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Structure/Activity Studies Related to 2-(3,4-Dichlorophenyl)-*N*-methyl-*N*-[2-(1-pyrrolidinyl)-1-substituted-ethyl]acetamides: A Novel Series of Potent and Selective κ-Opioid Agonists

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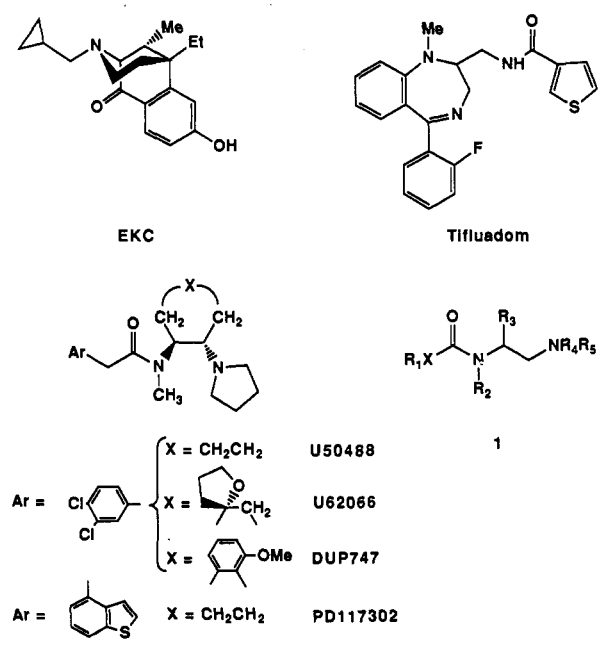
This paper describes the synthesis of a series of *N*-[2-(1-pyrrolidinyl)ethyl]acetamides **1**, variously substituted at the carbon adjacent to the amide nitrogen (C1), and related analogues, together with their biological evaluation as opioid κ agonists. In the first part of the study, the variants in *N*-acyl, *N*-alkyl, and amino functions were explored when the substituent at C1 was 1-methylethyl and the optimum was found to be exemplified by 2-(3,4-dichlorophenyl)-*N*-methyl-*N*-[(1*S*)-1-(1-methylethyl)-2-(1-pyrrolidinyl)ethyl]acetamide (**13**). Subsequently, racemic or chiral amino acids were used to introduce other alkyl and aryl substituents at C1 of the ethyl linking moiety. A series of potent compounds, bearing substituted-aryl groups at C1, were discovered, typified by 2-(3,4-dichlorophenyl)-*N*-methyl-*N*-[(1*R*,*S*)-1-(3-aminophenyl)-2-(1-pyrrolidinyl)ethyl]acetamide (**48**), which was 5-fold more active as the racemate than **13** in vitro and exhibited potent naloxone-reversible analgesic effects (ED_{50} = 0.04 mg/kg sc) in a mouse abdominal constriction model.

Since the existence of multiple subtypes of opioid receptors was first proposed,[1,2] three subclasses of opioid receptor have gained widespread acceptance,[3] namely μ, δ, and κ. Agonists, partial agonists, and antagonists have been described for each receptor, and agonist occupancy at all three gives rise to analgesic effects.[4] Unfortunately, serious side effects can result from the administration of potent μ agonists such as morphine to animals and man, most notably dependence and respiratory depression.[5] In the search for improved analgesic agents, it has been shown that κ agonists can cause centrally mediated analgesia, though different side effects, such as sedation, dysphoria, and diuresis, have been reported in animal studies.[6] In addition to a number of naturally occurring and synthetic peptides related to dynorphin,[7] three structurally dissimilar classes of compound, exemplified by ethylketocyclazocine (EKC),[8] tifluadom,[9] and U-50488,[10] have emerged as κ agonists capable of producing analgesia in experimental models. The most selective of these, 2-(3,4-dichlorophenyl)-*N*-methyl-*N*-[2-(1-pyrrolidinyl)cyclohexyl]acetamide (U-50488), has relatively poor affinity but good selectivity for the receptors labeled by [^{3}H]bremazocine.[11] Initially, the potential for modification of this novel structure was explored by the addition of substituents in the cyclohexane ring, as with U-62066 (spiradoline),[12] and later by simple acyl variants, as exemplified by PD117302.[13] More recently, the cyclohexane ring has been replaced by a tetrahydronaphthyl moiety, giving DU-P747.[14] In addition, piperidine analogues, such as



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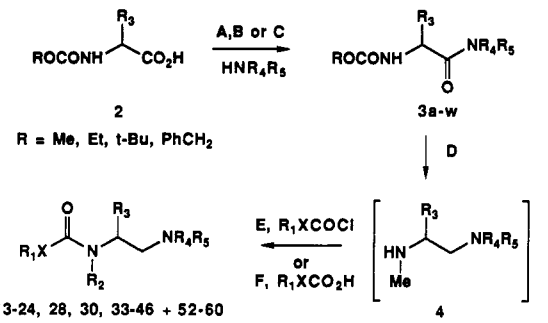
ZT52656A[15] (1, R_1X = [4-(trifluoromethyl)phenyl]methyl, NR_4R_5 = pyrrolidine, R_2R_3 = $-(CH_2)_4-$) and a piperazine, GR103545[16] (1, R_1X = (3,4-dichlorophenyl)methyl, NR_4R_5 = pyrrolidine, R_2R_3 = $-(CH_2)_2N(CO_2Me)CH_2-$), have been reported to possess κ agonist properties. These ethylenediamines do not incorporate the cyclohexane ring of U50488 but utilize ring formation between the *N*-alkyl substituent and the α-carbon of the ethyl chain, linking amide and pyrrolidine functions, to restrict conformation.

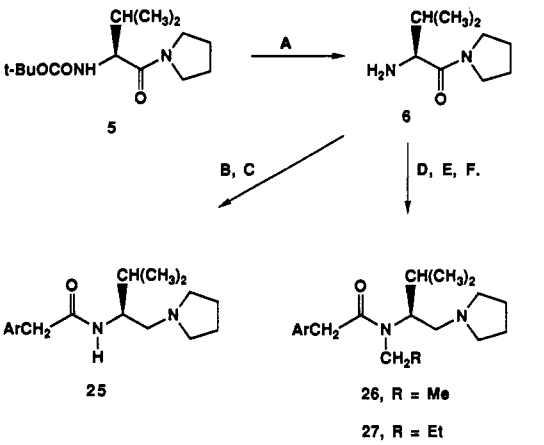
We have described conformational studies with acylated ethylenediamines of general structural formula 1 in an attempt to determine whether the cyclohexane ring was necessary for κ agonist activity.[17] The introduction of alkyl or phenyl substituents on the carbon α to the amide (R_3) gave potent κ agonists which were analgesic in animal models. The objective of the present study was to explore the effect of further variations in the substituent R_3 on biological activity, an option not readily accessible for U50488 itself. This evaluation was subsequent upon an examination of the effects of modifying other parts of the structure, to ensure a rational choice of the most appropriate parent. The established activity of 2-(3,4-dichlorophenyl)-*N*-methyl-*N*-[(1*S*)-1-(1-methylethyl)-2-(1-pyrrolidinyl)ethyl]acetamide (13) and the ready availability of *S*-valine made compounds in which R_3 = *i*-Pr the logical starting point for the first part of the study, in which R_1, R_2, NR_4R_5, and X were varied, each in turn. We report herein the SAR of analogues of general formula 1 resulting from both aspects of the current investigation which culminated in the discovery of compounds such as 2-(3,4-dichlorophenyl)-*N*-methyl-*N*-[(1*R*,*S*)-1-(3-aminophenyl)-2-(1-pyrrolidinyl)ethyl]acetamide (48), which, even as the racemate, was 5-fold more potent than 13 as a κ agonist in vitro and exhibited potent naloxone-reversible analgesic effects (ED_{50} = 0.04 mg/kg sc) in an abdominal constriction model in the mouse.

Scheme I[a]



[a] (A) HOBT, DCCI, CH_2Cl_2; (B) CDI, EtOAc; (C) isobutyl chloroformate, *N*-methylmorpholine, CH_2Cl_2; (D) LAH, THF; (E) CH_2Cl_2; (F) HOBT, DCCI, CH_2Cl_2.

Scheme II[a]



[a] (A) 2 M HCl/EtOAc; (B) 3,4-dichlorophenylacetyl chloride, NEt_3, CH_2Cl_2; (C) BH_3, THF; (D) RCOCl (R = Me or Et), NEt_3, CH_2Cl_2; (E) LAH, THF; (F) 3,4-dichlorophenylacetyl chloride, CH_2Cl_2.

Chemistry

The majority of compounds were prepared by the route depicted in Scheme I. Various urethane-protected amino acids 2 were coupled to secondary amines R_4R_5NH using one of the three standard methods A–C shown in Scheme I to give amides 3 (Table IV). Where R_3 was aryl, method B was suitable only for use with racemic amino acids, as considerable loss of chiral integrity occurred during the coupling. Chiral purity of 3 (R = $PhCH_2$, R_3 = Ph, NR_4R_5

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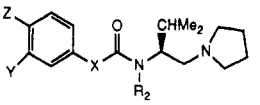
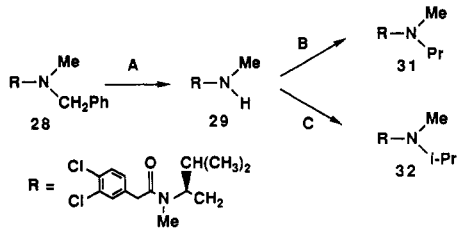
Table I. Biological Activity in κ Binding, Mouse Vas Deferens, Analgesia, and Sedation Screens for Compounds of the General Formula Shown



no.	substituents Y	Z	X	R_2	κ binding; IC_{50}, nM	mouse vas deferens: potency[a] vs EKC	mouse vas deferens: K_e naloxone,[b] nM	ED_{50}, mg/kg: analgesia sc	ED_{50}, mg/kg: sedation sc
13	Cl	Cl	CH_2	Me	6.9 (3.7–10.7)	4.3 ± 0.83	14.9 ± 2.7	0.05 (0.02–0.06)	0.78 (0.4–1.5)
14	H	H	CH_2	Me	656 (315–1370)	0.016 ± 0.007	ND[c]	~10	12.55 (8.63–19.21)
15	Cl	H	CH_2	Me	99 (33–303)	0.49 ± 0.05	12.1 ± 0.3	0.33 (0.2–0.54)	0.77 (0.17–1.98)
16	H	Cl	CH_2	Me	37.2 (16.7–83.4)	0.4 ± 0.24	16.3 ± 3.9	0.09 (0.04–0.17)[d]	1.4 (0.91–2.35)[d]
17	F	F	CH_2	Me	101 (50–208)	0.1 ± 0.03	NT[e]	0.23 (0.14–0.37)[d]	1.18 (0.24–2.42)[d]
18	H	CN	CH_2	Me	277 (76–1650)	0.08 ± 0.03	16.5 ± 5.3	0.84 (0.34–1.98)	9.31 (6.28–13.73)
19	H	NO_2	CH_2	Me	92 (18.2–457)	0.24 ± 0.05	16.9 ± 5.7	0.3 (0.23–0.38)	0.87[f]
20	H	CF_3	CH_2	Me	14.3 (3.6–28.9)	0.97 ± 0.19	15.5 ± 0.75	0.07 (0.06–0.08)	0.56 (0.39–0.82)
21	H	OMe	CH_2	Me	909 (315–2630)	0.06 ± 0.02	14.3 ± 3.5	3.3 (2.6–4.2)	10.61 (7.56–15.11)
22	H	H	$(CH_2)_2$	Me	420 (252–700)	*g*	NT[e]	NT[e]	NT[e]
23	H	H	OCH_2	Me	20.9 (12.6–34.8)	1.7 ± 0.05	21.8 ± 8.1	0.13 (0.12–0.16)	0.73[f]
24	H	H	SCH_2	Me	206 (136–319)	0.63 ± 0.3	15.2 ± 1.7	0.27 (0.05–0.7)[h]	9.71 (6.54–14.43)[h]
25	H	H	CH_2	H	485 (316–744)	0.08 ± 0.06	ND[c]	1.3 (0.4–3.5)[h]	29.7 (13.76–219)[h]
26	H	H	CH_2	Et	322 (44–2356)	0.07 ± 0.02	16 ± 2.1	0.32 (0.15–0.62)[h]	8.72 (5.36–13.76)[h]
27	H	H	CH_2	*n*-Pr	1440 (1230–1690)	0.021 ± 0.01	ND[c]	>10	NT[e]
U-50488					95.5 (63.8–143)	0.11 ± 0.02	15.5 ± 1.6	1.1 (0.6–2.2)	7.37 (5.5–9.87)
EKC					28.6 (19.2–42.8)	1	15.8 ± 1.6	0.17 (0.12–0.23)	0.46 (0.31–0.68)
morphine					2390 (2099–2721)	0.13 ± 0.03	4.2 ± 2.0	0.4 (0.3–0.6)	*i*

[a] Results expressed as the molar potency ratio to EKC assayed in the same tissues. The mean IC_{50} value for EKC = 64.2 ± 6.6 nM. [b] Values of ca. 15 nM are indicative of κ receptor antagonism.[11] [c] ND = not determined due to poor shape of the dose–response curve. [d] Not completely reversed by naloxone. [e] NT = not tested. [f] Confidence intervals not determined due to the shape of the dose–response curve. [g] Weak antagonist, $K_e \approx 2$ μM. [h] Not tested for naloxone reversal. [i] Motor stimulation at 5 mg/kg, no sedation observed.

Scheme III[a]



[a] (A) H_2, 5% Pd/C, aqueous dioxane; (B) EtCHO, $Na(BH_3)CN$; (C) Me_2CO, $Na(BH_3)CN$.

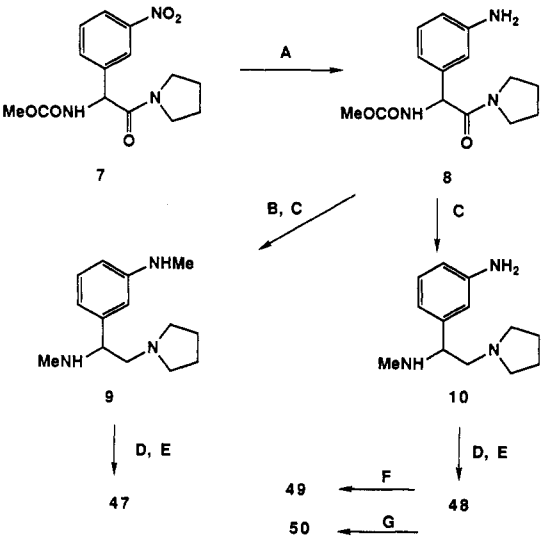
= pyrrolidine), obtained from method C, was assessed by HPLC assay of an α-phenylethyl isocyanate derivative of diamine **4** (R_3 = Ph, NR_4R_5 = pyrrolidine). In each case the product **3** was reduced with LAH to *N*-methyldiamine **4**, which was acylated without full characterization with either 3,4-dichlorophenylacetyl chloride or the corresponding acid, activated with carbonyldiimidazole. The acid chloride method had the advantage that the products **1** were isolated as hydrochloride salts which were frequently crystalline.

Coupling of Boc-*S*-valine with pyrrolidine gave **5**, which was subjected to acid deprotection to give primary amine **6**. This was either acylated directly and then partially reduced to give **25** in low yield or acylated, reduced to *N*-alkylamine, and reacylated to give analogues **26** and **27**, containing alternative R_2 substitutents (Scheme II).

When examining the SAR of the amino substitutent NR_4R_5, *N*-methyl-*N*-benzylamine (**28**), obtained by the above route, was hydrogenated to *N*-methylamine (**29**) and then subjected to reductive alkylation with either propanal or acetone in the presence of sodium cyanoborohydride, affording amines **31** and **32**, respectively (Scheme III).

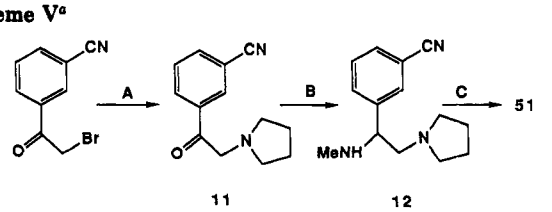
Intermediate **7** was hydrogenated to aniline **8** (Scheme IV). This was acylated with methyl chloroformate and the product reduced with LAH to give bis-methylamino intermediate **9**. Diacylation with 2 equiv of 3,4-dichloro-

Scheme IV[a]



[a] (A) H_2, Pd; (B) MeOCOCl; (C) LAH, Et_2O; (D) 2 equiv of 3,4-dichlorophenylacetyl chloride; (E) KOH; (F) MeCOCl; (G) HCl, $NaNO_2$, CuCN, KCN.

Scheme V[a]



[a] (A) pyrrolidine; (B) $MeNH_2$, $MeNH_2$·HCl, $Na(BH_3)CN$, MeOH; (C) 3,4-dichlorophenylacetyl chloride, CH_2Cl_2.

phenylacetyl chloride followed by selective base hydrolysis gave *N*-methylamine analogue **47**. LAH reduction of **8** gave diamine **10**. Diacylation, as above, gave a bis-amide, from which the more labile acyl group was removed by base

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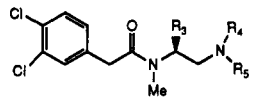
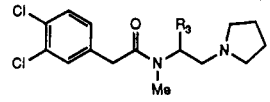


no.	substituents R_3	substituents NR_4R_5	κ binding; IC_{50}, nM	mouse vas deferens: potency[a] vs EKC	mouse vas deferens: K_e naloxone,[b] nM	ED_{50}, mg/kg: analgesia, sc	ED_{50}, mg/kg: sedation, sc
28	*i*-Pr	N(Me)CH_2Ph	1610 (330–7890)	*c*		>10	NT[d]
29	*i*-Pr	NHMe	625 (334–1170)	0.003 ± 0.001	ND[e]	>10	NT[d]
30	*i*-Pr	NMe_2	105 (55–200)	0.32 ± 0.02	27.2 ± 8.3	0.16 (0.07–0.37)[f]	1.15 (0.52–2.99)[f]
31	*i*-Pr	N(Me)*n*-Pr	71 (29–172)	1.18 ± 0.19	8.9 ± 4.0	0.58 (0.38–0.87)	2.42 (1.21–4.29)
32	*i*-Pr	N(Me)*i*-Pr	14.6 (4.5–47)	3.84 ± 0.8	15.1 ± 2.4	0.065 (0.04–0.11)	0.18[g]
33	*i*-Pr	NEt_2	81 (20.2–321)	0.3 ± 0.1	14.2 ± 3.0	1.52 (0.96–2.37)	1.18 (1.11–3.89)
34	*i*-Pr	piperidine	10.8 (3.8–31.1)	1.45 ± 0.15	24.4 ± 6.6	0.075 (0.03–0.16)	0.46 (0.27–0.77)
35	Ph	N(Me)allyl	8.2 (2.4–28)	10.3 ± 4.8	11.8 ± 1.1	NT[d]	0.71 (0.29–1.38)[h]
36	Ph	3-pyrroline	10.8 (5.6–20.8)	40.9 ± 4.1	26.1 ± 6.3	0.005 (0.003–0.008)	0.04 (0.03–0.08)

[a] Results expressed as the molar potency ratio to EKC assayed in the same tissues. The mean IC_{50} value for EKC = 64.2 ± 6.6 nM. [b] Values of ca. 15 nM are indicative of κ receptor antagonism. [c] Weak antagonist, K_e = 530 nM. [d] NT = not tested. [e] ND = not determined. [f] Not completely reversed by naloxone. [g] 95% confidence intervals not determined due to poor shape of the dose–response curve. [h] Not tested for naloxone reversal.

Table III. Biological Activity in κ Binding, Mouse Vas Deferens, Analgesia, and Sedation Screens for Compounds of the General Formula Shown



no.	R_3	isomer	κ binding; IC_{50}, nM	mouse vas deferens: potency[a] vs EKC	mouse vas deferens: K_e naloxone,[b] nM	ED_{50}, mg/kg: analgesia, sc	ED_{50}, mg/kg: sedation, sc
37	Me	*S*	52.5 (13.5–99)	0.14 ± 0.02	18.5 ± 6.6	0.86 (0.74–0.98)	1.98 (1.4–2.8)
38	Et	*S*	65.4 (17.8–240)	0.14 ± 0.07	19.9 ± 6.9	0.43 (0.27–0.66)	2.76[c]
39	*n*-Pr	*S*	38.7 (13.3–112)	0.9 ± 0.45	16.1 ± 4.4	0.12 (0.08–0.19)	0.8 (0.46–1.3)
40	*i*-Pr	*R*	1020 (768–1340)	0.015 ± 0.005	17.1 ± 6.1	>10	33.1 (22.5–49.3)
41	*s*-Bu	*S*	10.1 (6.9–14.8)	8.5 ± 1.4	22.2 ± 0.4	0.012 (0.007–0.02)	0.16 (0.003–0.56)
42	*i*-Bu	*S*	14 (5.8–34)	3.2 ± 0.96	*d*	0.01 (0.009–0.012)[e]	0.37 (0.21–0.62)[e]
43	*t*-Bu	*R,S*	24.5 (13–45.6)	2.5 ± 0.1	11 ± 2.4	0.03 (0.01–0.65)	0.13 (0.04–0.32)
44	Ph	*R*	2750 (1060–7110)	*f*		>10	NT[g]
45	Ph	*R,S*	12.2 (3.1–48)	5.2 ± 0.04	3.4 ± 1.5	0.007 (0.005–0.01)	0.15 (0.07–0.32)[h]
46	Ph	*S*	6.9 (3.4–14.4)	16.1 ± 5.7	17.8 ± 3.6	0.004 (0.002–0.007)[h]	0.05 (0.03–0.06)[h]
47	3-NH(Me)C_6H_4	*R,S*	39.1 (13–113)	7.7 ± 1.6	16.8 ± 3.3	0.081 (0.05–0.13)[h]	0.63[c,h]
48	3-$NH_2C_6H_4$	*R,S*	14.3 (11.6–17.5)	24 ± 3.1	11.3 ± 1.6	0.041 (0.02–0.07)	0.17[c]
49	3-NH(Ac)C_6H_4	*R,S*	5.5 (2.33–13.1)	21.4 ± 4.62	*i*	0.03 (0.015–0.06)	0.19[c,h]
50	3-ClC_6H_4	*R,S*	57.8 (43.7–76.5)	4.65 ± 0.15	5.7 ± 0.4	0.086 (0.06–0.13)	0.68[c]
51	3-CNC_6H_4	*R,S*	25 (9–69)	0.53 ± 0.12	NT[g]	NT[g]	NT[g]
52	2-$MeOC_6H_4$	*R,S*	16.8 (9–31.1)	7.5 ± 1	11.6 ± 2.9	0.04 (0.02–0.07)	0.22 (0.1–0.39)
53	3-$MeOC_6H_4$	*R,S*	31.2 (11–88.5)	2.45 ± 1.3	18.5 ± 5.1	0.03 (0.02–0.05)	0.39[c]
54	4-$MeOC_6H_4$	*R,S*	73.2 (36.7–146)	2.9 ± 0.6	12.9 ± 4.0	0.12 (0.08–0.18)	0.55 (0.33–0.83)
55	2-HOC_6H_4	*R,S*	21.7 (10.7–44.1)	0.4 ± 0.22	*j*	NT[g]	NT[g]
56	3-HOC_6H_4	*R,S*	11.5 (8.6–15.3)	6.5 ± 1.2	*j*	0.055 (0.02–0.11)[h]	0.53[h]
57	4-HOC_6H_4	*R,S*	9.8 (3.5–27.3)	11 ± 2.4	52.7 ± 11	0.045 (0.03–0.06)	0.33 (0.2–0.55)[e]
58	4-$MeSC_6H_4$	*R,S*	124 (71.4–216)	0.48 ± 0.1	13.8 ± 2.9	0.32 (0.14–0.62)	3.3 (1.99–6.05)
59	2,4-$(MeO)_2C_6H_3$	*R,S*	248 (124–495)	1.8 ± 0.43	21.4 ± 9.7	0.19 (0.09–0.38)	1.5[c]
60	3,4-$(MeO)_2C_6H_3$	*R,S*	32.8 (26.9–54)	21.3 ± 7.8	16 ± 5.1	0.05 (0.03–0.07)	0.13 (0.09–0.21)

[a] Results expressed as the molar potency ratio to EKC assayed in the same tissues. The mean IC_{50} value for EKC = 64.2 ● 6.6 nM. [b] Values of approximately 15 nM are indicative of κ receptor antagonism. [c] 95% confidence intervals not determined due to the poor shape of the dose–response curve. [d] Antagonism not competitive. [e] Not tested for naloxone reversal. [f] Weak antagonist, $K_e \approx 2$ μM. [g] NT = not tested. [h] Not completely reversed by naloxone. [i] Compound would not wash out. [j] Naloxone K_e variable.

hydrolysis affording **48**, acetylation of which gave **49**. Attempted Sandmeyer reaction of **48** to give **51** failed, giving instead chloro derivative **50**. Therefore, 3-cyanophenacyl bromide was converted to amino ketone **11** which was alkylated reductively to methylamine **12**, acylation of which yielded **51** (Scheme V).

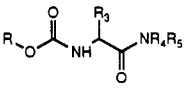
The reaction conditions, yields, and physical properties of analogues **13–60** are listed in Table V.

Pharmacology

Binding. Opioid κ receptor affinities were determined by displacement of [^{3}H]bremazocine of specific activity 15–30 Ci/mmol using guinea pig brain membranes.[18] [D-Ala,D-Leu]enkephalin (DADLE) was included at a concentration of 3 μM to suppress binding to μ and δ sites. At concentrations above 1 μM, DADLE, normally considered to be δ selective, binds to both μ and δ receptors in guinea pig brain membranes. Results are expressed in

(18) Magnan, J.; Paterson, S. J.; Tavani, A.; Kosterlitz, H. W. The Binding Spectrum of Narcotic Analgesic Drugs With Different Agonist and Antagonist Properties. *Naunyn-Schmiedebergs Arch. Pharmacol.* **1982**, *319*, 197–205.

Table IV. Physical Properties of Intermediates 3a–w[a]



no.	R	R_3	NR_4R_5	isomer	$[\alpha]^{20}_D$,[b] deg	method[c]	% yield[d]	mass spec,[e] m/e
3a	$PhCH_2$	*i*-Pr	pyrrolidine	*S*	ND[f]	A	96	305
3b	$PhCH_2$	*i*-Pr	$N(Me)CH_2Ph$	*S*	+10.1	A	93	355
3c	$PhCH_2$	*i*-Pr	NMe_2	*S*	+30.0	A	83	279
3d	$PhCH_2$	*i*-Pr	NEt_2	*S*	*g*	A	67	307
3e	$PhCH_2$	*i*-Pr	piperidine	*S*	+31.8	A	47	319
3f	$PhCH_2$	Ph	N(Me)allyl	*S*	+11.7	A	74	339
3g	$PhCH_2$	Ph	3-pyrroline	*S*	+16.1	A	48	337
3h	$PhCH_2$	Et	pyrrolidine	*S*	+9.5	A	59	291
3i	$PhCH_2$	*n*-Pr	pyrrolidine	*S*	+4.8	A	63	305
3j	$PhCH_2$	*i*-Pr	pyrrolidine	*R*	ND[f]	C	63	305
3k	$PhCH_2$	*s*-Bu	pyrrolidine	*S*	ND[f]	A	83	318[h]
3l	$PhCH_2$	*i*-Bu	pyrrolidine	*S*	ND[f]	A	82	319
3m	$PhCH_2$	Ph	pyrrolidine	*R*	ND[f]	C	100	339
3n	*t*-Bu	Ph	pyrrolidine	*R,S*		A	30	ND[f]
3o	$PhCH_2$	$2\text{-}MeOC_6H_4$	pyrrolidine	*R,S*		B	100	ND[f]
3p	$PhCH_2$	$3\text{-}MeOC_6H_4$	pyrrolidine	*R,S*		B	98	379
3q	Et	$4\text{-}MeOC_6H_4$	pyrrolidine	*R,S*		B	70	321
3r	Me	$2\text{-}HOC_6H_4$	pyrrolidine	*R,S*		A	50	279
3s	Me	$3\text{-}HOC_6H_4$	pyrrolidine	*R,S*		A	45	ND[f]
3t	Me	$4\text{-}HOC_6H_4$	pyrrolidine	*R,S*		A	37	ND[f]
3u	Me	$4\text{-}MeSC_6H_4$	pyrrolidine	*R,S*		A	89	ND[f]
3v	Et	$2,4\text{-}(MeO)_2C_6H_3$	pyrrolidine	*R,S*		C	70	337
3w	Me	$3,4\text{-}(MeO)_2C_6H_3$	pyrrolidine	*R,S*		B	97	323

[a] The products were isolated mainly as oils, which were homogeneous by TLC and characterized satisfactorily by NMR. [b] *c* 1%, $CHCl_3$. [c] Coupling method in Scheme I. [d] Crude yield of product used directly in the next stage. [e] $(M + H)^+$ unless otherwise stated, as determined by low-resolution mass spectrometry; fragmentation pattern consistent with expected structure. [f] ND = not determined. [g] Cotton effect. [h] M^+ value.

Tables I–III as IC_{50} values (nM) with 95% confidence intervals.

Mouse Vas Deferens. Agonist activity was determined on the field-stimulated mouse vas deferens preparation,[19] and antagonist K_e values (nM) were recorded with the standard opioid antagonist naloxone. Results are expressed in Tables I–III as the molar potency ratio relative to the standard agonist EKC, which was used to calibrate each tissue. This assay provides a measure of efficacy in vitro and, as proposed,[11] K_e values for naloxone versus the test agonist of ca. 15 nM are characteristic of κ compounds while values of 1–4 nM are indicative of μ opioid effects.

Analgesia. Compounds were administered by the sc route to female mice of the Alderley Park Strain weighing between 22 and 25 g. Antinociceptive activity was determined by using the acetic acid (0.4%) induced abdominal constriction assay, observed over a period of 15 min commencing 30 min after dosing.[20] The results are expressed in Tables I–III as ED_{50} values in mg/kg with 95% confidence intervals. The effects of all compounds active in this assay were abolished by naloxone administered at 3 mg/kg (sc) at the same time as the agonist in a separate experiment, except where shown in Tables I–III.

Sedation. Compounds were administered by the sc route to female mice of the Alderley Park strain. Thirty minutes after dosing, mice were placed in a Perspex box measuring 30 × 30 × 30 cm, the floor of which was marked with a 1 cm^2 grid. The number of squares crossed in a 1-min period was recorded for both control and test groups ($n = 6$). Sedation was assessed by the difference in locomotor activity between control and treated groups. The results are expressed in Tables I–III as ED_{50} values in mg/kg with 95% confidence intervals. Active compounds were assessed for naloxone reversal in a separate experiment, in which naloxone was predosed at 0.5 mg/kg (sc) 15 min before the agonist and the above protocol observed, resulting in no observed sedative effect in many cases. Those compounds whose sedative effects were not abolished completely by this dose of naloxone are indicated in Tables I–III.

Structure/Activity Relationships (SAR)

Compound **13** has been identified previously,[17] in binding and in vitro models, as a potent κ agonist which produces analgesia in vivo. In the present study, a preliminary examination was undertaken into the effect of varying R_1, X, R_2, and NR_4R_5 in structure **1**, each in turn, on the activity of **13**. The initial aims were to explore the SAR of these substituents and establish the most appropriate combination for the subsequent study into the effect of varying R_3 on κ activity. For the purpose of discussion of the SAR, we have selected the effect in the mouse vas deferens assay, which expresses both affinity and efficacy. Potency in this assay broadly parallels the affinity observed in the κ binding assay and gives a reasonable indication of activity in the analgesic test (Tables I–III).

Changes in R_1 were limited to variations in aryl substitution (Table I). Complete removal of the halogens (**14**) produces a 170-fold fall in activity in comparison with **13**, while replacement of either of the two chlorines with hydrogen (**15** and **16**, respectively) results in approximately a 10-fold drop. Replacement of both chlorines with fluorine (**17**) gives a 40-fold drop in activity. In comparison with 4-chloro analogue **16**, introduction of more strongly electron withdrawing substituents such as cyano (**18**) and nitro (**19**), which lower lipophilicity, reduces activity. In contrast, trifluoromethyl (**20**), which is both more electron-withdrawing and more lipophilic than chlorine, enhances activity 2-fold. Replacement of 4-chloro by a less

(19) Miller, L.; Shaw, J. S.; Whiting, E. M. The Contribution of Intrinsic Activity to the Action of Opioids In Vitro. *Br. J. Pharmacol.* **1986**, *87*, 595–601.

(20) Hayashi, G.; Takemori, A. E. Type of Analgesic-Receptor Interaction Involved in Certain Analgesic Assays. *Eur. J. Pharmacol.* **1971**, *16*, 63–66.

Table V. Physical Porperties of Compounds of Formula 1

no.	mp, °C	$[\alpha]^{20}_D$,[a] deg	cryst solv	method[b]	% yield[c]	formula	anal.[d]
13	174–175	−64.4	MeOH/EtOAc	I, E	90	$C_{18}H_{26}Cl_2N_2O\cdot HCl$	C, H, N, Cl
14	162–164	−61.3	EtOH/Et_2O	I, E	80	$C_{18}H_{28}N_2O\cdot HCl$	C, H, N
15	150–153	−59.0	MeCN/Et_2O	I, E	97	$C_{18}H_{27}ClN_2O\cdot HCl\cdot 0.1H_2O$	C, H, N, H_2O
16	207–209	−60.9	MeOH/EtOAc	I, E	97	$C_{18}H_{27}ClN_2O\cdot HCl$	C, H, N
17	196–197	−50.8	Me_2CO	I, F	67	$C_{18}H_{26}F_2N_2O\cdot C_4H_4O_4$	C, H, N, F
18	185–187	−88.2	MeOH/EtOAc	I, E	*e*	$C_{19}H_{27}N_3O\cdot C_4H_4O_4$	C, H, N
19	177–180	−66.4	MeCN/Et_2O	I, E	96	$C_{18}H_{27}N_2O_3\cdot HCl$	C, H, N
20	159–161	−54.6	EtOAc/Et_2O	I, E	99	$C_{19}H_{27}F_3N_2O\cdot HCl$	C, H, N
21	221–224	−57.8	*f*	I, E	99	$C_{19}H_{30}N_2O\cdot HCl$	C, H, N
22	181–182	−20.1[g]	EtOAc	I, E	67	$C_{19}H_{28}Cl_2N_2O\cdot HCl$	C, H, N
23	103–104	−25.5[h]	EtOAc/Et_2O	I, E	46	$C_{18}H_{26}Cl_2N_2O_2\cdot HCl$	C, H, N
24	174–176	+24.6[h]	EtOAc/Et_2O	I, E	60	$C_{18}H_{26}Cl_2N_2OS\cdot HCl$	C, H, N, S
25	189–190	+6.1[h]	MeOH/EtOAc	II, B–C	9	$C_{17}H_{24}Cl_2N_2O\cdot HCl$	C, H, N
26	166–167	−18.5[h]	MeOH/EtOAc	II, D–F	16	$C_{19}H_{28}Cl_2N_2O\cdot C_2H_2O_4$	C, H, N
27	125–126	−10.1[i]	EtOAc	II, D–F	22	$C_{20}H_{30}Cl_2N_2O\cdot C_2H_2O_4$	C, H, N
28	185–187	−52.3	*f*	I, E	85	$C_{22}H_{28}Cl_2N_2O\cdot HCl$	C, H, N, Cl
29	162–163	−57.8	MeOH/EtOAc	III, A	89	$C_{15}H_{22}Cl_2N_2O\cdot HCl$	C, H, N, Cl
30	175–177	−73.6	*f*	I, E	68	$C_{16}H_{24}Cl_2N_2O\cdot HCl$	C, H, N
31	142–143	−47.6[j]	MeOH/EtOAc	III, B	70	$C_{18}H_{28}Cl_2N_2O\cdot C_2H_2O_4\cdot 0.25H_2O$	C, H, N, Cl, H_2O
32	164–165	−44.4[j]	MeOH/EtOAc	III, C	53	$C_{18}H_{28}Cl_2N_2O\cdot C_2H_2O_4$	C, H, N, Cl
33	85–87	+24.5[f]		I, E	48	$C_{18}H_{28}Cl_2N_2O$	C, H, N
34	173–175	−61.8[f]		I, E	71	$C_{19}H_{28}Cl_2N_2O\cdot HCl$	C, H, N
35	169–171	+104.3	MeOH/EtOAc	I, E	76	$C_{21}H_{24}Cl_2N_2O\cdot HCl$	C, H, N
36	214–216	+210.8[j]	MeCN	I, E	80	$C_{21}H_{22}Cl_2N_2O\cdot HCl$	C, H, N, Cl
37	167–169	−55.7	MeOH/EtOAc	I, A, D–E	24	$C_{16}H_{22}Cl_2N_2O\cdot HCl\cdot H_2O$	C, H, N, H_2O
38	218–219	−53.1	EtOH/Et_2O	I, A, D–E	45	$C_{17}H_{24}Cl_2N_2O\cdot HCl$	C, H, N
39	194–195	−43.1	EtOH/Et_2O	I, A, D–E	34	$C_{18}H_{26}Cl_2N_2O\cdot HCl$	C, H, N
40	169–170	+60.2	MeOH/EtOAc	I, D–E	12	$C_{18}H_{26}Cl_2N_2O\cdot HCl$	C, H, N
41	190–192	−37.6	CH_2Cl_2/Et_2O	I, D–E	97	$C_{19}H_{28}Cl_2N_2O\cdot HCl\cdot H_2O$	C, H, N, H_2O
42	174–176	−32.5	CH_2Cl_2/Et_2O	I, D–E	89	$C_{19}H_{28}Cl_2N_2O\cdot HCl\cdot 0.5H_2O$	C, H, N, H_2O
43	215–217		MeOH/EtOAc	I, A, D, E	24	$C_{19}H_{28}Cl_2N_2O\cdot HCl$	C, H, N
44	225–226	−127.8	MeOH/EtOAc	I, C–E	34	$C_{21}H_{24}Cl_2N_2O\cdot HCl$	C, H, N, Cl
45	245–247		MeOH/EtOAc	I, E	40	$C_{21}H_{24}Cl_2N_2O\cdot HCl$	C, H, N
46	225–226	+129.0	MeOH/EtOAc	I, A, D–E	38	$C_{21}H_{24}Cl_2N_2O\cdot HCl$	C, H, N
47	242–244		MeOH/EtOAc	IV, A–C	13	$C_{22}H_{27}Cl_2N_3O\cdot 2HCl$	C, H, N
48	248–249		MeOH/EtOAc	IV, A–E	6	$C_{21}H_{25}Cl_2N_3O\cdot 2HCl\cdot H_2O$	C, H, N, H_2O
49	231–232		MeOH/EtOAc	IV, F	52	$C_{23}H_{27}Cl_2N_3O_2\cdot HCl\cdot 0.5H_2O$	C, H, N, H_2O
50	173–175		EtOAc	IV, G	13	$C_{21}H_{23}Cl_3N_2O\cdot C_2H_2O_4$	C, H, N
51	266–268		MeCN	V	6	$C_{22}H_{23}Cl_2N_3O\cdot HCl$	C, H, N
52	171–173		MeOH/EtOAc	I, C–E	69	$C_{22}H_{26}Cl_2N_2O_2\cdot HCl\cdot 0.1H_2O$	C, H, N, H_2O
53	221–222		MeOH/EtOAc	I, B, D–E	84	$C_{22}H_{28}Cl_2N_2O_2\cdot HCl$	C, H, N
54	222–223		MeCN	I, D–E	20	$C_{22}H_{28}Cl_2N_2O_2\cdot HCl$	C, H, N
55	250–252		MeOH/EtOAc	I, D–E	13	$C_{21}H_{24}Cl_2N_2O_2\cdot HCl$	C, H, N
56	228–230		CH_2Cl_2/Et_2O	I, D–E	34	$C_{21}H_{24}Cl_2N_2O_2\cdot HCl$	C, H, N
57	229–230		MeOH/EtOAc	I, D–E	18	$C_{21}H_{24}Cl_2N_2O_2\cdot HCl$	C, H, N
58	193–195		MeOH/EtOAc	I, D–E	53	$C_{22}H_{26}Cl_2N_2OS\cdot HCl$	C, H, N
59	186–188		MeCN	I, D–E	8	$C_{23}H_{28}Cl_2N_2O_3\cdot HCl$	C, H, N
60	186–187		MeCN	I, D–E	17	$C_{23}H_{28}Cl_2N_2O_3\cdot HCl$	C, H, N

[a] c 1.0%, $CHCl_3$, except where indicated. [b] Scheme number, experimental conditions. [c] Overall yield for the steps quoted in method. [d] All analyses within ±0.4% of the theoretical value. [e] HCl salt obtained as a glass (overweight), an aliquot of which was converted to the maleate salt. [f] Pure product crystallized from the reaction mixture. [g] c 0.7%, MeOH. [h] c 1.1%, MeOH. [i] c 1.2%, MeOH. [j] c 1.0%, MeOH.

lipophilic, electron-donating substituent such as methoxy (**21**) decreases activity. Thus, it appears that both the $+\pi$ and $+\sigma$ effects of aromatic substituents are important for good activity in vitro.

The group linking the phenyl ring of R_1 to the amide moiety was varied in length and character; X and Y were maintained as chlorines (Table I). Only chain extensions were considered in this part of the study, as we have observed previously that removing the methylene linking group from **37** gave a compound which showed neither agonist activity nor antagonist effects versus the agonists EKC (κ), glyol (μ), or ICI 176032 (δ) in the mouse vas deferens (result not tabulated). Using **13** as the standard for comparison, the addition of a methylene unit (**22**) results in poor activity in binding (IC_{50} = 420 nM), while inclusion of an ether link (**23**) reduces activity in vitro to less than half and a thioether (**24**) causes a 7-fold decrease in activity.

The substituent R_3 on the amide nitrogen was investigated next (Table I). Replacement of the methyl group of **13** with either hydrogen or ethyl (**25** or **26**, respectively) results in approximately a 55-fold decrease in activity. An even greater loss is observed as the chain length is increased to *n*-propyl. Thus R_3 appears relatively sensitive to small changes in substituent.

As a result of the above observations, the amide moiety was maintained as 2-(3,4-dichlorophenyl)-*N*-methylacetamide and the consequence of varying NR_4R_5 was studied next (Table II). When R_3 = isopropyl, poor activity is observed as a result of replacing the pyrrolidine of **13** with either methylamino (**29**) or its precursor *N*-benzylamine (**28**). Progressively better in vitro results are observed as the size of the substituent on nitrogen is increased from NMe_2 (**30**) through N(Me)*n*-Pr (**31**) to N(Me)*i*-Pr (**32**), which is equipotent with **13** in vitro. Little difference is seen between the dimethyl- and diethylamines (**30** and **33**, respectively), which are both some 13-fold less active than **13**. Increasing the size of the cyclic amine from pyrrolidine (**13**) to piperidine (**34**) results in a 3-fold loss in potency. Later in the study, the effect of introducing unsaturated alkyl groups on nitrogen was explored. In morphine, replacement of *N*-methyl with, for example allyl, results in

antagonist properties, as with nalorphine.[21] In this case, *N*(Me)allyl analogue **35**, where R_3 is now phenyl rather than isopropyl, appears 1.5-fold less potent than parent **46**. The inclusion of a double bond in the pyrrolidine ring (**36**) gives a 2.5-fold increase in activity in vitro, affording one of the most potent analogues found in this study.

To evaluate changes in R_3 the other substituents were kept constant as R_1 = 3,4-dichlorophenyl, R_2 = Me, and NR_4R_5 = pyrrolidine; substitution in the R_3 position has a very marked effect (Table III). In agreement with previous work only the *S* enantiomers bind to κ receptors (**40** vs **13**, and **46** vs **44**), the racemate **45** having approximately the activity predicted for a 1:1 mixture of **46** and **44**. For this reason, compounds which are not derived from natural amino acids (**47–60**) were prepared as racemates, and their activity compared to that of the racemic unsubstituted phenyl compound **45**, with the assumption that the pure *S* enantiomer would be twice as potent.

When R_3 is alkyl, increasing the length of the chain causes some improvement in potency (**37–39**), and α-branching causes a further increase; thus **13**, **41**, and **42** are all potent κ agonists. Further branching, as in *tert*-butyl analogue **43**, does not cause any further improvement, though activity is maintained.

Aromatic substituents at R_3 behave very like α-branched alkyl groups, and produce potent compounds. Even the least active derivatives, **51** and **58**, are considerably more potent then the reference compound U-50488. No clear pattern of SAR is observed in the aryl series, both electron donating (e.g. **49**) and withdrawing (e.g. **50**) substituents give good activity, and the methoxy derivatives (**51–53**) show that all the ring positions may be substituted to give compounds of comparable potency. This is confirmed by the hydroxy analogues **56** and **57**; the drop in potency with **55** is likely to be due to the poor solubility of the compound, as it tended to precipitate from the test solution. Both **55** and **56** were too insoluble for in vivo testing.

The reasons for the lower activity of **51** and **58** are not clear. Although **51** binds to κ receptors fairly well, the activity is not expressed in the mouse vas deferens, so metabolism is a possibility. The MeS group is fairly large, and it may be that the 4-position of the ring cannot tolerate a substituent of this size.

It seems likely that the aryl ring is acting mainly by restricting the conformation of the ethylenediamine chain, and that substituents affect activity largely in terms of bioavailability and metabolism, rather than intrinsic potency, particularly in vivo.

The most potent compounds we have found are **36**, **48**, **49**, and **60**, all of which are more than 40 times as potent as the standard EKC, allowing that the latter three are racemates. All are very effective in the in vivo analgesic test but, unfortunately, they are also very potent in the sedation test (Tables II and III). In every case potency as an analgesic is mirrored by sedative potency, suggesting that the analgesia is centrally mediated and that both effects are a direct result of agonist activity at κ receptors in the CNS. This suggests that separation of beneficial and unwanted effects may not be possible.

In conclusion, we have demonstrated that the cyclohexane ring in U-50488 is not necessary for activity at the κ receptor. Linear [(acylamino)ethyl]pyrrolidines, suitably substituted on the carbon adjacent to the amide nitrogen to restrict rotation and/or introduce hydrophobic interactions, can give compounds which are very potent agonists at the κ opioid receptor, mediating centrally induced analgesia and, unfortunately, sedative side effects. Many of the compounds reported in this study are more than 20 times more potent than U-50488 as analgesics.

Experimental Section

Melting points (uncorrected) were determined in open capillary tubes with a Buchi-Tottoli apparatus. Optical rotations were determined in a Perkin-Elmer 241 polarimeter at the sodium D line in either $CHCl_3$ or MeOH solution. NMR spectra were obtained with either a JEOL FX 90Q or a Bruker AM 200 spectrometer in $CDCl_3$, DMSO-d_6 or DMSO-d_6/AcOH-d_4. Chemical shifts are reported in δ values (ppm) relative to internal Me_4Si. Low resolution mass spectra were determined for intermediates and final products on Varian VG 1212 or VG70-250SE instruments, giving anticipated molecular ions and fragmentation patterns. Analytical TLC was performed on 0.25 mm silica gel plates (Merck, Kieselgel 60 F-254). Evaporations were performed under reduced pressure and all oily products were dried at 0.1 Torr for 16 h. Flash column chromatography was carried out on silica (Merck Kieselgel 60, 230–400 mesh). Elemental analyses were performed by B. Crooks and his associates, ICI Pharmaceuticals. All final products were characterized by NMR, MS, and elemental analysis. The carbamates **3a–w** were isolated mainly as viscous oils and characterized by NMR and the majority by low-resolution MS in addition. The corresponding amines **4**, which were homogeneous by TLC, were used directly without further characterization.

[(3,4-Dichlorophenyl)thio]methanecarboxylic acid required in the synthesis of **24** was prepared by the literature procedure.[22] Amino acids which were not available commercially were prepared by the literature routes: 2- and (3-methoxyphenyl)glycine,[23] [4-(methylthio)phenyl]glycine,[24] and (3-nitrophenyl)glycine.[25] The protected (dimethoxyphenyl)glycines were synthesized as described below.

***N*-(Methoxycarbonyl)-(*R*,*S*)-(3,4-dimethoxyphenyl)-glycine.** *N*-(Methoxycarbonyl)-2-hydroxyglycine (11.0 g, 60 mmol) was added to a stirred mixture of AcOH (52 mL) and concentrated H_2SO_4 (5.82 mL) under an argon atmosphere. 1,2-Dimethoxybenzene (9.39 mL, 73 mmol) was then added portionwise with cooling to keep the temperature below 25 °C. The mixture was stirred for 16 h and shaken with EtOAc (500 mL) and H_2O (500 mL), and the organic layer was washed with water (250 mL) and brine (250 mL), dried ($MgSO_4$), and evaporated to give a brown oil (16 g) which crystallized on standing. Recrystallization from EtOH (150 mL) gave a white solid (4.6 g, 27%): mp 134–136 °C; NMR ($CDCl_3$) δ 3.7 (s, 3 H, CO_2CH_3), 3.9 (s, 6 H, 2 OCH_3), 5.3 (br d, J = 6 Hz, 1 H, CHAr), 5.8 (br s, 1 H, NH), 6.7–7.0 (cmplx, 3 H, Ar), 7.7 (s, 1 H, CO_2H); MS m/e 270 $(M + H)^+$. Anal. ($C_{12}H_{14}NO_6 \cdot 0.5H_2O$) C, H, N.

***N*-(Ethoxycarbonyl)-(*R*,*S*)-(2,4-dimethoxyphenyl)glycine** was prepared by an analogous procedure to the above, affording a yellow oil which was used directly without characterization in the synthesis of **59**. The intermediate pyrrolidine **3v**, obtained by the method described below for **3j**, was purified by flash chromatography using 2% MeOH/CH_2Cl_2 as eluant, affording an oil: NMR ($CDCl_3$) δ 1.2 (t, J = 8 Hz, 3 H, $CO_2CH_2CH_3$), 1.8 (bcmplx, 4 H, 2 CH_2CH_2N), 2.8–3.7 (cmplx, 4 H, 2 CH_2CH_2N), 3.8 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 4.05 (q, J = 8 Hz, 2 H,

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$CO_2CH_2CH_3$), 5.7 (d, J = 9 Hz, 1 H, CHAr), 5.9 (d, J = 9 Hz, 1 H, NH), 6.5 (cmplx, 2 H, Ar), 7.25 (cmplx, 1 H, Ar); MS m/e 337 $(M + H)^+$.

1-[(2*R*)-2-Phenyl-2-(methylamino)ethyl]pyrrolidine (4, R_3 = Ph, NR_4R_5 = pyrrolidine): Chiral Assay. Compound 4 (R_3 = Ph, NR_4R_5 = pyrrolidine) (2 mg) was dissolved in MeOH (300 μL) and treated with (*R*)-(+)-1-phenylethyl isocyanate (3 μL), and the solution stood for 30 min. A sample of this solution (10 μL) was applied to a 25-cm C_{18} reverse-phase (CO-PEL) HPLC column and eluted with $MeCN/H_2O/Et_3N$ (80/20/0.1) at a flow rate of 2 mL/min. A single sharp peak was seen, t_R = 5.5 min. Repeating the above with (*S*)-(−)-1-phenylethyl isocyanate gave a derivative with t_R = 4.75 min. From these traces the optical purity of the *R* isomer was estimated to be ca. 99% (98% ee).

Benzyl *N*-[(1*S*)-2-Methyl-1-(1-pyrrolidinylcarbonyl)-propyl]carbamate (3a) [Coupling Method A]. 1-Hydroxybenzotriazole (29.7 g, 0.2 mol) was added to a solution of (*S*)-*N*-(benzyloxycarbonyl)valine (55.2 g, 0.2 mol) in dry CH_2Cl_2 (400 mL) while being stirred under an atmosphere of argon with ice-bath cooling. Dicyclohexylcarbodiimide (DCCI) (45.3 g, 0.2 mol) in dry CH_2Cl_2 (300 mL) was added to the mixture at a fast drop rate and the reaction stirred for 1 h at 0 °C. Pyrrolidine (14.2 g, 0.2 mol) was added and the mixture stirred for a further 18 h at 20 °C. Dicyclohexylurea (DCU) was removed by filtration and washed with a little CH_2Cl_2. The combined filtrate was evaporated and the residue taken up in EtOAc (1.5 L), washed successively with saturated aqueous $NaHCO_3$ (2 × 300 mL), water (300 mL), 2 M HCl (2 × 300 mL), and brine (300 mL), and then dried ($MgSO_4$), filtered, and evaporated. The residue was dissolved in Et_2O (200 mL) and filtered to remove a small amount of insoluble DCU. Removal of the solvent under reduced pressure afforded 64.0 g (96%) of a colorless viscous oil: NMR ($CDCl_3$) δ 0.98 (d, J = 7 Hz, 3 H, one of $(CH_3)_2CH$), 1.00 (d, J = 7 Hz, 3 H, one of $(CH_3)_2CH$), 1.7–2.25 (cmplx, 5 H, 2 CH_2CH_2N + $CH(CH_3)_2$), 3.25–3.9 (m, 4 H, CH_2NCO), 4.15–4.5 (m, 1 H, CONHCHCO), 5.15 (s, 2 H, CH_2Ar), 5.6 (br d, J = 9 Hz, 1 H, NHCO), 7.35 (br s, 5 H, aromatic); MS m/e 305 $(M + H)^+$.

1-[(2*S*)-3-Methyl-2-(methylamino)butyl]pyrrolidine (4, R_3 = $CH(CH_3)_2$, NR_4R_5 = pyrrolidine). A solution of **3** (64 g, 0.21 mol) in dry THF (500 mL) was added dropwise, over a period of 30 min, to a stirred suspension of LAH (25 g, 0.658 mol) in dry THF (600 mL) at 0 °C and the mixture stirred for 16 h at 20 °C. Saturated aqueous Na_2CO_3 was added cautiously until effervescence ceased, the mixture filtered through Celite, and the filter cake washed thoroughly with Et_2O. The combined filtrate was evaporated to give an oil which was redissolved in Et_2O (1 L) and extracted with 2 M HCl (3 × 400 mL). The combined aqueous extracts were washed with Et_2O (2 × 400 mL), basified to pH 11 with solid NaOH, and extracted with Et_2O (3 × 400 mL). After drying (K_2CO_3), the combined extracts were evaporated to give 24.14 g (67%) of **4** (R_3 = *i*-Pr, NR_4R_5 = 1-pyrrolidinyl) as a clear oil. A small sample (0.85 g) was treated with ethereal HCl and the product recrystallized from MeOH/EtOAc to give 0.83 g (68%) of the dihydrochloride salt: mp 170–172 °C; $[\alpha]^{20}_D$ = 20° (*c* 1.0, MeOH); NMR (DMSO-d_6) δ 0.95 (d, J = 7 Hz, 3 H, one of $(CH_3)_2CH$), 0.98 (d, J = 7 Hz, 3 H, one of $(CH_3)_2CH$), 1.75–2.15 (cmplx, 4 H, 2 CH_2CH_2N), 2.18–2.35 (m, 1 H, $CH(CH_3)_2$), 2.65 (s, 3 H, $CH_3NH_2^+$), 2.85–3.25 (br d, 1 H, $CHNH_2^+$), 3.25–3.85 (cmplx, 6 H, 3 CH_2NH^+), 9.1–9.7 (br m, 2 H, 2 NH^+). Anal. ($C_{10}H_{22}N_2$·2HCl) C, H, Cl, N.

2-(3,4-Dichlorophenyl)-*N*-methyl-*N*-[(1*S*)-1-(1-methylethyl)-2-(1-pyrrolidinyl)ethyl]acetamide Hydrochloride (13). A solution of 3,4-dichlorophenylacetyl chloride (13.4 g, 60 mmol) in dry CH_2Cl_2 (75 mL) was added to a solution of **4** (R_3 = *i*-Pr, NR_4R_5 = 1-pyrrolidinyl) (10.2 g, 60 mmol) in dry CH_2Cl_2 (100 mL) and the mixture was left at 20 °C for 0.5 h. The reaction mixture was evaporated and the residue dissolved in water, basified to pH 11 with 2 M NaOH solution, and extracted with Et_2O (6 × 100 mL). The combined extracts were dried ($MgSO_4$) and evaporated to give 20.0 g (94%) of a viscous yellow oil. This free base (18 g) was treated with ethereal HCl to give 17.9 g (90%) of the hydrochloride salt, recrystallized from MeOH/EtOAc to afford 15.3 g of pure **13** as a white solid: mp 174–175 °C; $[\alpha]^{20}_D$ = −64.4° (*c* 1.0, $CHCl_3$); NMR (DMSO-d_6) δ 0.74 (d, J = 7 Hz, 3 H, one of $(CH_3)_2CH$), 0.95 (d, J = 7 Hz, 3 H, one of $(CH_3)_2CH$), 1.64–1.85 (m, 1 H, $CH(CH_3)_2$), 1.87–2.05 (cmplx, 4 H, 2 $CH_2CH_2NH^+$), 2.95 (s, 3 H, CH_3NCO), 2.80–3.15 (cmplx, 6 H, 3 CH_2NH^+), 3.88 (AB q, J = 16.5 Hz, Δδ = 60 Hz, 2 H, CH_2Ar), 4.91 (dt, J = 3 Hz, J = 10 Hz, 1 H, CHN), 7.23–7.58 (m, 3 H, aromatic), 10.63 (br s, 1 H, NH^+). Anal. ($C_{18}H_{26}Cl_2N_2O$·HCl) C, H, Cl, N.

Benzyl *N*-[(1*R*,*S*)-(3-Methoxyphenyl)(1-pyrrolidinylcarbonyl)methyl]carbamate (3p) [Coupling Method B]. *N*-(Benzyloxycarbonyl)-(*R*,*S*)-(3-methoxyphenyl)glycine (31.5 g, 0.1 mol) in EtOAc (300 mL) was cooled in an ice/water bath and treated with carbonyldiimidazole (17.8 g, 0.11 mol). After stirring for 2 h at 10–15 °C, pyrrolidine (9.2 mL, 7.8 g, 0.11 mol) was added. A slight exotherm (to 23 °C) was noted. After 1 h the solution was washed with 2 M HCl (3 × 300 mL), aqueous $NaHCO_3$ (300 mL), and H_2O (300 mL), dried ($MgSO_4$), treated with charcoal, and evaporated to give 36.1 g (98%) of a pale green oil: NMR ($CDCl_3$) δ 1.8 (cmplx, 4 H, 2 CH_2CH_2N), 2.9–3.7 (cmplx, 4 H, 2 CH_2CH_2N), 3.8 (s, 3 H, CH_3O), 5.05 (d, J = 3 Hz, 2 H, $ArCH_2$), 5.35 (d, J = 9 Hz, 1 H, NHCH), 6.3 (d, J = 9 Hz, 1 H, NHCH), 6.8–7.4 (cmplx, 9 H, aromatic); MS m/e 379 $(M + H)^+$.

Benzyl *N*-[2-Methyl-1-(1*R*)-(1-pyrrolidinylcarbonyl)-propyl]carbamate (3j) [Coupling Method C]. *N*-(Benzyloxycarbonyl)-*R*-valine (2.85 g, 10 mmol) and *N*-methylmorpholine (1.01 g, 11 mmol) in dry THF (25 mL) were stirred at −20 °C and treated carefully with isobutyl chloroformate (1.37 g, 10 mmol) over 5 min. After stirring for 0.5 h at −20 °C pyrrolidine (0.91 mL, 0.78 g, 11 mmol) was added and the mixture was stirred for 0.5 h at −20 °C and allowed to warm to 20 °C overnight. The mixture was diluted with water (150 mL) and extracted with Et_2O (200 mL). The Et_2O extract was washed with 2 M HCl (200 mL), aqueous $NaHCO_3$ (200 mL), and water (200 mL), dried ($MgSO_4$), and evaporated to give a colorless oil (3.64 g, 100%) which was used directly, without characterization, in the synthesis of **40**.

(2*S*)-(2-Amino-3-methylbutyryl)pyrrolidine Hydrochloride (6). Compound **5** (47.6 g 0.175 mol) was treated with 2 M HCl in EtOAc (500 mL) at 20 °C for 1 h and then evaporated and the product recrystallized from MeOH/EtOAc, affording 28.2 g (78%) of **6** as a white solid: mp 177–179 °C; NMR ($CDCl_3$) δ 1.1 (d, J = 9 Hz, 6 H, $(CH_3)_2CH$), 1.75–2.15 (cmplx, 4 H, 2 CH_2CH_2N), 2.15–2.55 (m, 1 H, $CH(CH_3)_2$), 3.2–4.1 (cmplx, 4 H, 2 CH_2NCO), 4.25 (t, J = 6 Hz, 1 H, COCHNH$^+$), 8.4 (br s, 3 H, NH_3^+). Anal. ($C_9H_{18}N_2O$·HCl) C, H, N.

2-(3,4-Dichlorophenyl)-*N*-[(1*S*)-1-(1-methylethyl)-2-(1-pyrrolidinyl)ethyl]acetamide Hydrochloride (25). Et_3N (8 mL, 56 mmol) was added to a solution of **6** (5.38 g, 26 mmol) in dry CH_2Cl_2 (150 mL) and the mixture cooled to 0 °C while 3,4-dichlorophenylacetyl chloride (6.0 g, 29 mmol) in dry CH_2Cl_2 (50 mL) was added dropwise with stirring. After a further 2 h at 20 °C, the resulting solution was washed with water (100 mL), 1 M NaOH (100 mL), and water (100 mL), dried ($MgSO_4$), and then evaporated to give an oil (8.65 g). A portion of this (2.57 g, 7.2 mmol) was dissolved in dry THF (35 mL) and treated dropwise under argon with 1 M BH_3/THF (24 mL, 24 mmol) at 20 °C. The stirred reaction mixture was heated to reflux for 3 h and cooled, and MeOH (25 mL) was added and then it was heated to reflux once more for 30 min. The mixture was evaporated to dryness and the residue submitted to gravity chromatography on aluminia (Woelm N-32-63) eluting with 1/1 EtOAc/petroleum ether (bp 60–80 °C). Fractions containing the product were combined and evaporated, and the residue was treated with ethereal HCl to give 0.25 g (9%) of **25** after recrystallization from MeOH/EtOAc: mp 189–190 °C; $[\alpha]^{20}_D$ = +6.1° (*c* 1.1, MeOH); NMR ($CDCl_3$) δ 0.83 (d, J = 7 Hz, 3 H, one of $(CH_3)_2CH$), 0.86 (d, J = 7 Hz, 3 H, one of $(CH_3)_2CH$), 1.7–1.95 (cmplx, 5 h, 2 $CH_2CH_2N^+$ + $CH(CH_3)_2$), 2.37–2.8 (cmplx, 6 H, 3 CH_2N^+), 3.57 (s, 2 H, CH_2Ar), 3.82–4.0 (m, 1 H, CHNHCO), 6.10 (br d, J = 8.5 Hz, NHCO), 7.13–7.45 (cmplx, 3 H, aromatic). Anal. ($C_{17}H_{24}Cl_2N_2O$·HCl) C, H, N.

(2*S*)-1-[2-(Acetylamino)-3-methylbutyryl]pyrrolidine (*N*-acetyl-6). Amine **6** (2.06 g, 10 mmol) was dissolved in dry CH_2Cl_2 (25 mL) and Et_3N (3 mL, 21 mmol) added. The resulting solution was cooled to 0 °C and stirred while acetyl chloride (0.78 mL, 11 mmol) was added dropwise over 5 min. After stirring at 20 °C for 16 h the solvent was evaporated and the residue submitted to flash chromatography on silica eluting with EtOAc to give 0.8 g (38%) of *N*-acetyl-**6** as an oil: NMR ($CDCl_3$) δ 0.91 (d, J = 7 Hz, 3 H, one of $(CH_3)_2CH$), 0.93 (d, J = 7 Hz, 3 H, one of $(CH_3)_2CH$), 1.88–2.10 (cmplx, 5 h, 2 CH_2CH_2NCO + $CH(CH_3)_2$),

1.99 (s, 3 H, CH_3CO), 3.31–3.57 (cmplx, 3 H, 3 of 2 NCH_2), 3.66–3.88 (m, 1 H, one of NCH_2), 4.57 (dd, J = 7 Hz, J = 9 Hz, 1 H, NHCHCO), 6.55 (br d, J = 9 Hz, 1 H, NHCHCO).

2-(3,4-Dichlorophenyl)-*N*-ethyl-*N*-[(1*S*)-1-(1-methylethyl)-2-(1-pyrrolidinyl)ethyl]acetamide Oxalate (26). *N*-Acetyl-6 (0.77 g, 3.6 mmol) was dissolved in dry THF (20 mL) and added to a stirred suspension of LAH (0.3 g, 8 mmol) in dry THF (50 mL) under an argon atmosphere and then stirred at 20 °C for 72 h. Aqueous NaOH solution (10%) was added dropwise and the precipitate formed was filtered through a Celite bed. Evaporation of the solvent gave an oil (0.67 g) which was reacted directly with 3,4-dichlorophenylacetyl chloride (0.81 g, 3.6 mmol) in CH_2Cl_2 (30 mL) as previously described affording 0.56 g (43%) of **26** free base which was converted to a crystalline oxalate salt: mp 166–167 °C; $[\alpha]^{22}_D$ = −18.5° (*c* 1.1, MeOH); NMR ($CDCl_3$) δ 0.76 (d, J = 7 Hz, 3 H, one of $(CH_3)_2CH$, 40% minor rotamer), 0.83 (d, J = 7 Hz, 3 H, one of $(CH_3)_2CH$, 60% major rotamer), 0.97 (d, J = 7 Hz, 3 H, one of $(CH_3)_2CH$, 60% major rotamer), 0.99 (d, J = 7 Hz, 3 H, one of $(CH_3)_2CH$, 40% minor rotamer), 1.20 (t, J = 7 Hz, 3 H, CH_3CH_2, 40% minor rotamer), 1.25 (t, J = 7 Hz, 3 H, CH_3CH_2, 60% major rotamer), 2.2–4.3 (cmplx, 11 H, 3 CH_2N^+ + CH_2NCO + $ArCH_2$ + CHNCO), 7.04–7.40 (cmplx, 3 H, aromatic). Anal. ($C_{19}H_{28}Cl_2N_2O{\cdot}C_2H_2O_4$) C, H, N.

2-(3,4-Dichlorophenyl)-*N*-propyl-*N*-[(1*S*)-1-(1-methylethyl)-2-(1-pyrrolidinyl)ethyl]acetamide Oxalate (27). Amine **6** was treated with propanoyl chloride and the product reduced and acylated by an analogous procedure to the above, affording **27** oxalate.

2-(3,4-Dichlorophenyl)-*N*-methyl-*N*-[(1*S*)-1-(1-methylethyl)-2-(*N*-methylamino)ethyl]acetamide Hydrochloride (29). *N*-Benzylamine hydrochloride **28** (15.0 g, 34 mmol) was dissolved in 10% aqueous dioxane (330 mL) containing 2 N HCl (17 mL) and 5% Pd/C (1.7 g) was added. The mixture was hydrogenated at atmospheric pressure, resulting in the uptake of hydrogen (820 mL) over a period of 6 h. The catalyst was removed by filtration through Celite and the filtrate basified to pH 11 with 2 M NaOH and then extracted with Et_2O (3 × 100 mL). Combined Et_2O extracts were back-washed with water (100 mL), dried ($MgSO_4$), and evaporated to give 11.3 g (100%) of a pale yellow oil. Nine grams of this was treated with ethereal HCl, affording an HCl salt which was recrystallized from MeOH/EtOAc to give 4.5 g product as white crystals: mp 162–163 °C; $[\alpha]^{20}_D$ = −57.8° (*c* 1.0, $CHCl_3$); NMR (DMSO-d_6) δ 0.57 (d, J = 7 Hz, 3 H, one of $(CH_3)_2CH$, 20% minor rotamer), 0.73 (d, J = 7 Hz, 3 H, one of $(CH_3)_2CH$, 80% major rotamer), 0.92 (d, J = 7 Hz, 3 H, one of $(CH_3)_2CH$, 80% major rotamer), 0.95 (d, J = 7 Hz, 3 H, one of $(CH_3)_2CH$, 20% minor rotamer), 1.66–1.88 (m, 1 H, $CH(CH_3)_2$), 2.50 (s, 3 H, $CH_3NH_2^+$, 80% major rotamer) 2.59 (s, 3 H, $CH_3NH_2^+$, 20% minor rotamer), 2.67 (s, 3 H, CH_3NCO, 20% minor rotamer), 2.90 (s, 3 H, CH_3NCO, 80% major rotamer), 3.0–3.25 (m, 2 H, $CH_2NH_2^+$), 3.84 (AB q, J = 16.5 Hz, Δδ = 27 Hz, 2 H, CH_2Ar, 80% major rotamer), 3.97 (AB q, J = 16 Hz, Δδ = 40 Hz, 2 H, CH_2Ar, 20% minor rotamer), 4.33 (dt, J = 3 Hz, J = 10 Hz, 1 H, CHNCO), 7.20–7.65 (cmplx, 3 H, aromatic), 8.8 (br s, 2 H, NH_2^+). Anal. ($C_{15}H_{22}Cl_2N_2O{\cdot}HCl$) C, H, Cl, N.

2-(3,4-Dichlorophenyl)-*N*-methyl-*N*-[(1*S*)-1-(1-methylethyl)-2-(*N*-propyl-*N*-methylamino)ethyl]acetamide Oxalate (31). To a solution of **29** (0.35 g, 1 mmol) in EtOH (5 mL) was added freshly distilled propanal (0.35 mL, 0.29 g, 5 mmol). After stirring for 10 min, $Na(BH_3)CN$ (0.19 g, 3 mmol) was added followed by glacial AcOH (5 drops) to pH 5 and stirring was continued for 1 h. Removal of the solvent under vacuum gave an oily residue which was treated with aqueous saturated K_2CO_3 (10 mL) and extracted with Et_2O (5 × 10 mL). Combined extracts were dried ($MgSO_4$) and evaporated to give an oil which was subjected to flash chromatography on silica eluting with CH_2Cl_2/MeOH/NH_4OH (97/2/1). Fractions containing the product were combined and evaporated affording 0.25 g (70%) of a colorless oil. A 0.21-g portion of this was treated with oxalic acid (80 mg) in MeOH/EtOAc, affording 0.12 g of **29**-oxalate: mp 142–143 °C; $[\alpha]^{20}_D$ = −47.4° (*c* 1.0, MeOH); NMR (DMSO-d_6) δ 0.74 (d, J = 7 Hz, 3 H, one of $(CH_3)_2CH$), 0.86 (t, J = 7 Hz, 3 H, CH_3CH_2), 0.95 (d, J = 7 Hz, 3 H, one of $(CH_3)_2CH$), 1.5–1.9 (cmplx, 3 H, $CH(CH_3)_2$ + CH_2CH_3), 2.68 (s, 3 H, CH_3NH^+), 2.87 (s, 3 H, CH_3NCO), 2.8–3.4 (cmplx, 4 H, 2 CH_2N^+), 3.80 (s, 2 H, CH_2Ar), 4.45 (dt, J = 3 Hz, J = 10 Hz, 1 H, CHNCO), 7.16–7.6 (m, 3 H, aromatic). Anal. ($C_{18}H_{28}Cl_2N_2O{\cdot}C_2H_2O_4{\cdot}0.25H_2O$) C, H, Cl, N, H_2O.

2-(2,3-Dichlorophenyl)-*N*-[(1*S*)-1-(1-methylethyl)-2-[*N*-(1-methylethyl)-*N*-methylamino]ethyl]acetamide Oxalate (32). Acetone was reacted with **29** and the product was reduced with $Na(BH_3)CN$, as described above to give **32**.

2-(3,4-Dichlorophenyl)-*N*-methyl-*N*-[(1*R*,*S*)-1-[3-(methylamino)phenyl]-2-(1-pyrrolidinyl)ethyl]acetamide Dihydrochloride (47). Compound **7** (1.7 g, 6.1 mmol), 10% palladium/carbon catalyst (300 mg), and AcOH (20 mL) were stirred, at 20 °C, under H_2 at atmospheric pressure until absorption ceased. After filtration and evaporation of the solvent, the product was partitioned between 2 M HCl (50 mL) and EtOAc (50 mL). The aqueous extract was washed with EtOAc (50 mL) and basified with aqueous NaOH to give an oil which was extracted with EtOAc (100 mL). The extract was dried over anhydrous Na_2SO_4 and evaporated to give 900 mg (56%) of **8** as an oil which crystallized on standing. This product (2.9 g, 10.4 mmol) in CH_2Cl_2 (30 mL) was treated with Et_3N (1.53 mL, 11 mmol), followed by methyl chloroformate (0.85 mL, 11 mmol). The mixture was stirred for 16 h at 20 °C, evaporated, and partitioned between EtOAc (100 mL) and H_2O (100 mL). The organic phase was washed with H_2O (100 mL), 2 M HCl (100 mL), H_2O (100 mL), dried ($MgSO_4$), and evaporated to give a foam (1.7 g) which was purified by flash chromatography using EtOAc/CH_2Cl_2 (3/1) to give 850 mg (25%) of a foam which was used directly. The accumulated product from several runs (2.0 g, 7.2 mmol), LAH (1.5 g, 39 mmol), and dry THF (100 mL) were refluxed and stirred for 16 h under argon. Excess LAH was destroyed with saturated Na_2CO_3 solution and the mixture filtered. The filtrate was evaporated to give 1.0 g of crude diamine **9**, which was dissolved in CH_2Cl_2 (10 mL), cooled in an ice bath, and treated with 3,4-dichlorophenylacetyl chloride (2.3 g, 10 mmol) in CH_2Cl_2 (10 mL). After 30 min the mixture was evaporated, converted to free base with 10% KOH solution (10 mL), and extracted into EtOAc (50 mL). After washing with water (50 mL), drying ($MgSO_4$), and evaporating, the product was purified by flash chromatography eluting with 5% MeOH in CH_2Cl_2 to give 1.6 g of the diacyl derivative. This was dissolved in a mixture of H_2O (10 mL) and EtOH (40 mL) containing KOH (5.0 g, 89 mmol), and the mixture refluxed for 16 h. After cooling and evaporation, the product was extracted into EtOAc (50 mL), washed with water (50 mL), dried ($MgSO_4$), and evaporated. The residue was dissolved in Et_2O (50 mL) and treated with HCl/Et_2O, affording a hygroscopic solid which was crystallized twice from MeOH/EtOAc to give 175 mg (13%) of **47**: mp 242–244 °C; NMR (DMSO-d_6) δ 1.88–2.12 (cmplx, 4 H, CH_2CH_2), 2.82–2.88 (2 s, 6 H, 2 NCH_3), 3.05–4.16 (cmplx, 8 H, $ArCH_2CO$ + 3 CH_2N), 6.1 (br d, J = 10 Hz, 1 H, CHAr), 6.98–7.64 (cmplx, 7 H, aromatic). Anal. ($C_{22}H_{27}Cl_2N_3O{\cdot}2HCl$) C, H, N.

2-(3,4-Dichlorophenyl)-*N*-methyl-*N*-[(1*R*,*S*)-1-(3-aminophenyl)-2-(1-pyrrolidinyl)ethyl]acetamide Hydrochloride (48). Compound **8** was reduced with LAH, in the standard manner, to give **10**. This was diacylated with 3,4-dichlorophenylacetyl chloride, and the more labile anilide acyl group was removed by KOH hydrolysis, by the same method used for the synthesis of **47**, giving pure **48**: mp 248–249 °C; NMR (DMSO-d_6) δ 1.9–2.1 (cmplx, 4 H, CH_2CH_2), 2.86 (s, 3 H, NCH_3), 3.0–3.3 (cmplx, 2 H, CH_2N^+), 3.4–4.2 (cmplx, 6 H, CH_2N^+ + CH(Ar)-CH_2N^+ + $ArCH_2CO$), 6.12 (dd, J = 2 Hz, J = 8 Hz, 1 H, CONCHAr), 7.15–7.6 (cmplx, 7 H, aromatic). Anal. ($C_{21}H_{25}Cl_2N_3O{\cdot}2HCl{\cdot}H_2O$) C, H, N, H_2O.

2-(3,4-Dichlorophenyl)-*N*-methyl-*N*-[(1*R*,*S*)-1-(3-acetamidophenyl)-2-(1-pyrrolidinyl)ethyl]acetamide Hydrochloride (49). The free base of **48** (406 mg, 1 mmol) in CH_2Cl_2 (5 mL) was treated with AcCl (0.1 mL, 1.25 mmol) in CH_2Cl_2 (2 mL) with ice cooling. After 1 h the solution was evaporated and the residue recrystallized from MeOH/EtOAc to give 250 mg (52%) of **49**: mp 231–232 °C dec; NMR (DMSO-d_6) δ 2.0 (cmplx, 4 H, CH_2CH_2), 2.05 (s, 3 H, CH_3CO), 2.8 (s, 3 H, NCH_3), 3.1–4.15 (cmplx, 8 H, 3 NCH_2 + $ArCH_2CO$), 6.1 (br d, J = 11 Hz, 1 H, NCHAr), 6.9–7.6 (cmplx, 7 H, aromatic). Anal. ($C_{23}H_{27}Cl_2N_3O_2{\cdot}HCl{\cdot}0.5H_2O$) C, H, N, H_2O.

2-(3,4-Dichlorophenyl)-*N*-methyl-*N*-[(1*R*,*S*)-1-(3-chlorophenyl)-2-(1-pyrrolidinyl)ethyl]acetamide Oxalate (50). A suspension of **48** (0.5 g, 1.1 mmol) in 50% aqueous HCl (10 mL) was stirred at 0–5 °C and treated slowly with $NaNO_2$ (76 mg, 1.1

mmol) in cold water (5 mL). After 1 h the solution was added to a solution of CuCN (180 mg, 2.2 mmol) and KCN (180 mg, 2.75 mmol) in H_2O (10 mL) at 70 °C. The mixture was then heated on a steam bath for 0.5 h, cooled, basified with Na_2CO_3 solution, and extracted with EtOAc (3 × 20 mL). The solution was dried ($MgSO_4$) and evaporated to give an oil (350 mg) which was purified by flash chromatography eluting with 5% MeOH/CH_2Cl_2, to give a yellow oil (83 mg) which was dissolved in EtOAc and treated with oxalic acid monohydrate (23 mg), which led to a solid that was recrystallized from EtOAc to give 65 mg (13%) of **50**·oxalate: mp 173–175 °C; NMR (DMSO-d_6) δ 1.9 (br s, 4 H, CH_2CH_2), 2.8 (s, 3 H, NCH_3), 3.2–3.4 (cmplx, 4 H, 2 CH_2N^+), 3.45–3.65 (cmplx, 1 H, one of N(Me)CHCH_2), 3.85–4.05 (cmplx, 3 H, one of N(Me)CHCH_2 + ArCH_2CO), 4.8 (br peak, 8 H, oxalate + H_2O), 6.1 (dd, J = 7 Hz, J = 3 Hz, 1 H, CHAr), 7.2–7.6 (cmplx, 7 H, aromatic). Anal. ($C_{21}H_{23}Cl_3N_2O·C_2H_2O_4$) C, H, N.

2-(3,4-Dichlorophenyl)-*N*-methyl-*N*-[(1*R*,*S*)-1-(3-cyanophenyl)-2-(1-pyrrolidinyl)ethyl]acetamide Hydrochloride (51). Pyrrolidine (3.4 mL, 40 mmoL) in Et_2O (100 mL) was stirred with ice cooling and 3-cyanophenacyl bromide[26] (4.48 g, 20 mmol) added. The solution was stirred for 1 h and acidified with HCl in EtOH. The product was collected and washed with EtOAc to give **11** (3.25 g, 15 mmol), which was stirred in MeOH (75 mL) with methylamine hydrochloride (6.5 g, 0.1 mol), and methylamine (33% in EtOH) was added dropwise to adjust the pH to 6. $Na(BH_3)CN$ (1.0 g, 15 mmol) was added and the mixture stirred for 48 h. The pH had drifted to 7.4 and was adjusted back to 6 with HCl/EtOH and the mixture stirred a further 48 h. The solution was acidified to pH 2 with aqueous HCl and evaporated. The residue was dissolved in water (50 mL), washed twice with Et_2O (50 mL), and made basic with 2 M NaOH. The solution was extracted with Et_2O (3 × 50 mL), and the extracts were dried over K_2CO_3 and evaporated to give **12** (2.2 g) as a light brown oil which was not characterized but acylated in the usual fashion with 3,4-dichlorophenylacetyl chloride to give **51**: mp 266–268 °C; NMR (DMSO-d_6) δ 2.0 (br, 4 H, pyrrolidine CH_2CH_2) 2.88 (s, 3 H, N-CH_3), 3.0–4.2 (cmplx, 8 H, 3 CH_2N + ArCH_2CO), 6.18 (m, 1 H, NCHAr), 7.3–7.9 (cmplx, 7 H, aromatic). Anal. ($C_{22}H_{23}Cl_2N_3O·HCl$) C, H, N.

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Registry No. **3a**, 56414-68-7; **3b**, 136329-23-2; **3c**, 42718-52-5; **3d**, 56414-64-3; **3e**, 135415-78-0; **3f**, 136329-24-3; **3g**, 136329-25-4; **3h**, 136329-26-5; **3i**, 136329-27-6; **3j**, 56414-69-8; **3k**, 136329-28-7; **3l**, 56414-66-5; **3m**, 136329-29-8; **3h**, 136329-30-1; **3o**, 136329-31-2; **3p**, 125207-72-9; **3q**, 136329-32-3; **3r**, 136329-33-4; **3s**, 136329-34-5; **3t**, 136329-35-6; **3u**, 136329-36-7; **3v**, 136329-37-8; **3w**, 115201-10-0; (*R*)-**4**, R_3 = Ph, NR_4R_5 = pyrrolidine, 136329-39-0; (*RS*)-**4**, R_3 = Ph, NR_4R_5 = pyrrolidine, 136378-39-7; (*S*)-**4**, R_3 = $CH(CH_3)_2$, NR_4R_5 = pyrrolidine, 136329-40-3; **5**, 130013-62-6; **6**, 115201-28-0; *N*-acetyl-**6**, 115201-30-4; **7**, 115201-25-7; **8**, 115201-24-6; **9**, 115201-33-7; **10**, 125190-71-8; **11**, 136328-62-6; **12**, 136328-63-7; **13**, 136328-64-8; **13**, 136328-64-8; **13**·HCl, 115199-69-4; **14**, 136328-65-9; **14**·HCl, 115199-88-7; **15**, 136328-66-0; **15**·HCl, 115199-99-0; **16**, 136328-67-1; **16**·HCl, 115200-00-5; **17**, 115200-03-8; **17**·$C_4H_4O_4$, 136329-01-6; **18**, 115200-07-2; **18**·$C_4H_4O_4$, 136329-02-7; **19**, 136328-68-2; **19**·HCl, 115199-90-1; **20**, 136328-69-3; **20**·HCl, 115199-82-1; **21**, 136328-70-6; **21**·HCl, 115199-70-7; **22**, 136328-71-7; **22**·HCl, 136329-03-8; **23**, 136328-72-8; **23**·HCl, 136329-04-9; **24**, 136328-73-9; **24**·HCl, 136329-05-0; **25**, 136328-74-0; **25**·HCl, 136329-06-1; **26**, 136328-75-1; **26**·$C_2H_2O_4$, 136329-07-2; **27**, 136328-76-2; **27**·$C_2H_2O_4$, 136329-08-3; **28**, 136328-77-3; **28**, 136328-77-3; **28**·HCl, 136329-09-4; **29**, 136328-78-4; **29**·HCl, 136329-10-7; **30**, 136328-79-5; **30**·HCl, 115200-62-9; **31**, 136328-80-8; **31**·$C_2H_2O_4$, 136329-11-8; **32**, 115200-67-4; **32**·$C_2H_2O_4$, 136329-12-9; **33**, 115200-63-0; **34**, 136328-81-9; **34**·HCl, 115200-61-8; **35**, 136328-82-0; **35**·HCl, 115200-69-6; **36**, 115200-94-7; **36**·HCl, 115200-73-2; **37**, 115200-95-8; **37**·HCl, 115199-66-1; **38**, 136328-83-1; **38**·HCl, 115200-02-7; **39**, 136328-84-2; **39**·HCl, 115200-01-6; **40**, 136328-85-3; **40**·HCl, 136329-13-0; **41**, 136328-86-4; **41**·HCl, 136329-14-1; **42**, 136328-87-5; **42**·HCl, 115199-74-1; **43**, 136328-88-6; **43**·HCl, 115199-96-7; **44**, 136328-89-7; **44**·HCl, 136329-15-2; **45**, 136378-37-5; **45**·HCl, 136378-38-6; **46**, 116508-24-8; **46**·HCl, 115199-84-3; **47**, 136328-90-0; **47**·2HCl, 136329-16-3; **48**, 115200-89-0; **48**·2HCl, 125190-65-0; **49**, 136328-91-1; **49**·HCl, 136329-17-4; **50**, 136328-92-2; **50**·$C_2H_2O_4$, 136329-18-5; **51**, 136328-93-3; **51**·HCl, 136329-19-6; **52**, 136328-94-4; **52**·HCl, 136329-20-9; **53**, 125190-68-3; **53**·HCl, 115200-21-0; **54**, 136328-95-5; **54**·HCl, 115200-22-1; **55**, 136328-96-6; **55**·HCl, 136329-21-0; **56**, 115201-26-8; **56**·HCl, 115199-91-2; **57**, 136328-97-7; **57**·HCl, 115199-85-4; **58**, 136328-98-8; **58**·HCl, 115199-95-6; **59**, 136328-99-9; **59**·HCl, 136329-22-1; **60**, 136329-00-5; **60**·HCl, 115200-30-1; *N*-(methoxycarbonyl)-2-hydroxyglycine, 115201-13-3; 1,2-dimethoxybenzene, 91-16-7; *N*-(methoxycarbonyl)-(*R*,*S*)-(3,4-dimethoxyphenyl)glycine, 115201-12-2; *N*-(ethoxycarbonyl)-(*R*,*S*)-(2,4-dimethoxyphenyl)-glycine, 136329-38-9; (*S*)-*N*-(benzyloxycarbonyl)valine, 1149-26-4; pyrrolidine, 123-75-1; 3,4-dichlorophenylacetyl chloride, 6831-55-6; *N*-(benzyloxycarbonyl)-(*R*,*S*)-(3-methoxyphenyl)glycine, 125190-66-1; *N*-(benzyloxycarbonyl)-(*R*)-valine, 1685-33-2; isobutyl chloroformate, 543-27-1; 2-(3,4-dichlorophenyl)-*N*-[(1*S*)-1-(1-methylethyl)-2-(1-pyrrolidinyl)ethyl]acetamide, 115201-27-9; 3-cyanophenacyl bromide, 50916-55-7.

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