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# Generation of Polysubstituted 2-Pyridinecarboxylic Acid Derivatives from the Reaction of (Functionalised) 2-Oxa-5-azabicyclo[2.2.2]oct-5-en-3-ones with Various Nucleophiles.

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**Abstract:** By selective reaction of the chlorimine function in the adducts **2** from 3,5-dichloro-2*H*-1,4-oxazin-2-ones and double bond systems, a series of 6-substituted 2-oxa-5-azabicyclo[2.2.2]oct-5-en-3-ones **3** could be generated. Lactone cleavage of the latter with alcohols or amines yielded variously substituted 4,5-dihydro-5-hydroxy-2-pyridinecarboxylic acid derivatives which were dehydrated to afford the corresponding pyridine systems. Some 6-amino substituted 2-pyridinecarboxamides could be obtained in a one step procedure by reacting **2** with $Me_3Al$/amine.
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Recently we reported a general method for the generation of variably substituted 1,6-dihydro-6-oxo-2-pyridine- and 6-oxo-2-piperidinecarboxylates via an alcohol mediated lactone cleavage of (±)-4,6-dichloro-2-oxa-5-azabicyclo-[2.2.2]oct-5-en-3-ones **2** made by cycloaddition of 3,5-dichloro-2*H*-1,4-oxazin-2-ones and olefins.[1,2] These cycloadducts **2** could also be used to synthesize variously substituted 6-chloro-2-pyridinecarboxylic acid derivatives.[3] In this paper we deal with the functionalisation of the chlorimine in the adducts **2** and the use of the derived compounds **3** in the generation of 2-pyridinecarboxylic acid derivatives with a wide variation of substituents in positions 3-6. Many 6-substituted-2-pyridinecarboxylic acid derivatives are known to be useful compounds as pharmaceutics or as agrochemicals[4] but most of the existing methods for the synthesis of multisubstituted-2-pyridinecarboxylic acid derivatives have a rather narrow scope.[5]

The (±)-4,6-dichloro-2-oxa-5-azabicyclo[2.2.2]oct-5-en-3-ones **2a,b** and the (±)-4,6-dichloro-2-oxa-5-azatricyclo[5.2.2.$0^{7,8}$]undec-5-en-3-ones **2c** (*endo*) and **2d** (mixture of *endo* and *exo*) were prepared from the reaction of 3,5-dichloro-2*H*-1,4-oxazin-2-ones **1a,b** with ethene (20 atm) in toluene at 110 °C or with cyclopentene in refluxing $CHCl_3$.[1] These cycloadducts have bielectrophilic characteristics, due to a lactone function and a chlorimine function. We attempted a selective reaction of the chlorimine function with amines and other nucleophiles, as shown in table 1 and scheme 1, to yield adducts **3** of potential interest. It should be noted that naturally occuring aminoglycoside antibiotics such as fortimycin AH, AI[6] and a gentamycin[7,8] contain a

2-oxa-5-azabicyclo[2.2.2]oct-5-ene ring system. Derivatives of these bicyclic compounds have also been used in the synthesis of polyamides with biomedical interest[9] and analogues of sialic acid.[10]

Because of competitive attack on the lactone, reaction of primary amines such as propylamine gave low yields of **3a** but this could be improved (48 %) when using only 1.2 equivalents instead of two. High yields of **3b-e** could be realised with aniline and secondary amines whereas *t*-$BuNH_2$ and 2,6-diethylaniline did not react. Activation of the chlorimine function with a Lewis acid such as $AlCl_3$ was required in the cases of 2,4-difluoroaniline, benzyl mercaptan and anisole. A catalytic amount of 18-crown-6-ether was added to the reaction mixture when cyanide was used as nucleophile. As stated in a previous article[2] **2a** could be converted into the labile iminoether **3j** (53 %) after one hour of stirring with NaOMe in dry THF at 0 °C. Other attempts to improve the yield for the conversion into an iminoether failed even when catalysed with $AlCl_3$ (comparable with the functionalisation with thiols), fluoride or iodide. Reaction with other alcoholates (such as NaOPh or NaO*i*-Pr) were not successful. The structure of the compounds **3**, was confirmed by their spectral characteristics. Their IR-spectra show typical absorptions around 1795-1760 $cm^{-1}$ and 1500-1610 $cm^{-1}$ which can be attributed to the lactone carbonyl and the imine function, respectively. In the $^1$H-NMR spectrum of the isolated compounds **3**, signals corresponding with the introduced groups are found along with the characteristic absorptions for the ethylene bridge (1.8 ppm - 2.5 ppm). The mass spectra (electron impact) show an easy loss of $CO_2$. $^{13}$C-NMR spectra of the substituted adducts also reveal signals consistent with an ethylene bridge (31 ppm - 34 ppm), a lactone carbonyl (163 ppm - 169 ppm), an imine (154 ppm - 163 ppm) and two quaternary carbon atoms C-1 and C-4 (79 ppm - 84 ppm).

Treatment of **2a** with 1.2 equivalents potassium thiocyanate in refluxing acetonitrile for four days failed to give the expected product **3k** ($R^6$ = SCN). In the $^1$H-NMR spectrum of the isolated product **4** (41 %) a broad singlet at 9.1 ppm was observed along with the characteristic absorptions for the ethylene bridge. The infrared absorption at 1795 $cm^{-1}$ (lactone) was present but the the typical values for the thiocyanate (2175 $cm^{-1}$ and 2140 $cm^{-1}$) were missing. The absorption at 1500 $cm^{-1}$ was indicative of a thioamide function just like the $^{13}$C-NMR absorption at 199.6 ppm. We presume that an attack of KSCN on the chlorimine function was followed by an easy hydrolysis of **3k**.

As stated in a recent paper the lactone function in the non-functionalised adducts **2** can be cleaved selectively with alcohols and amines to yield substituted 6-chloro-2-pyridinecarboxylic acid derivatives.[3] We applied the method (lactone cleavage, HCl and $H_2O$ elimination) to the functionalised bicyclic adducts **3**, to provide a series of 6-substituted 2-pyridinecarboxylic acid derivatives **5** and **6** (Scheme 2). However treatment of the amino substituted adduct **3c** with four or more equivalents of methanol in refluxing $CHCl_3$ (or neat) did not yield compounds of type **5** or **6** even after two weeks. Only when adding an equimolar amount of DBU to make the alcohol more nucleophilic, adduct **3c** gave compound **6a** in 81 % yield after two days reaction in refluxing THF. In refluxing $CHCl_3$ as solvent the reaction ran more slowly.

**Scheme 1.** Reaction conditions and yield for the substitution of 4,6-dichloro-2-oxa-5-azabicyclo[2.2.2]oct-5-en-3-ones **2**.

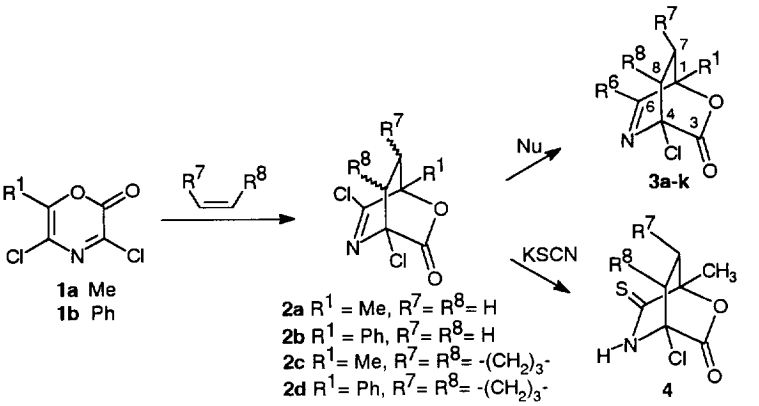



**Table 1.**

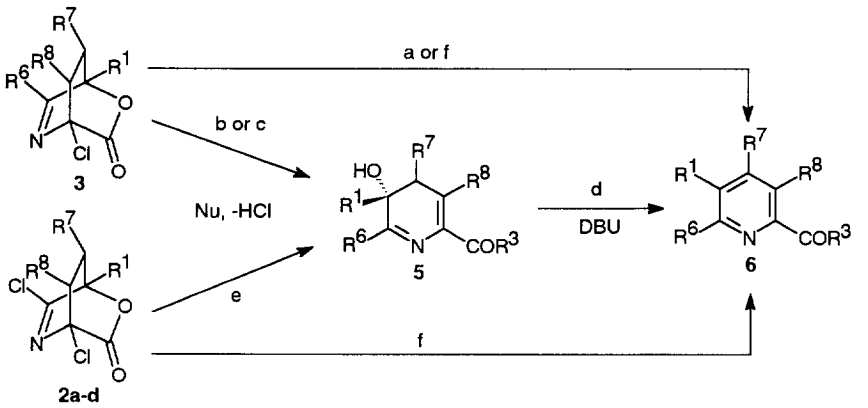
| Comp. | $R^1$ | $R^6$ | $R^7$, $R^8$ | Reaction conditions | Yield (%) |
|---|---|---|---|---|---|
| **3a** | Me | NHPr | H | 2 (1,2) eq. $NH_2Pr$, 1 eq. $NEt_3$, $CH_2Cl_2$ reflux, 15 min | 27(48) |
| **3b** | Me | $NEt_2$ | H | 2 eq. $NHEt_2$, 1 eq. $NEt_3$, $CH_2Cl_2$ reflux, 2h | 80 |
| **3c** | Me | 1-piperidinyl | H | 2 eq. piperidine, 1 eq. $NEt_3$, $CH_2Cl_2$ reflux, 20 min | 96 |
| **3d** | Me | 1-piperidinyl | $-(CH_2)_3-$ | 2 eq. piperidine, 1 eq. $NEt_3$, THF reflux, 1d | 86 |
| **3e** | Me | NHPh | H | 2 eq. aniline, 1 eq. $NEt_3$, $CH_2Cl_2$, RT. 1d | 83 |
| **3f** | Me | 2,4-diFAn [a] | H | 2.1 eq. $AlCl_3$, 2 eq. 2,4-difluoroaniline, $CH_2Cl_2$, RT, 4h | 72 |
| **3g** | Me | SBn | H | 2.1 eq. $AlCl_3$, 2 eq. BnSH, $CH_2Cl_2$ RT, 30 min | 88 |
| **3h** | Me | 4-MeOPh | H | 2.1 eq. $AlCl_3$, 2 eq. anisole, $CH_2Cl_2$ 0 °C, 2h | 47 |
| **3i** | Me | CN | H | 1.2 eq. KCN, 18-crown-6-ether, MeCN 60 °C, 1d | 96 |
| **3j** | Me | OMe | H | 2 eq. NaOMe, THF 0 °C, 1h [b] | 53 |
| **3k** | Me | SCN | H | 1.2 eq. KSCN, MeCN reflux, 4d | 0 |
| **4** | Me | | H | 1.2 eq. KSCN, MeCN reflux, 4d | 41 |

[a] 2,4-diFAn = 2,4-difluoroanilino; [b] see ref 2

The *endo* 7,8-disubstituted adduct **3d** and also adduct **3i** was treated in the same way for two days to yield the *c*-annelated pyridine **6b** (44 %) and the pyridine **6c** (48 %). We suppose that the reaction proceeds via intermediates of type **5a-c** which are probably dehydrated by a DBU catalysed $E_{1cb}$-mechanism.

However reaction of the thio imino ether **3g** with ethanol (DBU) in THF did not yield **6d**, but a complex reaction mixture was observed. We believe that the thio imino ether is affected by ethanol.[2] The $^1$H-NMR spectrum of compounds **6a-c** shows the typical absorptions for the protons on C-3 and C-4 at around 7.5 ppm (**6a,c**), the piperidinyl group (± 1.50 ppm, m, 6H and ± 3.10 ppm, m, 4H; **6a,b**) and the ester function. The characteristic absorptions for the pyridine carbon atoms of in the $^{13}$C-NMR spectra of **6a-c** are consistent with literature data.[11]

**Scheme 2.** Lactone cleavage of the adducts **2** and the functionalised derivatives **3** with alcohols and amines(/$Me_3Al$)




[a] 8 eq. DBU-ROH, THF, reflux; [b] 4 eq. ROH, $CHCl_3$ r.t.; [c] 3 eq. $NH_2Pr$, $CHCl_3$, reflux, 3u; [d] 3 eq. DBU, MeCN or toluene, reflux; [e] 2.2 eq. $Me_3Al$/HNR'R'', $CH_2Cl_2$ or toluene., r.t. or reflux; [f] 4 eq. $Me_3Al$/HNR'R'', toluene reflux, 4 days.

**Table 2.**

| Adduct | 5, 6 | $R^1$ | $R^6$ | $R^3$ | $R^{7,8}$ | Yield 5, % | Yield 6, % |
|---|---|---|---|---|---|---|---|
| **3c** | **a** | Me | 1-piperidinyl | OMe | H | / | 81[a] |
| **3d** | **b** | Me | 1-piperidinyl | OEt | $-(CH_2)_3-$ | / | 44[a] |
| **3i** | **c** | Me | CN | OEt | H | / | 48[a] |
| **3g** | **d** | Me | SBn | OEt | H | / | /[a or b] |
| **3a** | **e** | Me | NHPr | NHPr | H | 69[c] | 65[c,d] |
| **3g,i** | | Me | CN, SR | NR'R'' | H | / | /[c,d] |
| **3g** | **f** | Me | SBn | NH*t*-Bu | H | / | 62[c,d] |
| **3b** | **g** | Me | $NEt_2$ | 2,6-diEtAn | H | 82[e] | 68[e,d] |
| **3f** | **h** | Me | 2,4-diFAn | 3-$CF_3$An | H | / | 82[f] |
| **2a** | **i** | Me | 2,4-diFAn | 2,4-diFAn | H | / | 91[f] |
| **2c** | **j** | Me | NHBn | NHBn | $-(CH_2)_3-$ | / | 96[f] |
| **2d** | **k** | Ph | 3-$CF_3$An | 3-$CF_3$An | $-(CH_2)_3-$ | / | 89[f] |
| **2b** | **l** | Ph | 2,6-diEtAn | 2,6-diEtAn | H | 69[e] | |

The adducts **2** and **3** could also be reacted with amines. Treatment of adduct **3a** with three equivalents propylamine in refluxing $CHCl_3$ provided successfully the new dihydro-2-pyridinecarboxamide **5e** (69 %) after 3 hours reaction. In the $^1$H-NMR spectrum of compound **5e** an ABX-pattern for the protons in position 3 and 4 and a broad singulet at 3.0 ppm (OH) was observed. The dehydration of **5e** was performed with three equivalents of DBU in refluxing toluene providing 94 % of **6e** after one day. However treatment of the adducts

**3g,i** with amines led to complex reaction mixtures probably due to cleavage of the lactone and substitution of the thiobenzyl or cyano group. Moreover, attempts to cleave the lactone bridge in some amino substituted adducts with other amines such as the sterically hindered 2,6-diethylaniline, *t*-butylamine and the less nucleophilic 3-(trifluoromethyl)aniline also failed. This problem was overcome by reacting the required amine dissolved in dry dichloromethane with an equimolar amount of trimethylaluminum in hexane affording the amide.[12] The lactone was then added dropwise to the amide and the mixture was stirred at room or reflux temperature. After completion the mixture was treated with diluted HCl and extracted with dichloromethane. Treatment of **3b** and **3g** with 2.2 equivalents $NH_2$-*t*-Bu/$AlMe_3$ or 2,6-diethylaniline/$AlMe_3$ led to a selective lactone cleavage but failed in the case of **3i**, probably due to side reactions of the cyano function.[13] As exemplified for **5g**, compounds of type **5** can be isolated if required: dehydration of the crude reaction mixture (after workup procedure) with DBU in refluxing toluene, provided 62 % of **6f** and 68 % **6g**.

We found that lactone cleavage, HCl elimination and dehydration could be realised in one step by using an excess of amine/$Me_3Al$ and refluxing in toluene for a prolonged period. Thus 83 % of **6h** was isolated using four equivalents of 3-(trifluoromethyl)aniline/$Me_3Al$. Cleavage of the lactone, HCl elimination, dehydration and even functionalisation could be done in one step by treating the non-functionalised adducts **2a,c,d** using the above described procedure with an excess of amine/$Me_3Al$. Even with some less nucleophilic or sterically hindered amines, excellent yields of (*c*-annelated) 5-substituted 6-amino-2-pyridinecarboxamides **6h-k** with equal groups $R^6 = R^3$ were obtained. If required the precursors, 4,5-dihydro-5-hydroxy-2-pyridinecarboxamides **5**, could be isolated (e.g. **5l**) by using only 2.2 equivalents of amine/$Me_3Al$.

In conclusion we can state that the new functionalised bi(tri)cyclic adducts **3** and their precursors **2** are interesting synthons in the preparation of some variably substituted 2-pyridinecarboxylic acid derivatives **6** of interest for (phyto)pharmacalogical screening. This method can also give access to 4,5-dihydro-5-hydroxy-2-pyridinecarboxylic acid derivatives **5** which to our knowledge have scarcely been described. The remarkable direct formation of pyridines **6i-k** with equal groups $R^6 = R^3$ is possible by treatment of the non functionalised adducts **2** with an excess of amine/$Me_3Al$ in refluxing toluene for a prolonged period.

## EXPERIMENTAL SECTION

Infrared spectra were recorded on a Perkin-Elmer 297 grating IR spectrophotometer and a Perkin-Elmer 1720 Fourier transform spectrometer. $^1$H-NMR spectra and $^{13}$C-NMR spectra were recorded on a Bruker WM 250 or on a Bruker AMX 400 instrument. The $^1$H and $^{13}$C chemical shifts are reported in ppm relative to tetramethylsilane or the deuterated solvent as an internal reference. Mass spectra were run by using a Kratos MS50TC instrument and a DS90 data system. For the chromatography analytical TLC plates (Alugram Sil G/$UV_{254}$) and 70-230 mesh silica gel 60 (E.M. Merck) were used. Melting points were taken using a Reichert-Jung Thermovar apparatus and an Electrothermal IA 9000 digital melting point apparatus and are uncorrected.

Microanalyses were performed by Janssen Pharmaceutica on a Carlo Erba elemental analyser type 1106. Synthesis and spectroscopic data of the cycloadducts **2** (except **2d**) of **3j** are described in a previous article.[1,2]

*I. Synthesis of (±)-endo, -exo 4,6-dichloro-1-methyl-2-oxa-5-azatricyclo[5.2.2.0$^{7,8}$]undec-5-en-3-one* ***2d.***

Cyclopentene (0.017 mmol, 1.5 ml) was added at once to a stirred solution of 3,5-dichloro-6-phenyl-2*H*-1,4-oxazin-2-one[5] **1b** (1.0 g, 5.6 mmol) in $CHCl_3$ (5 ml). After reflux for one day the solvent was evaporated and the crude reaction mixture purified by crystallisation in $CCl_4$.

mp: 112 °C ($CCl_4$); IR (KBr) cm$^{-1}$: 1751 (s), 1608 (s); $^1$H NMR ($CDCl_3$) δ: 1.42 - 3.41 (m, 8H, H-7 ,H-8 and ($C\underline{H}_2$)$_3$), 7.45 (m, 5H, $H_{arom}$); $^{13}$C NMR ($CDCl_3$): *endo*-isomer: 27.0, 28.5, 31.0 ($CH_2$), 49.1, 50.2 (C-7 and C-8), 87.2, 89.4 (C-1 and C-4), 128.2, 128.5, 130.1, 132.8 ($C_{arom}$, $C_{ipso}$), 163.6 (C-6), 165.1 (C-3); *exo*-isomer: 27.2, 27.5, 28.8 ($CH_2$), 46.8, 50.7 (C-7 and C-8), 88.7, 89.2 (C-1 and C-4), 126.8, 128.7, 129.6, 132.6 ($C_{arom}$ and $C_{ipso}$), 164.5 (C-3), 165.8 (C-6); evidence for a 7,8-disubstituted *endo* structure: 165.1 ppm: d, $^3J_{C3\text{-}H8exo}$ = 2 Hz; 163.6 ppm: d, $^3J_{C6\text{-}H7exo}$ = 8.5 Hz; evidence for a 7,8-disubstituted *exo* structure: 164.5 ppm, d, $^3J_{C3\text{-}H8endo}$ = 7 Hz; 165.8 ppm, br s $^3J_{C6\text{-}H7endo} \approx 0$ Hz.; m/z (%): 309 ($M^+$, 1), 265 (100), 230 (81); exact mass cald for $C_{15}H_{13}Cl_2NO_2$: 309.0323: found: 309.0320

*II. Synthesis of the 6-functionalised-4-chloro-2-oxa-5-azabicyclo[2.2.2]oct-5-en-3-ones 3 and 4.*

**(±)-6-Propylamino, (±)-6-diethylamino, (±)-6-(1-piperidinyl), (±)-6-phenylamino substituted -4-chloro-2-oxa-5-azabicyclo[2.2.2]oct-5-en-3-ones 3a-c, 3e and (±)-*endo* 4-chloro-1-methyl-2-oxa-6-(1-piperidinyl)-5-aza-tricyclo[5.2.2.0$^{7,8}$]undec-5-en-3-one 3d. General procedure:**

The amine (10 mmol) dissolved in $CH_2Cl_2$ or THF (5 ml) was added dropwise to a refluxing (r.t.; **3e**) mixture of adduct **2a** or **2c** (5 mmol) and $Et_3N$ (0.71 ml, 5 mmol) dissolved in $CH_2Cl_2$ (**3a-c, 3e**) or THF (**3d**) (10 ml). In the case of **3a** 1.2 eq. propylamine was used. After 15 min - 1 d the solvent was removed at reduced pressure and the residue purified by chromatography on silica gel with $CH_2Cl_2$/EtOAc (95:5) as eluent (yields: 48-96 %) (Table 1).

**(±)-4-Chloro-1-methyl-2-oxa-6-propylamino-5-azabicyclo[2.2.2]oct-5-en-3-one 3a.**

mp: 107 °C (*n*-Hex/$CH_2Cl_2$); IR (KBr) cm$^{-1}$: 3410 (m), 1760 (s),1610 (s), 1545 (s); $^1$H NMR ($CDCl_3$) δ: 0.93 (t, 3H, $J$ = 7.0 Hz, $CH_2CH_2C\underline{H}_3$), 1.60 (sext, 2H, $J$ = 7.0 Hz, $CH_2C\underline{H}_2CH_3$), 1.67 (s, 3H, 1-$CH_3$), 1.82 (ddd, 1H, $J$ = 14.0, 11.0, 3.6 Hz, H-7), 2.09 (ddd, 1H, $J$ = 14.0, 10.0, 5.5 Hz, H-7), 2.26 (ddd, 1H, $J$ = 13.0, 11.0, 5.5 Hz, H-8), 2.34 (ddd, 1H, $J$ = 13.0, 10.0, 3.6 Hz, H-8), 3.24 (m, 2H, $C\underline{H}_2CH_2CH_3$), 4.89 (br s, 1H, NH); $^{13}$C NMR ($CDCl_3$): 11.2 ($CH_3$), 18.3 ($CH_2$), 21.8 (1-$CH_3$), 31.8, 34.0 (C-7) and (C-8), 42.8 ($CH_2N$), 79.1, 83.1 (C-1) and (C-4), 161.7 (C-6), 168.8 (C-3); m/z (%): 230 ($M^+$, 6), 186 (100), 171 (17), 157 (47); exact mass cald for $C_{10}H_{15}ClN_2O_2$: 230.0820; found: 230.0818; anal cald for $C_{10}H_{15}ClN_2O_2$: C 52.07, H 6.55, N 12.14; found: C 51.86, H 6.67, N 11.94

**(±)4-chloro-6-diethylamino-1-methyl-2-oxa-5-azabicyclo[2.2.2]oct-5-en-3-one 3b.**

mp: 53 °C (*n*-Hex/$Et_2O$); IR (KBr) cm$^{-1}$: 3450 (m), 1775 (s), 1577 (s); $^1$H NMR ($CDCl_3$) δ: 1.16 (t, 6H, $J$ = 7.0 Hz, 2 x $CH_2C\underline{H}_3$), 1.87 (s, 3H, 1-$CH_3$), 1.89 (ddd, H, $J$ = 13.5, 11.5, 3.5 Hz, H-7), 2.06 (ddd, 1H, $J$ = 13.5, 10.0, 5.5 Hz, H-7), 2.21 (ddd, 1H, $J$ = 12.5, 11.5, 5.5 Hz, H-8), 2.38 (ddd, 1H, $J$ = 12.5, 10.0, 3.5 Hz, H-8), 3.46 (q, 4H, $J$ = 7.0 Hz, 2 x $C\underline{H}_2CH_3$); $^{13}$C NMR ($CDCl_3$): 13.3 ($CH_3$), 22.5 (1-$CH_3$), 33.4 (C-7), 33.9 (C-8),

43.5 ($CH_2N$), 81.7 (C-4), 83.2 (C-1), 163.2 (C-6), 168.2 (C-3); m/z (%): 244 ($M^+$, 7), 202 (32), 200 (100), 185 (33), 172 (39); exact mass cald for $C_{11}H_{17}ClN_2O_2$: 244.0974: found: 244.0972; anal cald for $C_{11}H_{17}ClN_2O_2$: C 53.99, H 7.00, N 11.45; found: C 53.97, H 7.07, N 11.37

**(±)-4-chloro-1-methyl-2-oxa-6-(1-piperidinyl)-5-azabicyclo[2.2.2]oct-5-en-3-one 3c.**

mp: 95 °C ($CCl_4$): IR (KBr) $cm^{-1}$: 1762 (s), 1564 (s); $^1H$ NMR ($CDCl_3$) δ: 1.63 (m, 6H, γ,β-$CH_2$-pip, 1.82 (s, 3H, 1-$CH_3$), 1.83 - 2.40 (m, 4H, H-7 and H-8), 3.27 (m, 4H, α-$CH_2$-pip); $^{13}C$ NMR ($CDCl_3$): 22.3 (1-$CH_3$), 24.1, 25.3 ($CH_2$), 33.0 (C-7), 33.7 (C-8), 48.8 ($CH_2N$), 81.7 (C-1), 83.5 (C-4), 166.2 (C-6), 167.8 (C-3); m/z (%): 256 ($M^+$, 4), 212 (74), 197 (43), 177 (35), 69 (100); exact mass cald for $C_{12}H_{17}ClN_2O_2$: 256.0978; found: 256.0980; anal cald for $C_{12}H_{17}ClN_2O_2$: C 56.14, H 6.67, 10.91; found: C 56.03, H 6.67, N 10.77

**(±)-*Endo* 4-chloro-1-methyl-2-oxa-6-(1-piperidinyl)-5-aza-tricyclo[5.2.2.$0^{7,8}$]undec-5-en-3-one 3d.**

oil; IR (NaCl, film) $cm^{-1}$: 1769 (s), 1560 (s); $^1H$ NMR ($CDCl_3$) δ:1.00 - 2.45 (m, 12H, γ,β-$CH_2$-pip and $(CH_2)_3$), 1.80 (s, 3H, 1-$CH_3$), 2.61 (dt, 1H, $J$ = 10.0, 8.0 Hz, H-7), 2.81 (dt, 1H, $J$ = 10.0, 8.0 Hz, 1H, H-8), 3.36 (m, 4H, α-$CH_2$-pip); $^{13}C$ NMR ($CDCl_3$): 21.6 (1-$CH_3$), 23.7, 25.3, 26.4, 27.5, 28.9 ($CH_2$), 48.2 (N-$CH_2$), 48.6 (C-7) 51.1 (C-8), 84.1 (C-1), 86.1 (C-4), 164.9 (C-6), 168.5 (C-3); m/z (%): 296 ($M^+$, 2), 252 (65), 217 (100); exact mass cald for $C_{15}H_{21}ClN_2O_2$: 296.1292; found: 296.1293

**(±)-4-Chloro-1-methyl-2-oxa-6-phenylamino-5-azabicyclo[2.2.2]oct-5-en-3-one 3e.**

mp: 169 °C (*n*-Hex/$CH_2Cl_2$); IR (KBr) $cm^{-1}$: 3445 (m), 1780 (s), 1600 (s), 1545 (s); $^1H$ NMR ($CDCl_3$) δ: 1.78 (s, 3H, 1-$CH_3$), 1.90 - 2.50 (m, 4H, H-7 and H-8), 5.45 (br s, 1H, NH), 7.10 - 7.70 (m, 5H, $H_{arom}$); $^{13}C$ NMR ($CDCl_3$): 19.5 (1-$CH_3$), 32.5 (C-7), 35.0 (C-8), 81.7 (C-1), 84.9 (C-4), 121.9, 125.1, 129.8, 140.0 ($C_{arom}$ + $C_{ipso}$), 161.3 (C-6), 169.6 (C-3); m/z (%): 264 ($M^+$, 85), 220 (70), 185 (40), 117 (100); exact mass cald for $C_{13}H_{13}ClN_2O_2$: 264.0662; found: 264.0665; anal cald for $C_{13}H_{13}ClN_2O_2$: C 58.99, H 4.95, N 10.58; found: C 58.80, H 4.79, N 10.46

**(±)-6-[(2,4-Difluorophenyl)amino], (±)-6-phenylmethylthio and (±)-6-(4-methoxyphenyl) substituted -4-chloro-1-methyl-2-oxa-5-azabicyclo[2.2.2]oct-5-en-3-ones (3f-h). General procedure:**

2,4-Difluoroaniline, benzyl mercaptan or anisole (2.8 mmol) dissolved in $CH_2Cl_2$ (5 ml) was added dropwise to a stirred mixture of adduct **2a** (0.3 g, 1.4 mmol) and $AlCl_3$ (0.4 g, 3.0 mmol) in $CH_2Cl_2$ (10 ml) at r.t. (0 °C, **3h**). After reaction for 15 min to 4 h the mixture was poured into an ice bath and extracted with $CH_2Cl_2$ (3 x 50 ml). The combined $CH_2Cl_2$ portions were dried ($MgSO_4$). Evaporation of the solvent under reduced pressure afforded a residue that was purified by chromatography on silica gel with $CH_2Cl_2$/EtOAc (95:5) as eluent (yields: 47-88 %) (Table 1).

**(±)-4-Chloro-6-[(2,4-difluorophenyl)amino]-1-methyl-2-oxa-5-azabicyclo[2.2.2]oct-5-en-3-one 3f.**

mp: 133 °C ($CH_2Cl_2$/*n*-Hex); IR (KBr) $cm^{-1}$: 3225 (m), 1785 (s), 1603 (s), 1521 (s); $^1H$ NMR ($CDCl_3$) δ: 1.82 (s, 3H, 1-$CH_3$), 1.95 - 2.38 (m, 4H, H-7 and H-8), 3.60 (br s, 1H, NH), 6.69 - 8.40 (m, 3H, $H_{arom}$); $^{13}C$ NMR ($CDCl_3$): 18.3 (1-$CH_3$), 31.9 (C-7), 33.6 (C-8), 79.3 (C-1), 82.3 (C-4), 103.6, 110.7, 122.4, 122.8 ($C_{arom}$ + $C_{ipso}$), 152.5 (CF), 158.4 (CF), 158.7 (C-6), 167.8 (C-3); m/z (%): 300 ($M^+$, 47), 256 (87), 221 (27), 180 (47), 117 (100); exact mass cald for $C_{13}H_{11}ClF_2N_2O_2$: 300.0477; found: 300.0478; anal cald for $C_{13}H_{11}ClF_2N_2O_2$: C 51.93, H 3.69, N 9.32; found: C 51.55, H 3.58, N 9.15

**(±)-4-Chloro-1-methyl-2-oxa-6-phenylmethylthio-5-azabicyclo[2.2.2]oct-5-en-3-one 3g.**

oil; IR (NaCl, film) $cm^{-1}$: 1785 (s), 1560 (s); $^1H$ NMR ($CDCl_3$) δ: 1.70 (s, 3H, 1-$CH_3$), 1.79 - 2.34 (m, 4H, H-7 and H-8), 4.25 (s, 2H, $CH_2S$), 7.30 (m, 5H, $H_{arom}$); $^{13}C$ NMR ($CDCl_3$): 18.6 (1-$CH_3$), 31.3 (C-7) 33.1 (C-8)

34.2 ($SCH_2$), 81.7 (C-1) 85.2 (C-4) 127.6, 128.5, 129.1, 135.2 ($C_{arom}$) 166.4 (C-3) 174.2 (C-6); m/z (%): 295 ($M^+$, 58), 251 (6), 218 (22), 91 (100); exact mass cald for $C_{14}H_{14}ClN_2O_2S$: 295.0429; found: 295.0433

**(±)-4-Chloro-6-(4-methoxyphenyl)-1-methyl-2-oxa-5-azabicyclo[2.2.2]oct-5-en-3-one 3h.**

oil; IR (NaCl, film) $cm^{-1}$: 1775 (s), 1610 (s); $^1H$ NMR ($CDCl_3$) δ: 1.85 (s, 3H, 1-$CH_3$), 1.80 - 2.50 (m, 4H, H-7 and H-8), 3.85 (s, 3H, $OCH_3$), 6.93 (d, 2H, $J$ = 7.5 Hz, $H_{arom}$), 7.48 (d, 2H, $J$ = 7.5 Hz, $H_{arom}$); $^{13}C$ NMR ($CDCl_3$): 21.6 (1-$CH_3$), 32.3 (C-7), 32.7 (C-8), 55.3 ($CH_3O$), 81.9 (C-1), 84.5 (C-4), 113.9, 125.7, 129.7, 161.7 ($C_{arom}$), 166.9 (C-3), 174.1 (C-6); m/z (%): 279 ($M^+$, 16), 235 (100), 220 (22), 200 (24); exact mass cald for $C_{14}H_{14}ClNO_3$: 279.0662; found: 279.0661

**(±)-4-Chloro-6-cyano-1-methyl-2-oxa-5-azabicyclo[2.2.2]oct-5-en-3-one 3i.**

A mixture of **2a** (0.3 g, 1.4 mmol), KCN (0.09 g, 1.7 mmol) and a catalytic amount of 18-crown-6 ether in $CH_3CN$ (5ml) was stirred for 24 h at r.t.. After removal of the salts by filtration and evaporation of the filtrate under reduced pressure the residue was purified by chromatography on silica gel with $CH_2Cl_2$/EtOAc (95:5) as eluent (0.26 g, yield: 96 %) (Table 1).

mp: 127 °C ($CCl_4$); IR (KBr) $cm^{-1}$: 1790 (s), 1600 (s); $^1H$ NMR ($CDCl_3$) δ: 1.90 (s, 3H, 1-$CH_3$), 1.90 -2.60 (m, 4H, H-7 and H-8); $^{13}C$ NMR ($CDCl_3$): 19.5 (1-$CH_3$), 31.1 (C-7), 32.3 (C-8), 80.1 (C-1), 84.5 (C-4), 110.5 (CN), 154.3 (C-6), 163.8 (C-3); m/z (%): 154 ($M^+$-$CO_2$, 97), 139 (33), 119 (100); exact mass cald for $C_7H_7ClN_2$ [$M^+$ -$CO_2$]: 154.0296; found: 154.0304 ; anal cald for $C_8H_7ClN_2O_2$: C 48.08, H 3.55, N 14.10; found: C 47.72, H 3.58, N 13.95

**(±)-4-Chloro-1-methyl-2-oxa-6-thioxo-5-azabicyclo[2.2.2]oct-5-en-3-one 4.**

A mixture of **2a** (0.3 g, 1.4 mmol) and KSCN (0.16 g, 1.7 mmol) in $CH_3CN$ (5ml) was stirred for 4 days at 80 °C. Then $H_2O$ (15 ml) was added, the resulting mixture extracted with $CH_2Cl_2$ (3 x 50 ml) and dried ($MgSO_4$). After removal of the solvent at reduced pressure, chromatography on silica gel with $CH_2Cl_2$/EtOAc (95:5) as eluent gave **4** as a pure solid (0.12 g, yield: 41 %) (Table 1).

mp: 152 °C (*n*-Hex/$CH_2Cl_2$); IR (KBr) $cm^{-1}$: 3100 (s), 1795 (s), 1500 (s); $^1H$ NMR ($CDCl_3$) δ: 1.85 (s, 3H, 1-$CH_3$), 1.80 - 2.70 (m, 4H, H-7 and H-8), 9.10 (br s, 1H, NH); $^{13}C$ NMR ($CDCl_3$): 22.1 (1-$CH_3$), 31.4 (C-7), 34.6 (C-8), 74.5 (C-4), 86.8 (C-1), 164.2 (C-3), 198.7 (C-6); m/z (%): 205 ($M^+$, 60), 161 (20), 126 (100), 98 (11); exact mass cald for $C_7H_8ClNO_2S$: 204.9962; found: 204.9970; anal cald for $C_7H_8ClNO_2S$: C 40.88, H 3.92, N 6.81; found: C 40.73, H 3.94, N 6.70

*III. Synthesis of (4,5-Dihydro-)(3,4,)6-substituted-5-methyl(or phenyl)-2-pyridinecarboxylic acid derivatives* ***5*** *and* ***6****.*

**Procedure a:**

A stirred mixture of the **3c,d** or **3i** (1.4 mmol), DBU (1.7 ml, 11.2 mmol) and ROH (11.2 mmol) in THF (10 ml) was refluxed for 2 days (r.t., **3i**). Evaporation of the solvent under reduced pressure afforded a residue that was purified by chromatography on silica gel with $CH_2Cl_2$/EtOAc (8:2) as eluent (Table 2) yielded compounds **6a-c**.

**Procedure c-d:**

To the adduct **3a** (1.0 g, 4.3 mmol) dissolved in $CHCl_3$ (10 ml) propylamine (1.06 ml, 12.9 mmol) was added. After reflux for 3 hours, the solvent was evaporated under reduced pressure; the residue was purified by chomatography on silica gel with $CH_2Cl_2$/EtOAc (7:3-1:9) as eluent providing compound **5e** (0.75 g, 69 %). The latter was disolved in toluene (10 ml) and 3 equiv of DBU were added. Reflux for two days, work-up and

purification as above yielded pyridine **6e** (procedure d) in the same way compounds **6f** and **6g** were isolated from the crude reaction mixture obtained by procedure e.

**Procedure e and f: reaction of adducts 2a-d and 3b,f,g with amine/$Me_3Al$**

A hexane solution (2M) of trimethylaluminum (4.5 mmol in procedure e **5g**, **5l**, **6f**, 8.0 mmol in procedure f, **6h,k**) was slowly added at r.t. to a solution of an equimolar amount of the amine in dry $CH_2Cl_2$ (10 ml; **5g**, **5l**) or toluene (10 ml; **6f,h-k**) under nitrogen atmosphere. The mixture was stirred at r.t. for 15 min and a $CH_2Cl_2$ or toluene (10 ml) solution of the adduct **2** or **3** (2.0 mmol) was added. After 1 day (**5g, 5l**), 3 days (**6f**) or 4 days (**6h-k**) reaction at r.t. (**5g,l**) or reflux temperature (**6f, 6h-k**) the reaction mixture was quenched with 1N HCl solution and extracted with $CH_2Cl_2$ (3 x 50 ml). The combined $CH_2Cl_2$ layers were dried ($MgSO_4$) and concentrated under reduced pressure. The 4,5-dihydro pyridines **5g,l** were isolated by chromatography on silica gel with $CH_2Cl_2$/EtOAc (8:2) as eluent (yields: 69-82%); applying procedure d the crude compound **5f,g** led to the pyridines **6f,g**. In the case procedure f (using 8.0 mmol of trimethylaluminum), dehydration took place *in situ* on reflux. Workup procedure and repeated washing of the crude residue with with $CH_2Cl_2$/Diisopropylether (1:5) (**6j**) or chromatography on silicagel with $CH_2Cl_2$/EtOAc (8:2) as eluent provided the pure pyridines **6h-k** (Table 2).

**(±)-4,5-Dihydro-5-hydroxy-5-methyl-*N*-propyl-6-propylamino-2-pyridinecarboxamide 5e.**

mp: 135 °C ($CH_2Cl_2$/*n*-Hex); IR (KBr) $cm^{-1}$: 3360 (m), 1665 (s), 1625 (s), 1595 (s); $^1H$ NMR ($CDCl_3$) δ: 0.97 (m, 6H, 2 x $CH_2CH_2C\underline{H}_3$), 1.27 (s, 3H, 5-$CH_3$), 1.61 (m, 6H, $CH_2C\underline{H}_2CH_3$), 2.30 (dd, 1H, $J$ = 20, 6 Hz, H-4), 2.49 (dd, 1H, $J$ = 20, 3.5 Hz, H-4), 3.00 (br s, 1H, OH), 3.30 (m, 4H, 2 x $C\underline{H}_2CH_2CH_3$), 6.00 (br t, 1H, NH), 6.25 (dd, 1H, $J$ = 6, 3.5 Hz, H-3), 7.80 (br s, 1H, CONH); $^{13}C$ NMR ($CDCl_3$): 11.2, 11.4 ($CH_3$), 22.1, 22.6 ($CH_2$), 25.2 (5-$CH_3$), 36.1 (C-4), 40.7, 42.1 ($NCH_2$), 68.2 (C-5), 109.3 (C-3), 138.6 (C-2), 164.5 (C-6), 165.7 (CO); m/z (%): 253 ($M^+$, 100), 224 (31), 196 (28), 168 (90); exact mass cald for $C_{13}H_{23}N_3O_2$: 253.1790; found: 253.1789

**(±)-6-Diethylamino-*N*-(2,6-diethylphenyl)-4,5-dihydro-5-hydroxy-5-methyl-2-pyridinecarboxamide 5g.**

oil; IR (KBr) $cm^{-1}$: 3400 (m), 3300 (m), 1635 (s), 1550 (s), 1495 (s); $^1H$ NMR ($CDCl_3$) δ: 1.20 (m, 12H, 4 x $CH_2C\underline{H}_3$), 1.34 (s, 3H, 5-$CH_3$), 2.28 (dd, 1H, $J$ = 18.0, 6.5 Hz, H-4), 2.53 (dd, 1H, $J$ = 18.0, 2.5 Hz, H-4), 2.62 (q, 4H, $J$ = 7.5 Hz, 2 x $C\underline{H}_2CH_3$), 2.90 (br s, 1H, OH), 3.50 (m, 4H, 2 x $C\underline{H}_2CH_3$), 6.27 (dd, 1H, $J$ = 6.5, 2.5 Hz, H-3), 7.15 (m, 3H, $H_{arom}$), 9.20 (br s, 1H, CONH); $^{13}C$ NMR ($CDCl_3$): 12.9, 14.3 ($CH_3$), 24.6 (5-$CH_3$), 24.9 ($CH_2$), 39.9 (C-4), 43.0 ($CH_2N$), 69.1 (C-5), 109.5 (C-3), 126.0, 127.1, 133.1, 141.4 ($C_{arom}$ + $C_{ipso}$), 138.2 (C-2), 163.4 (C-6) 164.4 (CO); m/z (%): 357 ($M^+$, 65), 342 (20), 328 (52), 43 (100); exact mass cald for $C_{21}H_{31}N_3O_2$: 357.2415; found: 357.2417

**(±)-*N*-(2,6-Diethylphenyl)-6-[(2,6-diethylphenyl)amino]-4,5-dihydro-5-hydroxy-5-phenyl-2-pyridinecarboxamide 5l.**

oil; IR (NaCl, film) $cm^{-1}$: 3350 (s), 3300 (s), 1660 (s), 1605 (s); $^1H$ NMR ($CDCl_3$) δ: 1.00 (m, 12H, 4x $CH_2C\underline{H}_3$), 2.40 (m, 10H, 4x $C\underline{H}_2CH_3$ + H-4), 2.78 (br s, 1H, OH), 5.25 (br s, 1H, NH), 6.95 (m, 1H, H-3), 7.04 - 7.40 (m, 11H, $H_{arom}$), 8.90 (br s, 1H, CONH); $^{13}C$ NMR ($CDCl_3$): 14.1, 14.6 ($CH_3$), 24.5, 24.9 ($CH_2$), 38.0 (C-4), 71.6 (C-5), 110.7 (C-3), 125.0, 126.0, 126.1, 127.1, 127.3, 127.9, 128.1, 132.9, 133.6, 138.7, 140.9, 141.7, 141.9 ($C_{arom}$ + $C_{ipso}$, C-2), 161.1 (C-6), 163.9 (CO); m/z (%): 495 ($M^+$, 100), 477 (42), 466 (20), 449 (50); exact mass cald for $C_{32}H_{37}N_3O_2$: 495.2877; found: 495.2885

**Methyl 5-methyl-6-(1-piperidinyl)-2-pyridinecarboxylate 6a.**

mp: 104 °C (*n*-Hex/$CCl_4$); IR (KBr) $cm^{-1}$: 1731 (s), 1575 (s); $^1H$ NMR ($CDCl_3$) δ: 1.63 (m, 2H, γ-$CH_2$-pip, 1.70 (m, 4H, β-$CH_2$-pip), 2.32 (s, 3H, 5-$CH_3$), 3.15 (m, 4H, α-$CH_2$-pip), 3.94 (s, 3H, $OCH_3$), 7.45 (d, 1H, $J$ = 7.5 Hz, H-4), 7.63 (d, 1H, $J$ = 7.5 Hz, H-3); $^{13}C$ NMR ($CDCl_3$): 18.7 (5-$CH_3$), 24.2, 26.2 ($CH_2$), 50.6 ($NCH_2$), 52.6 ($OCH_3$), 119.0 (C-3), 129.6 (C-5), 139.5 (C-4), 143.8 (C-2), 162.5 (C-6), 166.4 (CO); m/z (%): 234 ($M^+$, 48), 205 (41), 151 (44), 84 (100); exact mass cald for $C_{13}H_{18}N_2O_2$: 234.1364; found: 234.1369; anal cald for $C_{13}H_{18}N_2O_2$: C 66.64, H 7.74, N 11.96; found: C 66.87, H 7.89, N 12.02

**Ethyl 6,7-dihydro-4-methyl-3-(1-piperidinyl)-5*H*-2-pyrindine-1-carboxylate 6b.**

oil; IR (NaCl, film) $cm^{-1}$: 1735 (s), 1713 (s), 1595 (m); $^1H$ NMR ($CDCl_3$) δ: 1.40 (t, 3H, $J$ = 7 Hz, $CH_2C\underline{H}_3$), 1.59 (m, 2H, γ-$CH_2$-pip), 1.70 (m, 4H, β-$CH_2$-pip), 2.06 (pent, 2H, $J$ = 7.5 Hz, $CH_2C\underline{H}_2CH_2$), 2.22 (s, 3H, 4-$CH_3$), 2.78 (t, 2H, $J$ = 7.5 Hz, $C\underline{H}_2CH_2CH_2$), 3.10 (m, 4H, α-$CH_2$-pip), 3.22 (t, 2H, $J$ = 7.5 Hz, $CH_2CH_2C\underline{H}_2$), 4.38 (q, 2H, $J$ = 7 Hz, $C\underline{H}_2CH_3$); $^{13}C$ NMR ($CDCl_3$): 15.2 ($CH_3$), 14.4 (4-$CH_3$), 24.2, 26.3, 31.7, 32.6 ($CH_2$), 51.2 ($NCH_2$), 60.8 ($OCH_2$), 125.2 (C-4), 136.9 (C-7a), 138.4 (C-1), 156.3 (C-4a), 160.9 (C-3), 166.5 (CO); m/z (%): 288 ($M^+$, 69), 259 (71), 232 (51), 84 (100); exact mass cald for $C_{17}H_{24}N_2O_2$: 288.1838; found: 288.1841

**Ethyl 6-cyano-5-methyl-2-pyridinecarboxylate 6c.**

mp: 127 °C ($CCl_4$); IR (KBr) $cm^{-1}$: 2240 (w), 1740 (s), 1571 (m); $^1H$ NMR ($CDCl_3$) δ: 1.35 (t, 3H, $J$ = 7 Hz, $CH_2C\underline{H}_3$), 2.56 (s, 3H, 5-$CH_3$), 4.38 (q, 2H, $J$ = 7 Hz, $C\underline{H}_2CH_3$), 7.92 (d, 1H, $J$ = 8 Hz, 1H, H-4), 8.12 (d, 1H, $J$ = 8 Hz, H-3); $^{13}C$ NMR ($CDCl_3$): 13.9 ($CH_3$), 18.5 (5-$CH_3$), 62.0 ($OCH_2$), 115.3 (CN), 127.3 (C-3), 133.7 (C-5), 139.1 (C-4), 141.7 (C-2), 147.0 (C-6), 163.3 (CO); m/z (%): 190 ($M^+$, 8), 146 (16), 118 (100), 91 (11); exact mass cald for $C_{10}H_{10}N_2O_2$: 190.0740; found: 190.0743

**5-Methyl-*N*-propyl-6-propylamino-2-pyridinecarboxamide 6e.**

mp: 105 °C ($CH_2Cl_2$/*n*-Hex); IR (KBr) $cm^{-1}$: 3420 (m), 1680 (s), 1610 (s); $^1H$ NMR ($CDCl_3$) δ: 0.88 (m, 6H, 2 x $CH_2CH_2C\underline{H}_3$), 1.54 (m, 4H, 2 x $CH_2C\underline{H}_2CH_3$), 1.98 (s, 3H, 5-$CH_3$), 3.30 (m, 4H, 2 x $C\underline{H}_2CH_2CH_3$), 4.60 (br s, 1H, NH), 7.12 (d, 1H, $J$ = 7 Hz, H-4), 7.26 (d, $J$ = 7 Hz, 1H, H-3), 7.96 (br t, 1H, CONH); $^{13}C$ NMR ($CDCl_3$): 10.8, 11.1 ($CH_3$), 16.4 (5-$CH_3$), 22.2, 22.5 ($CH_2$), 40.4, 43.0 ($NCH_2$), 110.2 (C-3), 119.8 (C-5), 136.8 (C-4), 145.2 (C-2), 155.1 (C-6), 164.8 (CO); m/z (%): 235 ($M^+$, 100), 220 (46), 206 (69), 193 (88); exact mass cald for $C_{13}H_{21}N_3O$: 235.1684; found: 235.1686; anal cald for $C_{13}H_{21}N_3O$: C 66.35, H 8.99, N 17.96; found: C 66.55, H 9.04, N 17.97

***N*-*t*-Butyl-5-methyl-6-phenylmethylthio-2-pyridinecarboxamide 6f.**

oil; IR (NaCl, film) $cm^{-1}$: 3381 (m), 1739 (m), 1677 (s), 1577 (s); $^1H$ NMR ($CDCl_3$) δ: 1.45 (s, 9H, $(C\underline{H}_3)_3C$), 2.32 (s, 3H, 5-$CH_3$), 4.45 (s, 2H, $SCH_2$), 7.28 (d, 1H, $J$ = 7.5 Hz, H-4), 7.35 (m, 5H, $H_{arom}$), 7.75 (br s, 1H, CONH), 7.83 (d, 1H, $J$ = 7.5 Hz, H-3); $^{13}C$ NMR ($CDCl_3$): 18.3 (5-$CH_3$), 28.7 ($CH_3$), 34.2 ($SCH_2$), 50.6 ($\underline{C}(CH_3)_3$), 117.5 (C-3), 127.2, 128.5, 128.6 ($C_{arom}$), 133.4 (C-5), 137.3 ($C_{ipso}$), 137.4 (C-4), 148.1 (C-2), 156.3 (C-6), 163.3 (CO); m/z (%): 314 ($M^+$, 37), 258 (14), 225 (36), 91 (100); exact mass cald for $C_{18}H_{22}N_2OS$: 314.1453: found: 314.1458

**6-Diethylamino-*N*-(2,6-diethylphenyl)-5-methyl-2-pyridinecarboxamide 6g.**

oil; IR (NaCl, film) $cm^{-1}$: 3360 (m), 1700 (s), 1595 (s), 1505 (s); $^1H$ NMR ($CDCl_3$) δ:1.22 (t, 6H, $J$ = 7 Hz, $CH_2C\underline{H}_3$), 1.28 (t, 6H, $J$ = 7 Hz, $CH_2C\underline{H}_3$), 2.40 (s, 3H, 5-$CH_3$), 2.74 (q, 4H, $J$ = 7 Hz, 2x $C\underline{H}_2CH_3$), 3.35 (q, 4H, $J$ = 7 Hz, 2x $C\underline{H}_2CH_3$), 7.25 (m, 3H, $H_{arom}$), 7.60 (d, 1H, $J$ = 7.5 Hz, H-4), 7.81 (d, 1H, $J$ = 7.5 Hz, H-3), 8.47 (br s, 1H, CONH); $^{13}C$ NMR ($CDCl_3$): 12.9, 14.3 ($CH_3$), 19.0 (5-$CH_3$), 25.0 ($CH_2$), 44.8 ($CH_2N$), 115.4 (C-3), 126.3, 127.5, 133.1, 141.4 ($C_{arom}$ + $C_{ipso}$), 128.8 (C-5), 140.6 (C-4), 145.1(C-2), 159.6 (C-6), 163.6 (CO);

m/z (%): 339 ($M^+$, 100), 310 (94), 296 (30), 282 (74); exact mass cald for $C_{11}H_{17}ClN_2O_2$: 339.2310: found: 339.2302

**6-[(2,4-Difluorophenyl)amino]-5-methyl-*N*-[(3-trifluoromethyl)phenyl]-2-pyridinecarboxamide 6h.**

mp: 162 °C (THF/Diisopropylether); IR (KBr) $cm^{-1}$: 3383 (m), 3304 (m), 1675 (s), 1598 (s); $^1H$ NMR ($CDCl_3$) δ: 2.37 (s, 3H, 5-$CH_3$), 6.24 (br s, 1H, NH), 7.01 - 7.95 (m, 9H, $H_{arom}$ + H-3,4), 9.85 (br s, 1H, CONH); $^{13}C$ NMR ($CDCl_3$): 16.8 (5-$CH_3$), 104.0 ($C_{arom}$), 110.4 ($C_{arom}$), 114.4 (C-3), 115.6 ($C_{arom}$), 120.3 ($C_{arom}$), 121.7 ($C_{arom}$), 122.1 ($C_{arom}$), 122.3 (C-5), 123.6 ($CF_3$), 124.1 ($C_{ipso}$), 129.4 ($C_{arom}$), 131.3 (C-$CF_3$), 138.2 ($C_{ipso}$), 139.3 (C-4) 144.5 (C-2), 154.3 (CF), 158.3 (CF), 159.4 (C-6), 162.2 (CO); m/z (%): 407 ($M^+$, 28), 388 (20), 359 (9), 219 (100); exact mass cald for $C_{20}H_{14}F_5N_3O$: 407.1057; found: 407.1064; anal cald for $C_{20}H_{14}F_5N_3O$: C 58.97, H 3.46, N 10.32; found: C 58.66, H 3.35, N 10.23

***N*-(2,4-Difluorophenyl)-6-[(2,4-difluorophenyl)amino]-5-methyl-2-pyridinecarboxamide 6i.**

mp: 170 °C ($CH_2Cl_2$/Diisopropylether); IR (KBr) $cm^{-1}$: 3447 (m), 3342 (m), 1702 (s), 1598 (s), 1544 (s); $^1H$ NMR ($CDCl_3$) δ: 2.37 (s, 3H, 5-$CH_3$), 6.28 (s, 1H, NH), 6.93, 8.05, 8.59 (m, 6H, 2 x $C_6H_3F_2$), 9.92 (s, 1H, CONH); $^{13}C$ NMR ($CDCl_3$): 17.0 (5-$CH_3$), 103.3, 104.2, 110.8, 111.2 ($C_{arom}$), 114.5 (C-3), 121.3 ($C_{arom}$), 122.4 (C-5), 123.1, 123.6, 124.4 ($C_{arom}$), 139.3 (C-4), 144.9 (C-2), 150.5 (CF), 152.1 (C-6), 154.2 (CF), 154.4 (CF), 156.1 (CF), 162.3 (CO); m/z (%): 375 ($M^+$, 55), 219 (100); exact mass cald for $C_{19}H_{13}F_4N_3O$: 375.0995; found: 375.1002; anal cald for $C_{19}H_{13}F_4N_3O_1$: C 60.80, H 3.49, N 11.20; found: C 60.56, H 3.38, N 11.12

**6,7-Dihydro-4-methyl-*N*-phenylmethyl-6-phenylmethylamino-5*H*-2-pyridine-1-carboxamide 6j.**

mp: 203 °C (THF/MeOH); IR (KBr) $cm^{-1}$: 3407 (m), 3346 (m), 1656 (s), 1609 (s), 1533 (s); $^1H$ NMR ($CDCl_3$) δ: 1.94 (pent, 2H, $J$ = 7.5 Hz, $CH_2C\underline{H}_2CH_2$), 2.10 (s, 3H, 5-$CH_3$), 2.73 (t, 2H, $J$ = 7 Hz, $C\underline{H}_2CH_2CH_2$), 3.10 (t, 2H, $J$ = 7 Hz, $CH_2CH_2C\underline{H}_2$), 4.41 (d, 2H, $J$ = 7 Hz, $CH_2Ar$), 4.56 (d, 2H, $J$ = 7 Hz, $CH_2Ar$), 6.48 (br t, 1H, NH), 7.20 (m, 10H, $H_{arom}$), 8.30 (br s, 1H, CONH); $^{13}C$ NMR ($CDCl_3$): 12.8 (4-$CH_3$), 24.3, 30.2, 31.0 ($CH_2$), 41.7, 44.8 ($NCH_2$), 115.7 (C-4), 125.7, 126.4, 126.7, 126.8, 127.6, 127.9, 128.6 ($C_{arom}$), 137.9, 139.9 ($C_{ipso}$), 141.3 (C-7a), 152.0 (C-1), 153.7 (C-4a), 154.0 (C-3), 165.2 (CO); m/z (%): 371 ($M^+$, 100), 328 (31), 280 (13), 238 (95); exact mass cald for $C_{24}H_{25}N_3O$: 371.1998; found: 371.1991

**6,7-dihydro-4-phenyl-*N*-[3-trifluoromethyl)phenyl]-6-[(3-trifluoromethyl)phenyl)amino]-5*H*-2-pyrindine-1-carboxamide 6k.**

mp: 179 °C ($CH_2Cl_2$/Diisopropylether); IR (KBr) $cm^{-1}$: 3420 (m), 3290 (m), 1688 (s), 1596 (s), 1525 (s); $^1H$ NMR ($CDCl_3$) δ: 2.19 (pent, 2H, $J$ = 7.5 Hz, $CH_2C\underline{H}_2CH_2$), 2.69 (t, 2H, $J$ = 7.5 Hz, $C\underline{H}_2CH_2CH_2$), 3.48 (t, 2H, $J$ = 7.5 Hz, $CH_2CH_2C\underline{H}_2$), 6.40 (s, 1H, NH), 7.30 - 8.07 (m, 13H, $C_6H_5$ + 2 x $C_7H_4F_3$), 10.0 (s, 1H, CONH); $^{13}C$ NMR ($CDCl_3$): 25.1 (C-6), 32.0, 32.1 (C-5, C-7), 116.0, 116.1, 118.9, 120.4, 122.3, 122.9 ($C_{arom}$), 124.0 (C-4), 124.6 ($CF_3$), 124.7 ($CF_3$), 129.3, 129.7, 129.0, 128.9 ($C_{arom}$), 134.5 (C-7a), 135.0, 139.3, 138.5 ($C_{ipso}$), 140.9 (C-1), 149.1 (C-4a), 157.7 (C-3), 163.4 (CO); m/z (%): 541 ($M^+$, 53), 351 (100); exact mass cald for $C_{29}H_{21}F_6N_3O_1$: 541.1589: found: 541.1591; anal cald for $C_{29}H_{21}F_6N_3O_1$: C 64.33, H 3.91, N 7.76; found: C 64.40, H 3.66, N 7.68

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