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Application of a Novel Design Paradigm to Generate General Nonpeptide Combinatorial Scaffolds Mimicking Beta Turns: Synthesis of Ligands for Somatostatin Receptors

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Abstract—Nonpeptide compounds that mimic bioactive peptides are desirable for a number of clinical indications. We report a new practical method for the design of scaffolds exhibiting drug-like properties that are suitable for the display of peptide pharmacophores. The synthesis of various synthons of 7′-hydroxy-2′,3′-dihydro-1′H,2H,5H-spiro[imidazolidine-4,4′-quinoline]-2,5-dione (**1**) and methods for the introduction of several mimics of amino acid side-chains are described. This method is exemplified by derivatives that show agonist activity for the somatostatin type 2 receptor.

Introduction

An important goal in medicinal chemistry has been to develop an understanding and a set of tools that will allow for the planned introduction of the important pharmacophores exhibited by the numerous potent bioactive peptides onto small synthetic drug-like scaffolds.[1] The development of nonpeptide agonists at peptide receptors has represented a particular challenge in medicinal chemistry. Recently there has been impressive progress in this area, as exemplified by the development of potent nonpeptide agonists of specific sub-types of important targets such as the melanocortin receptor (MC4),[2] growth hormone secretagogue peptide receptor (GHSP-6),[3] opioid (δ),[4,5] urotensin II,[6] and somatostatin receptors (hSST 1-5).[7–9] Despite these significant accomplishments in the stepwise introduction of such activity into small molecules, much of the progress in the discovery of nonpeptide agonists has relied on the iterative development of peptide analogues containing modified α-amino acids coupled with specific building blocks.[1,8] There have been relatively few examples of the use of clearly defined general methods that allow for the design and preparation of compounds that would be useful for the general exploration of the numerous interesting potential combinatorial pharmacophoric possibilities that do not include α-amino acids in the scaffold. One early notable example of such an approach is that of Hirschmann and co-workers.[9] We sought the development and application of a practical method for the design of scaffolds, based on fundamental principles, which would be useful to medicinal and combinatorial chemists. We preferred a design that would not include any α-amino acids in the scaffold since such compounds usually do not have the desired physiochemical properties. We initially chose to target somatostatin receptors, since the ligand pharmacophores are well studied.[10] As a starting point in our effort to develop a conceptual approach to this important problem, we noted the recent groundbreaking work of Garland and Dean.[11] These authors demonstrated that cluster analysis and recombination of the observed patterns yielded a consensus positioning of the C-α atoms among the various beta-turn types. They also showed that this relationship could be visualized as three independent specific three-point (triangular) distance-geometries that are common to all beta-turn types. These authors also demonstrated that these triangles could be used as queries to search 3D databases and find existing compounds that match the consensus positioning of the C-α atoms of beta-turns. These authors clearly demonstrated the utility of this method

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as a screen for existing compounds that possess the rather rare combination of: (1) the very specific constrained atomic positioning required mimicking the main-chain arrangement observed in beta turns, and (2) the capacity for the synthetic introduction of the required groups to mimic the side chain interactions.

We report here the extension of the Garland–Dean approach to the design of novel scaffolds, such as **1**, which contain multiple substitution points that match several of the Garland–Dean geometries (see Fig. 1). This design paradigm allows for the construction of other scaffolds that, like **1**, are suitable for the exhibition of many of the interesting combinatorial pharmacophoric possibilities that may be observed in bioactive peptides. We also report for the first time the synthesis of several active novel somatostatin agonists, using our design paradigm. This type of approach can be useful for the de novo design of ligands and for targeted library design.

Results

Our design of synthetically tractable templates containing the correct geometry that could be modified to be suitable for substitution with reagents that mimic the side-chains of the natural amino acids, is a stepwise process; First we searched >450,000 compounds from our internal 3D database of library screening structures, to seek structural starting points following the published method that had been previously applied to a subset from the compounds in the Available Chemical Directory (ACD).[11] We performed our 3D searches in Chem-X.[12] The structures that matched were ranked giving priority to molecules containing the fewest number of rotatable bonds. The top fifty structures were selected for evaluation based on their suitability for redesign, by inspection. In addition to the general types of structures that were previously reported[11] we also observed matches with numerous bicyclic (and spirobicyclic) ring systems. The various ring systems that matched were then combined and modified with the introduction of heteroatoms, where needed, until structures that contained multiple Garland–Dean geometries in the same template were designed. After several iterations of design, modeling, synthetic analysis, followed by redesign, we developed several potential molecular targets including the novel general scaffold **1** (see Fig. 1).

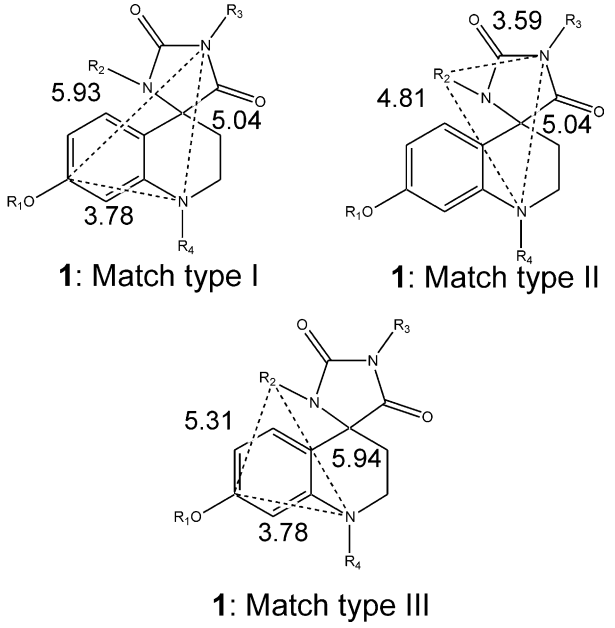
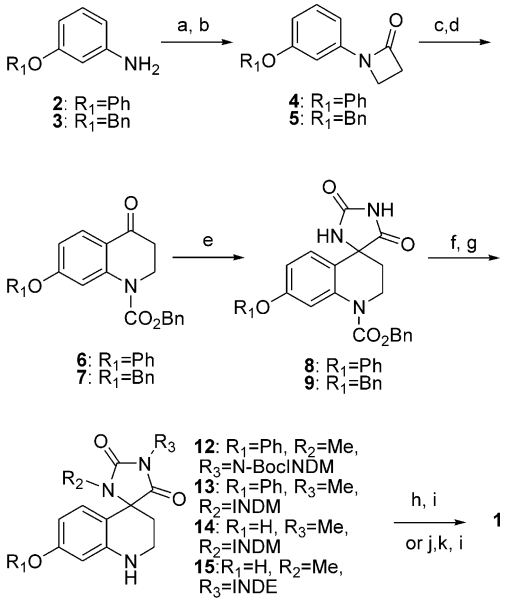


Figure 1. The general structure of the template 1 along with overlays representing the atoms mimicking the positions of the C-α atoms, and the distances in Angstroms between these atoms. The Garland–Dean class 3 distances that are the best match (with standard deviations in parentheses) are 5.42 (±0.57), 3.82 (±0.01), 5.44 (±0.55).

Our approach to the synthesis of derivatives of **1** is shown in Scheme 1 and begins with either 3-phenoxyaniline (**2**) or 3-benzyloxyaniline (**3**), which are both readily available. The corresponding beta-lactams **4** and **5** could then be prepared according to established methods.[13] We developed conditions for the acid catalyzed Fries rearrangement of these substrates[13] that cleanly gave the desired isomer (e.g., 7-(phen- and benzyl)-oxy-2,3-dihydro-1H-quinolin-4-one) in useful yields (35%). These intermediates were then converted to the corresponding benzyloxy-carbonyl derivatives **6** or **7**. Conversion of the dihydroquin-4-one derivatives to the corresponding hydantoin intermediates could then be accomplished by the treatment of the corresponding ketone with KCN and ammonium carbonate in ethanol,[14] to give the key intermediates **8** or **9**. These intermediates were then suitable for the step-wise regioselective introduction of substituents R_2 and R_3 in high yield, as shown.



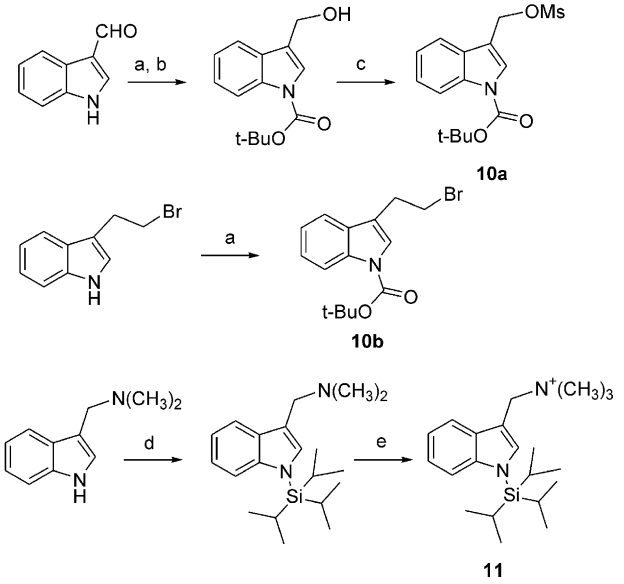
Scheme 1. The synthesis of compounds of the general structure **1** (see Table 1). Reagents: (a) 3-bromopropionic acid/EDC/TEA/DMAP; DCM; (b)TBACl/KOH/DCM; (c) PPE/DCE; (d) CBZ-Cl/DIEA/DCM; (e) KCN/NH_4CO_3/EtOH/70 °C; (f) (i) $R_3X/CsHCO_3$ (ii) K_2CO_3/R_2X or 11/NaH/TBAF/THF; (g) H_2/Pd; (h) EDC/TEA/DMAP/R_4-OH; (i) TFA/DCM; (j) $ArB(OH)_2/Cu(OAc)_2$; (k) $NaB(OAc)_3H$/DCM. Abbreviations: Ph = phenyl; Me = methyl; INDM = indolemeth-3-yl; INDE = indole-3-(eth-2-yl).

In order to present the pharmacophores that would be specifically desirable for some well studied cases such as somatostatin,[10] the opioid receptors[5] and the melanocortin receptors[2,15,16] we needed methods that would allow us to introduce building-blocks that would mimic the analogous side-chains found in the corresponding bioactive peptides. For the introduction of the side chain of mimics of tryptophan three different building blocks may be used (**10a**, **10b** or **11**: see Scheme 2).[17,18] Removal of the benzyloxycarbonyl group with hydrogen and palladium following alkylation of **8** and **9** then gave compounds **12**–**15**. Alkylation of compound **9** followed by hydrogenolysis removed both the benzyloxy-carbonyl group and the O-benzyl group, giving intermediates such as **14** and **15**. We found that these derivatives could undergo the copper catalyzed coupling specifically on the phenolic oxygen with electron rich boronic acids.[19] This allowed for the chemoselective introduction of numerous O-aryl substituents to mimic the side-chains of amino acids such as phenylalanine or tyrosine.

The building blocks that mimic the side-chain of lysine could then be introduced by acylation or reductive amination, followed by deprotection, to give final compounds that mimic the pharmacophores of bioactive somatostatin peptides. This synthetic scheme also allows for the introduction of groups that contain conformational constraints such as the 4-methylpiperidine group. This approach allowed for the synthesis of funtionalized beta turn mimics **16**–**22** (see Table 1).

Discussion

Table 1 shows the compounds that were prepared. While Table 2 shows a summary of the results of bioassays with the human somatostatin receptors (hSST) for



Scheme 2. The synthesis of tryptophan side-chain analogue building blocks **10a**, **10b** and **11**. Reagents: (a) Boc_2O/TEA/DMAP; DCM; (b); $NaBH_4$/EtOH (c) MsCl/TEA/DCM; (d) TIPSCl/DIEA/DCM; (e) CH_3I/THF.

Table 1. Summary of derivatives of the general structure 1[a]

Compd	R_1	R_2	R_3	R_4
16	Ph	Me	INDM	4-ABC
17	Ph	INDM	Me	4-ABC
18	Ph	INDM	Me	4-AB
19	Tol	INDM	Me	4-AB
20	Ph	INDM	Me	PIPM
21	Tol	Me	INDE	4-AB
22	MDP	Me	INDE	4-AB

[a]Abbreviations: Ph = phenyl; Me = methyl; INDM = indole-3-meth-3-yl; 4-ABC = 4-$H_2N(CH_2)_3CO$-; 4-AB = 4-aminobutan-1-yl; PIPM = piperidinemeth-4-yl; Tol = 4-methylphenyl; INDE = indole-3-(eth-2-yl) MDP = 2,4-methylenedioxyphenyl.

binding in hSST1, hSST3, hSST4,[20] as well as the guinea pig receptor agonist assay data for gpSST2 and gpSST5.[21] Compound **16** (shown in Fig. 1) that correctly fits Match Type I, shows binding to all of the hSST receptors investigated as well as agonist activity at the gpSST2 receptor. Compound **17** fits match type III, but is one atom short in the R_2 side-chain. This compound shows, at best, only very weak activity to the SST receptors, as expected. Interestingly the more conformationally flexible compound **18** does show binding to hSST1 and hSST3 but only weak activity at the hSST4 and gpSST2 receptors. Small modifications can have significant effects as shown by compound **19**, which only differs from **18** by the addition of a methyl group at the 4-position of the phenyl group. This conservative modification allows for much more potent SST1 binding, with a modest associated enhancement in gpSST2 agonist activity. Compound **20**, which contains a specific side-chain constraint, shows enhanced activity when compared to compound **18**, which lacks this ring constraint. Compounds **21** and **22** fit match I (Fig. 1) but have an additional atom in the R_3 side-chain, and therefore more conformational freedom. Both of these compounds show significantly enhanced activity when compared to compound **16** in binding at the hSST1 and hSST4 receptors but reduced agonist activity at the gpSST2 receptor. Compounds **16**, **18**, **19**, **20**, and **22** showed 61%, 114%, 68%, 82% and 55% agonist activity against gpSST2, respectively (% relative to $somatostatin_{28}$ contraction response, data not shown[21]). Table 2 also shows data on compound **23** (see Fig. 2) that was previously reported as the result of screening a highly targeted library of β-turn mimics.[22] It can be seen that the activity that we observed from a much smaller set of compounds is generally similar to that seen with derivatives such as **23**, despite the desirable conformationally constrained nature of our template, and the desired absence of any amino acids in our compounds.

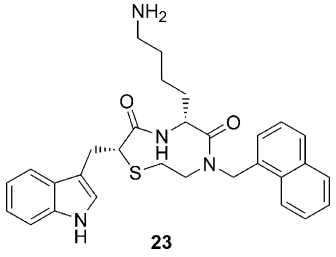


Figure 2. The structure of the known SST5 ligand.[22]

Table 2. Summary of the binding and agonist activity for the SST receptors (μM)

Compd	K_i[a] [IC_{50}][d] hSST1	IC_{50}[b] gpSST2	K_i[a] [IC_{50}][d] hSST3	K_i[a] [IC_{50}][d] hSST4	IC_{50}[c] gpSST5
16	6.1	2.9	5.9	5.3	>10
17	>10	>30	>10	>10	ND
18	3.1	>30	5.2	>10	ND
19	0.65	23.3	6.3	4.5	ND
20	1.8	10.5	1.3	1.4	ND
21	1.2	>30	6.7	0.57	ND
22	0.66	22.9	3.3	0.66	>10
23[22]	[0.5]	—	[3.1]	[1.0]	—

[a]Binding (μM).
[b]Agonist activity in guinea pig ileum (μM).
[c]Agonist activity in guinea pig vas deferens (μM).
[d]Binding for compound **23** (μM) as previously reported in reference 22.

Conclusion

We have developed a method for the design of nonpeptide templates, such as **1**, that may be elaborated to mimic the activity of peptides, as exemplified by compounds **16**–**22** these compounds show significant activity, *and contain no amino acids*. Thus we have outlined an approach that can, in at least these receptors, produce 'hits' de novo (with no high-throughput screening). We have shown, by partial exploration of a few of the numerous combinatorial positional and substitution possibilities, that the selectivity and potency to even closely related receptors could be modulated. These examples indicate that this design paradigm, and templates such as **1**, show great potential for the exploration and discovery of new active pharmacophores, and corresponding new chemical entities with activity at protein families that recognize the beta-turn motif. Additional exploration and refinement should lead to more potent and selective compounds active at the somatostatin receptor and other receptors of interest. Extension of this work to other peptide GPCRs is currently in progress in our labs.

Experimental

General

Melting points were determined on an Electrothermal MEL-TEMP capillary melting point apparatus and are uncorrected. Thin-layer chromatography (TLC) was performed on silica gel 60F-254 plate purchased from E-Merck and Co. Separation by column chromatography was performed on Merck silica gel 60 for flash chromatography. Nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Brucker AMX 300 or AMX 500 spectrometer. Chemical shifts were expressed in part per million (δ) with tetramethylsilane (TMS) as an internal standard; s = singlet; d = doublet; dd = doublet of doublets; t = triplet; m = multiplet; bs = broad singlet. Low Resolution mass spectra (ESI) were obtained with PE SCIEX API 150 EX. Microanalyses were performed at NuMega Resonance Labs, Inc. Chemicals (including compounds **2** and **3**) and solvents were purchased from Aldrich Chemical Co. and used without further purification. Biological evaluation was performed by MDS Pharma Services and full detailed descriptions are available from MDS Pharma (http://www.mdsps.com). The K_i determinations were made using a five point curve (n = 2). I^{125} Somatostatin$_{14}$ was used as the radioligand for the binding assays (hSST 1, hSST 3 and hSST 4) with IC_{50}'s of 3.7 ± 2.5 nM (n = 61), 0.47 ± 0.25 nM (n = 68), and 4.6 ± 2.1 nM (n = 37) respectively. Somatostatin$_{28}$ (at 30 nM) was used as the ligand for the agonism assays (gpSST 2, and gpSST 5) with IC_{50}'s of 69 ± 10 nM (n = 20), and 68 ± 12 nM (n = 15) respectively.

4-Phenoxyaniline-3′-bromopropionamide (2A). A well stirred solution of 3-phenoxyaniline (1.85 g, 10 mmol) in 20 mL of dichloromethane (DCM) was treated successively with 3-bromopropionic acid (1.74 g, 11 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide HCl (EDC) (2.35 g, 12 mmol) and 4-dimethylaminopyridine (0.06 g, 0.5 mmol), under an atmosphere of dry nitrogen. The resulting solution was allowed to stir for 30 min at room temperature. The mixture was then poured into 150 mL of chloroform and washed successively with 50 mL 1 N HCl, 50 mL water, satd aqueous $NaHCO_3$ (2×50 mL), 50 mL brine then dried (Na_2SO_4) and evaporated. This oil (2.4 g, 100% crude yield) was used directly in the next steps. ^{1}H NMR ($CDCl_3$) δ: 7.33 (m, 2H), 7.22 (m, 2H), 7.16 (m, 2H), 7.01 (m, 2H), 6.71 (m, 1H), 3.88 (s, 2H), 3.74 (t, J = 3.9 Hz, 2H), 2.97 (t, J = 3.9 Hz, 2H); ESI-MS m/z 321 $[M+H]^+$.

4-Benzyloxyaniline-3′-bromopropionamide (3A). A well stirred solution of 3-benzyloxyaniline (5.08 g, 25 mmol) in 40 mL of DCM was treated successively with 3-bromopropionic acid (4.34 g, 27.5 mmol), 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide HCl (EDC) (5.61 g, 28.7 mmol) and 4-dimethylaminopyridine (0.305 g, 2.5 mmol), under an atmosphere of dry nitrogen. The resulting solution was allowed to stir for 30 min at room temperature. The mixture was then poured into 150 mL of chloroform and washed successively with 50 mL 1 N HCl, 50 mL water, satd. aqueous $NaHCO_3$ (2×50 mL), 50 mL brine then dried (Na_2SO_4), filtered though a pad of silica gel and the filtrate evaporated. This oil (8 g, 96% yield) was used directly in the next steps. ^{1}H NMR ($CDCl_3$) δ: 7.43 (m, 4H), 7.36 (m, 1H), 7.22 (m, 2H), 6.99 (d, J = 4.8 Hz, 1H), 6.76 (d, J = 4.8 Hz, 1H), 5.06 (s, 2H), 3.71 (t, J = 3.9 Hz, 2H), 2.93 (t, J = 3.9 Hz, 2H); ESI-MS m/z 335 $[M+H]^+$.

1-(3-Phenyloxy-phenyl)-azetidin-2-one (4). A well-stirred solution of Compound **2A**, (3.2 g, 10 mmol) in 100 mL of DCM was treated successively with KOH (0.589 g, 10.5 mmol), and 18-crown-6 (2.77 g, 10.5 mmol) under an atmosphere of dry nitrogen. The resulting solution was allowed to stir for 3 h at room temperature. The mixture was then poured into 150 mL of DCM and washed successively 50 mL water, satd. aqueous NH_4Cl (2×50 mL) and 50 mL brine then dried (Na_2SO_4) and evaporated. This residue was then purified by column chromatography (methanol/DCM 1/200) to give 2.3 g (100%) of pure material. Mp = 102–103 °C. ^1H NMR ($CDCl_3$) δ 7.33 (app t, J = 4.8 Hz, 2H), 7.16–7.09 (m, 2H), 7.00 (m, 2H), 6.70 (dd, J = 1.5 and 4.8 Hz), 3.59 (t, J = 2.4 Hz, 2H), 3.10 (t, J = 2.4 Hz, 2H); ESI-MS m/z 335 $[M+H]^+$; CHN calcd for $C_{23}H_{19}NO_4$: C 73.98%, H 5.13%, N 3.75%; Found C 74.02%, H 5.29%, N 3.74%.

1-(3-Benzyloxy-phenyl)-azetidin-2-one (5). A well stirred solution of Compound **3A** prepared as above (8.35 g, 25 mmol) in 150 mL of DCM was treated successively with KOH (1.4 g, 25 mmol), and tetrabutylammonium bromide (8.06 g, 25 mmol) under an atmosphere of dry nitrogen. The resulting solution was allowed to stir for 3 h at room temperature. The mixture was then poured into 150 mL of DCM and washed successively 50 mL water, satd. aqueous NH_4Cl (2×50 mL) and 50 mL brine then dried (Na_2SO_4) and evaporated. This residue was then purified by column chromatography (methanol/DCM 1/300) to give 4.5 g (74%) of pure material. Mp = 96–98 °C. ^1H NMR ($CDCl_3$) δ 7.44 (m, 2H), 7.40 (app t, J = 4.8 Hz), 7.34 (m, 1H0, 7.24 (m, 1H0, 7.10 (m, 1H), 6.90 (m, 1H), 6.72 (m, 1H),. 5.06 (s, 2H), 3.60 (t, J = 2.4 Hz, 2H), 3.10 (t, J = 2.4 Hz, 2H); ESI-MS m/z 254 $[M+H]^+$; calcd for $C_{16}H_{15}NO_2$; C 75.87%, N 5.53%, H 5.97%; Found: C 75.60%, H 5.97%, N 5.48%.

7-Phenoxy-2,3-dihydro-1H-quinolin-4-one (4A). A well-stirred solution of 1-(3-phenoxy-phenyl)-azetidin-2-one (2.3 g, 9.6 mmol) in 30 mL of trifluoroacetic acid (TFA) was refluxed for 1 h under an atmosphere of dry nitrogen. The resulting solution was diluted with ice/water, treated with 35 mL of 28% aqueous NH3 and extracted with chloroform (2×100 mL). The combined extracts were dried (Na_2SO_4) and evaporated. This residue was then purified by column chromatography (methanol/DCM 1/4) to give 0.85 g (36% yield) of 7-phenoxy-2,3-dihydro-1H-quinolin-4-one; ^1H NMR ($CDCl_3$) δ 7.82 (d, J = 5.4 Hz, 1H), 7.31 (t, J = 4.8 Hz, 1H), 7.13 (t, J = 4.5 Hz, 2H), 6.37 (m, 1H), 6.10 (bs, 1H), 4.33 (bs, 1H), 3.55 (t, J = 4.2 Hz, 2H), 2.66 (t, J = 4.2 Hz, 2H); ESI-MS m/z 240 $[M+H]^+$.

A related by-product 5-phenoxy-2,3-dihydro-1H-quinolin-4-one was also isolated and characterized (0.44 g, 18%); ^1H NMR ($CDCl_3$) δ 7.31 (m, 2H), 7.13 (m, 1H), 7.07 (t, J = 4.5 Hz, 1H), 7.00 (d, J = 4.5 Hz, 2H), 6.39 (d, J = 4.9 Hz, 1H), 6.13 (d, J = 4.9 Hz, 1H), 4.50 (bs, 1H), 3.57 (t, J = 4.2 Hz, 2H), 2.68 (t, J = 4.2 Hz, 2H); ESI-MS m/z 240 $[M+H]^+$.

7-Benzyloxy-2,3-dihydro-1H-quinolin-4-one (5A). A well-stirred solution of 1-(3-benzyloxy-phenyl)-azetidin-2-one, (10 g, 39.5 mmol) in 300 mL of dichloroethane was treated with polyphosphoric ester (PPE) (100 g,) under an atmosphere of dry nitrogen. The resulting solution was allowed to stir then heated to reflux for 1.5 h. The mixture was then evaporated to approximately 100 mL and poured into 500 mL of ice/water. This was extracted with ethyl acetate (3×150 mL), these combined extracts were washed with 150 mL water, satd. aqueous $NaHCO_3$ (2×50 mL) and 50 mL brine, then dried (Na_2SO_4) and evaporated. The residue was then purified by column chromatography (methanol/DCM 1/300, then hexane/ethyl acetate with 2% isopropanol) to give 3 g (30% yield) of pure material. ^1H NMR ($CDCl_3$) δ 7.82 (d, J = 5.4 Hz, 1H). 7.39–7.38 (m, 5H), 6.40 (dd, J = 5.1 and 1.2 Hz, 1H), 6.15 (bs, 1H), 5.06 (bs, 2H) 4.33 (bs, 1H), 3.55 (t, J = 4.2 Hz, 2H), 2.66 (t, J = 4.2 Hz, 2H); ESI-MS m/z 254 $[M+H]^+$.

1-Benzyloxycarbonyl-7-benzyloxy-4-3,4-dihydro-2H-quinoline (7). A well-stirred solution of **5A**, (2 g, 7.89 mmol) in 30 mL of DCM containing diisopropylethylamine (4.1 g, 31.56 mmole) was treated dropwise with benzyl chloroformate (4.0 g, 23.68 mmol) under an atmosphere of dry nitrogen. The resulting mixture was allowed to stir for 48 h then diluted with 20 mL of DCM. This mixture was then washed with 100 mL of water, 150 mL of 1 N HCl, and satd aqueous $NaHCO_3$ (2×50 mL), then dried (Na_2SO_4) and evaporated. This residue was then purified by column chromatography (hexane/ethyl acetate 5/1 to 4/1) to give 3.0 g (98% yield) of pure material. ^1H NMR ($CDCl_3$) δ: 7.95 (d, J = 5.1 Hz, 1H). 7.3–7.5 (m, 11H), 6.78 (m, 1H), 5.28 (s, 2H), 4.99 (s, 2H), 4.21 (t, J = 3.6 Hz, 2H), 2.72 (t, J = 3.6 Hz, 2H); ESI-MS m/z 386 $[M-H]^-$.

1-Benzyloxycarbonyl-7-phenoxy-4-3,4-dihydro-2H-quinoline (6). Prepared as **7**, (95%), ^1H NMR ($CDCl_3$) δ: 7.97 (d, J = 5.1 Hz, 1H). 7.3–7.4 (m, 7H), 7.22 (t, J = 4.5 Hz, 1H), 7.06 (d, J = 5.1 Hz, 2H), 6.76 (dd, J = 5.1 and 1.2 Hz, 1H), 5.22 (s, 2H), 4.21 (t, J = 3.6 Hz, 2H), 2.74 (t, J = 3.6 Hz, 2H); ESI-MS m/z 274 $[M+H]^+$, 396 $[M+H]^+$.

7-Phenoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester-4-spiro-5′-imidazolidine-2′,4′-dione (8). A well-stirred solution of **6**, (0.3 g, 0.80 mmol) in 5 mL of 95% ethanol containing 5% water, was treated with ammonium carbonate (1.42 g, 14.77 mmol) and KCN (208 mg, 3.19 mmol). This was heated in a sealed pressure tube for 72 h then poured into dilute aqueous HCl and extracted with ethyl acetate (3×150 mL), these combined extracts were dried (Na_2SO_4) and evaporated. This residue was then purified by column chromatography ($CHCl_3$/methanol 60/1 to 50/1) to give 250 mg (70% yield) of pure 7-phenoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester-4-spiro-5′-imidazolidine-2′,4′-dione (52% yield). ^1H NMR ($CDCl_3$) δ: 8.41 (bs, 1H), 7.52 (bs, 1H), 7.3–7.4 (m, 7H), 7.12–7.08 (m, 2H), 6.99 (d, J = 4.8 Hz, 2H), 6.72 (dd, J = 5.1 and 1.0 Hz, 1H), 6.24 (bs, 1H), 5.18 (s, 2H), 4.21 (m, 1H), 3.95 (m, 1H), 2.36 (m, 1H), 2.14 (m, 1H); ESI-MS m/z 466 $[M+Na]^+$.

7-Benzyloxy-3, 4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester-4-spiro-5′-imidazolidine-2′,4′-dione (9). A well-stirred solution of **7** (1 g, 2.58 mmol) in 20 mL of

absolute ethanol was treated with ammonium carbonate (2.48 g, 25.8 mmol) and KCN (670 mg, 10.32 mmol). This was heated in a sealed pressure tube for 72 h then poured into dilute aqueous HCl and extracted with ethyl acetate (3×150 mL), these combined extracts were dried ($NaSO_4$) and evaporated. This residue was then purified by column chromatography ($CHCl_3$/methanol 100/1 to 60/1) gave 1 g (85% yield) of pure title compound. ^{1}H NMR ($CDCl_3$) δ: 8.26 (bs, 1H), 7.51 (bs, 1H), 7.40 (m, 9H), 7.04 (d, J=3.0 Hz, 1H), 6.71 (dd, J=1.2 and 5.1 Hz, 1H), 6.09 (s, 1H), 5.23 (s, 2H), 4.89 (s, 2H), 4.22 (m, 1H), 3.93 (m, 1H), 2.35 (m, 1H), 2.12 (m, 1H); ESI-MS m/z 480.5 $[M+Na]^+$.

7-Phenoxy-3, 4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester-4-spiro-5′-3′-(3-methyl-1H-indole-1-carboxylic acid *tert*-butyl ester)-imidazolidine-2′,4′-dione (8A). A well-stirred solution of **8**, (208 mg, 0.469 mmol) in 3 mL of anhydrous dimethylformamide (DMF) was treated with cesium bicarbonate (180 mg, 0.938 mmol) and 3-methansulfonyl-oxymethyl-indole-1-carboxylic acid *tert* ester (170 mg, 0.522 mmol). This was allowed to stir under nitrogen at room temperature for 48 h. The mixture was poured into satd aqueous NH_4Cl and extracted with ethyl acetate (3×25 mL). The combined extracts were washed with water then brine, dried (Na_2SO_4) and evaporated. Chromatography (Hexane: EtOAc 4:1) gave the title compound (240 mg, 76%) as thick oil. ^{1}H NMR ($CDCl_3$) δ: 8.13 (bs 1H). 7.72 (s, 1H), 7.69 (s, 1H), 7.60 (bs, 1H), 7.4 (m, 15H), 7.10 (t, 4.5 Hz, 1H), 6.96 (d, J=9.0 Hz, 1H), 6.78 (d, J=9 Hz, 1H), 6.52 (dd, J=2, 4 and 8.4 Hz, 1H), 5.60 (s, 1H), 5.15 (s, 2H), 4.86 (m, 2H), 4.28 (m, 1H), 3.97 (m, 1H), 2.30 (m, 1H), 2.02 (m, 1H), 1.66 (s, 9H); ESI-MS m/z 695 $[M+Na]^+$.

7-Benzyloxy-3, 4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester-4-spiro-5′-3′-(3-methyl-1H-indole-1-carboxylic acid *tert*-butyl ester)-imidazolidine-2′,4′-dione (9A). (76%). The reaction was carried out using the same procedure used to obtain **8A**. ^{1}H NMR ($CDCl_3$) δ: 8.15 (d, J=9.0 Hz, 1H), 7.71 (s, 1H), 7.69 (s, 1H), 7.60 (bs, 1H), 7.47 (m, 13H), 6.72 (d, J=9 Hz, 1H), 6.50 (dd, J=3 and 9 Hz, 1H), 5.59 (s, 1H), 5.22 (s, 2H), 4.87 (m, 4H), 4.29 (m, 1H), 3.97 (m, 1H), 2.33 (m, 1H), 2.08 (m, 1H), 1.85 (s, 9H); ESI-MS m/z 709 $[M+Na]^+$.

7-Phenoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester-4-spiro-5′-3′-(3-methyl-indole-1-carboxylic acid *tert*-butyl ester)-1′-methyl-imidazolidine-2′,4′-dione (12A). A well-stirred solution of compound **8A**, (270 mg, 0.393 mmol) in 5 mL of anhydrous DMF was treated with K_2CO_3 (109 mg, 0.78 mmol) and iodomethane (73 uL, 1.17 mmol). The solution was stirred at room temperature for 18 h. The mixture was poured into saturated aqueous NH_4Cl and extracted with ethyl acetate (3×25 mL), the combined extracts were washed with water then brine, dried (Na_2SO_4) and evaporated. Chromatography (hexane:ethyl acetate 5:1) yielded 300 mg (100% yield) of pure title compound. ^{1}H NMR ($CDCl_3$) δ: 8.13 (d, J=9 Hz, 1H), 7.74 (m., 2H), 7.58 (bs, 1H), 7.35 (m, 13H), 7.00 (d, J=9 Hz, 1H) 6.61 (m, 2H), 5.18 (s, 2H), 4.84 (m, 2H), 4.27 (M, 2H), 2.69 (s, 3H), 2.30 (m, 2H), 1.65 (s, 9H); ESI-MS m/z 709 $[M+Na]^+$.

7-Benzyloxy-3,4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester-4-spiro-5′-3′-(3-methyl-indole-1-carboxylic acid tert-butyl ester)-1′-methyl-imidazolidine-2′,4′-dione (12B). (85%). ^{1}H NMR ($CDCl_3$) δ: 8.13 (d, J=9 Hz, 1H), 7.69 (m., 2H), 7.58 (bs, 1H), 7.39 (m, 13H), 7.21 (t, J=5.4 Hz, 1H), 6.61 (m, 2H), 5.23 (m, 2H), 4.94 (m, 4H), 4.19 (m, 2H), 2.67 (s, 3H), 2.15 (m, 2H), 1.65 (s, 9H); ESI-MS m/z 760 $[M-H]^-$.

7-Benzyloxy-3,4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester-4-spiro-5′-3-[(indol-3-yl-ethyl)-1-carboxylic acid *tert*-butyl ester] 1′-methyl-imidazolidine-2′,4′-dione (12C). (92%). ^{1}H NMR ($CDCl_3$) δ: 8.2 (bs, 1H), 7.62 (d, J=9.0 Hz, 1H); 7.51 (s, 1H), 7.45 (s, 1H), 7.38 (m, 10H), 7.31 (m, 1H), 6.59 (m, 2H), 5.25 (q, J=12 Hz, 2H), 4.90 (s, 2H), 4.23 (m, 1H), 4.15 (m, 1H), 3.38 (m, 2H), 3.11 (m, 2H), 2.68 (s, 3H), 2.09 (m, 1H), 2.00 (m, 1H), 1.62 (s, 9H); ESI-MS m/z 732 $[M+NH_4]^+$.

7-Phenoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester-4-spiro-5′-3-methyl-imidazolidine-2′,4′-dione (8B). A mixture of **8** (0.52 g; 0.6 mmol), MeI (0.15 mL, 2.35 mmol), and $CsHCO_3$ (0.45 g, 1.35 mmol) in anhydrous DMF (8 mL) was stirred at room temperature for 24 h. The mixture was quenched with H_2O and extracted with EtOAc (3×30 mL). The combined EtOAc layer was washed with water, brine, dried over Na_2SO_4, and evaporated to dryness under vacuum. Chromatography on SiO_2 (hexanes/EtOAc 7:3) gave the title compound (0.53 g, 99%). ^{1}H NMR (CDCl3) δ: 7.55 (bs. 1H); 7.36–-7.30 (m, 9H); 7.15–7.10 (m, 1H); 7.03–6.98 (m, 2H); 6.72 (dd, 1H, J=2.4 and 8.7 Hz); 5.59 (bs. 1H); 5.19 (bs. 2H); 4.32–-4.23 (m, 2H); 4.01–3.94 (m, 2H); 3.09 (s, 3H); 2.38-–2.33 (m, 2H); 2.16-–2.08 (m, 2H); ESI-MS m/z 458 $[M+H]^+$.

7-Benzyloxy-3, 4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester-4-spiro-5′-3-methyl-imidazolidine-2′,4′-dione (9B). (79%). ^{1}H NMR ($CDCl_3$) δ: 7.53 (bs.1H), 7.36 (m, 9H), 7.15 (m, 1H), 6.97 (d, J=9.0 Hz, 2H), 6.70 (dd, J=3 and 9.0 Hz, 1H), 5.63 (bs. 1H), 5.25 (s. 2H), 4.32 (m, 1H), 4.01 (m, 1H), 3.09 (s, 3H), 2.38 (m, 1H), 2.16 (m, 21H); ESI-MS: m/z 472 $[M+H]^+$.

7-Benzyloxy-3, 4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester-4-spiro-5′-3-[2-(1H-indol-3-yl)-ethyl-1-carboxylic acid *tert*-butyl ester]-imidazolidine-2′,4′-dione (9C). (58%). To a solution of **9** (1 g, 2.1 mmol) in anhydrous DMF (5 mL) $CsHCO_3$ (850 mg, 4.3 mmol) was added followed by 3-(2-bromo-ethyl)-indole-1-carboxylic acid tert-butyl ester (780 mg, 2.4 mmol). The reaction was stirred at room temperature for 5 h. The reaction mixture was quenched with water and extracted with ETOAc (3×50 mL). The combined extracts were washed, dried and evaporated. Chromatography using DCM/ ETOAc 9:1 gave **9C** (830 mg, 55% yield). ^{1}H NMR ($CDCl_3$) δ: 8.12 (bs. 1H), 7.63 (d, J=9.0 Hz, 1H), 7.48 (bs, 1H), 7.46 (s, 1H), 7.38 (m, 11H), 3.31(m, 1H), 6.68 (d, J=9.0 Hz, 1H), 6.58 (dd, J=3.0 and 9.0 Hz, 1H), 5.45 (s. 1H), 5.25 (s. 2H), 4.8 (s,

2H), 4.23 (m, 1H), 3.92 (m, 3H), 3.11 (m, 2H), 2.23 (m, 1H), 2.02 (m, 1H), 1.63 (s, 9H); ESI-MS *m/z* 699 $[M-H]^-$.

7-Phenoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester-4-spiro-5′-1′-(1H-indol-3-ylmethyl)-3′-methyl-imidazolidine-2′,4′-dione (13A). To a solution of **8B** (0.44 g, 0.96 mmol) in anhydrous DMF (8 mL) and cooled at 0 °C, NaH (0.027 g, 1.15 mmol) was added portion wise. The suspension was stirred for 30 min. To this solution, a solutions of trimethyl-(1-triisopropylsilanyl)-1-H-indol-3-ylmethyl) ammonium iodide (0.5 g, 1.06 mmol) in DMF (4 mL), and 1M solution TBAF (1.2 mL, 1.15 mmol) were slowly added simultaneously. After the addition was completed the reaction mixture was allowed to stir at room temperature for 8 h. The mixture was diluted with water and extracted with EtOAc (3×30 mL). The combined EtOAc layer was washed with water, brine, dried over Na_2SO_4 and evaporated to dryness under vacuum. Chromatography on silica gel (hexanes/ethyl acetate 7:3) yielded (0.35 g, 62% yield). ^{1}H NMR ($CDCl_3$) δ: 7.59 (d, $J=9$ Hz, 1H), 7.42 (m, 7H), 7.22 (m, 5H), 6.72 (d, $J=9$ Hz, 1H), 6.61 (d, $J=9.1$ Hz, 1H), 6.52 (dd, $J=1.8$, and 9.0 Hz, 1H), 5.20 (m 2H), 4.93 (m, 1H), 4.23 (m, 1H), 4.12 (m, 1H), 3.89 (m, 1H), 3.12 (s, 3H), 76 (m, 2H); ESI-MS: *m/z* 587 $[M+H]^+$.

7-Benzyloxy-3,4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester-4-spiro-5′-1′-(1H-indol-3-ylmethyl)-3′-methyl-imidazolidine-2′,4′-dione (13B). (71%). ^{1}H NMR (CDCl3) δ: 7.60 (d, $J=9$ Hz, 1H), 7.42 (m, 7H), 7.40 (m, 12H), 7.18 (m, 4H), 6.69 (d, $J=9$ Hz, 1H), 6.57 (m, 2H), 5.24 (s, 2H), 4.96 (s, 2H), 4.09 (m, 1H), 3.85 (m, 1H), 3.12 (s, 3H), 1.90 (m, 2H); ESI-MS: *m/z* 601$[M+H]^+$.

7-Phenoxy-3,4-dihydro-2H-quinoline-4-spiro-5′-3′-(1H-indol-3-ylmethy-1-carboxylic acid *tert*-butyl ester)-1′-methyl-imidazolidine-2′,4′-dione (14A). A well stirred solution of **12A** (220 mg, 0.32 mmol), and ammonium formate (180 mg, 0.96 mmol) in 7 mL of MeOH in a capped vial was treated with solid 10% Pd/C (0.1g). The mixture was heated at 60 °C for 1 h with stirring, filtered through a Celite bed, washed with MeOH, and concentrated under reduced pressure to afford **14A** (180 mg, 100% yield). ^{1}H NMR ($CDCl_3$) δ: 8.10 (m, 2H), 7.76–7.70 (m, 2H), 7.32 (m, 9H), 6.52 (d, $J=7.0$ Hz 1H), 6.16 (m, 2H), 6.83 (m, 2H), 4.00 (m, 1H), 3.8 (bs, 1H), 3.32 (m, 1H), 2.27 (s, 3H), 1.96 (m, 2H), 1.48 (s, 9H); ESI-MS *m/z* 553 $[M+H]^+$.

7-Hydroxy-3,4-dihydro-2H-quinoline-4-spiro-5′-3′-(3-methyl-indole-1-carboxylic acid tert-butyl ester)-1′-methyl-imidazolidine-2′,4′-dione (14B). (90%). ^{1}H NMR ($CDCl_3$) δ: 8.13 (bs, 1H), 7.73 (d, $J=9.0$ Hz, 1H), 7.60 (s, 1H), 7.30 (m, 1H) 7.22 (m, 2H), 6.41 (d, $J=9.0$ Hz, 1H), 5.98 (m, 2H), 5.05 (bs, 1H), 4.87 (m, 2H), 3.96 (m, 3H), 3.23 (m, 1H), 2.76 (s, 3H), 2.17 (m, 1H), 1.93 (m, 1H), 1.64 (s, 9H); ESI-MS *m/z* 477$[M+H]^+$.

7-Hydroxy-3,4-dihydro-2H-quinoline-4-spiro-5′-3′-[2(−1H-indol-3-yl)-ethyl-1-carboxylic acid *tert*-butyl ester] 1′-methyl-imidazolidine-2′,4′-dione (14C). (90%). ^{1}H NMR ($CDCl_3$) δ 7.66 (d, $J=9$ Hz, 1H), 7.45 (d, $J=9$ Hz, 1H) 7.35 (s, 1H), 7.30 (m, 12H), 6.55 (d, $J=9$ Hz, 1) 6.24 (m, 2H), 3.89 (m, 3H), 3.29 (m, 1H), 3.07 (m, 2H), 2.79 (s, 3H), 2.40 (m, 1H), 1.86 (m, 1H), 1.64 (s, 9H); ESI-MS *m/z*: 491 $[M+H]^+$.

7-Phenoxy-3,4-dihydro-2H-quinoline-4-spiro-5′-1′-(1H-indol-3-yl-methyl)-3′-methyl-imidazolidine-2′,4′-dione (15A). (83%). ^{1}H NMR ($CDCl_3$) δ: 8.05 (s, 1H), 7.68 (d, $J=9.0$ Hz, 1H), 7.32 (m, 9H), 6.68 (d, $J=9.0$ Hz, 1H), 6.22 (m, 2H), 5.02 (d, $J=15.5$ Hz, 1H), 4.24 (d, $J=15.5$ Hz, 1H), 3.88 (m, 2H), 3.49 (m, 1H), 3.12 (s, 3H), 2.14 (m, 1H), 1.73 (m, 1H); ESI-MS *m/z* 453 $[M+H]^+$.

7-Hydroxy-3,4-dihydro-2H-quinoline-4-spiro-5′-1′-(1H-indol-3-yl-methyl)-3′-methyl-imidazolidine-2′,4′-dione (15B). (79%). ^{1}H NMR (CD_3OD) δ: 7.61 (d, $J=9.0$ Hz, 1H), 7.33 (d, $J=9.0$ Hz, 1H), 7.05 (m, 3H), 6.51 (d, $J=9.0$ Hz, 1H), 6.12 (m, 2H), 4.97 (d, $J=15.5$ Hz, 1H), 4.21 (d, $J=15.$ 5 Hz, 1H), 3.59 (m, 1H), 3.096 (s, 3H), 2.97 (m, 1H), 2.13 (m, 1H), 1.75 (m, 1H); ESI-MS *m/z* 377 $[M+H]^+$.

7-Phenoxy-3,4-dihydro-2H-quinoline-1-(4-oxo-1-yl-butyl-carbamic acid *tert* butyl ester)-4-spiro-5′-1′-methyl-3′-(1H-indol-3yl-metyl-1carboxylic acid *tert* butyl ester)-imidazoline-2′4′-dione (16A). To a stirred solution of **14A** (90 mg, 0.163 mmol) and 4-Boc-amino butyric acid (36 mg, 0.179 mmol) in anhydrous DCM, (2 mL), 1-(3-dimethylaminopropyl)-3-ethycarbodiimide (0.048 g, 0.245 mmol), disopropylethyl amine (1 equiv), dimethyl amino pyridine (catalytic amount) were added. The reaction mixture was stirred at rt for 24 h. After this time the mixture was quenched with a satd solution $NaHCO_3$ (5 mL and extracted with CH_2Cl_2 (3×10 mL). The combined extracts were washed, dried over Na_2SO_4, and purified by chromatography (hexanes/ethyl acetate 7:3) to yield **16A** (0.01 g, 25% yield, based on recovered starting material). ^{1}H NMR ($CDCl_3$) δ: 8.12 (d, 1H, $J=7.8$ Hz), 7.74 (m, 2H), 7.41 (m, 10H), 7.04 (m, 2H), 4.86 (m, 2H), 4.34 (bs, 1H), 3.80 (m, 1H), 3.15 (m, 2H), 2.49 (s, 3H), 2.57 (m, 2H), 2.22 (bs, 1H), 2.15 (m, 1H), 1.87 (m, 2H), 1.65 (s, 9H), 1.49 (s, 9H), 1.28 (m, 2H); ESI-MS *m/z* 737 (M + H +), 760 $(M+Na^+)$.

7-Phenoxy-3,4-dihydro-2H-quinoline-1-(4-oxo-1-butyl-benzyl-carbamic acid *tert*-butyl ester)-4-spiro-5′-1′-(1H-indol-3-ylmethyl)-3′-methyl-imidazolidine-2′,4′-dione (17A). Prepared as **16A**, (52%). ^{1}H NMR ($CDCl_3$) δ: 8.39 (bs 1H), 7.67 (m, 1H), 7.36 (m, 15H), 6.86 (b.s., 1H), 6.68 (d, $J=8.2$ Hz, 1H), 6.30 (b.s, 1H), 4.85 (d, $J=15.9$ Hz, 1H), 4.45 (b.s.,2H), 4.35 (d, $J=15.9$ Hz, 1H), 4.15 (m, 2H), 3.63 (m, 2H), 3.22 (m, 3H), 3.13 (s, 3H), 1.45 (s, 9H), 1.33 (m, 2H), 0.88 (m, 2H); ESI-MS *m/z* 728 $[M+H]^+$.

7-Phenoxy-3, 4-dihydro-2H-quinoline-1-(4-amino-1yl-butan-1-one) 4-spiro-5′-1′-methyl-3′-(1H-indol-3-ylmethyl)-imidazoline-2′4′-dione triflate salt (16). A solution of **16A**, (10 mg, 0.0135 mmol), in DCM (1 mL) was treated with trifluoro acetic acid (0.3 mL). The reaction mixute

was stirred at room temperature for 20 min. After that the solvent was removed under vacuum and dried under high vacuum. The brown residue was then tritated with diethyl ether to afford **16**, (7 mg, 70% yield) as TFA salt. ^{1}H NMR (DMSO) δ: 11.02 (s, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.42 (m, 2H), 7.35 (d, J = 6.4 Hz, 1H), 7.29 (m, 2H), 7.08 (m, 2H), 6.98 (m, 1H), 6.76 (d, J = 6.8 Hz, 1H), 6.11 (dd, J = 2.0 and 7.0 Hz, 1H), 4.74 (s, 2H), 4.11 (m, 1H), 3.77 (bs, 1H), 2.75 (m, 2H), 2.70 (m, 4H), 2.26 (m, 1H), 2.17 (m, 1H), 1.77 (m, 2H); MS MS: m/z 538 $[M+H]^+$.

7-Phenoxy-3,4-dihydro-2H-quinoline-1-(4-benzylamino-1yl-butan-1-one)-4-spiro-5′-1′-(1H-indol-3-ylmethyl)-3′-methyl-imidazolidine-2′,4′-dione (17B). Prepared as **16**, (92%). ^{1}H NMR ($CDCl_3$) δ: 9.77 (bs, 1H), 9.40 (bs, 1H), 8.28 (bs, 1H), 7.60 (m, 1H), 7.37 (m, 12H), 7.12 (m, 1H), 6.94 (d, J = 7.8 Hz, 1H), 6.61 (s, 1H), 6.33 (d, J = 7.5 Hz, 1H), 5.83 (m, 1H), 4.81 (d, J = 15.4 Hz, 1H), 4.57 (d, J = 15.4 Hz, 1H) 4.08 (bs, 2H), 3.90 (m, 1H) 3.42 (m, 1H), 6.50 (m, 6H), 2.79 (m, 1H), 2.61 (m, 1H), 2.15 (m, 3H); ESI-MS m/z 628 $[M+H]^+$.

7-Phenoxy-3,4-dihydro-2H-quinoline-1-(4-amino-1yl-butan-1-one)-4-spiro-5′-1′-(1H-indol-3-ylmethyl)-3′-methyl-imidazolidine-2′,4′-dione (17). Prepared as **14A**, (90%). ^{1}H NMR ($CDCl_3$) δ: 8.36 (bs, 1H), 7.89 (d, J = 7.8 Hz, 1H), 7.34 (m, 10H), 4.94 (m, 3H), 3,75 (m, 4H), 3.28 (m, 1H), 2.67 (m, 2H), 2.36 (m, 2H), 2.05 (bs, 2H), 1.78 (m, 3H), 1.59 (m, 3H); ESI-MS m/z 628 $[M+H]^+$.

7-Phenoxy-3′-4′-dihydro-2H-quinoline-1-(butyl-1-yl-benzylcarbamic acid *tert* butyl ester)-4-spiro-5′-1′-(1H-indol-3-yl-methyl)-3′-methy-imidazolidine-2′4′-dione (18A). To a solution of **15A** (0.036 g, 0.08 mmol), *N*-benzyl-*N*-(*t*-butoxycarbonyl)-4-amino-1-butanal (0.033 g, 0.12 mmol) in anhydrous DCM (2 mL), and $NaBH(OAc)_3$ were added all in once. The reaction mixture was let to stir at room temperature for 8 h. The reaction mixture was diluted with ethyl acetate and washed with water and a 5% $NaHCO_3$, dried over Na_2SO_4, and evaporated to dryness under vacuum brine. Chromatography on silica gel (hexanes/ethyl acetate 6:4) yielded **18A** (0.03 g, 73.2% yield based on recovered SM). ^{1}H NMR ($CDCl_3$) 7.67 (m, 1H), 7.36 (m, 15H), 6.86 (b.s, 1H), 6.68 (d, J = 8.2 Hz, 1H), 6.30 (b.s, 1H), 6.14 (m, 1H), 4.42 (b.s.,2H), 3.63 (bs, 2H) 3.22 (m, 5H) 1.45 (s, 14H) 1.33 (m, 2H); ESI-MS m/z 714 $[M+H]^+$.

7-Phenoxy-3′-4′-dihydro-2H-quinoline-1-(4-benzylamino-butan-1yl-)-4-spiro-5′-1′-(1H-indol-3-yl-methyl)-3′-methy-imidazolidine-2′4′-dione (18B). Prepared as **16**, (91%). ^{1}H NMR ($CDCl_3$) δ: 9.36 (bs, 1H), 7.66 (d, J = 7.8 Hz, 1H), 7.33 (m, 7H), 7.21 (d, J = 7.8 Hz), 7.15 (m, 1H), 7.10 (m, 2H), 7.02 (d, J = 7.7 Hz, 1H), 6.33 (m, 1H), 6.17 (m, 1H), 5.17 (d, J = 15.4 Hz, 1H), 4.13 (d, J = 15.4 Hz, 1H), 3.81 (m, 2H), 3.78 (m, 1H), 3.28 (m, 1H), 3.05 (s, 3H), 3.00 (m, 1H), 2.79 (m, 1H), 2.67 (m, 4H), 1.84 (m, 1H), 1.57 (m, 2H); ESI-MS m/z 614 $[M+H]^+$.

7-Phenoxy-3′-4′-dihydro-2H-quinoline-1-(4-amino-butan-1yl-)-4-spiro-5′-1′-(1H-indol-3-yl-methyl)-3′methy-imidazolidine-2′4′-dione (18). Prepared as **14A**, (94%). ^{1}H NMR ($CDCl_3$) δ: 8.74 (bs, 1H), 7.60 (m, 1H), 7.31 (m, 4H), 7.05 (m, 5H), 6.46 (m, J = 8.5 Hz, 1H), 625 (s, 1H), 6.11 (m, 1H), 5.07 (d, J = 15.4 Hz, 1H), 4.23 (d, J = 15.4 Hz, 1H), 3.70 (m, 2H), 3.07 (s, 3H), 2.83 (m, 6H), 2.67 (m, 2H), 1.84 (m, 1H), 1.57 (m, 4H); ESI-MS m/z 524 $[M+H]^+$ and 546 $[M+Na]^+$.

7-(Tolyloxy)-3′-4′-dihydro-2H-quinoline-1′-(1H-indol-3-yl-methyl)-3′-methy-imidazolidine-2′4′-dione (19A). A mixture of compound **15B**, (80 mg, 0.21 mmol), $Cu(OAc)_2$ (78 mg, 0.40 mmol), *p*-tolyl boronic acid (60 mg, 0.44 mmol) and 20 mg of powdered 4 Å molecular sieves in 2 mL of anhydrous CH_2Cl_2 in a capped vial was added of triethylamine (58 mL, 0.410 mmol) in an atmosphere of air The mixture was stirred vigorously at room temperature for 24 h (during which the color was observed changing from blue to green) and filtered through silica bed, washing with $CHCl_3$/MeOH (10:1). Chromatography of the filtrate on silica gel (Hexane/EtOAc 3:1) afforded **19A** (35% yield). ^{1}H NMR ($CDCl_3$) δ: 8.02 (bs, 1H), 7.69 (m, 1H), 7.32 (m, 5H), 7.08 (m, 2H0, 6.67 (d, J = 8.4 Hz, 1H), 6.18 (m, 2H), 5.07 (d, J = 15.6 Hz, 1H), 4.25 (d, J = 15.5 Hz, 1H), 3.84 (m, 2H), 3.11 (s, 3H), 2.34 (s, 3H), 2.15 (m, 1H), 1.78 (m, 1H); ESI-MS m/z 467 $[M+H]^+$.

7-Tolyxoy-3′-4′-dihydro-2H-quinoline-1-(4-butan-1yl-benzylcarbamic acid *tert*-butyl ester)-4-spiro-5′-1′-(1H-indol-3-yl-methyl)-3′-methy-imidazolidine-2′4′-dione (19B). Prepared as decribed for **18A**. (38%). ^{1}H NMR ($CDCl_3$) δ 7.68 (m, 1H), 7.46 (m, 13H), 7.04 (d, J = 8.3 Hz, 1H), 6.31 (bs, 1H), 6.12 (m, 1H), 5.01 (d, J = 15.6 Hz, 1H), 4.32 (m, 2H), 4.16 (d, J = 15.6 Hz, 1H), 3.98 (m, 1H), 3.66 (m, 3H), 3.10 (m, 5H, 2.34 (s, 3H), 2.04 (m, 1H, 1.77 (m, 5H), 1.45 (s, 9H); ESI-MS: m/z 727 $[M+H]^+$.

7-Tolyxoy-3′-4′-dihydro-2H-quinoline-1-(4-benzylamino-butan-1yl)-4-spiro-5′-1′-(1H-indol-3-yl-methyl)-3′methy-imidazolidine-2′4′-dione (19C). (68%). ^{1}H NMR ($CDCl_3$) δ: 8.02 (bs, 1H), 7.69 (m, 1H), 7.32 (m, 5H), 7.08 (m, 2H), 6.67 (d, J = 8.4 Hz, 1H), 6.18 (m, 2H), 5.07 (d, J = 15.6 Hz, 1H), 4.25 (d, J = 15.5 Hz, 1H), 3.84 (m, 2H), 3.70 (m, 1H), 3.28 (m, 1H), 3.08 (s, 3H), 2.79 (m, 1H), 2.60 (m, 4H), 2.34 (s, 3H), 2.15 (m, 1H), 1.78 (m, 1H); ESI-MS m/z 467 $[M+H]^+$.

7-Tolyloxy-3′-4′-dihydro-2H-quinoline-1-(aminobutan-1yl)-4-spiro-5′-1′-(1H-indol-3-yl-methyl)-3′methy-imidazolidine-2′4′-dione (19). Prepared as **14A**, (43%). ^{1}H NMR ($CDCl_3$) δ: 9.30 (bs, 1H), 7.65 (m, 1H), 7.30 (m, 1H), 7.03 (m, 5H), 6.90 (m, 3H), 6.65 (m, 1H), 6.29 (m, 1H), 6.10 (m, 2H), 5.29 (m, 1H), 4.18 (m, 1H), 3.47 (m, 1H), 3.14 (s, 3H), 2.82 (m, 2H), 2.54 (m, 3H), 2.33(s, 3H), 1.62 (m, 4H); ESI-MS m/z 538 $[M+H]^+$.

7-Hydroxy-3′-4′-dihydro-2H-quinoline-1-(butyl-1-yl-benzylcarbamic acid tert butyl ester)-4-spiro-5′-1′-methyl-3′ [2(−1H-indol-3-yl)-ethyl-1-carboxylic acid *tert*-butyl ester]-imidazolidine-2′4′-dione (21A). Prepared as **18A**, (65%). ^{1}H NMR ($CDCl_3$) δ: 8.14 (d, J = 8.3 Hz, 1H), 7.64 (d, J = 8.6 Hz, 1H), 7.44 (s, 1H), 7.32 (m, 7H), 6.98 (m, 1H), 6.47 (m, 1H), 6.08 (m, 1H), 4.43 (s, 2H), 3.83

(m, 2H), 3.63 (m, 2H), 3.26 (m, 3H), 3.05 (m, 3H), 2.77 (s, 3H), 2.15 (m, 1H), 1.87 (m, 1H), 1.64 (s, 9H), 1.56 (m, 15H); ESI-MS m/z 752 $[M+H]^+$.

7-Tolyloxy-3′-4′-dihydro-2H-quinoline-1-(butyl-1-yl-benzyl carbamic acid tert butyl ester)-4-spiro-5′-1′-methyl-3′ [2(−1H-indol-3-yl)-ethyl-1-carboxylic acid *tert*-butyl ester]-imidazolidine-2′4′-dione (21B). Prepared from **21A** following the same procedure as for **19A**, (90%). ^{1}H NMR ($CDCl_3$) δ 8.12 (d, $J=7.8$ Hz, 1H), 7.65 (d, $J=7.8$ Hz, 1H), 7.44 (s, 1H), 7.35 (m, 7H), 7.12 (m, 2H), 6.89 (m, 2H), 6.52 (d, $J=8.4$ Hz, 1H), 6.26 (m, 1H), 6.10 (m, 1H), 4.41 (s, 2H), 3.90 (m, 3H), 3.07 (m, 7H), 2.74 (s, 3H), 2.31 (s, 3H), 1.84 (m, 1H), 1.79 (m, 2H), 1.63 (s, 18H); ESI-MS m/z 842 $[M+H]^+$, 864 $[M+Na]^+$.

7-Tolyloxy-3′-4′-dihydro-2H-quinoline-1-(4-benzylamino-butan-1yl)-4-spiro-5′-1′-methyl-3′ [2(−1H-indol-3-yl)-ethyl-1-carboxylic acid *tert*-butyl ester]-imidazolidine-2′4′-dione (21C). Prepared as **16**, (89%). ^{1}H NMR ($CDCl_3$) δ 8.01 (bs, 1H), 7.69 (m, 1H), 7.33 (m, 6H), 7.14 (m, 5H), 6.92 (m, 2H), 6.39 (m, 1H), 6.27 (bs, 1H), 6.01 (m, 1H), 4.23 (bs., 2H), 3.84 (m, 3H), 3.23 (m, 4H), 2.74 (s, 3H), 2.63 (m, 2H), 2.32 (s, 3H), 2.06 (m, 2H), 1.58 (m, 5H); ESI-MS m/z 642 $[M+H]^+$.

7-Tolyloxy-3′-4′-dihydro-2H-quinoline-1-(4-amino-butan-1-yl)-4-spiro-5′-1′-methyl-3′ [2-(1H-indol-3-yl)-ethyl-1-carboxylic acid *tert*-butyl ester]-imidazolidine-2′4′-dione (21). Prepared as **14A**, (83%). ^{1}H NMR ($CDCl_3$) δ 7.67 (m, 1H), 7.19 (m, 7H), 6.89 (m, 2H), 6.41(m, 1H), 6.26 (m, 2H), 5.99 (m, 1H), 3.84 (m, 2H), 3.26 (m, 3H), 2.73 (s, 2H), 2.62 (bs, 1H), 2.32 (s, 3H), 1.70 (m, 10H); ESI-MS m/z 552 $[M+H]^+$.

7-(Benzo [1,3] dioxol-5-yloxy)-3′-4′-dihydro-2H-quinoline-1-(butyl-1-yl-benzyl carbamic acid tert butyl ester)-4-spiro-5′-1′-methyl-3′ [2-(−1H-indol-3-yl)-ethyl-1-carboxylic acid *tert*-butyl ester]-imidazolidine-2′4′-dione (22A). Prepared from **21A** following the same procedure as for **19A**, (62%). ^{1}H NMR ($CDCl_3$) δ 8.12 (m, 1H), 7.65 (d, $J=7.8$ Hz, 1H), 7.44 (s, 1H), 7.35 (m, 7H), 6.75 (d, $J=9$ Hz < 1H), 6.57 (m, 1H), 6.49 (m, 2H), 6.24 (bs, 1H), 6.05 (m, 1H), 5.97 (s, 2H), 4.44 (s, 2H), 3.87 (m, 3H), 3.20 (5H), 2.96 (2H), 2.74 (s, 3H), 2.14 (m, 1H), 1.84 (m, 1H), 1.64 (bs, 20H); ESI-MS m/z 872 $[M+H]^+$.

7-(Benzo [1,3] dioxol-5-yloxy)-3′-4′-dihydro-2H-quinoline-1-(4-benzyl amino-butan-1yl)-4-spiro-5′-1′-methyl-3′ [2-(−1H-indol-3-yl)-ethyl-1-carboxylic acid *tert*-butyl ester]-imidazolidine-2′4′-dione (22B). Prepared as **16**, (87%). ^{1}H NMR ($CDCl_3$) δ 8.08 (s, 1H), 7.68 (m, 1H), 7.32 (m, 6H), 7.16 (m, 4H), 6.75 (m, 1H), 6.56 (m, 1H), 6.48 (m, 1H), 6.38 (m, 1H), 6.25 (m, 1H), 5.98 (s, 2H), 3.87 (m, 5H), 3.21 (m, 5H), 2.71 (s, 3H), 2.65 (m, 2H), 2.06 (m, 2H) 1.62 (m, 3H); ESI/MS: m/z 672 $[M+H]^+$.

7-(Benzo [1,3] dioxol-5-yloxy)-3′-4′-dihydro-2H-quinoline-1-(4-amino-butan-1yl)-4-spiro-5′-1′-methyl-3′ [2-(−1H-indol-3-yl)-ethyl-1-carboxylic acid *tert*-butyl ester]-imidazolidine-2′4′-dione (22). Prepared as **14A**, (76%). ^{1}H NMR ($CDCl_3$) δ 7.60 (m, 2H), 7.21 (m, 6H), 6.79 (m, 1H), 6.46 (m, 4H), 6.30 (m, 1H), 5.96 (s, 2H), 3.13 (m, 2H), 2.77 (m, 6H), 1.63 (m, 6H), 1.32 (m, 6H); ESI-MS m/z 582 $[M+H]^+$.

3-Methanesulfonyloxymethyl-indole-1carboxylic acid *tert*-butyl ester (10a). A well-stirred solution of 3-hydroxymethyl-indole-1-carboxylic acid *tert*-butyl ester (**10**, 450 mg, 1.82 mmol) in 10 mL of dichloromethane was cooled in an ice-bath, then treated successively with triethylamine (TEA) (283 mg, 2.18 mmol) and methanesulfonyl chloride (229 mg, 2.0 mmol). This was allowed to stir under nitrogen for 15 min diluted with dichloromethane, then washed with saturated $NaHCO_3$, dried (Na_2SO_4) and evaporated. This residue was purified by chromatography to give 0.43 g (73% yield) of the desired compound as an unstable brown solid. ^{1}H NMR ($CDCl_3$) δ 1.67 (s, 12H), 4.79 (s, 2H), 7.28 (m, 1H), 7.36 (m, 1H), 7.67 (m, 2H), 7.51 (bd, 1H).

Dimethyl-(1-triisopropylsilanyl)-1-H-indol-3-ylmethyl)amine (11a).[17] To a solution of gramine (2 g, 11 mmol) in anhydrous DMF (10 mL) and cooled at 0 °C in an ice-water bath, NaH (0.46 g, 15 mmol) was added portion wise over a 10 min period. The red reaction mixture was then stirred for 30 min. Tri-isopropyl-silyl-chloride (2.9 mL, 13 mmol) in DMF (5 mL) was added dropwise. After the addition was completed, the reaction mixture was stirred for 2 h at room temperature. The mixture was then quenched with water and extracted with EtOAc (3×40 mL). The combined organic layer was washed with water, brine, dried over Na_2SO_4 and evaporated to dryness under vacuum. Chromatography on silica gel of the crude material (hexane/ethyl acetate 90:10) afforded the title compound (3.3 g, 87.3%). ^{1}H NMR ($CDCl_3$) 7.67–7.64 (m, 3H); 7.49–7.46 (m, 1H); 7.17 (s, 1H); 7.14–7.11 (m, 2H); 3.65 (s. 2H); 2.28 (s. 6H); 1.7 (sept, 3H, $J=9$ Hz); 1.36 (d, 18H, $J=9$ Hz). ESI-MS m/z 661 $[2M+H]^+$.

Trimethyl-(1-triisopropylsilanyl)-1-H-indol-3-ylmethyl)-ammonium iodide (11).[17] To a solution of **11a** (0.812 g, 2.45 mmol) in anhydrous benzene (15 mL), MeI (0.69 g, 4.9 mmol) was added. After the addition was completed, a white solid precipitated out of the solution. The suspension was stirred for 2 h. The solvent was removed under vacuum to yield trimethyl-(1-triisopropylsilanyl)-1-H-indol-3-ylmethyl)1-ammonium iodide (1.1 g, 99%) as white powder.

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