Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry. This journal is © The Royal Society of Chemistry 2019

Supporting Information

Synthesis of diphenylamine macrocycles and their antiinflammatory effect

Alejandra Chávez-Riveros, *^a Eduardo Hernández-Vázquez, ^a Antonio Nieto-Camacho, ^a Teresa Ramírez-Apan^a and Luis D. Miranda *^a

^a Instituto de Química Univerisdad Nacional Autónoma de México, Circuito Exterior S.N., Ciudad Universitaria, Coyoacan, Ciudad de México, 04510, México.

Table of Contents

Description	Pg.
Table 1. Data of 12-O-tetradecanoylphorbol acetate induced mouse ear edema. Screening at $1 \mu M$	S1
Table 2. Data of the determination of ID ₅₀ of compounds 5e and 5n.	S2
Table 3. Data of the Myeloperoxidase assay.	S3
Table 4. Data of the Nitrite assay and cell viability.	S4
Table 5. Percentage of cytotoxicity screening of macrocycles 5a-n	S5
Figure 1. 400 MHz ¹ H NMR spectra of <i>tert</i> -butyl (4-(N-(2-(tert-butylamino)-2-oxoethyl)-3-	S6
iodobenzamido)butyl)carbamate (2).	
Figure 2. 100 MHz ¹³ C NMR spectra in CDCl ₃ of <i>tert</i> -butyl (4-(N-(2-(tert-butylamino)-2-oxoethyl)-3-	S7
iodobenzamido)butyl)carbamate (2).	
Figure 3. 300 MHz ¹ H NMR spectra of 3-amino-N-(2-(tert-butylamino)-2-oxoethyl)-N-(4-(N-(2-(tert-	S8
butylamino)-2-oxoethyl)-3-iodobenzamido)butyl)benzamide (4a).	
Figure 4. 75 MHz ¹³ C NMR spectra in CDCl ₃ of 3-amino-N-(2-(tert-butylamino)-2-oxoethyl)-N-(4-(N-	S9
(2-(tert-butylamino)-2-oxoethyl)-3-iodobenzamido)butyl)benzamide (4a).	
Figure 5. 300 MHz ¹ H NMR spectra of 3-amino-N-(2-(tert-butylamino)-2-oxoethyl)-N-(4-(N-(2-	S10
(hexylamino)-2-oxoethyl)-3-iodobenzamido)butyl)benzamide (4b).	
Figure 6. 75 MHz ¹³ C NMR spectra in CDCl ₃ of 3-amino-N-(2-(tert-butylamino)-2-oxoethyl)-N-(4-(N-	S11
(2-(hexylamino)-2-oxoethyl)-3-iodobenzamido)butyl)benzamide (4b).	
Figure 7. 400 MHz ¹ H NMR spectra of 3-amino-N-(2-(tert-butylamino)-2-oxoethyl)-N-(4-(N-(2-	S12
(heptylamino)-2-oxoethyl)-3-iodobenzamido)butyl)benzamide (4c).	
Figure 8. 100 MHz ¹³ C NMR spectra in CDCl ₃ of 3-amino-N-(2-(tert-butylamino)-2-oxoethyl)-N-(4-(N-	S13
(2-(heptylamino)-2-oxoethyl)-3-iodobenzamido)butyl)benzamide (4c).	
Figure 9. 300 MHz ¹ H NMR spectra of 3-amino-N-(2-(tert-butylamino)-2-oxoethyl)-N-(4-(3-iodo-N-	S14
(2-(octylamino)-2-oxoethyl)benzamido)butyl)benzamide(4d).	
Figure 10. 75 MHz ¹³ C NMR spectra in CDCl ₃ of 3-amino-N-(2-(tert-butylamino)-2-oxoethyl)-N-(4-(3-	S15
iodo-N-(2-(octylamino)-2-oxoethyl)benzamido)butyl)benzamide(4d).	
Figure 11. 400 MHz ¹ H NMR spectra of 3-amino-N-(2-(tert-butylamino)-2-oxoethyl)-N-(4-(N-(2-	S16
(decylamino)-2-oxoethyl)-3-iodobenzamido)butyl)benzamide(4e).	
Figure 12. 100 MHz ¹³ C NMR spectra in CDCl ₃ of 3-amino-N-(2-(tert-butylamino)-2-oxoethyl)-N-(4-	S17
(N-(2-(decylamino)-2-oxoethyl)-3-iodobenzamido)butyl)benzamide(4e).	
Figure 13. 400 MHz ¹ H NMR spectra of 3-amino-N-(2-(tert-butylamino)-2-oxoethyl)-N-(4-(3-iodo-N-	S18
(2-oxo-2-(undecylamino)ethyl)benzamido)butyl)benzamide (4f).	
Figure 14. 100 MHz ¹³ C NMR spectra in CDCl ₃ of 3-amino-N-(2-(tert-butylamino)-2-oxoethyl)-N-(4-	S19
(3-iodo-N-(2-oxo-2-(undecylamino)ethyl)benzamido)butyl)benzamide (4f).	
Figure 15. 300 MHz ¹ H NMR spectra of 3-amino-N-(2-(tert-butylamino)-2-oxoethyl)-N-(4-(N-(2-	S20
(dodecylamino)-2-oxoethyl)-3-iodobenzamido)butyl)benzamide (4g).	
Figure 16. 75 MHz ¹³ C NMR spectra in CDCl ₃ of 3-amino-N-(2-(tert-butylamino)-2-oxoethyl)-N-(4-(N-	S21
(2-(dodecylamino)-2-oxoethyl)-3-iodobenzamido)butyl)benzamide (4g).	
Figure 17. 300 MHz ¹ H NMR spectra of 3-amino-N-(2-(tert-butylamino)-2-oxoethyl)-N-(4-(N-(2-	S22
(cyclohexylamino)-2-oxoethyl)-3-iodobenzamido)butyl)benzamide (4h).	
Figure 18 . 75 MHz ¹³ C NMR spectra in CDCl ₃ of 3-amino-N-(2-(tert-butylamino)-2-oxoethyl)-N-(4-(N-	S23
(2-(cyclohexylamino)-2-oxoethyl)-3-iodobenzamido)butyl)benzamide (4h).	
Figure 19. 300 MHz ¹ H NMR spectra of 3-amino-N-(2-(tert-butylamino)-2-oxoethyl)-N-(4-(N-(2-	S24
(cyclopentylamino)-2-oxoethyl)-3-iodobenzamido)butyl)benzamide (4i).	
Figure 20. 75 MHz ¹³ C NMR spectra in CDCl ₃ of 3-amino-N-(2-(tert-butylamino)-2-oxoethyl)-N-(4-(N-	S25
(2-(cyclopentylamino)-2-oxoethyl)-3-iodobenzamido)butyl)benzamide (4i).	
Figure 21. 400 MHz ¹ H NMR spectra of 3-amino-N-(4-(N-(2-(benzylamino)-2-oxoethyl)-3-	S26
iodobenzamido)butyl)-N-(2-(tert-butylamino)-2-oxoethyl)benzamide (4j).	
Figure 22. 100 MHz ¹³ C NMR spectra in CDCl ₃ of 3-amino-N-(4-(N-(2-(benzylamino)-2-oxoethyl)-3-	S27
iodobenzamido)butyl)-N-(2-(tert-butylamino)-2-oxoethyl)benzamide (4j).	

Figure 23. 300 MHz ¹ H NMR spectra of 3-amino-N-(2-(tert-butylamino)-2-oxoethyl)-N-(4-(3-iodo-N-	S28
(2-oxo-2-(phenylamino)ethyl)benzamido)butyl)benzamide(4k).	
Figure 24 . 75 MHz ¹³ C NMR spectra in CDCl ₃ of 3-amino-N-(2-(tert-butylamino)-2-oxoethyl)-N-(4-(3-	S29
iodo-N-(2-oxo-2-(phenylamino)ethyl)benzamido)butyl)benzamide(4k).	
Figure 25. 300 MHz ¹ H NMR spectra of 3-amino-N-(4-(N-(2-(tert-butylamino)-2-oxoethyl)-3-	S30
iodobenzamido)butyl)-N-(2-((4-methoxyphenyl)amino)-2-oxoethyl)benzamide (41).	
Figure 26 . 75 MHz ¹³ C NMR spectra in CDCl ₃ of 3-amino-N-(4-(N-(2-(tert-butylamino)-2-oxoethyl)-3-	S31
iodobenzamido)butyl)-N-(2-((4-methoxyphenyl)amino)-2-oxoethyl)benzamide (41).	
Figure 27. 400 MHz ¹ H NMR spectra of methyl6-(3-aminobenzoyl)-11-(3-iodobenzoyl)-15,15-	S32
dimethyl-4,13-dioxo-3,6,11,14-tetraazahexadecan-1-oate (4m).	
Figure 28. 100 MHz ¹³ C NMR spectra in CDCl₃ of methyl6-(3-aminobenzoyl)-11-(3-iodobenzoyl)-	S33
15,15-dimethyl-4,13-dioxo-3,6,11,14-tetraazahexadecan-1-oate (4m).	
Figure 29. 300 MHz ¹ H NMR spectra of 3-amino-N-(4-(N-(2-(tert-butylamino)-2-oxoethyl)-3-	S34
iodobenzamido)butyl)-N-(2-(morpholinoamino)-2-oxoethyl)benzamide (4n).	
Figure 30 . 75 MHz ¹³ C NMR spectra in CDCl ₃ of 3-amino-N-(4-(N-(2-(tert-butylamino)-2-oxoethyl)-3-	S35
iodobenzamido)butyl)-N-(2-(morpholinoamino)-2-oxoethyl)benzamide (4n)	
Figure 31. 300 MHz ¹ H NMR spectra of 2,2'-(4,11-dioxo-2,5,10-triaza-1,3(1,3)-	S36
dibenzenacycloundecaphane-5,10-diyl)bis(N-(tert-butyl)acetamide) (5a).	
Figure 32. 75 MHz ¹³ C NMR spectra in CDCl ₃ of 2,2'-(4,11-dioxo-2,5,10-triaza-1,3(1,3)-	S37
dibenzenacycloundecaphane-5,10-diyl)bis(N-(tert-butyl)acetamide) (5a).	
Figure 33. 300 MHz ¹ H NMR spectra of N-(tert-butyl)-2-(10-(2-(hexylamino)-2-oxoethyl)-4,11-dioxo-	S38
2,5,10-triaza-1,3(1,3)-dibenzenacycloundecaphane-5-yl)acetamide (5b).	
Figure 34. 75 MHz ¹³ C NMR spectra in CDCl ₃ of N-(tert-butyl)-2-(10-(2-(hexylamino)-2-oxoethyl)-	S39
4,11-dioxo-2,5,10-triaza-1,3(1,3)-dibenzenacycloundecaphane-5-yl)acetamide (5b).	
Figure 35. 300 MHz ¹ H NMR spectra of N-(tert-butyl)-2-(10-(2-(heptylamino)-2-oxoethyl)-4,11-	S40
dioxo-2,5,10-triaza-1,3(1,3)-dibenzenacycloundecaphane-5-yl)acetamide (5c).	
Figure 36. 75 MHz ¹³ C NMR spectra in CDCl ₃ of N-(tert-butyl)-2-(10-(2-(heptylamino)-2-oxoethyl)-	S41
4,11-dioxo-2,5,10-triaza-1,3(1,3)-dibenzenacycloundecaphane-5-yl)acetamide (5c).	
Figure 37. 300 MHz ¹ H NMR spectra of N-(tert-butyl)-2-(10-(2-(octylamino)-2-oxoethyl)-4,11-dioxo-	S42
2,5,10-triaza-1,3(1,3)-dibenzenacycloundecaphane-5-yl)acetamide (5d).	
Figure 38. 75 MHz ¹³ C NMR spectra in CDCl ₃ of N-(tert-butyl)-2-(10-(2-(octylamino)-2-oxoethyl)-	S43
4,11-dioxo-2,5,10-triaza-1,3(1,3)-dibenzenacycloundecaphane-5-yl)acetamide (5d).	
Figure 39. 400 MHz ¹ H NMR spectra of N-(tert-butyl)-2-(10-(2-(decylamino)-2-oxoethyl)-4,11-dioxo-	S44
2,5,10-triaza-1,3(1,3)-dibenzenacycloundecaphane-5-yl)acetamide (5e).	
Figure 40. 100 MHz ¹³ C NMR spectra in CDCl ₃ of N-(tert-butyl)-2-(10-(2-(decylamino)-2-oxoethyl)-	S45
4,11-dioxo-2,5,10-triaza-1,3(1,3)-dibenzenacycloundecaphane-5-yl)acetamide (5e).	
Figure 41. 400 MHz ⁺ H NMR spectra of N-(tert-butyl)-2-(4,11-dioxo-10-(2-oxo-2-	S46
(undecylamino)ethyl)-2,5,10-triaza-1,3(1,3)-dibenzenacycloundecaphane-5-yl)acetamide (5f).	
Figure 42. 100 MHz 13 C NMR spectra in CDCI ₃ of N-(tert-butyI)-2-(4,11-dioxo-10-(2-oxo-2-	547
(undecylamino)ethyl)-2,5,10-triaza-1,3(1,3)-dibenzenacycloundecaphane-5-yl)acetamide (5f).	6.40
Figure 43. 300 MHz ⁻ H NMR spectra of N-(tert-butyl)-2-(10-(2-(dodecylamino)-2-oxoethyl)-4,11-	548
dioxo-2,5,10-triaza-1,3(1,3)-dibenzenacycioundecaphane-5-yi)acetamide (5g).	640
Figure 44 . 75 MHz ²³ C NMR spectra in CDCI ₃ of N-(tert-butyi)-2-(10-(2-(dodecylamino)-2-oxoetnyi)-	549
4,11-dioxo-2,5,10-triaza-1,3(1,3)-dibenzenacycioundecaphane-5-yi)acetamide (5g).	650
Figure 45. 300 MHZ ⁻ H NMR spectra of N-(tert-butyl)-2-(10-(2-(cyclonexylamino)-2-oxoethyl)-4,11-	350
a(x) - 2, 5, 10 - triaza - 1, 3(1, 3) - a(x) - a(CE 4
Figure 46. 75 MHzC NMR spectra in CDCI3 of N-(tert-butyi)-2-(10-(2-(cyclonexylamino)-2-	221
oxoethylj-4,11-uloxo-2,5,10-thaza-1,3(1,3)-ulbenzenacycloundecaphane-5-yljacetamide (5n).	653
FIGURE 47. SOU MIRZ IT INVIK SPECIA OF N-(TEFT-DUTY)-2-(TU-(Z-(CYCIOPENTYIAMINO)-Z-OXOETNYI)-4,11-	352
$u_{10x0-2,3,10-11}$ and $u_{1,3,1,3,1-10}$ and $u_{1,2,1,3,1-10}$	552
$r_{Igure +0.75} r_{IIII2} = C r_{IIIIIII} spectra in CDCI3 of re-(iCFCDU(y))-2-(iDFC)(UC)Pericyal (IIIIIO)-2-$	323
0,0emyij-4,11-ul0,0-2,3,10-ulaza-1,3(1,3)-ulbenzenacyclounuecaphane-3-yijacetannue (5i).	

Figure 49. 300 MHz ¹ H NMR spectra of N-benzyl-2-(10-(2-(tert-butylamino)-2-oxoethyl)-4,11-dioxo-	S54
2,5,10-triaza-1,3(1,3)-dibenzenacycloundecaphane-5-yl)acetamide (5j).	
Figure 50. 75 MHz ¹³ C NMR spectra in CDCl ₃ of N-benzyl-2-(10-(2-(tert-butylamino)-2-oxoethyl)-	S55
4,11-dioxo-2,5,10-triaza-1,3(1,3)-dibenzenacycloundecaphane-5-yl)acetamide (5j).	
Figure 51. 300 MHz ¹ H NMR spectra of N-(tert-butyl)-2-(4,11-dioxo-10-(2-oxo-2-	S56
(phenylamino)ethyl)-2,5,10-triaza-1,3(1,3)-dibenzenacycloundecaphane-5-yl)acetamide (5k).	
Figure 52. 75 MHz ¹³ C NMR spectra in CDCl ₃ of N-(tert-butyl)-2-(4,11-dioxo-10-(2-oxo-2-	S57
(phenylamino)ethyl)-2,5,10-triaza-1,3(1,3)-dibenzenacycloundecaphane-5-yl)acetamide (5k).	
Figure 53. 400 MHz ¹ H NMR spectra of N-(tert-butyl)-2-(10-(2-((4-methoxyphenyl)amino)-2-	S58
oxoethyl)-4,11-dioxo-2,5,10-triaza-1,3(1,3)-dibenzenacycloundecaphane-5-yl)acetamide (5I).	
Figure 54. 100 MHz ¹³ C NMR spectra in CDCl ₃ of N-(tert-butyl)-2-(10-(2-((4-methoxyphenyl)amino)-	S59
2-oxoethyl)-4,11-dioxo-2,5,10-triaza-1,3(1,3)-dibenzenacycloundecaphane-5-yl)acetamide (5l).	
Figure 55. 300 MHz ¹ H NMR spectra of methyl(2-(10-(2-(tert-butylamino)-2-oxoethyl)-4,11-dioxo-	S50
2,5,10-triaza-1,3(1,3)-dibenzenacycloundecaphane-5-yl)acetyl)glycinate (5m).	
Figure 56. 75 MHz ¹³ C NMR spectra in CDCl ₃ of methyl(2-(10-(2-(tert-butylamino)-2-oxoethyl)-4,11-	S61
dioxo-2,5,10-triaza-1,3(1,3)-dibenzenacycloundecaphane-5-yl)acetyl)glycinate (5m).	
Figure 57. 300 MHz ¹ H NMR spectra of N-(tert-butyl)-2-(10-(2-((2-morpholinoethyl)amino)-2-	S62
oxoethyl)-4,11-dioxo-2,5,10-triaza-1,3(1,3)-dibenzenacycloundecaphane-5-yl)acetamide (5n).	
Figure 58. 75 MHz ¹³ C NMR spectra in CDCl ₃ of N-(tert-butyl)-2-(10-(2-((2-morpholinoethyl)amino)-	S63
2-oxoethyl)-4,11-dioxo-2,5,10-triaza-1,3(1,3)-dibenzenacycloundecaphane-5-yl)acetamide (5n).	
Crystallographic data of compound 5a.	S64

Compound	Compound Control (mg)		Inhibition (%)
Indomethacin		2.88±0.73	78.76±
5a	14.17±1.00	9.73±0.67*	31.29±4.76*
5b	14.07±1.09	1.33±0.61**	90.52±3.72**
5c	14.07±1.09	1.43±0.03**	89.81±0.24**
5d	14.17±1.00	4.20±0.91**	70.35±6.41**
5e	14.07±1.09	0.33±0.29**	97.63±0.07**
5f	14.07±1.09	1.63±0.52**	88.39±3.72**
5g	14.17±1.00	1.90±0.45**	86.59±3.18**
5h	14.07±1.09	5.47±0.98**	66.32±6.06**
5i	15.58±0.33	3.63±1.32**	76.68±8.49**
5j	14.07±1.09	4.37±1.28**	68.95±9.11**
5k	14.07±1.09	4.67±1.49**	66.82±10.59**
51	14.07±1.09	2.27±0.33*	83.89±2.37**
5m	14.07±1.09	5.50±0.61**	60.92±4.33**
5n	14.07±1.09	1.10±0.17**	92.18±1.23**

Table 1. Data of 12-O-tetradecanoylphorbol acetate induced mouse ear edema. Screening at 1 μM

Compound	Dose (µmol/ear)	Edema (mg)	Inhibition (%)	DI ₅₀ (µmol/ear)
ТРА		14.75±1.13		
	0.031	12.78±1.21	13.36	0.236
	0.1	10.74±1.13*	27.19*	R ² =0.966
Indomethacin	0.31	5.62±0.89**	61.90**	R=0.983
	1	2.88±0.73**	78.76**	

Table 2. Data of the determination of $ID_{50}\, of$ compounds 5e and 5n.

Compound	Dose (µmol/ear)	Edema (mg)	Inhibition (%)	DI₅₀ (µmol/ear)
ТРА		15.58±0.33		
	0.031	11.76±2.15	24.52±13.8	0.18
	0.1	8.80±2.04*	43.52±13.12*	R ² =0.78
5e	0.31	7.60±1.23**	51.22±7.89**	R=0.88
	1	2.42±0.68**	84.47±2.10**	

Compound	Dose (µmol/ear)	Edema (mg)	Inhibition (%)	DI ₅₀ (µmol/ear)
ТРА		13.98±0.72		
	0.031	12.00±0.42	14.46±2.99	0.29
	0.1	9.00±1.01**	35.62±7.23**	R ² =0.79
5n	0.31	7.92±1.51**	43.35±10.79**	R=0.89
	1	3.38±1.13**	75.82±8.06**	

Table 3. Data of the myeloperoxidase assay

Sample	Dosis	MPO	MPO
	(µmol/ear)	(OD _{450nm} /biopsy)	(% of inhibition)
Basal	-	0.013±0.004	-
ТРА	-	0.202±0.055	-
	0.031	0.104±0.017	48.5
TPA +	0.1	0.087±0.034	56.93
Indomethacin	0.31	0.039±0.012	80.69
	1	0.018±0.006	91.08

Sample	Dosis	MPO	MPO
	(µmol/ear)	(OD _{450nm} /biopsy)	(% of inhibition)
Basal	-	0.128±0.028	-
ТРА	-	0.619±0.157	-
	0.031	0.369±0.102	40.39±16.54
TPA + 5e	0.1	0.147±0.026	76.19±4.25
	0.31	0.228±0.008	63.10±1.34
	1	0.157±0.019	74.63±3.05

Sample	Dosis	MPO	MPO
	(µmol/ear)	(OD _{450nm} /biopsy)	(% of inhibition)
Basal	-	0.099±0.006	-
ТРА	-	0.447±0.131	-
	0.031	0.342±0.068	23.53±15.16
TPA + 5n	0.1	0.161±0.024	63.94±5.29
	0.31	0.151±0.035	66.22±7.87
	1	0.145±0.028	67.61±6.25
	1	0.145±0.028	67.61±6.25

Compound	Concentration (µM)	Nitrite (µM)	Inhibition Production (%)	Viability
LPS (1µg/ml)		6.53±0.2		
Aminoguanidina	100	0.54±0.1	91.8	82.9±5.4
Aminoguanidine	31	2.0±0.4	69.4	84.7±5.6
	10	3.53±0.2	45.9	88.7±3.7
	3.1	4.47±0.4	31.6	88.1±3.9
	31	4.16±0.2	36.3	71.0±6.2
50	18	5.54±0.7	15.1	71.8±7.9
	10	6.0±0.2	8.1	70.2±4.1
	3.1	6.4±0.2	2.7	68.1±4.5
 50	31	5.18±0.2	20.7	73.3±5.3
Je	18	5.23±0.3	19.9	71.3±5.7
	10	5.52±0.2	15.4	76.3±4.5
	3.1	5.49±0.3	16.0	77.4±3.7
 5n	31	4.74±0.5	27.5	83.0±4.0
511	18	4.13±0.15	36.8	84.1±6.1
	10	5.41±0.4	17.2	82.1±3.8
	3.1	5.38±0.4	17.7	86.9±6.1

Table 4. Data of the Nitrite assay and cell viability

Table 5. Percentage o	f cytotoxicity sc	reening of macroo	cycles 5a-n
-----------------------	-------------------	-------------------	-------------

Comp.	U251 (50μM)	ΡC-3 (50μM)	К562 (50µМ)	HCT-15 (50μM)	MCF-7 (50μM)	SKLU-1 (50μM)	COS-7 (25μM)	FGH (25µM)
5a	3.8	18.3	28.7	1.6	13.2	29.5	12.3	NC
5b	NC	96.5	NC	100	65.9	44.2	52.6	11.1
5c	70.5	100	100	50.6	44.8	20.6	NC	37.9
5d	39.9	86.7	100	56.3	91.7	68.9	52.3	17.1
5e	32.0	73.8	100	66.2	58.6	5.6	51	30.4
5f	97.9	100	100	59.8	77.6	78.3	62.6	23.5
5g	39.0	70.7	20.8	35.0	21.8	10.7	46.3	NC
5h	27.2	61.1	100	28.5	85.0	50.1	50.4	NC
5i	16.6	33.8	92.8	22.4	77.6	46.9	NC	NC
5j	54.4	81.2	100	56.9	44.3	7.5	51.8	24.3
5k	NC	34.4	100	27.5	14.7	NC	50.4	19.8
51	NC	12.78	23.0	12.29	13.4	16.43	NC	NC
5m	NC	NC	9.66	2.31	13.48	21.74	NC	38.5
5n	NC	NC	30.0	6.23	10.39	34.46	NC	24.6



Figure 1. 400 MHz ¹H NMR spectra in CDCl₃ of *tert*-butyl (4-(N-(2-(tert-butylamino)-2-oxoethyl)-3-iodobenzamido)butyl)carbamate (2)



Figure 2. 100 MHz ¹³C NMR spectra in CDCl₃ of *tert*-butyl (4-(N-(2-(tert-butylamino)-2-oxoethyl)-3-iodobenzamido)butyl)carbamate (2)



Figure 3. 300 MHz ¹H NMR spectra in CDCl₃ of 3-amino-N-(2-(tert-butylamino)-2-oxoethyl)-N-(4-(N-(2-(tert-butylamino)-2-oxoethyl)-3-iodobenzamido)butyl)benzamide (**4a**).



Figure 4. 75 MHz ¹³C NMR spectra in CDCl₃ of 3-amino-N-(2-(tert-butylamino)-2-oxoethyl)-N-(4-(N-(2-(tert-butylamino)-2-oxoethyl)-3-iodobenzamido)butyl)benzamide (**4a**).



Figure 5. 300 MHz ¹H NMR spectra in CDCl₃ of 3-amino-N-(2-(tert-butylamino)-2-oxoethyl)-N-(4-(N-(2-(hexylamino)-2-oxoethyl)-3-iodobenzamido)butyl)benzamide (**4b**)



Figure 6. 75 MHz ¹³C NMR spectra in CDCl₃ of 3-amino-N-(2-(tert-butylamino)-2-oxoethyl)-N-(4-(N-(2-(hexylamino)-2-oxoethyl)-3-iodobenzamido)butyl)benzamide (**4b**)



Figure 7. 400 MHz ¹H NMR spectra in CDCl₃ of 3-amino-N-(2-(tert-butylamino)-2-oxoethyl)-N-(4-(N-(2-(heptylamino)-2-oxoethyl)-3-iodobenzamido)butyl)benzamide (**4c**).



Figure 8. 100 MHz ¹³C NMR spectra in CDCl₃ of 3-amino-N-(2-(tert-butylamino)-2-oxoethyl)-N-(4-(N-(2-(heptylamino)-2-oxoethyl)-3-iodobenzamido)butyl)benzamide (**4c**).



Figure 9. 300 MHz ¹H NMR spectra in CDCl₃ of 3-amino-N-(2-(tert-butylamino)-2-oxoethyl)-N-(4-(3-iodo-N-(2-(octylamino)-2-oxoethyl)benzamido)butyl)benzamide(**4d**).



Figure 10. 75 MHz ¹³C NMR spectra in CDCl₃ of 3-amino-N-(2-(tert-butylamino)-2-oxoethyl)-N-(4-(3-iodo-N-(2-(octylamino)-2-oxoethyl)benzamido)butyl)benzamide(4d).



Figure 11. 400 MHz ¹H NMR spectra in CDCl₃ of 3-amino-N-(2-(tert-butylamino)-2-oxoethyl)-N-(4-(N-(2-(decylamino)-2-oxoethyl)-3-iodobenzamido)butyl)benzamide(**4e**).



Figure 12. 100 MHz ¹³C NMR spectra in CDCl₃ of 3-amino-N-(2-(tert-butylamino)-2-oxoethyl)-N-(4-(N-(2-(decylamino)-2-oxoethyl)-3-iodobenzamido)butyl)benzamide(**4e**).



Figure 13. 400 MHz ¹H NMR spectra in CDCl₃ of 3-amino-N-(2-(tert-butylamino)-2-oxoethyl)-N-(4-(3-iodo-N-(2-oxo-2-(undecylamino)ethyl)benzamido)butyl)benzamide (**4f**).



Figure 14. 100 MHz ¹³C NMR spectra in CDCl₃ of 3-amino-N-(2-(tert-butylamino)-2-oxoethyl)-N-(4-(3-iodo-N-(2-oxo-2-(undecylamino)ethyl)benzamido)butyl)benzamide (**4f**).



Figure 15. 300 MHz ¹H NMR spectra in CDCl₃ of 3-amino-N-(2-(tert-butylamino)-2-oxoethyl)-N-(4-(N-(2-(dodecylamino)-2-oxoethyl)-3-iodobenzamido)butyl)benzamide (**4g**).



Figure 16. 75 MHz ¹³C NMR spectra in CDCl₃ of 3-amino-N-(2-(tert-butylamino)-2-oxoethyl)-N-(4-(N-(2-(dodecylamino)-2-oxoethyl)-3-iodobenzamido)butyl)benzamide (**4g**).



Figure 17. 300 MHz ¹H NMR spectra in CDCl₃ of 3-amino-N-(2-(tert-butylamino)-2-oxoethyl)-N-(4-(N-(2-(cyclohexylamino)-2-oxoethyl)-3-iodobenzamido)butyl)benzamide (**4h**).



Figure 18. 75 MHz ¹³C NMR spectra in CDCl₃ of 3-amino-N-(2-(tert-butylamino)-2-oxoethyl)-N-(4-(N-(2-(cyclohexylamino)-2-oxoethyl)-3-iodobenzamido)butyl)benzamide (**4h**).



Figure 19. 300 MHz ¹H NMR spectra in CDCl₃ of 3-amino-N-(2-(tert-butylamino)-2-oxoethyl)-N-(4-(N-(2-(cyclopentylamino)-2-oxoethyl)-3-iodobenzamido)butyl)benzamide (**4i**).



Figure 20. 75 MHz ¹³C NMR spectra in CDCl₃ of 3-amino-N-(2-(tert-butylamino)-2-oxoethyl)-N-(4-(N-(2-(cyclopentylamino)-2-oxoethyl)-3-iodobenzamido)butyl)benzamide (**4i**).



Figure 21. 400 MHz ¹H NMR spectra in CDCl₃ of 3-amino-N-(4-(N-(2-(benzylamino)-2-oxoethyl)-3-iodobenzamido)butyl)-N-(2-(tert-butylamino)-2-oxoethyl)benzamide (**4j**).



Figure 22. 100 MHz ¹³C NMR spectra in CDCl₃ of 3-amino-N-(4-(N-(2-(benzylamino)-2-oxoethyl)-3-iodobenzamido)butyl)-N-(2-(tert-butylamino)-2-oxoethyl)benzamide (4j).



Figure 23. 300 MHz ¹H NMR spectra in CDCl₃ of 3-amino-N-(2-(tert-butylamino)-2-oxoethyl)-N-(4-(3-iodo-N-(2-oxo-2-(phenylamino)ethyl)benzamido)butyl)benzamide(**4k**).



Figure 24. 75 MHz ¹³C NMR spectra in CDCl₃ of 3-amino-N-(2-(tert-butylamino)-2-oxoethyl)-N-(4-(3-iodo-N-(2-oxo-2-(phenylamino)ethyl)benzamido)butyl)benzamide(**4k**).



Figure 25. 300 MHz ¹H NMR spectra in CDCl₃ of 3-amino-N-(4-(N-(2-(tert-butylamino)-2-oxoethyl)-3-iodobenzamido)butyl)-N-(2-((4-methoxyphenyl)amino)-2-oxoethyl)benzamide (**4**)



Figure 26. 75 MHz ¹³C NMR spectra in CDCl₃ of 3-amino-N-(4-(N-(2-(tert-butylamino)-2-oxoethyl)-3-iodobenzamido)butyl)-N-(2-((4-methoxyphenyl)amino)-2-oxoethyl)benzamide (**4**)



Figure 27. 400 MHz ¹H NMR spectra in CDCl₃ of methyl6-(3-aminobenzoyl)-11-(3-iodobenzoyl)-15,15-dimethyl-4,13-dioxo-3,6,11,14-tetraazahexadecan-1-oate (**4m**)



Figure 28. 100 MHz ¹³C NMR spectra in CDCl₃ of methyl6-(3-aminobenzoyl)-11-(3-iodobenzoyl)-15,15-dimethyl-4,13-dioxo-3,6,11,14-tetraazahexadecan-1-oate (**4m**)



Figure 29. 300 MHz ¹H NMR spectra in CDCl₃ of 3-amino-N-(4-(N-(2-(tert-butylamino)-2-oxoethyl)-3-iodobenzamido)butyl)-N-(2-(morpholinoamino)-2-oxoethyl)benzamide (**4n**)



Figure 30. 75 MHz ¹³C NMR spectra in CDCl₃ of 3-amino-N-(4-(N-(2-(tert-butylamino)-2-oxoethyl)-3-iodobenzamido)butyl)-N-(2-(morpholinoamino)-2-oxoethyl)benzamide (**4n**)

Figure 31. 300 MHz ¹H NMR spectra in CDCl₃ of 2,2'-(4,11-dioxo-2,5,10-triaza-1,3(1,3)-dibenzenacycloundecaphane-5,10-diyl)bis(N-(tertbutyl)acetamide) (**5a**)

Figure 32. 75 MHz ¹³C NMR spectra in CDCl₃ of 2,2'-(4,11-dioxo-2,5,10-triaza-1,3(1,3)-dibenzenacycloundecaphane-5,10-diyl)bis(N-(tert-butyl)acetamide) (**5a**)

Figure 33. 300 MHz ¹H NMR spectra in CDCl₃ of N-(tert-butyl)-2-(10-(2-(hexylamino)-2-oxoethyl)-4,11-dioxo-2,5,10-triaza-1,3(1,3)dibenzenacycloundecaphane-5-yl)acetamide (**5b**)

Figure 34. 75 MHz ¹³C NMR spectra in CDCl₃ of N-(tert-butyl)-2-(10-(2-(hexylamino)-2-oxoethyl)-4,11-dioxo-2,5,10-triaza-1,3(1,3)dibenzenacycloundecaphane-5-yl)acetamide (**5b**)

Figure 35. 300 MHz ¹H NMR spectra in CDCl₃ of N-(tert-butyl)-2-(10-(2-(heptylamino)-2-oxoethyl)-4,11-dioxo-2,5,10-triaza-1,3(1,3)dibenzenacycloundecaphane-5-yl)acetamide (**5c**)

Figure 36. 75 MHz ¹³C NMR spectra in CDCl₃ of N-(tert-butyl)-2-(10-(2-(heptylamino)-2-oxoethyl)-4,11-dioxo-2,5,10-triaza-1,3(1,3)dibenzenacycloundecaphane-5-yl)acetamide (**5c**)

Figure 37. 300 MHz ¹H NMR spectra in CDCl₃ of N-(tert-butyl)-2-(10-(2-(octylamino)-2-oxoethyl)-4,11-dioxo-2,5,10-triaza-1,3(1,3)dibenzenacycloundecaphane-5-yl)acetamide (**5d**)

Figure 38. 75 MHz ¹³C NMR spectra in CDCl₃ of N-(tert-butyl)-2-(10-(2-(octylamino)-2-oxoethyl)-4,11-dioxo-2,5,10-triaza-1,3(1,3)dibenzenacycloundecaphane-5-yl)acetamide (**5d**)

Figure 39. 400 MHz ¹H NMR spectra in CDCl₃ of N-(tert-butyl)-2-(10-(2-(decylamino)-2-oxoethyl)-4,11-dioxo-2,5,10-triaza-1,3(1,3)dibenzenacycloundecaphane-5-yl)acetamide (**5e**)

Figure 40. 100 MHz ¹³C NMR spectra in CDCl₃ of N-(tert-butyl)-2-(10-(2-(decylamino)-2-oxoethyl)-4,11-dioxo-2,5,10-triaza-1,3(1,3)-dibenzenacycloundecaphane-5-yl)acetamide (**5e**)

Figure 41. 400 MHz ¹H NMR spectra in CDCl₃ of N-(tert-butyl)-2-(4,11-dioxo-10-(2-oxo-2-(undecylamino)ethyl)-2,5,10-triaza-1,3(1,3)dibenzenacycloundecaphane-5-yl)acetamide (**5f**)

Figure 42. 100 MHz ¹³C NMR spectra in CDCl₃ of N-(tert-butyl)-2-(4,11-dioxo-10-(2-oxo-2-(undecylamino)ethyl)-2,5,10-triaza-1,3(1,3)dibenzenacycloundecaphane-5-yl)acetamide (**5f**)

Figure 43. 300 MHz ¹H NMR spectra in CDCl₃ of N-(tert-butyl)-2-(10-(2-(dodecylamino)-2-oxoethyl)-4,11-dioxo-2,5,10-triaza-1,3(1,3)dibenzenacycloundecaphane-5-yl)acetamide (**5g**)

Figure 44. 75 MHz ¹³C NMR spectra in CDCl₃ of N-(tert-butyl)-2-(10-(2-(dodecylamino)-2-oxoethyl)-4,11-dioxo-2,5,10-triaza-1,3(1,3)dibenzenacycloundecaphane-5-yl)acetamide (**5g**)

Figure 45. 300 MHz ¹H NMR spectra in CDCl₃ of N-(tert-butyl)-2-(10-(2-(cyclohexylamino)-2-oxoethyl)-4,11-dioxo-2,5,10-triaza-1,3(1,3)dibenzenacycloundecaphane-5-yl)acetamide (**5h**)

Figure 46. 75 MHz ¹³C NMR spectra in CDCl₃ of N-(tert-butyl)-2-(10-(2-(cyclohexylamino)-2-oxoethyl)-4,11-dioxo-2,5,10-triaza-1,3(1,3)dibenzenacycloundecaphane-5-yl)acetamide (**5h**)

Figure 47. 300 MHz ¹H NMR spectra in CDCl₃ of N-(tert-butyl)-2-(10-(2-(cyclopentylamino)-2-oxoethyl)-4,11-dioxo-2,5,10-triaza-1,3(1,3)dibenzenacycloundecaphane-5-yl)acetamide (**5i**)

Figure 48. 75 MHz ¹³C NMR spectra in CDCl₃ of N-(tert-butyl)-2-(10-(2-(cyclopentylamino)-2-oxoethyl)-4,11-dioxo-2,5,10-triaza-1,3(1,3)dibenzenacycloundecaphane-5-yl)acetamide (**5i**)

Figure 49. 300 MHz ¹H NMR spectra in CDCl₃ of N-benzyl-2-(10-(2-(tert-butylamino)-2-oxoethyl)-4,11-dioxo-2,5,10-triaza-1,3(1,3)dibenzenacycloundecaphane-5-yl)acetamide (**5j**)

Figure 50. 75 MHz ¹³C NMR spectra in CDCl₃ of N-benzyl-2-(10-(2-(tert-butylamino)-2-oxoethyl)-4,11-dioxo-2,5,10-triaza-1,3(1,3)dibenzenacycloundecaphane-5-yl)acetamide (**5**j)

Figure 51. 300 MHz ¹H NMR spectra in CDCl₃ of N-(tert-butyl)-2-(4,11-dioxo-10-(2-oxo-2-(phenylamino)ethyl)-2,5,10-triaza-1,3(1,3)dibenzenacycloundecaphane-5-yl)acetamide (**5k**)

Figure 52. 75 MHz ¹³C NMR spectra in CDCl₃ of N-(tert-butyl)-2-(4,11-dioxo-10-(2-oxo-2-(phenylamino)ethyl)-2,5,10-triaza-1,3(1,3)-dibenzenacycloundecaphane-5-yl)acetamide (**5k**)

Figure 53. 400 MHz ¹H NMR spectra in CDCl₃ of N-(tert-butyl)-2-(10-(2-((4-methoxyphenyl)amino)-2-oxoethyl)-4,11-dioxo-2,5,10-triaza-1,3(1,3)dibenzenacycloundecaphane-5-yl)acetamide (**5**I)

Figure 54. 100 MHz ¹³C NMR spectra in CDCl₃ of N-(tert-butyl)-2-(10-(2-((4-methoxyphenyl)amino)-2-oxoethyl)-4,11-dioxo-2,5,10-triaza-1,3(1,3)dibenzenacycloundecaphane-5-yl)acetamide (**5**I)

Figure 55. 300 MHz ¹H NMR spectra in CDCl₃ of methyl(2-(10-(2-(tert-butylamino)-2-oxoethyl)-4,11-dioxo-2,5,10-triaza-1,3(1,3)-dibenzenacycloundecaphane-5-yl)acetyl)glycinate (**5m**)

Figure 56. 75 MHz ¹³C NMR spectra in CDCl₃ of methyl(2-(10-(2-(tert-butylamino)-2-oxoethyl)-4,11-dioxo-2,5,10-triaza-1,3(1,3)dibenzenacycloundecaphane-5-yl)acetyl)glycinate (**5m**)

Figure 57. 300 MHz ¹H NMR spectra in CDCl₃ of N-(tert-butyl)-2-(10-(2-((2-morpholinoethyl)amino)-2-oxoethyl)-4,11-dioxo-2,5,10-triaza-1,3(1,3)dibenzenacycloundecaphane-5-yl)acetamide (**5n**)

Figure 58. 75 MHz ¹³C NMR spectra in CDCl₃ of N-(tert-butyl)-2-(10-(2-((2-morpholinoethyl)amino)-2-oxoethyl)-4,11-dioxo-2,5,10-triaza-1,3(1,3)-dibenzenacycloundecaphane-5-yl)acetamide (**5n**)

Crystal data and structure refinement for Macrocycle 5a.

Identification code	337MGL17			
Empirical formula	$C_{120} \ H_{164} \ N_{20} \ O_{18}$			
Formula weight	2174.70			
Temperature	298(2) K			
Wavelength	1.54178 Å			
Crystal system	Orthorhombic			
Space group	Fdd2			
Unit cell dimensions	$a = 27.0176(6) \text{ Å}$ $\alpha = 90^{\circ}.$			
	$b = 36.9735(8) \text{ Å} \qquad \beta = 90^{\circ}.$			
	$c = 14.7072(3) \text{ Å} \qquad \qquad \gamma = 90^{\circ}.$			
Volume	14691.5(5) Å ³			
Z	4			
Density (calculated)	0.983 Mg/m^3			
Absorption coefficient	0.540 mm ⁻¹			
F(000)	4672			
Crystal size	0.330 x 0.289 x 0.179 mm ³			
Theta range for data collection	3.624 to 68.386°.			
Index ranges	-32<=h<=32, -40<=k<=44, -16<=l<=17			
Reflections collected	27876			
Independent reflections	6518 [R(int) = 0.0443]			
Completeness to theta = 67.679°	99.9 %			
Absorption correction	Semi-empirical from equivalents			
Max. and min. transmission	0.7531 and 0.6681			
Refinement method	Full-matrix least-squares on F ²			
Data / restraints / parameters	6518 / 70 / 414			
Goodness-of-fit on F ²	1.123			
Final R indices [I>2sigma(I)]	R1 = 0.0701, $wR2 = 0.1767$			
R indices (all data)	R1 = 0.0866, wR2 = 0.1927			
Absolute structure parameter	0.15(11)			
Largest diff. peak and hole	0.430 and -0.172 e.Å ⁻³			

