Induced Fit Selection of a Barbiturate Receptor from a Dynamic Structural and Conformational/Configurational Library

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The selection of the receptor presenting the strongest affinity for a barbiturate substrate from a dynamic combinatorial library of constituents differing in structure and conformation/configuration is described. The gradual addition of the barbiturate to an equilibrating mixture of hydrazone isomers leads to the quantitative shift towards a single species, **3**, which presents highest complementarity to the substrate and yields the supramolecular entity **3:4**.

Introduction

The reversible covalent or non-covalent combination of molecular components generates a potential diversity defining a dynamic combinatorial library of molecular or supramolecular constituents that may be real or virtual depending on whether or not they already exist in absence of the target or are expressed in its presence. This dynamic approach to combinatorial chemistry has recently been explored for both inorganic[1][2] and organic,[3−8] molecular or supramolecular entities.[9] It bypasses the need for synthesizing all constituents of a combinatorial library by allowing the target to select or express the most suitable component out of the equilibrating mixture.

On the other hand, structural diversity may also be generated through conformational and/or configurational exchange processes, generating a thermodynamically driven conformational/configurational dynamic library through (thermal or photo-induced) isomerization around single or double bonds, site inversion, or ring inversion. In this case, receptor−substrate interaction may be expected to be strongest for a given member of the set of conformationally or configurationally different species (conformational or configurational isomers) resulting in the displacement of the equilibrating mixture towards the preferential expression of the optimal partner. This amounts to an induced-fit process which may be of single or double (multiple) type, depending on whether only one partner, or both (several) partners are present in conformationally or configurationally different forms.

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Induced-fit processes, or the specific structural adaptation of a host molecule upon interaction with the guest to form a more stable complex, are widespread in nature, and are essential to the function of enzymes or biological receptors.[10] These processes have been mimicked in synthetic systems[11] in order to gain insight into the biological phenomena. In this communication, we describe an induced-fit process which leads to the substrate-driven selection of a receptor from a dynamic library of conformational and configurational isomers. Photo-isomerization around carbon−carbon double bonds has been used to induce the formation of a preferred receptor−substrate pair.[5]

Results and Discussion

Diversity Generation

As depicted in Scheme 1, the system studied here involves the equilibration between different condensation products of 5,5-dimethyl-1,3-cyclohexanedione (**1**) and 2-hydrazinopyridine (**2**). In a 1:2 ratio in chloroform, these compounds yield the (*Z*/*Z*), (*E*/*E*), and (*E*/*Z*) dihydrazone isomers. The equilibrated mixture also contains a substantial amount of the (*E*) and (*Z*) isomers of the monohydrazone monoketone, as well as of its hydrazino−enone tautomer.[12] The conjugated tautomers of the dihydrazones were not detected. A number of equilibration processes can be envisaged: tautomerism, *cis*/*trans* isomerization about the hydrazone double bond, hydrolysis to the monohydrazone monoketone, or transamination[13] by the remaining 2-hydrazinopyridine (**2**).

The complexity of the mixture is well illustrated by its ^{1}H-NMR spectrum (Figure 1A). Slow equilibration between these compounds on the NMR time-scale results in numerous signals which could only be partially assigned to the different species.

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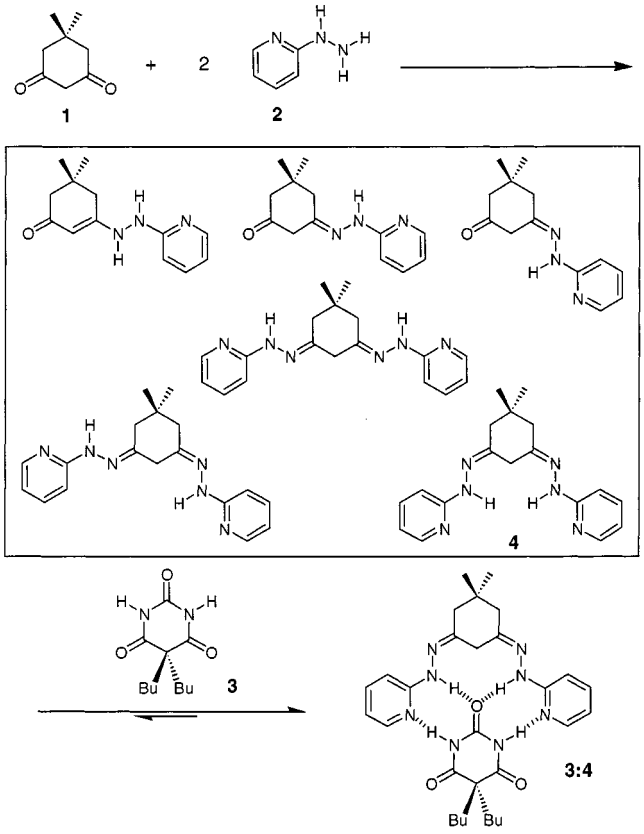


Scheme 1. Equilibrating product mixture obtained from 5,5-dimethyl-1,3-cyclohexanedione (**1**) and 2-hydrazinopyridine (**2**) in a 1:2 ratio, and binding of dibutylbarbiturate to the (*Z*/*Z*) dihydrazone isomer

Induced Fit Substrate Binding

Progressive addition of dibutylbarbiturate **3**[14] to the equilibrating mixture of the various isomers and tautomers leads to a dramatic simplification of the ^{1}H-NMR spectrum, with the gradual disappearance of the different products, accompanied by the emergence of a single new species (Figure 1). At one equivalent of **3**, this species has nearly quantitatively replaced all the components initially present in the mixture. Its sharp ^{1}H-NMR spectrum (Figure 1E) is consistent with a 1:1 complex between dibutylbarbiturate **3** and a symmetrical dihydrazone. The (*Z*/*Z*) isomer (**4**) with convergent hydrazone NH groups could be unambiguously identified, and the (*E*/*E*) isomer ruled out, after NOESY experiments revealed a strong correlation between the hydrazone N*H* and the cyclohexane *H*2 protons in the complex. Accordingly, no correlation was observed with the cyclohexane *H*4 and *H*6 protons.

The amplitude of the effect of the barbiturate (**3**) on the mixture is remarkable. Not only does configurational isomerisation of the dihydrazones lead to a quantitative shift towards the (*Z*/*Z*) isomer (**4**), but the barbiturate (**3**) also promotes the reaction of the monocondensation products with the remaining hydrazino-pyridine (**1**) (Figure 1, disappearance of the alkene proton signal at 5.38 ppm). No such equilibrium shift was observed when acetic acid or 1-benzyluracil was used instead of **3**. These compounds have pK_a′s similar to that of **3**, but lack some of its recognition elements and its complementarity to the target receptor. Their presence causes shifts of NMR signals due to non-specific associations, but no enrichment in a particular species.

Strong and specific hydrogen-bonding in the **3:4** supermolecule is supported by the following observations: (i) the NMR signals of the barbiturate N*H* (δ = 13.71), the hydrazone N*H* (δ = 9.95), and the pyridine *H*6 (δ = 8.34) protons are markedly deshielded; (ii) from zero to one equivalent, the barbiturate induces a stoichiometric formation of host; (iii) at more than one equivalent of barbiturate, slow exchange between bound and unbound barbiturate is observed on the NMR spectrum at 256 K or below; (iv) dilution from 10 mM to 0.156 mM causes neither shifts in the ^{1}H-NMR spectrum, nor appearance of other isomers after 6 h, which implies an association constant K_a in excess of 6400 M^{-1} for the **3**:**4** substrate:receptor pair.

The strength of association between **3** and **4**, as well as the reversibility of the various equilibria involved, were further established in a series of competition experiments involving the barbiturate receptor **6**[15] (Scheme 2). The association constant for the complex **3:6** was determined by analysis of the ^{1}H-NMR titration values obtained by progressive addition of **3** to **6** in $CDCl_3$. The resulting value of $5.8 \cdot 10^4$ M^{-1} is consistent with values reported in the literature for related systems.[17] When **6** (1 equiv.) is initially present in the mixture of **1** and **2**, addition of barbiturate *does not* favor the formation of the (*Z*/*Z*) isomer **4**. Instead, the barbiturate preferentially binds to **6**, and the mixture of products formed by **1** and **2** remains practically unchanged.

The same preferential binding was observed when **6** (1 equiv.) was added to a solution of a preformed complex between barbiturate **3** and induced receptor **4**. Shortly after the addition, the slowly equilibrating mixture contains free receptor **4** and free receptor **6**, as well as complexes **3**:**4** and **3**:**6**. The proportions between these species at this early stage allows us to estimate the association constant between barbiturate **3** and receptor **4** at about $1.5 \cdot 10^4$ M^{-1}. Upon standing a further 8 days, receptor **4** "diversifies back" into the original mixture of dihydrazones. A similar behavior can be observed, when [D_4]methanol (40 vol%) is added to a solution with complex **3:4** in [D]chloroform. The single species initially present is gradually replaced by the original diversity of isomers, as the association constant is decreased by interaction of the hydrogen-bonding sites with methanol.

All sets of experiments establish the strong affinity of receptor **4** for the barbiturate. The four hydrogen bonds involved in the **3**:**4** pair provide almost as much binding energy as the six hydrogen bonds formed by receptor **6**. When association occurs in the context of the reversible formation of **4**, it leads to its selective stabilization, and eventually its quantitative emergence from the original mixture. This phenomenon presents itself as an efficient way of recruiting and identifying a receptor from a pool of equilibrating molecules through a *molding process*.[3]

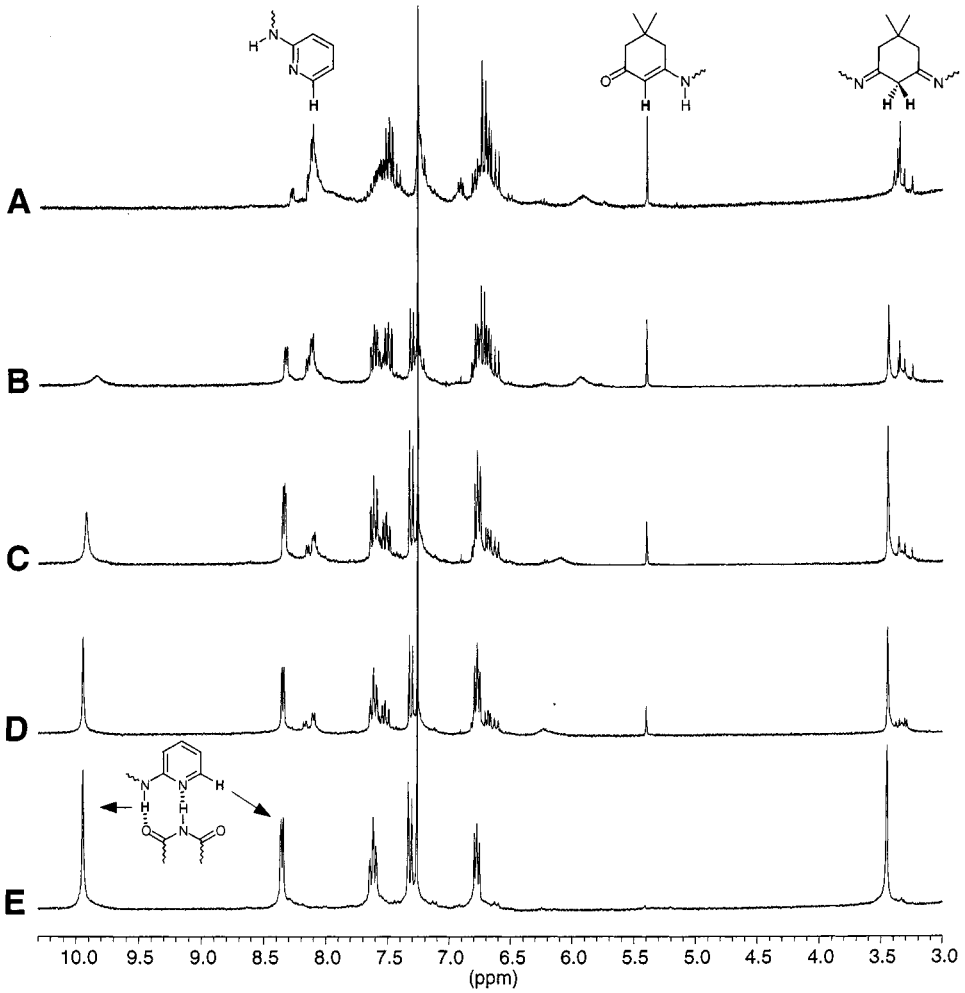
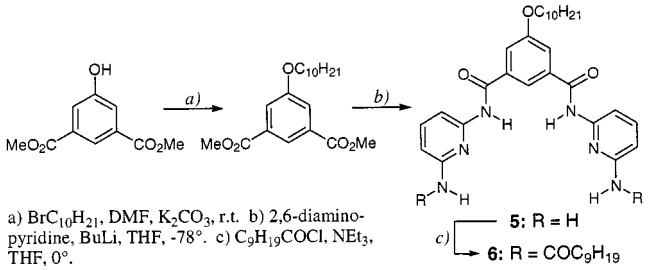
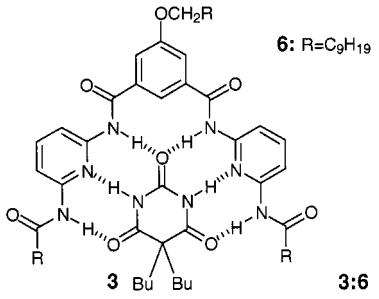


Figure 1. (A) 300 MHz ^{1}H NMR spectrum (δ = 3−10.5) of the mixture in $CDCl_3$ after two days of equilibration of 5,5-dimethyl-1,3-cyclohexanedione (**1**) (10 mM) and 2-hydrazinopyridine (**2**) (20 mM) under an oxygen free atmosphere; − (B), (C), (D), and (E) evolution of the spectrum after addition of 0.25, 0.5, 0.75, and 1.0 equivalent of dibutylbarbiturate (**3**), respectively. The structures indicate the assignment of some of the signals.



Scheme 2. Synthesis of compound **6**



Structural Data on the Substrate:Receptor Pair 3:4. Crystal Structure of 7

Attempts to crystallize the **3:4** substrate:receptor pair failed until now, but instead, single crystals suitable for X-ray analysis of the dimerized substrate−receptor complex $\mathbf{3}_2$**:7**[18] (Figure 2) could be obtained from a 1:1 solution of **3** and **4** in 40 mM CH_2Cl_2/hexane solution by solvent diffusion upon standing for 6 months. The crystal structure was not that of the expected monomeric **3:4** complex, but of a dimeric entity $\mathbf{3}_2$**:7** resulting from the formation of a C−C connection between two units of **4** to give **7**. It nevertheless confirms the solution studies on the **3:4** complex, as it shows the expected selection and conformational locking of the (*Z*/*Z*)-isomer by the barbiturate, also in the solid state. The hydrogen bonds in this new 2:1 three-component supermolecule ($\mathbf{3}_2$**:7**) are nearly linear and of the expected length (NH−N: 2.84 Å, 169°; O−HN: 2.97 Å, 173°), which is in agreement with the relatively high binding constant displayed by the **3:4** complex. The formation of **7** was observed in none of the solution studies, but the oxidative carbon−carbon bond formation, previously reported only for

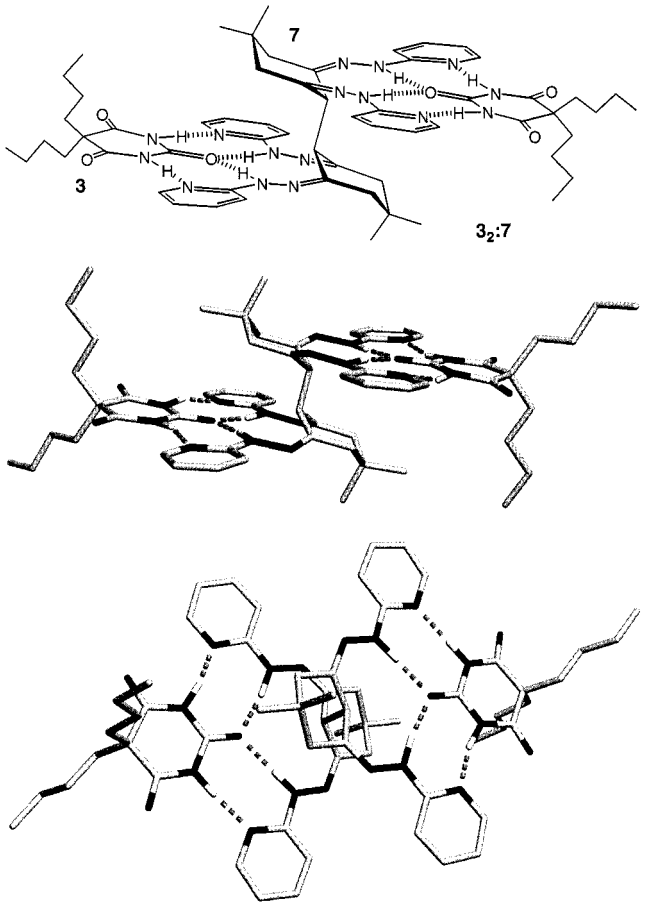
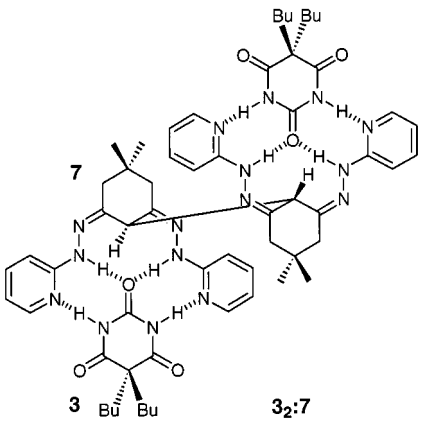


Figure 2. Schematic drawing (top) and crystal structure of the dimeric supermolecule $\mathbf{3}_2$:7 in cylindrical bond representation, side view (center) and top view (bottom).

cyclic 1,3-diones,[19] could be confirmed by letting samples of preformed **3:4** complex age in the presence of 2 equivalents of triethylamine under an oxygen atmosphere. Under these conditions, oxidative formation of dimer **7** was completed after 6 days at room temperature. Thus, the basic character of the hydrazines themselves make the slow formation of dimeric complex $\mathbf{3}_2$**:7** likely, even without the presence of additional base over a longer period of time in the crystallization assays.



Conclusion

The present results demonstrate the substrate-driven selection of the optimal receptor from a *dynamic structural and conformational/configurational library.* The simultaneous operation of conformational/configurational isomerizations within a species together with the establishment of molecular or supramolecular connections between components gives more efficient access to increased diversity in dynamic combinatorial chemistry. Thus, the present system may be extended by using several different hydrazines and diones in order to evaluate the selection procedure in the context of a large structural and conformational diversity. Furthermore, it is clear that other conformational processes (such as hindered bond rotation for instance[20]) may be implemented in order to give access to a variety of shapes and spatial arrangements for an increased real/virtual dynamic diversity. From a more general point of view, developments in dynamic processes involving induced-fit events provide entries towards *adaptive chemistry.*[21]

Experimental Section

General Methods: [D]Chloroform for all NMR studies on hydrazone compounds was passed through a short column of dry aluminium oxide 90 (Merck; 70−230 mesh, standardized activity II-III) and was subsequently degassed with argon for 30 min. During the equilibration periods, NMR-tubes were carefully kept under argon. − 2-Hydrazinopyridine (**2**) was purchased from Aldrich (pyridine as impurity) and purified by multiple extraction with small portions of boiling hexane under argon, and subsequent solvent removal under reduced pressure. − THF was distilled over sodium/benzophenone. − Triethylamine (Lancaster, 99%) was used as received. − Flash column chromatography was performed using silica gel (Geduran, SI 60 (40−63 μm, Merck). − Infrared spectra were recorded as thin films on NaCl discs on a Perkin−Elmer 1600 Series FTIR. − 500 MHz ^{1}H NOESY spectra were recorded on a Bruker ARX 500 spectrometer, 300 MHz ^{1}H NMR spectra on a Bruker AM 300 spectrometer, and 200 MHz ^{1}H NMR and 50.3 MHz ^{13}C NMR spectra on a Bruker SY 200 spectrometer. The solvent signal was used as an internal reference for both ^{1}H- and ^{13}C-NMR spectra. The following notation is used for the ^{1}H NMR spectral splitting patterns: singlet (s), doublet (d), triplet (t), multiplet (m). − EI and FAB-mass spectrometric measurements were performed by the Service de Spectrométrie de Masse, Institut de Chimie, Université Louis Pasteur. − Melting points (m.p.) were recorded on an electrothermal Digital Melting Point Apparatus and are uncorrected. − Elemental analyses were performed by the Service de Microanalyse, Institut Charles Sadron, Strasbourg.

5,5-Dibutylpyrimidine-2,4,6-trione (3) (Dibutylbarbiturate): This known compound was prepared according to a literature procedure[14] from diethyl dibutylmalonate and urea.

Complex 3:4. − Data for 4 in Complex 3:4: ^{1}H NMR (500 MHz, $CDCl_3$, 10 mM): δ = 9.95 (s, 2 H, H−N); 8.34 (dd, $^3J_{H6-H5}$ = 5.3 Hz, $^4J_{H6-H4}$ = 1.4 Hz, 2 H, H-6); 7.62 (ddd, $^3J_{H4-H3}$ = 8.9 Hz, $^3J_{H4-H5}$ = 6.8 Hz, $^4J_{H4-H6}$ = 1.7 Hz, 2 H, H-4); 7.31 (d, $^3J_{H3-H4}$ = 8.6 Hz, 2 H, H-3); 6.77 (ddd, $^3J_{H5-H6}$ = 5.1 Hz, $^3J_{H5-H4}$ = 7.1 Hz, $^4J_{H5-H3}$ = 0.8 Hz, 2 H, H-5); 3.44, (s, 2 H, H-2′); 2.44 (s, 4 H, H-4′); 1.01 (s, 6 H, CH_3).

Data for 3 in Complex 3:4: ^{1}H NMR (500 MHz, $CDCl_3$, 10 mM): δ = 13.71 (s, 2 H); 2.00 (m, 4 H); 1.33−1.16 (m, 8 H); 0.85 (t, ^3J = 7.2 Hz, 6 H, CH_3).

Dimethyl 5-Decyloxyisophthalate (Scheme 2): To a flask charged with dimethyl 5-hydroxyisophthalate (8.74 g, 41.48 mmol, 115 mol-%), 1-bromodecane (7.99 g, 36.10 mmol, 100 mol-%), K_2CO_3 (7.48 g, 54.12 mmol, 150 mol-%), and DMF (36 mL, 1 M) was added, and the mixture stirred at room temperature for 48 h. Et_2O (150 mL) was added and the organic phase washed twice with sat. aq. brine. The ether layer was dried with $MgSO_4$, filtered, evaporated to dryness, and purified by chromatography (SiO_2; EtOAc/hexane, 10:90 → 15:85) to provide dimethyl 5-decyloxyisophthalate (5.90 g, 41% yield) as a white powder. − M.p. 47−48 °C. − IR (thin film): $\tilde{\nu}$ = 2953 cm^{-1}, 2920, 2841, 1715, 1583, 1454, 1423, 1334, 1302, 1237, 1216, 1112, 1099, 1048, 1037, 1005, 994, 870, 788, 757, 720. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.24 (t, J = 1.4 Hz, 1 H); 7.72 (d, J = 1.4 Hz, 2 H); 4.04 (t, J = 6.5 Hz, 2 H); 3.92 (s, 6 H); 1.76 (m, 2 H); 1.26 (m, 14 H); 0.87 (t, J = 6.4 Hz, 3 H). − ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 166.3; 159.3; 131.77; 122.8; 119.9; 68.7; 52.4; 32.0; 29.6; 29.4; 29.2; 26.0; 22.7; 14.2. − EI-MS: m/z 351.1 ([M + H]$^+$, 100%). − $C_{20}H_{30}O_5$ (350.46): calc. C 68.55, H 8.63; found C 68.52, H 8.66.

***N,N′*-Bis(6-aminopyridin-2-yl)-5-decyloxyisophthalamide (5):**[16] To a solution of 2,6-diaminopyridine (recrystallized from boiling $CHCl_3$) (5.00 g, 45.82 mmol, 800 mol-%) in dry THF (46 mL, 1 M) at −78 °C was added a 1.6 M solution of *n*BuLi (44.20 mmol, 26.3 mL) in hexane. After 20 min at −78 °C, a solution of dimethyl 5-decyloxyisophthalate (2.00 g, 5.72 mmol, 100 mol-%) in dry THF (20 mL) was added dropwise. The reaction mixture was stirred at −78 °C for 8 h and then gradually warmed to room temp. and stirred over night. The reaction was then quenched with a 1 M solution of $NaHCO_3$ (100 mL) and extracted with EtOAc. The combined organic extracts were washed with sat. aq. brine and water, dried with $MgSO_4$, filtered, evaporated to dryness, and purified using flash chromatography (SiO_2; EtOAc/hexane, 2:1) to give *N,N′*-bis(6-aminopyridin-2-yl)-5-decyloxyisophthalamide (**5**) (2.63 g, 91% yield) as a pale yellow powder. − M.p. 132−133 °C. − IR (thin film): $\tilde{\nu}$ = 3362 cm^{-1}, 3205, 2951, 2923, 2854, 1681, 1620, 1593, 1538, 1456, 1337, 1303, 1247, 1166, 1134, 1051, 989, 864, 788, 744, 722, 707. − ^{1}H NMR (200 MHz, [D$_6$]DMSO): δ = 10.22 (s, 2 H); 8.11 (s, 1 H); 7.60 (d, J = 0.5 Hz, 2 H); 7.41 (m, 4 H); 6.28 (dd, J = 6.5 Hz, 1.5 Hz, 2 H); 5.79 (br. s, 4 H); 4.10 (t, J = 5.3 Hz, 2 H); 1.74 (m, 2 H); 1.25 (m, 14 H); 0.84 (t, J = 6.4 Hz, 3 H). − ^{13}C NMR (50.3 MHz, [D$_6$]DMSO): δ = 164.5; 158.7; 158.5; 150.2; 138.9; 135.6; 118.8; 116.9; 104.1; 101.8; 67.9; 31.2; 28.9; 28.6; 28.5; 25.4; 22.0; 13.9. − FAB-MS: m/z 505.3 [M + H]$^+$ (100%). − $C_{28}H_{36}N_6O_3$ (504.63): calc. C 66.64, H 7.19; found C 66.48, H 7.31.

5-Decyloxy-*N,N′*-bis[6-(decanoylamino)pyridin-2-yl]-isophthalamide (6): To a solution of **5** (0.5 g, 0.99 mmol, 100 mol-%) and triethylamine (0.20 g, 1.98 mol, 200 mol-%) in dry THF (20 mL) was added dropwise a solution of decanoyl chloride (0.38 g, 1.99 mmol, 200 mol-%) in THF (5 mL) at 0°C and the reaction stirred for 1 h, before warming to room temp. The reaction mixture was filtered, evaporated to dryness, and applied to a column (SiO_2; EtOAc/hexane, 1:3) to provide **6** (0.68 g, 84% yield) as a white powder. − M.p. 158−159 °C. − IR (thin film): $\tilde{\nu}$ = 3405 cm^{-1}, 3300, 2956, 2924, 2854, 1674, 1586, 1514, 1451, 1378, 1334, 1315, 1301, 1243, 1155, 1121, 1051, 883, 801, 722. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.65 (br. s, 2 H); 8.44 (br. s, 2 H); 7.83 (m, 5 H); 7.55 (t, J = 8.0 Hz, 2 H); 7.44 (s, 2 H); 3.85 (t, J = 6.4 Hz, 2 H); 2.33 (t, J = 7.4 Hz, 4 H); 1.65 (m, 6 H); 1.23 (m, 38 H); 0.84 (m, 9 H). − ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 172.2; 164.6; 159.7; 149.9; 149.2; 140.5; 135.6; 117.2; 110.3; 109.6; 68.7; 37.5; 31.8; 29.5; 29.4; 29.0; 25.9; 25.3; 22.6; 14.0. − FAB-MS: m/z 813.6 [M + H]$^+$ (100%). − $C_{48}H_{72}N_6O_5$ (813.13): calc. C 70.9, H 8.92; found C 70.79, H 8.98.

Formation of 7 by Oxidative Coupling of 4: To a solution of preformed **3:4** (**1**: 0.05 mmol, 7.0 mg; **2**: 0.1 mmol, 10.9 mg; **3**: 0.05 mmol, 12.0 mg, aged for 2 days under argon) in [D]chloroform (5 mL, 10 mM), was added NEt_3 (10.1 mg, 0.1 mmol, 200 mol-%) and the solution allowed to age under an oxygen atmosphere. After 6 days at room temp., **3:4** was quantitatively oxidized to **3**$_2$:**7**, as followed by ^{1}H-NMR spectroscopy.

Data for 7 in Complex 3$_2$:7: ^{1}H NMR (200 MHz, $CDCl_3$, 10 mM): δ = 10.50 (s, 4 H, H-N); 8.35 (dd, $^3J_{H6-H5}$ = 5.4 Hz, $^4J_{H6-H4}$ = 1.2 Hz, 4 H, H-6); 7.58 (ddd, $^3J_{H4-H3}$ = 7.8 Hz, $^3J_{H4-H5}$ = 7.2 Hz, $^4J_{H4-H6}$ = 1.7 Hz, 4 H, H-4); 7.12 (d, $^3J_{H3-H4}$ = 8.3 Hz, 4 H, H-3); 6.79 (ddd, $^3J_{H5-H6}$ = 5.5 Hz, $^3J_{H5-H4}$ = 5.9 Hz, $^4J_{H5-H3}$ = 0.8 Hz, 4 H, H-5); 5.20 (s, 2 H, H-2′); 2.95 (d, ^2J = 13.9 Hz, 4 H, CH_2); 2.19 (d, ^2J = 13.9 Hz, 4 H, CH_2); 1.02 (s, 6 H, CH_3); 0.72 (s, 6 H, CH_3).

Data for 3 in Complex 3$_2$:7: ^{1}H NMR (200 MHz, $CDCl_3$, 10 mM): δ = 14.42 (s, 4 H); 2.15 (m, 8 H); 1.40−1.10 (m, 16 H); 0.82 (t, ^3J = 6.6 Hz, 12 H).

Acknowledgments

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[15] The synthesis of the barbiturate receptor **6** is achieved in 3 steps starting from dimethyl 5-hydroxyisophthalate, which is O-alkylated with decyl bromide and K_2CO_3 in DMF at room temp. The resulting dimethyl-5-decyloxy-isophthalate is then treated with an access of 2,6-diaminopyridine monolithium salt in dry

THF at −78 °C.[16] The resulting diamine is acylated with decanoyl chloride in THF at room temp. to give **6** (see Experimental Section).

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[18] Crystal data for $\mathbf{3}_2$:**7** complex: $C_{30}H_{41}N_8O_3$, M_r 561.71, monoclinic, space group $P2_1/n$, a = 10.1810(3), b = 16.2190(4), c = 18.4800(5) Å, β = 95.490(1)°, V = 3037.5(3) Å^3, Z = 4, μ(Mo-K_α) = 0.082 mm^{-1}, ρ_{calc} = 1.23 gcm^{-3}. Orange crystals of dimensions 0.20 × 0.20 × 0.15 mm. 46830 Reflections collected, 2.5° ≤ θ ≤ 32.49°. 4428 Independent reflections having $I > 3\,\sigma(I)$. No absorption corrections. 370 Parameters. Final results: $R(F)$ = 0.064, $Rw(F)$ = 0.072, GOF = 1.064, maximal residual electron density = 0.687 eÅ^{-3}. Data were recorded with a *Nonius−KappaCCD* diffractometer, using graphite monochromatized Mo-K_α radiation (λ = 0.71071 Å), phi scans, 173 K. The structures were solved using direct methods and refined against $|F|$. H-Atoms were introduced as fixed contributors. For all computations, the *Enraf−Nonius* OpenMolN Package was used (OpenMoleN, Interactive Structure Solution, Nonius B.V., Delft, The Netherlands, 1997). Crystallographic data (excluding structure factors) for the structure of complex $\mathbf{3}_2$:**7** have been deposited with the *Cambridge Crystallographic Data Centre* as supplementary publication no. CCDC-127340. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0)1223/ 336-033; E-mail: deposit@ccdc.cam.ac.uk].
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