1,2-Dihydro-3,1-benzoxazin-4-one and 4*H*-1,2-Dihydro-pyrido-[2,3-*d*]-[1,3]-oxazin-4-one Derivatives as Potential Prodrugs Part I: Synthesis

Gerhard Schwenker* and Jianbing Chen[1)]

Pharmazeutisch-chemisches Institut der Universität Heidelberg, Im Neuenheimer Feld 364, D-6900 Heidelberg

Received September 18, 1990

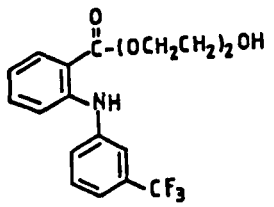
1-Mono- and previously unknown 1,2-disubstituted 1,2-dihydro-3,1-benzoxazin-4-ones **7** and **9**, potential prodrugs of flufenamic acid (**6**) and mefenamic acid (**8**), and 4*H*-1,2-dihydro-pyrido-[2,3-*d*]-[1,3]-oxazin-4-ones **11**, potential prodrugs of niflumic acid (**10**), were prepared; the structures of all new compounds wereconfirmed by spectroscopic methods.

1,2-Dihydro-3,1-benzoxazin-4-on- und 4*H*-1,2-Dihydro-pyrido-[2,3-*d*]-[1,3]-oxazin-4-on-Derivate als potentielle Prodrugs, Teil I: Synthesen

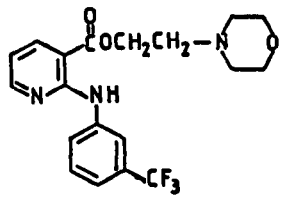
1-Mono- und bis jetzt unbekannte 1,2-disubstituierte 1,2-Dihydro-3,1-benzoxazin-4-on- **7a-7f** und **9a-9g** und 4*H*-1,2-dihydro-pyrido-[2,3-*d*]-[1,3]-oxazin-4-on-derivate **11a-11e** wurden als potentielle Prodrugs aus Flufenaminsäure, Mefenaminsäure bzw. Niflumінsäure hergestellt, ihre Strukturen wurden spektroskopisch gesichert.

According to the gastro-intestinal side effects and poor percutaneous permeability of the Non-Steroidal Antirheumatics (NSAR), a lot of potential prodrugs were synthesized. Most of them are carboxylic esters, for example, etofenamat[2)] (**1**), morniflumat[3)] (**2**), acetylosalicylic methylthiomethylester[4)] (**3**), and acemetacin[5)] (**4**). It was reported that the 1,3-benzodioxan-4-one derivatives[6)] (**5**) were potential prodrugs of acetylosalicylic acid. These compounds are cyclic condensation products of acetylosalicylic acid and alcohol (R = OEt).

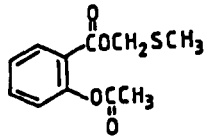
Due to the structural similarity to salicylic acid, 1-mono- and previously unknown 1,2-disubstituted 1,2-dihydro-3,1-benzoxazin-4-ones **7** and **9**, potential prodrugs of flufenamic acid (**6**) and mefenamic acid (**8**), and 4*H*-1,2-dihydro-pyrido-[2,3-*d*]-[1,3]-oxazin-4-ones **11**, potential prodrugs of niflumic acid (**10**), were prepared. The kinetics of hydrolysis of the new potential prodrugs in buffered aqueous media (30% methanol) were investigated. The results show that most of the new compounds are fast hydrolysized to deliver their parent acids. The percutaneous permeation of some of the new potential prodrugs through excised human skin was measured by an *in vitro* technique. Their permeabilities are at least twice as large as the permeability of the parent acid. Here we wish to report first the syntheses and spectroscopic properties of the new compounds.



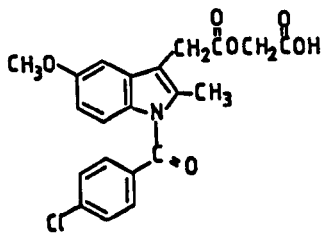
1



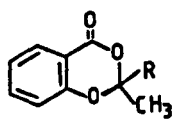
2



3



4

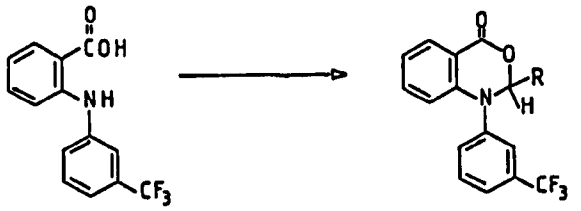


5

The starting compounds were the known NSAR flufenamic acid (**6**), mefenamic acid (**8**), and niflumic acid (**10**). *Dell* and *Kamp*[7)] prepared compound **7a** from **6** and 37% formaldehyde-solution in methanol in 50% yield. We found that the compounds **7a**, **9a**, and **11a** were formed by treatment of **6**, **8**, and **10**, resp., with paraformaldehyde in dry dichloromethane or chloroforme in the presence of dry $ZnCl_2$ in over 93% yield. Temp. and reaction time were dependent on the starting materials, in the case of **6** the reaction was carried out at room temp. within 2 h. The condensation of the starting compounds with aldehyde acetals or trialkyl orthoformate took place in dry toluene using *p*-toluenesulfonic acid as catalyst, and yielded products **7b-f**, **9b-g**, and **11b-e**. Due to the lower reactivity of **10**, the preparation of compounds **11** needed more vigorous conditions than required by compounds **7** and **9**. Most of the newly synthesized compounds are stable with the exception of **7b** and **7c**, which decompose on the TLC-surface to **6**.

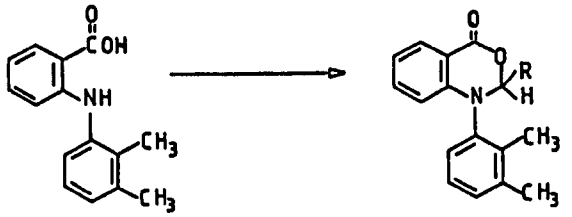
The NMR-spectroscopic evidence for the structures of the compounds was difficult to achieve due to the two aromatic rings, a newly produced chiral center and steric hinderance by the two substituents at N-1 and C-2 of compounds **7b-g**. In these cases the rotation around the N-C-1'-bond is not free at room temp. and some of the carbon- and hydrogen-atomes have doubled signals in their ^{13}C- or ^{1}H-NMR-spec-

  0365-6233/91/1010-0821 $ 3.50+.25/0



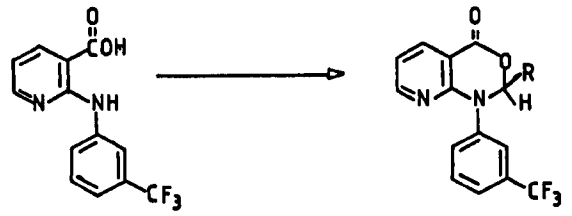
6 7a-7f

	R
a	H
b	OCH_3
c	OC_2H_5
d	CH_2Cl
e	CH_2OCH_3
f	$CO_2C_2H_5$



8 9a-9g

	R
a	H
b	OCH_3
c	OC_2H_5
d	CH_2Cl
e	CH_2OCH_3
f	$CO_2C_2H_5$
g	CH_3



10 11a-11e

	R
a	H
b	OCH_3
c	OC_2H_5
d	CH_2Cl
e	CH_3

tra, respectively. By modern analytical techniques, however, for example two dimensional and double-resonance spectra, and measurements at elevated temp., the structures of all new compounds were confirmed[1].

Experimental Part

1-(3'-Trifluoromethyl-phenyl)-1,2-dihydro-3,1-benzoxazin-4-one(7a)

To a solution of 4.2 g of 6 (15 mmol) and 0.9 g of paraformaldehyde in 150 ml of dichloromethane a catalytic quantity of dry $ZnCl_2$ powder was added. The mixture was stirred at room temp. for 2 h and then washed with 5% Na_2CO_3 solution and water. The org. phase was dried and evaporated to dryness under reduced pressure. Crystallization of the solid residue from petroleum ether/ether yielded 4.1 g of 7a (93%) as white crystals, m.p. 84-85°C.- $C_{15}H_{10}F_3NO_2$ (293.2) calcd. C 61.4 H 3.44 N 4.8 found C 61.3 H 3.55 N 4.8.- IR (KBr): 3050; 2960; 1725; 1610; 1580; 1500; 1235; 1150; 1120; 800; 755; 740, and 700 cm^{-1}.- ^{1}H-NMR (250.13 MHz, $CDCl_3$): δ = 5.60 (s, 2H, H-2), 7.06 (d, 1H, H-8, $^3J_{7,8}$ = 8.3 Hz), 7.20 (t, 1H, H-6), 7.30-7.55 (m, 5H, H-7,2',4',5',6'), 8.12 (d, 1H, H-5, $^3J_{5,6}$ = 7.85 Hz).- ^{13}C-NMR (62.89 MHz, $CDCl_3$): δ = 80.6 (t, C-2), 117.8 (s, $C\text{-}4_a$), 118.7 (d, C-8), 119.3 (q, C-2'), 121.8 (q, C-4'), 123.6 (q, CF_3), 123.7 (d, C-6), 125.8 (d, C-6'), 130.5 (d, C-5'), 131.3 (d, C-5), 132.7 (q, C-3'), 135.1 (d, C-7), 144.8 (s, C-1'), 145.7 (s, $C\text{-}8_a$), 163.5 (s, C-4).- MS (80 eV, 90°C): m/z (%) = 293 (78, M^+), 292 (2), 264 (19), 263 (100), 248 (27), 244 (1), 243 (6), 235 (9), 216 (4), 195 (1), 194 (4), 180 (29), 167 (3), 166 (10), 145 (16), 125 (3), 95 (8), 92 (18), 77 (9), 51 (10).

1-(3'-Trifluoromethyl-phenyl)-2-methoxy-1,2-dihydro-3,1-benzoxazin-4-one (7b)

4.2 g of 6 (15 mmol), 7.0 ml of trimethyl orthoformate and a catalytic amount of p-toluenesulfonic acid were added to 150 ml of dry toluene under dry conditions. The mixture was then refluxed for 4 h. After cooling to room tep. the mixture was washed with 5% cold Na_2CO_3 solution and cold water. The org. phase was dried and evaporated to dryness under reduced pressure. The solid residue was recrystallized from petroleum ether giving 4.3 g of 7b (89%) as a white powder, m.p. 63-64°C.- $C_{16}H_{12}F_3NO_3$ (323.3) calcd. C 59.5 H 3.74 N 4.3 found C 59.7 H 3.80 N 4.2.- IR (KBr): 3020; 2960; 1740; 1615; 1585; 1500; 1230; 1170; 1130; 800; 755; 740; 700 cm^{-1}.- ^{1}H-NMR (250.13 MHz, $CDCl_3$): δ = 3.60 (s, 3H, OCH_3), 6.00 (s, 1H, H-2), 6.71 (d, 1H, H-8, $^3J_{7,8}$ = 8.2 Hz), 7.05 (t, 1H, H-6), 7.30-7.65 (m, 5H, H-7,2',4',5',6'), 8.07 (d, 1H, H-5, $^3J_{5,6}$ = 7.88 Hz).- ^{13}C-NMR (62.89 MHz, $CDCl_3$): δ = 54.4 (q, OCH_3), 106.0 (d, C-2), 113.5 (s, $C\text{-}4_a$), 114.9 (d, C-8), 121.5 (q, C-2'), 122.1 (q, C-4'), 123.7 (q, CF_3), 123.7 (d, C-6), 128.8 (d, C-6'), 130.5 (d, C-5'), 130.8 (d, C-5), 132.6 (q, C-3'), 135.8 (d, C-7), 141.2 (s, C-1'), 143.7 (s, $C\text{-}8_a$), 160.9 (s, C-4).- MS (80 eV, 80°C): m/z (%) = 323 (4, M^+), 292 (9), 264 (20), 263 (100), 248 (1), 244 (2), 243 (4), 235 (9), 216 (4), 195 (1), 194 (2), 167 (6), 166 (7), 145 (7), 125 (1), 95 (4), 92 (11), 77 (4), 51 (4).

1-(3'-Trifluoromethyl-phenyl)-2-ethoxy-1,2-dihydro-3,1-benzoxazin-4-one (7c)

This compound was prepared as described for 7b, from 5.6 g of 6 (20 mmol), 10.0 ml of triethyl orthoformate and p-toluenesulfonic acid in 150

ml of dry toluene. The solid residue was recrystallized from petroleum ether giving 6.0 g of **7c** (89%) as a white powder, m.p. 40-41°C.- $C_{17}H_{14}F_3NO_3$ (337.3) calcd. C 60.5 H 4.18 N 4.2 found C 60.8 H 4.23 N 4.0.- IR (KBr): 3020; 2960; 1740; 1615; 1585; 1500; 1230; 1170; 1130; 800; 755; 740; 700 cm^{-1}.- ^{1}H-NMR (250.13 MHz, $CDCl_3$): δ = 1.28 (t, 3H, CH_3), 3.70-3.90 (m, 1H, H_a/H_b-CH_2CH_3), 3.90-4.05 (m, 1H, H_a/H_b-CH_2CH_3), 6.09 (s, 1H, H-2), 6.71 (d, 1H, H-8, $^3J_{7,8}$ = 8.36 Hz), 7.04 (t, 1H, H-6), 7.40-7.61 (m, 5H, H-7,2',4',5',6'), 8.06 (d, 1H, H-5, $^3J_{5,6}$ = 7.87 Hz).- ^{13}C-NMR (62.89 MHz, $CDCl_3$): δ = 14.9 (q, CH_3), 61.3 (t, CH_2CH_3), 104.9 (d, C-2), 113,4 (s, C-4_a), 114.8 (d, C-8), 121.3 (q, C-2'), 122.3 (q, C-4'), 123.5 (q, CF_3), 123.7 (d, C-6), 128.8 (d, C-6'), 130.6 (d, C-5'), 130.7 (d, C-5), 132.7 (q, C-3'), 135.7 (d, C-7), 141.3 (s, C-1'), 143.9 (s, C-8_a), 161.1 (s, C-4).- MS (80 eV, 75°C): m/z (%) = 337 (4, M^+), 292 (16), 264 (23), 263 (100), 248 (1), 244 (2), 243 (3), 235 (7), 216 (4), 195 (1), 194 (2), 167 (7), 166 (6), 145 (6), 125 (1), 95 (3), 92 (8), 77 (4), 51 (3).

1-(3'-Trifluoromethyl-phenyl)-2-chloromethyl-1,2-dihydro-3,1-benzoxazin-4-one (**7d**)

This compound was prepared as described for **7b**, from 4.2 g of **6** (15 mmol), 5.0 ml of 1,1-dimethoxy-2-chloro-ethane and p-toluenesulfonic acid in 150 ml of dry toluene. The solid residue was recrystallized from hexane/chloroforme giving 4.4 g of **7d** (86%) as light-yellow crystals, m.p. 118-119°C.- $C_{16}H_{11}ClF_3NO_2$ (341.7) calcd. C 56.2 H 3.24 N 4.1 found C 56.4 H 3.47 N 4.0.- IR (KBr): 3060; 2980; 1755; 1610; 1590; 1500; 1230; 1185; 1130; 785; 765; 740; 700 cm^{-1}.- ^{1}H-NMR (250.13 MHz, $CDCl_3$): δ = 3.89 (d, 2H, $^3J_{2, CH2Cl}$ = 6.75 Hz, H-2) 3.90 (dd, 1H, H_a/H_b-CH_2Cl), 5.86 (t, 1H $^3J_{2, CH2Cl}$ = 6.75 Hz, H-2), 7.05 (d, 1H, H-8, $^3J_{7,8}$ = 7.89 Hz), 7.22 (t, 1H, H-6), 7.47-7.60 (m, 5H, H-7,2',4',5',6'), 8.10 (d, 1H, H-5, $^3J_{5,6}$ = 7.76 Hz).- ^{13}C-NMR (62.89 MHz, $CDCl_3$): δ = 41.9 (t, CH_2Cl), 90.5 (d, C-2), 117.6 (s, C-4_a), 120.2 (q, C-2'), 121.2 (d, C-8), 122.4 (q, C-4'), 123.5 (q, CF_3), 124.1 (d, C-6), 126.7 (d, C-6'), 130.5 (d, C-5'), 130.7 (d, C-5), 131.9 (q, C-3'), 135.8 (d, C-7), 142.9 (s, C-1'), 145.9 (s, C-8_a), 161.0 (s, C-4).- MS (80 eV, 110°C): m/z (%) = 341 (9, M^+, ^{35}Cl), 292 (100), 264 (33), 263 (12), 244 (5), 235 (4), 216 (3), 195 (2), 194 (1), 167 (4), 166 (4), 145 (6), 125 (2), 95 (4), 92 (6), 77 (5), 51 (3).

1-(3'-Trifluoromethyl-phenyl)-2-methoxymethyl-1,2-dihydro-3,1-benzoxazin-4-one (**7e**)

This compound was prepared as described for **7b**, from 5.6 g of **6** (20 mmol), 4.0 g of 1,1,2-trimethoxy-ethane and p-toluenesulfonic acid in 150 ml of dry toluene. The viscous, light yellow oil was purified by cc (silica gel; petroleum ether/ethyl acetate (7/3)) giving 5.5 g of **7e** (82%) as a viscous and nearly colourless oil.- $C_{17}H_{14}F_3NO_3$ (337.3) calcd. C 60.5 H 4.18 N 4.2 found C 60.2 H 4.43 N 4.3.- IR (Film): 3080; 2940; 1740; 1610; 1585; 1490; 1230; 1170; 1130; 800; 750; 700 cm^{-1}.- ^{1}H-NMR (250.13 MHz, $CDCl_3$): δ = 3.39 (s, 3H, OCH_3), 3.76 (m, 2H, H_a and H_b-CH_2OCH_3), 5.80 (dd, $^3J_{2\ CH2OCH3}$ = 7.60 Hz, 1H, H-2), 7.00 (d, 1H, H-8, $^3J_{7,8}$ = 8.20 Hz), 7.14 (t, 1H, H-6), 7.44-7.58 (m, 5H, H-7,2',4',5',6'), 8.07 (d, 1H, H-5, $^3J_{5,6}$ = 7.90 Hz).- ^{13}C-NMR (62.89 MHz, $CDCl_3$): δ = 59.5 (q, OCH_3), 70.5 (t, CH_2OCH_3), 89.0 (d, C-2), 116.7 (s, C-4_a), 119.4 (d, C-8), 120.6 (q, C-2'), 122.1 (q, C-4'), 122.9 (d, C-6), 123.6 (q, CF_3), 127.0 (d, C-6'), 130.3 (d, C-5'), 130.6 (d, C-5), 132.3 (q, C-3'), 135.4 (d, C-7), 143.6 (s, C-1'), 145.3 (s, C-8_a), 161.9 (s, C-4).- MS (80 eV, 133°C): m/z (%) = 337 (6, M^+), 292 (100), 264 (34), 263 (4), 248 (1), 244 (4), 235 (3), 216 (3), 195 (2), 167 (7), 166 (3), 145 (5), 125 (1), 95 (1), 92 (3), 77 (4), 51 (1).

1-(3'-Trifluoromethyl-phenyl)-2-ethoxycarbonyl-1,2-dihydro-3,1-benzoxazin-4-one (**7f**)

4.2 g of **6** (15 mmol), 5.0 ml of ethyl 1,1-diethoxyacetate and p-toluenesulfonic acid were added to 150 ml of dry toluene. After refluxing for 3 h additional 2.0 ml of ethyl 1,1-diethoxy-acetate are added. The mixture was further refluxed for 2 h. After cooling to room temp. the mixture was washed with cold 5% Na_2CO_3 solution and cold water. The org. phase was dried and evaporated to dryness under reduced pressure. The solid residue was purified by cc (silica gel; chloroforme/ethyl acetate (9.5/0.5)). The main fraction was evaporated under reduced pressure. The product was crystallized from n-hexane giving 4.7 g of **7f** (86%) as white crystals; m.p. 78-79°C.- $C_{18}H_{14}F_3NO_4$ (365.3) calcd. C 59.2 H 3.86 N 3.8 found C 59.1 H 3.88 N 3.6.- IR (KBr): 3020; 2980; 1765; 1610; 1590; 1500; 1230; 1175; 1130; 800; 760; 740, 700 cm^{-1}.- ^{1}H-NMR (250.13 MHz, $CDCl_3$): δ = 1.23 (t, 3H, J = 7 Hz, CH_3), 4.20-4.32 (m, 2H, H_a and H_b-CH_2CH_3), 6.04 (s, 1H, H-2), 6.98 (d, 1H, H-8, $^3J_{7,8}$ = 8.20 Hz), 7.15 (t, 1H, H-6), 7.45-7.61 (m, 5H, H-7,2',4',5',6'), 8.07 (d, 1H, H-5, $^3J_{5,6}$ = 7.90 Hz).- ^{13}C-NMR (62.89 MHz, $CDCl_3$): δ = 13.9 (q, CH_3), 63.1 (t, O CH_2H_3), 86.4 (d, C-2), 116.7 (s, C-4_a), 118.1 (d, C-8), 119.9 (q, C-2'), 122.4 (q, C-4'), 123.4 (d, C-6), 123.6 (q, CF_3), 126.3 (d, C-6'), 130.6 (d, C-5'), 130.8 (d, C-5), 132.4 (q, C-3'), 135.4 (d, C-7), 143.0 (s, C-1'), 144.4 (s, C-8_a), 161.4 (s, C-4), 166.8 (s, COOEt).- MS (80 eV, 75°C): m/z (%) = 365 (4, M^+), 292 (100), 264 (26), 263 (4), 244 (2), 235 (3), 216 (3), 195 (1), 167 (9), 166 (3), 145 (4), 95 (1), 92 (2), 77 (4), 51 (1).

1-(1',2'-Dimethyl-phenyl)-1,2-dihydro-3,1-benzoxazin-4-one (**9a**)

This compound was prepared as described for **7a**, from 3.6 g of **8** (15 mmol), 0.9 g of paraformaldehyde and $ZnCl_2$ powder in 150 ml of dry dichloromethane. The solid residue was purified by crystallization from n-hexane giving 3.6 g of **9a** (95%) as white crystals, m.p. 82.5-83.5°C.- $C_{16}H_{15}NO_2$ (253.3) calcd. C 75.9 H 5.97 N 5.5 found C 75.7 H 6.01 N 5.2.- IR (KBr): 3020; 2980; 1725; 1610; 1575; 1495; 1225; 780; 765; 750; 715 cm^{-1}.- ^{1}H-NMR (250.13 MHz, $CDCl_3$): δ = 2.18 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 5.39 (s, 2H, H-2), 6.45 (d, 1H, $^3J_{7,8}$ = 8.35 Hz, H-8), 6.90-7.30 (m, 4H, H-6,4',5',6'), 7.35 (t, 1H, H-7), 8.04 (d, 1H, $^3J_{5,6}$ = 7.25 Hz, H-5).- ^{13}C-NMR: (62.89 MHz, $CDCl_3$): δ = 14.3 (q, CH_3-aryl), 20.6 (q, CH_3-aryl), 80.3 (t, C-2), 114.1 (s, C-4_a), 115.7 (d, C-8), 120.5 (d, C-6'), 124.8 (d, C-6), 126.8 (d, C-4'), 129.3 (d, C-5'), 131.1 (d, C-5), 134.6 (s, C-2'), 135.1 (d, C-7), 139.1 (s, C-3'), 140.8 (s, C-1'), 148.6 (s, C-8_a), 164.3 (s, C-4).- MS (80 eV, 86°C): m/z (%) = 253 (100, M^+), 252 (8), 224 (18), 223 (79), 209 (17), 208 (48), 195 (8), 194 (42), 180 (18), 105 (2), 77 (26), 51 (11).

1-(1',2'-Dimethyl-phenyl)-2-methoxy-1,2-dihydro-3,1-benzoxazin-4-one (**9b**)

4.8 g of **8** (20 mmol), 5.0 ml of trimethyl orthoformate and p-toluenesulfonic acid in 150 ml of dry toluene were refluxed for 3 h. Then 2.0 ml of trimethyl orthoformate were added and the mixture was further heated under reflux for 2 h. After cooling to room temp., the mixture was treated as described for **7b**. The residue was at first purified by cc (silica gel; petroleum ether/ethyl acetate 7.5/2.5) and then by crystallization from n-hexane/ethyl acetate giving 5.2 g of **9b** (92%) as white crystals, m.p. 115-116°C.- $C_{17}H_{17}NO_3$ (283.3) calcd. C 72.1 H 6.05 N 4.9 found C 72.2 H 6.03 N 4.8.- IR (KBr): 3010; 2970; 1740; 1610; 1580; 1490; 1230; 790; 780; 750; 720 cm^{-1}.- ^{1}H-NMR (250.13 MHz, $CDCl_3$): δ = 2.09 (s, 3H, CH_3-aryl), 2.34 (s, 3H, CH_3-aryl), 3.45 (s, 3H, OCH_3), 5.83 (s, 1H, H-2), 6.22 (d, 1H, $^3J_{7,8}$ = 8.44 Hz, H-8), 6.92 (t, 1H, $^3J_{6,5}$ = $^3J_{6,7}$ = 7.50 Hz, H-6), 7.20-7.40 (m, 4H, H-7,4',5',6'), 8.03 (d, 1H, $^3J_{5,6}$ = 7.50 Hz, H-5).- ^{13}C-NMR (62.89 MHz, $CDCl_3$): δ = 14.4 (q, CH_3-aryl), 20.1 (q, CH_3-aryl), 53.8 (q, OCH_3), 105.2 (d, C-2), 111.2 (s, C-4_a), 113.7 (d, C-8), 119.6 (d, C-6'), 125.8 (d, C-6), 126.9 (d, C-4'), 129.5 (d, C-5'), 129.8 (d, C-5), 134.7 (s, C-2'), 136.0 (d, C-7), 137.5 (s, C-3'), 138.6 (s, C-1'), 144.7 (s, C-8_a), 162.3 (s, C-4).- MS (80 eV, 73°C): m/z (%) = 283 (9, M^+), 253 (3), 252 (15), 224 (22), 223 (100), 209 (5), 208 (19), 195 (2), 194 (9), 180 (12), 105 (3), 77 (12), 51 (4).

1-(1',2'-Dimethylphenyl)-2-ethoxy-1,2-dihydro-3,1-benzoxazin-4-one(**9c**)

This compound was prepared as described for **9b**, from 3.6 g of **8** (15 mmol), 7.0 ml of triethyl orthoformate and p-toluenesulfonic acid in 150 ml of dry toluene. The solid residue was first flash chromatographed (silica gel; chloroforme/ethyl acetate 9.5/0.5) and crystallized from n-hexane giving 4.1 g of **9c** (91%) as white crystals, m.p. 119.0-120.5°C.- $C_{18}H_{19}NO_3$ (297.4) calcd. C 72.7 H 6.44 N 4.7 found C 72.4 H 6.36 N 4.5.- IR (KBr): 3040; 2990; 1740; 1610; 1580; 1495; 1230; 795; 780; 760; 730 cm^{-1}.- ^{1}H-NMR (250.13 MHz, $CDCl_3$): δ = 1.24 (t, 3H, J = 7 Hz, $CH_2\underline{CH_3}$), 2.12 (s, 3H, CH_3-aryl), 2.35 (s, 3H, CH_3-aryl), 3.64-3.78 (m, 1H, H_a/H_b-$\underline{CH_2}CH_3$), 3.86-4.10 (m, 1H, H_a/H_b-$\underline{CH_2}CH_3$), 5.92 (s, 1H, H-2), 6.22 (d, 1H, $^3J_{7,8}$ = 8.25 Hz, H-8), 6.90 (t, 1H, $^3J_{6,5}$ = $^3J_{7,8}$ = 7.88 Hz, H-6), 7.20-7.40 (m, 4H, H-7,4',5',6'), 8.04 (d, 1H, $^3J_{5,6}$ = 7.88 Hz, H-5).- ^{13}C-NMR (62.89 MHz, $CDCl_3$): δ = 14.1 (q, CH_3), 14.9 (q, CH_3-aryl), 20.6 (q, CH_3-aryl), 62.9 (t, $O\underline{CH_2}CH_3$), 105.1 (d, C-2), 111.9 (s, C-4_a), 114.0 (d, C-8), 119.6 (d, C-6'), 126.4 (d, C-6), 126.8 (d, C-4'), 130.0 (d, C-5'), 130.3 (d, C-5), 135.4 (s, C-2'), 135.6 (d, C-7), 138.1 (s, C-3'), 139.0 (s, C-1'), 145.3 (s, C-8_a), 161.9 (s, C-4).- MS (80 eV, 73°C): m/z (%) = 297 (5, M^+), 253 (3), 252 (16), 224 (23), 223 (100), 209 (6), 208 (20), 195 (2), 194 (9), 180 (11), 105 (2), 77 (9), 51 (2).

1-(1',2'-Dimethylphenyl)-2-chloromethyl-1,2-dihydro-3,1-benzoxazin-4-one (**9d**)

This compound was prepared from 4.8 g of **8** (20 mmol) and 5.0 ml of 1,1-dimethoxy-2-chloroethane in 150 ml of dry toluene. Two drops of conc. H_2SO_4 were used as catalyst. After refluxing for 6 h the mixture was treated as described for **7a**. The solid residue was purified by crystallization from chloroforme/n-hexane giving 4.5 g of **9d** (75%) as light yellow crystals, m.p. 131-132°C.- $C_{17}H_{16}ClNO_2$ (310.8) calcd. C 67.7 H 5.34 N 4.6 found C 67.5 H 5.40 N 4.4.- IR (KBr): 3040; 2930, 1725; 1610; 1560; 1490; 1240; 800; 785; 770; 730 cm^{-1}.- ^{1}H-NMR (250.13 MHz, $CDCl_3$): δ = 2.12 (s, 3H, CH_3-aryl), 2.35 (s, 3H, CH_3-aryl), 3.78 (d, 2H, $^3J_{2,\ CH2Cl}$ = 5.66 Hz, $C\underline{H_2}$ Cl) (dd, 1H, H_a/H_b-CH_2Cl), 5.62 (t, 1H, $^3J_{2,\ CH2Cl}$ = 5.66 Hz, H-2), 6.40 (d, 1H, $^3J_{8,7}$ = 8.31 Hz, H-8), 6.90-7.40 (m, 5H, H-6,7,4',5',6'), 8.03 (d, 1H, $^3J_{5,6}$ = 7.53 Hz, H-5).- ^{13}C-NMR (62.89 MHz, $CDCl_3$): δ = 14.1 (q, CH_3-aryl), 20.6 (q, CH_3-aryl), 42.8 (t, CH_2Cl), 88.8 (d, C-2), 112.7 (s, C-4_a), 115.5 (d, C-8), 120.2 (d, C-6'), 125.8 (d, C-6), 128.5 (d, C-4'), 130.5 (d, C-5'), 130.8 (d, C-5), 135.7 (d, C-7), 136.0 (s, C-2'), 139.1 (s, C-3'), 139.4 (s, C-1'), 146.6 (s, C-8_a), 162.3 (s, C-4).- MS (80 eV, 95°C): m/z (%) = 301 (13, M^+, ^{35}Cl, 253 (17), 252 (100), 224 (37), 223 (4), 209 (9), 208 (7), 195 (1), 194 (4), 180 (6), 105 (4), 77 (10), 51 (3).

1-(1',2'-Dimethylphenyl)-2-methoxymethyl-1,2-dihydro-3,1-benzoxazin-4-one (**9e**)

This compound was prepared from 4.8 g of **8** (20 mmol), 4.0 ml of 1,1,2-trimethoxy-ethane, and p-toluenesulfonic acid in 150 ml of dry toluene. After refluxing for 5 h, the mixture was treated as described for **7a**. The solid residue was first purified by cc (silica gel; petroleum ether/ethyl acetate 8/2) and then by crystallization from dichloromethane/petroleum ether giving 4.9 g of **9e** (83%) as white crystals, m.p. 60.5-61.5°C.- $C_{18}H_{19}NO_3$ (297.4) calcd. C 72.7 H 6.44 N 4.7 found C 72.7 H 6.55 N 4.5.- IR (KBr): 3080; 2920; 1730; 1610, 1575; 1485; 1225; 790; 775; 760; 725 cm^{-1}.- ^{1}H-NMR (250.13 MHz, $CDCl_3$): δ = 2.12 (s, 3H, CH_3-aryl), 2.34 (s, 3H, CH_3-aryl), 3.31 (s, 3H, OCH_3), 3.60-3.80 (m, 2H, H_a and H_b-CH_2OCH_3), 5.60 (t, 1H, $^3J_{2,\ CH2OCH3}$ = 5.63 Hz, H-2), 6.36 (d, 1H, $^3J_{8,7}$ = 8.44 Hz, H-8), 6.85-7.36 (m, 5H, H-6,7,4',5',6'), 8.02 (d, 1H, $^3J_{5,6}$ = 8.25 Hz, H-5).- ^{13}C-NMR (62.89 MHz, $CDCl_3$): δ = 14.7 (q, CH_3-aryl), 20.6 (q, CH_3-aryl), 59.0 (q, OCH_3), 71.3 (t, CH_2OCH_3), 88.0 (d, C-2), 113.0 (s, C-4_a), 115.4 (d, C-8), 119.7 (d, C-6'), 126.7 (d, C-6), 126.8 (d, C-4'), 130.0 (d, C-5'), 130.3 (d, C-5), 135.3 (d, C-7), 136.0 (s, C-2'), 139.1 (s, C-3'), 139.6 (s, C-1'), 147.2 (s, C-8_a), 163.3 (s, C-4).- MS (80 eV, 108°C): m/z (%) = 297 (6, M^+), 253 (20), 252 (100), 224 (48), 223(7), 209 (13), 208 (7), 195 (1), 194 (4), 180 (7), 105 (3), 77 (8), 51 (1).

1-(1',2'-Dimethylphenyl)-2-ethoxycarbonyl-1,2-dihydro-3,1-benzoxazin-4-one (**9f**)

This compound was prepared from 2.4 g of **8** (10 mmol), 3.0 ml of 1,1,2-trimethoxy-ethane, and p-toluenesulfonic acid in 150 ml of dry toluene. The mixture was refluxed for 18 h. After cooling to room temp. the mixture was treated as described for **7a**. The solid residue was first purified by cc (silica gel; n-hexane/ethyl acetate 6.5/3.5) and then by crystallization from n-hexane giving 2.5 g of **9f** (77%) as white crystals, m.p. 116-117°C.- $C_{19}H_{19}NO_4$ (325.4) calcd. C 70.1 H 5.89 N 4.3 found C 70.2 H 5.9 N 4.2.- IR (KBr): 3010; 2950; 1740; 1610; 1580; 1490; 1210 790; 760; 750; 720 cm^{-1}.- ^{1}H-NMR (250.13 MHz, $CDCl_3$): δ = 1.22 (t, 3H, J = 7 Hz, CH_3), 2.09 (s, 3H, CH_3-aryl), 2.34 (s, 3H, CH_3-aryl), 4.25 (m, 2H, H_a and H_b-CH_2CH_3), 5.75 (s, 1H, H-2), 6.42 (d, 1H, $^3J_{7,8}$ = 8.25 Hz, H-8), 6.90-7.55 (m, 5H, H-6,7,4',5',6'), 8.02 (d, 1H, $^3J_{5,6}$ = 7.50 Hz, H-5).- ^{13}C-NMR (62.89 MHz, $CDCl_3$): δ = 14.0 (q, CH_3), 14.6 (q, CH_3-aryl), 20.6 (q, CH_3-aryl), 62.6 (t, CH_2CH_3), 87.7 (d, C-2), 113.5 (s, C-4_a), 115.0 (d, C-8), 120.4 (d, C-6'), 126.7 (d, C-6), 127.1 (d, C-4'), 130.1 (d, C-5'), 130.8 (d, C-5), 135.2 (s, C-2'), 135.5 (d, C-7), 139.4 (s, C-3'), 139.7 (s, C-1'), 146.0 (s, C-8_a), 163.6 (s, C-4), 167.5 (s, COOEt.).- MS (80 eV, 90°C): m/z (%) = 325 (6, M^+), 253 (18), 252 (100), 224 (35), 223 (1), 209 (10), 208 (4), 195 (1), 194 (3), 180 (8), 105 (4), 77 (7), 51 (1).

1-(1',2'-Dimethylphenyl)-2-methyl-1,2-dihydro-3,1-benzoxazin-4-one(**9g**)

This compound was prepared from 2.4 g of **8** (10 mmol), 5.0 ml of 1,1-dimethoxyethane, and p-toluenesulfonic acid in 150 ml of dry chloroforme by refluxing for 5 h. After cooling to room temp., the mixture was treated as described for **7a**. The solid residue was first purified by cc (silica gel; dichloromethane) and then by crystallization from dichloromethane/petroleum ether giving 2.3 g of **9g** (86%) as white crystals, m.p. 99-100°C.- $C_{17}H_{17}NO_2$ (267.3) calcd. C 76.4 H 6.41 N 5.2 found C 76.3 H 6.36 N 5.3.- IR (KBr): 3030; 2950; 1725; 1610; 1575; 1490; 1235; 790; 780; 750; 725 cm^{-1}.- ^{1}H-NMR (250.13 MHz, $CDCl_3$): δ = 1.42 (d, 3H, $^3J_{2,\ CH3}$ = 5.90 Hz, CH_3), 2.18 (s, 3H, CH_3-aryl), 2.37 (s, 3H, CH_3-aryl), 5.70 (q, 1H, $^3J_{2,\ CH3}$ = 5.90 Hz, H-2), 6.18 (d, 1H, $^3J_{7,8}$ = 8.35 Hz, H-8), 6.86-7.40 (m, 5H, H-6,7,4',5',6'), 8.04 (d, 1H, $^3J_{5,6}$ = 7.87 Hz, H-5).- ^{13}C-NMR (62.89 MHz, $CDCl_3$): δ = 14.8 (q, CH_3-aryl), 19.0 (q, CH_3), 20.6 (q, CH_3-aryl), 85.8 (d, C-2), 112.7 (s, C-4_a), 115.0 (d, C-8), 119.4 (d, C-6'), 126.8 (d, C-6), 127.0 (d, C-4'), 129.9 (d, C-5'), 130.2 (d, C-5), 135.3 (d, C-7), 136.3 (s, C-2'), 138.4 (s, C-3'), 138.6 (s, C-1'), 149.2 (s, C-8_a), 163.6 (s, C-4).- MS (80 eV, 86°C): m/z (%) = 267 (53, M^+), 253 (6), 252 (32), 224 (30), 223 (100), 209 (12), 208 (45), 195 (4), 194 (16), 180 (17), 105 (4), 77 (30).

1-(3'-Trifluoromethylphenyl)-4-H-1,2-dihydro-pyrido-[2,3-d]-[1,3]-oxazin-4-one (**11a**)

This compound was prepared from 4.2 g of **10** (15 mmol), 0.9 g of paraformaldehyde and $ZnCl_2$ powder in 150 ml of dry chloroforme by refluxing for 24 h. After cooling to room temp., the mixture was treated as described for **7a**. The solid residue was first purified by flash chromatography (silica gel; ethyl acetate/n-hexane 4/6) and then by crystallization from dichloromethane/petroleum ether giving 4.2 g of **11a** (93%) as white crystals, m.p. 102-103°C.- $C_{14}H_9F_3N_2O_2$ (294.2) calcd. C 57.2 H 3.08 N 9.5 found C 57.0 H 3.15 N 9.5.- IR (KBr): 3090; 2960; 1730; 1610; 1580; 1490; 1235; 1160; 1120; 800; 780; 745; 700 cm^{-1}.- ^{1}H-NMR (250.13 MHz, $CDCl_3$): δ = 5.67 (s, 2H, H-2), 7.10 (dd, 1H, H-6, $^3J_{5,6}$ = 7.75 Hz, $^3J_{6,7}$ = 4.76 Hz), 7.47-7.57 (m, 4H, H-2', H-4', H-5', H-6'), 8.38 (dd, 1H, H-5, $^4J_{5,7}$ = 1.95 Hz), 8.46 (dd, 1H, H-7).- ^{13}C-NMR (62.89 MHz, $CDCl_3$): δ = 79.3 (t, C-2), 110.2 (s, C-4_a), 118.5 (d, C-6), 121.0 (q, C-2'), 122.8 (q, C-4'), 123.8 (q, CF_3), 127.5 (d, C-6'), 130.0 (d, C-5'), 132.0 q, C-3'), 140.3 (d, C-5), 141.6 (s, C-1'), 154.6 (d, C-7), 156.1 (s, C-8_a), 163.1 (s, C-4).- MS

80 eV, 91°C): m/z (%) = 294 (80, M^+), 293 (12), 265 (8), 264 (14), 245 (2), 237 (16), 236 (100), 195 (4), 167 (7), 145 (41), 125 (9), 93 (13), 78 (7), 77 (6), 52 (8), 51 (16).

1-(3'-Trifluoromethylphenyl)-2-methoxy-4-H-1,2-dihydro-pyrido-[2,3-d][1,3]-oxazin-4-one (**11b**)

This compound was prepared as described for **7b** from 4.2 g of **10** (15 mmol), 9.0 ml of trimethyl orthoformate, and p-toluenesulfonic acid in 150 ml of dry toluene. The mixture was refluxed for 8 h. The solid residue was first chromatographed (silica gel; dichloromethane) and then crystallized from dichloromethane/petroleum ether giving 3.80 g of **11b** (78%), m.p. 84.5-86.0°C.- $C_{15}H_{11}F_3N_2O_3$ (324.3) calcd. C 55.6 H 3.42 N 8.6 found C 55.3 H 3.44 N 8.5.- IR (KBr): 3025; 2980; 1740; 1610; 1590; 1480; 1235; 1150; 1120; 800; 775; 730; 705 cm^{-1}.- ^{1}H-NMR (250.13 MHz, $CDCl_3$): δ = 3.61 (s, 3H, OCH_3), 6.09 (s, 1H, H-2), 7.02 (dd, 1H, H-6, $^3J_{5,6}$ = 7.72 Hz; $^3J_{6,7}$ = 4.89 Hz), 7.59-7.64 (m, 4H, H-2', H-4', H-5', H-6'), 8.32 (dd, 1H, H-5, $^4J_{5,7}$ = 1.95 Hz), 8.39 (dd, 1H, H-7).- ^{13}C-NMR (62.89 MHz, $CDCl_3$): δ = 54.6 (q, OCH_3), 105.7 (d, C-2), 108.2 (s, C-4_a), 117.5 (d, C-6), 123.1 (q, C-2'), 123.9 (q, CF_3), 124.0 (q, C-4'), 129.7 (d, C-6'), 130.0 (d, C-5'), 132.1 (q, C-3'), 139.2 (d, C-5), 139.6 (s, C-1'), 153.8 (s, C-8_a), 154.7 (d, C-7), 160.9 (s, C-4).- MS (80 eV, 86°C): m/z (%) = 324 (7, M^+), 293 (9), 265 (24), 264 (71), 245 (7), 237 (17), 236 (100), 195 (2), 167 (7), 145 (25), 125 (5), 93 (8), 78 (7), 77 (3), 52 (3), 51 (8).

1-(3'-Trifluoromethylphenyl)-2-ethoxy-4-H-1,2-dihydro-pyrido-[2,3-d]-[1,3]-oxazin-4-one (**11c**)

This compound was prepared as described for **9b** from 4.2 g of **10** (15 mmol), 9.0 ml of triethyl orthoformate, and p-toluenesulfonic acid in 150 ml of dry toluene. The mixture was refluxed for 8 h. The solid residue was first chromatographed (silica gel; dichloromethane) and then crystallized from dichloromethane/petroleum ether giving 3.8 g of **11c** (73%), m.p. 78-79°C.- $C_{16}H_{13}F_3N_2O_3$ (338.3) calcd. C 56.8 H 3.87 N 8.3 found C 56.9 H 4.00 N 8.2.- IR (KBr): 3020; 2980; 1735; 1605; 1580; 1500; 1235; 1160; 1120; 800; 760; 730; 700 cm^{-1}.- ^{1}H-NMR (250.13 MHz, $CDCl_3$): δ = 1.28 (t, 3H, J = 7 Hz, CH_3), 3.75-3.88 (m, 1H, H_a/H_b-C$\underline{H}_2$$CH_3$), 3.94-4.06 (m, 1H, H_a/H_b-C$\underline{H}_2$$CH_3$), 6.18 (s, 1H, H-2), 7.02 (dd, 1H, H-6, $^3J_{5,6}$ = 7.74 Hz, $^3J_{6,7}$ = 4.85 Hz), 7.57-7.69 (m, 4H, H-2', H-4', H-5', H-6'), 8.32 (dd, 1H, H-5, $^4J_{5,7}$ = 1.94 Hz), 8.39 (dd, 1H, H-7).- ^{13}C-NMR (62.89 MHz, $CDCl_3$): δ = 14.8 (q, CH_3), 63.4 (t, OCH_2CH_3), 104.7 (d, C-2), 108.2 (s, C-4_a), 117.4 (d, C-6), 123.1 (q, C-2'), 123.6 (q, CF_3), 124.0 (q, C-4'), 129.8 (d, C-6'), 129.9 (d, C-5'), 131.9 (q, C-3'), 139.1 (d, C-5), 139.7 (s, C-1'), 153.9 (s, C-8_a), 154.7 (d, C-7), 161.1 (s, C-4).- MS (80 eV, 91°C): m/z (%) = 338 (8, M^+), 293 (18), 265 (31), 264 (94), 245 (7), 237 (20), 236 (100), 195 (1), 167 (3), 145 (17), 125 (3), 93 (6), 78 (5), 77 (2), 52 (1), 51 (4).

1-(3'-Trifluoromethylphenyl)-2-chloromethyl-4-H-1,2-dihydro-pyrido-[2,3-d]-[1,3]-oxazin-4-one (**11d**)

4.2 g of **10** (15 mmol), 5.0 ml of 1,1-dimethoxy-2-chloro-ethane and two drops of conc. H_2SO_4 were added to 150 ml of dry toluene. The mixture was refluxed for 40 h. After cooling to room temp. the mixture was treated as described for **7a**. The solid residue was chromatographed (silica gel; dichloromethane, n-hexane, and ethyl acetate 7.0/3.0/0.5) and afterwards crystallized from chloroforme/n-hexane giving 2.5 g of **11d** (49%), m.p. 81.5-83.0°C.- $C_{15}H_{10}ClF_3N_2O_2$ (342.7) calcd. C 52.6 H 2.94 N 8.2 found C 52.8 H 3.03 N 8.1.- IR (KBr): 3030; 2980; 1740; 1610; 1595; 1580; 1500; 1235; 1160; 1120; 800; 785; 740; 700 cm^{-1}.- ^{1}H-NMR (250.13 MHz, $CDCl_3$): δ = 3.90 (d, 2H, $^3J_{CH_2Cl,\ 2}$ = 5.65 Hz, CH_2Cl) 3.91 (dd, 1H, H_a/$H_b$$CH_2Cl$), 5.96 (dd, 1H, $^3J_{2,\ CH_2Cl}$ = 5.65 Hz, H-2), 7.09 (dd, 1H, H-6, $^3J_{5,6}$ = 7.75 Hz, $^3J_{6,7}$ = 4.84 Hz), 7.58-7.67 (m, 4H, H-2', H-4', H-5', H-6'), 8.34 (dd, 1H, H-5, $^4J_{5,7}$ = 1.95 Hz), 8.47 (dd, 1H, H-7).- ^{13}C-NMR (62.89 MHz, $CDCl_3$): δ = 42.8 (t, CH_2Cl), 89.2 (d, C-2), 109.7 (s, C-4_a), 118.4 (d, C-6), 123.1 (q, C-2'), 123.9 (q, C-4'), 124.0 (q, CF_3), 129.5 (d, C-6'), 129.9 (d, C-5'), 130.2 (q, C-3'), 139.5 (d, C-5), 142.0 (s, C-1'), 154.5 (s, C-8_a), 155.3 (d, C-7), 161.0 (s, C-4).- MS (80 eV, 91°C): m/z (%): 342 (10, M^+, ^{35}Cl), 293 (100), 265 (67), 264 (2), 245 (7), 237 (3), 236 (18), 195 (2), 167 (2), 145 (16), 125 (3), 93 (4), 78 (7), 77 (1), 52 (1), 51 (5).

1-(3'-Trifluoromethylphenyl)-2-methyl-4-H-1,2-dihydro-pyrido-[2,3-d]-[1,3]-oxazin-4-one (**11e**)

5.6 g of **10** (20 mmol), 8.0 ml of 1,1-diethoxyethane, p-toluenesulfonic acid, and 150 ml of dry toluene were refluxed for 4 h. After cooling to room temp. the mixture was treated as described for **7a**. The solid residue was crystallized from n-hexane giving 5.1 g of **11e** (83%), m.p. 89-90°C.- $C_{15}H_{11}F_3N_2O_2$ (308.3) calcd. C 58.5 H 3.60 N 9.1 found C 58.4 H 3.74 N 9.1.- IR (KBr): 3020; 2990; 1725; 1620; 1600; 1580; 1500; 1235; 1160; 1120; 800; 785; 730; 700 cm^{-1}.- ^{1}H-NMR (250.13 MHz, $CDCl_3$): δ = 1.51 (d, 3H, $^3J_{CH3,\ 2}$ = 5.94 Hz, CH_3), 6.18 (q, 1H, $^3J_{2,\ CH3}$ = 5.94 Hz, H-2), 7.12 (dd, 1H, H-6, $^3J_{5,6}$ = 7.73 Hz, $^3J_{6,7}$ = 4.82 Hz), 7.63-7.74 (m, 4H, H-2', H-4', H-5', H-6'), 8.27 (dd, 1H, H-5, $^4J_{5,7}$ = 1.91 Hz), 8.42 (dd, 1H, H-7).- ^{13}C-NMR (62.89 MHz, $CDCl_3$): δ = 19.3 (q, CH_3), 86.1 (d, C-2), 108.8 (s, C-4_a), 117.3 (d, C-6), 123.2 (q, C-2'), 124.1 (q, C-4'), 124.2 (q, CF_3), 130.4 (d, C-6'), 131.5 (d, C-5'), 132.1 (q, C-3'), 139.0 (d, C-5), 140.8 (s, C-1'), 154.5 (d, C-7), 156.1 (s, C-8_a), 162.5 (s, C-4).- MS (80 eV, 91°C): m/z (%) = 308 (34, M^+), 293 (16), 265 (22), 264 (51), 245 (3), 237 (14), 236 (100), 195 (2), 167 (3), 145 (21), 125 (3), 93 (8), 78 (5), 77 (2), 52 (1), 51 (4).

References

1 Part of the doctoral thesis of Jianbing Chen, 1989, Heidelberg.
2 K.H. Boltze and H. Kreisfeld, Arzneim.-Forsch. *27*, 1300 (1977).
3 A. Robert, Prostaglandins, 21, Suppl. 89 (1981).
4 T. Loftsson, J.J. Kaminski, and N. Bodor, J. Pharm. Sci *70*, 743 (1981).
5 K.H. Boltze, O. Brendler, H. Jacobi, W. Opitz, S. Raddatz, P.-R. Seidel, and D. Vollbrecht, Arzneim.-Forsch. *30*, 1314 (1980).
6 L. Zambaletti, Belg. P. 890730; C.A. *96*, 199707 (1982).
7 H.D. Dell and Kamp, Arch. Pharm. (Weinheim) *303*, 785 (1970).

[Ph873]