1,4-Benzodiazepines as Inhibitors of Respiratory Syncytial Virus

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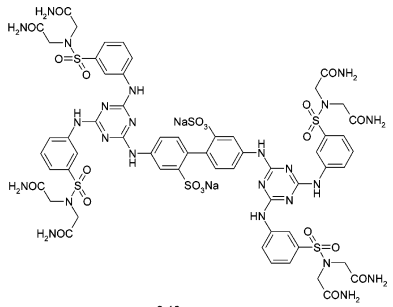
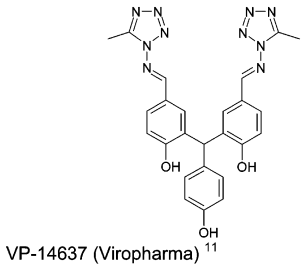
Respiratory syncytial virus (RSV) is the cause of one-fifth of all lower respiratory tract infections worldwide and is increasingly being recognized as a serious threat to patient groups with poorly functioning immune systems. Our approach to finding a novel inhibitor of this virus was to screen a 20 000-member diverse library in a whole cell XTT assay. Parallel assays were carried out in the absence of virus in order to quantify any associated cell toxicity. This identified 100 compounds with IC_{50}'s less than 50 μM. A-33903 (**18**), a 1,4-benzodiazepine analogue, was chosen as the starting point for lead optimization. This molecule was moderately active and demonstrated good pharmacokinetic properties. The most potent compounds identified from this work were A-58568 (**47**), A-58569 (**44**), and A-62066 (**46**), where modifications to the aromatic substitution enhanced potency, and A-58175 (**42**), where the amide linker was modified.

Introduction

Respiratory syncytial virus (RSV) is a seasonal disease that is highly predictable, occurring in the winter season in both hemispheres, and throughout the year in tropical climates. RSV is the leading cause of serious respiratory tract infections in infants and children worldwide.[1] The highest morbidity and mortality occurs in those born prematurely and those with chronic heart or lung disease. There is also increasing evidence linking severe RSV infection and the development of childhood asthma.[2] RSV is a major cause of morbidity and mortality in the elderly and in immunocompromised patients, as well as those with chronic obstructive pulmonary disease (COPD) and congestive heart failure (CHF).[3] Among immunocompromised adults, those having had stem cell transplant therapy are at highest risk, with one study[4] suggesting that as many as 15% of bone marrow transplant patients experience respiratory virus infection each season. The most common infection virus isolated with the highest mortality rate was RSV (35% of respiratory infections). Once infected with RSV, half the patients will develop pneumonia, resulting in a mortality rate of up to 80% in this group. The only significant product currently sold for RSV is the monoclonal antibody "Synagis" marketed by Abbott. This product is used only for prophylaxis in premature and other high-risk infants. Unlike many other viral diseases, production of a vaccine for RSV has proved to be unsuccessful,[5] so there is a huge unmet need for medication to treat this disease. Recently several companies have developed small molecule inhibitors of RSV (Figure 1) that have shown potency against the virus (IC_{50}'s in the range 0.5−50 nM). These molecules have not been successful as a potential treatment for a number of reasons. Most or all of them are inhibitors of viral fusion, a feature of which is the rapid emergence of highly resistant virus in cell culture. Many of them also have poor pharmacokinetic properties that would prevent them from being dosed orally to patients. With this background, there existed a clear need to identify orally active inhibitors of RSV targeting a mechanism distinct from those found thus far.

Screening Campaign. At Arrow we employed a 20 000-member diverse molecule screen against RSV in a whole cell assay. A colorimetric read-out utilizing XTT (2,3-bis(2-methoxy-4-nitro-5-sulfophenyl)-2*H*-tetrazolium-5-carboxanilide, disodium salt) was employed to measure compound-mediated cell survival. This process was laborious and provided a relatively high hit rate, with several hit series being identified. Secondary testing in ELISA and plaque[6] reduction assays allowed us to eliminate certain classes from our investigation, and subsequently we identified a lead series of 1,4-benzodiazepines. These compounds, as exemplified by A-33903 (**18**), displayed antiviral activity in all three of our assays with virtually no associated





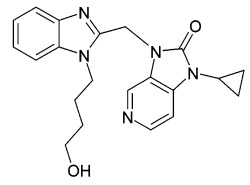


Figure 1. Structures of recently described fusion inhibitors of RSV.

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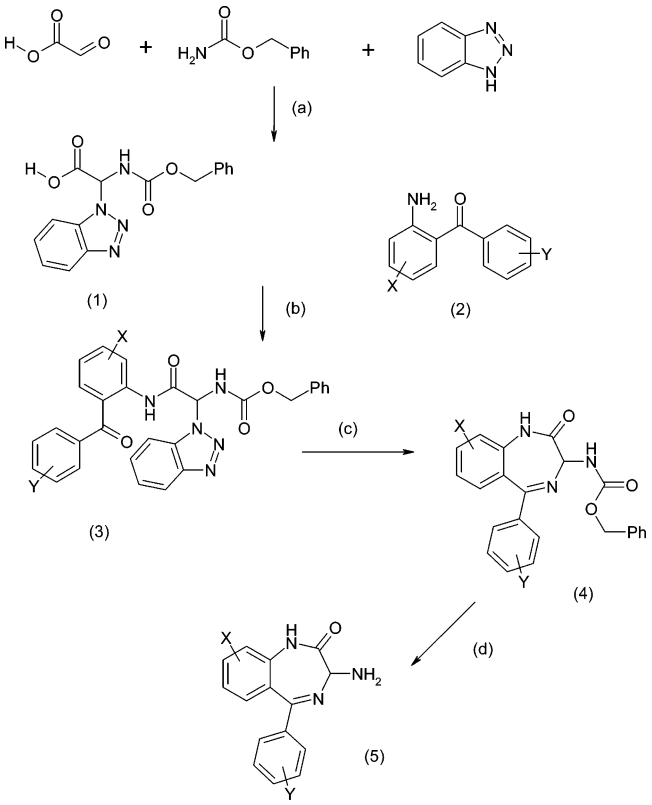
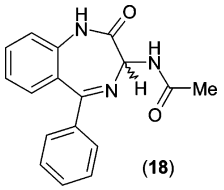
Scheme 1[a]



[a] Reagents and conditions: (a) toluene, reflux; (b) (i) oxalyl chloride, THF, DCM, 0 °C, (ii) (2) *N*-methylmorpholine, DCM; (c) (i) NH_3/MeOH, (ii) NH_4OAc, AcOH; (d) HBr/AcOH.

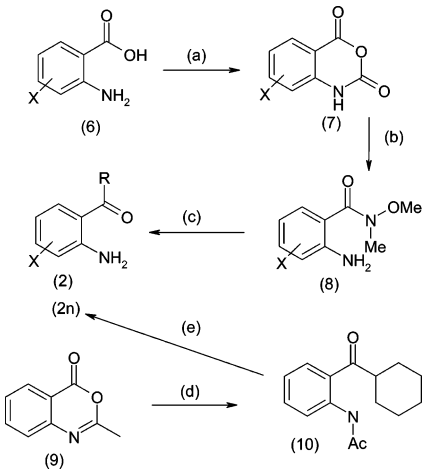
cell toxicity. The structure−activity relationships of this series were investigated, and potent ($IC_{50} \sim 1\ \mu M$) inhibitors were prepared. These compounds were found to possess good pharmacokinetic properties and, unlike most recently described small-molecule inhibitors of RSV, were not viral fusion inhibitors. We observed a relatively slow onset of resistance and were able to show that (**18**) and its analogues caused mutations in the nucleocapsid protein, an essential component of the viral replication complex.[7] These molecules all contained a chiral center at the 3-position of the diazepine ring. Subsequently, we have prepared the individual enantiomers of the most promising molecules and the antiviral activity has been shown to reside solely in the (*S*)-enantiomer.[8]



(**18**)

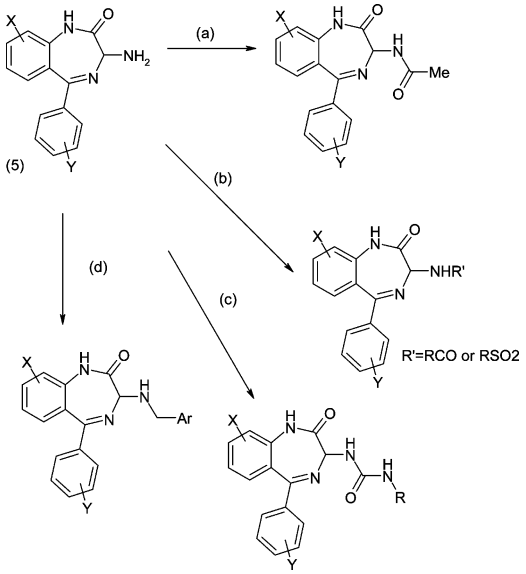
Synthetic Chemistry. Many routes to 1,4-benzodiazepines have been described in recent years. We chose to follow the route described by Sherrill and Sugg[13] (Scheme 1). This utilized the α-benzotriazolylglycine intermediate (**1**), which was readily prepared in a one-pot process on a large scale. Conversion of this to the acyl chloride and then reaction with an appropriate aminobenzophenone (**2**) gave the amide (**3**), which was routinely used crude in the following cyclization step. Reaction of ammonia gas in methanol, followed by ammonium acetate in acetic acid, furnished the protected benzodiazepine (**4**). The amine (**5**) was then prepared by the action of either trifluoroacetic acid or hydrogen bromide in acetic acid.

Scheme 2[a]



[a] Reagents and conditions: (a) triphosgene, THF; (b) dimethyl hydroxylamine, aq EtOH, reflux; (c) ArLi, THF, −100 °C; (d) cyclohexyl magnesium bromide, THF; (e) HCl, reflux.

Scheme 3[a]



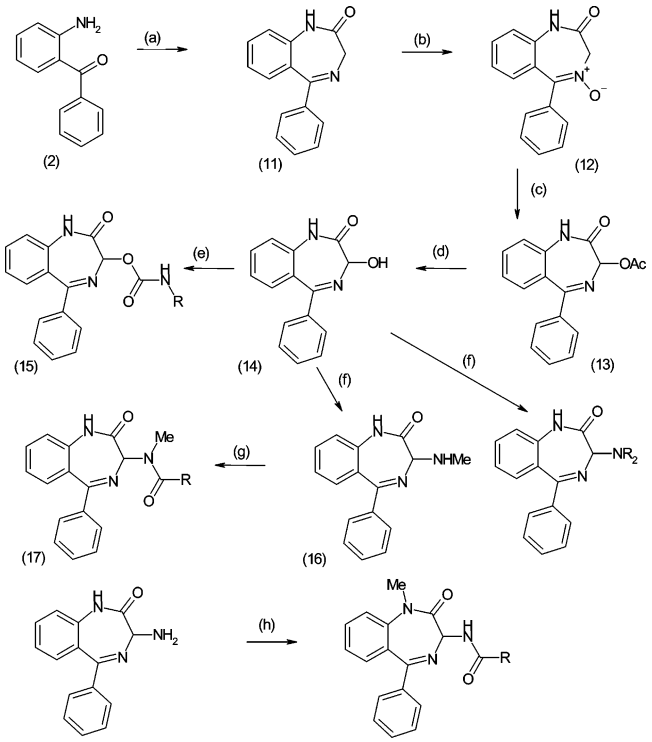
[a] Reagents and conditions: (a) acetic anhydride, pyridine; (b) RCOCl, Et_3N, THF or HBTU,[17] RCO_2H, DMF; (c) RCNO, DMF or THF; (d) ArCHO, $Na(OAc)_3BH$, AcOH, DCM.

Where possible, commercially available aminobenzophenones (**2**) were used. Commercially unavailable aminobenzophenones were prepared by the action of aryllithiums on the appropriate Weinreb amides[14] (**8**) derived from isatoic anhydrides (**7**), themselves prepared from the anthranilic acids (**6**). For the cyclohexyl derivative (**2n**), reaction of a Grignard reagent with the oxazinone (**9**) gave the required intermediate (**10**), which could then be progressed in an analogous manner. (Scheme 2).

Various amides, amines, ureas, and sulfonamides of this amine (**5**) were then synthesized (Scheme 3).

Synthesis of the methylated analogues and the carbamate is shown in Scheme 4. Acylation of aminobenzophenone (**2**) followed by ammonolysis led to the unsubstituted benzodiazepine (**11**).[15] Reaction with *m*-chloroperbenzoic acid gave the *N*-oxide (**12**), which underwent rearrangement to the C-3 acetoxy derivative (**13**) on heating with acetic anhydride.[16] Hydrolysis furnished the alcohol (**14**), which was transformed into carbamates, (e.g. **15**), upon reaction with isocyanates. Alcohol (**14**) was activated with methanesulfonyl chloride and reaction of

Scheme 4[a]



[a] Reagents and conditions: (a) (i) $BrCOCH_2Br$, DCM, water, (ii) NH_3; (b) *m*-CPBA, DCM; (c) Ac_2O 70°C; (d) NaOH, MeOH; (e) RCNO, THF; (f) (i) $MeSO_2Cl$, THF, (ii) $MeNH_2$ or R_2NH; (g) RCNO or RCO_2H, HBTU; (h) (i) NaH, MeI, DMF, (ii) amide/urea formation as in Scheme 3.

the unstable mesylate with methylamine gave amine (**16**), which allowed synthesis of amides and ureas (**17**). The mesylate was also used to prepare the tertiary amines (**75**, **76**). Ring amide methylation was achieved using 1 equiv of sodium hydride followed by methyl iodide. Under these conditions no other alkylation products were observed.

Biology. Routinely the RSS strain of RSV was used in the primary assay. Compounds that showed activity (less than 10 μM) were taken into secondary and tertiary assays as described in the Experimental Section. A further subset of particularly interesting compounds was then evaluated in assays where various strains of RSV (A and B subgroups) were used in order to demonstrate their spectrum of activity (see Table 6). Resistant viruses were generated to lead molecules, and cross-resistance studies were carried out.

Results and Discussion

The acetamido-1,4-benzodiazepine analogue (**18**) exhibited IC_{50}'s in the range of 10−20 μM over all three assays routinely used. This molecule also demonstrated excellent pharmacokinetic properties in the rat with a half-life of approximately 6 h and an oral bioavailability of 76%. This suggested that the core benzodiazepine was relatively stable to metabolism and a good starting point for lead optimization. Increasing the size of the alkyl chain or branching the chain gave a modest decrease in potency, as did incorporation of a cyclic substituent (Table 1). Noticeable increases in potency were seen, however, when aromatic amides were tested, especially those containing electron-donating substituents. The *o*-methoxybenzamide (**25**) was the most potent analogue of this type. However it showed a very poor pharmacokinetic profile with low bioavailability (4%) and extremely high clearance (71 mL/min/kg) when dosed in the rat (Table 7). Addition of a second methoxy group gave a very active compound (**31**), and while replacement of methoxy with ethoxy (**29**) retained activity, lengthening of the chain to propoxy (**30**) or modification to trifluoromethoxy (**32**, **33**) reduced potency. Other electron-donating substituents (methylamino and dimethylamino) also led to reasonably potent molecules (**34**, **35**); movement of the basic center one carbon atom away from the ring reduced activity, as demonstrated by the morpholinylmethyl analogue (**37**). Incorporation of a lipophilic electronically neutral substituent (cyclohexyl, **36**) led to a further loss in potency.

Heteroaromatic compounds (**38**−**40**) also demonstrated excellent activity, but the tetrahydrofuranyl derivative (**41**) was less effective. Both the heteroaromatic and electron-rich aromatic amides suffered from poor pharmacokinetics, however. Addition of halogens as groups blocking potential aromatic hydroxylation or of electron-withdrawing substituents led to very potent molecules (**44**−**47**) with a wide range of metabolic vulnerability. The 5-fluoro analogue (**47**) was virtually undetectable (see Table 8) after oral dosing to rats, whereas incorporation of a 4-nitro substituent (**44**) gave a potent molecule that demonstrated good exposure combined with a low clearance and a 5.8 h half-life when orally dosed to rats at 25 mg/kg. Incorporation of a 4-trifluoromethyl group gave a compound that although having potent antiviral activity was shown to be highly cell-toxic (data not shown). Generally, the series exhibited good half-lives and volumes of distribution in conjunction with low to moderate clearances, suggesting that these molecules would be well distributed in tissues relevant to RSV infection. Aromatic ureas were also shown to possess excellent activity with good pharmacokinetic properties and a lack of toxicity, as demonstrated by the 2-fluoro analogue (**42**). Replacement of the amide moiety with a sulfonamide led to loss of activity (data not shown) and to a general increase in cell toxicity. A similar pattern emerged when reduction of the amide carbonyl was carried out, leading to benzylamines (**48** and **49**).

Unless stated otherwise, all molecules exhibited no cell toxicity at 50 μM.

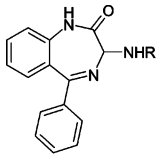
Replacement of the pendant phenyl ring with a methyl group led to poor activity (**52**), and an identical result was seen when the phenyl ring was reduced to cyclohexyl (**50**, **51**). (Table 2) Recent results also show a similar trend when R is a benzyl substituent or a pyridine ring (data not shown).

Substitution on the pendant phenyl ring generally lead to a lowering of potency. Only substitution at the meta-position with electron-withdrawing groups (**53**, **54**, **56**), or at the para-position with groups as small as fluorine (**60**) maintained any measurable antiviral activity, as shown in Table 3.

Substitution on the fused phenyl ring has also been investigated both with and without substitution on the pendant phenyl. Substitution at the 7-position with chlorine gives a slight loss in activity (**61**); however, when accompanied by ortho-substitution in the pendant phenyl ring (**62**, **63**), a marked reduction in potency is observed. All other substituents investigated to date at either the 7- or 8-position have led to reduction of antiviral activity (see Table 4).

The importance of the NH groups in both the ring and substituent amide (or urea) was well demonstrated (Table 5) by the reduction in activity when either of these moieties was methylated (**68**−**70**). In the urea series, activity was retained, however, when the remote NH was absent, as shown by both the cyclic and noncyclic analogues (**71**−**73**). Interestingly, the carbamate analogue (**74**) of the most potent urea (**42**) still showed antiviral potency, although an order of magnitude lower. Related tertiary amine analogues (**75**, **76**) showed poor activity.

Table 1.[a]



Compound no.	R	IC_{50} (μM)
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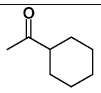
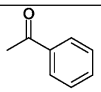
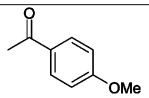
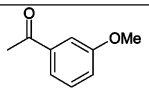
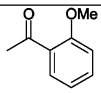
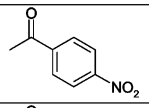
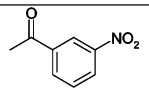
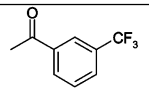
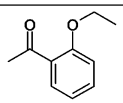
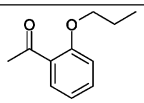
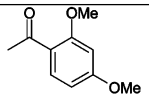
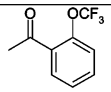
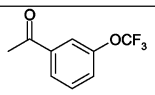
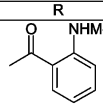
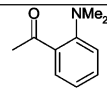
20	CO^{t}Bu	16.7
21		12.5
22		5.5
23		3.6
24		6.6
25		2.3
26		6.7
27		7.4
28		7.5
29		3.6
30		40.2
31		2.1
32		14.4
33		14.6

Compound no.	R	IC_{50} (μM)
34		9.6
35		4.8
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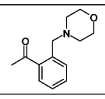
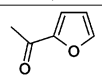
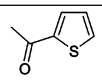
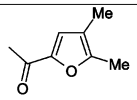
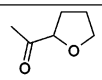
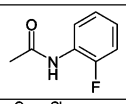
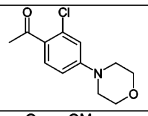
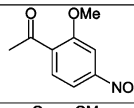
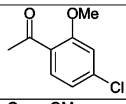
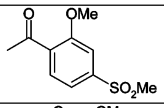
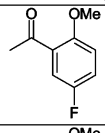
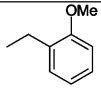
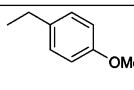
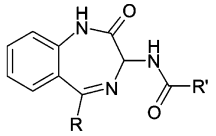
37		20.7
38		3.2
39		5.6
40		2.8
41		17.4
42		3.3
43		3.4
44		2.0
45		5.9
46		2.0
47		1.5
48		27.3
49		toxic

[a] All IC_{50}'s shown are a mean of $n = 3$.

The most interesting compounds from the XTT assay were taken forward into both ELISA and plaque assays to confirm activity. In general, the SAR from the XTT was consistent with both other assays, with good antiviral activity demonstrated. These compounds also showed excellent activity against a range of RSV strains (Long, B, and A2 strains; see Table 6) and also

Table 2



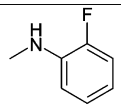
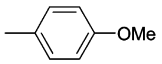
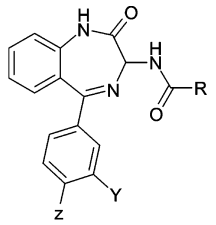
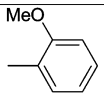
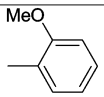
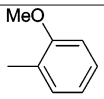
Compound no.	R	R'	IC_{50} (μM)
50			>50
51			>50
52	Me		>50

Table 3

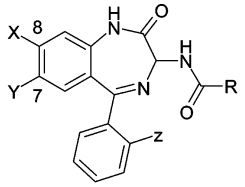


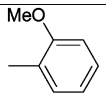
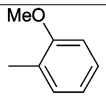
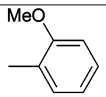
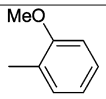
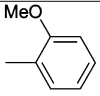
Compound no.	Y	Z	R	IC_{50} (μM)
53	Cl	H		6.9
54	CF_3	H		16.7
55	MeO	H		>50
56	CF_3	H		18.8
57	H	MeO		>50
58	H	CF_3		>50
59	H	CF_3		>50
60	H	F		16.5

against a number of both A- and B-strain clinical isolates (data not shown).

Compound Selectivity. As the benzodiazepine skeleton is well-documented as having high promiscuity in terms of pharmacological activity, we decided to test a number of our

Table 4



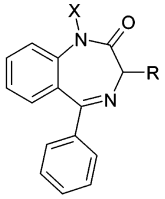
Compound no.	X	Y	Z	R	IC_{50} (μM)
61	H	Cl	H		6.1
62	H	Cl	F		26.2
63	H	Cl	F		41.3
64	H	MeO	H		>50
65	Cl	H	H		26.7
66	Me	H	H		19.2
67	MeO	MeO	H		>50

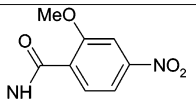
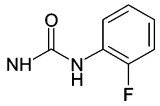
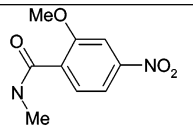
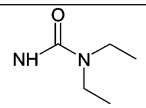
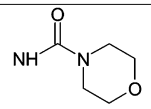
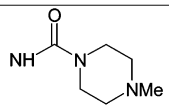
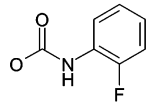
lead molecules in a Cerep diversity profile screen. This protocol involved testing molecules at a concentration of 10 μM against 68 receptors and 17 enzyme targets. Affinity for each target is measured by displacement of a radiolabeled ligand specific for each particular receptor or enzyme. The results are expressed in terms of percentage of displaced ligand, and results of 50% or less are considered to be insignificant. The overall profile was very clean and a notable lack of affinity for the central benzodiazepine receptor was demonstrated.

Mechanism of Action. To determine the molecular target of these molecules, resistant virus was generated. If successful, any mutations seen would indicate that the compounds potentially interact with that portion of the virus and thus how viral replication is inhibited.

Cells were infected with RSV (RSS strain) at a MOI of 0.01 and incubated in the presence of the acetamide analogue (**18**), initially at about half the IC_{50} concentration and then doubling the concentration at each passage. This procedure was carried out up to a final drug concentration of 70 μM (ca. 15 × IC_{50}). At each passage the IC_{50} of both (**18**) and the furan derivative (**38**) on the virus population was determined. No apparent shift in IC_{50} was observed until passage 9, when the IC_{50} had increased >10-fold (See Tables 9 and 10). Virus from the resistant population was plaque picked for expansion and further characterization. The genome of the mutant virus was sequenced and compared to the wild-type virus. Three nucleotide changes were consistently obtained in the resistant genotype that resulted in nonconserved amino acid substitutions: Val to Ala in the

Table 5



Compound no.	X	R	IC_{50} (μM)
68	Me		>50
69	Me		>50
70	H		25.1
71	H		20.7
72	H		9.7
73	H		9.3
74	H		16.1
75	H		>50
76	H		>50

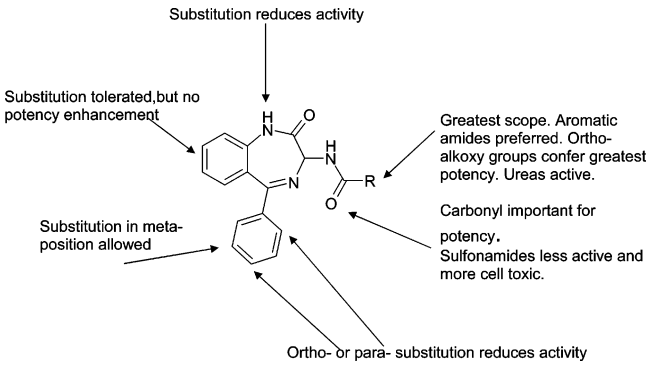


Figure 2. General SAR.

F-protein, Leu to Ile in the N-protein, and Glu to Gly in the L-protein.

The resistant phenotype can be attributed to all, one, or a combination of these mutations. The mutation in the F-gene was observed after passage 4, when no increase in IC_{50} was seen, while mutations in N and L occurred around passage 8 or 9, concomitant with a change in the IC_{50}, and are more likely to be the cause of the resistance. In addition, we observed that viruses at the late stage of the selection process reverted to the wild-type genotype of the L gene. All together these data strongly indicate that the molecular target of this series of compounds is the N-protein.

After the discovery of these mutations, reverse genetics studies are underway wherein three separate mutant viruses are generated by transfection with mutated viral genomic constructs, each possessing one single-point change from wild type. IC_{50}'s against all three mutants will then be determined in order to identify which mutation is responsible for the altered sensitivity.

Table 6.[a]

		ELISA			plaque			
compd	XTT	RSS	Long	B	A2	RSS	Long	B
18	8.6	9.3	17.6	17.8	NT	7.1	7.2	3.6
42	3.3	2.7	2.5	1.9	2.8	3.0	2.2	0.75
44	2.0	2.5	1.2	1.3	NT	1.8	0.9	<0.3

[a] NT = not tested. All figures quoted are IC_{50} values (μM).

Table 7. Intravenous and Oral PK Properties of Selected Molecules in Rat[a]

compd	C_{max} (ng/mL)	T_{max} (h)	$T_{1/2}$ (h)	CL* (mL/min/kg)	V_d (L/kg)	*F* (%)
18 (po)[b]	7930	1.5	4.4	7.3	2.7	–
18 (iv)	2400	0.08	5.0	5.3	2.2	
18 (po)	616	2.6	5.9	4.9	4.2	77
25 (iv)	798	0.08	0.4	71.2	2.4	
25 (po)	19.3	0.8	ND	ND	ND	4
42 (iv)	1533	0.08	3.7	7.8	2.5	
42 (po)	386	2.6	8.1	9.5	7.5	76

[a] All compounds dosed at 2 mg/kg unless stated. CL/*F* for oral dose. ND = not determined. Oral dose is as suspension in 1% CMC at 2 mg/mL concentration. iv dose made by diluting 100% DMSO solution of compound into 10% w/v solution of hydroxypropyl β-cyclodextrin in phosphate-buffered saline to give a total volume of 5 mL. [b] Dosed at 25 mg/kg.

Table 8. Oral PK Properties of Selected Compounds in Rat[a]

compd	C_{max} (ng/mL)	T_{max} (h)	$T_{1/2}$ (h)	CL/*F* (mL/min/kg)	V_d (L/kg)
44	1671	3.0	5.8	18.8	9.8
45	273	1.0	2.7	288.5	98.3
47	10.3	3.33	ND	980.7	1804.3

[a] All compounds dosed at 20 mg/kg. Oral dose is as suspension in 1% CMC at 2 mg/mL concentration. ND = not determined.

Table 9. Cross-Resistance Studies by Plaque Assay

	IC_{50} (μM)		
compd	unselected virus	selected virus	fold resistance
18	5	50	10
38	1.5	20	13

Table 10. Cross-Resistance Studies by ELISA Assay

	IC_{50} (μM)		
compd	unselected virus	selected virus	fold resistance
18	6	50	8
38	1.8	25	14

Conclusion

We have investigated the antiviral SAR of approximately 650 closely related 1,4-benzodiazepines and found that an *o*-methoxybenzamide containing a suitably positioned electron-withdrawing group gave both excellent in vitro activity and good

pharmacokinetic properties. Other heteroaromatic amides were also shown to have good activity, as were aromatic ureas. Substitution around the bicyclic template, however, gave no improvement in activity, showing that preferably the core should remain unsubstituted. Alkylation of either the ring or substituent amide NH groups also led to a loss of activity.

Experimental Section

Biology. XTT Assay. 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.

Plaque Assay. Monolayer cultures of Hep-2 cells were infected with RSV. Following adsorption for 2 h, compounds were added in medium containing 0.6% agarose. After 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 RSV and exposed to test compound for 3 days at 37 °C. Monoclonal antibodies to the 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} determined.

Pharmacokinetic Determination. Pharmacokinetic studies were carried out at BioDynamics of Rushden, Northants, UK. Albino rats (Sprague−Dawley, approximately 2 months old) were dosed with test material. The oral dose solution was prepared by suspending the test material in 1% carboxymethylcellulose at a concentration of 2 mg/mL. The dose was administered as a single bolus dose given by oral gavage. Blood samples (∼0.3 mL) were then collected at the following time points: 15, 30, 60, 120, 240, 360, 480 min and 24 h. The samples thus collected were analyzed by LC−MS and LC−MS/MS and compared to a reference sample and an internal standard using an Agilent HP1100 autosampler and binary HPLC pump with LG-980-02 ternary gradient unit linked to a PE Sciex API-3000 triple quadrupole mass spectrometer.

Intravenous doses were prepared as follows. Test material was dissolved in 100% DMSO at a concentration of 20 mg/mL, and 100 μL of this stock solution was mixed with 10% w/v hydroxypropyl β-cyclodextrin in phosphate-buffered saline to give a total volume of 5 mL. This dose was administered into a lateral tail vein. Blood samples were then taken at the following time points: 5, 15, 30, 60, 120, 240, 480 min and 24 h. The samples were then analyzed as described above.

Chemistry. ^{1}H NMR and ^{13}C 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.

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. Solid-phase extraction (SPE) chromatography was carried out using Jones chromatography (Si) cartridges under 15 mmHg vacuum with stepped gradient elution. All chemicals were purchased from commercial suppliers and used directly without further purification.

6-Methoxy-1*H*-benzo[*d*][1,3]oxazine-2,4-dione (7b). Method A. A suspension of 2-amino-5-methoxybenzoic acid (**6b**, 4.35 g, 26 mmol) in dry THF (100 mL) was treated with triphosgene (2.6 g, 0.34 equiv) and the mixture stirred at room temperature for 18 h. The solvent was then evaporated and the residue triturated with diethyl ether, giving the title compound as a pale brown solid (4.88 g, 97%). ^{1}H NMR (DMSO-d_6): δ 3.81 (s, 3H) 7.11 (d, 1H, J = 8.84 Hz) 7.33−7.41 (m, 2H) 11.62 (s, 1H).

2-Amino-5,*N*-dimethoxy-*N*-methylbenzamide (8b). Method B. A solution of *O*,*N*-dimethylhydroxylamine hydrochloride (4.9 g, 2 equiv) in 90% aqueous ethanol (140 mL) was treated with triethylamine (6.9 mL, 2 equiv) and was stirred at room temperature for 10 min. **7b** (4.8 g, 25 mmol) was then added and the mixture heated to reflux for 3 h. The mixture was allowed to cool and was then basified with sodium bicarbonate solution (4%, 150 mL). The ethanol was then evaporated and the aqueous layer extracted with EtOAc. The dried extract was evaporated and the residue chromatographed on silica gel. Gradient elution with 0−10% MeOH in DCM gave an impure sample of the title compound as a brown oil (3.04 g, 58%). This material was used without further purification in the following step. ^{1}H NMR ($CDCl_3$): δ 3.36 (s, 3H) 3.61 (s, 3H) 3.75 (s, 3H) 4.10 (brs, 2H) 6.68 (d, 1H, J = 8.84 Hz) 6.84 (dd, 1H, J = 8.84, 3.16 Hz) 6.93 (d, 1H, J = 3.16 Hz)

(2-Amino-5-methoxyphenyl)phenylmethanone (2b). Method C. A solution of **8b** (3.04 g, 14.47 mmol) and bromobenzene (1.65 mL, 1.1 equiv) in dry THF (140 mL) was cooled (−100 °C), treated with n-BuLi (1.6 M in hexanes, 26 mL, 3 equiv), and then stirred for a further 1 h at −100 °C. HCl (1 M) was then added, and the mixture was allowed to warm to room temperature and was then extracted with EtOAc. The dried extracts were evaporated, and the residue was chromatographed on silica gel. Gradient elution with 5% EtOAc/petrol to neat EtOAc gave an impure sample of the title compound as a dark yellow oil (2.05 g, 62%). This material was used without further purification in the following step.

(2-Aminophenyl)cyclohexylmethanone (2n). A solution of 2-methylbenzo[*d*][1,3]oxazin-4-one (1 g, 6.2 mmol) in dry THF (20 mL) at 0 °C was treated dropwise with cyclohexylmagnesium bromide (2 M in ether, 3.1 mL, 1 equiv). The mixture was stirred for 3 h, slowly warming to 20 °C. HCl (2 M) was then added and the mixture extracted with EtOAc. The solvent was evaporated and the residue chromatographed on silica gel. Elution with 25% EtOAc in petrol gave a colorless oil (530 mg). This material was dissolved in 1:1 acetone:6 M HCl (14 mL) and was heated to reflux for 2 h. The mixture was cooled, basified (K_2CO_3), and extracted with DCM. The solvent was evaporated and the residue partially purified on silica gel. Elution with petrol gave a bright yellow oil (415 mg, 33%). This material was used without further purification or characterization in the preparation of **4n**.

(2-Oxo-5-phenyl-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-3-yl)-carbamic Acid Benzyl Ester (4a). Method D. A cold (0 °C) solution of **1** (11.6 g, 37.26 mmol) in dry THF (100 mL) under nitrogen was stirred and treated dropwise with a solution of oxalyl chloride (4.4 g) in dry dichloromethane (50 mL), followed by dry dimethylformamide (2 mL). This resulting mixture was stirred for 2 h and then treated with a solution of 2-(aminophenyl)phenylmethanone (6.1 g) and *N*-methylmorpholine (7.07 g) in dry THF (50 mL) over 30 min. The reaction mixture was then allowed to warm to room temperature and was then filtered to remove inorganic salts. The mother liquors were then treated with 7 M ammonia in methanol (100 mL) and stirring continued for 18 h. The solvents were then evaporated, and the residue was partitioned between ethyl acetate and 1 M sodium hydroxide. The dried extracts were evaporated, and the crude oil dissolved in acetic acid (200 mL) containing ammonium acetate (13.4 g). This mixture was then stirred at room temperature for 18 h. The solvents were then evaporated, and the residue was suspended in ethyl acetate:diethyl ether (1:3) (200 mL). Sodium hydroxide (1 M) was added until pH 8 was reached, and then the mixture was cooled to 0−5 °C and the resulting solid collected by filtration (6.94 g, 48%). ^{1}H NMR (DMSO-d_6): δ 5.05 (s, 1H) 5.09 (m, 2H) 7.25−7.69 (m, 14H) 8.38 (d, 1H) 10.85 (s, 1H). MS: found $[M + H]^+$ = 386.

3-Amino-5-phenyl-1,3-dihydrobenzo[*e*][1,4]diazepin-2-one (5a) Method E. 4a (1.07 g, 2.77 mmol) was dissolved in 48% hydrobromic acid in acetic acid (30 mL) and was heated to 70 °C for 30 min. The mixture was then allowed to cool and was diluted with diethyl ether (30 mL). This led to the formation of a yellow solid, which was collected by filtration. This material was then partitioned between ethyl acetate and 1 M potassium carbonate

solution. The extracts were dried and then evaporated, giving an oil which was triturated with diethyl ether giving an off-white solid (305 mg, 33%). ^{1}H NMR (DMSO-d_6): δ 4.25 (s, 1H) 7.17−7.66 (m, 9H) 10.65 (brs, 1H).

3-Amino-1-methyl-5-phenyl-1,3-dihydrobenzo[*e*][1,4]diazepin-2-one (5p). To a cold (0 °C) stirred solution of **5a** (325 mg, 1.295 mmol) in dry DMF (20 mL) was added sodium hydride (60% in oil, 52 mg, 1 equiv). The mixture was stirred for 30 min and then methyl iodide (2 M in TBME, 0.65 mL, 1 equiv) was added. The mixture was then allowed to warm slowly to room temperature and was stirred for 18 h. This mixture was then partitioned between ammonium chloride solution and DCM. The dried organic layer was evaporated and the residue chromatographed on silica gel. Gradient elution with DCM:EtOH:NH_3 400:8:1 to 200:8:1 gave a pale brown gum (213 mg, 41%). ^{1}H NMR ($CDCl_3$): δ 3.39 (s, 3H), 5.23 (s, 1H), 7.13 (dt, 1H, J = 1.26, 6.95 Hz), 7.24−7.39 (m, 6H), 7.46−7.58 (m, 4H).

4-Oxy-5-phenyl-1,3-dihydrobenzo[*e*][1,4]diazepin-2-one (12). *m*-Chloroperbenzoic acid (50−55%, 11 g, 1 equiv) in DCM (75 mL) was treated dropwise, with stirring, with a solution of 5-phenyl-1,3-dihydrobenzo[*e*][1,4]diazepin-2-one (**11**) (7.5 g, 31.78 mmol) in DCM (380 mL) over 1 h. Stirring was maintained for 18 h, and then ammonium hydroxide (25%) was added until pH 8 was reached. The precipitate that formed was then collected by filtration, washed with DCM and water, and then dried, giving the title compound as a pale yellow solid (9.4 g, >100%). This material was then used without further purification or characterization in the preparation of **13**.

Acetic Acid 2-Oxo-5-phenyl-2,3-dihydro-1*H*-benzo[*e*][1,4]-diazepin-3-yl Ester (13). A suspension of **12** (9.3 g) in acetic anhydride (90 mL) was heated to 70 °C for 3 h, producing a clear solution. The mixture was cooled and the solvent evaporated. The orange oil produced was dissolved in hot EtOH and then stored at 4 °C overnight. The colorless solid was then collected by filtration and dried (5.26 g, 56%). A further 5 g of crude material was obtained from evaporation of the mother liquor. ^{1}H NMR (DMSO-d_6): δ 2.1 (3H, s), 5.58 (1H, s), 7.13−7.60 (m, 9H), 10.89 (s, 1H).

3-Hydroxy-5-phenyl-1,3-dihydrobenzo[*e*][1,4]diazepin-2-one (14). A mixture of **13** (10.2 g) in MeOH (100 mL) and 4 M NaOH (60 mL) was stirred for 2 h. Water (400 mL) was then added, and the mixture was acidified to pH 3 with acetic acid and then extracted with DCM. The solvent was evaporated and the residue chromatographed on silica gel. Elution with DCM followed by gradient elution with DCM:EtOH:NH_3 800:8:1 to 50:8:1 gave the title compound as a pale yellow solid (900 mg, 10%). ^{1}H NMR (DMSO-d_6): δ 4.58 (1H, d, J = 8.2 Hz), 6.14 (d, 1H, J = 8.8 Hz), 7.03−7.43 (9H, m), 10.58 (1H, s).

3-Methylamino-5-phenyl-1,3-dihydrobenzo[*e*][1,4]diazepin-2-one (16). A stirred solution of **14** (100 mg, 0.39 mmol) in dry THF (10 mL) containing triethylamine (0.08 mL) was treated with methanesulfonyl chloride (0.046 mL). The mixture was stirred for 30 min, and then methylamine (2M in THF, 1 mL, 5 equiv) was added. After 18 h the mixture was partitioned between aqueous K_2CO_3 and DCM. The solvent was evaporated and the residue purified on a silica gel SPE cartridge. Elution with DCM:EtOH:NH_3 200:8:1 gave the title compound as a pale yellow solid (55 mg, 53%). ^{1}H NMR (DMSO-d_6): δ 2.62 (3H, s), 4.17 (s, 1H), 7.09−7.64 (m, 9H), 8.88 (s, 1H).

***N*-(2-Oxo-5-phenyl-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-3-yl)acetamide (18).** A solution of **5a** (300 mg, 1.19 mmol) in pyridine (5 mL) was treated with acetic anhydride (183 mg). The mixture was stirred at room temperature for 1.5 h and was then evaporated. The residue was partitioned between water and dichloromethane. The dried extract was evaporated and the residue triturated with petroleum ether, giving a colorless solid (231 mg, 66%). MS: found $[M - H]^-$ = 292. NMR (DMSO-d_6): δ 1.99 (s, 3H), 5.25 (d, 1H, J = 8.21 Hz), 7.21−7.66 (m, 9H), 9.06 (d, 1H, J = 8.21 Hz), 10.81 (s, 1H). Anal. ($C_{17}H_{15}N_3O_2 \cdot 0.42H_2O$) C, H, N.

***N*-(2-Oxo-5-phenyl-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-3-yl)isobutyramide (19) Method F.** A solution of **5a** (100 mg, 0.398 mmol) and diisopropyl ethylamine (62 mg, 1.2 equiv) in 9:1 DCM:DMF (2 mL) was treated with isobutyryl chloride (0.041 mL, 1 equiv). The mixture was stirred at room temperature for 18 h and was then partitioned between water and DCM. The solvent was evaporated and the residue purified on a silica gel SPE cartridge. Gradient elution with 5% EtOAc/petrol to neat EtOAc gave the title compound as a colorless solid (35 mg, 27%). MS: found $[M + H]^+$ =322. ^{1}H NMR (DMSO-d_6): δ 1.03 (d, 6H, J = 7.58 Hz), 2.72 (septet, 1H, J = 1.89 Hz), 5.23 (d, 1H, J = 8.21 Hz), 7.20−7.68 (m, 9H), 8.90 (d, 1H, J = 8.21 Hz), 10.77 (brs, 1H). Anal. ($C_{19}H_{19}N_3O_2 \cdot 0.55H_2O$) C, H, N.

2-Methoxy-*N*-(2-oxo-5-phenyl-2,3-dihydro-1*H*-benzo[*e*][1,4]-diazepin-3-yl)benzamide (25). This material was prepared as described in method F except that 2-methoxybenzoyl chloride (0.059 mL) was used. The title compound was a colorless solid (69 mg, 46%). MS: found $[M + H]^+$ = 386. ^{1}H NMR (DMSO-d_6): δ 4.05 (s, 3H), 5.44 (d, 1H, J = 7.58 Hz), 7.11 (t, 1H), 7.24−7.70 (m, 11H), 7.97 (dd, 1H, J = 7.58, 1.89 Hz), 9.50 (d, 1H, J = 6.95 Hz), 10.97 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 56.75, 68.36, 112.91, 121.05, 121.28, 122.01, 123.80, 126.92, 128.70, 129.77, 130.79, 130.92, 131.59, 132.50, 133.33, 133.86, 138.56, 138.95, 158.11, 164.37, 167.10, 167.99. Anal. ($C_{23}H_{19}N_3O_3 \cdot 0.3H_2O$) C, H, N.

2-Ethoxy-*N*-(2-oxo-5-phenyl-2,3-dihydro-1*H*-benzo[*e*][1,4]-diazepin-3-yl)benzamide (29) Method G. **5a** (40 mg, 0.159 mmol), 2-ethoxybenzoic acid (40 mg, 1.5 equiv), *O*-benzotriazol-1-yl-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (121 mg, 2 equiv), and triethylamine (0.07 mL, 3 equiv) in dry DMF (1 mL) was stirred at room temperature for 1 h. Water (10 mL) was then added and stirring continued for 10 min. The colorless precipitate was collected by filtration and then partitioned between dichloromethane and water. The dried organic phase was evaporated and the residue purified on a silica gel SPE cartridge. Elution with ethyl acetate:petrol 1:1 gave the title compound as a colorless solid (46 mg, 72%). ^{1}H NMR (DMSO-d_6): δ 1.56 (t, 3H, J = 6.95 Hz), 4.31 (q, 2H, J = 6.95 Hz), 5.43 (d, 1H, J = 6.95 Hz), 7.07−7.70 (m, 12H), 8.03 (dd, 1H, J = 1.89, 8.21 Hz), 9.75 (d, 1H, J = 6.95 Hz), 11.03 (s, 1H). Anal. ($C_{24}H_{21}N_3O_3 \cdot 0.15H_2O$) C, H, N.

2-Morpholin-4-ylmethyl-*N*-(2-oxo-5-phenyl-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-3-yl)benzamide (37). A mixture of 2-formylbenzoic acid (500 mg, 3.33 mmol) and morpholine (0.29 mL, 1 equiv) in dry THF (10 mL) and acetic acid (1 mL) was treated with sodium (triacetoxy)borohydride (1.4 g, 2 equiv). The mixture was stirred for 18 h and was then partitioned between DCM and pH 7.4 buffer. Evaporation of the extracts gave very little material, so the aqueous layer was evaporated and the residue stirred in DCM/MeOH. Filtration of the insoluble inorganic material and evaporation gave a colorless gum (impure); 88 mg of this material and 50 mg (0.198 mmol) of **5a** were reacted together as described in Method G. The title compound was isolated as a colorless solid (47 mg, 52%). ^{1}H NMR (DMSO-d_6): δ 2.48−2.60 (m, 4H), 3.48−3.62 (m, 4H), 3.69 (d, 1H, J = 12.00 Hz), 3.92 (d, 1H, J = 12.00 Hz), 5.47 (d, 1H, J = 7.58 Hz), 7.26−7.42 (m, 3H), 7.44−7.56 (m, 8H), 7.65−7.77 (m, 2H), 10.94 (s, 1H), 11.66 (d, 1H, J = 7.58 Hz). Anal. ($C_{27}H_{26}N_4O_3 \cdot 0.79H_2O$) C, H, N.

Furan-2-carboxylic Acid (2-Oxo-5-phenyl-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-3-yl)amide (38). This material was prepared as described in method F except that furan-2-carbonyl chloride (0.039 mL) was used. The title compound was a colorless solid (17 mg, 31%). LC−MS: t_R = 4.53 min, found ES+ = 346. ^{1}H NMR (DMSO-d_6): δ 5.42 (d, 1H, J = 8.21 Hz), 6.68 (m, 1H), 7.24−7.70 (m, 10H), 7.90 (m, 1H), 9.02 (d, 1H, J = 8.21 Hz), 10.95 (s, 1H). Anal. ($C_{20}H_{15}N_3O_3 \cdot 0.37H_2O$) C, H, N.

1-(2-Fluorophenyl)-3-(2-oxo-5-phenyl-2,3-dihydro-1*H*-benzo-[*e*][1,4]diazepin-3-yl)urea (42) Method H. A mixture of **5a** (30 mg, 0.12 mmol) and triethylamine (0.05 mL) in dry THF (4 mL) was treated with 1-fluoro-2-isocyanatobenzene (0.011 mL) and was left to stir at room temperature for 24 h. The mixture was then partitioned between water and DCM. The dried organic layer was

evaporated and the residue triturated with petrol, giving the title compound as a beige solid (29 mg, 63%). ^{1}H NMR (DMSO-d_6): δ 5.10 (d, 1H, J = 8.21 Hz), 6.81−6.92 (m 1H), 6.98 (t, 1H, J = 7.58 Hz), 7.07−7.26 (m, 4H), 7.32−7.45 (m, 5H), 7.55 (t, 1H, J = 8.21 Hz), 7.93−8.03 (m, 2H), 8.82 (s, 1H), 10.84 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 68.70, 115.24 (d, J_{C-F} = 19 Hz) 120.70, (d, $J_{C-F} \sim$ 1 Hz), 121.89, 122.33 (J_{C-F} = 7.5 Hz), 123.71, 124.72 (J_{C-F} = 3.3 Hz), 126.90, 128.21, 128.38, 128.69, 129.72, 130.75, 130.85, 132.43, 138.85 (J_{C-F} = 24 Hz), 152.10 (d, J_{C-F} = 241 Hz), 154.57, 166.66, 168.45. Anal. ($C_{22}H_{17}FN_4O_2 \cdot 0.4H_2O$) C, H, N.

2-Methoxy-4-nitro-*N*-(2-oxo-5-phenyl-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-3-yl)benzamide (44). A mixture of **5a** (40 mg, 0.158 mmol) and 2-methoxy-4-nitrobenzoic acid (47 mg) was reacted together as described in method G. The title compound was isolated as a colorless solid (51 mg, 75%). ^{1}H NMR (DMSO-d_6): δ 4.08 (s, 3H), 5.69 (d, 1H, J = 6.95 Hz), 7.08−7.52 (m, 9H), 7.80−7.87 (m, 2H), 8.29 (brs, 1H), 8.31 (d, 1H, J = 8.84 Hz), 9.84 (d, 1H, J = 6.95 Hz). ^{13}C NMR (DMSO-d_6): δ 57.48, 68.59, 107.86, 115.91, 122.01, 123.82, 126.83, 127.93, 128.71, 129.79, 130.83, 130.98, 132.39, 132.57, 138.47, 138.94, 150.38, 158.08, 163.38, 167.36, 167.79. Anal. ($C_{23}H_{18}N_4O_5 \cdot 0.48H_2O$) C, H, N.

5-Fluoro-2-methoxy-*N*-(2-oxo-5-phenyl-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-3-yl)benzamide (47). A mixture of **5a** (40 mg, 0.158 mmol) and 5-fluoro-2-methoxybenzoic acid (41 mg) was reacted together as described in method G. The title compound was isolated as a colorless solid (41 mg, 64%). ^{1}H NMR ($CDCl_3$): δ 4.23 (s, 3H), 5.97 (d, 1H, J = 7.58 Hz), 7.18 (dd, 1H, J = 3.79, 8.84 Hz), 7.32−7.76 (m, 10 H), 8.92 (dd, 1H, J = 3.16, 9.48 Hz), 8.76 (s, 1H), 8.95 (d, 1H, J = 6.95 Hz). Anal. ($C_{23}H_{18}FN_3O_3 \cdot 0.24H_2O$) C, H, N.

3-(2-Methoxybenzylamino)-5-phenyl-1,3-dihydrobenzo[*e*][1,4]-diazepin-2-one (48). Method I. A solution of **5a** (50 mg, 0.2 mmol), 2-methoxybenzaldehyde (41 mg, 1.5 equiv), and sodium (triacetoxy)borohydride (106 mg, 2.5 equiv) in a mixture of DCM (6 mL) and acetic acid (1 mL) was stirred at room temperature for 18 h. The mixture was then partitioned between aqueous $NaHCO_3$ and DCM. The organic layer was evaporated and the residue chromatographed on silica gel. Elution with DCM:EtOH:NH_3 200:8:1 gave the title compound as a colorless solid (48 mg, 65%). ^{1}H NMR (DMSO-d_6): δ 3.09 (brs, 1H), 3.73 (s, 3H), 3.96 (q, 2H, J = 13.90, 36.01 Hz), 4.16 (s, 1H), 6.84−6.94 (m, 2H), 7.16−7.36 (m, 5H), 7.45−7.63 (m, 6H), 10.71 (s, 1H). Anal. ($C_{23}H_{21}N_3O_2$) C, H, N.

3-Diethylamino-5-phenyl-1,3-dihydrobenzo[*e*][1,4]diazepin-2-one (75). Method J. A stirred solution of **14** (50 mg, 0.2 mmol) in dry THF (2 mL) containing triethylamine (0.04 mL) was treated with methanesulfonyl chloride (0.023 mL). The mixture was stirred for 30 min, and then diethylamine (0.07 mL, 3.5 equiv) was added and the mixture stirred for 5 h. The mixture was partitioned between water and DCM. The organic layer was evaporated and the residue chromatographed on silica gel. Elution with DCM:EtOH:NH_3 200:8:1 gave the title compound as a colorless solid (21 mg, 34%). ^{1}H NMR (DMSO-d_6): δ 1.27 (t, 6H, J = 6.95 Hz), 3.16 (q, 4H, J = 6.95 Hz), 4.42 (s, 1H), 7.38−7.54 (m, 3H), 7.63−7.85 (m, 6H), 10.76 (s, 1H). Anal. ($C_{19}H_{21}N_3O \cdot 0.11H_2O$) C, H, N.

Supporting Information Available: Chemical intermediate synthesis, final compound synthesis and analytical characterization, biological assay protocols, and a list of receptors and enzymes screened in the Cerep diversity profile. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Greenough, A. Respiratory Syncytial Virus Infection: Clinical Features, Management and Prophylaxis. *Curr. Opin. Pulm. Med.* **2002**, *8*, 214−217.
(2) Sigurs, N. Epidemiologic and Clinical Evidence of a Respiratory Syncytial Virus−Reactive Airways Disease Link. *Am. J. Crit. Care Med*. **2001**, 163 (no 3), S2−6.
(3) Falsey, A. R.; Walsh, E. Respiratory Syncytial Virus in Adults. *Clin. Microbiol. Rev.* **2000**, *July*, 371−384
(4) Bowden, R. A. Respiratory Virus Infections after Marrow Transplant: The Fred Hutchinson Research Center Experience. *Am. J. Med.* **1996**, *102*, 27−30.
(5) Hall, C. B. Prospects for a Respiratory Syncytial Virus Vaccine. *Science* **1994**, *265*, 1393−1394.
(6) McKimm-Breschkin, J. L. A Simplified Plaque Assay for Respiratory Syncytial Virus−Direct Visualisation of Plaques without Immunostaining. *J. Virol. Methods* **2004**, *120* (1), 113−117.
(7) *Fields Virology*, 4th ed.; Knipe, D. M., Howley, P. M., Eds.; Lippincott Williams & Wilkins: Philadelphia, 2001; Volume 1, Chapter 45, pp 1443−1485.
(8) Henderson, E. A.; Alber, D. G.; Baxter, R. C.; Bithell, S. K.; Carter, M. C.; Cockerill, G. S.; Dowdell, V. C. L.; Harris, R. A.; Keegan, S. J.; Kelsey, R. D.; Lumley, J. A.; Stables, J. N.; Weerasekera, N.; Wood, L. J.; Powell, K. L. 1,4-Benzodiazepines as Inhibitors of Respiratory Syncytial Virus. The Identification of a Clinical Candidate. Manuscript in preparation.
(9) Ding, W.-D.; et al. Novel and Specific Respiratory Syncytial Virus Inhibitors That Target Virus Fusion. *J. Med. Chem*. **1998**, *41*, 2671−2675.
(10) Razinkov, R.; et al., RFI-641 Inhibits Entry of Respiratory Syncytial Virus via Interactions with Fusion Protein. *Chem. Biol*. **2001**, 645−659.
(11) Douglas, J. L.; et al. Inhibition of Respiratory Syncytial Virus Fusion by the Small Molecule VP-14637 via Specific Interactions with F Protein. *J Virol*. **2003**, *77* (9), 5054−5064.
(12) Cianci, C.; et al. Orally Active Fusion Inhibitor of Respiratory Syncytial Virus. *Antimicrob. Agents Chemother*. **2004**, 413−422.
(13) Sherrill, R. G.; Sugg, E. E. An Improved Synthesis and Resolution of 3-Amino-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-ones. *J. Org. Chem*. **1995**, *60*, 730−734.
(14) Nahm, S.; Weinreb, S. M. *N*-Methoxy-*N*-methylamides as Effective Acylating Agents. *Tetrahedron Lett*. **1981**, *22*, 3815−3818.
(15) Bock, M. G.; et al. Synthesis and Resolution of 3-Amino-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-ones. *J. Org. Chem*. **1987**, *52* (15), 3232−3239.
(16) Köves, G. J. Synthesis of Deuterium Labelled Lorazepam. *J. Labelled Compds Radiopharm.* **1992**, *29*, 15−22
(17) Dourtoglou, V.; Gross, B. *O*-Benzotriazolyl-*N*,*N*,*N*′,*N*′-tetramethyluronium Hexafluorophosphate as Coupling Reagent for the Synthesis of Peptides of Biological Interest. *Synthesis* **1984**, 572−574.

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