1,4-Benzodiazepines as Inhibitors of Respiratory Syncytial Virus. The Identification of a Clinical Candidate

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Respiratory syncytial virus (RSV) is the cause of one-fifth of all lower respiratory tract infections worldwide and is increasingly being recognized as representing a serious threat to patient groups with poorly functioning or immature immune systems. Racemic 1,4-benzodiazepines show potent anti-RSV activity in vitro. Anti-RSV evaluation of 3-position *R*- and *S*-benzodiazepine enantiomers and subsequent optimization of this series resulted in selection of a clinical candidate. Antiviral activity was found to reside mainly in the *S*-enantiomer, and the *R*-enantiomers were consistently less active against RSV. Analogues of 1,4-(*S*)-benzodiazepine were synthesized as part of the lead optimization program at Arrow and tested in the XTT assay. From this exercise, (*S*)-1-(2-fluorophenyl)-3-(2-oxo-5-phenyl-2,3-dihydro-1*H*-benzo[*e*][1,4]-diazepin-3-yl)-urea, **17b** (RSV-604) was identified as a clinical candidate, exhibiting potent anti-RSV activity in the XTT assay, which was confirmed in secondary assays. Compound **17b** also possessed a good pharmacokinetic profile and has now progressed into the clinic.

Introduction

The preceding paper in this series[1] described the lead optimization program based on racemic benzodiazepines identified as inhibitors of RSV in an XTT[a] based cell screen. This activity was confirmed in secondary assays (plaque and ELISA), and the compounds exhibited good pharmacokinetic (PK) properties when dosed in the rat.

Synthesis and evaluation of 3*R*- and 3*S*-enantiomers of lead compounds showed that *S*-enantiomers were consistently more active against RSV than *R*-enantiomers. Subsequent lead optimization of these enantiomers led to the identification of **17b** (RSV-604), (*S*)-1-(2-fluorophenyl)-3-(2-oxo-5-phenyl-2,3-dihydro-1*H*-benzo[*e*][1,4]-diazepin-3-yl)-urea, as a candidate compound for clinical evaluation.

Chemistry

The unsubstituted, racemic benzodiazepine (**1a**) was synthesized as described in the previous paper.[1] Initial attempts to separate the isomers via crystallization with chiral salts[2] were unsuccessful, so a synthetic route was developed involving the synthesis of diastereomeric analogues coupled to *S*-phenylalanine[3] (Scheme 1).

The racemic amine **1a** was coupled to *N*-Boc-*S*-phenylalanine using HBTU,[4] followed by deprotection with hydrogen chloride in ethyl acetate to yield amines **3b** and **3c**. At this stage, repeated crystallizations using methanol and ethyl acetate yielded diastereomerically pure quantities of each diastereomeric amine.

Amines **3b** and **3c** were independently treated with isothiocyanatobenzene to yield the thioureas, **4b** and **4c**, which yielded the enantiomeric amines **1b** and **1c** upon Edman degradation.[5] The enantiomeric purity of intermediates **1b** and **1c** was analyzed using chiral HPLC, and both were found to have enantiomeric excesses greater than 99.9%.

Enantiomerically pure amide and urea derivatives were prepared as shown in Schemes 2 and 3.[6] Several specific carboxylic acids were required as part of the lead optimization program. 2-Methoxy-4-methylsulfanylbenzoic acid was oxidized with oxone to produce 4-methanesulfonyl-2-methoxybenzoic acid,[7] which was used in the synthesis of compound **18**. Cyclization of ethenesulfonyl ethane onto 2-amino-5-chlorobenzoic acid afforded the intermediate acid[8] required for the synthesis of compound **19**. Microwave heating of 2,4-difluorobenzoic acid with piperidine resulted in the formation of 4-fluoro-2-piperidin-1-ylbenzoic acid,[9] which was used in the synthesis of compound **22**. Functionalization at the *N*-1 position was carried out as in Scheme 4.[10] Compound **17b** was deprotonated with sodium hydride and treated with methyl bromoacetate to yield intermediate **11**. Deprotection of the ester with lithium hydroxide[11] followed by coupling with a variety of amines in the presence of HBTU yielded the desired products of the general structure of **13**.

Structure Confirmation. To obtain preliminary identification of the isomers, compounds analogous to **3b** and **3c** were synthesized using *N*-Boc-D-phenylalanine instead of *N*-Boc-L-phenylalanine, so that comparison with a published crystal structure could be used to assign stereochemistry. The isomers were separated and N^1-methylated, and ^{1}H NMR in $CDCl_3$ was performed. This data was compared to previously published structural analyses on the N^1-methylated derivative of compound **3b**[12] and, as the diastereoisomers showed differing signals, it was possible to assign the stereochemistry of these analogues. Both isomers were deprotected to give compounds **1b** and **1c**. These samples were compared by chiral HPLC to samples of **1b** and **1c** derived from the route using *N*-Boc-L-phenylalanine, which resulted in compound **3b** being identified as the *S*-isomer. The most pronounced difference in the spectra is the signal due to the C^3 proton; in the *S*-isomer, this is quoted as 5.55 ppm, and we found that in the *R*-isomer it lay at 5.57 ppm (Figure

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[a] Abbreviations: XTT, 2,3-bis-(2-methoxy-4-nitro-5-sulfophenyl)-2*H*-tetrazolium-5-carboxanilide disodium salt; HBTU, *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate; HEp-2, human respiratory epithelial cells; F-protein, fusion protein; N-protein, nucleocapsid protein; P-protein, phosphoprotein.

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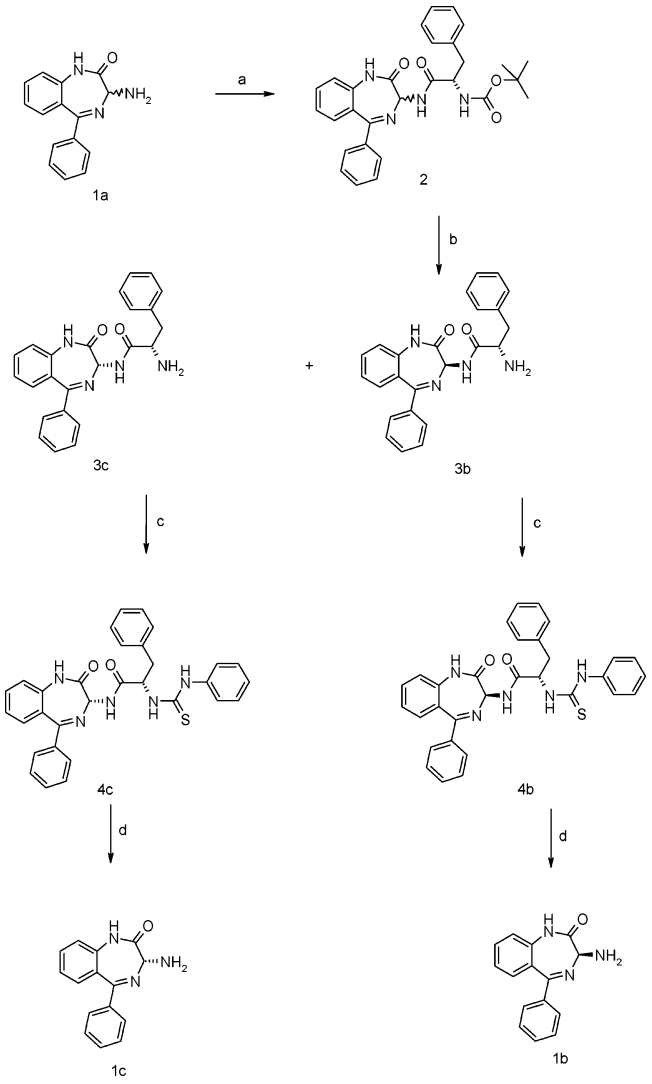
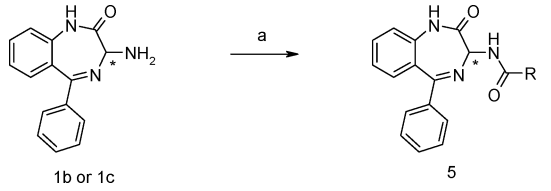
Scheme 1[a]



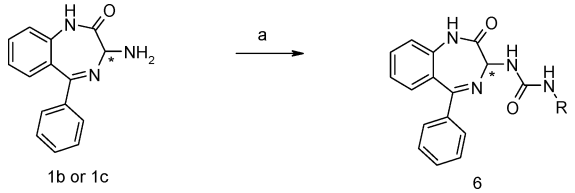
[a] Reagents and conditions: (a) *N*-Boc-L-Phe, HBTU, Et_3N, CH_2Cl_2; (b) HCl, EtOAc; (c) PhNCS, CH_2Cl_2; (d) TFA.

Scheme 2[a]



[a] Reagents and conditions: (a) R−COOH, HBTU, Et_3N.

Scheme 3[a]

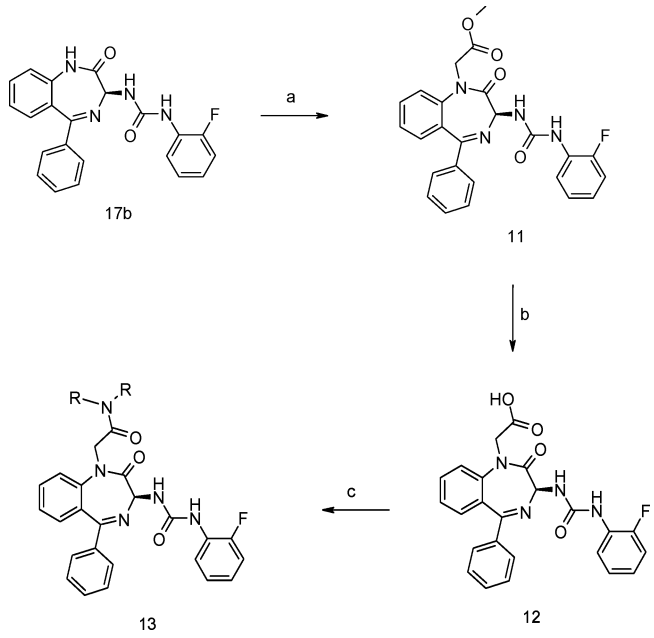


[a] Reagents and conditions: (a) R−NCO, Et_3N.

1). The NMR sample of **3b** was spiked with a small quantity of **3c** to confirm the differences in the spectra.

To unequivocally confirm this assignment, a crystal structure determination was obtained. To obtain satisfactory resolution, it was necessary to synthesize a derivative with at least one heavy heteroatom incorporated into the structure to ensure scattering of the X-rays.[13] Compound **14** (Figure 2) was synthesized from intermediate **1b**, and 4-bromo-2-chlorophenyl isocyanate and crystals of suitable quality for X-ray crystal

Scheme 4[a]



[a] Reagents and conditions: (a) NaH, methyl bromoacetate, DMF; (b) LiOH, THF, H_2O; (c) R_2−NH, HBTU, Et_3N, DMF.

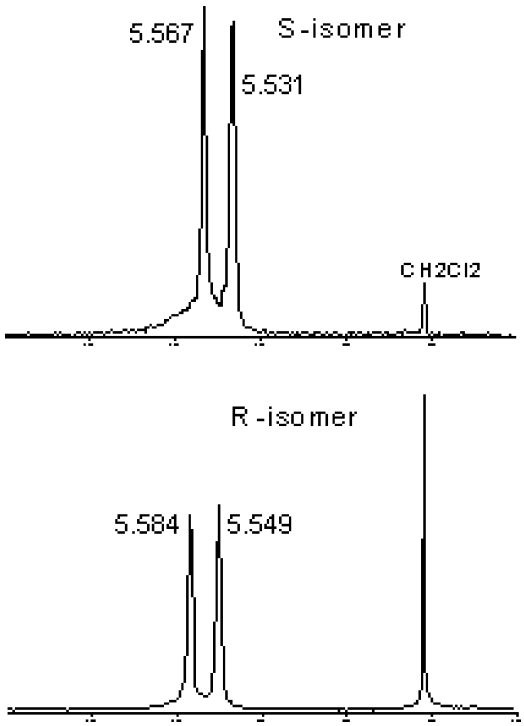


Figure 1. ^1H NMR of diastereomers derived from intermediates **3b** and **3c**.

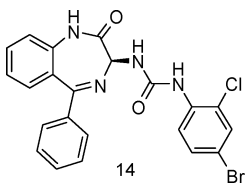


Figure 2. Structure for X-ray crystallography.

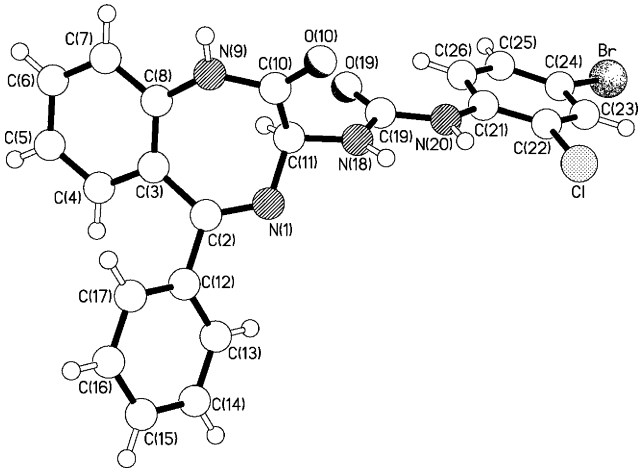


Figure 3. Structure determination by X-ray crystallography.

structure determination were produced. The X-ray crystal structure (Figure 3) confirmed that compound **14** had the expected *S*-stereochemistry at the C-3 position of the benzodiazepine ring system (shown as C-11 in Figure 3).

Computational conformational analysis utilizing the MMFF94s forcefield[14] identified the low-energy conformations for *R*- and *S*-isomers of compound **14**. In each case, the pendent phenyl amide was maintained in the equatorial position by an alternate "boat"-shaped conformation of the seven-membered heterocyclic ring. The boat-shaped conformation of the benzodiazepine seen here is consistent with previously published structural reports.[15] A clear energetic preference of over 10 kcal mol^{-1} was seen for the *R*- or *S*-equatorial over the axial isomer.

Biology

XTT Assay. All compounds were tested against the RSS strain of RSV in the XTT (2,3-bis-(2-methoxy-4-nitro-5-sulfophenyl)-2*H*-tetrazolium-5-carboxanilide disodium salt) assay. Because this metabolic assay cannot distinguish between virally induced cell death and cell death due to toxic effects of compound, the XTT assay was simultaneously run in the absence of virus to allow a preliminary toxicity assessment of the compounds.

HEp-2 cells were infected with RSV in the presence of compound and incubated for 6 days at 37 °C. Residual cell viability was then measured by metabolism of the XTT substrate to a colored product, and 50% inhibitory concentrations (IC_{50}) were determined. Toxicity was measured as TD_{50} and defined as the concentration of compound required for 50% cell death in the absence of virus.

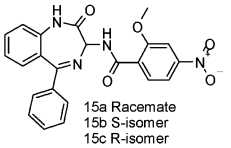
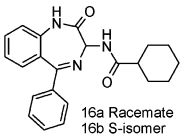
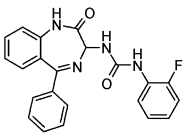
Plaque Assay. Monolayer cultures of HEp-2 cells were infected with the RSS strain of RSV. Following adsorption for 2 h, compounds were added in medium containing 0.6% agarose. After a 5-day incubation at 37 °C, the monolayers were fixed and the overlay was removed. Plaques were visualized by staining with methylene blue.

ELISA Assay. HEp-2 cells were infected with the RSS strain of RSV and exposed to test compound for 3 days at 37 °C. Monoclonal antibodies to the RSV F-, N-, and P-proteins were used and detected with an enzyme-linked secondary antibody. Subsequent conversion of substrate to a colored product was measured by optical density, and the IC_{50} was determined.

Results and Discussion

The structure−activity relationship (SAR) of racemic benzodiazepines is described in detail in the preceding paper in this series.[1] A series of compounds that showed a range of activities in addition to structural differences in the side chain and linker were chosen to be synthesized as chirally pure enantiomers to quickly examine any enantiomeric preference and trends. The results of three of these enantiomeric pairs are presented in Table 1. It was observed that in all three cases the relative potency across the chiral and achiral forms remained the same, but the *S*-isomer showed higher potency than the racemate, and the *R*-isomer was consistently less potent.

Table 1. Activity Against RSV in XTT Assay of Racemates and Separate Enantiomers

Structure	XTT Assay					
	Racemate		*S*-isomer		*R*-isomer	
	IC_{50} μM	TD_{50} μM	IC_{50} μM	TD_{50} μM	IC_{50} μM	TD_{50} μM
 15a Racemate 15b S-isomer 15c R-isomer	2.0	>50	0.9	>50	21.2	>50
 16a Racemate 16b S-isomer 16c R-isomer	12.6	>50	3.3	>50	>50	>50
 17a Racemate 17b S-isomer 17c R-isomer	3.5	>50	0.9	>50	27.8	>50

With this initial indication of enantiospecific anti-RSV activity and trends in place, the strategy within the chiral series was to optimize utilizing the SARs gleaned from the racemic optimization.[1] Particular attention was paid to substituents that would potentially modify physical properties and maintain or improve the PK profile of the series. Therefore, 5-phenyl-1,3-dihydrobenzo[*e*][1,4]diazepin-2-one was used as the core structure for this optimization.

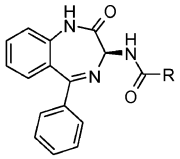
From the SAR in the racemic series it was known that electron-rich side chain substituents were favorable for greater potency against RSV. However, some of these electron-rich substituents exhibited poor PK profiles so further analogues were synthesized with substituents that could potentially block metabolically vulnerable sites.[16]

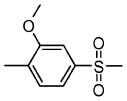
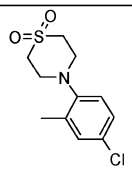
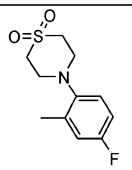
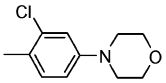
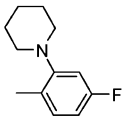
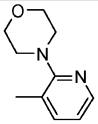
The strategy was that by using side chains containing sulfones and amines (Table 2), as well as increasing potency, the PK profile of the compounds could be improved by increasing solubility and lowering CLogP[17] while maintaining the electron-rich status of the aromatic ring.[18]

Replacing the nitro-substituent of compound **15b** with another electron-withdrawing group, methyl sulfone **18**, resulted in an equipotent compound (Table 2) with none of the potential toxicity issues that are associated with the metabolic reduction of aromatic nitro groups.[19]

From CLogP calculations it was predicted that compounds containing a thiomorpholine *S*,*S*-dioxide substituent, for example **19** and **20** (CLogPs of 2.53 and 1.96, respectively) could prove

Table 2. Activity Against RSV with Varying Substituents at C-3



R-Substituent	XTT IC_{50} (μM)	TD_{50} (μM)
18 	0.5	>50
19 	2.2	>50
20 	0.7	>50
21 	1.4	>50
22 	7.5	>50
23 	2.9	>50

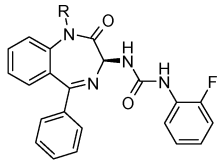
to be more water soluble than compound **15b** (CLogP of 3.13). Potential metabolically vulnerable sites were blocked with halogens to produce active analogues with fluorine, **20**, being preferred over chlorine, **19**.

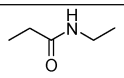
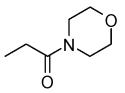
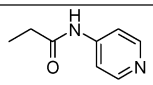
A range of other potentially solubilizing substituents on the aromatic ring gave varying results. A morpholine group on either a phenyl ring, **21**, or a pyridyl ring, **23**, showed potent activity against RSV, but when the phenyl ring was substituted with piperidine, **22**, a significant decrease in potency was observed.

It has been demonstrated in benzodiazepines targeted as CCK-B antagonists that *N*-1 substitution on the benzodiazepine core can enhance activity.[10] In the previous paper in this series,[1] it was shown that *N*-1 methylation reduced potency against RSV. To further investigate this observation, a number of compounds were synthesized with *N*-1 amide substituents that were analogous to those published as CCK-B antagonists.

The unsubstituted compound, **17b**, was a potent RSV inhibitor, but all other substitutions at this position resulted in a significant reduction of activity against RSV, Table 3. The only exception was when the substituent was pyridinylamide, **26**, but this was still significantly less active than the unsubstituted analogue, **17b**.

Table 3. Activity against RSV with Varying Substituents at N-1



R-substituent	XTT IC50 (μM)	TD50 (μM)
17b H	0.9	>50
24 	>50	>50
25 	>50	>50
26 	14.2	>50

It was concluded that the benzodiazepine core with no substitution at the *N*-1 position was optimum for activity against RSV, and three of the most potent compounds (**15b**, **17b**, and **21**) were chosen to proceed to secondary assays (ELISA and plaque) and PK profiling, Table 4.

All three compounds showed excellent potency against RSV in the primary and secondary assays with IC_{50} values in the range of 0.5−1.5 μM, and the calculated logP of the compounds were within an acceptable range. The initial PKs showed that compound **15b** reached a relatively high C_{max} compared to the other two analogues. However, the presence of the aromatic nitro substituent and the associated developability issues[19] precluded further interest in this compound. The PK profile of the other two compounds showed that **17b** had higher exposure and also a higher solubility in water than compound **21**. Compound **17b**, (*S*)-1-(2-fluorophenyl)-3-(2-oxo-5-phenyl-2,3-dihydro-1*H*-benzo[*e*][1,4]-diazepin-3-yl)-urea, was, therefore, chosen to proceed into further studies.

As part of the preclinical and clinical candidate selection process, an early assessment of the ADME characteristics of **17b** was undertaken. In a focused selection of in vivo and in vitro experiments, the suitability for progression into safety assessment studies and, ultimately, clinical evaluation was determined.

When a high throughput equilibrium dialysis approach with LC-MS/MS detection was used, **17b** showed high binding to serum proteins; fu = 0.05 (95% protein bound), with equivalence observed in rat dog and human sera.

The susceptibility of **17b** for oxidative metabolism was assessed in vitro using rat and human microsomes. Turnover of compound was slow for both species, with the apparent intrinsic clearance (disregarding fraction unbound in the microsomal protein incubations) of 23.5 ± 2.8 and 4.5 ± 2.4 μL/min/mg of rat and human microsomal protein, respectively.

Early in vivo PK characterization of **17b** was undertaken in the rat using both oral and intravenous routes of administration, with the parameters obtained detailed in Table 5.

The plasma clearance (CLp) was shown to be low in the rat at 7.2 mL/min/kg, which supported the findings of the microso-

Table 4. Biological Evaluation of Lead Compounds

	XTT (μM)		ELISA (μM)		plaque (μM)			aqueous solubility pH 7	plasma levels[a]
cmpd	IC_{50}	TD_{50}	IC_{50}	TD_{50}	IC_{50}	TD_{50}	CLogP	(μg/mL)	C_{max} (ng/mL)
15b	0.9	>50	1.0	>50	0.5	>50	3.13	–	C_{max} 6172 T_{max} 6 h
17b RSV-604	0.9	>50	1.4	>50	0.7	>50	3.02	4.1	C_{max} 1023 T_{max} 4 h
21	1.4	>50	1.5	>50	0.8	>50	2.67	0.9	C_{max} 204 T_{max} 6 h
18 A-315	0.6	>50	0.6	>50	0.5	>50	1.88	22.0	C_{max} 2197 T_{max} 8 h

[a] 20 mg/kg dosed orally as a suspension in 5% PEG400 with 1% CMC.

Table 5. Pharmacokinetic Parameters of **17b** Following Intravenous and Oral Administration to Rat ($n = 3$)

route	dose (mg/kg of body wt)	$AUC_{0-\infty}$ (μg·hr/mL)	C_{max} (μg/mL)	CLp (mL/min/kg)	V_{ss} (L/kg)	$t_{1/2}$ (hours)
PO	5	10.9 (± 1.5)	0.91 (± 0.10)	ND[a]	ND[a]	2.6 (± 0.2)
IV	5	11.7 (± 1.4)	3.3 (± 0.48)	7.2 (± 0.87)	2.2 (± 0.12)	3.8 (± 0.9)

[a] ND = not determinable following oral administration.

mal turnover screen. Compound **17b** exhibited a high volume of distribution (V_{ss}), which at 2.2 L/kg was much greater than total body water. This finding implied that compound **17b** was unlikely to be restricted to the systemic circulation and could have significant tissue distribution.

This observation was further supported following oral PK studies in colostrum deprived calves where nasal mucosa showed significant levels of parent compound at trough.[20] These data helped support the decision to progress **17b** into clinical development, as the findings in calves suggested the compound was capable of reaching the target site of RSV infection at concentrations that exceed the bovine IC_{50} (123 ng/mL) at 24 h post-dose. These data provided confidence that efficacious target tissue concentrations could readily be achieved using an appropriate dosing regimen, thus providing an opportunity to demonstrate in vivo potency assuming these observations extrapolate to man.

The oral dose was given in a lipid-based formulation to enhance bioavailability (F) and maximize exposure and circulating plasma levels of **17b**. The compound showed good absorption, with $F > 90\%$ at 5 mg/kg. When **17b** was administered as a suspension in 1% carboxymethylcellulose (CMC), bioavailability was reduced to <40% at an equivalent dose but dose proportionality in this formulation was demonstrated from 2 to 20 mg/kg. The apparent high bioavailability in the solubilized form correlated well with the low clearance and the in vitro experimentally determined apparent permeability coefficient (P_{app}) using a MDCK cell line of 13×10^{-6} cm/sec, indicating that **17b** had moderate to high passive permeability characteristics.

Although **17b** has low plasma clearance, it has been shown to be a substrate for cytochrome P450 (CYP450) metabolism using the Bactosome recombinant isoform expression system. CYP450 3A4 was established to be the major contributor to the compound's metabolism, with both 2C19 and 2D6 also implicated in metabolic turnover in vitro. To further assess the potential for **17b** to undergo drug interaction when dosed in combination with other CYP450 metabolized therapeutics, CYP inhibition and induction were assessed. Compound **17b** was found to be a moderate inducer of CYP3A4 and CYP1A in a concentration-dependent manner but was demonstrated to have no inhibitory effect on the metabolism of specific probe substrates for CYPs 3A4, 1A2, 2D6, 2C9, or 2C19.

These preclinical data aided the selection of **17b** for preclinical study and its move into the clinical arena, where it has successfully progressed through phase I and into phase II clinical development. PK data thus far obtained from these studies correlates well with the preclinical findings reported from these early ADME characterizations.

No cellular toxicity was observed in the three antiviral in vitro assays for either of the enantiomers or the racemate of compound **17**.

The racemate (**17a**) and the *S*-isomer (**17b**) have been screened against a wide range of receptors in a CEREP screen.[21] The racemate, **17a**, was shown to hit CCKa receptors at low levels as well as CCKb and the benzodiazepine receptor. (*S*)-1-(2-Fluorophenyl)-3-(2-oxo-5-phenyl-2,3-dihydro-1*H*-benzo[*e*]-[1,4]-diazepin-3-yl)-urea, **17b**, showed a cleaner profile than the racemate when tested in the CEREP screen. It showed marginal activity at CCKa and CCKb receptors, and there was no effect observed on the benzodiazepine receptor.

Resistant mutant studies on compounds **15b** and **17b** showed amino acid changes in the same region of the N-protein as the original lead compound in this series,[1] indicating the same mode of action.

A subsequent program at Arrow Therapeutics identified (*S*)-4-methanesulfonyl-2-methoxy-*N*-(2-oxo-5-phenyl-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-3-yl)-benzamide, **18** (A-315), as a back-up molecule to **17b**. Compound **18** showed potent anti-RSV activity across the primary and secondary assays, with a different PK profile and improved aqueous solubility over **17b**.

Conclusion

Separation of the *R*- and *S*-enantiomer of intermediates **3b** and **3c** followed by synthesis of a variety of analogues resulted in the discovery that the RSV activity resides mainly in the *S*-enantiomer of these benzodiazepine derivatives. Optimization of this series produced compounds with comparable activity, with a range of physicochemical properties, and with increased solubility. Substitution at the *N*-1 position was found to greatly reduce RSV activity. Compound **17b**, (*S*)-1-(2-Fluorophenyl)-3-(2-oxo-5-phenyl-2,3-dihydro-1*H*-benzo[*e*][1,4]-diazepin-3-yl)-urea, was selected as a clinical candidate, as it showed potent anti-RSV activity across a range of in vitro assays as well as a good PK profile. It was subsequently tested in CEREP screens and shown to have a clean in vitro toxicity profile. This

compound has now successfully finished Phase I and entered into Phase II clinical trials. Further work allowed us to identify **18**, (*S*)-4-methanesulfonyl-2-methoxy-*N*-(2-oxo-5-phenyl-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-3-yl)-benzamide, as a back up compound to **17b**. This compound possesses potent anti-RSV activity across the primary and secondary assays as well as improved solubility and a different PK profile.

Experimental Section

Chemistry. ^{1}H NMR spectra were recorded on a Bruker Avance spectrometer at 250 MHz and chemical shifts are reported in ppm relative to DMSO-d_6 or $CDCl_3$. Elemental analyses were performed by G. A. Maxwell at University College London. Thin-layer chromatography was performed on precoated silica gel F-254 plastic plates (0.2 mm, Macherey-Nagel) and was visualized with UV light. LC/MS conditions: Samples were run on a Micromass ZMD, using electrospray with simultaneous positive−negative ion detection. Column, YMC-PACK FL-ODS AQ, 50 × 4.6 mm I.D. S-5 μm; gradient, 95:5 to 5:95 v/v H_2O/CH_3CN + 0.05% formic acid over 4.0 min, hold 3 min, return to 95:5 v/v H_2O/CH_3CN + 0.05% formic acid over 0.2 min and hold at 95:5 v/v H_2O/CH_3CN + 0.05% formic acid over 3 min; detection, PDA 250−340 nm; flow rate, 1.5 mL/min.

Chiral high-performance liquid chromatography (HPLC) was carried out on a HP1090 chromatograph equipped with a UV detector (λ = 280 nm and 254 nm). Enantiomeric excess of final compounds was measured using a 250 × 4 mm Chiralpak AD column with an isocratic mobile phase of 50:50 propan-2-ol/hexane.

All temperatures are in °C. Solid-phase extraction (SPE) chromatography was carried out using Jones chromatography (Si) cartridges under 15 mmHg vacuum with stepped gradient elution. Temperature-controlled microwave heating was carried out using a CEM Discover single-mode synthesizer. All the organic phases were dried over $MgSO_4$ or by passing through a hydrophobic, single-fritted column (Isolute SPE accessories). All chemicals were purchased from commercial suppliers and used directly without further purification.

General Procedure 1. A solution of amine (1 equiv), acid (1 equiv), triethylamine (0.07 mL), and *O*-benzotriazol-1-yl-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (121 mg) in dry tetrahydrofuran (3 mL) was stirred at ambient temperature for 18 h under a nitrogen atmosphere. The mixture was then partitioned between potassium carbonate solution (15 mL) and dichloromethane (15 mL). The organic phase was passed through a hydrophobic frit and evaporated. The residue was purified on a silica gel SPE cartridge, eluting with dichloromethane followed by dichloromethane/ethanol: 0.880 ammonia 400:8:1 and then 200:8:1, to yield the title compound.

General Procedure 2. A solution of amine (1 equiv) in tetrahydrofuran (2 mL) containing triethylamine (0.085 mL) was treated with acid chloride (1 equiv) and stirred at ambient temperature under a nitrogen atmosphere for 18 h. The mixture was partitioned between water (10 mL) and dichloromethane (10 mL). The organic extract was evaporated, and the residue was purified on a silica gel SPE cartridge, eluting with dichloromethane followed by dichloromethane/ethanol: 0.880 ammonia 400:8:1 and then 200:8:1, to yield the title compound.

General Procedure 3. A mixture of amine (1 equiv) and isocyanate (1 equiv) in dry tetrahydrofuran (4 mL) was treated with triethylamine (1 equiv) and stirred at ambient temperature for 18 h. The mixture was partitioned between water (10 mL) and dichloromethane (10 mL). The organic extract was dried by filtration through a hydrophobic frit and concentrated in vacuo. The residue was triturated with petroleum ether to yield the final compound.

General Procedure 4. (*S*)-3-Amino-5-phenyl-1,3-dihydro-benzo-[*e*][1,4]diazepin-2-one, **1b** (100 mg), *O*-benzotriazol-1-yl-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (150 mg), triethylamine (0.083 mL), and acid (1 equiv) in dry *N*,*N*-dimethylformamide (1 mL) was stirred at ambient temperature for 1 h. Water (10 mL) was added and stirring was continued for 10 min. The colorless precipitate was collected by filtration and partitioned between dichloromethane (25 mL) and water (25 mL). The organic phase was dried by filtration through a hydrophobic frit and evaporated, and the residue was purified on a silica gel SPE cartridge. Elution with ethyl acetate/petrol 1:1 gave the title compound.

General Procedure 5. A solution of {3-[3-(2-fluorophenyl)-ureido]-2-oxo-5-phenyl-2,3-dihydrobenzo [*e*][1,4]diazepin-1-yl} acetic acid, **12** (40 mg), in dry *N*,*N*-dimethylformamide (1.5 mL) was treated with *O*-benzotriazol-1-yl-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (37 mg), triethylamine (0.018 mL), and amine (1 equiv) and stirred at ambient temperature under a nitrogen atmosphere for 2 h. Water (10 mL) was added and the product was collected by filtration.

(*S*,*S*)- and (*R*,*S*)-[1-(2-Oxo-5-phenyl-2,3-dihydro-1*H*-benzo-[*e*][1,4]diazepin-3-ylcarbamoyl)-2-phenylethyl] Carbamic Acid *tert*-Butyl Ester, 2. A solution of 3-amino-5-phenyl-1,3-dihydro-benzo[*e*][1,4]diazepin-2-one, **1** (34.9 g), (*S*)-2-*tert*-butoxycarbonyl-amino-3-phenylpropionic acid (55.3 g), triethylamine (100 mL), and *O*-benzotriazol-1-yl-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (116 g) in dichloromethane (1 L) was stirred at ambient temperature for 18 h under a nitrogen atmosphere. The solvent was evaporated, and the residue was partitioned between 10% citric acid solution and ethyl acetate. The organic phase was further washed with 2 M sodium hydroxide, water, and brine before being dried ($MgSO_4$). The organic phase was evaporated, giving an oil that was used crude in the following step. LC/MS ES$^+$ = 498. ^{1}H NMR (DMSO-d_6) δ 1.29 (s, 9H), 2.72−2.84 (m, 1H), 3.05−3.18 (m, 1H), 4.32−4.44 (m, 1H), 5.20−5.25 (m, 1H), 6.97−7.05 (m, 1H), 7.16−7.68 (m, 14H), 9.17−9.21 (d, 1H, J = 7.0 Hz), 10.90 (s, 1H).

(*S*,*S*)-2-Amino-*N*-(2-oxo-5-phenyl-2,3-dihydro-1*H*-benzo[*e*]-[1,4]diazepin-3-yl)-2-phenylpropionamide, 3b, and (*R*,*S*)-2-Amino-*N*-(2-oxo-5-phenyl-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-3-yl)-2-phenylpropionamide, 3c. [1-(2-Oxo-5-phenyl-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-3-ylcarbamoyl)-phenylethyl] carbamic acid *tert*-butyl ester, **2**, was added in a single portion to a cooled (−10 °C) solution of HCl (34 g) in ethyl acetate (1 L). The reaction was stirred at this temperature for 1 h, before being warmed to 20 °C and stirred for a further 2 h. The reaction was cooled to 0 °C, and water (300 mL) was added at a rate that maintained a temperature below 10 °C. The aqueous layer was washed with ethyl acetate (2 × 150 mL), and the aqueous layer was returned to the reaction flask. The reaction was again cooled to 0 °C, and concentrated aqueous ammonia was added at a rate that maintained the temperature below 5 °C until pH 9.0 had been achieved. The reaction was washed with ethyl acetate (5 × 150 mL), the combined organic extracts were washed with brine (100 mL) and dried with magnesium sulfate, and the solvent was evaporated, producing a yellow oil. The yellow oil was stirred rapidly with a 5% solution of methanol in ethyl acetate until a thick white precipitate formed. The precipitate was filtered, and the mother liquor was evaporated. The residual gum was again stirred with 5% methanol in ethyl acetate until a thick precipitate had formed. This sequence was repeated several times. On each occasion, the precipitate was analyzed to assess the diastereomeric excess by TLC (SiO_2, DCM/EtOH/NH_3, 200:8:1). Pure, or mostly pure, batches of each diastereomer were kept aside, and mixtures were returned to the precipitation procedure at the evaporation stage after first dissolving in a mixture of 5% methanol in dichloromethane. The combined batches that contained pure or mainly pure **3b** (*S*,*S*)-diastereomer (R_f = 0.25, higher spot) were stirred as a slurry in 5% methanol in ethyl acetate for 10 min and filtered to produce **3b** (*S*,*S*)-diastereomer (>99% d.e.), a pure sample as a white powder (26.1 g, 47% over two steps). LC/MS ES$^+$ = 399. ^{1}H NMR ($CDCl_3$) δ 1.45 (br s, 2H), 2.81 (dd, 1H, J = 13.9 Hz, 10.1 Hz), 3.33 (dd, 1H, J = 13.9 Hz, 3.8 Hz), 3.72 (dd, 1H, J = 9.5 Hz, 3.8 Hz), 5.55 (d, 1H, J = 8.2 Hz), 7.53−7.12 (m, 14H), 8.52 (s, 1H), 8.88 (d, 1H, J = 8.8 Hz).

Compound **3c** (*R*,*S*)-diastereomer (R_f = 0.22, lower spot) was isolated by recrystallization (as described above) as a white solid (15.4 g, 28% over two steps). LC/MS ES$^+$ = 399. ^{1}H NMR ($CDCl_3$)

δ 1.48 (br s, 2H), 2.76 (dd, 1H, J = 13.3 Hz, 10.1 Hz), 3.40 (dd, 1H, J = 13.3 Hz, 3.8 Hz), 3.79 (dd, 1H, J = 10.1 Hz, 3.8 Hz), 5.57 (d, 1H, J = 8.2 Hz), 7.17−7.56 (m, 14H), 8.91 (d, 1H, J = 8.2 Hz), 9.02 (s, 1H).

(*S*,*S*)-*N*-(2-Oxo-5-phenyl-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-3-yl)-3-phenyl-2-(3-phenylthioureido)propionamide, 4b. A solution of (*S*,*S*)-2-amino-*N*-(2-oxo-5-phenyl-2,3-dihydro-1*H*-benzo[*e*]-[1,4]-diazepin-3-yl)-2-phenylpropionamide, **3b** (27.1 g), in dichloromethane (500 mL) was treated with isothiocyanatobenzene (14.7 g), and the mixture was stirred at ambient temperature for 18 h. The solvent and excess reagent were removed by evaporation, and the residue was redissolved in dichloromethane and then precipitated with petrol, giving a colorless solid that was collected by filtration (36.1 g, 99%). LC/MS ES$^-$ = 532. ^{1}H NMR ($CDCl_3$) δ 3.25−3.30 (m, 2H), 5.35−5.41 (m, 2H), 6.66 (d, 1H, J = 7.6 Hz), 6.94−7.50 (m, 19H), 7.83 (s, 1H), 8.61 (br s, 1H).

(*R*,*S*)-*N*-(2-Oxo-5-phenyl-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-3-yl)-3-phenyl-2-(3-phenylthioureido)propionamide, 4c. This compound was prepared as described for compound **4b** using (*R*,*S*)-2-amino-*N*-(2-oxo-5-phenyl-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-3-yl)-2-phenylpropionamide, **3c** (15 g). The title compound was isolated as a white solid (18.7 g, 93%). LC/MS ES$^+$ = 534. ^{1}H NMR ($CDCl_3$) δ 3.20−3.52 (m, 2H), 5.41 (d, 1H, J = 7.6 Hz), 5.62 (m, 1H), 6.84−7.53 (m, 20H), 7.80 (m, 1H), 8.10 (m, 1H), 9.21 (br s, 1H).

(*S*)-3-Amino-5-phenyl-1,3-dihydrobenzo[*e*][1,4]diazepin-2-one, 1b. (*S*,*S*)-*N*-(2-Oxo-5-phenyl-2,3-dihydro-1*H*-benzo[*e*][1,4]-diazepin-3-yl)-2-phenyl-2-(3-phenylthioureido)propionamide, **4b** (24 g), was heated to 50 °C and treated with trifluoroacetic acid (64 mL). The mixture was stirred rapidly for 40 min and evaporated to dryness, giving a yellow oil. This material was purified by silica gel chromatography. Elution with dichloromethane/methanol/acetic acid/water, 90:10:1:1, gave the acetate salt of the amine as a pale yellow foam (13.1 g, 94%). LC/MS ES$^+$ = 252. ^{1}H NMR ($CDCl_3$) δ 2.17 (s, 3H), 4.68 (br s, 1H), 6.98−7.47 (m, 9H), 9.56 (br s, 1H), 10.68 (br s, 1H). HPLC: retention time, 6.16 min (e.e. >99%).

The free base of **1b** was isolated as follows: 0.5 g of the acetate salt of **1b** was dissolved in dichloromethane (1 mL) and basified by the addition of 0.880 ammonia (1 mL), giving a colorless precipitate that was collected by filtration and dried (380 mg, 94%).

(*R*)-3-Amino-5-phenyl-1,3-dihydrobenzo[*e*][1,4]diazepin-2-one, 1c. A solution of (*R*,*S*)-*N*-(2-oxo-5-phenyl-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-3-yl)-2-phenyl-2-(3-phenylthioureido)propionamide, **4c** (5 g), in dichloromethane (35 mL) was treated with trifluoroacetic acid (3.5 mL) and stirred at ambient temperature for 6 h. The reaction was quenched with ice water (60 mL), and the organic extract was washed with water (40 mL). The combined aqueous extracts were basified to pH 9 with 10% aq potassium carbonate, and the precipitate was collected by filtration to yield the title compound as a white solid (1.3 g, 55%). LC/MS ES$^+$ = 252. ^{1}H NMR (DMSO-d_6) δ 2.58 (br s, 2H), 4.24 (s, 1H), 7.15−7.29 (m, 3H), 7.43−7.62 (m, 6H), 10.69 (br s, 1H). HPLC: retention time, 4.40 min (e.e. >98%).

2-Methoxy-4-nitro-*N*-(2-oxo-5-phenyl-2,3-dihydro-1*H*-benzo-[*e*][1,4]-diazepin-3-yl)benzamide, 15a. This material was prepared as described in General Procedure 1, using 3-amino-5-phenyl-1,3-dihydrobenzo[*e*][1,4]diazepin-2-one, **1a** (40 mg), and 2-methoxy-4-nitrobenzoic acid (47 mg). The title compound was isolated as a colorless solid (51 mg, 74%). LC/MS ES$^+$ = 431. ^{1}H NMR (DMSO-d_6) δ 4.09 (s, 3H), 5.69 (d, 1H, J = 7.0 Hz), 7.08−7.49 (m, 9H), 7.80−7.86 (m, 2H), 8.27 (s, 1H), 8.31 (s, 1H), 9.52 (d, 1H, J = 7.1 Hz). Anal. ($C_{23}H_{18}N_4O_5 \cdot 0.48H_2O$) C, H, N. HPLC: retention time, 10.39 min (49.9%), 22.92 min (50.1%).

(*S*)-2-Methoxy-4-nitro-*N*-(2-oxo-5-phenyl-2,3-dihydro-1*H*-benzo[*e*][1,4]-diazepin-3-yl)benzamide, 15b. This material was prepared as described in General Procedure 1, using (*S*)-3-amino-5-phenyl-1,3-dihydrobenzo[*e*][1,4]diazepin-2-one, **1b** (40 mg), and 2-methoxy-4-nitrobenzoic acid (47 mg). The title compound was isolated as a colorless solid (37 mg, 54%). LC/MS ES$^+$ = 431. ^{1}H NMR (DMSO-d_6) δ 4.13 (s, 3H), 5.44 (d, 1H, J = 7.0 Hz), 7.29−7.70 (m, 9H), 7.97−8.10 (m, 3H), 9.63 (d, 1H, J = 7.0 Hz), 11.05 (s, 1H). Anal. ($C_{23}H_{18}N_4O_5 \cdot 0.36H_2O$) C, H, N. HPLC: retention time, 10.21 min (e.e. >99%).

(*R*)-2-Methoxy-4-nitro-*N*-(2-oxo-5-phenyl-2,3-dihydro-1*H*-benzo[*e*][1,4]-diazepin-3-yl-benzamide, 15c. This material was prepared as described in General Procedure 1, using (*R*)-3-amino-5-phenyl-1,3-dihydrobenzo[*e*][1,4]diazepin-2-one, **1c** (40 mg), and 2-methoxy-4-nitrobenzoic acid (47 mg). The title compound was isolated as a white solid (57 mg, 83%). LC/MS ES$^+$ = 431. ^{1}H NMR (DMSO-d_6) δ 4.13 (s, 3H), 5.45 (d, 1H, J = 7.0 Hz), 7.27−7.70 (m, 9H), 7.98−8.09 (m, 3H), 9.67 (d, 1H, J = 7.6 Hz), 11.01 (s, 1H). Anal. ($C_{23}H_{18}N_4O_5 \cdot 0.15H_2O$) C, H, N. HPLC: retention time, 22.82 min (e.e. >99%).

Cyclohexanecarboxylic Acid (2-Oxo-5-phenyl-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-3-yl-amide, 16a. This material was prepared as described in General Procedure 2, using 3-amino-5-phenyl-1,3-dihydrobenzo[*e*][1,4]diazepin-2-one, **1a** (100 mg), and cyclohexanecarbonyl chloride (0.053 mL). The title compound was isolated as a colorless solid (57 mg, 40%). LC/MS ES$^+$ = 362. ^{1}H NMR (DMSO-d_6) δ 1.10−1.43 (m, 5H), 1.60−1.82 (m, 5H), 2.44 (m, 1H), 5.22 (d, 1H, J = 7.6 Hz), 7.20−7.67 (m, 9H), 8.81 (d, 1H, J = 7.6 Hz), 10.75 (s, 1H). Anal. ($C_{22}H_{23}N_3O_2 \cdot 0.50H_2O$) C, H, N. HPLC: retention time, 4.45 min (53.3%), 5.61 min (46.7%).

(*S*)-Cyclohexanecarboxylic Acid (2-Oxo-5-phenyl-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-3-yl-amide, 16b. This material was prepared as described in General Procedure 2, using (*S*)-3-amino-5-phenyl-1,3-dihydrobenzo[*e*][1,4]diazepin-2-one, **1b** (40 mg), and cyclohexanecarbonyl chloride (0.021 mL). The title compound was isolated as a white solid (28 mg, 49%). LC/MS ES$^+$ = 362. ^{1}H NMR (DMSO-d_6) δ 1.20−1.43 (m, 5H), 1.60−1.82 (m, 5H), 2.47 (m, 1H), 5.29 (d, 1H, J = 8.2 Hz), 7.25−7.72 (m, 9H), 8.93 (d, 1H, J = 8.2 Hz), 10.85 (s, 1H). Anal. ($C_{22}H_{23}N_3O_2$) C, H, N. HPLC: retention time, 4.45 min (e.e. >99%).

(*R*)-Cyclohexanecarboxylic Acid (2-Oxo-5-phenyl-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-3-yl-amide, 16c. This material was prepared as described in General Procedure 2, using (*R*)-3-amino-5-phenyl-1,3-dihydrobenzo[*e*][1,4]diazepin-2-one, **1c** (100 mg), and cyclohexanecarbonyl chloride (0.053 mL). The title compound was isolated as a white solid (42 mg, 29%). LC/MS ES$^+$ = 362. ^{1}H NMR (DMSO-d_6) δ 1.16−1.40 (m, 5H), 1.60−1.81 (m, 5H), 2.43 (m, 1H), 5.21 (d, 1H, J = 7.5 Hz), 7.21−7.67 (m, 9H), 8.86 (d, 1H, J = 7.5 Hz), 10.78 (s, 1H). Anal. ($C_{22}H_{23}N_3O_2$) C, H, N. HPLC: retention time, 5.62 min (e.e. >99%).

1-(2-Fluorophenyl)-3-(2-oxo-5-phenyl-2,3-dihydro-1*H*-benzo-[*e*][1,4]-diazepin-3-yl)-urea, 17a. This material was prepared as described in General Procedure 3, using 3-amino-5-phenyl-1,3-dihydrobenzo[*e*][1,4]diazepin-2-one, **1a** (30 mg), and 2-fluoroisocyanatobenzene (0.010 mL). The title compound was isolated as a beige solid (29 mg, 62%). LC/MS ES$^+$ = 389. ^{1}H NMR (DMSO-d_6) δ 5.21 (d, 1H, J = 8.2 Hz), 6.90−7.70 (m, 12H), 8.07 (m, 2H), 8.93 (s, 1H), 10.94 (s, 1H). Anal. ($C_{22}H_{17}FN_4O_2 \cdot 0.40H_2O$) C, H, N. HPLC: retention time, 7.52 min (49.4%), 8.65 min (50.6%).

(*S*)-1-(2-Fluorophenyl)-3-(2-oxo-5-phenyl-2,3-dihydro-1*H*-benzo[*e*][1,4]-diazepin-3-yl)-urea, 17b. This material was prepared as described in General Procedure 3, using (*S*)-3-amino-5-phenyl-1,3-dihydrobenzo[*e*][1,4]diazepin-2-one, **1b** (30 mg), and 2-fluoroisocyanatobenzene (0.010 mL). The title compound was isolated as a white solid (34 mg, 73%). LC/MS ES$^+$ = 389. ^{1}H NMR (DMSO-d_6) δ 5.24 (d, 1H, J = 7.5 Hz), 6.90−7.75 (m, 12H), 8.11−8.17 (m, 2H), 8.95 (d, 1H, J = 2.5 Hz), 10.95 (s, 1H). Anal. ($C_{22}H_{17}FN_4O_2$) C, H, N. HPLC: retention time, 8.64 min (e.e. >99%).

(*R*)-1-(2-Fluorophenyl)-3-(2-oxo-5-phenyl-2,3-dihydro-1*H*-benzo[*e*][1,4]-diazepin-3-yl)-urea, 17c. This material was prepared as described in General Procedure 3, using (*R*)-3-amino-5-phenyl-1,3-dihydrobenzo[*e*][1,4]diazepin-2-one, **1c** (30 mg), and 2-fluoroisocyanatobenzene (0.010 mL). The title compound was isolated as a white solid (32 mg, 69%). LC/MS ES$^+$ = 389. ^{1}H NMR (DMSO-d_6) δ 5.20 (d, 1H, J = 8.2 Hz), 6.90−7.68 (m, 12H), 8.05−8.11 (m, 2H), 8.92 (s, 1H), 10.93 (s, 1H). Anal. ($C_{22}H_{17}FN_4O_2$; 0.37 H_2O) C, H, N. HPLC: retention time, 7.52 min (e.e. >99%).

(*S*)-4-Methanesulfonyl-2-methoxy-*N*-(2-oxo-5-phenyl-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-3-yl)-benzamide, 18. This mate-

rial was prepared as described as in General Procedure 2, using (*S*)-3-amino-5-phenyl-1,3-dihydro-benzo[*e*][1,4]diazepin-2-one, **1b** (100 mg), and 4-methanesulfonyl-2-methoxybenzoic acid, **8** (46 mg). The title compound was isolated as a colorless solid (55 mg, 30%). LC/MS $ES^+ = 464$. ^1H NMR (DMSO-d_6) δ 3.33 (s, 3H), 4.13 (s, 3H), 5.44 (d, 1H, $J = 7.5$ Hz), 7.33−7.71 (m, 11H), 8.10 (d, 1H, $J = 10.0$ Hz), 9.61 (d, 1H, $J = 7.5$ Hz), 11.06 (s, 1H). Anal. ($C_{24}H_{21}N_3O_5S \cdot 1.19H_2O$) C, H, N. HPLC: retention time, 8.28 min (e.e. >99%).

(*S*)-2-Chloro-4-morpholin-4-yl-*N*-(2-oxo-5-phenyl-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-3-yl)-benzamide, 21. This material was prepared as described in General Procedure 4, using 2-chloro-4-morpholin-4-yl benzoic acid (86 mg). The title compound was isolated as a colorless solid (112 mg, 59%). LC/MS $ES^+ = 475$. ^1H NMR (DMSO-d_6) δ 3.21 (m, 4H), 3.70 (t, 4H, $J = 4.7$ Hz), 5.36 (d, 1H, $J = 8.2$ Hz), 6.90−6.97 (m, 2H), 7.21−7.66 (m, 10H), 9.21 (d, 1H, $J = 8.2$ Hz), 10.86 (s, 1H). Anal. ($C_{26}H_{23}ClN_4O_3 \cdot 1.0H_2O$) C, H, N. HPLC: retention time, 14.08 min (e.e. >99%).

(*S*)-{3-[3-(2-Fluorophenyl)ureido]-2-oxo-5-phenyl-2,3-dihydro-benzo[*e*][1,4]diazepin-1-yl}-acetic Acid Methyl Ester, 11. A solution of (*S*)-1-(2-fluorophenyl)-3-(2-oxo-5-phenyl-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-3-yl)-urea, **17b** (500 mg), in dry *N*,*N*-dimethylformamide (15 mL) was treated with 60% sodium hydride in mineral oil and stirred at ambient temperature for 30 min under a nitrogen atmosphere. Methyl bromoacetate (0.13 mL) was added, and the solution was stirred for 3 h. Water (70 mL) was added, and the crude product was collected by filtration. Purification on a silica gel SPE, eluting with dichloromethane followed by dichloromethane/ethanol/0.880 ammonia 200:8:1, yielded the title product as a pale yellow solid (385 mg, 65%). LC/MS $ES^+ = 461$. ^1H NMR ($CDCl_3$) δ 3.62 (s, 3H), 4.63 (ABq, 2H, $J = 17.3$ Hz), 5.62 (d, 1H, $J = 8.3$ Hz), 6.75 (d, 1H, $J = 8.2$ Hz), 6.89−7.12 (m, 4H), 7.22−7.70 (m, 9H), 7.99 (t, 1H, $J = 8.2$ Hz).

(*S*)-{3-[3-(2-Fluorophenyl)-ureido]-2-oxo-5-phenyl-2,3-dihydro-benzo[*e*][1,4]diazepin-1-yl} Acetic Acid, 12. A solution of (*S*)-{3-[3-(2-fluorophenyl)ureido-2-oxo-5-phenyl-2,3-dihydro-benzo-[*e*][1,4]diazepin-1-yl} acetic acid methyl ester, **11** (50 mg), in tetrahydrofuran (1 mL) and water (3 mL) was treated with lithium hydroxide (50 mg) and stirred at ambient temperature for 1 h. The solution was cooled to 0 °C and acidified to pH 2, and the precipitate was collected by filtration to yield the title compound as a pale yellow solid (41 mg, 85%). LC/MS $ES^+ = 447$. ^1H NMR (DMSO-d_6) δ 4.66 (ABq, 2H, $J = 19.0$ Hz, 17.7 Hz), 5.33 (d, 1H, $J = 8.9$ Hz), 6.90−7.73 (m, 12H), 8.00−8.11 (m, 2H), 8.94 (s, 1H), 13.14 (br s, 1H).

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Supporting Information Available: Experimental procedures for the synthesis of intermediates and characterization of final products, including X-ray crystal structure determination. This material is available free of charge via the Internet at http://pubs.acs.org.

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