2,5-Diketopiperazines as Potent, Selective, and Orally Bioavailable Oxytocin Antagonists. 2. Synthesis, Chirality, and Pharmacokinetics

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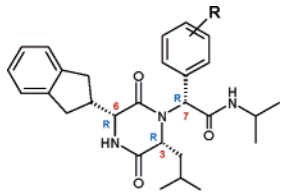
A short stereoselective synthesis of a series of chiral 7-aryl-2,5-diketopiperazines oxytocin antagonists is described. Varying the functionality and substitution pattern of substituents in the 7-aryl ring and varying the chirality of this exocyclic ring have produced potent oxytocin antagonists ($pK_i > 8.5$). SAR and pharmacokinetic profiling of this series of (3*R*,6*R*,7*R*)-2,5-diketopiperazines together with the introduction of an ortho F group in the 7-aryl ring to improve rat p*K* has culminated in the 2′,4′-difluorophenyldiketopiperazine derivative **37**, a highly potent oxytocin antagonist against the human oxytocin receptor ($pK_i = 8.9$) that has >1000-fold selectivity over all three vasopressin receptors V1a, V2, and V1b. It has good bioavailability (46%) in the rat and moderate bioavailability (13−31%) in the dog and is more active in vivo in the rat than atosiban (rat $DR_{10} = 0.44$ mg/kg iv).

Introduction

Preterm labor is a major clinical problem leading to death and disability in newborns. It accounts for 10% of all births and causes 70% of all infant mortality and morbidity.[1] It is the major cause of long-term handicap, particularly cerebral palsy. Intensive care in incubators is usually required, and even those diagnosed as healthy need long-term medical support. Preterm labor has been characterized as labor between 24 and 36 weeks of gestation, with fetal survival increasing from 15% at 24 weeks gestation to 95% at 32 weeks. There is a huge health burden associated with it, and delaying premature labor could dramatically reduce mortality, morbidity, and healthcare costs. Hence, there is an unmet need for an effective long-term treatment of uncomplicated preterm labor.[2,3]

Oxytocin, a nonapeptide hormone, is a potent stimulant of uterine contractions and is responsible for the initiation of labor via the interaction with the oxytocin receptors in the mammalian female uterus. The oxytocin receptor is a seven-transmembrane (7TM) (G_q-coupled) receptor with no subtypes but related to the vasopressin receptors.[17] Oxytocin antagonists have been shown to inhibit uterine contractions and delay preterm delivery.[2c] Hence, there is increasing interest in oxytocin antagonists as a result of their potential application in the prevention of preterm labor. Several templates have been investigated as potential oxytocin antagonists,[5−7] all with different levels of vasopressin antagonist activity. Although several tocolytics (uterine contraction inhibtors) have already been approved in clinical practice, they have harmful maternal or fetal side effects.[2b] The first clinically tested oxytocin antagonist atosiban (Tractocile) has a more tolerable side effect profile and has recently been approved for use in Europe. However, atosiban is a peptide and a mixed oxytocin/vasopressin V1a antagonist that has to be given by iv infusion and is less likely to be suitable for long-term maintenance treatment because it is not orally bioavailable.[4] Our target was a potent, orally active oxytocin antagonist with high levels of selectivity over vasopressin receptors, which would safely delay labor by greater than 7 days and improve infant outcome.

We recently reported[8] on the identification of a novel series of 2,5-diketopiperazine derivatives with antagonist activity at the human oxytocin receptor. The initial structure−activity relationships and stereochemistry were defined, and the most potent template was identified as the (3*R*,6*R*,7*R*)-6-indanyl-3-isobutyl-2,5-diketopiperazine-7-arylisopropylamide **1**.



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We now report on the synthesis, further SAR studies, and preliminary pharmacokinetics of these novel 2,5-diketopiperazine oxytocin antagonists. This has given orally active compounds that are >1000-fold selective for the human oxytocin receptor relative to all three

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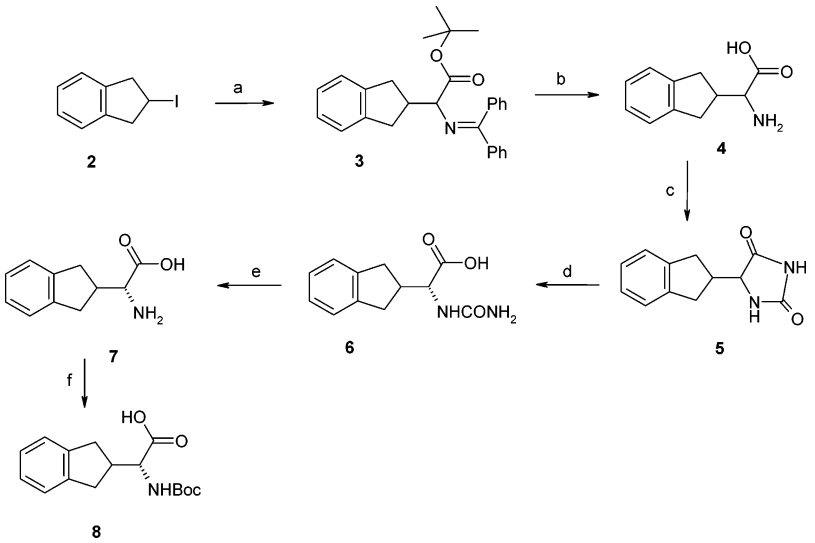
Scheme 1[a]



[a] Reagents and conditions: (a) $(Ph)_2CH{=}NCH_2CO_2CMe_3$, LDA, THF; (b) TFA, CH_2Cl_2; (c) KOCN, H_2O, 90 °C, 3 h, then concentrated HCl, 20 °C, 1.3 h, then at 90 °C, 15 h; (d) D-hydantoinase, pH 10.5; (e) D-carbamoylase, pH 8.5; (f) $(Boc)_2O$, THF, Et_3N, 16 h, room temp.

vasopressin receptors V1a, V2, and V1b, with greater in vivo potency than atosiban in animal models.

Chemistry

The synthesis of the Boc-protected homochiral *R*-indanylglycine is outlined in Scheme 1. The known racemic indanylglycine **4**[9] was prepared by alkylation of the benzhydrylimine of Boc-glycine with 2-iodoindane **2** to give **3**, followed by acid hydrolysis.[9] Reaction of **4** with potassium cyanate gave an intermediate urea that cyclized under acidic conditions at 90 °C to give the racemic hydantoin **5** in 91% yield. Dynamic kinetic resolution of the racemic hydantoin **5** with D-hydantoinase[10,11] gave the chiral urea **6** (90% ee, 93% yield), which was converted by D-carbamoylase to the *R*-indanylglycine **7** (>99% ee, 85% yield). Boc protection of **7** gave *N*-*tert*-butoxycarbonyl-D-indanylglycine **8** in 95% yield.

The two-stage synthesis of indanyldiketopiperazines is outlined in Scheme 2. The first stage used a four-component Ugi reaction where the imine formed by the initial reaction of the arylaldehyde **9** and amine **10** D-leucine methyl ester reacted with the isonitrile **11** (R_1 = isopropyl or tertiary butyl), and the resulting intermediate imminium ion then further reacted with the acid **8** (Boc-protected indanyl-*R*-glycine), which rearranged to give the tripeptide **12**. In the second stage deprotection of the Boc-amine in **12** with TFA followed by cyclization in the presence of Et_3N gave a 1:3 mixture of the 3*R*,6*R*,7*R* **13**−**42** and 3*R*,6*R*,7*S* **14**−**38**, isomers, respectively. The minor 3*R*,6*R*,7*R* isomers **13**−**42** were isolated in ≤25% yield. Changing the methyl ester of leucine to the more bulky tertiary butyl ester improved the ratio of (3*R*,6*R*,7*R*)/(3*R*,6*R*,7*S*) isomers from ∼1:3 to ∼2:3. Changing the solvent of the reaction from methanol to trifluoroethanol shortened the time of the reaction and decreased the volume required. However, attempts to increase further the isomer ratio in favor of the required (3*R*,6*R*,7*R*) isomer by changing the reaction time and temperature or by further changing solvent were unsuccessful.

The stereochemistry of the tertiary butylamide **17** was determined to be 3*R*,6*R*,7*R* by an alternative stereospecific synthesis,[12] and the configuration of this amide **17** was confirmed as 3*R*,6*R*,7*R* for C104, C102, C125 by single-crystal X-ray analysis (Figure 1). It is of interest to note the presence of two unique molecules of **17** per asymmetric unit, molecule A and molecule B, which differ in the conformation of the indanyl side chain relative to the 2,5-diketopiperazine ring. The main distinguishing feature between the two molecules is the magnitude of the torsion angle between the plane of the indane ring and the 2,5-diketopiperazine ring. For molecule A, ω_1 is 93.8° for torsion angle C107−C106−C105−C104. For molecule B, ω_1 is 157.4° for torsion angle C207−C206−C205−C704 (Figure 1). To assess the relative energies of the two conformations, molecular orbital calculations[13] were conducted and the energies of the two distinct conformers in the unit cell were compared. The energy-optimized structure calculated for each conformer was comparable to that of the solid state, confirming that both molecules of the unit cell are low-energy conformers. The two energy-optimized conformations were shown to have an energy difference of 1.1 kcal/mol.

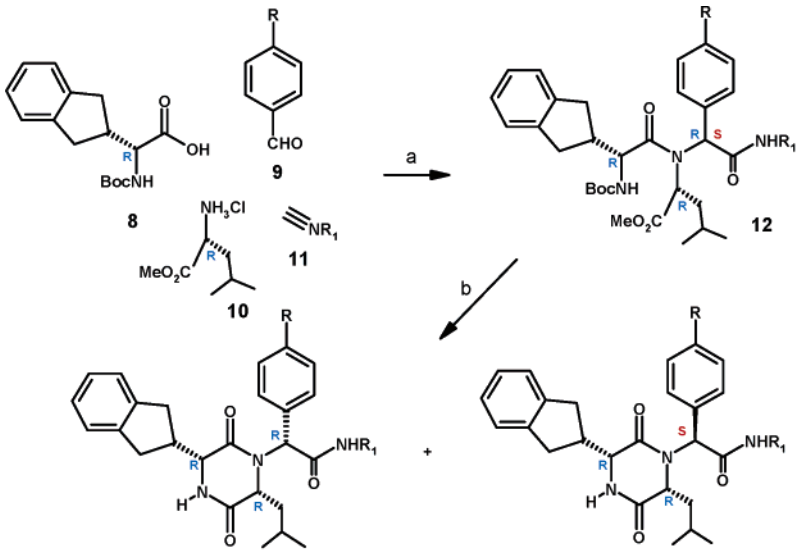
Comparison of the CD spectra of **17** and **37** showed that the configuration of the 7-aryl substituent and the 3,6-substituents on the diketopiperazine ring were the same (*RRR*) in both compounds and different from the 3*R*,6*R*,7*S* isomer **18**.

Reduction of **15** with $LiAlH_4$ gave the monoketopiperazine **45** in 31% yield (Scheme 3). Alkylation of **15** with allyl iodide gave **44** selectively in 35% yield. This occurred at the 1-position of the diketopiperazine ring. In contrast, alkylation of **15** with methyl iodide gave the tertiary amide **43** in 32% yield where the smaller methyl group had preferentially alkylated the exocyclic amide.

Results and Discussions

SAR, Structure, and Stereochemistry. The most potent homochiral template recently identified[8] from a

Scheme 2[a]



[a] Reagents and conditions: (a) Et_3N, methanol, room temp, 16 h; (b) TFA, CH_2Cl_2, then Et_3N, room temp, 16 h.

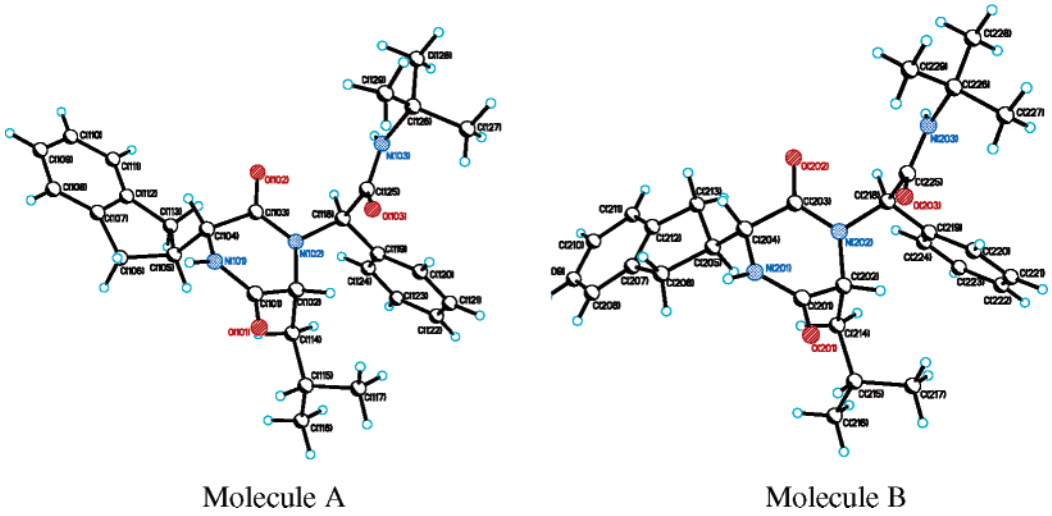
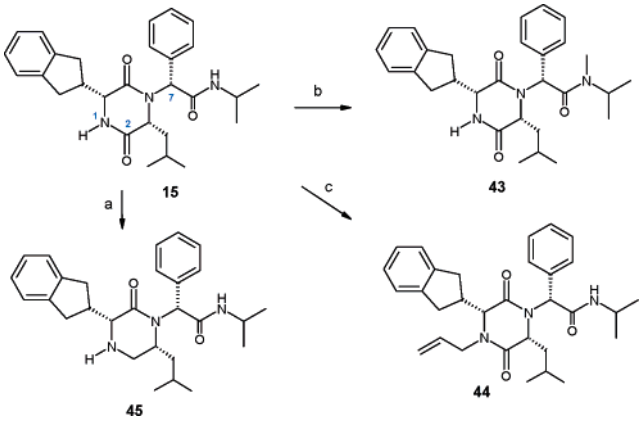


Figure 1. Molecules A and B.

series of 2,5-diketopiperazine oxytocin antagonists is exemplified by the (3*R*,6*R*,7*R*)-6-indanyl-3-isobutyl-2,5-diketopiperazine-7-phenylisopropylamide **15**. Some initial SAR analysis of this template established that 6-indanyl > 6-phenethyl > 6-benzyl in terms of potency, and a four-carbon branched alkyl was optimal for potency at the 3-position. Also, for this semirigid molecule the relative stereochemistry of the substituents and their chirality was crucial for potency. For both the 3,6-subsituents the potency of cis was greater than that of trans and for the 7-phenyl substituent the potency of *R* was greater than that of *S* by an order of

Scheme 3[a]



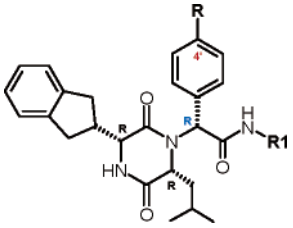
[a] Reagents and conditions: (a) $LiAlH_4$ (3 equiv)/THF, −78 °C; (b) LHMDS (1.3 equiv)/THF, −78 °C, then MeI (17 equiv); (c) LHMDS (1.3 equiv)/THF, −78 °C, then allyl iodide (17 equiv).

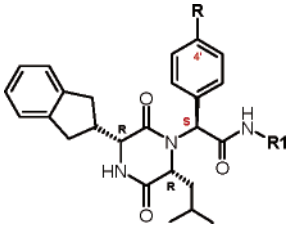
magnitude. An aromatic group at the 7-position with *R* chirality was required for good potency. To extend the SAR and find out what functionality was tolerated, an additional set of chirally pure single isomers of the indanyldiketopiperazines with a wide spread of electronic properties, lipophilic properties, and size was prepared and tested for activity against the human oxytocin receptor (Table 1).

Exploration of the para position of the aryl ring revealed that the acetamide **13** (NHCOMe) was more potent than carboxamide **29** ($CONH_2$) and was similar in potency to our previous lead,[15] the benzoxazine **46** (Scheme 4), while the rest had a similar potency of pK_i = 8.6−8.0 for a range of electron-withdrawing and -donating substituents at this position except **29** ($CONH_2$), pK_i = 7.6. All *R* isomers were greater in potency in the range of 1.8−1.1 log units compared to the *S* isomers. A similar level of potency was exhibited by the isopropylamides and tertiary butylamides (**15** and **17**) and (**13** and **39**). The meta-substituted derivatives **40** and **42** were less active than the corresponding para-substituted analogues **39** and **41**. Hence, a whole range of substituents at the para position of the aryl ring maintain potency and the para-substituted aromatic rings are more potent than meta-substituted aromatic rings and the *R* isomers are more potent than the *S* isomers.

In addition to the chirality of the exocyclic 7-phenyl substituent, the relative stereochemistry of the 3- and 6-substituents is crucial for potency. To verify the stereochemistry of the substituents and conformation of the diketopiperazine ring,[12] an X-ray crystal structure of **17** was obtained (Figures 1 and 2). This confirmed the relative stereochemistry as cis for the 3 and 6 centers, which was supported in solution by strong NOEs between the protons at the 2′ position of the indane ring and the methylene of the 3-isobutyl group. The X-ray crystal structure of **17** showed that the 3 and the 6 substituents are on the same face of the DKP ring, which is puckered. Also, strong NOEs between the protons at the 3 and 7 positions and the 7 position and the methylene of the 3-isobutyl substituent support the buttressing effect on the leucine seen in the X-ray crystal structure of **17** (Figure 2). The key functionality of the puckered diketopiperazine ring, the lactam carbonyl and NH groups at the 1 and 2 positions, are also

Table 1. Inhibition of the Binding of Oxytocin by 7-Aryl-(*R*)- and 7-Aryl-(*S*)-2,5-diketopiperazines at the Human Oxytocin (hOT) Receptor[a]





compd	R	chirality	R_1	pK_i hOT[b]	compd	R	chirality	R_1	pK_i hOT[b]
13	NHCOMe	3*R*,6*R*,7*R*	$CHMe_2$	8.8	**14**	NHCOMe	3*R*,6*R*,7*S*	$CHMe_2$	6.9
15	H	3*R*,6*R*,7*R*	$CHMe_2$	8.4	**16**	H	3*R*,6*R*,7*S*	$CHMe_2$	7.3
19	F	3*R*,6*R*,7*R*	$CHMe_2$	8.4	**20**	F	3*R*,6*R*,7*S*	$CHMe_2$	7.0
21	CF_3	3*R*,6*R*,7*R*	$CHMe_2$	8.3	**22**	CF_3	3*R*,6*R*,7*S*	$CHMe_2$	7.1
23	Me	3*R*,6*R*,7*R*	$CHMe_2$	8.4	**24**	Me	3*R*,6*R*,7*S*	$CHMe_2$	7.3
25	NMe_2	3*R*,6*R*,7*R*	$CHMe_2$	8.5	**26**	NMe_2	3*R*,6*R*,7*S*	$CHMe_2$	7.6
27	SO_2Me	3*R*,6*R*,7*R*	$CHMe_2$	8.0	**28**	SO_2Me	3*R*,6*R*,7*S*	$CHMe_2$	7.0
29	$CONH_2$	3*R*,6*R*,7*R*	$CHMe_2$	7.5	**30**	$CONH_2$	3*R*,6*R*,7*S*	$CHMe_2$	6.8
17	H	3*R*,6*R*,7*R*	CMe_3	8.3	**18**	H	3*R*,6*R*,7*S*	CMe_3	7.1
31	Cl	3*R*,6*R*,7*R*	CMe_3	8.6	**32**	Cl	3*R*,6*R*,7*S*	CMe_3	6.8
33	OMe	3*R*,6*R*,7*R*	CMe_3	8.6	**34**	OMe	3*R*,6*R*,7*S*	CMe_3	7.4
35	OCF_3	3*R*,6*R*,7*R*	CMe_3	8.3	**36**	OCF_3	3*R*,6*R*,7*S*	CMe_3	6.8
39	NHCOMe	3*R*,6*R*,7*R*	CMe_3	8.7					
40	3′-NHCOMe	3*R*,6*R*,7*R*	CMe_3	8.2					
41	4′–N NMe	3*R*,6*R*,7*R*	CMe_3	7.6					
42	3′–N NMe	3*R*,6*R*,7*R*	CMe_3	6.8					
46	benzoxazine[c]			8.7					

[a] Displacement of [^{3}H]oxytocin from hOT by the test compound.[14] [b] pK_i values are reported as the mean value of three or more determinations, and all results were obtained in binding assays with a standard deviation in pK_i of less than 0.25. [c] Standard from previous series.[15]

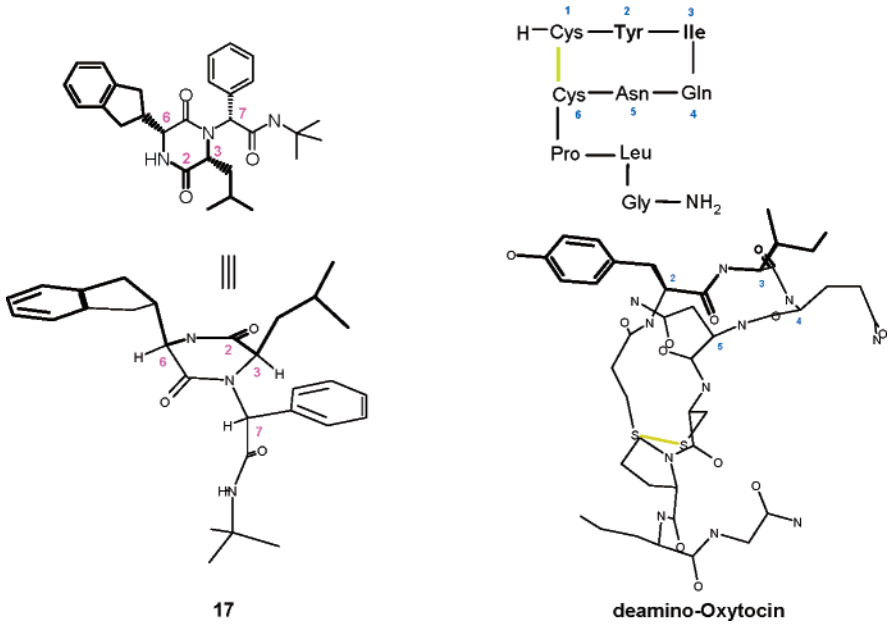
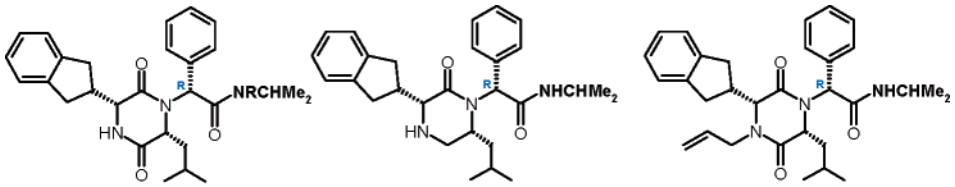


Figure 2. X-ray crystal structures of 2,5-diketopiperazine **17** and deamino-oxytocin.[16]

Table 2. Activity of Ring Modified Diketopiperazines



15 R = H hOT pK_i = 8.4
43 R = Me hOT pK_i = 8.4

45 hOT pK_i = 6.5

44 hOT pK_i = 7.2

important for activity. Removal of the 6-carbonyl from **15** to give the monoketopiperazine **45** resulted in a greater than 10-fold loss in potency (Table 2). Similarly, alkylation of **15** with allyl iodide to give the *N*-allyl lactam **44** resulted in a loss in potency by 10-fold. Interestingly, the tertiary amide **43** retained activity.

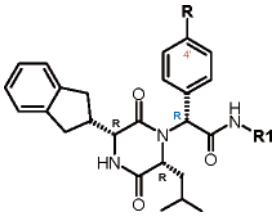
In these diketopiperazine oxytocin antagonists the *RRR* stereochemistry of the three chiral centers at the 3, 6, and 7 postions and the key functionality (the carbonyl at the 2-position and the NH at the 1-position) of the diketopiperazine ring are essential for high antagonist potency and hence must be crucial elements in binding to the oxytocin receptor.

The oxytocin receptor contains seven transmembrane domains and is a member of the class 1 family of G-protein-coupled receptors (GPCRs). The agonist oxytocin binds to the extracellular region and transmembrane domain of the receptor, which enables the intracellular part to couple to the G proteins and initiate a cascade of events liberating Ca^{2+}, which causes contractions.[17] The 2-Tyr and 3-Ile are the key amino acids in oxytocin (Figure 2) for this interaction with the receptor, generating agonist activity. Modification at the 2-position of oxytocin produces antagonist activity. The deamino OEt-Tyr^2 oxytocin analogue is a potent antagonist of oxytocin-induced contractions in the rat uterus in vitro and in vivo.[18] Modification of the 4 and 8 positions of this deamino OEt-Tyr^2 oxytocin analogue gave the antagonist atosiban.[19] In addition, structure−activity studies of oxytocin analogues have revealed that the antagonist property depends on a specific conformation, and the appropriate modification of the Tyr^2 plays a crucial role in this function. The incorporation of bulky apolar side chain amino acids in position 2 increased potency and made more effective oxytocin antagonists. The use of D-indanylglycine (D-IgL) as a rigid homophenylalanine analogue resulted in OT receptor affinity higher than that of D-Phe^2 with greater selectivity for the oxytocin over the vasopressin receptors.[20] This agrees with what we have found in the diketopiperazine series of oxytocin antagonists where 6-indanyl > 6-phenethyl > 6-benzyl in terms of potency.

To understand the importance of the stereochemistry of the three chiral centers for activity in the diketopiperazine oxytocin antagonists, the X-ray crystal structure of the anatagonist **17** was compared to the known crystal structure of the agonist deamino oxytocin[16] (Figure 2). This shows that they have similar pharamacophores (those in bold) that can be overlaid. Hence, there is a similar stereochemical relationship of the required aryl ring, peptide backbone, and isoleucine in oxytocin and the required aryl ring, part of diketopiperazine and leucine in our diketopiperazines. However the 2,5-diketopiperazine template with three chiral centers is a more rigid system, where the stereochemistry of 3,6 substituents and the vectors these take up are highly important for potency.

The phenyl ring with the *R* configuration in the exocyclic phenylisopropylamide restricts the conformational mobility of the leucine (3-isobutyl) group which

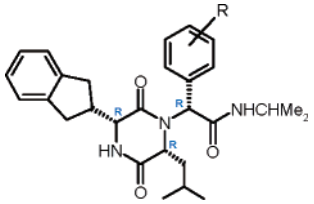
Table 3. Pharmacokinetics of Monoaryl-Substituted (3*R*,6*R*,7*R*)-2,5-Diketopiperazines in the Rat



				rat[b]						
compd	R	R_1	pK_i hOT[a]	AUC po	Cl	V_{dss}	$t_{1/2}$	*F*, %	CHI log *D* [c]	sol[d]
39	NHCOMe	CMe_3	8.7	59					2.4	0.079
15	H	$CHMe_2$	8.4	114	29	0.8	1.0	5	3.2	0.02
19	F	$CHMe_2$	8.4	421	23	0.8	0.9	13	3.2	0.03
21	CF_3	$CHMe_2$	8.3	280					3.7	0.001
23	Me	$CHMe_2$	8.4	nd[e]	37	0.6	0.6		3.5	0.02
31	Cl	CMe_3	8.6	95	43	0.4	0.7	2	4.0	0.001
33	OMe	CMe_3	8.6	101					3.4	0.001
35	OCF_3	CMe_3	8.3	85					4.1	0.001
25	NMe_2	$CHMe_2$	8.5	287	48	2.3	1.2	5	3.4	0.02
27	SO_2Me	$CHMe_2$	8.0	60	21	0.7	1.5	3	2.4	0.22
29	$CONH_2$	$CHMe_2$	7.5	44					1.8	0.25

[a] Displacement of [^{3}H]oxytocin from hOT by the test compound.[14] pK_i values are reported as the mean of three or more determinations, and all results were obtained in binding assays with a standard deviation in pK_i of less than 0.25. [b] Rat PK (n = 2): AUC (h ng mL^{-1}) at 5 mg kg^{-1}, 5% DMSO/95% PEG400 formulation; Cl in mL min^{-1} kg^{-1}; V_{dss} in L kg^{-1}; $t_{1/2}$ in h. [c] An HPLC method based measurement of lipophilicity.[21] [d] Solubility (μg/mL), a precipitation/HPLC based measurement.[22] [e] nd = not determined.

Table 4. Pharmacokinetic Profile of 2′,5′-Diketopiperazine Oxytocin Antagonists in the Rat and Dog and the Inhibition of OT Binding at the Human OT (hOT) and Vasopressin at the Human (V1a, V1b, and V2) Receptors[a]



			vasopressin pK_i[a]			rat[b,c]				dog[c,d]			
compd	R	oxytocin pK_i hOT[a]	hV1a	hV1b	hV2	AUC po	Cl	V_{dss}	*F*, %	AUC po	Cl	V_{dss}	*F*, %
19	4-F	8.4	<5.2	<5.2	5.9	421	23	0.8	13	259	5	0.8	13
25	4-NMe_2	8.5	<4.4	<4.3	<4.1	287	48	2.3	5	335	15	1.7	50
37	2,4-diF	8.9	5.2	<5.2	6.2	1088	36	2	46	121	11	1.2	13
										291[e]			33[e]

[a] Displacement of [^{3}H]oxytocin from hOT or vasopressin from hV1a, hV1b, and hV2 by the test compound.[14] pK_i values are reported as mean values of three or more determinations, and all results were obtained in binding assays with a standard deviation in pK_i of less than 0.25. [b] Rat PK (n = 2): AUC (h ng mL^{-1}) at 5 mg/kg, 5% DMSO/95% PEG400 formulation. [c] Cl in mL min^{-1} kg^{-1}. V_{dss} in L kg^{-1}. [d] Dog PK(n = 1): AUC (h ng mL^{-1}) at 0.6 mg/kg, 5% DMSO/95% PEG400 formulation. [e] AUC (h ng mL^{-1}) at 0.6 mg/kg, 5% DMSO/95% labrafil formulation.

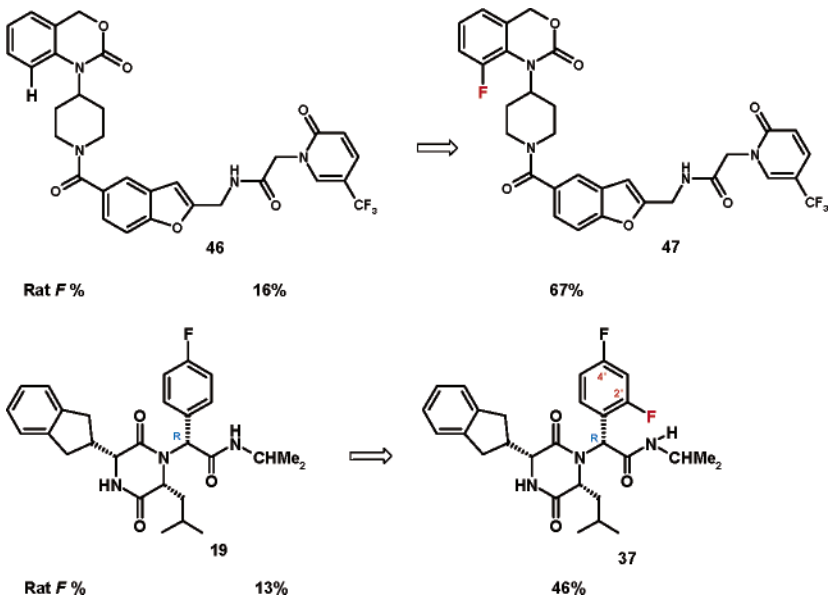
facilitates its interaction at the oxytocin receptor. The *R* configuration of the exocyclic phenylisopropylamide allows the exocyclic amide (which is below the plane of the diketopiperazine ring) to occupy the same space as the hexapeptide in oxytocin, whereas in the 3*R*,6*R*,7*S* diastereoisomer the inversion of the exocyclic center does not allow these favorable interactions.

Pharmacokinetics. Because the potency was found to be associated with the *R* isomer of a 4′-substituted phenyl ring, a range of these (3*R*,6*R*,7*R*)-diketopiperazine derivatives were looked at in the rat to estimate their pharmacokinetic profiles (Table 3). These were chosen to give a spread of polarity, lipophiliciy (chromatographic hydrophobicity index (CHI) log D[21]), and solubility.[22] All these compounds had a lower rat oral exposure than the F derivative **19** (AUC 421 h·ng/mL). Also, with the exception of the primary amide **27**, all the derivatives measured had a higher clearance than **19**, and this compound was the best in this group with a bioavailability of 13%. Although it would be useful to increase water solubility, it can be seen from the data that hydrophilic electron-withdrawing groups gave low values for rat oral exposure.

The two diketopiperazines with the largest exposure in the rat, the 4′-fluorophenyl derivative **19** and the 4′-dimethylaminophenyl derivative **25**, were tested in the dog (Table 4). Whereas the 4′-fluorophenyl derivative **19** had similar bioavailability in both species, the 4′-dimethylaminophenyl derivative **25** had much better bioavailability in the dog than the rat.

The highly potent mono-4′-substituted phenyldiketopiperazines with the best pharmacokinetic profile were the 4′-F and 4′-NMe_2 derivatives, but they had low bioavailability in the rat. The question of how to improve the bioavailability of this template was addressed by analogy with a previous class of oxytocin antagonists[15] where an aromatic fluoro substituent next to the ring junction had a dramatic effect on the bioavailability, increasing it from **46** (16%) to **47** (54%) (Scheme 4). This is due to the increased permeability of **47** (AUC = 7901

Scheme 4

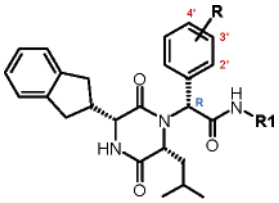


h·ng/mL) compared to **46** (AUC = 1360 h·ng/mL) because the clearance of these are essentially the same (11 and 10 mL min^{-1} kg^{-1}, respectively). A similar situation was seen recently[28] where an ortho fluoro substitution in a aryl ring of factor Xa inhibitors significantly improved Caco-2 permeability. This suggested that the 2′,4′-difluorophenyldiketopiperazine derivative should have increased bioavailability. This proved to be the case; the ortho fluoro effect improved the bioavailability of the diketopiperazine template in the rat (Table 3) where the 13% seen in the 4′-fluorophenyl derivative **19** was increased to 46% in the 2′,4′-difluorophenyl analogue **37** (Scheme 4). A different formulation (DMSO/labrafil) gave higher oral exposures and improved the bioavailability to 33% for **37** in the dog compared with 13% obtained with conventional formulation (DMSO/PEG400) (Table **4**). Overall, **37** has good pharmacokinetics (PK) in rat (Cl 36 mL min^{-1} kg^{-1}, $t_{1/2}$ = 2 h, F = 46%, oral formulation (DMSO/PEG400) and dogs (Cl 10 mL min^{-1} kg^{-1}, $t_{1/2}$ = 1 h, F = 33%, oral formulation (DMSO/labrafil).

Selectivity vs Human Vasopressin Receptors and Activity in the Presence of HSA. Selectivity relative to human vasopressin receptors for a range of diketopiperazines (Table 4) has been established by measuring the pK_i against the human vasopressin receptors V1a, V1b, and V2. The 2′,4′-difluorophenyldiketopiperazine derivative **37** was >10^4-fold selective for the human oxytocin receptor over the vasopressin V1a in the SPA receptor assay. All the diketopiperazines measured (Table 4) are >1000-fold selective for the human oxytocin receptor relative to all three vasopressin receptors V1a, V2, and V1b.

The lead compound **46** in our previous class of oxytocin antagonists had insufficient in vivo activity to be progressed because of the influence of protein binding. Therefore, activity in the presence of human serum albumin (HSA) became an essential part of the screening protocol for the advancement of lead compounds. A range of 2,5-diketopiperazine derivatives binding to purified human serum albumin (HSA) was measured on a HSA immobilized column. A similar exercise was also carried out using rat serum albumin (RSA), and rat was seen to parallel human protein binding (Table 5). This did not, however, differentiate between the classes of oxytocin antagonists, so the activity of a range of diketopiperazines against the human oxytocin receptor was also measured in the presence and absence of physiological concentrations of HSA and the loss in activity was represented as a shift in hOT IC_{50} (Table 5). The diketopiperazines as a class have a minimal loss in human oxytocin antagonist activity in the presence of HSA (hOT IC_{50} shift < 2.3, relative to the previous class lead benzoxazine, e.g., **46** hOT IC_{50} shift = 46). Human serum albumin showed little effect on the potency of the lead 2′,4′-difluorophenyldiketopiperazine derivative **37** with a shift of only 2.2 in its hOT IC_{50}.

Table 5. Protein Binding and Potency of OT Antagonists at the hOT Receptor

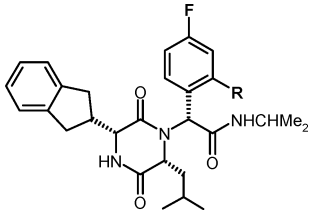


compd	R	R1	% HSA[a]	% RSA[b]	pK_i hOT[c]	hOT IC_{50} shift + HSA[d]	CHI[e] log D, pH 7.4
46	benzoxazine		95.3	90.1	8.7	46	2.2
25	4-NMe_2	$CHMe_2$	93.8	90.7	8.5		3.4
19	4-F	$CHMe_2$	90.3	87.0	8.4	2.2	3.2
37	2,4-diF	$CHMe_2$	93.4	90.2	8.9	2.2	3.4

[a] Human serum albumin binding.[23] [b] Rat serum albumin binding.[23] [c] Displacement of [^{3}H]oxytocin from hOT by the test compound.[14] pK_i values are reported as mean values of three or more determinations, and all results were obtained in binding assays with a standard deviation in pK_i of less than 0.25. [d] HSA shift = ratio of displacement of [^{3}H] oxytocin from hOT by the test compound in the presence and absence of 50 mg/mL human serum albumin.[24] [e] An HPLC method based measurement of lipophilicity.[21]

In Vivo Potency. The in vivo efficacy of the 2′,4′-difluorophenyldiketopiperazine derivative **37** was estimated in an anesthetized rat model where uterine contractions were elicited by iv administration of oxy-

Table 6. Potency at the Human Oxytocin Receptor Compared with the Efficacy Obtained in the Rat Uterine Contractility Model



		rat, iv		
compd	R	DR_{10},[a] mg/kg	IC_{50},[b] ng/mL	pK_i hOT[c]
37	F	0.44		8.9
19	H	0.61	50	8.4
atosiban		0.63	140	7.4

[a] DR_{10} determination.[26] [b] Plasma IC_{50}.[25] [c] Displacement of [^{3}H]oxytocin from hOT by the test compound.[14] pK_i values are reported as mean values of three or more determinations, and all results were obtained in binding assays with a standard deviation in pK_i of less than 0.25.

tocin. The reduction in uterine contractility was measured after subsequent iv administrations of increasing doses of **37**. Two methods were used for the measurement of in vivo activity, plasma IC_{50} determination[25] (plasma concentration that causes 50% inhibition of response to standard OT dose), and DR_{10} determination (dose that shifts agonist dose response to oxytocin 10-fold).[26] The 2′,4′-difluorophenyldiketopiperazine derivative **37** was more potent than atosiban in vitro and in vivo (Table 6).

Conclusions

Substitution in the para position of the 7-aryl ring of the (3*R*,6*R*,7*R*)-diketopiperazines has produced a wide range of potent oxytocin antagonists with pK_i values greater than 8.5. SAR studies have shown that the potency of compounds with *R* chirality at the 7-position is greater than the corresponding *S* isomers and that the potency at the oxytocin receptor with para substitution is greater than that with meta substitution in the 7-aryl ring. The relative stereochemistry and chirality of the substituents on the semirigid DKP ring, shown to be important for antagonist potency at the oxytocin receptor, have been rationalized as mimicking the 2-Tyr and 3-Ile key amino acids in oxytocin required for agonist binding. Pharmacokinetic profiling of the (3*R*,6*R*,7*R*)-diketopiperazines identified the 4′-F and 4′-NMe_2 phenyl derivatives with moderate oral exposures in the rat. Increased bioavailability was achieved by substitution in the 2′ position with fluorine, which gave the 2′,4′-difluorophenyldiketopiperazine derivative **37**. This is highly potent against the human oxytocin receptor (pK_i = 8.9), is active in the presence of HSA (only a 2.2-fold shift in IC_{50}), and has good bioavailability (46%) in rat and moderate bioavailability (13−31%) in the dog. It is >1000-fold selective for the human oxytocin receptor relative to all three vasopressin receptors V1a, V2, and V1b and is more active in vivo in the rat than atosiban (rat DR_{10} = 0.44 mg/kg iv). It is also available in a short two-stage synthesis from Boc-protected homochiral *R*-indanylglycine.

Experimental Procedures

General Procedures. Melting points were obtained using an Electrothermal digital melting point apparatus and are uncorrected. All purifications by flash chromatography were performed using Kieselgel 60, Merck 9385 silica gel. Preparative plate chromatography was performed using Whatman PK6F silica gel 60A plates, with the sample eluting with ethyl acetate/cyclohexane or 2-propanol/dichloromethane mixtures. Monitoring of reactions by TLC used Merck 60 F254 silica gel glass backed plates (5 × 10 cm), with samples eluting with mixtures of ethyl acetate and cyclohexane and visualized by UV light followed by heating with aqueous phosphomolybdic acid. Analytical HPLC experiments were run on a Hewlett-Packard 1090 HPLC instrument, equipped with a Intersil M column ODS2. Standard conditions were eluent systems A (H_2O, 0.1% H_3PO_4) and B (95% MeCN/H_2O, 0.1% H_3PO_4): gradient 0% B in 2 min, 0−100% B in 40 min, 100% B in 10 min, flow rate = 1 mL/min, λ = 215 nm). Retention times (t_r) are given in minutes. LCMS were run on a Hewlett-Packard 1050 coupled with a Micromass Platform II equipped with a Supelco ABZplus column. Standard conditions were eluent systems A (H_2O, 0.1% formic acid, 10 mmol of ammonium acetate) and B (MeCN, 0.05% formic acid): gradient 1 100% A in 0.7 min, 100% A to 100% B in 3.5 min, 100% B in 3.5 min, 100−0% B in 0.3 min, flow rate = 1 mL/min); gradient 2, 100% A in 0.7 min, 100% A to 100% B in 4.2 min, 100% B in 1.1 min, 100−0% B in 0.2 min, flow rate = 1 mL/min); gradient 3, 100% A in 3 min, 100% A to 100% B in 20 min, 100% B in 5 min, 100−0% B in 2 min, flow rate = 1 mL/min). All NMR spectra were run on a Bruker 400 MHz instrument generally as solutions in $CDCl_3$ unless otherwise stated. IR spectra were recorded on a Bio-rad FTS7 spectrometer from thin films on NaCl plates, a KBr mix, or solutions in the solvent specified. Mass spectra were run by an electrospray Hewlett-Packard 5989B instrument. CD spectra were recorded in acetonitrile on a Jasco J-720A spectropolarimeter. Optical rotations were taken with a Perkin-Elmer model 241 polarimeter. Enantiomeric excess (% ee) was determined by chiral HPLC anaylsis using a Chiracel OJ or Chiral Pak AD464 column with a UV detector, λ = 215 nm, and with eluents and flow rates as indicated in each case. Final organic solutions were dried over $MgSO_4$ before filtration and evaporation using a Buchi Rotavapor. Ambient temperature was 20 °C. All solvents used were Fisons analytical reagents except for pentane (Aldrich Chemical Co.) and anhydrous THF (Fluka sureseal). All other reagents were usually obtained from Aldrich, Fluka, or Lancaster. Elemental microanalyses were determined by the Microanalytical Laboratory, GlaxoSmithKline Stevenage.

***tert*-Butyl *N*-(Diphenylmethylene)-2-(2-indanyl)glycinate (3).** To a solution of *N*-(diphenylmethylene)glycine *tert*-butyl ester (20 g, 68 mmol, 1 equiv) in dry THF (340 mL) at −70 °C was added a solution of 1.6 M LDA (108.5 mL, 1.1 equiv) in THF/hexane (1:1) over 10 min. After the addition was complete, the cooling was removed and the mixture was allowed to warm to 10 °C over 1.5 h. A solution of iodoindane **2**[27] (19.9 g, 81.6 mmol, 1.2 equiv) in THF (210 mL) was added over 30 min. The mixture was then allowed to stir at ambient temperature overnight. The reaction was quenched with glacial acetic acid (5.2 mL). The mixture was washed with water (130 mL), and the aqueous portion was extracted with EtOAc (250 mL). The combined organics were washed with saturated $NaHCO_3$ (400 mL), then brine (400 mL). The organic phases was separated, dried (Na_2SO_4), filtered, and evaporated to give the crude product as an orange oil. Flash chromatography (Merck 9385 silica, eluting with 12:1 cyclohexane/EtOAc) and evaporation gave, after trituration under cyclohexane, the pure product **3** as an off-white solid (9.1 g, 33%). ^{1}H NMR ($CDCl_3$) δ 7.69−7.07 (m, 14H, *arylH*), 4.03 (d, *J* = 6.9 Hz, NC*H*indanyl), 3.27−3.15, 3.07−2.92, and 2.75−2.62 (3m, 5H, indanyl-*3H*, *-1H*, *-2H*), 1.46 (s, 9H, *Bu*^{t}); LCMS *m/z* 412 (MH^+) single component 99.8%, gradient 2 (t_R = 4.24 min); HRMS calcd for $C_{28}H_{29}NO_2$ (MH^+) 412.2277, found 412.2278; HPLC 100% (t_R = 20.79 min).

***rac*-Indanylglycine (4).** To diphenyliminoindanylglycine *tert*-butyl ester 3 (79.9 g, 0.19 mol) was added 10:1 TFA/water (242 mL). The mixture was stirred at room temperature for 5.5 h, at which point TFA (73 mL, 5 equiv) was added and the

mixture was stirred at ambient temperature overnight. The mixture was poured into water (1.5 L), and the pH was adjusted to 8. A precipitate formed. This was filtered and washed with diethyl ether. The cake was slurried in diethyl ether, filtered, and washed. Drying under vacuum gave the product **4** as a white solid (32.1 g, 86%). ^{1}H NMR (DMSO-d_6 + TFA) δ 8.41 (s,3H, NH_3^+), 7.26−7.12 (m, 4H, *arylH*), 4.12−4.04 (m, 1H, NC*H*indanyl), 3.05−2.88 (m, 5H, indanyl-*3H*, *-1H*, *-2H*); LCMS *m/z* 192 (MH^+) single component, gradient 2 (t_R = 1.42min); HRMS calcd for $C_{11}H_{13}NO_2$ (MH^+) 192.1025, found 192.1025; HPLC 99.52% (t_R = 2.32 min).

***rac*-Indanylglycine Hydantoin (5).** To a solution of potassium cyanate (127.5 g, 1.57 mol) and water (1.6 L) was added racemic indanylglycine **4** (100 g, 0.52 mol), and the mixture was heated to 90 °C over 1 h and held at this temperature for 2 h (92.8% conversion. HPLC analysis). The mixture was cooled to 20 °C, and concentrated aqueous hydrochloric acid (400 mL) was added over 1 h, maintaining the temperature at 20 °C (±2 °C). After being stirred at 21 °C for 20 min, the mixture was heated to 90 °C over 1.25 h and held at this temperature for 15 h. The mixture was cooled to 37 °C, and water (1 L) was added to the thick white slurry. After cooling at 10 °C for 4 h, the mixture and vessel washings with water (500 mL) were filtered and the cake was washed with water (2 × 500 mL). The cake was dried under vacuum at 45 °C overnight to give the title compound **5** as a white solid (102.8 g, 91%). ^{1}H NMR (DMSO-d_6) δ 10.71 (br s, 1H, CON*H*CO), 8.09 (br s, 1H, CON*H*), 7.21−7.06 (m, 4H, *arylH*), 4.20−4.17 (m, 1H, NC*H*indanyl), 3.04−2.96 and 2.89−2.69 (2m, 5H, indanyl-*3H*, *-1H*, *-2H*); chiral HPLC 49.77% (t_R = 10.26 min) and 50.23% (t_R = 13.85 min) (Chiralpak AD, 30% EtOH/heptane); LCMS *m/z* 234 (MNH_4^+) single component, gradient 2 (t_R = 2.46min); HRMS calcd for $C_{12}H_{12}N_2O_2$ (MH^+) 217.0977, found 217.0973; HPLC 99.08% (t_R = 1.20 min).

***R*-*N*-Carbamylindanylglycine (6).** To a solution of Borax (disodium tetraborate decahydrate) (104 g, 0.272mol) and water (2.75 L) at 43 °C was added dropwise concentrated aqueous sodium hydroxide (~40 mL) until the pH was 10.5. To this solution was added racemic indanylglycine hydantoin **5** (103.6 g, 0.479 mol) in dimethylsulfoxide (690 mL), a white precipitate formed. Polymer-supported hydantoinase (69 g) was added, and the slurry was stirred at 45 °C for 23 h. A further charge of polymer-supported hydantoinase (69 g) was added, and the mixture was stirred for 22 h (91% conversion HPLC). The mixture was filtered hot through a Celite pad, and the filter bed was washed with water (1.5 L). The temperature of the filtrate was adjusted to 25 °C, and concentrated aqueous hydrochloric acid (~100 mL) was slowly added until pH 1.53 was obtained. The white precipitate formed was stirred for 45 min, filtered, washed with water, and dried under vacuum at room temperature overnight to give the crude indanylglycine carbamate **6** as a white solid (106.4 g). ^{1}H NMR (DMSO-d_6) δ 12.64 (br s,1H, CO_2H), 7.28−7.16 and 7.13−7.08 (2m, 4H, *arylH*), 6.40 (d, J = 9 Hz, 1H, N*H*CONH$_2$), 5.61(s, 2H, NHCON*H*$_2$), 4.20 (dd, J = 9 Hz, 6 Hz, 1H, NC*H*indanyl), 2.95−2.82 and 2.80−2.70 (2m, 5H, indanyl-*3H*, *-1H*, *-2H*); chiral HPLC 90.2% (t_R = 7.62 min) and 9.8% (t_R = 8.41 min) (Chiracel OD-R, 20% MeCN/$HClO_4$/$NaClO_4$ (0.5 M), aqueous, pH 2); LCMS *m/z* 235 (MH^+) single component, gradient 2 (t_R = 2.41min); HRMS calcd for $C_{12}H_{14}N_2O_3$ (MH^+) 235.1083, found 235.1084.

***R*-Indanylglycine (7).** A solution of Borax (disodium tetraborate decahydrate) (243 g, 0.637 mol) and water (6.40 L) was heated to 42 °C, and the pH was adjusted to 8.02 using dropwise addition of concentrated aqueous hydrochloric acid (~70 mL). To this solution was added crude indanylglycine carbamate (106.4 g, 0.454mol) in dimethyl sulfoxide (700 mL). Resin-supported d-carbamoylase was filtered, and 120 g was added to the mixture. The mixture was stirred at 45 °C for 36 h under an air atmosphere. The mixture was cooled to 25 °C and left overnight. After division into into two equal halves, each was worked up as follows. Dimethyl sulfoxide (900 mL) was added followed by concentrated aqueous hydrochloric acid (200 mL), and the mixture was stirred until no white solid remained (20 min). The resin was filtered throught Celite, and concentrated aqueous sodium hydroxide was added to the filtrate until pH 7.0 was obtained. The prepcipate that formed was left at 18 °C for 1 h, filtered, and dried under vacuum at room temperature overnight to give the chiral indanylglycine **7** as a beige solid (73.8 g, 85%). ^{1}H NMR (DMSO-d_6 + TFA) δ 8.37 (br s, 3H (+water)), 7.19−7.16 and 7.11−7.06 (2m, 4H, *arylH*), 4.06−3.99 (m,1H, NC*H*indanyl), 3.03−2.80 (m, 5H, indanyl-*3H*, *-1H*, *-2H*); HPLC 97.5% (t_R = 0.93 min) (generic fast method); chiral HPLC 100% (t_R = 5.42min) (Chirobotic T, 20% MeCN/TEAA (0.1%), pH 4.1); LCMS *m/z* 192 (MH^+) single component, gradient 2 (t_R = 1.43min); HRMS calcd for $C_{11}H_{13}NO_2$ (MH^+) 192.1025, found 192.1023; $[\alpha]^{23}_D$ −28° (*c* 0.20 in 1 N aqueous HCl, 10 cm cell).

***N*-*tert*-Butoxycarbonyl-D-2-indanylglycine (8).** To a stirred suspention of *R*-indanylglycine (15.1 g, 79 mmol) in tetrahydrofuran (75 mL) and water (75 mL) at room temperature was added triethylamine (13 mL, 93.3 mmol, 1.18 equiv). The mixture was cooled to 2 °C, and a solution of di-*tert*-butyl dicarbonate (27.9 g, 127.8 mmol, 1.62 equiv) in tetrahydrofuran (50 mL) was added over 40 min. The mixture was sitrred at room temperature for 16 h. Water (150 mL) and ethyl acetate (700 mL) were added. The pH was adjusterd to pH 5 by the addition of 0.5 M citric acid (75 mL), and the organic phase was separated. The aqueous phase was extracted with ethyl acetate (2 × 300 mL), and the combined organic phase was washed with brine (400 mL), dried ($NaSO_4$), and evaporated. The residue was dissolved in ether (140 mL), hexane (650 mL) was added, and the organic phase was washed with sodium bicarbonate (158 mmol, 2 equiv) in water (2 L). The aqueous phase was acidified with 0.5 M citric acid (280 mL) to pH 5 and extracted with ether (3 × 650 mL), and the combined organic phase was washed with brine (500 mL), dried ($NaSO_4$), and evaporated to give **8** (23.81 g, 96%). ^{1}H NMR (DMSO-d_6) δ 12.58 (br s,1H, CO_2H), 7.26 (d, J = 8 Hz,1H, BocNH), 7.19−7.16 and 7.11−7.06 (2m, 4H, *arylH*), 3.99 (t, J = 8 Hz,1H, NC*H*indanyl), 2.96−2.85 and 2.78−2.72 (2m, 5H, indanyl-*3H*, *-1H*, *-2H*), 1.39(s, 9H, Bu^t); HPLC 98.10% (t_R = 1.61 min); chiral HPLC 100.00%, (t_R = 9.98 min) (Chiralpak ADRHCD-JE039 50% MeCN/H_3PO_4 0.1% at 215 nm) 100.0% ee; LCMS *m/z* 292 (MH^+) single component, gradient 2 (t_R = 3.26min); HRMS calcd for $C_{16}H_{21}NO_4$ (MNa^+) 314.1368, found 314.1368. $[\alpha]^{23}_D$ −11° (*c* 1.0 in MeOH, 10 cm cell).

(2*R*)-2-[(3*R*,6*R*)-3-(2,3-Dihydro-1*H*-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-*N*-isopropyl-2-phenylethanamide (15) and ((2*S*)-2-[(3*R*,6*R*)-3-(2,3-Dihydro-1*H*-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-*N*-isopropyl-2-phenylethanamide (16). To a solution of D-leucine methyl ester hydrochloride (182 mg) in methanol (3 mL) was added triethylamine (140 μL) and benzaldehyde (102 μL). The mixture was stirred for 2.5 h before the acid **8** (291 mg) and isopropylisonitrile (150 μL) were sequentially added. After the mixture was stirred for 16 h, the solvent was removed in vacuo and the residue was dissolved in dichloromethane (20 mL). This solution was washed with a saturated aqueous sodium hydrogen carbonate solution (×2), dried over magnesium sulfate, and evaporated in vacuo. The residue was dissolved in dichloromethane (3 mL) and trifluoroacetic acid (4 mL), and the mixture was stirred for 3 h at ambient temperature. After this time, the solvent was removed in vacuo and the residue was re-evaporated from dichloromethane (10 mL × 2). The residue was treated with triethylamine in dioxane (5% solution, 10 mL) and was left to stir overnight. After this time, the dioxane was removed in vacuo and the residue was dissolved in dichloromethane (50 mL). The solution was washed with 0.1 M hydrochloric acid solution (10 mL × 2), and the organic phase was separated using a hydrophobic frit and evaporated in vacuo to give a yellow gum. This crude material was purified by preparative plate chromatography, eluting with 2.5% 2-propanol in dichloromethane (×3) to give the less polar diastereomer **15** as a colorless solid (81 mg, 17.6%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45−7.41 (m, 5H, phenyl-*arylH*), 7.24−7.14 (m, 4H, indanyl-*arylH*), 6.58 (d, J = 4.0 Hz, 1H, lactamN*H*), 5.59 (d, J = 8.0 Hz, 1H, N*H*CHMe$_2$),

5.20 (s, 1H, NC*H*phenyl), 4.15−4.06 (m, 1H, NHC*H*Me$_2$), 4.00−3.95 (m, 2H, NC*H*isobutyl, NC*H*indanyl), 3.20−3.02 (m, 3H, indanyl-*3H*, *-1H*), 2.97−2.85 (m, 1H, indanyl-*2H*), 2.82−2.73 (m, 1H, indanyl-*1H*), 1.86−1.65 (m, 2H, C*H*HCHMe$_2$, CH$_2$-C*H*Me$_2$), 1.42−1.34 (m, 1H, CH*H*CHMe$_2$), 1.13 and 1.12 (2d, J = 6.5 Hz, NHCH*Me$_2$*), 0.81 and 0.74 (2d, J = 6.5 Hz, 3H, CH$_2$CH*Me$_2$*); LCMS *m/z* 462 (MH$^+$) single component, gradient 2 (t_R = 3.40 min); HRMS calcd for $C_{28}H_{35}N_3O_3$ (MH$^+$) 462.2757, found 462.2765; HPLC 100% (t_R = 13.62 min).

The more polar diastereomer **16** (162 mg, 35.2%) was isolated as a colorless solid. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.59 (broad s, 1H, lactamN*H*), 7.45−7.34 (m, 5H, phenyl-*arylH*), 7.20−7.10 (m, 4H, indanyl-*arylH*), 6.08 (broad s, 1H, N*H*-CHMe$_2$), 5.51 (s, 1H, NC*H*phenyl), 4.17−4.07 (m, 1H, NH-C*H*Me$_2$), 4.00−3.93 (m, 1H, NC*H*indanyl), 3.71−3.65 (m, 1H, NC*H*isobutyl), 3.17−2.78 (m, 5H, indanyl-*3H*, *-1H*, indanyl-*2H*), 1.98−1.89 (m, 1H, C*H*HCHMe$_2$), 1.78−1.65 (m, 2H, CH*H*CHMe$_2$, CH$_2$C*H*Me$_2$), 1.16 and 1.13 (2d, J = 6.5 Hz, NHCH*Me$_2$*), 0.80 and 0.62 (2d, J = 6.5 Hz, 6H, CH$_2$CH*Me$_2$*); LCMS *m/z* 462 (MH$^+$) single component, gradient 2 (t_R = 3.36 min); HRMS calcd for for $C_{28}H_{35}N_3O_3$ (MH$^+$) 462.2757, found 462.2765; HPLC 100% (t_R = 13.53 min).

The following compounds were similarly prepared.

(2*R*)-2-[4-(Acetylamino)phenyl]-2-[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-*N*-isopropylethanamide (13) and (2*S*)-2-[4-(Acetylamino)-phenyl]-2-[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-2,5-dioxo-1-piperazinyl]-*N*-(1-methylethyl)ethanamide (14). Compound **8** was reacted with 4-acetamidobenzaldehyde as described for compound **15** to give **13** as a colorless solid (14%). ^{1}H NMR (CD$_3$OD) δ 8.36 (s, 1H, AcN*H*), 7.59 and 7.38 (pseudo-ABq, J = 8.5 Hz, 4H, acetamidophenyl-*H*), 7.24−7.13 (m, 4H, indanyl-*arylH*), 7.10 (d, J = 4.0 Hz, lactamN*H*), 5.92 (d, J = 8.0 Hz, 1H, N*H*CHMe$_2$), 5.20 (s, 1H, NC*H*acetamidopheny), 4.11−4.00 (m, 1H, NHC*H*Me$_2$), 3.98−3.92 (m, 2H, NC*H*isobutyl, NC*H*indanyl), 3.19−3.00 (m, 3H, indanyl-*3H*, *-1H*), 2.93−2.75 (m, 2H, indanyl-*2H*, indanyl-*1H*), 2.18 (s, 3H, *Me*CO), 1.80−1.61 (m, 2H, C*H*HCHMe$_2$, CH$_2$-C*H*Me$_2$), 1.37−1.28 (m, 1H, CH*H*CHMe$_2$), 1.10 (pseudo-t, 2 overlapping d, J = 6.5 Hz, 6H, NHCH*Me$_2$*), 0.78 and 0.68 (2d, J = 6.5 Hz, 6H, CH$_2$CH*Me$_2$*); LCMS *m/z* 519 (MH$^+$) single component, gradient 2 (t_R = 3.02 min); HRMS calcd for $C_{30}H_{39}N_4O_4$ (MH$^+$) 519.2971, found 519.2966; HPLC 100% (t_R = 13.60 min).

The diastereomer **14** (34%) was isolated as a white solid. ^{1}H NMR (CDCl$_3$) δ 8.36 (s, 1H, AcN*H*), 7.58 and 7.33 (pseudo-ABq, J = 8.5 Hz, 4H, acetamidophenyl-*H*), 7.23−7.13 (m, 4H, indanyl-*arylH*), 6.05 (broad s, 1H, lactamN*H*), 5.46 ((s, 1H, NC*H*acetamidopheny), 4.14−4.04 (m, 1H, NHC*H*Me$_2$), 3.94 (d, J = 10.0 Hz, 1H, NC*H*indanyl), 3.74−3.69 (m, 1H, NC*H*isobutyl), 3.19−2.75 (m, 5H, indanyl-*3H*, *-1,H*, *-2H*), 2.18 (s, 3H, *Me*CO), 1.94−1.64 (m, 3H, C*H$_2$*CHMe$_2$, CH$_2$C*H*Me$_2$), 1.15 and 1.13 (2d, J = 6.5 Hz, 6H, NHCH*Me$_2$*), 0.79 and 0.68 (2d, J = 6.5 Hz, 6H, CH$_2$CH*Me$_2$*); LCMS *m/z* 519 (MH$^+$) single component, gradient 2 (t_R = 2.93 min); HRMS calcd for $C_{30}H_{39}N_4O_4$ (MH$^+$) 519.2971, found 519.2974; HPLC 100% (t_R = 13.46 min).

(2*R*)-*N*-(*tert*-Butyl)-2-[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-phenylethanamide (17) and (2*S*)-*N*-(*tert*-Butyl)-2-[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-phenylethanamide (18). Compound **8** was reacted with benzaldehyde as described for compound **15** to give **17** as a white solid (19%). ^{1}H NMR (CDCl$_3$) δ 7.45−7.38 (m, 5H, *phenylH*), 7.24−7.13 (m, 4H, indanyl *arylH*), 6.72 (d, 1H, J = 4 Hz, lactamN*H*), 5.67 (s, 1H, CON*H*Bu^t), 5.21 (s, 1H, NC*H*phenyl), 4.01−3.94 (m, 2H, NC*H*isobutyl, NC*H*indanyl), 3.19−2.75 (m, 5H, indanyl-*3H*, *-1,H*, *-2H*), 1.83−1.64 (m, 2H, C*H*HCHMe$_2$, CH$_2$C*H*Me$_2$), 1.68 (m, 1H), 1.37−1.28 (m, 1H, CH*H*CHMe$_2$), 1.32 (s, 9H, *Bu^t*), 0.80 and 0.71 (2d, J = 6.5 Hz, 6H, CH$_2$CH*Me$_2$*); LCMS *m/z* 476 (MH$^+$) (t_R = 3.54 min); HRMS calcd for $C_{29}H_{38}N_3O_3$ (MH$^+$) 476.2913, found 476.2906; HPLC >99.5% (t_R = 14.3min); circular dichroism (CH$_3$CN) λ_{max} = 204.0 nm, dE 22.73, E31923, λ_{max} = 228.2 nm, dE −15.52, E4355.

The diastereomer **18** (40%) was isolated as a white solid. ^{1}H NMR (CDCl$_3$) δ 7.45−7.38 (m, 5H, *phenylH*), 7.24−7.13 (m, 4H, indanyl *arylH*), 6.67 (d, 1H, J = 4 Hz, lactamN*H*), 5.80 (s, 1H CON*H*Bu^t), 5.42 (s, 1H, NC*H*phenyl), 3.98, (dd, 1H, J = 9.5 Hz, 4 Hz, NC*H*indanyl), 3.75 (m, 1H, NC*H*isobutyl), 3.18−2.76 (m, 5H, indanyl-*3H*, *-1,H*, *-2H*), 1.91−1.65 (m, 3H, C*H$_2$*CHMe$_2$, CH$_2$C*H*Me$_2$), 1.36 (s, 9H), 0.80 and 0.64 (2d, J = 6.5 Hz 6H, CH$_2$CH*Me$_2$*); LCMS *m/z* 476 (MH$^+$) (t_R = 3.59min); HRMS calcd for $C_{29}H_{38}N_3O_3$ (MH$^+$) 476.2913, found 476.2915; HPLC >99.5% (t_R =14.5min); circular dichroism (CH$_3$CN) λ_{max} = 206.0 nm, dE 2.92, E28846, λ_{max} = 219.0 nm, dE −3.17, E13945, λ_{max} = 226.6 nm, dE −3.47, E3857.

(2*R*)-2-[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(4-fluorophenyl)-*N*-isopropylethanamide (19) and (2*S*)-2-[(3*R*,6*R*)-3-(2,3-Dihydro-1*H*-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(4-fluorophenyl)-*N*-isopropylethanamide (20). Compound **8** was reacted with 4-fluorobenzaldehyde as described for compound **15** to give **19** as a colorless solid (18%). ^{1}H NMR (CDCl$_3$) δ 7.46−7.41 (m, 2H, fluorophenyl-*2H*, *-6H*), 7.25−7.07 (m, 6H, fluorophenyl-*3H*, -5H, indanyl-*arylH*), 6.51 (d, J = 3.5 Hz, 1H, lactamN*H*), 5.60 (d, J = 7.5 Hz, 1H, N*H*CHMe$_2$), 5.10 (s, 1H, NC*H*fluorophenyl), 4.15−4.05 (m, 1H, NHC*H*Me$_2$), 3.98−3.93 (m, 2H, NC*H*isobutyl, NC*H*indanyl), 3.20−3.02 (m, 3H, indanyl-*3H*, *-1H*), 2.96−2.84 (m, 1H, indanyl-*2H*), 2.82−2.73 (m, 1H, indanyl-*1H)*, 1.82−1.63 (m, 2H, C*H*HCHMe$_2$, CH$_2$C*H*Me$_2$), 1.47−1.39 (m, 1H, CH*H*CHMe$_2$), 1.14−1.10 (m, 6H, NH-CH*Me$_2$*), 0.84 and 0.79 (2d, J = 6.5 Hz, 6H, CH$_2$CH*Me$_2$*); LCMS *m/z* 480 (MH$^+$) single component, gradient 2 (t_R 3.42 min); HRMS calcd for $C_{28}H_{35}FN_3O_3$ (MH$^+$) 480.2662, found 480.2661; HPLC 100% (t_R = 13.71 min).

The diastereomer **20** (33%) was isolated as a colorless solid. ^{1}H NMR (CDCl$_3$) δ 7.47−7.42 (m, 2H, fluorophenyl-*2H*, *-6H*), 7.24−7.08 (m, 6H, fluorophenyl-*3H*, -5H, indanyl-*arylH*), 6.75 (d, J = 4.0 Hz, 1H, lactamN*H*), 5.84 (d, J = 7.5 Hz, 1H, N*H*CHMe$_2$), 5.49 (s, 1H, NC*H*fluorophenyl), 4.15−4.06 (m, 1H, NHC*H*Me$_2$), 3.99 (dd, J = 9.5 Hz, 4.0 Hz, 1H, NC*H*indanyl), 3.73 (dd, J = 11.0 Hz, 4.0 Hz, 1H, NC*H*isobutyl), 3.18−2.88 (m, 4H, indanyl-*3H*, *-1H*, indanyl-*2H*), 2.83−2.76 (m, 1H, indanyl-*1H)*, 1.91−1.65 (m, 3H, C*H$_2$*CHMe$_2$, CH$_2$C*H*Me$_2$), 1.16 (pseudo-t, 2 overlapping d, J = 6.5 Hz, 6H, NHCH*Me$_2$*), 0.82 and 0.72 (2d, J = 6.5 Hz, 6H, CH$_2$CH*Me$_2$*); LCMS *m/z* 480 (MH$^+$) single component, gradient 2 (t_R = 3.42 min); HRMS calcd for $C_{28}H_{35}FN_3O_3$ (MH$^+$) 480.2662, found 480.2645; HPLC 100% (t_R = 13.68 min).

((2*R*)-2-[(3*R*,6*R*)-3-(2,3-Dihydro-1*H*-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-*N*-isopropyl-2-[4-(trifluoromethyl)phenyl]ethanamide (21) and ((2*S*)-2-[(3*R*,6*R*)-3-(2,3-Dihydro-1*H*-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-*N*-isopropyl-2-[4-(trifluoromethyl)phenyl]ethanamide (22). Compound **8** was reacted with 4-trifluoromethylbenzaldehyde as described for compound **15** to give **21** as a colorless solid (18%). ^{1}H NMR (CDCl$_3$) δ 7.75 (d, J = 3.5 Hz, 1H, lactamN*H*), 7.68 and 7.56 (pseudo-ABq, J = 8.0 Hz, 4H, trifluoromethylphenyl-*H*), 7.22−7.13 (m, 4H, indanyl-*arylH*), 6.01 (d, J = 8.0 Hz, 1H, N*H*CHMe$_2$), 5.22 ((s, 1H, NC*H*trifluoromethylphenyl), 4.16−4.06 (m, 1H, NHC*H*Me$_2$), 4.02−3.97 (m, 2H, NC*H*isobutyl, NC*H*indanyl), 3.17−2.98 (m, 3H, indanyl-*3H*, *-1H*), 2.95−2.78 (m, 2H, indanyl-*2H*, indanyl-*1H*), 1.89−1.71 (m, 2H, C*H*HCHMe$_2$, CH$_2$C*H*Me$_2$), 1.47−1.39 (m, 1H, CH*H*CHMe$_2$), 1.15 and 1.14 (2d, J = 6.5 Hz, 6H, NH-CH*Me$_2$*), 0.85 and 0.79 (2d, J = 6.5 Hz, 6H, CH$_2$CH*Me$_2$*); LCMS *m/z* 530 (MH$^+$) single component, gradient 2 (t_R = 3.77 min); HRMS calcd for $C_{29}H_{35}F_3N_3O_3$ (MH$^+$) 530.2631, found 530.2629; HPLC 100% (t_R = 16.85 min).

The diastereomer **22** (47%) was isolated as a white solid. ^{1}H NMR (CDCl$_3$) δ 8.23 (d, J = 3.5 Hz, 1H, lactamN*H*), 7.68 and 7.55 (pseudo-ABq, J = 8.0 Hz, 4H, trifluoromethylphenyl-*H*), 7.20−7.10 (m, 4H, indanyl-*arylH*), 6.53 (d, J = 5.0 Hz, 1H, N*H*CHMe$_2$), 5.56 ((s, 1H, NC*H*trifluoromethylphenyl), 4.16−4.06 (m, 1H, NHC*H*Me$_2$), 3.99 (dd, J = 9.5 Hz, 4.5 Hz, 1H, NC*H*indanyl), 3.73−3.67 (m, 1H, NC*H*isobutyl), 3.19−2.84 (m, 5H, indanyl-*3H*, *-1H*, *-2H*), 1.97−1.68 (m, 3H, C*H$_2$*CHMe$_2$, CH$_2$C*H*Me$_2$), 1.47−1.39 (m, 1H, CH*H*CHMe$_2$), 1.16 and 1.12

(2d, J = 6.5 Hz, 6H, NHCH*Me*$_2$), 0.82 and 0.65 (2d, J = 6.5 Hz, 6H, CH$_2$CH*Me*$_2$); LCMS *m/z* 530 (MH$^+$) single component, gradient 2 (t_R = 3.77 min); HRMS calcd for $C_{29}H_{35}F_3N_3O_3$ (MH$^+$) 530.2631, found 530.2630; HPLC 100% (t_R = 16.73 min).

(2*R*)-2-[(3*R*,6*R*)-3-(2,3-Dihydro-1*H*-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-*N*-isopropyl-2-(4-methylphenyl)ethanamide (23) and (2*S*)-2-[(3*R*,6*R*)-3-(2,3-Dihydro-1*H*-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-*N*-isopropyl-2-(4-methylphenyl)ethanamide (24). Compound **8** was reacted with 4-methylbenzaldehyde as described for compound **15** to give **23** as a colorless solid (19%). ^{1}H NMR (CDCl$_3$) δ 7.33−7.13 (m, 7H, methylphenyl-*H*, indanyl-*arylH*), 6.99 (d, J = 4.0 Hz, 1H, lactamN*H*), 5.62 (d, J = 8.0 Hz, 1H, N*H*CHMe$_2$), 5.16 ((s, 1H, NC*H*methylphenyl), 4.14−4.04 (m, 1H, NHC*H*Me$_2$), 3.99−3.93 (m, 2H, NC*H*isobutyl, NC*H*indanyl), 3.18−3.01 (m, 3H, indanyl-*3H*, *-1H*), 2.95−2.75 (m, 2H, indanyl-*2H*, indanyl-*1H*), 2.37 (s, 3H, *methyl*phenyl), 1.84−1.65 (m, 2H, C*H*HCHMe$_2$, CH$_2$C*H*Me$_2$), 1.43−1.35 (m, 1H, CH*H*CHMe$_2$), 1.12 and 1.11 (2d, J = 6.5 Hz, 6H, NHCH*Me*$_2$), 0.81 and 0.74 (2d, J = 6.5 Hz, 6H, CH$_2$CH*Me*$_2$); LCMS *m/z* 476 (MH$^+$) single component, gradient 2 (t_R = 3.65 min); HRMS calcd for $C_{29}H_{38}N_3O_3$ (MH$^+$) 476.2913, found 476.2914; HPLC 100% (t_R = 16.47 min).

The diastereomer **24** (38%) was isolated as a white solid. ^{1}H NMR (CDCl$_3$) δ 7.33−7.04 (m, 9H, methylphenyl-*H*, indanyl-*arylH*, NHC*H*Me$_2$), 5.81 (d, J = 4.0 Hz, 1H, lactamN*H*), 5.48 (s, 1H, NC*H*methylphenyl), 4.16−4.06(m, 1H, NHC*H*Me$_2$), 4.01−3.94 (m, 1H, NC*H*indanyl), 3.72−3.66 (m, 1H, NC*H*isobutyl), 3.18−2.75 (m, 5H, indanyl-*3H*, *-1H*, *-2H*), 2.37 (s, 3H, *methyl*phenyl), 1.96−1.64 (m, 3H, C*H*$_2$CHMe$_2$, CH$_2$C*H*Me$_2$), 1.20−1.10 and 1.10 (m, 6H, NHCH*Me*$_2$), 0.80 and 0.66 (2d, J = 6.0 Hz, 6H, CH$_2$CH*Me*$_2$); LCMS *m/z* 476 (MH$^+$) single component, gradient 2 (t_R = 3.65 min); HRMS calcd for $C_{29}H_{38}N_3O_3$ (MH$^+$) 476.2913, found 476.2912; HPLC 100% (t_R = 16.28 min).

((2*R*)-2-[(3*R*,6*R*)-3-(2,3-Dihydro-1*H*-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-[4-(dimethylamino)phenyl]-*N*-isopropylethanamide (25) and ((2*S*)-2-[(3*R*,6*R*)-3-(2,3-Dihydro-1*H*-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-[4-(dimethylamino)phenyl]-*N*-isopropylethanamide (26). Compound **8** was reacted with 4-dimethylaminobenzaldehyde as described for compound **15** to give **25** as a colorless solid (12%). ^{1}H NMR (CDCl$_3$) δ 730−7.26 (m, 2H, dimethylaminophenyl-*2H*, *-6H*), 7.25−7.14 (m, 4H, indanyl-*arylH*), 6.72−6.68 (m, 2H, dimethylaminophenyl-*3H*, *-5H*), 6.11 (d, J = 3.5 Hz, 1H, lactamN*H*), 5.45 (d, J = 8.0 Hz, 1H, N*H*CHMe$_2$), 5.11 ((s, 1H, NC*H*dimethylaminophenyl), 4.14−4.04 (m, 1H, NHC*H*Me$_2$), 3.97−3.91 (m, 2H, NC*H*isobutyl, NC*H*indanyl), 3.20−3.06 (m, 3H, indanyl-*3H*, *-1H*), 2.98 (s, 6H, *Me*$_2$N), 2.96−2.71 (m, 2H, indanyl-*2H*, indanyl-*1H*), 1.84−1.63 (m, 2H, C*H*HCHMe$_2$, CH$_2$C*H*Me$_2$), 1.42−1.34 (m, 1H, CH*H*-CHMe$_2$), 1.12 and 1.10 (2d, J = 6.5 Hz, 6H, NHCH*Me*$_2$), 0.80 and 0.75 (2d, J = 6.5 Hz, 6H, CH$_2$CH*Me*$_2$); LCMS *m/z* 505 (MH$^+$) single component, gradient 2 (t_R = 2.78 min); HRMS calcd for $C_{30}H_{40}N_4O_3$ (MNa$^+$) 527.2998, found 527.3000; HPLC 100% (t_R = 12.87 min).

The diastereomer **26** (18%) was isolated as a colorless solid. ^{1}H NMR (CDCl$_3$) δ 7.25−7.14 (m, 6H, dimethylaminophenyl-*2H*, *-6H*, indanyl-*arylH*), 6.70 (1/2 pseudo-ABq, J = 8.5 Hz, 2H, dimethylaminophenyl-*3H*, -5H), 6.29 (d, J = 3.5 Hz, 1H, lactamN*H*), 5.59 (d, J = 8.0 Hz, 1H, N*H*CHMe$_2$), 5.49 (s, 1H, NC*H*dimethylaminophenyl), 4.15−4.06 (m, 1H, NHC*H*Me$_2$), 3.96 (dd, J = 9.5 Hz, 4.0 Hz, 1H, NC*H*indanyl), 3.72−3.68 (m, 1H, NC*H*isobutyl), 3.19−2.94 (m, 10H, *Me*$_2$N, indanyl-*3H*, *-1H*, indanyl-*2H*), 2.81−2.73 (m, 1H, indanyl-*1H)*, 1.97−1.89 (m, 1H, C*H*HCHMe$_2$), 1.79−1.65 (m, 2H, CH*H*CHMe$_2$, CH$_2$C*H*Me$_2$), 1.15 and 1.14 (2d, J = 6.5 Hz, 6H, NHCH*Me*$_2$), 0.83 and 0.70 (2d, J = 6.5 Hz, 6H, CH$_2$CH*Me*$_2$); LCMS *m/z* 505 (MH$^+$) single component, gradient 2 (t_R = 3.55 min); HRMS calcd for $C_{30}H_{40}N_4O_3$ (MNa$^+$) 527.2998, found 527.3000; HPLC 100% (t_R = 13.71 min).

(2*R*)-2-[(3*R*,6*R*)-3-(2,3-Dihydro-1*H*-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-*N*-isopropyl-2-[4-(methylsulfonyl)phenyl]ethanamide (27) and (2*S*)-2-[(3*R*,6*R*)-3-(2,3-Dihydro-1*H*-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-*N*-isopropyl-2-[4 (methylsulfonyl)phenyl]ethanamide (28). Compound **8** was reacted with 4-methylsulfonylbenzaldehyde as described for compound **15** to give **27** as a colorless solid (13%). ^{1}H NMR (CDCl$_3$) δ 7.99 and 7.64 (pseudo-ABq, J = 8.5 Hz, 4H, methylsulfonylphenyl-*H*), 7.25−7.16 (m, 4H, indanyl-*arylH*), 6.30 (d, J = 4.0 Hz, lactamN*H*), 5.97 (d, J = 8.0 Hz, 1H, N*H*CHMe$_2$), 5.00 ((s, 1H, NC*H*methylsulfonylphenyl), 4.17−4.08 (m, 1H, NHC*H*Me$_2$), 4.00−3.94 (m, 2H, NC*H*isobutyl, NC*H*indanyl), 3.22−3.15 (m, 1H, indanyl-*3H*), 3.09−3.03 (m, 5H, *Me*SO$_2$, indanyl-*3H*, *-1H*), 2.97−2.75 (m, 2H, indanyl-*2H*, indanyl-*1H*), 1.95−1.78 (m, 2H, C*H*HCHMe$_2$, CH$_2$C*H*Me$_2$), 1.65−1.56 (m, 1H, CH*H*CHMe$_2$), 1.16 (d, J = 6.5 Hz, 6H, NHCH*Me*$_2$), 0.89 and 0.86 (2d, J = 6.5 Hz, 6H, CH$_2$-CH*Me*$_2$); LCMS *m/z* 540 (MH$^+$) single component, gradient 2 (t_R = 3.00 min); HRMS calcd for $C_{29}H_{37}N_3O_5S$ (MH$^+$) 540.2532, found 540.2534; HPLC 100% (t_R = 12.12 min).

The diastereomer **28** (41%) was isolated as a white solid. ^{1}H NMR (CDCl$_3$) δ 7.79 and 7.65 (pseudo-ABq, J = 8.5 Hz, 4H, methylsulfonylphenyl-*H*), 7.25−7.16 (m, 4H, indanyl-*arylH*), 6.43 (d, J = 4.5 Hz, lactamN*H*), 6.09 (d, J = 8.0 Hz, 1H, N*H*CHMe$_2$), 5.55 (s, 1H, NC*H*methylsulfonylphenyl), 4.16−4.06 (m, 1H, NHC*H*Me$_2$), 4.04 (dd, J = 9.5 Hz, 4.0 Hz, 1H, NC*H*indanyl), 3.88−3.83 (m, 1H, NC*H*isobutyl), (m, 1H, indanyl-*3H*), 3.22−2.91 (m, 7H, *Me*SO$_2$, indanyl-*3H*, *-1H*, *-2H*), 2.85−2.77 (m, 1H, indanyl-*1H*), 1.85−1.68 (m, 3H, C*H*$_2$CHMe$_2$, CH$_2$C*H*Me$_2$), 1.18 and 1.16 (2d, J = 6.5 Hz, 6H, NHCH*Me*$_2$), 0.84 and 0.77 (2d, J = 6.5 Hz, 6H, CH$_2$CH*Me*$_2$); LCMS *m/z* 540 (MH$^+$) single component, gradient 2 (t_R = 3.25 min); HRMS calcd for $C_{29}H_{37}N_3O_5S$ (MH$^+$) 540.2532, found 540.2523; HPLC 100% (t_R = 12.16 min).

4-[(1*R*)-1-[(3*R*,6*R*)-3-(2,3-Dihydro-1*H*-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(isopropylamino)-2-oxoethyl]benzamide (29) and 4-{(1*S*)-1-[(3*R*,6*R*)-3-(2,3-Dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-2,5-dioxo-1-piperazinyl]-2-[(1-methylethyl)amino]-2-oxoethyl}benzamide (30). Compound **8** was reacted with 4-carboxamidobenzaldehyde as described for compound **15** to give **29** as a colorless solid (10%). ^{1}H NMR (CD$_3$OD) δ 7.91 and 7.53 (pseudo-ABq, J = 8.5 Hz, 4H, carboxamidophenyl-*H*), 7.25−7.15 (m, 4H, indanyl-*arylH*), 6.75 (d, J = 8.0 Hz, 1H, N*H*CHMe$_2$), 5.47 ((s, 1H, NC*H*carboxamidophenyl), 4.10−3.94 (m, 3H, NHC*H*Me$_2$, NC*H*isobutyl, NC*H*indanyl), 3.20−3.00 (m, 3H, indanyl-*3H*, *-1H*), 2.91−2.78 (m, 2H, indanyl-*2H*, indanyl-*1H*), 1.72−1.67 (m, 2H, C*H*H-CHMe$_2$, CH$_2$C*H*Me$_2$), 1.21−1.12 (m, 4H, CH*H*CHMe$_2$, NHCH-*Me*Me), 1.09 (d, J = 6.5 Hz, 3H, NHCHMe*Me*), 0.74 and 0.59 (2d, J = 6.5 Hz, 6H, CH$_2$CH*Me*$_2$); LCMS *m/z* 505 (MH$^+$) single component, gradient 2 (t_R = 3.57 min); HRMS calcd for $C_{29}H_{36}N_4O_4$ (MH$^+$) 505.2815, found 505.2825; HPLC 100% (t_R = 11.07 min).

The diastereomer **30** (37%) was isolated as a white solid. ^{1}H NMR (CDCl$_3$) δ 7.86 and 7.49 (pseudo-ABq, J = 8.0 Hz, 4H, carboxamidophenyl-*H*), 7.23−7.05 (m, 6H, indanyl-*arylH*, lactam *NH*, N*H*CHMe$_2$), 6.45−5.90 (broad m, 2H, CO*NH*$_2$), 5.58 (broad s, 1H, NC*H*carboxamidophenyl), 4.16−4.06 (m, 1H, NHC*H*Me$_2$), 3.97 (dd, J = 9.0 Hz, 4.0 Hz, 1H, NC*H*indanyl), 3.77−3.69 (m, 1H, NC*H*isobutyl), 3.21−2.79 (m, 5H, indanyl-*3H*, *-1H*, *-2H*), 2.04−1.66 (m, 3H, C*H*$_2$CHMe$_2$, CH$_2$C*H*Me$_2$), 1.16 and 1.12 (2d, J = 6.5 Hz, 6H, NHCH*Me*$_2$), 082 and 0.71 (2d, J = 6.5 Hz, 6H, CH$_2$CH*Me*$_2$); LCMS *m/z* 505 (MH$^+$) single component, gradient 2 (t_R = 3.12 min); HRMS calcd for $C_{29}H_{36}N_4O_4$ (MH$^+$) 505.2815, found 505.2823; HPLC 100% (t_R = 11.20 min).

(2*R*)-*N*-(*tert*-Butyl)-2-(4-chlorophenyl)-2-[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide (31) and (2*S*)-*N*-(*tert*-Butyl)-2-(4-chlorophenyl)-2-[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide (32). Compound **8** was reacted with 4-chlorobenzaldehyde as described for compound **15** to give **31** as a colorless solid (3%). ^{1}H NMR (CDCl$_3$) δ 7.41−7.35 (m, 4H, chlorophenyl-*H*), 7.24−7.15 (m, 4H, indanyl-*arylH*), 6.26 (d, J = 3.5 Hz, 1H, lactam N*H*), 5.76 (s, 1H, N*H*CMe$_3$), 5.04 (s, 1H, NC*H*chlorophenyl), 3.98−3.92 (m, 2H, NC*H*isobutyl, NC*H*indanyl), 3.20−3.04 (m, 3H, inda-

nyl-*3H*, *-1H*), 2.95−2.73 (m, 2H, indanyl-*2H*, indanyl-*1H)*, 1.86−1.68 (m, 2H, C*H*HCHMe$_2$, CH$_2$C*H*Me$_2$), 1.47−1.40 (m, 1H, CH*H*CHMe$_2$), 1.33 (s, 9H, N*H*CMe$_3$), 0.84 and 0.78 (2d, *J* = 7.0 Hz, 3H, CH$_2$CH*Me$_2$*); LCMS *m/z* 510/512 (MH$^+$) single component, gradient 2 (t_R = 3.85 min); HRMS calcd for $C_{29}H_{37}ClN_3O_3$ (MH$^+$) 510.2523, found 510.2529; HPLC 100% (t_R = 17.85 min).

The diastereomer **32** (12%) was isolated as a white solid. ^{1}H NMR (CDCl$_3$) δ 7.43−7.37 (m, 4H, chlorophenyl-*H*), 7.25−7.16 (m, 4H, indanyl *aryl-H*), 6.44 (d, *J* = 4.0 Hz, lactam N*H*), 5.94 (s, 1H, N*H*CMe$_3$), 5.42 (s, 1H, NC*H*chlorophenyl), 4.00 (dd, *J* = 9.5 Hz, 4.0 Hz, 1H, NC*H*indanyl), 3.78 (dd, *J* = 11.0 Hz, 3.0 Hz, 1H, NC*H*isobutyl), 3.20−2.89 (m, 4H, indanyl-*3H*, *-1H*, *-2H*), 2.82−2.74 (m, 1H, indanyl-*1H)*, 1.87−1.65 (m, 3H, C*H$_2$*CHMe$_2$, CH$_2$C*H*Me$_2$), 1.36 (s, 9H, N*H*CMe$_3$), 0.83 and 0.74 (2d, *J* = 6.0 Hz, 6H, CH$_2$CH*Me$_2$*); LCMS *m/z* 510/512 (MH$^+$) single component, gradient 2 (t_R = 364 min); HRMS calcd for $C_{29}H_{37}ClN_3O_3$ (MH$^+$) 510.2523, found 510.2521; HPLC 100% (t_R = 17.42 min).

(2*R*)-*N*-(*tert*-Butyl)-2-[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(4-methoxyphenyl)ethanamide (33) and (2*S*)-*N*-(*tert*-Butyl)-2-[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(4-methoxyphenyl)ethanamide (34). Compound **8** was reacted with 4-methoxybenzaldehyde and *tert*-butylisonitrile as described for compound **15** to give **33** as a colorless solid (8%). ^{1}H NMR (CDCl$_3$) δ 7.38−7.34 (m, 2H, methoxyphenyl-*2H*, *-6H*), 7.23−7.14 (m, 4H, indanyl-*arylH*), 6.94−6.90 (m, 2H, methoxyphenyl-*3H*, *-5H*), 6.30 (d, *J* = 3.5 Hz, 1H, lactam N*H*), 5.56 (s, 1H, N*H*CMe$_3$), 5.14 (s, 1H, NC*H*methoxyphenyl), 3.98−3.92 (m, 2H, NC*H*isobutyl, NC*H*indanyl), 3.83 (s, 3H, O*Me*), 3.19−3.05 (m, 3H, indanyl-*3H*, *-1H*), 2.95−2.72 (m, 2H, indanyl-*2H*, indanyl-*1H)*, 1.83−1.65 (m, 2H, C*H*HCHMe$_2$, CH$_2$C*H*Me$_2$), 1.37−1.29 (m, 10H, CH*H*CHMe$_2$, N*H*CMe$_3$), 0.80 and 0.72 (2d, *J* = 7.0 Hz, 3H, CH$_2$CH*Me$_2$*); LCMS *m/z* 505 (MH$^+$) single component, gradient 2 (t_R = 3.50 min); HRMS calcd for $C_{30}H_{40}N_3O_4$ (MH$^+$) 506.3024, found 506.3017; HPLC 100% (t_R = 14.08 min).

The diastereomer **34** (11%) was isolated as a white solid. ^{1}H NMR (CDCl$_3$) δ 7.38−7.34 (m, 2H, methoxyphenyl-*2H*, *-6H*), 7.23−7.14 (m, 4H, indanyl-*arylH*), 6.94−6.90 (m, 2H, methoxyphenyl-*3H*, *-5H*), 6.27 (d, *J* = 3.5 Hz, 1H, lactam N*H*), 5.78 (s, 1H, N*H*CMe$_3$), 5.42 (s, 1H, NC*H*methoxyphenyl), 3.97 (dd, *J* = 9.5 Hz, 4.0 Hz, 1H, NC*H*indanyl), 3.83 (s, 3H, O*Me*), 3.74 (dd, *J* = 10.5 Hz, 3.5 Hz, 1H, NC*H*isobutyl), 3.19−2.90 (m, 4H, indanyl-*3H*, *-1H*, *-2H*), 2.80−2.73 (m, 1H, indanyl-*1H)*, 1.90−1.63 (m, 3H, C*H$_2$*CHMe$_2$, CH$_2$C*H*Me$_2$), 1.36−1.29 (s, 9H, N*H*CMe$_3$), 0.81 and 0.69 (2d, *J* = 6.5 Hz, 6H, CH$_2$CH*Me$_2$*); LCMS *m/z* 505 (MH$^+$) single component, gradient 2 (t_R = 3.50 min); HRMS calcd for $C_{30}H_{40}N_3O_4$ (MH$^+$) 506.3024, found 506.3023; HPLC 100% (t_R = 17.02 min).

(2*R*)-*N*-(*tert*-Butyl)-2-[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-[4-(trifluoromethoxy)phenyl]ethanamide (35) and (2*S*)-*N*-(*tert*-butyl)-2-[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-[4-(trifluoromethoxy)phenyl]ethanamide (36). Compound **8** was reacted with 4-trifluoromethoxybenzaldehyde and *tert*-butylisonitrile as described for compound **15** to give **35** as a colorless solid (21%). ^{1}H NMR (CDCl$_3$) δ 8.08 (d, *J* = 3.5 Hz, 1H, lactam N*H*), 7.51−7.47 (m, 2H, trifluoromethoxyphenyl-*2H*, *-6H*), 7.19−7.13 (m, 4H, indanyl-*arylH*), 6.94−6.90 (m, 2H, trifluoromethoxyphenyl-*3H*, *-5H*), 6.00 (s, 1H, N*H*CMe$_3$), 5.30 (s, 1H, NC*H*trifluoromethoxyphenyl), 4.04−3.95 (m, 2H, NC*H*isobutyl, NC*H*indanyl), 3.16−2.29 (m, 3H, indanyl-*3H*, *-1H*), 2.92−2.79 (m, 2H, indanyl-*2H*, indanyl-*1H)*, 1.85−1.64 (m, 2H, C*H*HCHMe$_2$, CH$_2$C*H*Me$_2$), 1.35−1.24 (m, 10H, CH*H*CHMe$_2$, N*H*CMe$_3$), 0.82 and 0.74 (2d, *J* = 7.0 Hz, 3H, CH$_2$CH*Me$_2$*); LCMS *m/z* 560 (MH$^+$) single component, gradient 2 (t_R = 3.65 min); HRMS calcd for $C_{xx}H_{xx}N_3O_3$ (MH$^+$) 560.2736, found 560.2736; HPLC 100% (t_R = 15.75 min).

The diastereomer **36** (31%) was isolated as a white solid. ^{1}H NMR (CDCl$_3$) δ 8.36 (d, *J* = 3.5 Hz, 1H, lactam N*H*), 7.51−7.47 (m, 2H, trifluoromethoxyphenyl-*2H*, *-6H*), 7.19−7.13 (m, 4H, indanyl-*arylH*), 6.94−6.90 (m, 2H, trifluoromethoxyphenyl-*3H*, *-5H*), 6.46 (s, 1H, N*H*CMe$_3$), 5.64 (s, 1H, NC*H*trifluoromethoxyphenyl), 3.96 (dd, *J* = 9.0 Hz, 4.0 Hz, 1H, NC*H*indanyl), 3.69 (dd, *J* = 10.5 Hz, 3.5 Hz, 1H, NC*H*isobutyl), 3.17−2.84 (m, 5H, indanyl-*3H*, *-1H*, *-2H*), 1.94−1.66 (m, 3H, C*H$_2$*CHMe$_2$, CH$_2$C*H*Me$_2$), 1.36 (s, 9H, N*H*CMe$_3$), 0.81 and 0.60 (2d, *J* = 7.0 Hz, 6H, CH$_2$CH*Me$_2$*); LCMS *m/z* 560 (MH$^+$) single component, gradient 2 (t_R = 3.79 min); HRMS calcd for $C_{30}H_{37}F_3N_3O_4$ (MH$^+$) 560.2736, found 560.2737; HPLC 100% (t_R = 18.48 min).

(2*R*)-2-(2,4-Difluorophenyl)-2-[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-*N*-isopropylethanamide (37) and (2*S*)-2-(2,4-Difluorophenyl)-2-[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-*N*-isopropylethanamide (38). Compound **8** was reacted with 2,4-difluorobenzaldehyde as described for compound **15** to give **37** as a colorless solid (7%). ^{1}H NMR (CDCl$_3$) δ 7.71−7.64 (m, 1H, difluorophenyl-*6H*), 7.24−7.14 (m, 4H, indanyl-*arylH*), 6.98−6.86 (m, 2H, difluorophenyl-*3H*, -5H), 6.69 (d, *J* = 3.5 Hz, 1H, lactamN*H*), 5.89 (d, *J* = 8.0 Hz, 1H, N*H*CHMe$_2$), 5.34 (s, 1H, NC*H*difluorophenyl), 4.17−4.08 (m, 1H, NHC*H*Me$_2$),4.02 (dd, *J* = 10.0 Hz, 3.5 Hz, 1H, NC*H*isobutyl), 3.93 (dd, *J* = 9.5 Hz, 4.0 Hz, 1H, NC*H*indanyl), 3.20−3.03 (m, 3H, indanyl-*3H*, *-1H*), 2.97−2.85 (m, 1H, indanyl-*2H*), 2.82−2.74 (m, 1H, indanyl-*1H)*, 1.90−1.74 (m, 2H, C*H*HCHMe$_2$, CH$_2$C*H*Me$_2$), 1.53−1.45 (m, 1H, CH*H*CHMe$_2$), 1.16 (pseudo-t, 2 overlapping d, *J* = 6.5 Hz, 6H, NHCH*Me$_2$*), 0.87 and 0.82 (2d, *J* = 6.5 Hz, 6H, CH$_2$CH*Me$_2$*); LCMS *m/z* 498 (MH$^+$) single component, gradient 2 (t_R = 3.57 min); HRMS calcd for $C_{28}H_{33}F_2N_3O_3$ (MH$^+$) 498.2568, found 498.2578; HPLC 100% (t_R = 14.11 min); circular dichroism (CH$_3$CN) λ_{max} = 202.0 nm, dE 12.75, E38105, λ_{max} = 228.0 nm, dE −7.33, E4077.

The diastereomer **38** (26%) was isolated as a white solid. ^{1}H NMR (CDCl$_3$) δ 7.72−7.65 (m, 1H, difluorophenyl-*6H*), 7.24−7.14 (m, 4H, indanyl-*arylH*), 7.07 (d, *J* = 3.5 Hz, 1H, lactamN*H*), 6.99−6.86 (m, 2H, difluorophenyl-*3H*, -5H), 5.97 (d, *J* = 7.8 Hz, 1H, N*H*CHMe$_2$), 5.37 (s, 1H, NC*H*difluorophenyl), 4.17−4.08 (m, 1H, NHC*H*Me$_2$), 4.03 (dd, *J* = 10.6 Hz, 3.5 Hz, 1H, NC*H*isobutyl), 3.93 (dd, *J* = 9.4 Hz, 4.0 Hz, 1H, NC*H*indanyl), 3.20−3.03 (m, 3H, indanyl-*3H*, *-1H*), 2.97−2.85 (m, 1H, indanyl-*2H*), 2.82−2.74 (m, 1H, indanyl-*1H)*, 1.90−1.74 (m, 2H, C*H*HCHMe$_2$, CH$_2$C*H*Me$_2$), 1.52−1.43 (m, 1H, CH*H*CHMe$_2$), 1.16 (pseudo-t, 2 overlapping d, *J* = 6.5 Hz, 6H, NHCH*Me$_2$*), 0.87 and 0.82 (2d, *J* = 6.5 Hz, 6H, CH$_2$CH*Me$_2$*); LCMS *m/z* 498 (MH$^+$) single component, gradient 2 (t_R = 3.36 min); HRMS calcd for $C_{28}H_{33}F_2N_3O_3$ (MH$^+$) 498.2568, found 498.2556; HPLC 100% (t_R = 13.82 min).

(2*R*)-2-[4-(Acetylamino)phenyl]-*N*-(*tert*-butyl)-2-[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide (39). Compound **8** was reacted with 4-acetamidobenzaldehyde and *tert*-butylisonitrile as described for compound **15** to give **39** as a colorless solid (19%). ^{1}H NMR (CDCl$_3$) δ 8.48 (s, 1H, AcNH), 7.59 and 7.32 (pseudo-ABq, *J* = 8.5 Hz, 4H, acetamidophenyl-*H*), 7.24−7.13 (m, 5H, indanyl-*arylH*, lactamN*H*), 5.90 (s, 1H, N*H*CMe$_3$), 5.21 (s, 1H, NC*H*acetamidophenyl), 3.98−3.92 (m, 2H, NC*H*isobutyl, NC*H*indanyl), 3.18−3.00 (m, 3H, indanyl-*3H*, *-1H*), 2.92−2.75 (m, 2H, indanyl-*2H*, indanyl-*1H*), 2.18 (s, 3H, *Me*CO), 1.77−1.58 (m, 2H, C*H*HCHMe$_2$, CH$_2$C*H*Me$_2$), 1.33−1.22 (m, 10H, CH*H*-CHMe$_2$, NHC*Me$_3$*), 0.76 and 0.64 (2d, *J* = 6.5 Hz, 6H, CH$_2$-CH*Me$_2$*); LCMS *m/z* 533 (MH$^+$) single component, gradient 2 (t_R = 3.27 min); HRMS calcd for $C_{31}H_{40}N_4O_4$ (MH$^+$) 533.3128, found 533.3120; HPLC 100% (t_R = 12.34 min).

(2*R*)-2-[3-(Acetylamino)phenyl]-*N*-(*tert*-butyl)-2-[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide (40). Compound **8** was reacted with 3-acetamidobenzaldehyde and *tert*-butylisonitrile as described for compound **15** to give **40** as a colorless solid (11%). ^{1}H NMR (CDCl$_3$) δ 7.87−7.80 (m, 2H, AcNH, acetamidophenyl-*4H*), 7.56 (s, 1H, acetamidophenyl-*2H*), 7.36 (pseudo-t, *J* = 8.0 Hz, acetamidophenyl-*5H*), 7.22−7.09 (m, 5H, indanyl-*arylH*, acetamidophenyl-*5H*), 6.71 (d, *J* = 4.0 Hz, lactamN*H*), 5.75 (s, 1H, N*H*CMe$_3$), 5.06 ((s, 1H, NC*H*acetamidophenyl), 3.98−3.90

(m, 2H, NC*H*isobutyl, NC*H*indanyl), 3.19−3.00 (m, 3H, indanyl-*3H*, *-1H*), 2.95−2.78 (m, 2H, indanyl-*2H*, indanyl-*1H*), 2.15 (s, 3H, *Me*CO), 1.82−1.65 (m, 2H, C*H*HCHMe$_2$, CH$_2$C*H*Me$_2$), 1.45−1.37 (m, 1H, CH*H*CHMe$_2$), 1.33 (s, 9H, NHC*Me$_3$*), 0.80 and 0.74 (2d, J = 6.5 Hz, 6H, CH$_2$CH*Me$_2$*); LCMS *m/z* 533 (MH$^+$) single component, gradient 2 (t_R = 3.21 min); HRMS calcd for $C_{31}H_{40}N_4O_4$ (MH$^+$) 533.3128, found 533.3130; HPLC 100% (t_R = 12.69 min).

(2*R*)-2-[(3*R*,6*R*)-3-(2,3-Dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-2,5-dioxo-1-piperazinyl]-*N*-(1,1-dimethylethyl)-2-[4-(4-methyl-1-piperazinyl)phenyl]ethanamide (41). Compound **8** was reacted with 4-(4-methyl-1-piperazinyl)-benzaldehyde and *tert*-butylisonitrile as described for compound **15** to give **41** as a colorless solid (11%). ^{1}H NMR (CDCl$_3$) δ 7.32−7.14 and 6.95−6.90 (2m, 8H, aryl*H*), 6.13 (d, J = 4.5 Hz, lactamN*H*), 5.52 (s, 1H, N*H*CMe$_3$), 5.14 (s, 1H, NC*H*piperazinophenyl), 3.97−3.90 (m, 2H, NC*H*isobutyl, NC*H*indanyl), 3.45−2.54 (4m, 13H, indanyl-*3H*, *-1H*, *-2H*, piperazine 4 × C*H*$_2$), 2.36 (s, 3H, N*Me*), 1.78−1.50 (m, 3H, C*H*$_2$HCHMe$_2$), 1.31 (s, 9H, NHC*Me$_3$*), 0.77 and 0.69 (2d, J = 6.5 Hz, 6H, CH$_2$CH*Me$_2$*); LCMS *m/z* 574 (MH$^+$) single component, gradient 2 (t_R = 2.48 min); HRMS calcd for $C_{34}H_{48}N_5O_3$ (MH$^+$) 574.3757, found 574.3751; HPLC 100% (t_R = 10.21 min).

(2*R*)-2-[(3*R*,6*R*)-3-(2,3-Dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-2,5-dioxo-1-piperazinyl]-*N*-(1,1-dimethylethyl)-2-[3-(4-methyl-1-piperazinyl)phenyl]ethanamide (42). Compound **8** was reacted with 3-(4-methyl-1-piperazinyl)-benzaldehyde and *tert*-butylisonitrile as described for compound **15** to give **42** as a colorless solid (14%). ^{1}H NMR (CDCl$_3$) δ 7.30−7.15 and 7.00−6.85 (2m, 8H, aryl*H*), 6.07 (d, J = 4.0 Hz, lactamN*H*), 5.56 (s, 1H, N*H*CMe$_3$), 5.24 ((s, 1H, NC*H*piperazinophenyl), 4.03−3.94 (m, 2H, NC*H*isobutyl, NC*H*indanyl), 3.25−2.55 (4m, 13H, indanyl-*3H*, *-1H*, *-2H*, piperazine 4 × C*H*$_2$), 2.36 (s, 3H, N*Me*), 1.65−1.30 (m, 3H, C*H*$_2$HCHMe$_2$), 1.32 (s, 9H, NHC*Me$_3$*), 0.76 and 0.68 (2d, J = 6.5 Hz, 6H, CH$_2$CH*Me$_2$*); LCMS *m/z* 574 (MH$^+$) single component, gradient 2 (t_R = 2.53 min); HRMS calcd for $C_{34}H_{48}N_5O_3$ (MH$^+$) 574.3757, found 574.3761; HPLC 100% (t_R = 10.57 min).

(2*R*)-2-[(3*R*,6*R*)-3-(2,3-Dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-2,5-dioxo-1-piperazinyl]-*N*-methyl-*N*-(1-methylethyl)-2-phenylethanamide (43). Compound **15** (60 mg) and methyl iodide (0.016 mL) were dissolved in dry tetrahydrofuran (1 mL), and the solution was stirred at −20 °C under dry nitrogen. A solution of lithium hexamethyldisilazide (1.0 M in tetrahydrofuran, 0.100 mL) was added via syringe. The mixture was kept between −20 and −10 °C for 3 h and then allowed to warm to room temperature. The reaction was quenched with saturated aqueous ammonium chloride (0.5 mL). The quenched reaction mixture was diluted with ethyl acetate (50 mL) and dried over anhydrous sodium sulfate. The mixture was evaporated under reduced pressure, and the crude product was purified by preparative layer chromatography on silica (eluted with 3% 2-propanol in dichloromethane) to give the title compound as a colorless solid (20 mg, 32%). ^{1}H NMR (CDCl$_3$) (rotameric forms present) δ 7.45−7.39 and 7.25−7.13 (m, 9H, phenyl-*arylH*, indanyl-*arylH*), 6.85−6.79 (broad m, 1H, lactamN*H*), 6.63 and 6.37 (2s, 1H, NC*H*phenyl), 494 (septet, 1H, NMeC*H*Me$_2$), 4.20−4.06 (dd, J = 12.1 Hz, 4.0 Hz, 1H, NC*H*isobutyl), 3.99 (dd, J = 10.5 Hz, 4.5 Hz, 1H, NMeC*H*Me$_2$), 3.21−3.03 and 2.93−2.73 (2m, 5H, indanyl-*3H*, *-1H*, *-2H*), 2.82 and 2.60 (2s, 3H, N*Me*CH*Me$_2$*), 1.53−1.35 (m, 2H, C*H*HCHMe$_2$, CH$_2$C*H*Me$_2$), 1.22, 1.10, 1.00 and 0.68 (4d, J = 6.5 Hz, 6H, NMeCH*Me$_2$*), 0.62−0.53 (m, 4H, CH$_2$CH*Me*Me, CH*H*CHMe$_2$), 0.35 (d, J = 6.5 Hz, 3H, CH$_2$CHMe*Me*); LCMS *m/z* 476 (MH$^+$) major component, gradient 2 (t_R = 3.54 min). HRMS calcd for $C_{29}H_{38}N_3O_3$ (MH$^+$) 476.2913, found 476.2907; HPLC 95% (t_R = 14.36 min).

(2*R*)-2-[(3*R*,6*R*)-3-(2,3-Dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-2,5-dioxo-4-(2-propen-1-yl)-1-piperazinyl]-*N*-(1-methylethyl)-2-phenylethanamide (44). Compound **15** (42 mg) and allyl bromide (0.060 mL) were dissolved in dry tetrahydrofuran (2 mL), and the solution was stirred at −78 °C under dry nitrogen. A solution of lithium hexamethyldisilazide (1.0 M in tetrahydrofuran, 0.100 mL) was added via syringe. The mixture was allowed to warm to room temperature over 2 h, then stirred at room temperaure for 30 min. The solution was cooled to −30 °C. Then the reaction was quenched with saturated aqueous ammonium chloride (2 mL). The reaction mixture was diluted with ethyl acetate (50 mL) and dried over anhydrous sodium sulfate. The mixture was evaporated under reduced pressure, and the crude product was purified by preparative layer chromatography on silica (eluted with 2% 2-propanol in dichloromethane) to give the title compound as a colorless solid (16 mg, 35%). ^{1}H NMR (CDCl$_3$) δ 7.41 (s, 5H, phenyl-*arylH*), 7.28−7.14 (m, 4H, indanyl-*arylH*), 5.76−5.65 (m, 1H, C*H*=CH$_2$), 5.46 (d, J = 7.8 Hz, 1H, N*H*CHMe$_2$), 5.22 (s, 1H, NC*H*phenyl), 5.20 (broad d, J = 11.3 Hz, 1H, CH=C*H*H (cis to C*H*=CH$_2$)), 5.09 (broad d, J = 17.3 Hz, 1H, CH=CH*H* (trans to C*H*=CH$_2$)), 4.85−4.78 (m, 1H, C*H*HCH=CH$_2$), 4.16−4.06 (m, 1H, NHC*H*Me$_2$), 4.05 (dd, J = 10.8 Hz, 4.0 Hz, 1H, NC*H*isobutyl), (d, J = 9.0 Hz, 1H, NC*H*indanyl), 3.42−3.35 (m, 1H, C*H*HCH=CH$_2$), 3.20−2.84 (m, 5H, indanyl-*3H*, *-1H*, *-2H*), 1.81−1.66 (m, 2H, C*H*HCHMe$_2$, CH$_2$C*H*Me$_2$), 1.34−1.26 (m, 1H, CH*H*CHMe$_2$), 1.12 and 1.09 (2d, J = 6.5 Hz, 6H, NHCH*Me$_2$*), 0.80 and 0.75 (2d, J = 6.5 Hz, 6H, CH$_2$CH*Me$_2$*); LCMS *m/z* 502 (MH$^+$) major component, gradient 2 (t_R = 3.57 min). HRMS calcd for $C_{31}H_{40}N_3O_3$ (MH$^+$) 502.3070, found 502.3065; HPLC 100% (t_R = 14.74 min).

(2*R*)-2-[(3*R*,6*R*)-3-(2,3-Dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-2-oxo-1-piperazinyl]-*N*-(1-methylethyl)-2-phenylethanamide (45). Compound **15** (70 mg) was dissolved in dry tetrahydrofuran (3 mL), and the solution was stirred at room temperature under dry nitrogen. A solution of borane (1.0 M in tetrahydrofuran, 0.84 mL) was added via syringe over 1 min (effervescence was observed). The mixture was left at room temperature overnight, and then the excess borane was destroyed by addition of 0.5 M hydrochloric acid (2 mL, effervescence). After the mixture was stirred at room temperature for 2 h, the reaction mixture was evaporated under reduced pressure and the residue was partitioned between saturated aqueous sodium hydrogen carbonate (5 mL) and dichloromethane (10 mL). The organic extract was separated using a hydrophobic frit and evaporated under reduced pressure. The crude product was purified by preparative layer chromatography on silica (eluted with 2.5% 2-propanol in dichloromethane) to give the title compound as a colorless gum (21 mg, 31%). ^{1}H NMR (CDCl$_3$) δ 7.43−7.32 and 7.23−7.11 (2m, 9H, phenyl-*arylH*, indanyl-*arylH*), 5.90 (d, J = 7.5 Hz, 1H, N*H*CHMe$_2$), 5.37 (s, 1H, NC*H*phenyl), 4.15−4.05 (m, 1H, NHC*H*Me$_2$), 3.77 (d, J = 4.5 Hz, 1H, NC*H*indanyl), 3.46−3.36 (m, 1H, NHC*H*HCHisobutyl), 3.17−2.88 (m, 7H, NC*H*isobutyl, NHCH*H*CHisobutyl, indanyl-*3H*, *-1H*, *-2H*),1.89−1.67 (m, 2H, C*H*HCHMe$_2$, CH$_2$C*H*Me$_2$), 1.35−1.25 (m, 1H, CH*H*CHMe$_2$), 1.13 and 1.10 (2d, J = 6.5 Hz, 6H, NHCH*Me$_2$*), 0.74 and 0.58 (2d, J = 6.5 Hz, 6H, CH$_2$CH*Me$_2$*); LCMS *m/z* 448 (MH$^+$) major component, gradient 2 (t_R = 3.02 min); HRMS calcd for $C_{28}H_{38}N_3O_2$ (MH$^+$) 448.2964, found 448.2972; HPLC 94% (t_R = 11.55 min).

X-ray Crystallographic Analysis of 17. Crystals of **17** grew as colorless prisms by slow evaporation of 1,2-dimethoxyethane. The data crystal was a prism with approximate dimensions of 0.90 × 0.22 × 0.14 mm^3. Crystal data are the following: empirical formula, $C_{31}H_{42}N_3O_4$; M = 520.68; monoclinic; space group $P2_1$; a = 12.7167(7) Å; b = 19.3272(11) Å; c = 13.8360(8) Å; α = 90°; β = 117.124(2)°; γ = 90°; volume, 3026.6(3) Å^3; Z = 4; D_c = 1.143 g/cm^3; F(000) = 1124. The data were collected at 160(2) K on a Bruker SMART 1K CCD diffractometer using Mo Kα, radiation (λ = 0.710 73 Å). Data reduction was performed using SAINT, version 6.63 (from Bruker AXS). The structure was solved by direct methods using SHELXTL and refined by full-matrix least-squares on F^2 with anisotropic displacement parameters for the non-H atoms using SHELXTL. The structure was refined to R = 0.0474 (10 899 reflections with $F^2_o > 2\sigma(F_o)$]), wR2 = 0.1048, and a goodness of fit = 1.055 for 714 refined parameters. The absolute structure parameter, Flack, was refined to −0.1(8); this was not sufficient to assign the absolute stereochemistry. Neutral atom scattering factors and values used to calculate

the linear absorption coefficient are from the International Tables for X-ray Crystallography. The crystal structure has been deposited at the Cambridge Crystallographic Data Centre, and the allocated deposition number is CCDC 272988.

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Supporting Information Available: Details of the X-ray crystallographic determination of **17** and the CD spectra of **17**, **18**, and **37**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(24) Ratio of the IC_{50} hOT in the presence of 50 mg/mL HSA to IC_{50} hOT in the absence of 50 mg/mL HSA. Method is as in ref 14. The ligand [^{3}H]oxytocin was made up in buffer containing 100 mg/mL HSA. HSA was obtained from Sigma (Poole, Dorset, U.K.).

(25) IC_{50} is the serum concentration for 50% inhibition of uterine contractility response to oxytocin in an OT induced rat uterus contraction model (see ref 15).

(26) DR_{10} determination: Adult female AHA rats were anesthetized with sodium pentobarbitone (60 mg/kg ip, then 10 mg kg^{-1} h^{-1} i.v.) 18 h after pretreatment with diethylstilbestrol (250 μg/kg ip). Arterial blood pressure was recorded from a femoral artery. The left uterine horn was anchored in the abdominal cavity at the ovarian end, and uterine contractility was recorded via a ligature tied approximately 2 cm distally and connected to a strain gauge under 1−2 g resting tension. Two consecutive two-point dose-response curves to either iv OT were constructed and uterine contractile responses quantified by recording the area under the contractile response for the 10 min period immediately postdose. Cumulative doses of antagonist or vehicle were then injected iv, and oxytocin dose-response curves were repeated 15 min later. Dose ratios were calculated for each dose of antagonist by comparison with the second agonist dose-response curve and the DR10 (antagonist dose required to shift the agonist dose-response curve 10-fold), calculated by linear interpolation of log(DR − 1) plotted against dose (mg/kg).

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