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Original article

Imidazo[2,1-*b*]thiazepines: synthesis, structure and evaluation of benzodiazepine receptor binding

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Abstract

As a continuation of our search for new ligands acting on benzodiazepine receptors among the fused 2-thiohydantoin derivatives, a series of 5-substituted imidazo[2,1-*b*]thiazepines was synthesized and investigated in radioligand binding studies at the benzodiazepine binding site of $GABA_A$ receptors in rat brain cortical membranes. Among ortho-substituted 5-arylidene-imidazo[2,1-*b*]thiazepines compounds could be identified which exhibit affinity for the benzodiazepine binding site at low micromolar concentrations. X-ray structure analyses for two compounds (**6ae** and **6ag**) have been performed. In order to analyze the structure–activity relationships, 3D models of all compounds have been completed (using X-ray data). Physicochemical properties calculated (log *P* and log *D*) as well as experimental thin layer chromatography data were examined.

Keywords: Benzodiazepine receptor; $GABA_A$ receptor; Imidazo[2,1-*b*]thiazepines; Structure–activity relationships; X-ray structure analysis

1. Introduction

γ-Aminobutyric acid acts on the $GABA_A$ chloride ion channel; GABA is the principal inhibitory transmitter of many CNS pathways regulating numerous neurological functions including convulsions, anxiety and sleep activity as well as memory and learning processes [1,2]. Present molecular biology studies have demonstrated that several different receptor subunits (α_{1-6}, β_{1-4}, γ_{1-3}, δ, ε, π, ρ) combine to form the $GABA_A$ receptor complex with a number of native receptor subtypes identified thus far [3–6]. Numerous structural classes of chemical compounds bind to the $GABA_A$ chloride ion channel complex including the benzodiazepines, neurosteroids and barbiturates. Ligands acting at the benzodiazepine binding site of the $GABA_A$ receptor allosterically modulate the action of GABA on neuronal chloride ion flux. They show a wide variety of pharmacological actions ranging in a continuum from full agonists (sedative/hypnotic, anxiolytic and anticonvulsant activities) to inverse agonists (anxiogenic, and proconvulsant activities). Antagonists do not exhibit any direct pharmacological effects but can antagonize the actions of both agonists and inverse agonists [1–8]. Partial agonists lie within this continuum and may have reduced benzodiazepine-mediated side effects such as physical dependence, amnesia, oversedation and muscle relaxation [8,9]. Recently the development of partial agonists/antagonists [10–13] as well as receptor subtype selective ligands [14,15] has been the aim of several research groups.

In our research program, bicyclic heterocyclic compounds consisting of condensed 5 + 5, 5 + 6 and 5 + 7 ring systems were examined (Fig. 1). Derivatives of imidazo[2,1-b]thiazoles, -thiazines and -thiazepines possessing additional aromatic substituent(s) in quadrants A, B, C, D (see Fig. 1) were synthesized and compared [16–19]. The sulfur atom was bioisosterically exchanged by nitrogen in the imidazo[2,1-b]imidazole, -pyrimidinone and -diazepinone series [19]. In the course of our research it was found that benzylidene derivatives of imidazo[2,1-b]thiazine exhibit affinity for benzodiazepine receptors (BzR) [16]. Their activity was strongly dependent on the substitution pattern of the

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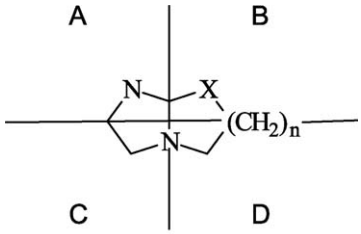


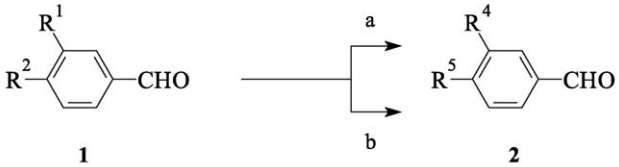
Fig. 1. Basic skeleton of the synthesized bicyclic structures [16–19].

benzylidene residue. Their profile of action was characterized as partially agonistic at the BzRs on the basis of the GABA shift [16]. Continuing our research on these classes of compounds we have now explored imidazo[2,1-b]thiazepine bicyclic ring system in more detail because enlargement of the ring annelated to the imidazole ring—thiazole toward thiazine—had been found to increase the BzR affinity [16,19].

2. Chemistry

The designed imidazo[2,1-*b*]thiazepine derivatives **6–8** (Figs. 3 and 4) were obtained by methods described in the literature [16,20,36]. As starting materials for the synthesis of imidazo[2,1-*b*]thiazepines **6** and **7** (Fig. 3) appropriate aldehydes or ketones were used. Non-commercial derivatives of meta- or para-hydroxybenzaldehydes **2** were synthesized as described in Fig. 2. The ethers **2a–d** were obtained by the reactions of the appropriate hydroxybenzaldehydes with alkylating agents performed in ethanol in the presence of potassium carbonate. Esters **2e–g** resulted from the reactions of benzoyl chlorides with 4-hydroxybenzaldehyde carried out in pyridine at room temperature. A series of 2-thiohydantoin derivatives **5** (Figs. 3 and 4) was prepared by the Knoevenagel condensation of aldehydes or ketones **3** (methods A–C) with 2-thiohydantoin. Aldehydes **3** were reacted with 2-thiohydantoin in stoichiometric amounts (method A) or with 10% excess in water (method B) in the presence of alanine and sodium carbonate (method A), or in acetic acid in the presence of sodium acetate (method B) used as basic reaction catalysts. Condensation with ketones (method C) was performed in toluene. Cyclization of 2-thiohydantoin derivatives with 1,4-dibromobutane under phase transfer catalysis conditions (acetone, potassium carbonate, benzyl triethylammonium chloride [BTEA] catalyst) provided the desired imidazo[2,1-*b*]thiazepines **6–8** (Figs. 3 and 4). In the synthesis of the isomers **8** (Fig. 4) 5,5-diphenyl-2-thiohydantoin was used. [20,21].

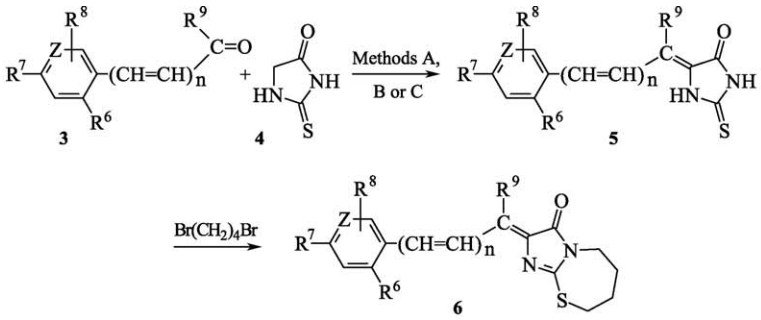
In order to confirm the structural assignment and to determine the conformational properties of the imidazo[2,1-*b*]thiazepines, X-ray structure analyses for two derivatives were performed. For this analysis, the ortho-substituted derivatives **6ae** and **6ag** were selected taking into account their important biological activity (Table 4) and the degree to which the conformation is influenced by ortho-substitution. Generally for the *Z*-isomers, due to the free rotation of the phenyl ring attached to the exocyclic methylene bond (Fig. 5), two planar conformations (*syn* and *anti*) should be taken into consideration and the *anti* conformation was expected to be energetically favored. In the case of the ortho-substituted derivatives, due to steric repulsion, deviation from planarity is expected and X-ray studies of **6ae** and **6ag** confirm this. The respective ORTEP drawings with atom numbering are shown in Fig. 6. All X-ray details, non-hydrogen atoms fractional coordinates and selected geometrical data are collected in Tables 1–3. Firstly the *Z*-configuration for derivatives **6a–h** has been confirmed by X-ray structure analysis (see Fig. 6 and corresponding torsion angles in Table 3). Moreover, in both derivatives the ortho-substituents (*o*-OCH_3 **6ae**; *o*-CF_3 **6ag**) are *anti* with



1a	$R^1 = OH$	$R^2 = H$	**2a**	$R^4 = 4\text{-}ClC_6H_4CH_2O$	$R^5 = H$
1b	$R^1 = H$	$R^2 = OH$	**2b**	$R^4 = 2,4\text{-}diClC_6H_3CH_2O$	$R^5 = H$
			2c	$R^4 = H_5C_2OOCH_2O$	$R^5 = H$
			2d	$R^4 = H$	$R^5 = H_5C_2OOCCH_2O$
			2e	$R^4 = H$	$R^5 = C_6H_5COO$
			2f	$R^4 = H$	$R^5 = 4\text{-}ClC_6H_4COO$
			2g	$R^4 = H$	$R^5 = 2\text{-}ClC_6H_4COO$

(a) – (un)substituted benzoyl chloride, pyridine, room temperature;
(b) – R^3X, ethanol, K_2CO_3, reflux.

Fig. 2. Procedure for the preparation of substituted meta- (**2a–2c**) or para- (**2d–2g**) hydroxy-benzaldehydes.



Methods: (A) aldehyde (1 mmol), 2-thiohydantoin (1 mmol), alanine (1 mmol), Na_2CO_3 (0.5 mmol), water, reflux; (B) aldehyde (1.1 mmol), 2-thiohydantoin (1 mmol), CH_3COONa (4.4 mmol), acetic acid, reflux; (C) ketone (1.6 mmol), 2-thiohydantoin (2.6 mmol), NH_4OAc (2.5 mmol), toluene, reflux.

Compound	n	Z	R^6	R^7	R^8	R^9
6aa *	0	CH	H	H	H	H
6ab	0	CH	2–F	H	H	H
6ac	0	CH	2–Cl	H	H	H
6ad	0	CH	2–Br	H	H	H
6ae	0	CH	2–OCH_3	H	H	H
6af	0	CH	2–CH_3	H	H	H
6ag	0	CH	2–CF_3	H	H	H
6ah	0	CH	2–OCH_3	4–OCH_3	H	H
6ai	0	CH	2–Cl	H	3–Cl	H
6aj	0	CH	2–CH_3	4–OCH_3	5–CH_3	H
6ba	0	CH	H	H	3–Cl	H
6bb	0	CH	H	H	3–NO_2	H
6bc	0	CH	H	H	3–PhO	H
6bd	0	CH	H	H	3–CH_3	H
6be	0	N	H	H	H	H
6bf	0	CH	H	H	3–(4–ClC_6H_4)CH_2O	H
6bg	0	CH	H	H	3–(2,4diClC_6H_3)CH_2O	H
6bh	0	CH	H	H	3–($EtOOCCH_2O$)	H
6ca	0	CH	H	4–Cl	H	H
6cb	0	CH	H	4–OCH_3	H	H
6cc	0	CH	H	4–OEt	H	H
6cd	0	CH	H	4–($EtOOCCH_2O$)	H	H
6ce	0	CH	H	4–$N(CH_3)_2$	H	H
6cf	0	CH	H	4–PhCOO	H	H
6cg	0	CH	H	4–(4–ClC_6H_4)COO	H	H
6ch	0	CH	H	4–(2–ClC_6H_4)COO	H	H
6ci	0	CH	H	4–$COOCH_3$	H	H
6cj	0	CH	H	4–Ph	H	H
6ck	0	CH	H	4–$PhCH_2O$	H	H
6da	1	CH	H	H	H	H
6db	0	CH	H	H	H	CH_3
6dc	0	CH	H	4–Cl	H	CH_3

* The same description applies to the commercially available aldehydes or ketones **3** used as starting compounds for the intermediate 2-thiohydantoin derivatives **5**. Index **a** is reserved for ortho-, **b** for meta- and **c** for para-substituted arylidene derivatives. Index **d** describes different derivatives (**6da** – cinnamylidene, **6db** and **6dc** – ketone derivatives).

Fig. 3. Two-step procedure for the preparation of imidazo[2,1-*b*]thiazepines **6** and **7**.

respect to the seven-membered thiazepine ring. The thermodynamic stability for the *anti*-conformation with the C62–C61–C6–C5 torsion angle close to 180° is confirmed by the potential energy distribution presented in Fig. 7. In the crystals phenyl and the imidazolone rings are not exactly coplanar with dihedral angles between phenyl and the planar five-membered imidazolone rings equaling 14.7(2)° in compound **6ae** and 5.7(3)° in compound **6ag**, respectively. As the torsion angles collected in Table 3 suggest, the thiazepine rings in both structures possess a half-chair form flattened at the C2 atom.

3. Biological assays

Compounds series **6, 7** and **8** were investigated in radioligand binding assays at rat brain cortical membranes for their affinity to the benzodiazepine binding sites of the $GABA_A$ receptor. All compounds were screened for their ability to displace [^{3}H]diazepam from its binding site at a single concentration (Table 4). K_i values were determined from a dose–response curve for the most potent compounds of the present series, **6aa, 6ab, 6ac, 6ad, 6ae, 6ag, 6ah, 6aj, 6bd, 6bh, 6cb, 6cd, 6ce** and **8a**. The most active compounds **6aa, 6ab,**

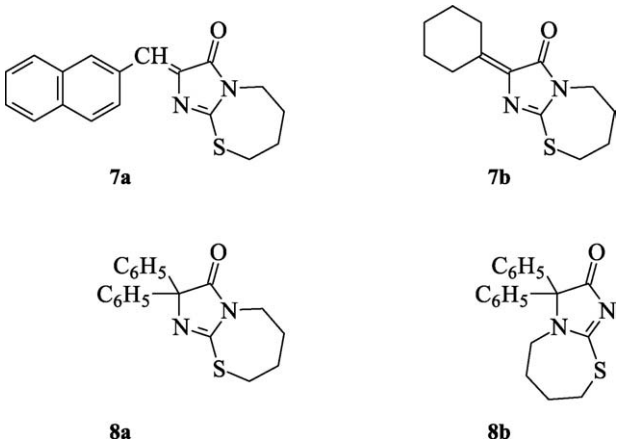


Fig. 4. Structures of further investigated imidazo[2,1-*b*]thiazepines; for **8a** and **8b** see ref. [20].

6ac and **6cb** were evaluated for their profile of action by means of their GABA shift [22].

The highest affinity compounds in vitro, **6aa, 6ab, 6ac, 6ad, 6ah, 6bb**,and **6cb,** were evaluated in vivo for their anticonvulsant activity and neurological toxicity according to the Antiepileptic Drug Development (ADD) Program, using published testing procedures [23,24]. Phase I of the evaluation included three tests: maximal electroshock (MES), subcutaneous pentylenetetrazol (ScMet), and rotorod test for neurological toxicity (Tox).

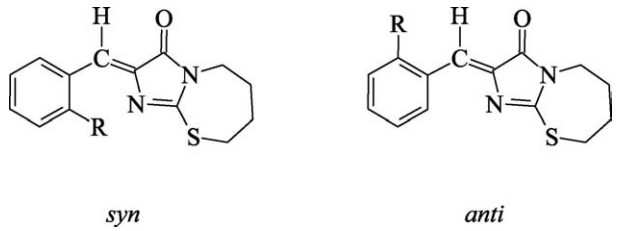


Fig. 5. *Syn*- and *anti*-conformations of the ortho-substituted derivatives of imidazo[2,1-*b*]thiazepines.

Table 1
X-ray structure analysis of **6ag** and **6ae**

	6ae	**6ag**
(A) *Crystal parameters*		
Formula	$C_{15}H_{16}N_2O_2S$	$C_{15}H_{13}F_3N_2OS$
Molecular weight	288.36	326.33
Crystallization medium	Dioxane	Dioxane
Colour	Lemon yellow	Lemon yellow
Crystal size, mm	0.1 × 0.1 × 0.3	0.2 × 0.2 × 0.4
Cell dimensions	a = 9.343(2) Å	a = 9.734(2) Å
	b = 12.684(3) Å	b = 13.549(3) Å
	c = 12.184(2) Å	c = 11.313(2) Å
	β = 103.81(3)°	β = 103.23(3)°
Space group	$P2_1/n$	$P2_1/c$
Molecules/unit cell	4	4
Density calculated	1.366 Mg/m^3	1.492 Mg/m^3
Linear absorption factor, mm^{-1}	2.078	2.333
(B) *Refinement parameters*		
Number of reflections	1840	3030
Non-zero reflections [$I > 4\ \sigma(I)$]	1745	2866
R-index	0.068	0.067
GOF	1.010	1.019
Secondary extinction factor	0.0014 (2)	0.0006 (3)

4. Results and discussion

The in vitro results obtained for the newly synthesized and screened compounds are presented in the Table 4. Compounds with affinities in low micromolar concentrations were obtained; based on their GABA shift ratios [22] they were classified either as weak partial agonists (**6aa, 6ac**), or neutral antagonists **(6ab, 6cb)**, respectively.

Lipophilicity parameters are important physicochemical properties in (Q)SAR studies. Lipophilicity expressed as log P values was calculated [25], log P values equaled log D since the analyzed compounds did not possess any acidic or basic functionalities. Lipophilicities expressed by R_{mo} values were determined by reversed phase thin layer chromatography (RP-TLC) on the basis of the relationships of the R_m values and the content of organic modifier in the mobile

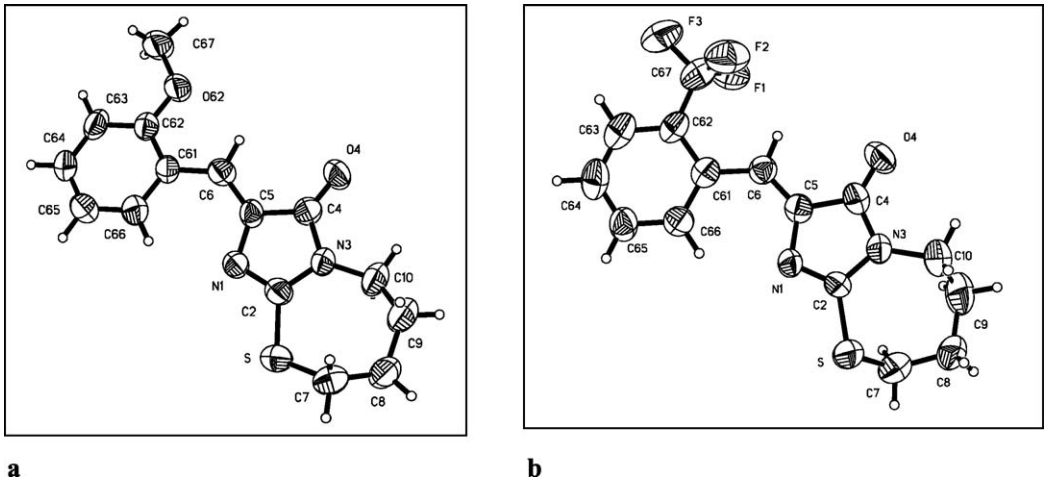


Fig. 6. The structures of (a) **6ae** and (b) **6ag**.

Table 2
Atomic coordinates (×10^4) and equivalent isotropic displacement parameters (Å^2 × 10^3)

	x	*y*	*z*	*U* (eq)
Compound **6ae**				
S	1961 (2)	8248 (1)	261 (1)	91 (1)
N(1)	1551 (3)	10011 (2)	–933 (3)	56 (1)
C(2)	1060 (4)	9060 (3)	–829 (3)	57 (1)
N(3)	–219 (3)	8807 (2)	–1629 (3)	58 (1)
C(4)	–623 (4)	9674 (3)	–2319 (4)	60 (2)
O(4)	–1707 (3)	9733 (2)	–3107 (3)	76 (1)
C(5)	545 (4)	10449 (3)	–1855 (3)	49 (1)
C(6)	558 (4)	11432 (3)	–2276 (3)	51 (1)
C(7)	1796 (5)	6973 (3)	–332 (4)	84 (2)
C(8)	304 (5)	6441 (3)	–569 (4)	74 (2)
C(9)	–780 (6)	6890 (4)	–1598 (5)	129 (3)
C(10)	–1232 (5)	7929 (3)	–1585 (5)	102 (2)
C(61)	1596 (4)	12285 (3)	–1901 (3)	44 (1)
C(62)	1229 (4)	13312 (3)	–2267 (3)	53 (1)
C(63)	2162 (5)	14139 (3)	–1846 (4)	66 (2)
C(64)	3451 (5)	13971 (4)	–1034 (4)	75 (2)
C(65)	3821 (4)	12964 (4)	–668 (4)	70 (2)
C(66)	2920 (4)	12138 (3)	–1084 (3)	61 (2)
O(62)	–55 (3)	13426 (2)	–3070 (2)	70 (1)
C(67)	–464 (5)	14473 (3)	–3491 (4)	82 (2)
Compound **6ag**				
S(1)	454 (1)	156 (1)	7922 (1)	86 (1)
N(1)	–1700 (3)	243 (2)	5983 (3)	53 (1)
C(2)	–672 (4)	–280 (2)	6598 (3)	57 (1)
N(3)	–498 (3)	–1192 (2)	6092 (3)	61 (1)
C(4)	–1502 (3)	–1253 (2)	5007 (3)	54 (1)
O(4)	–1628 (3)	–1930 (2)	4295 (2)	80 (1)
C(5)	–2285 (3)	–319 (2)	4959 (3)	50 (1)
C(6)	–3424 (3)	–128 (3)	4070 (3)	52 (1)
C(7)	658 (5)	–881 (3)	8905 (4)	90 (2)
C(8)	1632 (5)	–1686 (3)	8678 (4)	84 (2)
C(9)	976 (6)	–2319 (3)	7589 (5)	107 (2)
C(10)	703 (5)	–1880 (3)	6446 (5)	99 (2)
C(61)	–4353 (3)	720 (2)	3895 (3)	53 (1)
C(62)	–4233 (3)	1455 (2)	4786 (3)	58 (1)
C(63)	–5118 (4)	2276 (3)	4628 (4)	70 (1)
C(64)	–6135 (4)	2371 (3)	3592 (4)	78 (1)
C(65)	–6293 (4)	1668 (3)	2701 (4)	74 (1)
C(66)	–5432 (4)	843 (3)	2839 (3)	60 (1)
C(67)	–5666 (4)	102 (4)	1841 (4)	82 (2)
F(1)	–6022 (3)	–783 (2)	2182 (2)	96 (1)
F(2)	–4545 (3)	–26 (2)	1377 (2)	100 (1)
F(3)	–6712 (3)	377 (3)	898 (2)	121 (1)

phase [26]. Corrected log *P* (*c* log *P*) values were determined on the basis of experimental RP-TLC data [27].

Preliminary analysis of structure–affinity relationships revealed that enlargement of the annelated ring (thiazole and thiazine toward thiazepine) was beneficial for the receptor affinity. Dissimilarity between the structures (determined with semi-empirical calculations) of arylidene bicyclic derivatives 5 + 5, 5 + 6 and 5 + 7 is presented in Fig. 8. Contrary to the almost flat inactive imidazothiazole structure (5 + 5), among the more puckered imidazothiazine (5+6) and especially the thiazepine (5 + 7) derivatives (Fig. 8), active compounds were found. Presumably, more spatially voluminous derivatives fit better into the lipophilic pocket of the BzR receptor (Fig. 9). The position of the annelated ring is important as shows the comparison of the activity of compounds **8a** and **8b**: The 1,2-substituted derivative **8b** was less potent than the 2,3-substituted compound (**8b**). A flat, substituted aromatic ring connected by an exocyclic double bond was important for high activity, whereas the folded cycloalkylidene derivative **7b** was less active. A greater distance of the aromatic ring from the bicyclic skeleton in **6da** caused a decrease in BzR affinity, as did the introduction of a methyl substituent into the exocyclic methylene group (compounds **6db** and **6dc**).

Table 3
Selected geometrical data: dihedral and torsion angles (°)

6ae		**6ag**	
Dihedral angle between Ph/imidazole rings	14.7(2)		5.7(3)
C5–C6–C61–C62	–164.9 (4)	C5–C6–C61–C62	–7.3 (6)
C7–S–C2–N3	37.8 (5)	C7–S–C2–N3	–45.0 (4)
C2–S–C7–C8	–72.9 (4)	C2–S–C7–C8	76.7 (4)
S–C7–C8–C9	75.8 (5)	S–C7–C8–C9	–75.9 (5)
C7–C8–C9–C10	–66.8 (7)	C7–C8–C9–C10	66.6 (6)
C8–C9–C10–N3	72.4 (8)	C(8)–C9–C10–N3	–74.3 (6)
C2–N3–C10–C9	–65.2 (8)	C2–N3–C10–C9	65.1 (6)
S–C2–N3–C10	14.8 (7)	S–C2–N3–C10	–8.6 (6)

The size and substitution pattern of the arylidene ring has been shown to greatly influence the receptor affinity of the investigated compounds [16,19]. Introduction of an additional aromatic ring in the meta- (**6bc, 6bf, 6bg)** as well as in the para-position (**6cf, 6cg, 6ch, 6cj**, and **6ck)** was not advantageous. The lipophilicity (calculated log *P* values are in the range of 4.12–5.81) was very high causing problems with the determination of the BzR affinity in some cases (e.g. **6bf**). The affinity had to be determined at a lower concentration (2.5 μM) for compounds **6cf, 6cg** and **6ck** and it was low to negligible at that concentration. Compounds **6bc, 6bg, 6ch, 6cj** also showed low affinity in a concentration of 25 μM. Ortho-substituted arylidene derivatives were among the most active compounds (e.g. **6ab, 6ac, 6ad, 6ae, 6ah**). The ortho-substituent should have a limited size. Thus, compound **6ab** fits better into the small lipophilic pocket of the Cook and coworkers model of the BzR (Fig. 9) [28] than compounds **6ae** and **6ag** with larger substituents. A similar conclusion can be made by the comparison of the affinity of the halogen containing derivatives (2-F > 2-Cl > 2-Br) with K_i values of 0.93, 2.2, and 4.5 μM, respectively.

In the meta- and para-position larger substituents, such as OCH_2COOEt (compare **6bh** and **6cd)** -are better tolerated.

QSAR studies were performed for a number of derivatives from series **6** with determined K_i values. At a first step π—constants for substituents in ortho-, meta- and para-positions [29] were examined (Table 5). For the selection of further similarity descriptors of the analyzed derivatives, it was decided to consider quantum chemistry calculation re-

Table 4
Physicochemical properties and inhibition of [^{3}H]diazepam binding to rat brain cortical membranes by arylidene (**6, 7**) and diphenyl (**8**) imidazo[2, 1-*b*]thiazepines

Compound	Test concentration (μM)	Percent specific inhibition	K_i (μM) (GABA shift)	Log *P*	R_{mo}	*c* log*P*
6aa	25	81 ± 3	1.5 ± 0.5 [1.5]	2.63	1.91	2.98
6ab	25	92 ± 3	0.93 ± 0.39 [0.8]	2.79	2.05	3.31
6ac	25	83 ± 2	2.2 ± 0.5 [1.7]	3.35	2.19	3.65
6ad	25	71 ± 1	4.5 ± 1.9	3.51	2.27	3.84
6ae	25	59 ± 3	11.4 ± 2.1	2.59	1.90	2.96
6af	25	36 ± 12		3.07	1.55	2.14
6ag	25	53 ± 6	42.3 ± 13.2 [c]	3.78	1.84	2.83
6ah	25	83 ± 7	2.0 ± 0.3	2.53	1.75	2.59
6ai	25	0 ± 2 [a]		3.90	2.11	3.47
6aj	25	51 ± 20	2.8 ± 1.2	3.55	1.89	2.94
6ba	25	39 ± 23 [a]		3.41	2.05	3.31
6bb	25	61 ± 4		2.61	2.07	3.36
6bc	25	0 [a]		4.32	2.52	4.44
6bd	25	54 ± 3	10.6 ± 2.1	3.17	2.07	3.36
6be	25	48 ± 16			n.d.	n.d.
6bf	25	n.d.		5.03	2.83	5.17
6bg	25	7 ± 7 [a]		5.81	3.17	5.99
6bh	25	51 ± 6	11.9 ± 3.7	3.04	2.08	3.40
6ca	25	47 ± 3.4		3.36	2.24	3.78
6cb	25	74 ± 7	2.5 ± 1.0 [0.9]	2.59	1.83	2.79
6cc	25	16 ± 6		2.60	1.94	3.07
6cd	25	45 ± 3	6.4 ± 0.83	2.94	1.30	1.54
6ce	25	53 ± 5	23.6 ± 10.9	2.60	1.68	2.43
6cf	2.5	16 ± 3		4.12	2.38	4.11
6cg	2.5	5 ± 5		4.80	2.87	5.28
6ch	25	8 ± 3		4.67	2.62	4.68
6ci	25	28 ± 2		2.79	1.79	2.70
6cj	25	3 ± 3		4.59	2.51	4.42
6ck	2.5	4 ± 4		4.30	2.52	4.44
6da	25	32 ± 9		3.28	1.91	2.98
6db	25	22 ± 3		3.11	1.73	2.55
6dc	25	16 ± 4		3.75	2.37	4.08
7a	25	n.d.		3.85	2.32	3.97
7b	25	27 ± 1		2.95	1.35	[b]
8a	25	61 ± 10	30.3 ± 6.3	3.25	1.97	3.12
8b	25	35 ± 11		3.08	3.08	[b]
Diazepam		n.d.	0.025 ± 0.006[d] [3.4]	3.21		

n.d., not detected, compound insoluble at test concentrations.
[a] Inhibition of [^{3}H]diazepam binding may be underestimated due to low solubility of the compound.
[b] Compounds were not chromatographically congeneric.
[c] Estimated K_i-value by extrapolation; determination of full inhibition curve was precluded by limited solubility.
[d] Ref. [16].

sults based on our previous studies [30] on BzR ligands. Consequently starting from crystallographic data the molecules from series **6** with determined K_i values were roughly modelled [PCMODEL] and optimised with the AM1 semiempirical quantum chemistry method in aqueous environment [MOPAC.6]. At the same time two compounds **6bh** and **6cd** were rejected from the calculations, as their arylidene substituent OCH_2COOEt was too flexible for simple geometry optimisation without careful conformation analysis. For that reason only 11 (instead of 13) derivatives were selected for QSAR studies. After geometry optimization electronic similarity parameters (dipole moment μ and HOMO energies), gathered in Table 5 and tested for QSAR utility did not allow to obtain good correlations, as well as considered lipophilicity descriptors (log *P* calculated with PALLAS program and experimental values R_{mo} and *c* log *P*).

The investigated compounds tested in vivo according to the ADD Program of the NIH in Bethesda, MD, USA, were devoid of anticonvulsant activity (in doses up to 300 mg/kg) in maximal electroshock seizures and subcutaneous pentylenetetrazole (ScMet) tests. This result maybe reasoned by their pharmacokinetic properties (metabolism, low penetration into the brain). It could be also taken into the discussion their more expressed activity through the respective $GABA_A$. subunits. As it was stated, while $GABA_A$-α_1-receptor is more engaged in anticonvulsant and sedative effects, the $GABA_A$-α_2 is more connected with attenuation of anxiety

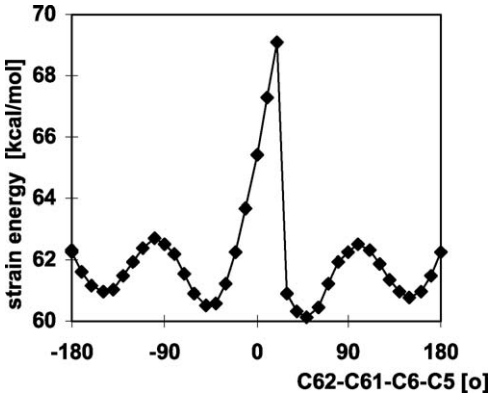


Fig. 7. The strain energy (as astimated using AM1 Hamiltonian) of **6ae** as a function of phenyl ring rotation round the C61–C6 bond.

Table 5
The parameters applied for QSAR analysis for 11 derivatives from series **6**

Compound	K_i	Substituent constans			$c\log P$	μ (debay)	HOMO (kcal/mol)
		π_o	π_p	π_m			
6aa	1.5	0	0	0	2.98	4.53	–8.87
6ab	0.93	0.14	0	0	3.31	5.78	–8.80
6ac	2.2	0.71	0	0	3.65	5.79	–8.95
6ad	4.5	0.86	0	0	3.84	6.08	–8.99
6ae	11.4	–0.02	0	0	2.96	3.14	–8.78
6ag	42.3	0.88	0	0	2.83	8.13	–8.99
6ah	2.0	–0.02	–0.02	0	2.59	4.26	–8.68
6aj	2.8	0.56	–0.02	0.56	2.94	3.35	–8.71
6bd	10.6	0	0	0.56	3.36	4.37	–8.87
6cb	2.5	0	–0.02	0	2.79	3.17	–8.72
6ce	23.6	0	0.18	0	2.43	3.96	–8.40

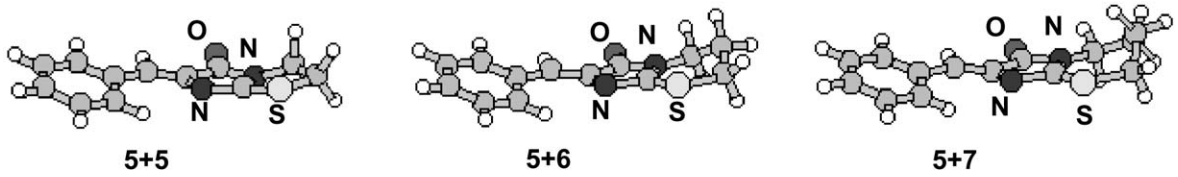


Fig. 8. Molecules of the arylidene bicyclic derivatives: 5 + 5, 5 + 6, and 5 + 7.

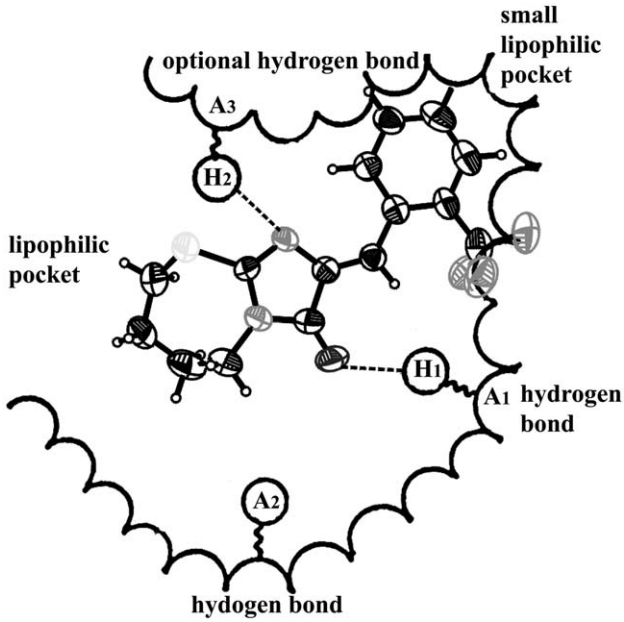


Fig. 9. The Cook model of BzR binding [28] applied to compound **6ag**.

[32,33].The investigated compounds have not shown neurological toxicity (in doses up to 300 mg/kg).

5. Experimental protocols

5.1. Chemistry

5.1.1. General remarks

Melting points were measured on Mel-Temp. II (LD Inc., USA) and were not corrected. The TLC was performed on Merck Silica gel GF_{254} precoated tlc Al Sheets; the used solvent systems were: A chloroform/ethyl acetate (1:1); B toluene/acetone (20:1.5); spots were visualized by UV absorption at 254 nm. Column chromatography was performed on Merck silica gel 60 (70–230 mesh) using the solvent methylene chloride/ethyl acetate (1:1).

Electron impact and electron spray mass spectra were recorded on an AMD-604, or a Finningan MAT 95S spectrometer respectively, with a direct inlet. Infrared spectra were measured with an FT IR 410 spectrometer (Jasco) in KBr pellets. The UV spectra were obtained for solutions of 10^{-4} mol/l concentration in methylene chloride with a UV Vis V-530 Jasco spectrometer. The ^{1}H-, and ^{13}C-NMR spectra were performed on a Bruker AC-200F, on a Bruker DPX 250 Avance, on a VARIAN MERCURY 300 MHz or on a Bruker DPX 400 Avance in $DMSOd_6$ (unless otherwise stated) using tetramethyl silane as an internal standard (chemical shifts are reported in δ units). The elemental analyses (performed at the Department of Pharmaceutical Chemistry of the Jagiellonian University, Kraków, Poland) indicated by the symbols of the elements were within ±0.4% of the theoretical values.

5.1.2. Preparation of 2-thiohydantoins

The starting 2-thiohydantoins **5** were obtained as recently described [18,19] or in analogy to the described procedures [31,34–36]. The following new derivatives were prepared:

*5.1.2.1. Z-5-(Pyridin-3-methylene)-2-thiohydantoin (**5be**).* A mixture of pyridine-3-carboxaldehyde (5.65 g, 0.05 mol), 2-thiohydantoin (5.8 g, 0.05 mol), alanine (4.46 g; 0.05 mol) and sodium carbonate (2.65 g, 0.025 mol) in 50 ml of water was refluxed for 3 h. Afterwards it was diluted with water. The precipitate was collected; cream-colored crystals, m.p.

297–298 °C (DMF + H_2O); yield 66%; ^{1}H-NMR (300 MHz) δ: 6.51 (s, 1H, ArCH=), 7.42–7.47 (m, 1H, H-4′), 8.18 (d, J = 8.0 Hz, 1H, H-3′), 8.54 (dd, J = 1.3 Hz, J = 4.7 Hz, 1H, H-5′), 8.86 (d, J = 1.9 Hz, 1H, H-1′), 12.30 (s, 1H, N_1–H), 12.46 (s, 1H, N_3–H); IR ν: 3169, 3072 (N–H), 2826 (C–H), 1735 (C=O), 1655 (ArCH=), 1532, 1348, 1194, 1089, 963 cm^{-1}; MS: *m/z* 205 ($M^{+\cdot}$), 145, 118, 91. Anal. ($C_9H_7N_3OS$) C, H, N.

*5.1.2.2. Z-5-(4-Benzoyloxybenzylidene)-2-thiohydantoin (**5cf**).*

(a) A mixture of 4-hydroxybenzaldehyde (9.76 g, 0.08 mol) and freshly distilled benzoyl chloride (14.4 g, 0.1 mol) in 200 ml of pyridine was stirred at room temperature for 24 h. The reaction mixture was poured on 200 ml of 2 N acetic acid solution cooled with ice. The precipitate (**2e**) was collected, washed thoroughly with water. Yield: 14.9 g (83%); m.p. 78–79 °C.

(b) A mixture of 4-benzoyloxybenzaldehyde (**2e**) (4.28 g, 0.018 mol), 2-thiohydantoin (1.97 g, 0.017 mol) and anhydrous sodium acetate (6.07 g, 0.073 mol) in 25 ml glacial acetic acid was refluxed for 2 h. On cooling, the precipitate was collected, washed thoroughly with water; yield 64%; yellow crystals, m.p. 251–254 °C (acetic acid). ^{1}H-NMR (200 MHz) δ: 6.53 (s, 1H, ArCH=), 7.35 (d, J = 8.5 Hz, 2H, H-3′, H-5′), 7.59 (t, J = 7.3 Hz, 2H, H-3″, H-5″), 7.74 (m, 1H, H-4″), 7.84 (d, J = 8.6 Hz, 2H, H-2′, H-6′), 8.13 (d, J = 7.3 Hz, 2H, H-2″, H-6″), 12.20 (br s, 1H, N_1–H), 12.32 (br s, 1H, N_3–H). Anal. ($C_{17}H_{12}N_2O_3S$) C, H, N.

*5.1.2.3. Z-5-[4-(4-Chlorobenzoyloxy)benzylidene]-2-thiohydantoin (**5cg**).*

(a) 4-(4-Chlorobenzoyloxy)benzaldehyde (**2f**) was obtained as described in 5.1.2.2.a; yield 93%; m.p. 104–107 °C

(b) **5cg** was obtained as described in Section 5.1.2.2(b); yield 76%; yellow crystals, m.p. 243–245 °C (acetic acid); ^{1}H-NMR (200 MHz) δ: 6.51 (s, 1H, ArCH=), 7.35 (d, J = 8.5 Hz, 2H, H-3′, H-5′), 7.62 (d, J = 8.5 Hz, 2H, H-3″, H-5″), 7.82 (d, J = 8.6 Hz, 2H, H-2′, H-6′), 8.09 (d, J = 8.5 Hz, 2H, H-2″, H-6″), 12.28 (br s, 2H, N_1–H, N_3–H). Anal. ($C_{17}H_{11}N_2O_3SCl$) C, H, N.

*5.1.2.4. Z-5-[4-(2-Chlorobenzoyloxy)benzylidene]-2-thiohydantoin (5**ch**).*

(a) 4-(2-Chlorobenzoyloxy)benzaldehyde (**2f**) was obtained as described in Section 5.1.2.2(a); yield 79%; m.p. 91–94 °C.

(b) **5ch** was obtained as described in Section 5.1.2.2(b); yield 80%; yellow crystals, m.p. 233–235 °C (acetic acid); ^{1}H-NMR (200 MHz) δ: 6.52 (s, 1H, ArCH=), 7.37 (d, J = 8.5 Hz, 2H, H-3′, H-5′), 7.49–7.59 (m, 1H, H-4″), 7.65 (def.d, J = 7.8 Hz, 2H, H-3″, H-5″), 7.85 (d, J = 8.5 Hz, 2H, H-6′, H-2′), 8.09 (d, J = 7.3 Hz, 1H, H-6″), 12.28 (s, 2H, N_1–H, N_3–H). Anal. ($C_{17}H_{11}N_2O_3SCl$) C, H, N.

*5.1.2.5. Z-5-[4-(Ethoxycarbonylmethoxy)benzylidene]-2-thiohydantoin (**5cd**).*

(a) A mixture of 4-hydroxybenzaldehyde (12.2 g, 0.1 mol), ethyl bromoacetate (16.7 g, 0.1 mol) and potassium carbonate (6.9 g, 0.05 mol) in 100 ml of ethanol was heated under reflux for 7 h. On cooling the solid was filtered off, the solvent was evaporated, the oily residue was dissolved in methylene chloride and washed with 2% NaOH solution and then with water, the solvent was dried over Na_2SO_4 and evaporated to yield 76% of **2d** as an oil.

(b) **5cd** was obtained as described in Section 5.1.2.2; yield 50%; yellow crystals, m.p. 205–207 °C (acetic acid); ^{1}H-NMR (200 MHz) δ: 1.20 (t, J = 7.1 Hz, 3H, CH_3CH_2), 4.16 (q, J = 7.1 Hz, 2H, CH_3CH_2), 4.85 (s, 2H, CH_2O), 6.45 (s, 1H, ArCH=), 6.96 (d, J = 8.8 Hz, 2H, H-3′, H-5′), 7.72 (d, J = 8.8 Hz, 2H, H-2′, H-6′), 12.15 (br s, 2H, N_1–H, N_3–H). Anal. ($C_{14}H_{14}N_2O_4S$) C, H, N.

*5.1.2.6. Z-5-[3-(Ethoxycarbonylmethoxy)benzylidene]-2-thiohydantoin (**5bh**).*

(a) 3-(Ethoxycarbonylmethoxy)benzaldehyde **2c** was obtained as described in Section 5.1.2.5; yield 52%; oil.

(b) **5bh** was obtained as described in 5.1.2.2 b; yield 62%; yellow crystals, m.p. 150–152 °C (acetic acid); ^{1}H-NMR (200 MHz) δ: 1.30 (t, J = 7.5 Hz, 3H, CH_3CH_2), 4.26 (q, J = 7.5 Hz, 2H, CH_3CH_2), 4.96 (s, 2H, CH_2O), 6.53 (s, 1H, ArCH=), 7.02–7.07 (m, 1H, H-5′), 7.33 (s, 1H, H-4′), 7.39 (d, J = 7.5 Hz, 1H, H-6′), 7.43 (s, 1H, H-2′), 12.38 (br s, 2H, N_1–H, N_3–H); IR ν: 3220, 3135, 3069 (N–H), 1741, 1722 (C=O), 1654 (ArCH=), 1373, 1216, 1085, 649 cm^{-1}. Anal. ($C_{14}H_{14}N_2O_4S$) C, H, N.

*5.1.2.7. Z-5-(2-Fluorobenzylidene)-2-thiohydantoin (**5ab**).* Obtained as described in Section 5.1.2.2(b) (refluxed for 2 h), cream-colored yellow crystals, m.p. 201–203 °C; analytically pure; yield 85%; ^{1}H-NMR (300 MHz) δ: 6.44 (s, 1H, ArCH=), 7.21–7.29 (m, 2H, H-3′, H-5′), 7.38–7.46 (m, 1H, H-4′), 7.80–7.85 (m, 1H, H-6′), 12.17 (s, 1H, N_1–H), 12.40 (s, 1H, N_3–H). Anal. ($C_{10}H_7N_2OSF$) C, H, N.

*5.1.2.8. Z-5-(2-Trifluoromethylbenzylidene)-2-thiohydantoin (**5ag**).* Obtained as described in Section 5.1.2.2(b) (refluxed for 1.5 h), cream-colored crystals, m.p. 289–291 °C; analytically pure; yield 83%; ^{1}H-NMR (300 MHz) δ: 6.49 (d, J = 1.9 Hz, 1H, ArCH=), 7.55 (t, J = 7.7 Hz, 1H, H-5′), 7.68–7.82 (m, 3H, H-3′, H-4′, H-6′), 12.38 (s, 2H, N_1–H, N_3–H). Anal. ($C_{11}H_7N_2OSF_3$) C, H, N.

*5.1.2.9. Z-5-(2-Methylbenzylidene)-2-thiohydantoin (**5af**).* Obtained as described in Section 5.1.2.2(b) (refluxed 2 h), cream-colored crystals, m.p. 241–243 °C analytically pure yield 85%; ^{1}H-NMR (300 MHz) δ: 2.33 (s, 3H, CH_3), 6.54 (s, 1H, ArCH=), 7.19–7.28 (m, 3H, H-3′, H-4′, H-5′), 7.58–7.61 (m, 1H, H-6′), 12.15 (s, 1H, N_1–H), 12.27 (s, 1H, N_3–H). Anal $C_{11}H_{10}N_2OS$) C, H, N.

5.1.3. Preparation of imidazo[2,1-b][1,3]thiazepinones

Compounds **6aa, 6ca** [36] **8a** and **8b** [20] were obtained as previously described. The following new derivatives were prepared in analogy to the described procedures [16,36].

*5.1.3.1. Z-2-(2-Fluorobenzylidene)-5,6,7,8-tetrahydro-5H-imidazo[2,1-b][1,3]thiazepin-3(2H)-one (**6ab**).* Yield 24%; cream-colored to yellow crystals, m.p. 149–151 °C (from dioxane + water); R_f 0.78 (A); ^{1}H-NMR (200 MHz) δ: 1.75–1.84 (m, 2H, $SCH_2C\underline{H}_2$), 1.99–2.10 (m, 2H, $NCH_2C\underline{H}_2$), 3.15–3.20 (m, 2H, SCH_2), 3.75 (m, 2H, NCH_2), 6.99 (s, 1H, CH=), 7.24–7.35 (m, 2H, H-4′, H-5′), 7.43–7.54 (m, 1H, H-3′), 8.69 (dt, J = 1.8 Hz, J = 8.0 Hz, H-6′); UV λ_{max} (log ε): 246 (3.57), 292 (4.02), 378 (4.34), 401 (4.13); IR ν: 2944, 2915 (C–H), 1708, 1639, 1486, 1357, 1330, 1209, 1149, 761 cm^{-1}. Anal. ($C_{14}H_{13}N_2OSF$) C, H, N.

*5.1.3.2. Z-2-(2-Chlorobenzylidene)-5,6,7,8-tetrahydro-5H-imidazo[2,1-b][1,3]thiazepin-3(2H)-one (**6ac**).* Yield 34%; cream-colored crystals, m.p. 148–150 °C (from dioxane); R_f 0.71 (A); ^{1}H-NMR (250 MHz) δ: 1.83–1.90 (m, 2H, $SCH_2C\underline{H}_2$), 2.06–2.15 (m, 2H, $NCH_2C\underline{H}_2$), 3.23–3.27 (def.t, 2H, SCH_2), 3.80–3.84 (def.t, 2H, NCH_2), 7.25 (s, 1H, CH=), 7.48–7.54 (m, 2H, H-4′, H-5′), 7.61–7.67 (m, 1H, H-3′), 8.82 (dd, J = 7.5 Hz, J = 2.5 Hz, 1H, H-6′); UV λ_{max} (log ε): 247 (3.79), 288 (3.85), 381 (3.98), 407 (3.65); IR ν: 2924, 2845 (C–H), 1733 (C=O), 1627 (ArCH=), 1556, 1478, 1441, 1353, 1324, 1188, 1120, 949, 752, 676 cm^{-1}; EI-MS: *m/z* (%): 292($M^{+\cdot}$, 17); 257 (100, M–Cl); 215 (12); 150 (4), 114 (4). Anal. ($C_{14}H_{13}N_2OSCl$) C, H, N.

*5.1.3.3. Z-2-(2-Bromobenzylidene)-5,6,7,8-tetrahydro-5H-imidazo[2,1-b][1,3]thiazepin-3(2H)-one (**6ad**).* Yield 23%; lemon-yellow crystals, m.p. 153–155 °C (from dioxane); R_f 0.80 (A); R_f 0.28 (B); ^{1}H-NMR (200 MHz) δ: 1.70–1.85 (m, 2H, $SCH_2C\underline{H}_2$), 1.98–2.10 (m, 2H, $NCH_2C\underline{H}_2$), 3.15–3.20 (m, 2H, SCH_2), 3.73–3.77 (m, 2H, NCH_2), 7.15 (s, 1H, CH=), 7.33 (dt, J = 1.7 Hz, J = 7.8 Hz, 1H, H-5′), 7.49 (def.t, J = 7.5 Hz, 1H, H-4′), 7.7 (dd, J = 1.1 Hz, J = 7.9 Hz, 1H, H-3′), 8.73 (dd, J = 1.6 Hz, J = 7.9 Hz, 1H, H-6′); UV λ_{max} (log ε): 241 (4.49), 282 (4.15), 381 (4.24); IR ν: 2920 (C–H), 1708 (C=O), 1648 (ArCH=), 1620, 1480, 1352, 1224, 1154, 840, 764, 560 cm^{-1}. Anal. ($C_{14}H_{13}N_2OSBr$) C, H, N.

*5.1.3.4. Z-2-(2-Methoxybenzylidene)-5,6,7,8-tetrahydro-5H-imidazo[2,1-b][1,3]thiazepin-3(2H)-one (**6ae**).* Yield 30%; lemon-yellow crystals, m.p. 183–184 °C (from dioxane); R_f 0.72 (A); ^{1}H-NMR (300 MHz) δ: 1.78 (m, 2H, $SCH_2C\underline{H}_2$), 2.03 (m, 2H, $NCH_2C\underline{H}_2$), 3.14 (m, 2H, SCH_2), 3.74 (m, 2H, NCH_2), 3.89 (s, 3H, OCH_3), 7.07 (m, 2H, H-5′, H-4′), 7.33 (s, 1H, ArCH=), 7.42 (t, J = 7.0 Hz, 1H, H-3′), 8.66 (d, J = 7.8 Hz, 1H, H-6′); UV λ_{max} (log ε): 250 (3.40), 294 (3.74), 382 (4.18), 407 (3.96); IR ν: 2934 (C–H), 2840 (C–H), 1708 (C=O), 1625 (ArCH=), 1484, 1302, 1249, 1223, 1190, 1161, 1021, 758 cm^{-1}; ^{13}C-NMR δ: 26.83 ($SCH_2\underline{C}H_2$), 30.08 ($SCH_2\underline{C}H_2$), 31.08 (SCH_2), 40.52 (NCH_2), 55.68 (OCH_3), 111.25 (ArCH=), 118.09 (C-12), 120.61 (C-14), 122.10 (C-10), 131.90 C-13), 132.05 (C-8), 138.15 (C-15), 158.41 (C-11), 165.31 (C-7), 168.71 (C-17); EI-MS: *m/z* (%): 288($M^{+\cdot}$, 100), 257 (40), 215 (7), 195 (9), 130 (8), 88 (15). Anal. ($C_{15}H_{16}N_2O_2S$) C, H, N.

*5.1.3.5. Z-2-(2-Methylbenzylidene)-5,6,7,8-tetrahydro-5H-imidazo[2,1-b][1,3]thiazepin-3(2H)-one (**6af**).* Yield 37%; pale lemon-yellow crystals, m.p. 129–131 °C (from dioxane + water); R_f 0.76 (A); ^{1}H-NMR (200 MHz) δ: 1.78–1.83 (m, 2H, $SCH_2C\underline{H}_2$), 1.96–2.06 (m, 2H, $NCH_2C\underline{H}_2$), 2.44 (s, 3H, CH_3), 3.11–3.17 (m, 2H, SCH_2), 3.74 (def.t, J = 5.0 Hz, 2H, NCH_2), 7.11 (s, 1H, CH=), 7.26–7.32 (m, 3H, H-3′, H-4′, H-5′), 8.56–8.61 (m, 1H, H-6′); IR ν: 3056, 2916 (C–H), 1698 (C=O), 1648 (ArCH=), 1620, 1590, 1488, 1444, 1376, 1352, 1312, 1196, 1180, 768, 756 cm^{-1}. Anal. ($C_{15}H_{17}N_2OS$) C, H, N.

*5.1.3.6. Z-2-(2-Trifluoromethylbenzylidene)-5,6,7,8-tetrahydro-5H-imidazo[2,1-b][1,3]thiazepin-3(2H)-one (**6ag**).* Yield 16%; lemon-yellow crystals, m.p. 144–146 °C (from dioxane + water); R_f 0.76 (A); ^{1}H-NMR (200 MHz) δ: 1.76–1.86 (m, 2H, $SCH_2C\underline{H}_2$), 1.99–2.07 (m, 2H, $NCH_2C\underline{H}_2$), 3.17–3.23 (m, 2H, SCH_2), 3.73–3.78 (m, 2H, NCH_2), 7.03 (d, J = 2.0 Hz, 1H, CH=), 7.60 (t, J = 7.6 Hz, 1H, H-5′), 7.80 (def.t, J = 8.0 Hz, 2H, H-3′, H-4′), 8.81 (d, J = 7.8 Hz, 1H, H-6′); UV λ_{max} (log ε): 252 (3,24), 291 (3.44), 376 (3.69); IR ν: 2920 (C–H), 1712 (C=O), 1648 (ArCH=), 1626, 1480, 1376, 1308, 1148, 1120, 1030, 770, 668 cm^{-1}. Anal. ($C_{15}H_{13}N_2OSF_3$) C, H, N.

*5.1.3.7. Z-2-(2,4-Dimethoxybenzylidene)-5,6,7,8-tetrahydro-5H-imidazo[2,1-b][1,3]thiazepin-3(2H)-one (**6ah**).* Yield 24%; orange-yellow crystals, m.p. 158–160 °C (from dioxane + water); R_f 0.70 (A); ^{1}H-NMR (250 MHz) δ: 1.79–1.85 (m, 2H, $SCH_2C\underline{H}_2$), 2.08–2.10 (m, 2H, $NCH_2C\underline{H}_2$), 3.14–3.18 (m, 2H, SCH_2), 3.77–3.81 (m, 2H, NCH_2), 3.90 (s, 3H, OCH_3), 3.95(s, 3H, OCH_3), 6.67–6.75 (m, 2H, H-3′, H-5′), 7.33 (s, 1H, CH=), 8.72 (d, J = 8.8 Hz, 1H, H-6′); UV λ_{max} (log ε): 261 (4.08), 310 (3.83), 399 (4.59), 408 (4.58); IR ν: 3002, 2937, 2842 (C–H), 1702 (C=O), 1689 (ArCH=), 1592, 1274, 1213, 1189, 1025, 835 cm^{-1}. Anal. ($C_{16}H_{18}N_2O_3S$) C, H, N.

*5.1.3.8. Z-2-(2,3-Dichlorobenzylidene)-5,6,7,8-tetrahydro-5H-imidazo[2,1-b][1,3]thiazepin-3(2H)-one (**6ai**).* Yield 28%; lemon-yellow crystals, m.p. 180–182 °C (from acetonitrile); R_f 0.81 (A); R_f 0.34 (B); ^{1}H-NMR (200 MHz) δ: 1.79–1.86 (m, 2H, $SCH_2C\underline{H}_2$), 2.02–2.07 (m, 2H, $NCH_2C\underline{H}_2$), 3.17–3.22 (def.t, J = 5.5 Hz, 2H, SCH_2), 3.75 (def.t, J = 5.1 Hz, 2H, NCH_2), 7.16 (s, 1H, ArCH=), 7.47 (t, J = 8.0 Hz, 1H, H-5′), 7.67 (dd, J = 8.0 Hz, J = 1.6 Hz, 1H, H-4′), 8.67 (dd, J = 8.0 Hz, J = 1.5 Hz, 1H, H-6′); UV λ_{max} (log ε): 257 (3.54), 296 (3.69), 384 (3.94); IR ν: 2905, 2852

(C–H), 1714 (C=O), 1625 (ArCH=), 1478, 1462, 1410, 1354, 1210, 1181, 1151, 1125, 787, 588 cm^{-1}. Anal. ($C_{14}H_{12}N_2OSCl_2$) C, H, N.

5.1.3.9. Z-*2-(4-Methoxy-2,5-dimethylbenzylidene)-5,6,7,8-tetrahydro-5*H-*imidazo[2,1-b][1,3]thiazepin-3(2*H*)-one* (***6aj***). Yield 46%; lemon-yellow crystals, m.p. 190–193 °C (methylene chloride + ethyl acetate); R_f 0.73 (A); ^{1}H-NMR (250 MHz) δ: 1.75–1.79 (m, 2H, $SCH_2C\underline{H}_2$), 1.98–2.03 (m, 2H, $NCH_2C\underline{H}_2$), 2.12 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 3.08–3.13 (m, 2H, SCH_2), 3.72–3.76 (m, 2H, NCH_2), 3.83 (s, 3H, OCH_3), 6.88 (s, 1H, ArCH=), 7.06 (s, 1H, H-3′), 8.50 (s, 1H, H-6′); UV λ_{max} (log ε): 261 (4.16), 399 (4.71), 423 (4.57); IR ν: 3062, 2938 (C–H), 1685 (C=O), 1625 (ArCH=), 1594, 1504, 1488, 1267, 1220, 1099, 1066, 838 cm^{-1}. Anal. ($C_{17}H_{20}N_2O_2S$) C, H, N.

5.1.3.10. Z-*2-(3-Chlorobenzylidene)-5,6,7,8-tetrahydro-5*H-*imidazo[2,1-b][1,3]thiazepin-3(2*H*)-one* (***6ba***). Yield 24%; pale lemon-yellow crystals, m.p. 110–112 °C (from dioxane + water); R_f 0.74 (A); ^{1}H-NMR (250 MHz) δ: 1.81–1.90 (m, 2H, $SCH_2C\underline{H}_2$), 2.06–2.15 (m, 2H, $NCH_2C\underline{H}_2$), 3.22–3.26 (m, 2H, SCH_2), 3.81 (def.t, J = 5.3 Hz, 2H, NCH_2), 7.04 (s, 1H, ArCH=), 7.52–7.55 (m, 2H, H-4′, H-5′), 8.14–8.17 (m, 1H, H-6′), 8.39 (s, 1H, H-2′); UV λ_{max} (log ε): 247 (4.00), 292 (4.09), 377 (4.42), 399 (4.25); IR ν: 2912 (C–H), 1712 (C=O), 1648 (ArCH=), 1632, 1564, 1480, 1346, 1184, 796, 672 cm^{-1}. Anal. ($C_{14}H_{13}N_2OSCl$) C, H, N.

5.1.3.11. Z-*2-(3-Nitrobenzylidene)-5,6,7,8-tetrahydro-5*H-*imidazo[2,1-b][1,3]thiazepin-3(2*H*)-one* (***6bb***). Yield 26%; lemon-yellow crystals, m.p. 182–184 °C (from dioxane + water); R_f 0.72 (A); R_f 0.11 (B); ^{1}H-NMR (300 MHz) δ: 1.78–1.82 (m, 2H, $SCH_2C\underline{H}_2$), 2.03–2.05 (m, 2H, $NCH_2C\underline{H}_2$), 3.16–3.20 (def.t, 2H, SCH_2), 3.27–3.76 (def.t, J = 4.3 Hz, 2H, NCH_2), 7.10 (s, 1H, ArCH=), 7.71 (t, J = 8.0 Hz, 1H, H-5′), 8.20 (dd, J = 8.2 Hz, J = 2.2 Hz, 1H, H-4′), 8.48 (d, J = 8.0 Hz, 1H, H-6′), 9.12 (s, 1H, H-2′); UV λ_{max} (log ε): 254 (4.25), 286 (4.29), 378 (4.41), 399 (4.25); IR ν: 3070, 2951, 2934, 2907 (C–H), 1716 (C=O), 1638 (ArCH=), 1520, 1483, 1347, 1193, 1161, 927, 740, 668 cm^{-1}. Anal. ($C_{14}H_{13}N_3O_3S$) C, H, N.

5.1.3.12. Z-*2-(3-Phenoxybenzylidene)-5,6,7,8-tetrahydro-5*H-*imidazo[2,1-b][1,3]thiazepin-3(2*H*)-one* (***6bc***). Yield 17%; yellow crystals, m.p. 127–129 °C (from dioxane + water); R_f 0.76 (A); ^{1}H-NMR (200 MHz) δ: 1.68–1.86 (m, 2H, $SCH_2C\underline{H}_2$), 1.97–2.11 (m, 2H, $NCH_2C\underline{H}_2$), 3.10–3.16 (m, 2H, SCH_2), 3.72 (def.t, J = 4.6 Hz, 2H, NCH_2), 6.98 (s, 1H, ArCH=), 7.01–7.06 (m, 3H, H-3″, H-4″, H-5″), 7.15 (t, J = 7.3 Hz, 1H, H-5′), 7.36–7.49 (m, 3H, H-4′, H-2″, H-6″), 7.87 (d, J = 7.8 Hz, 1H, H-6′), 8.01 (s, 1H, H-2′); UV λ_{max} (log ε): 359 (4.30), 378 (4.41), 399 (4.27); IR ν: 2944, 2916 (C–H), 1702 (C=O), 1628 (ArCH=), 1584, 1564, 1484, 1428, 1256, 1220, 1192, 1168, 1156, 1116, 760, 694 cm^{-1}. Anal. ($C_{20}H_{18}N_2O_2S$) C, H, N.

5.1.3.13. Z-*2-(3-Methylbenzylidene)-5,6,7,8-tetrahydro-5*H-*imidazo[2,1-b][1,3]thiazepin-3(2*H*)-one* (***6bd***). Yield 14%; pale lemon-yellow crystals, m.p. 104–105 °C (from dioxane + water); R_f 0.73 (A); ^{1}H-NMR (200 MHz) δ: 1.70–1.81 (m, 2H, $SCH_2C\underline{H}_2$), 1.97–2.08 (m, 2H, $NCH_2C\underline{H}_2$), 2.33 (s, 3H, CH_3), 3.11–3.16 (m, 2H, SCH_2), 3.74 (def.t, J = 5.0 Hz, 2H, NCH_2), 6.94 (s, 1H, ArCH=), 7.23 (d, J = 7.6 Hz, 1H, H-5′), 7.34 (t, J = 7.5 Hz, 1H, H-4′), 7.97 (s, 1H, H-2′), 8.00 (d, J = 7.8 Hz, 1H, H-6′); UV λ_{max} (log ε): 251 (3.61), 295 (3.86), 258 (4.15), 377 (4.25), 401 (4.03); IR ν: 2908 (C–H), 1704 (C=O), 1680, 1648 (ArCH=), 1626, 1480, 1348, 1192, 1118, 1040, 928, 836, 784, 696 cm^{-1}. Anal. ($C_{15}H_{17}N_2OS$) C, H, N.

5.1.3.14. Z-*2-(Pyridine-3-methylene)-5,6,7,8-tetrahydro-5*H-*imidazo[2,1-b][1,3]thiazepin-3(2*H*)-one* (***6be***). Yield 28%; lemon-yellow crystals, m.p. 148–150 °C (from acetonitrile); R_f 0.81 (A), R_f 0.34 (B); ^{1}H-NMR (200 MHz) δ: 1.79–1.98 (m, 2H, $SCH_2C\underline{H}_2$), 2.01–2.08 (m, 2H, $NCH_2C\underline{H}_2$), 3.17 (def.t, J = 5.4 Hz, 2H, SCH_2), 3.74 (def.t, J = 5.0 Hz, 2H, NCH_2), 7.02 (s, 1H, ArCH=), 7.45–7.51 (m, 1H, H-5′), 8.55 (dd, J = 1.6 Hz, J = 4.8 Hz, 1H, H-4′), 8.65 (dt, J = 1.8 Hz, J = 8.1 Hz, 1H, H-6′), 9.14 (d, J = 1.9 Hz, 1H, H-2′); UV λ_{max} (log ε): 253 (3.14), 296 (3.02), 359 (3.13), 405 (3.39); IR ν: 2946, 2907, 2853 (C–H), 1725 (C=O), 1637 (ArCH=), 1551, 1482, 1328, 1203, 1185, 1135, 951, 815, 715, 706 cm^{-1}. Anal. ($C_{13}H_{13}N_3OS$) C, H, N.

5.1.3.15. Z-*2-[3-(4-Chlorobenzyloxy)benzylidene)-5,6,7,8-tetrahydro-5*H-*imidazo[2,1-b][1,3]thiazepin-3(2*H*)-one* (***6bf***). Yield 34%; pale lemon-yellow crystals, m.p. 108–111 °C (from dioxane + water); R_f 0.82 (A); ^{1}H-NMR (250 MHz) δ: 1.81–1.89 (m, 2H, $SCH_2C\underline{H}_2$), 2.06–2.15 (m, 2H, $NCH_2C\underline{H}_2$), 3.20–3.24 (m, 2H, SCH_2), 3.81 (def.t, J = 5.0 Hz, 2H, NCH_2), 7.01 (s, 1H, ArCH=), 7.13 (dd, J = 2.0 Hz, J = 8.0 Hz, 1H, H-4′), 7.43 (t, J = 8.0 Hz, 1H, H-5′), 7.52 (d, J = 8.5 Hz, 2H, H-3″, H-5″), 7.58 (d, J = 8.5 Hz, 2H, H-2″, H-6″), 7.80 (d, J = 7.8 Hz, 1H, H-6′), 7.99 (s, 1H, H-2′); UV λ_{max} (log ε): 252 (4.10), 292 (4.05), 380 (4.46), 402 (4.33); IR ν: 2920 (C–H), 1696 (C=O), 1648 (ArCH=), 1630, 1564, 1488, 1288, 1250, 1152, 1036, 808, 784 cm^{-1}. Anal. ($C_{21}H_{19}N_2O_2SCl$) C, H, N.

5.1.3.16. Z-*2-[3-(2,4-Dichlorobenzyloxy)benzylidene]-5,6,7,8-tetrahydro-5*H-*imidazo[2,1-b][1,3]thiazepin-3(2*H*)-one* (***6bg***). Yield 10%; pale lemon-yellow crystals, m.p. 135–137 °C (from dioxane + water); R_f 0.88 (A); ^{1}H-NMR (250 MHz) δ: 1.77–1.81 (m, 2H, $SCH_2C\underline{H}_2$), 2.02–2.05 (m, 2H, $NCH_2C\underline{H}_2$), 3.13–3.17 (m, 2H, SCH_2), 3.73 (def.t, J = 5.0 Hz, 2H, NCH_2), 6.95 (s, 1H, ArCH=), 7.09 (dd, J = 2.0 Hz, J = 8.0 Hz, 1H, H-5″), 7.38 (t, J = 8.3 Hz, 1H, H-5′), 7.47 (dd, J = 2.0 Hz, J = 8.4 Hz, 1H, H-6″), 7.64 (d, J = 8.3 Hz, 1H, H-4′), 7.69 (d, J = 2.0 Hz, 1H, H-3″), 7.75 (d, J = 8.0 Hz, 1H, H-6′), 7.94 (d, J = 1.3 Hz, 1H, H-2′); UV λ_{max} (log ε): 249 (4.09), 292 (4.03), 379 (4.43), 401 (4.28); IR ν: 2915 (C–H), 1707 (C=O), 1633 (ArCH=), 1573, 1487, 1436,

1345, 1267, 1200, 1166, 1046, 835, 785, 707 cm^{-1}. Anal. ($C_{21}H_{18}N_2O_2SCl_2$) C, H, N.

*5.1.3.17. Z-2-[3-(Ethoxycarbomethoxy)benzylidene]-5,6,7,8-tetrahydro-5*H*-imidazo[2,1-b][1,3] thiazepin-3(2*H*)-one (**6bh**).* Yield 28%; lemon-yellow crystals, m.p. 107–109 °C (from methylene chloride); R_f 0.80 (A); ^{1}H-NMR (250 MHz) δ: 1.29 (t, J = 7.5 Hz, 3H, CH_3), 1.84–1.86 (m, 2H, $SCH_2C\underline{H}_2$), 2.09–2.11 (m, 2H, $NCH_2C\underline{H}_2$), 3.20–3.24 (s, 3H, SCH_3), 3.78–3.82 (m, 2H, NCH_2), 4.25 (q, J = 7.5 Hz, 2H, OCH_2CH_3), 4.86 (s, 2H, CH_2O), 7.01 (s, 1H, ArCH=), 7.04–7.08 (m, 1H, H-4′), 7.44 (t, J = 5.0 Hz, 1H, H-5′), 7.91 (s, 1H, H-2′), 7.80 (d, J = 5.0 Hz, 1H, H-6′); UV λ_{max} (log ε): 251 (3.91), 367 (4.37), 388 (4.51), 410 (3.36); IR v: 2967, 2917 (C–H), 1758 (COOEt), 1712 (C=O), 1627 (ArCH=), 1488, 1203, 1085, 777, 676 cm^{-1}. Anal. ($C_{18}H_{20}N_2O_4S$) C, H, N.

*5.1.3.18. Z-2-(4-Methoxybenzylidene)-5,6,7,8-tetrahydro-5*H*-imidazo[2,1-b][1,3]thiazepin-3(2*H*)-one (**6cb**).* Yield 21%; lemon-yellow crystals, m.p. 125–128 °C (from dioxane + water); R_f 0.72 (A); ^{1}H-NMR (200 MHz) δ: 1.70–1.85 (m, 2H, $SCH_2C\underline{H}_2$), 1.95–2.10 (m, 2H, $NCH_2C\underline{H}_2$), 3.09–3.14 (m, 2H, SCH_2), 3.74 (def.t, J = 4.6 Hz, 2H, NCH_2), 3.82 (s, 3H, OCH_3), 6.97 (s, 1H, ArCH=), 7.02 (d, J = 8.8 Hz, 2H, H-3′, H-5′), 8.16 (d, J = 8.8 Hz, 2H, H-2′, H-6′); IR v: 2920 (C–H), 1692 (C=O), 1648 (ArCH=), 1592, 1506, 1480, 1254, 1176, 1156, 1022, 836, 546 cm^{-1}. Anal. ($C_{15}H_{17}N_2O_2S$) C, H, N.

*5.1.3.19. Z-2-(4-Ethoxybenzylidene)-5,6,7,8-tetrahydro-5*H*-imidazo[2,1-b][1,3]thiazepin-3(2*H*)-one (**6cc**).* Yield 30%; lemon-yellow crystals, m.p. 170–173 °C (from dioxane + water); R_f 0.80 (A); ^{1}H-NMR (250 MHz) δ: 1.33 (t, J = 7.0 Hz, 3H, CH_3), 1.68–1.80 (m, 2H, $SCH_2C\underline{H}_2$), 1.90–2.05 (m, 2H, $NCH_2C\underline{H}_2$), 3.08–3.11 (m, 2H, SCH_2), 3.70–3.74 (def.t, J = 4.8 Hz, 2H, NCH_2), 4.08 (q, J = 7.0 Hz, 2H, CH_2CH_3), 6.95 (s, 1H, ArCH=), 6.99 (d, J = 8.8 Hz, 2H, H-3′, H-5′), 8.13 (d, J = 8.8 Hz, 2H, H-2′, H-6′); IR v: 2971, 2927 (C–H), 1702 (C=O), 1639 (ArCH=), 1630, 1598, 1251, 1178, 1043 cm^{-1}. Anal. ($C_{16}H_{18}N_2O_2S$) C, H, N.

*5.1.3.20. Z-2-[4-(Ethoxycarbomethoxy)benzylidene)]-5,6,7,8-tetrahydro-5*H*-imidazo[2,1-b][1,3] thiazepin-3(2*H*)-one (**6cd**).* Yield 31%; lemon-yellow crystals, m.p. 117–120 °C (from dioxane + water); R_f 0.84 (A); ^{1}H-NMR (250 MHz) δ: 1.28 (t, J = 5.0 Hz, 3H, CH_3), 1.83–1.86 (m, 2H, $SCH_2C\underline{H}_2$), 2.09 (m, 2H, $NCH_2C\underline{H}_2$), 3.16–3.21 (m, 2H, SCH_3), 3.78–3.82 (m, 2H, NCH_2), 4.23 (q, J = 7.5 Hz, 2H, OCH_2CH_3), 4.92 (s, 2H, OCH_2CO), 7.03 (s, 1H, ArCH=), 7.08 (d, J = 10.0 Hz, 2H, H-3′, H-5′), 8.22 (d, J = 10.0 Hz, 2H, H-2′, H-6′); IR v: 2911(C–H), 1766 (COOEt), 1704 (C=O), 1629 (ArCH=), 1598, 1492, 1205, 1176, 1085, 838 cm^{-1}. Anal. ($C_{18}H_{20}N_2O_4S$) C, H, N.

*5.1.3.21. Z-2-(4-Dimethylaminobenzylidene)-5,6,7,8-tetrahydro-5*H*-imidazo[2,1-b][1,3]thiazepin-3(2*H*)-one (**6ce**).* Yield 18%; dark orange crystals, m.p. 177–180 °C (from dioxane + water); R_f 0.63 (A); ^{1}H-NMR (250 MHz) δ: 1.71–1.76 (m, 2H, $SCH_2C\underline{H}_2$), 2.00–2.03 (m, 2H, $NCH_2C\underline{H}_2$), 3.01 (s, 6H, 2 × CH_3), 3.04–3.08 (m, 2H, SCH_2), 3.70–3.73 (m, 2H, NCH_2), 6.75 (d, J = 7.5 Hz, 2H, H-3′, H-5′), 6.90 (s, 1H, ArCH=), 8.04 (d, J = 7.5 Hz, 2H, H-2′, H-6′); UV λ_{max}(log ε); 263 (4.13), 322 (3.71), 448 (4.74); IR v: 2917 (C–H), 1693 (C=O), 1589 (ArCH=), 1529, 1444, 1380, 1322, 1195, 1184, 1153, 1116, 821 cm^{-1}. Anal. ($C_{16}H_{19}N_3OS$) C, H, N.

*5.1.3.22. Z-8-[(4-Benzoyloxy)-benzylidene]-2,3,4,5-tetrahydroimidazo[2,1-b]thiazepin-7-one (**6cf**).* Yield 12%; yellow crystals, m.p. 157–160 °C (from methylene chloride + ethyl acetate); R_f 0.82 (A); ^{1}H-NMR (200 MHz) δ: 1.79 (m, 2H, $SCH_2C\underline{H}_2$), 2.03 (m, 2H, $NCH_2C\underline{H}_2$), 3.13–3.18 (m, 2H, SCH_2), 3.75 (def.t, 2H, NCH_2), 7.04 (s, 1H, ArCH=), 7.40 (d, J = 8.7 Hz, 2H, H-3′, H-5′), 7.61 (t, J = 7.7 Hz, 2H, H-3″, H-5″), 7.73–7.76 (m, 1H, H-4″), 8.14 (def.d, 2H, H-2″, H-6″), 8.29 (d, J = 8.7 Hz, 2H, H-2′, H-6′); IR v: 1736 (COO), 1704 (C=O), 1631 (ArCH=), 1594 (C=N), 1416, 1384, 1254, 1200, 1167, 1080, 1024, 962, 711 cm^{-1}. Anal. ($C_{21}H_{18}N_2O_3S$) C, H, N.

*5.1.3.23. Z-2-[4-(4-Chlorobenzoyloxy)-benzylidene]-2,3,4,5-tetrahydroimidazo-[2,1-b]-thiazepin-7-one (**6cg**).* Yield 11%; lemon-yellow crystals, m.p. 184–187 °C (from methylene chloride); R_f 0.79 (A); ^{1}H-NMR (200 MHz) δ: 1.87 (m, 2H, $SCH_2C\underline{H}_2$), 2.13 (m, 2H, $NCH_2C\underline{H}_2$), 3.23 (def.t, 2H, SCH_2), 3.84 (t, 2H, NCH_2), 7.12 (s, 1H, ArCH=), 7.48 (d, J = 8.7 Hz, 2H, H-3′, H-5′), 7.77 (d, J = 8.5 Hz, 2H, H-3″, H-5″), 8.22 (d, J = 8.5 Hz, 2H, H-2″, H-6″), 8.37 (d, J =8.8 Hz, 2H, H-2′, H-6′); IR v: 1741 (COO), 1709 (C=O), 1636 (ArCH=), 1590 (C=N), 1482, 1385, 1259, 1208, 1188, 1167, 1086, 1064, 1012, 904, 871, 750, 676, 560. Anal. ($C_{21}H_{17}N_2O_3SCl$) C, H, N.

*5.1.3.24. Z-2-[4-(2-Chlorobenzoyloxy)benzylidene]-2,3,4,5-tetrahydroimidazo-[2,1-b]-thiazepin-7-one (**6ch**).* Yield 21%; lemon-yellow crystals, m.p. 152–154 °C (from methylene chloride); R_f 0.84 (A); ^{1}H-NMR (200 MHz) δ: 1.78–1.82 (m, 2H, $SCH_2C\underline{H}_2$), 2.02–2.05 (m, 2H, $NCH_2C\underline{H}_2$), 3.13–3.18 (m, 2H, SCH_2), 3.74 (t, 2H, NCH_2), 7.03 (s, 1H, CH=), 7.37 (d, J = 8.5 Hz, 2H, H-3′, H-5′), 7.53–7.58 (m, 1H, H-4″), 7.66–7.69 (m, 2H, H-3″, H-5″), 8.1 (d, J = 7.2 Hz, 1H, H-6″), 8.29 (d, J =8.8 Hz, 2H, H-2′, H-6′); IR v: 2941 (C–H), 1731, 1698 (C=O), 1633 (ArCH=), 1593 (C=N), 1493, 1433, 1381 (COO), 1279, 1213, 1186, 1166, 1119, 962, 869, 824, 777, 751, 715, 686, 648 cm^{-1}. Anal. ($C_{21}H_{18}N_2O_3S$) C, H, N.

*5.1.3.25. Z-2-(4-Carbomethoxybenzylidene)-5,6,7,8-tetrahydro-5*H*-imidazo[2,1-b][1,3]thiazepin-3(2*H*)-one (**6ci**).* Yield 32%; lemon-yellow crystals, m.p. 213–215 °C (from methylene chloride + ethyl acetate); R_f 0.77 (A); ^{1}H-NMR (200 MHz) δ: 1.75–1.84 (m, 2H, $SCH_2C\underline{H}_2$), 1.99–2.07 (m, 2H, $NCH_2C\underline{H}_2$), 3.16–3.21 (m, 2H, SCH_2), 3.76 (def.t,

J = 5.1 Hz, 2H, NCH_2), 7.01 (s, 1H, ArCH=), 8.00 (d, J = 8.2 Hz, 2H, H-3′, H-5′), 8.28 (d, J = 8.5 Hz, 2H, H-6′, H-2′); IR ν: 2946 (C–H), 1718 (COOMe, C=O), 1627 (ArCH=), 1477, 1274, 1108, 840, 711, 698 cm^{-1}. Anal. ($C_{16}H_{16}N_2O_3S$) C, H, N.

5.1.3.26. Z-*2-(4-Phenylbenzylidene)-5,6,7,8-tetrahydro-5*H-*imidazo[2,1-b][1,3]thiazepin-3(*2H*)-one* (***6cj***). Yield 34%; lemon-yellow crystals, m.p. 140–143 °C (from dioxane + water); R_f 0.75 (A); ^{1}H-NMR (250 MHz) δ: 1.70–1.80 (m, 2H, $SCH_2C\underline{H}_2$), 1.90–2.10 (m, 2H, $NCH_2C\underline{H}_2$), 3.12–3.16 (m, 2H, SCH_2), 3.74 (def.t, J = 5.0 Hz, 2H, NCH_2), 7.03 (s, 1H, ArCH=), 7.38–7.48 (m, 3H, H-3″, H-4″, H-5″), 7.71–7.78 (m, 4H, H-3′, H-5′, H-2′, H-6″), 8.26 (d, J = 8.5 Hz, 2H, H-2′, H-6′); IR ν: 3027, 2935, 2850 (C–H), 1712 (C=O), 1631 (ArCH=), 1598, 1475, 1357, 1321, 1193, 1128, 836, 763, 692 cm^{-1}. Anal. ($C_{20}H_{18}N_2OS$) C, H, N.

5.1.3.27. Z-*2-(4-Benzyloxybenzylidene)-5,6,7,8-tetrahydro-5*H-*imidazo[2,1-b][1,3]thiazepin-3(*2H*)-one* (***6ck***). Yield 25%; lemon-yellow crystals, m.p. 158–160 °C (from methylene chloride + ethyl acetate); R_f 0.80 (A); ^{1}H-NMR (200 MHz) δ: 1.76–1.80 (m, 2H, $SCH_2C\underline{H}_2$), 1.98–2.08 (m, 2H, $NCH_2C\underline{H}_2$), 3.08–3.14 (m, 2H, SCH_2), 3.71–3.75 (m, 2H, NCH_2), 5.17 (s, 2H, OCH_2), 6.97 (s, 1H, ArCH=), 7.10 (d, J = 8.8 Hz, 2H, H-3′, H-5′), 7.36–7.45 (m, 5H, C_6H_5), 8.16 (d, J = 8.9 Hz, 2H, H-2′, H-6′); IR ν: 2931 (C–H), 1698 (C=O), 1633 (ArCH=), 1594, 1490, 1247, 1174, 998, 833, 746, 698. Anal. ($C_{21}H_{20}N_2O_2S$) C, H, N.

5.1.3.28. Z-*2-(Cinnamylidene)-5,6,7,8-tetrahydro-5*H-*imidazo[2,1-b][1,3]thiazepin-3(*2H*)-one* (***6da***). Yield 28%; yellow crystals, m.p. 124–126 °C (from dioxane + water); R_f 0.75 (A); ^{1}H-NMR (400 MHz) δ: 1.75–1.78 (m, 2H, $SCH_2C\underline{H}_2$), 1.98–2.04 (m, 2H, $NCH_2C\underline{H}_2$), 3.10–3.13 (m, 2H, SCH_2), 3.65–3.73 (m, 2H, NCH_2), 6.91 (d, J = 11.4 Hz, 1H, H_a), 7.27 (d, J = 15.8 Hz, 1H, H_b), 7.34–7.45 (m, 1H, H-4′), 7.40 (d, J = 7.6 Hz, 2H, H-3′, H-5′), 7.49 (d, J = 11.5 Hz, 1H, H_c), 7.62 (d, J = 7.2 Hz, 2H, H-2′, H-6′); UV λ_{max} (log ε): 259 (3.38), 295 (3.50), 349 (3.63), 382 (3.85), 4.16 (4.00); IR ν: 2927 (C–H), 1706 (C=O), 1620 (ArCH=), 1485, 1328, 1190, 1156, 975, 755; EI-MS: m/z (%): 284 ($M^{+\cdot}$, 100); 255 (31); 229 (7); 185 (5); 155 (23); 142 (19); 115 (43); 72 (59); 55 (78). Anal. ($C_{16}H_{16}N_2OS$) C, H, N.

5.1.3.29. Z-*2-(Methylphenylmethylene)-5,6,7,8-tetrahydro-5*H-*imidazo[2,1-b][1,3]thiazepin-3(*2H*)-one* (***6db***). Yield 12%; cream-rose-colored crystals, m.p. 90–94 °C (from dioxane + water then ethyl acetate); R_f 0.77 (A); ^{1}H-NMR (250 MHz) δ: 1.73 (qui, J = 5.0 Hz, 2H, $SCH_2C\underline{H}_2$), 1.95–2.04 (m, 2H, $NCH_2C\underline{H}_2$), 2.66 (s, 3H, CH_3), 2.99–3.04 (m, 2H, SCH_2), 3.70–3.74 (m, 2H, NCH_2), 7.36–7.45 (m, 3H, H-3′, H-4′, H-5′), 7.69–7.76 (m, 2H, H-2′, H-6′); IR ν: 3054, 2944, 2915 (C–H), 1693 (C=O), 1610 (ArC=), 1492, 1232, 1213, 993, 850, 823, 676 cm^{-1}. Anal. ($C_{15}H_{16}N_2OS$) C, H, N.

5.1.3.30. Z-*2-[Methyl-(4-chlorophenyl)methylene]-5,6,7,8-tetrahydro-5*H-*imidazo[2,1-b][1,3]thiazepin-3(*2H*)-one* (***6dc***). Yield 5%; cream-rose-colored crystals, m.p. 119–122 °C (from ethyl acetate); R_f 0.77 (A); ^{1}H-NMR (250 MHz) δ: 1.78–1.83 (m, 2H, $SCH_2C\underline{H}_2$), 2.02–2.09 (m, 2H, $NCH_2C\underline{H}_2$), 2.72 (s, 3H, CH_3), 3.08–3.12 (m, 2H, SCH_2), 3.77–3.81 (m, 2H, NCH_2), 7.55 (d, J = 10.0 Hz, 2H, H-3′, H-5′), 7.85 (d, J = 10.0 Hz, 2H, H-2′, H-6′); IR ν: 2944, 2908 (C–H), 1697 (C=O), 1619 (ArC=), 1500, 1220, 1199, 1164, 1091, 1074, 954 cm^{-1}. Anal. ($C_{15}H_{15}N_2OSCl$) C, H, N.

5.1.3.31. Z-*2-(2-Naphtylmethylene)-5,6,7,8-tetrahydro-5*H-*imidazo[2,1-b][1,3]thiazepin-3(*2H*)-one* (***7a***). Yield 35%; yellow crystals, m.p. 166–168 °C (from dioxane); R_f 0.79 (A); ^{1}H-NMR (250 MHz) δ: 1.75–1.82 (m, 2H, $SCH_2C\underline{H}_2$), 1.99–2.07 (m, 2H, $NCH_2C\underline{H}_2$), 3.14–3.18 (m, 2H, SCH_2), 3.74–3.78 (m, 2H, NCH_2), 7.13 (s, 1H, ArCH=), 7.51–7.58 (m, 2H, H-6′, H-7′), 7.90–7.97 (m, 3H, H-4′, H-5′, H-8′), 8.48–8.55 (m, 2H, H-3′, H-1′); UV λ_{max} (log ε): 252 (4.21), 391 (4.43), 413 (4.32); IR ν: 2924 (C–H), 1692 (C=O), 1614 (ArCH=), 1488, 1330, 1152, 1116, 928, 828, 748 cm^{-1}. Anal. ($C_{18}H_{16}N_2OS$) C, H, N.

*5.1.3.32. 2-Cyclohexylidene-5,6,7,8-tetrahydro-5*H-*imidazo[2,1-b][1,3]thiazepin-3(*2H*)-one* (***7b***). Yield 22%; cream-colored crystals, m.p. 152–154 °C (from ethanol); R_f 0.72 (A); ^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 1.59–1.82 (m, 8H, 3 × CH_2, cyclohexyl, $SCH_2C\underline{H}_2$), 2.05–2.17 (m, 2H, $NCH_2C\underline{H}_2$), 2.75 (t, J = 5.8 Hz, 2H, H-2′), 2.90–2.95 (m, 2H, SCH_2), 3.07 (t, J = 5.5 Hz, 2H, H-6′), 3.82 (def.t, J = 5.0 Hz, 2H, NCH_2); IR ν: 2927, 2850 (C–H), 1691 (C=O), 1635 (C=), 1508, 1444, 1336, 1191, 1159, 964, 925 cm^{-1}. Anal. ($C_{13}H_{18}N_2OS$) C, H, N.

5.2. Benzodiazepine binding assays

Frozen rat brains were obtained from Pel-Freez®, Rogers, AR, USA. The cortex was dissected and inhibition of binding of [^{3}H]diazepam to rat brain cortical membranes was determined as previously described [18]. The compounds were dissolved in dimethyl sulfoxide (DMSO), and the final DMSO concentration in the assays was 1%. In a final volume of 1 ml, each test tube contained 790 μl of Tris–HCl (tris(hydroxymethyl)aminomethane hydrochloride) buffer (50 mM, pH 7.4), 10 μl of compound solution in DMSO, 100 μl of rat cerebral cortical membrane preparation with a protein concentration of ca. 100 μg per tube, and 100 μl of [^{3}H]diazepam solution, to give a final concentration of 1 nM. DMSO was necessary since the compounds possessed low water solubility.

Incubations were performed on an ice-bath for 1 h and were terminated by rapid filtration through GF/B glass fiber filters (Whatman, USA) using a Brandel 48-channel cell harvester (Brandel, Gaithersburg, MD, USA). Three 5 ml washes with ice-cold Tris–HCl buffer 50 mM, pH 7.4 were performed. Unlabelled diazepam (5 μM) was used to define

non-specific binding. All compounds were initially tested in a single concentration of 25 μM (or 2.5 μM) in at least three independent experiments each in triplicate. For selected compounds, a full inhibition curve was determined in 4–5 separate experiments in triplicate. K_i values were calculated from IC_{50} values, determined by the non-linear regression program Prism version 3.0 (Graphpad, San Diego, CA, USA), using the Cheng-Prusoff equation and a K_D value of 4 nM for diazepam [19].

5.3. In vivo tests

Evaluation for anticonvulsant activity was performed in male Carworth Farms no. 1 (CF 1) mice. Phase I of the evaluation was qualitative assay which used small groups of animals (1–8) and included three tests: maximal electroshock (MES), subcutaneous pentylenetetrazole (ScMet) and rotorod test for neurological toxicity (Tox). Compounds were suspended in 30% polyethylene glycol 400 and were administered by intraperitoneal injection at three dosage levels (30, 100 and 300 mg/kg) with anticonvulsant activity and neurotoxicity noted 30 min and 4 h after administration (according to published procedure [23,24]).

5.4. X-ray diffraction analysis of Z-2-(2-methoxybenzylidene)-5,6,7,8-tetrahydro-5H-imidazo[2,1-b][1,3]thiazepin-3(2H)-one (**6ae**) and Z-2-(2-trifluoromethylbenzylidene)-5,6,7,8-tetrahydro-5H-imidazo[2,1-b][1,3]thiazepin-3(2H)-one (**6ag**)

Crystals of **6ae** and **6ag** were obtained by slow evaporation of dioxane solutions of the compounds. Preliminary crystallographic data were obtained using a KM4 four-cycle diffractometer; the accurate cell dimensions were determined by the least-squares refinement from the angular settings of 25 reflections located within $10 < \Theta < 40°$. All crystal data are collected in Table 1. The crystals (dimensions of 0.10 × 0.10 × 0.30 mm for **6ae** and 0.2 × 0.2 × 0.4 mm for **6ag**) were used to collect diffraction data on a KM4 diffractometer by the $\omega/2\Theta$ scan technique using graphite monochromated CuKα radiation at room temperature. The data were collected for **6ae** in the range of $\Theta < 55°$ [*h*: -9/9, *k*: 0/13, *l*: 0/12] while for **6ag** in the range of $\Theta < 80^o$ [*h*: -12/12, *k*: 0/17, *l*: 0/14]; an absorption correction was not applied; the intensity of three standard reflections, monitored every 100 reflections, showed no significant fluctuations. For **6ae** 1840 reflections were measured, 1745 reflections were considered to be observed using the criterion $F_o > 4\sigma(F_o)$, while for **6ag** these values were 3030 and 2866 reflections, respectively. The structures were solved using a direct method (SHELXTL-PC) [37]. E-map provided positions for all non-H-atoms. The full-matrix least-squares refinement was carried out on F^2's using anisotropic temperature factors for all non-H-atoms. The H-atoms were located geometrically, then the positions of H-atoms were refined in the riding model with isotropic thermal parameters taken as 1.5 times the temperature factors for their parent-atoms. The refinement for **6ae** was finished at $R = 0.0676$, $wR^2 = 0.1496$ (with $w = 1/[\sigma^2(F_o^2)+(0.0835P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$ and empirical extinction correction coefficient $g = 0.0014(2)$, $S = 1.01$ (182 parameters); $\Delta\sigma\rho_{min} = -0.29$ e A^{-3}, $\Delta\rho_{max} = 0.37$ e A^{-3}. Corresponding data for **6ag** were $R = 0.0672$, $wR^2 = 0.1971$ (with $w = 1/[\sigma^2(F_o^2)+0.1454P)^2+1.1313P]$ where $P = (F_o^2 + 2F_c^2)/3$ and empirical extinction correction coefficient $g = 0.0006(3)$, $S = 1.02$ (200 parameters); $\Delta\rho_{min} = -0.51$ e A^{-3}, $\Delta\rho_{max} = 0.98$ e A^{-3}. The atomic scattering factors were taken from SHELXL-93 [38].

5.5. Analytical chromatographic measurements

Analytical TLC was performed on 20 × 20 cm pre-coated RP-TLC Al sheets of RP-18, F_{254S} (E. Merck); samples of 2.5 μl of the solutes (0.1 mg/ml in acetonitrile) were spotted with a Hamilton microliter syringe. The chromatograms were developed over a distance of 9.5 cm. The chambers were saturated with organic solvent vapour for 20 min. In the performed studies the water–acetonitrile mixtures were used as mobile phases. The concentration of the organic modifier in a mobile phase ranged from 65% to 90%. All TLC measurements were performed at 21 °C. Spots were visualised under UV light at 254 nm.

5.6. Computational procedures

The conformation analyses of **6ae** (starting with the crystallographically obtained geometry) were performed by molecular mechanics methods using the PCMOD.6 program [39]. The energy was minimized after each 10° clockwise rotation of one torsional angle in the 360° range. The geometry of the molecules were optimized with MOPAC 6.0 using AM1 Hamiltonians in an aqueous environment (dielectric constants equals 78.4) [40]. The values of log *P* for the compounds investigated were calculated by means of the PALLAS (version 1.2) program [25]. Multiple Linear Regression Equations were computed by means of the QSAR-PC:PAR program written by R.C. Coburn [41].

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