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Benzoazepine derivative as potent antagonists of the glycine binding site associated to the NMDA receptor

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Abstract

A series of benzoazepine derivatives, bearing suitable substituents at the C-3 position, was designed and evaluated by superimposition with the pharmacophore model of the glycine binding site. To fully explore the SAR of this class of compounds and to allow the preparation of new different compounds at the C-3 position, appropriate synthetic routes were set up. The benzoazepines were evaluated in terms of in vitro affinity using [^{3}H]glycine binding assay and in vivo potency by inhibition of convulsions induced by *N*-methyl-D-aspartate (NMDA) in mice. This further analysis confirmed the preliminary results previously reported and that compound **27** is the most promising compound (Ki = 32 nM, ED_{50} = 0.09 mg/kg, i.v.) in this series. Significant neuroprotective effect was observed after both pre- and post-ischaemia administration in the MCAo model. In particular, after post-ischaemia administration, it was found to be still effective when the administration was delayed up to 6 h after occlusion of the middle cerebral artery.

Keywords: NMDA receptor; Benzoazepine derivatives; Glycine

1. Introduction

In the last decade the modulation of the NMDA receptor has been proven, in animal models of cerebral ischaemia, to represent a valuable biological strategy to identify effective neuroprotective agents. In particular, antagonists acting at the non-competitive glycine binding site were found to counteract the excitotoxic cascade triggered by the stroke onset. These compounds, having been associated to a clean side-effects profile, might be able to offer similar efficacy, but greater therapeutic opportunities with respect to both competitive NMDA antagonists and NMDA channel blockers [1–15].

Considerable effort has then been devoted to find potent and selective ligands [16–26], resulting in the identification of several classes of glycine antagonists, and a selected number of these derivatives is shown in Fig. 1.

To a better understanding of the glycinergic mechanism, our research was focussed on the identification of novel classes of glycine antagonists devoid of the more classical indole scaffold [20] but with a comparable pharmacological profile. In particular, a class of benzo-[b]-azepine derivatives, substituted at the C-5 position with the same α,β-unsaturated chain present in the indole series, was designed (Fig. 2) [26]. The superimposition of this template with the pharmacophore model of the glycine binding site (Fig. 3) suggested that the presence of H-bond donor or a negatively charged R group at the C-3 position could be instrumental to maximise their affinity to the glycine binding site. Following this working hypothesis, the SAR of this class of C-3 substituted benzazepine derivatives was

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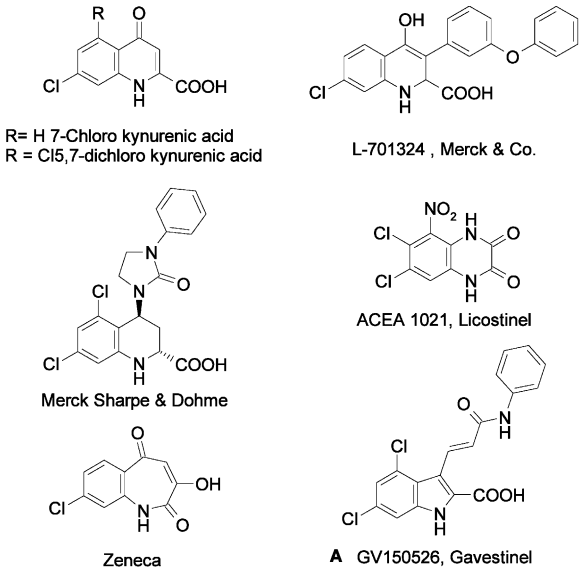


Fig. 1. Structures of various glycine antagonists.

explored in detail adding new selected derivatives with respect to those already published in a preliminary report [26].

Compound **27** (Table 1) confirmed to be the most promising derivative of this series and its pharmacological characterization confirmed the neuroprotective effect of this glycine antagonist.

2. Synthesis

To prepare the derivatives reported in Table 1, different synthetic approaches were set up, depending on the substituents in the C-3 position. As represented in Scheme 1, the key step of the synthetic route was represented by Heck-type cyclization reaction (step h) in which the *E* stereochemistry of the exocyclic double bond was controlled starting from the appropriate stereochemistry of the double bond of the acrylate intermediate. Moreover, to increase the efficiency of this cyclization, it was necessary to shift the cisoid/transoid equilibrium of the amide group towards the transoid rotamer (Fig. 4). To achieve this purpose, the *p*-methoxybenzyl (PMB) group was selected as an appropriate protecting group considering also the required chemical conditions for the final deprotective step. Thus, for the preparation of the C-3 substituted hydroxy derivative, 2-bromo-5-chloro aniline (**1**) was reacted, according to Weinreb conditions, with the substituted butyrolactone **2** to yield the amido intermediate **3**. Its primary alcoholic function was masked as *tert*-butyldimethylsilyl (TBDMS) ether, and the resulting compound **4** was protected as PMB derivative **5** generating the anion with NaH in THF and quenching the reaction adding PMB chloride. After deprotection of the primary alcoholic function, compound **6** was oxidized, under Swern conditions, to obtain the aldehyde **7**, which was submitted to a thermal Wittig-type olefination reaction to yield compound **8** [27]. Amidation reaction, according to the Weinreb's conditions [28], yielded compound **9**, which was submitted to the Heck-type cyclization reaction, using $Pd(PPh_3)_4$ as catalyst. The desired compound **10a** together with the undesired isomer **10b** was formed in 85/15 ratio; the latter was then easily removed by flash chromatography [29]. Finally, removal of the protecting groups with anisole in H_2SO_4/TFA at 80 °C yielded the target compound **11**.

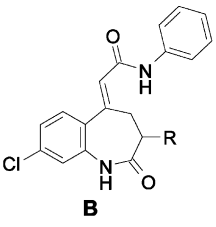


Fig. 2. Benzo-[b]-azepine template.

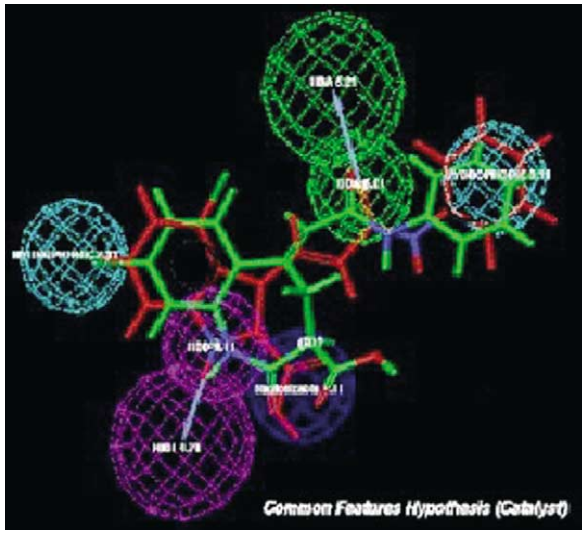
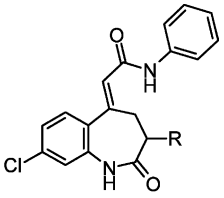


Fig. 3. Superimposition of **27** (Green) with GV150526A (Red) within the pharmacophore model of the glycine binding site. Common features are represented by H-bond acceptor (green), H-bond donor (purple), Hydrophobic (cyan) and Negative inonizable (blue) spheres.

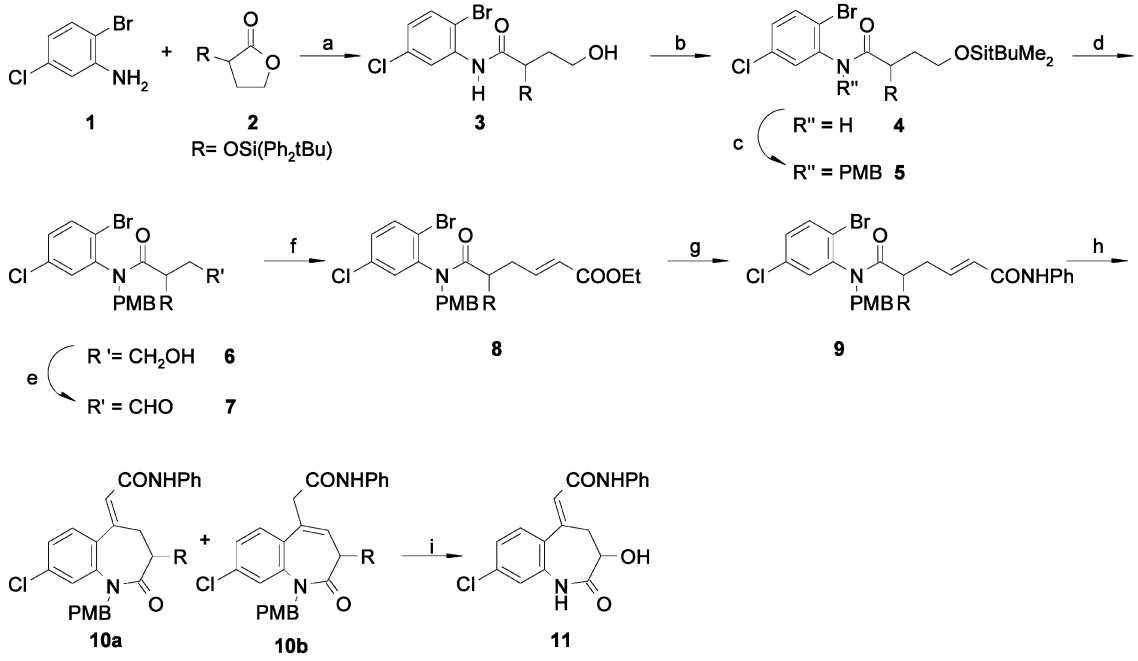
To prepare compounds **19a** and **19b** (R = $NHSO_2CH_3$ and $NHSO_2CF_3$, respectively) the synthetic route shown in Scheme 2 was followed. Alkylation of the aniline **1** with PMBCl in DMF in the presence of NaI at 80 °C gave compound **12**, which was acylated with *N*-benzyloxycarbonyl-allylglycyl chloride to obtain compound **13**. Then, the allylic double bond was transformed into the aldehyde **14** through ozonolysis. Sequential Wittig-type olefination reaction followed by deprotection of the *t*-butyl ester and amidation reaction

Table 1
Substitution at the C-3 position



Entry	R	K_i (nM) [a]	NMDA induced convulsions model in mice [b]	
11 #	OH	1288		
19a	$NHSO_2CH_3$	$>10^5$		
19b	$NHSO_2CF_3$	2692		
27 #	COOH	32		0.07 [c] (0.030–0.230)
28a	CONHOH	44	40%	
28b #	$CONH_2$	39	30%	
28c #	CONHPh	72	30%	
28d	$CON(CH_3)_2$	2239		
28e #	CN	339		
28f	$CONHSO_2Ph$	234		
35	COPh	20893		
GV150526		3		0.06 [c] (0.005–0.42)

[a] Inhibition of binding of [^{3}H]-glycine.
[b] Percentage of inhibition of convulsions at 0.1 mg/kg, i.v.
[c] ED_{50} (mg/kg).
Reported also in Ref. [26].



Scheme 1. [a] Reagents and conditions: (a) Et_2AlCl 1 M Hex, CH_2Cl_2; (b) TBDMSCl, imidazole, 4-(dimethylamino)pyridine, DMF; (c) NaH, NaI, 4(MeO)$PhCH_2Cl$ (PMBCl), DMF, 80 °C; (d) *p*-toluenesulfonic acid, MeOH; (e) DMSO, $(COCl)_2$, TEA, CH_2Cl_2, −78−−20 °C; (f) Ph_3P=CHCOOEt, toluene, 70 °C; (g) aniline, Et_2AlCl 1 M Hex, toluene, 80 °C; (h) $Pd(PPh_3)_4$, CH_3CN, TEA, reflux; (i) CF_3COOH, anisole, H_2SO_4,

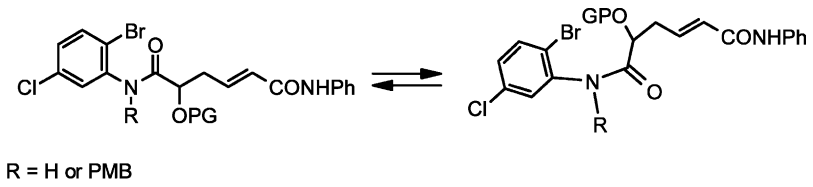
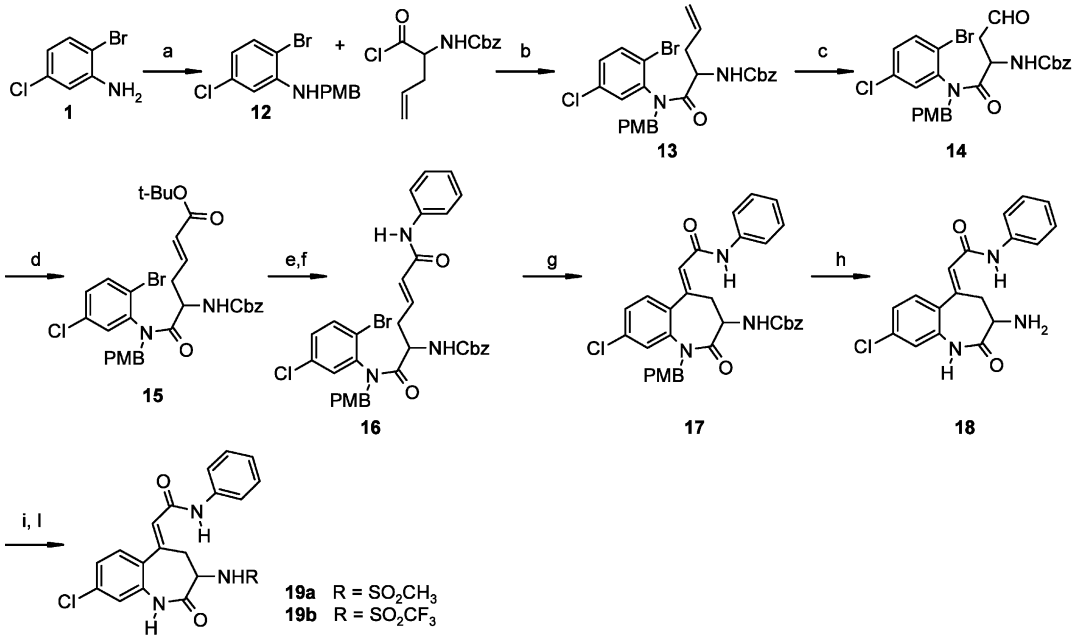


Fig. 4.

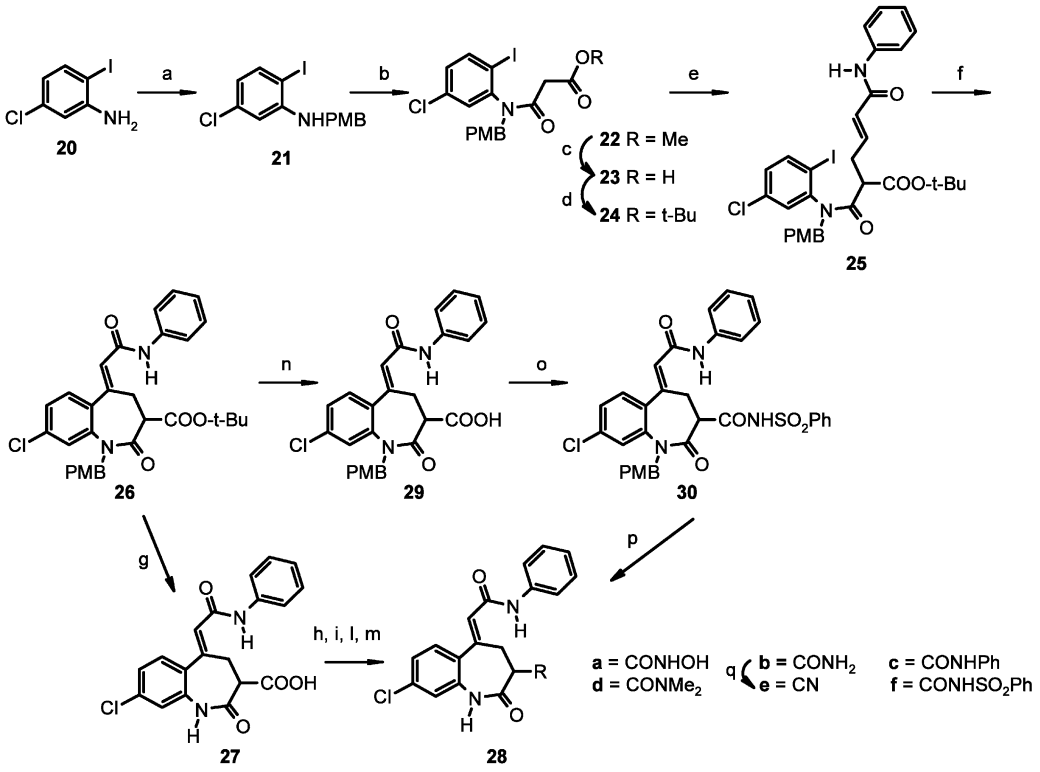
with aniline allowed the preparation of the key intermediate **16**. Heck-type cyclization reaction followed by removal of both N–Cbz and N–PMB protecting groups under acid conditions yielded the amino derivative **18**. The latter was transformed into the sulfonamide derivatives **19a** and **19b** by reaction with $(CF_3SO_2)_2O$ and CH_3SO_2Cl, respectively.

The benzoazepine derivatives **28a**–**f** were synthesized according to the synthetic sequence shown in Scheme 3. Protection of the aniline derivative **20** with PMBCl yielded the compound **21**, which was reacted with methyl malonyl chloride to give the intermediate **22**. Sequential hydrolysis of the methyl ester, activation of the acid function and reaction with *t*-butanol yielded intermediate **24** [30]. Taking advantage from the presence of the malonic moiety, treatment of the compound **24** with a 1 M sodium bis(trimethylsilyl)amide solution in THF followed by addition of E-4-bromo-crotonanilide allowed to prepare the open intermediate **25** which was submitted to the Heck-type cyclization reaction yielding the compound **26**. In this event, it is worth underlining that the Heck-type reaction on the iodine derivative **25** permitted shorter reaction times thus avoiding the formation of the endo double bond isomer. The final removal of the protecting groups in acid medium gave the carboxyl derivative **27**. This compound was then smoothly transformed into derivatives **28a**–**d** by simple activation of the carboxyl group and reaction with hydroxylamine, secondary or tertiary amines. The cyano derivative **28e** was obtained by treatment of the amido derivative **28b** with trifluoroacetic anhydride and pyridine in THF. The phenylsulfonylaminocarbonyl derivative **28f**, was prepared starting from the compound **26**. Thus, after deprotection of the *t*-butyl ester with formic acid and activation of the acid function, compound **29** was reacted with phenylsulfonylamine sodium salt to give the compound **30**; the latter was deprotected in acid medium to yield the desired derivative **28f**.

Finally, the synthesis of the C-3 benzoyl derivative is reported in the Scheme 4. Treatment of the malonic derivative **24** with a 1 M sodium bis(trimethylsilyl)amide solution in THF followed by addition of benzoyl chloride yielded the compound **31**. Deprotection of the



Scheme 2. [a] Reagents and conditions: (a) NaI, 4(MeO)PhCH$_2$Cl (PMBCl), DMF, 80 °C; (b) pyridine, CH_2Cl_2; (c) 1) ozone, −78 °C, 2) PPh_3; (d) PH_3 P=CHCOO*t*-Bu, toluene, reflux; (e) HCOOH; (f) 1-hydroxybenzotriazole, dicyclohexylcarbodiimide, aniline, DMF; (g) $Pd(PPh_3)_4$, DMF, TEA, 110 °C; (h) CF_3COOH, anisole, H_2SO_4, 80 °C; (i) $(CF_3SO_2)_2O$, TEA, THF, −78 °C; (j) CH_3SO_2Cl, TEA, THF, 0 °C.

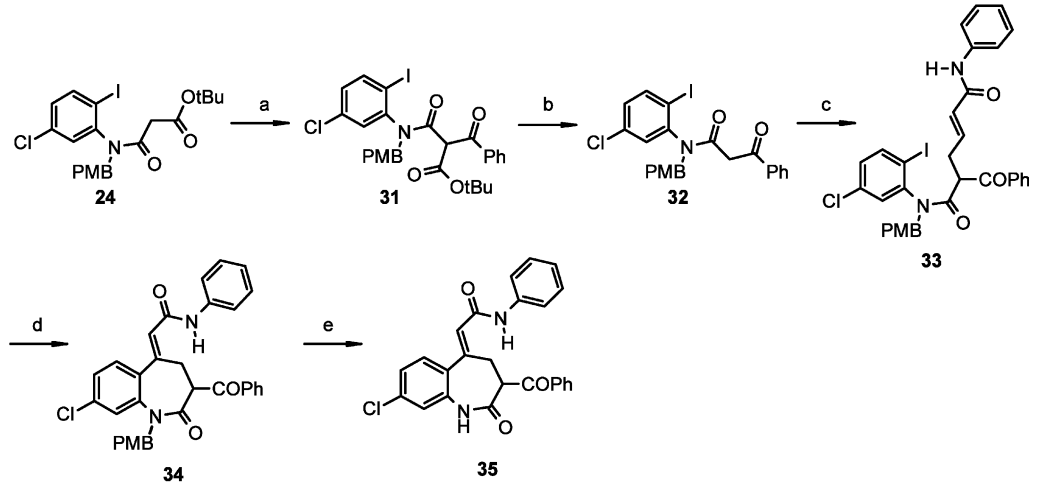


Scheme 3. [a] Reagents and conditions: (a) NaI, 4(MeO)PhCH$_2$Cl (PMBCl), DMF, 80 °C; (b) ClCOCH$_2$COOMe, pyridine, toluene, 0 °C; (c) LiOH, THF, H$_2$O; (d) 4-(dimethylamino)pyridine, 2-methyl-2-propanol, 1-[-3-(dimethylamino)propyl)]-3-ethylcarbodiimide HCl, CH$_2$Cl$_2$; (e) [(CH$_3$)$_3$Si]$_2$N-Na, BrCH$_2$CH=CHCONHPh, 0 °C; (f) Pd(PPh$_3$)$_4$, CH$_3$CN, TEA, reflux; (g) CF$_3$COOH, anisole, H$_2$SO$_4$, 80 °C; (h) 1-hydroxybenzotriazole, 1-[-3-(dimethylamino)propyl)]-3-ethylcarbodiimide HCl, (CH$_3$)$_3$CSiONH$_2$, TEA, CH$_3$CN; (i) 1-hydroxybenzotriazole, 1-[-3-(dimethylamino)propyl)]-3-ethylcarbodiimide HCl, (CH$_3$)$_3$SiNH$_2$, CH$_3$CN; (j) 1-hydroxybenzotriazole, 1-[-3-(dimethylamino)propyl)]-3-ethylcarbodiimide HCl, PhNH$_2$; (m) 1-hydroxybenzotriazole, 1-[-3-(dimethylamino)propyl)]-3-ethylcarbodiimide HCl, (CH$_3$)$_2$NH;(n) HCOOH;(o) carbonyldiimidazole, PhSO$_2$NHNa, DMF; (p) CF$_3$COOH, anisole, H$_2$SO$_4$, 80 °C; (CF$_3$CO)$_2$O, pyridine, THF.

t-butyl ester with trifluoroacetic acid afforded the acid derivative which easily decarboxylated in the reaction medium to yield the compound **32**. Sequential alkylation of the compound **32** with E-4-bromo-crotonanilide, Heck-type cyclization reaction and deprotection of the PMB function yielded the desired compound **35**.

3. Biology

The biological evaluation of the new chemical entities (NCEs) was performed according to the following screening cascade [20,31]: (a) binding assay to evaluate the affinity for the glycine site/functional activity; (b)



Scheme 4. [a] Reagents and conditions: (a) [(CH$_3$)$_3$Si]$_2$NNa, PhCOCl, THF, −78 °C to r.t.; (b) CF$_3$COOH; (c) [(CH$_3$)$_3$Si]$_2$NNa, BrCH$_2$CH=CHCONHPh, −78 to 0 °C; (d) Pd(PPh$_3$)$_4$, DMF, TEA, 110 °C; (e) CF$_3$COOH, anisole, H$_2$SO$_4$, 80 °C.

selectivity for the glutamate receptors (NMDA/AMPA/KA); (c) in vivo anticonvulsant activity in the NMDA induced convulsions model in CD-1 mice (i.v. and p.o.) to assess preliminary pharmacological profile; (d) in vivo evaluation of the neuroprotective activity in the middle cerebral artery occlusion (MCAo) model in male Sprague–Dawley rats as described by Tamura.

As far as the NMDA-induced convulsions model was concerned, to further increasing its throughput and based on the known anticonvulsant activity of the reference compound GV150526, all NCEs exhibiting suitable in vitro affinity (Ki < 100 nM) were tested iv at a single dose (0.1 mg/kg). Only compounds inhibiting 50% of convulsions, induced by the preemptive icv administration of the glycine binding site agonist NMDA, were fully characterized in terms of dose response curve to assess the ED_{50}. This model can be considered a surrogate of cerebral ischaemia in the animal that allow gathering rapid information on pharmacological/brain penetration profile of the NCEs in a very early phase of the screening cascade. Further, the evaluation of the ED_{50} was assessed only on the better compounds to rapidly obtain the selection the best compounds to eventually progress into the low throughput MCAo model in rats.

4. Results and discussion

The benzoazepine template [26], substituted at the C-5 position with the same α,β-unsaturated chain present in the indole series, was fitted on the known pharmacophore model of the glycine binding site built up in house [20]. As shown in Fig. 3, this template was superimposed to this model satisfying the observed pharmacophore arrangement. In particular, as far as the key carboxyl group present at the C-2 position of GV150526 was concerned, we argued that either the synergistic action of the C-2 carbonyl group with a suitable C-3 H-bond donor or a negatively charged substituent (R) could mimic the acid function. To test this hypothesis, the benzoazepine derivatives shown in Table 1 were characterized in vitro in terms of affinity to the glycine binding site. From the newly reported derivatives (Table 1) and from previously reported results [26], the following general comments can be addressed: (a) signs of activity were observed when an H-bond donor groups (R = OH and $NHSO_2CF_3$, entry **11** and **19b**, Ki = 1288 and 2692 nM, respectively) were introduced in this position; (b) a significant improvement in terms of in vitro affinity was observed with free carboxyl group confirming the working hypothesis (R = COOH, entry **27**, Ki = 32 nM); (c) notably, a comparable in vitro affinity to compound **27** was observed when the free acid was transformed into the corresponding hydroxamic acid (R = CONHOH, entry **28a**, Ki = 44 nM) or primary and secondary amides (R = $CONH_2$ and CONHPh, entry **28b** and **28c**, Ki = 39 and 72 nM, respectively). Moreover, the corresponding tertiary dimethylamide derivative [R = $CON(CH_3)_2$, entry **28d**, Ki = 2239] was significantly less active with respect to both the amides **28b** and **28c**, suggesting that the negatively charged carboxylate could be replaced by an amide group able to act as H-bond donor; (d) a significant decrease of affinity with respect to compound **27** was observed for alternative electron withdrawing substituents able to act as H-bond acceptors (R = COPh, CN, entry **35** and **28e**, Ki = 20893 and 339, respectively), further strengthening the previous hypothesis.

In summary, the presence at the position C-3 of a carboxylic group, negatively charged at physiological pH, (H-bond acceptor effect or coulombic interaction) or, conversely, of a primary and secondary amide (H-bond donor effect), seems to be crucial to maximize the in vitro affinity to the glycine binding site. This opposite electronic effect observed for the COOH and the CONHR groups, was difficult to explain based on the results available to date. However, it seems reasonable to hypothesize that the binding of both substituents could be mediated by H_2O, responsible for a 'bridging' effect between the molecule and the receptor pocket.

In contrast to the indole-2-carboxylates analogues of GV150526 [20], where the transformation of the carboxylic function into the amido function resulted in a loss of affinity (Ki = 3 nM and $> 10^5$, for R = COOH and $CONH_2$, respectively), the benzazepine derivative **27** and **28b** (R = COOH and $CONH_2$) show comparable in vitro activity. As a result, a different positioning of the indole and the benzazepine template within the glycine binding site pocket could be hypothesized.

5. Pharmacological characterization

The most in vitro potent benzazepine derivatives (Ki < 100 nM) were tested in the NMDA-induced convulsions in mice by i.v. route. The research complied with national legislation and with company policy on the Care and Use of Animals and with related codes of practice.

As shown in Table 1, all the compounds selected, (entry **27**, **28a**, **28b** and **28c**) exhibited good in vivo activity (greater than 30% inhibition of convulsion induced by the icv injection of NMDA). When the most potent compound of this series, the free carboxyl derivative **27**, was tested in the range of doses between 0.001 and 3 mg/kg, a dose-dependent inhibition of convulsions was observed reaching 80% of inhibition at 3 mg/kg, i.v. (ED_{50} by = 0.07 mg/kg). As previously reported [26], compound **27** was further progressed throughout the screening cascade assessing in vitro

both the degree of non-competitive antagonism and the glutamate receptor selectivity.

In vitro, this compound exhibited more than 1000-fold receptor selectivity for the strychnine-insensitive glycine binding site with respect to other glutamate binding sites ($Ki > 10^5$ for the NMDA, AMPA and kainate binding site, respectively). Moreover, by inhibition studies of the binding of [^{3}H]TCP in extensively washed cortical membranes preparation, this compound was confirmed to be a non-competitive antagonist acting at the glycine binding site with an estimated pA_2 of 6.4.

In the permanent MCAo model in rats, a significant neuroprotective effect was observed after both pre- and post-ischaemia administration. In the pre-ischaemia protocol (compound administered 5 min prior occlusion), as shown in Table 2, compound **27**, show a dose-dependent neuroprotective effect in the range between 0.1 and 3 mg/kg, i.v., with a maximal protection of 66% observed at 3 mg/kg ($ED_{50} = 0.6$ mg/kg). Post-ischaemia, a significant neuroprotective effect was seen at 2.5 mg/kg dose, when compound **27** was given as a single bolus, up to 6 h from occlusion. In these conditions a significant reduction of the volume of brain infarct (41%) was observed with respect to the control animals.

6. Conclusions

A class of glycine antagonists was designed by receptor mapping studies based on the pharmacophore model of the glycine binding site. A number of new derivatives were produced and new synthetic pathways designed. Notably, the in vitro affinity of this class of compounds was optimized by suitable modulation of the C-3 position. In particular, it was observed that the presence of an H-bond donor and/or a charged group in the position C-3, was found to be crucial to maximize the binding of the benzazepine template to the glycine site, gathering additional information on the glycine binding site associated to the NMDA receptor. Among the different compounds prepared, the free carboxyl derivative **27** confirmed [26] its outstanding neuroprotective profile when given both pre- and post-ischaemia in the MCAo model in rats. Notably, post-ischaemia, it was found to be still effective when its administration was delayed up to 6 h after the occlusion of the middle cerebral artery.

Therefore, as GV150526, compound **27** was able to block the progression of the cerebral damage even at delayed times from occlusion.

Table 2
Pharmacological profile of **27**

		27	GV150526
MCAo model			
Pre-ischaemia	ED_{50}	0.6 mg/kg	0.8 mg/kg
Post-ischaemia		2.5 mg/kg [a]	3 mg/kg [a]

[a] Single full protective dose given 6 h after occulsion. i.v. administration.

7. Experimental

7.1. Chemistry

In the preparations and examples, unless otherwise stated: melting points (m.p.) were determined on a Büchi melting point apparatus and are uncorrected. All temperatures refer to °C. Infrared spectra were measured on a Bruker IFS 48 (FT) spectrometer in chloroform-*d1* solutions or in Nujol mull. Proton magnetic resonance (^{1}H NMR) spectra were recorded either on a Varian PFG JNOVA 400 operating at 400 MHz or on a Varian VXRS 5000 operating at 300 MHz. Chemical shifts are expressed as δ units (part per million) downfield from Me_4Si and are assigned as singlets (s), doublets (d), doublet of doublets (dd), or multiplets (m). Mass spectra were recorded on a VG-4 triple quadrupole Fisons instrument. Elemental analyses (C, H, N) were performed by our analytical group on a CHNS-O EA-1108 Elemental Analyser and were within ± 0.4% of the theoretical values. TLC refers to the thin-layer chromatography on silica gel plates using Merck silica gel 60, F_{254} plates. Column chromatography was carried out over silica gel 60 (230–400 mesh, G60 Merck). Reagents were used as received unless otherwise stated.

7.2. 2-Bromo-5-chloro-aniline (*1*)

Iron powder (0.944 g, 16.9 mmol) was added to a solution of 2-bromo-5-chloronitrobenzene (1.5 g, 4.22 mmol) in AcOH/EtOH (14/14 ml) and the reaction mixture was heated at 100 °C for 1 h. Then, a saturated solution of $NaHCO_3$ was added and the resulting mixture was extracted with EtOAc. The organic phase was washed with brine, dried and evaporated under reduced pressure. The oil residue was purified by flash chromatography (eluant cyclohexane/EtOAc 8:2), yielding compound **1** as a brown oil (1.24 g, 97%): ^{1}H NMR δ ($CDCl_3$): 7.30 (d, 1H); 6.75 (d, 1H); 6.59 (dd, 1H); 4.14 (bs, 2H); IR ($CDCl_3$) $\nu_{max.}$ (cm^{-1}): 3493 and 3396 (NH_2); MS (EI/positive): *m/z* 205 [*M*; 1Br]$^+$. *Anal.* (C_6H_5BrClN) C, H, N.

7.3. α-(Diphenyl-tert-butylsilyloxy)-butyrolactone (*2*)

To a solution of α-hydroxy-butyrolactone (0.8 g, 7.84 mmol) in DMF (30 ml) were added diphenyl-*tert*-

butyldiphenylchlorosilane (4.07 ml, 15.9 mmol) and *N*,*N*-dimethylaminopyridine (0.095 g). The reaction mixture was stirred at room temperature (r.t.) for 12 h, then diluted with brine and extracted with EtOAc. The organic phase was collected and washed with brine, dried and evaporated under reduced pressure. The crude residue was purified by flash chromatography (eluant cyclohexane/EtOAc 95:5) to give compound **2** as colourless oil (2 g, 75%): ^{1}H NMR δ (DMSO-d_6): 7.80 (dd, 2H); 7.69 (dd, 2H); 7.5–7.35 (m, 6H); 4.36 (dd, 1H); 4.31 (m, 1H); 4.01 (ddd, 1H); 2.32–2.12 (m, 2H); 1.10 (s, 9H); IR (Nujol) $\nu_{max.}$ (cm^{-1}): 1790 (C=O); MS (FAB/NBA): *m*/*z* 283 $[M-t\text{Bu}]^+$; 340 $[M+\text{H}]$ defective. *Anal.* ($C_{20}H_{24}O_3Si$) C, H.

7.4. N-(2-Bromo-5-chlorophenyl)-2-(diphenyl-tert-butylsilyloxy)-4-hydroxy-butyramide (3)

To a solution of intermediate **1** (25 g, 12.1 mmol) in CH_2Cl_2 (80 ml) was added dropwise a 1 M solution of Et_2AlCl (18 ml, 18 mmol) in hexane. After 30 min, the reaction mixture was cooled to 0 °C and a solution of intermediate **2** (4.5 g, 13.3 mmol) in CH_2Cl_2 (40 ml) was carefully added. The resulting solution was stirred at r.t. for 3 h, then diluted with brine and extracted with EtOAc. The organic phase was washed with a 1 N solution of HCl, dried and evaporated under reduced pressure. The crude residue was purified by flash chromatography (eluant cyclohexane/EtOAc 8:2) to give compound **3** as white solid (2.6 g, 40%): m.p. 163–165 °C; ^{1}H NMR δ ($CDCl_3$): 9.24 (bs, 1H); 8.44 (d, 1H); 7.71 (dd, 2H); 7.63 (dd, 2H); 7.52–7.32 (m, 7H); 7.00 (dd, 1H); 4.47 (dd, 1H); 3.6 (m, 2H); 1.96 (dd, 1H); 2.00–1.85 (m, 1H); 1.85–1.7 (m, 1H); 1.2 (s, 9H); IR ($CDCl_3$) $\nu_{max.}$ (cm^{-1}): 1691 (C=O); MS (FAB/NBA): *m*/*z* 456 $[M+\text{H}]^+$. Anal. ($C_{26}H_{29}BrClNO_3Si$) C, H, N.

7.5. N-(2-Bromo-5-chlorophenyl)-2-(diphenyl-tert-butylsilyloxy)-4-(dimethyl-tert-butylsilyloxy)-butyramide (4)

To a solution of intermediate **3** (2.6 g, 4.76 mmol) in DMF (47 ml) were added *tert*-butyldimethylsilylchloride (1.43 g, 9.5 mmol), imidazole (3.24 g, 47.6 mmol) and a catalytic amount of dimethylaminopyridine (0.058 g, 0.47 mmol). The reaction mixture was stirred at r.t. for 12 h, then diluted with brine and extracted with EtOAc. The organic phase was washed with brine, dried and evaporated under reduced pressure. The crude residue was purified by flash chromatography (eluant cyclohexane/EtOAc 9:1) to give compound **4** as colourless oil (3.36 g, 99%): ^{1}H NMR δ ($CDCl_3$): 9.13 (s, 1H); 8.50 (d, 1H); 7.70 (m, 2H); 7.61 (m, 2H); 7.5–7.3 (m, 7H); 6.95 (dd, 1H); 4.45 (dd, 1H); 3.72 (m, 1H); 3.58 (m, 1H); 2.00 (m, 1H); 1.62–1.52 (m, 1H); 1.17 (s, 9H); 0.76 (s, 9H); 0.098 (s, 3H); −0.1 (s, 3H); IR (Nujol) $\nu_{max.}$ (cm^{-1}): 3366 (NH), 1705 (C=O); MS (FAB/NBA): *m*/*z* 662 $[M+\text{H}]^+$. *Anal*. ($C_{32}H_{43}BrClNO_3Si_2$) C, H, N.

7.6. N-(2-Bromo-5-chlorophenyl)-N-(4-methoxybenzyl)-2-(diphenyl-tert-butylsilyloxy)-4-(dimethyl-tert-butylsilyloxy)-butyramide (5)

To a solution of intermediate **4** (0.5 g, 0.76 mmol) in DMF (20 ml) was added NaH 60% (0.04 g, 1.0 mmol) and the reaction mixture was stirred at r.t. for 30 min. Then, 4-methoxybenzyl chloride (0.16 g, 1 mmol) and sodium iodide (0.12 g, 0.83 mmol) were added. The reaction mixture was heated at 80 °C for 2 h, then diluted with water and extracted with EtOAc. The organic phase was washed with brine, dried and evaporated under reduced pressure. The crude residue was purified by flash chromatography (eluant cyclohexane/EtOAc 8:2) to give compound **5** as colourless oil (0.3 g, 51%): ^{1}H NMR δ ($CDCl_3$): 7.63 (dd, 2H); 7.54 (dd, 2H); 7.40 (d, 1H); 7.4–7.23 (m, 6H); 7.00 (dd, 1H); 6.87 (d, 2H); 6.71 (d, 2H); 5.68 (d, 1H); 5.25 (d, 1H); 4.1 (dd, 1H); 4.00 (d, 1H); 3.79 (s, 3H); 3.62–3.48 (m, 2H); 1.84 (m, 2H); 1.03 (s, 9H); 0.76 (s, 9H); −0.098 (s, 3H); −0.1 (s, 3H); IR ($CDCl_3$) $\nu_{max.}$ (cm^{-1}): 1674 (C=O); MS (FAB/NBA): *m*/*z* 780 $[M+\text{H}]^+$. *Anal.* ($C_{40}H_{51}BrClNO_4Si_2$) C, H, N.

7.7. N-(2-Bromo-5-chlorophenyl)-2-(diphenyl-tert-butylsilyloxy)-4-hydroxy-N-(4-methoxybenzyl)-butyramide (6)

To a solution of intermediate **5** (1.9 g, 2.43 mmol) in MeOH (50 ml) was added *p*-toluensolphonic acid (0.278 g, 1.46 mmol) and the reaction mixture was stirred at r.t. for 1 h. The reaction mixture was poured into a buffered phosphate solution pH 7, the organic phase was extracted with EtOAc, dried and evaporated under reduced pressure. The crude residue was purified by flash chromatography (eluant cyclohexane/EtOAc 8:2) to give compound **6** as white foam (1.17 g, 72%): ^{1}H NMR δ ($CDCl_3$): 7.58 (m, 2H); 7.53 (m, 2H); 7.42 (d, 1H); 7.38 (m, 2H); 7.3–7.2 (m, 4H); 7.03 (dd, 1H); 7.01 (m, 2H); 6.79 (m, 2H); 5.57 (d, 1H); 5.37 (d, 1H); 4.08 (t, 1H); 4.00 (d, 1H); 3.82 (s, 3H); 3.80 (m, 1H); 3.64 (m, 1H); 2.12 (t, 1H); 1.75 (m, 2H); 1.07–1.06 (2s, 9H); MS (FAB/NBA): *m*/*z* 666 $[M+\text{H}]^+$. *Anal*. ($C_{34}H_{37}BrClNO_4Si$) C, H, N.

7.8. N-(2-Bromo-5-chlorophenyl)-2-(diphenyl-tert-butylsilyloxy)-N-(4-methoxybenzyl)-4-oxo-butyramide (7)

At −78 °C, oxalylchloride (0.19 ml, 2.25 mmol) was added to a solution of DMSO (0.32 ml, 4.5 mmol) in CH_2Cl_2 (20 ml) and the solution was stirred at the same temperature for 20 min. Then a solution of intermediate

6 (0.6 g, 0.9 mmol) in CH_2Cl_2 (15 ml) and TEA (0.62 ml, 4.5 mmol) were added and the solution was warmed to −20 °C. After 30 min a 3 N solution of HCl (20 ml) was added. The organic phase was extracted with CH_2Cl_2, dried and evaporated under reduced pressure. The crude residue was purified by flash chromatography (eluant cyclohexane/EtOAc 8:2) to give compound **7** as colourless oil (0.45 g, 75%): ^{1}H NMR δ ($CDCl_3$): 9.77 (m, 1H); 7.58 (d, 2H); 7.45 (d, 2H); 7.42–7.2 (m, 7H); 7.02 (dd, 1H); 7.00 (m, 2H); 6.78 (d, 2H); 5.71 (d, 1H); 5.19 (d, 1H); 4.25 (t, 1H); 4.11 (d, 1H); 3.81 (s, 3H); 2.67 (ddd, 1H); 2.52 (ddd, 1H); 1.003 (s, 9H); MS (FAB/NBA): *m/z* 664 $[M+H]^+$. *Anal*. ($C_{34}H_{35}BrClNO_4Si$) C, H, N.

*7.9. 6-[(2-Bromo-5-chlorophenyl)-(4-methoxybenzyl)-carbamoyl)-5-(diphenyl-tert-butylsilyloxy)-(E)-hex-2-enoic acid ethyl ester (**8**)*

To a solution of intermediate **7** (0.4 g, 0.6 mmol) in toluene (20 ml) was added (ethoxycarbonylmethylen)-triphenylphosphorane (0.21 g, 0.6 mmol). The reaction mixture was heated at 70 °C for 2 h, then the solvent was evaporated and the crude residue was purified by flash chromatography (eluant cyclohexane/EtOAc 9:1) to afford compound **8** as colourless oil (0.35 g, 80%): ^{1}H NMR δ ($CDCl_3$): 7.55 (dd, 2H); 7.45 (dd, 2H); 7.4–7.2 (m, 7H); 7.03 (dd); 7.00 (d, 2H); 6.77 (d, 2H); 6.67 (dt, 1H); 5.71 (d, 1H); 5.70 (d, 1H); 5.23 (d, 1H); 4.15 (q, 2H); 4.07 (d, 1H); 3.87 (m, 1H); 3.81 (s, 3H); 2.56 (m, 2H); 1.28 (t, 3H); 1.02 (s, 9H); MS (FAB/NBA): *m/z* 734 $[M+H]^+$. *Anal*. ($C_{38}H_{41}BrClNO_5Si$) C, H, N.

*7.10. (E)-Hex-2-enedioic acid, 6-[(2-bromo-5-chlorophenyl)-(4-methoxybenzyl)-amide]-5 (diphenyl-tert-butylsilyloxy)-1-phenylamide (**9**)*

To a solution of aniline (0.22 ml, 2.44 mmol) in CH_2Cl_2 (10 ml) was added Et_2AlCl (1 M solution in hexane, 3.67 ml, 3.67 mmol). The reaction mixture was stirred at r.t. for 30 min, then a solution of intermediate **8** (0.9 g, 1.22 mmol) in toluene (20 ml) was added and the resulting solution was heated at 80 °C for 1 h. A 1 M solution of HCl (20 ml) was added and the mixture was extracted with CH_2Cl_2; the organic phase was washed with brine, dried and evaporated under reduced pressure. The crude material was purified by flash chromatography (eluant cyclohexane/EtOAc 8:2) to give compound **9** as colourless oil (0.744 g, 78%): ^{1}H NMR δ ($CDCl_3$): 7.6–7.06 (m, 18H); 7.03 (d, 2H); 6.79 (d, 2H); 6.53 (m, 1H); 5.83 (d, 1H); 5.79 (d, 1H); 5.30 (d, 1H); 4.06 (d, 1H); 3.92 (t, 1H); 3.81 (s, 3H); 2.56 (m, 2H); 1.02 (s, 9H); IR ($CDCl_3$) $\nu_{max.}$ (cm^{-1}): 1678 and 1603 (C=O); MS (FAB/NBA): *m/z* 781 $[M+H]^+$. *Anal*. ($C_{42}H_{42}BrClN_2O_4Si$) C, H, N.

*7.11. 2-[8-Chloro-(4-methoxybenzyl)-2-oxo-3-(diphenyl-tert-butylsilyloxy)-1,2,3,4-tetrahydro-benzo-[b]-azepin-5-ylidene)]-N-phenyl-acetamide (**10a**)*

To a suspension of intermediate **9** (0.25 g, 3.02 mmol) in MeCN (90 ml) was added TEA (0.84 ml, 6.04 mmol) and $Pd(PPh_3)_4$ (0.17 g, 0.15 mmol). The reaction mixture was heated at reflux for 24 h, then poured into saturated solution of ammonium chloride and extracted with EtOAc. The organic phase was washed with brine, dried and evaporated under reduced pressure. The crude material was purified by flash chromatography (eluant cyclohexane/EtOAc 7:3) to obtain compound **10a** as white foam (0.52 g, 77%): ^{1}H NMR δ ($CDCl_3$): 7.6–7.57 (m, 4H); 7.55–7.3 (m, 10H); 7.21 (d, 1H); 7.16–7.1 (m, 1H); 7.07 (d, 2H); 6.97 (d, 2H); 6.78 (d, 1H); 6.73 (d, 2H); 6.69 (d, 2H); 6.62 (bs, 1H); 5.44–5.40 (d, 1H); 5.05 (d, 1H); 4.91 (d, 1H); 4.56 (dd, 1H); 4.30 (dd, 1H); 4.22–4.02 (m, 3H); 3.89 (d, 1H); 3.69–3.66 (s, 3H); 2.95 (tt, 1H); 2.74 (tt, 1H); 1.10/0.82 (s, 9H); IR ($CDCl_3$) $\nu_{max.}$ (cm^{-1}): 1682 (C=O); MS (FAB/NBA): *m/z* 700 $[M+H]^+$. *Anal*. ($C_{42}H_{41}ClN_2O_4Si$) C, H, N.

The endo isomer **10b** was also isolated as white foam (0.087 g, 13%).^{1}H NMR δ ($CDCl_3$): 7.69 (m, 3H); 7.6 (d, 2H); 7.44–7.12 (m, 12H); 7.06 (dd, 1H); 7.00 (d, 1H); 6.84 (d, 2H); 6.65 (d, 2H); 6.21 (d, 1H); 4.82 (m, 2H); 4.32 (d, 1H); 3.69 (s, 3H); 3.52 (d, 1H); 3.34 (d, 1H); 1.13 (s, 9H); IR (Nujol) $\nu_{max.}$ (cm^{-1}): 1691 and 1664 (C=O); MS (FAB/NBA): *m/z* 700 $[M+H]^+$. *Anal*. ($C_{42}H_{41}ClN_2O_4Si$) C, H, N.

*7.12. 2-[6-Chloro-2-oxo-3-hydroxy-1,2,3,4-tetrahydro-benzo-[b]-azepin-5-ylidene)]-N-phenyl-acetamide (**11**)*

To a solution of intermediate **10a** (0.1 g, 0.22 mmol) in CF_3COOH (8.6 ml) were added anisole (234 μl) and 12 N H_2SO_4 (359 μl). The reaction mixture was heated at 80 °C for 1 h, then poured into crushed ice. Saturated solution of $NaHCO_3$ was added until pH 7 and the resulting solution was extracted with EtOAc, washed with brine, dried and evaporated under reduced pressure. The crude residue was purified by flash chromatography (eluant cyclohexane/EtOAc) to obtain compound **11** as white solid (0.05 g, 67%): m.p. 243–245 °C; ^{1}H NMR δ (acetone-d_6): 9.33 (bs, 2H); 7.72 (d, 2H); 7.44 (d, 1H); 7.34–7.23 (m, 3H); 7.22 (d, 1H); 7.06 (t, 1H); 6.1 (dd, 1H); 4.45 (m, 1H); 3.98 (d, 1H); 3.79 (ddd, 1H); 3.60 (ddd, 1H); IR (Nujol) $\nu_{max.}$ (cm^{-1}): 3441–3198 (NH), 1670 and 1661 (C=O); MS (FAB/NBA): *m/z* 343 $[M+H]^+$. *Anal*. ($C_{18}H_{15}ClN_2O_3$) C, H, N.

*7.13. N-(4-Methoxy-benzyl)-2-bromo-5-chloro aniline (**12**)*

To a solution of intermediate **1** (2 g, 9.7 mmol) in DMF (35 ml) were added 4-methoxybenzylchloride (1.45 ml, 10.68 mmol) and NaI (1.6 g, 10.68 mmol). The reaction mixture was heated at 80 °C for 2 h, then diluted with water and extracted with EtOAc. The organic phase was washed with brine, dried and evaporated under reduced pressure. The crude residue was purified by flash chromatography (eluant petroleum/Et_2O 98:2) to give compound **12** as yellow oil (2.2 g, 70%): m.p. 67–69 °C; ^1H NMR δ ($CDCl_3$): 7.32 (d, 1H); 7.28 (d, 2H); 6.90 (d, 2H); 6.60 (d, 1H); 6.55 (dd, 1H); 4.69 (t, 1H); 4.29 (d, 2H); 3.82 (s, 3H); IR (Nujol) $\nu_{max.}$ (cm^{-1}): 3408 (NH); MS (EI/positive): *m/z* 325 [*M*, 1Br]$^+$. *Anal*. ($C_{14}H_{13}BrClNO$) C, H, N.

*7.14. {1-[(2-Bromo-5-chloro-phenyl)-(4-methoxy-benzyl)-carbamoyl]-but-3-enyl}-carbamic acid benzyl ester (**13**)*

To a solution of *N*-benzyloxycarbonyl-allylglycyl chloride (1.85 g, 6.9 mmol) in CH_2Cl_2, cooled to −40 °C, were added a solution of intermediate **12** (1.5 g, 4.6 mmol) in THF (25 ml) and Py (560 μl, 6.9 mmol). The reaction mixture was slowly warmed to r.t. and stirred for 12 h, then diluted with a saturated solution of $NaHCO_3$ and extracted with EtOAc. The organic phase was washed with brine, dried and evaporated under reduced pressure. The crude residue was purified by flash chromatography (eluant cyclohexane/EtOAc 80:20) to give compound **13** as white foam (2 g, 78%): ^1H NMR δ (acetone-d_6): 7.8 (d, 1H); 7.4–7.3 (m, 6H); 7.18 (m, 2H); 6.85 (d, 1H); 6.61 (d, 1H); 5.76–5.60 (m, 1H); 5.55 (d, 1H); 5.6–4.94 (m, 4H); 4.20 (d, 1H); 4.16 (m, 1H); 3.77 (s, 3H); 2.48 (m, 1H); 2.32 (m, 1H); IR ($CDCl_3$) $\nu_{max.}$ (cm^{-1}): 1682 (C=O); MS (FAB/NBA): *m/z* 557 [*M*+H]$^+$. *Anal*. ($C_{27}H_{26}BrClN_2O_4$) C, H, N.

*7.15. {1-[(2-Bromo-5-chloro-phenyl)-(4-methoxy-benzyl)-carbamoyl]-3-oxo-propyl}-carbamic acid benzyl ester (**14**)*

Ozone was bubbled through a cooled (−78 °C) solution of intermediate **12** (2 g, 3.6 mmol) in CH_2Cl_2 (40 ml) until a pale blue color appeared (approximately 30 min). Then, PPh_3 (1.4 g, 5.4 mmol) was added and the reaction mixture stirred at r.t. for 2 h. The solvent was evaporated under reduced pressure and the crude residue was purified by flash chromatography (eluant cyclohexane/EtOAc 80:20) to give compound **14** as white foam (1.5 g, 74%): ^1H NMR δ ($CDCl_3$): 9.71 (s, 1H); 7.8 (d, 1H); 7.45–7.3 (m, 6H); 7.22–7.1 (m, 2H); 6.94 (d, 1H); 6.9 (d, 1H); 5.53 (d, 1H); 4.9 (m, 2H); 4.74 (m, 1H); 4.15 (d, 1H); 3.79 (s, 3H); 3.13 (dd, 1H); 2.69 (m, 1H); MS (FAB/NBA): *m/z* 559 [*M*+H]$^+$. *Anal*. ($C_{26}H_{24}BrClN_2O_5$) C, H, N.

*7.16. (E)-5-Benzyloxycarbonylamino-5-[(2-bromo-5-chloro-phenyl)-(4-methoxy-benzyl)-carbamoyl]-pent-2-enoic acid tert-butyl ester (**15**)*

To a solution of intermediate **14** (1.4 g, 2.5 mmol) in toluene (25 ml) was added (*tert*-butoxycarbonyl methylene)-triphenyl phosphorane (1.035 g, 2.75 mmol) and the reaction mixture was heated at reflux for 2 h. The solvent was evaporated under reduced pressure and the crude residue was purified by flash chromatography (eluant cyclohexane/EtOAc 80:20) to give the title compound **15** as pale yellow oil (1.5 g, 92%); ^1H NMR δ (acetone-d_6): 7.8 (d, 1H); 7.4–7.28 (m, 6H); 7.14 (m, 2H); 6.80 (m, 3H); 6.68 (m, 1H); 5.75 (dt, 1H); 5.51 (d, 1H); 5.03 (s, 2H); 4.3–4.1 (m, 2H); 3.77 (s, 3H); 2.66 (m, 1H); 2.53 (m, 1H); 1.45 (s, 9H); MS (FAB/NBA): *m/z* 657 [*M*+H]$^+$. *Anal*. ($C_{32}H_{34}BrClN_2O_6$) C, H, N.

*7.17. (E)-{1-[(2-Bromo-5-chloro-phenyl)-(4-methoxy-benzyl)-carbamoyl]-4-phenylcarbamoyl-but-3-enyl}-carbamic acid benzyl ester (**16**)*

To a solution of intermediate **15** (1.5 g, 2.3 mmol) was added HCOOH (16 ml) and the reaction mixture stirred at r.t. for 2 h. The solvent was evaporated under reduced pressure and the crude residue was diluted with CH_2Cl_2, washed with brine, dried and evaporated under reduced pressure. The crude residue (1.3 g, 2.1 mmol) was dissolved in DMF (20 ml), then 1-hydroxybenzotriazole (0.315 g, 2.6 mmol), dicyclohexylcarbodiimide (0.54 g, 2.6 mmol) and aniline (0.236 ml, 2.6 mmol) were added. The reaction mixture was stirred at r.t. for 12 h then diluted with EtOAc, washed with a 1 N solution of HCl dried and evaporated under reduced pressure. The crude compound was triturated with Et_2O/petroleum (8/8 ml) to give compound **16** as white solid (1.13 g, 80%): ^1H NMR δ (acetone-d_6): 9.22 (s, 1H); 7.8–7.6 (m, 3H); 7.40–7.0 (m, 12H); 6.84–6.7 (m, 4H); 6.13 (d, 1H); 5.53 (d, 1H); 5.03 (s, 2H); 4.15 (m, 2H); 3.76 (s, 3H); 2.8–2.4 (m, 2H); IR (Nujol) $\nu_{max.}$ (cm^{-1}): 3323 (NH), 1720 and1661 (C=O); MS (FAB/NBA): *m/z* 676 [*M*+H]$^+$. *Anal*. ($C_{34}H_{31}BrClN_3O_5$) C, H, N.

*7.18. (E)-[8-Chloro-1-(4-methoxy-benzyl)-2-oxo-5-phenylcarbamoylmethylene-2,3,4,5-tetrahydro-1H-benzo[b]azepin-3-yl]-carbamic acid benzyl ester (**17**)*

To a solution of intermediate **16** (1.1 g, 1.6 mmol) in DMF (15 ml) were added $Pd(PPh_3)_4$ (0.093 g, 0.08 mmol) and TEA (0.45 ml, 3.2 mmol). The reaction mixture was heated at 110 °C for 2 h, then diluted with

brine and extracted with EtOAc. The organic layer was dried, evaporated and the crude residue was purified by flash chromatography (eluant cyclohexane/EtOAc 80:20) to give compound **17** as white solid (0.57 g, 60%): ^{1}H NMR δ (acetone-d_6): 9.21 (s, 1H); 7.73 (d, 2H); 7.57 (d, 1H); 7.4–7.2 (m, 9H); 7.09 (d, 2H); 7.08 (t, 1H); 6.74 (d, 2H); 6.67 (d, 1H); 5.83 (dd, 1H); 5.48 (d, 1H); 5.08 (s, 2H); 4.6 (d, 1H); 4.60 (m, 1H); 4.11(dd, 1H); 3.66 (s, 3H); 3.30 (m, 1H); IR (Nujol) $\nu_{max.}$ (cm^{-1}): 3325 (NH), 1720 (C=O); MS (FAB/NBA): *m/z* 596 $[M+H]^+$. *Anal*. ($C_{34}H_{30}ClN_3O_5$) C, H, N.

*7.19. (E)-2-(3-Amino-8-chloro-2-oxo-1,2,3,4-tetrahydro-benzo[b]azepin-5-ylidene)-N-phenyl-acetamide (**18**)*

Compound **18** was prepared using the same methods as compound **11** and used without further purification: MS (FAB/NBA): *m/z* 342 $[M+H]^+$.

*7.20. (E)-2-(8-Chloro-3-methanesulfonylamino-2-oxo-1,2,3,4-tetrahydro-benzo[b]azepin-5-ylidene)-N-phenyl-acetamide (**19a**)*

To a solution of intermediate **18** (0.1 g, 0.29 mmol) in THF (10 ml) was added TEA (0.061 ml, 0.44 mmol) and the reaction mixture was cooled to −78 °C. Trifluoromethanesulphonic anhydride (0.137 ml, 0.29 mmol) was added and the mixture stirred for 1 h, then diluted with a saturated solution of NH_4Cl and extracted with EtOAc. The organic layer was washed with brine, dried and evaporated under reduced pressure. The crude residue was purified by flash chromatography (eluant cyclohexane/EtOAc 80:20) to give compound **19a** as white solid (0.103 g, 75%): m.p. 225–227 °C; ^{1}H NMR δ (acetone-d_6): 9.33 (s, 1H); 9.30 (s, 1H); 7.71 (d, 2H); 7.45 (d, 1H); 7.32 (m, 2H); 7.30 (dd, 1H), 7.22 (d, 1H); 7.07 (m, 1H); 6.43 (d, 1H); 6.13 (m, 1H); 4.49 (m, 1H); 4.04 (m, 1H); 3.57 (m, 1H); 2.93 (s, 3H); MS (FAB/NBA): *m/z* 420 $[M+H]^+$. *Anal*. ($C_{19}H_{18}ClN_3O_4S$) C, H, N.

*7.21. (E)-2-(8-Chloro-2-oxo-3-trifluoromethanesulfonylamino-1,2,3,4-tetrahydro-benzo[b]azepin-5-ylidene)-N-phenyl-acetamide (**19b**)*

To a solution of intermediate **18** (0.1 g, 0.29 mmol) in THF (10 ml) was added TEA (0.061 ml, 0.44 mmol) and the reaction mixture was cooled to 0 °C. CH_3SO_2Cl (0.025 ml, 0.319 mmol) was added and the mixture stirred for 1 h, then diluted with a saturated solution of NH_4Cl and extracted with EtOAc. The organic layer was washed with brine, dried and evaporated under reduced pressure. The crude residue was purified by flash chromatography (eluant cyclohexane/EtOAc 50:50) to give compound **19b** as white solid (0.06 g, 80%): m.p. 240–242 °C;^{1}H NMR δ (acetone-d_6): 9.40 (s, 2H); 8.52 (s, 1H); 7.8 (d, 1H); 7.74 (d, 2H); 7.50 (d, 1H); 7.37 (dd, 1H); 7.35 (t, 2H); 7.30 (d, 1H); 7.11 (t, 1H); 6.20 (t, 1H); 4.60 (dd, 1H); 4.26 (dd, 1H); 3.59 (m, 1H); MS (FAB/NBA): *m/z* 474 $[M+H]^+$. *Anal*. ($C_{19}H_{15}ClF_3N_3O_4S$) C, H, N.

*7.22. (5-Chloro-2-iodo-phenyl)-(4-methoxy-benzyl)-amine (**21**)*

Compound **21** was prepared using the same methods as compound **12** and obtained, after purification by flash column chromatography (eluant petroleum/Et_2O 98:2), as colourless oil (3.37 g, 66%): ^{1}H NMR δ ($CDCl_3$): 7.55 (1H, d); 7.27 (2H, d); 6.90 (2H, d); 6.52 (1H, d); 6.45 (1H, dd); 4.55 (1H, t); 4.28 (2H, d); 3.81 (3H, s); MS (FAB/NBA): *m/z* 373 $[M+H]^+$. *Anal*. ($C_{14}H_{13}ClINO$) C, H, N.

*7.23. N-(5-Chloro-2-iodo-phenyl)-N-(4-methoxy-benzyl)-malonamic acid methyl ester (**22**)*

To a solution of intermediate **21** (3.37 g, 8.61 mmol) in toluene (60 ml), cooled to 0 °C, were added Py (0.91 ml, 11.5 mmol) and methyl malonyl chloride (1.2 ml, 11.19 mmol). The solution was stirred at 0 °C for 45 min, then poured into brine and extracted with EtOAc. The organic phase was washed with 0.5 N solution of HCl, dried and evaporated under reduced pressure. The crude residue was purified by flash column chromatography (eluant cyclohexane/EtOAc 9:1–8:2) to afford compound **22** as colourless solid (4.0 g, 97%): ^{1}H NMR δ ($CDCl_3$): 7.84 (1H, d); 7.13 (2H, d); 7.06 (1H, dd); 6.82 (2H, d); 6.75 (1H, d); 5.52 (1H, d); 3.96 (1H, d); 3.79 (3H, s); 3.68 (3H, s); 3.18 (1H, d); 3.04 (1H, d); IR (Nujol): $\nu_{max.}$ (cm^{-1}): 1734 and 1664 (C=O); MS (FAB/Thiogly.): *m/z* 474 $[M+H]^+$. *Anal*. ($C_{18}H_{17}ClINO_4$) C, H, N.

*7.24. N-(5-Chloro-2-iodo-phenyl)-N-(4-methoxy-benzyl)-malonamic acid (**23**)*

To a solution of intermediate **22** (3.99 g, 8.42 mmol) in THF (85 ml) was added 1 M solution of LiOH in water (16.85 ml, 16.5 mmol). The reaction was stirred at r.t. for 18 h, then poured into a saturated solution of NH_4Cl and acidified to pH 2 with 2 M solution of HCl. The solution was extracted with EtOAc and the organic phase was washed with brine, dried and evaporated under reduced pressure, obtaining compound **23** as colourless solid (3.56 g, 92%): m.p. 132–133 °C; ^{1}H NMR δ ($CDCl_3$): 7.87 (1H, d); 7.14 (1H, dd), 7.09 (2H, d); 6.84 (2H, d); 6.69 (1H, d); 5.50 (1H, d); 4.03 (1H, d); 3.81 (3H, s); 3.02 (2H, s); IR (Nujol) $\nu_{max.}$ (cm^{-1}): 1738 (C=O); MS (EI/positive): *m/z* 459 $[M]^+$. *Anal*. ($C_{17}H_{15}ClINO_4$) C, H, N.

7.25. N-(5-Chloro-2-iodo-phenyl)-N-(4-methoxy-benzyl)-malonamic acid tert-butyl ester (**24**)

A solution of intermediate **23** (2.30 g, 5.00 mmol) in CH_2Cl_2 (75 ml) was cooled to 0 °C, then were added 4-(dimethylamino)pyridine (0.30 g, 2.45 mmol), 2-methyl-2-propanol (0.93 g, 12.54 mmol) and 1-[-3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (1.29 g, 6.72 mmol). The mixture was stirred for 15 min at 0 °C and then at r.t. for 1 h. The reaction mixture was diluted with EtOAc, washed with 5% solution of $NaHCO_3$ and brine, dried and concentrated. The crude residue was purified by flash column chromatography (eluant cyclohexane/EtOAc 9:1–8:2) obtaining compound **24** as colourless solid (1.67 g, 65%): m.p. 83–85 °C; ^{1}H NMR δ ($CDCl_3$): 7.84 (1H, d); 7.14 (2H, d); 7.05 (1H, dd); 6.82 (2H, d); 6.78 (1H, d); 5.57 (1H, d); 3.91 (1H, d); 3.79 (3H, s); 3.11 (1H, d); 2.94 (1H, d); 1.41 (9H, s); IR (Nujol) $\nu_{max.}$ (cm^{-1}): 1728 and 1645 (C=O); MS (FAB/NBA): *m/z* 516 $[M+H]^+$. *Anal*. ($C_{21}H_{23}ClINO_4$) C, H, N.

7.26. (E)-2-[(5-Chloro-2-iodo-phenyl)-(4-methoxy-benzyl)-carbamoyl]-5-phenylcarbamoyl-pent-4-enoic acid tert-butyl ester (**25**)

To a solution of intermediate **24** (0.26 g, 0.50 mmol) in THF (5 ml), cooled to −50 °C, was added a 1 M solution of $[(CH_3)_3Si]_2NNa$ in THF (0.62 ml, 0.62 mmol). The reaction mixture was stirred at 0 °C for 1 h, then a solution of the bromocrotonate derivative (0.12 g, 0.50 mmol) in THF (10 ml) was added dropwise. The reaction mixture was stirred at 0 °C for 1 h then the resulting solution was poured into brine and extracted with EtOAc. The organic phase was dried, evaporated and purified by flash column chromatography (eluant cyclohexane/EtOAc 9:1–7:3) affording compound **25** as colourless solid (0.27 g, 80%): m.p. 63–65 °C; ^{1}H NMR (acetone-d_6): 9.19 (1H, bs); 8.05 (1H, d); 7.69 (2H, d); 7.28 (2H, t); 7.25 (1H, dd); 7.21 (2H, d); 7.03 (1H, t); 6.88 (4H, m); 6.14 (1H, d); 5.60 (1H, d); 3.92 (1H, d); 3.78 (3H, s); 3.07 (1H, t); 2.80 (2H, m); 1.38 (9H, s); IR (Nujol) $\nu_{max.}$ (cm^{-1}): 1700, 1670 and 1643 (C=O); MS (FAB/NBA): *m/z* 675 $[M+H]^+$. *Anal*. ($C_{31}H_{32}ClIN_2O_5$) C, H, N.

7.27. (E)-8-Chloro-1-(4-methoxy-benzyl)-2-oxo-5-phenylcarbamoylmethylene-2,3,4,5-tetrahydro-1H-benzo[b]azepine-3-carboxylic acid tert-butyl ester (**26**)

Compound **26** was prepared using the same methods as compound **10a** (refluxing for 2 h) and obtained as white solid (0.77 g, 93%): m.p. 188–191 °C; ^{1}H NMR (DMSO-d_6/70 °C): 9.86 (1H, bs); 7.63 (2H, d); 7.48 (1H, bs); 7.35–7.30 (1H, m); 7.31 (2H, t); 7.22 (1H, d); 7.05 (1H, t); 7.03 (2H, d); 6.75 (2H, d); 5.86 (1H, s); 5.09 (1H, d); 4.82 (1H, d); 3.88 (1H, bs); 3.71 (1H, t); 3.64 (3H, s); 3.5 (1H, bs); 1.4 (9H, bs); IR (Nujol) $\nu_{max.}$ (cm^{-1}): 3290 and 3130 (NH); 1736 (C=O); MS (FAB/NBA): *m/z* 547 $[M+H]^+$. *Anal*. ($C_{31}H_{31}ClN_2O_5$) C, H, N.

7.28. (E)-8-Chloro-2-oxo-5-phenylcarbamoylmethylene-1,2,3,4-tetrahydro-1H-benzo[b]azepine 3-carboxylic acid (**27**)

Compound **27** was prepared using the same methods as compound **11** and obtained as white solid (0.03 g, 74%): ^{1}H NMR (DMSO-d_6): 12.59 (1H, bs); 10.16 (1H, s); 10.06 (1H, s); 7.65 (2H, d); 7.38 (1H, d); 7.32 (2H, t); 7.29 (1H, dd); 7.08 (1H, d); 7.07 (1H, t); 6.08 (1H, t); 3.87 (1H, m); 3.65 (1H, dd); 3.47 (1H, m); IR (Nujol) $\nu_{max.}$ (cm^{-1}): 3242 (NH), 1747, 1676 and 1651 (C=O); MS (FAB/Thiogly.): *m/z* 371 $[M+H]^+$. *Anal*. ($C_{19}H_{15}ClN_2O_4$) C, H, N.

7.29. General procedure for the synthesis of the compounds **28a–c**

To a suspension of compound **27** (1 equiv.) in MeCN were added 1-hydroxybenzotriazole (1.2 equiv.) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (1.5 equiv.) and the reaction mixture was stirred for 1 h. The desired amine (1.5 equiv.) was added, the reaction mixture was stirred for 2 h then extracted with EtOAc. The organic layer was washed saturated $NaHCO_3$, brine, dried and evaporated under reduced pressure. The crude residue was purified by flash chromatography (eluant cyclohexane/EtOAc) or by trituration to give the desired compounds.

7.30. (E)-8-Chloro-2-oxo-5-phenylcarbamoylmethylene-2,3,4,5-tetrahydro-1H-benzo[b]azepine-3-carboxylic acid hydroxyamide (**28a**)

Compound **28a** was prepared from **27** (0.13 g, 0.35 mmol) in MeCN (15 ml), then adding a solution of Et_3N (0.1 ml, 0.7 mmol) and *O*-(*tert*-butyldimethylsilyl)-hydroxylamine in MeCN (5 ml), according to the general procedure. Compound **28a** was isolated by trituration in CH_2Cl_2 as white solid (0.04 g, 30%). In the mother liquor was recovered the O-silylated compound (0.04 g), which can be deprotected using tetrabutylammonium fluoride and AcOH to yield compound **28a** (0.028 g, 90%): ^{1}H NMR (DMSO-d_6): 10.28 (1H, d); 10.12 (1H, s); 10.00 (1H, s); 8.86 (1H, d); 7.62 (2H, d); 7.38 (1H, d); 7.30 (2H, t); 7.07 (1H, d); 6.06 (1H, bs); 3.93 (1H, d); 3.5–3.3 (2H, m); MS (FAB/NBA): *m/z* 386 $[M+H]^+$. *Anal*. ($C_{19}H_{16}ClN_3O_4$) C, H, N.

*7.31. (E)-8-Chloro-2-oxo-5-phenylcarbamoylmethylene-2,3,4,5-tetrahydro-1H-benzo[b]azepine-3-carboxylic acid amide (**28b**)*

Compound **28b** was prepared from **27** (0.37 g, 1.0 mmol) in MeCN (40 ml), then adding $[(CH_3)_3Si]_2NH$, according to the general procedure. Compound **28b** was isolated by trituration in Et_2O as white solid (0.17 g, 46%): m.p. decomp.; ^1H NMR (DMSO-d_6): 10.10 (1H, s); 9.96 (1H, s); 7.63 (2H, d); 7.38 (1H, d); 7.32 (1H, bs); 7.30 (2H, t); 7.28 (1H, dd); 7.05 (1H, d); 7.04 (1H, t); 6.94 (1H, bs); 6.05 (1H, s); 3.91 (1H, dd); 3.54 (1H, dd); 3.3 (1H, m); IR (Nujol) $\nu_{max.}$ (cm^{-1}): 3200–3315 (NH + NH_2), 1690 and 1660 (C=O); MS (FAB/NBA): *m/z* 370 $[M+H]^+$. *Anal*. ($C_{19}H_{16}ClN_3O_3$) C, H, N.

*7.32. (E)-8-Chloro-2-oxo-5-phenylcarbamoylmethylene-2,3,4,5-tetrahydro-1H-benzo[b]azepine-3-carboxylic acid phenylamide (**28c**)*

Compound **28c** was prepared from **27** (0.03 g, 0.08 mmol) in MeCN (5 ml), then adding aniline, according to the general procedure. Compound **28c** was isolated by flash chromatography as white solid (0.018 g, 50%): m.p. 229–230 °C; ^1H NMR (DMSO-d_6): 10.12 (1H, s); 10.08 (1H, s); 9.90 (1H, s); 7.63 (2H, dd); 7.53 (2H, dd); 7.41 (1H, d); 7.35–7.25 (5H, m); 7.11 (1H, d); 7.06–7.00 (2H, tt); 6.08 (1H, t); 4.07 (1H, ddd); 3.81 (1H, dd); 3.35 (1H, ddd); IR (Nujol) $\nu_{max.}$ (cm^{-1}): 3319 (NH); 1691 and 1678 (C=O); MS (FAB/NBA): *m/z* 446 $[M+H]^+$. *Anal*. ($C_{25}H_{20}ClN_3O_3$) C, H, N.

*7.33. (E)-8-Chloro-2-oxo-5-phenylcarbamoylmethylene-2,3,4,5-tetrahydro-1H-benzo[b]azepine-3-carboxylic acid dimethylamide (**28d**)*

Compound **28d** was prepared from **27** (0.13 g, 0.35 mmol) in MeCN (15 ml), then adding a 2 M solution of $(CH_3)_2NH$ in THF, according to the general procedure. Compound **28d** was isolated by trituration in Et_2O as white solid (0.1 g, 70%): ^1H NMR (DMSO-d_6): 10.14 (1H, s); 10.13 (1H, s); 7.64 (2H, d); 7.40 (1H, d); 7.30 (3H, m); 7.11 (1H, d); 7.05 (1H, tt); 6.08 (1H, m); 4.04–3.93 (2H, m); 3.21 (1H, m); 2.81 (3H, s); 2.76 (3H, s); IR (Nujol) $\nu_{max.}$ (cm^{-1}): 3452, 3190 (NH), 1676 (C=O); MS (FAB/NBA): *m/z* 398 $[M+H]^+$. *Anal*. ($C_{21}H_{20}ClN_3O_3$) C, H, N.

*7.34. (E)-2-(8-Chloro-3-cyano-2-oxo-1,2,3,4-tetrahydro-benzo[b]azepin-5-ylidene)-N-phenyl-acetamide (**28e**)*

At 0 °C, trifluoroacetic anhydride (0.023 ml, 0.165 mmol) was added to a solution of compound **28b** (0.055 g, 0.15 mmol) and Py (0.024 ml, 0.30 mmol) in THF (5 ml). The solution was stirred for 1 h at r.t., then diluted with EtOAc, washed with a 1 N solution of HCl and brine, then dried and evaporated. The crude compound was purified by flash column chromatography (eluant cyclohexane/EtOAc 7:3) affording compound **28e** as white solid (0.09 g, 60%): ^1H NMR (DMSO-d_6): 9.40 (1H, bs); 9.32 (1H, bs); 7.72 (2H, d); 7.46 (1H, d); 7.36–7.30 (3H, m); 7.23 (1H, d); 7.08 (1H, tt); 6.19 (1H, dd); 4.41 (1H, dd); 4.31 (1H, ddd); 3.79 (1H, ddd); IR (Nujol) $\nu_{max.}$ (cm^{-1}): 3196–3111 (NH); 1686 (C=O); MS (FAB/Thiogly.): *m/z* 352 $[M+H]^+$. *Anal*. ($C_{19}H_{14}ClN_3O_2$) C, H, N.

*7.35. (E)-8-Chloro-1-(4-methoxy-benzyl)-2-oxo-5-phenylcarbamoylmethylene-2,3,4,5-tetrahydro-1H-benzo[b]azepine-3-carboxylic acid (**29**)*

A suspension of compound **26** (0.054 g, 0.1 mmol) in formic acid (1 ml) was stirred for 1 h, then the acid was evaporated and the crude material was triturated in Et_2O/petroleum (1.5/1.5 ml) to yield compound **29** as white solid (0.04 g, 82%): m.p. 225–227 °C; ^1H NMR (acetone-d_6): 11.50 (1H, bs); 9.20 (1H, bs); 7.74 (2H, d); 7.56 (1H, m); 7.32 (2H, m); 7.30 (1H, m); 7.24 (1H, d); 7.10 (2H, d); 7.08 (1H, t); 6.74 (2H, d); 5.83 (1H, s); 5.40 (1H, bm); 4.714 (1H, bm); 3.85 (1H, m); 3.40 (1H, m); IR (Nujol) $\nu_{max.}$ (cm^{-1}): 2730 (COOH), 1724 and 1643 (C=O); MS (FAB/NBA): *m/z* 491 $[M+H]^+$. *Anal*. ($C_{27}H_{23}ClN_2O_5$) C, H, N.

*7.36. (E)-2-[3-Benzenesulfonylaminocarbonyl-8-chloro-1-(4-methoxy-benzyl)-2-oxo-1,2,3,4-tetrahydro-benzo[b]azepin-5-ylidene]-N-phenyl-acetamide (**30**)*

To a solution of **29** (0.035 g, 0.07 mmol) in DMF (2 ml) was added carbonyldiimidazole (0.024 g, 0.15 mmol) and the reaction mixture was stirred at 70 °C for 1 h. The solution was cooled to 0 °C, then was added a suspension of phenylsulphonylamine sodium salt in DMF (prepared from phenylsulphonyl amine (0.036 g, 0.24 mmol) and NaH 80% (0.01 g, 0.24 mmol) in DMF (2 ml)). The reaction mixture was stirred at r.t. for 4 h, then EtOAc was added and the organic phase was washed with 1 M solution of HCl and brine, dried and evaporated. The crude product was purified by flash column chromatography (eluant CH_2Cl_2/MeOH 9:1), affording compound **30** as white solid (14 mg, 30%): ^1H NMR (DMSO-d_6): 12.10 (1H, bs); 9.98 (1H, bs); 7.90 (1H, bs); 7.8–7.5 (3H, m); 7.36–7.26 (2H, m); 7.18 (1H, m); 7.04 (1H, t); 6.98 (2H, bm); 6.70 (2H, m); 5.77 (1H, s); 5.30 (1H, d); 4.62 (1H, d); 4.08 (1H, m); 3.60 (3H, s); 2.94 (1H, m); MS (FAB/NBA): *m/z* 630 $[M+H]^+$. *Anal*. ($C_{33}H_{28}ClN_3O_6S$) C, H, N.

*7.37. (E)-2-(3-Benzenesulfonylaminocarbonyl-8-chloro-2-oxo-1,2,3,4-tetrahydro-benzo[b]azepin-5-ylidene)-N-phenyl-acetamide (**28f**)*

Compound **28f** was prepared using the same methods as compound **11** and obtained as white solid (0.006 g, 63%): ^{1}H NMR (acetone-d_6): 10.96 (1H, bs); 9.33 (1H, bs); 9.17 (1H, bs); 8.06 (2H, d); 7.73 (2H, m); 7.70 (1H, m); 7.63 (2H, t); 7.44 (1H, d); 7.36–7.29 (3H, m); 7.20 (1H, d); 7.08 (1H, m); 6.15 (1H, t); 4.16 (1H, m); 3.95 (1H, dd); 3.50 (1H, m); IR (Nujol) $\nu_{max.}$ (cm^{-1}): 1668 and 1597 (C=O); MS (FAB/NBA): *m/z* 510 $[M+H]^+$. *Anal*. ($C_{25}H_{20}ClN_3O_5S$) C, H, N.

*7.38. 2-Benzoyl-N-(5-chloro-2-iodo-phenyl)-N-(4-methoxy-phenyl)-malonamic acid tert-butyl ester (**31**)*

A solution of **24** (0.6 g, 1.2 mmol) in THF (25 ml) was cooled at −78 °C then $[(CH_3)_3Si]_2NNa$ 1 M in THF (1.8 ml, 1.8 mmol) was added and the reaction warmed to 0 °C. Benzoyl chloride (0.42 ml, 3.6 mmol) was added and the reaction mixture stirred at r.t. for 15 min. The solution was diluted with brine, extracted with EtOAc and the organic layer was dried and evaporated. The crude compound was purified by flash column chromatography (cyclohexane/EtOAc 8:2) to obtain compound **31** (0.39 g, 52%) as yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.98 (d, 2H); 7.81 (d, 1H); 7.62 (t, 1H); 7.56 (d, 2H); 7.45 (t, 2H); 7.16 (d, 1H); 7.05 (d, 2H); 7.02 (dd, 1H); 5.59 (d, 1H), 4.19 (d, 1H); 3.79 (s, 1H); 3.72 (s, 3H); 1.03 (s, 9H); IR (Nujol) $\nu_{max.}$ (cm^{-1}): 1734, 1703 and 1660 (C=O); MS (FAB/NBA): *m/z* 620 $[M+H]^+$. *Anal*. ($C_{28}H_{27}ClINO_5$) C, H, N.

*7.39. N-(5-Chloro-2-iodo-phenyl)-N-(4-methoxy-phenyl)-3-oxo-3-phenyl-propionamide (**32**)*

Compound **31** (0.39 g, 0.63 mmol) was dissolved in CF_3COOH (25 ml) and the solution was stirred for 30 min, then concentrated, diluted with EtOAc (30 ml) and concentrated. The crude compound was purified by flash chromatography (cyclohexane/EtOAc 8:2) to obtain compound **32** (0.31 g, 95%) as yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.9–6.77 (m, 12H); 5.56 (d, 1H); 4.00 (d, 1H); 3.92 (d, 1H); 3.80 (s, 3H); 3.58 (d, 1H); IR (Nujol) $\nu_{max.}$ (cm^{-1}): 1691, 1661 and 1624 (C=O); MS (FAB/NBA): *m/z* 520 $[M+H]^+$. *Anal*. ($C_{23}H_{19}ClINO_3$) C, H, N.

*7.40. 5-Benzoyl-hex-2-enedioic acid 6-[(5-chloro-2-iodo-phenyl)-(4-methoxy-phenyl)-amide] 1-phenylamide (**33**)*

To a solution of compound **32** (0.25 g, 0.48 mmol) in THF, at −78 °C, $[(CH_3)_3Si]_2NK$ 0.5 M in toluene (1.3 ml, 0.67 mmol) was added and the solution was warmed to 0 °C in 1 h. 4-Bromo-but-2-enoic acid phenylamide (0.174 g, 0.72 mmol) was added and the reaction was stirred 2 h at 0 °C, then diluted with brine and extracted with EtOAc. The organic layer was dried and evaporated. The crude compound was purified by flash chromatography (cyclohexane/EtOAc 8:2) to obtain compound **33** (0.17 g, 98%) as white foam: ^{1}H NMR ($CDCl_3$) δ 7.76 (d, 1H), 7.52–7.44 (m, 5H), 7.33–7.3 (m, 4H), 7.22 (bs, 1H), 7.2–7.1 (m, 3H), 6.95 (m, 1H), 6.82 (m, 2H), 6.74 (dd, 1H), 6.32 (d, 1H), 6.06 (m, 1H), 5.56 (d, 1H), 4.16 (dd, 1H), 3.95 (d, 1H), 3.79 (s, 3H), 3.20 (m, 1H). IR (Nujol) $\nu_{max.}$ (cm^{-1}): 1686 and 1601 (C=O); MS (FAB/NBA): *m/z* 679 $[M+H]^+$. *Anal*. ($C_{33}H_{28}ClIN_2O_4$) C, H, N.

*7.41. 2-[3-Benzoyl-8-chloro-1-(4-methoxy-phenyl)-2-oxo-1,2,3,4,-tetrahydro-benzo[b]azepin-5-ylidene]-N-phenyl-acetamide (**34**)*

Compound **34** was prepared using the same methods as compound **17**, heating at 110 °C for 5 h and obtained, after purification by flash column chromatography (cyclohexane/EtOAc 7:3), as white foam (0.175 g, 70%): ^{1}H NMR ($CDCl_3$) δ 10.05 (bs, 1H), 7.8–7.5 (m, 8H), 7.4–7.25 (4H), 7.06 (t, 1H), 6.97 (d, 2H), 6.72 (d, 2H), 5.86 (s, 1H), 5.2 (m, 1H), 4.8 (m, 1H), 4.7 (m, 1H), 4.4 (m, 1H), 3.2 (m, 1H), 3.61 (s, 3H); MS (FAB/NBA): *m/z* 551 $[M+H]^+$. *Anal*. ($C_{33}H_{27}ClN_2O_4$) C, H, N.

*7.42. 2-(3-Benzoyl-8-chloro-2-oxo-1,2,3,4-tetrahydro-benzo[b]azepin-5-ylidene)-N-phenyl-acetamide (**35**)*

Compound **35** was prepared using the same methods as compound **11**, and obtained, after purification by flash column chromatography (cyclohexane/EtOAc 6:4), as a white solid (0.011 g, 50%): ^{1}H NMR ($CDCl_3$) δ 10.20 (bs, 1H), 10.14 (bs, 1H), 7.78 (d, 2H), 7.65 (d, 2H), 7.59 (t, 1H), 7.47 (t, 2H), 7.43 (d, 1H), 7.32 (t, 2H), 7.17 (d, 1H), 7.06 (t, 1H), 6.12 (bs, 1H), 4.79 (dd, 1H), 4.12 (m, 1H), 3.41 (m, 1H); MS (FAB/NBA): *m/z* 431 $[M+H]^+$. *Anal*. ($C_{25}H_{19}ClN_2O_3$) C, H, N.

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Appendix A

Comp.	Theor. (%)	Found (%)
1	C 34.90; H 2.44; N 6.78	C 35.01; H 2.42; N 6.71
2	C 77.50; H 7.10	C 76.99; H 7.12
3	C 57.09; H 5.34; N 2.56	C 57.11; H 5.33; N 2.58
4	C 58.13; H 6.55; N 2.12	C 58.10; H 6.52; N 2.14
5	C 61.49; H 6.58; N 1.79	C 61.52; H 6.60; N 1.78
6	C 61.22; H 5.59; N 2.10	C 61.21; H 5.57; N 2.07
7	C 61.40; H 5.30; N 2.11	C 61.44; H 5.29; N 2.13
8	C 62.08; H 5.62; N 1.91	C 62.00; H 5.58; N 1.88
9	C 64.49; H 5.41; N 3.58	C 64.39; H 5.43; N 3.62
10a	C 71.93; H 5.89; N 3.99	C 71.85; H 5.87; N 4.02
10b	C 71.93; H 5.89; N 3.99	C 72.00; H 5.92; N 3.93
11	C 63.07; H 4.41; N 8.17	C 63.10; H 4.38; N 8.16
12	C 51.48; H 4.01; N 4.29	C 51.50; H 4.00; N 4.29
13	C 58.13; H 4.70; N 5.02	C 58.08; H 4.76; N 5.05
14	C 55.78; H 4.32; N 5.00	C 55.83; H 4.30; N 4.96
15	C 58.41; H 5.21; N 4.26	C 58.53; H 5.19; N 4.29
16	C 60.32; H 4.62; N 6.21	C 60.40; H 4.61; N 6.23
17	C 68.51; H 5.07; N 7.05	C 68.48; H 5.05; N 7.09
19a	C 54.35; H 4.32; N 10.01	C 54.31; H 4.29; N 9.98
19b	C 48.16; H 3.19; N 8.87	C 48.18; H 3.17; N 8.91
21	C 45.01; H 3.51; N 3.75	C 44.98; H 3.54; N 3.77
22	C 45.64; H 3.62; N 2.96	C 45.68; H 3.60; N 3.00
23	C 44.42; H 3.29; N 3.05	C 44.44; H 3.29; N 3.03
24	C 48.90; H 4.49; N 2.72	C 48.95; H 4.51; N 2.71
25	C 55.16; H 4.78; N 4.15	C 55.19; H 4.80; N 4.12
26	C 68.06; H 5.71; N 5.12	C 68.11; H 5.77; N 5.10
27	C 61.55; H 4.08; N 7.55	C 61.57; H 4.09; N 7.53
28a	C 59.15; H 4.18; N 10.89	C 59.19; H 4.20; N 10.83
28b	C 61.71; H 4.36; N 11.36	C 61.76; H 4.33; N 11.41
28c	C 67.34; H 4.52; N 9.42	C 67.37; H 4.50; N 9.39
28d	C 63.40; H 5.07; N 10.56	C 63.41; H 5.06; N 10.53
28e	C 64.87; H 4.01; N 11.94	C 64.91; H 3.99; N 11.98
29	C 66.06; H 4.72; N 5.71	C 66.01; H 4.68; N 5.67
30	C 62.90; H 4.48; N 6.67	C 62.96; H 4.52; N 6.65
28f	C 58.88; H 3.95; N 8.24	C 58.94; H 3.92; N 8.19
31	C 54.25; H 4.39; N 2.26	C 54.19; H 4.41; N 2.29
32	C 53.15; H 3.68; N 2.69	C 53.10; H 3.69; N 2.74
33	C 58.38; H 4.16; N 4.13	C 58.33; H 4.15; N 4.11
34	C 71.93; H 4.94; N 5.08	C 72.12; H 4.99; N 4.97
35	C 69.69; H 4.44; N 6.50	C 69.91; H 4.48; N 6.54

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[30] The introduction of the *tert*-butyl ester protecting group was necessary in order to avoid the exo/endo isomerization of the double bond in the benzoazepine derivative observed in the final deprotection step under basic conditions.
[31] The research complied with national legislation and with company policy on the Care and Use of Animals and with related codes of practice.