

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 μ M. 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 study⁴ 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

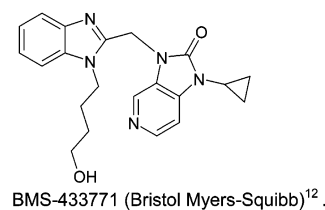
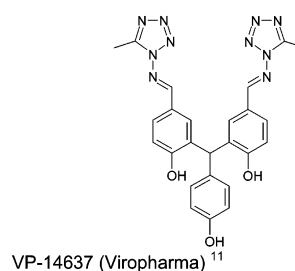
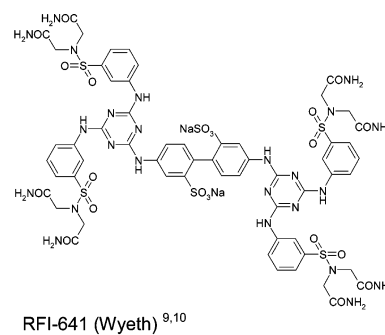
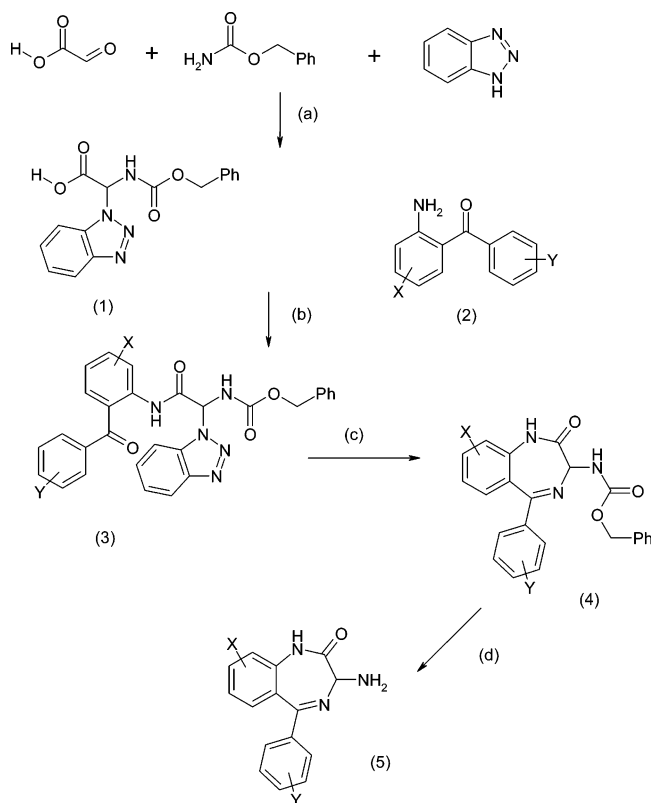


Figure 1. Structures of recently described fusion inhibitors of RSV.

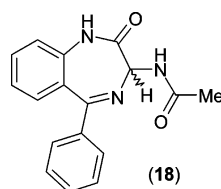
assay. A colorimetric read-out utilizing XTT (2,3-bis(2-methoxy-4-nitro-5-sulphophenyl)-2H-tetrazolium-5-carboxanilide, disodium salt) was employed to measure compound-mediated cell survival. This process was laborious and provided a relatively high hit rate, with several hit series being identified. Secondary testing in ELISA and plaque⁶ 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

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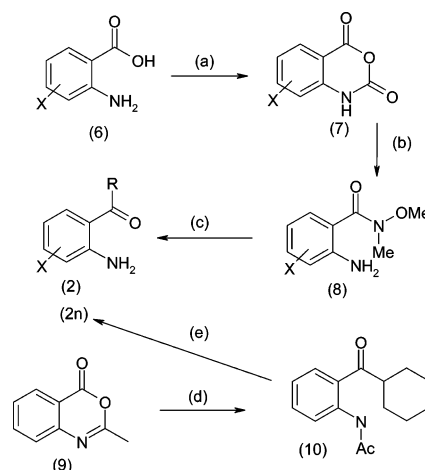
Scheme 1^a

^a Reagents and conditions: (a) toluene, reflux; (b) (i) oxalyl chloride, THF, DCM, 0 °C, (ii) (2) *N*-methylmorpholine, DCM; (c) (i) NH₃/MeOH, (ii) NH₄OAc, AcOH; (d) HBr/AcOH.

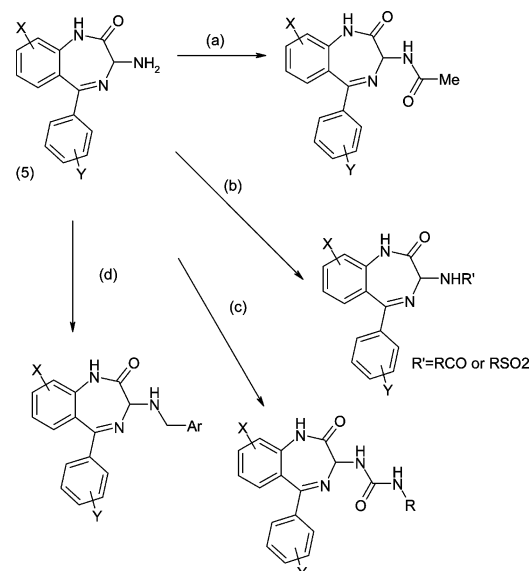
65 cell toxicity. The structure–activity relationships of this series
 66 were investigated, and potent (IC₅₀ ~ 1 μM) inhibitors were
 67 prepared. These compounds were found to possess good
 68 pharmacokinetic properties and, unlike most recently described
 69 small-molecule inhibitors of RSV, were not viral fusion inhibi-
 70 tors. We observed a relatively slow onset of resistance and were
 71 able to show that (**18**) and its analogues caused mutations in
 72 the nucleocapsid protein, an essential component of the viral
 73 replication complex.⁷ These molecules all contained a chiral
 74 center at the 3-position of the diazepine ring. Subsequently, we
 75 have prepared the individual enantiomers of the most promising
 76 molecules and the antiviral activity has been shown to reside
 77 solely in the (*S*)-enantiomer.⁸



78 **Synthetic Chemistry.** Many routes to 1,4-benzodiazepines
 79 have been described in recent years. We chose to follow the
 80 route described by Sherrill and Sugg¹³ (Scheme 1). This utilized
 81 the α-benzotriazolylglycine intermediate (**1**), which was readily
 82 prepared in a one-pot process on a large scale. Conversion of
 83 this to the acyl chloride and then reaction with an appropriate
 84 aminobenzophenone (**2**) gave the amide (**3**), which was routinely
 85 used crude in the following cyclization step. Reaction of
 86 ammonia gas in methanol, followed by ammonium acetate in
 87 acetic acid, furnished the protected benzodiazepine (**4**). The
 88 amine (**5**) was then prepared by the action of either trifluoro-
 89 acetic acid or hydrogen bromide in acetic acid.

Scheme 2^a

^a Reagents and conditions: (a) triphosgene, THF; (b) dimethyl hydroxyl-amine, aq EtOH, reflux; (c) ArLi, THF, -100 °C; (d) cyclohexyl magnesium bromide, THF; (e) HCl, reflux.

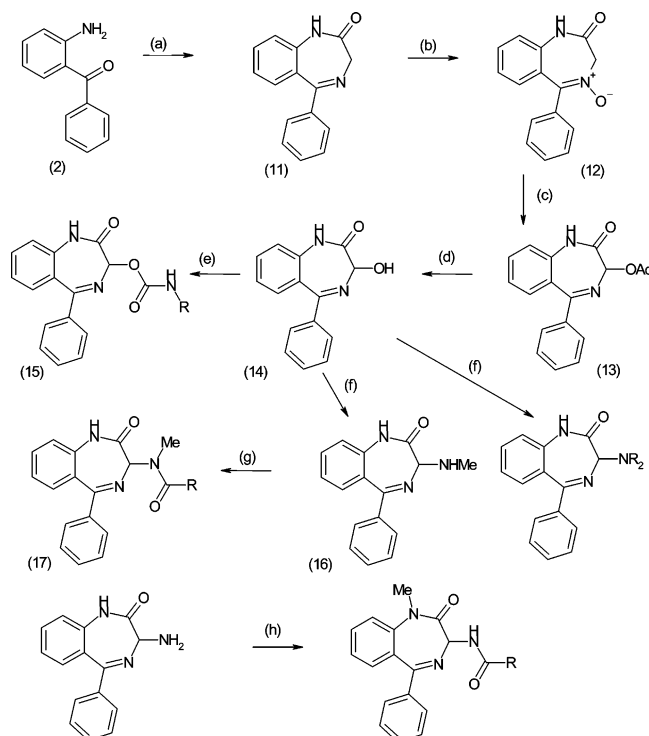
Scheme 3^a

^a Reagents and conditions: (a) acetic anhydride, pyridine; (b) RCOCl, Et₃N, THF or HBTU,¹⁷ RCO₂H, 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 amides¹⁴ (**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**) fol-
 lowed 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 car-
 bamates, (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) BrCOCH₂Br, DCM, water, (ii) NH₃; (b) *m*-CPBA, DCM; (c) Ac₂O 70°C; (d) NaOH, MeOH; (e) RCNO, THF; (f) (i) MeSO₂Cl, THF, (ii) MeNH₂ or R₂NH; (g) RCNO or RCO₂H, 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 IC₅₀'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.

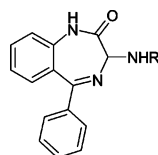
Replacement of the pendant phenyl ring with a methyl group led to poor activity (52), and an identical result was seen when the phenyl ring was reduced to cyclohexyl (50, 51). (Table 2) Recent results also show a similar trend when R is a benzyl substituent or a pyridine ring (data not shown).

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



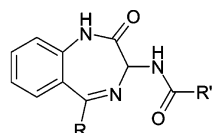
Compound no.	R	IC ₅₀ (μM)	Compound no.	R	IC ₅₀ (μM)
18	COMe	8.6	34		9.6
19	CO ^t Pr	9.5	35		4.8
20	CO ^t Bu	16.7	36		>50
21		12.5	37		20.7
22		5.5	38		3.2
23		3.6	39		5.6
24		6.6	40		2.8
25		2.3	41		17.4
26		6.7	42		3.3
27		7.4	43		3.4
28		7.5	44		2.0
29		3.6	45		5.9
30		40.2	46		2.0
31		2.1	47		1.5
32		14.4	48		27.3
33		14.6	49		toxic

^a All IC₅₀'s shown are a mean of $n = 3$.

205 The most interesting compounds from the XTT assay were taken
 206 forward into both ELISA and plaque assays to confirm activity.
 207 In general, the SAR from the XTT was consistent with both

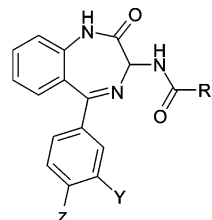
other assays, with good antiviral activity demonstrated. These
 208 compounds also showed excellent activity against a range of
 209 RSV strains (Long, B, and A2 strains; see Table 6) and also
 210

Table 2



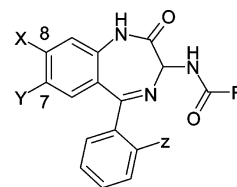
Compound no.	R	R'	IC ₅₀ (μM)
50			>50
51			>50
52	Me		>50

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

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.

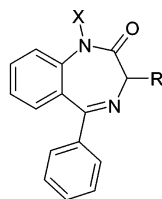
Cells were infected with RSV (RSS strain) at a MOI of 0.01 and incubated in the presence of the acetamide analogue (**18**), initially at about half the IC₅₀ concentration and then doubling the concentration at each passage. This procedure was carried out up to a final drug concentration of 70 μM (ca. 15 × IC₅₀). At each passage the IC₅₀ of both (**18**) and the furan derivative (**38**) on the virus population was determined. No apparent shift in IC₅₀ was observed until passage 9, when the IC₅₀ 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

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

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

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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

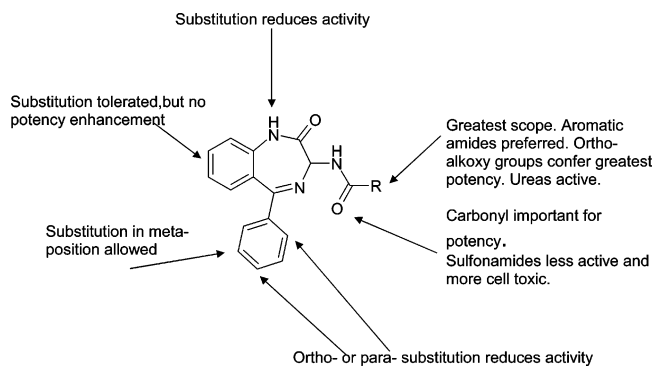


Figure 2. General SAR.

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

246 The resistant phenotype can be attributed to all, one, or a
247 combination of these mutations. The mutation in the F-gene
248 was observed after passage 4, when no increase in IC₅₀ was
249 seen, while mutations in N and L occurred around passage 8 or

Table 6.^a

compd	XTT	ELISA			plaque			
		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 IC₅₀ values (μM).

Table 7. Intravenous and Oral PK Properties of Selected Molecules in Rat^d

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^d

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

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

Table 10. Cross-Resistance Studies by ELISA Assay

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

9, concomitant with a change in the IC₅₀, and are more likely
251 to be the cause of the resistance. In addition, we observed that
252 viruses at the late stage of the selection process reverted to the
253 wild-type genotype of the L gene. All together these data
254 strongly indicate that the molecular target of this series of
255 compounds is the N-protein.

256 After the discovery of these mutations, reverse genetics
257 studies are underway wherein three separate mutant viruses are
258 generated by transfection with mutated viral genomic constructs,
259 each possessing one single-point change from wild type. IC₅₀'s
260 against all three mutants will then be determined in order to
261 identify which mutation is responsible for the altered sensitivity.

Conclusion

262 We have investigated the antiviral SAR of approximately 650
263 closely related 1,4-benzodiazepines and found that an *o*-methoxybenzamide
264 containing a suitably positioned electron-withdrawing group gave both excellent *in vitro* activity and good
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267 pharmacokinetic properties. Other heteroaromatic amides were
268 also shown to have good activity, as were aromatic ureas.
269 Substitution around the bicyclic template, however, gave no
270 improvement in activity, showing that preferably the core should
271 remain unsubstituted. Alkylation of either the ring or substituent
272 amide NH groups also led to a loss of activity.

273 Experimental Section

274 **Biology. XTT Assay.** Hep-2 cells were infected with RSV in
275 the presence of compound and incubated for 6 days at 37 °C.
276 Residual cell viability was then measured by metabolism of the
277 XTT substrate to a colored product, and 50% inhibitory concentra-
278 tions (IC₅₀) were determined.

279 **Plaque Assay.** Monolayer cultures of Hep-2 cells were infected
280 with RSV. Following adsorption for 2 h, compounds were added
281 in medium containing 0.6% agarose. After 5-day incubation at 37
282 °C, the monolayers were fixed, and the overlay was removed.
283 Plaques were visualized by staining with methylene blue.

284 **ELISA Assay.** Hep-2 cells were infected with RSV and exposed
285 to test compound for 3 days at 37 °C. Monoclonal antibodies to
286 the F-, N-, and P-proteins were used and detected with an enzyme-
287 linked secondary antibody. Subsequent conversion of substrate to
288 a colored product was measured by Optical Density and the IC₅₀
289 determined.

290 **Pharmacokinetic Determination.** Pharmacokinetic studies were
291 carried out at BioDynamics of Rushden, Northants, UK. Albino
292 rats (Sprague–Dawley, approximately 2 months old) were dosed
293 with test material. The oral dose solution was prepared by
294 suspending the test material in 1% carboxymethylcellulose at a
295 concentration of 2 mg/mL. The dose was administered as a single
296 bolus dose given by oral gavage. Blood samples (~0.3 mL) were
297 then collected at the following time points: 15, 30, 60, 120, 240,
298 360, 480 min and 24 h. The samples thus collected were analyzed
299 by LC–MS and LC–MS/MS and compared to a reference sample
300 and an internal standard using an Agilent HP1100 autosampler and
301 binary HPLC pump with LG-980-02 ternary gradient unit linked
302 to a PE Sciex API-3000 triple quadrupole mass spectrometer.

303 Intravenous doses were prepared as follows. Test material was
304 dissolved in 100% DMSO at a concentration of 20 mg/mL, and
305 100 μL of this stock solution was mixed with 10% w/v hydroxy-
306 propyl β-cyclodextrin in phosphate-buffered saline to give a total
307 volume of 5 mL. This dose was administered into a lateral tail vein.
308 Blood samples were then taken at the following time points: 5,
309 15, 30, 60, 120, 240, 480 min and 24 h. The samples were then
310 analyzed as described above.

311 **Chemistry.** ¹H NMR and ¹³C NMR spectra were recorded on a
312 Bruker Avance spectrometer at 250 MHz, and chemical shifts are
313 reported in ppm relative to DMSO-*d*₆ or CDCl₃. Elemental analyses
314 were performed by G. A. Maxwell at University College London.

315 **LC–MS Conditions.** Samples were run on a Micromass ZMD,
316 using electrospray with simultaneous positive–negative ion detec-
317 tion: column, YMC-PACK FL-ODS AQ, 50 × 4.6 mm I.D S-5
318 μm; gradient, 95:5 to 5:95 v/v H₂O/CH₃CN + 0.05% formic acid
319 over 4.0 min, hold 3 min, return to 95:5 v/v H₂O/CH₃CN + 0.05%
320 formic acid over 0.2 min, and hold at 95:5 v/v H₂O/CH₃CN +
321 0.05% formic acid over 3 min; detection, PDA 250–340 nm; flow
322 rate, 1.5 mL/min. Solid-phase extraction (SPE) chromatography was
323 carried out using Jones chromatography (Si) cartridges under 15
324 mmHg vacuum with stepped gradient elution. All chemicals were
325 purchased from commercial suppliers and used directly without
326 further purification.

327 **6-Methoxy-1H-benzo[d][1,3]oxazine-2,4-dione (7b). Method**
328 **A.** A suspension of 2-amino-5-methoxybenzoic acid (**6b**), 4.35 g,
329 26 mmol) in dry THF (100 mL) was treated with triphosgene (2.6
330 g, 0.34 equiv) and the mixture stirred at room temperature for
331 18 h. The solvent was then evaporated and the residue triturated
332 with diethyl ether, giving the title compound as a pale brown solid
333 (4.88 g, 97%). ¹H NMR (DMSO-*d*₆): δ 3.81 (s, 3H) 7.11 (d, 1H,
334 *J* = 8.84 Hz) 7.33–7.41 (m, 2H) 11.62 (s, 1H).

2-Amino-5,N-dimethoxy-N-methylbenzamide (8b). Method B. 335
A solution of *O,N*-dimethylhydroxylamine hydrochloride (4.9 g, 2 336
equiv) in 90% aqueous ethanol (140 mL) was treated with 337
triethylamine (6.9 mL, 2 equiv) and was stirred at room tempera- 338
ture for 10 min. **7b** (4.8 g, 25 mmol) was then added and the mix- 339
ture heated to reflux for 3 h. The mixture was then allowed to cool and 340
was then basified with sodium bicarbonate solution (4%, 150 341
mL). The ethanol was then evaporated and the aqueous layer 342
extracted with EtOAc. The dried extract was evaporated and the 343
residue chromatographed on silica gel. Gradient elution with 344
0–10% MeOH in DCM gave an impure sample of the title 345
compound as a brown oil (3.04 g, 58%). This material was used 346
without further purification in the following step. ¹H NMR 347
(CDCl₃): δ 3.36 (s, 3H) 3.61 (s, 3H) 3.75 (s, 3H) 4.10 (brs, 2H) 348
6.68 (d, 1H, *J* = 8.84 Hz) 6.84 (dd, 1H, *J* = 8.84, 3.16 Hz) 6.93 349
(d, 1H, *J* = 3.16 Hz) 350

(2-Amino-5-methoxyphenyl)phenylmethanone (2b). Method 351
C. A solution of **8b** (3.04 g, 14.47 mmol) and bromobenzene (1.65 352
mL, 1.1 equiv) in dry THF (140 mL) was cooled (–100 °C), treated 353
with *n*-BuLi (1.6 M in hexanes, 26 mL, 3 equiv), and then stirred 354
for a further 1 h at –100 °C. HCl (1 M) was then added, and the 355
mixture was allowed to warm to room temperature and was then 356
extracted with EtOAc. The dried extracts were evaporated, and the 357
residue was chromatographed on silica gel. Gradient elution with 358
5% EtOAc/petrol to neat EtOAc gave an impure sample of the title 359
compound as a dark yellow oil (2.05 g, 62%). This material was 360
used without further purification in the following step. 361

(2-Aminophenyl)cyclohexylmethanone (2n). A solution of 362
2-methylbenzo[d][1,3]oxazin-4-one (1 g, 6.2 mmol) in dry THF 363
(20 mL) at 0 °C was treated dropwise with cyclohexylmagnesium 364
bromide (2 M in ether, 3.1 mL, 1 equiv). The mixture was stirred 365
for 3 h, slowly warming to 20 °C. HCl (2 M) was then added and 366
the mixture extracted with EtOAc. The solvent was evaporated and 367
the residue chromatographed on silica gel. Elution with 25% EtOAc 368
in petrol gave a colorless oil (530 mg). This material was dissolved 369
in 1:1 acetone:6 M HCl (14 mL) and was heated to reflux for 2 h. 370
The mixture was cooled, basified (K₂CO₃), and extracted with 371
DCM. The solvent was evaporated and the residue partially purified 372
on silica gel. Elution with petrol gave a bright yellow oil (415 mg, 373
33%). This material was used without further purification or 374
characterization in the preparation of **4n**. 375

(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)- 376
carbamic Acid Benzyl Ester (4a). Method D. A cold (0 °C) 377
solution of **1** (11.6 g, 37.26 mmol) in dry THF (100 mL) under 378
nitrogen was stirred and treated dropwise with a solution of oxalyl 379
chloride (4.4 g) in dry dichloromethane (50 mL), followed by dry 380
dimethylformamide (2 mL). This resulting mixture was stirred for 381
2 h and then treated with a solution of 2-(aminophenyl)phenyl- 382
methanone (6.1 g) and *N*-methylmorpholine (7.07 g) in dry THF 383
(50 mL) over 30 min. The reaction mixture was then allowed to 384
warm to room temperature and was then filtered to remove 385
inorganic salts. The mother liquors were then treated with 7 M 386
ammonia in methanol (100 mL) and stirring continued for 18 h. 387
The solvents were then evaporated, and the residue was partitioned 388
between ethyl acetate and 1 M sodium hydroxide. The dried extracts 389
were evaporated, and the crude oil dissolved in acetic acid (200 390
mL) containing ammonium acetate (13.4 g). This mixture was then 391
stirred at room temperature for 18 h. The solvents were then 392
evaporated, and the residue was suspended in ethyl acetate:diethyl 393
ether (1:3) (200 mL). Sodium hydroxide (1 M) was added until 394
pH 8 was reached, and then the mixture was cooled to 0–5 °C and 395
the resulting solid collected by filtration (6.94 g, 48%). ¹H NMR 396
(DMSO-*d*₆): δ 5.05 (s, 1H) 5.09 (m, 2H) 7.25–7.69 (m, 14H) 8.38 397
(d, 1H) 10.85 (s, 1H). MS: found [M + H]⁺ = 386. 398

3-Amino-5-phenyl-1,3-dihydrobenzo[e][1,4]diazepin-2-one (5a) 399
Method E. **4a** (1.07 g, 2.77 mmol) was dissolved in 48% 400
hydrobromic acid in acetic acid (30 mL) and was heated to 70 °C 401
for 30 min. The mixture was then allowed to cool and was diluted 402
with diethyl ether (30 mL). This led to the formation of a yellow 403
solid, which was collected by filtration. This material was then 404
partitioned between ethyl acetate and 1 M potassium carbonate 405

406 solution. The extracts were dried and then evaporated, giving an
407 oil which was triturated with diethyl ether giving an off-white solid
408 (305 mg, 33%). ¹H NMR (DMSO-*d*₆): δ 4.25 (s, 1H) 7.17–7.66
409 (m, 9H) 10.65 (brs, 1H).

410 **3-Amino-1-methyl-5-phenyl-1,3-dihydrobenzo[*e*][1,4]diazepin-
411 2-one (5p).** To a cold (0 °C) stirred solution of **5a** (325 mg, 1.295
412 mmol) in dry DMF (20 mL) was added sodium hydride (60% in
413 oil, 52 mg, 1 equiv). The mixture was stirred for 30 min and then
414 methyl iodide (2 M in TBME, 0.65 mL, 1 equiv) was added. The
415 mixture was then allowed to warm slowly to room temperature
416 and was stirred for 18 h. This mixture was then partitioned between
417 ammonium chloride solution and DCM. The dried organic layer
418 was evaporated and the residue chromatographed on silica gel.
419 Gradient elution with DCM:EtOH:NH₃ 400:8:1 to 200:8:1 gave a
420 pale brown gum (213 mg, 41%). ¹H NMR (CDCl₃): δ 3.39 (s,
421 3H), 5.23 (s, 1H), 7.13 (dt, 1H, *J* = 1.26, 6.95 Hz), 7.24–7.39 (m,
422 6H), 7.46–7.58 (m, 4H).

423 **4-Oxy-5-phenyl-1,3-dihydrobenzo[*e*][1,4]diazepin-2-one (12).**
424 *m*-Chloroperbenzoic acid (50–55%, 11 g, 1 equiv) in DCM (75
425 mL) was treated dropwise, with stirring, with a solution of 5-phenyl-
426 1,3-dihydrobenzo[*e*][1,4]diazepin-2-one (**11**) (7.5 g, 31.78 mmol)
427 in DCM (380 mL) over 1 h. Stirring was maintained for 18 h, and
428 then ammonium hydroxide (25%) was added until pH 8 was
429 reached. The precipitate that formed was then collected by filtration,
430 washed with DCM and water, and then dried, giving the title
431 compound as a pale yellow solid (9.4 g, >100%). This material
432 was then used without further purification or characterization in
433 the preparation of **13**.

434 **Acetic Acid 2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[*e*][1,4]-
435 diazepin-3-yl Ester (13).** A suspension of **12** (9.3 g) in acetic
436 anhydride (90 mL) was heated to 70 °C for 3 h, producing a clear
437 solution. The mixture was cooled and the solvent evaporated. The
438 orange oil produced was dissolved in hot EtOH and then stored at
439 4 °C overnight. The colorless solid was then collected by filtra-
440 tion and dried (5.26 g, 56%). A further 5 g of crude material
441 was obtained from evaporation of the mother liquor. ¹H NMR
442 (DMSO-*d*₆): δ 2.1 (3H, s), 5.58 (1H, s), 7.13–7.60 (m, 9H), 10.89
443 (s, 1H).

444 **3-Hydroxy-5-phenyl-1,3-dihydrobenzo[*e*][1,4]diazepin-2-
445 one (14).** A mixture of **13** (10.2 g) in MeOH (100 mL) and 4 M
446 NaOH (60 mL) was stirred for 2 h. Water (400 mL) was then added,
447 and the mixture was acidified to pH 3 with acetic acid and then
448 extracted with DCM. The solvent was evaporated and the residue
449 chromatographed on silica gel. Elution with DCM followed by
450 gradient elution with DCM:EtOH:NH₃ 800:8:1 to 50:8:1 gave the
451 title compound as a pale yellow solid (900 mg, 10%). ¹H NMR
452 (DMSO-*d*₆): δ 4.58 (1H, d, *J* = 8.2 Hz), 6.14 (d, 1H, *J* = 8.8 Hz),
453 7.03–7.43 (9H, m), 10.58 (1H, s).

454 **3-Methylamino-5-phenyl-1,3-dihydrobenzo[*e*][1,4]diazepin-2-
455 one (16).** A stirred solution of **14** (100 mg, 0.39 mmol) in dry THF
456 (10 mL) containing triethylamine (0.08 mL) was treated with
457 methanesulfonyl chloride (0.046 mL). The mixture was stirred for
458 30 min, and then methylamine (2M in THF, 1 mL, 5 equiv) was
459 added. After 18 h the mixture was partitioned between aqueous
460 K₂CO₃ and DCM. The solvent was evaporated and the residue
461 purified on a silica gel SPE cartridge. Elution with DCM:EtOH:
462 NH₃ 200:8:1 gave the title compound as a pale yellow solid (55
463 mg, 53%). ¹H NMR (DMSO-*d*₆): δ 2.62 (3H, s), 4.17 (s, 1H),
464 7.09–7.64 (m, 9H), 8.88 (s, 1H).

465 ***N*-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[*e*][1,4]diazepin-3-
466 yl)acetamide (18).** A solution of **5a** (300 mg, 1.19 mmol) in
467 pyridine (5 mL) was treated with acetic anhydride (183 mg). The
468 mixture was stirred at room temperature for 1.5 h and was then
469 evaporated. The residue was partitioned between water and di-
470 chloromethane. The dried extract was evaporated and the resi-
471 due triturated with petroleum ether, giving a colorless solid (231
472 mg, 66%). MS: found [M – H][–] = 292. NMR (DMSO-*d*₆): δ
473 1.99 (s, 3H), 5.25 (d, 1H, *J* = 8.21 Hz), 7.21–7.66 (m, 9H), 9.06
474 (d, 1H, *J* = 8.21 Hz), 10.81 (s, 1H). Anal. (C₁₇H₁₅N₃O₂·0.42H₂O)
475 C, H, N.

***N*-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[*e*][1,4]diazepin-3-
476 yl)isobutyramide (19) Method F.** A solution of **5a** (100 mg, 0.398
477 mmol) and diisopropyl ethylamine (62 mg, 1.2 equiv) in 9:1 DCM:
478 DMF (2 mL) was treated with isobutyryl chloride (0.041 mL, 1
479 equiv). The mixture was stirred at room temperature for 18 h and
480 was then partitioned between water and DCM. The solvent was
481 evaporated and the residue purified on a silica gel SPE cartridge.
482 Gradient elution with 5% EtOAc/petrol to neat EtOAc gave the
483 title compound as a colorless solid (35 mg, 27%). MS: found [M
484 + H]⁺ = 322. ¹H NMR (DMSO-*d*₆): δ 1.03 (d, 6H, *J* = 7.58 Hz),
485 2.72 (septet, 1H, *J* = 1.89 Hz), 5.23 (d, 1H, *J* = 8.21 Hz), 7.20–
486 7.68 (m, 9H), 8.90 (d, 1H, *J* = 8.21 Hz), 10.77 (brs, 1H). Anal.
487 (C₁₉H₁₉N₃O₂·0.55H₂O) C, H, N.

488 **2-Methoxy-*N*-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[*e*][1,4]-
489 diazepin-3-yl)benzamide (25).** This material was prepared as
490 described in method F except that 2-methoxybenzoyl chloride
491 (0.059 mL) was used. The title compound was a colorless solid
492 (69 mg, 46%). MS: found [M + H]⁺ = 386. ¹H NMR (DMSO-
493 *d*₆): δ 4.05 (s, 3H), 5.44 (d, 1H, *J* = 7.58 Hz), 7.11 (t, 1H),
494 7.24–7.70 (m, 11H), 7.97 (dd, 1H, *J* = 7.58, 1.89 Hz), 9.50 (d,
495 1H, *J* = 6.95 Hz), 10.97 (s, 1H). ¹³C NMR (DMSO-*d*₆): δ 56.75,
496 68.36, 112.91, 121.05, 121.28, 122.01, 123.80, 126.92, 128.70,
497 129.77, 130.79, 130.92, 131.59, 132.50, 133.33, 133.86, 138.56,
498 138.95, 158.11, 164.37, 167.10, 167.99. Anal. (C₂₃H₁₉N₃O₃·0.3H₂O)
499 C, H, N.

500 **2-Ethoxy-*N*-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[*e*][1,4]-
501 diazepin-3-yl)benzamide (29) Method G.** **5a** (40 mg, 0.159 mmol),
502 2-ethoxybenzamide (40 mg, 1.5 equiv), *O*-benzotriazol-1-yl-
503 *N,N,N',N'*-tetramethyluronium hexafluorophosphate (121 mg, 2
504 equiv), and triethylamine (0.07 mL, 3 equiv) in dry DMF (1 mL)
505 was stirred at room temperature for 1 h. Water (10 mL) was then
506 added and stirring continued for 10 min. The colorless precipitate
507 was collected by filtration and then partitioned between dichlo-
508 romethane and water. The dried organic phase was evaporated and
509 the residue purified on a silica gel SPE cartridge. Elution with ethyl
510 acetate:petrol 1:1 gave the title compound as a colorless solid (46
511 mg, 72%). ¹H NMR (DMSO-*d*₆): δ 1.56 (t, 3H, *J* = 6.95 Hz),
512 4.31 (q, 2H, *J* = 6.95 Hz), 5.43 (d, 1H, *J* = 6.95 Hz), 7.07–7.70
513 (m, 12H), 8.03 (dd, 1H, *J* = 1.89, 8.21 Hz), 9.75 (d, 1H, *J* = 6.95
514 Hz), 11.03 (s, 1H). Anal. (C₂₄H₂₁N₃O₃·0.15H₂O) C, H, N.

515 **2-Morpholin-4-ylmethyl-*N*-(2-oxo-5-phenyl-2,3-dihydro-1H-
516 benzo[*e*][1,4]diazepin-3-yl)benzamide (37).** A mixture of 2-formyl-
517 benzoic acid (500 mg, 3.33 mmol) and morpholine (0.29 mL, 1
518 equiv) in dry THF (10 mL) and acetic acid (1 mL) was treated
519 with sodium (triacetoxy)borohydride (1.4 g, 2 equiv). The mixture
520 was stirred for 18 h and was then partitioned between DCM and
521 pH 7.4 buffer. Evaporation of the extracts gave very little material,
522 so the aqueous layer was evaporated and the residue stirred in DCM/
523 MeOH. Filtration of the insoluble inorganic material and evapora-
524 tion gave a colorless gum (impure); 88 mg of this material and 50
525 mg (0.198 mmol) of **5a** were reacted together as described in
526 Method G. The title compound was isolated as a colorless solid
527 (47 mg, 52%). ¹H NMR (DMSO-*d*₆): δ 2.48–2.60 (m, 4H), 3.48–
528 3.62 (m, 4H), 3.69 (d, 1H, *J* = 12.00 Hz), 3.92 (d, 1H, *J* = 12.00
529 Hz), 5.47 (d, 1H, *J* = 7.58 Hz), 7.26–7.42 (m, 3H), 7.44–7.56
530 (m, 8H), 7.65–7.77 (m, 2H), 10.94 (s, 1H), 11.66 (d, 1H, *J* = 7.58
531 Hz). Anal. (C₂₇H₂₆N₄O₃·0.79H₂O) C, H, N.

532 **Furan-2-carboxylic Acid (2-Oxo-5-phenyl-2,3-dihydro-1H-
533 benzo[*e*][1,4]diazepin-3-yl)amide (38).** This material was prepared
534 as described in method F except that furan-2-carbonyl chloride
535 (0.039 mL) was used. The title compound was a colorless solid
536 (17 mg, 31%). LC–MS: *t*_R = 4.53 min, found ES⁺ = 346. ¹H
537 NMR (DMSO-*d*₆): δ 5.42 (d, 1H, *J* = 8.21 Hz), 6.68 (m, 1H),
538 7.24–7.70 (m, 10H), 7.90 (m, 1H), 9.02 (d, 1H, *J* = 8.21 Hz),
539 10.95 (s, 1H). Anal. (C₂₀H₁₅N₃O₃·0.37H₂O) C, H, N.

540 **1-(2-Fluorophenyl)-3-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo-
541 [e][1,4]diazepin-3-yl)urea (42) Method H.** A mixture of **5a** (30
542 mg, 0.12 mmol) and triethylamine (0.05 mL) in dry THF (4 mL)
543 was treated with 1-fluoro-2-isocyanatobenzene (0.011 mL) and was
544 left to stir at room temperature for 24 h. The mixture was then
545 partitioned between water and DCM. The dried organic layer was
546

547 evaporated and the residue triturated with petrol, giving the title
548 compound as a beige solid (29 mg, 63%). ¹H NMR (DMSO-*d*₆):
549 δ 5.10 (d, 1H, *J* = 8.21 Hz), 6.81–6.92 (m, 1H), 6.98 (t, 1H, *J* =
550 7.58 Hz), 7.07–7.26 (m, 4H), 7.32–7.45 (m, 5H), 7.55 (t, 1H, *J* =
551 8.21 Hz), 7.93–8.03 (m, 2H), 8.82 (s, 1H), 10.84 (s, 1H). ¹³C
552 NMR (DMSO-*d*₆): δ 68.70, 115.24 (d, *J*_{C-F} = 19 Hz) 120.70, (d,
553 *J*_{C-F} ~ 1 Hz), 121.89, 122.33 (*J*_{C-F} = 7.5 Hz), 123.71, 124.72
554 (*J*_{C-F} = 3.3 Hz), 126.90, 128.21, 128.38, 128.69, 129.72, 130.75,
555 130.85, 132.43, 138.85 (*J*_{C-F} = 24 Hz), 152.10 (d, *J*_{C-F} = 241
556 Hz), 154.57, 166.66, 168.45. Anal. (C₂₂H₁₇FN₄O₂·0.4H₂O) C, H,
557 N.

558 **2-Methoxy-4-nitro-*N*-(2-oxo-5-phenyl-2,3-dihydro-1*H*-benzo-
559 [e][1,4]diazepin-3-yl)benzamide (44).** A mixture of **5a** (40 mg,
560 0.158 mmol) and 2-methoxy-4-nitrobenzoic acid (47 mg) was
561 reacted together as described in method G. The title compound was
562 isolated as a colorless solid (51 mg, 75%). ¹H NMR (DMSO-*d*₆):
563 δ 4.08 (s, 3H), 5.69 (d, 1H, *J* = 6.95 Hz), 7.08–7.52 (m, 9H),
564 7.80–7.87 (m, 2H), 8.29 (brs, 1H), 8.31 (d, 1H, *J* = 8.84 Hz),
565 9.84 (d, 1H, *J* = 6.95 Hz). ¹³C NMR (DMSO-*d*₆): δ 57.48, 68.59,
566 107.86, 115.91, 122.01, 123.82, 126.83, 127.93, 128.71, 129.79,
567 130.83, 130.98, 132.39, 132.57, 138.47, 138.94, 150.38, 158.08,
568 163.38, 167.36, 167.79. Anal. (C₂₃H₁₈N₄O₅·0.48H₂O) C, H, N.

569 **5-Fluoro-2-methoxy-*N*-(2-oxo-5-phenyl-2,3-dihydro-1*H*-benzo-
570 [e][1,4]diazepin-3-yl)benzamide (47).** A mixture of **5a** (40 mg,
571 0.158 mmol) and 5-fluoro-2-methoxybenzoic acid (41 mg) was
572 reacted together as described in method G. The title compound was
573 isolated as a colorless solid (41 mg, 64%). ¹H NMR (CDCl₃): δ
574 4.23 (s, 3H), 5.97 (d, 1H, *J* = 7.58 Hz), 7.18 (dd, 1H, *J* = 3.79,
575 8.84 Hz), 7.32–7.76 (m, 10H), 8.92 (dd, 1H, *J* = 3.16, 9.48 Hz),
576 8.76 (s, 1H), 8.95 (d, 1H, *J* = 6.95 Hz). Anal. (C₂₃H₁₈FN₃O₃·
577 0.24H₂O) C, H, N.

578 **3-(2-Methoxybenzylamino)-5-phenyl-1,3-dihydrobenzo[e][1,4]-
579 diazepin-2-one (48).** **Method I.** A solution of **5a** (50 mg, 0.2
580 mmol), 2-methoxybenzaldehyde (41 mg, 1.5 equiv), and sodium
581 (triacetoxo)borohydride (106 mg, 2.5 equiv) in a mixture of DCM
582 (6 mL) and acetic acid (1 mL) was stirred at room temperature for
583 18 h. The mixture was then partitioned between aqueous NaHCO₃
584 and DCM. The organic layer was evaporated and the residue
585 chromatographed on silica gel. Elution with DCM:EtOH:NH₃ 200:
586 8:1 gave the title compound as a colorless solid (48 mg, 65%). ¹H
587 NMR (DMSO-*d*₆): δ 3.09 (brs, 1H), 3.73 (s, 3H), 3.96 (q, 2H, *J*
588 = 13.90, 36.01 Hz), 4.16 (s, 1H), 6.84–6.94 (m, 2H), 7.16–7.36
589 (m, 5H), 7.45–7.63 (m, 6H), 10.71 (s, 1H). Anal. (C₂₃H₂₁N₃O₂)
590 C, H, N.

591 **3-Diethylamino-5-phenyl-1,3-dihydrobenzo[e][1,4]diazepin-
592 2-one (75).** **Method J.** A stirred solution of **14** (50 mg, 0.2 mmol)
593 in dry THF (2 mL) containing triethylamine (0.04 mL) was treated
594 with methanesulfonyl chloride (0.023 mL). The mixture was stirred
595 for 30 min, and then diethylamine (0.07 mL, 3.5 equiv) was added
596 and the mixture stirred for 5 h. The mixture was partitioned between
597 water and DCM. The organic layer was evaporated and the residue
598 chromatographed on silica gel. Elution with DCM:EtOH:NH₃ 200:
599 8:1 gave the title compound as a colorless solid (21 mg, 34%). ¹H
600 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. (C₁₉H₂₁N₃O·0.11H₂O) C, H, N. 601 602

Supporting Information Available: Chemical intermediate 603
synthesis, final compound synthesis and analytical characterization, 604
biological assay protocols, and a list of receptors and enzymes 605
screened in the Cerep diversity profile. This material is available 606
free of charge via the Internet at <http://pubs.acs.org>. 607

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