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Original article

Imidazo-thiazine, -diazinone and -diazepinone derivatives. Synthesis, structure and benzodiazepine receptor binding

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Abstract – In our search for new compounds acting on benzodiazepine receptors among the fused 2-thiohydantoin derivatives, a series of arylidene imidazo[2,1-*b*]thiazines was synthesized. The 1,2- and 2,3- cyclized derivatives of mono- and di-substituted *Z*-5-arylidene-2-thiohydantoins were examined (the X-ray crystal structure of *Z*-2-cinnamylidene-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]thiazin-3(2H)-one was determined) and compared with the diphenyl derivatives. To investigate the influence of the type of annelated ring on the biological activity, imidazo[2,1-*b*]pyrimidinone and imidazo[2,1-*b*]diazepinone derivatives were obtained. The method used in annelation (1,2- and 2,3-cyclized isomers with the exception of fused arylidene imidazothiazines), the substitution pattern (arylidene towards diphenyl) as well as the character of the annelated ring had minor influence on the benzodiazepine receptor affinity of the investigated compounds. It appears that the greatest influence on the biological activity has the character and position of the substituents on the arylidene ring. © 2001 Éditions scientifiques et médicales Elsevier SAS

benzodiazepine receptor / $GABA_A$ receptor / imidazo[2,1-*b*]thiazines / imidazo[2,1-*b*]pyrimidinone / imidazo[2,1-*b*]diazepinone

1. Introduction

γ-Aminobutyric acid acts on the γ-aminobutyric acid-A chloride ion channel ($GABA_A$ receptor) controlling the excitation of many central nervous system pathways [1]. Various classes of compounds, such as benzodiazepines, neurosteroids and barbiturates which interact with this macromolecular ionophore and modulate the action of γ-aminobutyric acid on the neuronal chloride flux, have a continuum of intrinsic activity ranging from full agonists (anxiolytic, hypnotic and anticonvulsant agents) through antagonists, to inverse agonists (proconvulsant and anxiogenic agents) [2, 3]. Partial agonists lie within this continuum and may have reduced typical benzodiazepine-mediated side effects such as physical dependence, amnesia, oversedation and muscle relaxation [4, 5]. As it would be useful to find partial agonists for the benzodiazepine binding site of the $GABA_A$ receptor for therapeutic use, several research groups have developed and characterized such ligands comprising different chemical structures, including β-carboline (Abecarnil) [6], imidazopyridine (Alpidem) [7], quinoxalinone (Panadiplon) [8], pyridobenzimidazole [9] and imidazoquinoxaline [10, 11] structures. Further, recent molecular biology studies, which demonstrated that the $GABA_A$ receptor is a hetero-oligomeric ligand-gated chloride channel consisting of α-, β-, γ- and δ-subunits, brought fresh impetus into this field of research concerning the identification of new selective ligands for certain subtypes of the $GABA_A$ receptor [12].

We have recently reported on the annelated 2-thiohydantoin derivatives being benzylidene substituted imidazo[2,1-*b*]thiazoles, -thiazines and -thiazepines

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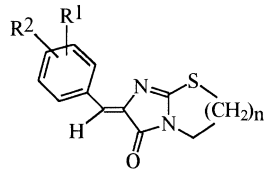


1 n = 1, 2, 3

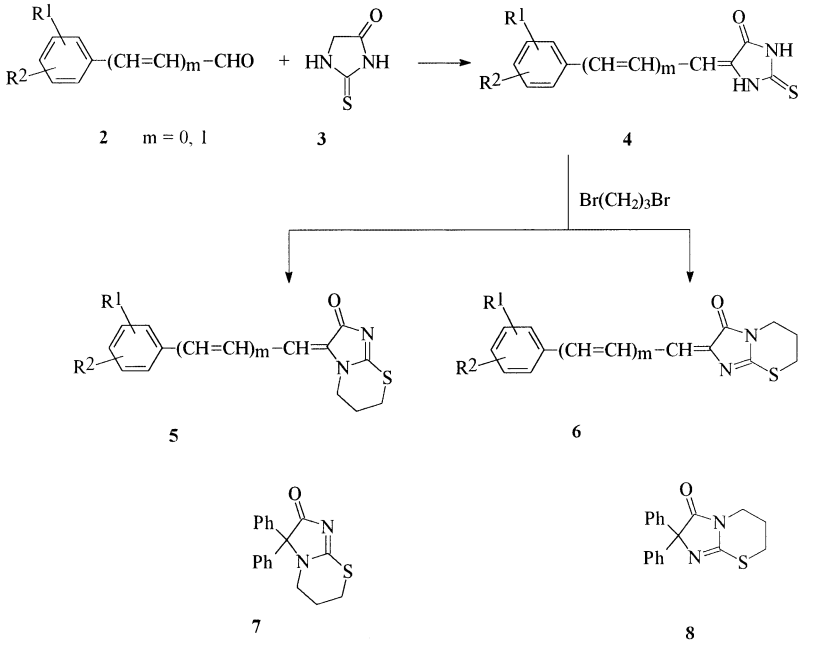
Figure 1. Structures of imidazo[2,1-*b*]thiazoles, -thiazines and -thiazepines.

with the general structure (**1**) given in *figure 1*, which displayed micromolar affinity for the benzodiazepine binding site of the $GABA_A$ receptors [13, 14]. Their profile of action was characterized on the basis of the $GABA_A$ shift [9] as partial agonists at the benzodiazepine-binding site of the $GABA_A$ receptors. Analysis of the structure–activity relationships revealed that thiazepine and thiazine derivatives were more potent than the analogous thiazole derivatives. Receptor affinity was strongly dependent on the substitution pattern of the benzylidene residue [13, 14].

In our present paper we report the further synthesis and biological activity of bicyclic imidazo[2,1-*b*]thiazines containing arylidene, cinnamylidene or diphenyl substituents of type **5**–**8** (*figure 2*). Bioisosteric replacement of sulfur with nitrogen yielding imidazo[2,1-*b*]pyrimidinone derivative (**11**) (*figure 3*) as well as enlargement of the annelated ring as in the imidazo[2,1-*b*]diazepinone derivative (**12**) was also investigated.

2. Chemistry

Bicyclic compounds of imidazo[2,1-*b*]thiazine type **5**–**8** were synthesized according to the procedures outlined in Refs. [15, 16]. Thus, *Z*-5-arylidene-, cinnamylidene-, or 5,5-diphenyl-2-thiohydantoins, respectively, was reacted with 1,3-dibromopropane under phase-transfer catalysis conditions (solid–liquid) in acetone in the presence of potassium carbonate and benzyltriethylammonium chloride as phase-transfer catalysts (*figure 2*). The initial *Z*-5-arylidene- and cinnamylidene-2-thiohydantoins were prepared by Knoevenagel condensation of the appropriate aldehydes with 2-thiohydantoin [17]. Earlier it was found by our research group [14, 16] that during the reaction of 5-arylidene-2-thiohydantoins with 1,2-dibromoethane two isomeric products were obtained: the products of 1,2-substitution in minority (Yield: 3–10%) and of 2,3-substitution of 5-arylidene-2-thiohydantoin in majority (Yield: 22–51%). In an



2 m = 0, 1 **3** **4** **5** **6** **7** **8**

Figure 2. Synthesis of imidazo[2,1-*b*]thiazines **5**–**8**; for substituents see *table I*.

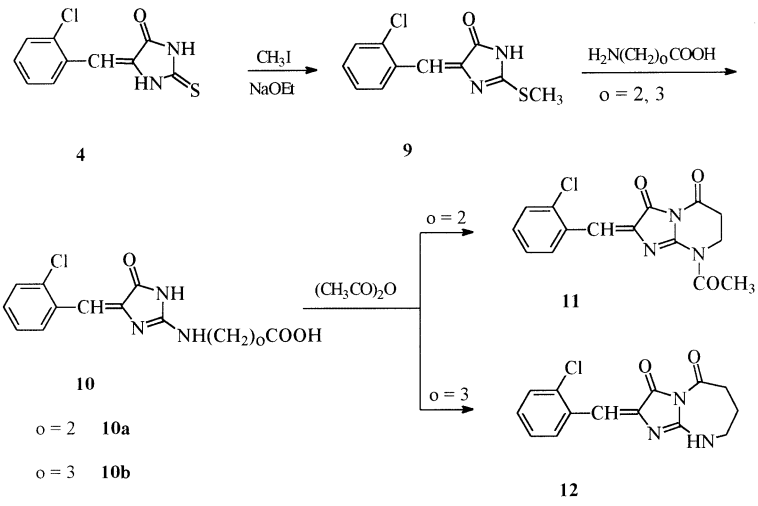


Figure 3. Synthesis of imidazo[2,1-*b*]pyrimidinone **11** and imidazo[2,1-*b*]diazepinone **12**.

analogous reaction with 1,3-dibromopropane the products of 1,2-substitution were obtained in very low yields (ca. 1%) or sometimes even difficult to detect. In the reaction of 1,3-dibromopropane with 5-cinnamylidene-2-thiohydantoin, the products of 1,2- (**5**) and 2,3-cyclization (**6**) were obtained in a 1:4 ratio in the same way as in the case of 5,5-diphenyl-2-thiohydantoin dialkylation with 1,3-dibromopropane where the ratio of the products **7** and **8** equaled 1:5 [18]. The dominance of the 2,3-cyclization products correlates with their higher thermodynamical stability. The heat of formation (AM1 approximation) for the major products was found to be 3 kcal mol^{-1}.

The structures of 5-cinnamylidene derivatives were confirmed by X-ray structure determination of one dominating product of cyclization (*figure 4*). The molecule of **6m** (in *Z*-configuration) contains two coplanar border cycles, phenyl and bicyclic imidazothiazinone (inclined at 5.8°) joined by the spacer –C8(H)=C7(H)–C6(H)=. Both the cyclic parts are in *cis*-configuration with respect to the three carbon-atom chain. This is clear from the values of the respective torsion angles: C7–C8–C21–C26 = 174.2(2)° defining the phenyl ring position and/or C7–C6–C5–C4 = 179.7(2)° for the bicyclic part. However, the respective *trans*-isomer is also thermodynamically possible, as concluded from the conformational analysis (molecular mechanics) for the phenyl ring rotation (*figure 5*). The two minima with almost equal energy at C7–C8–C21–C26 about 180° (*cis*) and 0° (*trans*) possess an energy barrier of only 1.5 kcal mol^{-1}. These observations appear to be important in the interpretation of the structure–activity relationships.

Imidazo[2,1-*b*]pyrimidinone (**11**) and imidazo[2,1-*b*]diazepinone (**12**) derivatives (*figure 3*) were prepared by the cyclization of appropriate imidazoline-4-one aminoacid derivatives **10a** and **10b** in acetic acid anhydride. 5-*ortho*-Chloro-substituted benzylidene 2-thiohydantoin was chosen as the initiating material as the *ortho*-chloro derivative (**6b**) belonged to the most active compounds. The required intermediate derivatives **10a** and **10b** were obtained according to the method described for the preparation of thiazolidinone derivatives [19]; thus 2-methylthio derivative (**9**), prepared by alkylation of

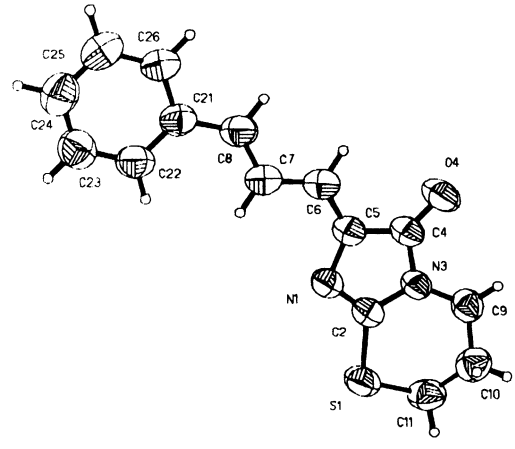


Figure 4. The molecule of **6m**.

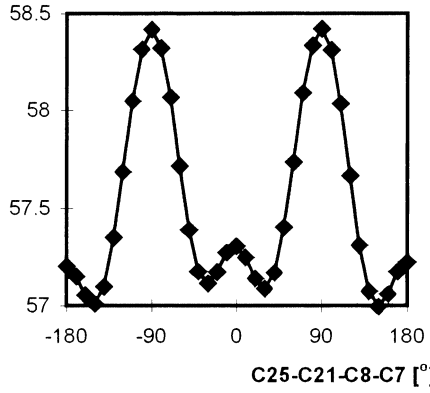
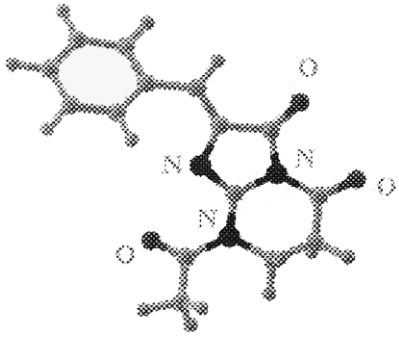


Figure 5. The strain energy of **6m** as a function of phenyl ring rotation round the C21–C8 bond.

arylidene-2-thiohydantoin (**4**) with methyl iodide, was reacted with 3-aminopropanoic acid or with 4-aminobutanoic acid for the preparation of **10a** and **10b**, respectively. Treatment of **10a** with acetic anhydride yielded the *N*-acetyl derivative of the bicyclic compound **11**, while in the synthesis using **10b** as an intermediate imidazo[2,1-*b*]diazepinone **12** was obtained. The structures of compounds **11** and **12** were confirmed on the basis of elemental and spectral analyses. The electron ionization mass spectra showed the expected molecular ions for **11** and **12**; in the ^{1}H NMR spectra, in addition to the common characteristic signals for the bicyclic structures, in the case of compound **11** a triproton singlet for the acetyl group was found. The models of both molecules **11** and **12** are given in *figure 6*. These models were built for the molecular modeling of ligand–receptor interactions (see below). For all the compounds considered calculations of their log *P* values were carried out [20] for a preliminarily estimate of their lipophilicity.



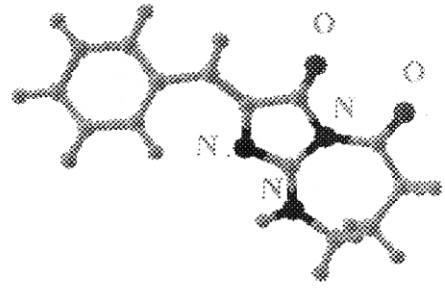


Figure 6. Models of **11** and **12**.

3. Biological assays

The compounds **5a**–**5c**, **6f**, **6h**–**6n**, **11** and **12** were investigated in radioligand binding assays in the rat brain cortical membranes for their affinity to the benzodiazepine binding sites of the $GABA_A$ receptor. All the compounds were screened for their potency to displace [^{3}H]diazepam from its binding site in a single concentration (*table I*), K_i values were determined for compounds, which inhibited the radioligand binding by more than 40% at a concentration of 25 μM. A typical displacement curve for the most potent compound of the series, **6b**, is shown in *figure 7*. The Scatchard plot showed that the inhibition of [^{3}H]diazepam binding was competitive (*figure 7*).

4. Results and discussion

4.1. Structure–activity relationships

The results obtained for the newly screened compounds are presented in *table I*. For comparison, the results obtained earlier for compounds **6a**–**6e** and **6g** are also included in *table I* [13]. The substitution pattern of the arylidene ring in derivatives **6a**–**6l** was shown to influence the receptor affinity of the investigated compounds significantly. This is visualized by the diagram given in *figure 8*. The diagram was prepared by a selection of seven derivatives displaying higher affinities (*table II*). The lowest K_i values were found for derivatives with a *meta*-substituted arylidene ring. The affinity sequence for chloro substitution was observed to be *ortho*<*para*<*meta* (*figure 8*).

Analysis of the calculated lipophilic properties of the examined imidazo[2,1-*b*]thiazines showed that the log *P* values of most of the compounds (**5a**, **5b**, **6a**–**6i** and **6m**)

Table I. Inhibition of [^{3}H]diazepam binding to rat brain by imidazo-thiazine **5–8**, -pyrimidinone **11** and -diazepinone **12** derivatives.

Compound	R^1	R^2	*m*	% [a]	References	K_i (μM) $n = 3$	log *P* [b]
5a	*o*-OCH_3	H	0	54 ± 5	[16]	n.d. [c]	1.84
6a	*o*-OCH_3	H	0	1.5 ± 3.1	[13]	>25	2.08
6b	*o*-Cl	H	0	73 ± 4	[13]	13 [13]	2.76
6c	*m*-Cl	H	0	69 ± 5	[13]	1.6 [13]	2.90
6d	*p*-Cl	H	0	49 ± 2 [d]	[13]	10.1 ± 3.9	2.76
6e	*p*-NO_2	H	0	0 ± 9 [e]	[13]	>25	2.04
6f	*m*-NO_2	H	0	62 ± 6	–	4.5 ± 0.4	2.10
6g	*p*-OCH_3	H	0	64 ± 6	[13]	6.0 ± 1.3	2.20
6h	*o*-OCH_3	*p*-OCH_3	0	63 ± 5	–	19.6 ± 4.2	2.02
6i	*m*-OCH_3	*p*-OCH_3	0	43 ± 6	–	8.8 ± 0.8	2.28
6j	*o*-Cl	*m*-Cl	0	3 ± 17	–	>25	3.39
6k	*m*-O–Ph	H	0	30 ± 13	–	>25	3.91
6l	*p*-$CH(CH_3)_2$	H	0	28 ± 17	–	>25	3.54
5b	H	H	1	10 ± 1	–	>25	2.52
6m	H	H	1	17 ± 8	–	>25	2.77
7	–	-	–	17 ± 16	[15, 21]	>25	2.57
8	–	–	–	1 ± 6	[15, 21]	>25	2.74
11	–	–	–	12 ± 4	–	>25	0.53
12	–	–	–	31 ± 6	–	>25	1.44
Diazepam	–	–	–	n.d.	–	0.025 [13]	3.21

[a] Percent specific inhibition of [^{3}H]diazepam binding to rat brain cortical membranes at drug concentration of 25 μM unless otherwise stated.
[b] log *P* values calculated by means of the PALLAS program [20].
[c] Inhibition curve could not be determined because of solubility problems.
[d] Drug concentration of 40 μM.
[e] Drug concentration of 100 μM.

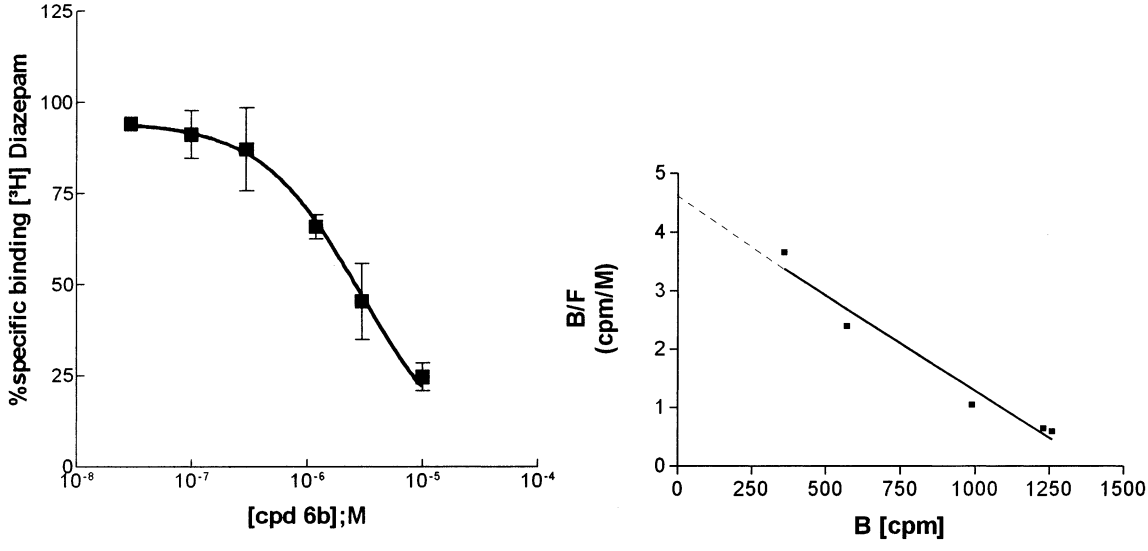


Figure 7. Radioligand binding curve and Scatchard plot of compound **6b**; full curve could not be determined owing to the limited solubility at higher concentrations.

were within the range of 1.84–2.90 required for the CNS-active compounds (log $P \approx 2.5$ [24]). Only the log *P* values of compounds **6j–6l** (3.39–3.91) were higher. On the other hand, the calculated log *P* values of the fused imidazo[2,1-*b*]pyrimidinone (**11**) and imidazo [2,l-*b*]diazepinone (**12**) derivatives were lower (0.53–

Table II. Parameters for selected molecules used in Eqs. (1) and (2).

Compound	π_o	π_m	π_p	log P	K_i
6b	0.76			2.76	13.0
6c		0.77		2.90	1.6
6d			0.73	2.76	10.1
6f		0.11		2.10	4.5
6g			−0.03	2.20	6.0
6h	−0.33		−0.03	2.02	19.6
6i		0.12	−0.03	2.28	8.8

1.44) than required. Such compounds have additional functional groups that may form hydrogen bonds, leading to the reduction of the in-brain penetration [25, 26]. The lipophilicity had a minor influence on the K_i values as shown by a second-degree polynomial fit, with poor agreement (Eq. (1)) describing the relationship between log P values and log K_i for the seven derivatives in *table II*.

$$\log K_i = 6.41 \log P - 1.37 \log P^2 - 6.46 \quad n = 7,\ r = 0.43 \tag{1}$$

At the same time, we have performed a QSAR study to explain the measured differences in affinity of arylidene derivatives. The multiple linear regression (MLR) model [22] with Hansch's constants corresponding to substituents in the *o*-, *m*- or *p*-positions of the arylidene ring was applied [23]. The values used in the correlation analysis are collected in *table II* and the results of the calculation are presented by the following equation (Eq. (2)):

$$\log K_i = -0.02\pi_o - 1.08\pi_m - 0.02\pi_p + 1.01 \quad n = 7\ \ r = 0.85 \tag{2}$$

Contrary to Eq. (1), the newly obtained Eq. (2) has an acceptable r-value worth discussing further. In the previous investigations (see *figure 8*) it was found that the position of the substituents on the benzylidene ring had a great influence on the activity of the compounds (see, e.g. *o*-, *m*-, *p*-chloro derivatives **6b**, **6c** and **6d**), the *meta*-substituted derivatives being the most potent (with the lowest K_i values). This corresponds excellently with the high negative contribution to the log K_i of the π_m positive constant for Cl in Eq. (2) (*table II*). Moreover *para*-nitro-substituted derivative **6e**, not used in this correlation, was much less active (K_i>25) but owing to the higher negative contribution weight for π_m a NO_2 group introduced in the *meta*-position gave the considerably more active compound **6f**. Derivatives containing a methoxy substituent in the *para*-position (**6g**) (small negative contribution for π_p in Eq. (2) and negative π-constant for OCH_3) as well as di-substituted methoxy derivatives **6h** and **6i** belong to the most active compounds in this series. In these two di-substituted derivatives different weights in Eq. (2) are compensated by the opposite signs of π_o and π_m for OCH_3 significantly. However, di-substitution with chlorine as in compound

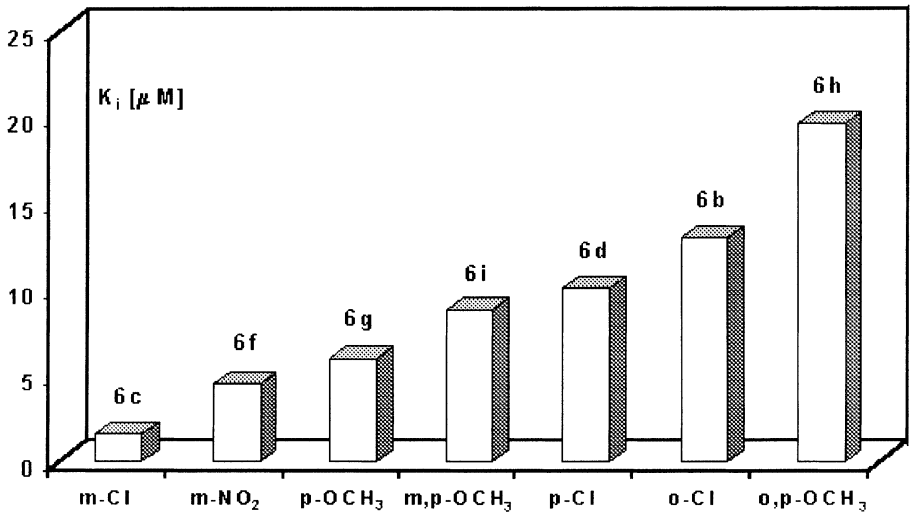


Figure 8. Graphical representation of K_i values of compounds **6** (see *tables I and II* and *figure 2*) with different substitution patterns (R^1, R^2) on the phenyl ring.

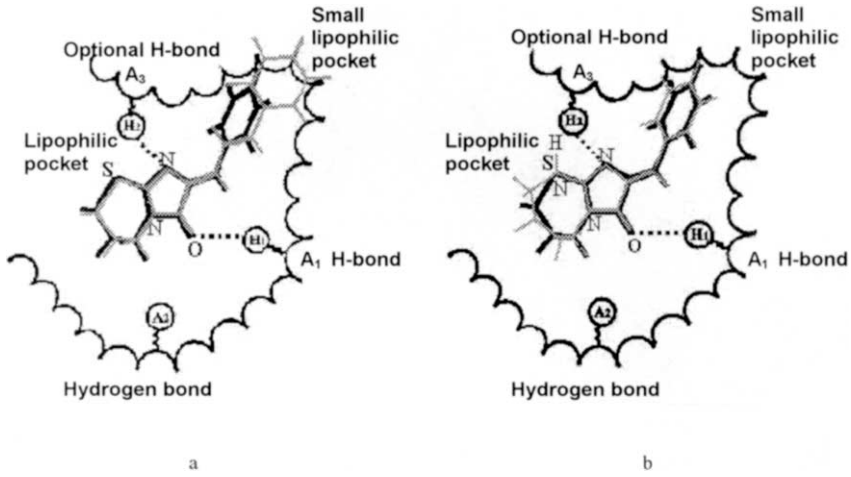


Figure 9. Binding interactions of *Z*-5-arylidene-, cinnamylidene imidazo[2,1-*b*]thiazines and *Z*-5-arylidene imidazo[2,1-*b*]pyrimidinone and imidazo[2,1-*b*]diazepinone derivatives with Cook et al. [30] model of BZR active sites.

6j combining interesting properties of the *ortho*- and the *meta*-substituted compounds **6b** and **6c** was unprofitable ($K_i > 25$).

Introducing a longer spacer between the phenyl ring and the bicyclic structure as in compounds **5b** and **6m** had no effect on activity. Analogous effects were observed for the diphenyl derivatives **7** and **8**. Moreover, it was found that the type of annelation of the thiazine ring also had no effect on the activity of the cinnamylidene and diphenyl derivative (see pairs of compounds **5b** and **6m**, and **7** and **8**). Replacement of the thiazine ring by pyrimidinone or diazepinone as in structures **11** and **12** also had no effect on the activity of the compounds. It means that both the molecules cannot fulfill all the spatial conditions required by the receptor (see below).

4.2. Interaction with the benzodiazepine receptor

The general concept of the structural requirements for benzodiazepin receptor ligands was presented in form of several models [27–29]. The models are characterized by a size-limited lipophilic region with π–π interaction volume, at least one hydrogen bond donor interaction site and one hydrogen bond acceptor. Such a model may be easily adapted to arylidene thiazolidinone derivatives as it is presented below.

The molecules highly active at the benzodiazepine receptor in most cases contain a planar or almost planar core. In the compounds studied, bicyclic and arylidene moieties are also nearly planar. This result was obtained from crystallography, and geometry optimization by quantum-chemistry calculations (see *figures 4* and *6*). It should be noted that the torsional angle describing non-planarity in low energy conformations (AM1 approximation) for **6a**–**6l** deviated by 148°. Independently of the arylidene ring substitution, the barrier of rotation for the ring was found to be as low as 2 kcal mol^{-1}. The planarity criterion is not fulfilled by the inactive bicyclic diphenyl derivatives **7** and **8** [15, 21]. This clearly indicates that the volume of the arylidene moiety in the *Z*-configuration presumably fills the size in the lipophilic pocket (the black contour in *figure 9a* represents the highly active molecule (**6b**)). On the other hand, compound **6m**, a derivative with a cinnamylidene moiety, which is about 3 Å longer than benzylidene, and is practically inactive (the grey contour in *figure 9a*). Thus, the benzylidene group may act as the hydrophobic π-electron fragment. Moreover, the mode of substitution in this fragment is important with regard to space (see Eq. (1)).

In all the molecules discussed there are two groups able to act as H-bond acceptors as confirmed by the electrostatic potential (MEP) distribution showing two common minima. The one minimum is localized at the carbonyl oxygen, the second appears near the nitrogen atom (N1). This is visualized in *figure 10* showing MEP distribution for one molecule (**6b**). In *figure 9* these two groups are marked as corresponding to the binding sites A_1 and A_3 in the benzodiazepine receptor. Having in view the A_2 pharmacophoric point (H-bond acceptor), derivatives **11** and **12** were svnthesized (*figure 6*). Especially compound **12** having a free NH group seemed to

be interesting as a potential benzodiazepine receptor ligand. However, superimposition with **6b** (*figure 10*) clearly indicates that for the *Z*-isomer of **12** this group and the phenyl ring are *cis*-configurated in the molecule. Consequently, the location of the H-bond acceptor in the receptor model is not close to the NH group in the molecule. The observed low activity of **12** supported this hypothesis.

In conclusion, we have described the synthesis of diphenyl and arylidene imidazothiazine, -diazinone and -diazepinone derivatives and the evaluation of their benzodiazepine receptor-binding activity. Analysis of the 3D structure of the compounds obtained and the structural requirements for benzodiazepine receptor binding revealed that for the activity the presence of diphenyl and cinnamylidene substituents as well as diazinone and diazepinone annelated rings was not advantageous. As a result of the QSAR analysis of the arylidene imidazothiazine derivatives it was found that a negative π-value for the *meta*-substituent in the arylidene group is an important parameter, which influences the binding of the compounds to the benzodiazepine receptors.

5. Experimental

5.1. Chemistry

Melting points (m.p. (dec.)) were measured on Mel-Temp. II (LD Inc. USA) and were not corrected. TLC was performed on Merck silica gel GF_{254} precoated TLC Al sheets; the solvent systems used were: (A) chloroform–ethyl acetate (1:1); (B) methylene chloride; (C) chloroform–isopropanol–25% (aq.) ammonia (9:11:2); and (D) toluene–acetone (20:1.5). Column chromatography was performed on Merck silica gel 60 (70–230 mesh) using solvents (A) or (B). Electron impact and electron spray mass spectra were recorded on an AMD-604, or a Finningan MAT 95S spectrometer, respectively, with a direct inlet. IR spectra were measured with an FTIR 410 spectrometer (Jasco) in KBr pellets. The UV spectra were obtained for solutions of 10^{-4} mol L^{-1} concentration with a UV–vis-spectrometer (UV–vis V-530 Jasco). The ^{1}H NMR spectra were performed on a Bruker AC-200F, a Bruker DPX 250 AVANCE or a VARIAN MERCURY 300 MHz spectrometer in DMSO-d_6 using tetramethyl silane as an internal standard (chemical shifts are reported in δ units. The elemental analyses were performed at the Department of Pharmaceutical Chemistry of the Jagiellonian University, Cracow (Poland) and were within $\pm$0.4% of the theoretical values.

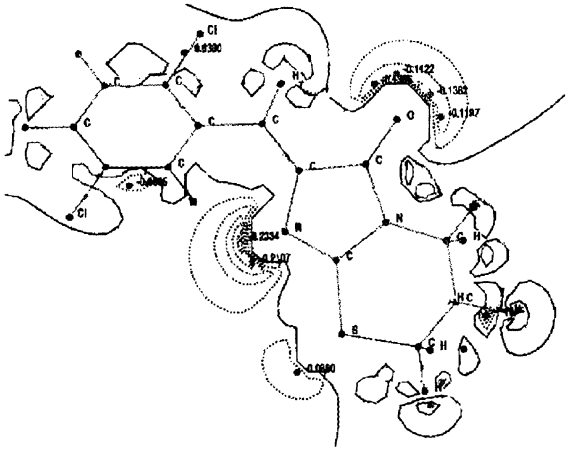


Figure 10. MEP distribution of compound **6b**.

The initial 2-thiohydantoins (**4**) were obtained as described earlier or in analogy to the procedure described in Ref. [17]. The following new derivatives were prepared.

5.1.1. Z-5-(3-Phenoxybenzylidene)-2-thiohydantoin

Cream-colored yellow crystals, m.p. (dec.) 200–203 °C; the raw product was analytically pure, Yield: 90%; TLC: R_f (A) 0.90; ^{1}H NMR (250 MHz): $\delta = 6.47$ (s, 1H, ArCH=), 6.95–7.02 (m, 3H, 2′-H, 3′-H, 4′-H), 7.13 (t, $J = 7.5$ Hz, 1H, 6′-H), 7.35–7.44 (m, 3H, 3″-H, 4″-H, 5″-H), 7.52 (d, $J = 10$ Hz, 2H, 2″-H, 6″-H), 12.22 (s, 1H, N_1H), 12.39 (s, 1H, N_3H); FTIR (ν, cm^{-1}): 3133 (N–H), 1728 (C=O), 1648 (ArCH=), 1481, 1371, 1245, 1195, 954, 694. Anal. ($C_{16}H_{12}N_2O_2S$) C, H, N.

5.1.2. Z-5-[4-(2-Propylo)benzylidene]-2-thiohydantoin

Yellow crystals, m.p. (dec.) 217–220 °C from acetic acid, Yield: 73%; TLC: R_f (A) 0.86; ^{1}H NMR (300 MHz): $\delta = 1.21$ (d, $J = 6.9$ Hz, 6H, $2CH_3$), 2.92 (sept, $J = 6.9$ Hz, 1H, $CH(CH_3)_2$), 6.47 (s, 1H, ArCH=), 7.30 (d, $J = 8.4$ Hz, 2H, 3′-H, 5′-H), 7.68 (d, $J = 8.4$ Hz, 2H, 2′-H, 6′-H); FTIR (ν, cm^{-1}): 3305 (N–H), 2958 (C–H), 1712 (C=O), 1645 (ArCH=), 1479, 1363, 1178, 761. Anal. ($C_{13}H_{14}N_2OS$) C, H, N.

5.1.3. Z-5-(2,3-dichlorobenzylidene)-2-thiohydantoin

Yellow crystals, m.p. (dec.) 286–288 °C; the raw product was analytically pure, Yield: 94%; TLC: R_f (D) 0.16; ^{1}H NMR (300 MHz): $\delta = 6.55$ (s, 1H, ArCH=),

7.42 (t, $J = 8.0$ Hz, 1H, 5′-H), 7.64 (dd, $J = 8.1$ Hz, 1H, 4′-H), 7.72 (dd, $J = 7.5$ Hz, 1H, 6′-H), 12.39 (br s, 2H, N_1H, N_3H); FTIR (ν, cm^{-1}): 3141 (N–H), 2857 (C–H), 1731 (C=O), 1670 (ArCH=), 1515, 1376, 1228, 908, 781. Anal. ($C_{10}H_6N_2OSCl_2$) C, H, N.

Compounds **5a**, **6a**, **6d**, **6e**, **6f** [16], **6b**, **6c** [13]. **6g** [31] and **5c**, **6n** [16, 21] were obtained as described earlier. The new derivatives **6h**–**6l** were prepared in analogy to the procedures described in Ref. [4].

*5.1.4. Z-2-(2,4-Dimethoxybenzylidene)-6,7-dihydro-5H-imidazo[2,1-b][1,3]thiazin-3(2H)-one (**6h**)*

This compound was obtained as yellow crystals after purification using column chromatography performed twice with eluent (A), Yield: 34%; m.p. (dec.) 204–205 °C; TLC: R_f (A) 0.38; ^{1}H NMR (200 MHz): $\delta =$ 2.16 (def qi, 2H, $CH_2CH_2CH_2$), 3.21 (t, $J = 5.4$ Hz, 2H, SCH_2), 3.61 (t, $J = 5.7$ Hz, 2H, NCH_2), 3.82 (s, 3H, 2′-OCH_3), 3.87 (s, 3H, 4′-OCH_3), 6.61 (dd, $J = 6.5$ Hz, $J = 2.4$ Hz, 1H, 5′-H), 6.66 (d, $J = 2.4$ Hz, 1H, 3′-H), 7.12 (s, 1H, ArCH=), 8.62 (d, $J = 6.8$ Hz, 1H, 6′-H); FTIR (ν, cm^{-1}): 1692 (C=O), 1648 (ArCH=), 1588, 1466 (C=N), 1270, 1238; MS; m/z: 304 [$M^{+\bullet}$], 273, 245, 181, 176, 160, 146, 121, 100, 72. Anal. ($C_{15}H_{16}N_2O_3S$) C, H, N.

*5.1.5. Z-2-(3,4-Dimethoxybenzylidene)-6,7-dihydro-5H-imidazo[2,1-b][1,3]thiazin-3(2H)-one (**6i**)*

This compound was obtained as yellow crystals after purification using column chromatography performed with eluent (A), Yield: 36%; m.p. (dec.) 212–214 °C; TLC: R_f (A) 0.45; ^{1}H NMR (200 MHz): $\delta = 2.16$ (def qi, 2H, $CH_2CH_2CH_2$), 3.22 (t, $J = 5.4$ Hz, 2H, SCH_2), 3.62 (t, $J = 5.6$ Hz, 2H, NCH_2), 3.77 (s, 3H, 3′-OCH_3), 3.81 (s, 3H, 4′-OCH_3), 6.80 (s, 1H, ArCH=), 7.02 (d, $J = 8.5$ Hz, 1H, 5′-H), 7.71 (dd, $J = 8.5$ Hz, $J = 1.5$ Hz, 1H, 6′-H), 7.87 (d, $J = 1.5$ Hz, 1H, 2′-H); FTIR (ν, cm^{-1}): 1710 (C=O), 1648 (ArCH=), 1590, 1508, 1484 (C=N), 1362, 1268, 1244, 1158, 1136, 1016; MS; m/z: 304 [$M^{+\bullet}$], 289, 275, 261, 233, 176, 100, 72. Anal. ($C_{15}H_{16}N_2O_3S$) C, H, N.

*5.1.6. Z-2-(2,3-Dichlorobenzylidene)-6,7-dihydro-5H-imidazo[2,1-b][1,3]thiazin-3(2H)-one (**6j**)*

A solution of 1,3-dibromopropane 3.08 g (0.015 mol) in acetone (10 mL) was added dropwise to a stirred suspension of 5-(2,3-dichlorobenzylidene)-2-thiohydantoin 4.11 g (0.015 mol), K_2CO_3 (6.0 g), and triethylbenzylammonium chloride 0.45 g (0.0015 mol) in acetone (60 mL). The mixture was stirred at room temperature (r.t.) for two days. The solid was removed, washed with water, and then subsequently with 1% NaOH and 1% HCl solutions. The remaining solid was suspended in chloroform (150 mL), stirred for 0.5 h, and the suspension was filtered. The solid was then discarded. The chloroform filtrate was evaporated to dryness. The precipitate obtained was recrystallized from dioxane, Yield: 2.8 g (60%); m.p. (dec.) 218–220 °C; TLC: R_f (A) 0.57; ^{1}H NMR (200 MHz): $\delta = 2.10$–2.25 (m, 2H, $CH_2CH_2CH_2$), 3.26 (t, $J = 5.5$ Hz, 2H, SCH_2), 3.65 (t, $J = 5.8$ Hz, 2H, NCH_2), 7.04 (s, 1H, ArCH=), 7.46 (t, $J = 8.0$ Hz, 1H, 5′-H), 7.64 (dd, $J = 8.0$ Hz, $J = 1.5$ Hz, 1H, 4′-H), 8.69 (dd, $J = 8.0$, 1.5 Hz, 1H, 6′-H); FTIR (ν, cm^{-1}): 1716 (C=O), 1631 (ArCH=), 1482 (C=N), 1461, 1238, 1166, 1151, 1122, 790. Anal. ($C_{13}H_{10}N_2OSCl_2$) C, H, N.

*5.1.7. Z-2-(3-Phenoxybenzylidene)-6,7-dihydro-5H-imidazo[2,1-b][1,3]thiazin-3(2H)-one (**6k**)*

Compound **6k** was obtained as yellow crystals after purification using column chromatography performed with eluent (A), Yield: 31%; m.p. (dec.) 144–146 °C (from acetonitrile); TLC: R_f (A) 0.65; ^{1}H NMR (300 MHz): $\delta = 2.14$–2.17 (m, 2H, $CH_2CH_2CH_2$), 3.22 (t, $J = 5.4$ Hz, 2H, SCH_2), 3.62 (t, $J = 5.6$ Hz, 2H, NCH_2), 6.82 (s, 1H, ArCH=), 6.99–7.05 (m, 3H, 3″-H, 4″-H, 5″-H), 7.16 (t, $J = 7.5$ Hz, 1H, 5′-H), 7.38–7.46 (m, 3H, 4′-H, 2″-H, 6″-H), 7.85 (d, $J = 8.2$ Hz, 1H, 6′-H), 7.97 (t, $J = 1.8$ Hz, 1H, 2′-H); FTIR (ν, cm^{-1}): 1714 (C=O), 1635 (ArCH=), 1569, 1488 (C=N), 1230, 898, 759, 692. Anal. ($C_{19}H_{16}N_2O_2S$) C, H, N.

*5.1.8. Z-2-[4-(2-Propylo)benzylidene]-6,7-dihydro-5H-imidazo[2,1-b][1,3]thiazin-3(2H)-one (**6l**)*

The compound was obtained as cream-colored yellow crystals after purification using column chromatogaphy performed consecutively with eluents (B) and (A), Yield: 40%; m.p. (dec.) 174–176 °C (from dioxane); TLC: R_f (A) 0.66; ^{1}H NMR (200 MHz): $\delta = 1.20$ (d, $J = 6.9$ Hz, 6H, $(CH_3)_2$), 2.05–2.22 (m, 2H, $CH_2CH_2CH_2$), 2.90 (sept, $J = 6.9$ Hz, 1H, $CH(CH_3)_2$), 3.23 (t, $J = 5.4$ Hz, 2H, SCH_2), 3.63 (t, $J = 5.7$ Hz, 2H, NCH_2), 6.81 (s, 1H, ArCH=), 7.30 (d, $J = 8.2$ Hz, 2H, 3′-H, 5′-H), 8.05 (d, $J = 8.2$ Hz, 2H, 2′-H, 6′-H); FTIR (ν, cm^{-1}): 2954 (C–H), 1710 (C=O), 1631 (ArCH=), 1486 (C=N), 1245, 1162, 890, 833. Anal. ($C_{16}H_{18}N_2OS$) C, H, N.

*5.1.9. Z-3-Cinnamylidene-6,7-dihydro-4H-imidazo-[2,1-b][1,3]thiazin-2(3H)-one (**5b**) and Z-2-cinnamylidene-6,7-dihydro-5H-imidazo[2,1-b]-[1,3]thiazin-3(2H)-one (**6m**)*

A solution of 1,3-dibromopropane 2.02 g (0.01 mol) in acetone (10 mL) was added dropwise to a stirred suspension of 5-cinnamylidene-2-thiohydantoin 2.30 g (0.01 mol), K_2CO_3 (4.0 g), and triethylbenzylammonium chloride 0.3 g (0.001 mol) in acetone (40 mL). The mixture was stirred at r.t. for two days. The solid was removed, washed with water, and then with 1% NaOH and 1% HCl solutions, and recrystallized from dioxane to yield 230 mg (8.5%) of yellow crystals of **5b**, m.p. (dec.) 265-268 °C; TLC: R_f (A) 0.07; ^{1}H NMR (200 MHz): $\delta = 2.27–2.32$ (m, 2H, $CH_2CH_2CH_2$), 3.23–3.26 (m, 2H, SCH_2), 4.18 (t, $J = 5.8$ Hz, 2H, NCH_2), 6.55 (d, $J = 12.2$ Hz, 1H, ArCH=), 7.16 (d, $J = 15.2$ Hz, 1H, –CH=CH–CH=), 7.34–7.50 (m, 4H, –CH=CH–CH=, 3′-H, 4′-H, 5′-H), 7.62–7.67 (m, 2H, 2′-H, 6′-H); FTIR (ν, cm^{-1}): 1673 (C=O), 1618 (ArCH=CH–CH=), 1434 (C=N), 1405, 1326, 1236, 1121, 976, 755; MS; m/z: 270 [$M^{+\bullet}$], 192, 154, 142, 128, 114. Anal. ($C_{15}H_{14}N_2OS$) C, H, N.

The combined precipitates obtained from the dioxane solution (precipitated with water) and from the acetone filtrate were recrystallized from acetone to yield 1.0 g (37%) of cream-colored yellow crystals of **6m**, m.p. (dec.) 184–187 °C; TLC: R_f (A) 0.57; ^{1}H NMR (200 MHz): $\delta = 2.05–2.25$ (m, 2H, $CH_2CH_2CH_2$), 3.21 (t, $J = 5.6$ Hz, 2H, SCH_2), 3.61 (t, $J = 5.8$ Hz, 2H, NCH_2), 6.75 (d, $J = 11.3$ Hz, 1H, ArCH=), 7.17 (d, $J = 15.8$ Hz, 1H, –CH=CH–CH=), 7.32–7.45 (m, 3H, 3′-H, 4′-H, 5′-H), 7.50 (d, $J = 11.3$ Hz, 1H, –CH=CH–CH=), 7.57–7.62 (m, 2H, 2′-H, 6′-H); FTIR (ν, cm^{-1}): 1702 (C=O), 1621 (ArCH=CH–CH=), 1484 (C=N), 1467, 1228, 1160, 968, 950, 908, 686. Anal. ($C_{15}H_{14}N_2OS$) C, H, N.

*5.1.10. 8-Acetylo-Z-2-(2-chlorobenzylidene)-5,6,7,8-tetrahydro-imidazo[2,1-b]pirymidin-3(2H),5-dione (**11**)*

Starting material in the synthesis of **11**: [*Z*-5-(2-Chlorobenzylidene)-4-oxoimidazolin-2-yl]-3-aminopropanoic acid (**10a**) was obtained following the procedure described in Ref. [19].

The suspension of 3-aminopropanoic acid (4.8 g, 0.054 mol) and potassium *tert*-butanolate (4.2 g, 0.036 mol) in 500 mL anhydrous ethanol was stirred at r.t. for 0.5 h. Then *Z*-5-(2-chlorobenzylidene)-2-methylthioimidazolin-4-one (**9**) [32] (7.5 g, 0.0297 mol) was added and the reaction mixture was refluxed for 4 h. From the clear reaction mixture the solvent was evaporated in vacuo. The solid obtained was dissolved in 100 mL of water, and the solution was acidified with 2% HCl solution to pH 6–7. The obtained precipitate was filtered off the next day to yield 6.34 g (72%) of intensive yellow crystals of **10a**, m.p. (dec.) 247–249 °C (from acetic acid); TLC: R_f (C) 0.15; ^{1}H NMR (250 MHz): $\delta = 2.46$ (s, 2H, CH_2COOH), 3.58 (s, 2H, $NHCH_2$), 6.53 (s, 1H, ArCH=), 7.20 (t, $J = 7.6$ Hz, 1H, 4′-H), 7.33 (d, $J = 7.6$ Hz, 1H, 3′-H), 7.42 (def t, 1H, 5′-H), 8.18 (br s, 1H, $NHCH_2$), 8.88 (br s, 1H, 6′-H), 11.38 (br s, 1H, NH); FTIR (ν, cm^{-1}): 3297 (NH), 1706 (C=O), 1664 (ArCH=), 1617, 1507, 1404, 1294, 1196, 1049, 989; MS; m/z (electron spray): 293 [$M^{+\bullet}$], 275, 258, 240, 198, 151. Anal. ($C_{13}H_{13}N_3O_3Cl$) C, H, N.

Method A. The suspension of propanoic acid derivative **10a** (1.5 g) in acetic acid anhydride (1.5 mL) and pyridine (2.25 mL) was left to stand with continuous stirring at r.t. for 3 days. The solid obtained was filtered off and recrystallized from ethanol to give 0.73 g (53%) of cream yellow crystals of **11**.

Method B. The suspension of propanoic acid derivative **10a** (1.0 g) in 10 mL of acetic acid anhydride was refluxed for 1.5 h. After cooling, the precipitate formed was filtered off and recrystallized from ethanol to give 0.52 g (37%) of **11**.

M.p. (dec.) 213–217 °C; TLC: R_f (C) 0.43; ^{1}H NMR (250 MHz): $\delta = 2.77$ (s, 3H, CH_3), 2.87 (t, $J = 6.5$ Hz, 2H, CH_2CO), 4.13 (t, $J = 6.5$ Hz, 2H, NCH_2), 7.24 (s, 1H, ArCH=), 7.43–7.55 (m, 2H, 4′-H, 5′-H), 7.63 (dd, $J = 7.3$ Hz, $J = 2.0$ Hz, 1H, 3′-H). 8.72 (dd, $J = 7.3$ Hz, $J = 2.0$ Hz, 1H, 6′-H); FTIR (ν, cm^{-1}): 1779, 1703 (C=O), 1648 (ArCH=), 1591, 1401, 1240, 1199, 1035, 975, 680; MS; m/z (electron spray): 317 [$M^{+\bullet}$] 277, 275, 240, 198, 186, 129, 116, 74; UV: λ_{max} (nm) ($\log \varepsilon$) (methylene chloride): 378 (4.441), 359 (4.545), 242 (4.433). Anal. ($C_{15}H_{12}N_3O_3Cl$) C, H, N.

*5.1.11. Z-2-(2-Chlorobenzylidene)-5,6,7,8-tetrahydro-imidazo[2,1-b][1,3]diazepin-3(2H),5-dione (**12**)*

Starting material in the synthesis of **12**: [*Z*-5-(2-Chlorobenzylidene)-4-oxoimidazolin-2-yl]-4-aminobutanoic acid (**10b**) was obtained following the procedure described in Ref. [19] analogous to that performed for **10a**.

10b: cream-colored crystals (from ethanol), m.p. (dec.) 134–137 °C; TLC: R_f (C) 0.11; ^{1}H NMR (250 MHz): $\delta = 1.84$ (m, 2H, CH_2CH_2COOH), 2.32 (t, $J = 7.2$ Hz, 2H, CH_2COOH), 3.30–3.50 (m, 2H, CH_2NH), 6.58 (s, 1H, ArCH=), 7.20 (dt, $J = 7.5$ Hz, $J = 1.5$ Hz, 1H, 5′-H), 7.32 (d, $J = 7.6$ Hz, 1H, 3′-H), 7.4 (def t, 1H, 4′-H), 8.40

Table III. Crystal data, structure refinement parameters and the summary of intensity data collection for **6m**.

Empirical formula	$C_{15}H_{14}N_2OS$
Formula weight	270.34
Crystallization medium	acetone–dioxane (2:1)
Color	cream-yellow
Crystal size (mm)	$0.4 \times 0.3 \times 0.3$
Unit cell dimensions	
a (Å)	8.632(2)
b (Å)	7.610(2)
c (Å)	20.635(4)
β (°)	96.96(3)
V (Å^3)	1345.5(5)
Molecules/unit cell	4
Density calculated (Mg m^{-3})	1.335
Linear absorption factor (mm^{-1})	2.074
Reflections collected	3428
Reflections observed [$I > 2\sigma(I)$]	2768
R-index	0.0602
Goodness-of-fit on F^2	1.135
Secondary extinction factor g	0.0147(19)

(br s, 1H, N*H*CH$_2$), 8.82 (br s, 1H, 6′-H), 10.75 (br s, 1H, NH); FTIR (ν, cm^{-1}): 1751, 1710 (C=O), 1617 (ArCH=), 1420, 1345, 1289, 1242, 1184, 1089, 1006, 833, 764, 691, 635. Anal. ($C_{14}H_{14}N_3O_3Cl$) C, H, N.

The cyclization of butanoic acid derivative **10b** was performed as described in method A for compound **11**.

12: yellow crystals (from ethanol), m.p. (dec.) 269–271 °C; TLC: R_f (C) 0.77; ^{1}H NMR (250 MHz): $\delta =$ 2.05–2.19 (m, 2H, CH$_2$), 2.59 (t, $J = 7.8$ Hz, 2H, CH$_2$CO), 3.96 (t, $J = 7.3$ Hz, 2H, NHC*H*$_2$), 7.02 (s, 1H, ArCH=), 7.30–7.48 (m, 2H, 4′-H, 5′-H), 7.52 (d, $J = 7.8$ Hz, 1H, 3′-H), 8.80 (d, $J = 8.0$ Hz, 1H, 6′-H), 11.3 (s, 1H, NH); FTIR (ν, cm^{-1}): 3436, 3267 (NH), 1730, 1698 (C=O), 1636 (ArCH=), 1586, 1449, 1384, 1282, 1092, 880, 768, 694, 578; MS; m/z (electron impact): 289 [M$^{+\bullet}$] 254, 74, 60, 57, 55; UV: λ_{max} (nm) (log ε) (methylene chloride): 388 (4.428), 368 (4.478), 359 (4.483), 244 (4.372). Anal. ($C_{16}H_{14}N_3O_3Cl$) C, H, N.

5.2. Benzodiazepine binding assays

Frozen rat brains were obtained from Pel-Freez®, Rogers, Arkansas, USA. The cortex was dissected and the inhibition of binding of [^{3}H]diazepam to rat brain cortical membranes were determined as described earlier in Ref. [13]. The compounds were dissolved in dimethyl sulfoxide and diluted further with tris(hydroxymethyl)aminomethane hydrochloride buffer (50 mM, pH 7.4); the final dimethyl sulfoxide concentration was 1%. In a final volume of 1 mL, each test tube contained 790 μL of tris(hydroxymethyl)aminomethane hydrochloride buffer (50 mM, pH 7.4), 10 μL of the compound solution, 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. Dimethyl sulfoxide was necessary as the compounds possessed low water solubility.

Incubations were carried out at 2 °C for 1 h and were terminated by rapid filtration through glass fiber filters (Schleicher & Schüll GF 51) using a Brandel cell harvester M-24 (Brandel, Gaithersburg, Maryland, USA). Three 5 mL washes with ice cold tris(hydroxymethyl)aminomethane hydrochloride buffer were carried out. Unlabeled diazepam (5 μM) was used to define the non-specific binding. All compounds were tested in a single concentration of 25 μM, in some cases 40 or 100 μM in at least three independent experiments each in triplicate. Inhibition curves for the more potent compounds were determined using at least 6–7 different concentrations each in triplicate spanning a concentration range of 3–4 orders of magnitude. Three independent experiments were carried out. The K_i values were calculated from the IC_{50} values as described in Ref. [13].

5.3. X-ray diffraction analysis of Z-2-cinnamylidene-6,7-dihydro-5H-imidazo[2,1-b][1,3]-thiazin-3(2H)-one (**6m**)

Crystals of **6m** were obtained by slow evaporation of an acetone–dioxane (2:1) solution. All the crystallographic data are given in *table III*. Preliminary crystallographic data were obtained from 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 $10 < \Theta < 40°$; a crystal of $0.4 \times 0.3 \times 0.3$ mm^3 was applied to collect diffraction data on KM4 diffractometer by the $\omega/2\Theta$ scan technique and using graphite monochromated Cu Kα radiation at r.t. for $\Theta < 84°$ [h: $-11 \rightarrow 11$, k: $0 \rightarrow 9$, l: $9 \rightarrow 26$]; an absorption correction was not applied; the intensity of the two standard reflections monitored every 100 reflections did not show significant fluctuations; 3428 reflections were measured, 2768 reflections were considered observed using the criterion $F_0 > 4\sigma(F_0)$. The structure was solved by a direct method (SHELXTL-PC) [33]. E-map provided positions for all non-H-atoms; full-matrix least-squares refinement was carried out on F^2s using anisotropic temperature factors for all non-H-atoms; the positions of all H-atoms were from $\Delta\rho$-maps;

misotropic thermal parameters of H-atoms were taken as 1.5 times of the temperature factors for their parent-atoms then the positions of H-atoms were refined in the riding model, being finished at $R_1 = 0.0602$, $wR_2 = 0.1780$ with $w = 1/[\rho^2(F_o^2) + (0.1128\ P)^2 + 0.2078\ P]$ where $P = (F_o^2 + F_c^2)/3$ and empirical extinction correction coefficient $g = 0.0147(19)$, $S = 1.135$ (173 parameter); final changes $\Delta/\rho_{min} < 0.01$; $\Delta\rho_{min} = -0.27$ e A^{-3}, $\Delta\rho_{max} = 0.22$ e A^{-3}. The atomic scattering factors were taken from SHELXL-97 [34]. The X-ray structure analysis results are presented in the form of non-H-atoms coordinates in *table IV* as well as in *figure 1*.

5.4. Computational procedures

The conformation analyses of **6m** (starting with the crystallographically obtained geometry) were carried out using molecular mechanics methods using the PCMOD.6 program [35]. The energy was minimized after each 10° clockwise rotation of two torsional angles in the 360° range. The geometry of the molecules was optimized with MOPAC 6.0 using AM1 Hamiltonians in an aqueous environment (dielectric constants equals 78.4) [36]. The molecular electrostatic distribution MEP was performed using the MOLDEN [37] program. The values of log *P* for the compounds investigated were calculated by means of PALLAS (version 1.2) program [20]. Multiple Linear Regression Equations were computed by means of the QSAR-PC:PAR program written by Coburn [22].

Table IV. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($Å^2 \times 10^3$) for **6m**.

	x	*y*	*z*	*U* (equiv.)
S(1)	374(1)	5316(1)	1937(1)	81(1)
N(1)	−53(2)	8308(3)	1273(1)	66(1)
C(2)	865(2)	7397(3)	1687(1)	60(1)
N(3)	2225(2)	8231(2)	1939(1)	59(1)
C(4)	2208(3)	9887(3)	1660(1)	65(1)
O(4)	3226(2)	10980(3)	1767(1)	88(1)
C(5)	713(3)	9916(3)	1229(1)	63(1)
C(6)	199(3)	11322 (3)	867(1)	71(1)
C(7)	−1231(3)	11444(3)	443(1)	70(1)
C(8)	−1688(3)	12932(3)	124(1)	73(1)
C(9)	3486(3)	7566(3)	2413(1)	70(1)
C(10)	2906(3)	6176(4)	2838(1)	78(1)
C(11)	2158(4)	4678(3)	2442(2)	84(1)
C(21)	−3120(3)	13249(3)	−312(1)	68(1)
C(22)	−4228(3)	11950(4)	−493(1)	79(1)
C(23)	−5606(4)	12377(5)	−874(1)	90(1)
C(24)	−5888(4)	14061(5)	−1092(1)	93(1)
C (25)	−4796(4)	15346(4)	−932(1)	89(1)
C(26)	−3436(3)	14942(3)	−547(1)	76(1)

6. Supplementary material

Crystallographic data for structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC no. 140168. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

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