Pergamon

Bioorganic & Medicinal Chemistry Letters 8 (1998) 3609–3614

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

THE SOLID PHASE SYNTHESIS OF A SERIES OF TRI-SUBSTITUTED HYDANTOIN LIGANDS FOR THE SOMATOSTATIN SST_5 RECEPTOR

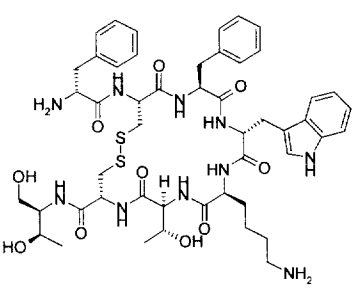
Jan J. Sciciński,[a]* Michael D. Barker,[b] Peter John Murray[a] and Emma M. Jarvie[c]

[a]*Glaxo Wellcome Cambridge Chemistry Laboratory, University Chemical Laboratories, Lensfield Rd, Cambridge, CB2 1EW, UK.* [b]*Medicines Research Centre, Gunnels Wood Rd, Stevenage, Hertfordshire, SG1 2NY, UK.* [c]*Glaxo Wellcome Institute of Applied Pharmacology, Tennis Court Rd, Cambridge, CB2 1QJ, UK.*

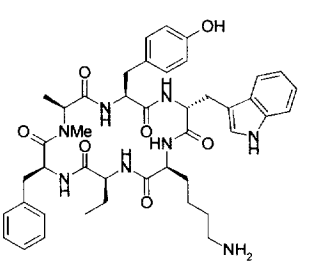
Received 17 September 1998; accepted 30 October 1998

Abstract: A series of trisubstituted hydantoins has been prepared by a versatile solid phase route employing primary alcohols, amines and amino acids as the monomeric building blocks. Several compounds showed sub-micromolar affinity in binding assays at recombinant human somatostatin receptors.

The endogenous neuropeptide hormone somatostatin (somatotrophin release inhibitory factor; SRIF) is an important natural ligand for which receptors are found in the central nervous system,[1] the stomach and the pancreas.[2] The two physiologically active forms of SRIF (SRIF 14 and SRIF 28) inhibit the release of growth hormone,[3] gastrin,[4] glucagon[5] and insulin[6] and therefore may be important in the treatment of diabetes.[7] Somatostatin receptors are also known to be expressed in a large number of hormone dependant tumours.[8] A metabolically stable peptide analogue of SRIF (octreotide, Sandostatin,® **1**) has been used in the clinic to treat growth hormone disorders[9,10] and although smaller cyclic peptidic analogues (eg BIM 23027, **2**) have also been shown to retain functional activity,[11] their clinical utility is limited by their lack of oral bioavailability. Our work has therefore been directed towards the discovery of non-peptidic ligands for somatostatin receptor subtypes.



1 Octreotide



2 BIM 23027

* JJS: **Fax:** + 44 (0)1223 331532; **E-mail:** jjs0985@glaxowellcome.co.uk

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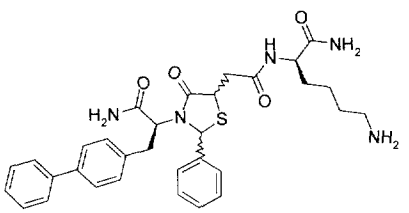
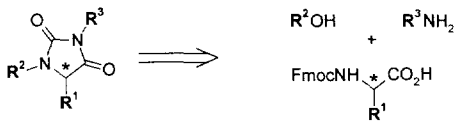
PII: S0960-894X(98)00647-7

The identification of the thiazolidinone AF 15831, **3**, as a potent and selective somatostatin receptor agonist (pIC_{50} = 5.85 at human recombinant sst_5 receptors) by colleagues at Affymax from screening generic libraries[12] demonstrated that small heterocylic scaffolds could provide SRIF receptor ligands. In order to resolve any stereochemical ambiguities associated with these structures and to explore other elements of diversity around **3**, we decided to transpose the thiazolidinone-derived ligands onto an alternative template, accessible by solid phase combinatorial chemistry.[13] The hydantoin scaffold was selected as it provided a chemically tractable molecular framework, maintained a similar display of key functional elements and is represented in a number of clinically useful compounds.[14] Herein we report a solid phase synthesis of tri-substituted hydantoins **4** and their affinity profile against human recombinant somatostatin receptors.



3 AF 15831



4 Proposed Hydantoin Template

Chemistry

We required a route to the generic structure **4** which maintained the requisite display of substituents around the central hydantoin motif and which utilised a broad range of commercially available monomeric building blocks in order to maximise the potential diversity of the products.

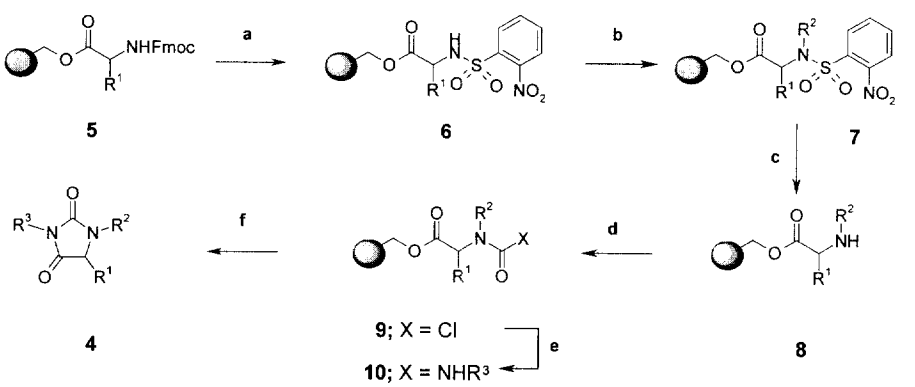
The solid phase synthesis of 4-imide,[15] 5-alkoxy[16] and 2-thiazolidine[17] trisubstituted hydantoins has been reported and recently synthetic routes to trialkyl substituted hydantoins **4** have appeared.[18,19] The key step in these strategies for construction of the *N,N'*-dialkylhydantoin nucleus relies on reductive *N*-alkylation of immobilised amino acids with aryl aldehydes or, under very carefully optimised conditions, with alkyl aldehydes.[20] However, in our hands, this reductive *N*-alkylation step using alkyl aldehydes, essential for the correct display of functional groups on the template, resulted exclusively in the isolation of *N,N'*-disubstituted products. We therefore employed an alternative procedure described by Fukuyama,[21] (Scheme, step b) which has recently been applied to both α-amino esters[22] and resin bound α-amino acid substrates,[23] followed by *in situ* urea formation *via* chlorocarbamate preparation (Scheme, step d) as the key steps. This alternative approach enabled the successful preparation of our target compounds from α-amino acids, alcohols and amines. Following the submission of this manuscript, a similar approach to hydantoins has been reported.[24]

After deprotection of *N*-Fmoc α-amino acids on WANG resin[25] (0.4 to 0.7 mmol g^{-1}), the free amines were reacted with *o*-nitrobenzenesulfonyl chloride, to provide the resin bound sulfonamides **6** (Scheme) which

were transformed into the secondary amines **8** using Fukuyama-Mitsunobu chemistry.[21] Using conditions optimised in our laboratory, primary alcohols alkylated **6** in the presence of tributylphosphine and *N,N,N',N'*-tetramethylazidodicarboxamide (TMAD)[26] in conversions greater than 95% (as determined by HPLC of a cleaved sample). Secondary alcohols and substrates containing tertiary alkylamino functionality did not alkylate the sulfonamides under these conditions.

Although these conditions gave excellent results when performed manually, lower conversions (30 – 50%) were obtained when the process was automated (Advanced ChemTech ACT 496). This could be improved by the slow addition of TMAD with vigorous agitation, which suggested that the lower conversions arose from radical anion formation arising from local excesses of the azodicarboxylate.[27] The difficulty of controlling these factors on the synthesiser led us to seek alternative conditions. Reaction optimisation with respect to phosphine and azodicarboxylate revealed that diisopropyl azodicarboxylate (DIAD) or TMAD with triphenylphosphine gave the highest yields and the latter system was chosen for the automated array[28] in which all reactions proceeded to greater than 95% completion, as determined by HPLC and LCMS of cleaved samples.

Scheme



Reagents and Conditions: a) i. 20% piperidine/DMF, ii. *o*-nitrobenzenesulfonyl chloride, Et_3N, DCM. b) R^2OH, PPh_3, TMAD, DCM. c) PhSH, K_2CO_3, DMF. d) triphosgene, pyridine, DCM. e) R^3NH_2, pyridine, DCM. f) 20% TFA/DCM or autocleavage.

Urea formation was carried out in a way analogous to that reported by Wang.[29] Treatment of the secondary amines with triphosgene in the presence of pyridine in dichloromethane gave the carbamoyl chloride intermediates **9** which were washed free of excess reagent then reacted with an equimolar solution of the required amine and pyridine.[30] In the case of simple amines, cleavage from the resin with 20% TFA in DCM afforded exclusively the corresponding hydantoins **4** on evaporation of the solvent. With 2-(aminoethyl)pyrrolidine as R^3NH_2, the basicity of the tertiary amine in the side chain was sufficient to catalyse cyclative autocleavage during the urea formation step. Analysis of the library (Table 1) was performed by LCMS and flow ^1H NMR spectroscopy to confirm identity and purity of all the products.

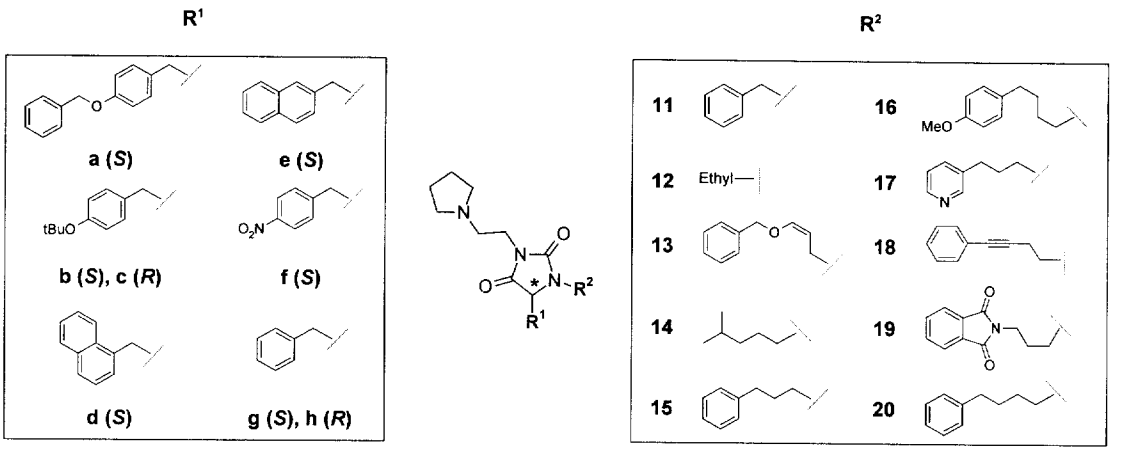
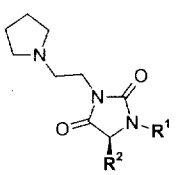


Table 1. Substitution Pattern Represented in the Hydantoin Library.

Biology

The test compounds were examined for their ability to inhibit specific [^{125}I] Tyr^{11}-SRIF binding (0.03 nM) to membranes prepared from CHO-K1 cells expressing human recombinant sst_2 and sst_5 receptors. The samples were initially examined at a single concentration of 10^{-6} M and full competition curves to determine pIC_{50} values were generated on compounds showing greater than 70% inhibition. No compounds showed more than 50% inhibition at human recombinant sst_2 receptors, however four compounds were found to possess submicromolar affinity to $hsst_5$ receptors (Table 2). Interestingly, $hsst_5$ activity was confined to those compounds in which the aromatic groups (R^1, R^2) were able to span a wider region in space. Short chain substituted derivatives were devoid of activity.

In conclusion, we have identified a series of potent and selective $hsst_5$ ligands based on the hydantoin scaffold, which has been constructed using novel, versatile solid phase chemistry. Further optimisation of these leads to increase potency while retaining selectivity is in progress and will be reported in due course.



R^1	R^2 a (S)	R^2 d (S)
16 MeO	6.3	60%[a]
18	6.5	6.4
20	6.5	49%[a]

[a] percentage inhibition of specific radioligand binding at 10^{-6}M.

Table 2. Affinity Values (pIC_{50}) For Selected Hydantoins.

Acknowledgements

The authors gratefully acknowledge Dr C. Holmes and our colleagues at The Affymax Research Institute for the identification of AF15831 as a somatostatin receptor agonist. The authors would also like to thank Mr I. Clemens and Mr J. Neesom for assistance in automating the chemistry, Mr M. Smith for LCMS and flow ^{1}H NMR spectroscopic analysis of the final compounds and Dr A. Merritt and Mr I. Campbell for helpful discussions.

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28. **Typical procedure:** To a suspension of the resin **6** (approx. 50 mg) in a 1.8 M solution of the alcohol (10 equiv.) in DCM was added a 1.8 M solution of triphenylphosphine (10 equiv.) in DCM followed by a 1.8M solution of TMAD (10 equiv.) in DCM. After agitating for 17 h the resin was washed successively with DMF, THF and DCM to give the product resin **7** which was agitated with the supernatant (1.5 mL) of a preformed suspension of potassium carbonate (3.4 g) and thiophenol (420 μL) in DMF (40 mL) for 16 h then washed in turn with DMF, THF and DCM to give the secondary amine resin **8**.

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30. **Typical procedure:** The resin **8** (approx. 50 mg) was suspended in a 0.44 M solution of pyridine in DCM (10 equiv.) then treated with a 0.15 M solution of triphosgene in DCM (3 equiv.) and agitated for 3 h then washed with DCM. The resin was resuspended in a 0.44 M solution of pyridine (10 equiv.) then treated with 2-aminoethylpyrrolidine (10 equiv.), agitated for 17 h the drained and washed with DCM. The combined filtrates were evaporated to give the required product hydantoins **4**.