Scientific paper

Synthesis of DDNP Analogs with an Aromatic Ring Attached via an Ethylidene Tether

Alenka Žabjek,[1] Jorge R. Barrio[2] and Andrej Petrič[1,*]

[1] *Faculty of Chemistry and Chemical Technology, University of Ljubljana, Aškerčeva 5, 1000 Ljubljana, Slovenia*

[2] *David Geffen School of Medicine at UCLA, Los Angeles, CA, USA*

* *Corresponding author: E-mail: andrej.petric@fkkt.uni-lj.si*

Received: 24-11-2008

Dedicated to Professor Branko Stanovnik on the occasion of his 70th birthday

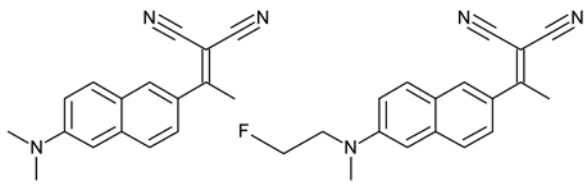
Abstract

The parent DDNP molecule was modified in such a manner that an aromatic or heteroaromatic ring was attached through an ethylidene tether. A series of analogs of FDDNP, a molecular probe for protein aggregate deposition in the central nervous system, was obtained. These analogs exhibit similar optical properties as DDNP/FDDNP and thus fulfill the optical requirements for successful application in fluorescence microscopy. The introduced aromatic ring offers an additional opportunity for π-interaction between the molecule and protein aggregates.

Keywords: DDNP, fluorescent probes, synthesis, fluorescence

1. Introduction

Starting from {1-[6-(dimethylamino)naphthalen-2-yl]ethylidene}propanedinitrile (DDNP)[1] as the lead compound, (1-{6-[(2-fluoroethyl)(methyl)amino]naphthalen-2-yl}ethylidene)propanedinitrile (FDDNP) was developed and successfully applied as a molecular probe for *in vitro* and *in vivo* assessment of amyloid protein aggregate deposition in the central nervous system (CNS) of patients with Alzheimer's and other neurodegenerative diseases with similar pathogenesis.[2–10]



To facilitate routine application in medical diagnostics and research, fully automated synthesis of radiolabeled [^{18}F]FDDNP was developed.[11] Besides FDDNP, four other compounds: 2-[4-(methylamino)phenyl]-1,3-benzothiazol-6-ol ([*N*-methyl-^{11}C]PIB), 5-{(*E*)-2-[6-(2-fluoroethoxy)-1,3-benzoxazol-2-yl]vinyl}-*N,N*-dimethyl-1,3-thiazol-2-amine ([^{11}C]BF-227), 4-{(*E*)-2-[4-(methylamino)phenyl]vinyl}phenol ([^{11}C]SB-13), and 4-[(*E*)-2-(4-{2-[2-([^{18}F]2-fluoroethoxy)ethoxy]ethoxy}phenyl)vinyl]-*N*-methylaniline ([^{18}F]-BAY94-9172) have been recently introduced.[12a] In this work we investigate the effect of molecular modifications in the parent structure (FDDNP) on the optical properties for their use with fluorescence microscopy of protein aggregation in the CNS.[12b] Molecules of the DDNP family bind strongly to protein aggregates (<nM) when two conditions are met: hydrophobic stacking of aromatic rings and relatively large dipole moment. The hydrophobic stacking is enhanced if the molecule can attain planar conformation, which also increases the probability of strong dipole moments. Polar interactions between the probe and amino acid residues within the binding site also contribute to stronger binding.

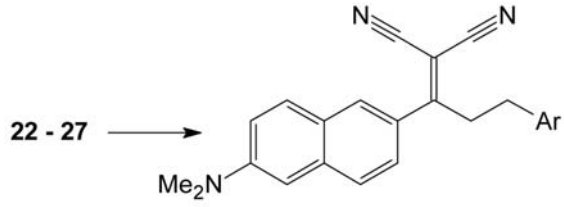
Several FDDNP analogs have already been prepared and characterized. Bifunctional heterocyclic or acyclic amino group were introduced instead of the dimethylamino group in DDNP thus enabling the preparation of pharmacophore-containing analogs, intended for structural and functional imaging of dopamine-D_2 receptors by fluo-

rescence microscopy.[13–15] Modifications of DDNP at the acceptor part of the molecule were also introduced utilizing the relatively high reactivity of the ethylidenemalononitrile side-chain resulting in the transformation of DDNP into highly fluorescent 2-hetaryl-6-dimethylaminonaphthalene derivatives. In contrast to the parent DDNP, functional groups in these compounds allow further synthetic elaboration.[16]

In this contribution we describe the synthesis of a series of DDNP derivatives with an additional aromatic ring attached via an ethylidene tether to the acceptor side-chain. We intended these derivatives to probe the impact of the additional aromatic ring on optical properties and on binding to protein aggregates.

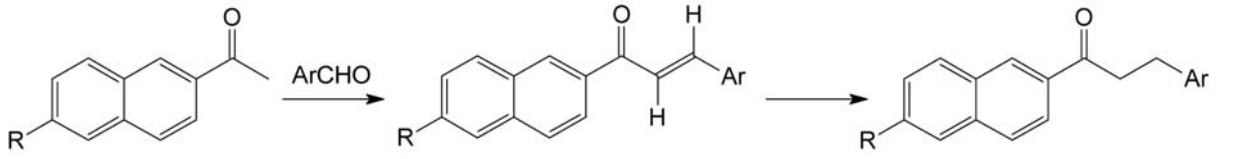
2. Results and Discussion

The synthetic approach is summarized in **Scheme 1**. Utilizing relatively high acidity of the methyl group in 1-[6-(dimethylamino)naphthalen-2-yl]ethanone (**2**) or its 6-methoxy precursor (**1**) in a Claisen-Schmidt condensation[17] with aromatic aldehydes, α,β-unsaturated ketones **3-15** were formed. The sodium hydroxide catalyzed reactions were run in ethanol at room temperature. Under these conditions the reactions yielded exclusively *E*-alkenes. For most compounds this was supported by the measured vicinal coupling constants between the alkene protons in ^{1}H NMR spectra. The coupling constants between 15 and 16.2 Hz were in the normal range for *E*-arrangement of protons. In some spectra the signals for alkene protons overlapped with other signals and such proof is lacking. In these cases we assumed *E*-stereochemistry by analogy. Alkenes **10–15** no longer exhibited the fluorescent properties of the precursor, but their intense yellow color indicated absorption red-shift of these derivatives in the visible region of the spectrum. The C=C bond was selectively reduced using iron pentacarbonyl[18] to give substituted naphthyl ethyl ketones **16–27**. The saturation of the exocyclic double bond enabled products **22–27** to exhibit similar visible fluorescence as observed in **2**. The methoxy derivatives **16–21** were prepared from **1** with the intent to serve as substrates for nucleophilic aromatic substitution with lithium salts of a series of secondary amines to yield novel fluorescent compounds with a reactive side chain. Low yields in experiments, in which we tried to prepare dimethylamino compounds **22–27** from their methoxy analogs, indicated that this wasn't the best synthetic approach. The yield was acceptable only in the case of transformation of **17** into **23**. As a result the introduction of the dimethylamino group at the beginning and performing the Claisen-Schmidt condensation as well as the reduction with this group already in place was the most efficient pathway. However, the methoxy group in **16–21** re-



28: Ar= phenyl
29: Ar= 3-hydroxyphenyl
30: Ar= 2,6-dichlorophenyl
31: Ar= biphenyl-4-yl
32: Ar= 2-naphthyl
33: Ar= quinolin-3-yl

Scheme 2.



1: R= OCH_3
2: R= NMe_2

3: R= OMe; Ar= phenyl
4: R= OMe; Ar= 3-hydroxyphenyl
5: R= OMe; Ar= 3-nitrophenyl
6: R= OMe; Ar= 2,6-dichlorophenyl
7: R= OMe; Ar= biphenyl-4-yl
8: R= OMe; Ar= 2-naphthyl
9: R= OMe; Ar= quinolin-3-yl
10: R= NMe_2; Ar= phenyl
11: R= NMe_2; Ar= 3-hydroxyphenyl
12: R= NMe_2; Ar= 2,6-dichlorophenyl
13: R= NMe_2; Ar= biphenyl-4-yl
14: R= NMe_2; Ar= 2-naphthyl
15: R= NMe_2; Ar= quinolin-3-yl

16: R= OMe; Ar= phenyl
17: R= OMe; Ar= 3-hydroxyphenyl
18: R= OMe; Ar= 2,6-dichlorophenyl
19: R= OMe; Ar= biphenyl-4-yl
20: R= OMe; Ar= 2-naphthyl
21: R= OMe; Ar= quinolin-3-yl
22: R= NMe_2; Ar= phenyl
23: R= NMe_2; Ar= 3-hydroxyphenyl
24: R= NMe_2; Ar= 2,6-dichlorophenyl
25: R= NMe_2; Ar= biphenyl-4-yl
26: R= NMe_2; Ar= 2-naphthyl
27: R= NMe_2; Ar= quinolin-3-yl

Scheme 1.

main a potential reactive site for e.g. demethylation and subsequent further transformations leading to other, reactive site containing, fluorescent analogues.

In the last step DDNP analogs were prepared in the Knoevenagel reaction of ketones **22–27** with malononitrile. (Scheme 2) Using this approach {1-[6-(dimethylamino)-2-naphthyl]-3-(3-aryl)propylidene}malononitrile derivatives **28–33** were obtained in moderate yields.

Measured fluorescence excitation and emission spectra of **28–33** (Table 1) revealed that the described structural modifications did not cause significant changes in the fluorophore. This suggests,[12] this these derivatives would have analogous binding characteristics to amyloid aggregates than other closer members of the DDNP family. However, it is anticipated that the additional tethered aromatic ring would play an important role in enhancing binding to protein aggregates through π-interactions.

Table 1. Excitation and emission maxima measured in methanol

Cmpd	λ_{exc}	λ_{em}
DDNP	433	580
28	441	588
29	440	587
30	439	604
31	433	578
32	439	611
33	446	589

3. Conclusions

We have prepared a series of DDNP analogues to probe their optical properties as predictor of their binding to amyloid aggregates. With an aromatic ring tethered to the parent molecule and additional binding point was introduced aiming for possible π-interaction with the protein aggregate. As hypothesized, the new analogs have optical properties resembling the optical properties of DDNP and its analogs described so far, making these compounds good candidates for successful application in fluorescence microscopy. The methoxy intermediates can serve for further synthetic elaboration at the donor part of the molecule, e.g. to introduce radiolabeling.

4. Experimental

NMR spectra were recorded on a Bruker DPX 300 spectrometer at 302 K using $CDCl_3$ as the solvent. ^{1}H chemical shifts are quoted in parts per million (ppm) downfield from TMS as internal standard, ^{13}C NMR spectra are referenced to the middle line of $CDCl_3$ signal (77.0 ppm). Mass spectra were measured at the Jožef Stefan institute using VG-Analytical AutospecQ spectrometer. Fluorescence spectra were measured on a Shimadzu RF 1501 spectrofluorimeter. 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 (T-Squared Technology, Inc., 903 Sneath Lane, Suite 125 San Bruno, Ca 94066). The rotors were prepared as recommended by the manufacturer using E. Merck Silica Gel (Cat. No. 7749-3) in 1, 2, or 4 mm layer thicknesses.

General procedure for the Claisen-Schmidt condensation of methyl ketones with aromatic aldehydes. An equimolar solution of a ketone and an aromatic aldehyde (1 mmol) in anhydrous ethanol (approximately 20 mL per one mmol) was cooled on ice, finely powdered NaOH (one tenth of the mass of the ketone) was added and the mixture was stirred on ice for 1 hour, followed by stirring at rt for additional 24 hours. The solid, which has separated was filtered off and chromatographed by radial chromatography to yield the products. In the case of reactions with 3-hydroxybenzaldehyde heating at 60–65 °C for 24 hours was required and the products were isolated by extraction (dichloromethane, anhydrous Na_2SO_4) followed by radial chromatography.

(2*E*)-1-(6-Methoxy-2-naphthyl)-3-phenylprop-2-en-1-one (3). Yield 78%; radial chromatography on a 2 mm thick silicagel layer using 30% petroleum ether in dichloromethane as the eluent; mp 124–126 °C (from benzene-petroleum ether), (lit.[19]125–126 °C); ^{1}H NMR δ 3.96 (s, 3H, OMe); 7.19 (d, 1H, *J* 2.6 Hz, H-5); 7.22 (dd, 1H, *J* 2.6 and 8.9 Hz, H-7); 7.42–7.46 (m, 3H, Ph'); 7.67–7.91 (m, 6H, H-4, H-8, 2H Ph', COCH=CH); 8.11 (1H, dd, *J* 1.6 and 8.7 Hz, H-3); 8.49 (d, 1H, *J* 1.6 Hz, H-1).

(2*E*)-3-(3-Hydroxyphenyl)-1-(6-methoxy-2-naphthyl) prop-2-en-1-one (4). Yield 62%; radial chromatography on 2 mm thick silicagel layer using 1% methanol in dichloromethane as the eluent; mp 197–199 °C (from dichloromethanehexane) Anal. Calcd for $C_{20}H_{16}O_3$: C 78.93, H 5.30. Found: C 79.28, H 5.27; ^{1}H NMR δ 3.96 (s, 3H, OMe); 6.89–6.93 (m, 1H, Ph'); 7.18 (d, 1H, *J* 2.4 Hz, H-5); 7.23 (dd, 1H, *J* 2.4 and 9.0 Hz, H-7); 7.27–7.38 (m, 3H, Ph'); 7.66 (d, 1H, *J* 15.0 Hz, COCH=CH); 7.81 (d, 1H, *J* 15.0 Hz, COCH=CH); 7.82 (d, 1H, *J* 8.7 Hz; H-4); 7.89 (d, 1H, *J* 9.0 Hz; H-8); 8.09 (dd, 1H, *J* 1.8 and 8.7 Hz, H-3); 8.48(d, 1H, *J* 1.8 Hz, H-1).

(2*E*)-1-(6-Methoxy-2-naphthyl)-3-(3-nitrophenyl)prop -2-en-1-one (5). Yield 70%; radial chromatography on 2 mm thick silicagel layer using 50% hexane in dichloromethane as the eluent; mp 183–184 °C (from dichloromethane-hexane); Anal. Calcd for $C_{20}H_{15}NO_4$: C 72.06, H 4.54, N 4.20. Found C 71.79, H 4.45, N 4.11; ^{1}H NMR δ

3.97 (s, 3H, OMe); 7.19 (d, 1H, *J* 2.4 Hz, H-5); 7.25 (dd, 1H, *J* 2.4 and 8.7 Hz, H-7); 7.63 (m, 1H, Ph'); 7.79–7.97 (m, 5H, H-4, H-8, 1H Ph', COCH=CH); 8.12 (dd, 1H, *J* 1.5 and 8.7 Hz, H-3); 8.25–8.29 (m, 1H, Ph'); 8.52 (1H, d, *J* 1.5 Hz, H-1); 8.56–8.58 (m, 1H, Ph').

(2*E*)-3-(2,6-Dichlorophenyl)-1-(6-methoxy-2-naphthyl) prop-2-en-1-one (6). Yield 50%; radial chromatography on 2 mm thick silicagel layer using 50% hexane in dichloromethane as the eluent; mp 122–123 °C (from dichloromethane-hexane); Anal. Calcd for $C_{20}H_{14}Cl_2O_2$: C 67.24, H 3.95. Found C 67.49, H 3.90; ^{1}H NMR δ 3.93 (s, 3H, OMe); 7.14–7.21 (m, 3H, H-5, H-7, 1H Ph'); 7.37 (m, 2H, Ph'); 7.79 (d, 1H, COCH=CH, *J* 16.2 Hz); 7.80 (d, 1H, H-4, *J* 8.7 Hz); 7.84 (d, 1H, H-8, *J* 9.0 Hz); 7.89 (d, 1H, COCH=CH, *J* 16.2 Hz); 8.08 (dd, 1H, *J* 1.5 and 8.7 Hz, H-3); 8.44 (1H, d, *J* 1.5 Hz, H-1); ^{13}C NMR δ 55.32, 105.77, 119.66, 125.08, 127.28, 127.75, 128.75, 129.65, 130.29, 130.46, 131.13, 132.73, 132.94, 135.09, 137.18, 137.28, 159.81, 189.39.

(2*E*)-3-Biphenyl-4-yl-1-(6-methoxy-2-naphthyl)prop-2-en-1-one (7). Yield 70%; radial chromatography on 2 mm thick silicagel layer using 50% hexane in dichloromethane as the eluent; mp 192–194 °C (from benzene-petroleum ether); Anal. Calcd for $C_{26}H_{20}O_2$: C 85.69, H 5.53. Found C 85.57, H 5.51; ^{1}H NMR δ 3.94 (s, 3H, OMe); 7.16 (d, 1H, H-5, *J* 2.64 Hz); 7.21 (dd, 1H, H-7, *J* 2.64 and 9.03 Hz); 7.34–7.39 (m, 1H, Ph'/Ph''); 7.42–7.48 (m, 2H, Ph'/Ph''); 7.61–7.66 (m, 4H, Ph'/Ph''); 7.71 (d, 1H, COCH=CH, *J* 15.5 Hz); 7.74 (m, 2H, Ph'/Ph''); 7.81 (d, 1H, H-4, *J* 8.7 Hz); 7.89 (d, 1H, H-8, *J* 8.9 Hz); 7.90 (d, 1H, –COCH=CH, *J* 15.5 Hz); 8.10 (dd, 1H, H-3, *J* 1.8 and 8.7 Hz); 8.48 (d, 1H, H-1, *J* 1.8 Hz); ^{13}C NMR δ 55.39, 105.82, 119.69, 121.85, 125.21, 127.03, 127.26, 127.54, 127.84, 127.89, 128.88, 128.94, 129.84, 131.10, 133.61, 134.02, 137.19, 140.15, 143.14, 143.80, 159.73, 189.69.

(2*E*)-1-(6-Methoxy-2-naphthyl)-3-(2-naphthyl)prop-2-en-1-one (8). Yield 66%; radial chromatography on 4 mm thick silicagel layer using 50% hexane in dichloromethane as the eluent; mp 190–192 °C (from benzene-petroleum ether); Anal. Calcd for $C_{24}H_{18}O_2$: C 85.18, H 5.36. Found C 85.44, H 5.29; ^{1}H NMR δ 3.97 (s, 3H, OMe); 7.19 (d, 1H, *J* 2.4 Hz, H-5); 7.23 (dd, 1H, *J* 2.4 and 9.0 Hz, H-7); 7.52–7.55 (2H, m, naphthyl'); 7.78–8.05 (m, 9H, H-4, H-8, 5H naphthyl', COCH=CH); 8.13 (dd, 1H, *J* 1.7 and 8.7 Hz, H-3); 8.53 (d, 1H, *J* 1.7 Hz, H-1); ^{13}C NMR δ 55.24, 105.87, 119.73, 122.20, 123.79, 125.27, 126.75, 127.31, 127.82, 127.95, 128.65, 128.72, 129.89, 130.54, 131.15, 132.61, 133.43, 133.67, 134.37, 137.24, 144.40, 159.78, 189.79.

(2*E*)-1-(6-Methoxynaphthalen-2-yl)-3-(quinolin-3-yl) prop-2-en-1-one (9). Yield 76%; radial chromatography on 2 mm thick silicagel layer using dichloromethane followed by 1% methanol in dichloromethane as the eluent; mp 261–263 °C (from dichloromethane); Anal. Calcd for $C_{23}H_{17}NO_2$: C 81.40, H 5.05, N 4.13. Found C 81.62, H 4.98, N 4.02; ^{1}H NMR: 3.97 (s, 3H, OMe); 7.19 (d, 1H, *J* 2.5 Hz, H-5); 7.24 (dd, 1H, *J* 2.5 and 9.03 Hz, H-7); 7.58–7.64 (m, 1H, quinolinyl); 7.75–7.80 (m, 1H, quinolinyl); 7.84 (d, 1H, *J* 8.7 Hz, H-4); 7.88–7.94 (m, 3H, COCH=CH, H-8, 1H quinolinyl); 8.02 (d, 1H, *J* 15.6 Hz, COCH=CH); 8.11–8.16 (m, 2H, H-3 and 1H quinolinyl); 8.38 (d, 1H, *J* 2.0 Hz, quinolinyl); 8.53 (d, 1H, *J* 1.1 Hz, H-1); 9.26 (d, 1H, *J* 2.0, quinolinyl); ^{13}C NMR δ 55.44, 105.88, 119.85, 123.60, 125.14, 127.44, 127.47, 127.76, 127.90, 128.10, 128.37, 129.43, 130.09, 130.65, 131.20, 133.22, 135.64, 137.39, 140.80, 148.59, 149.43, 159.94, 189.11.

(2*E*)-1-[6-(Dimethylamino)naphthalen-2-yl]-3-phenyl-prop-2-en-1-one (10). Yield 89%; radial chromatography on 2 mm thick silicagel layer using 3% dichloromethane in petroleum ether as the eluent; mp 186–187 °C (from dichloromethane-petroleum ether); Anal. Calcd for $C_{21}H_{19}NO$: C 83.69, H 6.35, N 4.65. Found C 83.85, H 6.27, N 4.70; ^{1}H NMR δ 3.06 (s, 6H, NMe_2); 6.85 (d, 1H, *J* 2.4 Hz, H-5); 7.13 (dd, 1H, *J* 2.4 and 9.2 Hz, H-7); 7.38–7.41 (m, 3H, Ph'); 7.64–7.71 (m, 4H, 1H-4, COCH=CH, 2H Ph'); 7.79 (d, 1H, *J* 9.2 Hz, H-8); 7.84 (d, 1H, *J* 15.8 Hz, COCH=CH); 8.01 (dd, 1H, *J* 1.5 and 8.7 Hz, H-3); 8.39 (d, 1H, *J* 1.5 Hz, H-1); ^{13}C NMR δ 40.29, 105.2, 116.17, 122.17, 125.03, 126.32, 128.29, 128.82, 130.10, 130.23, 130.67, 131.53, 135.26, 137.60, 143.38, 150.19, 189.25.

(2*E*)-1-[6-(Dimethylamino)naphthalen-2-yl]-3-(3-hydroxyphenyl)prop-2-en-1-one (11). Yield 78%; radial chromatography on 2 mm thick silicagel layer using 2% methanol in dichloromethane as the eluent; mp 209–211 °C (from dichloromethane-petroleum ether); Anal. Calcd for $C_{21}H_{19}NO_2 \times 0.5\ H_2O$: C 77.28; H 6.17; N 4.29. Found C 77.11; H 5.77; N 4.25; HRMS Calcd for $C_{21}H_{19}NO_2$: 317.1416, found 317.1427; ^{1}H NMR δ 3.12 (s, 6H, NMe_2); 5.33 (s, 1H, OH); 6.89–6.92 (m, 2H, H-5 and 1H Ph'); 7.16–7.21 (m, 2H, *J* 2.4 and 9.0 Hz, H-7, H-7 and 1H Ph'); 7.27–7.33 (m, 2H, Ph'); 7.66–7.71 (m, 2H, H-4 and COCH=CH); 7.82 (d, 1H, *J* 15.6 Hz, COCH=CH); 7.85(d 1H, *J* 9.0 Hz, H-8,); 8.02 (dd, 1H, *J* 1.8 and 8.7 Hz, H-3); 8.40 (d, 1H, *J* 1.8 Hz, H-1); ^{13}C NMR δ 104.34, 114.24, 115.52, 117.00, 118.85, 121.14, 124.06, 124.14, 125.55, 129.04, 129.47, 130.55, 135.54, 136.77, 142.78, 149.49, 157.07, 188.10.

(2*E*)-3-(2,6-Dichlorophenyl)-1-[6-(dimethylamino)-2-naphthyl]prop-2-en-1-one (12). Yield 74.4%; radial chromatography on 2 mm thick silicagel layer using 50% petroleum ether in dichloromethane as the eluent; mp 195–197 °C (from benzene-petroleum ether); Anal. Calcd

for $C_{21}H_{17}Cl_2NO$: C 68.12; H 4.63; Cl 19.15; N 3.78. Found C 68.38; H 4.45; N 3.84; ^{1}H NMR δ 3.10 (s, 6H, NMe_2); 6.88 (d, 1H, H-5, *J* 2.4 Hz); 7.16–7.24 (m, 2H, H-7 and 1H Ph'); 7.38–7.42 (m, 2H, Ph'); 7.67 (d, 1H, H-4, *J* 8.7 Hz); 7.80 (d, 1H, H-8, *J* 9.0 Hz); 7.80(d, 1H, CO<u>CH</u>=CH, *J* 16.0 Hz); 7.88 (1H, d, COCH=<u>CH</u>, *J* 16.0 Hz); 8.01 (dd, 1H, H-3, *J* 8.7 Hz), 8.39 (d, 1H, H-1, *J* 1.7 Hz); ^{13}C NMR δ 40.36, 105.33, 116.20, 125.03, 125.10, 126.37, 128.78, 129.53, 130.79, 130.86, 131.14, 133.12, 135,17 136.47, 137.80, 150.38, 189.06, 217.37.

(2*E*)-3-Biphenyl-4-yl-1-[6-(dimethylamino)-2-naphthyl]prop-2-en-1-one (13). Yield 80%; radial chromatography on 2 mm thick silicagel layer using 50% petroleum ether in dichloromethane as the eluent; mp 190–192 °C (from benzene-petroleum ether); Anal. Calcd for $C_{27}H_{23}NO$: C 85.91; H 6.14; N 3.71. Found C 85.89; H 5.96; N 3.94; ^{1}H NMR δ 3.09 (6H, s, NMe_2); 6.88 (d, 1H, H-5, *J* 2.6 Hz); 7.17 (dd, 1H, H-7, *J* 2.6 and 9.0 Hz); 7.34–7.39 (m, 1H, Ph'/Ph''); 7.43–7.48 (m, 2H, Ph'/Ph''); 7.61–7.76 (m, 8H, H-4, CO<u>CH</u>=CH, 6H Ph'/Ph''); 7.83 (d, 1H, H-8, *J* 9.0 Hz); 7.85 (d, 1H, COCH=<u>CH</u>, *J* 15.8 Hz); 8.04 (dd, 1H, H-3, *J* 1.7 and 8.7 Hz); 8.43 (d, 1H, H-1, *J* 1.7 Hz); ^{13}C NMR δ 40.42, 105.42, 116.28, 122.12, 125.17, 126.44, 127.07, 127.55, 127.82, 128.90, 128.91, 130.31, 130.79, 131.72, 134.32, 137.70, 140.27, 142.95, 143.07, 150.31, 189.33.

(2*E*)-1-[6-(Dimethylamino)-2-naphthyl]-3-(2-naphthyl) prop-2-en-1-one (14). Yield 67.8%; radial chromatography on 2 mm thick silicagel layer using 50% petroleum ether in dichloromethane as the eluent; mp 264–266 °C (from benzene-petroleum ether); Anal. Calcd for $C_{25}H_{21}NO \times 0.2\ H_2O$: C 84.57; H 6.08; N 3.95. Found C 84.50; H 5.91; N 4.21; HRMS Calcd for $C_{25}H_{21}NO$: 351.1623; found 351.1635; ^{1}H NMR δ 3.12 (s, 6H, NMe_2), 6.91 (d, 1H, H-5, *J* 2.1 Hz); 7.19 (dd, 1H, *J* 2.1 and 9.0 Hz, H-7); 7.51–7.54 (m, 2H, naphthyl'); 7.70 (d, 1H, *J* 8.7 Hz, H-4); 7.80–8.06 (m, 9H, CO<u>CH</u>=<u>CH</u>, H-8, H-3, 5H naphthyl'); 8.47 (bd, 1H, H-1); ^{13}C NMR δ 40.44, 105.44, 116.28, 122.43, 123.87, 125.18, 126.43, 126.67, 127.26, 127.79, 128.61, 128.64, 130.28, 130.30, 130.78, 131.76, 132.85, 133.46, 134.27, 137.69, 143.63, 150.31, 153.11, 189.38.

(2*E*)-1-[6-(Dimethylamino)-2-naphthyl]-3-quinolin-3-ylprop-2-en-1-one (15). Yield 60%; radial chromatography on 2 mm thick silicagel layer using 10% petroleum ether in dichloromethane, followed by pure dichloromethane and finally, 1% methanol in dichloromethane as the eluent; mp 237–239 °C (from dichloromethane-methanol); Anal. Calcd for $C_{24}H_{20}N_2O$: C 81.79; H 5.72; N 7.95. Found C 81.76; H 5.59; N 8.03; ^{1}H NMR δ 3.13 (s, 6H, NMe_2); 6.90 (d, 1H, H-5, *J* 2.5 Hz); 7.20 (dd, 1H, H-7, *J* 2.5 and 9.1 Hz); 7.57–7.6 (m 1H, quinolinyl); 7.71 (d, 1H, H-4, *J* 8.8 Hz); 7.74–7.81(m, 1H, quinolinyl,); 7.85–7.95 (m, 3H, H-8, 1H quinolinyl, CO<u>CH</u>=CH); 8.01 (d, 1H, *J* 15.7 Hz, COCH=<u>CH</u>); 8.06 (dd, 1H, H-3, *J* 1.7 and 9.2 Hz); 8.14 (d, 1H, quinolinyl, *J* 8.5 Hz); 8.38 (d, 1H, quinolinyl, , *J* 2.1 Hz); 8.47 (d, 1H, *J* 1.7 Hz, H-1); 9.26 (d, 1H, quinolinyl, *J* 2.1 Hz); ^{13}C NMR δ 40.41, 105.37, 116.31, 123.85, 125.08, 125.10, 126.55, 127.39, 127.82, 128.36, 129.45, 130.49, 130.54, 130.87, 135.73, 137.85, 139.93, 149.56, 150.43, 188.68.

General procedure for the reduction of α,β-unsaturated ketones. To a solution of 3 mmol KOH in 100 mL of ethanol, 1 mmol of $Fe(CO)_5$ was added and the mixture was stirred and gradually heated to boiling under argon. After 2 hours, an ethanolic solution of 1 mmol of the respective α,β-unsaturated ketone was added and reflux was continued for 2-4 hours. The volume of the reaction mixture was diminished to approximately 30 mL, triturated with water and extracted with diethyl ether. Combined ether extracts were dried and the solvent was removed. From the residue the products were isolated by radial chromatography and purified by recrystallization.

1-(6-Methoxy-2-naphthyl)-3-phenylpropan-1-one (16). Yield 77%; radial chromatography on 2 mm thick silicagel layer using 25% petroleum ether in dichloromethane as the eluent; mp 112–113 °C (from benzene-petroleum ether); Anal. Calcd for $C_{20}H_{18}O_2$: C 82.73, H 6.25. Found C 82.97, H 6.02; ^{1}H NMR δ 3.07–3.12 and 3.34–3.39 (m, 4H, $COCH_2CH_2$,); 3.90 (s, 3H,OMe); 7.11 (d, 1H, H-5, *J* 2.6 Hz); 7.17 (dd, 1H, H-7, *J* 2.6 and 8.9 Hz); 7.19–7.33 (m, 5H, Ph'); 7.72 (d, 1H, H-4, *J* 8.6 Hz); 7.78 (d, 1H, H-8, *J* 8.9 Hz); 7.98 (dd, 1H, H-3, *J* 1.7 and 8.6 Hz); 8.35 (d, 1H, H-1, *J* 1.7 Hz); ^{13}C NMR δ 30.29, 40.28, 55.32, 105.69, 119.62, 124.51, 126.05, 127.04, 127.76, 128.39, 128.46, 129.48, 131.02, 132.21, 137.18, 141.40, 159.66, 198.75.

3-(3-Hydroxyphenyl)-1-(6-methoxynaphthalen-2-yl) propan-1-one (17). Yield 33%; radial chromatography on 2 mm thick silicagel layer using 2% methanol in dichloromethane as the eluent; mp 121–123 °C (from dichloromethane-petroleum ether); Anal. Calcd for $C_{20}H_{18}O_3$: C 78.41, H 5.92. Found C 78.71, H 5.76; ^{1}H NMR δ 3.03–3.08 and 3.35–3.40 (m, 4H, $COCH_2CH_2$); 3.93 (m, 3H, OMe); 6.69–6.71 (m, 1H, Ph'); 6.78–6.84 (m, 2H, Ph'); 7.12–7.19 (m, 3H, H-5, H-7, 1Ph'), 7.73 (m, 1H, H-4, *J* 8.6 Hz); 7.79 (m, 1H, H-8, *J* 9.1 Hz); 7.98 (m, 1H, H-3, *J* 1.7 and 8.6 Hz); 8.36 (d, 1H, H-1, *J* 1.7 Hz).

3-(2,6-Dichlorophenyl)-1-(6-methoxynaphthalen-2-yl) propan-1-one (18). Yield 69%; radial chromatography on 4 mm thick silicagel layer using 50% petroleum ether in dich-loromethane as the eluent; mp 93–94 °C (from dichloromethane-hexane); Anal. Calcd for $C_{20}H_{16}Cl_2O_2$: C 66.87, H 4.49. Found C 67.25, H 4.44; HRMS Calcd for $C_{20}H_{16}Cl_2O_2$: 358.0527, found 358.0539; ^{1}H NMR δ

3.31–3.37 and 3.39–3.45 (m, 4H, –$COCH_2$–CH_2,); 3.95 (s, 3H, OMe,); 7.08–7.14 (m, 1H, H-4'), 7.15 (d, 1H, H-5, *J* 2.6 Hz); 7.19 (dd, 1H, H-7, *J* 2.6 and 8.8 Hz); 7.32 (d, 2H, H-3' and H-5'); 7.77 (d, 1H, H-4, *J* 8.7 Hz); 7.82 (d, 1H, H-8, *J* 8.8 Hz); 8.04 (dd, 1H, H-3, *J* 1.7 and 8.7 Hz); 8.42 (d, 1H, H-1, *J* 1.7 Hz).

3-(Biphenyl-4-yl)-1-(6-methoxynaphthalen-2-yl)propan-1-one (19). Yield 80%; radial chromatography on 4 mm thick silicagel layer using 50% petroleum ether in dichloromethane as the eluent; mp 171–172 °C (from benzene-petroleum ether); Anal. Calcd for $C_{26}H_{22}O_2$: C 85.22, H 6.05. Found C 85.45, H 6.01; ^{1}H NMR δ 3.13–3.18 and 3.41–3.46 (m, 4H, $COCH_2CH_2$,); 3.93 (s, 3H, OMe,); 7.14 (d, 1H, H-5, *J* 2.5 Hz); 7.19 (dd, 1H, H-7, *J* 2.5 and 8.9 Hz), 7.29–7.44 (m, 5H, Ph'/Ph''); 7.51–7.59 (m, 4H, Ph'/Ph''); 7.76 (d, 1H, H-4, *J* 8.7 Hz); 7.81 (d, 1H, H-8, *J* 8.9 Hz); 8.02 (dd, 1H, H-3, *J* 1.7 and 8.7 Hz); 8.39 (d, 1H, H-1, *J* 1.7 Hz); ^{13}C NMR δ 29.98, 40.30, 55.40, 105.77, 119.72, 124.60, 127.01, 127.08, 127.14, 127.27, 127.82, 128.72, 128.90, 129.58, 131.11, 132.29, 137.29, 139.14, 140.58, 141.02, 159.76, 198.80.

1-(6-Methoxynaphthalen-2-yl)-3-(naphthalen-2-yl)propan-1-one (20). Yield 68%; radial chromatography on 1 mm thick silicagel layer using 50% petroleum ether in dichloromethane as the eluent; mp 132–133 °C (from dichloromethane-hexane); Anal. Calcd for $C_{24}H_{20}O_2$: C 84.68, H 5.92. Found C 84.94, H 5.96; ^{1}H NMR δ 3.25–3.30 and 3.46–3.51 (m, 4H, $COCH_2CH_2$,); 3.93 (s, 3H, OMe,); 7.14 (d, 1H, H-5, *J* 2.5 Hz); 7.18 (dd, 1H, H-7, *J* 2.5 and 8.9 Hz); 7.39–7.49 (m, 3H, naphthyl'); 7.71–7.82 (m, 6H; H-4, H-8, 4H naphthyl'); 8.02 (dd, 1H, H-3, *J* 1.7 and 8.7 Hz); 8.39 (1H, H-1, *J* 1.7 Hz); ^{13}C NMR δ 30.69, 40.29, 55.40, 105.76, 129.72, 124.60, 125.29, 126.01, 126.52, 127.14, 127.22, 127.46, 127.62, 127.85, 128.11, 129.57, 131.11, 132.12, 132.30, 133.68, 137.28, 138.97, 159.76, 198.80.

1-(6-Methoxynaphthalen-2-yl)-3-(quinolin-3-yl)propan-1-one (21). Yield 75%; radial chromatography on 1 mm thick silicagel layer first using dichloromethane and later 1% methanol in dichloromethane as the eluent; mp 135–137 °C; Anal. Calcd for $C_{23}H_{19}NO_2$: C 80.92, H 5.61, N 4.10. Found 80.45, 5.43, N 4.33; HRMS Calcd for $C_{23}H_{19}NO_2$: 341.1416, found 341.1427; ^{1}H NMR δ 3.27–3.32 and 3.46–3.51 (m, 4H, $COCH_2CH_2$); 3.91 (s, OMe); 7.12 (d, 1H, *J* 2.4 Hz, H-5); 7.18 (dd, 1H, *J* 2.4 and 9.0 Hz, H-7); 7.47–7.53 (m, 1H, quinolinyl); 7.62–7.67 (m, 1H, quinolinyl); 7.76 (d, 1H, *J* 8.7 Hz, H-4); 7.78 (m, 1H, quinolinyl); 7.82 (d, 1H, *J* 9.0 Hz, H-8); 8.01 (dd, 1H, *J* 1.8 and 8.7 Hz, H-3), 8.05 (d, 1H, *J* 1.5 Hz, quinolinyl); 8.08 (d, 1H, *J* 8.7 Hz, quinolinyl); 8.39 (d, 1H, *J* 1.8 Hz, H-1); 8.90 (d, 1H, *J* 1.9 Hz, quinolinyl); ^{13}C NMR δ 27.38, 139.56, 55.34, 105.71, 119.73, 124.40, 126.59, 127.15, 127.32, 127.72, 128.04, 128.70, 129.12, 129.49, 130.94, 132.00, 134.04, 134.20, 137.28, 146.89, 151.84, 159.76, 197.94.

1-[6-(Dimethylamino)naphthalen-2-yl]-3-phenylpropan-1-one (22). Yield 72%; radial chromatography on 2 mm thick silicagel layer using 50% petroleum ether in dichloromethane as the eluent; mp 125–127 °C (from dichloromethane-petroleum ether); Anal. Calcd for $C_{21}H_{21}NO$: C 83.13, H 6.98; N 4.62. Found C 83.57, H 7.00, N 4.67; HRMS Calcd for $C_{21}H_{21}NO$: 303.1623, found 303.1612; ^{1}H NMR δ 3.13–3.17 (m, 8H, $\underline{CH_2}CH_2$ and NMe_2,); 3.38–3.43 (m, 2H, $\underline{CH_2}$–CH_2,); 6.89 (d, 1H, H-5, *J* 2.6 Hz); 7.18 (dd, 1H, H-7, *J* 2.6 and 9.0 Hz); 7.24–7.34 (m, 5H, Ph'); 7.66 (d, 1H, H-4, *J* 8.8 Hz); 7.79 (d, 1H, H-8, *J* 9.0 Hz); 7.96 (dd, 1H, H-3, *J* 1.8 and 8.8 Hz); 8.34 (d, 1H, H-1, *J* 1.8 Hz); ^{13}C NMR δ 30.53, 40.20, 40.4, 105.31, 116.26, 124.52, 125.06, 126.03, 126.19, 128.46, 128.49, 129.85, 130.41, 130.68, 137.66, 141.67, 150.24, 198.68.

1-[6-(Dimethylamino)naphthalen-2-yl]-3-(3-hydroxyphenyl)propan-1-one (23). Yield 52%; radial chromatography on 2 mm thick silicagel layer first using 30% hexane in dichloromethane, then dichloromethane and finally 1% methanol in dichloromethane as the eluent; mp 148–149 °C (from dichloromethane-petroleum ether); Anal. Calcd for $C_{21}H_{21}NO_2$: C 78.97; H 6.63; N 4.39. Found C 78.63; H 6.65; N 4.26; HRMS Calcd for $C_{21}H_{21}NO_2$: 319.1573, found 319.1585; ^{1}H NMR δ 3.01–3.07 (m, 8H, NMe_2 and $\underline{CH_2}$–CH_2); 3.31–3.36 (m, 2H, $\underline{CH_2}$–CH_2); 5.64 (s, 1H, OH); 6.69 (m, 1H, Ph'); 6.77–6.84 (m, 3H, H-5 and 2Ph'); 7.11–7.18 (m, 2H, H7, 1Ph'), 7.60 (d, 1H, H-4, *J* 8.7 Hz); 7.73(d, 1H, H-8, *J* 9.0 Hz); 7.90 (dd, 1H, H-3, *J* 1.9 and 8.7 Hz); 8.28 (d, 1H, H-1, *J* 1.9 Hz); ^{13}C NMR δ 30.41, 40.05, 40.55, 105.30, 113.14, 115.76, 116.27, 120.60, 124.47, 125.01, 126.22, 129.65, 130.08, 130.18, 130.72, 137.71, 143.33, 150.27, 155.98, 199.32.

Alternatively, **23** was prepared by nucleophilic aromatic substitution.[1] Dimethylamine was bubbled into a mixture of dry, freshly distilled HMPT (5 mL) and toluene (6 mL) until 1.6 g (35.6 mmol) was dissolved. To the solution, lithium metal (200 mg, 22.8 mmol) in small pieces was added and the mixture was stirred under argon until all the metal has dissolved. Methoxy derivative **17** was added (348 mg, 1.19 mmol) and stirring was continued for 48 hours. The reaction mixture was diluted with brine and extracted with dichloromethane (3 × 20 mL). Combined organic extracts were washed with brine, dried and evaporated. From the residue the compound **23** was isolated as described above in 49% yield.

3-(2,6-Dichlorophenyl)-1-[6-(dimethylamino)naphthalen-2-yl]propan-1-one (24). Yield 51%; radial chromatography on 4 mm thick silicagel layer using 50% petroleum ether in dichloromethane as the eluent; mp 148–149

°C (from dichloromethane-hexane); Anal. Calcd for $C_{21}H_{19}Cl_2NO$: C 67.75; H 5.14; N 3.76. Found C 67.77; H 5.09; N 3.57; ^{1}H NMR δ 3.096 (s, 6H, NMe_2); 3.28–3.34 and 3.38–3.44 (m, 4H, $COCH_2CH_2$); 6.86 (d, 1H, H-5, *J* 2.2 Hz); 7.07–7.17 (m, 2H, H-7 and 1Ph'); 7.31 (m, 2H, Ph'); 7.63 (d, 1H, H-4, *J* 8.7 Hz); 7.76 (d, 1H, H-8, *J* 9.0 Hz); 7.95 (dd, 1H, H-3, *J* 1.9 and 8.7 Hz); 8.34 (d, 1H, H-1; *J* 1.9 Hz); ^{13}C NMR δ 26.55, 36.42, 40.41, 105.33, 116.47, 124.50, 125.07, 126.22, 127.85, 127.94, 129.99, 130.21, 130.7, 135.46, 137.48, 137.73, 150.47, 198.14.

3-Biphenyl-4-yl-1-[6-(dimethylamino)-2-naphthyl] propan-1-one (25). Yield 75.4%; radial chromatography on 2 mm thick silicagel layer using 50% petroleum ether in dichloromethane as the eluent; mp 180–183 °C (from dichloromethane-hexane); Anal. Calcd for $C_{27}H_{25}NO$: C 85.45; H 6.64; N 3.69. Found C 85.4; H 6.64; N 3.56; ^{1}H NMR δ 3.05 (s, 6H, NMe_2); 3.11–3.16 and 3.35–3.41 (m, 4H, $COCH_2$–CH_2); 6.83 (1H, d, H-5, *J* 2.6 Hz); 7.11 (1H, dd, H-7, *J* 2.6 and 9.0 Hz); 7.28–7.43 (m, 5H, Ph'/Ph''), 7.50–7.58(m, 4H, Ph'/Ph''); 7.61 (1H, d, H-4, *J* 8.7 Hz); 7.74 (1H, d, H-8, *J* 9.0 Hz); 7.93 (1H, dd, H-3, *J* 1.6 and 8.7 Hz), 8.31(d, 1H, H-1, *J* 1.6 Hz); ^{13}C NMR δ 30.07, 40.04, 40.32, 105.24, 116.22, 124.46, 125.01, 126.17, 126.96, 127.00, 127.17, 128.67, 128.85, 129.84, 130.33, 130.63, 137.63, 138.97, 140.75, 140.99, 150.18, 198.54.

1-[6-(Dimethylamino)-2-naphthyl]-3-(2-naphthyl)propan-1-one (26). Yield 85%; radial chromatography on 4 mm thick silicagel layer using 50% hexane in dichloromethane as the eluent; mp 167–168 °C (from dichloromethane-hexane); Anal. Calcd for $C_{25}H_{23}NO$: C 84.95; H 6.56; N 3.96. Found C 85.02; H 6.54; N 4.16; HRMS Calcd for $C_{25}H_{23}NO$: 353.1780; found 353.1792; ^{1}H NMR δ 3.02 (s, 6H, NMe_2); 3.21–3.26 and 3.38–3.43 (m, 4H, $COCH_2CH_2$); 6.81 (d, 1H, H-5, *J* 2.5 Hz); 7.09 (dd, 1H, *J* 2.5 and 9.0 Hz, H-7); 7.36–7.45 (m, 3H, naphthyl'); 7.59 (d, 1H, *J* 8.7 Hz, H-4); 7.68–7.79 (m, 5H, H-8 and 4H naphthyl'); 7.93 (dd, 1H, *J* 1.5 and 8.7 Hz, H-3); 8.29 (d, 1H, *J* 1.5 Hz, H-1); ^{13}C NMR δ 30.57, 40.27, 105.18, 116.18, 124.45, 124.98, 125.18, 125.89, 126.15, 126.41, 127.22, 127.41, 127.55, 127.99, 129.81, 130.31, 130.61, 132.03, 133.61, 137.62, 139.13, 150.16, 198.50.

1-[6-(Dimethylamino)-2-naphthyl]-3-quinolin-3-ylpropan-1-one (27). Yield 52%; radial chromatography on 2 mm thick silicagel layer first using dichloromethane followed by 1% methanol in dichloromethane as the eluent; mp 155–158 °C (from dichloromethane-hexane); Anal. Calcd for $C_{24}H_{22}N_2O \times 0.3\ H_2O$ C 80.11; H 6.33; N 7.78. Found C 80.09; H 6.20; N 7.53; HRMS Calcd for $C_{24}H_{22}N_2O_1$: 354.1732; found 354.1745; ^{1}H NMR δ 3.08 (s, 6H, NMe_2); 3.27–3.32 and 3.45–3.50 (m, 4H, $COCH_2CH_2$); 6.84 (d, 1H, *J* 2.6 Hz, H-5); 7.14 (dd, 1H, *J* 2.6 and 9.0 Hz, H-7); 7.48–7.53 (m, 1H, quinolinyl); 7.60–7.67 (m, 2H, H-4, 1H quinolinyl); 7.74–7.77 (m, 2H, H-8, 1H quinolinyl); 7.92 (dd, 1H, *J* 1.7 and 9.0 Hz, H-3); 8.02 (d, 1H, *J* 1.5 Hz, quinolinyl); 8.08 (d, 1H, *J*= 8.6 Hz, quinolinyl), 8.31 (d, 1H, *J* 1.7 Hz, H-1); 8.89 (d, 1H, *J* 2.3 Hz, quinolinyl); ^{13}C NMR δ 27.59, 39.51, 40.34, 105.22, 116.27, 124.37, 124.95, 126.25, 126.57, 127.37, 128.10, 128.66, 129.15, 129.85, 130.13, 130.66, 134.29, 134.46, 137.72, 146.92, 150.27, 151.95, 197.77.

General procedure for the Knoevenagel condensation. To the solution of a ketone (1 mmol) in pyridine (5 mL) malononitrile (330 mg, 5 mmol) was added and the reaction mixture was heated at 78–80° for 57 hours. Pyridinie was removed under vacuum and from the residue the product was isolated by radial chromatography and re-crystallized.

{1-[6-(Dimethylamino)-2-naphthyl]-3-phenylpropylidene}malononitrile (28). Yield 69%; radial chromatography on 2 mm thick silicagel layer first using 30% petroleum ether in dichloromethane followed by 10% petroleum ether in dichloromethane as the eluent; mp 146–147 °C (from dichloromethane-hexane); Anal. Calcd for $C_{24}H_{21}N_3$: C 82.02%; H 6.02%; N 11.96%; found C 82.20%; H 5.99%; N 11.76%; ^{1}H NMR δ 2.76–2.81 and 3.30–3.35 (m, 4H, $COCH_2CH_2$); 3.12 (s, 6H, NMe_2); 6.87 (d, 1H, *J* 2.6 Hz; H-5); 7.10–7.13 (m, 2H, Ph'); 7.18 (dd, 1H, *J* 2.6 and 9.1 Hz, H-7); 7.25–7.31 (m, 3H, Ph'); 7.46 (dd, 1H, *J* 1.9 and 8.7 Hz, H-3); 7.69 (d, 1H, *J* 8.6 Hz, H-4); 7.76 (d, 1H, *J* 9.1 Hz, H-8); 7.91 (d, 1H, *J* 1.9 Hz, H-1); ^{13}C NMR δ 34.87, 38.84, 40.36, 105.14, 113.51, 113.89, 116.94, 124.44, 125.19, 126.79, 126.86, 126.98, 128.41, 128.67, 129.31, 130.40, 137.31, 138.90, 150.46, 177.94.

{1-[6-(Dimethylamino)-2-naphthyl]-3-(3-hydroxyphenyl)propylidene}malononitrile (29). Yield 25%; radial chromatography on 2 mm thick silicagel layer first using dichloromethane and later 1% methanol in dichloromethane as the eluent; mp 179–181 °C (from dichloromethane-methanol); Anal. Calcd for $C_{24}H_{21}N_3O \times 0.5\ H_2O$ C 76.57%; H 5.89%; N 11.16%; found C 76.15%; H 5.53%; N 11.03%; HRMS Calcd for $C_{24}H_{21}N_3O$: 367.1685 found 367.1692; ^{1}H NMR δ 2.72–2.77) and 3.29–3.35 (m, 4H, CH_2CH_2); 3.13 (s, 6H, NMe_2); 6.60–6.61 (m, 1H, Ph'); 6.66–6.71 (m, 2H, Ph'); 6.88 (d, 1H, *J* 2.6 Hz, H-5); 7.12–7.21 (m, 2H, H-7 and Ph'); 7.47 (dd, 1H, *J* 2.1 and 8.6 Hz, H-3); 7.69 (d, 1H, *J* 8.6 Hz, H-4); 7.77 (d, 1H, *J* 9.0 Hz, H-8); 7.92 (d, 1H, *J* 2.1 Hz, H-1); ^{13}C NMR δ 34.76, 38.733, 40.42, 81.85, 105.20, 113.60, 113.86, 115.36, 116.79, 120.87, 124.47, 125.24, 126.92, 126.98, 129.36, 129.95, 130.47, 137.17, 140.75, 150.52, 155.82, 177.94.

{3-(2,6-Dichlorophenyl)-1-[6-(dimethylamino)-2-naphthyl]propylidene}malononitrile (30). Yield 76%; radial chromatography on 1 mm thick silicagel layer using

40% petroleum ether in dichloromethane as the eluent; mp 158–161 °C (from dichloromethane-hexane); HRMS Calcd for $C_{24}H_{19}Cl_2N_3$: 419.0956; found 419.0968; ^{1}H NMR δ 3.08–3.12 (m, 8H, $\underline{CH_2}CH_2$ and NMe_2); 3.31–3.36 (m, 2H, $\underline{CH_2}CH_2$); 6.85 (d, 1H, *J* 2.6 Hz, H-5); 7.02–7.07 (m, 1H, Ph'); 7.15–7.25 (m, 3H, H-7 and Ph'); 7.61 (dd, 1H, *J* 1.9 and 8.7 Hz, H-3); 7.70 (m, 1H, H-4); 7.78 (m, 1H, H-8); 8.06 (d, 1H, *J* 1.9 Hz, H-1).

{3-Biphenyl-4-yl-1-[6-(dimethylamino)-2-naphthyl] propylidene}malononitrile (31). Yield 33%; radial chromatography on 1 mm thick silicagel layer first using 50% petroleum ether in dichloromethane followed by 10% petroleum ether in dichloromethane as the eluent; mp 171–173 °C (from dichloromethane-hexane); HRMS Calcd for $C_{30}H_{25}N_3$: 427.2048, found 427.2051; ^{1}H NMR δ 2.85–2.90 and 3.38–3.43 (m, 4H, CH_2CH_2); 3.17 (s, 6H, NMe_2); 6.90 (d, 1H, *J* 2.3 Hz, H-5); 7.19–7.22 (m, 3H, H-7, Ph'/Ph''); 7.35–7.59 (m, 8H, H-3, Ph'/Ph''); 7.72 (d, 1H, *J* 8.6 Hz, H-4); 7.78 (d, 1H, *J* 9.4 Hz, H-8); 7.95 (bd, 1H, H-1).

{1-[6-(Dimethylamino)-2-naphthyl]-3-(2-naphthyl) propylidene}malononitrile (32). Yield 40%; radial chromatography on 1 mm thick silicagel layer using 30% petroleum ether in dichloromethane as the eluent; mp 163–165 °C (from dichloromethane-hexane); Anal. Calcd for $C_{28}H_{23}N_3 \times 0.2H_2O$: C 83.02%; H 5.82%; N 10.37%; found C 82.90%; H 5.57%; N 10.02%; HRMS Calcd for $C_{28}H_{23}N_3$: 401.1892; found 401.1905; ^{1}H NMR δ 2.93–2.99 and 3.41–3.46 (m, 4H, CH_2CH_2); 3.13(s, 6H, NMe_2); 6.88(d, 1H, *J* 2.6 Hz, H-5); 7.20(dd, 1H, *J* 2.6 and 9.0 Hz, H-7); 7.28–7.50 (m, 5H, H-3, naphthyl'); 7.69–7.82 (m, 5H, H-4, H-8, 3H naphthyl'); 7.92(d, 1H, *J* 1.9 Hz, H-1); ^{13}C NMR δ 35.06, 38.74, 40.42, 105.21, 113.57, 113.85, 116.79, 124.49, 125.25, 125.70, 126.24, 126.68, 126.88, 126.94, 127.05, 127.52, 127.70, 128.477, 129.37, 130.44, 132.37, 136.35, 137.16, 178.01.

{1-[6-(Dimethylamino)-2-naphthyl]-3-quinolin-3-ylpropylidene}malononitrile (33). Yield 35%; radial chromatography on 2 mm thick silicagel layer first using dichloromethane and later 1% methanol in dichloromethane as the eluent; mp 208–210 °C (from dichloromethane-methanol); Anal. Calcd for $C_{27}H_{22}N_4$: C 80.57%; H 5.51%; N 13.92%; found C 80.37%; H 5.34%; N 13.65%; HRMS Calcd for $C_{27}H_{22}N_4$: 402.1844; found 402.1857; ^{1}H NMR δ 2.97–3.02 and 3.42–3.48(m, 4H, $COCH_2CH_2$); 3.13(s, 6H, NMe_2); 6.87(d, 1H, *J* 2.4 Hz, H-5); 7.19 (dd, 1H, *J* 2.4 and 9.1 Hz, H-7); 7.47(dd, 1H, *J* 1.87 and 8.6, H-3); 7.51–7.56(m, 1H, quinolinyl); 7.66–7.71(m, 2H, H-4, quinolinyl); 7.74–7.77 (m, 2H, H-8, quinolinyl); 7.91–7.94 (m, 2H, H-1, quinolinyl); 8.07(d, 1H, *J* 8.3 Hz, quinolinyl); 8.64(d, 1H, *J* 2.3 Hz, quinolinyl); ^{13}C NMR δ 32.08, 38.25, 40.39, 105.15, 113.49, 113.68, 116.86, 124.308, 125.21, 126.60, 126.98, 127.12, 127.47, 127.90, 129.27, 129.40, 130.48, 131.53, 134.81, 137.25, 147.25, 150.60, 151.14, 177.04.

5. Acknowledgment

Financial support from the Slovenian Research Agency (P1-0230-0103) is gratefully acknowledged. Special thanks are extended to Dr. B. Kralj and Dr. D. Žigon (Jožef Stefan Institute, Ljubljana, Slovenia) for MS measurements.

6. References

1. A. Jacobson, A. Petrič, D. Hogenkamp, A. Sinur, J. R. Barrio, *J. Am. Chem. Soc.* **1996**, *118*, 5572–5579.
2. E. D. Agdeppa, V. Kepe, J. Liu, S. Flores-Torres, N. Satyamurthy, A. Petrič, G. M. Cole, G. W. Small, S. C. Huang, J. R. Barrio, *J. Neurosci.* **2001**, *21*, RC189.
3. M. Bresjanac, L. M. Smid, T. D. Vovko, A. Petrič, J. R. Barrio, M. Popovic, *J. Neurosci.* **2003**, *23*, 8029–8033.
4. B. Ghetti, V. Kepe, J. R. Murrell, M. R. Farlow, F. Epperson, M. Bresjanac, G. Repovs, L. M. Smid, M. Popovic, A. Petrič, H. Sung-C, G. W. Small, N. Satyamurthy, M. E. Phelps, J. R. Barrio, *Brain Pathology* **2006**, *16*, S9–S9.
5. K. Shoghi-Jadid, G. W. Small, E. D. Agdeppa, V. Kepe, L. M. Ercoli, P. Siddarth, S. Read, N. Satyamurthy, A. Petrič, S. C. Huang, J. R. Barrio, *Amer. J. Geriatric Psychiatry* **2002**, *10*, 24–35.
6. G. W. Small, S. C. Huang, G. Cole, N. Satyamurthy, E. D. Agdeppa, Z. Kiziloglu, V. Kepe, A. Petrič, H. V. Vinters, M. E. Phelps, J. R. Barrio, *Neurobiol. Aging* **2001**, *22*, 335–335.
7. G. Small, E. Agdeppa, V. Kepe, K. Shoghi-Jadid, N. Satyamurthy, A. Petrič, S. C. Huang, J. Barrio, *Neurobiol. Aging* **2002**, *23*, S561–S562.
8. G. Small, V. Kepe, S. C. Huang, L. Ercoli, P. Siddarth, K. Miller, H. Lavretsky, B. C. Wright, N. Satyamurthy, H. H. Wu, K. Shoghi-Jadid, A. Petrič, M. E. Phelps, J. R. Barrio, *Neuropsychopharmacology* **2004**, *29*, S8–S8.
9. L. M. Smid, T. D. Vovko, M. Popovic, A. Petrič, V. Kepe, J. R. Barrio, G. Vidmar, M. Bresjanac, *Brain Pathology* **2006**, *16*, 124–130.
10. G. W. Small, V. Kepe, L. M. Ercoli, P. Siddarth, S. Y. Bookheimer, K. J. Miller, H. Lavretsky, A. C. Burggren, G. M. Cole, H. V. Vinters, P. M. Thompson, S. C. Huang, N. Satyamurthy, M. E. Phelps, J. R. Barrio, *N. England J. Med.* **2006**, *355*, 2652–2663.
11. J. Liu, V. Kepe, A. Žabjek, A. Petrič, H. C. Padgett, N. Satyamurthy, J. R. Barrio, *Molec. Imag. Biol.* **2007**, 9, 6–16.
12. a) A. Nordberg, *Neuropsychologia* **2008**, *46*, 1636–1641; b) A. Petrič, S. Čeh, A. Golobič, S. A. Johnson, Y. Li, K. N. Houk, E. D. Agdeppa, G. Timbol, J. Liu, G. Keum, N. Satyamurthy, V. Kepe, J. R. Barrio, manuscript in preparation.
13 A. Petrič, A. F. Jacobson, J. R. Barrio, *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1455–1460.

14. A. Petrič, T. Špes, J. R. Barrio, *Monatsh. Chem.* **1998**, *129*, 777–786.
15. A. Petrič, J. R. Barrio, *Acta Chim. Slov.* **1998**, *45*, 475–486.
16. P. Škofic, C. Dambrot, M. Koželj, A. Golobič, J. R. Barrio, A. Petrič, *Acta Chim. Slov.* **2005**, *52*, 391–397.
17. A. T. Nielsen, W. J. Houlihan, *Org. React.* **1968**, *16*, 1–442.
18. R. Noyori, I. Umeda, T. Ishigami, *J. Org. Chem.* **1972**, *37*, 1542–1545.
19. Kh. Yu. Yuldashev, *Dokl. Akad. Nauk Uzb. SSR* **1977**, *12*, 35–36; *Chem. Abstr.* **1979**, *91*, 74372y.

Povzetek

Molekulo spojine vodnice DDNP smo spremenili tako, da smo nanjo preko etilidenske skupine vezali aromatski obroč. Tako smo pripravili serijo analogov FDDNP, spojine, ki služi kot molekularna sonda za opazovanje izločanja proteinskih agregatov v centralnem živčnem sistemu. Sintetizirani analogi kažejo podobne optične lastnosti kot DDNP/FDDNP in tako izpolnjujejo pogoj za uspešno uporabo v fluorescenčni mikroskopiji. Dodatni aromatski obroč nudi dodatno možnost za π-interakcije med molekulo in proteinskimi agregati.