.7 ($\underline{C}$CHNH), 155.9 ($\underline{C}$C=O), 204.5 ($\underline{C}$=O). *m/z* 176.1070 (MH^+, expected: 176.1075).

3-Piperidin-1-yl-indan-1-one **1c** was prepared from 3-bromoindan-1-one (0.21 g, 1 mmol) and piperidine (0.08 g, 1 mmol). The product was isolated by flash chromatography with (hexane/ethyl acetate, 8:2) as a brown oil (0.18 g, 84%). IR (max (NaCl plate) 1715 (C=O), 2933 (aliphatic C–C) cm^{-1}. δ_H ($CDCl_3$) 1.45 (2H, m, NCH$_2$CH$_2$C$\underline{H}_2$), 1.56 (4H, m, NCH$_2$C$\underline{H}_2$), 2.30 (2H, m, NHC$\underline{H}_2$), 2.47 (2H, m, NHC$\underline{H}_2$), 2.61 (1H, dd, J_{gem} = 18.8, J_{vic} = 7.0, CHC$\underline{H}_2$C=O), 2.77 (1H, dd, J_{gem} = 18.8, J_{vic} = 3.5, CHC$\underline{H}_2$C=O), 4.53 (1H, dd, J = 3.5, 7.0, NC$\underline{H}$), 7.42 (1H, t, J = 7.52, C$\underline{H}$CHCHCC=O), 7.63 (1H, t, J = 7.52, C$\underline{H}$CHCC=O), 7.73 (2H, m, C$\underline{H}$CHCHC$\underline{H}$CC=O). δ_C ($CDCl_3$) 24.5 (NCH$_2$CH$_2$C$\underline{H}_2$), 26.2 (2C, NCH$_2$C$\underline{H}_2$), 36.4 (2C, NC$\underline{H}_2$CH$_2$), 49.7 (CH$\underline{C}$H$_2$C=O), 63.2 (N$\underline{C}$H), 123.0 ($\underline{C}$HCC=O), 126.7 ($\underline{C}$HCHCHCHCC=O), 128.4 ($\underline{C}$HCHCHCC=O), 134.5 ($\underline{C}$HCHCC=O), 137.5 ($\underline{C}$CHCHCHCHCC=O), 154.7 ($\underline{C}$C=O), 204.7 ($\underline{C}$=O). *m/z* 216.1393 (MH^+, expected: 216.1388).

3-[(*2-Hydroxy-1-methyl-2-phenyl-ethyl*)*-methyl-amino*]*-indan-1-one* or *3-ephedrin-indan-1-one* **1d** was prepared from ephedrine (0.21 g, 1 mmol) and 3-bromoindan-1-one (0.21 g, 1 mmol). Ephedrine has two chiral centres but consists in only one of the enantiomeric pairs (*R*,*S*:*S*,*R*). Therefore, the product of the reaction was obtained as four isomers or two pairs of enantiomers (*R*,*S*,*S*:*R*,*S*,*R*:*S*,*R*,*S*:*S*,*R*,*R*). The product was purified by flash chromatography (hexane/ethyl acetate, 8:2) and isolated as a mixture of isomers (0.12 g, 41%). After a few days, the mixture solidified affording a yellow solid. IR ν_{max} (KBr) 3429 (OH), 1692 (C=O) cm^{-1}. δ_H ($CDCl_3$) 1.06, 1.10 (3H, 2d, J = 7.0, C$\underline{H}_3$CH), 1.91, 2.16 (3H, 2s, NC$\underline{H}_3$) 2.52–2.75 (2H, m, C$\underline{H}_2$), 2.92, 3.14 (1H, 2m, NC$\underline{H}$CH$_3$), 4.74 (1H, m, NC$\underline{H}$CH$_2$), 4.87, 4.95 (1H, 2d, J = 5.5, J = 4.5). δ_C ($CDCl_3$) 11.8, 12.0 ($\underline{C}$H$_3$CH), 30.1 33.8 (N$\underline{C}$H$_3$) 37.2, 37.5 ($\underline{C}$H$_2$), 60.7 (CH$_2\underline{C}$HN), 63.6, 64.0 (CH$_3\underline{C}$HN) 73.8, 74.1 ($\underline{C}$HOH), 123.0, 123.1 7($\underline{C}$HCHCHCCHOH), 126.0 126.2 (2C, $\underline{C}$HCCHOH) 126.1, 126.2 ($\underline{C}$HCHCC=O), 127.1, 127.2 ($\underline{C}$HCC=O), 128.1, 128.2 (2C, $\underline{C}$HCHCCHOH), 128.5, 128.6 ($\underline{C}$HCHCHCHCC=O), 134.8, 134.9 ($\underline{C}$HCHCHCC=O), 137.1, 137.2 ($\underline{C}$CHCHCHCHCC=O), 142.0, 142.8 ($\underline{C}$CHOH), 155.5, 155.6 ($\underline{C}$C=O), 204 (C=O) *m/z* 296.1646 (MH^+, expected: 296.1651).

3-(*1H-Indol-3-yl*)*-2-*(*3-oxo-indan-1-ylamino*)*-propionic acid methyl ester*, or *3-*(*Tryptophan methyl ester*)*-indan-1-one* **1e** was prepared from D,L-tryptophan methyl ester hydrochloride (0.50 g, 2 mmol) and 3-bromoindan-1-one

(0.42 g, 2 mmol). Two racemic pairs were obtained and they were not separated. The product purified by flash chromatography (hexane/ethyl acetate 6:4) yielding an amber oil (0.61 g, 87%). IR ν_{max} (NaCl plate) 3040 (indole), 1714 (C=O) cm^{-1}. δ_H ($CDCl_3$) 2.22 (1H, br, s, NHCHCOOCH3), 2.35, (1H, dd, J_{gem} = 18.6, J_{vic} = 3.0, NHCHCH_2C=O), 2.48 (1H, dd, J_{gem} = 18.6, J_{vic} = 3.0, NHCHCH_2C=O), 2.87* (1H, dd, J_{gem} = 18.6, J_{vic} = 6.5, NHCHCH_2C=O), 2.91* (1H, dd, J_{gem} = 18.6, J_{vic} = 6.5, NHCHCH_2C=O), 3.14–3.33 (2H, m, CCH_2CHNH), 3.68, 3.77 (3H, 2s, CH_3), 3.80, 3.89 (1H, 2m, NHCHCOOCH_3), 4.39 (1H, m, NHCHCH_2C=O), 7.00, 7.06 (1H, dd, J = 1.5, J = 25.0 CNHCHC), 7.13–7.26, (2H, ArH), 7.28–7.43 (2H, ArH), 7.48, 7.46–7.70 (3H, m, ArH), 8.55, 8.62 (1H, d, J = 25.0, CNHCH). δ_C ($CDCl_3$) 29.5, 29.6 (CCH$_2$CHNH), 44.7, 45.2 (O=CCH$_2$CHNH), 51.8, 51.8 (CH$_3$), 54.6, 55.4 (O=CCH$_2$$C$HNH), 60.2, 60.8 (CCH$_2$$C$HNH), 110.5, 110.6 (CHC$C$CHNH), 111.2 (Ar$C$H), 118.3, 118.5 (Ar$C$H), 119.2, 119.2 (Ar$C$H), 121.9 (Ar$C$H), 122.9, 123.0 (Ar$C$H), 123.0, 123.1 (Ar$C$H), 125.5 126.0 (Ar$C$H), 127.1, 127.3 (C), 128.5, 128.6 (ArCH), 134.5, 134.8 (ArCH), 136.1 (C), 136.4, 136.5 (C), 155.2, 155.3 (CHCCHCH$_2$C=O), 175.3, 175.4 (O=COCH$_3$) 204.2, 204.3 (C=O). *m/z* 349.1563 (MH^+, expected: 349.1552).

2-(3-Oxo-indan-1-ylamino)-propionic acid methyl ester or *3-(alanine methyl ester)-indan-1-one* **1f** was prepared from D,L-alanine methyl ester (0.279 g, 2 mmol) and 3-bromoindanone (0.42 g, 2 mmol). The product was purified by flash chromatography (hexane/ethyl acetate, 2:1). An amber oil was obtained (0.12 g, 0.50 mmol) as a mixture of two pairs of enantiomers, which were not separated. 25%. IR ν_{max} (NaCl plate) 1715 (C=O) cm^{-1}. δ_H ($CDCl_3$) 1.18, (3H, d, J_{vic} = 4, CHCH_3) 1.22* (3H, d, J_{vic} = 4, CHCH_3), 2.11 (1H, br, s, NH), 2.42 (1H, dd, J_{gem} = 18.7, J_{vic} = 3.5, CH_2), 2.44 (1H, dd, J_{gem} = 18.7, J_{vic} = 2.9, CH_2), 2.85* (1H, dd, J_{gem} = 18.7, J_{vic} = 6.4, CH_2), 2.92* (1H, dd, J_{gem} = 18.7, J_{vic} = 7.0, CH_2), 3.45 (1H, q, J = 7.0, CH$_3$CHNH), 3.55* (1H, q, J = 7.0, CH$_3$CHNH), 4.31 (1H, dd, J = 2.9, 6.4, CHCH$_2$C=O), 4.41* (1H, dd, J = 3.5, 7.0, CHCH$_2$C=O), 7.41 (1H, m, CHCHCHCC=O), 7.63 (3H, m, CHCHCHCHCC=O), δ_C ($CDCl_3$) 19.2, 19.7 (CH_3CH), 44.9, 45.4 (CH_2), 52.0 (OCH_3), 54.3 (NCHCH$_2$), 54.7, 55.1 (NCHCH$_3$), 123.2, 123.4 (CHCC=O), 125.4, 126.2 (CHCHCHCHCC=O), 128.7, 128.8 (CHCHCHCC=O), 134.7, 135.0 (CHCHCC=O), 136.55, 136.6 (CCHCHCHCHCC=O), 155.2, 155.4 (CC=O), 176.0, 176.2 (COOCH$_3$), 204.0, 204.2 (C=O). *m/z* 234.1135 (MH^+, expected: 234.1130).

3-Phenethylamino-indan-1-one **1g** was prepared from phenylethylamine (0.12 g, 1 mmol) and 3-bromoindan-1-one (0.21 g, 1 mmol). The product isolated by flash chromatography (hexane/ethyl acetate, 8:2) as a brown oil (0.09 g, 36%). IR ν_{max} (NaCl plate) 1712 cm^{-1} (C=O). δ_H ($CDCl_3$) 2.50 (1H, dd, J_{gem} = 18.8, J_{vic} = 3.2, NHCHCH_2C=O), 2.84–3.05 (5H, NHCHCH_2C=O, NHCH_2CH_2), 4.48 (1H, dd, J = 3.2, 6.8, NHCHCH$_2$C=O), 7.22–7.28 (3H, m, CCHCHCHCHCH), 7.30 (2H, m, CCHCHCHCHCH), 7.43 (1H, t, J = 7.3, CHCHCHCC=O), 7.57–7.65 (2H, m, CHCHCHCHCC=O), 7.74 (1H, d, J = 7.5, CHCC=O). δ_C ($CDCl_3$) 36.3 (NCHCH$_2$), 44.4 (NCH$_2$$CH_2$), 48.3 (N$CH_2CH_2$), 55.8 (N$CHCH_2$), 123.2 ($C$HCC=O), 125.7 ($C$HCHCHCCH$_2CH_2$), 126.2 ($C$HCHCHCHCC=O), 128.4 (3C, CHCHCCH$_2$CH$_2$ and CHCHCHCC=O), 128.6 (2C, CHCCH$_2$CH$_2$), 134.8 (CHCHCC=O), 136.7 (CCH$_2$CH$_2$), 139.4 (CCHCHCHCHCC=O), 155.5 (CC=O), 204.4 (C=O). *m/z* 252.1386 (MH^+, expected: 252.1388).

2-(4-{2-Hydroxy-3-[isopropyl-(3-oxo-indan-1-yl)-amino]-propoxy}-phenyl)-acetamide, or, *3-atenolol-indan-1-one* **1h** was prepared from atenolol (RS) (0.27 g, 1 mmol) and 3-bromoindanone (0.21 g, 1 mmol). The evaporated residue was purified by flash chromatography using (DCM/methanol, 92.5:7.5) which yielded a single pair of enantiomers uncontaminated (the second pair were discarded) (0.094 g, 0.24 mmol, 11.8%). IR ν_{max} (NaCl plate) 1670, 1707, (C=O) 3354 (NH_2) cm^{-1}. δ_H ($CDCl_3$) 1.13 (3H, d, J = 6.4, CH_3), 1.25 (3H, d, J = 6.4, CH_3), 2.44 (1H, dd, J_{gem} = 13.6, J_{vic} = 6.1, NCH_2CH), 2.63 (1H, dd, J_{gem} = 13.6, J_{vic} = 6.1, NCH_2CH), 2.70 (1H, dd, J_{gem} = 19.1, J_{vic} = 3.4, CHCH_2C=O), 2.77 (1H, dd, J_{gem} = 19.1, J_{vic} = 6.8, CHCH_2C=O), 3.14 (1H, m, CH$_3$CHCH$_3$), 3.52 (2H, s, CH_2C=ONH$_2$), 3.66 (2H, m, CHCH_2O), 3.90 (1H, m, CHOH), 4.70 (1H, dd, J = 3.4, 6.8, NCHCH$_2$C=O), 5.48, (1H, s, br) 5.72 (1H, s, br), 6.75 (2H, d, J = 8.9, OCCHCHCCH$_2$), 7.16 (2H, d, J = 8.9, OCCHCHCCH$_2$), 7.40 (1H, t, J = 7.5, CHCHCC=O), 7.57 (1H, m, CHCHCHCC=O), 7.65 (1H, d, J = 4.1, CHCHCHCHCC=O), 7.73 (1H, d, J = 7.5, CHCC=O). *m/z* 397.2121 (MH^+, expected: 397.2127).

3-[4-(8-Chloro-5,6-dihydro-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)-piperidin-1-yl]-indan-1-one, or 3-desloratadine-indan-1-one **1i** was prepared from desloratadine (0.31 g, 1 mmol) and 3-bromoindan-1-one (0.21 g, 1 mmol). After evaporation, the reaction mixture residue was purified by flash column chromatography (DCM/methanol, 96:4). A reddish crystalline solid was obtained (0.38 g, 86%). IR ν_{max} (KBr) 1710 cm^{-1} (C=O). δ_H ($CDCl_3$), 2.27–2.50 (6H, m, CH_2), 2.5–2.77 (2H, m, CH_2) 2.79–2.96 (4H, m, CH_2), 3.31–3.42 (2H, m, CH_2), 4.62 (1H, m, CH$_2$NCH), 7.05–7.15 (4H, m, ArCH), 7.41–7.45 (2H, m, ArCH), 7.65 (1H, t, J = 7.9, ArCH), 7.72–7.77 (2H, m, ArCH), 8.38 (1H, m, ArCH). δ_C ($CDCl_3$) 31.3, 31.7 (2C, CCH$_2$$CH_2$C), 36.1, 36.3 (2C, CH$_2CCH_2$), 45.8 (NCHCH$_2$), 48.5, 48.6 (2C, NCH_2), 62.5 (NCHCH$_2$), 122.1 (ArCH), 123.1 (ArCH), 125.9 (ArCH), 126.7 (ArCH), 128.7 (ArCH), 128.9 (ArCH), 130.7 (ArCH), 132.6 (C), 133.0 (C), 133.4 (C), 134.8 (ArCH), 137.3 (ArCH), 137.5 (C), 138.3 (C), 139.4 (C), 146.5 (Ar-NCH), 157.3 (C), 175.0 (CC=O), 207.7 (C=O). *m/z* 441.1750 (MH^+, expected: 441.1734).

2-[2-(3,4-Dihydroxy-phenyl)-ethylamino]-indan-1-one, or *3-dopamine-indan-1-one* **1j** was prepared from dopamine hydrochloride (0.19 g, 1 mmol) and 3-bromoindan-1-one (0.21 g, 1 mmol) according to the described procedure

with the exception that the mixture was stirred for 3 days. The product was purified by flash chromatography (DCM/methanol 95:5) affording a yellowish solid (50 mg, 18%) with a melting point of 198–200 °C (with degradation). IR ν_{max} (KBr) 3311 (OH) 1693 (C=O) cm^{-1}. H–H and C–H COSY were used for assignment of the NMR signals. δ_H ($CDCl_3$/$(CD_3)_2SO$) 2.84 (2H, m, $NHCH_2C\underline{H}_2$), 2.85 (1H, dd, J_{gem} = 19.0, J_{vic} = 3.0, $CHC\underline{H}_2C$=O), 3.04 (1H, dd, J_{gem} = 19.0, J_{vic} = 7.5, $CHC\underline{H}_2C$=O), 3.15 (2H, m, $NHC\underline{H}_2CH_2$), 5.03 (1H, d, J = 6.0, $NC\underline{H}$), 6.48 (1H, dd, J = 2.0, 8.0, $CH_2CC\underline{H}CHCOH$), 6.65 (1H, d, J = 2.0, $CH_2CCHC\underline{H}COH$), 6.68 (1H, d, J = 8.0, $CH_2CC\underline{H}COH$), 7.59 (1H, t, J = 7.52, $C\underline{H}CHCC$=O), 7.72–7.77 (2H, m, $C\underline{H}C\underline{H}CHCHCC$=O), 8.05 (1H, d, J = 8.0, $C\underline{H}CC$=O), 8.46 (1H, s, $CO\underline{H}$), 8.48 (1H, s, $CO\underline{H}$). δ_C ($CDCl_3$/$(CD_3)_2SO$) 30.0 ($\underline{C}H_2CH_2NH$), 38.0 ($CH\underline{C}H_2C$=O), 45.9 ($CH_2\underline{C}H_2NH$), 53.5 ($\underline{C}HCH_2C$=O), 114.3 ($HOC\underline{C}HCCH_2CH_2NH$), 114.6 ($\underline{C}HCHCCH_2CH_2NH$), 118.0 ($CH\underline{C}HCCH_2CH_2NH$), 121.8 ($\underline{C}HCC$=O), 125.9 ($\underline{C}CH_2CH_2NH$), 126.2 ($\underline{C}HCHCHCHCC$=O), 129.0 ($\underline{C}HCHCHCC$=O), 133.6 ($\underline{C}HCHCC$=O), 136.1 ($\underline{C}CHCHCHCHCC$=O), 142.7 ($HO\underline{C}CHCHC$), 143.8 ($HO\underline{C}CHC$), 146.2 ($\underline{C}C$=O), 198.7 ($\underline{C}$=O). *m/z* 284.1295 ($MH^+$, expected: 284.1287).

3-(3,4-Dihydroxy-phenyl)-2-(3-oxo-indan-1-ylamino)-propionic acid ethyl ester, or *3-etilevodopa-indan-1-one* **1k** was prepared from L-dopa ethyl ester (etilevodopa) (0.26 g, 1 mmol) and 3-bromoindan-1-one (0.21 g, 1 mmol). The product was obtained following flash chromatography (DCM/methanol, 97.5:2.5) as a brown paste (0.16 g, 45%). According to the NMR integration, two diastereomers were obtained in a proportion of 34/66. IR ν_{max} (NaCl plate) 1707 cm^{-1} (C=O). Assignment of the NMR shifts to protons and carbons was confirmed by C–H and H–H COSY. δ_H ($CDCl_3$) 1.19* (3H, t, J = 7.2, $C\underline{H}_3$), 1.25 (3H, t, J = 7.2, $C\underline{H}_3$), 2.33–2.43* (1H, m, $NHCHC\underline{H}_2C$=O), 2.76–2.92* (3H, m, $C\underline{H}_2CHCOOC_2H_5$, $NHCHC\underline{H}_2C$=O), 3.55–3.61* (1H, m, $CH_2C\underline{H}COOC_2H_5$), 4.07–4.12*, 4.19–4.25 (2H, m, $C\underline{H}_2CH_3$), 4.33–4.39* (1H, m, $NHC\underline{H}CH_2C$=O), 6.52–6.54 (1H, dd, J = 1.8, 7.6, $CH_2CC\underline{H}CHCOH$), 6.59–6.61* (1H, dd, J = 1.8, 8.2, $CH_2CC\underline{H}CHCOH$), 6.65 (1H, m, $CH_2CCHC\underline{H}COH$), 6.71* (1H, m, $CH_2CCHC\underline{H}COH$) 6.73–6.78* (1H, d, J = 8.2, $CH_2CC\underline{H}COH$), 7.39–7.42* (1H, m, $C\underline{H}CHCHCC$=O), 7.53–7.57* (1H, m, $C\underline{H}CHCHCHCC$=O), 7.58–7.62* (1H, m, $C\underline{H}CHCC$=O), 7.69–7.72* (1H, m, $C\underline{H}CC$=O). δ_C ($CDCl_3$) 14.1*, 14.2 ($\underline{C}H_3$), 39.1, 39.2* ($\underline{C}H_2CHCOOC_2H_5$), 44.5, 45.1* ($NHCH\underline{C}H_2C$=O), 54.6, 55.4* ($NH\underline{C}HCH_2C$=O), 61.2*, 61.3 ($\underline{C}H_2CH_3$), 61.4, 61.4* ($\underline{C}HCOOC_2H_5$), 115.2* ($CH_2C\underline{C}HCOH$), 116.1,116.2* ($CH_2CCH\underline{C}HCOH$), 121.2, 121.3* ($CH_2CCH\underline{C}HCOH$), 123.4*, 123.5 ($\underline{C}HCC$=O), 125.7, 126.3* ($\underline{C}HCHCHCHCC$=O), 128.8*, 128.9 ($\underline{C}HCHCHCC$=O), 129.1 ($CH_2\underline{C}CHCOH$), 135.0*, 135.3 ($\underline{C}HCHCC$=O), 136.6 ($\underline{C}CHCHCHCHCC$=O), 143.0 ($CH_2\underline{C}CHCHCOH$), 144.0 ($CH_2CCH\underline{C}OH$), 155.1, 155.2* ($\underline{C}C$=O), 174.7,175.0* ($\underline{C}OOC_2H_5$), 205.0 ($CH_2\underline{C}$=O) *m/z* 356.1497 ($MH^+$, expected: 356.1498).

2.4. Kinetics experiments

2.4.1. Aqueous kinetics samples

The disappearance of the prodrugs was studied in the pH range of 0.5–11.7. For the preparation of the working buffers in the range 2–11.7, two stock solutions were used. Solution A was 0.05 M of citric acid monohydrate and 0.02 M of boric acid in distilled and deionised water. Solution B was 0.1 M in tripotassium-orthophosphate in distilled and deionised water. The two solutions were mixed and diluted in the necessary proportions to achieve the desired pHs and ionic strength of 0.154. For pH values under 2, HCl solutions were used: ionic strength was set by addition of NaCl where appropriate. Typically, stock solutions of the compounds under investigation of approximately 1–5 mg/ml in acetonitrile were prepared as appropriate. Stock solution (20–100 μl) were diluted in 1 ml of the working buffer and pre-warmed at 37 °C to obtain solutions with a final concentration of approximately 100 μg/ml. Each solution was introduced into the autosampler of the CE warmed to 37 °C and injections started immediately using the method described in 2.3.3.

2.4.2. Plasma kinetics samples

Citrated human blood was obtained from volunteers in the School of Pharmacy, Trinity College Dublin. Plasma was separated by centrifugation (3000 rpm for 10 min). Aminoindanone stock solutions (10–100 μl) were diluted in plasma (1–3 ml) to achieve the target concentration (0.4 mM). Aliquots from plasma samples were taken at time intervals and quenched with a 5% (v/v) perchloric acid solution or a 4% (v/v) perchloric acid and 1 g/l EDTA solution (1.5/1, v/v). These quenched samples were centrifuged for 3 min at 10,000 rpm and the supernatant analysed by CE or HPLC.

2.4.3. Capillary electrophoresis

CE was performed in a Beckman P/ACE system 5510 equipped with a UV filter detector set at 200 or 214 nm. The system also had an autosampler with cooling facility which was modified by connection to a water circulator. For kinetic tests the water temperature was set so that, inside the sample vials, a temperature of 37 ± 1 °C was achieved. The fused silica capillary was 12 cm effective length (20 cm total length) and an internal diameter of 50 μm. Samples were loaded by pressure injection for 5 s. Runs were carried out at 25 °C and at constant current of 100 or 150 μA in the direction of the cathode. New capillaries were conditioned beforehand with 0.1 M NaOH followed by deionised water for 5 min and the running buffer for 5 min. Between runs, the capillary was rinsed with the running buffer for 1 min. The running buffer was a phosphate buffer (pH 3, 100 mM) to which 100 mM tetrabutylammonium phosphate (TBA) was added. The buffer was filtered through a 0.45 μm membrane filter before use. Data acquisition was performed by the system Gold and peak areas were recorded at 200 or 214 for the original compound and the parent amine (when applicable).

For pK_a determination, CE and the method described in Simplício et al. (2004) was used.

2.4.4. HPLC

HPLC was performed using a system consisting of a Spectra System SCM1000 ultrasound, Spectra System P4000 pump and controller, Spectra System AS3000 autosampler and a Spectra System UV1000 detector controlled by Chromquest Chromatography Manager. The stationary phase was a C18 (4.6 mm × 250 mm) Waters Spherisorb with a 10 μm particle size column. A mixed gradient-isocratic mobile phase was employed which consisted of aqueous 42.5 mM orthophosphoric acid/6.1 mM triethylamine and acetonitrile in a ratio of 80:20 for 5 min then graded to 20:80 (aqueous: MeCN) over 10 min, maintained at that for 5 min then stepped back to initial conditions over 1 min and re-equilibrated for 9 min. The flow rate was 1.2 ml/min.

2.4.5. Non-linear regression

Graph Pad PRISM® 3.02 was used for fitting experimental data of the pH/rate profiles and the pH/mobility profiles.

3. Results and discussion

3.1. Elimination kinetics

The disappearance of the test compounds in aqueous solution over the pH range 0.5–11.7 at 37 °C was measured using CE or HPLC as appropriate; for some compounds both HPLC and CE were used. The identity of the amine was confirmed by running external standards in CE and HPLC. The presence of indenone was established by its PDA spectrum and retention time (HPLC), which coincided with that of an authentic sample of indenone prepared by treating 3-bromoindanone in diethyl ether with triethylamine (Marvel and Hinman, 1954).

The disappearance of aminoindanones was generally well described by apparent first-order kinetics up to around neutrality. First-order plots were constructed from the logarithm of % remaining compound versus time and the half-lives estimated using Eq. (1):

$$t^{1/2} = \frac{0.693}{k_{obs}} \tag{1}$$

This straightforward picture was not always adhered to. At higher pH, in some cases, there was evidence of the reverse reaction between the liberated amine and the indenone leading to an equilibrium (Fig. 1). The extent to which this occurred and the pH at which it began depended on the compound involved, but the behaviour was particularly marked for compounds **1i** (Fig. 3) and **1c**, compounds which share a nucleophilic piperidine moiety. Indeed, in the case of **1c** there was evidence of a further reaction between the liberated piperidine and the indenone.

When the degradation of **1c** was monitored at pH > 7 by HPLC, the indenone reaction product was consumed with

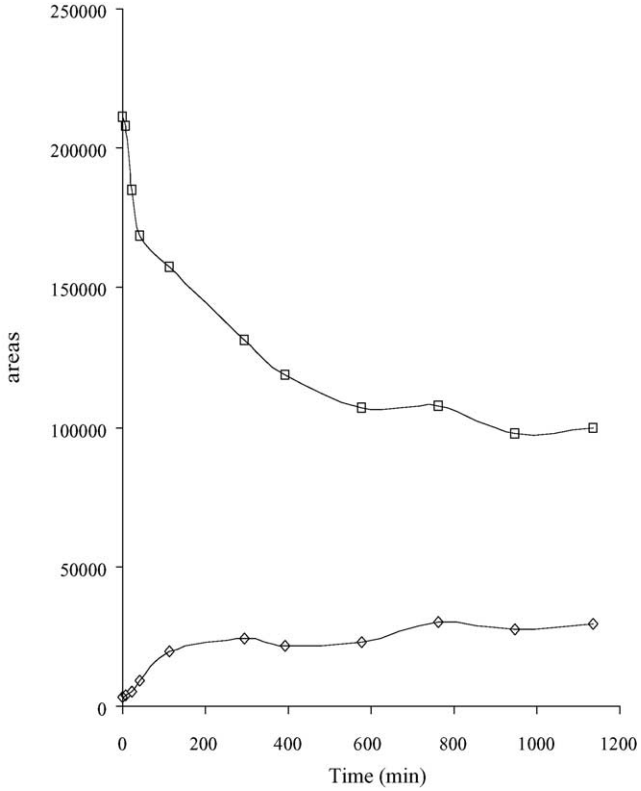

Fig. 3. Degradation profile of **1i** at pH 7.9 (◇, desloratadine; □ **1i**).

the formation of two later eluting unidentified components, resulting in complex kinetics. However, the degradation of **1c** followed apparent first-order kinetics up to pH 7.

The rate of the forward reaction (k_f) under apparent equilibrium conditions was measured using the following expression (Eq. (2)):

$$\ln\left(\frac{a_0 b_{eq} + b a_{eq}}{a_0(b_{eq} - b)}\right) = \frac{2a_0 - b_{eq}}{b_{eq}} k_f t \tag{2}$$

Since the concentration of **2** at equilibrium (b_{eq}) and at time t (b) can be related to the original concentration of **1** (a_0) by $b_{eq} = a_0 - a_{eq}$ and $b = a_0 - a$, Eq. (2) can be rewritten strictly as a function of the concentration of **1** (Eq. (3)):

$$\ln\left(\frac{a_0^2 - a a_{eq}}{a_0(a - a_{eq})}\right) = \frac{a_0 - a_{eq}}{a_0 - a_{eq}} k_f t \tag{3}$$

The graphical representation of this equation should provide a straight line for times preceding equilibrium. The first-order rate constant (k_f) for the forward reaction can be derived from the slope, m, of that line from Eq. (4):

$$k_f = m\frac{a_0 - a_{eq}}{a_0 + a_{eq}} \tag{4}$$

The decay plots of each compound at different pHs were evaluated and assigned to one of these assumptions; i.e. to completion or to an equilibrium situation. The extent of the

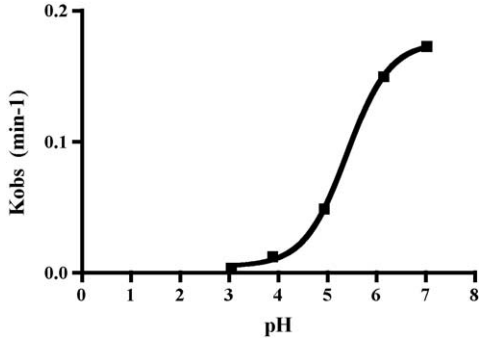

Fig. 4. Plot showing the pH-rate profile for the disappearance of compound **1h** (■) at 37 °C and μ = 0.154. The solid line was constructed using Eq. (5).

reverse reaction exhibited a marked dependence on pH. Under acid conditions the reverse reaction is suppressed because of amine protonation. Correspondingly, equilibria were most frequently observed at pH values in excess of amino pK_a when the amino group is mostly unionised. Amino nucleophilicity also seems likely to be important in determining the rate of the reverse reaction as evidenced here by the behaviour of **1i** and **1c**.

Further complications in measuring degradation rates were encountered with the amino esters **1e** and **1f**. At basic pH values these compounds degraded via a mixture of ester hydrolysis and amine elimination; only the behaviour up to the maximum pH at which elimination was apparently the exclusive mode of degradation is considered here. Finally, although the degradation of compound **1j** followed typical kinetics, the yield of liberated dopamine was low (∼40%).

pH-rate profiles were experimentally determined for all compounds in the study except for **1b**, which only slowly degraded across the pH range making measurement difficult. As previously stated (Simplício et al., 2004), pH rate profiles of the type depicted in Fig. 4 can be accounted for by assuming unimolecular decomposition of the protonated and unionised forms and may be mathematically represented in the form of a particular case of a Boltzmann sigmoid (Eq. (5)):

$$k_{obs} = k_2 - \frac{k_2 - k_1}{10^{(pH-pK_a)} + 1} \quad (5)$$

where k_1 and k_2 represent, respectively, the elimination rates from the protonated and the unprotonated aminoindanone, pK_a is the ionization constant of the compound and k_{obs} is the observed degradation rate constant at a particular pH.

Non-linear regression applied to the pH-rate profiles obtained for compounds **1a** and **1c**–**1k**, to Eq. (5), yielded values for k_1, k_2 and pK_a presented in Table 2. pK_a values were also determined using electrophoretic mobilities according to the method described in Simplício et al. (2004). Results of these determinations are presented in Table 3 and while there is generally good agreement between the two methods, the latter values are likely to be more accurate. Reductions of 3–4 pK_a units were observed for the aminoindanones in comparison with the corresponding free amines. This is likely to be advantageous for prodrugs intended for peroral administration because of the corresponding suppression of ionisation at intestinal pH.

The elimination rate for the ionised form (k_1) was generally very low with no significant reduction in concentration or emergence of parent amine at pH 0.5–1 over 24 h at 37 °C. The elimination rate was found to increase rapidly as the pH of the aqueous solution approached the pK_a of the amine. These rates varied significantly across the small amine set presented here. The compounds fell into two groups: (i) secondary derivatives of primary amines for which k_2 was low, leading to half-lives of 100–800 min, and; (ii) tertiary amines (**1d**, **1h**) for which half-lives at around neutrality were <5 min. Two further tertiary derivatives **1c** and **1i**, had longer half-lives but measurement in these cases was complicated by a prominent reverse reaction. These observations are consistent with the behaviour of a group of six promising anti-allergic/anti-inflammatory aminoindanones (Walsh et al., 2001) on which we have recently reported (Simplício et al., 2004). In that group, three tertiary amines had half-lives of <10 min at pH 7.4 whereas the corresponding

Table 2
Elimination rates k_1 and k_2 and pK_a values obtained by non-linear regression of experimental data to Eq. (5) along with projected half-lives based on the theoretical pseudo-first-order k_2 rate constants

	k_1 (min^{-1})	k_2 (min^{-1})	$t_{1/2}$ (min) k_2	$t_{1/2}$ (min) [experimental] 37 °C, low pH	$t_{1/2}$ (min) [experimental] 37 °C, pH 7.4	pK_a
1a	0 ± 0.0004	0.0029 ± 0.0003	238.97	Stable at pH < 4	266 (pH 7.8)	5.1 ± 0.4
1b	nd	nd	nd	Stable at pH 0.5	836	nd
1c	1e−7 ± 3e−5	0.0033 ± 3e−5	210	Stable at pH < 4	76	5.9 ± 0.03
1d	0 ± 0.03	0.13 ± 0.01	5.33	693 at pH 2.8	<5	4.5 ± 0. 6
1e	0 ± 0.001	0.0026 ± 0.0011	266.54	866 min at pH 3	277 (pH 5)	3.3 ± 0.9
1f	1e−7 ± 0.0003	0.0032 ± 0.0004	216.56	Stable at pH < 3	213 (pH 6.14)	4.3 ± 0.4
1g	0 ± 0.0006	0.0030 ± 0.0007	231	Stable at pH < 3	215	6.6 ± 0.6
1h	0.005 ± 0.007	0.18 ± 0.01	3.85	192 at pH 3 2310 at pH 0.5	1.1	5.3 ± 0.2
1i	0.0003 ± 0.0005	0.0064 ± 0.001	108.28	Stable at pH < 2	nd	5.0 ± 0.4
1j	0.0 ± 0.002	0.0067 ± 0.0003	103.43	Stable at pH < 4	120	6.6 ± 0.9
1k	0 ± 0.0003	0.0027 ± 0.0004	256.67	Stable at pH 0.5	240	3.7 ± 0.4

The experimentally determined k_2 disappearance rate is also presented along with stability characteristics at low pH. The statement that the material was stable means that there was no statistically significant change in concentration when a sample was incubated at that pH for 24 h.

Table 3
Experimental pK_a values of the amines and their indanone derivatives determined by CE, along with pK_a values available in the literature

Amine	pK_a amine (literature)	pK_a amine (experimental)	Compound	pK_a indanone (experimental)
Dimethylamine	10.73[a]	n.d.	**1a**	6.81 ± 0.06
Ethylamine	10.65[a]	n.d.	**1b**	7.67 ± 0.07
Piperidine	11.12[a]	n.d.	**1c**	7.15 ± 0.08
Ephedrine	9.6[a]	9.4 ± 0.8	**1d**	6.16 ± 0.07
Tryptophan methyl ester	7.29[b]	6. 9 ± 0.2	**1e**	3.9 ± 0.2
Alanine methyl ester	7.78[b]	n.d.	**1f**	5.04 ± 0.06
Phenethylamine	9.83[a]	10.0 ± 0.2	**1g**	6.82 ± 0.05
Atenolol	9.6[a]	9.6 ± 0.7	**1h**	5.75 ± 0.08
Desloratadine		n.d.	**1i**	5.07 ± 0.06
Dopamine	8.8, 10[a]	7.6 ± 0.2, n.d.	**1j**	6.8 ± 0.1, 8.5 ± 0.3
Etilevodopa	7.12[c]	6.74 ± 0.09, 8.9 ± 0.20	**1k**	4.2 ± 0.2, 8.1 ± 0. 2

[a] Albert and Serjeant (1984).
[b] Hay and Porter (1967).
[c] Beilstein.

secondary analogues degraded at pH 7.4 with half-lives of 200–500 min.

Steric factors are likely to play a significant role in determining the rate of elimination of amino drugs from their indanone derivatives. We were unable to establish any quantitative relationships in the present amino set because of the unavailability of appropriate parameters (Taft or Charton) for many of its members. Sets of stereoisomers were analysed in five cases; **1d**, **1e**, **1f**, **1h** and **1k**. The k_2 rates were fairly similar for both enantiomeric pairs of **1d** (0.0011, 0.0008 min^{-1}) and **1e** (0.0009, 0.0007 min^{-1}). The isomeric pairs of **1f** (the alanine compound) were not sufficiently well separated to determine if one pair degraded faster than the other. In the case of the L-dopa ethyl ester analogue, **1k** at pH > 7 the two diastereomers underwent degradation at different rates, but analysis was complicated at this pH by a competing ester hydrolysis. Thus, it was difficult to tell whether the isomers underwent elimination or hydrolysis at different rates.

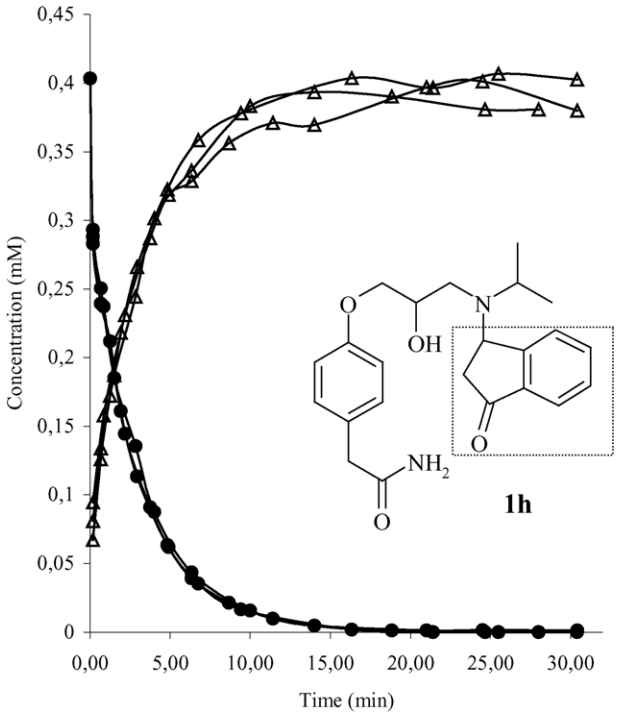

Fig. 5. Progress curves for the disappearance of **1h** (●) in plasma buffered at pH 7.4 and the appearance of atenolol (△) (mean, $n = 3$).

In terms of prodrug design, the amine release kinetics might be regarded as especially favourable for **1d** and **1h**, the indanone forms of ephedrine and the β-adrenergic blocking agent atenolol, respectively. Compound **1h** is stable at low pH but undergoes rapid elimination of the parent atenolol at higher pH ($t_{1/2}$ = 1.1 min at pH 7.4). The decomposition of **1h** was also studied in diluted human plasma at pH 7.4, where elimination of atenolol is quantitative (Fig. 5). For these tests, the samples had to be quenched in order to eliminate proteins before CE or HPLC tests. Perchloric acid was used for this according to the procedure described in 2.3.2. Buffered solutions were treated in the same way for comparison. The degradation rate in plasma was a little slower than in pH 7.4 buffer alone, probably due to protection of the compound while bound to plasma proteins.

4. Conclusions

The technology presented here adds to the armoury of chemistries available for reversibly masking amines. 3-Aminoindanones are stable at low pH but undergo elimination at blood pH, liberating the parent amine. Indanone attachment leads to significant suppression of ionisation relative to the parent amine and the compounds are also likely to be more lipophilic given the nature of the appended group. Caveats to the design include the following: little data is available concerning the toxicity characteristics of indenone; the half-lives of the tertiary compounds might be too short for peroral administration while the secondary compounds are potentially too stable.

The potential for β-amino ketones to undergo elimination is fairly well established (and predictable), though there have been few reports of this behaviour in an aqueous environment and the phenomenon has not been exploited previously

in the design of prodrug systems for amines (Tramontini and Angiolini, 1994). The unexpectedly rapid rates of elimination of the neutral tertiary aminoindanones appears to be connected with the extended conjugation available to the indenone side-product. In that sense there is probably a strong thermodynamic component to the elimination of aminoindanones. It is easy to imagine other arrangements in which amine elimination is similarly driven, and potentially at more readily modulated rates. We are currently evaluating structurally different carrier systems which fit this description.

Acknowledgements

This project was accomplished with the financial support of the Fundação para a Ciência e a Tecnologia, Portugal and the European Social Fund in the form of a scholarship.

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