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Synthesis of Hydrazinylpyridines via Nucleophilic Aromatic Substitution and Further Transformation to Bicyclo[2.2.2]octenes Fused with Two *N*-Aminosuccinimide Moieties

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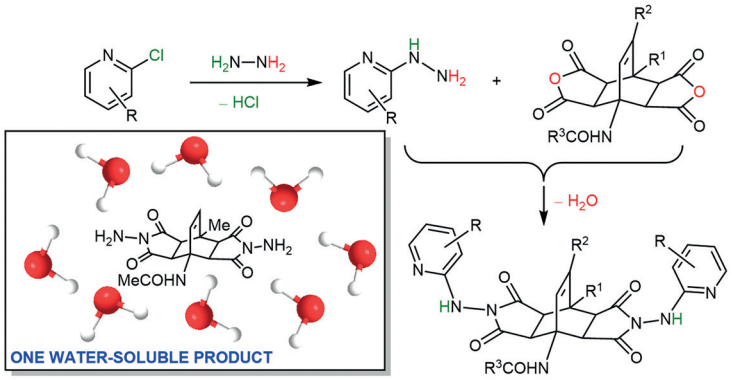

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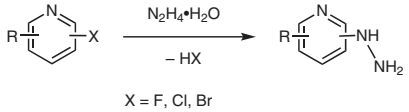
Abstract Efficient and reliable synthesis of substituted hydrazinylpyridines in thick-wall ACE tubes via nucleophilic substitution of a chlorine substituent in different chloropyridines is presented. Hydrazine hydrate and alkylhydrazines were used as nucleophiles and simple alcohols and diethyl ether were the only organic solvents necessary, making the process environmentally and user friendly, potentially reaching 100% atomic efficiency. In the next step, transformations of succinic anhydride moieties fused to the bicyclo[2.2.2]octene framework into succinimide moieties via nucleophilic substitution of oxygens were conducted. As nucleophiles two of the synthesized hydrazinylpyridines (2-hydrazinyl-3-nitropyridine and 2-hydrazinyl-5-nitropyridine) and also hydrazine hydrate, phenylhydrazine, and 4-nitrophenylhydrazine were used. Reactions were again carried out in ACE tubes and only simple alcohols, diethyl ether, and acetone were needed as solvents. One of the prepared bicyclo[2.2.2]octene adducts displayed water solubility thus being a promising candidate for future studies as a novel bidentate ligand for various metal cations in aqueous solutions or acting as an unprecedented halogen bond acceptor.

Key words green chemistry, chloropyridine, bicyclo[2.2.2]octene, water-soluble ligand, succinimide, nucleophilic substitution

Hydrazinylpyridines and their substituted analogues are simple organic molecules that can be used for many further transformations: acting as nucleophiles,[2–5] for the synthesis of more complex nitrogen heterocyclic compounds, mainly various [1,2,3]triazolopyridines[5–7] and azaindazoles,[8] or for hydrazone formation.[5] Hydrazine and its substituted analogues can be furthermore used for the synthesis of pyrazole and its derivatives.[9–12] Hydrazinyl group in hydrazinylpyridines can be substituted with a hydrogen, halogen, hydroxy, or phenyl group or reduced to an amine group.[5] 2-Hydrazinylpyridine can be used for the synthesis of organometallic complexes applied as antibiotics,[13,14] as a complexing site for technetium in molecules used in radioactive imaging in medicine,[15] and as a precursor in the synthesis of some pesticides.[5,16] Both 2- and 4-hydrazinylpyridines can be used in the synthesis of compounds that exhibit antitumor activity[17,18] and antidepressant characteristics.[19] Hydrazide derivatives of pyrimidine are used as precursors for the synthesis of various compounds of pharmacological interest.[20]

There are different options for the synthesis of hydrazinylpyridines. They (as well as the other aromatic hydrazines) can be prepared via formation of diazonium salts from aromatic amines, followed by reduction of the diazonium group using $SnCl_2$ and HCl,[5,21,22] PPh_3 and HCl[23] or Na_2SO_3[24–26] in combination with H_2SO_4,[24,25] HCl,[27] Zn dust and acetic acid[24] or NaOH and SO_2.[24] The main problem with this type of synthesis is an excessive amount of toxic waste generated in the form of inorganic salts.

Hydrazinylpyridines can be also prepared via nucleophilic aromatic substitution of a halogen in halopyridines with hydrazine (Scheme 1),[5] appropriate halogens being fluorine, chlorine, and bromine.[5] Besides hydrazine hydrate, substituted hydrazines can also be used, for example, methylhydrazine[28] and 4-tolylhydrazine.[29] Substitution most easily occurs on activated *ortho*- and *para*-positions regarding the nitrogen of pyridine ring, but can be in some cases achieved even on *meta*-position.[5]



Scheme 1 General reaction pathway of nucleophilic substitution of a halogen in halopyridine with hydrazine hydrate

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Nucleophilic substitution with hydrazine hydrate enabled preparation of many hydrazinylpyridines, for example, 4-hydrazinylpyridine from 4-chloropyridine,[30] 3-chloro-2-hydrazinylpyridine from 2,3-dichloropyridine,[31] and 3-chloro-2-fluoropyridine,[32] and 3,5-dichloro-2-hydrazinylpyridine from 2,3,5-trichloropyridine.[5] Appropriate reaction conditions can result even in substitution of two halogens as in the case of the synthesis of 2,6-dihydrazinylpyridine from 2,6-difluoropyridine.[33]

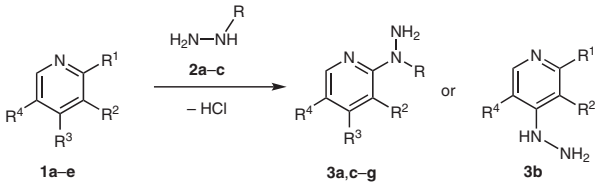
With perfluoro- and perchloropyridine substitution mainly takes place on *para*-position.[34] If perbromopyridine is used, *para*-product is still predominant, but the amount of *ortho*-product increases as a consequence of steric hindrance caused by the larger bromine substituents.[34,35] Pyridine ring is activated for the nucleophilic substitution if other electron-withdrawing substituents (nitro, cyano group) are present.[5] Examples of such compounds are 2-chloro-3-nitropyridine,[28] 2-bromo-5-chloro-3-nitropyridine,[28] and 3-carbonitrile-2,4,5,6-tetrachloropyridine.[5] Substitution of a halogen at *meta*-position was successful in the cases of 3-fluoro- and 3-chloro-2-nitropyridines[6] and also 3-fluoro- and 3-bromo-4-nitropyridine *N*-oxides.[29]

Most of the hydrazinylpyridine syntheses via nucleophilic substitution of a halogen are conducted in solvents such as simple alcohols (methanol, ethanol, *n*-propyl alcohol), THF, DMF, acetonitrile, dichloromethane, pyridine, or 1,4-dioxane,[5] under reflux,[30,34] at room temperature,[28] or at 0 °C[34] depending on the type and reactivity of starting halopyridines. Products are generally isolated by extraction into chloroform[28,34] followed by recrystallization[30,34] in some cases.

Our goal was to develop a simple, one-step synthesis of a set of hydrazinylpyridines **3a–g** starting from various chloro-substituted pyridines **1a–e** and hydrazines **2a–c**, where the desired aromatic nucleophilic substitution of the chloro substituent would take place under environmentally friendly conditions, including the consideration of the type and amount of waste. We decided to conduct all reactions in high-pressure ACE tubes, except in the case of the synthesis of 2-(1-methylhydrazinyl)-3-nitropyridine (**3f**), where room temperature turned out to be sufficient. *n*-Propyl alcohol was used as the solvent, except again in the case of **3f**, where methanol was selected. Closed high-pressure ACE tubes offer many advantages: reactions can be conducted at higher temperatures than the boiling point of the reaction mixture; any loss of reactants, products, and solvents can be prevented; pressure resistant (glass) equipment are available in a range of sizes (offering the possibility of scale-up). According to the reactivity of chloropyridines **1a–e** and the type of hydrazine **2a–c** used, the reaction temperature, time, and excess of hydrazines were adjusted (Table 1), enabling the synthesis of hydrazinylpyridines **3a–g** in excellent yields (60–93%, with the exception of **3g**).

In the cases when pyridine ring is inactivated (**1a**,**b**) or weakly activated (**1c**) for nucleophilic substitution, large excesses of hydrazine hydrate (**2a**) are needed for the complete transformation to **3a–c** (Table 1). When smaller amounts of hydrazine hydrate (2–3-fold excess) are used, the yields of **3a**,**b** decrease substantially to only 10–30%, but still depend upon the reaction temperature and time. In our cases, we were unable to replicate the results of a previous study stating that 1.1-fold excess of hydrazine hydrate is

Table 1 General Reaction Scheme for the Synthesis of Hydrazinylpyridines **3a–g**



Entry	Chloropyridine **1**					Hydrazine **2**		Molar ratio of **1**:**2**	Temp (°C)	Time	Product	Yield (%)
	R^1	R^2	R^3	R^4		R						
1	Cl	H	H	H	**1a**	H	**2a**	1:6	150	20 h	**3a**[a]	93
2	H	H	Cl	H	**1b**	H	**2a**	1:8	150	20 h	**3b**·HCl[a]	60
3	Cl	Cl	H	H	**1c**	H	**2a**	1:7	140	4 h	**3c**[a]	90
4	Cl	NO_2	H	H	**1d**	H	**2a**	1:3	60	30 min	**3d**[a]	79
5	Cl	H	H	NO_2	**1e**	H	**2a**	1:4	80	1 h	**3e**[a]	74
6	Cl	NO_2	H	H	**1d**	Me	**2b**	1:4	r.t.	30 min	**3f**[b]	72
7	Cl	H	H	NO_2	**1e**	CH_2CH_2OH	**2c**	1:3	100	45 min	**3g**[a]	32

[a] Reaction was conducted in a high pressure ACE tube, PrOH was used as the solvent.
[b] Reaction was conducted in an open vessel, MeOH was used as the solvent.

sufficient for the reaction with 4-chloropyridine (**1b**).[30] Obviously, at least 2-fold excess of hydrazine **2** is needed in all cases, because one equivalent of **2** is consumed for the neutralization of hydrogen chloride liberated as the side product of the nucleophilic substitution yielding **3**. In all cases, except for 4-hydrazinylpyridine hydrochloride (**3b**·HCl), pure hydrazinylpyridines **3** and not their salts were isolated demonstrating that products **3** are less basic (have lower pK_b values) than starting hydrazines **2**. On the other hand, as **3b** is more basic than hydrazine, a decreased amount of hydrazine is enough for the complete reaction (HCl formed does not decrease the nucleophilicity of the starting hydrazine **2**). Nevertheless, the use of 4-chloropyridine hydrochloride (**1b**·HCl) still requires an excess of hydrazine (**2a**), because in the first step an equivalent of **2a** is consumed for the neutralization of **1b**·HCl to form its free base **1b**.

The choice of the solvent (alcohol) also effects the overall yield. It turned out that all compounds **3**, including those containing nitro group (**3d**–**g**), are very polar. When the last step of isolation is filtration (for **3c**–**e**,**g**), application of higher alcohols such as *n*-propyl, isobutyl, and *n*-butyl alcohols improves the yield. In the cases of **3a**,**b**, the solvents are removed by vacuum distillation before the isolation, therefore the solubility of **3** in the solvents applied for the reactions does not affect the final yield. Alcohols with lower boiling points, such as ethyl, isopropyl and *n*-propyl alcohols are therefore favored.

Use of *N*-alkyl-substituted hydrazines, such as methylhydrazine (**2b**) and 2-hydrazinylethanol (**2c**), led, in accordance with the previous results,[6] to the substitution taking place on the secondary nitrogen as shown by the exclusive formation of products **3f**,**g**. Nucleophilicity of the secondary nitrogen in substituted hydrazines is increased (in comparison with the primary one) by the electron-donating properties of the additional alkyl substituent, as evident in the cases of **2b**,**c**, where electronic effects override the steric hindrance. These observations possibly explain the unsuccessful reaction of *N*,*N*-dimethylhydrazine.

Free rotation of 2-hydrazinyl-5-nitropyridine (**3e**) in DMSO-d_6 solution seems to be heavily hindered, as seen from the lack of fine structure in its ^{1}H NMR spectrum measured at 29 °C (Figure 1, red line). Furthermore, at 29 °C only two ^{13}C NMR signals were observed. Increasing the measurement temperature to 59 °C caused a drastic change in ^{1}H NMR spectrum, with nicely resolved fine structure observed (Figure 1, blue line), whereas in ^{13}C NMR spectrum five signals for five chemically inequivalent carbon nuclei were detected. This observation, unusual for a compound with so small molecular mass, could be due to strong intermolecular (hydrogen) bonds.

An unexpected wide variability was noted in the colors of compounds **3** in their pure crystalline forms (Figure 2). This observation might be as well explained with intermolecular (hydrogen) bonds forming in the solid state between hydrogens of NH_2 (or NH) groups and pyridine nitrogen or

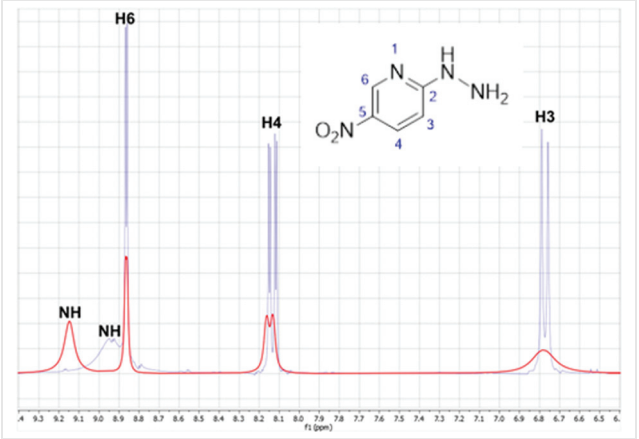


Figure 1 Assigned ^{1}H NMR spectra of 2-hydrazinyl-5-nitropyridine (**3e**) measured at 29 °C (red line) and 59 °C (blue line)

oxygens from NO_2 group. A long chain of molecules can form sufficiently small energy gap between HOMO and LUMO orbitals for coloration to appear. This could be supported by a previous report, that describes a derivative of hydrazinylpyridine already successfully implemented as a colorimetric sensor for carbonate ions due to its color changes upon the formation of hydrogen bonds with carbonate ion in an aqueous solution.[36]

Figure 2 Color variability of synthesized hydrazinylpyridines **3** (top row: **3a**–**c**, bottom row: **3d**–**g**) in their crystalline form

By optimizing synthetic procedures only small amounts of solvents (simple alcohols and diethyl ether) are needed; furthermore, they can be easily recycled. Products **3** are obtained pure even without recrystallization, the only by-product being hydrazine hydrochloride or the corresponding salt of alkylhydrazines **2b**,**c**, which are removed together with the aqueous phase (when extraction is used in the cases of **3a**–**c**) or washed away during the filtration of the final products (in the cases of **3d**–**g**). Hydrazine hydrochloride can be isolated from the aqueous phases; ^{1}H NMR analysis showed its purity to be around 90% and with further purification (or neutralization to regain hydrazine as a free base) can be efficiently reused. Consequently, the described synthetic process has 100% atomic efficiency if water, coming from the hydrazine hydrate, is not considered as a

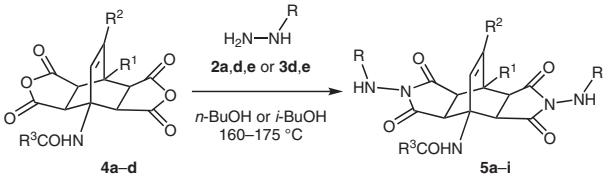
waste. The presence of water in the reaction mixture shifts the chemical equilibrium away from the products **3**. To lower the amount of hydrazine needed, from the two-phase system that appears during the synthesis of **3a–c**, continuous removal of water layer (containing mainly hydrazine hydrochloride) and continuous addition of fresh hydrazine hydrate is feasible. Such approach becomes attractive when the preparation of hydrazinylpyridines is taking place on a larger scale.

In the next step, hydrazine hydrate, two commercially available derivatives [phenyl- (**2d**) and 4-nitrophenylhydrazine (**2e**)] as well as two of the above prepared hydrazinylpyridines (i.e., **3d**,**e**) were selected for the transformation of succinic anhydride rings fused to the bicyclo[2.2.2]octene core of the compounds **4a–d** into corresponding *N*-substituted succinimides **5a–i**. These products contain *N*-amino (**5a**,**b**), *N*-phenylamino groups (**5c**,**d**), or its nitro analogue (**5e**,**f**) as well as *N*-nitropyridylamino groups (**5g–i**) that represent potential bidentate ligands for metal cations as demonstrated in similar, albeit more complex compounds.[37] Especially pyridine-containing derivatives **5g–i** are of great interest, as their heterocyclic nitrogen, having increased electron density, displays high affinity for coordination with various metal cations. Furthermore, such adducts can act as unprecedented double halogen bond acceptors with potential applicability in crystal engineering.[38,39] Adducts with free *N*-amino groups, on the other hand, are of interest as they offer easy entry into α-aminophosphine ligands showing a plethora of possible coordination modes as demonstrated recently for Pd(II) and Pt(II) complexes.[40]

The most straightforward approach towards the required symmetric *exo*,*exo*-bicyclo[2.2.2]octenes **4a–d** possessing two succinic anhydride moieties starts from the appropriate 2*H*-pyran-2-ones and maleic anhydride via double stereospecific thermal Diels–Alder cycloaddition.[41,42] Adducts **4** were in the next step transformed into succinimide derivatives **5** via nucleophilic attack of NH_2 group of amines, hydrazines, or hydrazides. Reactions with amines generally require harsh conditions; ethanamine, as an example, required 5 days (in water at 75 °C), whereas (pyridin-3-yl)methanamine required only 5 hours (in DMF at ca. 150 °C).[2] Reactions could be in some cases greatly accelerated by microwave heating (2 h at 160 °C in water was sufficient in most cases).[2,43] With hydrazine and its alkyl and aryl derivatives, being better nucleophiles than amines, transformations can be conducted more easily but microwave conditions still show good potential.[2–4] Reactions described in the literature were completed under microwave irradiation in 90 minutes or less (at 100–160 °C),[2,4] or with conventional heating in *n*-butyl alcohol in 3 hours (at 160 °C).[44]

For the transformations of **4a–d**, unsubstituted hydrazine (**2a**) and its aryl derivatives (**2d**,**e** and **3d**,**e**) were used as nucleophiles. Reactions were again conducted in high-

Table 2 Substituted Bicyclo[2.2.2]octenes **5a–i** Synthesized from **4a–d** and Substituted Hydrazines **2** or **3** via Nucleophilic Substitution of Oxygen with Nitrogen



Entry	Bicyclo[2.2.2]octene **4**				Hydrazines **2** or **3**		Molar ratio of **4**:hydrazine	Temp (°C)	Time (h)	Product	Yield (%)
	R^1	R^2	R^3		R						
1	Me	H	Me	**4a**	H	**2a**	1:20[a]	170	1.5	**5a**[b]	80
2	Et	Me	Ph	**4b**	H	**2a**	1:12	160	3	**5b**[c]	38
3	Me	H	Me	**4a**	Ph	**2d**	1:2.5	160	3	**5c**[c]	72
4	Et	Me	Ph	**4b**	Ph	**2d**	1:2.2	160	3	**5d**[c]	69
5	4-MeC_6H_4	H	Ph	**4c**	4-$NO_2C_6H_4$	**2e**	1:2.5	160	2.5	**5e**[c]	51
6	Me	CO_2Me	Ph	**4d**	4-$NO_2C_6H_4$	**2e**	1:3.6	170	2.5	**5f**[c]	56
7	Et	Me	Ph	**4b**	3-NO_2-pyridin-2-yl	**3d**	1:4	175	5	**5g**[b]	65
8	4-MeC_6H_4	H	Ph	**4c**	3-NO_2-pyridin-2-yl	**3d**	1:4	175	4	**5h**[b]	69
9	4-MeC_6H_4	H	Ph	**4c**	5-NO_2-pyridin-2-yl	**3e**	1:4	175	3	**5i**[b]	52

[a] For the reaction with 1 mol of bicyclo[2.2.2]octene, 2 mol of hydrazine were needed, so the ratio of 1:20 accounts for the 10-fold molar excess of hydrazine; analogously in the other cases as well.
[b] *i*-BuOH was used as the solvent.
[c] *n*-BuOH was used as the solvent.

pressure ACE tubes at 160–175 °C using *n*-butyl or isobutyl alcohol as the solvent yielding products **5a–i** in medium yields (Table 2). The main goal was to fine tune the substituent patterns of the products **5** to increase their solubility in aqueous media as this property plays an important role in the applicability as ligands for metal cations and inhibitors of various physiologically important enzymes. The aim was to prepare at least one water-soluble product; indeed, **5a** turned out to be soluble in water and partially in methanol, while insoluble in higher alcohols such as *n*-butyl or isobutyl alcohol. On the other hand, products **5b–i**, as well as their analogues previously reported in the literature, are completely insoluble in water and well soluble only in DMSO and DMF, greatly diminishing their potential applicability.

The *exo*,*exo* arrangement of the five-membered rings fused to the bicyclo[2.2.2]octene framework is conserved during the transformations **4** → **5**. This is confirmed by the value of the coupling constants in ^{1}H NMR spectra of products **5** for the doublets belonging to 3a-H and 4a-H (and also 7a-H and 8a-H) being around 8 Hz, consistent with the literature data (on the other hand, for *endo* arrangement these coupling constants are known to be around 10 Hz).[45]

^{1}H NMR spectrum of compound **5i** measured at 29 °C (Figure 3, red line) was again lacking any fine structure (except for the phenyl and *p*-tolyl group signals). Analogously, at 29 °C there were also signals missing in ^{13}C NMR spectrum. Increasing the measurement temperature to 59 °C caused the fine structure of ^{1}H NMR spectrum to appear, with better resolved and narrower signals (Figure 3, blue line). Additionally, in ^{13}C NMR spectrum at 59 °C signals for all chemically inequivalent carbons were observed. This behavior could again be explained by the heavily restricted free rotation in DMSO-d_6 solution as a consequence of strong intermolecular bonds.

Worth noting is that the hydrazine used in the preparation of **5i** was **3e**, the one for which restricted rotation was already demonstrated. It is interesting that molecules of **3e** do not show restricted free rotation in solution only, but also when representing a part (covalently bound fragment) of a larger organic molecule such as **5i**, when they affect bicyclo[2.2.2]octene skeleton as well (with only remote side groups staying unaffected).

Observation that methoxycarbonyl group of compound **5f** does not react with 4-nitrophenylhydrazine (**2e**), leads to the conclusion that the reaction conditions applied are not harsh enough for the ester groups to be transformed to corresponding hydrazides.

In conclusion, seven substituted hydrazinylpyridines **3a–g** were synthesized in very good yields (60–93%, with the exception of **3g**), starting from chloropyridines **1a–e** and hydrazines **2a–c** via nucleophilic substitution of chlorine. Simple isolation via filtration or vacuum distillation was sufficient, so no purifying of the products was needed, rendering the process environmentally friendly. Using selected hydrazine derivatives, including some hydrazinylpyridines **3** that we prepared, a set of nine bicyclo[2.2.2]octenes **5a–i** fused with two *N*-substituted succinimide moieties was obtained via nucleophilic substitution of the oxygen in succinic anhydride moieties. We managed to exchange the traditionally used solvents, such as decalin or tetralin (both of them classified as toxic to aquatic life with long-lasting effects and possibly fatal if swallowed, tetralin additionally causing skin and eye irritation and suspected of causing cancer, decalin being flammable) with environmentally friendly alcohols (isobutyl alcohol, *n*-butyl alcohol). Furthermore, our important goal of obtaining a water-soluble derivative was reached (i.e., product **5a** is very soluble in water and partially soluble in methanol), thus opening potential applications of such adducts as bidentate ligands for metal cations in aqueous solutions or as highly modular halogen bond acceptors, in both cases acting as unprecedented building blocks in crystal engineering capable of forming 1D molecular architectures. We also found that 2-hydrazinyl-5-nitropyridine (**3e**) displays heavily hindered rotation in a DMSO-d_6 solution at room temperature, this being unexpected for a molecule as small as **3e**. This behavior was observed in its adduct **5i** as well.

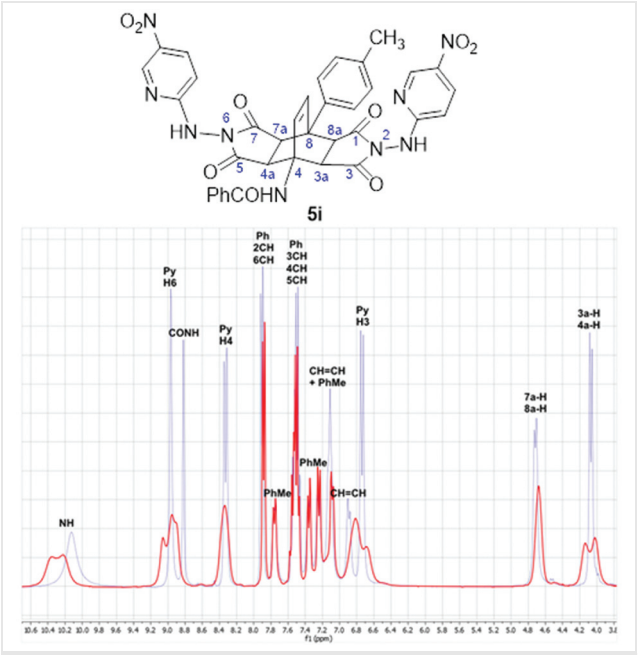


Figure 3 Assigned ^{1}H NMR spectra of compound **5i** measured at 29 °C (red line) and 59 °C (blue line)

Melting points were determined using an automatic OptiMelt MPA100 (Stanford Research System) instrument and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker Avance III spectrometer at 29 °C (unless stated otherwise) using Me_4Si as the internal standard at 300 MHz or 75.5 MHz, respectively. ^{13}C NMR spectra

are referenced against the central line of the solvent signal (DMSO-d_6 at 39.5 ppm). Mass spectra were recorded using an Agilent 6624 Accurate Mass TOF LC/MS spectrometer via ESI ionization. IR spectra of compounds as powders were recorded on a Bruker Alpha Platinum ATR FT-IR spectrophotometer. Elemental analyses were performed on a PerkinElmer 2400 Series II CHNS/O analyzer.

Reagents and solvents were used as received from commercial suppliers with purity of 98% or more. Bicyclo[2.2.2]octenes **4a**–**d** were prepared from appropriately substituted 2*H*-pyran-2-ones and maleic anhydride under reflux in tetralin according to the published procedure.[41] Commercially available thick-walled ACE glass tubes closed by a Teflon screw-plug were used.

2-Hydrazinylpyridine (3a) and 4-Hydrazinylpyridine Hydrochloride (3b·HCl)

For the synthesis of **3a**, hydrazine hydrate (**2a**; 2.92 mL, 3.00 g, 60.0 mmol) and PrOH (3 mL) were mixed in a 15 mL ACE tube. While stirring, 2-chloropyrdine (**1a**; 938 µL, 1.14 g, 10.0 mmol) was added.

For the synthesis of **3b**, hydrazine hydrate (**2a**; 972 µL, 1.00 g, 20.0 mmol) and PrOH (5 mL) were mixed in a 15 mL ACE tube. While stirring, 4-chloropyrdine hydrochloride (**1b**·HCl; 1.50 g, 10.0 mmol) was added. Two-phase system appeared and the bottom aqueous layer with hydrazine hydrochloride was removed with a syringe. Additional hydrazine hydrate (**2a**; 2.92 mL, 3.00 g, 60.0 mmol) was added.

Both the reaction mixtures were stirred for 20 h at 150 °C giving a two-phase system. The bottom aqueous layer, containing hydrazine hydrochloride, was removed and the upper layer evaporated under vacuum, yielding an orange oil that solidified at 4 °C (**3a**), or a white precipitate (**3b**·HCl). The latter was suspended in Et_2O (20 mL) and filtered.

3-Chloro-2-hydrazinylpyridine (3c)

2,3-Dichloropyridine (**1c**; 1.48 g, 10.0 mmol) was dissolved in PrOH (6 mL) in a 15 mL ACE tube. While stirring, hydrazine hydrate (**2a**; 3.40 mL, 3.51 g, 70.0 mmol) was added and the reaction mixture was stirred for 4 h at 140 °C giving a two-phase system. The bottom aqueous layer was removed and the upper layer was cooled to around 10 °C until white crystals were formed. This suspension was poured into distilled H_2O (6 mL). Crystals of **3c** were filtered and washed with Et_2O (6 mL).

2-Hydrazinyl-3-nitropyridine (3d), 2-Hydrazinyl-5-nitropyridine (3e), and 2-[1-(5-Nitropyridin-2-yl)hydrazinyl]ethanol (3g)

For the preparation of **3d**, 2-chloro-3-nitropyridine (**1d**; 0.793 g, 5.0 mmol) and for the preparation of **3e**,**g**, the same amount of 2-chloro-5-nitropyridine (**1e**; 0.793 g, 5.0 mmol) was suspended in PrOH (20 mL) in a 25 mL ACE tube, respectively. While stirring, hydrazine hydrate (**2a**; 729 µL, 0.751 g, 15.0 mmol for **3d** and 972 µL, 1.00 g, 20.0 mmol for **3e**) and 2-hydrazinylethanol (**2c**; 1.02 mL, 1.14 g, 15.0 mmol for **3g**) was added, respectively, and the respective reaction mixture was stirred at the specific temperature and time (Table 1). After reaction completion, in the case of **3d**,**e**, the resulting mixture was cooled to 4 °C, the precipitate filtered, suspended in distilled H_2O (15 mL), filtered again, then suspended in Et_2O (15 mL) and filtered once more. In the case of **3g**, the mixture was vacuum evaporated, the remaining red oil cooled in an ice-salt bath. After around 30 min, a yellow precipitate was formed, which was suspended in distilled H_2O (20 mL), filtered, then suspended in Et_2O (20 mL) and filtered again.

2-(1-Methylhydrazinyl)-3-nitropyridine (3f)

2-Chloro-3-nitropyridine (**1d**; 1.59 g, 10.0 mmol) was suspended in MeOH (5 mL). While stirring, methylhydrazine (**2b**; 2.11 mL, 1.84 g, 40.0 mmol) was slowly added. **Caution**: The reaction was heavily exothermic and the addition had to be slow. A red solution was formed and left stirring for 30 min at r.t. Distilled H_2O (15 mL) was added whereupon a red oil was formed. The mixture of MeOH and H_2O was removed with a syringe and the red oil was cooled in an ice-salt bath. The orange precipitate obtained was filtered and washed with distilled H_2O (10 mL).

Bicyclo[2.2.2]octene Derivatives 5a–d

Succinic anhydride adduct **4a**,**b** (1.0 mmol) was suspended in *i*-BuOH (6 mL, for **5a**) or BuOH (12 mL, for **5b**–**d**) inside a 15 mL ACE tube. While stirring, hydrazine hydrate (**2a**; 972 µL, 1.00 g, 20.0 mmol for **5a** and 583 µL, 0.601 g, 12.0 mmol for **5b**) and phenylhydrazine (**2d**; 246 µL, 0.270 g, 2.50 mmol for **5c** and 217 µL, 0.238 g, 2.20 mmol for **5d**), respectively, was added. The respective reaction mixture was stirred for 1.5 h at 170 °C (for **5a**) or for 3 h at 160 °C (for **5b**–**d**) and then cooled to 4 °C. The resulting precipitate was filtered and washed with MeOH (5 mL) and Et_2O (10 mL).

Bicyclo[2.2.2]octene Derivatives 5e–i

4-Nitrophenylhydrazine (**2e**; 0.383 g, 2.50 mmol for **5e** and 0.551 g, 3.60 mmol for **5f**), 2-hydrazinyl-3-nitropyridine (**3d**; 0.308 g, 2.00 mmol for **5g**,**h**), and 2-hydrazinyl-5-nitropyridine (**3e**; 0.308 g, 2.00 mmol for **5i**), respectively, was dissolved in the solvent (15 mL) given in Table 2 while heating in an open 25 mL ACE tube. While stirring, **4c** (0.457 g, 1.0 mmol for **5e**), **4d** (0.439 g, 1.0 mmol for **5f**), **4b** (0.205 g, 0.5 mmol for **5g**), and **4c** (0.229 g, 0.5 mmol for **5h**,**i**) was added, respectively. The respective reaction mixture was stirred at the specific temperature and time (Table 2). Thereafter, it was cooled to 10 °C, the resulting precipitate was filtered, and suspended in a mixture of MeOH (10 mL) and acetone (5 mL) for **5e** and **5f** and EtOH (10 mL) and acetone (10 mL) for **5g**–**i**. The precipitate formed was filtered again and washed with Et_2O (10 mL).

CAUTION! Care should be taken regarding boiling point of the alcohol, reaction temperature, and ACE tube strength to avoid an accidental explosion.

2-Hydrazinylpyridine (3a)

Yield: 1.01 g (93%); red solid; mp 44–46 °C (PrOH–EtOH–MeOH).

IR (neat): 3254, 3009, 1595, 1570 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 7.97 (ddd, J_1 = 5 Hz, J_2 = 2 Hz, J_3 = 1 Hz, 1 H, 6-H), 7.43 (ddd, J_1 = 8.5 Hz, J_2 = 7 Hz, J_3 = 2 Hz, 1 H, 4-H), 7.32 (s, 1 H, NH), 6.67 (dt, J_1 = 8.5 Hz, J_2 = 1 Hz, 1 H, 3-H), 6.53 (ddd, J_1 = 7 Hz, J_2 = 5 Hz, J_3 = 1 Hz, 1 H, 5-H), 4.07 (br s, 2 H, NH_2).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 162.3, 147.7, 137.3, 113.0, 106.9.

HRMS (ESI, TOF): m/z $[M + H]^+$ calcd for $C_5H_8N_3$: 110.0713; found: 110.0708.

4-Hydrazinylpyridine Hydrochloride (3b·HCl)

Yield: 0.875 g (60%); brown solid; mp 235–238 °C (MeOH–EtOH–Et_2O) [Lit.[30] mp 242–243 °C (MeOH)].

IR (neat): 3300, 3187, 2905, 2871, 2813, 1654, 1595, 1533 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 9.98 (s, 1 H, NH), 8.06 (d, J = 6.5 Hz, 2 H, 2-H, 6-H), 6.96 (d, J = 6.5 Hz, 2 H, 3-H, 5-H), 4.93 (br s, 2 H, NH_2).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 158.4, 144.7, 106.1.

HRMS (ESI, TOF): m/z [M – Cl]$^+$ calcd for $C_5H_8N_3$: 110.0713; found: 110.0711.

Anal. Calcd for $C_5H_8ClN_3$: C, 41.24; H, 5.54; N, 28.87; Cl, 24.35. Found: C, 41.54; H, 5.53; N, 28.76; Cl, 24.17.

3-Chloro-2-hydrazinylpyridine (3c)

Yield: 1.29 g (90%); white solid; mp 164–166.5 °C (PrOH) [Lit.[31] mp 169 °C (EtOH)].

IR (neat): 3284, 3195, 1917, 1890, 1865, 1622, 1592 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.05 (dd, J_1 = 5 Hz, J_2 = 1.5 Hz, 1 H, 6-H), 7.57 (dd, J_1 = 8 Hz, J_2 = 1.5 Hz, 1 H, 4-H), 7.56 (br s, 1 H, NH), 6.62 (dd, J_1 = 8 Hz, J_2 = 5 Hz, 1 H, 5-H), 4.22 (br s, 2 H, NH_2).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 156.2, 146.1, 136.7, 114.1, 113.7.

HRMS (ESI, TOF): m/z [M + H]$^+$ calcd for $C_5H_7ClN_3$: 144.0323; found: 144.0318.

2-Hydrazinyl-3-nitropyridine (3d)

Yield: 0.612 g (79%); orange solid; mp 166–167.5 °C (PrOH) [Lit.[28] mp 171–172 °C (EtOH)].

IR (neat): 3296, 3086, 1600, 1562 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.34 (s, 1 H, NH), 8.51 (dd, J_1 = 4 Hz, J_2 = 2 Hz, 1 H, 6-H), 8.39 (dd, J_1 = 8 Hz, J_2 = 2 Hz, 1 H, 4-H), 6.74 (dd, J_1 = 8 Hz, J_2 = 4 Hz, 1 H, 5-H), 4.88 (s, 2 H, NH_2).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 156.5, 152.5, 135.8, 127.0, 112.1.

HRMS (ESI, TOF): m/z [M + H]$^+$ calcd for $C_5H_7N_4O_2$: 155.0564; found: 155.0562.

Anal. Calcd for $C_5H_6N_4O_2$: C, 38.96; H, 3.93; N, 36.35. Found: C, 39.32; H, 3.48; N, 35.95.

2-Hydrazinyl-5-nitropyridine (3e)

Yield: 0.569 g (74%); green solid; mp 200–201.5 °C (PrOH).

IR (neat): 3334, 3215, 2974, 1665, 1606 cm^{-1}.

^{1}H NMR (300 MHz (59 °C, DMSO-d_6): δ = 8.93 (br s, 1 H, NH), 8.85 (d, J = 3 Hz, 1 H, 6-H), 8.13 (dd, J_1 = 9 Hz, J_2 = 3 Hz, 1 H, 4-H), 6.76 (d, J = 9 Hz, 1 H, 3-H), 4.59 (br s, 2 H, NH_2).

^{13}C NMR (75.5 MHz (59 °C, DMSO-d_6): δ = 163.9, 147.0, 134.9, 132.6, 105.3.

HRMS (ESI, TOF): m/z [M + H]$^+$ calcd for $C_5H_7N_4O_2$: 155.0564; found: 155.0563.

Anal. Calcd for $C_5H_6N_4O_2$: C, 38.96; H, 3.93; N, 36.35. Found: C, 39.11; H, 3.52; N, 36.34.

2-(1-Methylhydrazinyl)-3-nitropyridine (3f)

Yield: 1.21 g (72%); yellow solid; mp 59–60.5 °C (MeOH–H_2O) [Lit.[28] mp 60–61 °C (EtOH)].

IR (neat): 3338, 2976, 2884, 1636, 1591, 1553, 1514, 1487 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.22 (dd, J_1 = 5 Hz, J_2 = 2 Hz, 1 H, 6-H), 7.88 (dd, J_1 = 8 Hz, J_2 = 2 Hz, 1 H, 4-H), 6.73 (dd, J_1 = 8 Hz, J_2 = 5 Hz, 1 H, 5-H), 4.77 (s, 2 H, NH_2), 3.26 (s, 3 H, CH_3).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 153.8, 150.2, 134.6, 133.9, 112.3, 41.0.

HRMS (ESI, TOF): m/z [M + H]$^+$ calcd for $C_6H_9N_4O_2$: 169.0720; found: 169.0721.

Anal. Calcd for $C_6H_8N_4O_2$: C, 42.85; H, 4.80; N, 33.32. Found: C, 42.76; H, 4.78; N, 33.20.

2-[1-(5-Nitropyridine-2-yl)hydrazinyl]ethanol (3g)

Yield: 0.320 g (32%); yellow solid; mp 97.5–100 °C (PrOH).

IR (neat): 3302, 3182, 2862, 1591, 1567, 1485 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.88 (d, J = 3 Hz, 1 H, 6-H), 8.15 (dd, J_1 = 10 Hz, J_2 = 3 Hz, 1 H, 4-H), 7.18 (d, J = 10 Hz, 1 H, 3-H), 4.98 (s, 2 H, NH_2), 4.83 (br s, 1 H, OH), 3.91 (t, J = 6 Hz, 2 H, CH_2), 3.65 (t, J = 6 Hz, 2 H, CH_2).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 163.0, 146.5, 134.2, 132.5, 106.6, 58.3, 53.8.

HRMS (ESI, TOF): m/z [M + H]$^+$ calcd for $C_7H_{11}N_4O_3$: 199.0826; found: 199.0824.

Anal. Calcd for $C_7H_{10}N_4O_3$: C, 42.42; H, 5.09; N, 28.27. Found: C, 42.21; H, 4.97; N, 28.18.

***N*-(2,6-Diamino-8-methyl-1,3,5,7-tetraoxo-1,2,3,3a,4,4a,5,6,7,7a,8,8a-dodecahydro-4,8-ethenopyrrolo-[3,4-*f*]isoindol-4-yl)acetamide (5a)**

Yield: 0.277 g (80%); grey solid; mp 267.5–269.5 °C (*i*-BuOH).

IR (neat): 3349, 3281, 2980, 2929, 1772, 1690, 1670, 1535 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.35 (s, 1 H, CONH), 5.96 (d, J = 9 Hz, 1 H, CH=CH), 5.80 (d, J = 9 Hz, 1 H, CH=CH), 4.88 (s, 4 H, 2 × NH_2), 4.02 (d, J = 8 Hz, 2 H, 7a-H, 8a-H), 2.94 (d, J = 8 Hz, 2 H, 3a-H, 4a-H), 1.94 (s, 3 H, $COCH_3$), 1.72 (s, 3 H, CH_3).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 173.7, 172.3, 170.9, 134.7, 131.3, 57.5, 46.8, 42.3, 39.6, 24.0, 19.6.

HRMS (ESI, TOF): m/z [M + H]$^+$ calcd for $C_{15}H_{18}N_5O_5$: 348.1302; found: 348.1308.

***N*-(2,6-Diamino-8-ethyl-9-methyl-1,3,5,7-tetraoxo-1,2,3,3a,4,4a,5,6,7,7a,8,8a-dodecahydro-4,8-ethenopyrrolo-[3,4-*f*]isoindol-4-yl)benzamide (5b)**

Yield: 0.166 g (38%); white solid; mp 302.5–304 °C (dec.) (BuOH).

IR (neat): 3338, 3286, 3074, 2968, 2950, 1772, 1690, 1635, 1551 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.55 (s, 1 H, CONH), 7.88 (m, 2 H_{arom}, C_6H_5, 2-H, 6-H), 7.54 (m, 3 H_{arom}, C_6H_5, 3-H, 4-H, 5-H), 6.04 (s, 1 H, C=CH), 4.90 (s, 4 H, 2 × NH_2), 4.15 (d, J = 8 Hz, 2 H, 7a-H, 8a-H), 3.27 (d, J = 8 Hz, 2 H, 3a-H, 4a-H), 2.35 (q, J = 7 Hz, 2 H, CH_2), 1.55 (s, 3 H, CH_3), 1.18 (t, J = 7 Hz, 3 H, CH_2CH_3).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 173.6, 172.6, 168.4, 141.4, 136.3, 131.4, 128.4, 128.2, 124.7, 58.1, 44.7, 42.1, 41.8, 20.7, 18.6, 8.5.

HRMS (ESI, TOF): m/z [M + H]$^+$ calcd for $C_{22}H_{24}N_5O_5$: 438.1772; found: 438.1772.

***N*-[8-Methyl-1,3,5,7-tetraoxo-2,6-bis(phenylamino)-1,2,3,3a,4,4a,5,6,7,7a,8,8a-dodecahydro-4,8-ethenopyrrolo-[3,4-*f*]isoindol-4-yl]acetamide (5c)**

Yield: 0.360 g (72%); beige solid; mp 210.5–214.5 °C (BuOH).

IR (neat): 3296, 1779, 1718, 1662, 1602, 1539, 1496 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.50 (s, 1 H, CONH), 8.32 (s, 2 H, 2 × NH), 7.18 (t, J = 7.5 Hz, 4 H_{arom}, 2 × C_6H_5, 3-H, 5-H), 6.80 (t, J = 7.5 Hz, 2 H_{arom}, 2 × C_6H_5, 4-H), 6.63 (d, J = 7.5 Hz, 4 H_{arom}, 2 × C_6H_5, 2-H, 6-H), 6.32 (d, J = 9 Hz, 1 H, CH=CH), 6.21 (d, J = 9 Hz, 1 H, CH=CH), 4.31 (d, J = 8 Hz, 2 H, 7a-H, 8a-H), 3.21 (d, J = 8 Hz, 2 H, 3a-H, 4a-H), 1.94 (s, 3 H, $COCH_3$), 1.78 (s, 3 H, CH_3).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 174.4, 173.1, 171.1, 146.6, 135.9, 132.4, 129.3, 120.2, 113.1, 57.5, 47.1, 42.6, 39.8, 23.9, 19.5.

HRMS (ESI, TOF): *m*/*z* [M + H]$^+$ calcd for $C_{27}H_{26}N_5O_5$: 500.1928; found: 500.1926.

N-[8-Ethyl-9-methyl-1,3,5,7-tetraoxo-2,6-bis(phenylamino)-1,2,3,3a,4,4a,5,6,7,7a,8,8a-dodecahydro-4,8-ethenopyrrolo-[3,4-*f*]isoindol-4-yl]benzamide (5d)

Yield: 0.409 g (69%); white solid; mp 321.5–323.5 °C (BuOH).

IR (neat): 3296, 2960, 1775, 1705, 1661, 1601, 1495 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.79 (s, 1 H, CONH), 8.35 (s, 2 H, 2 × NH), 7.87 (m, 2 H_{arom}, C_6H_5, 2-H, 6-H), 7.52 (m, 3 H_{arom}, C_6H_5, 3-H, 4-H, 5-H), 7.19 (t, *J* = 7.5 Hz, 4 H_{arom}, 2 × NC_6H_5, 3-H, 5-H), 6.81 (t, *J* = 7.5 Hz, 2 H_{arom}, 2 × NC_6H_5, 4-H), 6.62 (d, *J* = 7.5 Hz, 4 H_{arom}, 2 × NC_6H_5, 2-H, 6-H), 6.47 (s, 1 H, C=CH), 4.45 (d, *J* = 8 Hz, 2 H, 7a-H, 8a-H), 3.54 (d, *J* = 8 Hz, 2 H, 3a-H, 4a-H), 2.37 (q, *J* = 7 Hz, 2 H, CH_2), 1.76 (s, 3 H, CH_3), 1.22 (t, *J* = 7 Hz, 3 H, CH_2CH_3).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 174.3, 173.4, 168.8, 146.6, 142.5, 136.3, 131.5, 129.3, 128.5, 128.1, 126.5, 120.3, 112.9, 58.1, 45.0, 42.2, 42.1, 20.7, 19.3, 8.4.

HRMS (ESI, TOF): *m*/*z* [M + H]$^+$ calcd for $C_{34}H_{32}N_5O_5$: 590.2398; found: 590.2392.

N-{2,6-Bis[(4-nitrophenyl)amino]-1,3,5,7-tetraoxo-8-(*p*-tolyl)-1,2,3,3a,4,4a,5,6,7,7a,8,8a-dodecahydro-4,8-ethenopyrrolo-[3,4-*f*]isoindol-4-yl}benzamide (5e)

Yield: 0.373 g (51%); orange solid; mp >320 °C (dec.) (BuOH).

IR (neat): 3318, 3263, 1790, 1721, 1661, 1599, 1500, 1483 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.44 (br s, 2 H, 2 × NH), 8.99 (s, 1 H, CONH), 8.12 (d, *J* = 9 Hz, 4 H_{arom}, 2 × 4-$NO_2C_6H_4$, 3-H, 5-H), 7.89 (d, *J* = 8 Hz, 2 H), 7.78 (d, *J* = 8 Hz, 1 H), 7.52 (m, 3 H), 7.37 (br s, 1 H), 7.36 (d, *J* = 8 Hz, 1 H), 7.26 (d, *J* = 8 Hz, 1 H), 7.10 (d, *J* = 8 Hz, 1 H), 6.99 (br s, 1 H): (CH=CH, C_6H_5, 4-MeC_6H_4), – 6.75 (d, *J* = 9 Hz, 4 H_{arom}, 2 × 4-$NO_2C_6H_4$, 2-H, 6-H), 4.72 (d, *J* = 8 Hz, 2 H, 7a-H, 8a-H), 4.07 (d, *J* = 8 Hz, 2 H, 3a-H, 4a-H), 2.31 (s, 3 H, CH_3).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 172.4, 172.3, 168.9, 152.4, 139.9, 136.1, 136.0, 135.3, 131.7, 129.5, 128.6, 128.5, 128.1, 127.9, 127.7, 126.2, 112.0, 58.7, 48.1, 46.3, 43.0, 21.1.

HRMS (ESI, TOF): *m*/*z* [M + H]$^+$ calcd for $C_{38}H_{30}N_7O_9$: 728.2100; found: 728.2098.

Methyl 4-Benzamido-8-methyl-2,6-bis[(4-nitrophenyl)amino]-1,3,5,7-tetraoxo-1,2,3,3a,4,4a,5,6,7,7a,8,8a-dodecahydro-4,8-ethenopyrrolo[3,4-*f*]isoindole-9-carboxylate (5f)

Yield: 0.400 g (56%); brown solid; mp >325 °C (dec.) (BuOH).

IR (neat): 3413, 3304, 2936, 1788, 1737, 1703, 1662, 1599, 1497 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.53 (s, 2 H, 2 × NH), 9.08 (s, 1 H, CONH), 8.06 (d, *J* = 9 Hz, 4 H_{arom}, 2 × 4-$NO_2C_6H_4$, 3-H, 5-H), 7.88 (d, *J* = 8 Hz, 2 H_{arom}, C_6H_5, 2-H, 6-H), 7.79 (s, 1 H, C=CH), 7.53 (m, 3 H_{arom}, C_6H_5, 3-H, 4-H, 5-H), 6.75 (br s, 4 H_{arom}, 2 × 4-$NO_2C_6H_4$, 2-H, 6-H), 4.69 (d, *J* = 8 Hz, 2 H, 7a-H, 8a-H), 3.78 (s, 3 H, OCH_3), 3.52 (d, *J* = 8 Hz, 2 H, 3a-H, 4a-H), 2.05 (s, 3 H, CH_3).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 173.2, 172.0, 168.7, 163.8, 152.3, 141.9, 140.1, 135.7, 131.8, 128.6, 128.0, 125.9, 112.0, 58.6, 52.9, 48.1, 42.3, 41.7, 18.6; one aromatic signal is hidden.

HRMS (ESI, TOF): *m*/*z* [M + H]$^+$ calcd for $C_{34}H_{28}N_7O_{11}$: 710.1841; found: 710.1839.

N-{8-Ethyl-9-methyl-2,6-bis[(3-nitropyridine-2-yl)amino]-1,3,5,7-tetraoxo-1,2,3,3a,4,4a,5,6,7,7a,8,8a-dodecahydro-4,8-ethenopyrrolo[3,4-*f*]isoindol-4-yl}benzamide (5g)

Yield: 0.444 g (65%); yellow solid; mp >330 °C (dec.) (*i*-BuOH).

IR (neat): 3365, 3247, 2969, 2955, 1782, 1723, 1665, 1602, 1539, 1483 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.16 (br s, 2 H, 2 × NH), 8.76 (s, 1 H, CONH), 8.54 (dd, J_1 = 8 Hz, J_2 = 2 Hz, 2 H, 2 × Py, 4-H), 8.44 (dd, J_1 = 5 Hz, J_2 = 2 Hz, 2 H, 2 × Py, 6-H), 7.85 (m, 2 H_{arom}, C_6H_5, 2-H, 6-H), 7.49 (m, 3 H_{arom}, C_6H_5, 3-H, 4-H, 5-H), 7.08 (dd, J_1 = 8 Hz, J_2 = 5 Hz, 2 H, 2 × Py, 5-H), 6.31 (s, 1 H, C=CH), 4.43 (d, *J* = 8 Hz, 2 H, 7a-H, 8a-H), 3.60 (d, *J* = 8 Hz, 2 H, 3a-H, 4a-H), 2.32 (q, *J* = 7 Hz, 2 H, CH_2), 1.76 (s, 3 H, CH_3), 1.21 (t, *J* = 7 Hz, 3 H, CH_2CH_3).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 173.0, 172.3, 168.8, 155.4, 149.7, 141.5, 136.2, 136.0, 131.4, 129.5, 128.4, 128.2, 125.5, 116.5, 57.8, 45.0, 42.1, 20.9, 19.3, 8.5; one aliphatic signal is hidden.

HRMS (ESI, TOF): *m*/*z* [M + H]$^+$ calcd for $C_{32}H_{28}N_9O_9$: 682.2004; found: 682.1999.

N-{2,6-Bis[(3-nitropyridine-2-yl)amino]-1,3,5,7-tetraoxo-8-(*p*-tolyl)-1,2,3,3a,4,4a,5,6,7,7a,8,8a-dodecahydro-4,8-etheno-pyrrolo[3,4-*f*]isoindol-4-yl}benzamide (5h)

Yield: 0.500 g (69%); brown solid; mp >200 °C (dec.) (*i*-BuOH).

IR (neat): 3349, 3322, 1790, 1731, 1653, 1602, 1573, 1526, 1476 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.06 (br s, 2 H, 2 × NH), 8.99 (s, 1 H, CONH), – 8.49 (m, 4 H), 7.88 (d, *J* = 9 Hz, 2 H), 7.76 (d, *J* = 8 Hz, 1 H), 7.52 (m, 3 H), 7.33 (d, *J* = 8 Hz, 1 H), 7.23 (d, *J* = 8 Hz, 1 H), 7.07 (m, 3 H), 6.94 (dd, J_1 = 8 Hz, J_2 = 4 Hz, 1 H), 6.80 (m, 1 H): (CH=CH, C_6H_5, 4-MeC_6H_4, 2 × Py) – 4.65 (d, *J* = 8 Hz, 2 H, 7a-H, 8a-H), 4.06 (d, *J* = 8 Hz, 2 H, 3a-H, 4a-H), 2.31 (s, 3 H, CH_3).

HRMS (ESI, TOF): *m*/*z* [M + H]$^+$ calcd for $C_{36}H_{28}N_9O_9$: 730.2004; found: 730.1995.

N-{2,6-Bis[(5-nitropyridine-2-yl)amino]-1,3,5,7-tetraoxo-8-(*p*-tolyl)-1,2,3,3a,4,4a,5,6,7,7a,8,8a-dodecahydro-4,8-etheno-pyrrolo[3,4-*f*]isoindol-4-yl}benzamide (5i)

Yield: 0.383 g (52%); beige solid; mp >300 °C (dec.) (*i*-BuOH).

IR (neat): 3411, 3308, 1790, 1723, 1653, 1601, 1585, 1507, 1485 cm^{-1}.

^{1}H NMR (300 MHz (59 °C, DMSO-d_6): δ = 10.12 (br s, 2 H, 2 × NH), 8.97 (s, 2 H, 2 × Py, 6-H), 8.82 (s, 1 H, CONH), 8.33 (d, *J* = 9 Hz, 2 H, 2 × Py, 4-H), 7.91 (d, *J* = 7 Hz, 2 H_{arom}, C_6H_5, 2-H, 6-H), 7.76 (d, *J* = 8 Hz, 1 H_{arom}, 4-MeC_6H_4), 7.52 (m, 3 H_{arom}, C_6H_5, 3-H, 4-H, 5-H), 7.36 (d, *J* = 8 Hz, 1 H_{arom}, 4-MeC_6H_4), 7.25 (d, *J* = 8 Hz, 1 H_{arom}, 4-MeC_6H_4), 7.11 (br s, 2 H, CH=CH, 4-MeC_6H_4), 6.89 (d, *J* = 9 Hz, 1 H, CH=CH), 6.74 (d, *J* = 9 Hz, 2 H, 2 × Py, 3-H), 4.72 (d, *J* = 8 Hz, 2 H, 7a-H, 8a-H), 4.07 (d, *J* = 8 Hz, 2 H, 3a-H, 4a-H), 2.32 (s, 3 H, CH_3).

^{13}C NMR (75.5 MHz (59 °C, DMSO-d_6): δ = 171.8, 171.7, 168.9, 160.2, 145.9, 138.3, 136.2, 136.0, 135.4, 133.8, 132.9, 131.5, 131.1, 129.3, 128.5, 128.1, 127.9, 107.0, 58.7, 48.0, 46.3, 43.0, 21.0.

HRMS (ESI, TOF): *m*/*z* [M + H]$^+$ calcd for $C_{36}H_{28}N_9O_9$: 730.2004; found: 730.2004.

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Supporting Information

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