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Short communication

Synthesis and evaluation of 4-amino-3,4-dihydro-2*H*-naphthalen-1-one derivatives as mast cell stabilising and anti-inflammatory compounds

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Abstract

A novel series of amine and amide derivatives of 4-amino-3,4-dihydro-2*H*-naphthalen-1-one were synthesised. The amine derivatives were evaluated for mast cell stabilising activity in rodent mast cell preparations against the reference compound disodium cromoglycate and found to possess significant activity in vitro. The amide compounds were evaluated in an in vivo murine model for anti-inflammatory activity.

Keywords: 4-Amino-3,4-dihydro-2*H*-naphthalen-1-one; Mast cell stabilising; Anti-inflammatory

1. Introduction

The classical role of the mast cell as the origin of mediators involved in allergic disease and the response to parasitic infestation has been significantly expanded in the recent past, and new potential roles continue to be elucidated for this heterogeneous cell type and its circulating counterpart, the basophil. For instance, important contributory roles in autoimmune diseases such as multiple sclerosis and rheumatoid arthritis have been ascertained [1], and also in biological processes including wound healing and angiogenesis [2]. Increased proliferation and activation of mast cells occur in conditions such as irritable bowel syndrome [3]. Potential therapeutic intervention during both developmental and maturational stages of mast cell development may provide future therapies, while established agents including cromoglycate and nedocromil target the activation and degranulation of these cells. Indeed, the search for more potent and efficacious small molecule therapies for the treatment of allergic and inflammatory disease has in recent years seen the development of several new generation antihistamines and immunomodulating molecules, both for topical and systemic application [4,5]. In addition, the newer class of leukotriene antagonists represents an advance in the adjunctive treatment of asthma [6]. Novel immunological therapies, such as the use of the *anti*-IgE therapy Omalizumab [7] are undoubtedly exciting developments, yet the associated costs with biotechnological therapies can be prohibitive. Thus the development of novel small molecules for the treatment of allergic disease remains an important area of research.

In traditional medicine systems, members of the Pteridaceae have been utilised as smooth muscle relaxants. Activity has been ascribed to the presence of indane sesquiterpenes [8]. Synthetic indane derivatives based on the indanone pterosin Z, found in *Pityrogramma* and *Pteris* species were then investigated for their activities as smooth muscle relaxants [9,10]. Further research into the development of synthetic indane and aminoindane analogues of these molecules has resulted in the discovery of several active molecules [11,12], including aminoindanone **1** (Fig. 1). Interestingly, these molecules exhibited a pharmacological profile encompassing not only smooth muscle relaxant, but also marked anti-inflammatory and mast cell stabilising activities. In light of these discoveries, the present study describes the synthesis and preliminary pharmacological screening of a series of tetralone derivatives, to investigate the effect of ring expansion of

Abbreviations: AA, arachidonic acid; ACN, 1,1′-azobis(cyclohexanecarbonitrile); DCM, dichloromethane; DMAP, 4-(dimethylamino)pyridine; DSCG, disodium cromoglycate; NBS, *N*-bromosuccinimide; RPMC, rat peritoneal mast cell.

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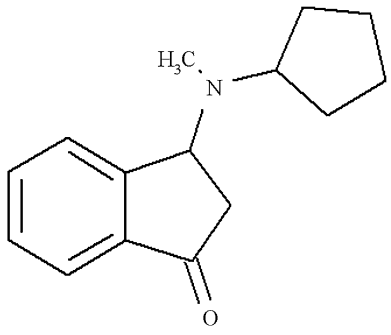

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Fig. 1. Aminoindanone **1**.

the core indanone skeleton on pharmacological activity, concentrating on their protective effects in models of inflammation and immunological phenomena.

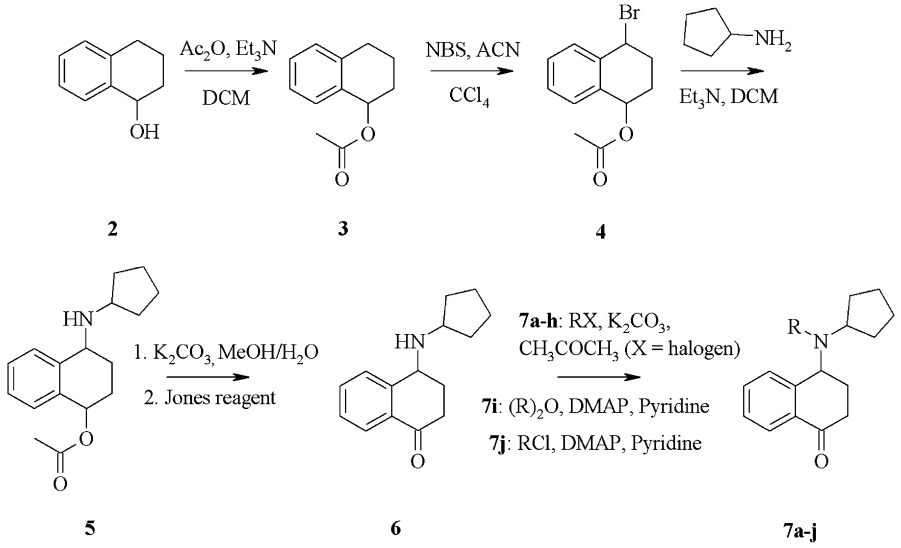
2. Chemistry

Two primary synthetic routes to the novel tetralone derivatives were employed; that for the tertiary amine and amide derivatives is shown in Scheme 1 and that for secondary amides is shown in Scheme 2. Direct bromination and substitution of α-tetralone, akin to the methodology used by Walsh and co-workers [12] in their synthesis of indanone **1** was precluded due to the formation of unacceptable quantities of aromatised product (1-naphthol) upon substitution with amine nucleophiles. Therefore, the selected starting material was alcohol **2**. Wohl–Ziegler bromination [13] of the protected alcohol **3** afforded the bromo acetate **4**. Incorporation of the cyclopentylamino ring was achieved by substitution of **4** with cyclopentylamine in basic media. Acyl hydrolysis using K_2CO_3 in methanol followed by oxidation with Cr(VI) (Jones reagent) in acetone [14] yielded ketone **6** in acceptable yield. Alkylation (**7a–h**) or acylation (**7i** and **j**) was accomplished using standard *N*-alkylation or *N*-acylation conditions [15]. Some of the amides of Scheme 2 **11a**, **b** and **e** have already been reported in the patent literature [16], where they have been utilized as intermediates in the synthesis of 1,2,3,4-tetrahydro-4-oxo-1-naphthylureas and thioureas, developed for use as animal growth promoters. Their preparation involved the benzylic oxidation of tetrahydro-1-naphthylamines using one of a variety of oxidants. In contrast, our synthesis of amide derivatives **11a–e**, as depicted in Scheme 2, involved benzylic bromination of α-tetralone and reaction with a strong nucleophile, azide. Reductive coupling of azide **10** under hydrogenation conditions (H_2/Pd/C/EtOAc/EtOH) using either anhydride for **11a** and **b** or pentafluorophenyl esters for **11c–e** of the parent acids afforded good yields of the required amides. To investigate the importance of the intact ring structure in derivatives of **6**, molecules **12** and **14** were synthesized, as shown in Schemes 3 and 4. Benzylic bromination of α-tetralone and substitution with *N*-benzylmethylamine afforded compound **12**, while compound **14** was obtained via bromination of 2′-methylacetophenone, and reaction with *N*-benzylmethylamine [17].

3. Pharmacology

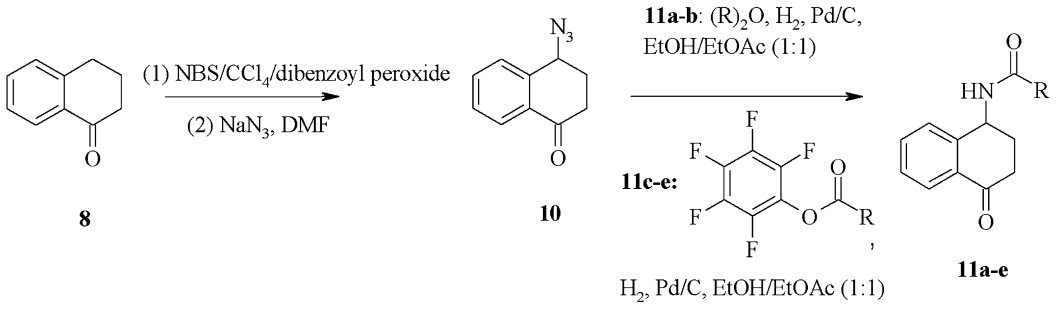
3.1. Mast cell stabilising activity

Test compounds were evaluated for inhibition of Compound 48/80-induced degranulation of rat peritoneal mast cells (RPMC), isolated as previously reported [11]. Cell populations



R= a) CH_3; b) $CH_2CH{=}CH_2$; c) CH_2Ph; d) 4-$CNC_6H_4CH_2$; e) 4-$CH_3C_6H_4CH_2$;
f) 4-$NO_2C_6H_4CH_2$; g) 3,4,5-$(CH_3O)_3C_6H_2CH_2$; h) 2-naphthyl; i) CH_3CO; j) $PhCH_2CO$

Scheme 1. Synthetic methods for the preparation of 4-(cyclopentylamino)-1,2,3,4-tetrahydro-1-naphthalenone derivatives **7a–j**.



R= a) CH_3CO; b) CH_3CH_2CO; c) CH_2Ph; d) CH_2CH_2Ph; e) 3,4-$(Cl)_2C_6H_3$

Scheme 2. Synthetic methods for the preparation of secondary amides **11a–e**.

were of >90% viability and mast cells comprised 1.4% of the total cell count. The results are shown in Table 1. Compound **7c** was also evaluated in more detail using three elicitors of histamine release in the same cell population; in addition to dose–response studies using Compound 48/80, these studies were additionally performed using the degranulating agents calcium ionophore A23187 and the lectin Concanavalin A. The IC_{50} values using each of these elicitors are shown in Table 2.

3.2. Inhibition of murine ear oedema

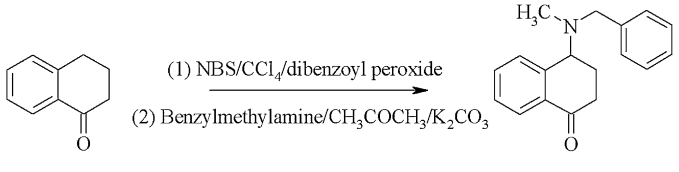
Inflammation of murine ears was achieved by topical application of arachidonic acid (AA) using a previously reported method [18]. Test compounds were evaluated for ability to inhibit oedema and compared to the standard inhibitor indomethacin. Compounds showing activity in this study are shown in Table 3.

4. Results

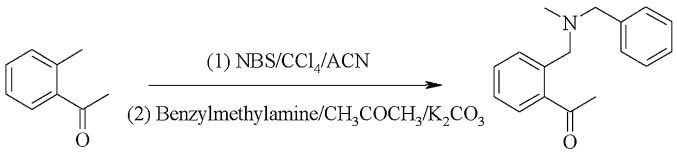
Several of the novel amine derivatives of α-tetralone (**7a**, **c**, **d**, **f** and **h**) displayed strong in vitro inhibitory effects against secretagogue-induced degranulation of rat peritoneal mast cells, as illustrated in Table 1. The methylated derivative **7a** was capable of inhibiting histamine release from rat peritoneal cells by 43%, whereas allylation to yield **7b** actually had the opposite effect within this series of molecules. Introduction of a bulky planar benzyl **7c** had a profound effect on activity, resulting in complete inhibition of histamine release at the concentration tested. Activity was reduced slightly by the presence of electron-withdrawing *para*-substituents on the benzyl ring such as nitrile (**7d**) or nitro (**7f**), although both compounds retained significant activity (67% and 65% inhibition, respectively). Conversely, substitution of the benzyl group by electron-donating trimethoxy groups (**7g**) resulted in abolition of mast cell stabilising activity. Finally, a large planar 2′-naphthalenyl substituent on the amino group (**7h**) did not greatly reduce activity as compared to the benzyl group, affording 77% protection against degranulation. The dose–response studies undertaken with the most active compound tested, **7c**, exhibited in all cases dose-dependent inhibition of histamine release, with IC_{50} values of 2.4 μM, 0.28 μM and 7.2 μM against Compound 48/80, ionophore and concanavalin A, respectively, as shown in Table 2. Amide compounds **7i** and **j** and **11a–e** were not tested for mast cell stabilising activity and although acetamide **7i** did not affect oedema induced by arachidonic acid, phenylacetamide **7j** significantly reduced the oedema (Table 3). Within the secondary amide series **11a–e**, compound **11b** showed mild (11%) inhibition of arachidonic acid-induced oedema.

5. Discussion

Five of the novel amines tested as described above were better than the reference compound disodium cromoglycate (DSCG), which inhibited histamine release by 10% in the mast cell stabilising assay. In addition, within the analogous indanone series, both *N*-methyl and *N*-allyl derivatives exhibited mast cell stabilising activity, the reported inhibitory effect of **1** being 90%, albeit using slightly different challenge conditions [12]. In the same work, the benzylated indanone analogue of **7c** inhibited release by 83% whereas the indanone amides were wholly ineffective; therefore amides **7i** and **j** were not evaluated in the present study for mast cell stabilising activity. The requirement for the core skeletal structure of the

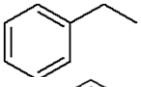
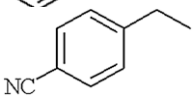
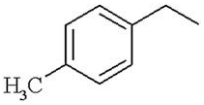
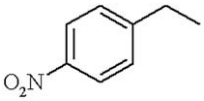
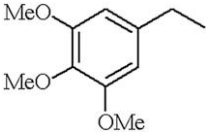
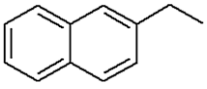


Scheme 3. Synthetic method for the preparation of **12**.



Scheme 4. Synthetic method for the preparation of **14**.

Table 1
Mast cell stabilising activity of synthesised compounds and the reference compound disodium cromoglycate in RPMC stimulated by Compound 48/80

Compound	N–R (**7a–h**)	% Inhibition
7a	CH_3	43 (17)
7b	$CH_2{=}CHCH_2$	NI
7c		99 (1)
7d		67 (5)
7e		NT
7f		65 (7)
7g		NI
7h		77 (4)
12		NI
14		NI
DSCG		10 (3)

Values are mean of at least five experiments, standard error in parentheses; test compounds and DSCGat a concentration of 2×10^{-5} M; challenge with Compound 48/80 at a concentration of 0.2μg ml^{-1} for 5 min; NI, no inhibition at concentration tested; NT, not tested.

most active compounds, as typified by **7c**, was seen from the fact that neither compound **12** nor compound **14** possessed any ability to prevent Compound 48/80-induced mast cell degranulation. Neither of these molecules possessed any mast cell stabilising activity, emphasising the need for the core ring system. The dose–response studies undertaken with **7c** revealed interesting results. Compound **7c** prevented release by all three elicitors in a dose-dependent fashion. As these releasing agents act through different pathways to induce histamine release, it is difficult to speculate on the manner by which the compounds are stabilising the RPMCs. Compound 48/80 is a hypotensive polymer amine which induces histamine release with similar kinetic characteristics to those

Table 2
Protective activity of **7c** against degranulation of RPMC induced by various elicitors

Elicitor	IC_{50} (μM)
Compound 48/80	2.4
Calcium ionophore A23187	0.28
Concanavalin A	7.2

Best-fit values were obtained from a mean of four experiments; calcium ionophore and Concanavalin A used at concentrations of 1 and 20 μg ml^{-1}, respectively; buffer system used with both elicitors was mast cell medium (MCM).

Table 3
Inhibition of arachidonic acid-induced mouse ear oedema

Compound	% Inhibition	*P*
7i	2	NS
7j	53	<0.05
11b	11	NS
Indomethacin	74	<0.0001

Values are the mean of at least 5 animals; test compounds and indomethacin administered at a dose of 300 μg ear^{-1}; arachidonic acid administered at a dose of 1 mg ear^{-1}; NS, not significant.

caused by antigen, in an energy-dependent process [19]. However, mast cells from all species do not respond equally to Compound 48/80. Therefore, we employed degranulating agents operating through different mechanisms. Unlike Compound 48/80, concanavalin A induces the cross-linking of IgE molecules on the mast cell membrane, leading to the activation of the adenylate cyclase system, and subsequent histamine release [20]. The intracellular [Ca^{2+}] is known to increase following antigen–antibody interactions, and selective ionophores such as A23187 have an important role in mechanistic studies [21]. It is interesting to note that **7c** inhibited histamine release induced by all three elicitors employed in the study.

The results of the anti-inflammatory assay contrast with those observed for the indanone congeners. In this study, **7i** did not prevent arachidonic acid-induced oedema, whereas in previous work the indanone analogue of **7i** afforded almost complete protection from arachidonic acid provocation, albeit at less than half the challenge dose of elicitor [12].

6. Conclusions

Of the novel amine derivatives of 4-amino-3,4-dihydro-2*H*-naphthalen-1-one tested, the benzylated derivative **7c** showed the best ability to inhibit degranulation of Compound 48/80-induced rat peritoneal mast cell degranulation. The abolition of activity seen with compounds **12** and **14** demonstrates the need for both the tetralone nucleus and the aminocyclopentyl substituent. Further studies to ascertain whether compound **7c** possesses ability to prevent degranulation caused by other secretagogues are envisaged. However, it has been ascertained that the expansion of the indanone ring, as contained in the patented compounds referenced above [12], is permissible without loss of mast cell stabilising activity. The amide derivatives tested in the murine oedema assay, however, displayed less anti-inflammatory activity than their indanone congeners, only the *N*-phenylacetamide (**7j**) showing significant inhibition.

7. Experimental protocols

7.1. Chemistry

Melting points were obtained using an Electrothermal apparatus, and are uncorrected. Infrared spectroscopy (IR) of test samples was performed on a Perkin Elmer Paragon 1000

FT-IR. Nuclear magnetic resonance (NMR) spectroscopy was performed using a Bruker DPX-400 instrument, at 400.13 MHz for proton (^{1}H) magnetic resonance and 100.61 MHz for carbon (^{13}C) spectra. Gas chromatographic-mass spectral data (GCMS) were obtained using a Saturn GC/MS 2000 [CP-3800 Gas Chromatograph]. High resolution mass spectroscopy (HRMS) was performed using a Micromass LCT instrument, operating in ES$^+$ mode. Flash column chromatography was performed using Silica Gel, Grade 9385, 230–400 mesh, 60 Å (Merck Laboratories). For thin layer chromatographic (TLC) procedures, aluminium foil plates pre-coated with Silica Gel 60 F_{254} were used (Merck Laboratories). TLC plates were visualised under ultraviolet light at 254 nm.

*7.1.1. 4-Bromo-1,2,3,4-tetrahydro-1-naphthalenyl acetate (**4**)*

To a stirred solution of **3** (1 g, 5.26 mmol) in carbon tetrachloride (30 ml) was added *N*-bromosuccinimide (g, 7.89 mmol) and a catalytic amount of 1,1′-azobis(cyclohexanecarbonitrile) (ACN). The reaction mixture was heated under reflux, and upon reaching reflux, the heat source was removed and replaced by two 240 W lamps, the light from these focused on the reaction, stirring vigorously all the time. On completion of the reaction a colour change from deep orange to clear was observed. The reaction mixture was then filtered to remove the insoluble *N*-hydrosuccinimide, and the solvent was removed in vacuo, using the lowest temperature possible. The residue was purified by flash column chromatography on silica gel (eluant: pet ether/ethyl acetate, 10:1) to yield the benzylic bromide as a stereoisomeric mixture (0.83 g, 59%). The bromide was isolated as oil, with the following physical properties: IR (CCl_4, ν) 2960, 1732, 1438, 1370, 1236, 1025, 964 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) $\delta_{ppm} = 2.05$, 2.18 (each s, 3H, C*H*$_3$), 2.03–2.12 (m, 2H, C*H*$_2$), 2.29 (m, 1H, C*H*$_2$), 2.47 (m, 1H, C*H*$_2$), 5.50, 5.61 (each bm, 1H, BrC*H*CH$_2$), 6.07 (m, 1H, OC*H*CH$_2$), 7.25–7.35 (m, 3H, 3 × Ar-*H*), 7.42 (m, 1H, Ar-*H*); ^{13}C NMR $\delta_{ppm} = 20.9 \times 2$ (*C*H$_3$), 24.4 and 25.2 (*C*H$_2$), 27.9 and 30.7 (*C*H$_2$), 49.4 and 49.8 (Br*C*HCH$_2$), 67.7 and 69.7 (O*C*HCH$_2$), 127.3, 127.8, 128.3, 128.5, 128.6, 130.1, 130.1, 130.2 (4 × *tert*. C), 132.8, 134.2 (*quat*. C), 137.0, 137.1 (*quat*. C), 169.8 and 170.4 (*C*=O).

*7.1.2. 4-(Cyclopentylamino)-1,2,3,4-tetrahydro-1-naphthalenyl acetate (**5**)*

To a solution of **4** (0.83 g, 3.08 mmol) in DCM (10 ml) was added cyclopentylamine (0.60 ml, 6.16 mmol) and triethylamine (0.86 ml, 6.16 mmol). The reaction was refluxed for 9 h, 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 stereoisomeric mixture (0.25 g, 30%) a brown oil, with the following physical properties: IR (CCl_4, ν) 2954, 2867, 1733, 1452, 1371, 1240 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) $\delta_{ppm} = 1.27$–2.12 (m, 12H, 6 × C*H*$_2$), 2.07, 2.09 (each s, 3H, C*H*$_3$), 3.29, 3.35 (each quintet, $J \sim 6.4$ Hz, 1H, NC*H*), 3.75, 3.86 (each t, $J =$ 5.3 Hz, 1H, NC*H*Ar), 5.95, 6.02 (each t, $J = 5.0$ Hz, 1H, OC*H*), 7.20–7.30 (m, 3H, 3 × Ar-*H*), 7.38, 7.55 (each d, $J =$ 7.5 Hz, 1H, Ar-H$_8$); ^{13}C NMR $\delta_{ppm} = 20.9$ (*C*H$_3$), 23.4, 23.5 × 2, 23.8, 24.4, 25.4, 25.6 (4 × *C*H$_2$), 32.8, 33.8, 33.9 (2 × *C*H$_2$), 52.9 and 53.4 (N*C*H), 56.7 and 56.9 (N*C*HAr), 69.3 and 69.9 (O*C*HAr), 126.5 and 126.7 (*tert*. C), 127.7, 127.9, 128.2, 128.5, 128.8 (3 × *tert*. C), 134.1 and 134.4, 140.2 and 140.7 (2 × *quat*. C), 170.1 and 170.2 (*C*=O); MS, *m/z*, (RI) 274 (M + 1, 25), 213 (100), 185 (5), 129 (13), 86 (14).

*7.1.3. 4-(Cyclopentylamino)-1,2,3,4-tetrahydro-1-naphthalenone (**6**)*

To a solution of **5** (0.25 g, 0.92 mmol) in methanol/water (10 ml, 1:1) was added excess potassium carbonate (0.25 g, 1.83 mmol). The reaction was heated under reflux for 1 h, monitored by GCMS. On completion, the reaction mixture was filtered and the solvent removed in vacuo, using toluene to azeotropically distil any residual water. To the residue was added acetone (10 ml) and Jones reagent (1.4 ml), the latter was added drop-wise over 30 min to the ice-cooled reaction. On appearance of the green $Cr_2(SO_4)_3$, anhydrous sodium sulphate (0.30 g, 2.12 mmol) was added. After 2 h, the solvent was evaporated, and the reaction separated using ether/water. After three washings with ether (3 × 20 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, which crystallised slowly on standing (83 mg, 60%): IR (CCl_4, ν) 2955, 2868, 1689, 1600, 1453, 1284 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta_{ppm} = 1.35$ (m, 2H, CH$_2$), 1.53 (m, 2H, CH$_2$), 1.69 (m, 2H, CH$_2$), 1.84 (m, 2H, CH$_2$), 2.04–2.24 (m, 2H, COCH$_2$C*H*$_2$), 2.49 (dd, $J = 7$, 4.5 Hz, 1H, C*H*$_2$CO), 2.93 (dd, $J = 10$, 4.5 Hz, 1H, C*H*$_2$CO), 3.25 (quintet, $J = 6.5$ Hz, 1H, CH$_2$C*H*CH$_2$), 3.91 (dd, $J = 6.0$, 3.5 Hz, 1H, C*H*CH$_2$CH$_2$CO), 7.29 (m, 1H, Ar-H), 7.47 (m, 2H, 2 × Ar-H), 7.95 (d, $J = 7.5$ Hz, 1H, COAr-H); ^{13}C NMR $\delta_{ppm} = 23.4$, 23.5, 28.2, 32.9, 33.6, 34.5 (5 × CH$_2$), 53.5, 56.9 (2 × CH), 126.6, 127.0, 127.6 (3 × *tert*. C), 131.4 (*quat*. C), 133.0 (*tert*. C), 146.1 (*quat*. C), 197.6 (C=O); MS, *m/z*, (RI) 230 (M + 1, 100), 229 (M$^+$, 44), 115 (4); HRMS (M + H)$^+$ 230.1561, $C_{15}H_{20}NO$ requires 230.1545.

*7.1.4. General procedure for the preparation of tertiary amines (**7a–h**)*

Mixtures of 4-(Cyclopentylamino)-1,2,3,4-tetrahydro-1-naphthalenone (1 mmol), appropriate alkyl halide, namely methyl iodide, allyl iodide, benzyl bromide, 4-(bromomethyl)-benzonitrile, 4-methylbenzyl bromide, 4-nitrobenzyl bromide, 3,4,5-trimethoxybenzyl bromide or 2-(bromomethyl)naphthalene (1 mmol) and anhydrous potassium carbonate (3 mmol) were stirred at room temperature for 7 days in acetone (10 ml). The reaction mixture was filtered, the solvent removed in vacuo, and the residue purified by flash column chromatography on silica gel (eluant: pet ether/ethyl acetate, 10:1) to

yield the pure amines pure **7a–h** which were routinely converted to their hydrochloride salts.

*7.1.4.1. 4-[Cyclopentyl(methyl)amino]-1,2,3,4-tetrahydro-1-naphthalenone (**7a**).* Yield: 94%; IR (CCl_4, ν) 2958, 2873, 2791, 1691, 1598, 1453, 1285 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) $\delta_{ppm} = 1.56$ (m, 4H, CH_2CH_2), 1.74 (m, 2H, CH_2), 1.89 (m, 2H, CH_2), 2.02 (m, 1H, CH_2CH_2CO), 2.15 (s, 3H, CH_3), 2.27 (m, 1H, CH_2CH_2CO), 2.54 (m, 1H, CH_2CO), 2.86 (2 × dd, $J = 16.1$, 3.6 Hz, 1H, CH_2CO), 3.06 (quintet, $J = 7.5$ Hz, 1H, CH_2CHCH_2), 4.21 (dd, $J = 11.4$, 4.0 Hz, 1H, ArCHN), 7.33 (dd, $J = 8.2$, 7.5 Hz, 1H, Ar-$C_{(7)}H$), 7.56 (dd, $J = 8.0$, 7.5 Hz, 1H, Ar-$C_{(6)}H$), 7.90 (d, $J = 8.0$ Hz, 1H, Ar-$C_{(5)}H$), 8.02 (d, $J = 8.0$ Hz, 1H, Ar-$C_{(8)}H$); ^{13}C NMR $\delta_{ppm} = 21.8$, 23.8, 23.9, 30.8, 31.7, 34.6 (CH_3), 38.1 (CH_2CO), 60.1 (*C*H), 63.0 (*C*H), 126.3, 126.6, 127.1 (3 × *tert*. C), 132.4 (*quat*. C), 133.1 (*tert*. C), 146.3 (*quat*. C), 197.5 (*C*=O); MS, *m/z*, (RI) 244 (M + 1, 100), 243 (M^+, 61), 214 (45), 186 (11), 146 (18), 100 (49); HRMS $(M + H)^+$ 244.1682, $C_{16}H_{22}NO$ requires 244.1701.

*7.1.4.2. 4-[Allyl(cyclopentyl)amino]-1,2,3,4-tetrahydro-1-naphthalenone (**7b**).* Yield: 60%; IR (CCl_4, ν) 2957, 2869, 1692, 1598, 1550, 1452, 1284 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) $\delta_{ppm} = 1.34–1.89$ (m, 8H, $CH_2CH_2CH_2CH_2$), 1.98 (m, 1H, CH_2CH_2CO), 2.34 (m, 1H, CH_2CH_2CO), 2.54 (m, 1H, CH_2CO), 2.86 (2 × dd, $J = 16.1$, 3.5 Hz, 1H, CH_2CO), 3.13 (quintet, $J = 7.9$ Hz, 1H, CH_2CHCH_2), 3.22 (dd, $J = 15.2$, 7.9 Hz, 1H, CH_2N), 3.35 (m, $J = 15.2$ Hz, 1H, CH_2N), 4.21 (dd, $J = 11.6$, 3 Hz, 1H, $COCH_2CH_2CH$), 5.07 (d, $J = 10.4$ Hz, 1H, CH_2=CH), 5.22 (d, $J = 17.3$ Hz, 1H, CH_2=CH), 5.92 (1H, m, CH_2=CH), 7.34 (dd, $J = 8.0$, 7.5 Hz, 1H, Ar-$C_{(7)}H$), 7.58 (dd, $J = 8.2$, 7.5 Hz, 1H, Ar-$C_{(6)}H$), 7.94 (d, $J = 8.0$ Hz, 1H, Ar-$C_{(5)}H$), 8.03 (d, $J = 8.0$ Hz, 1H, Ar-$C_{(8)}H$); ^{13}C NMR $\delta_{ppm} = 23.2$, 24.2 (2 × cyclopentyl CH_2), 25.0 (CH_2 tetralin), 28.3, 31.5 (2 × cyclopentyl CH_2), 38.2 (CH_2CO), 49.3 (CH_2N), 58.1 ($CHCH_2CH_2CO$), 59.7 (CH_2CHCH_2), 115.3 (CH_2=CH), 126.3 (Ar-$C_{(7)}$H), 126.7 (Ar-$C_{(8)}$H), 126.9 (Ar-$C_{(5)}$H), 132.6 (*quat*. C), 133.1 (Ar-$C_{(6)}$H), 138.1 (CH_2=CH), 147.1 (*quat*. C), 197.3 (*C*=O); MS, *m/z*, (RI) 270 (M + 1, 25), 269 (M^+, 34), 227 (67), 126 (100); HRMS $(M + H)^+$ 270.1866, $C_{18}H_{24}NO$ requires 270.1858.

*7.1.4.3. 4-[Benzyl(cyclopentyl)amino]-1,2,3,4-tetrahydro-1-naphthalenone (**7c**).* Yield: 55%; IR (CCl_4, ν) 2956, 2869, 1691, 1597, 1452, 1284 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) $\delta_{ppm} = 1.39$ (m, 1H, CH_2), 1.55–1.73 (m, 6H, CH_2), 1.93–2.06 (m, 2H, CH_2), 2.47 (m, 2H, CH_2CH_2CO), 2.88 (m, 1H, CH_2CO), 3.20 (quintet, $J \sim 7$ Hz, 1H, CH_2CHCH_2), 3.80, 3.97 (each d, $J = 14.5$ Hz, 2H, NCH_2), 4.03 (1H, dd, $J = 12$, 3.5 Hz, $CHCH_2CH_2CO$), 7.26 (1H, dd, $J = 8.1$, 7.5 Hz, Ar-CH), 7.33–7.37 (3H, m, 3 × Ar-*H*), 7.51 (2H, m, 2 × Ar-*H*), 7.62 (1H, dd, $J = 8.5$, 8 Hz, Ar-CH), 8.03 (2H, m, 2 × Ar-*H*); ^{13}C NMR $\delta_{ppm} = 23.7$, 25.1, 25.3, 27.8, 32.1 (4 × CH_2 cyclopentyl and CH_2CH_2CO), 38.6 (CH_2CO), 49.9 (NCH_2), 58.1, 59.2 (2 × *C*H), 126.4, 126.5, 126.8, 127.9, 127.9 (8 × *tert*. C), 132.6 (*quat*. C), 133.2 (*tert*. C), 140.5, 146.9 (2 × *quat*. C), 197.3 (*C*=O); MS, *m/z*, (RI) 320 (M + 1, 42), 319 (M^+, 27), 290 (29), 228 (36), 177 (100); HRMS $(M + H)^+$ 320.1997, $C_{22}H_{26}NO$ requires 320.2014.

*7.1.4.4. 4-[Cyclopentyl(4-oxo-1,2,3,4-tetrahydro-1-naphthalenyl)amino]methylbenzonitrile (**7d**).* Yield: 78%; m.p. 186–188 °C; IR (KBr, ν); 2947, 2865, 2227, 1686, 1596 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) $\delta_{ppm} = 1.38$ (m, 1H, CH_2), 1.49–1.66 (m, 6H, CH_2), 1.93 (m, 1H, CH_2), 2.02 (m, 1H, CH_2CH_2CO), 2.45 (m, 2H, CH_2CH_2CO), 2.87 (m, 1H, CH_2CO), 3.19 (quintet, $J = 7.9$ Hz, 1H, CH_2CHCH_2), 3.84, 3.95 (each d, $J = 15$ Hz, 2H, NCH_2), 3.94 (dd, 1H, $CHCH_2CH_2CO$, signal overlap), 7.35 (dd, $J = 8.3$, 7.5 Hz, 1H, Ar-*H*), 7.58–7.63 (m, 5 × Ar-*H*), 7.92 (d, $J = 8.0$ Hz, 1H, Ar-*H*), 8.01 (dd, $J = 7.8$, 1 Hz, 1H, Ar-*H*); ^{13}C NMR $\delta_{ppm} = 23.2$, 24.6, 24.7, 27.6, 31.7 (5 × CH_2), 38.0 (CH_2CO), 49.7 (NCH_2), 58.3 (*C*H), 59.2 (*C*H), 110.2 (*C*C≡N), 118.5 (*C*≡N), 126.4, 126.7, 127.0 (3 × *tert*. C), 128.3, 131.8 (4 × *tert*. C), 132.6 (*quat*. C), 133.3 (*tert*. C), 145.9, 146.6 (2 × *quat*. C), 196.9 (*C*=O); MS, *m/z*, (RI) 344 (M^+, 20), 315 (29), 228 (36), 199 (86), 171 (100), 145 (47), 116 (91), 89 (51); HRMS $(M + H)^+$ 345.1986, $C_{23}H_{25}N_2O$ requires 345.1967.

*7.1.4.5. 4-[Cyclopentyl(4-methylbenzyl)amino]-1,2,3,4-tetrahydro-1-naphthalenone (**7e**).* Yield: 80%; IR (HCl salt, KBr, ν); 3422, 2960, 1691, 1590, 1452, 1421 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) $\delta_{ppm} = 1.36$ (m, 1H, CH_2), 1.54–1.73 (m, 6H, CH_2), 1.91–2.04 (m, 2H, CH_2), 2.35 (s, 3H, CH_3), 2.42–2.51 (m, 2H, CH_2CH_2CO), 2.87 (m, 1H, CH_2CO), 3.18 (quintet, $J = 8$ Hz, 1H, CH_2CHCH_2), 3.84 (each d, $J = 14.2$ Hz, 2H, NCH_2), 4.03 (dd, $J = 3.5$ Hz, 1H, $CHCH_2CH_2CO$), 7.16 (m, 2H, 2 × Ar-*H*), 7.32–7.39 (m, 3H, 3 × Ar-*H*), 7.60 (dd, $J_1 = 8.5$, 7.5 Hz, 1H, Ar-*H*), 8.01 (m, 2H, 2 × Ar-*H*); ^{13}C NMR $\delta_{ppm} = 20.6$ (CH_3), 23.3, 24.7, 24.8, 27.4, 31.6 (5 × CH_2), 38.2 (CH_2CO), 49.2 (NCH_2), 57.6 (*C*H), 58.9 (*C*H), 126.3, 126.7, 126.8 (3 × *tert*. C), 127.8 (2 × *tert*. C), 128.6 (2 × *tert*. C), 132.6 (*quat*. C), 133.1 (*tert*. C), 136.0, 137.3, 147.0 (3 × *quat*. C), 197.3 (*C*=O); MS, *m/z*, (RI) 333 (M+, 18), 304 (15), 276 (8), 229 (30), 190 (100), 105 (46); HRMS $(M + H)^+$ 334.2144, $C_{23}H_{28}NO$ requires 334.2171.

*7.1.4.6. 4-[Cyclopentyl(4-nitrobenzyl)amino]- 1,2,3,4-tetrahydro-1-naphthalenone (**7f**).* Yield: 53%; IR (CCl_4, ν) 2959, 2871, 1692, 1526, 1346 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) $\delta_{ppm} = 1.41$ (m, 1H of CH_2), 1.52–1.70 (m, 6H, 3 × CH_2 cyclopentyl), 1.94 (m, 1H, CH_2), 2.05 (m, 1H, CH_2CH_2CO), 2.42–2.51 (m, 2H, CH_2CH_2CO), 2.88 (m, 1H, CH_2CO), 3.23 (quintet, $J = 7.8$ Hz, 1H, CH_2CHCH_2), 3.90, 3.99 (each d, $J = 15.6$ Hz, 2H, NCH_2), 3.99 (dd, 1H, $CHCH_2CH_2CO$, signal overlap), 7.36 (dd, $J = 8.2$, 7.5 Hz, 1H, Ar-*H*), 7.59–7.65 (m, 3H, 3 × Ar-*H*), 7.93 (d, $J = 8.0$ Hz, 1H, Ar-*H*), 8.02 (dd, $J = 7.8$, 1 Hz, 1H, Ar-*H*), 8.19 (m, 2H, 2 × Ar-*H*); ^{13}C NMR $\delta_{ppm} = 23.1$, 24.5, 24.8, 27.8, 31.7 (5 × CH_2), 37.9 (CH_2CO), 49.7 (NCH_2), 58.5 (*C*H), 59.5 (*C*H), 123.2 (2C), 126.4, 126.7,

127.0, 128.2 (2C) (7 × *tert*. C), 132.6 (*quat*. C), 133.2 (*tert*. C), 145.7 (*quat*. C), 148.7 (*quat*. C), 151.4 (*quat*. C), 196.7 (*C*=O); MS, *m/z*, (RI) 364 (M^+, 17), 335 (22), 307 (13), 228 (28), 221 (100), 191 (52), 145 (27), 117 (45), 89 (24); HRMS $(M+H)^+$ 365.1837, $C_{22}H_{25}N_2O_3$ requires 365.1865.

*7.1.4.7. 4-Cyclopentyl[3,4-dimethoxy-5-(methoxymethyl)benzyl]amino-1,2,3,4-tetrahydro-1-naphthalenone (**7g**)*. Yield: 70%; IR (CCl_4, *ν*) 2957, 2870, 1692, 1593, 1508, 1465, 1228, 1133 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) $\delta_{ppm} = 1.37$ (m, 1H, CH_2), 1.54–1.64 (m, 6H, CH_2), 1.91–2.05 (2H, m, CH_2), 2.44–2.51 (m, 2H, CH_2CH_2CO), 2.86 (m, 1H, CH_2CO), 3.20 (1H, quintet, $J = 7$ Hz, CH_2CHCH_2), 3.75 (d, $J = 14.6$ Hz, 1H, NCH_2), 3.83–3.93 (m, 10H, 3 × Ar-OCH_3, 1H of NCH_2, signal overlap), 4.04 (m, 1H, CHCH_2CH_2CO), 6.73 (s, 2H, 2 × $(CH_3O)_3$Ar-*H*), 7.34 (dd, $J = 8.5$, 7.5 Hz, 1H, Ar-*H*), 7.59 (1H, dd, $J = 8.5$, 7.5 Hz, Ar-*H*), 8.01 (m, 2H, 2 × Ar-*H*); ^{13}C NMR $\delta_{ppm} = 23.3$, 24.8, 24.8, 27.5, 31.6 (5 × *C*H_2), 38.1 (*C*H_2CO), 49.7 (NCH_2), 55.6, 55.7, 57.9 (3 × Ar-OCH_3), 58.8, 60.3 (2 × *C*H), 104.3 (2 × $(CH_3O)_3$Ar-*C*H), 126.4 (2C), 126.9 (3 × *tert*. C), 132.7 (*quat*. C), 133.0 (*tert*. C), 136.2, 146.7 (2 × *quat*. C), 152.3 (2 × *quat*. C), 197.1 (*C*=O), one *quat*. signal obscured due to peak overlapping; MS, *m/z*, (RI) 409 (M^+, 1), 264 (9), 229 (51), 181 (100), 117 (12); HRMS $(M+Na)^+$ 432.2114, $C_{25}H_{31}NO_4Na$ requires 432.2151.

*7.1.4.8. 4-[Cyclopentyl(2-naphthylmethyl)amino]-1,2,3,4-tetrahydro-1-naphthalenone (**7h**)*. Yield: 27%; IR (CCl_4, *ν*) 2957, 2869, 1692, 1550, 1284 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) $\delta_{ppm} = 1.41$ (m, 1H, CH_2), 1.58–1.76 (m, 6H, CH_2), 1.97–2.08 (m, 2H of CH_2), 2.41–2.53 (m, 2H, CH_2CH_2CO), 2.88 (m, 1H, CH_2CO), 3.23 (quintet, $J = 7.5$ Hz, 1H, CH_2CHCH_2), 3.97, 4.10 (each d, $J = 14$ Hz, 2H, NCH_2), 4.08 (m, 1H, CHCH_2CH_2CO), 7.33 (dd, $J = 8.5$ Hz, 1H, Ar-*H*), 7.47 (m, 2H, 2 × Ar-*H*), 7.61 (d, $J = 9$ Hz, 1H, Ar-*H*), 7.70 (d, $J = 8$ Hz, 1H, Ar-*H*), 7.85 (m, 4H, 4 × Ar-*H*), 8.03 (m, 2H, 2 × Ar-*H*); ^{13}C NMR $\delta_{ppm} = 23.3$, 24.8, 24.8, 27.5, 31.7, 38.2 (6 × *C*H_2), 49.8 (*C*H_2Ar), 57.6, 59.0 (2 × *C*H), 125.1, 125.5, 126.3 (2C), 126.4, 126.7, 126.8, 127.1, 127.2, 127.7 (10 × *tert*. C), 132.4, 132.6, 132.9 (3 × *quat*. C), 133.1 (*tert*. C), 138.0, 146.8 (2 × *quat*. C), 197.1 (*C*=O); MS, *m/z*, (RI) 370 (M + 1, 5), 340 (12), 228 (100), 141 (30), 115 (20); HRMS $(M+H)^+$ 370.2194, $C_{26}H_{28}NO$ requires 370.2171.

*7.1.5. General procedures for the preparation of amides (**7i** and **j**)*

Amides **7i** and **j** were prepared by adding to a solution of **6** in pyridine (5 ml) 5 mol equivalents of anhydride and a catalytic amount of DMAP. The reaction was stirred at room temperature for 3 h. The pyridine was removed by washing the organic phase (diluted with 20 ml DCM) three times with 2 M HCl (3 × 20 ml); the organic layer was then concentrated in vacuo, and the residue purified by flash column chromatography on silica gel (eluant: pet ether/ethyl acetate, 5:1) to yield amides **7i** and **j**.

*7.1.5.1. N1-Cyclopentyl-N1-(4-oxo-1,2,3,4-tetrahydro-1-naphthalenyl)acetamide (**7i**)*. Yield: 57%; m.p. 131–132 °C; IR (KBr, *ν*) 2946, 2869, 1688, 1644, 1597, 1434, 1285 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) $\delta_{ppm} = 1.45$–2.48 (br. m), 2.21 (s, 3H, COCH_3), 2.57–2.75 (m), 2.78–2.91 (m), 3.07 (br. s, CH), 5.15 (br. s, CH), 7.21 (m, 1H, 1 × Ar-*H*), 7.38 (m, 1H, 1 × Ar-*H*), 7.53 (m, 1H, 1 × Ar-*H*), 8.05 (dd, $J = 8.0$ Hz, 1H, Ar-*H*); ^{13}C NMR $\delta_{ppm} = 23.0$ (*C*H_3), 23.3 (br.), 23.4 (br.), 25.0 (br.), 25.3 (br.), 28.0, 28.8 (br.), 29.2 (br.), 30.2 (br.), 37.6 (br.), 38.2 (*C*H_2CO), 53.2 (*C*H), 57.6 (br.), 58.3 (br.), 126.3 (br.), 127.1, 127.4, 127.5, 133.0 (4 × *tert*. C), 133.5 (br.), 195.4, 196.2 (*C*=O); MS, *m/z*, (RI) 272 (M + 1, 100), 271 (M^+, 15), 160 (12), 115 (13), 84 (9); HRMS ($+H^+$) 272.1646, $C_{17}H_{22}NO_2$ requires 272.1651; $(M+Na)^+$ 294.1454, $C_{17}H_{21}NO_2Na$ requires 294.1470.

*7.1.5.2. N1-Cyclopentyl-N1-(4-oxo-1,2,3,4-tetrahydro-1-naphthalenyl)-2-phenylacetamide (**7j**)*. Yield: 68%; IR (CCl_4, *ν*) 2956, 1694, 1646, 1599, 1456, 1284, 1140 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) $\delta_{ppm} = 1.39$, 1.58, 1.71, 1.95 (4 × br m, 8H, 4 × CH_2), 2.19 (m, 1H, CH_2), 2.40 (m, 1H, CH_2), 2.77 (m, 2H, CH_2), 3.06 (CH), 3.83 (m, 3H, CH and CH_2, peaks overlapping), 7.25–7.48 (m, 7H, 7 × Ar-*H*), 7.56 (dd, $J = 8.5$, 7.5 Hz, 1H, Ar-*H*), 8.07 (1H, COAr-*H*); ^{13}C NMR $\delta_{ppm} = 25.2$, 25.5, 28.8, 29.1, 30.1 (5 × *C*H_2), 37.4, 43.4 (2 × *C*H_2CO), 57.8 (2C, 2 × *C*H), 126.2, 126.6, 127.4, 127.5, 127.9, 128.2, 128.3, 128.5 (8 × *tert*. C), 132.9 (*quat*. C), 133.3 (*tert*. C), 134.7 (*quat*. C), 169.9 (NC=O), 195.4 (*C*=O), one *quat*. signal obscured due to peak overlapping; MS, *m/z*, (RI) 348 (M + 1, 100), 347 (M^+, 7), 115 (11); HRMS $(M+H)^+$ 348.1950, $C_{23}H_{26}NO_2$ requires 348.1964.

*7.1.6. 4-Azido-3,4-dihydro-2H-naphthalen-1-one (**10**)*

Benzylic bromination of α-tetralone (**8**) yielded (**9**). To a solution of (**9**) (3 g, 13.3 mmol) in DMF (20 ml) was added sodium azide (8.6 g, 133 mmol). The resultant slurry was heated on an oil bath for 2 h at 50 °C, and then partitioned between water and ether. The aqueous layer was washed twice with ether (2 × 20 ml portions) and the combined ethereal layers dried over sodium sulphate and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (eluant: pet ether/ethyl acetate, 20:1) to yield azide (**10**) as a yellow oil (2.73 g, 89%), with the following physical properties: IR (CCl_4, *ν*) 2944, 2100, 1686, 1600, 1455, 1283 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) $\delta_{ppm} = 2.24$ (m, 1H, CH_2), 2.38 (m, 1H, CH_2), 2.60 (dd, $J = 7$, 4.5 Hz, 1H, COCH_2), 2.89 (dd, $J = 10$, 4.5 Hz, 1H, COCH_2), 4.75 (dd, $J = 6.3$, 3.8 Hz, 1H, CHN$_3$), 7.41–7.46 (m, 2H, 2 × Ar-*H*), 7.58 (m, 1H, Ar-*H*), 8.04 (dd, $J = 8.04$, 1 Hz, 1H, Ar-*H*); ^{13}C NMR $\delta_{ppm} = 28.1$ (CH_2CHN_3), 34.0 (*C*H_2CO), 58.4 (*C*HN$_3$), 127.2, 127.6, 128.7, 133.5 (4 × *tert*. C), 131.1, 139.6 (2 × *quat*. C), 195.7 (*C*=O).

*7.1.7. General procedures for the preparation of amides (**11a–e**)*

For amides **11a** and **b**, mixtures of 4-azido-3,4-dihydro-2*H*-naphthalen-1-one (1 mmol), appropriate anhydride, namely acetic or propionic (1 mmol) and a catalytic amount of 10% Pd/C were stirred at room temperature overnight in EtOH/EtOAc

(10 ml, 1:1) under an atmosphere of hydrogen, filtered, and the solvent was removed in vacuo. The residue was purified by flash column chromatography on silica gel (eluant: pet ether/ethyl acetate, 10:1) to yield amides **11a** and **b**.

For amides **11c–e**, mixtures of 4-azido-3,4-dihydro-2*H*-naphthalen-1-one (1 mmol), appropriate pentafluorophenyl ester, namely phenylacetic acid [22], 3-phenylpropionic acid [23] or 3,4-dichlorobenzoic acid (1 mmol) and a catalytic amount of 10% Pd/C were stirred at room temperature overnight in EtOH/EtOAc (10 ml, 1:1) under an atmosphere of hydrogen, filtered, and the solvent was removed in vacuo. The residue was purified by flash column chromatography on silica gel (eluant: pet ether/ethyl acetate, 10:1) to yield amides **11c–e**.

*7.1.7.1. N1-(4-Oxo-1,2,3,4-tetrahydro-1-naphthalenyl)acetamide (**11a**).* Yield: 50%; m.p. 138–139 °C; IR (CCl_4, ν) 3252, 2929, 1689, 1637, 1543 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) $\delta_{ppm} = 2.05$ (s, 3H, C*H*$_3$), 2.10 (m, 1H, C*H*$_2$), 2.32 (m, 1H, C*H*$_2$), 2.62 (m, 1H, C*H*$_2$CO), 2.75 (m, 1H, C*H*$_2$CO), 5.32 (1H, C*H*), 6.43 (N*H*), 7.35 (m, 2H, 2 × Ar-*H*), 7.54 (m, 1H, Ar-*H*), 7.94 (m, 1H, Ar-*H*); ^{13}C NMR $\delta_{ppm} = 22.8$ (*C*H$_3$), 29.2 (*C*H$_2$), 35.7 (*C*H$_2$CO), 46.9 (*C*H), 126.8 (*tert*. C), 126.9 (*tert*. C), 127.6 (*tert*. C), 131.5 (*quat*. C), 133.6 (*tert*. C), 142.9 (*quat*. C), 169.5 (NH*C*=O), 196.5 (*C*=O); MS, *m/z*, (RI) 204 (M + 1, 100), 203 (M^+, 21), 144 (70), 115 (25); HRMS $(M + Na)^+$ 226.0839, $C_{12}H_{13}NO_2Na$ requires 226.0844.

*7.1.7.2. N1-(4-Oxo-1,2,3,4-tetrahydro-1-naphthalenyl)propanamide (**11b**).* Yield: 40%; m.p. 142–143 °C; IR (CCl_4, ν) 3274, 1692, 1645, 1541 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) $\delta_{ppm} = 1.24$ (t, $J = 7.5$ Hz, 3H, C*H*$_3$), 2.13 (m, 1H, CHC*H*$_2$), 2.33 (q, $J = 7.5$ Hz, 2H, C*H*$_2$CH$_3$), 2.38 (m, 1H, CHC*H*$_2$), 2.76 (m, 2H, C*H*$_2$CO), 5.41 (br. s, 1H, C*H*), 5.92 (N*H*), 7.38 (m, 2H, 2 × Ar-*H*), 7.57 (dd, $J = 9.4$, 7.5 Hz, 1H, Ar-*H*), 8.03 (br. s, COAr-*H*); ^{13}C NMR $\delta_{ppm} = 9.4$ (*C*H$_3$), 29.4 (2C, 2 × *C*H$_2$), 35.8 (*C*H$_2$CO), 46.8 (*C*H), 126.7 (*tert*. C), 126.9 (*tert*. C), 127.7 (*tert*. C), 131.6 (*quat*. C), 133.6 (*tert*. C), 143.0 (*quat*. C), 173.1 (NH*C*=O), 196.3 (*C*=O); MS, *m/z*, (RI) 218 (M + 1, 100), 217 (M^+, 18), 144 (16), 115 (17); HRMS $(M + Na)^+$ 240.1012, $C_{13}H_{15}NO_2Na$ requires 240.1000.

*7.1.7.3. N1-(4-Oxo-1,2,3,4-tetrahydro-1-naphthalenyl)-2-phenylacetamide (**11c**).* Yield: 64%; IR (CCl_4, ν) 3267, 2929, 1690, 1640, 1542 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) $\delta_{ppm} = 1.97$ (m, 1H, C*H*$_2$CH$_2$CO), 2.28 (m, 1H, C*H*$_2$CH$_2$CO), 2.58 (m, 1H, C*H*$_2$CO), 2.68 (m, 1H, C*H*$_2$CO), 3.63 (s, 2H, PhC*H*$_2$CO), 5.32 (1H, m, NHC*H*), 6.24 (br. s, 1H, N*H*), 7.21 (1H, d, $J = 7.7$ Hz, Ar-*H*), 7.26–7.36 (6H, m, 6 × Ar-*H*), 7.48 (dd, $J = 8.5$, 7.5 Hz, 1H, Ar-*H*), 7.94 (d, $J = 8$ Hz, 1H, Ar-*H*); ^{13}C NMR $\delta_{ppm} = 29.3$ (*C*H$_2$CH$_2$CO), 35.9 (*C*H$_2$CO), 43.3 (*C*H$_2$CO), 47.0 (*C*H), 126.4, 126.9, 127.0, 127.5, 128.6 (2C), 128.7 (2C) (8 × *tert*. C), 131.5 (*quat*. C), 133.5 (*tert*. C), 134.3, 142.9 (2 × *quat*. C), 170.5 (NH*C*=O), 196.3 (*C*=O); MS, *m/z*, (RI) 280 (M + 1, 100), 279 (M^+, 40), 115 (16), 89(15); HRMS $(M + Na)^+$ 302.1143, $C_{18}H_{17}NO_2Na$ requires 302.1157.

*7.1.7.4. N1-(4-Oxo-1,2,3,4-tetrahydro-1-naphthalenyl)-3-phenylpropanamide (**11d**).* Yield: 69%; m.p. 110–112 °C; IR (CCl_4, ν) 3279, 2929, 1689, 1633, 1542 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) $\delta_{ppm} = 1.97$ (m, 1H, C*H*$_2$), 2.24 (m, 1H, C*H*$_2$), 2.51–2.66 (m, 4H, ArC*H*$_2$ and C*H*$_2$CO, signal overlap), 3.02 (ddd, $J = 8.5$, 7.4, 2.3 Hz, 2H, C*H*$_2$CO), 5.30 (dt, $J = 8.6$, 4.5 Hz, 1H, C*H*), 6.05 (N*H*), 7.04 (d, $J = 8$ Hz, 1H, Ar-*H*), 7.21–7.34 (m, 6H, 6 × Ar-*H*), 7.44 (dd, $J = 8.5$, 7.5 Hz, 1H, Ar-*H*), 7.93 (d, $J = 7.5$ Hz, 1H, COAr-*H*); ^{13}C NMR $\delta_{ppm} = 29.2$ (*C*H$_2$), 31.3 (*C*H$_2$), 35.7 (*C*H$_2$CO), 38.1 (*C*H$_2$CO), 46.8 (*C*H), 125.9 (*tert*. C), 126.7 (*tert*. C), 126.8 (*tert*. C), 127.5 (*tert*. C), 128.0 (2 × *tert*. C), 128.1 (2 × *tert*. C), 131.4 (*quat*. C), 133.5 (*tert*. C), 140.0 (*quat*. C), 142.8 (*quat*. C), 171.4 (NH*C*=O), 196.5 (*C*=O); MS, *m/z*, (RI) 294 (M + 1, 100), 293 (M^+, 43), 249 (23), 218 (27), 249 (23), 160 (20), 128 (25); HRMS $(M + Na)^+$ 316.1307, $C_{19}H_{19}NO_2Na$ requires 316.1313.

*7.1.7.5. N1-(4-Oxo-1,2,3,4-tetrahydro-1-naphthalenyl)-3,4-dichlorobenzamide (**11e**).* Yield: 81%; m.p. 165–167 °C; IR (CCl_4, ν) 3252, 2929, 1689, 1637, 1543 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) $\delta_{ppm} = 2.25$ (m, 1H, C*H*$_2$), 2.45 (m, 1H, C*H*$_2$), 2.70 (m, 1H, C*H*$_2$CO), 2.83 (m, 1H, C*H*$_2$CO), 5.55 (m, 1H, C*H*), 6.94 (N*H*), 7.40 (m, 2H, 2 × Ar-*H*), 7.48–7.59 (m, 2H, 2 × Ar-*H*), 7.67 (m, 1H, Ar-*H*), 7.97 (m, 2H, 2 × Ar-*H*); ^{13}C NMR $\delta_{ppm} = 29.2$ (*C*H$_2$), 35.7 (*C*H$_2$CO), 47.7 (*C*H), 125.9, 126.8, 127.0, 127.9, 128.8, 130.2 (6 × *tert*. C), 131.6, 132.7, 133.3 (3 × *quat*. C), 133.8 (*tert*. C), 135.9, 142.4 (2 × *quat*. C), 164.7 (NH*C*=O), 196.3 (*C*=O); MS, *m/z*, (RI) 334 (M + 1, 15), 333 (M^+, 10), 144 (100), 115 (25).

*7.1.8. 4-[Benzyl(methyl)amino]-1,2,3,4-tetrahydro-1-naphthalenone (**12**)*

To compound **9** (obtained from 1 g α-tetralone), was immediately added acetone (10 ml), *N*-benzylmethylamine (1.76 ml, 13.7 mmol) and anhydrous K_2CO_3 (4.7 g, 34.2 mmol). The reaction was stirred overnight at room temperature, and separated by sequential acid (2 M HCl) and base (2 M NaOH) washings, extracting the organic phase three times in each case with ether (3 × 20 ml). The combined organic extracts were dried over anhydrous sodium sulphate and the solvent was removed in vacuo. The residue was purified by flash column chromatography on silica gel (eluant: pet ether/ethyl acetate, 10:1) to yield the tertiary amine, a colourless oil that solidified on standing (0.45 g, 25%): IR (CCl_4, ν) 2647, 2797, 1693, 1599, 1545, 1285, 1026 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) $\delta_{ppm} = 2.18$ (m, 1H, C*H*$_2$CH), 2.26 (s, 3H, C*H*$_3$), 2.36 (m, 1H, C*H*$_2$CH), 2.55 (m, 1H, C*H*$_2$CO), 2.93 (m, 1H, C*H*$_2$CO), 3.73 (dd, $J = 13.8$ Hz, 2H, NC*H*$_2$Ar), 4.08 (dd, $J = 10.9$, 3.2 Hz, 1H, C*H*), 7.26–7.44 (m, 6H, 6 × Ar-*H*), 7.60 (dd, $J = 8.3$, 7.4 Hz, 1H, Ar-*H*), 7.96 (d, $J = 8.0$ Hz, 1H, Ar-*H*), 8.05 (d, $J = 8.0$ Hz, 1H, Ar-*H*); ^{13}C NMR $\delta_{ppm} = 21.3$ (CH*C*H$_2$), 37.0 (CO*C*H$_2$), 37.0 (*C*H$_3$), 57.7 (NC*H*$_2$Ar), 60.8 (*C*H), 126.6, 126.7, 126.8, 127.2, 127.9 (2C), 128.0 (2C) (9 ×

tert. C), 132.5, 139.2, 145.3 (3 × *quat*. C); MS, *m/z*, (RI) 265 (M^+, 15), 146 (100), 120 (86), 91 (30); HRMS $(M+H)^+$ 266.1527, $C_{18}H_{20}NO$ requires 266.1545.

*7.1.9. 1-(2-{[Benzyl(methyl)amino]methyl} phenyl)1-ethanone (**14**)*

To a solution of 2′-methylacetophenone **13** (1.5 g, 11.2 mmol) in CCl_4 (30 ml) was added NBS (2.99 g, 16.8 mmol) and a catalytic amount of ACN. The reaction mixture was heated under reflux, and upon reaching reflux conditions the heat source was removed and replaced by two 240 W lamps, the light from these focussed on the reaction, stirring vigorously all the time. On completion of the reaction a colour change from deep orange to clear was observed. The reaction mixture was then filtered to remove the insoluble *N*-hydrosuccinimide, and the solvent removed in vacuo. To the residue were added *N*-benzylmethylamine (2.9 ml, 22.4 mmol), acetone (10 ml) and anhydrous K_2CO_3 (3.09 g, 22.3 mmol). The reaction was stirred overnight at room temperature, filtered and purified by flash column chromatography on silica gel (eluant: pet ether/ethyl acetate, 10:1) to yield the tertiary amine, a colourless oil that solidified on standing (0.74 g, 26%): ^{1}H NMR ($CDCl_3$, 400 MHz) $\delta_{ppm} = 2.09$ (s, 3H, NC*H*$_3$), 2.58 (s, 3H, COC*H*$_3$), 3.53 (C*H*$_2$), 3.79 (C*H*$_2$), 7.25–7.35 (m, 6H, 6 × Ar-*H*), 7.41 (d, $J = 7.5$ Hz, 1H, Ar-*H*), 7.54 (m, 2H, 2 × Ar-*H*); ^{13}C NMR $\delta_{ppm} = 29.5$ (CO*C*H$_3$), 41.0 (N*C*H$_3$), 59.5 (*C*H$_2$), 61.5 (*C*H$_2$), 126.5 (2C), 127.1, 129.5 (2C), 129.9 (2C), 130.2, 130.3 (9 × *tert*. C), 138.2, 138.4, 140.0 (3 × *quat*. C), 202.9 (*C*=O).

7.2. Mast cell stabilising activity

A 250–300 g female Wistar rat was selected, and sacrificed by CO_2 inhalation. The animal was immediately injected with 15 ml of HEPES buffer solution (at 37 °C) into the peritoneal cavity, and massaged gently in this region for 90 s, to facilitate cell recovery. A midline incision was made and the peritoneum was exposed. The pale fluid was aspirated using a blunted plastic Pasteur pipette, and collected in a plastic centrifuge tube. The fluid was then centrifuged at 1000 rpm for 5 min, and the supernatant discarded to reveal a pale cell pellet. The cell pellets were re-suspended in fresh buffer and re-centrifuged. Cell suspensions of this nature appeared to be relatively consistent, as judged by basal and total readings for histamine content, and were not routinely purified further. Aliquots of the cell suspension were incubated with the test compounds or the control, disodium cromoglycate, before challenge with Compound 48/80. The reaction was terminated by addition of iced buffer, and aliquots centrifuged and analysed spectrophotometrically for released histamine after complexation with *o*-phthalaldehyde.

7.3. Inhibition of murine ear oedema

Male Laca mice weighing 25–30 g were divided into groups of five and sedated using sodium pentobarbitone, at a dose of 60 mg kg^{-1} via the intraperitoneal route. Test compounds, the control (indomethacin), and arachidonic acid (AA) were dissolved in acetone. All individual applications to an ear consisted of a 20 μL volume, 10 μL of which was applied evenly to each ear surface. The amount of arachidonic acid to be applied was determined from a standard curve. One hour after application of arachidonic acid, the animals were sacrificed by cervical dislocation. Using a 5 mm surgical punch, tissue sections were removed from both ears of each animal, and carefully weighed. The weights of the left ears were subtracted from those of the right, and a mean value obtained for the difference in weights in each group. The reduction in swelling was obtained by comparison of the weight differences in the positive control group (AA only), with those in the indomethacin and test groups.

7.4. Statistical analysis

Statistical analysis was performed using GraphPAD Prism software Version 3.02 (GraphPAD, San Diego, CA, USA). The RPMC experiments were repeated on the cells of 5 animals. Graphical data were obtained from the mean +/− the standard error of the mean (S.E.M.). Statistical analysis of arachidonic acid-induced mouse ear oedema was performed using Students *t*-test when comparing untreated (positive control) groups with treated groups. P values of <0.05 were considered significant.

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