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Synthesis and anxiolytic activity of 1-phenyl-2-(4-aryl-1,3,4,5-tetrahydropyrido[2,3-*b*][1,4]diazepin-2-ylidene)-ethanone

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A two-step, general synthesis of 1-phenyl-2-(4-aryl-1,3,4,5-tetrahydropyrido[2,3-*b*][1,4]diazepin-2-ylidene)-ethanones **3**–**9** is presented. This synthesis employs a condensation of 2,3-diaminopyridine with benzoylacetone followed by a basic-activated cyclization reaction with substituted benzaldehydes for final closure of the seven-membered ring. Molecular diversity is fixed by appropriate aldehydes: 2-chloro-, 4-chloro-, 2-bromo-, 4-bromo-, 4-fluoro-, 4-trifluoro- and 3-bromo-4,5-dimethoxybenzaldehyde. Compounds **4**, **6**, **8**, **9** and **10** were examined for their anxiolytic activity. The most active was the compound with the chlorophenyl substituent i.e. 1-phenyl-2-{4-(4-chlorophenyl)-1,3,4,5-tetrahydropyrido[2,3-*b*][1,4]diazepin-2-ylidene}-ethanone (**4**).

1. Introduction

Large numbers of both natural and synthetic compounds with a diazepine skeleton are known and many of them are recognized as influential participants in a variety of biological processes. A fused framework of the aromatic and seven-membered diazepine rings can be found in drugs which are implicated in neuropsychiatry disorders for years (Honigfeld 1996). Moreover, it appears recently that compounds based on a pyridodiazepine scaffold have revealed diverse biological effects ranging from antidepresant (Liegeois et al. 2002) to effective treatment in peptic ulcer diseases (Carmine and Broaden 1985). The different nature of the substituent gives rise to the various members of the pyridodiazepine family and modifies their biological functions. Numerous papers describe their synthesis and possible usefulnees as components of new therapeutic agents (Liegeois et al. 2002; Link et al. 1990; Sochaczewski et al. 2003; Hargrawe et al. 1991; Woolard et al. 1995; Proudfoot et al. 1995).

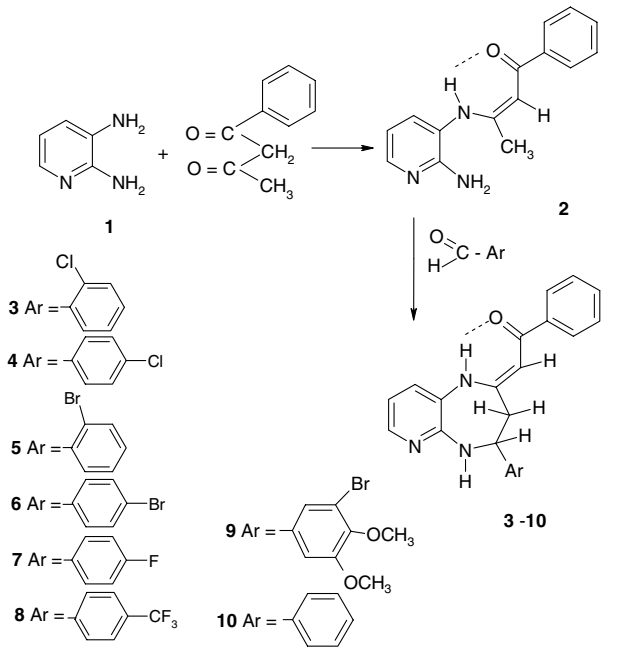
In our laboratory, previous works have led to new compounds with some psychotropic activity (Liszkiewicz et al. 1999; Nawojski et al. 1983). In an attempt to achieve new compounds with possible anxiolytic properties we investigated a novel class of 1,4-pyridodiazepines which was considered an attractive template in view of combining the high flexibility in the substitution pattern and the potentially straightforward synthesis and high-yielding processes to be applied for their preparation.

2. Investigations, results and discussion

2.1. Chemistry

A synthetic route for the target pyridodiazepines **3**–**9** is outlined in the Scheme. Reaction of 2,3-diaminopyridine (**1**) with benzoylacetone furnished ketone **2**. The seven-membered ring formation was achieved by a basic-activated cyclocondensation reaction of ketone **2** with an appropriately substituted benzaldehyde to form a range of new pyridodiazepines **3**–**9** (Liszkiewicz et al. 2002). The electron-withdrawing groups were chosen as substituents because they affect the electron density distribution pat-

Scheme 1



tern. The difference in the electronic effects is often the basis for the major varieties in the pharmacological properties of drugs. Due to their electronegativity, halogens exert strong field and inductive effects on the adjacent carbon atom. However, halogens substitution exhibit a diminished electron-withdrawing effect at distal sites. Thus the expected enhancement of biological activity of obtained pyridodiazepines can be attributed to the influence of the electron-withdrawing effect that the halogen substitution causes on interaction with either a biological receptor or enzyme, as well as its ability to alter the metabolic pathways (Zhang et al. 1994; Zhao and Uetrecht 1995). It has been shown that the replacement of C−H bond with C−F bond can significantly slow down the enzymatic oxidation (Ojima et al. 1996). There are also some recent reports in the literature wherein fluorinated analogues have improved the biological activity profile of some pharmacologically important compounds (Pu Yu et al. 1995; O'Neil et al. 2003). In addition to halogens also a trifluoromethyl group was chosen as a substituent to examine the influence not only of the electronegativity but also the size of substituent on the molecule biological properties. A strong electron-withdrawing CF_3 group is considered to be similar in size to an isopropyl group (Bott et al. 1980). Representative reaction conditions are provided in the Experimental Section. Molecular structure of all synthesized compounds was confirmed by elemental analysis and IR, ^{1}H NMR and MS spectra. All compounds show well-defined molecular ions and characteristic molecular-ion fragmentation patterns. In all cases the ^{1}H NMR spectra were assigned by inspection on the basis of known substituent effects and values of spin coupling constants. At the first place an effect of used electrophilic substituents can be seen from chemical shifts of the proton H-4. In 1-phenyl-2-(4-phenyl-1,3,4,5-tetrahydropyrido-[2,3-*b*][1,4]diazepin-2-ylidene)-ethanone (Liszkiewicz et al. 2002) (which in our point of view is unsubstituted) proton H-4 resonates at $\delta = 5.02$ ppm in DMSO solution. For all studied pyridodiazepines this proton indicated small deshielding. For compounds **3** and **5** the H-4 protons are most deshielded by 0.38 and 0.33 ppm, respectively. This observation supports an opinion that both *o*-Cl and *o*-Br substitution in the aromatic ring induce clear deshielding effects on the α-proton in the side-chain. This effect is probably caused by the electron withdrawal of the halogen substituents transmitted to the side-chain, mainly through *p*-orbital interaction between the α- and *ipso*-carbons (Laatikainen et al. 1985). The chemical shifts of the H-1 protons showed no essential substituent and solvent dependence and exhibited a very marked deshielding. For compounds **3**, **7** and **10** in DMSO-d_6 or $CDCl_3$ solution the H-1 proton resonates at $\delta = 12.80$ or 12.85 ppm, $\delta = 12.88$ or 13.09 ppm and $\delta = 12.91$ or 13.03 ppm, respectively. This proton resonates at $\delta =$ 12.85 and 13.09 ppm for compound **6** in solutions of DMSO-d_6 and acetone-d_6, respectively. This observation confirmed the presence of intramolecular hydrogen bonding between the carbonyl oxygen and the neighbouring nitrogen of diazepine ring what stabilizes a molecule conformation. The differences of splitting pattern for methylene protons (H-3) appeared to be the most diagnostic for observed structure of a particular compound. Only compound **9** displayed a coalescence effect in its ^{1}H NMR spectrum at room temperature. For this compound a doublet at $\delta \sim 3$ ppm is assigned for averaged methylene protons (H-3). For remaining compounds (**3**–**8**) distinguishing splitting patterns of two doublets for each of two methylene (H-3a and H-3b) protons were observed. The geminal coupling constant between them is $J \cong 14$ Hz and their vicinal coupling constants to H-4 are $J = 6.8 \div 6.4$ Hz and $J = 3.5 \div 2.7$ Hz for H-3a and H-3b, respectively. These values of vicinal couplings indicated that substituted phenyl at C-4 position retains in quasi-equatorial position (Malik et al. 1989; Stara et al. 1994). The spectra of compounds **6** and **7** were measured at a series of temperatures up to 373 K, and although some line broadening occurred, changes were observed consistent with inversion of the fused pyridodiazepine ring. In summary, coupling constants and chemical shifts are similar for hydrogen atoms located at the same relative positions in each compound, indicating that all compounds in our study possess a fixed conformation with very similar conformational dynamics at room temperature.

2.2. Pharmacology

2.2.1. Acute toxicity

For new compounds **4**, **6**, **8**, **9** and previously synthesized **10** (Liszkiewicz et al. 2002) doses up to 1 g/kg were not lethal to the animals and their LD_{50} values were not determined.

2.2.2. Anxiolytic activity

Anxiolytic activity has been evaluated using the light-dark box, a model of anxiety in which mice are exposed to a conflict represented by the novelty and aversive characteristic of the lit compartment of the box. An increased exploratory activity in brighty-lit environment, measured as a rearing behavior, line crossing and time spent in light section, was an index of anxiolytic action.

In the present study compound **4** at doses of 10, 50 mg/kg increased the proportion of time the mice spent in the light section. This was associated with an increase in both rearings and line crossings with corresponding decreased reaction in the dark section. A dose of 100 mg/kg prolonged the latency of the initial movement from the light to the dark area, prolonged the whole time of staying in the light part of the box and caused motor depression. A dose of 5 mg/kg was ineffective (Liszkiewicz et al. 2005). Compounds **6** at doses of 50 and 100 mg/kg and **9** at a dose of 100 mg/kg prolonged latency of initial movement from the light to the dark area possibly related to a sedative effect. Compound **8** at doses of 10, 50 and 100 mg/kg increased the latency of initial movement from the light to the dark area and dose-dependently reduced mobility of animals. At a dose of 10 mg/kg it also increased the whole time of staying in the light part of the box. Compound **10** only at a dose of 10 mg/kg caused specific changes in mouse exploratory activity in the test box. It increased the latency of the initial movement from the light to the dark area, increased the whole time of staying in the light part of the box and enhanced rearings, with a decrease in rearings and line crossings in the dark section (Fig. 1, Fig. 2).

In summary, from the tested 1-phenyl-2-(4-aryl-1,3,4,5-tetrahydro-2*H*-pyrido[2,3-*b*][1,4]-diazepin-2-ylidene)-ethanones the most active was compound **4** which at doses of 10 and 50 mg/kg exhibits a selective anxiolytic action and non-specific sedative effect at the dose of 100 mg/kg.

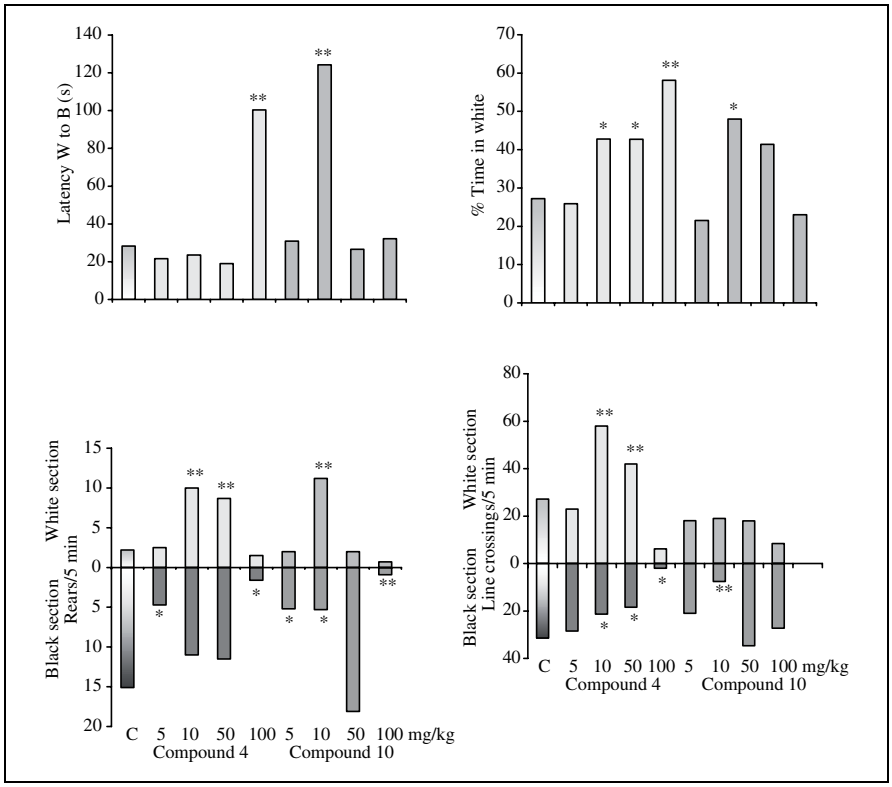


Fig. 1:
The effects of compounds **4** and **10** on the behavior of mice in the light-dark box test. C – control. Asterisks indicate statistical significance (* – $p < 0.05$, ** – $p < 0.001$) versus control

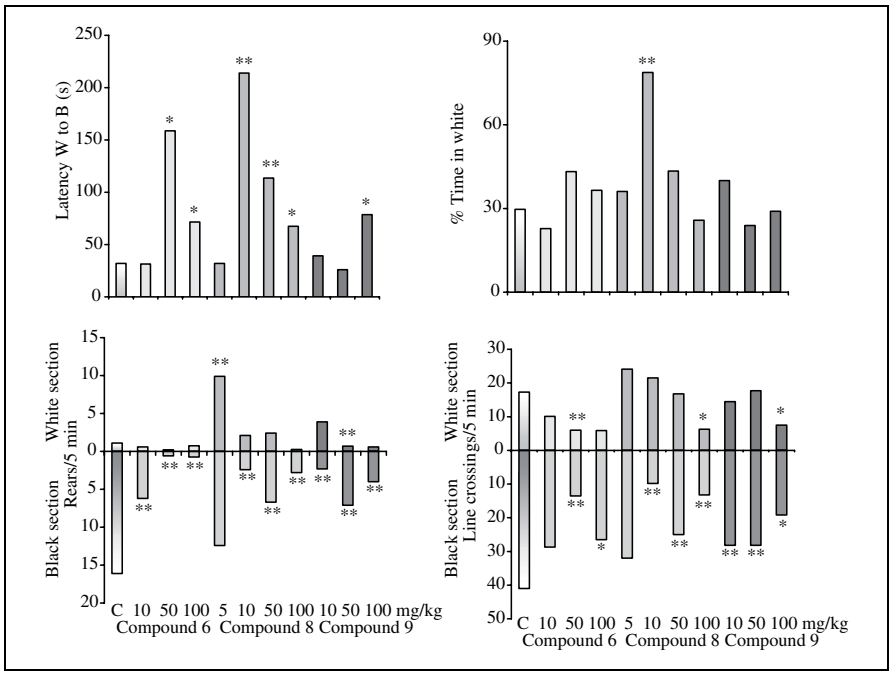


Fig. 2:
The effects of compounds **6**, **8** and **9** on the behavior of mice in the light-dark box test. C – control. Asterisks indicate statistical significance (* – $p < 0.05$, ** – $p < 0.001$) versus control

3. Experimental

3.1. Chemistry

Melting points (uncorrected) were measured with a Boethius melting point apparatus. Analyses were performed on a Perkin Elmer 2400 analyzer and satisfactory results within ±0.4% calculated values were obtained for the new compounds. IR spectra (in KBr) were recorded with an IR 75 spectrophotometer. ^{1}H NMR spectra – on a Bruker Avance 500 MHz using $CDCl_3$, DMSO-d_6 and acetone-d_6 as solvents at room temperature and chemical shifts are referred to the residual solvent signal at δ 7.24, 2.50 and 2.04 ppm, respectively. Mass spectra were determined on a GCMS-LK 82091 spectrometer at the ionization energy 70 eV. The course of reaction and the purity of products were checked by TLC (Kieselgel G, Merck) in diethyl ether : ethanol = 5 : 1 for eluation.

Compound **2** (10 mmol) (Liszkiewicz et al. 2002), appropriate aldehyde (10 mmol), KOH (10 mmol) in methanol (30 ml) were refluxed for 4 h. The solid precipitate was filtered, decolorized with charconal and recrystallized from toluene to yield compounds **3**–**9**.

3.1.1. 1-Phenyl-2-{(Z)-(4RS)-4-(2-chlorophenyl)-1,3,4,5-tetrahydro-2H-pyrido[2,3-b][1,4]diazepin-2-ylidene}-ethanone (**3**)

Yield: 2.9 g (64%), m.p. 186–187 °C. IR (KBr) ν cm^{-1}: 3300, 3020, 1660, 1580. ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 12.85 (s, 1 H, NH), 7.84 (dd, J = 4.7 Hz, J = 1.5 Hz, 1 H, H-7), 7.74 (dd, J = 7.1 Hz, 1.4 Hz, 2 H, ArH), 7.63 (dd, J = 7.5 Hz, 1.7 Hz, 1 H, ArH), 7.39 (lt, J_{av} = 6.7 Hz, 1 H, ArH), 7.37–7.34 (m, 3 H, ArH), 7.28 (dd, J = 7.60 Hz, 1.5 Hz, 1 H, H-9), 7.22–7.15 (m, 2 H, ArH), 6.73 (dd, J = 4.7 Hz, J = 7.60 Hz, 1 H, H-8), 5.68 (d,

J = 3.2 Hz, 1 H, NH), 5.61 (s, 1 H, =CHCOPh), 5.52–5.50 (m, 1 H, H-4), 2.94 (dd, J = 14.1 Hz, 3.2 Hz, 1 H, H-3a), 2.89 (dd, J = 14.1 Hz, 7.0 Hz, 1 H, H-3b). (DMSO, 500 MHz) δ (ppm): 12.80 (s, 1 H, NH), 7.95 (dd, J = 4.8 Hz, J = 1.1 Hz, 1 H, H-7), 7.71 (d, J = 7.3 Hz, 2 H, ArH), 7.48–7.39 (m, 6 H, H-9 + ArH), 7.28–7.21 (m, 2 H, ArH), 7.05 (d, J = 4.9 Hz, 1 H, NH), 6.78 (dd, J = 7.7 Hz, 4.80 Hz, 1 H, H-8), 5.63 (s, 1 H, =CHCOPh), 5.40 (m, 1 H, H-4), 3.07 (dd, J = 14.2 Hz, 2.7 Hz, 1 H, H-3a), 2.99 (dd, J = 14.2 Hz, 6.5 Hz, 1 H, H-3b). MS (70 eV) m/z (%): 377 ($M^+ + 2$, 35), 376 ($M^+ + 1$, 26), 375 (M^+, 100), 340 (M^+−Cl, 14).
$C_{22}H_{18}ClN_3O$ (375.9)

3.1.2. 1-Phenyl-2-{4-(4-chlorophenyl)-1,3,4,5-tetrahydropyrido[2,3-b][1,4]-diazepin-2-ylidene}-ethanone (**4**)

Yield: 2.3 g (63%), m.p. 204–206 °C. IR (KBr) ν cm^{-1}: 3320, 3020, 1600, 1590, 1540, 1460, 1180. ^1H NMR (DMSO, 500 MHz) δ (ppm): 12.87 (s, 1 H, NH), 7.92 (d, J = 4.8 Hz, 1 H, H-7), 7.79 (d, J = 7.8 Hz, 2 H, ArH), 7.50–7.34 (m, 8 H, H-9 + ArH), 7.02 (d, J = 4.2 Hz, 1 H, NH), 6.75 (dd, J = 7.4 Hz, 4.8 Hz, 1 H, H-8), 5.84 (s, 1 H, =CHCOPh), 5.10 (m, 1 H, H-4), 3.04 (dd, J = 14.2 Hz, 3.0 Hz, 1 H, H-3a), 3.00 (dd, J = 14.2 Hz, 6.7 Hz, 1 H, H-3b). MS (70 eV) m/z (%): 377 ($M^+ + 2$, 33), 376 ($M^+ + 1$, 25), 375 (M^+, 100).
$C_{22}H_{18}ClN_3O$ (375.9)

3.1.3. 1-Phenyl-2-{4-(2-bromophenyl)-1,3,4,5-tetrahydropyrido[2,3-b][1,4]-diazepin-2-ylidene}-ethanone (**5**)

Yield: 2.7 g (64%), m.p. 176–178 °C. IR (KBr) ν cm^{-1}: 3220, 3040, 1600, 1590, 1550, 1530, 1345, 1175. ^1H NMR (DMSO, 500 MHz) δ (ppm): 12.80 (s, 1 H, NH), 7.95 (dd, J = 4.7 Hz, 1.3 Hz, 1 H, H-7), 7.72 (d, J = 7.2 Hz, 2 H, ArH), 7.60 (d, J = 7.9 Hz, 1 H, ArH), 7.48–7.40 (m, 5 H, H-9 + ArH), 7.31 (lt, J_{av} = 7.6 Hz, 1 H, ArH), 7.16 (lt, J_{av} = 7.8 Hz, 1 H, ArH), 7.04 (d, J = 4.7 Hz, 1 H, NH), 6.79 (dd, J = 7.7 Hz, 4.7 Hz, 1 H, H-8), 5.63 (s, 1 H, =CHCOPh), 5.36–5.33 (m, 1 H, H-4), 3.05 (dd, J = 14.1 Hz, 2.8 Hz, 1 H, H-3a), 2.98 (dd, J = 14.1 Hz, 6.6 Hz, 1 H, H-3b).
$C_{22}H_{18}BrN_3O$ (420.3)

3.1.4. 1-Phenyl-2-{4-(4-bromophenyl)-1,3,4,5-tetrahydropyrido[2,3-b][1,4]-diazepin-2-ylidene}-ethanone (**6**)

Yield: 3.0 g (72%), m.p. 200–202 °C. IR (KBr) ν cm^{-1}: 3240, 3200, 1660, 1580, 1530, 1480, 1320, 1180. ^1H NMR (DMSO, 500 MHz) δ (ppm): 12.85 (s, 1 H, NH), 7.92 (dd, J = 4.6 Hz, 1.3 Hz, 1 H, H-7), 7.77 (d, J = 7.3 Hz, 2 H, ArH), 7.50 (m, 3 H, ArH), 7.43 (lt, J_{av} = 7.4 Hz, 7.3 Hz, 2 H, ArH), 7.37 (d, J = 7.6 Hz, 1 H, H-9), 7.34 (d, J = 8.3 Hz, 2 H, ArH), 7.00 (d, J = 4.4 Hz, 1 H, NH), 6.75 (dd, J = 7.6 Hz, 4.6 Hz, 1 H, H-8), 5.82 (s, 1 H, =CHCOPh), 5.08 (m, 1 H, H-4), 3.01 (dd, J = 14.4 Hz, 3.2 Hz, 1 H, H-3a), 2.99 (dd, J = 14.4 Hz, 6.6 Hz, 1 H, H-3b). MS (70 eV) m/z (%): 422 ($M^+ + 2$, 94), 420 (M^+, 100).
$C_{22}H_{18}BrN_3O$ (420.3)

3.1.5. 1-Phenyl-2-{4-(4-fluorophenyl)-1,3,4,5-tetrahydropyrido[2,3-b][1,4]-diazepin-2-ylidene}-ethanone (**7**)

Yield: 2.4 g (68%), m.p. 208–209 °C. IR (KBr) ν cm^{-1}: 3240, 3020, 1605, 1545, 1510, 1440, 1240, 1190. ^1H NMR (DMSO, 500 MHz) δ (ppm): 12.89 (s, 1 H, NH), 7.93 (dd, J = 4.6 Hz, 1.4 Hz, 1 H, H-7), 7.79 (d, J = 7.2 Hz, 2 H, ArH), 7.49 (lt, J_{av} = 7.2 Hz, 1 H, ArH), 7.45–7.37 (m, 5 H, H-9 + ArH), 7.13 (lt, J_{av} = 8.8 Hz, 2 H, ArH), 6.96 (d, J = 4.1 Hz, 1 H, NH), 6.76 (dd, J = 7.6 Hz, 4.6 Hz, 1 H, H-8), 5.85 (s, 1 H, =CHCOPh), 5.08 (m, 1 H, H-4), 3.03 (dd, J = 14.2 Hz, 3.5 Hz, 1 H, H-3a), 2.99 (dd, J = 14.2 Hz, 6.4 Hz, 1 H, H-3b). MS (70 Ev) m/z (%): 360 ($M^+ + 1$, 84), 358 ($M^+ - 1$, 21).
$C_{22}H_{18}FN_3O$ (359.4)

3.1.6. 1-Phenyl-2-{4-(4-trifluoromethylphenyl)-1,3,4,5-tetrahydropyrido[2,3-b][1,4]diazepin-2-ylidene}-ethanone (**8**)

Yield: 2.3 g (55%), m.p. 183–185 °C. IR (KBr) ν cm^{-1}: 3260, 3080, 1605, 1550, 1520, 1370, 1290, 1190. ^1H NMR (DMSO, 500 MHz) δ (ppm): 12.78 (s, 1 H, NH), 7.94 (dd, J = 4.7 Hz, 1.5 Hz, 1 H, H-7), 7.72 (d, J = 7.1 Hz, 2 H, ArH), 7.68 (d, J = 8.2 Hz, 2 H, ArH), 7.61 (d, J = 8.2 Hz, 2 H, ArH), 7.48 (lt, J_{av} = 7.2 Hz, 1 H, ArH), 7.43–7.39 (m, 3 H, H-9 + ArH), 7.07 (d, J = 4.6 Hz, 1 H, NH), 6.77 (dd, J = 7.7 Hz, 4.7 Hz, 1 H, H-8), 5.77 (s, 1 H, =CHCOPh), 5.21 (m, 1 H, H-4), 3.09 (dd, J = 14.2 Hz, 2.9 Hz, 1 H, H-3a), 3.03 (dd, J = 14.2 Hz, 6.8 Hz, 1 H, H-3b). MS (70 eV) m/z (%): 411 ($M^+ + 2$, 19), 410 ($M^+ + 1$, 100).
$C_{23}H_{18}FN_3O$ (409.1)

3.1.7. 1-Phenyl-2-{4-(3-bromo-4,5-dimethoxyphenyl)-1,3,4,5-tetrahydropyrido[2,3-b][1,4]-diazepin-2-ylidene}-ethanone (**9**)

Yield: 2.8 (59%) g (%), m.p. 203–204 °C. IR (KBr) ν cm^{-1}: 3320, 3000, 1610, 1590, 1540, 1410, 1300, 1190. ^1H NMR (DMSO, 500 MHz) δ (ppm): 12.78 (s, 1 H, NH), 7.97 (dd, J = 4.7 Hz, 1.1 Hz, 1 H, H-7), 7.81 (d, J = 7.3 Hz, 2 H, ArH), 7.50 (lt, J_{av} = 7.2 Hz, 1 H, ArH), 7.46–7.41 (m, 3 H, H-9 + ArH), 7.19 (d, J = 1.6 Hz, 1 H, ArH), 7.12 (d, J = 1.6 Hz, 1 H, ArH), 6.89 (d, J = 3.7 Hz, 1 H, NH), 6.78 (dd, J = 7.6 Hz, 4.7 Hz, 1 H, H-8), 5.92 (s, 1 H, =CHCOPh), 5.05 (dt, J = 5.1 Hz, 3.7 Hz, 1 H, H-4), 3.78 (s, 3 H, OCH_3), 3.64 (s, 3 H, OCH_3), 2.99 (d, J = 5.1 Hz, 2 H, H-3). MS (70 eV) m/z (%): 482 ($M^+ + 2$, 19), 481 ($M^+ + 1$, 89), 480 (M^+, 26).
$C_{24}H_{22}$ BrN_3O_3 (480.4)

3.1.8. 1-Phenyl-2-(4-phenyl-1,3,4,5-tetrahydropyrido[2,3-b][1,4]diazepin-2-ylidene)-ethanone (**10**)

Analytical data see Liszkiewicz et al. (2002).

3.2. Biological test procedures

The experiments were carried out on male BALB/c mice (20–24 g) kept under standard laboratory conditions, with free access to food and water. The experimental and control groups contained 8–10 animals each. The investigated compounds were administered intraperitoneally (ip) as suspensions in an 1% aqueous solution of Tween 80 in a volume of 10 ml/kg. Control animals were given appropriate amounts of the vehicle.
The protocol of experiments was approved by the local Ethical Commitete.

3.2.1. Acute toxicity

LD_{50} were calculated according to the method of Litchfield and Wilcoxon (1959). Dead mice were counted 24 h after ip administration.

3.2.2. Light-dark box test

The mice were observed over a 5 min period and 4 behaviors were noted: the latency of the initial movement from the light to the dark area, the time spent in the light area, the number of exploratory rearings and the number of line crossings in the light and dark areas (Costall et al. 1989). The investigated compounds were injected 1 h before the test. Data were analyzed using a one-way ANOVA with Dunnett's post-hoc analysis.

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