Further Studies of the Structure–Activity Relationships of 1-[1-(2-Benzo[*b*]thienyl)cyclohexyl]piperidine. Synthesis and Evaluation of 1-(2-Benzo[*b*]thienyl)-*N*,*N*-dialkylcyclohexylamines at Dopamine Uptake and Phencyclidine Binding Sites

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We previously reported (*J. Med. Chem.* **1993**, *36*, 1188–1193) that changes to the ring size of the piperidine and cyclohexyl rings of the high-affinity and selective dopamine (DA)-uptake inhibitor 1-[1-(2-benzo[*b*]thienyl)cyclohexyl]piperidine (BTCP, **2**) caused different, and in some cases opposite, changes in affinity for sites on the DA transporter labeled by [^{3}H]BTCP and [^{3}H]-cocaine. These results suggested that the radioligands label different sites on the transporter. In the present study, we extend the structure–activity relationships (SAR) of BTCP by studying the binding characteristics of a series of N,N-disubstituted 1-(2-benzo[*b*]thienyl)cyclohexylamines **7–32** at the DA transporter. Cyclohexyl was selected as opposed to other ring sizes since it corresponds to BTCP. The binding results indicate that a considerable degree of structural variation is permitted for the N-substituents, while still retaining nanomolar affinity for sites on the transporter (studied in rat forebrain homogenates). As observed in our earlier study, the differential effects of structural change on binding to sites on the DA transporter labeled by these radioligands suggests that they are different and distinct binding sites. In general, and up to a point, increasing the size and lipophilicity of the *N* substituents resulted in improvements in binding but appeared to have less predictable effects on DA-uptake inhibition (as measured in rat brain synaptosomes). The binding of these compounds to sites labeled by [^{3}H]BTCP appeared to correlate best with IC_{50} for DA-uptake inhibition. To our surprise, the monoalkyl N-substituted BTCP derivatives displayed the highest affinity for the DA transporter of all the compounds in this series. For example, the *N*-(cyclopropylmethyl) derivative **14** displayed IC_{50}'s = 23 nM ([^{3}H]cocaine) and 1 nM ([^{3}H]-BTCP), and the *N*-butyl derivative **10** showed IC_{50}'s = 60 nM ([^{3}H]cocaine) and 0.3 nM ([^{3}H]-BTCP). BTCP exhibited IC_{50}'s of 39 nM ([^{3}H]cocaine) and 5 nM ([^{3}H]BTCP) in this assay. The observation that *N*,*N*-dibutyl derivative **31** exhibited low ratios of IC_{50} [^{3}H]cocaine/IC_{50} DA reuptake and IC_{50} [^{3}H]BTCP/IC_{50} DA reuptake suggests that it may be a potential candidate for cocaine antagonism studies. The effect of additional amino, amide, and aromatic groups on the N-substituents was examined, and the results are discussed. The failure of all of the compounds in this series to bind phencyclidine receptors coupled with their high affinity and range of selectivities at the DA transporter identifies many of them as useful tools for probing the mode of action of BTCP at this site.

Introduction

Intensive structure–activity (SAR) studies of the drug of abuse phencyclidine (**1**) have furthered our knowledge of its mechanism of action at PCP binding sites on the *N*-methyl-D-aspartate/Ca^{2+} channel complex.[1] These studies have furnished novel compounds showing both improved affinity and improved selectivity for PCP binding sites.[1,2] Several of these compounds, including dizocilpine (MK801),[3] are effective noncompetitive inhibitors of the excitotoxic effects of endogenously released excitatory amino acids (EAA).[4]

The structurally related 1-[1-(2-benzo[*b*]thienyl)cyclohexyl]piperidine (BTCP, **2**; Chart I)[5] binds potently and selectively with central dopamine (DA) uptake sites ("cocaine receptors") but fails to interact with PCP receptors. Like cocaine, BTCP inhibits the uptake of DA into dopaminergic neurons.[6] Koek et al.[7] found that BTCP elicits cocaine-like behavioral effects in rodents and birds.

Chart I

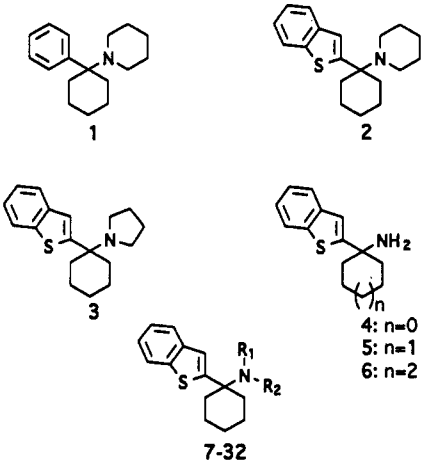

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Table I. Physical and Chemical Properties of Target Compounds and Their Intermediates

compd	salt[a]	solvent	mp (°C)	method[b]	MS	formula[c]	yield (%)[l]
7	fumarate	MeOH/2-PrOH	173–173.5	G	$MH^+(C_{18}H_{19}NS)$	$C_{18}H_{23}NO_4S$	91.5
8[d]	fumarate	EtOH	161.5–163	H	$M^+(C_{18}H_{21}NS)$	$C_{20}H_{25}NO_4S$	80
9	fumarate	EtOAc/2-PrOH	177–178	H	$MH^+(C_{17}H_{23}NS)$	$C_{21}H_{27}NO_4S$	83
10	fumarate	EtOH	141–142	H	$MH^+(C_{18}H_{25}NS)$	$C_{22}H_{29}NO_4S$	71
11	fumarate	2-PrOH	145–146	H	$MH^+(C_{18}H_{27}NS)$	$C_{23}H_{31}NO_4S{\cdot}0.25H_2O$	58
12[d]	fumarate	2-PrOH	175–176.5	I	$MH^+(C_{17}H_{21}NS)$	$C_{21}H_{25}NO_4S$	58
13	HCl	2-PrOH	220–221	G	$MH^+(C_{19}H_{25}NS)$	$C_{18}H_{26}ClNS$	100
14[d]	fumarate	EtOAc	177.5–178	H	$MH^+(C_{18}H_{23}NS)$	$C_{22}H_{27}NO_4S{\cdot}0.25H_2O$	75
15	fumarate	EtOAc/2-PrOH	166–167	H	$MH^+(C_{18}H_{25}NS)$	$C_{23}H_{29}NO_4S$	83
16[d]	fumarate	EtOAc	172–173	H	$MH^+(C_{21}H_{23}NS)$	$C_{25}H_{27}NO_4S$	22
17	fumarate	2-PrOH	180–180.5	G	$MH^+(C_{22}H_{23}Cl_2NS)$	$C_{26}H_{27}Cl_2NO_4S$	82
18	free base	hexane/EtOAc	147–148	A	$MH^+(C_{24}H_{26}Cl_2N_2OS)$	HRMS[e]	31
19	fumarate	2-PrOH	185–186	G	$M^+(C_{24}H_{23}Cl_2N_2S)$	HRMS[f]	82
20[d]	fumarate	2-PrOH	145–147	F	$MH^+(C_{18}H_{20}N_2OS)$	$C_{20}H_{24}N_2O_5S{\cdot}H_2O$	83
21	HCl	2-PrOH	250–251 dec	H	$MH^+(C_{18}H_{22}N_2S)$	$C_{18}H_{24}Cl_2N_2S$	66
22[d]	fumarate	2-PrOH	177–178	H	$MH^+(C_{17}H_{24}N_2S)$	$C_{25}H_{32}N_2O_8S$	41
23[g]	HCl	EtOAc	171–173	F	$MH^+(C_{17}H_{24}N_2S)$	$C_{17}H_{26}Cl_2N_2S$	86
24	fumarate	2-PrOH	161–163	H	$MH^+(C_{18}H_{28}N_2S)$	$C_{26}H_{24}N_2O_8S{\cdot}0.5H_2O$	28
25	HCl	2-PrOH	261–262	H	$MH^+(C_{18}H_{28}N_2S)$	$C_{18}H_{30}Cl_2N_2S$	72
26	fumarate	2-PrOH	179–181	H	$M^+(C_{18}H_{21}NS)$	$C_{20}H_{25}NO_4S$	44
27[h]	fumarate	2-PrOH	150–151	D	$MH^+(C_{18}H_{25}NS)$	$C_{22}H_{29}NO_4S$	76
28[d]	HCl	EtOAc	151–152	E	$MH^+(C_{18}H_{27}NS)$	$C_{18}H_{28}ClNS$	94
29[i]	HCl	EtOAc	154–156	D	$MH^+(C_{20}H_{28}NS)$	$C_{20}H_{31}ClNS{\cdot}0.25H_2O$	92
30	fumarate	EtOAc	156–157	E	$MH^+(C_{18}H_{27}NS)$	$C_{23}H_{31}NO_4S$	91
31	$HClO_4$	EtOAc	134–136	E	$MH^+(C_{22}H_{33}NS)$	$C_{22}H_{34}ClNO_4S$	88
32[d]		EtOAc/hexane	207–208	H	$MH^+(C_{17}H_{20}N_2OS)$	$C_{17}H_{20}N_2OS$	37
33[d]		EtOAc	144–145	C	$MH^+(C_{18}H_{17}NOS)$	$C_{18}H_{17}NOS$	97
34		hexane	157–158	A	$MH^+(C_{18}H_{19}NOS)$	$C_{18}H_{19}NOS$	92
35		hexane	177–178	A	$MH^+(C_{17}H_{21}NOS)$	$C_{17}H_{21}NOS$	96
36[d]		hexane	131.5–132	A	$MH^+(C_{18}H_{23}NOS)$	$C_{18}H_{23}NOS$	97
37		hexane	156–157	A	$MH^+(C_{18}H_{25}NOS)$	$C_{18}H_{25}NOS$	100
38[d]		hexane	178–179	A	$MH^+(C_{18}H_{21}NOS)$	$C_{18}H_{21}NOS$	96
39[j]		hexane	170–171	A	$MH^+(C_{18}H_{23}NOS)$	$C_{18}H_{23}NOS$	94
40		hexane	163–164	A	$MH^+(C_{21}H_{21}NOS)$	$C_{21}H_{21}NOS$	98
41		hexane/$CHCl_3$	214–215	A	$MH^+(C_{22}H_{21}Cl_2NOS)$	$C_{22}H_{21}Cl_2NOS{\cdot}0.25H_2O$	87
42		hexane	177.5–178.5	A	$M^+(C_{17}H_{19}NOS)$	$C_{17}H_{19}NOS{\cdot}0.25H_2O$	99
43		hexane	142–143	A	$MH^+(C_{18}H_{23}NOS)$	$C_{18}H_{23}NOS$	92
44[d,k]		oil		B	$MH^+(C_{21}H_{28}N_2O_3S)$	$C_{21}H_{28}N_2O_3S$	100
45		hexane	139–140	B	$MH^+(C_{22}H_{30}N_2O_3S)$	$C_{22}H_{30}N_2O_3S$	68
46		hexane	116–117	B	$MH^+(C_{23}H_{32}N_2O_3S)$	$C_{23}H_{32}N_2O_3S$	100
47		foam		C	$MH^+(C_{18}H_{19}NOS)$	$C_{18}H_{19}NOS$	81
48[d]	fumarate	2-PrOH	209–210 dec	H	$MH^+(C_{22}H_{32}N_2O_2S)$	$C_{26}H_{36}N_2O_6S$	25
49[d]	fumarate	2-PrOH	174–175	G	$MH^+(C_{22}H_{24}ClNS)$	mixture of 3- and 4-isomers	5

[a] Salts were crystallized from ca. 1:10 weight/volume ratio of salt to solvent. [b] Methods as described in the Experimental Section. [c] Elemental analyses were determined to be within ±0.4% of the theoretical values for C, H, and N unless indicated otherwise. [d] See ref 13 for ^{1}H-NMR spectral data. [e] HRMS MH^+ (calcd for $C_{24}H_{26}Cl_2N_2OS$) 461.1221, MH^+ (found) 461.1225. [f] HRMS M^+ (calcd for $C_{24}H_{28}Cl_2N_2S$) 446.1350, M^+ (found) 446.1358. [g] Anal. Calcd for $C_{17}H_{26}Cl_2N_2S$: C, 56.50; H, 7.25; N, 7.75. Found: C, 57.26; H, 7.48; N, 6.67 (due to extensive solvation). [h] Previously reported compound (ref 5b); lit. mp of 27·HCl 160–161 °C. [i] Previously reported compound (ref 5b); lit. mp of 29·HCl: 157–158 °C. [j] Anal. Calcd for $C_{18}H_{23}NOS$: C, 72.80; H, 7.40; N, 4.47. Found: C, 72.36; H, 7.36; N, 4.43 (due to solvation). [k] Anal. Calcd for $C_{21}H_{28}N_2O_3S{\cdot}0.6CH_2Cl_2$: C, 59.03; H, 6.70; N, 6.38. Found: C, 58.95; H, 6.61; N, 6.55 (due to solvation). [l] All yields are nonoptimized.

In view of the wealth of SAR studies of PCP, it appeared to us that similar studies for BTCP were conspicuously lacking. We therefore pursued a limited SAR study to investigate the optimal ring sizes for binding of BTCP to the DA transporter.[8] A certain degree of correlation between binding affinity and their potency as DA-uptake inhibitors was evident from this study. More interestingly, certain of the compounds in this study were more potent in binding to the transporter than their DA-uptake inhibitory potency would predict.

In our earlier study,[8] we established that BTCP and cocaine bind to different sites on the transporter and that the cyclohexane and piperidine rings already present in BTCP are optimal for its high affinity at sites labeled by [^{3}H]BTCP but not [^{3}H]cocaine since **3** (Chart I), which contains a pyrrolidine ring, was the highest-affinity ligand at sites labeled by [^{3}H]cocaine.

In order to further the SAR of **2** and possibly to identify potential cocaine antagonists, we report here the synthesis and interaction at the DA-uptake site of a series of ring-opened or N,N-disubstituted derivatives (**7–32**) of BTCP (Chart I and Table II). The impetus for the present investigation was our observation[8] that the primary amine derivatives (**4–6**) still possessed good affinity for sites on the transporter labeled by [^{3}H]BTCP and [^{3}H]-cocaine. Additionally, the *N,N*-diethyl and *N,N*-dipropyl derivatives (**27** and **29**) were reported to have almost equipotent (with BTCP) binding at the DA-uptake site.[5b] In pursuing the present study, we also noted that **4–6** were more potent at inhibiting DA uptake than their binding affinity would suggest.

Chemistry

N-Formylation of **5**[9] with refluxing ethyl formate in the presence of a trace of formic acid gave N-formamide **33** (Scheme I) in 97% yield, while treatment of **5** with the appropriate acid chloride in the presence of Et_3N gave amides **34–43** (87–100% yield) (Schemes I and II). 1-[3-(Dimethylamino)propyl]-3-ethylcarbodiimide-mediated coupling of **5** with *N*-Boc-protected glycine, β-alanine, and γ-aminobutyric acid afforded amides **44–46** (68–100%

Table II. Dopamine-Uptake Inhibition and Binding Affinity of Cocaine, BTCP (2), and 7–32 at Sites Labeled by [^{3}H]Cocaine, [^{3}H]BTCP, and [^{3}H]TCP[b]

compd	NR_1R_2 (in Chart I)	IC_{50} (nM)[a] [^{3}H]Coc	[^{3}H]BTCP	[^{3}H]DA-uptake inhibition	ratio IC_{50} [^{3}H]BTCP/ IC_{50} [^{3}H]DA uptake	ratio IC_{50} [^{3}H]Coc/ IC_{50} [^{3}H]DA uptake
2 (BTCP)	$(CH_2)_5$	39 ± 5	5 ± 0.4	11 ± 1	0.45	3.5
3	NH_2	684[c]	123[c]	78[c]	1.6	8.8
cocaine		82 ± 7	179 ± 14	296 ± 19	0.60	0.28
7	NHMe	270 ± 28	101 ± 2	57 ± 6	1.8	4.7
8	NHEt	165 ± 17	22 ± 4	22 ± 3	1.0	7.5
9	NHPr	57 ± 12	4 ± 0.9	5 ± 1	0.8	11
10	NHBu	60 ± 14	0.3 ± 0.03	7 ± 1	0.043	8.6
11	NHPent	337 ± 36	24 ± 5	34 ± 7	0.71	9.9
12	NHAllyl	57 ± 3	7 ± 0.6	11 ± 0.5	0.64	5.2
13	$NHCH_2CH{=}CMe_2$	50 ± 3	8 ± 0.5	14 ± 7	0.57	3.6
14	NHCyclopropylmethyl	23 ± 5	1 ± 0.2	4 ± 0.5	0.25	5.8
15	NHCyclobutylmethyl	37 ± 2	4 ± 1	7 ± 1	0.57	5.3
16	$NHCH_2Ph$	1651 ± 148	143 ± 14	196 ± 23	0.73	8.4
17	$NH(CH_2)_2$-3,4-Cl_2Ph	>5000	1002 ± 138	>5000	<0.20	
18	$NH(CH_2)_2NHCOCH_2$-3,4-Cl_2Ph	1476 ± 140	579 ± 56	947 ± 100	0.61	1.6
19	$NH(CH_2)_2NH(CH_2)_2$-3,4-Cl_2Ph	713 ± 96	211 ± 10	174 ± 17	1.2	4.1
20	$NHCOCH_2NH_2$	841 ± 167	114 ± 9	138 ± 12	0.83	6.1
21	$NH(CH_2)_2NH_2$	170 ± 41	30 ± 6	88 ± 14	0.34	1.9
22	$NH(CH_2)_2NHMe$	63 ± 12	17 ± 1	29 ± 4	0.59	2.2
23	$NH(CH_2)_3NH_2$	930 ± 150	58 ± 10	33 ± 4	1.8	28
24	$NH(CH_2)_3NHMe$	746 ± 98	8 ± 0.7	89 ± 13	0.090	8.4
25	$NH(CH_2)_4NHMe$	328 ± 43	50 ± 7	33 ± 4	1.5	9.9
26	NMe_2	84 ± 17	27 ± 5	51 ± 7	0.50	1.6
27[d]	NEt_2	42 ± 6	12 ± 0.5	12 ± 2	1.0	3.5
28	NEtPr	207 ± 34	20 ± 1	17 ± 2	1.2	12
29[d]	NPr_2	220 ± 37	37 ± 6	81 ± 9	0.46	2.7
30	NMeBu	161 ± 21	21 ± 2	33 ± 9	0.64	4.9
31	NBu_2	386 ± 75	124 ± 7	1363 ± 183	0.091	0.28
32	$(CH_2)_2NHCO$	>5000	1744 ± 270	2124 ± 368	0.82	>2.4

[a] Each value is the result of three experiments, each performed in triplicate (rat forebrain). The [^{3}H]cocaine and [^{3}H]BTCP binding and [^{3}H]DA uptake was performed as described in our earlier study.[8] [b] All compounds exhibited k_i values >10 000 nM for sites labeled by [^{3}H]TCP in rat brain homogenates; the binding was performed as described previously.[8,12] [c] Previously reported data.[8] [d] Previous reported compound.[5b]

yield). The amide carbonyl of these intermediates was readily reduced with $LiAlH_4$ in THF to give the target compounds **22**, **24**, and **25**, some of which were further transformed (Scheme III). Compounds **7–11**, **13–17**, **19**, and **21** (22–100%) (Schemes I–III) were prepared via AlH_3[10] or $LiAlH_4$ reduction of the appropriate amide precursors.

Compound **12** was obtained by N-alkylation of **5** with allyl bromide since attempted reduction of the acrylamide **42** proved unsuccessful (Scheme II). The more hindered **13**, however, was readily prepared via AlH_3 reduction of the dimethylacrylamide intermediate **43** (Scheme II). Interestingly, $LiAlH_4$ reduction of **44** to **22** (Scheme III) gave the imidazolone **32** as a side product (37%) due to the more rapid reduction of the amide (compared to the tBoc carbamate) carbonyl. Compound **32** exhibited a characteristic IR absorption at 1696.4 cm^{-1} for the urea carbonyl stretch. The greater resistance of the carbamate carbonyl to reduction was also evident during the $LiAlH_4$ reduction of **45** to **24** (Scheme III) in which **48** was formed as the major product.

Reduction of **41** (Scheme II) with AlH_3[10] afforded **17** as the major product together with a trace of monochloro mixture **49**. The formation of **49** is surprising in view of the lack of reactivity we have typically observed for the (3,4-dichlorophenyl)ethyl group to AlH_3.[11]

The sequence of N-formylation of amine **7** followed by reduction with $LiAlH_4$ gave *N,N*-dimethyl derivative **26**. Dialkyl-substituted amines **27–31** were obtained from primary amine **5** or monoalkyl-substituted amines **8** and **10** (Scheme I) by reductive alkylation with the appropriate aldehyde in the presence of AcOH and $Na(CN)BH_4$.

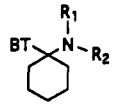
Results and Discussion

The results (Table II) indicate that a considerable degree of structural variation is permitted for the N-substituents while still retaining nanomolar affinity at the DA transporter. Varying the N-substituents has differential effects on binding ([^{3}H]BTCP and [^{3}H]cocaine). This suggests that these radioligands are interacting at distinct sites on the transporter.

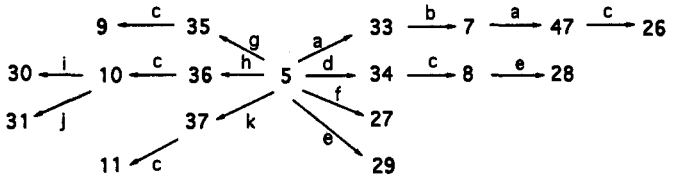
Increasing the size, to a certain point, of the *N*-alkyl groups (as in **7**, **26**, **28**, **29**, etc.) resulted in improvements in binding to the transporter. Further increases in the size of the alkyl groups beyond *N,N*-diethyl resulted in reductions in binding affinity at sites labeled by both [^{3}H]-BTCP and [^{3}H]cocaine, suggesting the existence of a boundary condition at the binding site. The results of increasing alkyl size on IC_{50} value for DA reuptake appeared to be less predictable.

Surprisingly, the monoalkyl-substituted derivatives furnished the highest-affinity ligands for the DA transporter in this series. The *N*-(cyclopropylmethyl) derivative **14** displayed the highest affinity (IC_{50} = 23 nM) for sites labeled by [^{3}H]cocaine while the *N*-butyl derivative **10** showed the highest affinity (IC_{50} = 0.3 nM) for sites on the transporter labeled by [^{3}H]BTCP. Further increases in the size of the *N*-alkyl group of the monoalkyl derivatives (e.g. **11**) resulted in reductions in affinity. As for the dialkyl-substituted compounds, increasing the size of the monoalkyl congeners failed to have predictable effects on DA-uptake inhibitory potency.

Scheme I[a]



Compd	R_1	R_2
5	H	H
7	H	Me
8	H	Et
9	H	nPr
10	H	nBu
11	H	nPent
26	Me	Me
27	Et	Et
28	Et	nPr
29	nPr	nPr
30	Me	nBu
31	nBu	nBu
33	H	CHO
34	H	MeCO
35	H	EtCO
36	H	nPrCO
37	H	nBuCO
47	Me	CHO

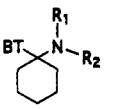


[a] (a) EtOCHO, HCOOH, reflux; (b) AlH_3, THF, room temperature; (c) $LiAlH_4$, THF, reflux; (d) MeCOCl, Et_3N, THF, room temperature; (e) EtCHO, AcOH, MeCN, $Na(CN)BH_3$, room temperature; (f) MeCHO, AcOH, MeCN, $Na(CN)BH_3$, room temperature; (g) EtCOCl, Et_3N, THF, room temperature; (h) PrCOCl, Et_3N, THF, room temperature; (i) HCHO, AcOH, MeCN, $Na(CN)BH_3$, room temperature; (j) PrCHO, AcOH, MeCN, $Na(CN)BH_3$, room temperature; (k) BuCOCl, Et_3N, THF, room temperature.

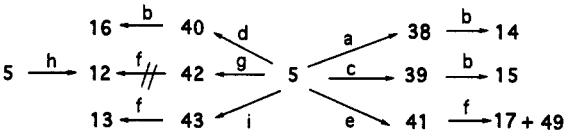
The presence of unsaturation as in **12** and **13** failed to improve either binding activity or DA-transport inhibitor activity, while addition of a phenyl ring to **7** as in **16** caused a reduction in binding affinity. The failure of unsaturation or phenyl substituents to improve the binding interaction indicates the absence of additional π-bonding groups at the receptor site. Similarly, the failure of additional amino groups (as in **21**, **22**, **24**, and **25**) to improve binding and transport inhibitory activity indicates the absence of additional H-bonding sites.

It is interesting to note differential affects such as the 12-fold reduction ([^{3}H]cocaine displacement) and the 2-fold increase ([^{3}H]cocaine displacement) in binding on addition of a single methylene group to **22** (as in **22** → **24**). However, binding activity at sites labeled by both of these radioligands roughy doubles on extending **24** by one further methylene group to give **25**. [^{3}H]DA-uptake inhibitory activity appears to correlate with the displacement activity of these diamines at sites labeled by [^{3}H]cocaine. Addition of a methyl group to the terminal N atom of these diamines results in an overall improvement in both binding and DA-uptake inhibitory activity. However, addition of a methyl group to the terminal N atom of **23** (to give **24**) caused an improvement in binding but a decrease in uptake inhibitor activity. The unpredictable, and in some cases

Scheme II[a]



Compd	R_1	R_2
5	H	H
12	H	allyl
13	H	3,3-dimethylallyl
14	H	cyclopropylmethyl
15	H	cyclobutylmethyl
16	H	Bn
17	H	2-(3,4-dichlorophenyl)ethyl
38	H	cyclopropylCO
39	H	cyclobutylCO
40	H	Bz
41	H	3,4-dichlorophenylacetyl
42	H	acryl
43	H	Me_2C=CHCO
49	H	2-(3- and 4-chlorophenyl)ethyl mixture



[a] (a) cyclopropylcarbonyl chloride, Et_3N, THF, room temperature; (b) $LiAlH_4$, THF; (c) cyclobutylcarbonyl chloride, Et_3N, THF, room temperature; (d) benzoyl chloride, Et_3N, THF, room temperature; (e) 3,4-dichlorophenylacetyl chloride, Et_3N, THF, room temperature; (f) AlH_3, THF, room temperature; (g) acroyl chloride, Et_3N, THF, room temperature; (h) allyl bromide, K_2CO_3, EtOH, reflux; (i) 3,3-dimethylacroyl chloride, Et_3N, THF, room temperature.

opposing, effects on radioligand binding in homologous diamines **22**, **24**, and **25** suggests that they have complex interactions with the DA transporter.

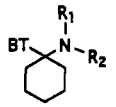
The addition of a large lipophilic N-substituent such as in compound **17** abolished activity at the DA transporter, again indicating an upper limit to size and/or lipophilicity of the *N*-alkyl group. Insertion of an aminomethyl moiety into **17** (resulting in **19**) caused improvement in binding, perhaps due to a reduction in lipophilicity.

The relatively high potency of **21** suggests a degree of tolerance to the location of the basic amine nitrogen. The weak, but nonetheless significant, activity of **32** indicates that an H-bonding amide group may serve some of the function of a basic N atom in binding.

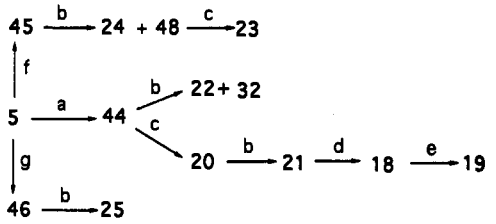
It is notable that the lowest ratios of IC_{50} [^{3}H]BTCP/IC_{50} [^{3}H]DA reuptake occurred with **10**, **24**, and **31** while the lowest ratios of IC_{50} [^{3}H]cocaine/IC_{50}[^{3}H]DA reuptake occurred with cocaine and compound **31**. Since **31** exhibited favorable (low) ratios for both [^{3}H]cocaine and [^{3}H]BTCP binding, it may be a good candidate for evaluation as a cocaine antagonist. The very high (subnanomolar) affinity of **10** for sites labeled by [^{3}H]BTCP compared with its high potency at inhibiting DA reuptake identifies it as a useful probe for study of the DA transporter.

Inspection of the data reveals that in general (with a few exceptions) there exists a good correlation between IC_{50} for inhibition of DA reuptake and IC_{50} for displacement of [^{3}H]BTCP, suggesting that this site may mediate

Scheme III[a]



Compd	R_1	R_2
5	H	H
18	H	$(CH_2)_2NHCOCH_2$-3,4-Cl_2Ph
19	H	$(CH_2)_2NH(CH_2)_2$-3,4-Cl_2Ph
20	H	$COCH_2NH_2$
21	H	$(CH_2)_2NH_2$
22	H	$(CH_2)_2NHMe$
23	H	$(CH_2)_3NH_2$
24	H	$(CH_2)_3NHMe$
25	H	$(CH_2)_4NHMe$
32	R_1,R_2N =	
44	H	$COCH_2NHtBOC$
45	H	$CO(CH_2)_2NHtBOC$
46	H	$CO(CH_2)_3NHtBOC$
48	H	$(CH_2)_3NHtBOC$



[a] (a) Boc-glycine, $Me_2N(CH_2)_3N{=}C{=}NEt{\cdot}HCl$, CH_2Cl_2, Et_3N, room temperature; (b) $LiAlH_4$, THF, reflux; (c) CF_3CO_2H, $CHCl_3$, room temperature; (d) 3,4-dichlorophenylacetyl chloride, Et_3N, THF, room temperature; (e) AlH_3, THF, room temperature; (f) Boc-β-alanine, $Me_2N(CH_2)_3N{=}C{=}NEt{\cdot}HCl$, Et_3N, CH_2Cl_2, room temperature; (g) Boc-γ-aminobutyric acid, $Me_2N(CH_2)_3N{=}C{=}NEt{\cdot}HCl$, CH_2Cl_2, Et_3N, room temperature.

inhibition of DA reuptake in the BTCP-type compounds. This is further supported by compound **23** which has weak binding to sites labeled by [^{3}H]cocaine and yet is a potent inhibitor of DA uptake.

The diversity of potency of these BTCP congeners at sites labeled by [^{3}H]BTCP and [^{3}H]cocaine coupled with their high selectivity for the transporter versus PCP receptors identifies this series, particularly certain compounds such as **10** and **31**, as tools for further study of the transporter. The inability of these compounds to bind PCP receptors was not unexpected since previous studies,[5,8] indicated that the 1-(2-benzo[*b*]thienyl)cyclohexylamines possessed negligible affinity (IC_{50} > 10 000 nM, [^{3}H]TCP) for PCP receptors.

Experimental Section

Chemistry: Materials and Methods. Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Elemental analyses were performed at Atlantic Microlabs, Atlanta, GA. Chemical ionization mass spectra (CIMS) were obtained using a Finnigan 1015 mass spectrometer. Electron ionization mass spectra (EIMS) and high-resolution mass measurements (HRMS) were obtained using a VG-Micro Mass 7070F mass spectrometer. IR spectra were recorded from $CHCl_3$ solutions of compounds using a Bio-Rad FTS-45 FTIR spectrometer. ^{1}H-NMR spectra were recorded from $CDCl_3$ solutions using a Varian XL-300 spectrometer; results are recorded as ppm downfield of the TMS signal. Spectral data (^{1}H-NMR and IR) for all amines is reported for the free base form. Thin-layer chromatography (TLC) was performed on 250 μM Analtech GHLF silica gel plates. TLC solvent system A refers to concentrated aqueous ammonia–MeOH–$CHCl_3$ (1:9:90). TLC solvent system B refers to ethyl acetate–hexane (1:3). No attempt was made to optimize the yields.

Preparation of *N*-[1-(2-Benzo[*b*]thienyl)cyclohexyl]-amides (18, 34–43, Schemes I–III). General Method A. To a stirred solution of amine **5** (4.62 g, 20 mmol) and triethylamine (6 g, 60 mmol) in dry THF (80 mL) was added dropwise at room temperature a solution of acid chlorides (24 mmol) in THF (20 mL). Progress of the reaction mixture was monitored by TLC (solvent system A). After 1 h, at room temperature, the white precipitate of $Et_3N{\cdot}HCl$ was removed by filtration, and the filter cake was washed with a little dry THF. The filtrate was evaporated in vacuo to give the crude products as oils. These were dissolved in $CHCl_3$ (100 mL), washed with 15% aqueous citric acid (50 mL) and water (50 mL), and dried (Na_2SO_4). Evaporation of the solvent afforded the purified products **34–43**, which were crystallized from the appropriate solvent (see Table I).

In the case of **18**, the starting material was **21** instead of **5**.

Preparation of *N*-[1-(2-Benzo[*b*]thienyl)cyclohexyl]-amides (44–46, Scheme III). General Method B. To a stirred solution of *N*-tBoc-protected amino acid (26 mmol) in alcohol-free CH_2Cl_2 (100 mL) was added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (5.0 g, 26 mmol). After 5 min of stirring at room temperature, a solution of **5** (4.62 g, 20 mmol) in CH_2Cl_2 (50 mL) was added followed by triethylamine (6 g, 60 mmol) in CH_2Cl_2 (40 mL). The reaction mixture was stirred overnight at room temperature when TLC (solvent system A) indicated the reaction to be complete. The reaction mixture was evaporated, and the residue was taken up in ethyl acetate (100 mL). The solution was washed with 10% aqueous Na_2CO_3 (50 mL), 15% aqueous citric acid (2 × 50 mL), and water (50 mL) and dried (Na_2SO_4). Evaporation of the solvent in vacuo afforded the products (44–76%) as colorless oils, some of which were crystallized from the appropriate solvents (Table I).

Preparation of *N*-[1-(2-Benzo[*b*]thienyl)cyclohexyl]formamides (33, 47, Scheme I). General Method C. To a stirred solution of amine (20 mmol) in ethyl formate (50 mL) was added 0.5 mL of formic acid (88%), and the reaction mixture was boiled under reflux overnight, after which time TLC (solvent system A) indicated the reaction to be complete. The solvent was evaporated in vacuo to give the products as colorless oils. Further purification could be achieved by crystallization (Table I).

Preparation of 27 and 29 (Scheme I) by Reductive Dialkylation of Primary Amine 5. General Method D. To a stirred solution of primary amine **5** (700 mg, 3 mmol) in dry acetonitrile (20 mL) at 4 °C was added aldehyde (50 mmol). After the reaction mixture was stirred for 15 min at 4 °C, $Na(CN)BH_3$ (570 mg, 9.1 mmol) was added in one portion. The pH was adjusted to 6 by addition of glacial acetic acid, and stirring was continued for a further 4 h when TLC (solvent system A) indicated complete reaction. The solution was adjusted to pH = 9 by dropwise addition of concentrated aqueous NH_3 solution, and then water (100 mL) was added. The aqueous mixture was extracted with ether (2 × 100 mL). The combined ethereal extract was back-washed with water (50 mL) and dried (Na_2SO_4), and the solvent was evaporated in vacuo to give the crude products as pale yellow oils which were purified further by column chromatography on silica gel eluting with solvent system B. Suitable salts were formed in an appropriate solvent (see Table I).

Preparation of 28, 30, and 31 (Scheme I) by Reductive Alkylation of Secondary Amines 8 and 10. General Method E. Secondary amine (2 mmol) in dry acetonitrile (15 mL) at 4 °C was treated with aldehyde (40 mmol), and the reaction mixture was stirred at this temperature for 15 min and then treated with $Na(CN)BH_3$ (380 mg, 6 mmol) in one portion. The solution was adjusted to pH = 5 by dropwise addition of acetic acid. The reaction was allowed to proceed for 6 h at 4 °C and then quenched by the addition of concentrated aqueous NH_3 solution (to pH = 9) followed by water (100 mL). The aqueous mixture was

extracted with ether (2 × 100 mL), and the combined ethereal extracts were back-washed with water (50 mL), dried (Na_2SO_4), and evaporated in vacuo to give the crude products as oils. Further purification was achieved by column chromatography on silica gel eluting with solvent system B followed by salt formation (see Table I).

Synthesis of 20 and 23 (Scheme III) by N-Deprotection of t-Boc-Protected Amines 44 and 48. General Method F. Carbamates 44 and 48 (20 mmol) in hydrocarbon-stabilized $CHCl_3$ (100 mL) were treated dropwise at room temperature with CF_3CO_2H (40 mL), and the reactions were monitored by TLC (solvent system A) until complete (ca. 20 min). The solvent was evaporated in vacuo, and the residue was dissolved in $CHCl_3$ (100 mL) and washed with 10% aqueous Na_2CO_3 (3 × 50 mL) to remove CF_3COOH, followed by 15% aqueous citric acid (3 × 70 mL). The combined aqueous citric acid extract was washed with ether (2 × 50 mL), and the ether extracts were discarded. The aqueous layer was rendered basic by addition of concentrated aqueous NH_3 and extracted with $CHCl_3$ (100 mL). The $CHCl_3$ extract was back-washed with water (50 mL) and dried (Na_2SO_4) and the solvent was evaporated in vacuo to give the products as colorless oils which were obtained in crystalline form as suitable salts (Table I).

Synthesis of Amines 7, 13, 17, 19, and 49 (Schemes I–III) by Alane Reduction of Amides 18, 33, 41, and 43. General Method G. To a stirred solution of AlH_3 in THF (10 mL of a 1.0 M solution, 10 mmol prepared as described in ref 10) at room temperature was added a solution of amides (2 mmol) in dry THF (10 mL). The solution was stirred for 20 min at room temperature or until TLC (solvent system A) indicated the reaction to be complete. The reaction mixture was poured into 30 mL of cold (0 °C) 15% aqueous NaOH and extracted with $CHCl_3$ (50 mL). The organic extract was dried (Na_2SO_4) and evaporated in vacuo to give the crude amine products as oils which were further purified by column chromatography (solvent system B) and suitable salt formation (see Table I).

Synthesis of Amines 8–11, 14–16, 21, 22, 24–26, and 48 (Schemes I–III) by $LiAlH_4$ Reduction of Amides 20, 34–40, and 44–47. General Method H. To a stirred solution of $LiAlH_4$ in THF (20 mL of a 1.0 M solution, 20 mmol) at room temperature was added dropwise during 10 min a solution of amides (4 mmol) in dry THF (20 mL). The reaction mixture was boiled under reflux for 2 h at room temperature, cooled to 0 °C, and then treated dropwise with water (0.76 mL), 15% aqueous NaOH (0.76 mL), and finally water (2.28 mL). The mixture was stirred for 45 min at room temperature and then filtered. The filtrate was washed with a little THF, and the combined filtrate and washings were evaporated in vacuo to yield the products as colorless oils which were obtained in crystalline form by salt formation (see Table I). Compounds 24 and 28 required purification by column chromatography prior to salt formation.

Formation of 1-[1-[2-(Benzo[*b*]thienyl)cyclohexyl]]imidazolin-2-one (32) from $LiAlH_4$ Reduction of 44. Treatment of 44 with $LiAlH_4$ as described in method H above gave a 1:1 (^{1}H-NMR) mixture of the required diamine 22 together with 32. These were separated by column chromatography on silica gel, eluting with solvent system B. Compounds 22 and 32 exhibited spectral characteristics as in Table I and ^{1}H-NMR signals as in ref 13; compound 32 exhibited the following spectral characteristics: ^{13}C-NMR δ 162.8 (weak), 150.5 (weak), 139.7 (weak), 139.3 (weak), 124.3, 124.2, 123.7, 122.4, 120.7, 60.1 (weak), 43.3, 37.8, 37.0, 25.7, 22.9; FTIR (KBr) 3455.6 (NH str), 2940.1, 2860.2, 1696.4 (strong, characteristic for urea C=O str), 1417.8, 1267.6 cm^{-1}.

***N*-Allyl-1-(2-benzo[*b*]thienyl)cyclohexylamine (12). Method I.** A mixture of 5 (2.31 g, 10 mmol), allyl bromide (1.33 g, 11 mmol), and anhydrous K_2CO_3 (4.14 g, 30 mmol) in anhydrous ethanol (30 mL) was boiled under reflux overnight. The reaction mixture was cooled, the solvent was evaporated to vacuo, and the residue was taken up in water (50 mL) and extracted with ether (2 × 50 mL). The ether layer was dried (Na_2SO_4) and evaporated, and the crude product was purified by chromatography on silica gel, eluting with solvent system B to give 12 as a colorless oil (1.57 g, 58%) which was further purified by salt formation (Table I).

Biological Methods. Tissue Preparation, Binding ([^{3}H]-Cocaine/[^{3}H]BTCP), and [^{3}H]Dopamine (DA)-Uptake Studies. The [^{3}H]BTCP displacement in rat forebrain was performed using a modification[8] of the previously described method.[5a] The [^{3}H]cocaine displacement in rat forebrain, and inhibition of [^{3}H]-DA uptake in rat synaptosomes, was evaluated as described previously.[8]

Phencyclidine (PCP) Binding. Binding (K_i values) of all the compounds in Table II to rat brain homogenates was determined as described previously.[8,12]

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(13) ^{1}H-NMR ($CDCl_3$) of selected compounds from Table I: **8** δ 7.79 (d, J = 7.5 Hz, 1H, Ar*H*), 7.68 (dd, J = 1.6, 7.3 Hz, 1H, Ar*H*), 7.28 (m, 2H, Ar*H*), 7.09 (s, 1H, Ar*H*), 2.40 (q, J = 7.1 Hz, 2H, NCH_2CH_3), 1.86–2.06 (m, 4H), 1.50–1.72 (m, 4H), 1.43 (m, 2H), 1.03 (t, J = 7.1 Hz, 3H, NCH_2CH_3); **12** δ 7.79 (d, J = 7.7 Hz, 1H, Ar*H*), 7.69 (dd, J = 1.5, 7.3 Hz, 1H, Ar*H*), 7.29 (m, 2H, Ar*H*), 7.11 (s, 1H, Ar*H*), 5.84 (m, 1H, $NCH_2CH{=}CH_2$), 5.00–5.17 (m, 2H, $NCH_2CH{=}CH_2$), 3.00 (d, J = 5.8 Hz, 2H, $NCH_2CH{=}CH_2$), 1.95 (m, 4H), 1.32–1.74 (complex m, 6H); **14** δ 7.79 (d, J = 7.8 Hz, 1H, Ar*H*), 7.68 (dd, J = 1.5, 6.8 Hz, 1H, Ar*H*), 7.28 (m, 2H, Ar*H*), 7.07 (s, 1H, Ar*H*), 2.20 (d, J = 6.8 Hz, 2H, NCH_2), 1.86–2.03 (m, 4H), 1.32–1.72 (complex m, 6H), 0.89 (m, 1H, cyclopropylC*H*), 0.41 (m, 2H, cyclopropylCH_2), –0.02 (m, 2H, cyclopropylCH_2); **16** δ 7.81 (d, J = 7.6 Hz, 1H, Ar*H*), 7.71 (d, J = 7.8 Hz, 1H, Ar*H*), 7.18–7.37 (complex m, 7H, Ar*H*), 7.16 (s, 1H, Ar*H*), 3.52 (s, 2H, $PhCH_2$), 1.93–2.10 (m, 4H), 1.32–1.77 (complex m, 6H); **17** δ 7.78 (d, J = 8.7 Hz, 1H, Ar*H*), 7.67 (dd, J = 1.8, 7.4 Hz, 1H, Ar*H*), 7.24–7.35 (m, 2H, benzothienylAr*H*), 7.29 (d, J = 8.1 Hz, 1H, 3,4-dichlorophenylArH[5]), 7.22 (d, J = 2.1 Hz, 1H, 3,4-dichlorophenylArH[2]), 7.03 (s, 1H, benzothienylAr*H*), 6.95 (dd, J = 2.1, 8.1 Hz, 1H, 3,4-dichlorophenylArH[6]), 2.67 (dist t, J_{app} = 5.4 Hz, 2H), 2.61 (dist t, J_{app} = 5.4 Hz, 2H), 1.82–2.00 (m, 4H), 1.32–1.63 (complex m, 6H); **20** δ 7.74 (d, J = 7.4 Hz, 1H, Ar*H*), 7.68 (d, J = 7.8 Hz, 1H, Ar*H*), 7.63 (br s, 1H, N*H*CO), 7.27 (m, 2H, Ar*H*), 7.21 (s, 1H, Ar*H*), 3.31 (s, 2H, $COCH_2$), 2.62 (dm, J_{gem} = 13 Hz, 2H), 1.97 (m, 2H), 1.29–1.76 (complex m, 6H); **22** 7.78 (d, J = 7.3 Hz, 1H, Ar*H*), 7.68 (d, J = 8.6 Hz, 1H, Ar*H*), 7.28 (m, 2H, Ar*H*), 7.09 (s, 1H, Ar*H*), 2.62 (dist t, J = 5.6 Hz, 2H, NCH_2CH_2N), 2.48 (dist t, J = 5.6 Hz, 2H, NCH_2CH_2N), 2.36 (s, 3H, NCH_3), 1.95 (m, 4H), 1.48–1.72 (complex m, 4H), 1.40 (m, 2H); **28** δ 7.78 (d, J = 7.8 Hz, 1H, Ar*H*), 7.71 (dd, J = 1.5, 7.4 Hz, 1H, Ar*H*), 7.28 (m, 2H, Ar*H*), 7.10 (s, 1H, Ar*H*), 2.53 (q, J = 7.2 Hz, 2H, NCH_2CH_3), 2.42 (t, J = 7.9 Hz, 2H, $NCH_2CH_2CH_3$), 2.14 (m, 2H), 1.91 (m, 2H), 1.73 (m, 2H), 1.45 (m, 6H), 1.02 (t, J = 7.06 Hz, 3H, NCH_2CH_3), 0.83 (t, J = 7.3 Hz, 3H, $NCH_2CH_2CH_3$); **32** δ 7.78 (d, J = 7.2 Hz, 1H, Ar*H*), 7.72 (dd, J = 1.5, 7.7 Hz, 1H, Ar*H*), 7.30 (m, 2H, Ar*H*), 7.24 (s, 1H, Ar*H*), 4.29 (br s, 1H, CON*H*) ($NaOD/D_2O$ exchangeable), 3.41 (dist t, J = 7.4 Hz, 2H), 3.30 (dist t, J = 7.4 Hz, 2H), 2.83 (m, 2H), 2.01 (m, 2H), 1.35–1.75 (complex m, 6H); **33** δ 8.21 (59%), 8.17 (41%) (s, 1H, NC*H*O), 7.67–7.81 (m, 2H, Ar*H*), 7.26–7.38 (m, 2H, Ar*H*), 7.24 (59%), 7.25 (41%) (s, 1H, Ar*H*), 6.23 (59%) (d, J = 12 Hz, N*H*), 5.63 (41%) (br s, N*H*), 2.57 (m, 1H), 1.94–2.20 (complex m, 4H), 1.32–1.76 (complex m, 5H); **36** δ 7.74 (d, J = 7.6 Hz, 1H, Ar*H*), 7.67 (d, J = 7.4 Hz, 1H, Ar*H*), 7.27 (m, 2H, Ar*H*), 7.19 (s, 1H, Ar*H*), 5.58 (br s, 1H, N*H*CO), 2.57 (m, 2H), 2.17 (t, J = 7.4 Hz, 2H, $COCH_2CH_2CH_3$), 1.95 (m, 2H), 1.46–1.74 (complex m, 7H), 1.37 (m, 1H), 0.95 (t, J = 7.4 Hz, 3H, CH_3); **38** δ 7.75 (d, J = 7.3 Hz, 1H, Ar*H*), 7.68 (dd, J = 1.6, 7.2 Hz, 1H, Ar*H*), 7.26 (m, 2H, Ar*H*), 7.19 (s, 1H, Ar*H*), 5.78 (br s, 1H, N*H*), 2.56 (m, 2H), 1.97 (m, 2H), 1.52–1.74 (complex m, 6H), 1.38 (tt, J = 4.4, 7.8 Hz, 1H, COC*H*), 0.91 (m, 2H, cyclopropylCH_2), 0.70 (m, 2H, cyclopropylCH_2); **44** δ 7.74 (d, J = 7.7 Hz, 1H, Ar*H*), 7.67 (d, J = 7.4 Hz, 1H, Ar*H*), 7.27 (m, 2H, Ar*H*), 7.19 (s, 1H, Ar*H*), 6.56 (br s, 1H, $NHCOCH_2NHBOC$), 5.23 (br s, 1H, $NHCOCH_2NHBOC$), 3.73 (d, J = 6.0 Hz, 2H, CH_2NHBOC), 2.54 (dm, J_{gem} = 14 Hz, 2H), 1.92 (m, 2H), 1.49–1.75 (complex m, 4H), 1.47 (s, 9H, OtBu), 1.36 (m, 2H); **48** δ 7.78 (d, J = 7.5 Hz, 1H, Ar*H*), 7.68 (dd, J = 1.8, 7.1Hz, 1H, Ar*H*), 7.29 (m, 2H, Ar*H*), 7.08 (s, 1H, Ar*H*), 5.18 (s, 1H, N*H*BOC), 3.19 (m, 2H, CH_2NHBOC), 2.42 (t, J = 6.3 Hz, 2H, $NHCH_2$), 1.95 (m, 4H), 1.47–1.74 (complex m, 8H), 1.42 (s, 9H, *t*Bu); mixture **49** δ 7.79 (d, J = 7.4 Hz, 1H, Ar*H*), 7.67 (dd, J = 1.5, 7.8 Hz, 1H, Ar*H*), 7.29 (m, 2H, Ar*H*), 7.20 (s, 1H, Ar*H*[2]) (*m*-monochloro isomer), 7.17 (s, 1H, Ar*H*), 7.00–7.07 (complex m, 3H, Ar*H*) (mixture of *m*- and *p*-monochloro isomers), 2.70 (dist t, 2H, CH_2CH_2), 2.62 (dist t, 2H, CH_2CH_2), 1.83–2.00 (m, 4H), 1.44–1.62 (m, 6H).