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BICYCLO[2.2.2]OCT-7-ENE DERIVATIVES: A GREEN PREPARATION OF THE FUSED SUCCINIMIDE RING[#]

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Abstract – The reaction of differently substituted bicyclo[2.2.2]oct-7-ene-2*exo*,3*exo*,5*exo*,6*exo*-tetracarboxylic acid 2,3:5,6-dianhydrides (**1a**–**g** and **4**) with various hydrazines was investigated. The starting **1a**–**g** were transformed in an aqueous solution under microwave irradiation conditions to the corresponding fused *N*-aminosuccinimides with high yields. The derivative (**4**) also reacted at the additional carbonyl moiety to give **5a**–**c** as the sole products.

INTRODUCTION

Bicyclo[2.2.2]octenes and their fused derivatives have been shown to serve as useful building blocks in organic syntheses.[1] Among them, bicyclo[2.2.2]oct-7-enes (bicyclo[2.2.2]oct-2-enes when unsubstituted) containing a free or protected amino group at the bridgehead carbon atom are very rare compounds[2a] and can be found in the skeleton of naturally occurring *Kopsia* alkaloids.[2b] During our recent investigation of the transformations of the 2*H*-pyran-2-ones and fused pyran-2-ones[3–4] we synthesized a series of aminobicyclo[2.2.2]oct-7-enes bearing fused heterocyclic rings in their structure, such as a fused maleic anhydride moiety[4a] or a fused substituted succinimide moiety.[4b,c] The transformation of the bicyclo[2.2.2]oct-7-ene-2*exo*,3*exo*,5*exo*,6*exo*-tetracarboxylic acid 2,3:5,6-dianhydrides (**1**)[4a] with hydrazine derivatives resulted in the preparation of the corresponding fused succinimides.[5] Though the derivatives (**1**) possess in their structure various functionalities (a double-bond C=C, a substituted amino group, two fused succinic anhydride units and a heterocyclic moiety) and, therefore, might serve as multifunctional building blocks in the synthesis, they were very selectively transformed to the corresponding fused imides. The anhydrides are known to react with amines and hydrazines producing the corresponding amides and imides,[6] but prior to our investigation[5] there was only a single previous report utilizing a fused bicyclo[2.2.2]octene system (but not containing an amino group at the bridgehead carbon

[#] Dedicated to Professor Yoshito Kishi on the occasion of his 70th birthday.

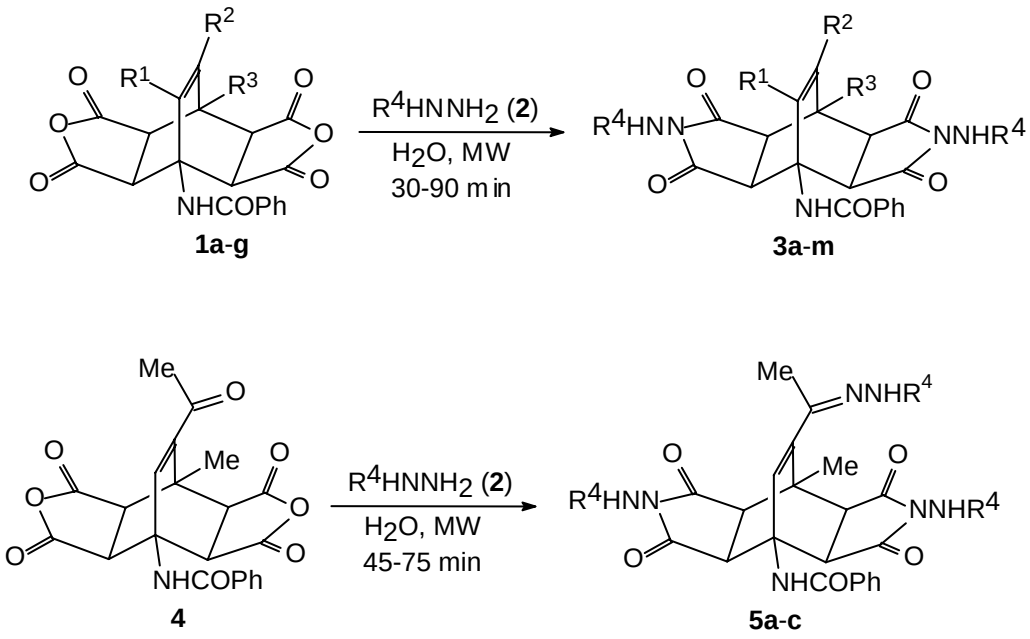
atom) in a reaction with hydrazine hydrate and phenylhydrazine in an ethanolic solution.[7] Two products were prepared in this investigation, but no details about the reaction times were given. Therefore, we decided to extend our study to look at different substrates and hydrazines and to investigate the scope and limitations of this method.

RESULTS AND DISCUSSION

Here we report on the transformations of a series of prochiral derivatives of bicyclo[2.2.2]oct-7-enes (**1a**−**g**) and a related keto moiety containing derivative (**4**) with a wider variety of hydrazines (**2**) (hydrazine hydrate, aryl- and heteroarylhydrazines) toward the corresponding fused succinimides (**3a**−**m**) and their hydrazono-substituted derivatives (**5a**−**c**) (Scheme 1, Table 1). We again applied a green concept to the reaction conditions,[4c,5,8,9] by using water as the reaction medium and microwaves (MWs) as the source of heating. The initial experiment with **1a** and hydrazine hydrate (1.2 mmol of hydrazine hydrate / 0.5 mmol of **1a**) was conducted at 100 °C, and the ^{1}H NMR analysis of the crude product obtained after 50 min of irradiation with MWs showed a relatively large conversion (above 90%), but some remaining starting **1a** could still be detected. Therefore, we decided to increase the reaction temperature to 150 °C, and in this case the reaction was finished after 40 min (Table 1, Run 1). A similar experiment with **1d** (at 100 °C) showed an approximately 90% conversion after 1 h; however, with the increased temperature (150 °C) the reaction was finished after 55 min (Run 4). The same reaction temperature was then applied to the synthesis of a set of products (**3a**−**e**) obtained from **1a**−**e** with hydrazine hydrate. The reaction times needed for the complete conversion of the substrates were between 30 and 55 min and the yields of the isolated products (**3**) were high (83−91%). The generally lower yields obtained in the reactions with hydrazine hydrate might be attributed to the slightly higher solubility of the products (**3a**−**e**) in water in comparison with other products (**3f**−**m**) and also (**5a**−**c**), which were almost completely insoluble in water.

With the conditions firmly established for the reaction with hydrazine hydrate, we decided to perform more transformations with substituted hydrazines. A preliminary experiment with **1c** and phenylhydrazine showed that after 45 min of MW irradiation at 160 °C the conversion leading to the product (**3g**) was again above 90%, but some of the **1c** still remained unreacted. In this case, as the temperature was already relatively high (and close to the maximum value that can be sustained in this MW reactor with water in a closed vessel), we decided to increase the reaction time. Indeed, after 75 min (at 160 °C) the transformation was completed (Run 7). The starting compound (**1e**), containing a cyclohexane ring fused to the bicyclo[2.2.2]octene system, also seemed to be an interesting example for the transformation with hydrazines. After 60 min of MW irradiation of an aqueous mixture of **1e** and phenylhydrazine at 150 °C an approximately 95% conversion was obtained, whereas at 160 °C the reaction was complete after 45 min and

pure **3i** was isolated in a 91% yield (Run 9). A set of products (**3f**−**i**) was obtained with phenylhydrazine after 45−75 min of MW irradiation at 160 °C in very high yields (91−98%) (Runs 6–9).



Scheme 1

Analogous reaction conditions were then applied to the synthesis of the derivatives (**3j**−**m**) that were obtained in the reaction of bicyclo[2.2.2]octenes (**1a**, **1c**, and **1f**, respectively) with 2-pyridylhydrazine, 4-bromophenylhydrazine and 4-flourophenylhydrazine. Though somewhat longer reaction times were needed (75−90 min), the products were isolated in high yields (86−99%) from the reaction mixtures irradiated by the MWs at 160 °C. The indispensability of the longer reaction time was clearly demonstrated in the transformation between **1f** and 2-pyridylhydrazine, where after 60 min at 160 °C the conversion was around 90%, but after 90 min it was complete (Run 10).

We were also curious to check the possible chemoselectivity when reacting different hydrazines with the starting bicyclo[2.2.2]octene derivative (**4**), which besides both maleic anhydride rings also contained an acetyl moiety in its structure. Here we anticipated a higher reactivity of one type of the reactive group in comparison with the other (anhydride *versus* keto group), and thought about the possibility of an eventual chemoselective conversion of the compound (**4**). However, the reaction between **4** and hydrazine hydrate at 100 °C did not stop at the first stage and after 60 min we obtained the product (**5a**) containing the acetyl moiety transformed in the hydrazono form and also containing two fused succinimide rings. The conversion was 90% and the remaining material was unchanged starting **4**. Therefore, it was clearly evident that this reaction, under the applied conditions, could not be undertaken in a chemoselective way. The

complete transformation with different hydrazines produced the corresponding hydrazono compounds (**5a**−**c**) in high yields (87−96%) (Runs 14–16).

Table 1: Reaction times and yields of products under microwave reaction conditions

Run	Starting **1** or **4**				**2**	Prod.	*T* (°C)	*t*/min[a]	Yield (%)[b]
	R^1	R^2	R^3		R^4				
1	H	H	2-furyl	**1a**	H	**3a**	150[c]	40	83
2	H	H	2-thienyl	**1b**	H	**3b**	150[c]	45	88
3	Me	H	Ph	**1c**	H	**3c**	150[c]	30	87
4	Me	H	2-thienyl	**1d**	H	**3d**	150[c]	55	86
5	H	-[CH_2]$_4$-		**1e**	H	**3e**	150[d]	45	91
6	H	H	Ph	**1f**	Ph	**3f**	160[e]	45	98
7	Me	H	Ph	**1c**	Ph	**3g**	160[e]	75	97
8	H	4-MeO-C_6H_4	Me	**1g**	Ph	**3h**	160[f]	75	96
9	H	-[CH_2]$_4$-		**1e**	Ph	**3i**	160[d]	45	91
10	H	H	Ph	**1f**	2-Py	**3j**	160[f]	90	99
11	Me	H	Ph	**1c**	2-Py	**3k**	160[f]	90	86
12	H	H	2-furyl	**1a**	4-Br-C_6H_4	**3l**	160[f]	75	93
13	H	H	2-furyl	**1a**	4-F-C_6H_4	**3m**	160[f]	90	95
14	H	COMe	Me	**4**	H	**5a**	150[c]	60	87
15	H	COMe	Me	**4**	2-Py	**5b**	160[f]	75	95
16	H	COMe	Me	**4**	4-Br-C_6H_4	**5c**	135[c]	45	96

[a] Microwave irradiation in aqueous suspension (1.5 mL) in a pressurized tube with 20% excess of hydrazines. [b] Yield of isolated compounds. [c] Power set to 120 W. [d] Power set to 130 W. [e] Power set to 160 W. [f] Power set to 140 W.

When we applied 4-hydrazinobenzoic acid under the above neutral reaction condition for the transformation of **1f** the reaction did not take place, and after 60 min of MW irradiation at 150 °C only the starting bicyclo[2.2.2]octene was detected by ^{1}H NMR. The same happened in the reaction between acetohydrazide and **1f**; again only starting material was detected.

Some of the hydrazines (*i.e.*, 4-bromophenylhydrazine and 4-fluorophenylhydrazine) are commercially available in the form of their hydrochloride salts, from which free hydrazines can be obtained with neutralization by Na_2CO_3 and subsequent extraction. However, we thought that this step might be incorporated together with the reaction with hydrazines into a single one-pot operation. To verify this

assumption we added an equimolar amount of Na_2CO_3 to the aqueous mixture of bicyclo[2.2.2]octene (**1a**) and 4-bromophenylhydrazine hydrochloride in water and stirred for 5 min at room temperature followed by irradiation with MWs as before (Run 12). Though the ^{1}H NMR spectrum of the crude product (**3l**) did not exhibit any remaining **1a** (and practically no other impurities), the yield in this case was significantly lower (around 60%). A possible explanation for this might be that under basic conditions and MW irradiation some of the starting compound is destroyed into the side product(s) that is (are) more soluble in water than **3l**. A similar result was also obtained with a smaller quantity (half molar amount) of Na_2CO_3 or when an equimolar amount of K_2CO_3 was used. An analogous reduction of the yield (to around 45%) was also observed when 4-fluorophenylhydrazine hydrochloride reacted with **1a**.

To further explore these transformations, we performed a comparison of the results for the reaction under conventional thermal reaction conditions (reflux in water) and those obtained with MW irradiation. For the reaction between the acetyl-substituted starting compound (**4**) and 2-pyridylhydrazine in water after 1 h of reflux the conversion was around 83%, whereas the same reaction with MW irradiation (at 160 °C) was nearly finished (conversion above 95%).

In conclusion, we have demonstrated that the presented method could be successfully applied to the transformation of the fused anhydride moiety (and also a carbonyl group) with hydrazine and its derivatives in a variety of bicyclo[2.2.2]octenes containing a benzoylamino group at the bridgehead carbon and different additional substituents (methyl, phenyl, 2-furyl, 2-thienyl, 4-methoxyphenyl and acetyl) or even an additional fused cyclohexane ring. The use of water as the solvent and MWs as the energy source renders this synthesis eco-friendly and concomitantly simplifies the isolation giving the products (**3a**−**m**) and (**5a**−**c**) in very high yields. It has also been shown that it is better to carry out the reaction with isolated free hydrazines instead of their preparation *in situ* from hydrochloric salts and the appropriate amount of a base.

EXPERIMENTAL

Melting points were determined on a Kofler micro hot stage, and are uncorrected. ^{1}H NMR spectra were recorded with a Bruker Avance DPX 300 spectrometer at 29 °C (unless otherwise stated) and 300 MHz using TMS as an internal standard. ^{13}C NMR spectra were recorded on the same instrument at 75.5 MHz and are referenced against the central line of the solvent signal (DMSO-d_6 septet at δ = 39.5 ppm). The coupling constants (*J*) are given in Hz. IR spectra were obtained with a Bio-Rad FTS 3000MX (KBr pellets for all products). MS spectra were recorded with a VG-Analytical AutoSpec Q (EI and FAB) or Q-TOF Premier instrument (ESI). Elemental analyses (C, H, N) were performed with a Perkin Elmer 2400 Series II CHNS/O Analyzer. TLC was carried out on Fluka silica-gel TLC-cards. The starting compounds (**1** and **4**) were prepared according to the published procedures;[4a] in two cases hydrazines (**2**) (*i.e.*, 4-bromophenylhydrazine and 4-fluorophenylhydrazine) were obtained in the free form from the

commercially available hydrochloride salts by neutralization with Na_2CO_3 and subsequent extraction into CH_2Cl_2; all other reagents and solvents were used as received from commercial suppliers. MW reactions were conducted in air using a focused MW unit (Discover by CEM Corporation, Matthews, NC). The machine consists of a continuous, focused microwave power delivery system with an operator-selectable power output from 0 to 300 W. Reactions were performed in glass vessels (capacity 10 mL) sealed with a septum. The pressure was controlled by a load cell connected to the vessel *via* the septum. The temperature of the contents of the vessel was monitored using a calibrated infrared temperature controller mounted under the reaction vessel. All the mixtures were stirred with a Teflon-coated magnetic stir bar in the vessel. Temperature, pressure and power profiles were recorded using commercially available software provided by the manufacturer of the MW unit.

General procedure for the preparation of 3a–m and 5a–c.

A mixture of the starting fused succinic anhydride derivative (**1** or **4**) (0.5 mmol) and hydrazines (**2**) (1.2 mmol for **1** or 1.8 mmol for **4**) in 1.5 mL of distilled water was irradiated in the focused MW equipment. For the time, temperature and power settings see Table 1. The ramp time was set to 5 min. Thereafter, the reaction mixture was cooled; the precipitated solid was filtered off and washed with distilled water (3−5 mL). For typical temperature, pressure and power profiles, see Figure 1.

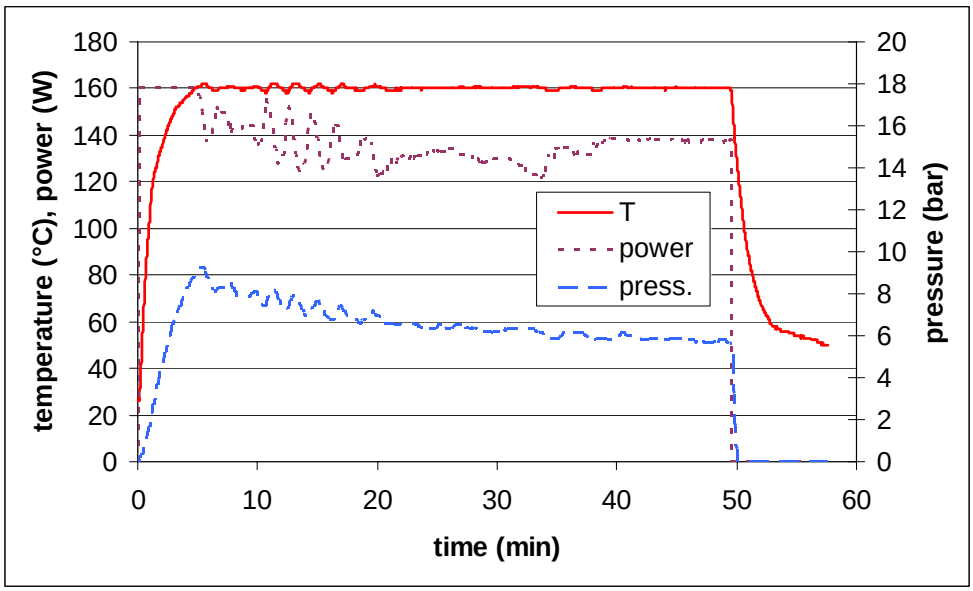
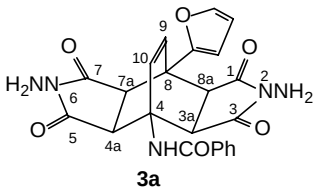


Figure 1. Typical temperature (red), power (violet) and pressure (blue) profiles for the microwave irradiated synthesis of **3f**.

Analytical and spectroscopic data of products:

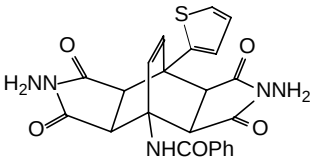
***N*-[2,6-Diamino-8-(2-furyl)-2,3,3a,4a,5,6,7,7a,8,8a-decahydro-1,3,5,7-tetraoxo-4,8-ethenobenzo-**

[1,2-*c*:4,5-*c*′]dipyrrol-4(1*H*)-yl]benzamide (3a): mp 274–276 °C (EtOH); IR (KBr) ν_{max}/cm^{-1}: 1774, 1713, 1694, 1653, 1539; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.59 (d, J = 8.3 Hz, 2H, 7a-H, 8a-H), 4.38 (d, J = 8.3 Hz, 2H, 3a-H, 4a-H), 4.85 (s, 4H, 2 × NH_2), 6.47 (m, 4H), 7.54 (m, 3H), 7.68 (m, 1H), 7.91 (m, 2H) (Ph, 9-H, 10-H, 3′-H, 4′-H, 5′-H), 8.78 (s, 1H, NH); ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 41.6, 42.5, 46.0, 58.0, 107.7, 110.3, 127.6, 128.0, 129.0, 131.0, 132.1, 135.6, 142.1, 151.7, 167.9, 171.4, 171.7; MS (*m/z*, %) 461 (M^+, 3), 105 (100). *Anal.* Calcd for $C_{23}H_{19}N_5O_6$: C, 59.87; H, 4.15; N, 15.18. Found: C, 59.81; H, 4.26; N, 15.11.



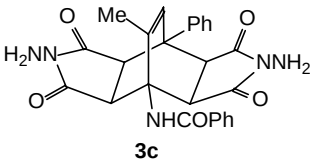
3a

***N*-[2,6-Diamino-2,3,3a,4a,5,6,7,7a,8,8a-decahydro-1,3,5,7-tetraoxo-8-(2-thienyl)- 4,8-ethenobenzo-[1,2-*c*:4,5-*c*′]dipyrrol-4(1*H*)-yl]benzamide (3b):** mp 297–298 °C (EtOH); IR (KBr) ν_{max}/cm^{-1}: 1775, 1713, 1692, 1635, 1532; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.61 (d, J = 8.1 Hz, 2H, 7a-H, 8a-H), 4.38 (d, J = 8.1 Hz, 2H, 3a-H, 4a-H), 4.81 (s, 4H, 2 × NH_2), 6.55 (m, 2H), 7.03 (m, 1H), 7.18 (m, 1H), 7.54 (m, 4H), 7.91 (m, 2H) (Ph, 9-H, 10-H, 3′-H, 4′-H, 5′-H), 8.78 (s, 1H, NH); ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 42.1, 44.2, 49.1, 58.0, 125.3, 127.7, 128.0, 130.6, 131.0, 131.9, 135.6, 143.8, 168.0, 171.43, 171.48 (2 signals are hidden); MS (*m/z*, %) 477 (M^+, 2), 105 (100). *Anal.* Calcd for $C_{23}H_{19}N_5O_5S$: C, 57.85; H, 4.01; N, 14.67. Found: C, 57.64; H, 4.06; N, 14.87.



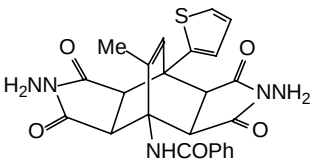
3b

***N*-[2,6-Diamino-2,3,3a,4a,5,6,7,7a,8,8a-decahydro-10-methyl-1,3,5,7-tetraoxo-8-phenyl-4,8-etheno-benzo[1,2-*c*:4,5-*c*′]dipyrrol-4(1*H*)-yl]benzamide (3c):** mp 244–246 °C (EtOH); IR (KBr) ν_{max}/cm^{-1}: 1774, 1711, 1637, 1528; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.93 (s, 3H, Me), 3.73 (d, J = 8.0 Hz, 2H, 7a-H, 8a-H), 4.44 (d, J = 8.0 Hz, 2H, 3a-H, 4a-H), 4.79 (s, 4H, 2 × NH_2), 6.49 (s, 1H, 9-H), 7.34 (m, 4H), 7.58 (m, 3H), 7.80 (m, 1H), 7.88 (m, 2H) (2 × Ph), 7.47 (s, 1H, NH); ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 18.1, 41.8, 45.8, 47.3, 59.7, 123.1, 126.3, 127.2, 127.5, 127.6, 127.9, 128.3, 131.3, 135.6, 138.1, 138.6, 168.0, 171.93, 171.98 (For 8-Ph 5 signals were observed.); MS-FAB (*m/z*, %) 486 (MH^+, 49), 105 (100). *Anal.* Calcd for $C_{26}H_{23}N_5O_5 \times ¼\ H_2O$: C, 63.73; H, 4.83; N, 14.29. Found: C, 63.49; H, 4.79; N, 14.07.



3c

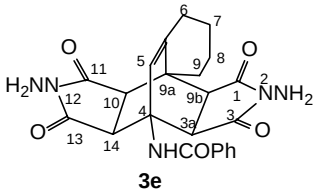
***N*-[2,6-Diamino-2,3,3a,4a,5,6,7,7a,8,8a-decahydro-10-methyl-1,3,5,7-tetraoxo-8-(2-thienyl)-4,8-ethenobenzo[1,2-*c*:4,5-*c*′]dipyrrol-4(1*H*)-yl]benzamide (3d)**: mp 287–290 °C (EtOH); IR (KBr) ν_{max}/cm^{-1}: 1771, 1703, 1601, 1526; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.91 (br d, J = 1.1 Hz, 3H, Me), 3.58 (br, 2H, 7a-H, 8a-H), 4.46 (d, J = 8.1 Hz, 2H, 3a-H, 4a-H), 4.82 (s, 4H, 2 × NH_2), 6.24 (m, 1H), 7.02 (m, 1H), 7.47 (br s, 1H), 7.57 (m, 5H), 7.87 (m, 2H) (Ph, NH, 9-H, 3′-H, 4′-H, 5′-H); ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 17.9, 41.9, 44.3, 49.1, 59.6, 124.2, 125.1, 127.7, 128.3, 131.3, 135.5, 138.5, 143.7, 168.0,



3d

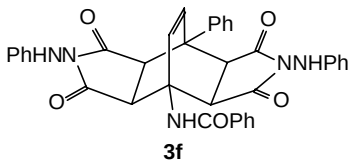
171.4, 171.8 (2 signals are hidden); MS (*m/z*, %) 491 (M^+, 4), 105 (100). *Anal.* Calcd for $C_{24}H_{21}N_5O_5S$: C, 58.65; H, 4.31; N, 14.25. Found: C, 58.55; H, 4.48; N, 14.33.

***N*-[2,12-Diamino-2,3,3a,6,7,8,9,9b,11,12,13,14-dodecahydro-1,3,11,13-tetraoxo-10*H*-4,9a[3′,4′]-*endo*-pyrrolo-9a*H*-benz[*e*]isoindol-4(1*H*)-yl]benzamide (3e):** mp 258–261 °C (EtOH); IR (KBr) ν_{max}/cm^{-1}: 1771, 1711, 1632, 1551; ^1H NMR (300 MHz, DMSO-d_6): δ1.32 (m, 2H, CH_2), 1.60 (m, 2H, CH_2), 2.09 (m, 2H, CH_2), 2.63 (m, 2H, CH_2), 3.03 (d, J = 7.9 Hz, 2H, 9b-H, 10-H), 4.14 (d, J = 7.9 Hz, 2H, 3a-H, 14-H), 4.91 (s, 4H, 2 × NH_2), 5.99 (s, 1H, 5-H), 7.52 (m, 3H, Ph), 7.88 (m, 2H, Ph), 8.55 (s, 1H, NH); ^{13}C NMR (75.5 MHz, DMSO-d_6): δ20.9, 22.6, 26.5, 28.7, 40.4, 42.1, 47.3, 57.4, 123.2, 127.6, 127.9, 130.8, 135.8, 140.7, 167.8, 172.0, 173.9; MS (*m/z*, %) 449 (M^+, 4), 105 (100). *Anal.* Calcd for $C_{23}H_{23}N_5O_5$ × EtOH: C, 60.60; H, 5.90; N, 14.13. Found: C, 60.52; H, 5.91; N, 14.22.



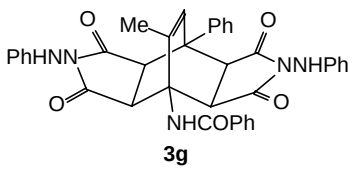
3e

***N*-[2,3,3a,4a,5,6,7,7a,8,8a-Decahydro-1,3,5,7-tetraoxo-8-phenyl-2,6-bis(phenylamino)-4,8-etheno-benzo[1,2-*c*:4,5-*c*']dipyrrol-4(1*H*)-yl]benzamide (3f):** mp 277–280 °C (AcOEt); IR (KBr) ν_{max}/cm^{-1}: 3333, 1780, 1720, 1659, 1602, 1542, 1469; ^1H NMR (300 MHz, DMSO-d_6): δ4.01 (d, J = 8.4 Hz, 2H, 7a-H, 8a-H), 4.64 (d, J = 8.4 Hz, 2H, 3a-H, 4a-H), 6.59 (m, 4H), 6.77 (m, 2H), 6.90 (m, 1H), 7.15 (m, 5H), 7.25 (m, 2H), 7.46 (m, 5H), 7.87 (m, 3H) (4 × Ph, 9-H, 10-H), 8.23 (s, 2H, 2 × NH), 8.97 (s, 1H, NH); ^{13}C NMR (75.5 MHz, DMSO-d_6): δ42.3, 45.9, 47.5, 58.3, 112.6, 119.7, 126.6, 127.4, 127.5, 127.7, 128.1, 128.9, 130.6, 131.1, 132.8, 135.7, 138.1, 146.1, 168.4, 172.5, 172.7; MS-FAB (*m/z*, %) 624 (MH^+, 36), 105 (97), 71 (100). *Anal.* Calcd for $C_{37}H_{29}N_5O_5 \times H_2O$: C, 69.26; H, 4.87; N, 10.91. Found: C, 69.34; H, 5.00; N, 10.83.



3f

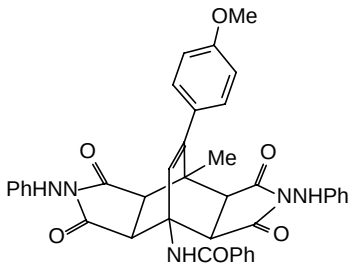
***N*-[2,3,3a,4a,5,6,7,7a,8,8a-Decahydro-10-methyl-1,3,5,7-tetraoxo-8-phenyl-2,6-bis(phenylamino)-4,8-ethenobenzo[1,2-*c*:4,5-*c*']dipyrrol-4(1*H*)-yl]benzamide (3g):** mp 336–339 °C (EtOH); IR (KBr) ν_{max}/cm^{-1}: 3347, 1786, 1732, 1655, 1601, 1528, 1493; ^1H NMR (300 MHz, DMSO-d_6): δ2.10 (s, 3H, Me), 4.01 (d, J = 7.8 Hz, 2H, 7a-H, 8a-H), 4.71 (d, J = 7.8 Hz, 2H, 3a-H, 4a-H), 6.56 (m, 4H, Ph), 6.78 (m, 2H, Ph), 6.97 (s, 1H, 9-H), 7.16 (m, 4H, Ph), 7.26 (m, 2H, Ph), 7.48 (m, 5H, Ph), 7.70 (s, 1H, NH), 7.84 (m, 3H, Ph) 8.19 (s, 2H, 2 × NH); ^{13}C NMR (75.5 MHz, DMSO-d_6, 59 °C): δ18.4, 41.9, 45.8, 47.2, 59.7, 112.3, 119.6, 124.6, 126.3, 127.1, 127.3, 127.7, 128.0, 128.6, 131.1, 135.3, 137.9, 139.3, 145.9, 168.1, 172.2, 172.3; MS-FAB (*m/z*, %) 638 (MH^+, 1), 71 (100). *Anal.* Calcd for $C_{38}H_{31}N_5O_5$: C, 71.57; H, 4.90; N, 10.98. Found: C, 71.66; H, 5.15; N, 10.64.



3g

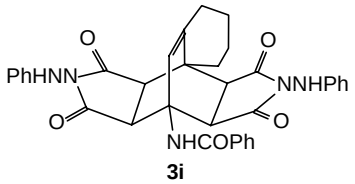
***N*-[2,3,3a,4a,5,6,7,7a,8,8a-Decahydro-9-(4-methoxyphenyl)-8-methyl-1,3,5,7-tetraoxo-2,6-bis(phenyl amino)-4,8-ethenobenzo[1,2-*c*:4,5-*c*']dipyrrol-4(1*H*)-yl]benzamide (3h):** mp 328–331 °C (MeOH); IR (KBr) ν_{max}/cm^{-1}: 3343, 1776, 1720, 1634, 1603, 1510; ^1H NMR (300 MHz, DMSO-d_6): δ1.83 (s, 3H, Me), 3.44 (d, J = 8.4 Hz, 2H, 7a-H, 8a-H), 3.74 (s, 3H, OMe), 4.59 (d, J = 8.4 Hz, 2H, 3a-H, 4a-H), 6.52 (s, 1H,

10-H), 6.63 (m, 4H), 6.74 (m, 2H), 6.84 (m, 2H), 7.00 (m, 6H), 7.49 (m, 3H), 7.88 (2H, m) (3 × Ph, C_6H_4), 8.45 (s, 2H, 2 × NH), 8.77 (s, 1H, NH); ^{13}C NMR (75.5 MHz, DMSO-d_6): δ18.9, 42.2, 42.4, 47.6, 55.1, 58.2, 112.7, 113.5, 119.8, 127.61, 127.66, 128.0, 128.7, 129.2, 129.5, 131.0, 135.8, 145.7, 145.9, 158.9, 168.3, 172.7, 174.4; MS-ESI (*m/z*, %) 690 (MNa^+, 89), 668 (MH^+, 100), 353 (18). HRMS Calcd for $C_{39}H_{34}N_5O_6$ (MH^+): 668.2509. Found: 668.2526. *Anal.* Calcd for $C_{39}H_{33}N_5O_6 \times$ MeOH: C, 68.66; H, 5.33; N, 10.01. Found: C, 68.87; H, 4.97; N, 9.82.



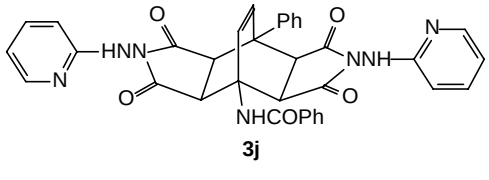
3h

***N*-[2,3,3a,6,7,8,9,9b,11,12,13,14-Dodecahydro-1,3,11,13-tetraoxo-2,12-bis(phenylamino)-10*H*-4,9a-[3′,4′]-*endo*-pyrrolo-9a*H*-benz[*e*]isoindol-4(1*H*)-yl]benzamide (3i):** mp 277–280 °C (MeOH); IR (KBr) ν_{max}/cm^{-1}: 3412, 1779, 1720, 1647, 1603, 1535, 1495; ^{1}H NMR (300 MHz, DMSO-d_6): δ1.28 (m, 2H, CH_2), 1.56 (m, 2H, CH_2), 2.30 (m, 2H, CH_2), 2.67 (m, 2H, CH_2), 3.31 (d, J = 8.1 Hz, 2H, 9b-H, 10-H), 4.42 (d, J = 8.1 Hz, 2H, 3a-H, 14-H), 6.37 (s, 1H, 5-H), 6.62 (m, 4H), 6.79 (m, 2H), 7.17 (m, 4H), 7.47 (m, 3H), 7.84 (m, 2H) (3 × Ph), 8.33 (s, 2H, 2 × NH), 8.75 (s, 1H, NH); ^{13}C NMR (75.5 MHz, DMSO-d_6): δ20.6, 22.6, 26.3, 29.3, 40.5, 42.2. 47.6, 57.4, 112.3, 119.7, 124.7, 127.6, 127.9, 128.7, 130.9, 135.8, 141.7, 146.1, 168.1, 172.6, 174.7; MS-ESI (*m/z*, %) 624 (MNa^+, 100), 602 (MH^+, 44). HRMS Calcd for $C_{35}H_{32}N_5O_5$ (MH^+): 602.2403. Found: 602.2415.



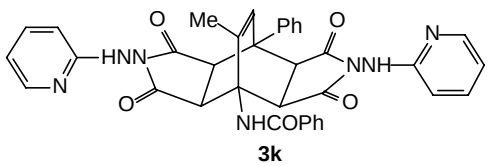
3i

***N*-[2,3,3a,4a,5,6,7,7a,8,8a-Decahydro-1,3,5,7-tetraoxo-8-phenyl-2,6-bis(2-pyridylamino)-4,8-ethenobenzo[1,2-*c*:4,5-*c*']dipyrrol-4(1*H*)-yl]benzamide (3j):** mp 306–307 °C (MeOH); IR (KBr) ν_{max}/cm^{-1}: 3293, 1758, 1724, 1642, 1605, 1555; ^{1}H NMR (300 MHz, DMSO-d_6): δ4.06 (d, J = 8.4 Hz, 2H, 7a-H, 8a-H), 4.63 (d, J = 8.4 Hz, 2H, 3a-H, 4a-H), 6.55 (m, 2H), 6.76 (m, 2H), 6.83 (m, 1H), 7.09 (m, 1H), 7.26 (m, 2H), 7.51 (m, 7H), 7.89 (m, 3H), 8.02 (m, 2H) (2 × Ph, 2 × Py, 9-H, 10-H), 8.96 (br s, 3H, 3 × NH); ^{13}C NMR (75.5 MHz, DMSO-d_6, 59 °C): δ42.0, 45.7, 47.1, 58.0, 107.0, 115.4, 126.3, 127.0, 127.3, 127.4, 127.7, 129.9, 130.7, 132.1, 135.5, 137.3, 137.9, 147.2, 156.1, 168.1, 171.8, 172.0; MS-FAB (*m/z*, %) 626 (MH^+, 44), 71 (100). *Anal.* Calcd for $C_{35}H_{27}N_7O_5$: C, 67.19; H, 4.35; N, 15.67. Found: C, 66.92; H, 4.32; N, 15.44.



3j

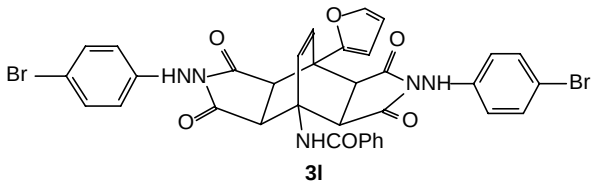
***N*-[2,3,3a,4a,5,6,7,7a,8,8a-Decahydro-10-methyl-1,3,5,7-tetraoxo-8-phenyl-2,6-bis(2-pyridylamino)-4,8-ethenobenzo[1,2-*c*:4,5-*c*']dipyrrol-4(1*H*)-yl]benzamide (3k):** mp 322–324 °C (AcOEt); IR (KBr) ν_{max}/cm^{-1}: 3349, 1784, 1728, 1639, 1599, 1530; ^{1}H NMR (300 MHz, DMSO-d_6): δ2.12 (s, 3H, Me), 4.03 (d, J = 8.4 Hz, 2H, 7a-H, 8a-H), 4.71 (d, J = 8.4 Hz, 2H, 3a-H, 4a-H), 6.56 (m, 2H), 6.78 (m, 3H), 7.26 (m, 2H), 7.43 (m, 2H), 7.55 (m, 6H), 7.86 (m, 3H),



3k

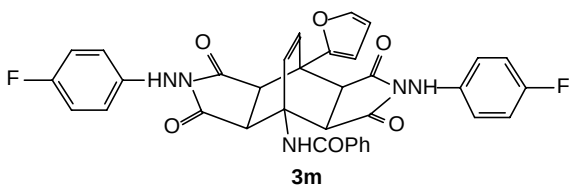
8.05 (m, 2H) (2 × Ph, 2 × Py, 9-H, NH), 8.95 (s, 2H, 2 × NH); ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 18.9, 42.0, 45.8, 47.3, 59.8, 107.1, 115.7, 124.3, 126.5, 127.3, 127.4, 127.5, 127.7, 128.0, 128.2, 131.4, 135.5, 137.7, 138.4, 138.7, 147.5, 156.3, 168.3, 172.4, 172.5 (For 8-Ph 6 signals were observed.); MS-FAB (*m/z*, %) 638 ((M−H)$^+$, 1), 71 (100). *Anal.* Calcd for $C_{36}H_{29}N_7O_5 \times$ ¾ AcOEt: C, 66.37; H, 5.00; N, 13.89. Found: C, 66.76; H, 4.78; N, 13.84.

***N*-[2,6-Bis(4-bromophenylamino)-8-(2-furyl)-2,3,3a,4a,5,6,7,7a,8,8a-decahydro-1,3,5,7-tetraoxo-4,8-ethenobenzo[1,2-*c*:4,5-*c*']dipyrrol-4(1*H*)-yl]benzamide (3l):** mp 315–318 °C (MeOH); IR (KBr) ν_{max}/cm^{-1}: 3442, 1790, 1732, 1648, 1596, 1528, 1490; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.84 (d, J = 8.4 Hz, 2H, 7a-H, 8a-H), 4.64 (d, J = 8.4 Hz, 2H, 3a-H, 4a-H), 6.41 (m, 1H, 1H of furyl), 6.48 (m, 1H, 1H of furyl), 6.59 and 7.32 (AA'XX', J = 8.5 Hz, 8H, 2 × C_6H_4Br), 6.84 (s, 2H, 9-H, 10-H), 7.50 (m, 3H, Ph), 7.68 (m, 1H, 1H of furyl), 7.86 (m, 2H, Ph), 8.50 (s, 2H, 2 × NH), 8.93 (s, 1H, NH); ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 41.9, 42.6, 46.3, 58.0, 108.1, 110.4, 110.8, 114.7, 127.6, 128.0, 130.2, 131.1, 131.4, 133.3, 135.5, 142.3, 145.5, 151.1, 168.2, 171.8, 172.3; MS-ESI (*m/z*, %) 794 (MNa$^+$, 37), 298 (100). *Anal.* Calcd for $C_{35}H_{25}N_5O_6Br_2$: C, 54.49; H, 3.27; N, 9.08. Found: C, 54.36; H, 3.34; N, 9.03.



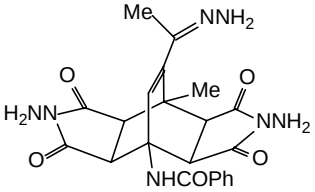
3l

***N*-[2,6-Bis(4-fluorophenylamino)-8-(2-furyl)-2,3,3a,4a,5,6,7,7a,8,8a-decahydro-1,3,5,7-tetraoxo-4,8-ethenobenzo[1,2-*c*:4,5-*c*']dipyrrol-4(1*H*)-yl]benzamide (3m):** mp 305–306 °C (MeOH); IR (KBr) ν_{max}/cm^{-1}: 3419, 1782, 1728, 1667, 1544, 1508; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.83 (d, J = 8.4 Hz, 2H, 7a-H, 8a-H), 4.63 (d, J = 8.4 Hz, 2H, 3a-H, 4a-H), 6.42 (m, 1H, 1H of furyl), 6.49 (m, 1H, 1H of furyl), 6.63 (m, 4H, 2 × C_6H_4F), 6.82 (s, 2H, 9-H, 10-H), 7.00 (m, 4H, 2 × C_6H_4F), 7.50 (m, 3H, Ph), 7.68 (m, 1H, 1H of furyl), 7.87 (m, 2H, Ph), 8.29 (s, 2H, 2 × NH), 8.93 (s, 1H, NH); ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 41.9, 42.6, 46.2, 58.0, 108.1, 110.4, 114.0 (d, J = 7.7 Hz), 115.3 (d, J = 22.6 Hz), 127.6, 128.0, 130.1, 131.1, 133.1, 135.6, 142.3, 142.5 (d, J = 1.7 Hz), 153.0 (d, J = 274.6 Hz), 157.9, 168.2, 172.0, 172.4; MS-ESI (*m/z*, %) 672 (MNa$^+$, 100), 650 (MH$^+$, 26). *Anal.* Calcd for $C_{35}H_{25}N_5O_6F_2 \times H_2O$: C, 62.97; H, 4.08; N, 10.49. Found: C, 63.22; H, 3.88; N, 10.62.



3m

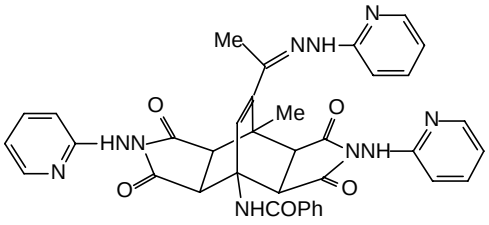
***N*-[2,6-Diamino-9-ethanehydrazonoyl-2,3,3a,4a,5,6,7,7a,8,8a-decahydro-8-methyl-1,3,5,7-tetraoxo-4,8-ethenobenzo[1,2-*c*:4,5-*c'*]dipyrrol-4(1*H*)-yl]benzamide (5a):** mp 271–275 °C (EtOH/H_2O); IR (KBr) ν_{max}/cm^{-1}: 1771, 1713, 1644, 1629, 1568; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.57 (s, 3H, Me), 1.89 (s, 3H, Me), 2.98 (d, J = 8.1 Hz, 2H, 7a-H, 8a-H), 4.18 (d, J = 8.1 Hz, 2H, 3a-H, 4a-H), 4.84 (s, 4H, 2 ×



5a

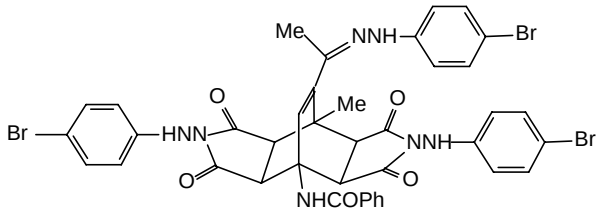
NH_2), 6.13 (s, 2H, NH_2), 6.23 (s, 1H, 10-H), 7.52 (m, 3H, Ph), 7.90 (m, 2H, Ph), 8.61 (s, 1H, NH); ^{13}C NMR (75.5 MHz, DMSO-d_6): δ13.2, 19.7, 41.6, 42.4, 47.7, 57.7, 125.9, 127.6, 128.0, 131.0, 135.7, 141.1, 143.5, 167.8, 171.9, 173.0; MS (*m/z*, %) 465 (M^+, 0.3), 69 (100). HRMS Calcd for $C_{22}H_{23}N_7O_5$: 465.1760. Found: 465.1772. *Anal.* Calcd for $C_{22}H_{23}N_7O_5 \times 2\ H_2O$: C, 52.69; H, 5.43; N, 19.55. Found: C, 52.88; H, 5.67; N, 19.56.

***N*-[2,3,3a,4a,5,6,7,7a,8,8a-Decahydro-8-methyl-1,3,5,7-tetraoxo-2,6-bis(2-pyridylamino)-9-(*N*-(2-pyridyl)ethanehydrazonoyl)-4,8-ethenobenzo[1,2-*c*:4,5-*c*']dipyrrol-4(1*H*)-yl]benzamide (5b):** mp 258–262 °C (MeOH); IR (KBr) ν_{max}/cm^{-1}: 3270, 1782, 1732, 1646, 1602, 1579; ^{1}H NMR (300 MHz, DMSO-d_6): δ2.08 (s, 3H, Me), 2.19 (s, 3H, Me), 3.39 (d, J = 8.4 Hz, 2H, 7a-H, 8a-H), 4.50 (d, J = 8.4 Hz, 2H, 3a-H, 4a-H), 6.52 (m, 2H), 6.75 (m, 4H), 7.09 (m, 1H), 7.49 (m, 6H), 7.88 (m, 2H), 8.00 (m, 2H), 8.14 (m, 1H), 8.82 (s, 1H), 9.03 (br s, 2H), 9.64 (s, 1H) (Ph, 3 × Py, 4 × NH, 10-H); ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 13.8, 21.1, 41.7, 42.5, 47.9, 57.9, 107.1, 107.3, 115.3, 115.6, 127.6, 128.0, 128.8, 131.1, 135.5, 137.5, 137.9, 142.1, 142.3, 147.3, 147.4, 156.4, 157.5, 168.1, 172.3, 173.5; MS-ESI (*m/z*, %) 697 (MH^+, 100), 593 (92). *Anal.* Calcd for $C_{37}H_{32}N_{10}O_5 \times 2\ H_2O$: C, 60.65; H, 4.95; N, 19.12. Found: C, 60.93; H, 4.95; N, 18.98.



5b

***N*-[2,6-Bis(4-bromophenylamino)-9-(*N*-(4-bromophenyl)ethanehydrazonoyl)-2,3,3a,4a,5,6,7,7a,8,8a-decahydro-8-methyl-1,3,5,7-tetraoxo-4,8-ethenobenzo[1,2-*c*:4,5-*c*']dipyrrol-4(1*H*)-yl]benzamide (5c):** mp 195−197 °C (EtOH/H_2O); IR (KBr) ν_{max}/cm^{-1}: 3424, 1781, 1724, 1650, 1594, 1488; ^{1}H NMR (300 MHz, DMSO-d_6): δ1.98 (s, 3H, Me), 2.21 (s, 3H, Me), 3.34 (d, J = 8.4 Hz, 2H, 7a-H, 8a-H), 4.46 (d, J = 8.4 Hz, 2H, 3a-H, 4a-H), 6.49 and 7.21 (AA'XX', J = 8.9 Hz, 8H, 2 × C_6H_4Br), 6.79 (s, 1H, 10-H), 7.05 and 7.33 (AA'XX', J = 8.9 Hz, 4H, C_6H_4Br), 7.50 (m, 3H, Ph), 7.85 (m, 2H, Ph), 8.47 (s, 2H, 2 × NH), 8.73 (s, 1H, NH), 9.35 (s, 1H, NH); ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 13.5, 21.6, 41.8, 42.6, 48.2, 57.8, 110.4, 110.9, 114.7, 115.1, 127.5, 128.1, 131.1, 131.3, 131.5, 135.6, 139.7, 142.4, 144.8, 145.6, 168.0, 172.5, 173.5 (1 signal hidden); MS-ESI (*m/z*, %) 932 (MH^+, 37), 263 (100). HRMS Calcd for $C_{40}H_{33}N_7O_5Br_3$ (MH^+): 928.0093. Found: 928.0106.



5c

ACKNOWLEDGEMENTS

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