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β-Lactam derivatives as potential anti-cancer compounds

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Abstract A number of 1,4-diaryl-3-methylene substituted β-lactams, the addition products obtained from their reactions with N-, S-, and C-nucleophiles, and diverse related compounds were prepared, and a selection of 43 compounds was screened in preliminary tests as anti-tumor compounds by using 4 or 5 human cancer cell lines of diverse origins. Twelve compounds were highly active against all cell lines, 6 showed low activity, 12 no activity, and 13 exhibited a selective activity against a human small cell lung carcinoma cell line.

Keywords β-Lactams; Anti-cancer compounds.

Introduction

The β-lactam ring is known as an important structural part of the highly active and clinically useful β-lactam antibiotics [1]. Apart from clinical use as antibacterials, β-lactams serve as synthons in the synthesis of other biological active heterocycles [2], and in many examples the biological activity can be interpreted as an interaction between the β-lactam ring and a serine containing enzyme (serine protease) like elastase [3]. Therefore, the search for clinical useful β-lactams is a growing field of interest. We have described a number of β-lactam derivatives [4] and studied their properties as elastase inhibitors. During the last decade a few papers were published reporting on the cytotoxicity and anticancer activity of β-lactams [5]. Extending our research in this field, we describe herein preliminary results concerning substituted β-lactams and some derivatives thereof and their biological evaluation regarding their activity against tumor cell lines [6].

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Results and discussion

Chemistry

As starting material for most syntheses substituted (*RS*)-1,4-diphenylazetidin-2-ones (**1**) were used. These were transformed either *via* the 3-trimethylsilyl compounds (**2**) and their reaction with carbonyl compounds in the presence of *LDA* or *Bu*Li or *via* the aldols (**3**, Table 1) obtained by reaction with aldehydes followed by dehydration into the substituted 3-methylene derivatives (**4**, Table 2). These compounds were isolated as mixtures of the *E*- and *Z*-diastereoisomers, and were either separated and the diastereoisomers or the mixtures were tested.

Compounds **4** allowed nucleophilic additions of C-, N-, or S-nucleophiles at C-3 of the β-lactam ring if at least one of the substituents R' and R'' is an electron withdrawing group, yielding compounds of the general structure **5** and the oxidation products **6** (Table 3). From a few reactions we obtained different products. When **4o** and **4s** reacted under iden-

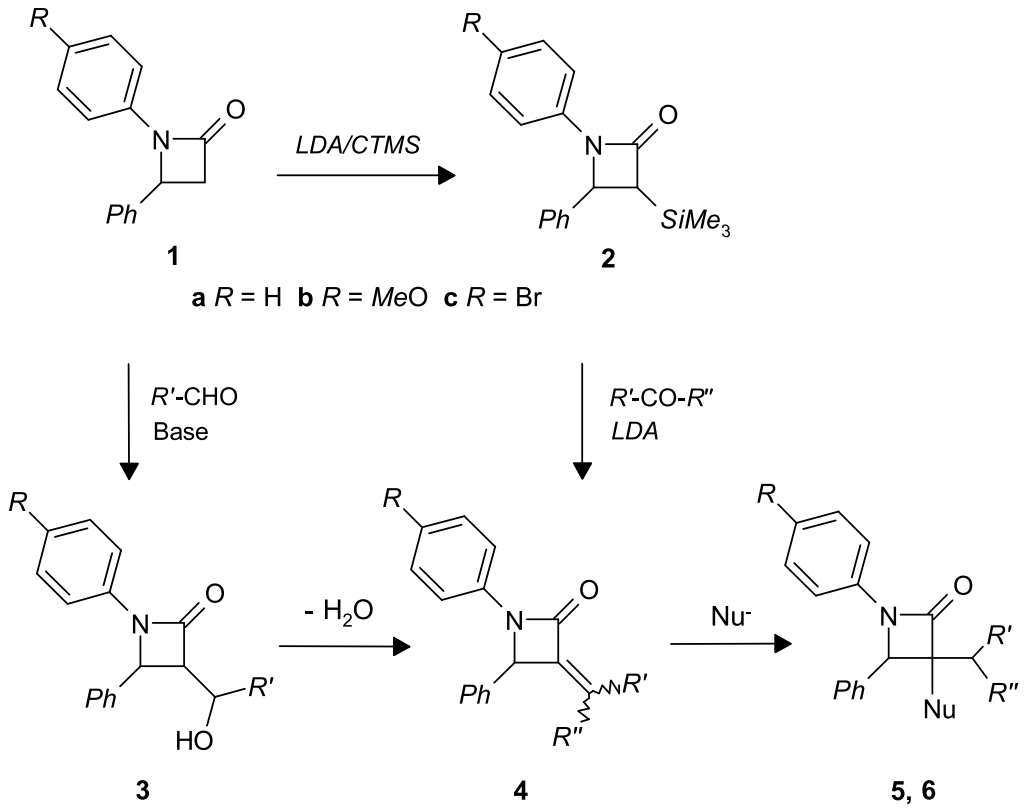


Table 1 1,4-Diaryl-3-(subst.-α-hydroxybenzyl)-β-lactams and diverse compounds*

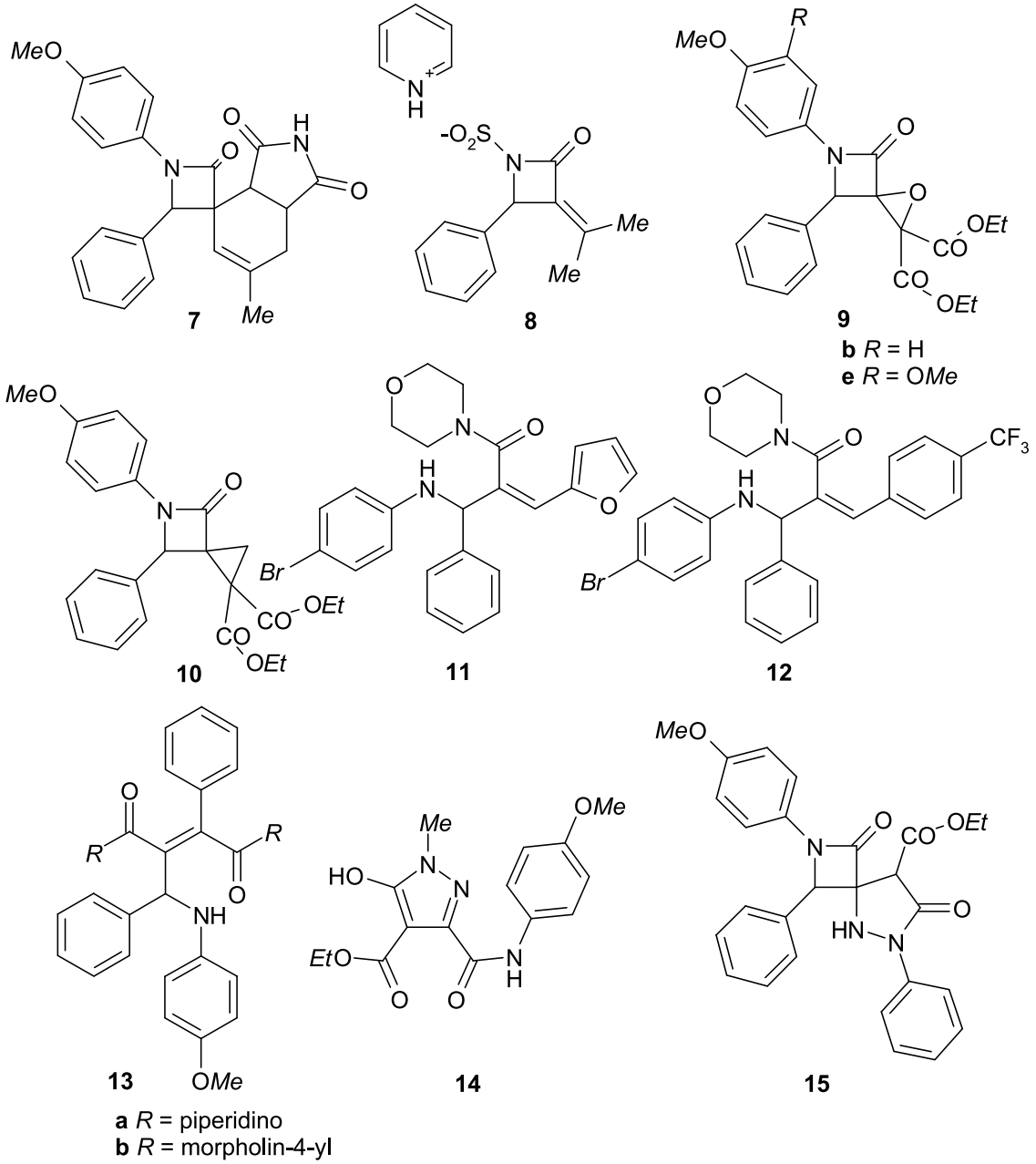
Cpd.	*R*	*R′*	Mol. formula	Mol. weight	Ref.
3a	H	CH=CH–*Ph*	$C_{24}H_{19}NO_2$	353.42	[6d]
3b	Br	4-O_2N–*Ph*	$C_{22}H_{17}BrN_2O_4$	453.30	[6d]
3c	Br	2-O_2N–*Ph*	$C_{22}H_{17}BrN_2O_4$	453.29	–
7			$C_{24}H_{22}N_2O_4$	402.45	[6a]
8			$C_{17}H_{18}N_2O_4S$	346.41	[6b]
9a	H		$C_{23}H_{23}NO_7$	425.44	[6c]
9b	*Me*O		$C_{24}H_{25}NO_8$	455.47	[6c]
10			$C_{24}H_{25}NO_6$	423.47	[6c]
11			$C_{24}H_{23}BrN_2O_3$	467.36	–
12			$C_{27}H_{24}BrF_3N_2O_2$	545.39	–
13a			$C_{34}H_{39}N_3O_3$	537.70	–
13b			$C_{32}H_{35}N_3O_5$	541.65	–
14			$C_{15}H_{17}N_3O_5$	319.32	[6c]
15			$C_{27}H_{25}N_3O_5$	471.52	[6c]

* Cpds without a ref. see 'Experimental' of this paper

tical conditions with morpholine, we isolated the products **11** and **12** formed by an attack of the nucleophile to the carbonyl group and not to the double bond. The 2-butene derivatives **13a** and **13b** were formed from **5l** to **5m** by an attack of the amine to the ester group followed by a ring opening with migration of the amine from the quaternary C-atom to the lactam carbonyl group. **7** was prepared by cycloaddition of maleinimide [7a], **8** according to Ref. [7b], **9a** and **9b** by epoxidation and **10** by carben addition to the exocyclic double bond [7c]. Two products, **14** and **15**, obtained as rearrangement products from the reaction of 3-methylidene β-lactams with hydrazines [7c] were included in the biological testing.

Biology

With the goal of obtaining information on the potential antitumor activity of the new compounds, all compounds were tested at a concentration of 20 μM in an *in vitro* screening method with the following human cancer cell lines of diverse origins: 5637 (urinary bladder carcinoma), RT-4 (urinary bladder carcinoma), A-427 (lung carcinoma), LCLC-103H (large cell lung carcinoma), and compounds **4n**–**4z** were additionally tested against MCF-7 (breast adenocarcinoma). The method has been previously described and validated in [8], and the results are summarized in Tables 4 and 5. Values are the averages from 2 to 5 independent experiments.



A first interpretation of the obtained values yielded the following four groups of compounds. No activity against all cell lines was found for compounds **3a**, **4g**, (*Z*)-**4j**, **4k**, **5q**, **6b**, **7**, **8**, **9a**, **9b**, **9b**, **10**, **14**, and **15** (Table 4); the data in Table 5 also showed no activity for compounds (*Z*)-**4o**, (*Z*)-**4t**, (*Z*)-**4u**, (*Z*)-**4w**, and (*Z*)-**4y**. We do not intend to continue studying these compounds. A high activity against all cell lines was exhibited by **3b**, **4a**, (*E*)-**4n**, **5a**, **5b**, **5c**, **5d**, **5e**, **5y**, and **5z** (Table 4); a similar result was found in Table 5 for compounds (*Z*)-**4n**, (*Z*)-**4p**, (*Z*)-**4q**, and, less clear, (*Z*)-**12**. This high activity against all cell lines might be interpreted as an indication for general toxicity. The remaining compounds seem to form the most interesting group, as they exhibited a differentiated behavior, *i.e.*, we found growth inhibitory effects only against one cell line, the small cell lung cancer line A-427. Compounds (Table 4) (*E*)-**4b**, (*Z*)-**4l**, (*Z*)-**4m**, **5f**, **5m**, **5n**, **5o**, and **5u** exhibited a significant effect only against this cell line. A similar effect was seen for compounds **4u**, **4x**, (*Z*)-**4z**, and (*Z*)-**11** in Table 5 in A-427 cells. A fourth group of

Table 2 1,4-Diaryl-3-(subst. methylene)-β-lactams (**4**)*

Cpd.	*R*	*R′*	*R″*	Mol. formula	Mol. weight	Ref.
(*Z*)-**4a**	*Me*O	CHO	H	$C_{19}H_{17}NO_3$	307.35	[6b]
(*E*)-**4b**	*Me*O	H	1-propenyl	$C_{20}H_{19}NO_2$	305.38	[6a]
4c	H	CO_2CH_3	*Ph*	$C_{24}H_{19}NO_3$	369.42	[6e]
4d	*Me*O	CO_2CH_3	*Ph*	$C_{25}H_{21}NO_4$	399.45	[6e]
4e	*Me*O	CO_2CH_3	*Me*	$C_{20}H_{19}NO_4$	227.38	[6e]
4f	*Me*O	CONH*Ph*	*Me*	$C_{25}H_{22}N_2O_3$	398.47	–
4g	*Me*O	*Ph*	CONH*Ph*	$C_{30}H_{24}N_2O_3$	460.54	–
4h	*Me*O	$CONHC_6H_{11}$	*Me*	$C_{25}H_{28}N_2O_3$	404.51	–
4i	*Me*O	CONH*Bn*	*Ph*	$C_{31}H_{26}N_2O_3$	474.56	–
(*Z*)-**4j**	H	*Et*	H	$C_{18}H_{17}NO$	263.34	[6e]
4k	*Me*O	H	1-pyrrolidinyl	$C_{21}H_{22}N_2O_2$	334.42	[6e]
(*Z*)-**4l**	*Me*O	CO_2CH_3	*Ph*	$C_{25}H_{21}NO_4$	399.45	[6e]
(*Z*)-**4m**	*Me*O	CO_2CH_3	*Me*	$C_{20}H_{19}NO_4$	337.38	[4]
(*E*)-**4n**	*Me*O	H	2-furyl	$C_{21}H_{17}NO_3$	331.37	–
(*Z*)-**4o**	Br	2-furyl	H	$C_{20}H_{14}BrNO_2$	380.24	–
(*E*)-**4p**	*Me*O	H	5-O_2N-2-furyl	$C_{21}H_{16}N_2O_5$	376.36	–
(*Z*)-**4q**	Br	5-O_2N-2-furyl	H	$C_{20}H_{13}BrN_2O_4$	425.23	–
(*Z*)-**4r**	Br	2-thienyl	H	$C_{20}H_{14}BrNOS$	396.30	–
4s**	Br	H	4-F_3C–*Ph*	$C_{23}H_{15}BrF_3NO$	458.27	–
(*Z*)-**4t**	*Me*O	4-O_2N–*Ph*	H	$C_{23}H_{18}N_2O_4$	386.40	–
4u**	Br	H	4-O_2N–*Ph*	$C_{22}H_{15}BrN_2O_3$	435.27	–
(*E*)-**4v**	Br	H	5-Br-2-furyl	$C_{20}H_{13}Br_2NO_2$	459.13	–
(*Z*)-**4w**	Br	4-Cl–*Phe*	H	$C_{22}H_{15}BrClNO$	424.72	–
4x	Br	2-O_2N–*Phe*	H	$C_{22}H_{15}BrN_2O_3$	435.27	–
(*Z*)-**4y**	Br	2,4-di–Cl–*Phe*	H	$C_{22}H_{14}BrCl_2NO$	459.16	–
(*Z*)-**4z**	Br	2-Cl–*Phe*	H	$C_{22}H_{15}BrClNO$	424.72	–

* Cpds without a ref. see 'Experimental' of this paper. ** *E*/*Z*-mixture

two compounds, (*Z*)-**4o** and (*Z*)-**4r**, showed a moderate growth inhibitory effect against the cell line 5637. Comparing the values of (*E*)-**4n** (Table 4) with those of (*Z*)-**4n** (Table 5) one might suggest, at least in this example, that the (*Z*)-isomer is the slightly more active form. In a following paper (in preparation) one of us will report on potency studies with detailed IC_{50} values and studies about a possible mechanism of action.

Experimental

General

Mp Mel-Temp-II Laboratory Devices Inc., USA. IR Spectra: Perkin-Elmer FTIR 1600; in KBr (cm^{-1}), if not noted otherwise. NMR Spectra: Bruker WP 80 (80 MHz), DPX 200 (200 MHz), WM 400 (400 MHz) for ^1H and DPX 200 (50 MHz) for ^{13}C; δ (ppm) rel. to *TMS* as internal standard; values from DPX 200 (200/50 MHz) spectra in $CDCl_3$, if not noted otherwise. MS: M40 AMD Intectra, EI 70 eV. Elementary analyses: Perkin-Elmer Analyzer 2400 CHN, Pharmazeutisches Institut der Universität Greifswald. All compounds gave satisfactory elemental analyses. Column chromatography (CC): Silica gel 60 (Merck 7734). HPLC with LaChrom apparatus series 7000 Merck Hitachi, LiChrospher 250-4, RP-18, 5 μm, LiChroCART 250-4 (S,S)-Whelk-O1, 5 μm, and DIACEL® ChiraCel® OJ–R™, 5 μm. HPLC experiments were done using [a] *Me*CN/H_2O (7/3) or [b] *Me*CN/H_2O (4/1) and detection by UV if not noted otherwise.

THF was stored with KOH, then refluxed with Na and benzophenone, and distilled prior to use. Other solvents were dried/purified according to literature procedures. *LDA* (lithium diisopropylamide) was freshly prepared by mixing of equivalent amounts of freshly distilled diisopropylamine and *n-Bu*Li (15% in hexane) at −78°C.

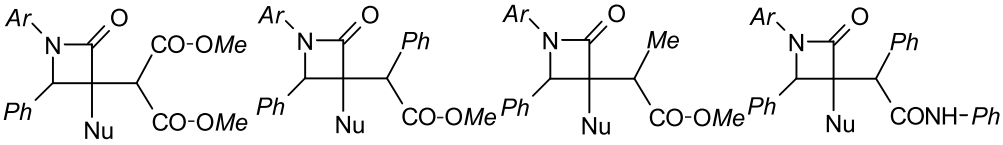
Abbreviations: *Ac*O*Et* = Ethyl acetate; *CTMS* Chlorotrimethylsilane; *PE* Petroleum ether; *ar* = Aromatic.

The following compounds were prepared according to literature: (*RS*)-1,4-diphenylazetidin-2-one (**1a**) [9], (*RS*)-1-(4-Methoxyphenyl)-4-phenylazetidin-2-one (**1b**) [10], (*RS*)-1-(4-Bromophenyl)-4-phenylazetidin-2-one (**1c**), *cis*-1,4-Diphenyl-3-(trimethylsilyl)azetidin-2-one (**2a**), *cis*-1-(4-Methoxyphenyl)-4-phenyl-3-(trimethylsilyl)azetidin-2-one (**2b**) [7b], *cis*-1-(4-Bromophenyl)-4-phenyl-3-(trimethylsilyl)azetidin-2-one (**2c**) [7h], (*Z*/*E*)-3-(Furan-2-ylmethylene)-1-(4-methoxyphenyl)-4-phenylazetidin-2-one (**4n**) [7b].

*Reaction of **2** with carbonyl compounds. General procedure*

At −78°C, a solution of **2** in *THF* (1 cm^3/mmol) was added drop by drop with stirring to a solution of 2 equivalents *LDA*

Table 3 β-Lactams of structure **5***



Ar = p-*Me*O-*Ph*

Cpd.	Structure	Nu	Mol. formula	Mol. weight	Ref.
5a	A	NH–NH–*Ph*	$C_{29}H_{31}N_3O_6$	517.59	[6f]
5b	A	NH–NH–CO_2Me	$C_{25}H_{29}N_3O_8$	499.53	[6c]
5c	A	$CH(CO_2Me)(CH_2)_2SMe$	$C_{29}H_{36}N_2O_8S$	572.68	[6c]
5d	A	S–*Ph*	$C_{29}H_{29}NO_6S$	519.62	[6c]
5e	A	S–$CHMe_2$	$C_{26}H_{31}NO_6S$	485.60	[6c]
5f	B	$N(CHMe_2)_2$	$C_{31}H_{36}N_2O_4$	500.64	–
5g	B	$N(C_6H_{11})_2$	$C_{37}H_{44}N_2O_4$	580.77	–
5h	B	NEt_2	$C_{29}H_{32}N_2O_4$	472.59	–
5i	B	pyrrolidino	$C_{29}H_{30}N_2O_4$	470.57	–
5j	C	pyrrolidino	$C_{24}H_{28}N_2O_4$	408.50	–
5k	B**	piperidino	$C_{29}H_{30}N_2O_3$	454.57	–
5l	B	piperidino	$C_{30}H_{32}N_2O_4$	484.60	–
5m	B	4-morpholino	$C_{29}H_{30}N_2O_5$	486.57	–
5n	D	pyrrolidino	$C_{34}H_{33}N_3O_3$	531.66	–
5o	C	S-*Ph*	$C_{26}H_{25}NO_4S$	447.56	–
5p	B	S–$CHMe_2$	$C_{28}H_{29}NO_4S$	475.61	–
5q	B	S–CH_2–CH=CH_2	$C_{28}H_{27}NO_4S$	473.60	–
5r	B	S–$(CH_2)_2$–CO_2Me	$C_{29}H_{29}NO_6S$	519.62	–
5s	C	S–$(CH_2)_2$–CO_2Me	$C_{24}H_{27}NO_6S$	457.55	–
5t	B	S–CMe_3	$C_{29}H_{31}NO_4S$	489.64	–
5u	B	S–*Bu*	$C_{29}H_{31}NO_4S$	489.64	–
5v	B	*Bu*	$C_{29}H_{31}NO_4$	457.57	
5y	A	NH_2	$C_{23}H_{26}N_2O_6$	426.47	[6e]
5z	A	4-morpholino	$C_{27}H_{32}N_2O_7$	496.57	[6e]
6a	A	SO_2–*Ph*	$C_{29}H_{29}NO_8S$	551.62	–
6b	B	SO_2–$(CH_2)_2CO_2Me$	$C_{29}H_{29}NO_8S$	551.62	–
6c	C	SO_2Ph	$C_{26}H_{25}NO_6S$	479.56	–
6d	S	SO_2–$(CH_2)_2$–CO_2Me	$C_{24}H_{27}NO_8S$	489.55	–

* Cpds without a ref. see 'Experimental' of this paper. ** $Ar = Ph$

in *THF*. After 15 min, an equivalent amount of the carbonyl compounds (freshly distilled or a solution in *THF*) was added slowly and with stirring. Stirring was continued until the mixture was warmed to room temperature (*ca.* 1 h); a solution of NH_4Cl was added until *pH* 7.5–8 was reached. The organic layer was separated, the aqueous layer was extracted (2–3×) with *Ac*O*Et*, the combined organic layers were dried (Na_2SO_4), evaporated *in vacuo*, and the residue was purified as noted below.

1-(4-Bromophenyl)-3-[hydroxy(2-nitrophenyl)methyl]-4-phenylazetidin-2-one (**3c**, $C_{22}H_{17}BrN_2O_4$)
From 1.9 g (5 mmol) **2c** and 7.5 g (50 mmol) 2-nitrobenzaldehyde. Yield 1.3 g (58%); yellow crystals; mp 230°C (dec., *Et*OH); IR: $\bar{\nu} = 3334$ (OH), 3036, 2934, 2850 (CH), 1717 (CO), 1589, 1522, 1491 (NO_2) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 3.47$ (ddd, $^3J_{3,\alpha} = 3.7$, $^3J_{3,4} = 2.6$, $^5J_{3,OH} = 0.7$ Hz, 3-H), 5.46 (d, $^3J_{4,3} = 2.6$ Hz, 4-H), 5.64 (dd, $^3J_{\alpha,OH} = 4.8$, $^3J_{\alpha,3} = 3.7$ Hz, α-H), 6.35 (dd, $^3J_{OH,\alpha} = 4.8$, $^3J_{OH,3} = 0.7$ Hz, OH), 7.12–7.31 (m, 7 *ar* H), 7.50 (dd, $^3J = 6.8$, $^4J = 2.1$ Hz, 2 *ar* H), 7.55 (m, 4′-H), 7.84 (ddd, $^3J = 7.8$, $^3J = 7.6$, $^4J = 1.3$ Hz, 5′-H), 7.94 (dd, $^3J = 8.1$, $^4J = 1.3$ Hz, 3′-H), 8.19 (dd, $^3J = 7.8$, $^4J = 1.3$ Hz, 6′-H) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 54.86$ (C-3), 64.13 (C-4), 65.62 (C–OH), 115.32, 118.54, 124.24, 126.03, 126.98, 127.19, 128.04, 128.75, 128.86, 128.98, 131.92, 132.12, 133.35, 133.62, 136.29, 137.37, 137.66, 146.81 (C–NO_2), 164.54 (CO) ppm; HPLC: RP-18[b]: $t_0 = 1.83$ min, $k' = 4.18$, $\lambda_{max} = 331.4$ nm.

Table 4 Cell growth relative to untreated controls/% after application of 20 μM compounds **3a**–**15** for 96 h

Compounds	Cell lines			
	5637	RT-4	A-427	LCLC-103H
3a	81	79	10	46
3b	0	−5	−5	3
4a	−3	−5	−3	−2
(*E*)-**4b**	90	79	−4	74
4g	91	88	56	76
(*Z*)-**4j**	95	91	52	81
4k	80	93	48	65
(*Z*)-**4l**	56	60	−4	44
(*Z*)-**4m**	83	79	8	67
(*E*)-**4n**	6	7	1	9
5a	−3	−6	−5	−2
5b	−3	−6	−5	−2
5c	−3	−6	−5	−2
5d	−3	−6	−5	−2
5e	−3	−6	−5	−2
5f	23	41	−4	33
5m	33	31	−1	31
5n	54	64	8	42
5o	61	39	2	65
5q	90	50	14	57
5u	26	32	3	44
5y	−3	−8	−5	−3
5z	−3	−8	−5	−3
6b	98	74	64	85
7	97	93	81	65
8	107	102	89	90
9a	104	94	81	73
9b	107	87	92	74
10	78	84	42	72
14	93	98	112	90
15	96	97	114	91

Table 5 Cell growth relative to untreated controls/% after application of 20 μM compounds **4n**–**4z**, (*Z*)-**11**, and (*Z*)-**12** for 96 h

	5637	RT-4	A-427	LCLC-103H	MCF-7
(*Z*)-**4n**	−2	−11	−2	0	−1
(*Z*)-**4o**	10	63	67	56	23
(*Z*)-**4p**	−4	−9	−4	−3	8
(*Z*)-**4q**	−3	−14	−4	−3	−14
(*Z*)-**4r**	8	85	59	68	74
(*Z*)-**4s**	64	93	11	76	70
(*Z*)-**4t**	85	85	30	82	56
(*Z*)-**4u**	42	85	15	61	54
4u	55	81	8	59	47
(*Z*)-**4v**	76	47	−1	60	18
(*Z*)-**4w**	63	79	70	83	82
4x	94	88	2	90	53
(*Z*)-**4y**	72	81	33	81	77
(*Z*)-**4z**	48	85	8	72	64
(*Z*)-**11**	54	78	6	57	27
(*Z*)-**12**	21	15	−2	1	2

(Z/E)-1-(4-Bromophenyl)-3-(furan-2-ylmethylene)-4-phenylazetidin-2-one (**4o**, $C_{20}H_{14}BrNO_2$)
From 6 g (16 mmol) **2c** and 15 cm^3 (160 mmol) furfural as **4n**. Ratio of isomers (HPLC) *E*/*Z* 1:1. Yield 3.2 g (42%); light yellow crystals; mp (*Z*): 206–207°C (*Me*OH), (*E*): 178–183°C (*Me*OH); IR: $\bar{\nu} = 3144$, 3033 (CH), 1889, 1804, 1724 (CO), 1687 (C=C) cm^{-1}; ^{1}H NMR (*Z*): $\delta = 5.37$ (d, $^4J_{4,\alpha} = 1.0$ Hz, 4-H), 6.24 (dd, $^4J_{\alpha,4} = 1.0$, $^5J_{\alpha,F4} = 0.6$ Hz, α-H), 6.50 (ddd, $^3J_{F4,F3} = 3.5$, $^3J_{F4,F5} = 1.8$, $^5J_{F4,\alpha} = 0.6$ Hz, 4-H_F), 7.20–7.30 (m, 3-H_F, 1 *ar* H), 7.47 (dd, $^3J_{F5,F4} = 1.8$, $^4J_{F5,F3} = 0.6$ Hz, 5-H_F), 7.30–7.44 (m, 8 *ar* H) ppm; (*E*): $\delta = 5.66$ (d, $^4J_{4,\alpha} = 1.4$ Hz, 4-H), 6.35 (dd, $^3J_{F4,F3} = 3.4$, $^3J_{F4,F5} = 1.7$ Hz, 4-H_F), 6.44 (d, $^3J_{F3,F4} = 3.4$ Hz, 3-H_F), 6.91 (d, $^4J_{\alpha,4} = 1.4$ Hz, α-H), 7.51 (d, $^3J_{F5,F4} = 1.7$ Hz, 5-H_F), 7.15–7.58 (m, 9 *ar* H) ppm; ^{13}C NMR (*Z*): $\delta = 62.44$ (C-4), 112.68 (C-4_F), 114.72 (C-3_F), 116.56 (C–Br), 117.06 (C-α), 118.37, 126.70, 129.02, 129.26, 132.19, 136.45, 136.91, 137.42, 144.13 (C-5_F), 150.12 (C-2_F), 159.97 (CO) ppm; (*E*): $\delta = 64.43$ (C-4), 112.24, 112.82 (C-4_F), 114.98 (C-3_F), 116.43 (C–Br), 117.06 (C-α), 118.41, 126.71, 127.76, 128.82, 128.91, 132.12, 136.35, 136.81, 137.78, 144.78 (C-5_F), 149.64 (C-2_F), 161.96 (CO) ppm; HPLC (*Z*) RP-18[a]: $t_0 = 1.79$ min, $k' = 11.73$, $\lambda_{max} = 341.1$ nm; RP-18[b]: $t_0 = 1.83$ min, $k' = 3.43$; (*E*) RP-18[a]: $t_0 = 1.79$ min, $k' = 7.35$, $\lambda_{max} = 333.8$ nm; RP-18[b]: $t_0 = 1.83$ min, $k' = 2.36$.

(Z/E)-1-(4-Bromophenyl)-3-(5-nitrofuran-2-ylmethylene)-4-phenylazetidin-2-one (**4p**, $C_{21}H_{16}N_2O_5$)
From 1.6 g (5 mmol) **2b** and 2 g (14 mmol) 5-nitro-2-furfural. CC (*n*-hexane/CH_2Cl_2 1/1). Yield 150 mg (8%); orange crystals, >90% (*Z*); mp 180–183°C (*Me*OH); IR: $\bar{\nu} = 3113$, 2927, 2836 (CH), 1731 (CO), 1610 (C=C), 1582, 1573 (NO_2), 1510, 1474, 1380, 1353 (NO_2), 1245 (O*Me*) cm^{-1}; ^{1}H NMR (*Z*): $\delta = 3.76$ (s, O*Me*), 5.45 (d, $^4J_{4,\alpha} = 1.1$ Hz, 4-H), 6.24 (dd, $^4J_{\alpha,4} = 1.1$, $^4J_{\alpha,F4} = 0.5$ Hz, α-H), 6.83 (dd, $^3J = 6.8$, $^4J = 2.3$ Hz, 2 *ar* H), 7.32 (dd, $^3J = 6.8$, $^4J = 2.3$ Hz, 2 *ar* H), 7.37 (dd, $^3J_{F4,F3} = 3.9$, $^5J_{F4,\alpha} = 0.5$ Hz, 4-H_F), 7.37–7.43 (m, 5 *ar* H), 7.83 (d, $^3J_{F3,F4} = 3.9$ Hz, 3-H_F) ppm; (*E*): $\delta = 3.75$ (s, O*Me*), 5.80 (d, $^4J_{4,\alpha} = 1.4$ Hz, 4-H), 6.56 (d, $J = 3.7$ Hz, 3-H_F), 6.80 (dd, $^3J = 6.8$, $^4J = 2.3$ Hz, 2 *ar* H), 6.83 (d, $^4J_{\alpha,4} =$ 1,4 Hz, α-H), 7.23 (d, $^3J_{F4,F3} = 3.7$ Hz, 4-H_F), 7.31 (dd, $^3J = 6.8$, $^4J = 2.3$ Hz, 2 *ar* H), 7.27–7.40 (m, 5 *ar* H), 7.63–7.70 (m, 2 *ar* H) ppm; ^{13}C NMR: (*Z*): $\delta = 55.49$ (O*Me*), 62.70 (C-4), 113.79, 114.66, 115.89, 118.60 (C-α), 126.62, 129.34, 129.39, 130.77, 135.62, 145.92 (C-2_F), 152.16 (C-4_F), 156.82 (C-5_F), 158.26 (CO) ppm; (*E*): $\delta = 55.47$ (O*Me*), 64.53 (C-4), 109.12, 113.12, 114.59, 115.42, 118.68 (C-α), 128.05, 128.92, 129.14 ppm; HPLC (*Z*) RP-18[a]: $t_0 = 1.78$ min, $k' = 5.45$, $\lambda_{max} = 384.3$ nm; (*E*) RP-18[a]: $t_0 = 1.78$ min, $k' = 3.50$.

(Z)-1-(4-Bromophenyl)-3-(5-nitrofuran-2-ylmethylene)-4-phenylazetidin-2-one (**4q**, $C_{20}H_{13}BrN_2O_4$)
From 1.87 g (5 mmol) **2c** and 3.5 g (25 mmol) 5-nitro-2-furaldehyde as **4p**. CC (*n*-Hexane/CH_2Cl_2 2/1). Yield 340 mg (16%); yellow crystals; mp *ca.* 250°C (dec., *Me*OH); IR: $\bar{\nu} = 3154$, 1724 (CO), 1632 (C=C), 1586, 1574 (NO_2), 1518, 1489, 1354 (NO_2) cm^{-1}; ^{1}H NMR: $\delta = 5.47$ (d, $^4J_{4,\alpha} = 1.1$ Hz, 4-H), 6.29 (dd, $^4J_{\alpha,4} = 1.1$, $^5J_{\alpha,F4} = 0.6$ Hz, α-H), 7.20–7.30 (m, 5 *ar* H), 7.34–7.47 (m, 5 *ar* H, 4-H_F), 7.81 (d, $^3J_{F3,F4} =$ 4.0 Hz, 1H, 3-H_F) ppm; ^{13}C NMR: $\delta = 62.76$ (C-4), 113.65,

114.91, 116.20 (C–Br), 117.64 (C-3_F), 118.69 (α-CH), 126.56, 129.53, 129.57, 132.41, 135.12, 136.21, 145.26 (C-2_{Furan}), 151.75 (C-4_F), 159.83 (CO) ppm; HPLC RP-18[a]: $t_0 = 1.79$ min, $k' = 10.76$, $\lambda_{max} = 377.0$ nm; RP-18[b]: $t_0 = 1.83$ min, $k' = 2.99$; ChiralCel OJ–R[a]: $t_0 = 2.01$ min, $k_1' = 4.47$, $k_2' = 4.90$.

(Z/E)-1-(4-Bromophenyl)-4-phenyl-3-(thien-2-ylmethylene)-azetidin-2-one (**4r**, $C_{20}H_{14}BrNOS$)
From 6 g (16 mmol) **2c** and 14.5 cm^3 (160 mmol) thiophene-2-carbaldehyde. First the (*Z*)-isomer was obtained by crystallization of the residue from propanol, then the filtrate was evaporated *in vacuo*, and the residue crystallized from *Me*OH. Yield 2.1 g (33%); mp (*Z*) 248°C (Propanol); light yellow crystals; mp (*E*) 224°C (*Me*OH); light yellow plats; IR: $\bar{\nu} = 3082$, 3031, 2962 (CH), 1885, 1725 (CO), 1678 (C=C) cm^{-1}; ^{1}H NMR (*Z*): $\delta = 5.38$ (d, $^4J_{4,\alpha} = 1.2$ Hz, 4-H), 6.43 (dd, α-H), 7.06 (dd, $^3J_{T4,T5} = 5.1$, $^3J_{T4,T3} = 3.7$ Hz, 4-H_T), 7.20–7.44 (m, 9 *ar* H), 7.43 (dd, $^3J_{T5,T4} = 5.1$ Hz, 5-H_T), 7.72 (ddd, $^3J_{T3,T4} = 3.7$ Hz, 3-H_T) ppm; (*E*): $\delta = 5.58$ (d, $^4J_{4,\alpha} = 1.6$ Hz, 4-H), 6.95 (dd, $^3J_{T4,T5} = 5.1$, $^3J_{T4,T3} = 3.7$ Hz, 4-H_T), 7.09 (ddd, 3-H_T), 7.20–7.44 (m, 9 *ar* H), 7.56 (d, $^4J_{\alpha,4} = 1.6$ Hz, Hz, α-H), 7.59 (m, 5-H_T) ppm; ^{13}C NMR (*Z*): $\delta = 62.48$ (C-4), 116.58 (C–Br), 118.39 (C-α), 122.00, 126.76, 128.09, 129.02, 129.28, 129.66, 131.81, 132.19, 136.52, 136.92, 137.26, 137.72, 160.12 (CO) ppm; (*E*): $\delta = 64.28$ (C-4), 116.50 (C–Br), 118.32, 118.39 (C-α), 118.89, 126.76, 127.76, 128.49, 128.53, 129.06, 129.27, 129.43, 129.85, 131.72, 132.12, 132.18, 135.22, 136.63, 136.79, 137.79, 162.12 (CO) ppm; HPLC (*Z*) RP-18[a]: $t_0 = 1.79$ min, $k' = 14.76$, $\lambda_{max} = 341.1$ nm; RP-18[b]: $t_0 = 1.83$ min, $k' = 4.19$; ChiralCel OJ–R[b]: $t_0 = 1.89$ min, $k_1' = 2.72$, $k_2' = 3.39$; (*E*) RP-18[a]: $t_0 = 1.79$ min, $k' = 10.70$, $\lambda_{max} = 338.6$ nm; RP-18[b]: $t_0 = 1.83$ min, $k' = 2.86$.

(Z/E)-1-(4-Bromophenyl)-3-(4-trifluoromethylbenzylidene)-4-phenylazetidin-2-one (**4s**, $C_{23}H_{15}BrF_3NO$)
From 1.9 g (5 mmol) **2c** and 6.7 cm^3 (50 mmol) 4-trifluoromethylbenzaldehyde. The residue was crystallized from *Me*OH. The first fraction was pure (*Z*)-isomer, the following fractions contained mixtures of (*E*)- and (*Z*)-isomer, ratio *ca.* 1:3. Yield 1.2 g (53%); colorless crystals; mp (*Z*) 176.5°C (*Me*OH); IR: $\bar{\nu} = 3059$ (CH), 1807, 1734, 1720 (CO), 1616 (C=C) cm^{-1}; ^{1}H NMR (*Z*): $\delta = 5.41$ (d, $^4J_{4,\alpha} = 1.1$ Hz, 4-H), 6.32 (m, α-H), 7.27 (dd, 2 *ar* H), 7.35–7.47 (m, 7 *ar* H), 7.63 (d, $^3J = 8.2$ Hz, 2 *ar* H), 8.09 (d, $^3J = 8.2$ Hz, 2 *ar* H) ppm; (*E*): $\delta = 5.72$ (d, $^4J_{4,\alpha} = 1.5$ Hz, 4-H), 7.18 (d, $^4J_{\alpha,4} = 1.5$ Hz, α-H), 7.20–7.57 (m, 13 *ar* H) ppm; ^{13}C NMR (*Z*): $\delta = 62.55$ (C-4), 117.16 (C–Br), 118.51, 118.63, 125.51 (CF_3), 125.66, 125.73, 126.66, 126.74, 129.22, 129.38, 129.56, 130.13, 130.84, 132.29, 136.15, 136.57, 142.98, 159.69 (CO) ppm; HPLC (*Z*) RP-18[a]: $t_0 = 1.69$ min, $k' = 23.51$, $\lambda_{max} = 322.6$ nm; RP-18[b]: $t_0 = 1.83$ min, $k' = 7.56$; ChiralCel OJ–R[a]: $t_0 = 2.01$ min, $k_1' = 6.79$, $k_2' = 7.20$; (*E*) RP-18[a]: $t_0 = 1.69$ min, $k' = 11.61$, $UV_{max} = 322.6$ nm; ChiralCel OJ–R[a]: $t_0 = 2.01$ min, $k_1' = 2.81$, $k_2' = 3.64$.

(Z/E)-1-(4-Methoxyphenyl)-3-(4-nitrobenzylidene)-4-phenylazetidin-2-one (**4t**, $C_{23}H_{18}N_2O_4$)
From 3.25 g (10 mmol) **2b** and 15 g (100 mmol) 4-nitrobenzaldehyde. Ratio of isomers (HPLC) *Z*/*E* 2:1. Yield 1.2 g (31%); yellow needles; mp 179°C (*Me*OH, (Z)); IR: $\bar{\nu} = 3108$, 3064, 2934, 2907, 2838 (CH), 1806, 1730 (CO), 1594 (C=C), 1512, 1467, 1382, 1340 (NO_2) cm^{-1}; ^{1}H NMR (*Z*): $\delta = 3.76$ (s, O*Me*), 5.41 (d, $^4J_{4,\alpha} = 1.0$ Hz, 4-H), 6.29 (d, $^4J_{\alpha,4} = 1.0$ Hz, α-H), 6.83 (dd, $^3J = 7.0$, $^4J = 2.2$ Hz, 2 *ar* H), 7.34 (dd, $^3J = 7.0$, $^4J = 2.2$ Hz, 2 *ar* H), 7.37–7.47 (m, 5 *ar* H), 8.16 (dd, $^3J = 6.8$, $^4J = 2.5$ Hz, 2 *ar* H), 8.23 (dd, $^3J = 6.8$, $^4J = 2.5$ Hz, 2 *ar* H) ppm; (*E*): $\delta = 3.75$ (s, O*Me*), 5.73 (d, $^4J_{4,\alpha} = 1.4$ Hz, 4-H), 7.15 (d, $^4J_{\alpha,4} = 1.4$ Hz, α-H), 6.75–7.58 (m, 9 *ar* H), 8.05 (dd, $^3J = 7.0$, $^4J = 1.9$ Hz, 2 *ar* H), 8.09 (dd, $^3J = 7.0$, $^4J = 1.9$ Hz, 2 *ar* H) ppm; ^{13}C NMR (*Z*): $\delta = 55.49$ (O*Me*), 62.59 (C-4), 114.61, 118.59, 123.89, 126.78, 127.27, 127.89, 129.15, 129.34, 130.59, 136.32, 140.11, 145.25, 147.76 (C–NO_2), 156.69 (C–O*Me*), 158.92 (CO) ppm; HPLC (*Z*) RP-18[a]: $t_0 = 1.79$ min, $k' = 8.09$, $\lambda_{max} = 363.7$ nm; RP-18[b]: $t_0 = 2.40$ min, $k' = 2.07$; (*E*) RP-18[a]: $t_0 = 1.79$ min, $k' = 3.97$, $\lambda_{max} = 363.7$ nm, RP-18[b]: $t_0 = 2.40$ min, $k' = 1.00$.

(Z/E)-1-(4-Bromophenyl)-3-(4-nitrobenzylidene)-4-phenylazetidin-2-one (**4u**, $C_{22}H_{15}BrN_2O_3$)
From 3.74 g (10 mmol) **2c** and 15 g (100 mmol) 4-nitrobenzaldehyde. Ratio of isomers (HPLC) *Z*/*E* 2:1. Yield 2.9 g (66%); yellow crystals; mp 230–233°C (*Me*OH, (*Z*)); IR: $\bar{\nu} = 3105$, 3041, 2936, 2852 (CH), 1807, 1715 (CO), 1598 (C=C), 1520, 1488, 1375, 1343 (NO_2) cm^{-1}; ^{1}H NMR (*Z*): $\delta = 5.44$ (d, $^4J_{4,\alpha} = 1.1$ Hz, 4-H), 6.35 (d, $^4J_{\alpha,4} = 1.1$ Hz, α-H), 7.23–7.47 (m, 9 *ar* H), 8.15 (dd, $^3J = 6.9$, $^4J = 2.3$ Hz, 2 *ar* H), 8.24 (dd, $^3J = 6.9$, $^4J = 2.3$ Hz, 2 *ar* H) ppm; (*E*): $\delta = 5.74$ (d, $^4J_{4,\alpha} = 1.5$ Hz, 4-H), 7.20 (d, $^4J_{\alpha,4} = 1.5$ Hz, α-H), 7.21–7.57 (m, 11 *ar* H), 8.07 (dd, $^3J = 6.9$, $^4J = 1.9$ Hz, 2 *ar* H) ppm; ^{13}C NMR (*Z*): $\delta = 62.65$ (C-4), 117.46, 118.71, 123.92, 126.72, 128.47, 129.37, 129.46, 129.55, 130.68, 132.35, 135.80, 136.38, 139.72, 144.72, 147.97 (C–NO_2), 159.32 (CO) ppm; (*E*): $\delta = 64.74$ (C-4), 117.28, 118.57, 123.43, 123.84, 127.83, 129.90, 129.94, 132.29, 134.82, 139.02, 144.39, 147.87 (C–NO_2), 161.16 (CO) ppm; HPLC (*Z*) RP-18[a]: $t_0 = 1.83$ min, $k' = 6.74$, $\lambda_{max} = 346.3$ nm; RP-18[b]: $t_0 = 1.89$ min, $k' = 2.88$; (*E*) RP-18[b]: $t_0 = 1.89$ min, $k' = 2.37$, $\lambda_{max} = 346.3$ nm.

(Z/E)-3-(5-Bromofuran-2-ylmethylene)-1-(4-bromophenyl)-4-phenylazetidin-2-one (**4v**, $C_{20}H_{13}Br_2NO_2$)
From 430 mg (1.15 mmol) **2c** and 1 g (5.7 mmol) 5-bromfurfural. On crystallization from *Me*OH first the (*E*)- and then the (*Z*)-isomer was obtained. Yield 230 mg (44%); yellow brownish crystals; mp 180°C (dec., (*Z*)); IR: $\bar{\nu} = 3146$, 2359 (CH), 1786, 1721 (CO), 1681 (C=C) cm^{-1}; ^{1}H NMR (*Z*): $\delta = 5.37$ (d, $^4J_{4,\alpha} = 1.1$ Hz, 4-H), 6.18 (dd, $^4J_{\alpha,4} = 1.1$, $^5J_{\alpha,F4} = 0.6$ Hz, α-H), 6.43 (dd, $^3J_{F4,F3} = 3.6$, $^5J_{F4,\alpha} = 0.6$ Hz, 4-H_F), 7.15–7.43 (m, 9 *ar* H), 7.46 (d, $^3J_{F3,F4} = 3.6$ Hz, 3-H_F) ppm; (*E*): $\delta = 5.67$ (d, $^4J_{4,\alpha} = 1.4$ Hz, 4-H), 6.28 (d, $^3J_{F3,F4} = 3.5$ Hz, 3-H_F), 6.40 (d, $^3J_{F4,F3} = 3.5$ Hz, 4-H_F), 6.79 (d, $^4J_{\alpha,4} = 1.4$ Hz, α-H), 7.15–7.62 (m, 9 *ar* H); ^{13}C NMR (*Z*): $\delta = 62.38$ (C-4), 118.38 (α-CH), 152.03, 159.71 (CO) ppm; (*E*): $\delta = 64.37$ (C-4), 118.45 (α-CH), 151.38, 161.55 (CO); (*Z*/*E*): $\delta = 111.53$, 114.06, 114.58, 115.99, 116.58, 116.73, 116.81, 116.91, 124.20, 125.56, 126.64, 128.02, 128.88, 128.91, 129.12, 129.30, 132.15, 132.22, 135.85, 136.16, 136.69, 136.76, 137.75, 138.76 ppm; HPLC (*Z*) (RP-18[b]: $t_0 = 1.83$ min, $k' = 7.56$, $\lambda_{max} = 346.3$ nm; (*E*): (RP-18[b]: $t_0 = 1.83$ min, $k' = 4.92$, $\lambda_{max} = 343.7$ nm.

(Z/E)-1-(4-Bromophenyl)-3-(4-chlorobenzylidene)-4-phenylazetidin-2-one (**4w**, $C_{22}H_{15}BrClNO$)
From 1.9 g (5 mmol) **2c** and 7 g (50 mmol) 4-chlorobenzaldehyde. Yield 0.6 g (29%); colorless crystals; mp (*Z*) 234–235°C (2-Propanol); IR: $\bar{\nu} = 3061$, 2861 (CH), 1720 (CO), 1633 (C=C) cm^{-1}; ^1H NMR (*Z*): $\delta = 5.37$ (d, $^4J_{4,\alpha} = 1.1$ Hz, 4-H), 6.24 (dd, α-H), 7.21–7.45 (m, 11 *ar* H), 7.93 (dd, $J = 6.7$, 1.8 Hz, 2 *ar* H) ppm; ^{13}C NMR: $\delta = 62.45$ (C-4), 116.92, 118.39, 118.53, 126.74, 128.94, 129.09, 129.32, 130.03, 131.31, 132.24, 132.35, 135.73, 136.39, 140.88, 160.61 (CO) ppm; HPLC (*Z*) RP-18[b]: $t_0 = 2.40$ min, $k' = 7.53$, $\lambda_{max} = 322.5$ nm; (*E*) RP-18[b]: $t_0 = 2.40$ min, $k' = 3.81$, $\lambda_{max} = 320.5$ nm.

(Z)-1-(4-Bromophenyl)-3-(2-nitrobenzylidene)-4-phenylazetidin-2-one (**4x**, $C_{22}H_{15}BrN_2O_3$)
The mother liquor of **3c** was concentrated and then refluxed with 10% (m/m) conc. H_3PO_4 and *ca.* 1% (m/m) conc. H_2SO_4 with 3 Å mol. sieves for 2 h. After neutralization (Na_2CO_3) the mixture was extracted with *Ac*O*Et*, and the organic layer was evaporated *in vacuo*. Mp 177–178°C (*Me*OH); ^1H NMR (*DMSO*-d_6): $\delta = 5.88$ (d, $^4J_{4,\alpha} = 1.5$ Hz, 4-H), 6.86 (d, $^4J_{\alpha,4} = 1.5$ Hz, α-H), 7.20–7.60 (m, 9 *ar* H), 7.60–7.90 (m, 4′-H, 5′-H), 8.08 (dd, $^3J_{3',4'} = 8.0$, $^4J_{3',5'} = 1.3$ Hz, 3′-H), 8.26 (dd, $^3J_{6',5'} = 7.8$, $^4J_{6',4'} = 1.3$ Hz) ppm; HPLC: ((*S*,*S*)-Whelk 01, *n*-hexane/2-propanol 3/1): $t_0 = 2.24$ min, $k'_1 = 3.90$, $k'_2 = 4.15$, $\lambda_{max} = 336.1$ nm.

(Z/E)-1-(4-Bromophenyl)-3-(2,4-dichlorobenzylidene)-4-phenylazetidin-2-one (**4y**, $C_{22}H_{14}BrCl_2NO$)
From 1 g (2.7 mmol) **2c** and 3 g (17 mmol) 2,4-dichlorobenzaldehyde. Yield 210 mg (17%); colorless crystals; mp (*Z*) 212–214°C (2-Propanol); IR: $\bar{\nu} = 3087$, 3064, 3029 (CH), 1810, 1715 (CO), 1631 (C=C) cm^{-1}; ^1H NMR (*Z*): $\delta = 5.41$ (d, $^4J_{4,\alpha} = 1.1$ Hz, 4-H), 6.72 (dd, α-H), 7.18–7.50 (m, 10 *ar* H), 7.32 (d, $J = 8.5$ Hz, 5′-H), 8.67 (d, $J = 8.5$ Hz, 6′-H) ppm; (*E*): $\delta = 5.65$ (d, $^4J_{4,\alpha} = 1.5$ Hz, 4-H), 7.02 (d, $J = 1.5$ Hz, α-H), 7.02–7.50 (m, 11 *ar* H), 7.87 (d, $J = 8.5$ Hz, 6′-H) ppm; HPLC (*Z*) RP-18[b]: $t_0 = 1.90$ min, $k' = 14.94$, $\lambda_{max} = 326.9$ nm; (*E*) RP-18[b]: $t_0 = 1.90$ min, $k' = 7.20$, $\lambda_{max} = 322.6$ nm.

(Z/E)-1-(4-Bromophenyl)-3-(2-chlorobenzylidene)-4-phenylazetidin-2-one (**4z**, $C_{22}H_{15}BrClNO$)
From 1 g (2.7 mmol) **2c** and 3.5 cm^3 (31 mmol) 2-chlorobenzaldehyde. Yield 220 mg (19%); colorless crystals; mp 216°C (*Et*OH); IR: $\bar{\nu} = 3060$, 3025 (CH), 1814, 1717 (CO), 1678 (C=C) cm^{-1}; ^1H NMR (*Z*): $\delta = 5.43$ (d, $J = 1.2$ Hz, 4-H), 6.81 (d, $J = 1.2$ Hz, α-H), 8.68 (m, 6′-H), 7.20–7.48 (m, 12 *ar* H) ppm; ^{13}C NMR (*Z*): $\delta = 114.14$, 121.72, 127.99, 128.06, 128.27, 131.07, 137.61, 144.88 ppm; HPLC (*Z*) RP-18[b]: $t_0 = 1.90$ min, $k' = 8.32$, $\lambda_{max} = 322.6$ nm; (*E*) RP-18[b]: $t_0 = 1.90$ min, $k' = 4.38$.

Reactions with amines. General procedure
Under N_2 at −78°C, *n-Bu*Li was added to a solution of the amine (freshly distilled) in *THF*, and after 15 min stirring, a solution of **4** in *THF* was added drop by drop. After 30 min, the mixture was hydrolyzed with a solution of NH_4Cl (60 g dm^{-3}). The organic layer was separated, the aqueous layer was 3× washed with $CHCl_3$, the combined organic layers were dried (Na_2SO_4) and evaporated. The residue was crystallized or purified by CC as noted.

1-(4-Methoxyphenyl)-3-[α-(phenylcarbamoyl)ethylidene]-4-phenylazetidin-2-one (**4f**, $C_{25}H_{22}N_2O_3$)
From (*E*)-**4e** (1.0 g, 2.9 mmol), aniline (0.93 g, 10 mmol), and *n-Bu*Li (6.3 cm^3, 10 mmol). Yield 870 mg (76%); yellow crystals; mp 188°C (*Me*OH); IR: $\bar{\nu} = 3255$ (NH), 3130, 3060, 3040, 3017, 2990, 2965, 2930, 2840 (CH), 1740, 1640 (CO) cm^{-1}; ^1H NMR: $\delta = 2.40$ (s, *Me*), 3.70 (*s*, *Me*O), 5.60 (*s*, 4-H), 6.98 (*s*, NH), 6.59–7.55 (*m*, 14 *ar* H).

1-(4-Methoxyphenyl)-3-[α-(phenylcarbamoyl)benzylidene]-4-phenylazetidin-2-one (**4g**, $C_{30}H_{24}N_2O_3$)
From (*E*)-**4d** (1.0 g, 2.51 mmol), aniline (0.93 cm^3, 10 mmol), and *n-Bu*Li (6.3 cm^3, 10 mmol). Yield 980 mg (85%); yellow crystals; mp 133°C (*Me*OH); IR: $\bar{\nu} = 3400$, 3320 (NH), 3070, 3030, 3000, 2960, 2935, 2840 (CH), 1735, 1660 (CO), 1685 (C=C) cm^{-1}; ^1H NMR: $\delta = 3.67$ (s, *Me*O), 5.73 (s, 4-H), 6.61–7.83 (m, 19 *ar* H, NH).

3-[α-(Cyclohexylcarbamoyl)ethylidene)]-1-(4-methoxyphenyl)-4-phenylazetidin-2-one (**4h**, $C_{25}H_{28}N_2O_3$)
From (*E*)-**4e** (1.0 g, 2.97 mmol), cyclohexylamine (1.18 g, 11.88 mmol), and *n-Bu*Li (7.48 cm^3, 11.88 mmol). CC ($CHCl_3$). Yield 150 mg (12%); yellowish crystals; mp 98°C (*Me*OH); IR: $\bar{\nu} = 3250$ (NH), 3090, 3060, 3030, 2930, 2850 (CH), 1740, 1620 (CO) cm^{-1}; ^1H NMR: $\delta = 0.73$–1.69 (m, 11 cyclohexyl-H), 2.31 (s, *Me*), 3.70 (s, *Me*O), 5.25 (s, NH), 5.85 (s, 4-H), 6.68–7.50 (m, 9 *ar* H).

3-[α-(Benzylcarbamoyl)benzylidene]-1-(4-methoxyphenyl)-4-phenylazetidin-2-one (**4i**, $C_{31}H_{26}N_2O_3$)
From (*E*)-**4d** (1.0 g, 2.5 mmol), benzylamine (1.07 g, 10 mmol), and *n-Bu*Li (6.3 cm^3, 10 mmol). CC ($CHCl_3$). Yield 460 mg (39%); yellow crystals; mp 193°C (*Me*OH); IR: $\bar{\nu} = 3340$ (NH), 3080, 3030, 3000, 2860, 2940, 2840 (CH), 1740, 1655 (CO), 1690 (C=C) cm^{-1}; ^1H NMR: $\delta = 3.64$ (s, *Me*O), 4.20 (d, $J = 7$ Hz, CH_2), 5.64 (t, NH), 5.75 (s, 4-H), 6.60–7.59 (m, 19 *ar* H).

3-(Diisopropylamino)-3-[α-(methoxycarbonyl)benzyl]-1-(4-methoxyphenyl)-4-phenylazetidin-2-one (**5f**, $C_{31}H_{36}N_2O_4$)
From **4d** (1.0 g, 2.51 mmol), diisopropylamine (1.4 cm^3, 10 mmol), and *n-Bu*Li (6.3 cm^3, 10 mmol). Yield 900 mg (72%); colorless crystals; mp 175°C (*Me*OH); IR: $\bar{\nu} =$ 3060, 3020, 2950, 2860, 2830 (CH), 1760–1720 (CO) cm^{-1}; ^1H NMR (80 MHz): $\delta = 1.19$–1.37 (m, 2CH*Me*$_2$), 3.54, 3.70 (2s, 2*Me*O), 4.12 (s, α-H), 5.22 (s, 4-H), 6.55–7.30 (m, 14 *ar* H).

3-(Dicyclohexylamino)-3-[α-(methoxycarbonyl)benzyl]-1-(4-methoxyphenyl)-4-phenylazetidin-2-one (**5g**, $C_{37}H_{44}N_2O_4$)
From (*Z*)-**4d** (1.0 g, 2.51 mmol), dicyclohexylamine (1.8 cm^3, 10 mmol), and *n-Bu*Li (6.3 cm^3, 10 mmol). Yield 1.00 g (68%); colorless crystals; mp 181–182°C (*Me*OH); IR: $\bar{\nu} = 3060$, 3030, 2925, 2850 (CH), 1740 (CO) cm^{-1}; ^1H NMR (80 MHz): $\delta = 1.01$–2.05 (m, 22 cyclohexyl-H), 3.50, 3.69 (2s, 2*Me*O), 4.05 (s, α-H), 5.13 (s, 4-H), 6.63–7.31 (m, 14 *ar* H).

3-(Diethylamino)-3-[α-(methoxycarbonyl)benzyl]-1-(4-methoxyphenyl)-4-phenylazetidin-2-one (**5h**, $C_{29}H_{32}N_2O_4$)
From (*Z*)-**4d** (1.0 g, 2.51 mmol), diethylamine (740 mg, 10 mmol), and *n-Bu*Li (6.3 cm^3, 10 mmol). Yield 800 mg (68%); colorless crystals; mp 112–114°C (*Me*OH); IR: $\bar{\nu}$ = 3070, 3030, 2970, 2930, 2840 (CH), 1755–1745, 1720 (CO) cm^{-1}; ^{1}H NMR (80 MHz): δ = 1.07 (t, 2 *Me*), 2.75–3.05 (m, $2CH_2$), 3.52, 3.67 (2s, 2*Me*O), 3.97 (s, α-H), 5.00 (*s*, 4-H), 6.66–7.26 (m, 14 *ar* H).

3-[α-(Methoxycarbonyl)benzyl]-1-(4-methoxyphenyl)-4-phenyl-3-(pyrrolidin-1-yl)azetidin-2-one (**5i**, $C_{29}H_{30}N_2O_4$)
From a) (*Z*)-**4d** or b) (*E*)-**4d** (1.0 g, 2.51 mmol), pyrrolidine (720 mg, 10.04 mmol), and *n-Bu*Li (6.3 cm^3, 10 ml). Yield a) 720 mg (61%), b) 550 mg (47%); colorless crystals; mp 166–167°C (*Me*OH); IR: $\bar{\nu}$ = 3070, 3030, 2950, 2880, 2840, 2820 (CH), 1755, 1735 (CO) cm^{-1}; ^{1}H NMR (80 MHz): δ = 1.85 (m, $2CH_2$), 2.80 (m, $2CH_2$), 3.60, 3.72 (2s, 2*Me*O), 3.99 (s, α-H), 5.05 (s, 4-H), 6.67–7.35 (m, 14 *ar* H).

3-[α-(Methoxycarbonyl)ethyl]-1-(4-methoxyphenyl)-4-phenyl-3-(pyrrolidin-1-yl)azetidin-2-one (**5j**, $C_{24}H_{28}N_2O_4$)
From (*E*/*Z*)-**4e** (800 mg, 2.37 mmol), pyrrolidine (0.84 cm^3, 10 mmol), and *n-Bu*Li (6.32 cm^3, 10 mmol). Yield 520 mg (54%); colorless crystals; mp 104°C (*Me*OH); IR: $\bar{\nu}$ = 3060, 3030, 3010, 2980, 2950, 2900, 2840 (CH), 1760 (CO) cm^{-1}; ^{1}H NMR (80 MHz): δ = 1.13 (d, *J* = 7 Hz, *Me*), 1.81 (m, $2CH_2$), 2.94 (m, *J* = 7 Hz, $2CH_2$, α-H), 3.44, 3.77 (2s, 2*Me*O), 5.17 (s, 4-H), 6.70–7.43 (m, 9 *ar* H).

3-[α-(Methoxycarbonyl)benzyl]-1,4-diphenyl-3-piperidinoazetidin-2-one (**5k**, $C_{29}H_{30}N_2O_3$)
From (*E*/*Z*)-**4c** (1.0 g, (2.71 mmol), piperidine (460 mg, 5.42 mmol), and *n-Bu*Li (3.41 cm^3, 5.42 mmol), CC (cyclohexane/*Ac*O*Et* 4/1). Yield 340 mg (28%); colorless crystals; mp 185°C (dec., *Me*OH); IR: $\bar{\nu}$ = 3050, 3020, 2980, 2920, 2840 (CH), 1750, 1720 (CO) cm^{-1}; ^{1}H NMR (80 MHz): δ = 1.25–1.85 (m, $3CH_2$), 2.93 (s, $2CH_2$), 3.65 (s, *Me*O), 4.03 (s, α-H), 5.18 (s, 4-H), 6.80–7.74 (m, 15 *ar* H).

3-[α-(Methoxycarbonyl)benzyl]-1-(4-methoxyphenyl)-4-phenyl-3-piperidinoazetidin-2-one (**5l**, $C_{30}H_{32}N_2O_4$)
From a) (*E*/*Z*)-**4d** or b) (*Z*)-**4d** (1.0 g, 2.51 mmol), piperidine (1.28 cm^3, 10.84 mmol) and *n-Bu*Li (6.82 cm^3, 10.84 mmol): a) 900 mg (72%), b) 803 mg (66%), mixture of **5l** and **13a**. Separation CC (cyclohexane/*Ac*O*Et* 4/1). Yield a) 440 mg (36%), b) 290 mg (24%); colorless crystals; mp 175°C (*Me*OH); IR: $\bar{\nu}$ = 3060, 3030, 2930, 2860, 2800 (CH), 1745, 1720 (CO) cm^{-1}; ^{1}H NMR (80 MHz): δ = 1.56 (s, $3CH_2$), 2.91 (s, $4CH_2$), 3.62, 3.70 (2s, 2*Me*O), 4.04 (s, α-H), 5.14 (s, 4-H), 6.69–7.30 (m, 14 *ar* H).

3-[α-(Methoxycarbonyl)benzyl]-1-(4-methoxyphenyl)-3-(morpholin-4-yl)-4-phenylazetidin-2-one (**5m**, $C_{29}H_{30}N_2O_5$)
From a) (*E*/*Z*)-**4d** or b) (*Z*)-**4d** or c) (*E*)-**4d** (1.0 g, 2.51 mmol), morpholine (0.88 cm^3, 10.84 mmol) and *n-Bu*Li (6.82 cm^3, 10.84 mmol). Yield a) 800 mg (66%), b) 872 mg (72%), mixture of **5m** and **13b**, c) 260 mg (21%). CC (cyclohexane/*Ac*O*Et* 4/1). *Rf* = 0.75. Yield a) 300 mg (24%), b) 490 mg (39%); colorless crystals; mp 192°C (*Me*OH); IR: $\bar{\nu}$ = 3065, 3030, 2970, 2955, 2850 (CH), 1750, 1730 (CO) cm^{-1}; ^{1}H NMR (80 MHz): δ = 2.97 (m, $2CH_2$), 3.59–3.74 (m, $2CH_2$), 3.61, 3.67 (2s, 2*Me*O), 3.97 (s, α-H), 5.20 (s, 4-H), 6.70–7.31 (m, 14 *ar* H).

1-(4-Methoxyphenyl)-4-phenyl-3-[α-(phenylcarbamoyl)-benzyl]-3-(pyrrolidin-1-yl)azetidin-2-one (**5n**, $C_{34}H_{33}N_3O_3$)
From **4g** (500 mg, 1.1 mmol), pyrrolidine (0.42 cm^3, 5 mmol), and *n-Bu*Li (3.16 cm^3, 5 mmol). Yield 233 mg (40%); colorless crystals mp 212°C (*Me*OH); IR: $\bar{\nu}$ = 3390, 3260 (NH), 3130, 3060, 3030, 2970, 2830 (CH), 1735 (CO) cm^{-1}; ^{1}H NMR (80 MHz): δ = 1.50, 3.17 ($2m_c$, $4CH_2$), 3.67 (s, *Me*O), 4.77 (s, α-H), 6.00 (s, 4-H), 6.55–7.80 (m, NH, 19 *ar* H).

Addition of S-nucleophiles. General procedure
At −78°C, an equivalent amount of *n-Bu*Li was added to the thiol in 10 cm^3 *THF*, and after 15 min stirring, the β-lactam **4** in 20 cm^3*THF* was added drop by drop. After 10 min, the mixture was hydrolyzed with a solution of NH_4Cl (30 cm^3, 60 g dm^{-3}), the aqueous layer was once washed with $CHCl_3$, the organic layers were dried (Na_2SO_4) and evaporated.

3-[1-(Methoxycarbonyl)ethyl]-1-(4-methoxyphenyl)-4-phenyl-3-(phenylthio)azetidin-2-one (**5o**, $C_{26}H_{25}NO_4S$)
From thiophenol (1.2 cm^3, 10 mmol), (*Z*)-**4e** (700 mg, 2.06 mmol), and *n-Bu*Li (3.15 ml, 5 mmol). Yield 600 mg (65%); colorless crystals; mp 157–158°C (*Me*OH); IR: $\bar{\nu}$ = 3055, 3030, 3000, 2950, 2930, 2900, 2830 (CH), 1740, 1725 (CO) cm^{-1}; ^{1}H NMR (80 MHz): δ = 1.33 (d, *J* = 7 Hz, *Me*), 3.08 (q, *J* = 7 Hz, α-H), 3.73 (s, 2*Me*O), 5.70 (s, 4-H), 6.70–7.63 (m, 14 *ar* H).

3-Isopropylthio-3-[α-(methoxycarbonyl)benzyl]-1-(4-methoxyphenyl)-4-phenylazetidin-2-one (**5p**, $C_{28}H_{29}NO_4S$)
From 1-methylethanethiol (0.4 cm^3, 5 mmol), *n-Bu*Li (3.16 cm^3, 5 mmol), and (*Z*)-**4d** (500 mg, 1.25 mmol). Yield 346 mg (58%); colorless crystals; mp 127°C (*Me*OH); IR: $\bar{\nu}$ = 3060, 3030, 2950, 2930, 2910, 2860, 2830 (CH), 1745 (CO) cm^{-1}; ^{1}H NMR (80 MHz): δ = 1.25 (d, *J* = 7 Hz, 2 *Me*), 3.55 (mc, *J* = 7 Hz, $CHMe_2$), 3.60, 3.71 (2s, 2*Me*O), 4.55 (s, α-H), 5.33 (s, 4-H), 6.45–7.55 (m, 14 *ar* H).

3-Allylthio-3-[α-(methyoxycarbonyl)benzyl]-1-(4-methoxyphenyl)-4-phenylazetidin-2-one (**5q**, $C_{28}H_{27}NO_4S$)
From 2-propenethiol (0.6 cm^3, 5 mmol), *n-Bu*Li (3.15 cm^3, 5 mmol), and (*Z*)-**4d** (500 mg, 1.25 mmol). Yield 295 mg (50%); yellowish crystals; mp 93°C (*Me*OH); IR: $\bar{\nu}$ = 3060, 3030, 3010, 2950, 2835 (CH), 1735 (CO) cm^{-1}; ^{1}H NMR (80 MHz): δ = 3.50–3.74 (m, CH_2), 3.63, 3.73 (2s, *Me*O), 4.63 (s, α-H), 4.93–5.25 (m, CH_2), 5.34 (s, 4-H), 5.50–6.04 (m, –CH=), 6.48–7.55 (m, 14 *ar* H).

3-[α-(Methoxycarbonyl)benzyl]-3-[2-(methoxycarbonyl)-ethylthio]-1-(4-methoxyphenyl)-4-phenylazetidin-2-one (**5r**, $C_{29}H_{29}NO_6S$)
From methyl 3-mercaptopropionate (2.6 cm^3, 20 mmol), *n-Bu*Li (12.6 cm^3, 20 mmol), and (*Z*)-**4d** (1.0 g, 2.5 mmol). Yield

970 mg (75%); colorless crystals; mp 102°C (*Me*OH); IR: $\bar{\nu}$ = 3070, 3030, 3010, 2950, 2840 (CH), 1740 (CO) cm^{-1}; ^1H NMR (80 MHz): δ = 2.35–3.35 (m, CH_2–CH_2), 3.63 (s, $2CO_2Me$), 3.75 (s, *Me*O), 4.59 (s, α-H), 5.38 (s, 4-H), 6.49–7.58 (m, 14 *ar* H).

3-[1-(Methoxycarbonyl)ethyl]-3-[2-(methoxycarbonyl)-ethylthio]-1-(4-methoxyphenyl)-4-phenylazetidin-2-one (**5s**, $C_{24}H_{27}NO_6S$)
From (*Z*)-**4e** (560 mg, 1.66 mmol), methyl 3-mercaptopropionate (0.65 cm^3, 5 mmol), and *n-Bu*Li (3.15 cm^3, 5 mmol). Yield 620 mg (82%); colorless crystals; mp 116°C (*Me*OH); IR: $\bar{\nu}$ = 3090, 3070, 3040, 2990, 2955, 2850 (CH), 1745, 1700 (CO) cm^{-1}; ^1H NMR (80 MHz): δ = 1.43 (d, J = 7 Hz, *Me*), 2.55, 3.05 (mc, $2CH_2$), 3.38 (q, J = 7 Hz, α-H), 3.63 (s, *Me*O), 3.75 (s, $2CO_2Me$), 5.54 (s, 4-H), 6.70–7.38 (m, 9 *ar* H).

3-(t-Butylthio)-3-[α-(methoxycarbonyl)benzyl]-1-(4-methoxyphenyl)-4-phenylazetidin-2-one (**5t**, $C_{29}H_{31}NO_4S$)
From *t-Bu*SH (900 mg, 10 mmol), *n-Bu*Li (6.3 cm^3, 10 mmol), and (*Z*)-**4d** (1.0 g, 2.5 mmol). Yield 907 mg (74%); colorless crystals; mp 151–153°C (*Me*OH); IR: $\bar{\nu}$ = 3070, 3040, 3000, 2960 (CH), 1745 (CO) cm^{-1}; ^1H NMR (80 MHz): δ = 1.53 (s, CMe_3), 3.61, 3.74 (2s, 2*Me*O), 4.79 (s, α-H), 5.35 (s, 4-H), 6.45–7.50 (m, 14 *ar* H).

3-(n-Butylthio)-3-[α-(methoxycarbonyl)benzyl]-1-(4-methoxyphenyl)-4-phenylazetidin-2-one (**5u**, $C_{29}H_{31}NO_4S$)
From *n-Bu*SH (900 mg, 10 mmol), *n-Bu*Li (6.3 cm^3, 10 mmol), and (*Z*)-**4d** (1.0 g, 2.5 mmol). Yield 860 mg (70%); yellowish crystals; mp 115°C (*Me*OH); IR: $\bar{\nu}$ = 3085, 3040, 2970, 2950, 2880, 2855 (CH), 1750, 1730 (CO) cm^{-1}; ^1H NMR (80 MHz): δ = 0.69–0.94 (m, *Me*), 1.10–1.60 (m, CH_2–CH_2), 2.65–3.06 (m, SCH_2), 3.65, 3.75 (2s, 2*Me*O), 4.60 (s, α-H), 5.38 (s, 4-H), 6.53–7.63 (m, 14 *ar* H).

3-n-Butyl-3-[α-(methoxycarbonyl)benzyl]-1-(4-methoxyphenyl)-4-phenylazetidin-2-one (**5v**, $C_{29}H_{31}NO_4$)
At −78°C, *n-Bu*Li (6.3 cm^3, 10 mmol) was added to (*Z*)-**4d** (1.0 g, 2.51 mmol) in 20 cm^3 *THF*. After 10 min, the mixture was hydrolyzed with a solution of NH_4Cl (30 cm^3, 60 g dm^{-3}), the aqueous layer was once washed with $CHCl_3$, the combined organic layers were dried (Na_2SO_4) and evaporated. Yield 252 mg (21%); colorless crystals; mp 165°C (*Me*OH); IR: $\bar{\nu}$ = 3080, 3060, 3025, 2950, 2930, 2875, 2835 (CH), 1725 (CO) cm^{-1}; ^1H NMR (80 MHz): δ = 0.73–2.76 (m, CH_2–CH_2–CH_2–*Me*), 3.05 (s, CO_2Me), 3.68 (s, *Me*O), 3.95 (s, α-H), 5.03 (s, 4-H), 6.65–7.29 (m, 14 *ar* H); ^{13}C NMR: δ = 14.47 (*Me*), 23.54, 26.83, 28.99 (CH_2), 51.92 (CO_2Me), 52.35 (C-α), 55.86 (*Me*O), 63.15 (C-4), 64.49 (C-3), 114.80, 119.16, 128.08, 130.22 (*ar* C), 131.04, 134.62, 134.86 (quart. *ar* C), 156.51 (CO Lactam), 171.81 (CO Ester).

Oxidation with m-chloroperbenzoic acid (MPCBA). General procedure
A threefold excess of MCPBA was added to a solution of the sulfide in 20 cm^3 CH_2Cl_2. After stirring for 1 h the excess of MCPBA was destroyed by NaOH solution, the organic layer was dried (Na_2SO_4) and evaporated *in vacuo*.

Diethyl [1-(4-methoxyphenyl)-2-oxo-4-phenylsulfonyl-azetidin-3-yl]malonate (**6a**, $C_{29}H_{29}NO_8S$)
From **5d** (500 mg, 1 mmol) and MCPBA (492 mg, 3 mmol). Yield 375 mg (68%); light yellow crystals; mp 120°C (*Me*OH); IR: $\bar{\nu}$ = 3060, 2990, 2970, 2910, 2830 (CH), 1755 (CO), 1330, 1145 (SO_2) cm^{-1}; ^1H NMR (80 MHz): δ = 1.10, 1.40 (2t, J = 7 Hz, *Me*), 3.74 (s, *Me*O), 3.96–4.50 (m, $2OCH_2$), 4.10 (s, α-H), 6.23 (s, 4-H), 6.73–8.04 (m, 14 *ar* H).

3-[α-(Methoxycarbonyl)benzyl]-3-[2-(methoxycarbonyl)-ethylsulfonyl]-1-(4-methoxyphenyl)-4-phenylazetidin-2-one (**6b**, $C_{29}H_{29}NO_8S$)
From **5r** (400 mg, 0.77 mmol) and MCPBA (378 mg, 2.31 mmol). Yield 364 mg (81%); colorless crystals; mp 137–138°C (*Me*OH); IR: $\bar{\nu}$ = 3060, 3030, 3005, 2950, 2930, 2830 (CH), 1765 (CO Lactam), 1735 (CO Ester), 1310, 1125 (SO_2) cm^{-1}; ^1H NMR (80 MHz): δ = 2.33–3.44 (m, CH_2–CH_2), 3.64 (s, $2CO_2Me$), 3.79 (s, *Me*O), 4.88 (s, α-H), 5.76 (s, 4-H), 6.50–7.71 (m, 14 *ar* H).

3-[1-(Methoxycarbonyl)ethyl]-1-(4-methoxyphenyl)-4-phenyl-3-(phenylsulfonyl)azetidin-2-one (**6c**, $C_{26}H_{25}NO_6S$)
From **5o** (350 mg, 0.78 mmol) and MCPBA (438 mg, 2.34 mmol). Yield 233 mg (62%); colorless crystals; mp 150–152°C (dec, *Me*OH); IR: $\bar{\nu}$ = 3035, 3015, 3000, 2950, 2825 (CH), 1760 (CO Lactam), 1735 (CO Ester), 1325, 1140 (SO_2) cm^{-1}; ^1H NMR (80 MHz): δ = 1.35 (d, J = 7 Hz, *Me*), 3.23 (q, J = 7 Hz, α-H), 3.76, 3.85 (2s, 2*Me*O), 6.05 (s, 4-H), 6.74–8.05 (m, 14 *ar* H).

3-[1-(Methoxycarbonyl)ethyl]-3-[2-(methoxycarbonyl)-ethylsulfonyl]-1-(4-methoxyphenyl)-4-phenylazetidin-2-one (**6d**, $C_{24}H_{27}NO_8S$)
From **5s** (350 mg, 0.76 mmol) and MCPBA (375 mg, 2.28 mmol). Yield 360 mg (97%); colorless crystals; mp 150°C (*Me*OH); IR: $\bar{\nu}$ = 3070, 3040, 3000, 2960, 2850 (CH), 1750 (CO), 1330, 1140 (SO_2) cm^{-1}; ^1H NMR (80 MHz): δ = 1.45 (d, J = 7 Hz, *Me*), 2.48–3.90 (m, CH_2–CH_2, α-H), 3.64 (s, *Me*O), 3.73, 3.80 (2s, $2CO_2Me$), 5.88 (s, 4-H), 6.69–8.03 (m, 9 *ar* H).

2-[(4-Bromophenylamino)(phenyl)methyl)]-3-(furan-2-yl)-1-(morpholin-4-yl)-prop-2-en-1-one (**11**, $C_{24}H_{23}BrN_2O_3$)
From 0.8 g (2.1 mmol) (*Z*)-**4o** and 0.87 cm^3 (10 mmol) morpholine. Yield 710 mg (73%); colorless crystals; mp 208–209°C (*Me*OH); IR: $\bar{\nu}$ = 3398 (NH), 3060, 3019, 2977, 2926, 2863 (CH), 1613 (CO), 1594 (C=C) cm^{-1}; ^1H NMR Isomer 1: δ = 2.3–3.9 (m, $8H_M$), 5.10 (d, $^3J_{CH,NH}$ = 5.7 Hz, CH–NH), 5.93 (d, $^3J_{NH,CH}$ = 5.7 Hz, NH), 6.62 (s, α-H), 6.36–6.43 (m, 3-H_F, 4-H_F), 6.70 (dd, J = 6.8 Hz, 2 *ar* H), 7.26 (dd, J = 6.8 Hz, 2 *ar* H), 7.36 (m, 5-H_F), 7.20–7.45 (m, 5 *ar* H); Isomer 2: δ = 2.3–3.9 (m, $8H_M$), 4.31 (d, $^3J_{NH,CH}$ = 2.8 Hz, NH), 5.14 (m, $^3J_{CH,NH}$ = 2.8, $^4J_{CH,\alpha}$ = 1.2 Hz, CH–NH), 6.29 (d, $^3J_{F3,F4}$ = 3.3 Hz, 3-H_F), 6.36–6.43 (m, 4-H_F), 6.38 (dd, J = 6.8 Hz, 2 *ar* H), 6.54 (d, $^4J_{\alpha,CH}$ = 1.2 Hz, α-H), 7.14 (dd, J = 6.8 Hz, 2 *ar* H), 7.36 (m, 5-H_F), 7.20–7.45 (m, 5 *ar* H); ^{13}C NMR Isomer 1: δ = 64.76

(NH–CH), 131.79, 132.50, 139.53, 143.64 (C-5_F), 145.78 (p–*Ar*–C–NH), 149.73 (C-2_F), 167.52 (CO); Isomer 2: $\delta = 62.69$ (NH–CH), 131.96, 132.50, 139.53, 143.20 (C-5_F), 145.37 (p–*Ar*–NH), 150.34 (C-2_F), 168.76 (CO); Isomer 1 or 2: $\delta = 41.30$, 41.45, 46.21, 65.40, 65.70, 66.05, 66.32, 108.80, 110.27, 111.34, 111.76, 111.87, 112.14, 113.93, 114.90, 115.55, 117.69, 126.77, 127.59, 128.08, 128.63, 128.84, 129.02, 129.25, 130.84; HPLC RP-18, *Me*CN/H_2O: 1/1): $t_0 = 1.79$ min, $k' = 17.67$, $\lambda_{max} = 260.5$ nm; ChiralCel OJ–R, *Me*CN/H_2O: 2/3): $t_0 = 2.40$ min, $k_1' = 12.86$, $k_2' = 13.59$; MS (70 eV): m/z (%) = 468.7 (3.3, $^{13}C/^{81}Br–M^+$), 467.7 (16.1, $^{81}Br–M^+$), 466.7 (3.6, $^{13}C/^{79}Br–M^+$), 465.7 (16.4, $^{79}Br–M^+$), 176.0 (100%).

(Z)-2-[(4-Bromophenylamino)(phenyl)methyl)]-1-(morpholin-1-yl)-3-[4-(trifluoromethyl)phenyl]prop-2-en-1-one (**12**, $C_{27}H_{24}BrF_3N_2O_2$)

From 0.9 g (2 mmol) (*Z*)-**4s** and 0.87 cm^3 (10 mmol) morpholine. Yield 730 mg (67%); colorless crystals; mp 204°C (*Me*OH); IR: $\bar{\nu} = 3398$ (NH), 3061, 3020, 2978, 2925, 2864 (CH), 1613 (CO), 1594 (C=C) cm^{-1}; ^1H NMR: Isomer 1: $\delta = 2.3–3.9$ (m, $8H_M$), 5.20 (d, $^3J_{CH,NH} = 5.7$ Hz, CH–NH), 6.01 (d, $^3J_{NH,CH} = 5.7$ Hz, NH), 6.89 (s, α-H), 6.74 (dd, $J = 6.8$, $J = 2.1$ Hz, 2 *ar* H), 7.20–7.69 (m, 11 *ar* H); Isomer 2: $\delta = 2.3–3.9$ (m, $8H_M$), 4.32 (d, $^3J_{NH,CH} = 2.8$ Hz, NH), 5.25 (m, $^3J_{CH,NH} = 2.8$, $^4J_{CH,\alpha} = 1.2$ Hz, CH–NH), 6.42 (dd, $J = 6.8$, $J = 2.1$ Hz, 2 *ar* H), 6.84 (d, $^4J_{\alpha,CH} = 1.2$ Hz, α-H), 7.16 (dd, $J = 6.8$, $J = 2.1$ Hz, 2 *ar* H), 7.20–7.69 (m, 11 *ar* H); ^{13}C NMR: $\delta = 41.17$, 41.33, 45.77, 45.84, 62.78, 64.68, 65.34, 65.57, 65.76, 114.85, 115.04, 115.53, 124.11, 125.41, 125.49, 125.54, 125.62, 126.74, 127.10, 127.53, 128.19, 128.24, 128.28, 128.50, 128.81, 128.95, 129.11, 129.17, 129.36, 131.87, 132.03, 136.53, 139.01, 139.09, 145.23 (p–*Ar*–C–NH), 145.60 (p–*Ar*–C–NH), 167.30 (CO), 168.23 (CO); HPLC RP-18[b]: $t_0 = 1.79$ min, $k' = 8.80$, $\lambda_{max} = 258.6$ nm; ChiralCel OJ–R, *Me*CN/H_2O: 1/1): $t_0 = 2.01$ min, $k_1' = 12.31$, $k_2' = 13.07$.

2-[α-(4-Methoxyanilino)benzyl]-3-phenyl-1,4-dipiperidino-2-butenedicarboxamide (**13a**, $C_{34}H_{39}N_3O_3$)

As a by-product of the synthesis of **5l**. Yield a) 160 mg (21%), b) 142 mg (12%); colorless crystals, mp 224–225°C (*Me*OH); IR: $\bar{\nu} = 3370$ (NH), 3060, 3030, 3000, 2940, 2860 (CH), 1630, 1610, (CO) cm^{-1}; ^1H NMR (400 MHz): $\delta = 1.11–1.66$ (m, $6CH_2$), 2.41, 3.05 (mc, $J = 13.5$, 7.5, 3.3 Hz, $2H_{Pip}$), 3.17–3.56 (m, $3CH_2$), 3.65 (s, *Me*O), 5.29 (s, benzyl-CH), 5.98 (s, NH), 6.35–7.66 (m, 14 *ar* H); ^{13}C NMR: $\delta = 23.53$, 23.93, 24.37, 24.80, 25.11, 25.44 ($6 \times CH_2$), 41.36, 41.63, 47.18, 47.88 ($4 \times CH_2$), 55.18 (*Me*O), 57.26 (C–NHR), 114.23, 114.29, 126.84, 127.01, 127.97, 128.07, 128.12, 128.19 (*ar* C), 131.30, 133.25, 134.02 (quart. *ar* C), 139.37, 139.54 (C=C), 151.14 (*Me*O–C_{ar}), 166.17, 166.82 (N–*C*OR).

2-[α-(4-Methoxyanilino)benzyl]-1,4-bis(morpholin-4-yl)-3-phenyl-2-butenedicarboxamide (**13b**, $C_{32}H_{35}N_3O_5$)

As a by-product of the synthesis of **5m**. *Rf* = 0.43. Yield 140 mg (16%); colorless crystals; mp 227°C (*Me*OH); IR: $\bar{\nu} = 3270$ (NH), 3070, 3030, 3000, 2980, 2940, 2910, 2860 (CH), 1630 (CO) cm^{-1}; ^1H NMR (250 MHz): $\delta = 2.23$, 2.50 (mc, 2 morpholine-H), 3.19–3.78 (m, 14 morpholine-H), 3.68 (s, *Me*O), 5.36 (s, benzyl-CH), 5.79 (s, NH), 6.38–7.68 (m, 14 *ar* H); ^{13}C NMR: $\delta = 41.33$, 41.61, 46.75, 47.35 (morpholine-C), 55.57 (*Me*O), 57.52 (*C*H–N), 66.07, 66.10, 66.58, 66.72 (morpholine-C), 114.69, 114.86, 127.11, 128.39, 128.72, 128.89, 128.92 (*ar* C), 131.94, 133.46, 133.49 (quart. *ar* C), 139.32, 139.53 (C=C), 151.86 (*Me*O-*Car*), 166.84, 167.57 (NCO). MS: 541 (34, M^+), 542 (14, $[M+1]^+$), 70 (100).

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