2020

Novel Mast Cell-Stabilising Amine Derivatives of 3,4 Dihydronaphthalen-1(2H)-One and 6,7,8,9-Tetrahydro-5H-benzo[7]annulen-5-one

James W. Barlow
University of Dublin, Trinity College

Tao Zhang
Technological University Dublin, tao.zhang@tudublin.ie

Orla Woods
University of Dublin, Trinity College

See next page for additional authors

Recommended Citation

Barlow, J.W., Zhang, T., Woods, O., Byrne, A.J. and Walsh, J.J. (2011). Novel mast cell-stabilising amine derivatives of 3,4 dihydronaphthalen-1(2H)-one and 6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one. *Medicinal Chemistry*, 7, 213-223. doi:10.2174/157340611795564222

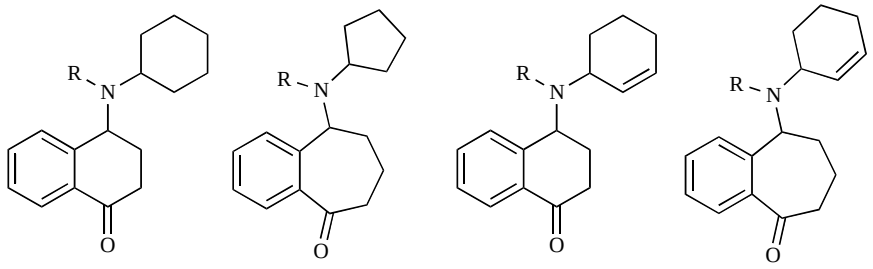
Funder: Enterprise Ireland

Novel Mast Cell-Stabilising Amine Derivatives of 3,4-Dihydronaphthalen-1(2*H*)-one and 6,7,8,9-Tetrahydro-5*H*-benzo[7]annulen-5-one

James W. Barlow, Tao Zhang, Orla Woods, Adam J. Byrne and John J. Walsh*

School of Pharmacy and Pharmaceutical Sciences, University of Dublin, Trinity College, Dublin 2, Ireland

Abstract: In an investigation of 4-amino-3,4-dihydronaphthalen-1(2*H*)-ones as novel modulators of allergic and inflammatory phenomena, we have investigated a series of cyclic analogues. Tertiary amines of structural types **9**, **10**, **20** and **21** were synthesised and evaluated for mast cell stabilising activity. *In vitro* and *in vivo* studies showed that of these compounds, the cyclohexenylamino derivatives of tetralone and benzosuberone of series **20** and **21** exhibited interesting activity both *in vitro* and *in vivo*.



9a-b R=Ar/Alkyl **10** R=CH_3 **20**a-f R=Ar/Alkyl **21**a-n R=Ar/Alkyl

Keywords: Anti-allergic, benzosuberone, mast cell, tetralone.

INTRODUCTION

Mast cells are densely granulated cells, historically associated with the pathogenesis of allergic reactions and protective responses to parasites; however, their further roles are increasingly being recognised. For example, mast cells are involved in cell-mediated immune reactions, are a component of the host reaction to infection, and have functions in angiogenesis and tissue repair after injury. Much interest focuses on their possible involvement in promoting persistent inflammation and remodeling in chronic airway disease [1]. Apart from lung disease, mast cells have been implicated in cardiovascular disease and cancer. Several studies point at their role in the pathogenesis of atherosclerosis and acute coronary syndromes [2]. Due to the association between inflammation and carcinogenesis, a possible contribution of these cells to tumour development has emerged, and it has been suggested that mast cells may even serve as a novel therapeutic target for cancer treatment [3]. Drugs in clinical use that modify the degranulation of both mast cells and their circulating counterparts the basophils include the prototypic agent sodium cromoglycate and its analogue nedocromil [4]. Additional agents including the cycloheptathiophene ketotifen, the phthalazin-1-one azelastine and the propylidene benzoxepin olopatadine exhibit both mast cell stabilising and antihistaminic properties, the latter effect mainly attributable to an additional diarylalkylamine pharmacophore [5]. It is now accepted that although mast cell stabilisation is a clinically relevant mechanism of cromoglycate-like drugs, it only partially explains the effects of these drugs *in vivo* and that other targets are important: one such is reflected by the recent demonstration that they suppress eicosanoid generation by promoting the release of the powerful anti-inflammatory protein annexin-A1 [6]. In addition to clinically established drugs, many diverse molecular entities have demonstrated both anti-allergic and anti-inflammatory activities, including natural products such as flavonoids and pterosins. Within the latter class of secondary metabolites, indane derivatives based on the indanone pterosin Z have been investigated as smooth muscle relaxants [7]; with both indanes and aminoindanes showing interesting activity [8]. Separately, it is of interest that the dual M2 / H1 receptor antagonist dimethindene maleate, possessing a 2-(1*H*-inden-2-yl)-ethylamine fragment in its structure, has also been shown to modulate mast cell histamine secretion and to produce a comparable, dose-dependent inhibition of anti-IgE-induced histamine release from the same cell type [9].

Our earlier work [10] showed that, among a series of 4-amino-3,4-dihydronaphthalen-1(2*H*)-ones, the tertiary benzylated compound **1** exhibited the most potent activity in anti-allergic assays (Fig. **1**). In addition, incorporation of the second *N*-benzyl within a second carbocyclic or heterocyclic architecture afforded dimeric compounds such as those

*Address correspondence to this author at the School of Pharmacy and Pharmaceutical Sciences, University of Dublin, Trinity College, Dublin 2, Ireland; Tel: +353 1 8962806; Fax: +353 1 896 2804;
E-mail: jjwalsh@tcd.ie (J. J. Walsh)

1573-4064/11 $58.00+.00

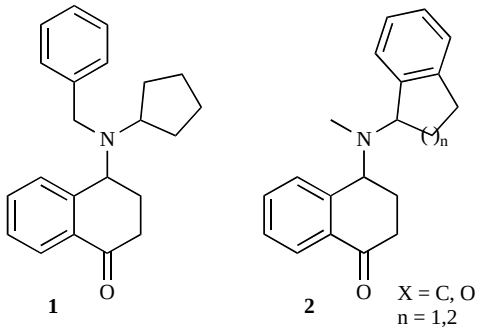


Fig. (1). Lead structural types **1** and **2**.

represented by the general structure **2**, and these also displayed interesting activities in preliminary screens [11]. In the present study, we developed a series of analogous cyclic compounds, varying the ring size of both hydroaromatic and alicyclic ring components of **1**, to investigate whether this would result in augmentation or annihilation of the requisite activity. There is no literature precedent for these molecules; although benzamido derivatives of 6,7,8,9-tetrahydro-(5*H*)-benzocycloheptene-5-one have been synthesized by Ritter reaction of 6,7-dihydro-(5*H*)-benzocycloheptene-5-ones with benzonitrile [12], and a non-pharmacophoric structural aminotetrahydro benzocycloheptenone motif occurs in compounds exhibiting effects as diverse as fungicidal [13] and 5HT-binding [14] activities.

CHEMISTRY

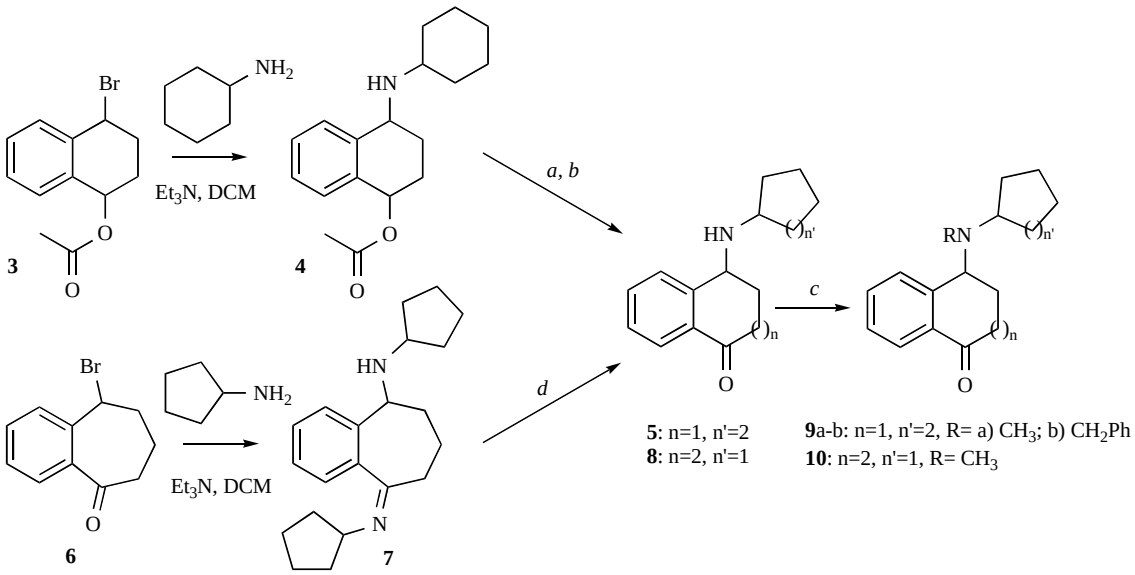
Using analogous methodology to the synthesis of the cyclopentyl derivatives [10], we obtained amines **9a-b** as outlined in Scheme **1**. Wohl-Ziegler bromination [15] of 1,2,3,4-tetrahydro-naphthalen-1-yl acetate gave bromo acetate **3**. Incorporation of the cyclohexylamino ring was achieved by substitution of **3** with cyclohexylamine in basic media. Acyl hydrolysis using K_2CO_3 in methanol followed by oxidation with Cr (VI) (Jones reagent) [16] yielded ketone **5**. Alkylation to **9a-b** was accomplished using standard *N*-alkylation conditions [17]. These compounds were isolated as diastereomeric mixtures of two enantiomeric pairs and were tested as such in the initial assays employed. Expansion of the hydroaromatic tetralone ring to that of a benzosuberyl moiety was the next synthetic target. Compared to 4-bromotetralone, the benzylic monobromide **6** of benzosuberone [18] is a more stable molecule, so much so that nucleophilic substitution with cyclopentylamine proceeded slowly and was not a clean transformation, producing considerable quantities of imine **7**. Acidic hydrolysis of the imine followed by methylation afforded **10**, as shown in Scheme **1**.

Introduction of unsaturation into the cyclohexyl ring of **5** to yield **18** was accomplished readily by reaction of 3-bromocyclohexene with 4-amino-3,4-dihydro-2*H*-naphthalen-1-one [19] **16** as shown in Scheme **2**. Alkylation as before gave tertiary amines **20a-f**. To complement the synthesis and testing of the cyclopentyl-substituted tetrahydro-benzocyclohepten-5-one **10**, it was decided to produce cyclohexenyl-substituted analogues. The synthetic rationale for the preparation of these compounds was similar to that used to generate **18**, namely the reaction of 3-bromocyclohexene with 9-amino-6,7,8,9-tetrahydro-benzocyclohepten-5-one **17**, which in turn was produced from **6**, as shown in Scheme **2**. As with the compounds of series **20**, compounds **21a-n** were isolated and tested as mixtures of stereoisomers.

PHARMACOLOGY

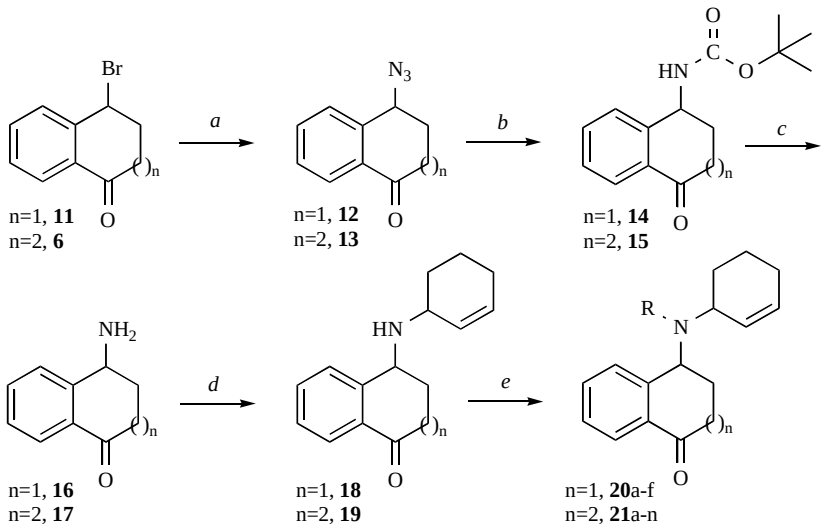
Mast Cell Stabilising Activity

Test compounds were evaluated for inhibition of compound 48/80-induced degranulation of rat peritoneal mast cells (RPMC), isolated as previously reported [20, 21]. Unpurified cell populations as used for initial screening (Table **1**) were of >90% viability and mast cells comprised 1.4% of the total cell count, whereas Percoll-purified cells (used to determine IC_{50} values, Table **2**) comprised 81.6% of



(a) K_2CO_3, MeOH, (b) Jones reagent, CH_3COCH_3, (c) RX, K_2CO_3, CH_3COCH_3, (d) 2M HCl/MeOH (1:1)

Scheme 1. Synthetic methods for the preparation of **9a-b** and **10**.



Series 20: R= a) CH_3; b) $CH_2CH=CH_2$; c) Bz; d) 4-CH_3Bz; e) 3,4,5-$(CH_3O)_3$Bz; f) 2'naphthylmethyl
Series 21: R= a) CH_3; b) $CH_2CH=CH_2$: c) Bz; d) 2,3,4-$(CH_3O)_3$Bz; e) 3,4,5-$(CH_3O)_3$Bz; f) 4-(OCF_3)Bz; g) 3-(OCF_3)Bz; h) 2,4,6-(F_3)Bz: i) 4-(COOMe)Bz; j) 4-(CH_2COOMe)Bz; k) 2-PhBz; l) $CH(Ph)_2$; m) 4-NO_2Bz; n) 4-CNBz

(a) NaN_3, DMF, <50ºC, (b) H_2, Pd/C, EtOH/EtOAc (2:1), Di-*tert*-butyl dicarbonate, R.T., (c) CF_3COOH, DCM, 0^{O}C-R.T., (d) 3-bromocyclohexene, Et_3N, DCM, R.T., (e) For **20**a-f: RX, K_2CO_3, CH_3COCH_3, Δ; For **21**a-n: RX, *N*,*N*-diisopropylethylamine, CH_3CN, N_2, Δ

Scheme 2. Synthetic Methods for the Preparation of **20a-f** and **21a-n**.

Table 1. Mast Cell Stabilising Activity of Novel Compounds[a,b]

Compounds	% Inhibitor	SEM
9a	NI	
9b	99 (NI)[c]	1
10	NI	
20a	13	8
20b	68	14
20c	100	
20d	77	10
20e	88 (64)[c]	6 (3)
21f	5	6
21a	NI	
21b	42	7
21c	99	1
21d	58	6
12e	101	10
21f	24	8
21h	90	5
21i	89	7
21j	95	11
21k	87	5
21l	11	4
21m	91	13
21n	90	14
DSCG	10	3

[a]Values are mean of at least n=5, test compounds and DSCG at 2 x 10^{-5}M, challenge with compound 48/80 at 0.2μg mL^{-1}, 5 min exposure; [b]NI, no inhibition at concentration tested; [c]Value in brackets reflect anti-IgE as clicitor.

the total cell count. The results were compared with the reference compound disodium cromoglycate (DSCG). The

Table 2. Protective Activity of Selected Compounds Against Degranulation of Percoll-purified RPMC Induced by Various Elicitors[a,b]

Compounds	Compound 48/80	Ca^{2+} ionophore A23187
	IC50 (μM)	
21d	1.5	8.2
21e	7.6	8.4
21f	1.2	20.7
21i	2.1	5.6
21l	-	2.6
21n	-	1.8

[a]value are obtained from a mean of four experiments
[b]Calcium ionophore used at 1 μg mL^{-1}

IC_{50} values of selected compounds (**21d-f**, **21i**, **21l** and **21n**) were determined using both compound 48/80 and the calcium ionophore A23187.

Passive Cutaneous Anaphylaxis (PCA)

Passive cutaneous anaphylaxis is an immediate type of hypersensitivity reaction caused by the interaction of antibodies with mast cells of the skin. This technique was developed in 1958 by Ovary [22]. In our study, an antiserum was raised by means of intraperitoneal inoculation of Wistar rats with 1 mL of heat-killed *Bordetella pertussis* suspension (10^{10} organisms per mL) and 0.5 mL of chicken egg albumin solution (1 mg per animal) in 0.5M NaCl. After 14 days, the animals were exsanguinated and the serum was isolated. The prepared serum was intradermally injected, and after 48 hours, the rats were intravenously challenged *via* the tail vein with 2.5 mg albumin in 0.25 mL 2% Evans Blue, with

simultaneous injection of 0.25 mL of vehicle (positive control) or test compound at a dose of 3 mg kg^{-1}. Thirty minutes after intravenous injection, the animals were sacrificed by cervical dislocation and the skin reflected. The vehicle control and test sites were measured and excised, and the tissue segments added to 1 mL of 1M KOH. Using the method of Katayama [23], the tissue was digested overnight at 37 ^{o}C, and to each digest was added 2.5 mL 0.6M H_3PO_4 and 6.5 mL acetone. The tubes were thoroughly shaken, and centrifuged at 3000 rpm for 15 minutes. The absorbance of each supernatant was measured using UV spectroscopy at 620 nm. As with the evaluation of mast cell stabilising activity, the standard used in this assay was DSCG.

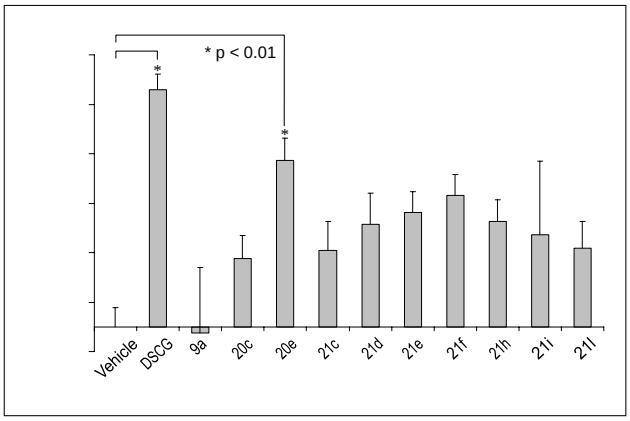


Fig. (2). Effect of novel compounds on PCA. Data were analysed by one-way ANOVA. Differences among means were considered significant at P<0.01.

RESULTS

In the preliminary assay with compound 48/80 as mast cell degranulating agent (Table **1**), *N*-methyl analogue **9a** was devoid of any mast cell-stabilising activity. However, *N*-benzyl analogue **9b** was remarkably effective at the dose level which tested (99% inhibition). The compounds of series **20** investigated the effect of unsaturation within the cyclohexyl ring of **9**. Methyl derivative **20a** only provided 13% inhibition of compound 48/80-induced degranulation. Allyl derivative **20b** offered 68% protection. As with **9b**, **20c** also completely abolished compound 48/80-induced degranulation, while substituted benzyl derivatives **20d-e** also retained activity. Enlargement of the hydroaromatic system alone, comparing **9a**, **10** and **21a**, did not affect mast cell-stabilising activity if the nitrogen was substituted with a small methyl group. However, in benzosuberone series **21**, the combination of an enlarged hydroaromatic ring coupled with a nitrogen bearing a more bulky planar benzyl or substituted benzyl moiety, inhibition was retained or even enhanced (**20e** vs. **21e**) in cyclohexenyl-substituted derivatives **21b-n**, the most active again being benzylated compound **21c** and substituted benzyl analogues **21e**, **h-k**, and **m-n**. Table **2** shows that while **21e** had comparable IC_{50}s against 48/80-and ionophore-induced degranulation; the other compounds tested showed an appreciable variation in protective ability against degranulation caused by ionophore A23187, most notably **20f**. The results from Fig. **2** show that *in vivo*, while both series **20** and **21** compounds offered protective effects, the most active compound tested was **20e**, inhibiting the reaction by 67%, compared to 28% for the unsubstituted benzyl **20c**.

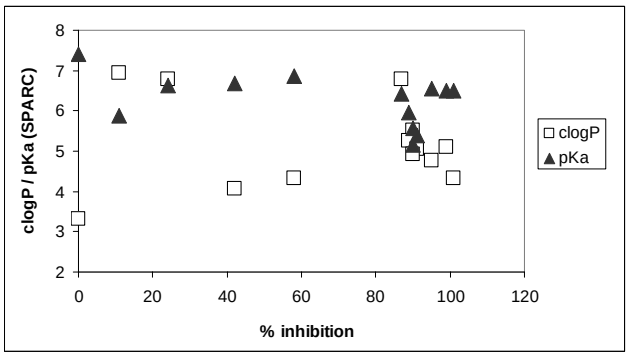


Fig. (3). Relationship of inhibitory activity (from Table **1**) *vs*. some predicted physicochemical parameters of compounds **21**a-n (clogP values calculated using MarvinSketch 5.1.4 from ChemAxon).

DISCUSSION

Analogously to the cyclopentyl series [10], the most active compounds tested in series **9**, **20** and **21** were benzylated derivatives, reinforcing that a tertiary *N*-benzyl group is a key structural element. Indeed compounds **9a**, **10**, **20a** and **21a**, all containing an *N*-methyl substituent, were largely devoid of activity. Within series **20**, contrasting somewhat with our earlier study, both allyl and trimethoxybenzyl derivatives offered good inhibition of mast cell degranulation (68% and 88%, respectively), whereas the 2′-methylnaphthalenyl derivative **20f** did not offer a significant protection (5%), in contrast to its *N*-cyclopentyl analogue. Incubation of RPMC suspensions with anti IgE caused a rapid (within 10 minutes) release of histamine (87%). Compound **20e**, unlike **9b**, exhibited a protective effect against degranulation by this elicitor, more reflective of mast cell degranulation *in vivo*. Use of an *in vivo* model (PCA) revealed that *N*-cyclopentyl derivative **1** was ineffective, despite being a potent inhibitor of compound 48/80-, Con A- and A23187-induced degranulation [10]. Promisingly however, **20e** was active against *in vivo* cutaneous anaphylaxis, inhibiting the extravasation reaction by 67%. The pattern of results for compounds **21a-n** mirrored those of series **20**, in that bulky benzylated substituents on the tertiary nitrogen retained their importance. Electronic effects do not appear to be strong predictors of *in vitro* activity, as compounds with either electron-donating (e.g. **21e**) or electron-withdrawing (e.g. **21m**) groups on the benzyl ring retained activity, and there is no obvious correlation between activity and polarizability. Fig. **3** shows that lipophilicity may have a role in predicting activity within compounds of type **21**: all compounds bar one that are potent *in vitro* have a clogP of around 5, obeying Lipinski predictors.

EXPERIMENTAL PROTOCOLS

All commercially available solvents and reagents were used without further purification. Reagents for synthesis and biological assays were purchased from Sigma–Aldrich. IR spectra were generated on a Perkin Elmer Paragon 1000 FT-

IR. NMR spectra were generated at Bruker DPX-400 instrument, at 400.13 MHz for proton (^{1}H) magnetic resonance and 100.61 MHz (unless otherwise specified) for carbon (^{13}C) spectra, in chloroform-d. Chemical shifts are expressed in δ units (ppm). Low-resolution mass spectra were obtained on a Saturn GC/MS 2000 [CP-3800 Gas Chromatograph], while high-resolution mass spectra (HRMS) were obtained on a Micromass LCT instrument.

4-(Cyclohexylamino)-1,2,3,4-tetrahydro-1-naphthalenyl acetate (4)

To a solution of **3** [10] (3g, 11.15 mmol) in DCM (10 mL) was added cyclohexylamine (2.54 mL, 22.3 mmol) and triethylamine (2.33 mL, 16.72 mmol). The reaction was refluxed for 9 hours, the solvent removed *in vacuo*, and the residue purified by flash column chromatography on silica gel (eluant: pet. ether:ethyl acetate, 2:1) to yield the amine as a 2:1 mixture of diastereomers, (1.66 g, 52%) a brown oil, with the following physical properties: IR (CCl_4) ν_{max} 2929, 2853, 1733, 1450, 1371, 1240, 1020; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_{ppm} = 1.11-1.40 (m, 6H, 3 x C<u>H</u>$_2$), 1.65-2.20 (m, 8H, 4 x C<u>H</u>$_2$), 2.08 and 2.12 (2 x s, 3H, C<u>H</u>$_3$), 2.30-2.40 (m, 1H, N<u>H</u>), 2.66-2.72 (m, 1H, $CH_2C\underline{H}CH_2$), 3.85-3.97 (m, 1H, NC<u>H</u>Ar), 5.96-6.02 (m, 1H, OC<u>H</u>), 7.21-7.32 (m, 3H, 3 x Ar-<u>H</u>), 7.39 and 7.55 (2 x d, 1H, *J*=7.8Hz, Ar-<u>H</u>); ^{13}C NMR ($CDCl_3$, 100MHz) δ_{ppm} = Diastereomer 1: 20.96 (<u>C</u>H$_3$), 24.4, 24.7, 25.4, 25.8, 25.8 (5 x <u>C</u>H$_2$), 33.0, 34.5 (2 x <u>C</u>H$_2$, <u>C</u>H$_2$<u>C</u>H$_2$CO), 51.7, 53.7, (2 x CH, <u>C</u>HNH<u>C</u>H), 70.0 (O<u>C</u>H), 126.5, 127.8, 127.9, 128.1 (4 x tert. <u>C</u>), 134.4, 141.0 (2 x quat. <u>C</u>), 170.3 (<u>C</u>=O); Diastereomer 2: 20.98 (<u>C</u>H$_3$), 24.1, 24.2, 24.5, 24.8, 25.8 (5 x <u>C</u>H$_2$), 33.1, 34.5 (2 x <u>C</u>H$_2$, <u>C</u>H$_2$<u>C</u>H$_2$CO), 51.0, 53.7, (2 x CH, <u>C</u>HNH<u>C</u>H), 69.3 (O<u>C</u>H), 126.7, 128.0, 128.5, 128.9 (4 x tert. <u>C</u>), 134.1, 140.6 (2 x quat. <u>C</u>), 170.2 (<u>C</u>=O); MS, m/z, (RI) 288 (M+1, 100), 287 (M^+, 18), 229 (13), 100 (13).

4-(Cyclohexylamino)-1,2,3,4-tetrahydro-1-naphthalenone (5)

To a solution of **4** (1.5 g, 5.23 mmol) in methanol/water (10 mL, 1:1) was added excess potassium carbonate (5.0 g, 36.2 mmol). The reaction was heated under reflux for 1 hour, monitoring by GCMS. On completion, the reaction was filtered and the solvent removed *in vacuo*, using toluene to azeotropically distill any residual water. To the residue containing the alcohol thus obtained, (0.91 g, 71%) was added acetone (10 mL) and Jones reagent (5 mL), the latter added drop-wise over 30 minutes to the ice-cooled reaction. On appearance of the green $Cr_2(SO_4)_3$, anhydrous sodium sulphate (1.5 g, 10.6 mmol) was added. After 2 hours, the solvent was evacuated, and the reaction separated using ether/water. After three washings with ether (3 x 50 mL), the combined organic extracts were filtered and the solvent removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 1:1) to yield the amine as a brown oil (0.49 g, 54%); IR (CCl_4) ν_{max} 2930, 2855, 1690, 1451, 1283; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_{ppm} = 1.10-1.39 (m, 5H, 5H of C<u>H</u>$_2$), 1.60-1.70 (m, 1H, 1H of C<u>H</u>$_2$), 1.74-1.84 (m, 2H, 2H of C<u>H</u>$_2$), 1.86-1.95 (m, 1H, 1H of C<u>H</u>$_2$), 1.98-2.07 (m, 1H, 1H of C<u>H</u>$_2$), 2.00-2.14 (m, 1H, $CH_2C\underline{H}CH_2$), 2.25-2.35 (m, 2H, N<u>H</u> and 1H of C<u>H</u>$_2$CH$_2$CO), 2.54 and 2.59 (2 x dd, 1H, J_1=6.3Hz, J_2=4.5Hz, 1H of C<u>H</u>$_2$CO), 2.65-2.75 (m, 1H, 1H of C<u>H</u>$_2$CH$_2$CO), 3.00 and 3.04 (2 x dd, 1H, J_1=9.5Hz, J_2=4.5Hz, 1H of C<u>H</u>$_2$CO), 4.08 (dd, 1H, J_1=6.4Hz, J_2=3.5Hz, 1H, NC<u>H</u>Ar), 7.37 (m, 1H, Ar-<u>H</u>), 7.53-7.57 (m, 2H, 2 x Ar-<u>H</u>), 8.03 (d, 1H, *J*=8.0Hz, COAr-<u>H</u>); ^{13}C NMR ($CDCl_3$, 100MHz) δ_{ppm} = 24.5 (<u>C</u>H$_2$), 24.7 (<u>C</u>H$_2$), 25.7 (<u>C</u>H$_2$), 28.4 (<u>C</u>H$_2$), 33.1 (<u>C</u>H$_2$), 34.3 (<u>C</u>H$_2$), 34.5 (<u>C</u>H$_2$), 51.7 (<u>C</u>H), 53.7 (<u>C</u>H), 126.7 (tert. <u>C</u>), 127.0 (tert. <u>C</u>), 127.5 (tert. <u>C</u>), 131.5 (quat. <u>C</u>), 133.2 (tert. <u>C</u>), 146.4 (quat. <u>C</u>), 197.9 (<u>C</u>=O); MS, m/z, (RI) 244 (M+1, 100), 100 (10).

4-[Cyclohexyl(methyl)amino]-1,2,3,4-tetrahydro-1-naphthalenone (9a)

To a solution of **5** (50 mg, 0.20 mmol) in acetone (10 mL) was added methyl iodide (0.06 ml, 0.96 mmol) and anhydrous potassium carbonate (0.15 g, 1.1 mmol). The reaction was stirred at room temperature for 24 hours, and filtered. The solvent was removed *in vacuo*, and the residue purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield the amine as a pale oil (46 mg, 88%); IR (CCl_4) ν_{max} 2933, 2856, 1692, 1598, 1452, 1284; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_{ppm} = 1.16-1.51 (m, 5H, 5H of 5 x C<u>H</u>$_2$), 1.62-1.65 (m, 1H, 1H of 5 x C<u>H</u>$_2$), 1.78-1.97 (m, 4H, 4H of 5 x C<u>H</u>$_2$), 2.14-2.24 (m, 5H, C<u>H</u>$_2$CH$_2$CO and C<u>H</u>$_3$, a singlet at 2.21), 2.53-2.62 (m, 2H, C<u>H</u>$_2$), 2.89 (2 x dd, 1H, J_1=5.5Hz, J_2=4.5Hz, $CH_2C\underline{H}CH_2$), 4.16 (dd, 1H, J_1=8.9Hz, J_2=6.5Hz, NC<u>H</u>Ar), 7.35 (dd, 1H, J_1=8.5Hz, J_2=7.5Hz, Ar-<u>H</u>), 7.55 (ddd, 1H, J_1=8.4Hz, J_2=7.5Hz, J_3=1.5Hz, Ar-<u>H</u>), 7.80 (d, 1H, *J*=7.6Hz, Ar-<u>H</u>), 8.03 (d, 1H, *J*=7.4Hz, Ar-<u>H</u>); ^{13}C NMR ($CDCl_3$, 100MHz) δ_{ppm} = 24.9 (<u>C</u>H$_2$), 2 x 25.3 (2 x <u>C</u>H$_2$), 25.8 (<u>C</u>H$_2$), 30.4 (<u>C</u>H$_2$), 30.9 (<u>C</u>H$_2$), 32.6 (<u>C</u>H$_3$), 37.1 (<u>C</u>H$_2$CO), 58.4 (<u>C</u>H), 59.9 (<u>C</u>H), 126.5 (tert. <u>C</u>), 126.7 (tert. <u>C</u>), 127.4 (tert. <u>C</u>), 2 x 132.5 (2 x quat. <u>C</u>), 132.9 (tert. <u>C</u>), 197.7 (<u>C</u>=O); MS, m/z, (RI) 258 (M+1), 257 (M^+, 100), 214 (71), 144 (10), 114 (50); HRMS $(M+H)^+$ 258.1864, $C_{17}H_{24}NO$ requires 258.1858.

4-[Benzyl(cyclohexyl)amino]-1,2,3,4-tetrahydro-1-naphthalenone (9b)

To a solution of **5** (50 mg, 0.20 mmol) in acetone (10 mL) was added benzyl bromide (0.12 mL, 1 mmol) and anhydrous potassium carbonate (0.15 g, 1.1 mmol). The reaction was stirred at reflux for 5 days, and filtered. The solvent was removed *in vacuo*, and the residue purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield the amine as a pale oil (24 mg, 36%): IR (CCl_4) ν_{max} 2932, 2855, 1691, 1599, 1495, 1452, 1284, 1101; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_{ppm} = 1.06-1.45 (m, 4H, 4H of C<u>H</u>$_2$), 1.51-1.63 (m, 2H, 2H of C<u>H</u>$_2$), 1.79-1.82 (m, 2H, 2H of C<u>H</u>$_2$), 1.95-2.04 (m, 2H, 2H of C<u>H</u>$_2$), 2.11-2.20 (m, 1H, 1H of C<u>H</u>$_2$), 2.40-2.61 (m, 3H, 3H of C<u>H</u>$_2$), 2.84-2.89 (m, 1H, C<u>H</u>), 3.82 and 3.90 (2 x d, 2H, *J*=14.2Hz, NC<u>H</u>$_2$), 4.14-4.17 (m, 1H, NC<u>H</u>Ar), 7.24 (dd, 1H, J_1=8.3Hz, J_2=7.5Hz, Ar-<u>H</u>), 7.28-7.61 (m, 6H, 6 x Ar-<u>H</u>), 8.02-8.06 (m, 2H, 2 x Ar-<u>H</u>); ^{13}C NMR ($CDCl_3$, 100MHz) δ_{ppm} = 25.7 (<u>C</u>H$_2$), 25.8 (<u>C</u>H$_2$), 26.1 (<u>C</u>H$_2$), 26.5 (<u>C</u>H$_2$), 30.6 (<u>C</u>H$_2$), 32.7 (<u>C</u>H$_2$), 38.1 (<u>C</u>H$_2$CO), 49.8 (N<u>C</u>H$_2$), 56.5 (<u>C</u>H), 57.2 (<u>C</u>H), 126.3 (tert. <u>C</u>), 126.4 (tert. <u>C</u>), 126.7 (tert. <u>C</u>), 127.1 (tert. <u>C</u>), 2 x 127.8 (2 x tert. <u>C</u>), 2 x 127.9 (2 x tert. <u>C</u>), 132.8 (quat. <u>C</u>), 133.0 (tert. <u>C</u>), 140.6 (quat. <u>C</u>), 147.0 (quat. <u>C</u>), 197.2 (<u>C</u>=O); MS, m/z, (RI) 334 (M+1), 333 (M^+, 63), 290 (38), 242 (45), 190 (100), 146 (33); HRMS $(M+H)^+$ 334.2184, $C_{23}H_{28}NO$ requires 334.2171.

9-(Cyclopentyl-methyl-amino)-6,7,8,9-tetrahydro-benzocyclohepten-5-one (10)

To a solution of **8** (1 g, 4.12 mmol) in acetone (10 mL) was added methyl iodide (2.92 g, 20.6 mmol) and anhydrous potassium carbonate (2 g, 14.5 mmol). The reaction was stirred at room temperature for 24 hours, and filtered. The solvent was removed *in vacuo*, and the residue purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield the amine as a pale oil (0.92 g, 87%); IR (CCl_4) ν_{max} 2957, 2869, 2790, 1687, 1451, 1279, 1246; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_{ppm} = 1.35-1.53 (m, 4H, 4H of $(CH_2)_4$), 1.53-1.69 (m, 4H, 4H of $(CH_2)_4$), 1.69-2.02 (m, 4H, C$\underline{H}_2$C$\underline{H}_2$CH$_2$CO), 2.05 (s, 3H, C$\underline{H}_3$), 2.50-2.52 and 2.75-2.90 (2 x m, 2H, C$\underline{H}_2$CO), 3.00-3.10 (m, 1H, CH$_2$C$\underline{H}$CH$_2$), 3.75 (dd, 1H, J_1=6.5Hz, J_2=3.5Hz, NC$\underline{H}$Ar), 7.28 (dd, 1H, J_1=8.5Hz, J_2=7.5Hz, Ar-$\underline{H}$), 7.39 (dd, 1H, J_1=8.5Hz, J_2=7.5Hz, Ar-$\underline{H}$), 7.48-7.53 (m, 2H, 2 x Ar-$\underline{H}$); ^{13}C NMR ($CDCl_3$, 100MHz) δ_{ppm} = 20.3 (CH$_2$C$\underline{H}_2$CH$_2$CO), 24.1 (C$\underline{H}_2$), 24.2 (C$\underline{H}_2$), 26.2 (C$\underline{H}_2$), 26.7 (C$\underline{H}_2$CH$_2$CH$_2$CO), 27.9 (C$\underline{H}_2$), 33.3 (C$\underline{H}_3$), 40.5 (C$\underline{H}_2$CO), 61.3 (CH$_2$C$\underline{H}$CH$_2$), 65.2 (NC$\underline{H}$Ar), 127.0, 127.7 (x2C), 130.7 (4 x tert. C$\underline{}$), 139.4 (quat. C$\underline{}$), 143.0 (quat. C$\underline{}$), 205.9 (C$\underline{}$=O); MS, m/z, (RI) 258 (M+1, 100), 257 (M^+, 48), 200 (28); HRMS $(M+H)^+$ 258.1873, $C_{17}H_{24}NO$ requires 258.1858.

***tert*-Butyl *N*-(4-oxo-1,2,3,4-tetrahydro-1-naphthalenyl) carbamate (14)**

To a solution of azide **12** [10] (3.19 g, 17.1 mmol) in 10 mL of a mixture of EtOH/EtOAc (1:1) was added di-*tert*-butyl dicarbonate (3.74 g, 17.1 mmol) and a catalytic quantity of 10% Pd/C. The reaction was stirred overnight under an atmosphere of hydrogen. On completion, the reaction was filtered to remove the catalyst, and the solvent removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 5:1) to yield the carbamate as a white crystalline solid: IR (KBr) ν_{max} 2974, 1684, 1508, 1166; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_{ppm} = 1.45 (s, 9H, (C$\underline{H}_3$)$_3$), 2.05-2.31 (m, 2H, C$\underline{H}_2$), 2.55 and 2.59 (2 x dd, 1H, J_1=10.5Hz, J_2=4.6Hz, 1H of C$\underline{H}_2$CO), 2.72 and 2.76 (2 x dd, 1H, J_1=6.5Hz, J_2=4.5Hz, 1H of C$\underline{H}_2$CO), 4.95 (br. s, 1H, C$\underline{H}$), 5.19 (br. s, 1H, N$\underline{H}$), 7.31 (dd, 1H, J_1=8.5Hz, J_2=7.5Hz, Ar-$\underline{H}$), 7.39 (d, 1H, J=7.4Hz, Ar-H), 7.49 (dd, 1H, J_1=8.5Hz, J_2=7.4Hz, Ar-$\underline{H}$), 7.92 (d, 1H, J=7.5Hz, COAr-$\underline{H}$); ^{13}C NMR ($CDCl_3$, 100MHz) δ_{ppm} = 27.9 (3C, 3 x C$\underline{H}_3$), 29.8 (C$\underline{H}_2$CHNH), 35.9 (CO$\underline{C}$H$_2$), 48.4 (C$\underline{H}$NH), 79.3 (C$\underline{(CH_3)_3}$), 126.6, 126.7, 127.4, 133.4 (4 x tert. C$\underline{}$), 131.3, 143.6 (2 x quat. C$\underline{}$), 155.2 (O$\underline{C}$O), 196.4 (Ar-C$\underline{}$O); MS, m/z, (RI) 206 (100), 162 (71), 144, (93), 115 (30).

4-(2-Cyclohexenylamino)-1,2,3,4-tetrahydro-1-naphthalenone (18)

To a solution of **15** (3.84 g, 14.7 mmol) in DCM (5 mL) at 0^{o}C was added 5 mL of trifluoroacetic acid (TFA). Deprotection afforded amine **16**. To a stirred solution of the amine in DCM (10 mL) was added triethylamine (4.1 mL, 29.4 mmol) and 3-bromocyclohexene (3.4 mL, 29.4 mmol). The reaction was stirred overnight at room temperature, and the solvent removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 2:1) to yield the secondary amine, a stereoisomeric mixture, as a brown oil (2.11g, 60%): IR (KBr) ν_{max} 2936, 2863, 1690, 1601, 1450; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_{ppm} = 1.16 (br., 1H, N$\underline{H}$), 1.47-1.66 (m, 2H, 2H of C$\underline{H}_2$), 1.73-1.84 (m, 1H, 1H of C$\underline{H}_2$), 1.89-1.98 (m, 1H, 1H of C$\underline{H}_2$), 1.99-2.06 (m, 2H, CH=CHC$\underline{H}_2$), 2.07-2.19 and 2.33-2.28 (2 x m, 2H, C$\underline{H}_2$CH$_2$CO), 2.51-2.59 and 3.02-3.12 (2 x m, 2H, C$\underline{H}_2$CO), 3.30-3.39 (m, 1H, C$\underline{H}$CH=CH), 4.08-4.13 (m, 1H, C$\underline{H}$CH$_2$CH$_2$CO), 5.67-5.82 (m, 2H, C$\underline{H}$=C$\underline{H}$), 7.35-7.39 (m, 1H, Ar-C$_5$$\underline{H}$), 7.46-7.56 (m, 2H, 2 x Ar-$\underline{H}$), 8.02-8.04 (m, 1H, Ar-C$_8$$\underline{H}$); ^{13}C NMR ($CDCl_3$, 100MHz) δ_{ppm} = 19.2 and 19.8 (C$\underline{H}_2$), 2 x 24.9 (C$\underline{H}_2$), 28.0 and 28.4 (C$\underline{H}_2$), 29.0 and 30.3 (C$\underline{H}_2$), 34.1 and 34.3 (C$\underline{H}_2$CO), 49.8 and 50.3 (C$\underline{H}$), 52.0 and 52.3 (C$\underline{H}$), 126.7 and 126.8 (tert. C$\underline{}$), 127.1 and 127.2 (tert. C$\underline{}$), 2 x 127.6 (tert. C$\underline{}$), 128.6 and 128.8 (tert. C$\underline{}$), 129.1 and 129.7 (tert. C$\underline{}$), 2 x 131.6 (quat. C$\underline{}$), 2 x 133.1 (tert. C$\underline{}$), 145.8 and 146.0 (quat. C$\underline{}$), 2 x 197.8 (C$\underline{}$=O); MS, m/z, (RI) 242 (M+1, 100), 98 (15).

General procedure for the preparation of tertiary amines (**20a–f**)

Amines **20a–f** were prepared by adding equimolar quantities of appropriate alkyl halide and anhydrous potassium carbonate to an acetone solution (10 mL) of **18**. The reaction was stirred at room temperature for 1-7 days, and filtered. The solvent was removed *in vacuo*, and the residue purified by flash column chromatography on silica gel (eluant: pet ether:ethyl acetate, 10:1) to yield amines **20a–f**, as oils, which were routinely converted to their hydrochloride salts.

4-[2-Cyclohexenyl(methyl)amino]-1,2,3,4-tetrahydro-1-naphthalenone (20a)

Yield: 72%; IR (CCl_4) ν_{max} 2933, 1689, 1598, 1452, 1329, 1284, 1041; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_{ppm} = 1.50-1.78 (m, 2H, CH$_2$C$\underline{H}_2$CH$_2$), 1.81-1.89 (m, 2H, CH$_2$CH$_2$C$\underline{H}_2$CHN), 1.95-2.04 (m, 2H, COCH$_2$C$\underline{H}_2$), 2.19-2.25 (m, 5H, C=CC$\underline{H}_2$ and C$\underline{H}_3$), 2.52-2.61 (m, 1H, COC$\underline{H}_2$), 2.87 and 2.91 (2 x dd, 1H, J_1=5.5, J_2=5Hz, COC$\underline{H}_2$), 3.30 and 3.46 (2 x br., 1H, NC$\underline{H}$C=C), 4.05-4.12 (m, 1H, C$\underline{H}$CH$_2$CH$_2$CO), 5.71-5.73 (m, 1H, C$\underline{H}$=CH), 5.81-5.84 (m, 1H, CH=C$\underline{H}$), 7.33-7.36 (m, 1H, Ar-$\underline{H}$), 7.52-7.56 (m, 1H, Ar-$\underline{H}$), 7.74-7.78 (m, 1H, Ar-$\underline{H}$), 8.00-8.03 (m, 1H, Ar-$\underline{H}$); ^{13}C NMR ($CDCl_3$, 100MHz) δ_{ppm} = 21.0 and 21.1, 24.7 and 24.8, 25.5 and 25.8, 25.9 and 26.2 (4 x C$\underline{H}_2$), 32.0 and 33.0 (C$\underline{H}_3$), 36.7 and 36.8 (C$\underline{H}_2$CO), 56.9 and 57.1 (C$\underline{H}$), 58.4 and 59.7 (C$\underline{H}$), 126.60 and 126.62 (tert. C$\underline{}$), 2 x 126.7 (tert. C$\underline{}$), 127.3 and 127.6 (tert. C$\underline{}$), 129.5 and 129.7 (tert. C$\underline{}$), 130.1 and 130.7 (tert. C$\underline{}$), 132.80 and 132.83 (tert. C$\underline{}$), 2 x 132.4 (quat. C$\underline{}$), 146.3 and 146.4 (quat. C$\underline{}$), 2 x 197.6 (C$\underline{}$=O); MS, m/z, (RI) 256 (M+1, 8), 255 (M^+, 8), 227 (100), 112 (17), 68 (23); HRMS $(M+H)^+$ 256.1692, $C_{17}H_{22}NO$ requires 256.1701.

4-[Allyl(2-cyclohexenyl)amino]-1,2,3,4-tetrahydro-1-naphthalenone (20b)

Yield: 66%; IR (CCl_4) ν_{max} 2933, 2863, 1691, 1598, 1452, 1286; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_{ppm} = 1.48-1.67 (m, 2H of C$\underline{H}_2$C$\underline{H}_2$C$\underline{H}_2$), 1.74-2.06 (m, 4H of C$\underline{H}_2$C$\underline{H}_2$C$\underline{H}_2$), 2.07-2.19 (m, 1H of CH$_2$C$\underline{H}_2$CO), 2.26- 2.41 (m, 1H of C$\underline{H}_2$CH$_2$CO), 2.51-2.62 (m, 1H of C$\underline{H}_2$CO), 2.82-2.89 (m, 1H of C$\underline{H}_2$CO), 3.27-3.54 (m, 3H, NC$\underline{H}_2$ and NC$\underline{H}$C=C), 4.21-4.25 (m, 1H, C$\underline{H}$CH$_2$CH$_2$CO), 5.06-5.09 (m, 1H, 1H of CH=C$\underline{H}_2$), 5.17-5.24 (m, 1H, 1H of CH=C$\underline{H}_2$), 5.68-5.92 (m,

3H, CH=CH and CH=CH_2), 7.32-7.36 (m, 1H, Ar-H), 7.55-7.59 (m, 1H, Ar-H), 7.92-7.96 (m, 1H, Ar-H), 8.02-8.04 (m, 1H, Ar-H); ^{13}C NMR ($CDCl_3$, 100MHz) δ_{ppm} = 21.5 and 21.8, 24.6 and 24.7, 26.2 and 26.4, 27.9 and 29.1, 2 x 38.1 (5 x CH_2), 48.8 and 49.0 (CH_2CO), 53.7 and 54.2 (CH), 56.4 and 57.5 (CH), 115.5 and 115.8 (CH_2=C), 126.39 and 126.42, 126.72 and 126.78, 126.95 and 127.06, 129.8 and 130.0, 129.9 and 132.1, 133.0 and 133.1, 137.8 and 138.0 (7 x tert. C), 2 x 132.7 (quat. C), 2 x 147.4 (quat. C), 2 x 197.3 (C=O); MS, m/z, (RI) 282 (M+1, 34), 281 (M^+, 34), 253 (83), 225 (37), 138 (100); HRMS $(M+H)^+$ 282.1877, $C_{19}H_{24}NO$ requires 282.1858.

4-[Benzyl(2-cyclohexenyl)amino]-1,2,3,4-tetrahydro-1-naphthalenone (20c)

Yield: 63%; IR (CCl_4) ν_{max} 2934, 1691, 1598, 1453, 1285; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_{ppm} = 1.48-1.59 (m, 1H, 1H of $CH_2CH_2CH_2$), 1.64-1.86 (m, 2H, 2H of $CH_2CH_2CH_2$), 1.91-2.09 (m, 3H, 3H of $CH_2CH_2CH_2$), 2.07-2.23 (m, 1H, 1H of CH_2CH_2CO), 2.41-2.58 (m, 2H; 1H of CH_2 and 1H of CH_2CO), 2.84-2.90 (m, 1H, 1H of CH_2CO), 3.34-3.36 and 3.45-3.49 (2 x br. m, 1H, NCHC=C), 3.81-3.95 (m, 2H, NCH_2), 4.12 and 4.19 (2 x dd, 1H, J_1=11Hz, J_2=3.5Hz, $CHCH_2CH_2CO$), 5.80-5.89 (m, 2H, CH=CH), 7.23-7.28 (m, 1H, Ar-H), 7.31-7.36 (m, 3H, 3 x Ar-H), 7.42-7.48 (m, 2H, 2 x Ar-H), 7.57-7.63 (m, 1H, Ar-H), 8.01-8.05 (m, 2H, 2 x Ar-H); ^{13}C NMR ($CDCl_3$, 100MHz) δ_{ppm} = 21.5 and 21.9, 2 x 24.6, 25.3 and 26.3, 27.2 and 29.5 (4 x CH_2), 38.0 and 38.1 (CH_2CO), 49.7 and 49.9 (NCH_2), 53.2 and 53.5 (CH), 56.6 and 57.7 (CH), 2 x 126.4, 2 x 126.5, 126.78 and 126.84, 2 x 127.0, (4 x tert. C), 127.8-128.0 (4 x tert. C, signal overlap), 129.7 and 130.3, 130.2 and 132.1 (2 x tert. C), 132.7 and 132.8 (quat. C), 133.0 and 133.1 (tert. C), 2 x 140.7, 2 x 146.6 (2 x quat. C), 197.18 and 197.23 (C=O); MS, m/z, (RI) 303 (100), 212 (19), 188 (42), 158 (19), 144 (15); HRMS $(M+H)^+$ 332.2007, $C_{23}H_{26}NO$ requires 332.2014.

4-[2-Cyclohexenyl(4-methylbenzyl)amino]-1,2,3,4-tetrahydro-1-naphthalenone (20d)

Yield: 18%; IR (CCl_4) ν_{max} 2934, 1691, 1598, 1514, 1453, 1330, 1284, 1150, 1022; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_{ppm} = 1.47-1.62 (m, 1H, 1H of CH_2), 1.66-2.23 (m, 6H, 6H of CH_2), 2.36 x 2 (2 x s, 3H, CH_3), 2.44-2.57 (m, 2H, 2H of CH_2), 2.87-2.91 (m, 1H, 1H of $COCH_2$), 3.36 and 3.49 (2 x br., 1H, NCHC=C), 3.79-3.93 (m, 2H, NCH_2), 4.14 and 4.20 (2 x dd, 1H, J_1=11Hz, J_2=3Hz, $CHCH_2CH_2CO$), 5.83-5.90 (m, 2H, CH=CH), 7.16-7.18 (m, 2H, 2 x Ar-H), 7.33-7.39 (m, 3H, 3 x Ar-H), 7.59-7.64 (m, 1H, Ar-H), 8.04-8.09 (m, 2H, Ar-H); ^{13}C NMR ($CDCl_3$, 100MHz) δ_{ppm} = 2 x 20.6 (CH_3), 21.5 and 22.0, 2 x 24.7, 25.3 and 26.3, 27.3 and 29.5 (4 x CH_2), 38.1 and 38.2 ($COCH_2$), 49.4 and 49.6 (NCH_2), 53.1 and 53.4, 56.5 and 57.6 (2 x CH), 126.42 and 126.44, 126.77 and 126.84, 2 x 127.1, 2 x 127.8, 2 x 128.0, 128.6 (2C) (7 x tert. C, signal overlap), 129.9 and 130.1, 130.2 and 132.3, 133.0 and 133.2 (3 x tert. C), 132.7 and 132.8, 2 x 135.9, 136.9 and 137.6, 146.7 and 147.1 (4 x quat. C), 197.1 and 197.2 (C=O); MS, m/z, (RI) 346 (M+1, 5), 317 (100), 202 (44), 105 (26); HRMS $(M+H)^+$ 346.2146, $C_{24}H_{28}NO$ requires 346.2171.

4-(2-Cyclohexenyl-3,4,5-trimethoxyanilino)-1,2,3,4-tetrahydro-1-naphthalenone (20e)

Yield: 14%; IR (CCl_4) ν_{max} 2935, 1693, 1591, 1505, 1464, 1419, 1329, 1236, 1132, 1011; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_{ppm} = 1.45-1.58 (m, 1H, 1H of CH_2), 1.61-1.73 (m, 1H, 1H of CH_2), 1.75-1.85 (m, 1H, 1H of CH_2), 1.89-2.06 (m, 3H, 3H of CH_2), 2.08-2.21 (m, 1H, 1H of CH_2), 2.38-2.53 (m, 2H, 2H of CH_2), 2.82-2.90 (m, 1H, 1H of CH_2), 3.35 and 3.49 (2 x br., 1H, NCHC=C), 3.73-3.93 (m, 11H, 3 x OCH_3 and NCH_2, with 3 x OCH_3 at 3.82, 3.84 and 3.85), 4.09-4.19 (m, 1H, $CHCH_2CH_2CO$), 5.77-5.88 (m, 2H, CH=CH), 6.65 (s, 1H, $(CH_3O)_3$Ar-H), 6.70 (s, 1H, $(CH_3O)_3$Ar-H), 7.28-7.34 (m, 1H, Ar-H), 7.54-7.59 (m, 1H, Ar-H), 7.97-8.05 (m, 2H, 2 x Ar-H); ^{13}C NMR ($CDCl_3$, 100MHz) δ_{ppm} = 21.4 and 21.9 (CH_2), 2 x 24.6 (CH_2), 25.4 and 26.3 (CH_2), 27.2 and 29.4 (CH_2), 37.90 and 37.95 (CH_2CO), 50.00 and 50.05 (NCH_2), 53.3 and 53.6 (CH), 55.6 and 60.3 (3 x OCH_3, signal overlap), 56.8 and 57.8 (CH), 2 x 104.3, 2 x 104.5 (2 x $(CH_3O)_3$-ArCH), 2 x 126.6, 126.7 and 126.88, 2 x 126.90, 129.6 and 130.2, 130.5 and 131.8, 132.86 and 132.90 (6 x tert. C), 2 x 132.79, 2 x 135.9, 136.3 and 136.5, 146.4 and 146.6, 2 x 152.68, 2 x 152.72 (6 x quat. C), 196.95 and 197.04 (C=O); MS, m/z, (RI) 422 (M+1, 1), 421 (M^+,1), 240 (75), 181 (100), 117 (8); HRMS $(M+H)^+$ 422.2329, $C_{26}H_{32}NO_4$ requires 422.2331.

4-[2-Cyclohexenyl(2-naphthylmethyl)amino]-1,2,3,4-tetrahydro-1-naphthalenone (20f)

Yield: 43%; IR (CCl_4) ν_{max} 2935, 1692, 1598, 1285; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_{ppm} = 1.46-2.27 (m, 7H, 7H of CH_2), 2.46-2.62 (m, 2H, CH_2), 2.83-2.93 (m, 1H, 1H of CH_2), 3.40 and 3.51 (2 x br., 1H, CH), 3.98-4.10 (m, 2H, NCH_2), 4.16 and 4.23 (2 x br.d, 1H, J=11Hz, CH), 5.85-5.94 (br., 2H, CH=CH), 7.31-7.37 (m, 1H, Ar-H), 7.42-7.51 (m, 2H, 2 x Ar-H), 7.59-7.69 (m, 2H, 2 x Ar-H), 7.78-7.87 (m, 4H, 4 x Ar-H), 8.00-8.04 (m, 1H, Ar-H), 8.07 and 8.10 (2 x d, 1H, J=8Hz, Ar-H); ^{13}C NMR ($CDCl_3$, 100MHz) δ_{ppm} = 21.5 and 21.9, 2 x 24.6, 25.3 and 26.4, 27.2 and 29.5 (4 x CH_2), 38.05 and 38.15 (CH_2CO), 50.0 and 50.1 (NCH_2), 53.2 and 53.6, 56.6 and 57.6 (2 x CH), 2 x 125.0, 2 x 125.5, 126.2 and 126.3, 126.4 and 126.5, 126.5 and 126.6, 126.8 and 126.9, 2 x 127.0, 2 x 127.1, 2 x 127.2, 2 x 127.6, 129.7 and 130.3, 130.4 and 132.1, 133.0 and 133.2 (13 x tert. C), 132.3 and 132.7, 132.8 and 132.9, 2 x 137.5, 2 x 138.1, 146.5 and 146.8 (5 x quat. C), 2 x 197.1 (C=O); MS, m/z, (RI) 382 (M+1, 2), 381 (M^+, 2), 353 (83), 240 (72), 208 (43), 141 (100), 115 (69); HRMS $(M+H)^+$ 382.2156, $C_{27}H_{27}NO$ requires 382.2171.

9-(Cyclohex-2-enylamino)-6,7,8,9-tetrahydro-benzocyclohepten-5-one (19)

To a solution of **17** (2.4 g, 13.7 mmol) in DCM (10 mL) was added 3-bromocyclohexene (1.57 mL, 13.7 mmol), and, dropwise, triethylamine (3.83 mL, 27.4 mmol). The reaction was stirred at reflux for twelve hours. The reaction mixture was then partitioned between 2M HCl (25 mL) and diethyl ether (3 x 20 mL), and the organic layers discarded. The aqueous layer was basified with 2M NaOH and extracted with diethyl ether (3 x 20 mL). The re-basified organic extract was columned on silica gel (eluant: pet ether:ethyl

acetate, 5:1) to yield the amine, a mixture of isomers, as a pale yellow oil (2.17g, 62%): IR (CCl_4) ν_{max} 2933, 2862, 1685, 1601, 1449, 1244, 1103; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_{ppm} = 1.01 (br., 1H, NH), 1.15-1.42 (m, 2H, 2H of CH_2), 1.50-1.58 (m, 1H, 1H of CH_2), 1.60-1.74 (m, 4H, 4H of CH_2), 1.80-1.89 (m, 2H, 2H of CH_2), 1.93-2.02 (m, 1H, 1H of CH_2), 2.45 and 2.49 (2 x d, 1H, *J*~4.5Hz, 1H of CH_2CO), 2.70-2.78 (br. m, 1H, NCHC=C), 2.85 and 2.90 (2 x d, 1H, *J*~9.1Hz, 1H of CH_2CO), 4.15-4.19 (m, 1H, NCHAr), 5.46-5.72 (m, 2H, CH=CH), 7.24-7.43 (m, 4H, 4 x Ar-H); ^{13}C NMR ($CDCl_3$, 100MHz) δ_{ppm} = 19.3 and 19.7 (CH_2), 19.8 and 19.9 (CH_2), 24.7 and 24.8 (CH_2), 27.8 and 29.6 (CH_2), 32.2 and 32.4 (CH_2), 40.5 and 40.6 (CH_2), 48.8 and 49.3 (CH), 56.3 and 56.9 (CH), 126.4 and 126.5 (tert. C), 2 x 127.1 (tert. C), 2 x 127.4 (tert. C), 128.0 and 128.2 (tert. C), 128.6 and 130.1 (tert. C), 130.69 and 130.72 (tert. C), 2 x 138.7 (quat. C), 141.1 and 141.5 (quat. C), 2 x 206.9 (C=O); MS, m/z, (RI) 256 (M+1, 100), 255 (M^+, 24); HRMS $(M+H)^+$ 256.1691, $C_{17}H_{22}NO$ requires 256.1701.

General procedures for the preparation of tertiary amines (**21a**–**n**)

Amines **21a**–**e** were prepared analogously to **20a-f**. For **21f-n**, to a stirred solution of **19** in acetonitrile (8 mL) was added appropriate alkyl halide (1.1 equiv.) and *N*,*N*-diisopropylethylamine (1.5 equiv.). The resulting mixture was heated to gentle reflux and kept under an atmosphere of nitrogen. After 1-12 days, the reaction solutions were quenched by the addition of 2M aq. HCl (20 mL) and the product was extracted with diethyl ether (3 x 25mL). The combined organic extracts were dried over magnesium sulphate, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (eluant: hexane:ethyl acetate). All homogenous fractions were collected and the solvent evaporated to afford a stereoisomeric mixture of the title compounds, as oils, which were routinely converted to their hydrochloride salts.

9-(Cyclohex-2-enyl-methyl-amino)-6,7,8,9-tetrahydro-benzocyclohepten-5-one (21a)

Yield: 79%; IR (CCl_4) ν_{max} 2934, 1686, 1450, 1278, 1245, 1008; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_{ppm} = 1.38-2.29 (m, 10H, 5 x CH_2), 1.97 and 2.23 (2 x s, 3H, CH_3), 2.50 and 2.54 (2 x dd, 1H, J_1~7.5Hz, J_2~3Hz, 1H of CH_2CO), 2.87-3.01 (m, 2H, 1H of CH_2CO and CH), 3.81-3.86 (m, 1H, CH), 5.38 and 5.56 (2 x d, 1H, *J*=10Hz, 1H of CH=CH), 5.70 and 5.79 (2 x m, 1H of CH=CH), 7.28-7.49 (m, 4H, 4 x Ar-H); ^{13}C NMR ($CDCl_3$, 100MHz) δ_{ppm} = 19.58 and 19.64, 20.0 and 21.1, 21.4 and 22.1, 24.6 and 24.7, 26.5 and 26.8 (5 x CH_2), 33.3 and 33.6 (CH_3), 39.7 and 39.8 (CH_2CO), 54.6 and 54.8 (CH), 63.9 and 64.3 (CH), 126.8 and 127.05, 127.07 and 127.12, 127.37 and 127.43, 128.6 and 128.8, 129.2 and 130.3, 130.4 and 130.8 (6 x tert. C), 139.0 and 139.2, 141.2 and 141.9 (2 x quat. C), 206.1 and 206.4 (C=O); MS, m/z, (RI) 270 (M+1, 37), 269 (M^+, 16), 241 (67), 213 (100); HRMS $(M+H)^+$ 270.1850, $C_{18}H_{24}NO$ requires 270.1858.

9-(Allyl-cyclohex-2-enyl-amino)-6,7,8,9-tetrahydro-benzocyclohepten-5-one (21b)

Yield: 30%; IR (CCl_4) ν_{max} 2934, 2865, 1686, 1458, 1280, 1242; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_{ppm} = 1.31-1.53 (m, 2H, 2H of CH_2), 1.69-2.14 (m, 8H, 4 x CH_2), 2.52-2.68 (m, 1H, 1H of CH_2CO), 2.80-2.96 (m, 1H, 1H of CH_2CO), 3.10-3.52 (m, 3H, NCH_2 and CHCH=CH), 4.11-4.16 (m, 1H, NCHAr), 4.95-5.15 (m, 2H, CH_2=CH), 5.54-5.63 (m, 1H, 1H of CH=CH), 5.71-5.80 (m, 1H, 1H of CH=CH), 5.79-5.98 (m, 1H, CH_2=CH), 7.27-7.34 (m, 1H, Ar-H), 7.40-7.46 (m, 1H, Ar-H), 7.51 and 7.69 (dd and d, 1H, J_{1dd}=7.5, J_{2dd}=1.5Hz, J_d=7.5Hz, COAr-H), 7.54-7.59 (m, 1H, Ar-H); ^{13}C NMR ($CDCl_3$, 100MHz) δ_{ppm} = 20.0 and 21.0 (CH_2), 21.5 and 21.6 (CH_2), 24.7 and 24.8 (CH_2), 25.1 and 25.5 (CH_2), 28.2 and 29.3 (CH_2), 40.1 and 40.2 (CH_2CO), 49.7 and 50.3 (CH_2N), 55.1 and 55.3 (CH), 60.3 and 61.3 (CH), 114.8 and 115.0 (CH_2=CH), 126.5 and 126.7, 127.2 and 127.4, 127.4 and 127.7, 129.2 and 129.8, 2 x 130.2, 130.6 and 130.7, 138.6 and 139.0 (7 x tert. C), 2 x 138.0, 142.6 and 143.8 (2 x quat. C), 205.5 and 206.3 (C=O); MS, m/z, (RI) 296 (M+1, 100), 295 (M^+, 18), 267 (22), 211 (24), 131 (19); HRMS $(M+H)^+$ 296.2006, $C_{20}H_{26}NO$ requires 296.2014.

9-(Benzyl-cyclohex-2-enyl-amino)-6,7,8,9-tetrahydro-benzocyclohepten-5-one (21c)

Yield: 25%; IR (CCl_4) ν_{max}.. 2933, 2864, 1686, 1599, 1495, 1453, 1280, 1124; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_{ppm} = 1.30-2.28 (m, 10H, 5 x CH_2), 2.52-2.68 (m, 1H, 1H of CH_2CO), 2.71-2.80 (m, 1H, 1H of CH_2CO), 3.35 and 3.42 (2 br., 1H, CHCH=CH), 3.76-4.02 (m, 2H, NCH_2), 4.17-4.24 (m, 1H, NCHAr), 5.69-5.87 (m, 2H, CH=CH), 7.22-7.28 (m, 1H, Ar-H), 7.32-7.38 (m, 3H, 3 x Ar-H), 7.44-7.63 (m, 4H, 4 x Ar-H), 7.86 and 7.96 (2 x d, 1H, *J*=7.5Hz, COAr-H); ^{13}C NMR ($CDCl_3$, 100MHz) δ_{ppm} = 20.0 and 20.3, 21.6 and 21.7, 24.7 and 24.8, 25.0 and 26.5, 29.1 and 29.9 (5 x CH_2), 40.2 and 40.3 (CH_2CO), 50.8 and 51.6 (NCH_2), 55.2 and 55.3, 60.9 and 61.5 (2 x CH), 126.06 and 126.11, 126.5 and 126.6, 127.2 and 127.3, 127.4 and 127.53, 127.53 and 127.66, 127.66 and 127.68, 127.8 (2C), 129.8 and 129.9, 2 x 130.2, 2 x 130.9 (11 x tert. C), 138.8 and 138.9, 141.1 and 141.8, 142.7 and 143.7 (3 x quat. C), 205.6 and 206.5 (C=O); MS, m/z, (RI) 346 (M+1, 100), 345 ($M^{+\cdot}$ 28), 317 (61), 289 (47), 266 (54), 246 (24), 186 (100), 158 (21); HRMS $(M+H)^+$ 346.2186, $C_{24}H_{28}NO$ requires 346.2171.

9-[Cyclohex-2-enyl-(2,3,4-trimethoxy-benzyl)-amino]-6,7,8,9-tetrahydro-benzocyclohepten-5-one (21d)

Yield: 54%; IR (DCM) ν_{max} 3396, 3063, 2938, 1683, 1600, 1466, 1287, 1101; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_{ppm} = 1.37-2.23 (4 x m, 10H, 5 x CH_2), 2.52-2.65 (m, 1H, 1H of CH_2CO), 2.68-2.75 (m, 1H, 1H of CH_2CO), 3.31 (br. m, 1H, NCHCH=CH), 3.68-3.86 (m, 2H, NCH_2), 3.87-3.89 (s overlapping, 9H, 3 x OCH_3), 4.13-4.18 (m, 1H, NCHAr), 5.65-5.80 (m, 2H, CH=CH), 6.72 (d, 1H, *J*=9.04Hz, Ar-H), 7.27 and 7.28 (1 x d, 1H, *J*=4.52Hz and 1 x d, *J*= 4.0Hz, Ar-H), 7.31-7.36 (m, 1H, Ar-H), 7.44-7.59 (m, 2H, 2 x Ar-H), 7.82 and 7.89 (2 x d, 1H, *J*=7.76Hz, COAr-H); ^{13}C NMR ($CDCl_3$, 100MHz) δ_{ppm} = 20.5 and 20.8 (CH_2), 22.1 and 22.2 (CH_2), 25.1 and 25.2 (CH_2), 25.4 and 27.1 (CH_2), 29.2 and 30.2 (CH_2), 40.6 and 40.7 (CH_2), 44.3 and 44.9 (CH_2), 55.3 and 55.4 (CH), 55.5, 60.3, 60.4 (3 x OCH_3), 60.7 and 61.1 (CH), 2 x 106.8 (tert. C), 123.3 and 123.5 (tert. C), 126.4 and 126.5 (tert. C), 126.6, 127.1, 127.2, 127.3 (1 x tert. C and 1 x quat. C), 127.4 and 127.5 (tert. C), 129.8, 129.9, 130.1, 130.3 (CH=CH), 2 x 131.3 (tert. C), 138.6 and 138.8 (quat. C), 2 x 141.4 (quat. C), 142.9 and 143.8 (quat. C), 150.8 and 151.1 (quat. C), 151.6 and 151.7 (quat. C), 206.1 and 206.9

(C=O); HRMS $(M+H)^+$ 436.2480, $C_{27}H_{34}NO_4$ requires 436.2488.

9-[Cyclohex-2-enyl-(3,4,5-trimethoxy-benzyl)-amino]-6, 7,8,9-tetrahydro-benzocyclohepten-5-one (21e)

Yield: 59%; IR (DCM) ν_{max} 3400, 3053, 2939, 1683, 1594, 1463, 1254, 1126; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_{ppm} = 1.40-2.16 (5 x m, 10H, 5 x CH_2), 2.53-2.58 (m, 1H, 1H of CH_2CO), 2.73-2.80 (m, 1H, 1H of CH_2CO), 3.30-3.36 (br. m, 1H, NCHCH=CH), 3.67-3.83 (m, 2H, NCH_2), 3.85 (s overlapping, 3H, OCH_3), 3.89 (s overlapping, 6H, 2 x OCH_3), 4.14-4.19 (m, 1H, NCHAr), 5.65-5.79 (m, 2H, CH=CH), 6.63 and 6.66 (2 x s, 2H, 2 x Ar-H), 7.32 and 7.34 (1 x d, 1H, *J*=7.52Hz, and 1 x d, *J*=7.56Hz, Ar-H), 7.45-7.55 (m, 2H, 2 x Ar-H), 7.77 (2 x d, 1H, *J*=7.78Hz, COAr-H); ^{13}C NMR ($CDCl_3$, 100MHz) δ_{ppm} = 20.4 and 20.6 (CH_2), 22.0 and 22.1 (CH_2), 25.1 and 25.2 (CH_2), 25.4 and 27.1 (CH_2), 29.2 and 29.9 (CH_2), 40.6 and 40.7 (CH_2), 51.7 and 52.4 (CH_2), 55.7 and 55.8 (CH), 3 x 56.0 (3 x OCH_3), 60.9 and 62.2 (CH), 2 x 103.8 (tert. C), 2 x 104.0 (tert. C), 2 x 126.8 (tert. C), 127.0 and 127.2 (tert. C), 127.4 and 127.6 (tert. C), 129.0, 130.0, 130.1 and 130.4 (CH=CH), 130.7 and 130.8 (tert. C), 2 x 135.8, 137.0 and 137.6, 138.8 and 140.0, 142.4 and 143.0 (4 x quat. C), 4 x 152.6 (2 x quat. C), 206.2 and 206.8 (C=O); HRMS $(M+Na)^+$ 458.2307, $C_{27}H_{33}NO_4Na$ requires 458.2322.

9-[Cyclohex-2-enyl-(4-trifluoromethoxy-benzyl)-amino]-6,7,8,9-tetrahydro-benzocyclohepten-5-one (21f)

Yield: 81%; IR (DCM) ν_{max} 3401, 3058, 2923, 1682, 1451, 1296, 1161; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_{ppm} = 1.39-2.18 (4 x m, 10H, 5 x CH_2), 2.55-2.63 (m, 1H, 1H of CH_2CO), 2.67-2.75 (m, 1H, 1H of CH_2CO), 3.35-3.41 (br. m, 1H, NCHCH=CH), 3.72-3.93 (m, 2H, NCH_2), 4.14-4.17 (m, 1H, NCHAr), 5.64-5.79 (m, 2H, 2H of CH=CH), 7.16 (2 x overlapping t, 2H, *J*=7.04Hz, 2 x Ar-H), 7.30 (dd, 1H, J_1=13.56Hz, J_2=6.52Hz, Ar-H), 7.38 (d, 1H, *J*=8.52Hz, Ar-H), 7.42-7.53 (m, 3H, 3 x Ar-H), 7.76 and 7.82 (2 x d, 1H, *J*=8.04Hz, COAr-H); ^{13}C NMR ($CDCl_3$, 100MHz) δ_{ppm} = 19.9 and 20.1 (CH_2), 21.4 and 21.5 (CH_2), 24.6 and 24.7 (CH_2), 24.8 and 26.1 (CH_2), 29.0 and 29.6 (CH_2), 40.2 and 40.3 (CH_2), 50.3 and 50.9 (CH_2), 55.3 and 55.4 (CH), 61.4 and 61.7 (CH), 116.2, 118.8, 121.3 and 123.9 (OCF_3, q, J_{CF}=252.3Hz), 4 x 120.3 (2 x tert. C), 126.7, 126.8, 127.0, 127.2, 127.3, 127.7, (3 x tert. C), 2 x 128.5 (tert. C), 2 x 128.7 (tert. C), 129.4, 129.8, 130.2, 130.5 (CH=CH) 2 x 130.9 (tert. C), 138.7 and 138.9 (quat. C), 139.9 and 140.7 (quat. C), 142.2 and 143.0 (quat. C), 2 x 147.3 (Ar-$COCF_3$), 205.8 and 206.6 (C=O); HRMS $(M+Na)^+$ 452.1813, $C_{25}H_{26}NO_2F_3$ requires 452.1813.

9-[Cyclohex-2-enyl-(3-trifluoromethoxy-benzyl)-amino]-6, 7,8,9-tetrahydro-benzocyclohepten-5-one (21g)

Yield: 73%; IR (DCM) ν_{max} 3063, 2925, 1688, 1450, 1261, 1216, 1164; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_{ppm} = 1.40-2.21 (4 x m, 10H, 5 x CH_2), 2.55-2.66 (m, 1H, 1H of CH_2CO), 2.69-2.77 (m, 1H, 1H of CH_2CO), 3.37-3.41 (br. m, 1H, NCHC=C), 3.75-3.98 (m, 2H, NCH_2), 4.15-4.19 (m, 1H, NCHAr), 5.65-5.82 (m, 2H, CH=CH), 7.07-7.09 (m, 1H, Ar-H), 7.27-7.39 (m, 4H, 4 x Ar-H), 7.48-7.56 (m, 2H, 2 x Ar-H), 7.79 and 7.85 (2 x d, 1H, *J*=7.76Hz, COAr-H); ^{13}C NMR ($CDCl_3$, 100MHz) δ_{ppm} = 20.3 and 20.6 (CH_2), 21.9 and 22.0 (CH_2), 25.1 and 25.2 (CH_2), 25.4 and 26.7 (CH_2), 29.7 and 30.3 (CH_2), 40.6 and 40.8 (CH_2), 50.9 and 51.5 (CH_2), 55.8 and 55.9 (CH), 61.7 and 61.9 (CH), 2 x 118.9 (tert. C), 116.7, 119.3, 121.2 and 124.3 (OCF_3, q, J_{CF}=255.6), 120.1 and 120.3 (tert. C), 126.1 and 126.2 (tert. C), 127.2, 127.3, 127.4, 127.6, 127.8, 128.1 (3 x tert. C), 2 x 129.5 (tert. C) 129.8, 130.2, 130.9, 131.1 (CH=CH) 131.4 and 131.5 (tert. C), 139.1 and 139.3 (quat. C), 142.3 and 143.4 (quat. C), 144.3 and 145.1 (quat. C), 149.3 (Ar-$COCF_3$), 206.3 and 207.1 (C=O); HRMS $(M+Na)^+$ 452.1813, $C_{25}H_{26}NO_2F_3$ requires 452.1813.

9-[Cyclohex-2-enyl-(2,3,6-trifluoro-benzyl)-amino]-6,7, 8,9-tetrahydro-benzocyclohepten-5-one (21h)

Yield: 70%; IR (DCM) ν_{max} 3400, 3058, 3019, 2930, 1684, 1496, 1246, 1033; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_{ppm} = 1.39-2.42 (3 x m, 10H, 5 x CH_2), 2.61-2.76 (m, 2H, CH_2CO), 3.27-3.47 (br. m, 1H, NCHCH=CH), 3.81-4.06 (2 x m, 3H, NCH_2 and NCHAr), 5.74-5.85 (m, 2H, CH=CH), 6.72-6.81 (m, 1H, Ar-H), 6.97-7.07 (m, 1H, Ar-H), 7.23-7.29 (m, 1H, Ar-H), 7.42 (t, 1H, *J*=7.34Hz, Ar-H), 7.52 (dd, 1H, J_1=2.51Hz, J_2=5.02Hz, Ar-H), 7.83 and 7.88 (2 x d, 1H, *J*=7.56Hz, COAr-H); ^{13}C NMR ($CDCl_3$, 100MHz) δ_{ppm} = 20.6 and 20.7 (CH_2), 22.0 and 22.2 (CH_2), 25.0 and 25.1 (CH_2), 25.4 and 27.1 (CH_2), 28.8 and 30.1 (CH_2), 2 x 39.1 (CH_2), 40.8 and 41.0 (CH_2), 55.7 and 55.9 (CH), 61.1 and 61.7 (CH), 110.2-110.6 (tert. C), 115.4-115.7 (tert. C), 117.8-118.0 (quat. C), 118.4-118.7 (quat. C), 126.7 and 126.2 (tert. C), 127.6 and 127.8 (tert. C), 2 x 128.4 (Ar-CHCCO), 129.6, 130.4, 130.6 (CH=CH), 2 x 130.9 (tert. C), 131.6 (CH=CH), 139.1 and 139.3 (quat. C), 143.7 and 144.1 (quat. C), 146.1 and 147.7 (2 x t, J_{CF}=161.9, CF), 148.6 and 150.2 (2 x m, J_{CF} ~160Hz, CF), 156.2 and 157.8 (d, J_{CF}= 161.9Hz, CF), 206.3 and 207.1 (C=O); HRMS $(M+H)^+$ 400.1877, $C_{25}H_{25}NOF_3$ requires 400.1697.

4-{[Cyclohex-2-enyl-(9-oxo-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-yl)-amino]-methyl}-benzoic acid methyl ester (21i)

Yield: 54%; IR (DCM) ν_{max} 3430, 3058, 3024, 2931, 1721, 1683, 1435, 1279; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_{ppm} = 1.34-2.11 (4 x m, 10H, 5 x CH_2), 2.46-2.58 (m, 1H, 1H of CH_2CO), 2.63-2.72 (m, 1H, 1H of CH_2CO), 3.31 (br. d, 1H, NCHCH=CH), 3.72-3.76 (m, 1H, NCHAr), 3.83-3.97 (s and m, signals overlapping, 4H, 3H of CH_3OCO- and 1H of NCH_2), 4.06-4.13 (m, 1H, 1H of NCH_2), 5.62-5.76 (m, 2H, CH=CH), 7.25-7.29 (m, 1H, Ar-H), 7.42-7.50 (m, 4H, 4 x Ar-H), 7.74 and 7.80 (2 x d, 1H, *J*=7.52Hz, Ar-H), 7.96 and 7.97 (2 x d, 2H, *J*=8.04Hz, 2 x Ar-H); ^{13}C NMR ($CDCl_3$, 100MHz) δ_{ppm} = 19.8 and 20.1 (CH_2), 21.4 and 21.5 (CH_2), 24.5, 24.6, 24.7, 26.4 (2 x CH_2), 29.1 and 29.7 (CH_2), 40.1 and 40.2 (CH_2), 2 x 50.8 (CH_2), 50.7 and 51.6 (CH_2), 51.5 (CH_3), 55.4 and 55.5 (CH), 61.5 and 61.8 (CH), 126.7 and 126.8 (tert. C), 126.9 and 127.1 (tert. C), 127.2, 2 x 127.3, 2 x 127.4, 127.6 (3 x tert. C), 2 x 128.0 (2 x quat. C), 4 x 129.1 (2 x tert. C), 129.1, 129.9, 2 x 130.3, 130.5 (CH=CH), 2 x 130.9 (tert. C), 138.7 and 138.8 (quat. C), 141.9 and 142.8 (quat. C), 146.9 and 147.7 (quat. C), 2 x 166.5 ($COOCH_3$),

205.7 and 206.6 (C=O); HRMS $(M+Na)^+$426.2053, $C_{26}H_{29}NO_3Na$ requires 426.2045.

4-{[Cyclohex-2-enyl-(9-oxo-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-yl)-amino]-methyl}-phenyl)-acetic acid methyl ester (21j)

Yield: 23%; IR (DCM) ν_{max} 3400, 3058, 3019, 2928, 1739, 1682, 1435, 1262; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_{ppm} = 1.28-2.22 (3 x m, 10H, 5 x CH_2), 2.56-2.60 (m, 1H, 1H of CH_2CO), 2.65-2.75 (m, 1H, 1H of CH_2CO), 3.35 (br. d, 1H, NCHCH=CH), 3.64 (2 x overlapping s, 2H, Ar-CH_2COO-), 3.71 (s, 3H, CH_3OCO-), 3.73-3.97 (m, 2H, NCH_2), 4.15-4.18 (m, 1H, NCHAr), 5.65-5.80 (m, 2H, CH=CH), 7.25 (2 x overlapping d, 2H, *J*=8.02Hz, 2 x Ar-H), 7.32 (t, 1H, *J*=7.52Hz, Ar-H), 7.39 and 7.41 (1 x d, *J*=8.00Hz and 1 x d *J*=9.56Hz, 2H, 2 x Ar-H), 7.48-7.63 (m, 2H, 2 x Ar-H), 7.84 and 7.94 (2 x d, 1H, *J*=8.02Hz, Ar-H); ^{13}C NMR ($CDCl_3$, 100MHz) δ_{ppm} = 20.4 and 20.7 (CH_2), 22.0 and 22.7 (CH_2), 25.1 and 25.2 (CH_2), 25.4 and 26.9 (CH_2), 29.6 and 30.4 (CH_2), 40.6 and 40.7 (CH_2), 2 x 40.8 (CH_2), 50.7 and 51.6 (CH_2), 52.1 (CH_3), 55.6 and 55.8 (CH), 61.0 and 61.6 (CH), 126.5 and 126.6 (tert. C), 2 x 127.1 (CH=CH), 2 x 127.3 (tert. C), 2 x 127.8 (CH=CH), 4 x 128.7 (2 x tert. C), 129.9 and 130.0 (tert. C), 130.2 and 130.3 (tert. C), 2 x 130.9 (tert. C), 131.6 and 131.7 (quat. C), 138.6 and 138.8 (quat. C), 139.9 and 140.8 (quat. C), 142.7 and 143.8 (quat. C), 2 x 171.8 ($COOCH_3$), 205.8 and 206.8 (C=O); HRMS $(M+Na)^+$440.2211, $C_{27}H_{31}NO_3Na$ requires 440.2202.

9-(Biphenyl-2-ylmethyl-cyclohex-2-enyl-amino)-6,7,8,9-tetrahydro-benzocyclohepten-5-one (21k)

Yield: 41%; IR (DCM) ν_{max} 3396, 3053, 2918, 1684, 1451, 1038; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_{ppm} = 1.26-1.95 (4 x m, 10H, 5 x CH_2), 2.44-2.65 (m, 2H, CH_2CO), 3.22 (br. m, 1H, NCHCH=CH), 3.62-3.69 (m, 1H, NCHAr), 3.83-3.98 (m, 2H, NCH_2), 5.48-5.73 (2H, m, CH=CH), 7.18 (d, 1H, *J*=7.32Hz, Ar-H), 7.27 (d overlapping signals, 4H, *J*=5.84Hz, 4 x Ar-H), 7.35-5.55 (m, 6H, 6 x Ar-H), 7.75 and 7.92 (2 x d, 1H, *J*=7.28Hz, Ar-H), 7.82 and 7.85 (2 x d overlapping, 1H, *J*=7.32Hz, *J*=8.04Hz, Ar-H); ^{13}C NMR ($CDCl_3$, 100MHz) δ_{ppm} = 20.3 and 20.6 (CH_2), 22.0 and 22.1 (CH_2), 2 x 25.1 (CH_2), 25.4 and 27.0 (CH_2), 29.1 and 30.1 (CH_2), 40.6 and 40.7 (CH_2), 47.7 and 48.3 (CH_2), 55.2 and 55.3 (CH), 60.6 and 60.9 (CH), 125.6 and 125.7 (tert. C), 126.4 and 126.5 (tert. C), 2 x 127.0 (tert. C), 2 x 127.2 (tert. C), 127.4, 127.5, 127.6, 128.6, 128.7, 8 x 128.9, 129.4, 129.5, 2 x 129.9, 130.1, 130.4, 130.9 (CH=CH and 9 x tert. C), 138.1 and 138.6 (quat. C), 138.8 and 138.9 (quat. C), 140.0 and 140.6 (quat. C), 140.9 and 141.0 (quat. C), 142.7 and 143.7 (quat. C), 206.0 and 206.9 (C=O); HRMS $(M+H)^+$ 422.2478, $C_{30}H_{32}NO$ requires 422.2484.

9-(Benzhydryl-cyclohex-2-enyl-amino)-6,7,8,9-tetrahydro-benzocyclohepten-5-one (21l)

Yield: 32%; IR (DCM) ν_{max} 3391, 3063, 3029, 2928, 1681, 1595, 1449, 1279; ^{1}H NMR ($CDCl_3$, 600 MHz) δ_{ppm} = 1.45-2.20 (5 x m, 10H, 5 x CH_2), 2.22-2.50 (m, 1H, 1H of CH_2CO), 2.54-2.66 (m, 1H, 1H of CH_2CO), 3.95 and 4.03 (2 x br. m, 1H, NCHCH=CH), 4.47-4.51 (m, 1H, $NCH(Ar)CH_2$), 5.41 and 5.50 (2 x s, 1H, NCH(Ar)Ar), 5.79-5.87 (m, 1H, CH=CH), 5.91-5.99 (m, 1H, CH=CH), 7.14-7.42 (m, 9H, 9 x Ar-H), 7.53 (t, 1H, *J*=7.70Hz, Ar-H), 7.57 (m, 1H, Ar-H), 7.63 (t, 1H, *J*=7.40Hz, Ar-H), 7.78, 7.84, 7.95 (3 x overlapping d, 2H, *J*=7.92Hz, *J*=7.14Hz, 2 x Ar-H); ^{13}C NMR ($CDCl_3$, 150Hz) δ_{ppm} = 20.1 and 20.3 (CH_2), 22.5 and 22.8 (CH_2), 25.0 and 25.1 (CH_2), 30.3 and 30.7 (CH_2), 32.1 and 32.2 (CH_2), 40.4 and 40.6 (CH_2), 55.5 and 55.7 (CH), 58.7 and 59.0 (CH), 65.7 and 65.9 (CH), 125.9, 2 x 126.3, 126.5, 126.7, 126.8, 127.0, 127.3, 127.4, 127.5, 127.7, 127.8, 127.9, 128.0, 2 x 128.1, 3 x 128.2, 128.3, 128.6, 128.9, 129.4, 130.1, 130.3, 130.4, 131.1, 131.4, 131.7, 132.4, 2 x 133.0 (CH=CH and 14 x tert. C), 138.1, 138.3, 143.5, 143.6, 144.0, 144.8, 144.9, 145.2 (4 x quat. C), 206.3 and 206.7 (C=O); HRMS $(M+Na)^+$ 444.2318, $C_{30}H_{31}NONa$ requires 444.32303.

9-[Cyclohex-2-enyl-(4-nitro-benzyl)-amino]-6,7,8,9-tetrahydro-benzocyclohepten-5-one (21m)

Yield: 64%; IR (DCM) ν_{max} 3406, 3063, 3015, 2929, 1683, 1599, 1518, 1344; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_{ppm} = 1.37-2.11 (2 x m, 10H, 5 x CH_2), 2.55-2.67 (m, 1H, 1H of CH_2CO), 2.68-2.71 (m, 1H, 1H of CH_2CO), 3.37-3.45 (br. m, 1H, NCHCH=CH), 3.81-3.97 (m, 2H, NCH_2), 4.14-4.17 (m, 1H, NCHAr), 5.64-5.82 (m, 2H, CH=CH), 7.25-7.31 (m, 1H, Ar-H), 7.41-7.50 (m, 3H, 3 x Ar-H), 7.53 (d, 1H, *J*=8.8Hz, Ar-H), 7.70 (d, 1H, *J*=7.76Hz, Ar-H), 8.08-8.15 (m, 2H, 2 x Ar-H); ^{13}C NMR ($CDCl_3$, 100MHz) δ_{ppm} = 20.2 and 20.4 (CH_2), 2 x 21.9 (CH_2), 2 x 25.1 (CH_2), 25.2 and 26.3 (CH_2), 29.6 and 30.0 (CH_2), 40.7 and 40.9 (CH_2), 51.5 and 51.9 (CH_2), 2 x 56.1 (CH), 62.7 and 62.9 (CH), 2 x 123.4 (tert. C), 2 x 123.5 (tert. C), 127.4 and 127.7 (tert. C), 2 x 127.5 (tert. C), 127.9 and 128.2 (tert. C), 2 x 128.3 (tert. C), 2 x 128.5 (tert. C), 129.3, 129.7, 130.5, 131.2 (CH=CH) 2 x 131.4 (tert. C), 139.2 and 139.5 (quat. C), 141.9 and 142.5 (quat. C), 146.6 and 146.7 (quat. C), 149.9 and 150.7 (quat. C), 206.4 and 207.1 (C=O); HRMS $(M+H)^+$ 391.2013, $C_{24}H_{27}N_2O_3$ requires 391.2314.

4-{[Cyclohex-2-enyl-(9-oxo-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-yl)-amino]-methyl}-benzonitrile (21n)

Yield: 85%; IR (DCM) ν_{max} 3428, 3067, 3024, 2929, 2226, 1683, 1606, 1449, 1100; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_{ppm} = 1.37-2.11 (3 x m, 10H, 5 x CH_2), 2.50-2.60 (m, 1H, 1H of CH_2CO), 2.65-2.75 (m, 1H, 1H of CH_2CO), 3.39 (br. m, 1H, NCHCH=CH), 3.75-3.93 (m, 2H, NCH_2), 4.11-4.14 (m, 1H, NCHAr), 5.62-5.80 (m, 2H, CH=CH), 7.28 (2 x overlapping t, 1H, *J*=8.00Hz, Ar-H), 7.39-7.49 (m, 4H, 4 x Ar-H), 7.54 and 7.58 (1 x d, *J*=8.04Hz and 1 x d, *J*=8.52Hz, 2H, 2 x Ar-H), 7.68 and 7.70 (2 x overlapping d, 1H, *J*=3.52Hz, COAr-H); ^{13}C NMR ($CDCl_3$, 100MHz) δ_{ppm} = 19.8 and 20.0 (CH_2), 21.4 and 21.5 (CH_2), 24.7 x 3, 25.9 (2 x CH_2), 29.1 and 29.5 (CH_2), 40.2 and 40.4 (CH_2), 51.2 and 51.6 (CH_2), 2 x 55.6 (CH), 62.2 and 62.3 (CH), 109.5 and 109.6 (quat. C), 118.7 (CN), 126.9, 2 x 127.0, 127.2, 127.3, 127.7 (3 x tert. C), 2 x 127.9 (tert. C), 2 x 128.0 (tert. C), 128.9, 129.3, 130.7, 130.8 (CH=CH), 130.9, 131.0 (tert. C), 2 x 131.5 (tert. C), 2 x 131.6 (tert. C), 138.7 and 139.0 (quat. C), 141.5 and 142.1 (quat. C), 147.2 and 148.0 (quat. C), 205.9 and 206.7 (C=O); HRMS $(M+Na)^+$ 393.1926, $C_{25}H_{26}N_2ONa$ requires 393.1943.

CONCLUSION

This paper presents the results of an assessment of the potential anti-allergic applications of a novel series of cyclohexenylamino derivatives of tetralone and benzosuberone. *In vitro* investigation of the mast cell-stabilising activity revealed that within series **20** and **21**, optimal activity appeared to reside in a tertiary amine bearing either parent bicyclic system, an unsaturated cyclohexene, and thirdly, a benzyl or substituted benzyl motif. It further appears that for *in vivo* activity the unsaturated alicyclic system on nitrogen is critical, both from results observed with **20e** and derivatives of **21**. This suggests that while ring expansion of the hydroaromatic core is permissible without loss of activity *in vivo*, there must be an unsaturated alicyclic component. We intend to expand on this premise in future studies.

ACKNOWLEDGMENTS

We acknowledge Enterprise Ireland (Research Innovation Fund IF/2001/014) for financial support.

ABBREVIATIONS

Con A = Concanavalin A

DSCG = Disodium cromoglycate

NBS = *N*-bromosuccinimide

RPMC = Rat peritoneal mast cell

REFERENCES

[1] Caughey, G.H. *Asthma and COPD: Basic Mechanisms and Clinical Management*, 2nd ed.; Elsevier Science & Technology Academic Press Inc., **2009**.

[2] Chester, A.H. Mast cells feel the strain. *Cardiovascular Res*., **2002**, *55*, 13-15.

[3] Ribatti, D.; Crivellato, E. The Controversial Role of Mast Cells in Tumor Growth. *Int. Rev. Cell Mol. Biol*., **2009**, *275*, 89-131.

[4] Leung, K.B.; Flint, K.C.; Brostoff, J.; Hudspith, B.N.; Johnson, N.M.; Lau, H.Y.; Liu, W.L.; Pearce, F.L. Effects of sodium cromoglycate and nedocromil sodium on histamine secretion from human lung mast cells. Thorax, **1988**, *43*, 756-761.

[5] Block, J.; Beale, J.M. *Wilson & Gisvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry*, 11th ed.; Lippincott Williams & Wilkins: **2003**.

[6] Yazid, S.; Solito, E.; Christian, H.; McArthur, S.; Goulding, N.; Flower, R. Cromoglycate drugs suppress eicosanoid generation in U937 cells by promoting the release of Anx-A1. *Biochem. Pharmacol*., **2009**, *77*, 1814-1826.

[7] Sheridan, H.; Frankish, N.; Farrell, R. Synthesis and antispasmodic activity of analogues of natural pterosins. *Eur. J. Med. Chem*., **1999**, *34*, 953-966.

[8] Walsh, J.; Frankish, N.; Sheridan, H.; Byrne, W. Indane compounds with smooth muscle relaxing and/or mast cell stabilizing and/or anti-inflammatory activity. U.S. Patent 6,297,399, October 2, **2001**.

[9] Liu, W.L.; Tainsh, K.R.; Towart, R.; Pearce, F.L. Inhibitory effect of the stereoisomers of dimethindene maleate (Fenistil®) on histamine release from rat peritoneal mast cells. *Inflamm. Res*. **1992**, *36*, Suppl. 2, C302-C304.

[10] Barlow, J.; Walsh, J. Synthesis and evaluation of 4-amino-3,4-dihydro-2*H*-naphthalen-1-one derivatives as mast cell stabilising and anti-inflammatory compounds. *Eur. J. Med. Chem*., **2008**, *43*, 2891-2900.

[11] Barlow, J.; Walsh, J. Synthesis and evaluation of dimeric 1,2,3,4-Tetrahydro-naphthalenylamine and Indan-1-ylamine derivatives with mast cell-stabilising and anti-allergic activity. *Eur. J. Med. Chem*., **2010**, *45*, 25-37.

[12] Kotkowska-Machnik, Z.; Zakrzewski, J. Reactions of some derivatives of dihydro- and tetrahydrobenzocycloheptenones. Part II. Synthesis of benzamido derivatives of 6,7,8,9-tetrahydro-(5H)-benzocycloheptene-5-one. *Pol. J. Chem*., **1979**, *53*, 2363-2366.

[13] Bruhn, J.A.; Pasteris, R.J. Fungicidal mixtures. International Patent WO2008/091594, July 31, **2008**.

[14] Kikuchi, C.; Ando, T.; Fuji, K.; Okuno, M.; Morita, E.; Imai, M.; Ushiroda, O.; Koyama, M.; Hiranuma, T. Tetrahydrobenzindole derivatives. U.S. Patent 6,498,251, December 24, **2002**.

[15] Djerassi, C. Brominations with N-bromosuccinimide and related compounds. *Chem. Rev*., **1948**, *43*, 271-317; Tanemura, K.; Suzuki, T.; Nishida, Y.; Satsumabayashi, K.; Horaguchi, T. A mild and efficient procedure for alpha-bromination of ketones using *N*-bromosuccinimide catalysed by ammonium acetate. *Chem. Commun*., **2004**, *4*, 470-471.

[16] Tojo, G.; Fernández, M. *Oxidation of alcohols to aldehydes and ketones*, 1st ed.; Springer: New York, **2006**.

[17] Wuts, P.G.M.; Greene, T.W. *Greene's Protective Groups in Organic Synthesis*, 4th ed.; Wiley & Sons, New Jersey, **2007**.

[18] Sedgeworth, J.; Proctor, G.R. Bridged-ring nitrogen compounds. Part 7. Synthesis of the 1,4-ethano-3-benzazepine ring system. *J. Chem. Soc., Perkin Trans. 1*, **1985**, 2677-2687; Crich, D.; Gastaldi, S. Reaction of Sodium Cyanide with 5-Bromobenzo-1-suberone: A Reappraisal. *New J. Chem*., **2000**, *24*, 249-250.

[19] Asato, G. Novel 1,2,3,4-tetrahydro-4-oxo-(oxy)-1-naphthylamines and method of preparation thereof. U.S. Patent 4,049,717, September 20, **1977**.

[20] Frankish, N.; Farrell, R.; Sheridan, H. Investigation into the mast cell stabilizing activity of nature-identical and synthetic indanones. *J. Pharm. Pharmacol*., **2004**, *56*, 1423-1427.

[21] Rickard, A.; Lagunoff, D. Eosinophil Peroxidase Accounts for Most if not All of the Peroxidase Activity Associated with Isolated Rat Peritoneal Mast Cells. *Int. Arch. All. Immunol*., **1994**, *103*, 365-369.

[22] Ovary, Z. Passive Cutaneous Anaphylaxis in the Mouse. *J. Immunol*., **1958**, *81*, 355-357.

[23] Katayama, S.; Shionoya, H.; Ohtake, S. A new method for extraction of extravasated dye in the skin and the influence of fasting stress on passive cutaneous allergy in guinea pigs and rats. *Microbiol Immunol*., **1978**, *22*, 89-101.

[24] Sparc On-Line Calculator. http://sparc.chem.uga.edu/sparc/ (Accessed July 28, June **2010**).

Received: August 20, 2010 Revised: October 28, 2010 Accepted: November 22, 2010