Scientific Paper

Syntheses of 4-(2-Naphthyl)pyridine Derivatives from DDNP

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Abstract

The ethylidenemalononitrile side-chain in {1-[6-(dimethylamino)-2-naphthyl]ethylidene}malononitrile (DDNP) was elaborated into a substituted pyridine ring in a two-step process. In this manner formal derivatives of a molecular probe (1-{6-[(2-fluoroethyl)(methyl)amino]-2-naphthyl}ethylidene)malononitrile (FDDNP), which is successfully applied in positron emission tomography to diagnose Alzheimer's Disease, were prepared. Chloroimidate intermediate in reaction of a nitrile group with HCl in alcoholic solution was trapped in the form of 2-chloro-4-[6-(dimethylamino)-2-naphthyl]nicotinonitrile, thus proving its existence in the Pinner synthesis. The structure of 2-methylamino derivative was also proven by X-ray analysis.

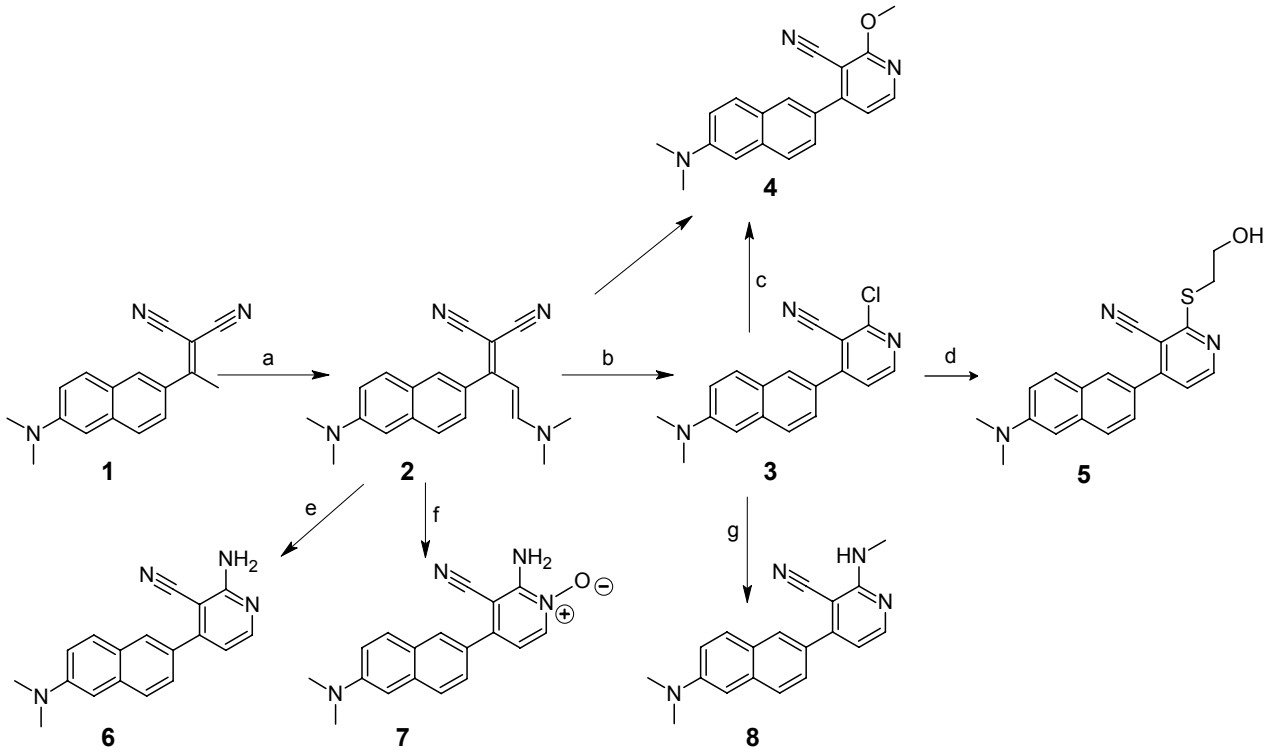
Key words: DDNP, molecular probes, ylidenmalononitriles, Pinner synthesis, X-ray

Introduction

The discovery of fluorescent {1-[6-(dimethylamino)-2-naphthyl]ethylidene}malononitrile, dubbed in literature as DDNP,[1] led to the design of novel fluorescent molecular probes for medical research. Our most successful compound to date, (1-{6-[(2-fluoroethyl)(methyl)amino]-2-naphthyl}ethylidene)malononitrile (FDDNP), has been utilized as a fluorescencent and, if stable isotope ^{19}F was replaced by radioactive ^{18}F, also as a radioligand, which binds to protein aggregates in the CNS of patients with neurodegenerative diseases.[2] It was used in *in vitro* experiments to determine the presence and localization of β-amyloid aggregates in brain slices of patients, diagnosed with Alzheimer's disease (AD) by fluorescence microscopy and autoradiography.[3] We have shown that FDDNP can be used as effectively in labeling the aggregates as standard fluorescent or immunofluorescent probes. Utilization of radio-labeled FDDNP in positron emission tomography (PET) led to the development of the first *in vivo* diagnostic method for the diagnosis of AD in living patients.[4] The research has been extended to the investigation of prion plaque deposition in the CNS of patients with other neurodegenerative diseases, e.g. variant Creutzfeld-Jacob disease (human variant of the Mad Cow Disease).[5]

To this day the mechanism of FDDNP binding to protein aggregates remains unknown. In the absence of this knowledge we decided to prepare DDNP derivatives in which the electron donor and/or the electron acceptor groups would be modified in hopes that the application of the modified ligands will at least partially reveal molecular requirements for successful binding to protein aggregates. Spatial arrangement of the donor and acceptor groups in DDNP allows for relatively large separation of partial positive and negative charges thus leading to substantial dipole moment of the molecule. This is a prerequisite for long wavelength absorption, fluorescence emissions[6] and possibly also very important for binding to protein aggregates.

In this contribution we describe the synthesis of DDNP derivatives, which were obtained through modification of the electron acceptor ethylidenemalononitrile side-chain. In the synthesized compounds the electron withdrawing ability of the pyridine ring is enhanced by a nitrile group in position 3 and also, in compound **7**, by the *N*-oxide functionality. The effect of the structural modifications will be assessed in the future through measurements of the optical properties and binding to protein aggregates. Functional groups in the new compounds, like the amino or hydroxy group, provide for reactive sites for eventual further synthetic elaboration.



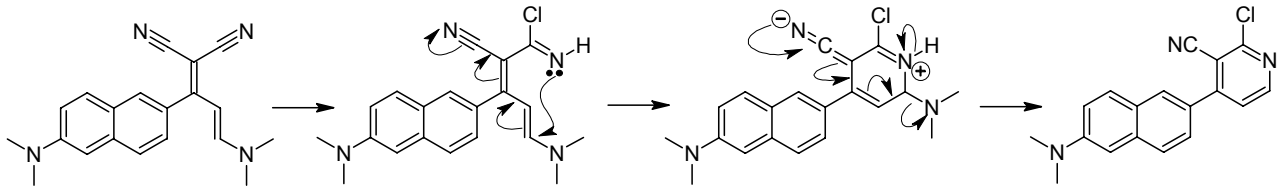
Scheme 1. a: DMFDMA, b: HCl/MeOH, c: NaOMe/MeOH, d: $NaSCH_2CH_2OH$/MeOH, e: NH_3/MeOH, f: $NH_2OH.HCl$/MeOH, g: $MeNH_2$/EtOH.

Results and discussion

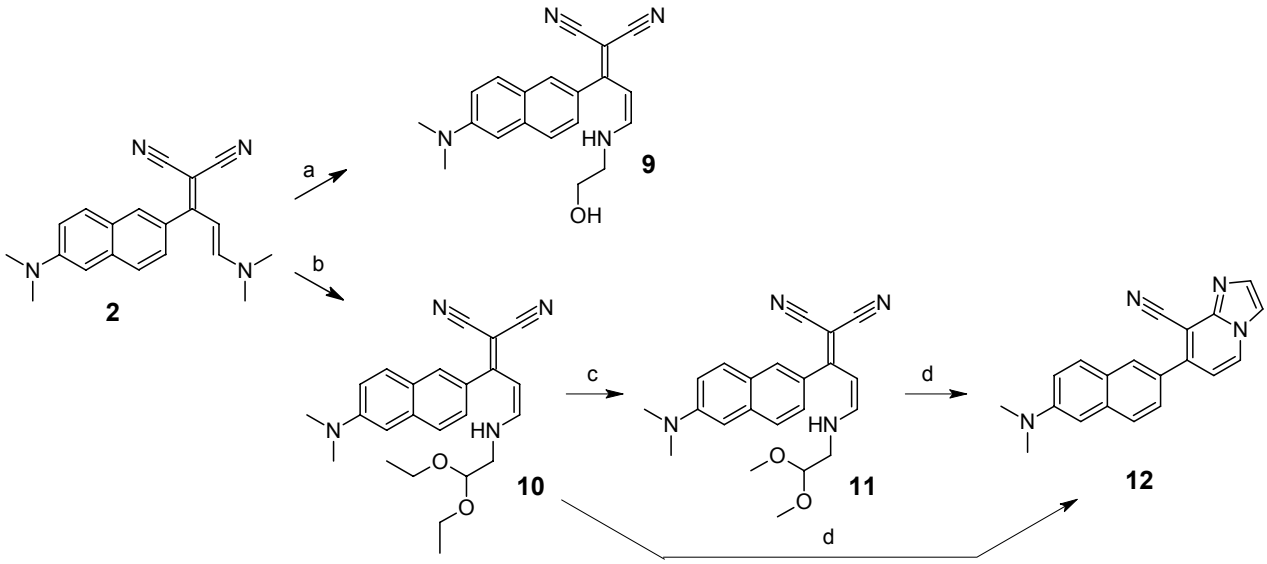
It has been extensively documented that ylidenmalononitriles react with *N,N*-dimethylformamide dimethyl acetal (DMFDMA) at the activated methyl group yielding highly substituted 1,3-butadiene, which can be further elaborated into a pyridine derivative.[7] In this manner we transformed DDNP[1] (**1**) into key intermediate **2** (Scheme 1). The latter was then subjected to the action of different nucleophiles.

In the presence of HCl gas at room temperature along with alcohols 2-chloropyridine derivative **3** was obtained. As determined by ^{1}H NMR, the crude product of the reaction in methanol contained 3–5% of 2-methoxypyridine derivative **4**. If the reaction was run in 2-propanol, exclusively the chloro compound **3** was obtained. These results can be explained by the initial reaction of one of the two nitrile groups with HCl giving the chloroimidate (or its hydrochloride), which then cyclizes with expulsion of dimethylamine to give **3** (Scheme 2). Alternatively, the chloroimidate intermediate can undergo nucleophilic displacement of the chloride by a reactive nucleophilic solvent like methanol to give imidate, which then cyclizes into **4**. In less nucleophilic 2-propanol, the entropy favored intramolecular cyclization is faster than the bimolecular nucleophilic displacement reaction leading to **3.** To support the above hypothesis and to exclude the possibility that the methoxy derivative **4** has been formed from **3**, the latter was dissolved in methanolic HCl and the reaction mixture was left at rt. Even after a prolonged period of time we could not detect any **4** in the reaction mixture thus supporting our explanation.

The two-step formation of the methoxypyridine derivative **4** offers an additional insight into the mechanism of the Pinner synthesis.[8] Although it is usually presented as a one step procedure from nitrile to the imidate, the reaction involves the formation of

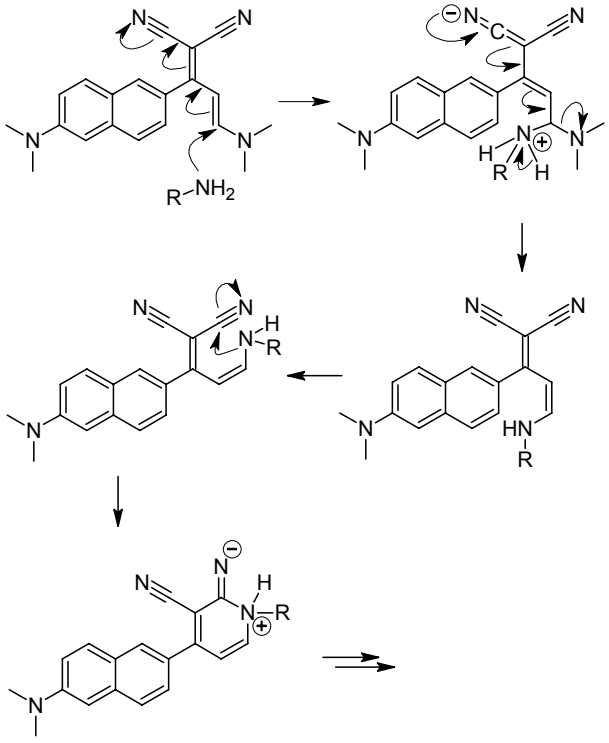


Scheme 2. Proposed reaction pathway for HCl-promoted cyclization.



Scheme 3. a: $NH_2CH_2CH_2OH$/MeOH, b: AADEA/MeOH, c: HCl/MeOH, rt, d: HCl/MeOH, reflux.

chloroimidate.[8] The chloropyridine derivative **3** in our hands represents a trapped chlorimidate intermediate and the admixed **4** represents the product of the Pinner reaction. The methoxypyridine derivative **4** can be prepared either by heating **2** or **3** with sodium methoxide in methanol. The chlorine atom in chloropyridine derivative **3** was also displaced by mercaptoethanol or methylamine to give the derivatives **5** and **8**, respectively.



Scheme 4. Proposed reaction pathway for the transformation of **2** with amines.

Nitrogen nucleophiles like ammonia, hydroxyammonium chloride, 2-aminoethanol and aminoacetaldehyde diethylacetal reacted with compound **2** in different manners. Ammonia and hydroxyammonium chloride gave 2-aminopyridine (**6**) and 2-aminopyridine-1-oxide (**7**) derivatives, while the dimethylamino group in **2** was substituted by 2-aminoethanol and aminoacetaldehyde diethylacetal, which gave acyclic compounds **9** and **10**, respectively (Scheme 3).

The formation of intermediates **9**-**10** and pyridine derivatives **6**-**7** can be explained by an initial nucleophilic attack at the C-4 of the diene, followed by the expulsion of dimethylamine. Sterically less hindered ammonia and hydroxyammonium chloride cyclization step into pyridine derivatives was fast and the intermediate was not isolated (Scheme 4).

On the other hand, the intermediates formed with sterically more hindered 2-aminoethanol and 2-aminoacetaldehyde diethyl acetal, were less reactive and could be isolated. If we treated compound **10** with methanolic HCl at rt in an attempt to promote the cyclization, only equilibration with excess of methanol took place giving the dimethyl acetal **11**. Upon heating **10** or **11** in a methanolic solution the imidazopyridine derivative **12** was formed.

The stereochemistry around the exocyclic double bond in compounds **2**, **9**, **10**, and **11** was deduced based on the size of the vicinal coupling constants. While the substitution pattern being very similar, the difference in the coupling constant of 12.5 in **2** and around 7 Hz in other three compounds is in accordance with the respective *E* and *Z* stereochemistry.

X-Ray diffraction analysis of compound **8** revealed its structural details. Basic crystal data are summarized

Table 1. Crystal data.

formula	$C_{19}H_{18}N_4$
formula wt.	302.38
crystal system	monoclinic
space group	$P2_1/n$, No. 14
a (Å)	10.2892(7)
b (Å)	9.643(1)
c (Å)	16.695(1)
β (°)	100.824(6)
Z	4
T (K)	293(2)
R	0.042
color	yellow

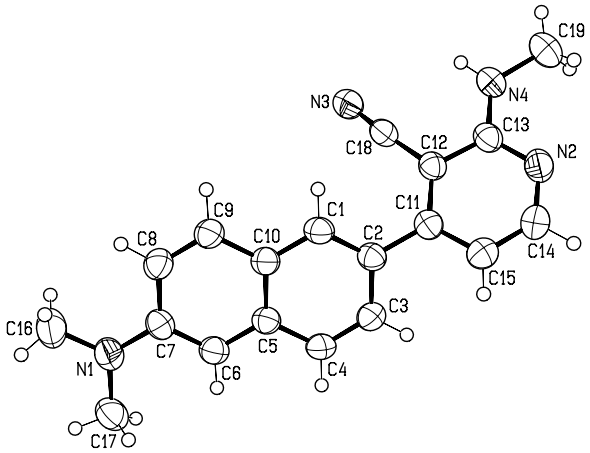


Figure 1. ORTEP drawing of compound **8**.

in Table 1. The groups around the dimethylamino nitrogen are in almost perfectly planar arrangement with the sum of the bond angles of 359°. This plane is twisted from the plane of the naphthalene ring by 6°. The planarity of the arrangement, co-planarity with the naphthalene ring, and relatively short C-N bond length between the dimethylamino group and the aromatic ring (1.381 Å) indicate substantial delocalization of the nitrogen lone-pair into the π-system. This delocalization causes additional shielding of H-5 and H-7 resulting in respective ^{1}H NMR chemical shifts of 6.92 and 7.20 ppm. In analogous compounds with the nitrogen of the amino group as a part of a six-member ring, which is restricted in a non-planar chair conformation, the delocalization of the lone pair is weakened; the corresponding chemical shifts are larger by approximately 0.1 ppm.[9] The plane of the pyridine ring, the acceptor of the dye, is twisted by approximately 32°.

Conclusions

Several 4-(2-naphthyl)pyridine derivatives were prepared from {1-[6-(dimethylamino)-2-naphthyl]-ethylidene}malononitrile (DDNP, **1**) either by elaboration of the ylidenemalononitrile side–chain or by further transformation of the intermediate 2-chloropyridine derivative. The formation of the pyridine ring was tentatively explained to occur via the addition of a nucleophile either directly to the nitrile triple bond or via a conjugate addition, followed by a cyclization step. The course of the reaction depended on the nucleophile selected. In the reaction with HCl the chloroimidate intermediate was trapped in the form of the 2-chloropyridine derivative. This offers a proof of the mechanism of the Pinner synthesis in which in the first step HCl addition across the triple bond occurs and in the second step the chlorine atom is substituted by a nucleophilic alcohol to give an imidate. The structures were proven by standard analytical and spectroscopic methods, and in the case of 4-[6-(dimethylamino)-2-naphthyl]-2-(methylamino)nicotinonitrile (**8**) also by X-ray analysis. All compounds exhibit visible wavelength fluorescence emissions and can be tested against FDDNP for applicability in fluorescence assay of protein aggregate formation.

Experimental

NMR spectra were recorded on Bruker AM360 WB or DPX 300 spectrometers. ^{1}H chemical shifts are quoted in parts per million (ppm) downfield from TMS as internal standard. Melting points were determined on a Kofler hot stage apparatus and are uncorrected. Elemental analyses were determined at the Faculty of Chemistry and Chemical Technology of the University of Ljubljana using a Perkin-Elmer 2400 CHN elemental analyzer. IR spectra were recorded on a Perkin Elmer 727B spectrometer. Radial chromatography was performed using Chromatotron (Harrison Research, 840 Moana Court, Palo Alto, CA 94306). The rotors were prepared as recommended by Harrison Research using E. Merck Silica Gel (Cat. No. 7749-3) in 1, 2, or 4 mm layer thicknesses.

X-ray structure analysis. Diffraction data for compound **8** were collected on Enraf Nonius CAD-4 diffractometer with graphite monochromatized MoKα radiation at room temperature. Intensities of reflections were corrected for decay and Lorentz-polarization effects, but not for absorption (due to the low value of the linear absorption coefficient). Structure was solved by direct methods using SIR92.[10] The positions of hydrogen atoms were obtained from difference Fourier maps. We employed full-matrix least-squares refinement on F magnitudes with anisotropic temperature factors for all non-hydrogen atoms. Only

positional parameters of hydrogen atoms were refined. The Xtal3.4[11] system of crystallographic programs was used for the correlation and reduction of data, structure refinement and interpretation. ORTEPII[12] was used to produce molecular graphics. Details of crystal data, data collection and refinement are given in Table 1. Final atomic coordinates, displacement parameters and geometry parameters have also been deposited with the Cambridge Crystallographic Data Center as supplementary material with the deposition number: CCDC 281787. These data can be obtained, free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html.

2-{(2*E*)-3-(Dimethylamino)-1-[6-(dimethylamino)-2-naphthyl]-2-propenylidene}-malononitrile (2). A solution of 2-{1-[6-(dimethylamino)-2-naphthyl]ethylidene}malononitrile[1] (**1**, 1 g, 3.8 mmol) in *N,N*-dimethlyformamide dimethyl acetal (DMFDMA, 5 mL) was stirred at rt overnight. The volatiles were removed *in vacuo* at rt and the residue was chromatographed by column chromatography (silica 70–230 mesh, 20×150 mm, chloroform) to give compound **2** (1.19 g, 98%). Mp 213–215 °C (from dichloromethane–petroleum ether mixture). Anal. Calcd for $C_{20}H_{20}N_4$: C 75.92, H 6.37, N 17.17. Found: C 76.28, H 6.04, N 17.57. IR (KBr) ν 2210 cm^{-1} (CN). ^{1}H NMR (360 MHz, $CDCl_3$) δ 3.02 (s, 6H, Me_2N), 3.1 (s, 6H, Me_2N), 5.86 and 6.72 (d, 2H, CH=CH), 6.91 (d, 1H, H-5), 7.20 (dd, 1H, H-7), 7.23 (dd, 1H, H-3), 7.62 (bs, 1H, H-1), 7.69 (d, 1H, H-8), 7.73(d, 1H, H-4). $J_{5,7}$ = 2.3 Hz, $J_{7,8}$ = 9.1 Hz, $J_{3,4}$ = 9.0 Hz, $J_{CH=CH}$ = 12.5 Hz. ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.1, 38.1, 41.1, 46.0, 65.1, 98.8, 106.1, 117.2, 126.1, 126.8, 127.0, 128.4, 129.0, 129.8, 136.1, 150.0, 156.5, 172.9.

2-Chloro-4-[6-(dimethylamino)-2-naphthyl]nicotinonitrile (3). A solution of 2-{(2*E*)-3-(dimethylamino)-1-[6-(dimethylamino)-2-naphthyl]-2-propenylidene}malononitrile (**2**, 603 mg, 1.9 mmol) in isopropanol (100 mL) was saturated with dry HCl gas at rt and then stirred overnight. The solvent was removed *in vacuo*, the solid residue was dissolved in dichloromethane and the solution was washed with saturated $NaHCO_3$ solution. The organic layer was dried and evaporated to leave compound **3** (402 mg, 69%). Mp 198–200 °C (from MeOH). Anal. Calcd for $C_{18}H_{14}N_3Cl$: C 70.24, H 4.58, N 13.65. Found: C 69.96, H 4.73, N 13.69. IR (KBr) ν 2250 cm^{-1} (CN). ^{1}H NMR (360 MHz, $CDCl_3$) δ 3.15 (s, 6H, Me_2N), 6.91 (d, 1H, H-5), 7.21 (dd, 1H, H-7), 7.47(d, 1H, H-5'), 7.57 (dd, 1H, H-3), 7.74 (d, 1H, H-8), 7.79 (d, 1H, H-4), 7.99 (d, 1 H, H-1), 8.53 (d, 1H, H-6). $J_{5,7}$ = 2.2 Hz, $J_{7,8}$ = 9.7 Hz, $J_{1,3}$ = 2.0 Hz, $J_{3,4}$ = 9.2 Hz, $J_{5',6'}$ = 5.1 Hz. ^{13}C NMR (75 MHz, $CDCl_3$) δ 40.5, 105.3, 108.7, 115.2, 116.9, 122.6, 125.3, 125.8, 127.1, 127.6, 128.7, 129.8, 135.9, 149.9, 151.1, 154.5, 156.6.

4-[6-(Dimethylamino)-2-naphthyl]-2-methoxynicotinonitrile (4). ***Method A.*** To a solution of compound **2** (82.5 mg, 0.26 mmol) in MeOH (15 mL) a solution of sodium methylate (1 mL, prepared by reacting 10 mg of sodium per mL of methanol) was added and the reaction mixture was heated under reflux for 20 h. The solvent was removed *in vacuo*, the residue was distributed between dichloromethane and brine, and the organic layer was dried and evaporated. The residue was chromatographed by radial chromatography (1 mm silica, dichloromethane–cyclohexane 1:1) to yield methoxy compound **4** (40 mg, 50%). ***Method B.*** A solution of the chloro compound **3** (58 mg, 0.19 mmol) in MeOH (10 mL) was heated under reflux with sodium methylate (0.9 mL of solution, prepared by reacting 10 mg of sodium per mL of methanol, 0.4 mmol) for 6.5 h. The crude **4** was isolated as described under *Method A* but was purified by recrystallization from MeOH. The yield was 34 mg (60%). Mp 150–151 °C (from MeOH). Anal. Calcd for $C_{19}H_{17}N_3O$ C 75.23, H 5.65, N 13.85. Found: C 74.99, H 5.59, N 13.73. IR (KBr) ν 2220 cm^{-1} (CN). ^{1}H NMR (360 MHz, $CDCl_3$) δ 3.1 (s, 6H, Me_2N), 4.11 (s, 3H, OMe), 6.9 (bs, 1H, H-5), 7.12 (d, 1H, H-5'), 7.20 (bd, 1H, H-7), 7.59 (d, 1H, H–3), 7.74 (d, 1H, H-4), 7.79 (d, 1H, H-8), 7.99 (bs, 1H, H-1), 8.31 (d, 1H, H-6'); $J_{7,8}$ = 9.2 Hz, $J_{3,4}$ = 8.6 Hz, $J_{5',6'}$ = 5,4 Hz. ^{13}C HMR (75 MHz, $CDCl_3$) δ 40.6, 54.7, 94.7, 105.5, 115.6, 116.8, 117.3, 125.6, 126.0, 126.9, 128.3, 128.7, 129.7, 135.7, 149.6, 150.0, 156.4, 165.6.

4-[6-(Dimethylamino)-2-naphthyl]-2-[(2-hydroxyethyl)sulfanyl]nicotinonitrile (5). To a solution of 2-mercaptoethanol (0.81 mL, 11.6 mmol) in a solution of sodium methylate (5 mL, prepared by reacting 10 mg of sodium per mL of MeOH, 2.17 mmol), a solution of compound **3** (273 mg, 0.89 mmol) in MeOH (20 mL) was added and the mixture was heated under reflux for 5 h. The solid, which separated from the reaction mixture, was filtered off and recrystallized from acetonitrile to give compound **5** (271 mg, 85%). Mp 210–212 °C. Anal. Calcd for $C_{20}H_{19}N_3OS$: C 68.74, H 5.48, N 12.02. Found: C 68.51, H 4.99, N 12.07. IR (KBr) ν 2220 cm^{-1} (CN), 3350 cm^{-1} (OH). ^{1}H NMR (360 MHz, $CDCl_3$) δ 3.1 (s, 6H, Me_2N), 3.5 (t, 2H, CH_2CH_2), 3.65 (b, 1H, OH), 4.0 (b, 2H, CH_2CH_2), 6.91 (d, 1H, H-5), 7.20 (dd, 1H, H-7), 7.25 (d, 1H, H-5'), 7.55 (d, 1H, H-3), 7.75 (d, 1H, H-4), 7.79 (d, 1H, H-8), 7.97 (bs, 1H, H-1), 8.50 (d, 1H, H-6'); $J_{7,8}$ = 7.8 Hz, $J_{3,4}$ = 8.6 Hz, $J_{5',6'}$ = 5.6 Hz, J_{CH2CH2} = 5.4 Hz. ^{13}C NMR (75 MHz, $CDCl_3$) δ 34.1, 40.6, 62.9, 105.5, 115.7, 116.9, 120.0, 125.5, 126.0, 127.0, 128.3, 128.5, 129.7, 135.8, 149.8, 150.7, 154.7, 160.8, 164.3. HRMS Calcd for $C_{20}H_{19}N_3OS$: 349.1256. Found: 349.1249.

2-Amino-4-[6-(dimethylamino)-2-naphthyl]nicotinonitrile (6). To a boiling solution of compound **2** (100 mg, 0.32 mmol) in MeOH (20 mL), ammonia gas was bubbled in for 30 min. Yellow crystals

of compound **6**, which started to separate from the solution during the reaction were filtered off (86 mg, 93%). Mp 256–257 °C (from MeOH). Anal. Calcd for $C_{18}H_{16}N_4$ C 74.98, H 5.59, N 19.43. Found: C 75.29, H 5.31, N 19.16. IR (KBr) ν 2210 cm^{-1} (CN), 3270 cm^{-1} ($ArNH_2$). ^1H NMR (360 MHz, $CDCl_3$) δ 3.1 (s, 6H, Me_2N), 5.27 (s, 2H, NH_2), 6.87 (d, 1H, H-5'), 6.92 (d, 1H, H-5), 7.20 (dd, 1H, H-7), 7.57 (dd, 1H, H-3), 7.74 (d, 1H, H-8), 7.79 (d, 1H, H-4), 7.97 (bs, 1H, H-1), 8. 42 (d, 1H, H-6); $J_{5,7}$= 2.3 Hz, $J_{7,8}$= 9.5 Hz, $J_{1,3}$= 2.0 Hz, $J_{3,4}$= 8.5 Hz, $J_{5',6'}$= 4.9 Hz.

2-Amino-4-[6-(dimethylamino)-2-naphthyl]nicotinonitrile 1-oxide (7). A solution of compound **2** (286 mg, 0.9 mmol) and hydroxyammonium chloride (94.5 mg, 1.36 mmol) in MeOH (20 mL) was heated under reflux for 70 h. After the reaction was complete the solvent was removed and the residue was solubilized in methanol, the solution was filtered and evaporated. The residue was distributed between chloroform and a saturated solution of sodium bicarbonate. The organic layer was dried and concentrated to a small volume. The compound was then purified using radial chromatography (2 mm thick layer of silica, application on a dry plate using chloroform followed by 2% MeOH in dichloromethane increasing to 5% MeOH in dichloromethane). The pure fractions were combined and recrystallized from methanol to give the *N*-oxide **7** (53 mg, 20%). Mp 248–250 °C (from MeOH). Anal. Calcd for $C_{18}H_{16}N_4O$: C 71.04, H 5.30, N 18.41. Found: C 70.59, H 5.59, N 18.19. IR (KBr) ν 2220 cm^{-1} (CN), 3310 cm^{-1} ($ArNH_2$). ^1H NMR (360 MHz, $CDCl_3$) δ 3.1 (s, 6H, Me_2N), 6.43 (s, 2H, NH_2), 6.86 (d, 1H, H-5'), 6.91 (d, 1H, H-5), 7.21 (dd, 1H, H-7), 7.55 (dd, 1H, H-3), 7.75 (d, 1H, H-8), 7.78 (d, 1H, H-4), 7.95 (bs, 1H, H-1), 8.12 (d, 1H, H-6); $J_{5,7}$= 2.4 Hz, $J_{7,8}$= 8.7 Hz, $J_{1,3}$= 2.0 Hz, $J_{3,4}$= 8.7 Hz, $J_{5',6'}$= 6.7 Hz. ^{13}C NMR (75 MHz, $CDCl_3$) δ 40.9, 91.8, 105.9, 113.7, 115.5, 117.3, 125.6, 126.4, 127.5, 128.3, 128.5, 130.0, 136.1, 140.4, 145.2, 150.1, 152.9. HRMS Calcd for $C_{18}H_{16}N_4O$: 304.1331. Found: 304.1324.

4-[6-(Dimethylamino)-2-naphthyl]-2-(methylamino)nicotinonitrile (8). Compound **3** (194.5 mg, 0.63 mmol) was suspended in ethanolic solution of methylamine (5 mL of 33% solution) and heated under reflux for 1 h. Additional 5 mL of methanolic methylamine was added and heating was continued for 9 h. After cooling product **8** was filtered off (147 mg, 77%). Additional amount of product (40 mg), leading to a total yield of 98%, was isolated from the mother liquor by radial chromatography (1 mm thick layer of silica, 1% of MeOH in dichloromethane). Mp 193–194 °C. Anal. Calcd for $C_{19}H_{18}N_4$: C 75.47, H 6.00, N 18.53. Found: C 75.28, H 5.99, N 18.48. IR (KBr) ν 2210 cm^{-1} (CN), 3270 cm^{-1} (NH). ^1H NMR (300 MHz, $CDCl_3$) δ 3.1 (s, 6H, NMe_2), 3.12 (d, 3H, MeNH, J= 4.8 Hz), 5.38 (bs, 1H, NH), 6.76 (d, 1H, H-5', J= 5.3 Hz), 6.92 (d, 1H, H-5, J= 2.5 Hz), 7.20 (dd, 1H, H-7, J= 2.5 and 9.1 Hz), 7.56 (dd, 1H, H-3, J= 1.9 and 8.6 Hz), 7.73 (d, 1H, H-4, J= 8.6 Hz), 7.78 (d, 1H, H-8, J= 9.1 Hz), 7.94 (d, 1H, H-1, J= 1.9 Hz), 8.29 (d, 1H, H-6', J= 5.3 Hz). Absorption λ_{max}= 362 nm, emission λ_{max}= 523 nm (in dichloromethane).

2-{(2Z)-1-[6-(Dimethylamino)-2-naphthyl]-3-[(2-hydroxyethyl)amino]-2-propenylidene}malononitrile (9). A solution of compound **2** (350 mg, 1.1 mmol) and 2-aminoethanol (0.4 mL, 6.6 mmol) in MeOH (50 mL) was heated under reflux for 24 h. The solvent was removed and the residue was chromatographed by radial chromatography (4 mm thick layer of silica, 5% MeOH in dichloromethane) to yield compound **9** (327 mg, 89%). Mp 168–170 °C (from EtOH). ^1H NMR (360 MHz, $CDCl_3$) δ 3.08 (s, 6H, Me_2N), 3.98 and 4.17 (bs, 4H, CH_2CH_2), 5.43 (b, 2H, OH, NH), 6.09 and 7.24 (d, 2H, CH=CH), 6.86 (bs, 1H, H-5), 7.16 (d, 1H, H-7), 7.51 (d, 1H, H-3), 7.68 (d, 1H, H-4), 7.74 (d, 1H, H-8), 7.94 (s, 1H, H-1); $J_{3,4}$= 8.6 Hz, $J_{7,8}$= 9.2 Hz, $J_{CH=CH}$= 6.9 Hz. ^{13}C NMR (75 MHz, $CDCl_3$) δ 40.5, 42.3, 57.2, 62.8, 98.8, 104.9, 105.4, 116.8, 124.93, 125.7, 126.8, 128.0, 128.4, 129.8, 136.15, 141.9, 149.8, 157.3, 158.6. HRMS Calcd for $C_{28}H_{20}N_4O$: 332.1645. Found: 332.1637.

2-{(2Z)-3-[(2,2-Diethoxyethyl)amino]-1-[6-(dimethylamino)-2-naphthyl]-2-propenylidene}malononitrile (10) and 2-{(2Z)-3-[(2,2-dimethoxyethyl)amino]-1-[6-(dimethylamino)-2-naphthyl]-2-propenylidene}malononitrile (11). A solution of compound **2** (100 mg, 0.316 mmol) and aminoacetaldehyde diethyl acetal (0.1 mL, 0.96 mmol) in MeOH (20 mL) was heated under reflux for 46 h. The solvent was removed in vacuo to leave an oily residue, which was chromatographed by radial chromatography (2 mm thick layer of silica, dichloromethane, followed by 5% MeOH in dichloromethane) to yield diethoxy compound **10** (111 mg, 87%). ^1H NMR (360 MHz, $CDCl_3$) δ 1.22 (t, 6H, t, $OCH_2\underline{CH_3}$, J = 7.1 Hz), 3.09 (s, 6H, Me_2N), 3.59 and 3.80 (m, 4H, $O\underline{CH_2}CH_3$), 4.05 (d, 2H, $\underline{CH_2}CH$), 4.92 (t, 1H, $CH_2\underline{CH}$), 5,95 and 7.23 (d, 2H, CH=CH), 6.90 (bs, 1H, H-5), 7.19 (dd, 1H, H-7), 7.55 (d, 1H, H-3), 7.71 (d, 1H, H-4), 7.77 (d, 1H, H-8), 7.97 (bs, 1H, H-1); $J_{CH=CH}$= 7.2 Hz, $J_{7,8}$= 9.1 Hz, $J_{3,4}$= 8.5 Hz, J_{CH2CH}= 5.1 Hz.

To a solution of **10** (19 mg, 0.05 mmol) in MeOH (5 mL) HCl gas was bubbled in for 5 min at rt. The reaction mixture was stirred at rt for additional 30 min and concentrated to leave an oily residue. It was distributed between ethyl acetate and ice-cold brine (40 mL each). The organic layer was dried and evaporated to yield compound **11** (12 mg, 66%). Compound **11** was also prepared directly from **2** using aminoacetaldehyde dimethyl acetal instead of the diethyl acetal and following the procedure for the synthesis of **10** except

that 0.3% of Et_3N was added to the solvent for radial chromatography after all the faster moving impurity had been removed from the plate. Mp 158–159 °C. IR (KBr) ν 2220 cm^{-1} (CN). ^1H NMR (360 MHz, $CDCl_3$) δ 3.1 (s, 6H, Me_2N), 3.48 (s, 6H, OCH_3), 4.06 (d, 2H, $\underline{CH_2}CH$), 4.78 (t, 1H, $CH_2\underline{CH}$), 5.96 and 7.24 (d, 2H, CH=CH), 6.89 (d, 1H, H-5), 7.18 (dd, 1H, H-7), 7.54 (d, 1H, H-3), 7.74 (d, 1H, H-4), 7.76 (d, 1H, H-8), 7.96 (s, 1H, H-1); $J_{5,7}$= 2.2 Hz, $J_{CH=CH}$= 7.0 Hz, $J_{7,8}$= 8.9 Hz, $J_{3,4}$= 8.5 Hz, J_{CH2CH}= 5.1 Hz. ^{13}C NMR (75 MHz, $CDCl_3$) δ 40.9, 53.9, 56.2, 99.2, 101.7, 103.8, 105.9, 117.1, 117.6, 125.4, 126.2, 127.1, 128.3, 129.4, 130.1, 136.4, 143.3, 150.1, 157.1, 157.3. HRMS Calcd for $C_{22}H_{24}N_4O_2$: 376.1906. Found: 376.1899.

7-[6-(Dimethylamino)-2-naphthyl]imidazo[1,2-*a*]pyridine-8-carbonitrile (12). A solution of **11** (53 mg, 0.14 mmol) in MeOH (15 mL) was heated under reflux for 2 h. During the first 30 min a stream of dry HCl gas was led through the reaction mixture. After the reaction was complete, the solvent was evaporated and the solid residue was distributed between dichloromethane and saturated solution of sodium bicarbonate. The organic layer was dried and evaporated. The residue was chromatographed by radial chromatography (1 mm thick layer of silica, 5% MeOH in dichloromethane) to give product **12** (25 mg, 57%). Mp 268–269 °C (from MeOH). Anal. Calcd for $C_{20}H_{16}N_4$: C 76.90, H 5.16, N 17.94. Found: C 76.23, H 5.22, N 17.62. IR (KBr) ν 2230 cm^{-1} (CN). ^1H NMR (360 MHz, $CDCl_3$) δ 3.07 (s, 6H, Me_2N), 7.02 (d, 1H, H-5'), 7.29 (d, 1H, H-6), 7.33 (dd, 1H, H-7'), 7.69 (d, 1H, H-3'), 7.74 (bs, 1H, H-2 or H-3), 7.84 (d, 1H, H-4'), 7.87 (d, 1H, H-8'), 8.11 (s, 1H, H-1'), 8.14 (bs, 1H, H-2 or H-3), 8.9 (d, 1H, H-5); $J_{5',7'}$= 2.0 Hz, $J_{7',8'}$= 9.4 Hz, $J_{3',4'}$= 8.6 Hz, $J_{5,6}$= 7.2 Hz. ^{13}C NMR (75 MHz, $CDCl_3$) δ 40.6, 99.1, 105.6, 113.3, 114.0, 115.4, 116.8, 125.9, 126.1, 127.0, 128.4, 129.1, 129.6, 135.4, 135.5, 144.3, 145.5, 149.6. HRMS Calcd for $C_{20}H_{16}N_4$: 312.1380. Found: 312.1375.

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References and Notes

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Povzetek

Etilidenmalononitrilno stransko verigo v {1-[6-(dimetilamino)-2-naftil]etiliden}malononitrilu (DDNP) smo v dvostopenjskem procesu pretvorili v substituiran piridinski obroč. Tako smo pripravili analoge molekularne probe (1-{6-[(2-fluoroetil)(metil)amino]-2-naftil}etiliden)malononitril (FDDNP), ki je bila uspešno uporabljena v diagnostiki Alzheimerjeve bolezni s pozitronsko emisijsko tomografijo. Pri reakciji s HCl smo izolirali 2-kloro-4-[6-(dimetilamino)-2-naftil]nikotinonitril, ki potrjuje nastanek kloroimidata kot intermediata pri Pinnerjevi sintezi. Strukturo 2-metilaminopiridinskega derivata smo dokazali tudi z rentgensko difrakcijsko analizo.