Synthesis of 5-Phenyl-5,6,7,8-tetrahydro-1,6-naphthyridines and 5-Phenyl-6,7,8,9-tetrahydro-5*H*-pyrido[3,2-*c*]azepines as Potential D1 Receptor Ligands

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A new access to 5-phenyl-5,6,7,8-tetrahydro-1,6-naphthyridines **25a**-**28a** (n=1) and 5-phenyl-6,7,8,9-tetrahydro-5*H*-pyrido[3,2-*c*]azepines **25b**-**28b** (n=2) has been developed by first preparing the functional pyridine moiety followed by intramolecular cyclization forming the partially reduced ring.

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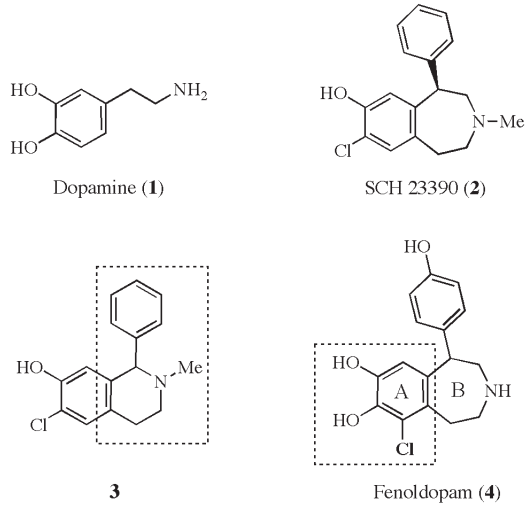
Introduction.

Dopamine (**1**) is a naturally occurring catecholamine which functions biochemically as neurotransmitter [1]. The dopamine receptors currently known are classified into five subtypes (D1-D5) [2,3].

Brain dopaminergic systems are implicated in a number of disorders, including psychomotor stimulant abuse, schizophrenia [4] and Parkinson's disease [5,6]. In the cardiovascular system, the administration of low doses of dopamine produces arteriolar dilation in certain organ beds, including the kidney [7].

In order to study physiological functions of dopamine receptors and to achieve new drugs for specific therapeutic use, highly selective and potent compounds have been developed. For example, the D1 receptor antagonist SCH23390 (**2**) plays an important role as radio ligand in receptor binding studies [8,9]. The phenyltetrahydroisoquinoline derivative **3**, its ring-contracted homolog, still possesses an antagonistic effect on D1 [10]. In contrast, Fenoldopam (**4**), a selective D1 agonist, is utilized in the United States to manage severe hypertensions [11] (Scheme 1). Our works have been concentrated on the development of further compounds with potential selectivity for the D1 receptor subtype based on a combination of lead structures **3** and **4**. The function of the electronegative chloro substituent in **4** should be replaced in terms of bioisosterical considerations inserting formally a nitrogen atom into aromatic ring A. As a consequence, in this paper we present a new access to 5-phenyltetrahydro-1,6-naphthyridines **25a-28a** (n=1) and the ring-extended phenyltetrahydropyrido[3,2-*c*]azepines **25b-28b** (n=2).

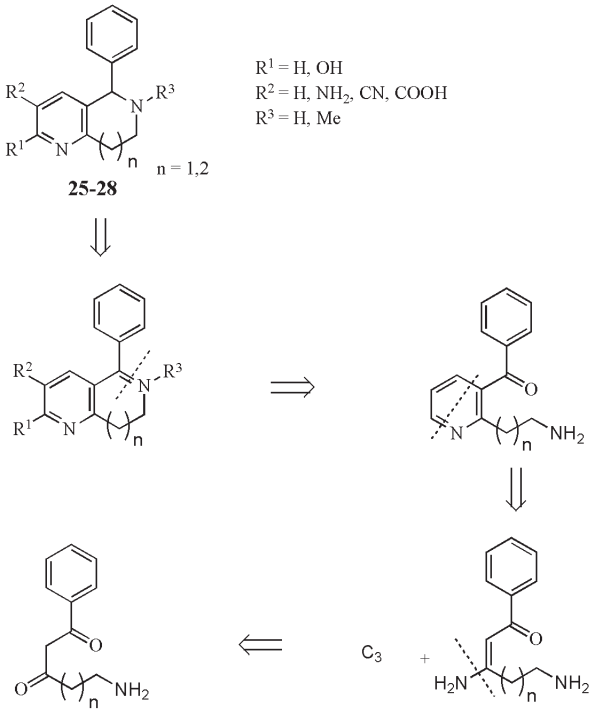
Scheme 1



Results and Discussion.

A short retrosynthetic consideration, outlined in scheme 2, clarifies our approach, *i.e.* first synthesis of a functional pyridine derivative and following intramolecular imine formation and further transformations. A dehydrogenation of title compounds **25a**,**b**-**28a**,**b** gives rise to those imines.

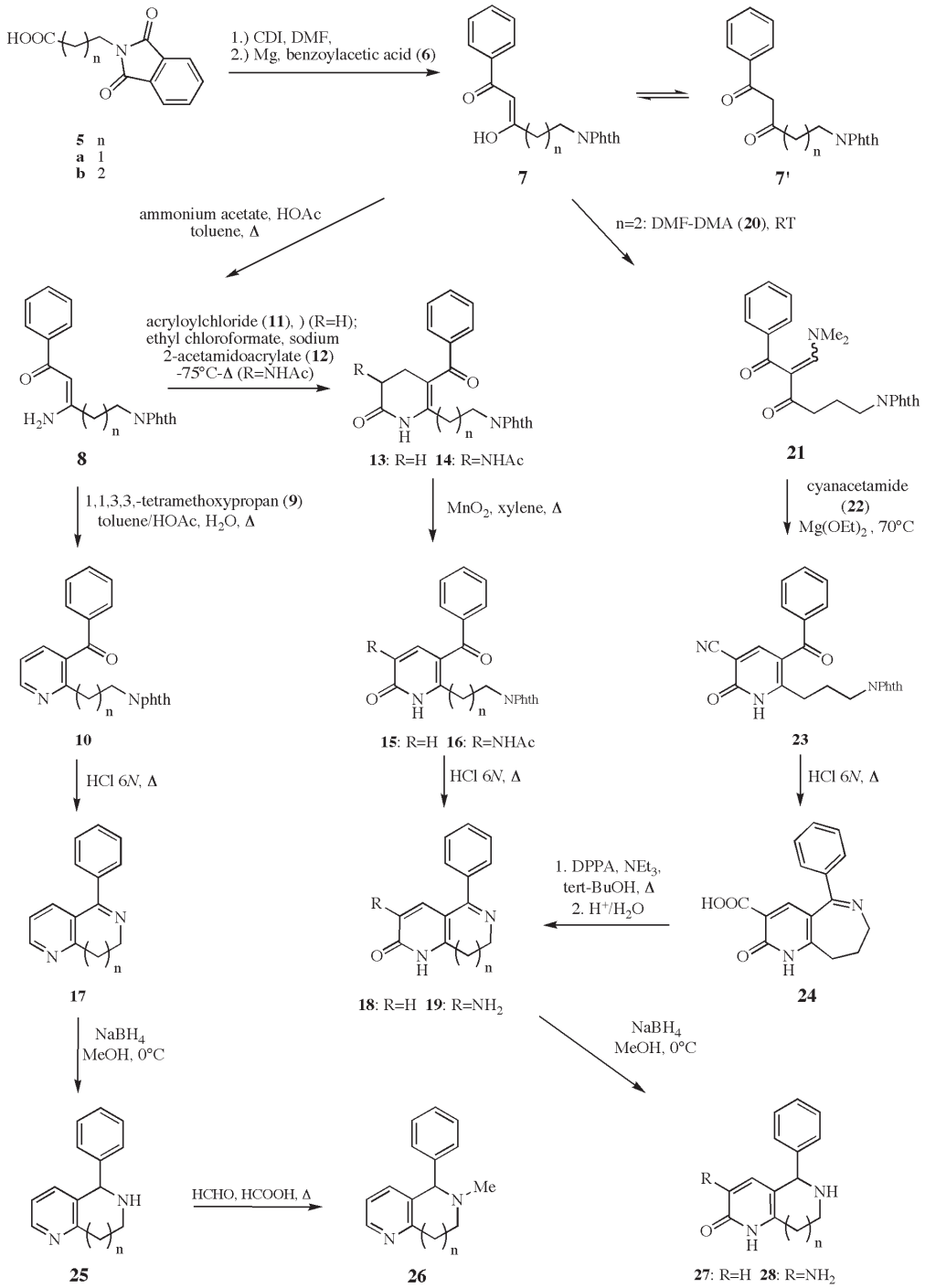
Scheme 2



Successive cleavage of both the imine bond and the pyridine ring, emphasized by broken lines, leads *via* 2-(aminoalkyl)-3-benzoylpyridines to C_3 building blocks and appropriate enaminones. The latter can be generated from diketones by ammonolysis.

As starting material, 1,3-diketones **7a**,**b** could be easily prepared by *in situ* activation of the *N*-phthaloyl protected amino acids **5a**,**b** using carbonyldiimidazole (CDI), and following addition of magnesium benzoylacetate (**6**) [12]. In ^{1}H nmr spectra **7a**,**b** were found to exist mainly as hydroxymethyleneketones, beside a small amount of diketones **7'a**,**b**. Compounds **7a,b** were converted into their appropriate enamines **8a,b** by an excess of ammonium acetate heating in toluene under azeotropic removal of

Scheme 3



water [13]. For ring closure to a pyridine derivative, these enamines were treated with different kinds of 1,3-biselectrophilic agents. By the use of 1,1,3,3-tetramethoxypropane (**9**), a diacetal of malonaldehyde, we isolated pyridines **10a**,**b** [14]. In order to achieve more functionalized pyridines, enamines **7a,b** were treated with substituted biselectrophilic C_3 compounds. Unfortunately, no suitable agents for a direct pyridine formation could be found, so we were forced to accept dihydropyridines as intermediates. According to this, dihydropyridones **13a**,**b** were prepared by refluxing acryloyl chloride (**11**) and **8a**,**b** in tetrahydrofuran [15,16]. For obtaining the 3-acetamidopyridones **14a**,**b**, commercially available 3-acetamidoacrylic acid (**12**) first was activated *in situ* to a mixed anhydride with ethyl chloroformate and reacted with enamines **8a**,**b** [17]. Resulting dihydropyridones **13a**,**b** and **14a**,**b** were oxidized with manganese (IV) oxide [17] and gave the desired 2-hydroxypyridines **15a**,**b** and **16a**,**b**, which were found to exist in their tautomeric 2(1*H*)-pyridone form according to ^{1}H nmr spectra. In the next step the *N*-phthalimido protecting group in **10a**,**b**,**15a**,**b**,**16a**,**b** was cleaved by refluxing in 6 *M* aqueous hydrochloric acid to reclaim a primary amino moiety for intramolecular ring closure with the benzoyl group [18]. Probably during neutralization of the reaction mixture the imines **17a**,**b**-**19a,b** were formed spontaneously.

In order to develop a method offering better results, we performed an alternative synthetic pathway by first considering aminopyridoazepine **19b** (R=NH_2, n=2) as target compound. Therefore, diketone **7b** (n=2) was stirred in *N*,*N*-dimethylformamide dimethyl acetal (DMF-DMA) (**20**) to get the dimethylaminomethylendiketone **21**, which was treated with the magnesium salt of cyanoacetamide (**22**) for ring closure in the next step [19]. The 3-cyanopyridone **23**, was refluxed in 6 *M* hydrochloric acid in order to cleave the phthalimido protecting group as well and to hydrolyze the cyano moiety. The resulting acid **24** was rearranged by a modified *Curtius* reaction employing diphenylphoshoryl azide (DPPA) and triethylamine in tertiary butanol leading to compound **19b** [20,21]. Due to no improvements in overall yield and an increased experimental effort, this way was not used for preparing other naphthyridines and pyridoazepines.

Finally, the dihydronaphthyridines **17a**-**19a** (n=1) and dihydropyridoazepines **17b**-**19b** (n=2) were reduced with $NaBH_4$ in methanol to give rise to the title compounds **25a**,**b**,**27a**,**b**,**28a,b** [22,23]. For further structural variation and for structure-activity-relationship studies, **25a**,**b** were *N*-methylated with formaldehyde/formic acid using the *Eschweiler-Clark* methodology to obtain **26a**,**b** [24,25]. (Scheme 3).

Dopamine D1 receptor binding was determined by measuring the ability to displace [^{3}H]SCH 23390 from porcine D1 receptors [26]. To assess D2long, D2short, [27] D3 [28] and D4.4 [29] affinities cloned human dopamine receptor subtypes stably expressed in Chinese hamster ovary cells (CHO) and the radioligand [^{3}H]spiperone were used for competition experiments.

The title compounds **25a**,**b**-**28a,b** showed no appreciable affinity to any of the dopamine receptors tested.

EXPERIMENTAL

Starting materials were obtained from commercial sources and were used without further purification. Solvents were dried by standard procedures. All anhydrous reactions were performed in oven-dried glassware. Reaction progress was observed by thin layer chromatography making use of commercial silica gel plates (Merck, silica gel F_{254} on aluminum sheets). All preparative chromatography was done on silica gel 60 (Merck). The medium pressure liquid chromatography (mplc) apparatus was composed of a Büchi B688 chromatography pump, a LKB Multirac 2111 fraction collector, and Buechi glass columns of different sizes. Melting points were determined in open capillary tubes on a Buechi 510 melting point apparatus and are uncorrected. Elemental analyses were performed by the Institut für Organische Chemie (university of Erlangen/Nuremberg) using Carlo Erba Elemental Analyzer 1108. ^{1}H nuclear magnetic resonance (^{1}H-nmr) spectra were determined with a Bruker AM 360 (360 MHz) spectrometer in appropriate deuterated solvents and are expressed in parts per million (δ, ppm) downfield from tetramethylsilane (internal standard). Nmr data are given as multiplicity (s, singlet; d, doublet; t, triplet; m, multiplet), coupling constants (J), and number of protons. Mass spectra (MS) were taken with a Finnigan MAT TSQ 70 mass spectrometer in the electron impact mode (70eV). Infrared (ir) spectra were obtained on a Jasco FT/IR 410 or Perkin-Elmer 1740 spectrometer.

2-[(3*Z*)-3-Hydroxy-5-oxo-5-phenylpent-3-en-1-yl)]-1*H*-isoindole-1,3(2*H*)-dione (**7a**).

3-Oxo-3-phenylpropionic acid (**6**) (19.70 g, 0.12 mole) was dissolved in 150 ml of dry tetrahydrofuran, and 6.87 g (60 mmoles) of magnesium ethoxide was added to the solution. After stirring for 4 hours, the mixture was concentrated *in vacuo*. Ethanol formed was aceotropically removed by using benzene as a co-solvent to give powdered magnesium 3-oxo-3-phenylpropionate. This was collected by filtration, washed profoundly with ether and dried *in vacuo*. *N*,*N*'-Carbonyldiimidazole (CDI) (17.84 g, 0.11 mole) of was added portion-wise to a solution of 21.92 g (0.1 mole) of 3-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)propionic acid (**5a**) in 200 ml of dry *N*,*N*-dimethylformamide under a nitrogen atmosphere. After stirring at room temperature for 1 hour, magnesium 3-oxo-3-phenylpropionate was added completely to the mixture. The whole was stirred for another 4 hours at room temperature, acidified with 2 *M* hydrochloric acid and extracted three times with ethyl acetate. The combined organic layer was washed with water, 5% aqueous sodium hydrogen carbonate, and brine, and then dried over sodium sulfate. Removal of the solvent gave crude **7a** which was purified by mplc using cyclohexane:ethyl acetate (7:3) as eluent to yield 24.4 g (76%) as colorless powder, mp 114-115 °C (MeOH); ir (potassium bromide): 1780 (phthaloyl), 1701 (CO), 1610 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 2.82 (t, J = 7 Hz, 2H, $COCH_2CH_2N$), 3.92 (t, J = 7 Hz, 2H, $COCH_2CH_2N$), 6.11 (s, 1H, =CH-), 7.50 - 7.72 (m, 3H, ben-

zoyl), 7.80 – 7.91 (m, 6H, benzoyl, phthaloyl), 15.78 (broad, s, 1H, OH, deuterium oxide-exchangeable); ms: m/z 321 (M^+), 174, 160.

Anal. Calcd. for $C_{19}H_{15}NO_4$ (321.34): C, 71.02; H, 4.71; N, 4.36. Found: C, 71.21; H, 4.58; N, 4.40.

2-[(4*Z*)-4-Hydroxy-6-oxo-6-phenylhex-4-en-1-yl)-1*H*-isoindole-1,3(2*H*)-dione (**7b**).

Preparation and purification according to **7a** using 23.32 g (0.1 mole) of 4-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)butyric acid (**5b**) to yield 26.2 g (78%) as colorless powder , mp 98-99 °C (MeOH); ir (potassium bromide): 1778 (phthaloyl), 1702 (CO), 1612 cm^{-1}; ^1H nmr ($CDCl_3$): δ 2.13 (tt, J_1 = 7 Hz, J_2 = 7 Hz, 2H, $COCH_2CH_2CH_2N$), 2.49 (t, J = 7 Hz, 2H, $COCH_2CH_2CH_2N$), 3.77 (t, J = 7 Hz, 2H, CO $CH_2CH_2CH_2N$), 6.21 (s, 1H, =CH-), 7.46 - 7.54 (m, 3H, benzoyl), 7.70 – 7.87 (m, 6H, phthaloyl), 15.99 (broad, s, 1H, OH, deuterium oxide-exchangeable); ms: m/z 335 (M^+), 175, 162, 105.

Anal. Calcd. for $C_{20}H_{17}NO_4$ (335.36): C, 71.63; H, 5.11; N, 4.18. Found: C, 72.00; H, 5.55; N, 3.99.

2-[(3*Z*)-3-Amino-5-oxo-5-phenylpent-3-en-1-yl)]-1*H*-isoindole-1,3(2*H*)-dione (**8a**).

2-[(3*Z*)-3-Hydroxy-5-oxo-5-phenylpent-3-en-1-yl)]-1*H*-isoindole-1,3(2*H*)-dione (**7a**) (14.45 g, 45 mmoles) and 17.34 g (0.3 mole) ammonium acetate were refluxed in 200 ml toluene adding 3 ml glacial acetic acid. Water was removed azeotropically using a Dean Stark apparatus. When separation of water was finished, the reactions mixture was cooled to room temperature, washed twice with saturated aqueous sodium hydrogen carbonate, once with water, and dried over sodium sulfate. After removal of the solvent, the residue was crystallized from ethanol to yield 10.62 g (74%) as pale yellow crystals, mp 119-121 °C (EtOH); ir (sodium chloride): 3583, 3403, 2926 (NH_2), 1772 (phthaloyl), 1712 (CO), 1610 cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.58 (t, = 7 Hz, 2H, $COCH_2CH_2N$), 3.90 (t, J = 7 Hz, 2H, $COCH_2CH_2N$), 5.58 (s, 1H, =CH-), 7.32 - 7.45 (m, 3H, benzoyl), 7.66-7.72 (m, 2H, benzoyl), 7.82 – 7.90 (m, 4H, phthaloyl), 7.96 (broad, s, 1H, NH_2, deuterium oxide-exchangeable), 9.89 (broad, s, 1H, NH_2, deuterium oxide-exchangeable); ms: m/z 320 (M^+), 172, 160.

Anal. Calcd. for $C_{19}H_{16}N_2O_3$ (320.35): C, 71.24; H, 5.03; N, 8.74. Found: C, 71.29; H, 4.77; N, 8.77.

2-[(4*Z*)-4-Amino-6-oxo-6-phenylhex-4-en-1-yl)]-1*H*-isoindole-1,3(2*H*)-dione (**8b**).

Preparation and purification according to **8a** using 15.08 g (45 mmoles) of 2-[(4*Z*)-4-hydroxy-6-oxo-6-phenylhex-4-en-1-yl)-1*H*-isoindole-1,3(2*H*)-dione (**7b**) to yield 10.38 g (69%) as pale yellow crystals, mp 126-128 °C (EtOH); ir (sodium chloride): 3395, 3059, 2934 (NH_2), 1769 (phthaloyl), 1713 (CO), 1607 cm^{-1}; ^1H nmr ($CDCl_3$): δ 2.04 (tt, J_1 = 7 Hz, J_2 = 6 Hz, 2H, $COCH_2CH_2CH_2N$), 2.33 (t, = 6 Hz, 2H, $COCH_2CH_2CH_2N$), 3.67 (t, J = 7 Hz, 2H, $COCH_2CH_2CH_2N$), 5.72 (s, 1H, =CH-), 5.80 (broad, s, 1H, NH_2, deuterium oxide-exchangeable), 7.40 - 7.47 (m, 3H, benzoyl), 7.70-7.75 (m, 2H, benzoyl), 7.81 – 7.90 (m, 4H, phthaloyl), 10.28 (broad, s, 1H, NH_2, deuterium oxide-exchangeable); ms: m/z 334 (M^+), 174, 161.

Anal. Calcd. for $C_{20}H_{18}N_2O_3$ (334.38): C, 71.84; H, 5.43; N, 8.38. Found: C, 71.75; H, 5.81; N, 7.99.

2-[2-(3-Benzoylpyridin-2-yl)ethyl]-1*H*-isoindole-1,3(2*H*)-dione (**10a**).

To a solution of 3.20 g (10 mmoles) 2-[(3*Z*)-3-amino-5-oxo-5-phenylpent-3-en-1-yl)]-1*H*-isoindole-1,3(2*H*)-dione (**8a**) in 50 ml of toluene:glacial acetic acid (7:3) was added 1.61 g (10 mmoles) 1,1,3,3-tetramethoxypropane and five drops of water. The reaction mixture was heated at reflux for 8 hours. Solvent was removed *in vacuo* and the residue was taken up in 20 ml of water. After neutralization with saturated aqueous sodium hydrogen carbonate, the mixture was extracted three times with ether. The combined organic layer was washed twice with saturated aqueous sodium hydrogen carbonate solution, once with water, and dried over sodium sulfate. Solvent was removed *in vacuo* and the oily residue was purified by mplc using cyclohexane:ethyl acetate (1:1) as eluent to yield 1.25 g (35%) as light yellow powder, mp 78-80 °C; ir (sodium chloride): 1772 (phthaloyl), 1713 (CO), 1665 cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.34 (t, J = 7 Hz, 2H, $ArCH_2CH_2N$), 3.93 (t, J = 7 Hz, 2H, $ArCH_2CH_2N$), 7.47 (dd, J_1 = 8 Hz, J_2 = 5 Hz, 1H, pyridine H-5), 7.45 - 7.48 (m, 2H, benzoyl), 7.63 – 7.70 (m, 3H, benzoyl), 7.76 (dd, J_1 = 8 Hz, J_2 = 2 Hz, 1H, pyridine H-4), 7.80 – 7.87 (m, 4H, phthaloyl), 8.65 (dd, J_1 = 5 Hz, J_2 = 2 Hz, 1H, pyridine H-6); ms: m/z 356 (M^+), 327, 196, 180.

Anal. Calcd. for $C_{22}H_{16}N_2O_3$ (356.38): C, 74.15; H, 4.53; N, 7.86. Found: C, 73.94; H, 4.42; N, 7.85.

2-[3-(3-Benzoylpyridin-2-yl)propyl]-1*H*-isoindole-1,3(2*H*)-dione (**10b**).

Preparation and purification according to **10a** using 3.34 g (10 mmoles) of 2-[(4*Z*)-4-amino-6-oxo-6-phenylhex-4-en-1-yl)]-1*H*-isoindole-1,3(2*H*)-dione (**7b**) to yield 1.20 g (32%) as light yellow powder, mp 91-93 °C; ir (sodium chloride): 1768 (phthaloyl), 1708 (CO), 1660 cm^{-1}; ^1H nmr ($CDCl_3$): δ 2.15 (tt, J_1 = 6 Hz, J_2 = 7 Hz, 2H, $ArCH_2CH_2CH_2N$), 2.87 (t, J = 7 Hz, 2H, $ArCH_2CH_2CH_2N$), 3.71 (t, J = 6 Hz, 2H, $ArCH_2CH_2CH_2N$), 7.22 (dd, J_1 = 7 Hz, J_2 = 4 Hz, 1H, pyridine H-5), 7.38 - 7.44 (m, 2H, benzoyl), 7.50 – 7.65 (m, 3H, benzoyl), 7.70 – 7.77 (m, 4H, phthaloyl), 7.81 (dd, J_1 = 7 Hz, J_2 = 2 Hz, 1H, pyridine H-4), 8.65 (dd, J_1 = 4 Hz, J_2 = 2 Hz, 1H, pyridine H-6); ms: m/z 370 (M^+), 341, 182.

Anal. Calcd. for $C_{23}H_{18}N_2O_3$ (370.41): C, 74.58; H, 4.90; N, 7.56. Found: C, 74.78; H, 4.58; N, 7.21.

2-[2-(3-Benzoyl-6-oxo-1,4,5,6-tetrahydropyridin-2-yl)ethyl)-1*H*-isoindole-1,3(2*H*)-dione (**13a**).

To a solution of 3.20 g (10 mmoles) of 2-[(3*Z*)-3-amino-5-oxo-5-phenylpent-3-en-1-yl)]-1*H*-isoindole-1,3(2*H*)-dione (**8a**) in 50 ml of dry tetrahydrofuran was added cautiously 1.18 g (13 mmoles) acryloyl chloride (**11**). The mixture was stirred for 15 minutes at room temperature and afterwards heated at reflux for 16 hours. After cooling, the reaction mixture was quenched with 100 ml of saturated aqueous sodium hydrogen carbonate solution. The organic layer was separated and the aqueous layer was extracted four times with chloroform. The combined organic layer was washed with water, and dried over sodium sulfate. The solvent was removed *in vacuo* and the residue was purified by flash chromatography using cyclohexane:ethyl acetate (1:1) as eluent to yield 2.54 g (68%) as colorless powder, mp 169-170 °C; ir (potassium bromide): 3286, 3222, 1772 (phthaloyl), 1718 (CO), 1659 (lactam) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.29 (t, J = 5 Hz, 2H, pyridine H-4), 2.35 (t, J = 5 Hz, 2H, pyridine H-3), 2.57 (t, J = 5 Hz, 2H, $ArCH_2CH_2N$), 3.80 (t, J = 5 Hz, 2H, $ArCH_2CH_2N$), 7.29 - 7.51 (m, 5H, benzoyl), 7.80 – 7.85 (m, 4H,

phthaloyl), 9.91 (s, broad, 1H, NH, deuterium oxide-exchangeable); ms: m/z 374 (M^+), 226, 214.

Anal. Calcd. for $C_{22}H_{18}N_2O_4$ (374.40): C, 70.58; H, 4.95; N, 7.48. Found: C, 70.49; H, 5.14; N, 7.46.

2-[3-(3-Benzoyl-6-oxo-1,4,5,6-tetrahydropyridin-2-yl)propyl)-1*H*-isoindole-1,3(2*H*)-dione (**13b**).

Preparation and purification according to **13a** using 3.34 g (10 mmoles) of 2-[(4*Z*)-4-amino-6-oxo-6-phenylhex-4-en-1-yl)]-1*H*-isoindole-1,3(2*H*)-dione (**8b**) to yield 2.46 g (66%) as colorless powder, mp 166-167 °C; ir (potassium bromide): 3116, 2934, 1774 (phthaloyl), 1718 (CO), 1666 (lactam) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.78 (tt, J_1 = 7 Hz, J_2 = 5 Hz, 2H, $ArCH_2CH_2CH_2N$), 2.16 (t, J = 7 Hz, 2H, $ArCH_2CH_2CH_2N$), 2.34 (t, J = 5 Hz, 2H, pyridine H-4), 2.46 (t, J = 5 Hz, 2H, pyridine H-3), 3.47 (t, J = 5 Hz, 2H, $ArCH_2CH_2CH_2N$), 7.32 – 7.41 (m, 3H, benzoyl), 7.51 – 7.59 (m, 2H, benzoyl), 7.81 – 7.85 (m, 4H, phthaloyl), 9.77 (s, broad, 1H, NH, deuterium oxide-exchangeable); ms: m/z 388 (M^+), 228, 214.

Anal. Calcd. for $C_{23}H_{20}N_2O_4$ (388.43): C, 71.12; H, 5.19; N, 7.21. Found: C, 71.04; H, 5.15; N, 7.54.

N-{5-Benzoyl-6-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-2-oxo-1,2,3,4-tetrahydropyridin-3-yl}acetamide (**14a**).

Sodium (506 g, 22 mmoles) was completely dissolved in 20 ml of dry ethanol; 2.84 g (22 mmoles) 2-acetamidoacrylic acid was added and the reaction mixture was stirred at room temperature for 30 minutes. Excess of solvent was removed and dried *in vacuo* to get crude sodium 2-acetamidoacrylate (**12**), which was suspended in 60 ml of dry tetrahydrofuran and cooled to –75 °C. Ethyl chloroformate (2.38 g, 22 mmoles) of was dropped cautiously into the suspension. After the addition was completed, the reaction mixture was, without cooling, allowed to warm to room temperature at which time 6.40 g (20 mmoles) of 2-[(3*Z*)-3-amino-5-oxo-5-phenylpent-3-en-1-yl)]-1*H*-isoindole-1,3(2*H*)-dione (**8a**) was added and the mixture was heated at reflux for 12 hours. After cooling, the reaction mixture was quenched with 50 ml of saturated aqueous sodium hydrogen carbonate. The organic layer was separated and the aqueous layer was extracted three times with chloroform. The combined organic layer was washed with water, and dried over sodium sulfate. The solvent was removed *in vacuo* and the residue was purified by flash chromatography using cyclohexane:ethyl acetate:methanol (5:4:1) as eluent to yield 6.07 g (64%) as colorless powder, mp 216-218 °C; ir (potassium bromide): 3336, 2945, 1772 (phthaloyl), 1707 (CO), 1655 (lactam) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.84 (s, 3H, acetyl), 2.31 (m, 1H, pyridine H-4), 2.50 (t, J = 5 Hz, 2H, $ArCH_2CH_2N$), 2.73 (m, 1H, pyridine H-4), 3.83 (t, J = 5 Hz, 2H, $ArCH_2CH_2N$), 4.36 (m, 1H, pyridine H-3), 7.31 - 7.53 (m, 5H, benzoyl), 7.79 – 7.86 (m, 4H, phthaloyl), 8.08 (s, broad, 1H, AcNH, deuterium oxide-exchangeable), 10.20 (s, broad, 1H, NH, deuterium oxide-exchangeable); ms: m/z 372 (M^+-$CH_2CONHNH_2^+$), 343, 212.

Anal. Calcd. for $C_{24}H_{21}N_3O_5$ (431.45): C, 66.81; H, 4.91; N, 9.74. Found: C, 66.99; H, 4.51; N, 9.78.

N-{5-Benzoyl-6-[3-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl) propyl]-2-oxo-1,2,3,4-tetrahydropyridin-3-yl}acetamide (**14b**).

Preparation and purification according to **14a** using 6.68 g (20 mmoles) of 2-[(4*Z*)-4-amino-6-oxo-6-phenylhex-4-en-1-yl)]-1*H*-isoindole-1,3(2*H*)-dione (**8b**) to yield 6.59 g (74%) as colorless powder, mp 183-185 °C; ir (potassium bromide): 3384, 3232, 1768 (phthaloyl), 1709 (CO), 1668 (lactam) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.81 (tt, J_1 = 7 Hz, J_2 = 6 Hz, 2H, $ArCH_2CH_2CH_2N$), 1.81 (s, 3H, acetyl), 2.12 (t, J = 7 Hz, 2H, $ArCH_2CH_2CH_2N$), 2.43 (m, 1H, pyridine H-4), 2.60 (m, 1H, pyridine H-4), 3.50 (t, J = 6 Hz, 2H, $ArCH_2CH_2CH_2N$), 4.43 (m, 1H, pyridine H-3), 7.33 – 7.42 (m, 5H, benzoyl), 7.84 – 7.86 (m, 4H, phthaloyl), 8.11 (s, broad, 1H, AcNH, deuterium oxide-exchangeable), 10.04 (s, broad, 1H, NH, deuterium oxide-exchangeable); ms: m/z 386 (M^+-$CH_2CONHNH_2^+$), 357, 226.

Anal. Calcd. for $C_{25}H_{23}N_3O_5$ (445.48): C, 67.41; H, 5.20; N, 9.43. Found: C, 67.33; H, 4.89; N, 9.55.

2-[2-(3-Benzoyl-6-oxo-1,6-dihydropyridin-2-yl)ethyl)-1*H*-isoindole-1,3(2*H*)-dione (**15a**).

2-[2-(3-Benzoyl-6-oxo-1,4,5,6-tetrahydropyridin-2-yl)ethyl)-1*H*-isoindole-1,3(2*H*)-dione (**13a**) (2.24 g, 6 mmoles) and 2.61 g (30 mmoles) of activated manganese (IV) oxide were suspended in 30 ml of dry *o*-xylene. The mixture was heated at reflux under an air atmosphere for 8 hours. Reaction water was separated using a Dean Stark apparatus. After cooling the solid phase was filtered off through a Celite® bed and washed profoundly with ethyl acetate. The filtrate was concentrated to dryness *in vacuo*. The residue was purified by flash chromatography using cyclohexane:ethyl acetate:methanol (5:4:1) as eluent to yield 1.52 g (68%) as colorless powder, mp 201-202 °C; ir (potassium bromide): 3463, 2951, 1774 (phthaloyl), 1713 (CO), 1669, 1646 cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.04 (t, J = 5 Hz, 2H, $ArCH_2CH_2N$), 3.91 (t, J = 5 Hz, 2H, $ArCH_2CH_2N$), 6.19 (d, J = 10 Hz, 1H, pyridine H-3), 7.31 (d, J = 10 Hz, 1H, pyridine H-4), 7.34 – 7.58 (m, 5H, benzoyl), 7.77 – 7.81 (m, 4H, phthaloyl), 12.28 (s, broad, 1H, NH, deuterium oxide-exchangeable); ms: m/z 372 (M^+), 343, 212.

Anal. Calcd. for $C_{22}H_{16}N_2O_4$ (372.38): C, 70.96; H, 4.33; N, 7.52. Found: C, 70.71; H, 4.56; N, 7.64.

2-[3-(3-Benzoyl-6-oxo-1,6-dihydropyridin-2-yl)propyl)-1*H*-isoindole-1,3(2*H*)-dione (**15b**).

Preparation and purification according to **15a** using 2.33 g (6 mmoles) of 2-[3-(3-benzoyl-6-oxo-1,4,5,6-tetrahydropyridin-2-yl)propyl)-1*H*-isoindole-1,3(2*H*)-dione (**13b**) to yield 1.55 g (67%) as colorless powder, mp 212-214 °C; ir (potassium bromide): 3442, 2924, 1769 (phthaloyl), 1719 (CO), 1668, 1650 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.91 (tt, J_1 = 6 Hz, J_2 = 8 Hz, 2H, $ArCH_2CH_2CH_2N$), 2.66 (t, J = 8 Hz, 2H, $ArCH_2CH_2CH_2N$), 3.60 (t, J = 6 Hz, 2H, $ArCH_2CH_2CH_2N$), 6.19 (d, J = 10 Hz, 1H, pyridine H-3), 7.39 (d, J = 10 Hz, 1H, pyridine H-4), 7.45 – 7.60 (m, 5H, benzoyl), 7.81 – 7.91 (m, 4H, phthaloyl), 12.12 (s, broad, 1H, NH, deuterium oxide-exchangeable); ms: m/z 386 (M^+), 238, 226.

Anal. Calcd. for $C_{23}H_{18}N_2O_4$ (386.42): C, 71.49; H, 4.70; N, 7.25. Found: C, 71.81; H, 4.66; N, 7.60.

N-{5-Benzoyl-6-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-2-oxo-1,2-dihydropyridin-3-yl}acetamide (**16a**).

Preparation and purification according to **15a** using 4.31 g (10 mmoles) of *N*-{5-benzoyl-6-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-2-oxo-1,2,3,4-tetrahydropyridin-3-yl}acetamide (**14a**) and 4.35 g (50 mmoles) of activated manganese (IV) oxide in 50 ml of toluene to yield 3.26 g (76%) as colorless powder, mp 245-247 °C; ir (potassium bromide): 3278, 1770 (phthaloyl), 1718 (CO), 1704 (AcNH), 1633 cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.02 (s, 3H, acetyl), 2.99 (t, J = 5 Hz, 2H, $ArCH_2CH_2N$), 3.93 (t, J = 5 Hz, 2H, $ArCH_2CH_2N$), 7.42 - 7.49 (m, 2H, benzoyl), 7.55 –

7.62 (m, 3H, benzoyl), 7.81 – 7.90 (m, 4H, phthaloyl), 8.22 (s, 1H, pyridine H-4), 9.32 (s, broad, 1H, AcNH, deuterium oxide-exchangeable), 12.39 (s, broad, 1H, NH, deuterium oxide-exchangeable); ms: m/z 429 (M^+), 269, 227.

Anal. Calcd. for $C_{24}H_{19}N_3O_5$ (429.44): C, 67.13; H, 4.46; N, 9.78. Found: C, 66.87; H, 4.10; N, 9.78.

N-{5-Benzoyl-6-[3-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-propyl]-2-oxo-1,2-dihydropyridin-3-yl}acetamide (**16b**).

Preparation and purification according to **16a** using 4.45 g (10 mmoles) of *N*-{5-benzoyl-6-[3-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)propyl]-2-oxo-1,2,3,4-tetrahydropyridin-3-yl} acetamide (**14b**) to yield 3.15 g (71%) as colorless powder, mp 267-269 °C; ir (potassium bromide): 3336, 1772 (phthaloyl), 1717 (CO), 1704 (AcNH), 1641 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.90 (tt, J_1 = 8 Hz, J_2 = 6 Hz, 2H, $ArCH_2CH_2CH_2N$), 2.05 (s, 3H, acetyl), 2.61 (t, J = 8 Hz, 2H, $ArCH_2CH_2CH_2N$), 3.59 (t, J = 6 Hz, 2H, $ArCH_2CH_2CH_2N$), 7.43 – 7.50 (m, 2H, benzoyl), 7.55 – 7.66 (m, 3H, benzoyl), 7.83 – 7.88 (m, 4H, phthaloyl), 8.18 (s, 1H, pyridine H-4), 9.34 (s, broad, 1H, AcNH, deuterium oxide-exchangeable), 12.41 (s, broad, 1H, NH, deuterium oxide-exchangeable); ms: m/z 443 (M^+), 283, 241.

Anal. Calcd. for $C_{25}H_{21}N_3O_5$ (443.46): C, 67.71; H, 4.77; N, 9.48. Found: C, 67.89; H, 4.99; N, 9.11.

5-Phenyl-7,8-dihydro-1,6-naphthyridine (**17a**).

2-[2-(3-Benzoylpyridin-2-yl)ethyl]-1*H*-isoindole-1,3(2*H*)-dione (**10a**) (1.07 g, 3 mmoles) was suspended in 30 ml of 6 *M* aqueous hydrochloride acid and heated at reflux for 14 hours. The reaction mixture was neutralized cautiously under ice-cooling by adding 6 *M* aqueous sodium hydroxide and extracted three times with diethyl ether. The combined organic layer was washed with saturated aqueous sodium hydrogen carbonate, dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified by mplc using cyclohexane:ethyl acetate:methanol (5:4:1) as eluent to yield 225 mg (36%) as colorless powder, 178-180 °C; ir (potassium bromide): 3058, 2952, 2845, 1609, 1578, 1562 cm^{-1}; ^1H nmr ($CDCl_3$): δ 3.03 (t, J = 7 Hz, 2H, H-8), 4.02 (t, J = 7 Hz, 2H, H-7), 7.22 (dd, J_1 = 8 Hz, J_2 = 4 Hz, 1H, H-3), 7.46 - 7.51 (m, 3H, phenyl), 7.55 – 7.61 (m, 3H, phenyl, H-4), 8.58 (dd, J_1 = 4 Hz, J_2 = 2 Hz, 1H, H-2); ms: m/z 208 (M^+), 180.

Anal. Calcd. for $C_{14}H_{12}N_2$ (208.27): C, 80.74; H, 5.81; N, 13.45. Found: C, 80.66; H, 5.58; N, 13.23.

5-Phenyl-8,9-dihydro-7*H*-pyrido[3,2-*c*]azepine (**17b**).

Preparation and purification according to **17a** using 1.11 g (3 mmoles) of 2-[3-(3-benzoylpyridin-2-yl)propyl]-1*H*-isoindole-1,3(2*H*)-dione (**10b**) and cyclohexane:ethyl acetate: methanol (50:35:15) as eluent to yield 206 mg (31%) as colorless powder, mp 183-185 °C; ir (potassium bromide): 3086, 2977, 1601, 1553 cm^{-1}; ^1H nmr ($CDCl_3$): δ 2.48 (tt, J_1 = 7 Hz, J_2 = 7 Hz, 2H, H-8), 2.87 (t, J = 7 Hz, 2H, H-9), 3.49 (t, J = 7 Hz, 2H, H-7), 7.26 (dd, J_1 = 7 Hz, J_2 = 4 Hz, 1H, H-3), 7.35 - 7.50 (m, 4H, phenyl, H-4), 7.60 – 7.65 (m, 2H, phenyl), 8.62 (dd, J_1 = 4 Hz, J_2 = 2 Hz, 1H, H-2); ms: m/z 222 (M^+-$CH_2COHNH_2^+$), 194.

Anal. Calcd. for $C_{15}H_{14}N_2$ (222.29): C, 81.05; H, 6.35; N, 12.60. Found: C, 81.00; H, 6.45; N, 12.25.

5-Phenyl-7,8-dihydro-1,6-naphthyridin-2(1*H*)-one (**18a**).

Preparation and purification according to **17a** using 1.12 g (3 mmoles) of 2-[2-(3-benzoyl-6-oxo-1,6-dihydropyridin-2-yl)ethyl)-1*H*-isoindole-1,3(2*H*)-dione (**15a**) and chloroform:methanol (95:5) as eluent to yield 215 mg (32%) as colorless powder, mp >300 °C (decomposition); ir (potassium bromide): 2435, 2954, 2790, 1678 (CO), 1621 cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.65 (t, J = 8 Hz, 2H, H-8), 3.72 (t, J = 8 Hz, 2H, H-7), 6.19 (d, J = 10 Hz, 1H, H-3), 7.20 (d, J = 10 Hz, 1H, H-4), 7.41 - 7.51 (m, 5H, phenyl), 12.18 (s, broad, 1H, NH, deuterium oxide-exchangeable); ms: m/z 224 (M^+), 223, 196, 195.

Anal. Calcd. for $C_{14}H_{12}N_2O$ (224.26): C, 74.98; H, 5.39; N, 12.49. Found: C, 74.78; H, 5.58; N, 12.21

5-Phenyl-1,7,8,9-tetrahydro-2*H*-pyrido[3,2-*c*]azepin-2-one (**18b**).

Preparation and purification according to **17a** using 772 mg (2 mmoles) of 2-[3-(3-benzoyl-6-oxo-1,6-dihydropyridin-2-yl)propyl)-1*H*-isoindole-1,3(2*H*)-dione (**15b**) and chloroform:methanol (95:5) as eluent to yield 114 mg (24%) as colorless powder, mp >300 °C (decomposition); ir (potassium bromide): 3440, 2951, 2860, 1668 (CO), 1608 cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.31 (tt, J_1 = 7 Hz, J_2 = 7 Hz, 2H, H-8), 2.50 (t, J = 7 Hz, 2H, H-9), 3.43 (t, J = 7 Hz, 2H, H-7), 6.24 (d, J = 10 Hz, 1H, H-3), 7.11 (d, J = 10 Hz, 1H, H-4), 7.39 - 7.47 (m, 3H, phenyl), 7.51 - 7.61 (m, 2H, phenyl), 12.05 (s, broad, 1H, NH, deuterium oxide-exchangeable) ms: m/z 238 (M^+), 237, 210.

Anal. Calcd. for $C_{14}H_{12}N_2O$ (224.26): C, 74.98; H, 5.39; N, 12.49. Found: C, 74.78; H, 5.58; N, 12.21.

3-Amino-5-phenyl-7,8-dihydro-1,6-naphthyridin-2(1*H*)-one (**19a**).

Preparation and purification according to **17a** using 2.14 g (5 mmoles) of *N*-{5-benzoyl-6-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-2-oxo-1,2-dihydropyridin-3-yl}acetamide (**16a**) and chloroform:methanol (9:1) as eluent to yield 347 mg (29%) as colorless powder; mp >300 °C (decomposition); ir (potassium bromide): 3463, 3364, 2891, 1641 (CO), 1595 cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.53 (t, J = 8 Hz, 2H, H-8), 3.67 (t, J = 8 Hz, 2H, H-7), 4.93 (s, broad, 2H, NH_2, deuterium oxide-exchangeable), 6.33 (s, 1H, H-4), 7.42 - 7.48 (m, 5H, phenyl), 11.91 (s, broad, 1H, NH, deuterium oxide-exchangeable) ms: m/z 239 (M^+), 238.

Anal. Calcd. for $C_{14}H_{13}N_3O$ (239.28): C, 70.28; H, 5.48; N, 17.56. Found: C, 70.11; H, 5.36; N, 17.51.

3-Amino-5-phenyl-1,7,8,9-tetrahydro-2*H*-pyrido[3,2-*c*]azepin-2-one (**19b**).

Method A: Preparation and purification according to **17a** using 2.22 g (5 mmoles) of *N*-{5-benzoyl-6-[3-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)propyl]-2-oxo-1,2-dihydropyridin-3-yl}acetamide (**16b**) and chloroform: methanol (9:1) as eluent to yield 304 mg (24%) as colorless powder. *Method B*: 2-Hydroxy-5-phenyl-8,9-dihydro-7H-pyrido[3,2-*c*]azepin-3-carboxylic acid (**24**) (85 mg, 0.3 mmole), 82 mg (0.3 mmole) diphenylphosphorylazid (DPPA) and 30 mg (0.3 mmole) triethylamine were dissolved in 10 ml of dry *tert*-butyl alcohol and heated at reflux for 3 hours. Water (10 ml) was added and heated at reflux for another 1.5 hour. After cooling 10 ml of 6 *M* aqueous hydrochloric acid was added and stirred for 1 hour. The reaction mixture was neutralized by portion-wise addition of sodium carbonate. Chloroform (10 ml) was added and the mixture was shaken well. The organic layer was separated, and the aqueous layer was extracted twice with chloroform. The combined organic layer was dried over sodium sulfate, and concentrated *in vacuo.* The residue was purified by column chromatography using chloroform:methanol (9:1) as eluent to yield 31

mg (41%) as colorless powder; mp >300 °C (decomposition); ir (potassium bromide): 3377, 3186, 2937, 1658 (CO), 1616, 1570 cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.24 (tt, J_1 = 8 Hz, J_2 = 7 Hz, 2H, H-8), 2.40 (t, J = 8 Hz, 2H, H-9), 3.40 (t, J = 7 Hz, 2H, H-7), 4.93 (s, broad, 2H, NH_2, deuterium oxide-exchangeable), 6.19 (s, 1H, H-4), 7.37 - 7.47 (m, 3H, phenyl), 7.54 – 7.59 (m, 2H, phenyl), 11.80 (s, broad, 1H, NH, deuterium oxide-exchangeable) ms: m/z 253 (M^+), 252, 225.

Anal. Calcd. for $C_{15}H_{15}N_3O$ (253.31): C, 71.13; H, 5.97; N, 16.59. Found: C, 70.92; H, 5.99; N, 16.91.

2-[5-Benzoyl-6-(dimethylamino)-4-oxohex-5-en-1-yl]-1*H*-isoindol-1,3(2*H*)-dione (**21**).

2-[(4*Z*)-4-Hydroxy-6-oxo-6-phenylhex-4-en-1-yl)-1*H*-isoindole-1,3(2*H*)-dione (**7b**) (3.66 g, 10.9 mmoles) was dissolved in 10 ml of dry tetrahydrofuran, 1.43 g (12 mmoles) of *N*,*N*-dimethylformamide dimethyl acetal (DMF-DMA) was added slowly, and stirred for 15 hours at room temperature. The mixture was concentrated *in vacuo*. The oily, red residue was taken up in *n*-butyl alcohol. The product was crystallized by drop-wise addition of *n*-hexane. The solid was collected by suction and recrystallized from ethanol/*n*-hexane to yield 2.61 g (60%) as yellow crystals, mp 107-109 °C; ir (potassium bromide): 3412, 2988, 2897, 1779 (phthaloyl), 1712 (CO), 1601 cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.66 (tt, J_1 = 7 Hz, J_2 = 7 Hz, 2H, $COCH_2CH_2CH_2N$), 2.33 (t, J = 7 Hz, 2H, $COCH_2CH_2CH_2N$), 2.91 (s, 6H, NMe_2), 3.54 (t, J = 7 Hz, 2H, $COCH_2CH_2CH_2N$), 7.33 - 7.48 (m, 5H, benzoyl), 7.64 – 7.89 (m, 5H, H-6, phthaloyl); ms: m/z 390 (M^+), 202, 105.

Anal. Calcd. for $C_{23}H_{22}N_2O_4$ (390.44): C, 70.75; H, 5.68; N, 7.17. Found: C, 71.14; H, 6.06; N, 6.84.

5-Benzoyl-6-[3-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)propyl]-2-oxo-1,2-dihydropyridine-3-carbonitrile (**23**).

Cyanoacetamide (420 mg, 5 mmoles) was added to a suspension of 570 mg (5 mmoles) of magnesium ethoxide in 30 ml of dry tetrahydrofuran and heated to 70 °C for 1 hour. 2-[5-Benzoyl-6-(dimethylamino)-4-oxohex-5-en-1-yl]-1*H*-isoindol-1,3(2*H*)-dione (**21**) (1.95 g, 5 mmoles) was added and heated at 70 °C for another 14 hours. After cooling the reaction mixture was acidified cautiously with 2 *N* aqueous sulfuric acid, and extracted three times with dichloromethane. The combined organic layer was washed with saturated aqueous sodium hydrogen carbonate, dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified by mplc using cyclohexane:ethyl acetate:methanol (50:45:5) as eluent to yield 781 mg (38%) as pale yellow powder, mp 213-214 °C (decomposition); ir (potassium bromide): 3463, 2228 (CN), 1770 (phthaloyl), 1713 (CO), 1658 (lactam) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.92 (tt, J_1 = 6 Hz, J_2 = 6 Hz, 2H, $ArCH_2CH_2CH_2N$), 2.67 (t, J = 6 Hz, 2H, $ArCH_2CH_2CH_2N$), 3.60 (t, J = 6 Hz, 2H, $ArCH_2CH_2CH_2N$), 7.46 - 7.53 (m, 2H, benzoyl), 7.59 – 7.69 (m, 3H, benzoyl), 7.83 – 7.90 (m, 4H, phthaloyl); ms: m/z 412 (M^++1), 411, 379.

Anal. Calcd. for $C_{24}H_{17}N_3O_4$ (411.42): C, 70.07; H, 4.16; N, 10.21. Found: C, 69.94; H, 4.55; N, 10.04.

2-Hydroxy-5-phenyl-8,9-dihydro-7*H*-pyrido[3,2-*c*]azepin-3-carboxylic Acid (**24**).

5-Benzoyl-6-[3-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)propyl]-2-oxo-1,2-dihydropyridin-3-carbonitrile (**23**) (617 g, 1.5 mmoles) was suspended in 15 ml of 6 *M* aqueous hydrochloride acid and heated at reflux for 12 hours. The mixture was neutralized with 6 *M* aqueous sodium hydroxide under ice-cooling, pH was adjusted to 3-4 using acetic acid and sodium acetate as buffer, and extracted five times with chloroform. The combined organic layer dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified by column chromatography using chloroform:methanol:acetic acid (85:15:0.5) as eluent to yield 97 mg (23%) as colorless powder, 250-251 °C (decomposition); ir (potassium bromide): 3435, 1731 (COOH), 1632, 1589 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.70 (tt, J_1 = 7 Hz, J_2 = 8 Hz, 2H, $ArCH_2CH_2CH_2N$), 2.02 (t, J = 8 Hz, 2H, $ArCH_2CH_2CH_2N$), 3.76 (t, J = 6 Hz, 2H, $ArCH_2CH_2CH_2N$), 7.44 – 7.59 (m, 6H, phenyl, 2-OH, 1H deuterium oxide-exchangeable), 8.64 (s, 1H, H-4), 13.22 (s, broad, 1H, COOH, deuterium oxide-exchangeable); ms: m/z 282 (M^+), 281, 263.

Anal. Calcd. for $C_{16}H_{14}N_2O_3$ (282.30): C, 68.00; H, 5.00; N, 9.92. Found: C, 68.23; H, 5.00; N, 10.11.

5-Phenyl-5,6,7,8-tetrahydro-1,6-naphthyridine (**25a**).

5-Phenyl-7,8-dihydro-1,6-naphthyridine (**17a**) (208 mg, 1 mmole) was dissolved in 10 ml of dry methanol and cooled to 0°C by an ice-bath. Sodium borohydride (38 mg, 1 mmole) was added and stirred for 30 minutes. The mixture was acidified by addition of 2 *N* aqueous sulfuric acid, pH was adjusted to about 8 with sodium carbonate, and extracted three times with diethyl ether. The combined organic layer was washed with saturated aqueous sodium hydrogen carbonate, dried over sodium sulfate, and concentrated *in vacuo* to yield 155 mg (74%) as pure, colorless powder, mp 168-170 °C (decomposition); ir (sodium chloride): 3244, 2877, 2841, 1551 cm^{-1}; ^1H nmr ($CDCl_3$): δ 2.05 (s, broad, 1H, NH, deuterium oxide-exchangeable), 2.95 – 3.40 (m, 4H, H-7, H-8), 5.08 (s, 1H, H-5), 6.99 (dd, J_1 = 8 Hz, J_2 = 4 Hz, 1H, H-3), 7.05 (dd, J_1 = 8 Hz, J_2 = 1 Hz, 1H, H-4), 7.23 – 7.38 (m, 5H, phenyl), 8.40 (dd, J_1 = 4 Hz, J_2 = 1 Hz, 1H, H-2); ms: m/z 210 (M^+), 180, 133.

Anal. Calcd. for $C_{14}H_{14}N_2$ (210.28): C, 79.97; H, 6.71; N, 13.32. Found: C, 80.12; H, 6.88; N, 12.92.

5-Phenyl-6,7,8,9-tetrahydro-5*H*-pyrido[3,2-*c*]azepine (**25b**).

Preparation according to **25a** using 222 mg (1 mmole) of 5-phenyl-8,9-dihydro-7*H*-pyrido[3,2-*c*]azepine (**17b**) to yield 155 mg (69%) as pure, colorless powder, mp 182-184 °C; ir (sodium chloride): 3273, 2927, 2848, 1573 cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.75 – 1.98 (m, 2H, H-8), 1.84 (s, broad, 1H, NH, deuterium oxide-exchangeable), 3.18 – 3.48 (m, 4H, H-7, H-9), 5.15 (s, 1H, H-5), 6.87 (dd, J_1 = 8 Hz, J_2 = 5 Hz, 1H, H-3), 6.95 (dd, J_1 = 8 Hz, J_2 = 2 Hz, 1H, H-4), 7.38 – 7.45 (m, 5H, phenyl), 8.34 (dd, J_1 = 5 Hz, J_2 = 2 Hz, 1H, H-2); ms: m/z 224 (M^+), 195.

Anal. Calcd. for $C_{15}H_{16}N_2$ (224.31): C, 80.32; H, 7.19; N, 12.49. Found: C, 80.11; H, 7.30; N, 12.13.

6-Methyl-5-phenyl-5,6,7,8-tetrahydro-1,6-naphthyridine (**26a**).

5-Phenyl-5,6,7,8-tetrahydro-1,6-naphthyridine (**25a**) (105 mg, 0.5 mmole) was heated at reflux in 4 ml of a mixture of aqueous formaldehyde (37%):formic acid (98%) (4:3) for 4 hours under a nitrogen atmosphere. After cooling the reaction mixture was concentrated *in vacuo*. The residue was taken up in 10 ml of saturated aqueous sodium carbonate, and extracted three times with dichloromethane. The combined organic layer was washed with saturated aqueous sodium carbonate, dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography using cyclohexane:ethyl acetate:methanol (50:45:5) as

eluent to yield 65 mg (58%) as colorless powder, mp 74-76 °C; ir (potassium bromide): 2983, 2949, 2795, 1574, 1446 cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.13 (s, 3H, Me), 2.50-2.60 (m, 2H, H-8), 3.09 – 3.19 (m, 2H, H-7), 4.30 (s, 1H, H-5), 6.90 (d, J = 8 Hz, 1H, H-4), 7.04 (dd, J_1 = 8 Hz, J_2 = 5 Hz, 1H, H-3), 7.23 – 7.38 (m, 5H, phenyl), 8.30 (d, J = 5 Hz, 1H, H-2); ms: m/z 224 (M^+), 180, 147.

Anal. Calcd. for $C_{15}H_{16}N_2$ (224.31): C, 80.32; H, 7.19; N, 12.49. Found: C, 79.99; H, 7.09; N, 12.18.

6-Methyl-5-phenyl-6,7,8,9-tetrahydro-5*H*-pyrido[3,2-*c*]azepine (**26b**).

Preparation according to **26a** using 112 mg (0.5 mmole) of 5-phenyl-6,7,8,9-tetrahydro-5*H*-pyrido[3,2-*c*]azepine (**25b**) to yield 61 mg (51%) as colorless powder, mp 103-104 °C; ir (sodium chloride): 2926, 2851, 1598, 1448 cm^{-1}; ^1H nmr ($CDCl_3$): δ 2.41 (s, 3H, Me), 2.90 – 3.24 (m, 4H, H-8, H-9), 4.72 – 5.01 (m, 2H, H-7), 5.04 (s, 1H, H-5), 7.09 (dd, J_1 = 8 Hz, J_2 = 5 Hz, 1H, H-3), 7.22 – 7.36 (m, 6H, phenyl, H-4), 8.42 (dd, J_1 = 5 Hz, J_2 = 2 Hz, 1H, H-2); ms: m/z 238 (M^+), 194, 161.

Anal. Calcd. for $C_{16}H_{18}N_2$ (238.34): C, 80.63; H, 7.61; N, 11.75. Found: C, 81.00; H, 7.71; N, 11.86.

5-Phenyl-5,6,7,8-tetrahydro-1,6-naphthyridin-2(1*H*)-one (**27a**).

Preparation according to **25a** using 112 mg (0.5 mmole) of 5-phenyl-7,8-dihydro-1,6-naphthyridin-2(1*H*)-one (**18a**). The product was purified by column chromatography using chloroform:methanol (9:1) as eluent to yield 94 mg (83%) as colorless powder, mp >300 °C (decomposition); ir (sodium chloride): 3446, 2921, 2850, 1654 (CO), 1618 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.24 (s, broad, 1H, NH, deuterium oxide-exchangeable), 2.42 – 3.09 (m, 4H, H-7, H-8), 4.75 (s, 1H, H-5), 6.03 (d, J = 10 Hz, 1H, H-4), 6.71 (d, J = 10 Hz, 1H, H-3), 7.20 – 7.39 (m, 5H, phenyl), 11.46 (s, broad, 1H, NH, 1H, deuterium oxide-exchangeable); ms: m/z 226 (M^+), 221, 92.

Anal. Calcd. for $C_{14}H_{14}N_2O$ (226.28): C, 74.31; H, 6.24; N, 12.38. Found: C, 74.23; H, 6.44; N, 12.03.

5-Phenyl-1,5,6,7,8,9-hexahydro-2*H*-pyrido[3,2-*c*]azepin-2-one (**27b**).

Preparation according to **25a** using 119 mg (0.5 mmole) of 5-phenyl-1,7,8,9-tetrahydro-2*H*-pyrido[3,2-*c*]azepin-2-one (**18b**). The product was purified by column chromatography using chloroform:methanol (9:1) as eluent to yield 100 mg (83%) as colorless powder, mp >300 °C (decomposition); ir (potassium bromide): 2962, 1639 (CO), 1614 cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.72 – 1.99 (m, 2H, H-8), 2.08 (s, broad, 1H, NH, deuterium oxide-exchangeable), 2.91 – 3.34 (m, 4H, H-7, H-9), 4.98 (s, 1H, H-5), 6.26 (d, J = 9 Hz, 1H, H-3), 6.85 (d, J = 9 Hz, 1H, H-4), 7.27 – 7.33 (m, 3H, phenyl), 7.35 – 7.41 (m, 2H, phenyl), 13.17 (s, broad, 1H, NH, deuterium oxide-exchangeable); ms: m/z 240 (M^+), 211, 163.

Anal. Calcd. for $C_{15}H_{16}N_2O$ (240.31): C, 74.97; H, 6.71; N, 11.66. Found: C, 74.78; H, 6.58; N, 11.61.

3-Amino-5-phenyl-5,6,7,8-tetrahydro,1,6-naphthyridin-2(1*H*)-one (**28a**).

Preparation and according to **25a** using 239 mg (1 mmole) of 3-amino-5-phenyl-7,8-dihydro-1,6-naphthyridin-2(1*H*)-one (**19a**). The product was purified by column chromatography using chloroform:methanol (82:18) as eluent to yield 202 mg (84%) as colorless powder, mp >300 °C (decomposition); ir (potassium bromide): 3319, 3257, 2875, 1651 (CO), 1591 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.94 (s, broad, 1H, NH, deuterium oxide-exchangeable), 3.30 – 3.03 (m, 4H, H-7, H-8), 4.63 (s, 1H, H-5), 4.69 (s, broad, 2H, NH_2, deuterium oxide-exchangeable), 5.81 (s, 1H, H-4), 7.17 – 7.43 (m, 5H, phenyl), 11.20 (s, broad, 1H, NH, 1H, deuterium oxide-exchangeable); ms: m/z 241 (M^+), 212, 271, 164.

Anal. Calcd. for $C_{14}H_{15}N_3O$ (241.30): C, 69.69; H, 6.27; N, 17.41. Found: C, 70.00; H, 6.01; N, 17.35.

3-Amino-5-phenyl-1,5,6,7,8,9-hexahydro-2*H*-pyrido[3,2-*c*]-azepin-2-one (**28b**).

Preparation and according to **25a** using 253 mg (0.5 mmole) of 3-amino-5-phenyl-1,7,8,9-tetrahydro-2*H*-pyrido[3,2-*c*]azepin-2-one (**19b**). The product was purified by column chromatography using chloroform:methanol (82:18) as eluent to yield 227 mg (89%) as colorless powder, mp 218-220 °C; ir (potassium bromide): 3340, 3354, 2925, 1645 (CO), 1587 cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.50 – 1.69 (m, 2H, H-8), 2.22 (s, broad, 1H, NH, deuterium oxide-exchangeable), 2.67 – 3.96 (m, 4H, H-7, H-9), 4.67 (s, broad, 2H, NH_2, deuterium oxide-exchangeable), 4.83 (s, 1H, H-5), 5.93 (s, 1H, H-4), 7.18 – 7.38 (m, 5H, phenyl), 11.24 (s, broad, 1H, NH, 1H, deuterium oxide-exchangeable); ms: m/z 255 (M^+), 238, 226.

Anal. Calcd. for $C_{15}H_{17}N_3O$ (255.32): C, 70.56; H, 6.71; N, 16.46. Found: C, 70.87; H, 6.82; N, 16.10.

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