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Original paper

1,4-Benzodiazepines and 1,5-benzodiazocines XI. Synthesis and biological activity

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Summary — The synthesis of a new class of anellated 1,4-benzodiazepines with anti-psychotic activity is exemplified by preparation of 10-fluoro-3-methyl-7-(2-thienyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-*a*][1,4]benzodiazepine (timelotem). The influence of variations of the fluoro-substitution pattern and variations of the fused ring system on the biological activity of the structural analogues is evaluated. *In vivo*, the potency of the compounds to antagonize apomorphine induced climbing (taken as being indicative of anti-psychotic activity) and their ability to inhibit pentetrazole-induced seizures (indicating similarities to benzodiazepine minor tranquilizers) are determined. *In vitro* the affinities of the compounds to both dopamine-D_2 and benzodiazepine receptors are measured.

Résumé — **Benzodiazépines-1,4 et benzodiazocines-1,5 XI. Synthèse et activité biologique.** *La synthèse d'une nouvelle classe de benzodiazépines-1,4 annélées douées d'activité anti-psychotique est présentée au moyen de l'exemple de la préparation de la fluoro-10 méthyl-3(thiényl-2)-7 hexahydro-1,2,3,4,4a,5 pyrazino[1,2-*a*]benzodiazépine-1,4 (timelotem).*

Les variations de la substitution par le groupe fluoro et par l'annélation des cycles condensés sont examinées pour montrer leur influence sur l'activité biologique. L'activité des composés est démontrée in vivo *par l'antagonisme de la réaction du grimper induite par l'apomorphine (indiquant une activité anti-psychotique) et par l'inhibition des convulsions induites par le pentétrazole (indiquant une ressemblance avec les benzodiazépines classées comme tranquillisants mineurs). L'affinité de ces composés est mesurée* in vitro *pour les récepteurs à la dopamine-D_2 et aux benzodiazépines.*

1,2,3,4,4a,5-hexahydropyrazino[1,2-*a*][1,4]benzodiazepines / timelotem / anti-psychotic activity / antagonism of apomorphine induced climbing / inhibition of pentetrazole induced seizures / dopamine-D_2 and benzodiazepine receptor binding

Introduction

Recently we showed, that anellated oxazino- and pyrazino-7-phenyl-1,4-benzodiazepines exhibit marked effects on the healing of experimentally-induced ulcers [1, 2], while showing only weak central nervous system (CNS) activity. This is in contrast to anellated triazolo-, imidazo- and pyrimido-1,4-benzodiazepines, which are classically equated with tranquilizing and anxiolytic drug activity [3].

Further investigations led us to the group of 7-heteroaryl substituted pyrazino- and oxazino-benzodiazepines [4] with anti-psychotic properties. Timelotem (10-fluoro-3-methyl-7-(2-thienyl)-1,2,3,4,4a,5-hexahydropyrazino-[1,2-*a*][1,4]benzodiazepine) was selected for in-depth pharmacological characterization in particular with respect to its psychotropic profile [4—8]. Here we will present the synthesis and some pharmacological properties of a selected group of derivatives out of this new chemical class.

Chemistry

As the synthesis of compounds **IV** following the classical route of preparing 1,4-benzodiazepines from 2-aminobenzophenones has proven to be unsuitable, two different approaches were chosen.

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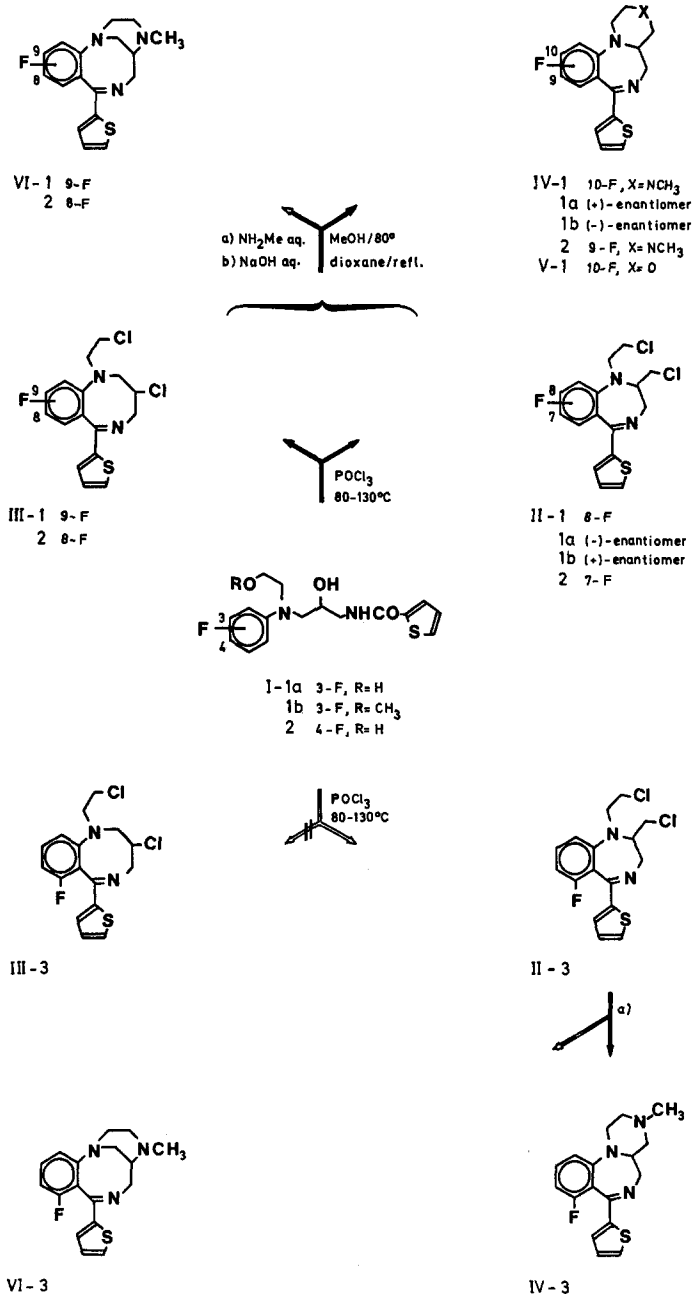
Abbreviations: **DMF:** dimethylformamide; **EtOH:** ethanol; **Et_2O:** diethylether; **EtOAc:** ethyl acetate; **iPrOH:** isopropanol; **MeOH:** methanol; **PE:** petroleum ether (bp: 50—70°C); **rt:** room temperature.

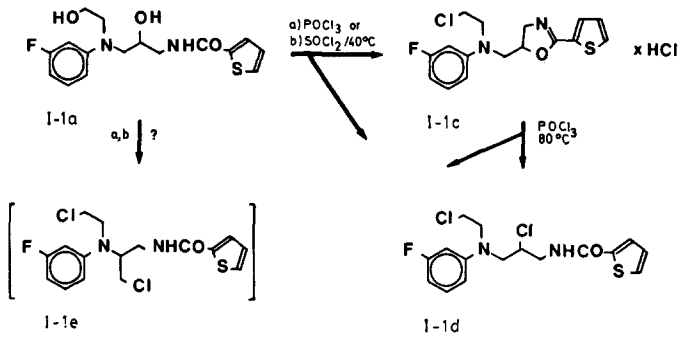
Method 1

As described for the synthesis of 1-methyl substituted 1,4-benzodiazepines [9, 10] with a functionalized side chain at carbon 2, the open chain amides **I** cyclize at 80—130°C in $POCl_3$ to yield a mixture of the 7- and 8-membered ring compounds **II** and **III**. The crude mixture of **II** and **III** is reacted subsequently either with methylamine or with aqueous NaOH to yield **IV** or **V**, respectively, as main products (Scheme 1).



Scheme 1. Method 1.

To elucidate the reaction pathway of this complex transformation, we tried to isolate some intermediates starting from **I-1a** (see Scheme 2). Under the cyclization conditions, two main intermediates were detected by high pressure liquid chromatography (HPLC). To isolate these compounds, we lowered the reaction temperature to 40°C. We isolated the oxazoline **I-1c** and the dichlorinated amide **I-1d**, which proved to be identical with both compounds found by HPLC. Using $SOCl_2$ instead of $POCl_3$ led to the advantage that the 2-oxazoline **I-1c** was obtained as a crystalline hydrochloride. The open chain amide **I-1d** was obtained as a minor by-product.



Scheme 2.

Due to the low stability of the dichlorinated amide **I-1d**, especially under chromatographic conditions, we did not try to prepare **I-1d** for subsequent cyclization.

The corresponding isomeric amide **I-1e**, as shown for *N*-methyl-amides [9], was not isolated.

I-1e is thought to be an intermediate to yield **II-1** at a temperature of about 80°C, because rearrangement of **III-1** was not observed at temperatures below 110°C.

The formation of both **I-1d** and **I-1e** can be explained by a common intermediate aziridinium compound formed by participation of the aniline nitrogen.

Thus, the 2-oxazoline **I-1c** is cyclized at 80°C in $POCl_3$, as well as the amide **I-1a**, to yield **III-1** as the main product and **II-1** as a by-product. When the temperature was raised to about 130°C, **II-1** became the main product.

Generally the cyclization reaction can be performed in two steps: starting with temperatures of about 80°C resulted in formation of **III-1** as the main product. Subsequent elevation of the temperature to about 130°C led to ring contraction and **II-1** was isolated preferentially.

Due to the asymmetric substitution pattern in the aromatic moiety of the amides **I-1**, the formation of the two isomers **III-3** and **II-3** can be expected. Whereas **III-3** was never observed, the formation of **II-3** depends upon the reaction temperature, *i.e.*, the amount of **II-3** is decreased by lowering the reaction temperature from 130°C to about 80°C. Since **III-1** was difficult to handle and the by-product **II-3** could be separated from **II-1** by crystallization, it was advisable to use the one-step preparation with preferential formation of **II-1** in good yield.

Compounds **II-2** and **III-2** were synthesized according to the same procedure, whereas **II-3** was separated from the mother liquors of **II-1** by repeated low pressure column chromatography.

When reacted with methylamine at 90°C, the dichlorides **II** and **III** yielded **IV** as the main product with various amounts of **VI** as a by-product. For example, starting with the ocine **III-1**, a slightly higher proportion of **VI-1**: **IV-1** (1:35) was observed, whereas **II-1** yielded a proportion of 1:60. This is in accordance with the literature [9, 11], where we discussed aziridinium structures as intermediates. Lowering the reaction temperature to 70°C did not influence the amount of **VI-1** significantly. At temperatures above 100°C, substitution of the 10-fluoro-substituent by the methylamino group was detected.

For synthesis of the oxazino compound **V-1** it is sufficient to use the raw cyclization mixture of **II-1** and **III-1** without further purification. Reaction with aqueous NaOH in boiling dioxan yielded **V-1**, whereas a compound corresponding to **VI** was not detected.

For the preparation of the enantiomers of timelotem **IV-1**, it is advisable to separate the enantiomers of **II-1** by crystallization as dibenzoyltartrates from dichloromethane by modifying the method of separation described in the literature [12]. The yields of **II-1a** and **II-1b** are 42 and 37%, respectively, relative to the racemate. The optical purity of the subsequently formed piperazines is $\geqslant$ 99% for **IV-1a** and $\geqslant$ 95% for **IV-1b**, as determined by HPLC. The absolute configuration of **I-1a** will be published elsewhere.

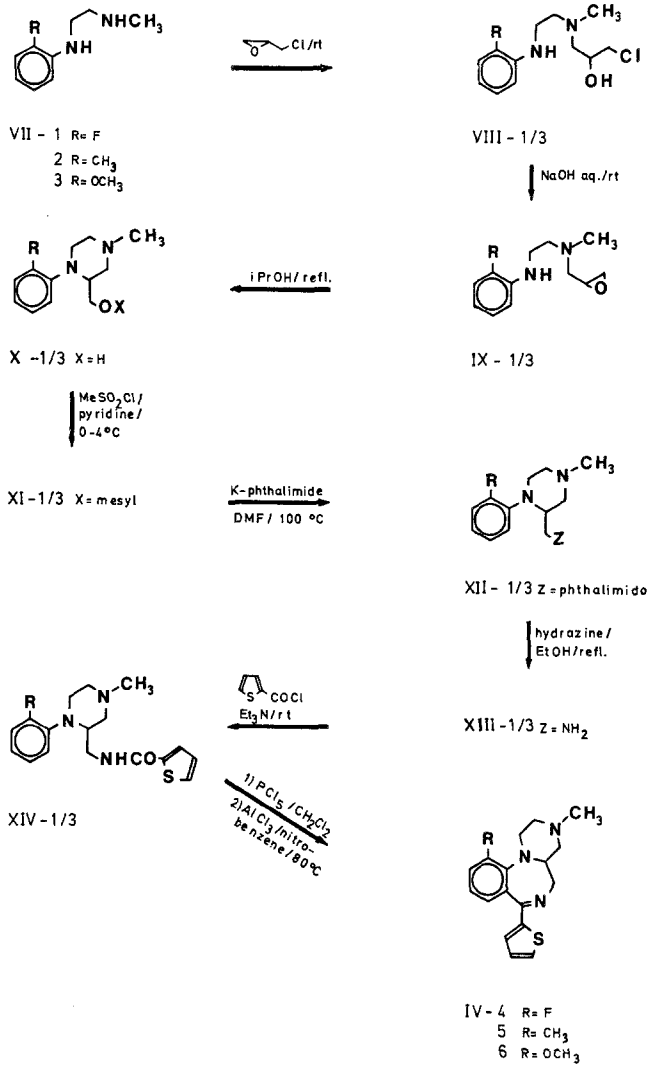
Method 2

For the isomeric 11-fluoro substituted benzodiazepine **IV-4**, a synthesis according to Scheme 3 was preferred. In a modification of the method reported in the literature [13], compound **VII-1** was synthesized by reaction of 2-fluoro-aniline with methylaminoethylchloride hydrochloride at 110°C.

The reaction of **VII-1** with wet epichlorohydrine was performed at 0—4°C. Without isolation of **VIII-1**, the chlorohydrine was changed into the epoxide **IX-1**, by treatment with an equimolar amount of NaOH in water. Subsequently, the isolated crude epoxide **IX-1** yielded **X-1** (55%, relative to **VII-1**) in boiling isopropanol.

The phthalimido compound **XII-1** was obtained *via* the mesylate **XI-1** with potassium—phthalimide in dimethylformamide (DMF) at 100°C. The main product **XII-1** (60%) crystallized from the reaction mixture. Compound **XII-1** was cleaved with hydrazine and reacted with 2-thienylcarbonylchloride to yield the amide **XIV-1** (80%).

Attempts to cyclize **XIV-1** using the conditions described in method 1 for amides **I** failed. In the literature [14], cyclization of the analogues 2-benzoylamino-1-(4-chlorophenyl)-4-methyl-piperazine is described under 'smooth' conditions in refluxing $POCl_3/P_2O_5$. This method was without any success when applied to **XIV-1**. Finally, we succeeded in ring closure *via* the imidoylchloride, which was prepared from **IV-1** by reaction with PCl_5. Without purification of the imidoylchloride, the subsequent Friedel—



Scheme 3. Method 2.

Crafts cyclization with $AlCl_3$ was carried out in nitrobenzene at 80°C as described for open chain amides [9] to yield **IV-4** (60%, relative to **XIV-1**).

To examine the scope of this synthetic approach, the 11-methyl- and 11-methoxy-substituted benzodiazepines **IV-5** (37%) and **IV-6** (32%) were synthesized.

For the synthesis of **IV-1**, method 2 is of no advantage because of lacking regioselectivity. Cyclization of the corresponding amide **XIV** with 3-fluorophenyl substitution gave a 60—70% yield of a mixture of **IV-1** and **IV-3** (about 7:1).

Results and interpretation of biological properties

Table I summarizes results from *in vivo* activity and *in vitro* receptor affinity evaluations of the described compounds, and the respective data of haloperidol (standard neuroleptic) and of diazepam (standard benzodiazepine minor tranquilizer). Clear-cut activity of the test com-

Table I. Biological activity of the compounds.

Compound	*In vivo* activity[a]			*In vitro* D_2 affinity[b]
	APO-climb	PTZ-ant		
rac. **IV-1** (dihydrogenmaleate)	0.55	>215	(10%)	20±4 (6)
(+)**IV-1a** (base)	0.60		(0%)	12 (1)
(—)**IV-1b** (base)	>215 (14%)		(0%)	6 300 (1)
IV-2 (dihydrochloride)	7.5		(0%)	32±4 (3)
V-1 (base)	>215 (23%)		(10%)	2 000±5 (3)
IV-3 (hydrogenmaleate)	37		(10%)	29±4 (4)
IV-4 (dihydrochloride)	26		(10%)	42±9 (4)
IV-5 (base)	>215 (0%)		(0%)	48±6 (3)
IV-6 (base)	>215 (0%)		(0%)	380±70 (3)
VI-1 (dihydrogenmaleate)	>215 (14%)		(0%)	4 900±720 (3)
Haloperidol	0.14	>147	(0%)	1.36±0.04 (168)
Diazepam	>215 (0%)	1.2		>10 000 (2)

[a] ED_{50}-values (μmol/kg, *p.o.*) or highest dose tested (μmol/kg, *p.o.*) and, between parentheses, the maximal effect (%). APO-climb: inhibition of apomorphine-induced climbing in mice. PTZ-ant: antagonism of pentetrazole-induced convulsions in mice.
[b] Average k_i values (nmol) ± SEM, number of independent determinations between parentheses. D_2: affinity for central dopamine-D_2 receptors.

pounds against apomorphine-induced climbing behavior (APO-climb) can be taken as being indicative of pronounced anti-psychotic potency. The potency of **IV-1** proved to be of the same order of magnitude as the potency of haloperidol. However, the anti-psychotic potency of the compounds is not paralleled by a strong affinity for central dopamine-D_2 receptors unlike the classical neuroleptics, *e.g.*, haloperidol. As one possible explanation, one might assume that extraordinary pharmacokinetic properties of the test compounds account for their unexpected high potency (as compared to their dopamine-D_2 receptor affinity and to typical neuroleptics). Evidence, however, could be established supporting the hypothesis that the anti-psychotic potency of the test compounds is not solely due to dopamine receptor blockade. Thus these compounds can be considered as atypical neuroleptics [5, 6, 8].

Testing the enantiomers of timelotem, **IV-1a** was shown to be the most effective component.

Despite of their benzodiazepine structure, the test compounds did not show any affinity for central benzodiazepine receptors (k_i > 10 000 nM; diazepam: k_i = 8.0 ± 0.2 nM). Furthermore, the compounds failed to inhibit pentetrazole-induced convulsions (PTZ-ant), a test particularly sensitive to benzodiazepine-like minor tranquilizers.

Conclusion

In conclusion compounds of the presented chemical class of anellated 1,4-benzodiazepines do not show the typical benzodiazepine profile. As a new property for benzodiazepines, they exhibit pronounced anti-psychotic potency. In contrast to typical neuroleptics, however, this activity is probably not solely linked to an interaction with D_2-receptors.

Experimental protocols

Chemistry

Melting points were determined on a Buchi apparatus (Dr. Tottoli) and are uncorrected. IR spectra (KBr or liquid film) were recorded on a Perkin—Elmer 157 G spectrophotometer, UV spectra (λ_{max} and sh = shoulder, (ε)) on a Leitz-Unicam SP 800 A spectrophotometer. Optical rotation was determined on a Perkin—Elmer 241 Polarimeter. Analyses were within ± 0.4% of the theoretical values. ^{13}C NMR data and EI mass spectra are reported in Tables II and III, respectively.

If not stated otherwise the reaction product was isolated in the following way. The crude reaction mixture was dissolved in a water non-miscible organic solvent. The organic layer was separated and, if necessary, treated with a diluted aqueous solution of sodium hydroxide or hydrochloric acid, respectively, washed with water or a saturated solution of sodium chloride, dried over sodium sulfate and filtered. The organic solvent was evaporated. For isolation, purification and identification the following techniques were used: 1) column chromatography (CC): Al_2O_3 Merck, standardized, activity II—III; 2) low pressure liquid chromatography (LPLC): Duramat® Colora Messtechnik GmbH, silica gel S, Riedel-de-Haën; 3) high pressure liquid chromatography (HPLC): Du Pont Liquid Chromatography System 8800, Du Pont UV Spectrophotometer Detector; column Knauer Patronensäule (30 + 100) × 4 mm, Machery-Nagel Nucleosil C 18, 0.005 mm. Experimental details see [15] and experimental protocol for **IV-1a,b** for analysis of enantiomers; 4) thin-layer chromatography (TLC): Merck silica gel 60 F_{254}, 0.25 mm-coated plates for analytical purposes or 2 mm-coated plates for preparative use. Spots were detected by direct observation under UV light (254 nm).

Hydrochlorides were prepared in the usual way.

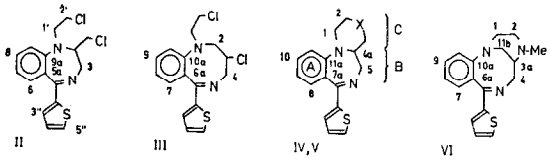
The amides **I** used as starting materials for the cyclization (method 1) were synthesized analogously to the *N*-methyl derivatives, according to an earlier published procedure [9].

The substituted N_1-methyl-N_2-phenyl-1,2-ethylene-diamines **VII-1/3** used as starting materials for method 2 were synthesized according to the published method [13] from the appropriate *ortho*-substituted aniline and methylaminoethylchloride hydrochloride.

Method 1

2-(2-Thienyl)-5-[N-*(3-fluorophenyl)*-N-*(2-chloroethyl)-aminomethyl*]-*1,3-oxazoline hydrochloride* ***I-1c*** *and* N_1-*(3-fluorophenyl)*-N_1-*(2-chloroethyl)*-N_2-*(2-thienylcarbonyl)-2-chloro-1,3-diaminopropane* ***I-1d***

Table II. ^{13}C NMR data.



II III IV,V VI

		phenyl ring						thienyl ring				$N-C_2H_4Cl$		oxazoline			
No	MHz	6	5	4	3	2	1	2′	3′	4′	5′	1″	2″	$N-CH_2$	5	4	2
I-1c	D	107.8 [2]	130.7 [10]	104.2 [22]	164.3 [243]	99.5_5 [26]	148.5 [10]	130.0_5	130.4	127.7	130.1	53.2_5*	39.8_5	55.7_5*	78.3	58.1	159.6

		phenyl ring						thienyl ring				$N-C_2H_4Cl$		1,3-diaminopropyl group			
		6	5	4	3	2	1	2′	3′	4′	5′	1″	2″	$N-CH_2$	CHCl	CH_2	CO
I-1d	B	108.2 [2]	130.8 [10]	104.4_5 [21]	164.1_5 [243]	99.8_5 [26]	147.8_5 [10]	138.1	128.5_5	127.7_5	130.6	53.8*	40.0_5	56.2*	58.7	43.8_5	162.2_5

		ring A						thienyl ring				$N-C_2H_4Cl$			ring B		
		5a	6	7	8	9	9a	2′	3′	4′	5′	1″	2″	CH_2Cl	2	3	5
II-1	A	126.7 [2]	131.7 [10]	110.1 [22]	164.4 [251]	110.5 [23]	148.2 [10]	144.6	129.6	127.4	130.5	52.2	40.7	44.5	70.3	52.5	165.8
II-2	D	133.6 [7]	116.5 [23]	159.0 [245]	118.0 [22]	126.7 [8]	141.8 [3]	144.3	130.4	127.5	129.6	53.1*	41.1	44.4	70.3	53.9*	165.2 [2]
II-3	D	119.8 [br]	159.4_5 [251]	111.6 [22]	131.9 [10]	119.4 [br]	146.9_5 [5]	143.8_5	129.3_5 [4]	127.4	128.8	52.7*	40.8_5	44.1	69.6_5	53.3*	162.1_5

		ring A						thienyl ring				$N-C_2H_4Cl$			ring B		
		6a	7	8	9	10	10a	2′	3′	4′	5′	1″	2″	2	3	4	6
III-1	D	116.6 [3]	134.5 [10]	103.0 [22]	164.7 [248]	103.9 [22]	149.4 [10]	147.3	131.7	127.4	129.8	56.9	39.8	54.4	52.0	55.4	161.3
conformer		114.4 [3]	135.1 [10]	102.4 [22]	164.6 [247]	99.9 [22]	148.3 [10]	nd	131.4	127.2	nd	56.9	39.6	55.0	55.3	53.3	166.3
III-2	D	131.6_5 [7]	116.2_5 [23]	158.4_5 [246]	118.5 [23]	125.8_5 [8]	144.5 [3]	145.5_5	131.1_5	127.5_5	130.1_5	59.3	41.6_5	57.0_5	54.0	58.7	163.7
conformer		nd	118.3_5 [22]	154.8_5 [240]	118.4 [23]	116.5 [7]	142.9_5 [br]	146.4	131.4	127.2_5	130.0	56.4	40.1_5	54.7	52.9	55.0	165.2

		ring A						thienyl ring				ring C			ring B			
		7a	8	9	10	11	11a	2′	3′	4′	5′	1	2	4	4a	5	7	N-Me
IV-1	B	124.3 [3]	131.2 [10]	107.9 [22]	164.3 [250]	105.6 [23]	151.8 [9]	145.4	129.9	127.1	128.9	49.0	54.2	59.4	71.2	53.0	165.2	45.8
IV-2	D	nd	116.2 [23]	157.7 [242]	117.6 [22]	119.1 [-7]	146.2 [br]	144.9	130.2	127.3	129.2	49.2	54.6	59.6	71.7	53.3	164.8	45.9
V-1	A	124.6 [2]	131.5 [10]	108.4 [22]	164.5 [250]	105.4 [23]	151.7 [9]	145.3	130.2	127.2	129.2	49.4	66.2	70.7	71.8	51.1	165.5	-
IV-3	D	116.1 [16]	159.5_5 [250]	110.9 [22]	131.9_5 [10]	113.8 [2]	151.3_5 [6]	144.2_5	129.3 [4]	127.2_5	128.5	49.2_5	54.6	59.7	70.9	53.2_5	161.6_5	45.8_5
IV-4	D	132.1 [2]	125.0_5 [3]	122.6 [9]	118.7_5 [22]	157.1_5 [246]	136.5 [10]	145.2	130.3	127.2_5	129.1	50.2_5 [11]	55.3_5 [4]	59.5_5	69.4	52.9	164.8_5	46.1
IV-5	D	132.7_5	127.1	122.7	134.5 11-Me :21.5	131.8_5	147.8_5	145.8_5	130.1	127.1_5	128.7	50.3	55.8	59.1	67.5	52.7_5	165.9	46.2_5
IV-6	C	131.9_5	121.8_5	123.0	115.0_5 11-OMe:56.2	155.0	138.3	145.7	130.2	127.2	128.7_5	50.4	55.5	59.6	68.8	53.1	165.5	46.3_5

		ring A						thienyl ring				ring C			ring B			
		6a	7	8	9	10	10a	2′	3′	4′	5′	1	2	11b	3a	4	6	N-Me
VI-1	D	116.2 [br]	135.1 [11]	104.1 [22]	164.3 [248]	103.0_5 [25]	152.0_5 [10]	147.1	130.6	127.2	128.9	52.7	46.6	48.7	53.3	45.1	165.8	42.6
VI-2	C	120.3_5 [6]	118.4* [22]	154.0 [238]	118.5* [23]	119.5 [7]	146.7 [2]	147.1	130.7_5	127.3	129.0_5	53.0_5	46.3_5	48.2	53.1_5	45.5_5	165.2_5	42.7
VI-3	D	109.5_5 [19]	161.7_5 [245]	104.3_5 [24]	131.0_5 [11]	114.0 [3]	151.7_5 [5]	147.0 [2]	129.0_5 [2]	127.2_5	128.3_5	53.7_5	46.8_5	48.2	54.6	46.5	161.6 [3]	42.6

		phenyl ring						piperazine ring							phthalimido group			
		6′	5′	4′	3′	2′	1′	2	3	5	6	N-Me	CH_2Z	C=O	1″	2″	3″	2′-R
X-1	D	124.5 [4]	121.9 [br]	123.2 [9]	116.1 [21]	156.3 [246]	138.2_5 [9]	56.6 [6]	57.7	55.0	47.8	46.2	63.9					F
X-2	D	122.3_5	126.6	124.4_5	131.1_5	134.5	149.0	57.8	58.4_5	55.6	51.6_5	46.3	62.6					17.6_5
X-3	D	121.2_5	124.4_5	122.7	111.7_5	153.7	139.3	57.0_5	57.8	55.2	49.2_5	46.3	63.6					55.5_5
XII-1	D	123.9_5 [4]	119.6 [br]	120.9 [8]	116.0 [21]	154.5 [246]	138.2_5 [8]	53.5 [8]	57.3	55.3	44.7	46.5	37.2_5	168.2_5	131.9	133.4_5	122.7_5	F
XII-2	D	121.1	126.3	123.2	131.0	nd	149.1	54.3	58.7	55.7	50.2	46.4	38.2	168.2	132.0	133.6	122.9	18.0
XII-3	D	119.4	121.4	120.7	111.4	151.2	139.3	51.9	57.7	55.6	45.3	46.5	37.4	168.2	132.0	133.2	122.6	55.2

		phenyl ring						piperazine ring							thienylcarbonyl group			
		6′	5′	4′	3′	2′	1′	2	3	5	6	N-Me	CH_2Z	C=O	2″	3″	4″	5″
XIV-1	D	124.8_5 [4]	122.7 [br]	124.1 [8]	116.5_5 [21]	156.7 [245]	138.0 [9]	55.1 [5.5]	57.7	55.0_5	48.5	46.3	40.6	161.7	139.2_5	127.7	127.5	129.7
XIV-2	D	122.3_5	127.0	124.9	131.5 2′-Me :17.6	134.3_5	148.5_5	55.9_5	58.8	55.7	52.5_5	46.3_5	40.4	161.6_5	139.1_5	127.8_5	127.6	129.7
XIV-3	D	121.6	123.3_5	125.2	112.3 2′-MeO:55.8	159.1	139.1_5	55.4_5	58.0	55.3_5	50.0	46.4	40.4_5	161.7_5	139.6_5	127.6_5	127.4	129.6

^{13}C NMR data of the bases were determined in $CDCl_3$ either A: on a Varian CFT 20 (20 MHz FT), B: Bruker HX 90R (22.63 MHz FT), C: Bruker AM 300 WB (75.47 MHz FT) or D: Bruker AM 400 (100.62 MHz FT) NMR spectrometer. Chemical shifts in ppm are referenced to internal TMS; J_{CF} (Hz) in brackets.
Abbreviations: nd = not detectable ; br = broad; * = might be exchanged; Me = methyl.

Table III. EI mass spectra.

I-1c,	$M^{+\cdot}$ 338 (5%), 340 (2%); 188 (32%), 187 (11%), 186 (100%), 151 (7%), 138 (10%), 124 (11%), 122 (7%), 111 (7%), 95 (7%), 63 (9%).
I-1d,	$M^{+\cdot}$ 374 (0.6%); 302 (19%), 212 (14%), 188 (32%), 186 (100%), 137 (13%), 124 (16%), 122 (14%), 111 (54%), 63 (18%), 39 (14%).
II-1,	$M^{+\cdot}$ 356 (30%), 360 (4%), 358 (21%); 330 (67%), 328 (100%), 292 (25%), 281 (30%), 279 (78%), 243 (26%), 230 (45%), 27 (51%).
III-1,	$M^{+\cdot}$ 356 (23%), 360 (3%), 358 (17%); 323 (37%), 321 (95%), 295 (37%), 293 (100%), 231 (39%), 123 (39%), 97 (34%), 39 (33%), 27 (71%).
IV-1,	$M^{+\cdot}$ 315 (100%); 287 (36%), 286 (20%), 285 (43%), 245 (30%), 244 (31%), 43 (25%), 42 (37%).
VI-1,	$M^{+\cdot}$ 315 (100%); 286 (32%), 285 (75%), 244 (32%), 243 (22%), 230 (21%), 42 (32%), 28 (16%).
VI-2,	$M^{+\cdot}$ 315 (100%); 286 (22%), 285 (54%), 245 (17%), 244 (42%), 243 (19%), 230 (20%), 42 (33%).
VI-3,	$M^{+\cdot}$ 315 (100%); 287 (17%), 286 (31%), 285 (66%), 244 (31%), 243 (18%), 230 (19%), 42 (33%).

EI mass spectra were recorded using a CH7 instrument (Finnigan MAT) with data system SS 166 (direct probe inlet, ion source temp. 200°C, electron energy 90 eV, electron emission 300 μA). Molecular ions and important fragment ions *(m/z)* are given, relative abundance between parentheses.

A solution of 23 g of **I-1a** and 24 g of $SOCl_2$ in 300 ml of CH_2Cl_2 was refluxed for 45 min. The hydrochloride of **I-1c** (16 g, 62.7%) crystallized from the cooled solution. The substance is sufficiently pure for subsequent use. From the mother liquor, another 4 g (17.4%) of **I-1c** as base were isolated according to the standard procedure and purified by CC with CH_2Cl_2 as the eluent.

From the first fraction of CC, an analytical sample of the less polar **I-1d** was separated. It is also formed from **I-1c** by thermal stress at about 80°C.

I-1c: mp: 118—120°C (iPrOH). $C_{16}H_{16}ClFN_2OS \cdot HCl$ (C, H, N, Cl, S). IR: 1640 (C=N), 1625, 1580 (C=C). UV (alk. EtOH): 252 (28800), 274 (12300).

I-1d oil: $C_{16}H_{17}Cl_2FN_2OS$ (C, H, N, Cl, S). IR: 3300 (NH), 1620 (CON), 1580 (C=C).

8-Fluoro-1-(2-chloroethyl)-2-chloromethyl-5-(2-thienyl)-2,3-dihydro-1H-1,4-benzodiazepine ***II-1*** *and 6-fluoro-1-(2-chloroethyl)-2-chloromethyl-5-(2-thienyl)-2,3-dihydro-1H-1,4-benzodiazepine* ***II-3***

56 g of **I-1b** were heated in 65 ml of $POCl_3$ at 140°C bath temperature for 16 h. Subsequently, 300 ml of $CHCl_3$ were added carefully. The organic layer was separated and treated with an aqueous solution of NaOH (10%) to liberate the base. The crude product which was isolated from the organic layer according to the standard procedure was redissolved in 100 ml of MeOH, filtered from insoluble residue. After evaporation of the solvent, the residue was purified by CC with CH_2Cl_2 as the eluent and yielded 42.3 g of an oil, which contained 5.2% **II-3** as a by-product. Two-fold crystallization yielded pure **II-1**. **II-3** was separated from the mother liquor by repeated LPLC with CH_2Cl_2 as the eluent.

II-1: yield: 31.8 g (56.0%); mp: 108—109°C (EtOH); $C_{16}H_{15}Cl_2FN_2S$ (C, H, N, Cl, S). IR: 1615 (C=N), 1600, 1580 (C=C). UV (EtOH): 242 (15800), 253 (15500), 340 sh (1600).

II-1 (hydrochloride): mp: 201—202°C (EtOH); $C_{16}H_{15}Cl_2FN_2S \cdot HCl$ (C, H, N, Cl, S). IR: 1610 (C=N), 1600, 1560 (C=C). UV (EtOH): 263.5 (14100), 310 sh (11000), 326 (11300), 416 (2700).

II-3: mp: 98—99°C (iPrOH); $C_{16}H_{15}Cl_2FN_2S$ (C, H, N, Cl, S). IR: 1610 (C=N), 1590, 1565 (C=C). UV (EtOH): 242.5 (13800), 262.5 (12100), 292 (8800), 348 sh (1200).

II-3 (hydrochloride): mp: 157-160°C (iPrOH/Et_2O); $C_{16}H_{15}Cl_2FN_2S \cdot HCl$ (C, H, N, Cl, S). IR: 1615 (C=N), 1560 (C=C). UV (EtOH): 246 sh (10000), 258.5 (11100), 299 (8400), 335 (8600), 426 (1200).

9-Fluoro-1-(2-chloroethyl)-3-chloro-6-(2-thienyl)-1,2,3,4-tetrahydro-1,5-benzodiazocine ***III-1***

1. 5 g of **I-1a** were heated in 10 ml of $POCl_3$ at 80°C for 16 h. Following the protocol for the preparation of **II-1**, 3.7 g (70.1%) of an oil were isolated. The main product **III-1** contained 7% **II-1** and less than 1% **II-3**. The product was sufficiently pure for subsequent reactions. An analytical sample was prepared by CC with CH_2Cl_2 as the eluent and crystallization as its hydrochloride.

III-1 (hydrochloride): mp: 160—163°C (iPrOH); $C_{16}H_{15}Cl_2FN_2S \cdot HCl$ (C, H, N, Cl, S). IR: 1610 sh (C=N), 1600, 1550 (C=C). UV (EtOH): 255 (18000), 290 (10000), 325 (8300), 430 (1600).

2. 3.7 g of **I-1c** (hydrochloride) were reacted in 6 ml of $POCl_3$ and 0.4 ml of water. As described above, 3.0 g (85.2%) of **III-1** were isolated, which contained 5% **II-1** and 1.4% **II-3** as by-products. For identification, **III-1** was separated by CC with CH_2Cl_2 as the eluent and crystallized as its hydrochloride.

7-Fluoro-1-(2-chloroethyl)-2-chloromethyl-5-(2-thienyl)-2,3-dihydro-1H-1,4-benzodiazepine ***II-2*** *and 8-fluoro-1-(2-chloroethyl)-3-chloro-6-(2-thienyl)-1,2,3,4-tetrahydro-1,5-benzodiazocine* ***III-2***

Cyclization of 50 g of **I-2** in 70 ml of $POCl_3$ at 130°C for 14 h yielded a mixture of **II-2** as the main product and **III-2** as a less polar by-product. The isolated oil (40 g, 75.8%) was sufficiently pure for subsequent use. Analytical samples were prepared after separation by CC with CH_2Cl_2 as the eluent. **II-2** was crystallized as its hydrochloride.

II-2 (hydrochloride): mp: 201—203°C (iPrOH); $C_{16}H_{15}Cl_2FN_2S \cdot HCl$ (C, H, N, Cl, S). IR: 1620 (C=N), 1605 sh, 1570 (C=C). UV (alk. EtOH): 238.5 (12800), 257 sh (10800), 290 (8900), 348 (1500).

III-2: mp: 84—87°C (Et_2O); $C_{16}H_{15}Cl_2FN_2S$ (C, H, N, Cl, S). IR: 1610 sh (C=N), 1595 (C=C), 1575 (C=C). UV (EtOH): 255.5 (12300), 264 sh (10000), 291.5 (9200), 356 sh (1000).

(—)-8-Fluoro-1-(2-chloroethyl)-2-chloromethyl-5-(2-thienyl)-2,3-dihydro-1H-1,4-benzodiazepine ***II-1a*** *and the corresponding (+)-enantiomer* ***II-1b***

To a solution of 87.5 g (0.245 mol) of the racemic base **II-1** in 1 l of CH_2Cl_2 was added a solution of 48.5 g (0.135 mol) of (—)-*O,O'*-dibenzoyl-L-tartaric acid. From the stirred solution, crystallization started at rt. The crystalline salt of **II-1a** was filtered off and washed with CH_2Cl_2 (3×80 ml). According to the standard procedure, the base was liberated and crystallized from iPrOH.

II-1a: yield: 36.5 g (41.7%); mp: 87—89°C; $[\alpha]_D^{22} = -482.1°$ (*c* = 1, MeOH); $C_{16}H_{15}Cl_2FN_2S$ (C, H, N, Cl, S).

The mother liquor from the salt precipitation was treated with dilute aqueous NaOH solution. The crude base of **II-1b** was isolated according to the standard procedure and then treated with (+)-*O,O'*-dibenzoyl-L-tartaric acid as described above.

II-1b: yield: 32.4 g (37%); mp: 87—89°C (iPrOH); $[\alpha]_D^{22} = +480.5°$ (*c* = 1, MeOH); $C_{16}H_{15}Cl_2FN_2S$ (C, H, N, Cl, S).

10-Fluoro-1,2,3,4,4a,5-hexahydro-3-methyl-7-(2-thienyl)-pyrazino[1,2-a][1,4]benzodiazepine ***IV-1*** *and 9-fluoro-1,2,3,3a,10a,10b-hexahydro-3-methyl-6-(2-thienyl)-4H-pyrazino[1,2,3-a,b][1,5]benzodiazocine* ***VI-1***

A solution of 5 g of **II-1** and 12 ml of an aqueous methylamine solution (40%) in 100 ml of MeOH was heated in an autoclave at 90°C for 14 h. The solvent was evaporated and the product isolated according to the standard procedure. The yield after filtration over Al_2O_3 with CH_2Cl_2 as the eluent was 3.6 g. HPLC analysis indicated a composition of **IV-1**:**VI-1** = 60:1. The main product was purified by crystallization from Et_2O. The by-product was isolated from the mother liquor by CC with CH_2Cl_2 as the eluent.

IV-1: yield: 3.0 g (68%); mp: 113—115°C (Et_2O); $C_{17}H_{18}FN_3S$ (C, H, N, S). IR: 1610 (C=N), 1595, 1575 (C=C). UV (EtOH): 240 (19600), 285 sh (10600), 340 sh (2000).

IV-1 (dihydrogenmaleate): mp: 171—172°C (EtOH); $C_{17}H_{18}FN_3S \cdot 2\,C_4H_4O_4$ (C, H, N, S). IR: 1690 (C=O), 1610 (C=N). UV (EtOH): 233.5 (20300), 266 (10100), 293.5 (8100).

VI-1: mp: 114—115°C (Et_2O); $C_{17}H_{18}FN_3S$ (C, H, N, S). IR: 1605 (C=N), 1590, 1570 (C=C). UV (EtOH): 237 sh (13500), 259 (20700), 287.5 (11000), 340 sh (1600).

VI-1 (dihydrogenmaleate): mp: 155—156°C (EtOH); $C_{17}H_{18}FN_3S \cdot 2\ C_4H_4O_4$ (C, H, N, S). IR: 1705 (C=O), 1610 (C=N). UV (EtOH): 250 (21000), 265 sh (13400), 285 sh (10200), 340 sh (2200).

9-Fluoro-1,2,3,4,4a,5-hexahydro-3-methyl-7-(2-thienyl)pyrazino[1,2-a]-[1,4]benzodiazepine ***IV-2*** *and 8-fluoro-1,2,3,3a,10a,10b-hexahydro-3-methyl-6-(2-thienyl)-4H-pyrazino[1,2,3-a,b][1,5]benzodiazocine* ***VI-2***

According to the protocol for the preparation of **IV-1**, 35 g of a mixture of **II-2** and **III-2** yielded 23 g (74.4%) of **IV-2**. From the mother liquor of the crystallization, **VI-2** was isolated as the less polar by-product in an analytical amount by preparative TLC with cyclohexane/EtOAc/EtOH (70/70/30) as the eluent.

IV-2: mp: 116-119°C (iPrOH); $C_{17}H_{18}FN_3S$ (C, H, N, S). IR: 1607 (C=N), 1595, 1570 (C=C). UV (EtOH): 234.5 (16700), 291 (8800), 265 sh (9000), 340 (2300).

IV-2 (dihydrochloride): mp: > 240°C (iPrOH/Et_2O); $C_{17}H_{18}FN_3S \cdot 2\ HCl \cdot 1.5\ H_2O$ (C, H, N, Cl, S). IR: 1607 (C=N), 1580 (C=C).

VI-2 oil: $C_{17}H_{18}FN_3S$ (MS). IR: 1595 (C=N), 1570 (C=C). UV (EtOH): 257.5 (14400), 297.5 (7900), 365 (1400).

(+)-10-Fluoro-1,2,3,4,4a,5-hexahydro-3-methyl-7-(2-thienyl)-pyrazino-[1,2-a][1,4]benzodiazepine ***IV-1a*** *and the corresponding (—) enantiomer* ***IV-1b***

IV-1a and **IV-1b** are synthesized in a way analogous to that used for **IV-1**, by reaction of **II-1a** and **II-1b** with methylamine.

IV-1a: yield: 65.2%; mp: 128—129°C (EtOH); $C_{17}H_{18}FN_3S$ (C, H, N, S). $[\alpha]_D^{22} = +359.7°$ (c = 1, MeOH). The optical purity of **IV-1a** was determined by HPLC to be ⩾ 99.5%.

IV-1b: yield: 71.2%; mp: 128—129°C (EtOH); $C_{17}H_{18}FN_3S$ (C, H, N, S). $[\alpha]_D^{22} = -356.3°$ (c = 1, MeOH). The optical purity of **IV-1b** was determined by HPLC to be ⩾ 95%.

HPLC analysis on column LKB Enantiopac, 100 × 4 mm, mobile phase: 0.008 M NaH_2PO_4, 0.008 M Na_2HPO_4, 0.1 M NaCl, 0.5% iPrOH, aqueous solution, adjusted to pH 5.3; flow rate: 0.3 ml/min; detection wavelength: 230 nm (0.08 absorbance units); sample size: 10 µl, respectively, 2 µg; detection limits: 0.5% **IV-1b** in **IV-1a**, 5% **IV-1a** in **IV-1b**.

8-Fluoro-1,2,3,4,4a,5-hexahydro-3-methyl-7-(2-thienyl)-pyrazino[1,2-a]-[1,4]benzodiazepine ***IV-3*** *and 7-fluoro-1,2,3,3a,10a,10b-hexahydro-3-methyl-6-(2-thienyl)-4H-pyrazino[1,2,3-a,b][1,5]benzodiazocine* ***VI-3***

20.9 g of **II-3** were reacted with methylamine, as described for **II-1**. 19.7 g (78.1%) of **IV-3** were obtained as its hydrogenmaleate. From the mother liquor of the crystallization, 150 mg of **VI-3** were isolated as base by preparative TLC with cyclohexane/EtOAc/EtOH (70/70/30) as the eluent. **VI-3** crystallizes as its dihydrochloride.

IV-3 (hydrogenmaleate): mp: 175—177°C (iPrOH/EtOH); $C_{17}H_{18}FN_3S \cdot C_4H_4O_4$ (C, H, N, S). IR: 1710 (C=O), 1610 (C=N), 1590, 1570 (C=C). UV (alk. EtOH): 237.5 (19800), 255 sh (13400), 292.5 (7700), 340 sh (1800). UV (EtOH): 235.5 (19400), 260 sh (10500), 295 (9200).

VI-3 (dihydrochloride): mp: 205—216°C (iPrOH/Et_2O); $C_{17}H_{18}FN_3S \cdot 2\ HCl \cdot 2\ H_2O$ (C, H, N, Cl, S). IR: 1605 (C=N), 1565 (C=C). UV (alk. EtOH): 245 sh (13800), 262.5 (18400), 297 (9900), 350 sh (1100).

10-Fluoro-1,2,4,4a-tetrahydro-7-(2-thienyl)-5H-[1,4]oxazino[4,3-a][1,4]-benzodiazepine ***V-1***

A solution of 17.5 g of **II-1** in 90 ml of dioxan was heated with 240 ml of an aqueous solution of NaOH (5%) under reflux for 6 h. The product was isolated according to the standard procedure and purified by CC on Al_2O_3 with CH_2Cl_2 as eluent.

V-1: yield: 8 g (54%); mp: 144—145°C, $C_{16}H_{15}FN_2OS$ (C, H, N, S). IR: 1610 (C=N), 1580, 1570 (C=C). UV (EtOH): 240 (16300), 280 sh (9000), 340 sh (1700).

Method 2

N_1-(2-Fluorophenyl)-N_4-methyl-2-hydroxymethyl-piperazine ***X-1***

37.5 g of **VII-1** were added dropwise to 20.6 g of epichlorohydrine and 0.5 ml of water at 20—25°C during 1 h. Subsequently, the temperature was kept at 25—30°C for 5 h. The product **VIII-1** showed less polarity than **VII-1** in TLC (cyclohexane/EtOAc/EtOH, 70/70/30).

Without isolation, the reaction mixture was treated with a solution of 10.7 g of NaOH in 19.8 ml of water at rt for 16 h. The reaction mixture was dissolved in CH_2Cl_2 and the epoxide **IX-1** isolated according to the standard procedure. The crude reaction product was refluxed in 300 ml of iPrOH for 16 h. After evaporation of the organic solvent, **X-1** was separated by CC on Al_2O_3 with CH_2Cl_2 as the eluent.

X-1: yield: 27.6 g (55.2%); mp: 106—107°C (iPrOH); $C_{12}H_{17}FN_2O$ (C, H, N).

N_1-(2-Fluorophenyl)-N_4-methyl-2-(N-phthalimidomethyl)-piperazine ***XII-1***

10.5 g of methanesulfonylchloride were added dropwise to a chilled solution of 18.0 g of **X-1** in 100 ml of pyridine. After 1.5 h, the crude reaction product **XI-1** was precipitated as its hydrochloride by adding Et_2O. 23 g of **XI-1** were obtained according to the standard procedure. **XI-1** was reacted without further purification with 13.4 g of potassium phthalimide in 100 ml of DMF at 100°C for 2 h. The solvent was evaporated and **XII-1** was isolated according to the standard procedure.

XII-1: yield: 17.7 g (62.4%); mp: 168—170°C (iPrOH); $C_{20}H_{20}FN_3O_2$ (C, H, N). IR: 1765, 1710 (CO—N—CO), 1605 (C=C).

2-(2-Thienylcarbonylaminomethyl)-1-(2-fluorophenyl)-4-methylpiperazine ***XIV-1***

18.5 g of **XII-1** were refluxed with 3.1 g of hydrazine hydrate in 100 ml of EtOH for 7 h. The cooled solution was acidified with conc. HCl and the precipitated phthalhydrazide filtered off. After evaporation of the filtrate, the amine **XIII-1** was isolated according to the standard procedure. Without further purification, 11.1 g of isolated **XIII-1** and 5.6 g of triethylamine were reacted with 7.3 g of 2-thienylcarbonylchloride in 100 ml of CH_2Cl_2 at rt for 2 h and **XIV-1** was isolated according to the standard procedure.

XIV-1: yield: 14.3 g (81.9%); mp: 111—112°C (Et_2O); $C_{17}H_{20}FN_3OS$ (C, H, N). IR: 3260 (NH), 1620 (CON), 1550 (C=C).

XIV-1 (dihydrochloride): mp: 189—192°C (EtOH); $C_{17}H_{20}FN_3OS \cdot 2\ HCl$ (C, H, N, Cl, S).

11-Fluoro-1,2,3,4,4a,5-hexahydro-3-methyl-7-(2-thienyl)-pyrazino[1,2-a]-[1,4]benzodiazepine ***IV-4***

11.3 g of **XIV-1** (base) were refluxed with 7.1 g of PCl_5 in 100 ml of CH_2Cl_2 for 3 h. The solvent was evaporated and the residue heated with 9.1 g of $AlCl_3$ in 80 ml of nitrobenzene at 80°C for 16 h. To the cooled solution, 100 g of ice were added and the product was isolated from the aqueous layer according to the standard procedure. Purification by CC with CH_2Cl_2/EtOH as the eluent, yielded 6.7 g (62.8%) of **IV-4**. The dihydrochloride crystallized from EtOH/Et_2O.

IV-4 (dihydrochloride): mp: > 240°C; $C_{17}H_{18}FN_3S \cdot 2\ HCl \cdot H_2O$ (C, H, N, Cl, S). IR: 1620 (C=N), 1600, 1570 (C=C). UV (alk. EtOH): 239 (13000), sh 257 (11000), 290 (6400), 350 (1000).

11-Methyl-1,2,3,4,4a,5-hexahydro-3-methyl-7-(2-thienyl)-pyrazino[1,2-a][1,4]benzodiazepine ***IV-5***

IV-5 was obtained according to the preparation of **IV-4**.

X-2: yield relative to **VII-2**: 63.7%; bp_1: 142—145°C, $C_{13}H_{20}N_2O$ (C, H, N).

XII-2: yield relative to **X-2**: 46.8%; mp: 122—124°C (Et_2O); $C_{21}H_{23}N_3O_2$ (C, H, N). IR: 1770, 1710 (CO—N—CO), 1600 (C=C).

XIV-2: yield relative to **XII-2**: 86.7%; mp: 146—147°C (iPrOH); $C_{18}H_{23}N_3OS$ (C, H, N, S). IR: 3260 (NH), 1640 (CON), 1550 (C=C).

IV-5 (dihydrochloride): yield relative to **XIV-2**: 37.3%; mp: 235—238°C (iPrOH; dec.); $C_{18}H_{21}N_3S \cdot 2\ HCl \cdot H_2O \cdot 0.25$ iPrOH (C, H, N, S, Cl). IR: 1640 (C=N), 1580 (C=C). UV (alk. EtOH): 252 (15400), sh 293 (7600), sh 350 (1200).

11-Methoxy-1,2,3,4,4a,5-hexahydro-3-methyl-7-(2-thienyl)pyrazino[1,2-a][1,4]benzodiazepine ***IV-6***

IV-6 was obtained according to the protocol used for the preparation of **IV-4**.

X-3: yield: 25.2% relative to **VII-3**; mp: 104—105°C (Et_2O), $C_{13}H_{20}N_2O_2$ (C, H, N).

XII-3: yield: 62% relative to **X-3**; mp: 137—138°C (Et_2O); $C_{21}H_{23}N_3O_3$ (C, H, N). IR: 1770, 1715 (CO—N—CO), 1615, 1590 (C=C).

XIV-3 (dihydrochloride): yield: 67% relative to **XII-3**; mp: 205—207°C (iPrOH); $C_{18}H_{23}N_3O_2S \cdot 2\ HCl \cdot H_2O$ (C, H, N, Cl, S). IR: 3230 (NH), 1635 (CON), 1600 (C=C).

IV-6: yield: 32.3% relative to **XIV-3**; mp: 126—128°C (Et_2O/PE); $C_{18}H_{21}N_3OS$ (C, H, N, S). IR: 1595 (C=N, C=C), 1575 (C=C). UV (EtOH): 252.5 (16600), sh 288 (10800), 348 (1500).

Biological tests

Inhibition of pentetrazole-induced convulsions
Convulsion inhibition was measured according to Blum *et al.* [16]. Male NMRI mice, $n = 10$/dose, body weight 19—25 g, were treated orally with test compounds suspended in an aqueous solution of 2% tylose® MH50 (methyl-hydroxyethyl-cellulose) and 0.2% Tween® 80 (polyoxyethylene-sorbitan-monooleat). Pentetrazole (100 mg/kg $= ED_{100}$; dissolved in distilled water) was given subcutaneously 60 min after administration of test compounds. Mice were then observed for 45 min for the occurrence of clonic convulsions. The dose of the test compound which reduced the number of mice affected by convulsions to 50% (ED_{50}) as compared to a tylose®/pentetrazole-treated control group was calculated by probit analysis.

Inhibition of apomorphine induced climbing
Inhibition was measured according to Protais *et al.* [17]. Male NMRI mice, $n = 10$/dose, body weight 18—28 g, were treated orally with test compounds suspended in an aqueous solution of 2% tylose® MH50 and 0.2% Tween® 80. Apomorphine (1 mg/kg $= ED_{100}$; dissolved in distilled water) was given subcutaneously 60 min after administration of the test compounds. Immediately after apomorphine injection, each mouse was placed individually inside an upright standing wire—mesh cylinder (diameter 13 cm; height 16 cm; top closed). Climbing behavior was rated 10, 20 and 30 min after apomorphine administration, according to the following scoring system: 0 = no paw at the grid; 1 = 1 or 2 paws touch the grid; 2 = 3 or all paws grasp the grid or animal climbs. The total score/dose group for all test times (max. 60 points) was used for calculation of *ED* values. ED_{50} was defined as the dose which reduced this total score to 50% compared to a vehicle/apomorphine-treated control group. *ED* values were calculated by probit analysis.

Dopamine-D_2 receptor affinity
Affinity for central dopamine-D_2 receptors was determined according to Creese *et al.* [18]; affinity for central benzodiazepine receptors according to Moehler and Okada [19]. All compounds were tested at at least 4 concentrations, each in triplicate. IC_{50} values were obtained by log—probit analysis of the displacement percentages. From these, k_i values were calculated with the Cheng—Prusoff equation: $k_i = IC_{50}/(I + S/K_d)$ in which S represents the concentration of the [^{3}H]-label, and K_d its equilibrium dissociation constant.

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