NEW TETRACYCLIC DERIVATIVES OF IMIDAZO-[1,5-*a*][1,4]BENZODIAZEPINES AND OF IMIDAZO-[1,5-*a*]THIENO[3,2-*f*][1,4]DIAZEPINES

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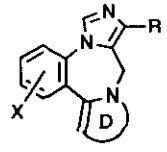
Dedicated to Prof. Arnold Brossi on the occasion of his 70th birthday

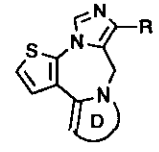
Abstract - The synthesis of new tetracyclic 1,4-diazepine derivatives is described. In these compounds, an additional five-membered heterocycle is fused on the known tricyclic ring systems imidazo[1,5-*a*][1,4]benzodiazepine and imidazo[1,5-*a*]thieno[3,2-*f*][1,4]diazepine. Many of these new compounds display a very high affinity to the benzodiazepine receptor in mammals.

Introduction

In the search for appropriate ligands of the benzodiazepine receptor with anxiolytic activity devoid of sedative effects and with optimal duration of action, we synthesized new tetracyclic compounds of general structure (**I**)and(**II**).



I



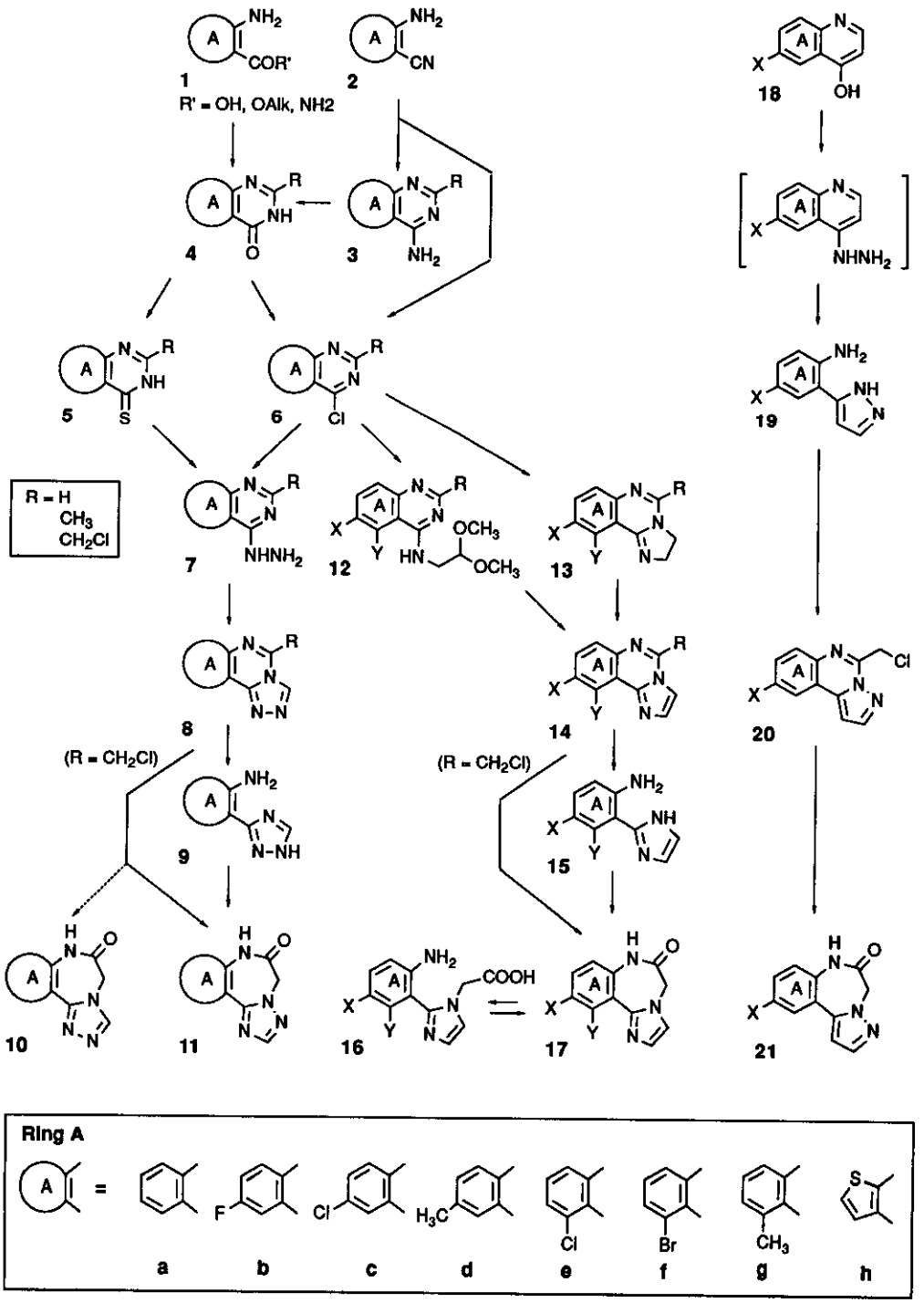
II

These compounds are characterized by an additional heterocyclic ring D (1,2,4-triazole, imidazole or pyrazole). In the following, we report on the synthesis of selected examples of several ring systems studied (for more examples, see ref.[1]).

Synthesis of tricyclic benzo- and thienodiazepinones (10, 11, 17 and 21)

Tricyclic 1,4-benzodiazepinone and thieno[3,2-*f*][1,4]diazepinone derivatives in which the diazepine ring is annelated with 1,2,4-triazole rings on the 4,5-bond have previously been described[2-5] Breuer[2] took advantage of a quinazoline-diazepine rearrangement to prepare compounds (**10a**, **10c**, **11a** and **11c**) (Scheme 1).

Scheme 1. Synthesis of the tricyclic benzo- and thienodiazepinones (**11**, **17** and **21**)



He started from the 4-chloro-2-chloromethylquinazolines (**6a** and **6c**, R = CH_2Cl) and built up the fused triazole ring by reacting them successively with hydrazine and trialkyl orthoformate. He reported that the rearrangement of **8a** or **8c** (R = CH_2Cl) with sodium hydroxide afforded a mixture of the isomeric triazolobenzodiazepinones (**10** and **11**, a and c) with **11** being the major product. In our hands, however, **11** was practically the only reaction product and **10** was obtained in such small amounts (less than 5 %) that a synthesis of **10** by this route was not convenient. Triazolo[4,3-*d*]benzodiazepinones of type (**10**), carrying an alkyl or an arylalkyl group on N-6, have been synthesized by Vogt *et al.*[3] and Wade *et al.*[4] following another route. However, this approach was not useful for our purposes, since we needed N-6-unsubstituted tricyclic benzodiazepinones. For the synthesis of substituted thienotriazolodiazepinones of type (**11h**), Shishoo *et al.*[5] used a route similar to that of Breuer.

Compounds (**4**, **6**, **7** and **8**) where R is a chloromethyl group are skin irritants. The use of those irritating intermediates could be avoided by performing the synthesis sequence with compounds carrying a hydrogen or a methyl group instead of the chloromethyl group. Subsequently, the triazoloquinazolines (**8**) were easily hydrolysed to the corresponding ring-open compounds (**9**). Condensing these compounds with chloroacetyl chloride and cyclising the chloroacetyl intermediate under alkaline conditions afforded **11** (in some cases together with small amounts of **10**) in yields comparable to those achieved by the direct rearrangement from **8** (R = CH_2Cl) to **11**.

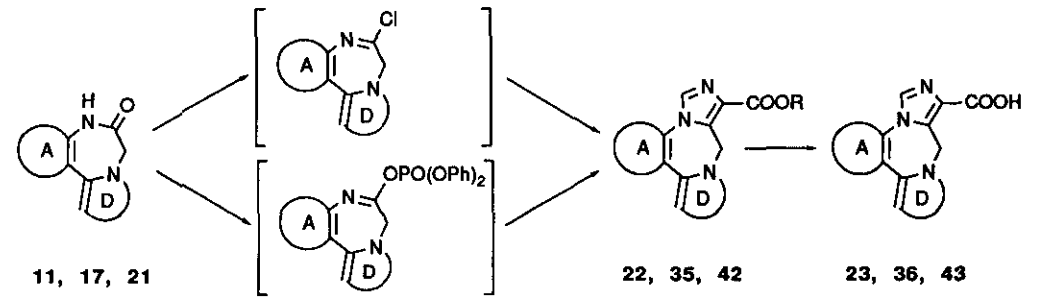
We prepared the new imidazo[1,2-*d*]benzodiazepinones (**17**) by following a similar pathway, where compounds (**6**) were reacted with 2-aminoacetaldehyde acetals instead of hydrazine; the relatively unstable intermediates (**12**) were in most cases cyclised without purification to the imidazo[1,2-*c*]quinazolines (**14**). Normally, acetic acid was used as cyclising agent; however, in the case of **12e** and **12g**, no cyclisation occurred with acetic acid and polyphosphoric acid was used. **6f** did not react with 2-aminoacetaldehyde acetal, possibly because of steric hindrance by the bromine atom. However, we were able to react **6f** with 2-bromoethylamine to yield the dihydro intermediate (**13**), which was then dehydrogenated using manganese dioxide to afford **14**. The transformation of **14** into **17** was conducted in two different ways as described above for the triazolo compounds. Compounds (**14**) with R = CH_2Cl were directly reacted with sodium hydroxide yielding **17**, compounds with R = H or CH_3 were first hydrolysed to **15**, and then reacted with chloroacetyl chloride under basic conditions. Under the strongly basic conditions described for the rearrangement of **14** to **17**, we observed a partial hydrolysis of the seven-membered ring to the amino acids (**16**). Ring closure of **16** to **17** was easily done with trifluoroacetic acid.

The synthesis of the pyrazolo[1,5-*d*]benzodiazepinones (**21**) started from 4-quinolinols (**18**). Heating the latter with hydrazine hydrate, a transposition to the 2-(3-pyrazolyl)anilines (**19**) occurred, as described by Alberti[6] and by de Stevens *et al.*[7] **19** was reacted with chloroacetyl chloride and cyclised, under acidic conditions, to the pyrazolo[1,5-*c*]quinazolines (**20**). The ring enlargement of **20** to **21** proceeded in a similar manner as described above for **11** and **17**.

Synthesis of the tetracyclic imidazo[1,5-*a*][1,4]diazepinecarboxylic acids (23, 32, 36 and 43)

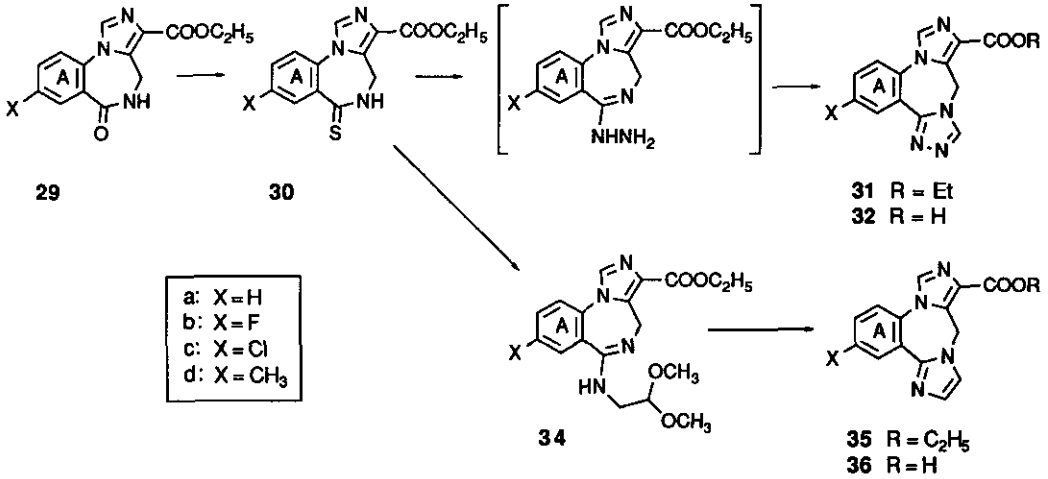
As shown in Scheme 2, the annelation of the tricyclic lactams (**11**, **17** and **21**) to the tetracyclic alkyl imidazo-[1,5-*a*][1,4]diazepinecarboxylates (**22**, **35** and **42**) was achieved by reaction of an activated form of these lactams with the anion of an isocyanoacetic ester, using a method first described by Walser and Fryer.[8]

Scheme 2. Annelation of the tricyclic benzo- and thienodiazepinones (**11**, **17** and **21**) with isocyanoacetic esters



The tetracyclic imidazo[1,5-*a*][1,2,4]triazolo[4,3-*d*][1,4]diazepines (**31**) were synthesized by another route (Scheme 3): the tricyclic imidazobenzodiazepinone esters (**29**)[9] were reacted with Lawesson's reagent in pyridine, producing the corresponding thiolactams (**30**). **30** was successively treated with hydrazine hydrate and then with trialkyl orthoformates providing the triazolo derivatives (**31**). The use of 2-aminoacetaldehyde acetals instead of hydrazine and cyclisation of the intermediates (**34**) with acetic acid led to the diimidazo esters (**35**).

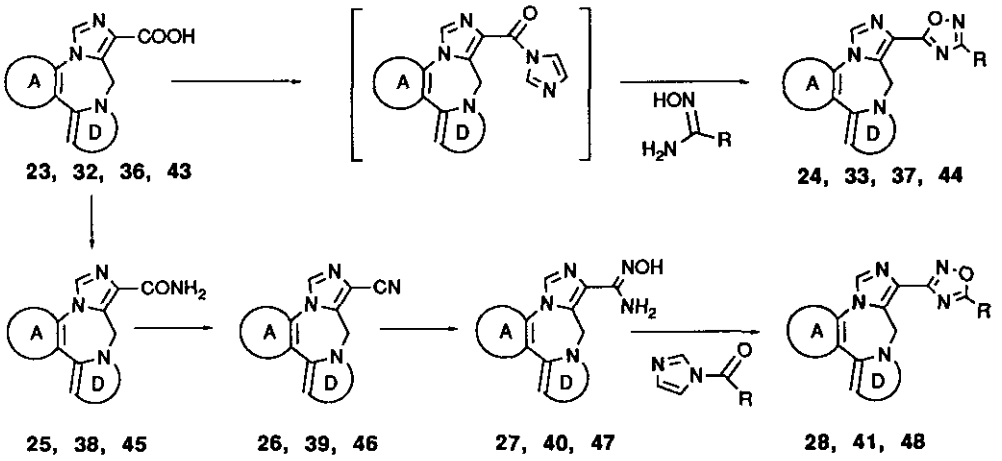
Scheme 3. Fusing a heterocyclic ring D (1,2,4-triazole or imidazole) on tricyclic imidazobenzodiazepinones (**29**)

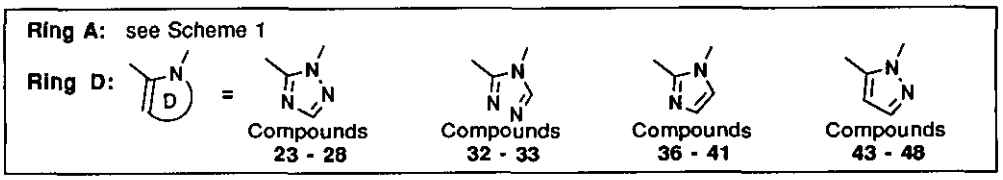


Synthesis of the oxadiazole rings, final compounds (24, 33, 37, 44, 28, 41 and 48)

The transformation of the acids (**23, 32, 36** and **43**) into the corresponding oxadiazolyl derivatives was achieved by known procedures (Scheme 4). Both isomeric substitutions with oxadiazole (**24, 33, 37, 44** and **28, 41, 48** respectively) were prepared, the key step being in both cases the reaction of an amidoxime with the imidazolide of a carboxylic acid.

Scheme 4. Synthesis of the 5- and the 3-(1,2,4)-oxadiazolyl rings from carboxylic acids





Conclusion

By the routes described above, we achieved the synthesis of new tetracyclic benzodiazepine and thienodiazepine derivatives. Most of them fulfilled our expectations regarding affinity to the benzodiazepine receptor and pharmacological profile.[a]

a) The final compounds (**24, 37, 44, 28, 41, 48**) are very good ligands to the BZR. Suprisingly, in contrast to the the [1,5-*d*]triazolo derivatives (**24**), the isomeric [4,3-*d*]triazolo derivatives (**33**) had a clearly lower affinity. Many of these compounds showed the desired pharmacological profile of a partial agonist at the benzodiazepine receptor.

EXPERIMENTAL

Melting points are not corrected. ^{1}H-Nmr spectra were recorded in $CDCl_3$ at 250 MHz. Chemical shifts are given in ppm relative to TMS. Mass spectra were recorded at 70 eV ionizing voltage. Ms spectra are presented as m/z (% rel. int.). Ir spectra were taken in KBr on a Nicolet FT IR apparatus. Abbreviations: r.t. means room temperature.

Starting materials: 2-amino-6-chlorobenzonitrile (**2e**), 2-amino-6-methylbenzonitrile (**2g**) and 4-quinolinol (**18a**) are commercially available.

The following compounds were prepared by literature methods: 2-amino-5-fluorobenzamide (**1b**, R' = NH_2),[10] methyl 2-amino-5-methylbenzoate (**1d**, R' = OMe),[11] 2-aminothiophene-3-carbonitrile (**2h**),[12] 6-fluoroquinazolin-4(3*H*)-one (**4b**, R = H),[13] 5-bromoquinazolin-4(3*H*)-one (**4f**),[14] 5*H*-[1,2,4]triazolo[1,5-*d*][1,4]benzodiazepin-6(7*H*)-one (**11a**) and 10-chloro-5*H*-[1,2,4]triazolo[1,5-*d*][1,4]benzodiazepin-6(7*H*)-one (**11c**),[2] 7-fluoroquinolin-4-ol (**18b**),[15] ethyl 5,6-dihydro-6-oxo-4*H*-imidazo[1,5-*a*]benzodiazepine-3-carboxylate (**29a**) and its 8-fluoro (**29b**), 8-chloro (**29c**) and 8-methyl (**29d**) analogs.[9]

Quinazolines and thienopyrimidines (6 and 12)

2-Chloromethyl-6-methylquinazolin-4(3*H*)-one (4d, R = CH_2Cl). A weak stream of dry HCl was introduced at 5° to 15°C for 8 h into a solution of methyl 2-amino-5-methylbenzoate (**1d**, R' = OCH_3, 91.4 g, 533 mmol) and chloroacetonitrile (23.4 ml, 372 mmol) in 1.0 l of abs. dioxane. After 4 h, further chloroacetonitrile (23.4 ml, 372 mmol) was added and the mixture stirred at r.t. for 18 h. The solvent was then evaporated in vacuo. The crystalline residue was suspended in 2.5 l of ice/water, adjusted to pH 8 to 9 with 25% NH_4OH and stirred at 5°C for 1 h. The crystals were filtered off, washed with water and dried, affording **4d** (R = CH_2Cl, 114.1 g, 98 %), mp 263-265°C. Anal. Calcd for $C_{10}H_9N_2OCl$: C 57.57, H 4.35, N 13.43. Found: C 57.66, H 4.35, N 13.13.

2,5-Dimethylquinazolin-4(3*H*)-one (4g, R = CH_3). A weak stream of dry HCl was introduced over 8 h at 5° to 7°C into a solution of 2-amino-6-methylbenzonitrile (**2g**, 26.5 g, 200 mmol) and acetonitrile (8.8 g, 214 mmol) in 300 ml of abs. dioxane. The mixture was then stirred at r.t. for 15 h. After cooling to 5°C, further acetonitrile (4.4 g, 107 mmol) was added, dry HCl was introduced for 8 h, and the mixture was stirred at r.t. for a further 15 h. The solvent was then removed under reduced pressure at 30°C. The crystalline residue was triturated with 280 ml of water, cooled below 5°C, neutralized with saturated $NaHCO_3$, filtered off, washed and dried, affording crude 4-amino-2,5-dimethylquinazoline (**3g**, R = CH_3, 42.8 g) containing some inorganic salts. (A sample recrystallized from EtOH melted at 198-199°C. (Anal. Calcd for $C_{10}H_{11}N_3$: C 69.34, H 6.40, N 24.26. Found C 69.15, H 6.44, N 24.21). 42 g of the crude **3g** (R = CH_3) were heated in 1.0 l of 6N HCl at 95°C for 20 h. The mixture was concentrated in vacuo and then neutralized with saturated $NaHCO_3$. The crystals were filtered off, washed with water and dried, affording **4g** (R = CH_3, 34 g, 90 %) mp 255-257°C (after recrystallisation in MeOH). Anal. Calcd for $C_{10}H_{10}N_2O$: C 68.95, H 5.79, N 16.08. Found: C 68.96, H 5.74, N 16.02.

In a similar manner, **2-chloromethyl-6-fluoroquinazoline-4(3*H*)-one (4b, R = CH_2Cl)**, mp 244-245°C (recryst. from ethyl acetate), was obtained in 64 % yield from 2-amino-5-fluorobenzamide (**1b, R' = NH_2**) by reacting with chloroacetonitrile and HCl. Anal. Calcd for $C_9H_6N_2OClF$: C 50.84, H 2.84, N 13.18. Found: C 50.66, H 3.09, N 13.13.

4-Chloro-2-(chloromethyl)thieno[2,3-*d*]pyrimidine (6h, R = CH_2Cl). A weak stream of dry HCl was bubbled into a solution of 2-aminothiophene-3-carbonitrile (**2h**, 17.3 g, 139 mmol) and chloroacetonitrile (13.3 g, 324 mmol) in abs. dioxane (1.5 l) at 5°C for 7 h. The mixture was stirred at r.t. for 15 h and then evaporated at 35°C in vacuo. The crystalline residue was triturated with 500 ml of ice-cold water, the crystals were filtered off, washed and dried, affording crude **6h** (R = CH_2Cl, 26.2 g). Yield: 85 %. A sample was recrystallized from hexane; mp 66-68°C. Anal. Calcd for $C_7H_4N_2Cl_2S$: C 38.38, H 1.84, N 12.79. Found C 38.36, H 2.01, N 12.76.

In a similar manner, **4,5-dichloro-2-chloromethylquinazoline (6e, R = CH_2Cl)**, mp 140-143°C (cryst. from Et_2O), was obtained in 72 % yield from 2-amino-6-chlorobenzonitrile (**2e**). Ms: 250, 248, 246 (16 / 50 / 52, M^+), 215, 213, 211 (14 / 66 / 100, M-Cl), 178, 176 (7.5 / 22), 138, 136 (5 / 19). Ir: 1598, 1564, 1542, 1479 (aromatic and heteroaromatic rings).

5-Bromo-4-chloroquinazoline (6f, R = H). *N,N*,4-Trimethylaniline (106 ml, 337 mmol) and $POCl_3$ (41 ml, 448 mmol) were added at r.t. to a suspension of **4f** (R = H, 33 g, 147 mmol) in $CHCl_3$ (1.2 l). The mixture was stirred at reflux for 16 h, then cooled and poured into 5 l of saturated $NaHCO_3$ and stirred for 30 min. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4 and chromatographed over silicagel (2 kg). First, *N,N*,4-trimethylaniline was eluted with CH_2Cl_2 and CH_2Cl_2/ethyl acetate 98:2, then **6f** (R = H, 29.0 g, 81 %) with CH_2Cl_2/ethyl acetate 9:4. After recrystallisation from Et_2O/iPr_2O, **6f** (R = H) melted at 124-126°C. Anal. Calcd for $C_8H_4N_2BrCl$: C 39.46, H 1.66, N 11.51. Found: C 39.60, H 1.70, N 11.53.

Table: Compounds (6), prepared from **4** in a similar manner to **6f**

Compound	R =	Reaction solvent	Conditions time (h)/ temp.(°C)	Yield (%)	mp (°C) (recryst. solvent)	Molecular formula	Microanalyses (%) C Calcd / Found	H Calcd / Found	N Calcd / Found
6b	CH_2Cl	$CHCl_3$	24 h / reflux	84	123-124 (iPr_2O)	$C_9H_5N_2Cl_2F$	46.78 / 46.71	2.18 / 2.11	12.12 / 12.00
6d	CH_2Cl	$CHCl_3$	24 h / reflux	81	111-112 (AcOEt)	$C_{10}H_8N_2Cl_2$	52.89 / 52.87	3.55 / 3.51	12.34 / 12.24
6g	CH_3	$CHCl_3$	20 h / reflux	73	76-77 (Et_2O/hexane)	$C_{10}H_9N_2Cl$	a)		

a) Ms: 194, 192 (7 / 22, M^+), 157 (100, M-Cl), 116 (13).
Ir: 1606, 1586, 1479 (aromatic and heteroaromatic rings).

6-Fluoro-quinazoline-4(3*H*)-thione (5b, R = H). Crude **4b** (R = H, 2.7 g, 16.4 mmol) and 2,4-bis(4-methoxyphenyl)-2,4-dithioxo-1,3,2,4-dithiophosphetane ("Lawesson's reagent", 7.5 g, 18.5 mmol) were stirred in pyridine (50 ml) for 8 h at 110°C bath temperature. The mixture was concentrated in vacuo, the residue taken up with saturated $NaHCO_3$ (80 ml) and stirred at r.t. for 30 min. The mixture was cooled to 15°C, the crystals were filtered off, washed with ice-cold water and dried, affording crude **5b** (R = H). After recrystallization from ethyl acetate, yellow crystals of **5b** (R = H, 2.8 g, 95 %) mp 294-297°C, were obtained. Anal. Calcd for $C_8H_5N_2FS$: C 53.32, H 2.80, N 15.55. Found: C 53.06, H 2.80, N 15.28.

Compounds (8, 14 and 20)

5-Chloromethyl-9-fluoro-1,2,4-triazolo[4,3-*c*]quinazoline (8b, R = CH_2Cl). To a cooled suspension of **6b** (R = CH_2Cl, 5.7 g, 247 mmol) in absolute THF (80 ml), a solution of hydrazine hydrate (2.4 ml, 484 mmol) in THF (10 ml) was added dropwise at 10-15°C within 5 min. A solution resulted thereby and the temperature rose to 20°C. The reaction mixture was stirred at r.t. for 3 h and then poured into a stirred mixture of saturated $NaHCO_3$ (150 ml) and $CHCl_3$. The crystals were filtered off, washed with water and dried. 4.8 g of **7b** (R = CH_2Cl) were obtained. The $CHCl_3$ phase of the filtrate was separated and the aqueous phase was extracted with $CHCl_3$. By evaporation of the organic phases, further **7b** (R = CH_2Cl, 0.6 g) was obtained. Total yield: 5.4 g of crude **7b** (R = CH_2Cl), which was suspended in ethyl orthoformate (150 ml) and refluxed for 1 h, then cooled and concentrated in vacuo. The precipitate was filtered off, yielding crude **8b** (R = CH_2Cl, 2.2 g). The filtrate was evaporated to dryness in vacuo and the residue crystallised from ethanol and diethyl ether, yielding a further 2.9 g of **8b** (R = CH_2Cl). Total yield: 5.1 g (87 %). A sample was recrystallized from EtOH, affording pure **8b** (R = CH_2Cl) mp 183°C (decomp.). Anal. Calcd for $C_{10}H_6N_4ClF$: C 50.76, H 2.56, N 23.68. Found: C 50.64, H 2.51, N 23.51.

Table: Compounds (8), prepared from **6** in a similar manner to **8b**

Compound	R =	Reaction solvent	Conditions time (h)/ temp.(°C)	Yield (%)	mp (°C) (recryst. solvent)	Molecular formula	Microanalyses (%) C Calcd / Found	H Calcd / Found	N Calcd / Found
8d	CH_2Cl	1) THF 2) HC(OEt)3	4 h / 15° 0.5 h / reflux	92	175 ($HC(OEt)_3/Et_2O$)	$C_{11}H_9N_4Cl$	56.78 57.04	3.90 4.10	24.00 23.80
8e	CH_2Cl	1) THF 2) HC(OEt)3	1.5 h / r.t. 0.5 h / reflux	76	184-186 ($CHCl_3$/EtOH)	$C_{10}H_6N_4Cl_2$ a)			
8h	CH_2Cl	1) THF 2) HC(OEt)3	3.5 h / r.t. 1.5 h / reflux	66	>120 decomp. (AcOEt)	$C_8H_5N_4ClS$	42.77 42.83	2.24 2.14	24.94 24.66

a) Ms: 256, 254, 252 (11 / 65 / 100, M^+), 219, 217 (5 / 14.5, M-Cl).
Ir: 1624, 1550, 1476 (aromatic & heteroaromatic rings).

9-Fluoro-1,2,4-triazolo[4,3-*c*]quinazoline (8b, R = H). To a suspension of 2.9 g (16.1 mmol) of crude **5b** in THF (75 ml), hydrazine hydrate (7.9 ml, 160 mmol) was added at r.t. while stirring. After about 15 min, a solution resulted for a short time, then a precipitate appeared. The mixture was stirred at r.t. for 3 h,

triethyl orthoformate (75 ml, 450 mmol) was then added and the THF was distilled off. The residual suspension was stirred at reflux temperature for 3 h. The solvent was removed in vacuo and the residue taken up in H_2O (300 ml), stirred at r.t. for 1 h, and then cooled to 15°C. The crystals were filtered off. Crude **8b** (R = H, 2.9 g) and, after recrystallization from ethanol, pure **8b** (R = H, 2.4 g, 80 %), mp 193-195°C, was obtained. Anal. Calcd for $C_9H_5N_4F$: C 57.45, H 2.68, N 29.78. Found: C 57.44, H 2.62, N 29.88.

5-Chloromethylimidazo[1,2-*c*]quinazoline (14a, R = CH_2Cl). To a suspension of **6a** (R = CH_2Cl, 88 g, 413 mmol) in THF (1 l), 2,2-dimethoxyethylamine (92 ml, 849 mmol) was added while stirring at 10°C. The mixture was stirred at r.t. for 2.5 h and then cooled to 0°C. The crystals were filtered off, the solvent was evaporated in vacuo and the residue taken up in ethyl acetate (3 l). An insoluble constituent was filtered off and the filtrate was evaporated in vacuo. The residue (containing **12a**, R = CH_2Cl) was heated in acetic acid (1.2 l) to 100°C for 3 h and then concentrated in vacuo. The residue was partitioned between $CHCl_3$ and saturated $NaHCO_3$. The $CHCl_3$ extract was chromatographed over silica gel. **14a** (R = CH_2Cl) was eluted with $CHCl_3$/EtOH 99.5:0.5. The eluates were crystallized from ether, affording **14a** (R = CH_2Cl, 30.2 g, 33 %) of mp 153-154°C. Anal. Calcd for $C_{11}H_8N_3Cl$: C 60.70, H 3.70, N 19.31. Found: C 60.77, H 3.97, N 19.36.

In a similar manner, **5-chloromethyl-9-fluoroimidazo[1,2-*c*]quinazoline (14b, R = CH_2Cl)**, mp 171-172°C (recryst. from ethyl acetate), was obtained in 36 % yield from **6b**. Anal. Calcd for $C_{11}H_7N_3ClF$: C 56.07, H 2.99, N 17.83. Found: C 55.75, H 3.12, N 17.69.

5,10-Dimethylimidazo[1,2-*c*]quinazoline (14g, R = CH_3). To a suspension of crude **6g** (R = CH_3, 12.8 g, 66 mmol) in THF (300 ml), 2,2-dimethoxyethylamine (17.4 ml, 160 mmol) was added at 5°C while stirring. The mixture was stirred at r.t. for 24 h, then further 2,2-dimethoxyethylamine (5 ml, 46 mmol) was added and the mixture stirred again for 40 h. The solvent was removed in vacuo and the residue partitioned between $CHCl_3$ and saturated $NaHCO_3$. $CHCl_3$ was evaporated in vacuo and the residue (21 g) chromatographed over silica gel (150 g). 4-(2,2-Dimethoxyethylamino)-2,5-dimethylquinazoline (**12g**, R = CH_3) was eluted with ethyl acetate. After recrystallization from hexane, **12g** (R = CH_3, 16.3 g, 94 %), mp 48-49°C, was obtained. 15.8 g (64.1 mmol) of **12g** (R = CH_3) were heated in polyphosphoric acid (300 g) at 155°C for 24 h, and then poured into a mixture of ice and aqueous 25% NH_4OH. The mixture was extracted four times with $CHCl_3$. $CHCl_3$ was evaporated in vacuo, affording crude **14g** (R= CH_3, 12.1 g). Chromatography through siliga gel (280 g), elution with dichloromethane and recrystallization from ethyl acetate afforded pure **14g** (R = CH_3, 10.1 g, 85% from **12g**), mp 159°C. Anal. Calcd for $C_{12}H_{11}N_3$: C 73.07, H 5.62, N 21.30. Found: C 73.08, H 5.77, N 21.51.

In a similar manner, **10-chloro-5-chloromethylimidazo[1,2-*c*]quinazoline (14e, R = CH_2Cl)**, mp 171-172°C (recryst. from ethyl acetate), was obtained in 66 % yield from **6e** (R = CH_2Cl). Anal. Calcd for $C_{11}H_7N_3Cl_2$: C 52.41, H 2.80, N 16.67. Found: C 52.21, H 2.99, N 16.66.

10-Bromo-2,3-dihydroimidazo[1,2-*c*]quinazoline (13f, R = H) A solution of **6f** (R = H, 5.63 g, 23.1 mmol) in THF (300 ml) was treated with $NaHCO_3$ (10.5 g, 125 mmol) and 2-bromoethylamine hydrobromide (5.76 g, 27.5 mmol) and stirred at r.t. for 66 h. The mixture was evaporated in vacuo and the residue was stirred in 300 ml of water. The crystals were filtered off, washed with water and dried, affording **13f** (R = H, 5.7 g, 98 %). After recryst. from ethyl acetate: mp 180-181°C. Anal. Calcd for $C_{10}H_8N_3Br$: C 48.02, H 3.22, N 16.80. Found: C 48.04, H 3.29, N 16.77.

10-Bromoimidazo[1,2-*c*]quinazoline (14f, R = H). MnO_2 (242 g, 2.78 mol) was added to a hot solution of **13f** (22 g, 88 mmol) in benzene (2 l) in a reaction vessel which was provided with a water separator. The mixture was heated at reflux for 15 h. Further MnO_2 (8 g, 9.2 mmol) was then added and the mixture was heated again at reflux for 1 h. The hot reaction mixture was filtered through Dicalite. The filter cake was rinsed with hot benzene (1 l), then again boiled up in 1.5 l of CH_2Cl_2/EtOH 199:1 and again filtered. The filtrate was concentrated to about 1.5 l in vacuo. A byproduct crystallized, which was filtered off (1.65 g). The filtrate was chromatographed over a column of silicagel (2 kg). 12.0 g of **14f** (R = H) were eluted with CH_2Cl_2/ethanol 99:1. After crystallization from AcOEt/Et_2O, 11.7 g (53 %) of **14f** (R = H), mp 214-216°C, were obtained. Anal. Calcd for $C_{10}H_6N_3Br$: C 48.42, H 2.44, N 16.94. Found: C 48.47, H 2.53, N 16.85.

2-(2*H*-Pyrazol-3-yl)aniline (19a). A mixture of 4-quinolinol (**18a**, 10.0 g, 82.5 mmol) and hydrazine hydrate (30 g, 100%, 0.6 mol) was heated to 170°C in an autoclave for 6 h. After cooling, the reaction mixture was dissolved in aqueous 3N HCl (total volume of the solution about 300 ml, pH about 1). The mixture was then made slightly alkaline (pH about 9) with 25% NH_4OH. The separated crystals were filtered off and dried, affording **19a** (8.0 g, 73 %) mp 122-123°C. Anal. Calcd for $C_9H_9N_3$: C 67.90, H 5.70, N 26.40. Found: C 67.93, H 5.47, N 26.50.

In an analogous manner, **4-fluoro-2-(2*H*-pyrazol-3-yl)aniline (19b)**, mp 91-92°C, was obtained in 33 % yield from 6-fluoro-4-quinolinol (**18b**). Anal. Calcd for $C_9H_8N_3F$: C 61.01, H 4.55, N 23.72. Found: C 61.08, H 4.41, N 23.66.

5-Chloromethylpyrazolo[1,5-*c*]quinazoline (20a). To a solution of **19a** (8.6 g, 54 mmol) in THF (800 ml), K_2CO_3 (75.3 g, 545 mmol) was added. After cooling to 5°C, a solution of chloroacetyl chloride (6.7 ml, 84 mmol) in ether (40 ml) was added dropwise within 10 min. After stirring at 5°C for 30 min, a further solution of chloroacetyl chloride (0.67 ml, 8.4 mmol) in ether (5 ml) was again added dropwise, and the mixture was stirred for a further 15 min. An insoluble constituent was filtered off, the filtrate evaporated in vacuo and the residue partitioned between saturated $NaHCO_3$ and CH_2Cl_2. The aqueous phase was extracted several times with CH_2Cl_2. The organic extracts were dried over Na_2SO_4 and evaporated in vacuo. The residue was taken up in 0.4 N HCl in dioxane (560 ml) and stirred at 90°C for 1 h. The solution was evaporated in vacuo and the residue was partitioned between saturated $NaHCO_3$ and CH_2Cl_2. The CH_2Cl_2 extract was evaporated in vacuo, affording **20a** (11.4 g, 97 %). After recrystallization from diisopropyl ether, the mp was 135-136°C. Anal. Calcd for $C_{11}H_8N_3Cl$: C 60.70, H 3.70, N 19.31. Found: C 60.89, H 3.61, N 19.25.

In an analogous manner, **5-chloromethyl-9-fluoropyrazolo[1,5-*c*]quinazoline (20b)**, mp 155-157°C, was obtained in 96 % yield from **19b**. Anal. Calcd for $C_{11}H_7N_3ClF$: C 56.07, H 2.99, N 17.83. Found: C 56.06, H 2.92, N 17.74.

2) Synthesis of 11, 17 and 21

10-Fluoro-5*H*-[1,2,4]triazolo[1,5-*d*][1,4]benzodiazepin-6(7*H*)-one (11b). 4.72 g (20 mmol) of **8b** (R = CH_2Cl) were dissolved in hot dioxane (140 ml). The solution was cooled to 10°C and then added to a mixture of 1N NaOH (40 ml) and dioxane (20 ml) in such a manner that the temperature rose to about 15°C. The mixture was stirred at r.t. for 45 min and then poured into 1.4 l of ice-cold water, and made neutral with 3N HCl. The solution was extracted with $CHCl_3$ (5 times). The solvent was washed with brine and evaporated in vacuo. The residue (4.35 g) was dissolved in AcOEt (250 ml) and chromatographed through silica gel (200 g). **11b** (3.7 g, 85 %) was eluted with mixtures of hexane and AcOEt 1:1 and 4:6. After recrystallization from AcOEt, **11b** melted at 243-245°C. Anal. Calcd for $C_{10}H_7N_4OF$: C 55.05, H 3.23, N 25.68. Found C 55.00, H 2.97, N 25.76.

Table: Compounds (11), prepared from **8** (R = CH_2Cl) in a similar manner to **11b**

Compound	Reaction solvent	Conditions time (h)/ temp.(°C)	Yield (%)	mp (°C) (recryst. solvent)	Molecular formula	Microanalyses (%) C Calcd / Found	H Calcd / Found	N Calcd / Found
11d	dioxane / 1 N NaOH	24 h / r.t.	62	206-208 (AcOEt)	$C_{11}H_{10}N_4O$	61.67 / 61.54	4.71 / 4.84	26.15 / 26.15
11e	dioxane / 1 N NaOH	10 h / r.t.	61	280-282	$C_{10}H_7N_4OCl$	a)		
11h	dioxane / 1 N NaOH	60 h / r.t.	48	260 (EtOH)	$C_8H_6N_4OS$	46.59 / 46.28	2.93 / 3.01	27.17 / 26.95

a) Ms: 236, 234 (33 / 100, M^+), 207, 205 (16 / 44, M - ·COH), 179 (51) 152 (42).
Ir: 1682 (C=O), 1599, 1575, 1495 (aromatic and heteroaromatic rings).

10-Fluoro-5*H*-[1,2,4]triazolo[1,5-*d*][1,4]benzodiazepin-6(7*H*)-one (11b). 5.0 g (30.5 mmol) of **8b** (R = H) were stirred in 6N HCl (90 ml) at 95°C for 1 h. After cooling to 5°C, the solution was poured into 25% NH_4OH (65 ml) and stirred in an ice bath for 10 min. The crystals were filtered off, washed with ice-cold water and dried, affording 4-fluoro-2-(1*H*-1,2,4-triazol-3-yl)aniline (**9b**, 4.35 g), mp 142.5-144.5°C (a sample recrystallized from water melted at 145-146°C).

A solution of **9b** (4.3 g, 24.1 mmol) in dioxane (200 ml) and abs. pyridine (2.3 ml) was cooled to 12°C. A solution of chloroacetyl chloride (2.2 ml, 27.6 mmol) in ether (8 ml) was then added dropwise within 5 min at 12° to 15°C. The mixture was stirred at 10° to 12°C for 15 min and then treated within 5 min with aqueous 2N NaOH (28.8 ml). The mixture was stirred at r.t. overnight. The pH thereby dropped to about 9. The mixture was adjusted to pH 8 with 3N HCl and evaporated at about 40°C in vacuo. The residue was stirred at 15°C for 30 min in 150 ml of water and 5 ml of ethyl acetate. The crystals were filtered off, washed with cold water and dried, affording **11b** (3.78 g, 65 % from **8b**, R = H), mp 232.5-238°C. This substance was

identical with **11b** obtained from **8b** (R = CH_2Cl). Further substance could be obtained from the aqueous phase as follows: it was evaporated to dryness in vacuo and the residue stirred in 10 ml of trifluoroacetic acid at r.t. overnight. The mixture was evaporated in vacuo, the residue was stirred at r.t. for 1 h in saturated Na_2CO_3 (60 ml) and ethyl acetate (2 ml). The crystals were filtered off, yielding further 0.5 g of **11b**. The mother liquor contained small amounts of **10b**, which was crystallised from EtOH; mp 325-326°C. Anal. Calcd for $C_{10}H_7N_4OF$: C 55.05, H 3.23, N 25.68. Found: C 55.06, H 3.02, N 25.50.

5*H*-Imidazo[1,2-*d*][1,4]benzodiazepin-6(7*H*)-one (17a). A solution of **14a** (R = CH_2Cl, 21.4 g, 98.3 mmol) in dioxane (500 ml) was added dropwise at 15°C to a mixture of 1N NaOH (197 ml) and dioxane (100 ml). The reaction mixture was stirred at r.t. for 2.5 h, then poured into 4 l of brine and extracted several times with $CHCl_3$. The dried $CHCl_3$ extracts were evaporated in vacuo and the residue (18.5 g) recrystallized from ethanol-ether, yielding **17a** (15.0 g, 76 %) of mp 265-266°C. Anal. Calcd for $C_{11}H_9N_3O$: C 66.32, H 4.55, N 21.09. Found: C 66.21, H 4.80, N 21.06.

Table: Compounds (17 and 21), prepared from **14** and **20** in a similar manner to **17a**

Compound	Reaction solvent	Conditions time (h)/ temp.(°C)	Yield (%)	mp (°C) (recryst. solvent)	Molecular formula	Microanalyses (%) C Calcd / Found	H Calcd / Found	N Calcd / Found
17b	dioxane / 1 N NaOH	4 h / r.t.	22	282-283 (AcOEt)	$C_{11}H_8N_3OF$	60.83 / 60.65	3.71 / 3.70	19.53 / 19.26
17e	dioxane / 1 N NaOH	24 h / r.t.	97	176-177 (AcOEt/Et2O)	$C_{11}H_8N_3OCl$	56.54 / 56.69	3.45 / 3.67	17.98 / 18.11
21a	dioxane / 1 N NaOH	2.5 h / r.t.	40	239-240 (EtOH)	$C_{11}H_9N_3O$	66.32 / 66.10	4.55 / 4.52	21.09 / 21.05
21b	dioxane / 1 N NaOH	2.75 h / r.t.	61	258-260 (EtOH)	$C_{11}H_8N_3OF$	60.83 / 60.69	3.71 / 3.84	19.35 / 19.39

3-Bromo-2-(1*H*-imidazol-2-yl)aniline (15f). A suspension of **14f** (R = H, 11.6 g, 46.7 mmol) was stirred in 6N HCl (170 ml) at 90°C for 6.5 h and then cooled in an ice bath. The solution was poured into a mixture of 25% NH_4OH (30 ml) and ice (50 g) and stirred for 10 min. The crystals were filtered off, washed with water and dried, affording **15f** (9.85 g). The aqueous phase was saturated with NaCl and extracted three times with $CHCl_3$. Further **15f** (1.5 g) was obtained after concentration of the organic extracts. Total yield: 11.35 g (~100 %). After recrystallization from water, **15f** melted at 164-165°C. Anal. Calcd for $C_9H_8N_3Br$: C 45.40, H 3.39, N 17.65. Found: C 45.46, H 3.41, N 17.58.

11-Bromo-5*H*-imidazo[1,2-*d*][1,4]benzodiazepin-6(7*H*)-one (17f). A solution of chloroacetyl chloride (2.4 ml, 30.1 mmol) in ether (10 ml) was added dropwise at 5°C within 15 min to a solution of crude **15f** (6.0 g, 24.2 mmol) in dioxane (150 ml) and pyridine (6.1 ml, 75 mmol). The mixture was stirred at 5°C for 10 min and then again, a solution of chloroacetyl chloride (0.25 ml, 3.1 mmol) in ether (5 ml) was added.

The mixture was stirred at 10° to 12°C for a further 30 min, then treated within 5 min with a mixture of 1N NaOH (75 ml) and dioxane (150 ml). The mixture was stirred at r.t. for 45 min, then poured into 1 l of water and extracted four times with $CHCl_3$. The $CHCl_3$ extracts were evaporated in vacuo. The oily residue was crystallized from CH_2Cl_2/ether. 0.99 g of **17f** of mp 234-235°C was obtained. The aqueous phase was evaporated to dryness in vacuo. The residue (containing **16f**) was dissolved in trifluoroacetic acid (150 ml) and left at r.t. for 16 h. The mixture was evaporated in vacuo and the residue was partitioned between saturated $NaHCO_3$ and $CHCl_3$. The residue from the $CHCl_3$ extracts was crystallized from CH_2Cl_2/ether, affording further 3.37 g of **17f**. Total yield 4.36 g (62 %). Anal. Calcd for $C_{11}H_8N_3OBr$: C 47.51, H 2.90, N 15.11. Found: C 47.66, H 3.15, N 14.86.

In a similar manner, **11-methyl-5*H*-imidazo[1,2-*d*][1,4]benzodiazepin-6(7*H*)-one (17g)**, was obtained in 61 % yield from **15g**. The intermediate 3-methyl-2-(1*H*-imidazol-2-yl)aniline (**15g**), mp 193-194°C, was reacted without purification with chloroacetyl chloride in dioxane and pyridine, followed by 1N NaOH to yield **17g**, mp 188-189°C (recrystallized from AcOEt). Anal. Calcd for $C_{12}H_{11}N_3O$: C 67.59, H 5.20, N 19.71. Found: C 67.51, H 5.24, N 19.82.

Imidazo[1,5-a]diazepine esters (22, 35 and 42) from tricyclic lactams (11, 17 and 21)

***tert*-Butyl 9*H*-Imidazo[1,5-*a*][1,2,4]triazolo[1,5-*d*][1,4]benzodiazepine-10-carboxylate (22a, R = tBu).** $POCl_3$ (23 ml, 251 mmol) was added to a suspension of **11a** [4] (16 g, 80 mmol) in $CHCl_3$ (1 l) and *N,N*,4-trimethylaniline (60 ml, 417 mmol) and the mixture refluxed for 16.5 h. A further 12 ml (83.4 mmol) of *N,N*,4-trimethylaniline and 4 ml (43.6 mmol) of $POCl_3$ were added and the mixture was refluxed for a further 1.5 h. The mixture was cooled, then poured into saturated $NaHCO_3$ (1 l) and stirred intensively for 30 min. The aqueous phase was separated and extracted with $CHCl_3$ (2 x 0.5 l). The combined $CHCl_3$ extracts were evaporated, leaving a mixture of 6-chloro-5*H*-[1,2,4]triazolo[1,5-*d*][1,4]benzodiazepine and *N,N*,4-trimethylaniline, which was dissolved in THF (100 ml) (Solution A).

A solution of *tert*-butyl isocyanoacetate (15.3 g, 108.4) in THF (40 ml) was cooled to -25°C. 13.4 g (119.4 mmol) of potassium *tert*-butylate were added (Solution B). Solution B was stirred at -10°C for 1 h, and then cooled to -60°C. Solution A, obtained as described above, was added to solution B, whereby the temperature rose to -15°C. The mixture was stirred at r.t. for a further 2.5 h and then poured into 5 l of brine. The mixture was extracted four times with $CHCl_3$. The solvent was removed in vacuo, the residue dissolved in $CHCl_3$ and chromatographed over silica gel. Elution with $CHCl_3$/EtOH (99.8:0.2 to 99:1) gave crude **22a** (R = tBu, 18.6 g). After recrystallization from ethyl acetate, pure **22a** (R = tBu, 15.1 g, 58 %), mp 247-249°C (decomp.), was obtained. Anal. Calcd for $C_{17}H_{17}N_5O_2$: C 63.15, H 5.30, N 21.66. Found: C 62.92, H 5.42, N 21.68.

Table: Compounds (22, R = tBu), prepared from **11** in a similar manner to **22a** (R = tBu)

Compound	R =	Reaction solvent	Conditions time (h)/ temp.(°C)	Yield (%)	mp (°C) (recryst. solvent)	Molecular formula	Microanalyses (%) C Calcd Found	H Calcd Found	N Calcd Found
22b	tBu	1) $CHCl_3$ 2) THF 1.5 h / r.t.	17 h / reflux start at -65°	58	192-193 (AcOEt/iPr_2O)	$C_{17}H_{16}N_5O_2F$	59.82 59.83	4.72 4.66	20.52 20.35
22c	tBu	1) $CHCl_3$ 2) DMF 1.5 h / r.t.	22 h / reflux start at -50°	30	217-218 (AcOEt)	$C_{17}H_{16}N_5O_2Cl$	57.07 57.08	4.51 4.39	19.57 19.52
22e	tBu	1) $CHCl_3$ 2) THF 2 h / r.t.	24 h / reflux start at -60°	34	271 (AcOEt)	$C_{17}H_{16}N_5O_2Cl$	57.07 57.12	4.51 4.64	19.57 19.45
22h	tBu	1) $CHCl_3$ 2) THF 2.5 h / r.t.	18 h / reflux start at -65°	69	217 (AcOEt)	$C_{15}H_{15}N_5O_2S$	54.70 54.56	4.59 4.80	21.26 21.22

Ethyl 3-Fluoro-9*H*-imidazo[1,5-*a*][1,2,4]triazolo[1,5-*d*][1,4]benzodiazepine-10-carboxylate (22b, R = ethyl). $POCl_3$ (12.5 ml, 136.5 mmol) was added to a suspension of **11b** (19.64 g, 90 mmol) in alcohol-free $CHCl_3$ (0.62 l) and *N,N*,4-trimethylaniline (32.8 ml, 228 mmol) and the mixture was refluxed for 24 h. Further *N,N*,4-trimethylaniline (6.6 ml, 45.8 mmol) and $POCl_3$ (2.5 ml, 27.3 mmol) were added and the mixture was refluxed for a further 7 h. The mixture was cooled to 30°C, poured into 1.3 l of 10% Na_2CO_3, stirred intensively for 45 min and then left to stand overnight. The $CHCl_3$ phase was separated. The aqueous phase was again extracted with 50 ml of $CHCl_3$ (alcohol-free). The combined $CHCl_3$ extracts were filtered through Dicalite and dried over 70 g of Na_2SO_4. About 650 ml of $CHCl_3$ were distilled off in vacuo at 35° to 40°C. The residual solution contained a mixture of 6-chloro-10-fluoro-5*H*-[1,2,4]triazolo[1,5-*d*][1,4]benzodiazepine and *N,N*,4-trimethylaniline (Solution A).

A solution of ethyl isocyanoacetate (11.3 g, 100 mmol) in THF (2.5 l) was stirred under argon and cooled to -25°C. KOtBu (11.4 g, 101 mmol) was added thereto, in portions, below -10°C. This suspension was stirred at -10°C for 45 min and then cooled to -65°C. The previously obtained solution A was added within 15 to 30 min at -35° to -30°C. The mixture was then stirred at 20°C for a further 1 h. Acetic acid (3.8 ml) was added, the mixture stirred for a further 15 min and then poured into a mixture of 1.0 l of 5% $NaHCO_3$ and 0.2 l of ethyl acetate. After standing overnight, the crystals were filtered off, washed successively with AcOEt (50 ml), with H_2O (100 ml) and with AcOEt (50 ml) and dried, yielding **22b** (13.65 g, R = Et, 48 %) of mp 254-258°C. A further 0.57 g of **22b** (R = ethyl) of mp 259-260°C could be obtained from the organic and aqueous phases. Anal. Calcd for $C_{15}H_{12}N_5O_2F$: C 57.51, H 3.86, N 22.35. Found: C 57.38, H 4.12, N 22.12.

Table: Compounds (22, R = Et), prepared from **11** in a similar manner to **22b** (R = Et)

Compound	R =	Reaction solvent	Conditions time (h)/ temp.(°C)	Yield (%)	mp (°C) (recryst. solvent)	Molecular formula	Microanalyses (%) C Calcd Found	H Calcd Found	N Calcd Found
22a	Et	1) $CHCl_3$ 2) THF 3 h / r.t.	20 h / reflux start at -60°	58	233-234 (EtOH)	$C_{15}H_{13}N_5O_2$	61.01 60.86	4.44 4.36	23.72 23.57
22c	Et	1) $CHCl_3$ 2) THF 2 h / r.t.	24 h / reflux start at -50°	56	255-256 (CH_2Cl_2/AcOEt)	$C_{15}H_{12}N_5O_2Cl$	54.64 54.49	3.67 3.63	21.24 21.14
22d	Et	1) $CHCl_3$ 2) THF 2 h / r.t.	20 h / reflux start at -50°	74	204-206 (AcOEt)	$C_{16}H_{15}N_5O_2$	62.13 62.32	4.89 4.94	22.64 22.81
22e	Et	1) $CHCl_3$ 2) THF 2 h / r.t.	14 h / reflux start at -60°	73	227-228 (AcOEt/EtOH)	$C_{15}H_{12}N_5O_2Cl$	54.64 54.77	3.67 3.60	21.24 21.20

Ethyl 1-Bromo-9*H*-diimidazo[1,5-*a*:1',2'-*d*][1,4]benzodiazepine-8-carboxylate (35f, R = ethyl). To a solution of ethyl isocyanoacetate (2.86 g, 52.3 mmol) in THF (120 ml), KOtBu (2.8 g, 25 mmol) was added at -15°C. The mixture was stirred at -10°C for 1 h. Separately, **17f** (5.56 g, 20.0 mmol) was dissolved in DMF (100 ml). NaH (0.85 g of an about 80% dispersion in mineral oil, about 28 mmol) was added at -15°C and the mixture stirred at -10°C for 1 h. The solution was cooled to -40°C, diphenylphosphoryl chloride (5.66 ml, 27.4 mmol) was added dropwise within 10 min, the mixture stirred at -40°C for 30 min and then cooled to -60°C. At this temperature, the previously prepared suspension of ethyl isocyanoacetate potassium salt was added. The cooling bath was then removed, the mixture stirred at r.t. for 2 h and then adjusted to pH 6 to 7 with acetic acid. The mixture was poured into 2 l of saturated $NaHCO_3$ and extracted four times with $CHCl_3$. The organic phases were washed once with saturated $NaHCO_3$, once with brine and then evaporated in vacuo. The residue was crystallized from AcOEt and diethyl ether, affording **35f** (R = ethyl, 4.8 g, 64 %) of mp 246-247°C. Anal. Calcd for $C_{16}H_{13}N_4O_2Br$: C 51.49, H 3.51, N 15.01. Found: C 51.57, H 3.52, N 14.89.

Table: Compounds (35 and 42, R = Et), prepared from **17** and **21** in a similar manner to **35f** (R = Et)

Compound	R =	Reaction solvent	Conditions time (h)/ temp.(°C)	Yield (%)	mp (°C) (recryst. solvent)	Molecular formula	Microanalyses (%) C Calcd Found	H Calcd Found	N Calcd Found
35a	tBu	DMF / THF	1) 1 h / -15° 2) -60° 3) 3 h / r.t.	45	188-190 (AcOEt / Et_2O / iPr_2O	$C_{18}H_{18}N_4O_2$	67.07 66.71	5.63 6.02	17.38 17.26

Table: Compounds (35 and 42, R = Et), prepared from **17** and **21** in a similar manner to **35f** (R = Et) (continued)

Compound	R =	Reaction solvent	Conditions time (h)/ temp.(°C)	Yield (%)	mp (°C) (recryst. solvent)	Molecular formula	Microanalyses (%) C Calcd / Found	H Calcd / Found	N Calcd / Found
35e	Et	DMF / THF	1) 1.5 h / -10° 2) -65° 3) 2 h / r.t.	44	213-215 (AcOEt)	$C_{16}H_{13}N_4O_2Cl$	58.45 / 58.36	3.99 / 3.78	17.04 / 16.79
35g	Et	DMF / THF	1) 2 h / -10° 2) -65° 3) 1 h / r.t.	76	220 (EtOH)	$C_{17}H_{16}N_4O_2$	66.22 / 65.97	5.23 / 5.36	18.17 / 18.03
42a	Et	DMF / THF	1) 2 h / -10° 2) -65° 3) 1 h / r.t.	66	180-182 ($AcOEt/Et_2O$)	$C_{16}H_{14}N_4O_2$	65.30 / 65.18	4.79 / 4.84	19.04 / 18.97
42b	Et	DMF / THF	1) 2.5 h / -14° 2) -60° 3) 2.5 h / r.t.	55	213-215 (AcOEt)	$C_{16}H_{13}N_4O_2F$	61.53 / 61.42	4.20 / 4.17	17.94 / 17.87

Imidazo[1,5-*a*]benzodiazepine esters (31 and 35) from 29

Ethyl 5,6-Dihydro-6-thioxo-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxylate (30a). A suspension of **29a** (10 g, 36.7 mmol) in pyridine (110 ml) was treated with 2,4-bis(4-methoxyphenyl)-2,4-dithioxo-1,3,2,4-dithiadiphosphetane ("Lawesson's reagent", 15 g, 37.1 mmol). The mixture was heated to 100°C for 48 h and then evaporated in vacuo. The residue was suspended in 120 ml of methanol and refluxed for 20 min. After cooling the crystals were filtered off, yielding crude **30a** (9.2 g, and after concentrating the filtrate, further 0.5 g). Recrystallization from ethanol gave pure **30a** (6.7 g, 63.5%), mp 273-274°C. Anal. Calcd for $C_{14}H_{13}N_3O_2S$: C 58.52, H 4.56, N 14.62. Found: C 58.37, H 4.58, N 14.65.

Table: Compounds (30), prepared from **29** in a similar manner to **30a**

Compound	Reaction solvent	Conditions time (h)/ temp.(°C)	Yield (%)	mp (°C) (recryst. solvent)	Molecular formula	Microanalyses (%) C Calcd / Found	H Calcd / Found	N Calcd / Found
30b	pyridine	120 h / 100°	80	302 decomp. (DMF/toluene)	$C_{14}H_{12}N_3O_2FS$	55.07 / 55.17	3.96 / 3.99	13.76 / 13.73
30c	pyridine	95 h / 100°	83	285-287 (DMF/toluene)	$C_{14}H_{12}N_3O_2ClS$	52.26 / 52.42	3.76 / 3.85	13.06 / 13.18

Table: Compounds (30), prepared from **29** in a similar manner to **30a** (continued)

Compound	Reaction solvent	Conditions time (h)/ temp.(°C)	Yield (%)	mp (°C) (recryst. solvent)	Molecular formula	Microanalyses (%) C Calcd Found	H Calcd Found	N Calcd Found
30d	pyridine	72 h / 100°	90	274-275 (AcOEt)	$C_{15}H_{15}N_3O_2S$	59.78 59.69	5.02 5.19	13.94 13.95

29c, mp 286-288 and **29d**, mp 277-279°C, were prepared in an analogous manner to that described for **29a.**[9]

Ethyl 3-Fluoro-9*H*-imidazo[1,5-*a*][1,2,4]triazolo[4,3-*d*][1,4]benzodiazepine-10-carboxylate (31b, R = Et). To a suspension of **30b** (15.4 g, 50.4 mmol) in THF (1 l), hydrazine hydrate (12.3 ml, 248 mmol) was added, and the mixture was refluxed for 20 h. The resulting solution was cooled to -10°C and ether (500 ml) was added. The crystals were filtered off, washed and dried. Ethyl 8-fluoro-6-hydrazino-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxylate (12.8 g), mp 232-233°C was obtained. By concentrating the mother liquor to about 150 ml and adding 150 ml of ether, further 1.8 g could be isolated.
Ethyl 8-fluoro-6-hydrazino-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxylate (14.6 g, 48.1 mmol) was suspended in ethanol (850 ml) and triethyl orthoformate (25 ml, 150 mmol) was added. The mixture was refluxed for 14 h. Charcoal was then added and the mixture filtered through Dicalite. The filtrate was concentrated to 150 ml and the crystals filtered off, washed and dried, yielding **31b** (R = Et, 12.1 g, 76 %) mp 233-234°C. Anal. Calcd for $C_{15}H_{13}N_5O_2F$: C 57.51, H 3.86, N 22.35. Found: C 57.27, H 3.60, N 22.25.

In an analogous manner, **ethyl 9*H*-imidazo[1,5-*a*][1,2,4]triazolo[4,3-*d*][1,4]benzodiazepine-10-carboxylate (31a**, R = Et), mp 263-264°C, was obtained in 42 % yield from **30a.** Anal. Calcd for $C_{15}H_{13}N_5O_2$: C 61.01, H 4.44, N 23.72. Found: C 60.72, H 4.83, N 23.61.

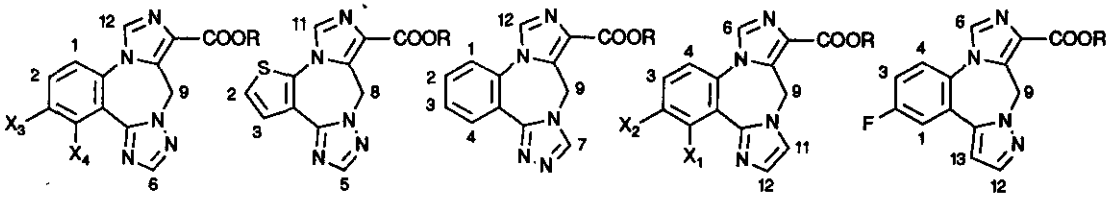
In an analogous manner, **ethyl 3-chloro-9*H*-imidazo[1,5-*a*][1,2,4]triazolo[4,3-*d*][1,4]benzodiazepine-10-carboxylate (31c**, R = Et), mp 226-227°C, was obtained in 70 % yield from **30c.** Anal. Calcd for $C_{15}H_{12}N_5O_2Cl$: C 54.64, H 3.67, N 21.24. Found: C 54.29, H 3.84, N 21.07.

Ethyl 2-Fluoro-9*H*-diimidazo[1,5-*a*:1',2'-*d*][1,4]benzodiazepine-8-carboxylate (35b, R = Et). A suspension of **30b** (30.0 g, 98.2 mmol) in 2,2-dimethoxyethylamine (150 ml, 1.38 mol) was stirred at 95°C for 57 h. The mixture was filtered from unreacted starting material (3.6 g) and the filtrate was evaporated in vacuo. The residue was dissolved in acetic acid (450 ml) and heated to 105°C for 2.5 h. The reaction mixture was evaporated in vacuo and the residue was partitioned between $CHCl_3$ and saturated $NaHCO_3$. The organic phases were washed with brine, dried and evaporated in vacuo. The residue was chromatographed through silica gel. **35b** (R = Et) was eluted with $CHCl_3$/EtOH 99.5:0.5 and crystallized from ethyl acetate, affording **35b** (R = Et, 9.2 g, 34 %) mp 213-215°C. Anal. Calcd for $C_{16}H_{13}N_4O_2F$: C 61.53, H 4.20, N 17.94. Found: C 61.66, H 4.29, N 18.13.

Table: Compounds (35, R = Et), prepared from 30 in a similar manner to 35b

Com- pound	R =	Reaction solvent	Conditions time (h)/ temp.(°C)	Yield (%)	mp (°C) (recryst. solvent)	Molecular formula	Microanalyses (%) C Calcd Found	H Calcd Found	N Calcd Found
35c	Et	AcOH	2 h / 100°	17	228-229 (AcOEt)	$C_{16}H_{13}N_4O_2Cl$	58.45 58.41	3.99 4.16	17.04 16.86
35d	Et	AcOH	69 h / 100°	64	221-222 (CH_2Cl_2/AcOEt)	$C_{17}H_{16}N_4O_2$	66.22 65.88	5.23 5.41	18.17 18.19

Table: ^{1}H-Nmr spectra of representative esters (**22, 31, 35** and **42**) ($CDCl_3$, 250 MHz)



22 a $X_3 = X_4 = H$ **22 h** **31 a** **35 b** $X_1 = H$, $X_2 = F$ **42b**
22 b $X_3 = F$, $X_4 = H$ **35 f** $X_1 = Br$, $X_2 = H$
22 e $X_3 = H$, $X_4 = Cl$ **35 g** $X_1 = CH_3$, $X_2 = H$

22a (R = tBu): δ 1.67 (9H, s, 3 C$\underline{H}_3$), 5.90 (2H, s, H-C(9)), 7.66 (3H, m, 3 arom. H), 7.88 (1H, s, H-C(12)), 7.98 (1H, s, H-C(6)), 8.20 (1H, m, arom. H).

22b (R = tBu): δ 1.66 (9H, s, 3 C$\underline{H}_3$), 5.70 (2H, s, H-C(9)), 7.40 (1H, m, H-C(2)), 7.62 (1H, m, H-C(1)), 7.84 (1H, s, H-C(12)), 7.90 (1H, m, H-C(4)), 7.97 (1H, s, H-C(6)).

22e (R = Et): δ 1.45 (3H, t, J = 7.1 Hz, -CH_2-C$\underline{H}_3$), 4.46 (2H, q, J = 7.1 Hz, -C$\underline{H}_2$-CH_3), 5.09 and 6.72 (2H, each d, J = 16 Hz, H-C(9)), 7.52 (1H, m, arom. H), 7.63 (1H, t, J = 8.0 Hz, H-C(2)), 7.75 (1H, m, arom. H), 7.86 (1H, s, H-C(12)), 8.07 (1H, s, H-C(6)).

22h (R = tBu): δ 1.66 (9H, s, 3 C$\underline{H}_3$), 5.93 (2H, s, H-C(9)), 7.29 and 7.57 (2H, each d, J = 5.5 Hz, H-C(2) and H-C(3)), 7.81 (1H, s, H-C(11)), 7.97 (1H, s, H-C(5)).

31a (R = Et): δ 1.46 (3H, t, J = 7.1 Hz, -CH_2-C$\underline{H}_3$), 4.46 (2H, q, J = 7.1 Hz, -C$\underline{H}_2$-CH_3), 5.75 (2H, broad, H-C(9)), 7.69 (3H, m, 3 arom. H), 7.89 (1H, s, H-C(12)), 8.33 (1H, m, arom. H), 8.36 (1H, s, H-C(7)).

35b (R = Et): δ 1.46 (3H, t, J = 7.1 Hz, -CH_2-C$\underline{H}_3$), 4.45 (2H, q, J = 7.1 Hz, -C$\underline{H}_2$-CH_3), 5.64 (2H, broad, H-C(9)), 7.18 and 7.21 (2H, each d, J = 0.4 Hz, H-C(11) and H-C(12)), 7.27 (1H, m, H-C(3)), 7.55 (1H, m, H-C(4)), 7.81 (1H, s, H-C(6)), 7.90 (1H, m, H-C(1)).

Table: ^{1}H-Nmr spectra of representative esters (**22, 31, 35** and **42**) ($CDCl_3$, 250 MHz)(continued)

35f (R = Et): δ 1.45 (3H, t, J = 7.1 Hz, $-CH_2-C\underline{H}_3$), 4.45 (2H, q, J = 7.1 Hz, $-C\underline{H}_2-CH_3$), 4.89 and 6.26 (2H, each d, J = 15.2 Hz, H-C(9)), 7.16 and 7.29 (2H, 2 s, H-C(11) and H-C(12)), 7.46 (2H, m, H-C(2) and H-C(3)), 7.80 (1H, s, H-C(6)), 7.92 (1H, m, H-C(4)).

35g (R = Et): δ 1.45 (3H, t, J = 7.1 Hz, $-CH_2-C\underline{H}_3$), 2.70 (3H, s, $C\underline{H}_3$-C(1)), 4.43 and 4.45 (2H, 2 q, J = 7.1 Hz, $-C\underline{H}_2-CH_3$), 4.83 and 6.21 (2H, each d, J = 15.1 Hz, H-C(9)), 7.11 and 7.21 (2H, AB, J = 1.1 Hz, H-C(11) and H-C(12)), 7.31 (1H, m, 1 arom H), 7.45 (2H, m, 2 arom. H), 7.79 (1H, s, H-C(6)).

42b (R = Et): δ 1.45 (3H, t, J = 7.1 Hz, $-CH_2-C\underline{H}_3$), 4.56 (2H, q, J = 7.1 Hz, $-C\underline{H}_2-CH_3$), 5.5 - 6.5 (2H, very broad, H-C(9)), 6.57 and 7.53 (2H, each d, J = 2.0 Hz, H-C(12) and H-C(13)), 7.27 (1H, m, 1 arom H), 7.42 (1H, m, 1 arom. H), 7.59 (1H, m, 1 arom. H), 7.83 (1H, s, H-C(6)).

Imidazo[1,5-*a*]diazepinecarboxylic acids (23, 32, 36 and 43) from 22, 31, 35 and 42)

9*H*-Imidazo[1,5-*a*][1,2,4]triazolo[1,5-*d*][1,4]benzodiazepine-10-carboxylic acid (23a). **22a** (R = tBu, 9.5 g, 29.4 mmol) was dissolved in trifluoroacetic acid (200 ml) and left to stand at r.t. for 5 h. The trifluoroacetic acid was evaporated in vacuo and the residue recrystallized from ethyl acetate, affording **23a** (7.5 g, 95 %) of mp 283-285°C (decomp.). Anal. Calcd for $C_{13}H_9N_5O_2$: C 58.43, H 3.39, N 26.21. Found: C 58.14, H 3.69, N 26.21.

Table: Compounds (23 and 36), prepared from **22** or **35** in a similar manner to **23a**

Compound	Reaction solvent	Conditions time (h)/ temp.(°C)	Yield (%)	mp (°C) (recryst. solvent)	Molecular formula	Microanalyses (%) C Calcd / Found	H Calcd / Found	N Calcd / Found
23h	CF_3COOH	2.5 h / r.t.	98	266-267 decomp. (AcOEt)	$C_{11}H_7N_5O_2S$	48.35 / 48.42	2.58 / 2.79	25.63 / 25.10 [a]
36a	CF_3COOH	3 h / r.t.	96	267-268 decomp. (H_2O)	$C_{14}H_{10}N_4O_2$	63.15 / 62.78	3.79 / 3.84	21.04 / 20.89

[a] Calc with 0.05 mol AcOEt: C 48.45, H 2.69, N 25.22.

3-Fluoro-9*H*-imidazo[1,5-*a*][1,2,4]triazolo[1,5-*d*][1,4]benzodiazepine-10-carboxylic acid (23b). To a solution of **22b** (R = Et, 17.0 g, 54.3 mmol) in hot abs. ethanol (0.5 l), a solution of NaOH (2.65 g, 66 mmol) in water (80 ml) was added and the mixture refluxed for 1 h. The solvent was removed in vacuo, the residue dissolved in water (0.5 l) and the solution acidified with conc. HCl (6.6 ml). The crystalline slurry was stirred at 10°C for 1 h and then filtered. The crystals were washed with ice-cold water and dried, affording **23b** (14.5 g, 94%) of mp 276°C (decomp). Anal. Calcd for $C_{13}H_8N_5O_2F$: C 54.74, H 2.83, N 24.55. Found: C 54.74, H 3.07, N 24.28.

Table: Compounds (23, 32, 36 and 43), prepared from **22, 31, 35** or **42** in a similar manner to **23b**

Compound	Reaction solvent	Conditions time (h)/ temp.(°C)	Yield (%)	mp (°C) (recryst. solvent)	Molecular formula	Microanalyses (%) C Calcd Found	H Calcd Found	N Calcd Found
23c	EtOH / H_2O	2.5 h / reflux	100	270-271 decomp. (H_2O)	$C_{13}H_8N_5O_2Cl$	51.76 51.66	2.67 2.89	23.21 22.89
23d	EtOH / H_2O	3 h / reflux	95	281-282 decomp. (H_2O)	$C_{14}H_{11}N_5O_2$	59.78 59.85	3.94 4.10	24.90 25.00
23e	EtOH / H_2O	2.5 h / reflux	96	277-279 decomp. (H_2O)	$C_{13}H_8N_5O_2Cl$	51.76 51.37	2.67 2.90	23.21 22.73
32a	EtOH / H_2O	4 h / reflux	99	256-257 decomp. (AcOEt/EtOH)	$C_{13}H_9N_5O_2$	58.43 57.45	3.39 3.98	26.21 a) 24.13
32b	EtOH / H_2O	1.5 h / reflux	100	272-273 decomp. (H_2O)	$C_{13}H_8N_5O_2F$	54.74 54.46	2.83 2.79	24.55 24.36
32c	EtOH / H_2O	2 h / reflux	100	282-283 decomp. (H_2O)	$C_{13}H_8N_5O_2Cl$	51.76 51.39	2.67 2.82	23.21 23.11
32d	EtOH / H_2O	1 h / reflux	100	276-277 decomp. (H_2O)	$C_{14}H_{11}N_5O_2$	59.78 59.61	3.94 4.31	24.90 24.99
36b	EtOH / H_2O	3 h / reflux	95	270-271 decomp. (H_2O)	$C_{14}H_9N_4O_2F$	59.16 58.94	3.19 3.31	19.71 19.70
36c	EtOH / H_2O	2 h / reflux	67	277-278 decomp. (H_2O)	$C_{14}H_9N_4O_2Cl$	55.92 55.27	3.02 3.23	18.63 18.31
36d	EtOH / H_2O	2 h / reflux	93	259-261 decomp. (H_2O)	$C_{15}H_{12}N_4O_2$	64.28 63.96	4.32 4.38	19.99 19.77
36e	EtOH / H_2O	2.5 h / reflux	97	300-302 decomp.	$C_{14}H_9N_4O_2Cl$	b)		
43a	EtOH / H_2O	0.75 h / reflux	95	257-258 decomp. (AcOEt)	$C_{14}H_{10}N_4O_2$	63.15 63.01	3.79 3.90	21.04 20.91
43b	EtOH / H_2O	1 h / reflux	98	258-260 decomp. (AcOEt)	$C_{14}H_9N_4O_2F$	59.16 59.03	3.19 3.02	19.71 19.43

a) Calcd with 0.5 mol EtOH: C 57.93, H 4.17, N 24.13. b) Ms: 302, 300 (33, 100, M^+), 284, 282 (14, 43, M - H_2O), 256 (72, M - CO_2), 254 (73, M - HCOOH), 228 (76). Ir: 2481, 1681, 1297, 1213 (-COOH).

Synthesis of 24, 33, 37 and 44

10-(3-Cyclopropyl-1,2,4-oxadiazol-5-yl)-3-fluoro-9*H*-imidazo[1,5-*a*][1,2,4]triazolo[1,5-*d*]-[1,4]benzodiazepine (24b, R = cyclopropyl). 1,1'-Carbonyldiimidazole (12.1 g, 74.6 mmol) was added to a suspension of **23b** (11.0 g, 38.5 mmol) in DMF (450 ml). After 15 to 30 min, a solution was obtained, whereafter the imidazolide of **23b** precipitated. Cyclopropanecarboxamidoxime (7.1 g, 70.8 mmol)

was then added and the mixture stirred at 80°C overnight. The solvent was removed, finally in high vacuum at 60°C. The residue was dissolved in acetic acid (250 ml) and stirred at 110°C for 2.5 h. The solution was evaporated to dryness in high vacuum. The residue was briefly suspended in hot ethyl acetate (80 ml), cooled to r.t. and poured slowly into 7% $NaHCO_3$ (200 ml). The mixture was stirred at r.t. for 1 h, the crystals filtered off, washed firstly with ethyl acetate (20 ml), then with water (2.0 l) and dried, affording **24b** (11.05 g, R = cyclopropyl) mp 215-218°C. By concentrating the organic phase and by chromatography of the residue, further **24b** (0.48 g, R = cyclopropyl) was obtained. Anal. Calcd for $C_{17}H_{12}N_7OF$: C 58.45, H 3.46, N 28.07. Found: C 58.37, H 3.67, N 28.03.

Table: Compounds (24, 33, 37 and 44), prepared from **23, 32, 36** and **43** in a similar manner to **24b**

Compound	R =	Reaction solvent Reactant	Conditions time (h)/ temp.(°C)	Yield (%)	mp (°C) (recryst. solvent)	Molecular formula	Microanalyses (%) C Calcd Found	H Calcd Found	N Calcd Found
24a	cPr [a]	1) DMF cPrC(NOH)NH_2	16 h / 80°	84	230-233 (AcOEt/ Et_2O)	$C_{17}H_{13}N_7O$	61.62 61.51	3.95 4.10	29.59 29.47
		2) AcOH	1.5 h / 110°						
24b	$(CH_2)_2OMe$								
		1) DMF 3-methoxypro-pionamide oxime	2 h / 90°	54	181-182 (AcOEt/ hexane)	$C_{17}H_{14}N_7O_2F$	55.58 55.63	3.84 3.81	26.69 26.72
		2) AcOH	2 h / 110°						
24c	cPr	1) DMF cPrC(NOH)NH_2	3 h / 70°	80	255-256 (AcOEt)	$C_{17}H_{12}N_7OCl$	55.82 55.77	3.31 3.35	26.81 26.60
		2) AcOH	2 h / 110°						
24d	cPr	1) DMF cPrC(NOH)NH_2	2 h / 90°	77	236-237 (AcOEt)	$C_{18}H_{15}N_7O$	62.60 62.56	4.38 4.48	28.39 28.44
		2) AcOH	3 h / 100°						
24e	cPr	1) DMF cPrC(NOH)NH_2	20 h / 80°	70	280-282 (EtOH)	$C_{17}H_{12}N_7OCl$	55.82 55.70	3.31 3.47	26.81 26.68
		2) AcOH	1 h / 100°						
24h	cPr	1) DMF cPrC(NOH)NH_2	16 h / 80°	65	219-220 (AcOEt)	$C_{15}H_{11}N_7OS$	53.40 53.11	3.29 3.43	29.06 29.09
		2) AcOH	1.5 h / 110°						
33a	cPr	1) DMF cPrC(NOH)NH_2	16 h / 80°	64	298-300 (EtOH /	$C_{17}H_{13}N_7O$	61.62 61.51	3.95 4.24	29.59 29.45
		2) AcOH	1.5 h / 110°		MeOH)				
33b	cPr	1) DMF cPrC(NOH)NH_2	2 h / 90°	73	253-254 (EtOH /	$C_{17}H_{12}N_7O_2F$	58.45 58.24	3.46 3.51	28.07 27.91
		2) AcOH	2 h / 110°		MeOH)				

[a] cPr = cyclopropyl

Table: Compounds (24, 33, 37 and 44), prepared from 23, 32, 36 and 43 in a similar manner to 24b (continued)

Compound	R =	Reaction solvent Reactant	Conditions time (h)/ temp.(°C)	Yield (%)	mp (°C) (recryst. solvent)	Molecular formula	Microanalyses (%) C Calcd Found	H Calcd Found	N Calcd Found
33c	cPr [a]	1) DMF cPrC(NOH)NH_2 2) AcOH	2 h / 90° 2 h / 110°	74	268-270 (EtOH)	$C_{17}H_{12}N_7OCl$	55.82 55.76	3.31 3.56	26.81 [b] 26.21
37a	cPr	1) DMF cPrC(NOH)NH_2 2) AcOH	16 h / 80° 2 h / 110°	63	224-226 (AcOEt)	$C_{18}H_{14}N_6O$	65.44 65.24	4.27 4.32	25.44 25.81
37b	cPr	1) DMF cPrC(NOH)NH_2 2) AcOH	16 h / 80° 1.5 h / 100°	73	226-227 (AcOEt)	$C_{18}H_{13}N_6OF$	62.07 62.04	3.76 3.85	24.13 24.00
37c	cPr	1) DMF cPrC(NOH)NH_2 2) AcOH	3 h / 90° 2 h / 110°	80	222 (EtOH)	$C_{18}H_{13}N_6OCl$	59.27 58.98	3.59 3.90	23.04 [c] 22.76
37d	cPr	1) DMF cPrC(NOH)NH_2 2) AcOH	2 h / 90° 3 h / 130°	73	270-271 (AcOEt)	$C_{19}H_{16}N_6O$	66.27 66.08	4.68 4.74	24.40 [d] 23.86
37e	cPr	1) DMF cPrC(NOH)NH_2 2) AcOH	20 h / 80° 1.5 h / 110°	63	247-248 (EtOH)	$C_{18}H_{13}N_6OCl$	59.27 59.01	3.59 3.44	23.04 22.90
44a	cPr	1) DMF cPrC(NOH)NH_2 2) AcOH	20 h / 80° 2.5 h / 110°	69	208-210 (AcOEt / EtOH)	$C_{18}H_{14}N_6O$	65.44 65.43	4.27 4.35	25.44 25.50
44b	cPr	1) DMF cPrC(NOH)NH_2 2) AcOH	16 h / 80° 4 h / 110°	70	217-218 (AcOEt)	$C_{18}H_{13}N_6OF$	62.07 61.86	3.76 3.79	24.13 23.98

[a] cPr = cyclopropyl. [b] Calcd with 0.18 mol EtOH: C 55.74, H 3.52, N 26.21. [c] Calcd with 0.1 mol EtOH: C 59.18, H 3.71, N 22.75. [d] Calcd with 0.18 mol AcOEt: C 66.06, H 4.76, N 23.96.

37f (R = cPr) from **35f (R = Et)**: **35f** (R = Et) was hydrolyzed to **36f** in the same manner as **22b** (R = Et) to **23b**. The acid **36f** (mp 304-306°C) was transformed without purification into **37f** (R = cPr) in a manner similar to that described above for **24b** from **23b**. Yield: 82% from **35f**. **37f (R = cPr)**: mp 243-244°C (recryst. from AcOEt). Anal. Calcd for $C_{18}H_{13}N_6OBr$: C 52.83, H 3.20, N 20.54. Found: C 52.86, H 3.28, N 20.48.

In a similar way, **37g (R = cPr)** was obtained in 69 % yield from **35g (R = ethyl). 37g (R = cPr)**: mp 200°C (recryst. from EtOH). Anal. Calcd for $C_{19}H_{16}N_6O$: C 66.27, H 4.68, N 24.40. Found: C 66.17, H 4.75, N 24.21.

Synthesis of 28, 41 and 48

9*H*-Imidazo[1,5-*a*][1,2,4]triazolo[1,5-*d*][1,4]benzodiazepine-10-carboxamide (25a). 1,1'-Carbonyldiimidazole (13.6 g, 83.8 mmol) was added to a solution of **23a** (10.9 g, 40.8 mmol) in DMF (700 ml). The mixture was stirred at r.t. for 4 h. and then 25% NH_4OH (485 ml) was added thereto. After stirring for 5 min, the solution was treated with water (1.2 l). The resulting precipitate was filtered off, washed with water and dried, affording **25a** (10.0 g, 92 %) of mp 324-329°C. Anal. Calcd for $C_{13}H_{10}N_6O$: C 58.64, H 3.79, N 31.56. Found: C 58.31, H 4.09, N 31.30.

Table: Compounds (25, 38 and 45), prepared from **23, 36** and **43** in a similar manner to **25a**

Compound	Reaction solvent	Conditions time (h)/ temp.(°C)	Yield (%)	mp (°C) (recryst. solvent)	Molecular formula	Microanalyses (%) C Calcd / Found	H Calcd / Found	N Calcd / Found
25b	1) DMF 2) conc. NH_4OH	3 h / r.t. 0.5 h / r.t.	97	340-343 (MeOH)	$C_{13}H_9N_6OF$	54.93 55.01	3.19 3.20	29.57 29.60
25c	1) DMF 2) conc. NH_4OH	3 h / r.t. 2 h / r.t.	95	>295 (DMF/H_2O)	$C_{13}H_9N_6OCl$	51.92 52.29	3.02 3.18	27.95 27.71
25d	1) DMF 2) conc. NH_4OH	3 h / r.t. 2 h / r.t.	98	>300 (H_2O)	$C_{14}H_{12}N_6O$	59.99 59.81	4.32 4.37	29.98 30.08
25e	1) DMF 2) conc. NH_4OH	4.5 h / r.t. 0.5 h / r.t.	76	309-311 (H_2O)	$C_{13}H_9N_6OCl$	51.92 51.95	3.02 3.14	27.95 27.78
38a	1) THF 2) conc. NH_4OH	16 h / r.t. 0.1 h / r.t.	83	276-279 (AcOEt)	$C_{14}H_{11}N_5O$	63.39 62.99	4.18 4.34	26.40 25.82
38b	1) DMF 2) conc. NH_4OH	3 h / r.t. 0.5 h / r.t.	96	287-289 (AcOEt)	$C_{14}H_{10}N_5OF$	59.36 58.83	3.56 3.48	24.72 24.85
38c	1) DMF 2) conc. NH_4OH	3 h / r.t. 1 h / r.t.	96	>295 (DMF/H_2O)	$C_{14}H_{10}N_5OCl$	56.10 55.87	3.36 3.52	23.37 22.99
38d	1) DMF 2) conc. NH_4OH	3 h / r.t. 2 h / r.t.	87	>295 (AcOEt)	$C_{15}H_{13}N_5O$	64.51 63.96	4.69 4.42	25.07 24.42 [a]
38e	1) DMF 2) conc. NH_4OH	4.5 h / r.t. 0.25 h / r.t.	85	342-343 (H_2O)	$C_{14}H_{10}N_5OCl$	56.10 55.92	3.36 3.41	23.37 23.13
45a	1) DMF 2) conc. NH_4OH	3 h / r.t. 1 h / r.t.	99	318-320 (AcOEt/EtOH)	$C_{14}H_{11}N_5O$	63.39 63.18	4.18 4.13	26.40 26.19
45b	1) DMF 2) conc. NH_4OH	3 h / r.t. 1 h / r.t.	100	342-344 (EtOH)	$C_{14}H_{10}N_5OF$	59.36 59.25	3.56 3.70	24.72 24.35

[a] Calcd with 0.05 mol AcOEt: C 63.98, H 4.73, N 24.55.

9*H*-Imidazo[1,5-*a*][1,2,4]triazolo[1,5-*d*][1,4]benzodiazepine-10-carbonitrile (26a) Trifluoroacetic anhydride (6.25 ml, 45 mmol) was added at 5° to 10°C within 15 min to **25a** (10.0 g, 37.5 mmol) in THF (280 ml) and pyridine (7.3 ml, 90 mmol) and the mixture was stirred at r.t. for 2 h. Further pyridine (1.45 ml, 18 mmol) and trifluoroacetic anhydride (1.4 ml, 10 mmol) were added. After stirring at r.t. for 1 h, the mixture was poured into ice-cold saturated $NaHCO_3$ (2.0 l) and extracted 5 times with $CHCl_3$. The $CHCl_3$ extracts were washed with brine and evaporated in vacuo. The residue was recrystallized from ethyl acetate/diisopropyl ether, affording **26a** (8.35 g, 89 %), mp 228-232°C. Anal. Calcd for $C_{13}H_8N_6$: C 62.90, H 3.25, N 33.85. Found: C 62.68, H 3.58, N 33.68.

Table: Compounds (26, 39 and 46), prepared from **25, 38** and **45** in a similar manner to **26a**

Compound	Reaction solvent	Conditions time (h)/ temp.(°C)	Yield (%)	mp (°C) (recryst. solvent)	Molecular formula	Microanalyses (%) C Calcd / Found	H Calcd / Found	N Calcd / Found
26b	dioxane/pyridine	2.5 h / r.t.	83	257-258 (AcOEt/iPr_2O)	$C_{13}H_7N_6F$	58.65 58.89	2.65 2.90	31.57 31.31
26c	DMF/pyridine	24 h / r.t.	80	255-256 (AcOEt)	$C_{13}H_7N_6Cl$	55.23 55.03	2.50 2.66	29.73 29.56
26d	DMF/pyridine	24 h / r.t.	88	275-276 (AcOEt)	$C_{14}H_{10}N_6$	64.11 64.20	3.84 4.07	32.04 32.04
26e	dioxane/pyridine	20 h / r.t.	76	283-285 (AcOEt)	$C_{13}H_7ClN_6$	55.23 55.16	2.50 2.59	29.73 29.71
39a	dioxane/pyridine	19 h / r.t.	85	226-228° (AcOEt)	$C_{14}H_9N_5$	68.01 66.62	3.67 4.20	28.32 a) 25.32
39b	dioxane/pyridine	19 h / r.t.	75	211-212 (AcOEt/iPr_2O	$C_{14}H_8N_5F$	63.39 63.22	3.04 2.95	26.40 26.38
39c	dioxane/pyridine	24 h / r.t.	57	231-232 (MeOH)	$C_{14}H_8N_5Cl$	59.69 59.34	2.86 3.23	24.86 b) 24.43
39d	DMF/pyridine	24 h / r.t.	74	267-269 (AcOEt)	$C_{15}H_{11}N_5$	68.95 69.10	4.24 4.09	26.80 26.43
39e	dioxane/pyridine	20 h / r.t.	82	207-208 (EtOH)	$C_{14}H_8N_5Cl$	59.69 59.57	2.86 2.98	24.86 c) 24.47
46a	dioxane/pyridine	16 h / r.t.	86	248-250 (AcOEt/Et_2O)	$C_{14}H_9N_5$	68.01 67.89	3.67 3.55	28.32 28.06
46b	dioxane/pyridine	16 h / r.t.	64	261-262 (AcOEt /Et_2O)	$C_{14}H_8N_5F$	63.39 63.26	3.04 3.05	26.40 26.44

a) Calcd with 0.3 mol AcOEt: C 66.71, H 4.20, N 25.59. b) Calcd with 0.1 mol MeOH: C 59.44, H 2.97, N 24.58. c) Calcd with 0.1 mol AcOEt: C 59.58, H 3.01, N 24.49.

10-(5-Cyclopropyl-1,2,4-oxadiazol-3-yl)-9*H*-imidazo[1,5-*a*][1,2,4]triazolo[1,5-*d*][1,4]benzodiazepine (28a, R = cyclopropyl). To a suspension of **26a** (8.35 g, 33.6 mmol) in ethanol (160 ml) were added hydroxylamine hydrochloride (2.7 g, 39 mmol) and then a solution of $NaHCO_3$ (3.34 g, 39.7 mmol) in water (40 ml). The mixture was stirred under reflux for 1.5 h. The resulting precipitate was filtered off and washed, affording crude 9*H*-imidazo[1,5-*a*][1,2,4]triazolo[1,5-*d*][1,4]benzodiazepine-10-carboxamidoxime **27a** (7.6 g). A further 0.5 g of **27a** could be obtained by concentrating the filtrate.
Cyclopropanecarboxylic acid (46 ml, 0.58 mmol) was dissolved in DMF (240 ml) and treated at 35°C with 1,1'-carbonyldiimidazole (7.0 g, 43.2 mmol). The mixture was stirred at 35°C for 1 h and at r.t. for 2 h, then crude **27a** (8.1 g, 28.8 mmol) was added thereto and the mixture stirred at 80°C for 15 h. The solvent was removed in vacuo, the residue dissolved in cyclopropanecarboxylic acid (50 ml) and heated at 130°C for 3.5 h. The solution was evaporated in vacuo and the residue chromatographed over silica gel. Elution with CH_2Cl_2/EtOH 99:1 yielded crude **28a** (R = cyclopropyl, 7.8 g). By recrystallization from EtOH, pure **28a** (R = cyclopropyl, 7.4 g, 66 %), mp 216-217°C, was obtained. Anal. Calcd for $C_{17}H_{13}N_7O$: C 61.62, H 3.95, N 29.59. Found: C 61.55, H 4.11, N 29.58.

Table: Compounds (28, 41 and 48, R= cPr), prepared from **26**, **39** and **46** in a similar manner to **28a**

Compound	R =	Reaction solvent	Conditions time (h)/ temp.(°C)	Yield (%)	mp (°C) (recryst. solvent)	Molecular formula	Microanalyses (%) C Calcd / Found	H Calcd / Found	N Calcd / Found
28b	cPr	1) EtOH/H_2O 2) DMF 3) cPrCOOH	2.5 h / reflux 16 h / 80° 4 h / 130°	65	223-224 (AcOEt)	$C_{17}H_{12}N_7OF$	58.45 58.33	3.46 3.64	28.07 27.94
28c	cPr	1) EtOH/H_2O 2) DMF 3) cPrCOOH	2 h / reflux 16 h / 80° 4 h / 130°	80	261-262 (AcOEt)	$C_{17}H_{12}N_7OCl$	55.82 55.53	3.31 3.41	26.81 26.64
28d	cPr	1) EtOH/H_2O 2) DMF 3) cPrCOOH	2 h / reflux 18 h / 80° 4 h / 130°	80	238-239 (AcOEt)	$C_{18}H_{15}N_7O$	62.60 62.42	4.38 4.34	28.39 28.34
28e	cPr	1) EtOH/H_2O 2) DMF 3) cPrCOOH	2 h / reflux 16 h / 80° 3.5 h / 130°	75	266-267 (EtOH)	$C_{17}H_{12}N_7OCl$	55.82 55.73	3.31 3.40	26.81 26.75
41a	cPr	1) EtOH/H_2O 2) DMF 3) cPrCOOH	2.5 h / reflux 16 h / 80° 4 h / 130°	51	187-189 (AcOEt/Et_2O)	$C_{18}H_{14}N_6O$	65.44 65.40	4.27 4.33	25.44 a) 25.11
41b	cPr	1) EtOH/H_2O 2) DMF 3) cPrCOOH	1.5 h / reflux 16 h / 80° 3 h / 130°	60	181-183 (AcOEt/iPr_2O)	$C_{18}H_{13}N_6OF$	62.07 62.03	3.76 3.67	24.13 23.98

a) Calcd with 0.4 mol AcOEt: C 65.33, H 4.32, N 25.17.

Table: Compounds (28, 41 and 48, R= cPr), prepared from **26**, **39** and **46** in a similar manner to **28a** (continued)

Compound	R =	Reaction solvent	Conditions time (h)/ temp.(°C)	Yield (%)	mp (°C) (recryst. solvent)	Molecular formula	Microanalyses (%) C Calcd / Found	H Calcd / Found	N Calcd / Found
41c	cPr	1) EtOH/H_2O 2) DMF 3) cPrCOOH	2 h / reflux 18 h / 80° 3 h / 130°	86	213-215 (AcOEt)	$C_{18}H_{13}N_6OCl$	59.27 59.17	3.59 3.59	23.04 22.93
41d	cPr	1) EtOH/H_2O 2) DMF 3) cPrCOOH	2 h / reflux 18 h / 80° 4 h / 130°	65	255-257 (AcOEt)	$C_{19}H_{16}N_6O$	66.27 65.70	4.68 4.65	24.40 [b] 24.08
41e	cPr	1) EtOH/H_2O 2) DMF 3) cPrCOOH	0.5 h / reflux 16 h / 80° 3 h / 130°	60	176-177 (EtOH)	$C_{18}H_{13}N_6OCl$	59.27 59.44	3.59 3.47	23.04 23.03
48a	cPr	1) EtOH/H_2O 2) DMF 3) cPrCOOH	1.25 h / reflux 18 h / 80° 3 h / 130°	52	207-209 (AcOEt)	$C_{18}H_{14}N_6O$	65.44 65.42	4.27 4.35	25.44 25.51
48b	cPr	1) EtOH/H_2O 2) DMF 3) cPrCOOH	1.5 h / reflux 3.5 h / 80°. 4 h / 130°	85	200-202 (AcOEt)	$C_{18}H_{13}N_6OF$	62.07 61.84	3.76 3.94	24.13 [c] 23.38

[b] Calcd with 0.16% of H_2O and 0.072 mol of AcOEt: C 66.06, H 4.76, N 23.97.
[c] Calcd with 3.65% of AcOEt: C 61.79 H 3.96, N 23.25.

Table: Compounds (28 and 41, R not cPr), prepared from **26** and **39** in a similar manner to **28a**: instead of cyclopropanecarboxylic acid, the corresponding acids R-COOH were used

Compound	R =	Reaction solvent	Conditions time (h)/ temp.(°C)	Yield (%)	mp (°C) (recryst. solvent)	Molecular formula	Microanalyses (%) C Calcd / Found	H Calcd / Found	N Calcd / Found
28b	Me	1) EtOH/H_2O 2) DMF 3) AcOH	3 h / reflux 18 h / 80° 6 h / 110°	78	293-294 (EtOH)	$C_{15}H_{10}N_7OF$	55.73 55.73	3.12 2.91	30.33 30.13
28b	Et	1) EtOH/H_2O 2) DMF 3) EtCOOH	3 h / reflux 17 h / 80° 6 h / 125°	72	267-269 (EtOH)	$C_{16}H_{12}N_7OF$	56.97 57.22	3.59 3.59	29.07 29.19
28b	iPr	1) EtOH/H_2O 2) DMF 3) iPrCOOH	3 h / reflux 20 h / 80° 6 h / 125°	76	207-209 (EtOH)	$C_{17}H_{14}N_7OF$	58.12 57.92	4.02 4.02	27.91 27.71

Table: Compounds (28 and 41, R not cPr), prepared from **26** and **39** in a similar manner to **28a**: instead of cyclopropanecarboxylic acid, the corresponding acids R-COOH were used (continued)

Compound	R =	Reaction solvent	Conditions time (h)/ temp.(°C)	Yield (%)	mp (°C) (recryst. solvent)	Molecular formula	Microanalyses (%) C Calcd Found	H Calcd Found	N Calcd Found
41e	iPr	1) EtOH/H_2O	1 h / reflux	55	156-157	$C_{18}H_{15}N_6OCl$	58.94	4.12	22.91
		2) DMF	20 h / 80°		(AcOEt)		58.92	4.13	22.87
		3) iPrCOOH	4 h / 125°						
41e	$EtOCH_2$								
		1) EtOH/H_2O	1 h / reflux	57	178-180	$C_{18}H_{15}N_6O_2Cl$	56.48	3.95	21.95
		2) DMF	20 h / 80°		(EtOH/AcOEt)		56.36	4.06	21.90
		3) ethoxy-acetic acid	4 h / 130°						
41e	2-Me-cPr								
		1) EtOH/H_2O	1 h / reflux	64	183-185	$C_{19}H_{15}N_6OCl$	60.24	3.99	22.19
		2) DMF	20 h / 80°		(iPrOH)		60.03	3.95	22.12
		3) rac trans-2-Me-cPrCOOH	2 h / 130°						

3-Fluoro-10-[5-(2-methoxyethyl)-1,2,4-oxadiazol-3-yl]-3-fluoro-9*H*-imidazo[1,5-*a*][1,2,4]-triazolo[1,5-*d*][1,4]benzodiazepine (28b, R = methoxyethyl). To a suspension of **26b** (3.63 g, 13.6 mmol) in ethanol (70 ml) were added hydroxylamine hydrochloride (1.2 g, 17.3 mmol) and then a solution of $NaHCO_3$ (5.82 g, 69.3 mmol) in water (70 ml). The mixture was stirred under reflux for 3 h. The resulting precipitate was filtered off and washed, affording crude 3-fluoro-9*H*-imidazo[1,5-*a*][1,2,4]triazolo-[1,5-*d*][1,4]benzodiazepine-10-carboxamidoxime **27b** (3.93 g). A further 0.07 g of **27b** could be obtained by concentrating the filtrate.

A solution of 3-methoxypropionic acid (1.9 ml, 20.2 mmol) in DMF (100 ml) was treated with 1,1'-carbonyl-diimidazole (3.2 g, 19.7 mmol). The mixture was stirred at r.t. for 3 h, then crude **27b** (4.0 g, 13.3 mmol) was added and the mixture stirred at 80°C for 18 h. The solvent was removed in vacuo, the residue dissolved in ethyl acetate (50 ml) and refluxed for 5 h. The solvent was removed in vacuo, the residue dissolved in CH_2Cl_2 and washed with saturated $NaHCO_3$. The organic phase was evaporated and the residue chromatographed over silica gel. CH_2Cl_2/methanol (99:1 to 97:3) eluted 3.6 g of product which, after recrystallization from ethyl acetate, afforded pure **28b** (R = methoxyethyl, 3.1 g) of mp 196-197°C. Anal. Calcd for $C_{17}H_{14}N_7O_2F$: C 55.58, H 3.84, N 26.69. Found: C 55.61, H 3.81, N 26.79.

Table: Compounds (28, R not cPr) prepared from **26** as described above; instead of 3-methoxypropionic acid, the corresponding acids R-COOH were used.

Compound	R =	Reaction solvent	Conditions time (h)/ temp.(°C)	Yield (%)	mp (°C) (recryst. solvent)	Molecular formula	Microanalyses (%) C Calcd Found	H Calcd Found	N Calcd Found
28b	$EtOCH_2$								
		1) EtOH/H_2O	2 h / reflux	60	187-188	$C_{17}H_{14}N_7O_2F$	55.58	3.84	26.69
		2) DMF	17 h / 80°		(AcOEt)		55.52	3.91	26.70
		3) AcOEt	4 h / 130°						
28b	Me_2NCH_2								
		1) EtOH/H_2O	2 h / reflux	38	196-197	$C_{17}H_{15}N_8OF$	55.73	4.13	30.59
		2) DMF	64 h / 80°		(AcOEt)		55.37	4.00	30.28
		3) AcOEt	5 h / 120°						
28b	2-thenyl								
		1) EtOH/H_2O	2 h / reflux	44	182-183	$C_{19}H_{12}N_7OFS$	56.29	2.98	24.19
		2) DMF	24 h / 80°		(AcOEt/hexane)		55.71	3.15	24.21
		3) AcOEt	2 h / 120°						
28b	benzyl								
		1) EtOH/H_2O	1.5 h / reflux	25	182-183	$C_{21}H_{14}N_7OF$	63.15	3.53	24.5
		2) DMF	18 h / 80°		(AcOEt/hexane)		63.07	3.38	24.37
		3) AcOEt	3 h / 120°						
28b	2-F-benzyl								
		1) EtOH/H_2O	1.5 h / reflux	50	202-204	$C_{21}H_{13}N_7OF_2$	60.43	3.14	23.49
		2) DMF	24 h / 80°		(AcOEt/hexane)		60.24	3.23	23.61
		3) AcOEt	3 h / 130°						
28b	3-F-benzyl								
		1) EtOH/H_2O	1.5 h / reflux	57	188-189	$C_{21}H_{13}N_7OF_2$	60.43	3.14	23.49
		2) DMF	24 h / 80°		(AcOEt/hexane)		60.44	3.23	23.55
		3) AcOEt	3 h / 130°						
28b	4-F-benzyl								
		1) EtOH/H_2O	1.5 h / reflux	51	191-192	$C_{21}H_{13}N_7OF_2$	60.43	3.14	23.49
		2) DMF	24 h / 80°		(AcOEt/hexane)		60.27	3.38	23.65
		3) AcOEt	3 h / 130°						
28b	4-MeO-benzyl								
		1) EtOH/H_2O	1.5 h / reflux	56	205-206	$C_{22}H_{16}N_7O_2F$	61.54	3.76	22.83
		2) DMF	24 h / 80°		(AcOEt/hexane)		61.44	3.88	22.83
		3) AcOEt	3 h / 130°						
28b	4-CF_3-benzyl								
		1) EtOH/H_2O	1.5 h / reflux	55	206-207	$C_{22}H_{13}N_7OF_4$	56.54	2.80	20.98
		2) DMF	18 h / 80°		(AcOEt/hexane)		56.30	2.85	20.82
		3) AcOEt	4 h / 130°						

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