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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

# Modifications to five-substituted 3,3-diethyl-4,5-dihydro-2(3*H*)-furanones *en* route to novel muscarinic receptor ligands

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**Abstract** Lead lactone-based ligands with modest affinity for muscarinic receptors were modified based on structure–activity relationship data in the literature to provide a new series of 5-substituted 4,5-dihydro-2(3*H*)-furanones. The modifications included the addition of various nitrogen-containing heterocycles attached to substituted and unsubstituted aromatic rings. The target compounds were synthesized in modest yields and evaluated in preliminary muscarinic binding assays. A lactone-based ligand containing a diphenylmethylpiperazine moiety was identified as a nonselective muscarinic ligand with $IC_{50}$ of 340 nM. The design of future ligands will be based, in part, on structure–activity data reported herein.

**Keywords** Muscarinic receptors · Lactone · Diphenylmethylpiperazine

## Introduction

Muscarinic receptors belong to the superfamily of G-protein coupled receptors and are classified into five receptor subtypes ($M_1$–$M_5$). In general, $M_1$, $M_3$, and $M_5$ receptor subtypes are coupled via Gq like proteins; while $M_2$ and $M_4$ subtypes are coupled to Gi-proteins (Burstein *et al.*, 1998; Koch *et al.*, 2005). Muscarinic receptors are widely distributed in the body where they are responsible for a variety of important physiological functions. The receptors have been targeted in drug discovery efforts for the treatment of various disorders including overactive bladder, Alzheimer's disease, pain, cognitive impairment, drug addiction, schizophrenia, and parkinson's disease (Abrams *et al.*, 2006; Wess *et al.*, 2007). To date, efforts to develop subtype selective ligands for muscarinic acetylcholine receptors (mAChRs) have been hampered by a lack of an X-ray crystal structures of the proteins and the high degree of homology among the receptor subtypes (Felder *et al.*, 2000).

The pharmacophoric requirements for cholinergic ligands have been reported by numerous investigators based on structure–activity relationship (SAR) and/or molecular modeling data of known muscarinic ligands. In general, the models propose that the pharmacophoric elements that should be present in muscarinic ligands include: (a) a quaternary ammonium group or its equivalent, (b) an unshared pair of electrons that can mediate a H-bond, (c) an appropriate distance between the H-bonding moiety and the center of the positive charge, and (d) the presence of a suitably located lipophilic/alkyl group (Beers and Reich, 1970; Marriott *et al.*, 1999; Peretto *et al.*, 2007). These fundamental requirements are useful when designing muscarinic ligands but have provided little guidance in the design of subtype selective compounds.

In recent years, molecular modeling and computational approaches have been used also to aid in the design of muscarinic ligands (Shapiro *et al.*, 1992; Nordvall and Hacksell, 1993; Peng *et al.*, 2006; Johren and Holtje, 2002; Ostopovici *et al.*, 2007). For example, 3D molecular modeling techniques and docking studies using a homology model of bovine rhodopsin have revealed unique interactions between acetylcholine (ACh) and the binding pockets of $M_1$–$M_5$ receptors (Pedretti *et al.*, 2006). Another study involved docking analysis of muscarinic receptors ($M_1$, $M_2$, and $M_5$) using known agonists with the goal of using the binding site geometry of the three receptors to design

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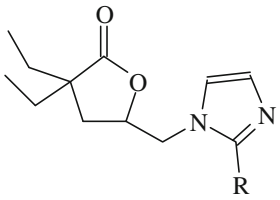


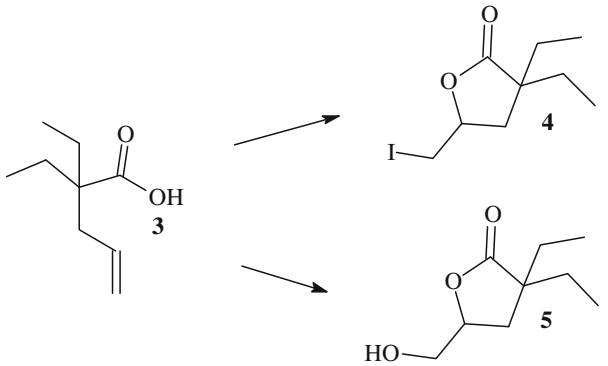

**Fig. 1** Structure of representative lactone-based leads reported previously

subtype selective ligands (Vistoli *et al.*, 2008). These modeling studies and SAR data provide important information with which to design novel muscarinic ligands. For example, aromatic groups are reported to play a critical role in the binding of ACh to muscarinic receptors in the modeling studies discussed above (Nordvall and Hacksell, 1993; Peng *et al.*, 2006; Ostopovici *et al.*, 2007). These interactions may serve as auxiliary binding sites that contribute to increase affinity and possibly increased selectivity for ligands with appropriately positioned complimentary groups (Pedretti *et al.*, 2006).

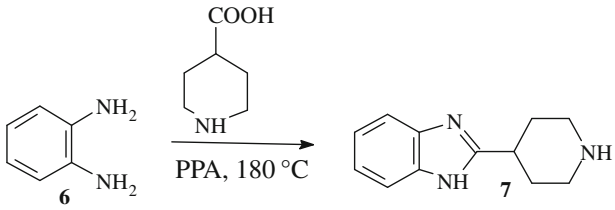
Our interest in developing novel muscarinic receptor ligands led to the design of lactone-based ligands using an approach similar to that reported by Kaiser *et al.* (1992) (Ahungena *et al.*, 2003). Hence, a series of semi-rigid muscarinic ligands were designed in which the lactone oxygens serve as a H-bond acceptor moieties while different nitrogen-containing heterocycles provide the requisite cationic group (see below). Preliminary binding studies indicate that several of the compounds were nonselective, low affinity ($IC_{50}$ = 1.81 and 1.56 μM for R = H and *i*-propyl, respectively) muscarinic agonists (based on preliminary in vivo data) (Ahungena *et al.*, 2003) (Fig. 1).

In this work, molecular modifications to our lead lactones have been made in order to increase receptor affinity. SAR data and molecular modeling experiments in the recent literature have been considered in the design of the novel compounds. The ligands contain a H-bond accepting moiety in the form of the lactone ring, a spacer ($CH_2$ in the present series), a cationic center in the form of nitrogen-containing heterocycles, and aromatic groups (Ahungena *et al.*, 2003; Kozlowski *et al.*, 2002; Ogino *et al.*, 2003; Lewis *et al.*, 2008) (Fig. 2).

An important distinction between the newly designed ligands and the lead lactones is the presence of substituted or unsubstituted aromatic systems that provide opportunities for interactions with auxiliary binding sites. The synthesis of the newly designed compounds and the effects of these molecular modifications on receptor affinity are reported herein.




**Scheme 1** Synthesis of precursors **4** and **5** (Ahungena and Canney, 1996)




**Scheme 2** Synthesis of precursor **7** [2-(4-piperidinyl)-1*H*-benzimidazole]

## Chemistry

Precursors **4** and **5** were synthesized from olefinic acid **3** as described previously (Scheme 1). Briefly epoxylactonization of olefinic acid **3** afforded hydroxy lactone **5** while iodolactonization of **3** provided iodolactone **4** in acceptable yields (Ahungena and Canney, 1996).

Benzimidazole **7** served as an intermediate for the synthesis of target compound **17** (Scheme 2) and was prepared by treating 1,2-diamino benzene **6** with 4-piperidine carboxylic acid in presence of polyphosphoric acid (PPA) (Orjales *et al.*, 1995).

Carbamate **13** (Scheme 3) was prepared by reacting alcohol **5** with the commercially available 4-piperidylbenzenisocyanate in dry dichloromethane at room temperature (Zhao, 2001).

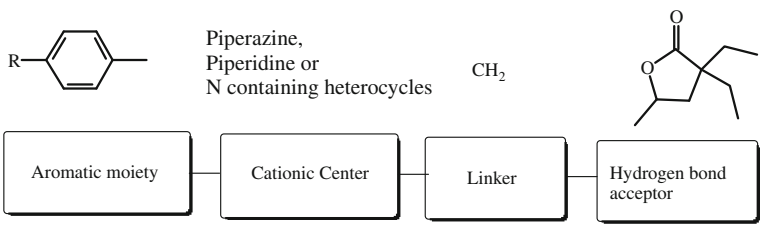
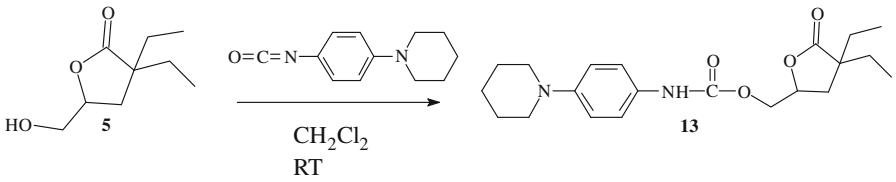
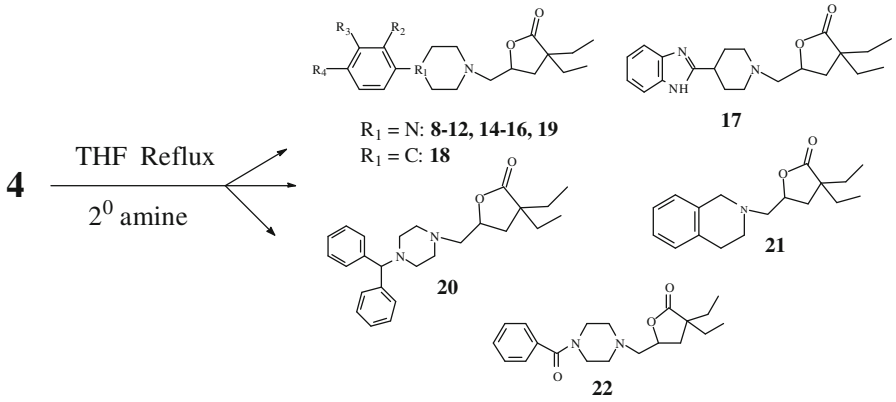



**Fig. 2** General structural features of the newly designed ligands

**Scheme 3** Synthesis of carbamate **13** from lactone **5** and commercially available 1-(4-isocyanatophenyl) piperidine




**Scheme 4** Synthesis of target compounds **8–12**, **14–22** from iodolactone **4**



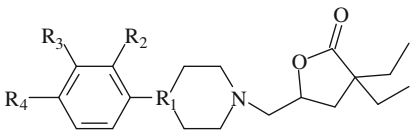

Compounds **8–12**, **14–22** were prepared as shown in Scheme 4 using precursor **4**. Hence, displacement of the iodine of lactone **4** by secondary amines under refluxing conditions (48 h) afforded the target ligands in 7–40% yield (Ahungena *et al.*, 2003; Ahungena and Canney, 1996).

## Results

A series of substituted furanones were prepared in modest yields using well precedented literature routes. The lactone-based ligands reported herein have pharmacophoric features in common but differ in potentially important ways. Compounds **8–12**, **14–16**, and **19** share a lactone ring coupled to phenyl piperazines containing a variety of electron withdrawing ($NO_2$, CN) or electron donating ($OCH_3$, OH) aromatic substituents. Compound **20** is an unsubstituted diphenylpiperazine. Compound **17** has a piperidine nitrogen and benzimidazole nitrogens as potential cationic centers. Compounds **18**, **21**, and **22** are similar in that each compound has only one nitrogen capable of forming a cationic center. Compounds **13** and **22** have additional opportunities for H-bond formation in their carbamate and amide moieties. Compound **13** is unique within the present series of ligands as its nitrogen-containing heterocycle is on the opposite side of the aromatic group.

Binding studies were preformed at CEREP using rat cerebral cortex membranes as per a previously published method (Richards, 1990). Preliminary data presented in Tables 1 and 2 represent the percent inhibition of specific binding of radioligand at a single concentration (10 μM) of test compound.

**Table 1** Preliminary binding data (% inhibition at 10 μM) for lactone-based compounds containing phenyl piperazines and piperidines



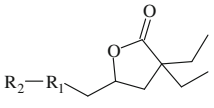

| Compound # | $R_1$ | $R_2$ | $R_3$ | $R_4$ | % Specific inhibition |
|---|---|---|---|---|---|
| **8** | N | H | H | $OCH_3$ | **26** |
| **9** | N | H | H | CN | 18 |
| **10** | N | H | H | $NO_2$ | 18 |
| **11** | N | H | H | H | 16 |
| **12** | N | $OCH_3$ | H | H | **32** |
| **14** | N | H | $OCH_3$ | H | 9 |
| **15** | N | H | H | OH | 7 |
| **16** | N | OH | H | H | **46** |
| **18** | C | H | H | H | **68** |
| **19** | N | CN | H | H | **31** |

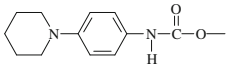
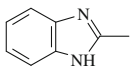
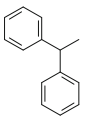
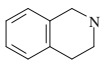
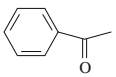
Bold value indicates % specific inhibition of more than 20%

For details regarding the evaluation of results, see "Experimental" section

Preliminary binding studies performed for the test compound at 10 μM revealed that both piperidine and piperazine containing compounds exhibited affinity for muscarinic receptors. Piperazines **8**, **12**, and **19** and piperidinyl phenyl carbamate **13** inhibited [$^3$H]-QNB binding to rat cerebral cortex membranes by 26–32%. Piperazine **16**, piperidine (benzimidazole) **17**, and 1,2,3,4-tetrahydroisoquinoline **21** were inhibitors of specific binding also with

**Table 2** Preliminary binding data (% inhibition at 10 μM) for lactone-based compounds **13**, **17**, **20–22**



| Compound # | $R_2$ | $R_1$ | % Specific inhibition |
|---|---|---|---|
| **13** |  | | **31** |
| **17** |  |  | **46** |
| **20** |  |  | **97** |
| **21** |  | | **44** |
| **22** |  |  | 5 |

Bold value indicates % specific inhibition of more than 20%

For details regarding the evaluation of results, see "Experimental" section

percent inhibition values ranging from 44 to 46%. In the present series of lactones, compounds **18** and **20** exhibited the highest % inhibition values (68 and 97%, respectively). Compound **20** was chosen for further evaluation and a full binding curve was generated. The $IC_{50}$ of biphenylmethylpiperazine **20** was determined to be 340 nM. Based on the guidelines suggested for interpretation of these data, the remaining piperazines **9**, **10**, **11**, **14**, **15**, and **22** (amide) were considered inactive.

## Discussion

The test compounds were prepared based on literature procedures and evaluated in preliminary binding assays. Molecular modifications to a series of lactone-based muscarinic leads were made in an effort to increase affinity. The original lead lactones contained various substituted amines and amine containing heterocycles and were found to have $IC_{50}$ values in 1–2 μM. The compounds reported herein differ from the leads in that all possess substituted or unsubstituted aromatic rings. The electronic nature of substituents on the test compounds vary from electron donating groups (e.g., **16**; OH) to strong electron withdrawing groups (e.g., **10**; $NO_2$). The position of the functional groups was varied also (e.g., **8**, **12**, and **14**). Generally, the % inhibition data provided herein is interpreted as follows: the baseline for % inhibition is considered −20 to 20% and compounds in this range are considered to be inactive; compounds in the range 20–49% are considered marginally active; while compounds exhibiting >50% inhibition are considered active and warrant further study.

With these limitations in mind, the binding data for this set of aromatic heterocycles suggest that the position of the substituent may hold precedent over the electronic nature. For example, the ortho substituted compounds **12** (32%), **16** (46%), and **19** (31%) were marginally active and were the only compounds in Table 1 to inhibit the binding by more than 30%. The corresponding derivatives with substituents at the para position (**9**, **10**, and **15**) were inactive (7–18%). Introduction of an additional hydrogen bond acceptor in the form of a carbamate in **13** did not improve activity. A comparison of the % inhibition for piperazine **11** with that for piperidine **18** reveals an improvement in activity. These results suggest that further evaluation of piperidine containing lactones is warranted. The addition of an imidazole ring in **17** resulted in marginal activity (46%). These results may suggest that the phenyl ring (without the imidazole) of **18** (68%) is better able to π–π stacking interaction with aromatic residues in the receptor pocket (additional work is required to test this hypothesis). Fusing the piperidine with an aromatic ring in **21** did not improve the activity and the introduction of an additional H-bond acceptor group (amide carbonyl) in **22** proved deleterious to binding. Of all the test compounds assayed, diphenylmethylpiperazine **20** was found to inhibit specific binding by 97% at 10 μM. Further evaluation to determine the $IC_{50}$ value revealed **20** to be the highest affinity lactone-based ligand identified in this series ($IC_{50}$ = 340 nM).

The affinity of ligand **20** ($IC_{50}$ = 340 nM) is improved compared to our previously reported ligands ($IC_{50s}$ of 1–2 μM). The data reported herein confirm that the lactone nucleus is a useful scaffold for the design of muscarinic ligands and indicate that the addition of appropriately positioned aromatic substituents can improve affinity. The % inhibition studies reported herein suggest that further structural modification to these lactone derivatives may

provide high affinity compounds that could be used in future efforts to develop subtype selective ligands. Compounds **18** and **20** will serve as leads in future efforts to design higher affinity muscarinic ligands.

## Experimental

### Chemical methods

Proton magnetic resonance spectra ($^1$H NMR) were measured in $CDCl_3$ on a Bruker WM-400 MHz instrument, data are presented as follows: chemical shift in parts per million (ppm) on the $\delta$ scale relative to internal tetramethylsilane (TMS) (coupling constant(s) in hertz). The following abbreviations are used to denote signal patterns: s = singlet, d = doublet, t = triplet, m = multiplet. Elemental analyses were performed by Atlantic Micolabs, Inc., Atlanta, GA, and were within ±0.4% of the theoretical values. All TLC was run using Silicycle precoated 60-F-254 silica plates (0.25 mm) with dichloromethane in methanol (9:1) solvent system and the components were visualized with iodine vapor and/or UV-light. Extractive workups culminated in washing the organic layer with brine, drying over $MgSO_4$, and evaporating the solvent at reduced pressure on a rotary evaporator. Flash column chromatography was carried out on Silia-P flash silica gel (40–63 μm) using methanol (0–3%) in dicloromethane solvent system. Preparative TLC was performed on Siliaplate TLC plates (particle size 1000 μm) using methanol (8%) in dichloromethane mobile phase (HPLC grade). HPLC analysis was performed using a Gilson 215 reversed phase chromatographic system equipped with a Sepax GP-C18 (21.2 × 100 mm 5 μm column) and a UV–Vis detector. The purity was analyzed using two mobile phases in 10–90% acetonitrile in water solvent gradient containing 0.1% formic acid (method A) and; 10–90% methanol in water solvent gradient containing 0.1% trifluroacetic acid (method B). The purity of compounds **10**, **12**–**22** was found to be >95%. Elemental analyses were performed on compounds **8**, **9**, and **11** and were found to be in acceptable range (±0.4%). LC–MS (ESI) analyses were done on an Agilent technologies 1200 series instrument using 95% acetonitrile in water solvent system. Compounds **4**, **5**, and **7** were prepared as described previously and spectroscopic data were identical to reported data (Ahungena and Canney, 1996; Orjales *et al.*, 1995).

## Binding studies

The target compounds **8**–**22** were evaluated in radioligand binding assays performed by CEREP, 86600 CELLE L'EVESCAULT, France using rat cerebral cortex membranes expressing muscarinic receptor subtypes $M_1$–$M_5$. The competitive binding assays were performed according to the previously reported method (Richards, 1990). The assays were done in duplicate and are presented as supplied by CEREP. Briefly, [$^3$H]-QNB (0.05 nM) and the test compound (10 μM) were incubated with rat cerebral cortex membranes for 90 min at room temperature. Following incubation, the reaction was terminated by filtration. Atropine (1 μM) was used to determine non-specific binding. The bound radioactivity was measured with scintillation counter. For interpretation of this type of preliminary data, CEREP suggests the following guidelines: 50% inhibition or higher represent significant effects (i.e., 50% is a common cut-off value for further investigation; determination of $IC_{50}$ or $EC_{50}$ values from concentration response curves). Results showing an inhibition between 20 and 50% indicate weak to moderate effects; inhibition less than 20% are considered inactive.

### Chemistry

*General procedure for compounds **8–12, 14–22***

Iodomethyl lactone **4** (1 Eq) and the appropriate secondary amine (5 Eq) in anhydrous tetrahydrofuran (THF; 35 ml) was stirred at reflux under a nitrogen atmosphere for 48 h. After 48 h, the mixture was filtered (when appropriate), concentrated under reduced pressure and the residue was dissolved in dichloromethane and purified by flash silica gel chromatography using methanol (0–3%) in dichloromethane.

*General procedure for compound **13***

To a solution of hydroxymethyl lactone **5** (1 Eq) in anhydrous dichloromethane (5 ml) was added 1-(4-isocyanatophenyl) piperidine (1 Eq) in dichloromethane (5 ml) with stirring. The reaction was stirred overnight, filtered, and the residue chromatographed on silica gel using methanol (1%) in dichloromethane.

*3,3-Diethyl-4,5-dihydro-5-(4-[4-methoxyphenyl]piperazinylmethyl)-2(3H)-furanone (**8**)* Pale yellow solid. Yield: 31.33%. $^1$H NMR: {$CDCl_3$, 400 MHz, $\delta$ (ppm)} 0.88–0.96 (m, 6H), 1.59–1.65 (m, 4H), 1.88–1.94 (m, 1H), 2.04–2.09 (m, 1H), 2.57–2.79 (m, 6H), 3.06–3.09 (m, 4H), 3.74 (s, 3H), 4.56–4.60 (m, 1H), 6.81–6.89 (m, 4H). Elemental analysis: calcd for $C_{20}H_{30}N_2O_3$: C, 69.33; H, 8.73; N, 8.09. Found: C, 69.11; H, 8.81; N, 8.01%.

*3,3-Diethyl-4,5-dihydro-5-(4-[4-cyanophenyl]piperazinylmethyl)-2(3H)-furanone (**9**)* Pale yellow liquid. Yield:

15.78%. $^1$H NMR: {$CDCl_3$, 400 MHz, $\delta$ (ppm)} 0.80–0.90 (m, 6H), 1.53–1.61 (m, 4H), 1.83–1.88 (m, 1H), 1.99–2.04 (m, 1H), 2.49–2.71 (m, 6H), 3.24–3.26 (m, 4H), 4.49–4.55 (m, 1H), 6.76–6.80 (d, 2H), 7.41–7.44 (d, 2H). Elemental analysis: calcd for $C_{20}H_{27}N_3O_2$: C, 70.35; H, 7.97; N, 12.31. Found: C, 70.07; H, 8.03; N, 12.11%.

*3,3-Diethyl-4,5-dihydro-5-(4-[4-nitrophenyl]piperazinylmethyl)-2(3H)-furanone (**10**)* Pale yellow liquid. Yield: 25.97%. $^1$H NMR: {$CDCl_3$, 400 MHz, $\delta$ (ppm)} 0.87–0.97 (m, 6H), 1.59–1.66 (m, 4H), 1.89–1.94 (m, 1H), 2.05–2.10 (m, 1H), 2.56–2.78 (m, 6H), 3.37–3.42 (m, 4H), 4.55–4.61 (m, 1H), 6.77–6.82 (d, 2H), 8.07–8.12 (d, 2H). LC–MS (ESI) (*m*/*z*) 362.3 $(M + H)^+$. HPLC analysis: >95% purity using two different mobile phases.

*3,3-Diethyl-4,5-dihydro-5-(4-[4-phenyl]piperazinylmethyl)-2(3H)-furanone (**11**)* Pale yellow solid. Yield: 22.02%. $^1$H NMR: {$CDCl_3$, 400 MHz, $\delta$ (ppm)} 0.89–0.98 (m, 6H), 1.60–1.66 (m, 4H), 1.90–1.96 (m, 1H), 2.06–2.11 (m, 1H), 2.58–2.80 (m, 6H), 3.14–3.21 (m, 4H), 4.57–4.63 (m, 1H), 6.85 (t, 1H), 6.92 (d, 2H), 7.26 (t, 2H). Elemental analysis: calcd for: $C_{19}H_{28}N_2O_2$: C, 72.12; H, 8.92; N, 8.85. Found: C, 72.40; H, 9.13; N, 8.65%.

*3,3-Diethyl-4,5-dihydro-5-(4-[2-methoxyphenyl]piperazinylmethyl)-2(3H)-furanone (**12**)* Pale yellow liquid. Yield: 17.04%. $^1$H NMR: {$CDCl_3$, 400 MHz, $\delta$ (ppm)} 0.89–0.97 (m, 6H), 1.60–1.65 (m, 4H), 1.88–1.91 (m, 1H), 2.05–2.10 (m, 1H), 2.60–2.81 (m, 6H), 3.08 (m, 4H), 3.85 (s, 3H), 4.58–4.62 (m, 1H), 6.84–7.01 (m, 4H). LC–MS (ESI) (*m*/*z*) 347.3 $(M + H)^+$. HPLC analysis: >95% purity using two different mobile phases.

*(4-Piperidinylphenyl)-1-carbamic acid 3,3-diethyl-4,5-dihydro-2(3H)-furanone methylester (**13**)* Pale yellow solid. Yield: 52.66%. $^1$H NMR: {$CDCl_3$, 400 MHz, $\delta$ (ppm)} 0.89–0.97 (m, 6H), 1.52–1.72 (m, 10H), 1.90–1.95 (m, 1H), 2.06–2.11 (m, 1H), 3.07–3.10, 4.12–4.16 (m, 1H), 4.38–4.42 (m, 1H), 4.61–4.67 (m, 1H), 6.57 (s, 1H), 6.89 (d, 2H), 7.22–7.23 (m, 2H). LC–MS (ESI) (*m*/*z*) 376.2 $(M + H)^+$. HPLC analysis: >95% purity using two different mobile phases.

*3,3-Diethyl-4,5-dihydro-5-(4-[3-methoxyphenyl]piperazinylmethyl)-2(3H)-furanone (**14**)* Pale yellow liquid. Yield: 40.54%. $^1$H NMR: {$CDCl_3$, 400 MHz, $\delta$ (ppm)} 0.87–0.96 (m, 6H), 1.58–1.64 (m, 4H), 1.88–1.93 (m, 1H), 2.03–2.08 (m, 1H), 2.55–2.76 (m, 6H), 3.12–3.18 (m, 4H), 3.76 (s, 3H), 4.56–4.59 (m, 1H), 6.38–6.53 (m, 3H), 7.12–7.16 (t, 1H). LC–MS (ESI) (*m*/*z*) 347.3 $(M + H)^+$. HPLC analysis: >95% purity using two different mobile phases.

*3,3-Diethyl-4,5-dihydro-5-(4-[4-hydroxyphenyl]piperazinylmethyl)-2(3H)-furanone (**15**)* Pale yellow solid. Yield: 7.79%. $^1$H NMR: {$CDCl_3$, 400 MHz, $\delta$ (ppm)} 0.85–0.92 (m, 6H), 1.55–1.62 (m, 4H), 1.82–1.88 (m, 1H), 2.01–2.06 (m, 1H), 2.54–2.81 (m, 6H), 3.02–3.05 (m, 4H), 4.55–4.62 (m, 1H), 6.71 (d, 2H), 6.78 (d, 2H). LC–MS (ESI) (*m*/*z*) 333.0 $(M + H)^+$. HPLC analysis: >95% purity using two different mobile phases.

*3,3-Diethyl-4,5-dihydro-5-(4-[2-hydroxyphenyl]piperazinylmethyl)-2(3H)-furanone (**16**)* Pale yellow liquid. Yield: 18.38%. $^1$H NMR: {$CDCl_3$, 400 MHz, $\delta$ (ppm)} 0.89–0.97 (m, 6H), 1.62–1.67 (m, 4H), 1.88–1.94 (m, 1H), 2.07–2.12 (m, 1H), 2.60–2.78 (m, 6H), 2.88–2.90 (m, 4H), 4.57–4.64 (m, 1H), 6.83–6.88 (m, 1H), 6.93–6.95 (m, 1H), 7.05–7.09 (m, 1H), 7.14–7.17 (m, 1H). LC–MS (ESI) (*m*/*z*) 333.3 $(M + H)^+$. HPLC analysis: >95% purity using two different mobile phases.

*3,3-Diethyl-4,5-dihydro-5-(2-[4-piperidinyl]benzimidazolylmethyl)-2(3H)-furanone (**17**)* Pale yellow solid. Yield: 10.15%. $^1$H NMR: {$CDCl_3$, 400 MHz, $\delta$ (ppm)} 0.85–0.96 (m, 6H), 1.57–1.65 (m, 4H), 1.86–2.28 (m, 9H), 2.51–2.64 (m, 2H), 2.88–3.09 (m, 3H), 4.52–4.58 (m, 1H), 7.15–7.25 (m, 2H), 7.51–7.54 (m, 2H). LC–MS (ESI) (*m*/*z*) 356.0 $(M + H)^+$. HPLC analysis: >95% purity using two different mobile phases.

*3,3-Diethyl-4,5-dihydro-5-(4-[4-phenyl]piperidinylmethyl)-2(3H)-furanone (**18**)* Pale yellow liquid. Yield: 23.74%. $^1$H NMR: {$CDCl_3$, 400 MHz, $\delta$ (ppm)} 0.93–1.01 (m, 6H), 1.63–1.69 (m, 4H), 1.81–1.95 (m, 5H), 2.09–2.14 (m, 1H), 2.23–2.29 (m, 2H), 2.51 (m, 1H), 2.64–2.67 (m, 2H), 3.05 (d, 11.2 Hz, 1H), 3.19 (d, 12.4 Hz, 1H), 4.62–4.63 (m, 1H), 7.22–7.34 (m, 5H). LC–MS (ESI) (*m*/*z*) 316.3 $(M + H)^+$. HPLC analysis: >95% purity using two different mobile phases.

*3,3-Diethyl-4,5-dihydro-5-(4-[2-cyanophenyl]piperazinylmethyl)-2(3H)-furanone (**19**)* Pale yellow liquid. Yield: 15.80%. $^1$H NMR: {$CDCl_3$, 400 MHz, $\delta$ (ppm)} 0.85–0.93 (m, 6H), 1.55–1.61 (m, 4H), 1.84–1.90 (m, 1H), 2.01–2.06 (m, 1H), 2.57–2.80 (m, 6H), 3.14–3.21 (m, 4H), 4.52–4.57 (m, 1H), 6.93–6.97 (m, 2H), 7.41–7.45 (m, 1H), 7.49 (dd, 8 and 4 Hz, 1H). LC–MS (ESI) (*m*/*z*) 342.2 $(M + H)^+$. HPLC analysis: >95% purity using two different mobile phases.

*3,3-Diethyl-4,5-dihydro-5-(4-[4-biphenylmethyl]piperazinylmethyl)-2(3H)-furanone (**20**)* Pale yellow liquid. Yield: 8.72%. $^1$H NMR: {$CDCl_3$, 400 MHz, $\delta$ (ppm)} 0.87–0.95 (m, 6H), 1.57–1.63 (m, 4H), 1.83–1.88 (m, 1H), 2.01–2.06 (m, 1H), 2.42–2.64 (m, 10H), 4.22 (s, 1H), 4.52–4.55 (m, 1 M), 7.14–7.18 (m, 2H), 7.24–7.27 (m, 4H), 7.40–7.42 (m, 4H). LC–MS (ESI) (*m/z*) 407.3 $(M + H)^+$. HPLC analysis: >95% purity using two different mobile phases.

*3,3-Diethyl-4,5-dihydro-5-([1,2,3,4-tetrahydroisoquinolyl]methyl)-2(3H)-furanone (**21**)* Pale yellow liquid. Yield: 7.4%. $^1$H NMR: {$CDCl_3$, 400 MHz, $\delta$ (ppm)} 0.90 (t, 3H), 0.96 (t, 3H), 1.59–1.66 (m, 4H), 1.91–1.97 (m, 1H), 2.08–2.13 (m, 1H), 2.72–2.90 (m, 6H), 3.70 (d, 1H), 3.81 (d, 1H), 4.62–4.68 (m, 1H), 7.01–7.03 (m, 1H), 7.03–7.13 (m, 3H). LC–MS (ESI) (*m/z*) 288.3 $(M + H)^+$. HPLC analysis: >95% purity using two different mobile phases.

*3,3-Diethyl-4,5-dihydro-5-(4-[4-phenylcarbonyl]piperazinylmethyl)-2(3H)-furanone (**22**)* Pale yellow liquid. Yield: 22.5%. $^1$H NMR: {$CDCl_3$, 400 MHz, $\delta$ (ppm)} 0.75–0.83 (m, 6H), 1.45–1.52 (m, 4H), 1.71–1.79 (m, 1H), 1.91–1.96 (m, 1H), 2.34–2.56 (m, 6H), 3.28–3.34 (m, 2H), 3.58–3.64 (m, 2H), 4.40–4.44 (m, 1H), 7.24–7.27 (m, 5H). LC–MS (ESI) (*m/z*) 345.3 $(M + H)^+$. HPLC analysis: >95% purity using two different mobile phases.

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