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1-(4-Methylphenyl)-2-pyrrolidin-1-yl-pentan-1-one (Pyrovalerone) analogs. A promising class of monoamine uptake inhibitors

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Abstract

Dopamine, serotonin and norepinephrine are essential for neurotransmission in the mammalian system. These three neurotransmitters have been the focus of considerable research since modulation of their production and their interaction at monoamine receptors has profound effects upon a multitude of pharmacological outcomes. Our interest has focused on neurotransmitter reuptake mechanisms in a search for medications for cocaine abuse. Herein we describe the synthesis and biological evaluation of an array of 2-aminopentanophenones. This array has yielded selective inhibitors of the dopamine and norepinephrine transporters with little effect upon serotonin trafficking. A subset of compounds had no significant affinity at $5HT_{1A}$, $5HT_{1B}$, $5HT_{1C}$, D_1, D_2, or D_3 receptors. The lead compound, racemic 1-(4-methylphenyl)-2-pyrrolidin-1-yl-pentan-1-one **4a**, was resolved into its enantiomers and the *S* isomer was found to be the most biologically active enantiomer. Among the most potent of these DAT/NET selective compounds are the 1-(3,4-dichlorophenyl)- (**4u**) and the 1-naphthyl- (**4t**) 2-pyrrolidin-1-yl-pentan-1-one analogs.

Introduction

The endogenous monoamines, dopamine, serotonin and norepinephrine are essential for neurotransmission in the mammalian system. These three neurotransmitters, their biological receptors, and their reuptake mechanisms are the focus of considerable research since modulation of their production and their interaction at monoamine receptors has profound effects upon a multitude of pharmacological outcomes.[1–8] Dopamine, serotonin and norepinephrine are released into the synapse where their concentrations are regulated, at least in part, by reuptake proteins located in the presynaptic membrane.[9,10] These reuptake mechanisms have been termed the dopamine transporter (DAT), serotonin transporter (SERT), and the norepinephrine transporter (NET). The DAT is the target of numerous therapeutic agents such as Ritalin® (methylphenidate), Adderral® (amphetamine), Wellbutrin® or Zyban® (bupropion). Our interest has focused on the DAT in a search for medications for cocaine abuse[2,11–14] since cocaine's reinforcing and stimulant properties have long been associated with its propensity to bind to and inhibit monoamine transport systems, especially the DAT.[15–24] Our work has concentrated on the design of compounds that inhibit all three monoamine uptake systems with different degrees of potency and selectivity. In the search for a new class of compounds that may provide a different access to agents that target the transport systems, our attention was drawn to bupropion (Figure 1), a compound marketed as an

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antidepressant (Wellbutrin®) as well as for smoking cessation (Zyban®). Bupropion is a 2-substituted aminopropiophenone,[25,26] that has been explored extensively. Interestingly, and of relevance to the work which we describe later, the enantiomers of bupropion may not differ in their ability to inhibit biogenic amines.[27] Bupropion is structurally closely related to a 2-substituted aminopentanophenone, pyrovalerone (Figure1).

In 1992 Lancelot reported that pyrovalerone inhibits the DAT and the NET, and is a weak inhibitor of the SERT.[28] Its synthesis was first reported by Heffe in 1964.[29] Stille[30] and Holliday[31] confirmed its stimulant activity in animals and humans in 1963. In 1971 pyrovalerone was demonstrated to reduce symptoms of chronic fatigue in humans.[32] Later studies in rat heart revealed that it inhibits NE uptake and effects the release of NE from storage or functional pools.[25,33] In 1993 Vaugeois et al.[34] reported that pyrovalerone stimulated locomotor activity in mice (2mg/Kg) for up to 1 hour and that this duration of action paralleled the time course of its DAT occupancy. Notwithstanding this early clinical interest, the literature reveals little SAR on pyrovalerone. Lancelot et al.[28] reported the exchange of the phenyl ring for a thiophenyl ring. This exchange resulted in analogs of similar potency for both inhibition of DA and NE uptake. Further, an increase of size of the nitrogen containing ring from a 5-membered pyrrolidine to a 6-membered piperidine caused a substantial loss in binding potency at all uptake mechanisms. These researchers also reported that their analogs inhibited both DA and NE uptake but were less potent at inhibition at SERT, a finding very similar to that now reported for the analogs of the present study. Since then, one pharmacological study has appeared[34] in which pyrovalerone was shown to occupy striatal sites labeled with GBR12783, and to manifest an increase in locomotor activity. However, there are no further reports concerning SAR or biological enantioselectivity of pyrovalerone or analogs. Consequently, there is little directly relevant SAR to guide the selection of pyrovalerone analogs for evaluation as potential cocaine medication.

Herein we describe the synthesis and biological evaluation of a family of analogs of 1-(4-methylphenyl)-2-pyrrolidin-1-yl-pentan-1-one (pyrovalerone) **4a** and show, in general, that these compounds are potent inhibitors of the dopamine transporter (DAT) and norepinephrine transporter (NET), but are relatively poor inhibitors of the serotonin transporter (SERT). In addition, certain compounds were evaluated for affinity at $5HT_{1A}$, $5HT_{1B}$, $5HT_{1C}$, D_1, D_2, and D_3 receptors and were found to be inactive.

Chemistry

The general route of synthesis of pyrovalerone and close analogs (Scheme 1) is straightforward and was first published by Heffe in 1964.[29] We have adopted this route wherever possible. The synthesis of target compounds **4** is presented in Scheme 1. Synthesis of **6, 7, 9f** and **9g** is shown in Scheme 2. Synthesis of compounds **9a–e** is presented in Scheme 3. The ketones (Scheme 1) **2d–f** are commercially available. Compound **2m** was prepared from **2k**. Ketones **2i–j** and **2n** were obtained from **2f** according to a literature procedure.[35] Other required ketones **2** were obtained either from aryl nitriles **1**, or by Friedel-Crafts acylation of suitably substituted aryl precursors.

Thus, arylnitriles **1** were subjected to reaction with *n*-BuMgCl, followed by acidic hydrolysis to afford ketones **2h, 2p, 2r–u** and **2w** in excellent yields. Alternatively, ketones **2a, 2g** and **2o** were prepared by Friedel-Crafts acylation of toluene, iodobenzene and acetanilide respectively with valeroyl chloride. These ketones **2** were then brominated selectively with bromine in the presence of a catalytic amount of aluminum trichloride to provide the α-bromoketones **3** quantitatively. Ring bromination did not occur under these conditions. The α-bromoketones were then used without further purification in the subsequent reactions with pyrrolidine at room temperature to provide **4a, d–j, m–p, r–u** and **4w**. Compounds **4k** and

4v were obtained by BBr_3 demethylation of **4m** and **4w** respectively. Sonogashira coupling of **4g** with propyne was used to prepare compound **4q**, and Stille coupling with the respective stannylated heterocycles was employed to prepare compounds **4x–z** from **4f**. Nitro compound **4l** was obtained by oxidation of compound **4o** with H_2O_2/trifluoroacetic anhydride.

The resolution of racemic 1-(4-methylphenyl)-2-pyrrolidin-1-yl-pentan-1-one **4a** was accomplished by recrystallization from CH_2Cl_2/hexane of the diastereomeric salts obtained upon reaction with dibenzoyl-D-tartaric acid in refluxing ethanol (Scheme 4).

This provided the (2*R*)-pyrovalerone dibenzoyl-D-tartrate salt. The purity was determined by ^{1}H-NMR spectroscopy. The diastereomeric salt mixture showed two sets of triplets at δ = 0.73 and 0.69 ppm ($CDCl_3$). These correspond to the ω-methyl protons of the pyrovalerone moieties of the (2*S*)-pyrovalerone dibenzoyl-D-tartrate and (2*R*)-pyrovalerone dibenzoyl-D-tartrate salts respectively. After four recrystallizations, the triplet at 0.73 ppm was no longer visible. The absence of the triplet attests to the diastereomeric purity of the compound, and this can be assumed to be >95% d.e. on the basis of the limits of sensitivity of the NMR experiment. It is noteworthy that the purified dibenzoyl-D-tartaric and L-tartaric acid diastereomeric salts of **4b** and **4c** are enantiomers and both resonate at δ 0.71 for the ω-methyl. The assignment of the absolute optical configuration of this diastereomer was confirmed by X-ray structural analysis as (2*R*) (optical rotation was $[\alpha]^{20}_D = +59.6°$ (c 1.06, EtOH)). Upon treatment with aqueous Na_2CO_3 and extraction into Et_2O, then treatment with HCl, this diastereomeric salt gave (2*R*)-pyrovalerone **4c**.

The (2*S*)-isomer **4b** was then obtained from the enriched mother liquors by reaction with dibenzoyl-L-tartaric acid, recrystallization of the diastereomeric salts (optical rotation was $[\alpha]^{20}_D = -61.1°$ (c 1.07, EtOH)) and liberation of **4b** upon treatment with aqueous sodium carbonate. The chiral center does not epimerize under these conditions. The enantiomeric purity of **4b** and **4c** can be anticipated to be >95% ee, that is the same as the diastereomeric purity of the precursor dibenzoyl tartrate salts. Enantiomeric purity was confirmed by HPLC chiral resolution using a Chiralpak AD column. Each isomer was thus confirmed to be >99% pure (ee > 98%).

α,β-Unsaturated ketones **5a** and **5 b** were obtained (Scheme 2) by dehydrobromination of **3a** and **3u** with Li_2CO_3/LiBr in DMF. Reaction with pyrrolidine then gave **6a** and **6b** respectively. Compounds **7a** and **7b** were accessible *via* Mannich reaction of **3a** and **3b** with paraformaldehyde and pyrrolidine hydrochloride. Compound **3u** was also used to provide **9f** (reaction with butylamine) and **9g** (reaction with piperidine). Compounds **9a** and **b** were prepared (Scheme 3) by reaction of the appropriate α-bromoketones with pyrrolidine. Compounds **9c–e** were prepared from the 2-pyrrolidinyl **8** [29] by alkylation with propargyl bromide in the presence of sodium amide or by alkylation with allyl bromide followed by treatment with aqueous sodium hydroxide. Reduction of **4a** with $LiAlH_4$ gave **9h** and **9j** as a mixture of diastereomers, which were separated by flash column chromatography. All amines were converted to their HCl salts and recrystallized from EtOH/Et_2O for biological assay with the exception of **4v** which was isolated as its HBr salt.

Biology

The ligand affinities (K_i, nM) for inhibition of the dopamine, serotonin and norepinephrine transporters were determined in competition studies with [^{125}I]RTI 55. Inhibition of monoamine uptake (IC_{50}, nM) was evaluated in competition with [^{3}H]dopamine, [^{3}H] serotonin, and [^{3}H]norepinephrine, and is presented in Table 1 and Table 2. In general, the analogs of 1-(4-methylphenyl)-2-pyrrolidin-1-yl-pentan-1-one provide numerous examples of compounds that are potent inhibitors of the dopamine transporter and of dopamine reuptake. These compounds also inhibit NE reuptake with some potency, but are generally inactive at the SERT and for serotonin reuptake inhibition. One notable exception to this selectivity is the naphthyl analog **4t**, which binds to all three transporters and inhibits reuptake at the nanomolar potency range. The lead compound, racemic pyrovalerone **4a**, has been demonstrated here to be biologically enantioselective since the DAT inhibitory potency of the racemic mixture of **4a** resides entirely with the 2*S*-enantiomer, **4b** (DAT K_i = 18.1 nM; DA IC_{50} = 16.3 nM). Of these DAT/NET compounds, the most potent is the 3,4-dichlorophenyl substituted **4u**, with DAT K_i= 11.5 nM and NET K_i = 37.8 nM. At this time it is unclear whether the inherent lipophilicity of both **4t** and **4u** is primarily responsible for their inhibitory potency. This question is currently being explored further.

Discussion

The lead compound for these studies was racemic 1-(4-methylphenyl)-2-pyrrolidin-1-yl-pentan-1-one (pyrovalerone) **4a** (Table 1). In our assays this compound proved a potent inhibitor of both RTI 55 binding (K_i = 21.4 nM, about 20-fold more potent than cocaine as measured in the same assay) and of dopamine (DA) uptake (IC_{50} = 52 nM, about 9-fold more potent than cocaine). Its potency of RTI 55 inhibition of the NET (K_i = 195 nM) as well as of norepinephrine (NE) uptake (IC_{50} = 28.3 nM) was also marked. It was found to be more potent than cocaine in this assay by about 11-fold and 13-fold respectively. The discrepancy between the inhibition of RTI 55 binding at the NET compared with inhibition of NE uptake was seen throughout this series of compounds. This discrepancy was first reported by Eshleman et al. in 1999.[36] They also noted that such differences were less evident in the case of the DAT and SERT. They suggested that this difference was likely a consequence of the ligand binding site on the NET being less closely linked to the sites of drug interactions with substrate and (NE) translocation than is the case for the DAT and the SERT.

Compound **4a** was relatively inert at the SERT, with potency in the micromolar range. Therefore racemic **4a** was potent at the DAT and NET, and selective against the SERT. Compound **4a** exists as two enantiomers; only racemic **4a** had been previously evaluated. The critical importance of absolute stereochemistry on biological function is well established. It is particularly relevant that both amphetamine (1-phenyl-2-aminopropane) and cathinone (1-phenyl-2-aminopropane-1-one) are biologically enantioselective with respect to their inhibition of DAT and NET.[37,38] Indeed, the *S*-enantiomers are the eutomers in both cases. These two compounds bear strong structural similarities to the 1-aryl-2-pyrrolidin-1-yl-pentan-1-one analogs of this study, and therefore it was likely that their binding to, and thus inhibition of these transporters may likewise be similar. However, the structural similarity of the 1-aryl-2-pyrrolidin-1-yl-pentan-1-ones to the 2β-carbomethoxy-3α-aryl-8-azabicyclo [3.2.1]octane (tropane) class of DAT inhibitors is less clear. It is therefore interesting to note a comparison that utilized Dreiding models of WIN 35,428 (Figure 1) with enantiomers 2*S*-**4b** and 2*R*-**4c** (Scheme 4). The pyrrolidine nitrogens and the centroids of the aromatic rings were held coincident. In this rudimentary analysis the propyl side chain in the 2*S*-configuration overlapped with the C2-β-carbomethoxy of the tropane. However the 2*R*-configured compound had the propyl chain in a position similar to that of the 2α-carbomethoxy of the tropane. It has been well established that the 2α-carbomethoxy tropane analogs are less potent at the DAT than their 2β-carbomethoxy counterparts. On this basis we had postulated that 2*S*-**4b** might be the active enantiomer at the DAT. As shown in Table 1, enantiopure (2*R*-**4c**) is a poor inhibitor of RTI 55 binding at both DAT (K_i = 1,330 nM) and SERT (K_i >10 μM). In contrast, enantiopure (2*S*-**4b**) was quite potent at DAT (K_i = 18.1 nM) and selective (SERT: K_i > 2 μM). It was interesting that this relative potency of the 2*S*-**4b** enantiomer extended to the NET. Here the 2*R*-**4c** enantiomer was effectively inert at NET inhibition and NE uptake and the potency of racemic **4a** resided exclusively in the 2*S*-**4b** enantiomer (NET: K_i = 109 nM; NE uptake: IC_{50} = 11.3 nM).

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It is evident from the biological data (Table 1) that the inhibitory activities of these compounds cannot be easily correlated with varying electron density on the aromatic ring, nor with lipophilicity, or molecular refractivity. To this extent, this family of 1-aryl-2-pyrrolidin-1-yl-pentan-1-one analogs differs from other monoamine uptake inhibitors such as the 8-oxa-, 8-thia-, 8-aza- bicyclo[3.2.1]octanes,[11,12,39,40] or methylphenidate analogs,[41,42] where Structure Activity Relationships (SAR) were more easily discerned. Notwithstanding, certain relationships were evident among these analogs. Most clear was the fact that these 1-aryl-2-pyrrolidin-1-yl-pentan-1-one analogs were generally poor inhibitors of the SERT. Only two compounds (**4t, 4u**) manifested SERT K_is of <200 nM. The naphthyl analog **4t** inhibited SERT with modest potency (K_i = 33.1 nM) and the high lipophilicity of this compound (cLogP = 4.77) may be partially responsible for this potency. However, the lipophilic dichlorophenyl analog **4u** (cLog P = 5.01) manifested lesser SERT potency (K_i = 199 nM). Therefore lipophilicity was likely not the only factor that determined potency for **4t**. Within the family of analogs evaluated, the 3,4-dichlorophenyl analog **4u** was the most potent at DAT (K_i = 11.5 nM), followed by the 4-methyphenyl analog **4a**. At NET, only **4q** (K_i = 69.8 nM) and **4u** (K_i = 37.8 nM) were potent inhibitors of RTI 55 binding, although many compounds manifested substantial inhibition of NE uptake (**4a** IC_{50} = 28.3; **4b** IC_{50} = 11.3 nM; **4d** IC_{50} = 56 nM; **4f** IC_{50} = 83 nM; **4g** IC_{50} = 46.5 nM; **4h** IC_{50} = 81 nM; **4j** IC_{50} = 12.4 nM; **4k** IC_{50} = 86.7 nM; **4n** IC_{50} = 22.8 nM; **4q** IC_{50} = 19.3 nM; **4r** IC_{50} = 19.7 nM; **4s** IC_{50} = 9.4 nM; **4t** IC_{50} = 11.7 nM; **4u** IC_{50} = 21 nM; **4v** IC_{50} = 7.6 nM; **4x** IC_{50} = 93 nM; **9a** IC_{50} = 18.5 nM; **9b** IC_{50} = 18.0 nM; **9c** IC_{50} = 88 nM; **9d** IC_{50} = 24.9 nM).

It was particularly interesting that the catechol analog **4v** was one of the most potent inhibitors of NE uptake (IC_{50} = 7.6 nM) of those evaluated. Protection as the dimethoxy compound **4w** completely obliterated potency at all three monoamine transporters. The contrast between inhibition of the RTI 55 binding at the NET and inhibition of NE uptake is quite marked in the comparison of the disubstituted compounds **4u** (3,4-dichloro substitution) and **4v** (catechol moiety). In the former, the ratio of inhibition of NET binding to NE inhibition is about 2-fold, while in the latter this ratio is closer to 30-fold. The significance of this is unclear although this may again imply that the ligand binding site on the NET is only loosely associated with the site that effects NE translocation.[36]

The position of the methyl substituent on the aromatic ring influenced NE uptake potency in an opposite sense to its influence on DAT inhibition, although DA uptake inhibition was similar. Thus, while the 3-methyl analog **4s** manifested an NE uptake IC_{50} = 9.4 nM, the 2-methyl **4r** and 4-methyl **4a** manifested IC_{50}s = 19.7, 28.3 nM respectively. A comparison of 4-methyl **4a** (DAT: K_i = 21.4 nM; NET: K_i = 195 nM), 2-methyl **4r** (DAT: K_i = 59.7 nM; NET: K_i = 425 nM), and 3-methyl **4s** (DAT: K_i = 51 nM; NET: K_i = 216 nM) 1-aryl-2-pyrrolidin-1-yl-pentan-1-ones showed that the 4-methyl **4a** was at least twice as potent as the 2-methyl **4r** and 3-methyl **4s** at DAT. The 3-methyl **4s** was about equipotent to the 4-methyl **4a** at the NET, although the 2-methyl **4r** remained about half as potent at the NET compared with **4a**. The most DAT vs. NET selective compound in this series was the 4-acetamido derivative **4o** with DAT K_i = 30.2 nM and NET K_i = 4 μM.

The search for medications for cocaine abuse has centered, primarily, about two approaches. The first is the design of compounds that can act as cocaine substitutes and that manifest, in contrast to cocaine, slow onset rates and long durations of action.[11,43–45] The second approach has been to seek cocaine antagonists.[13] These compounds would manifest high potency for inhibition of cocaine binding to the DAT and little or no effect on DA uptake (i.e. DA trafficking). This has been the focus of numerous studies, and Deutsch and Schweri[46] have described the Discrimination Ratio (DR) as a guiding measure of potential cocaine antagonism. They defined the DR as the IC_{50} of DA uptake inhibition/K_i for inhibition of DA uptake by the test compound. They pointed out that a DR< 10 is of little significance owing to differences in conditions of each assay protocol. By this standard, none of the compounds here showed a DR > 5, and therefore none can be regarded as cocaine antagonists. Their use as potential medications for cocaine addiction may derive from onset and duration of action extensions, and these factors are currently under investigation.

Of note, the biaryl compounds **4x–z** lacked impressive potency at all sites; this, again, is contrary to the effects of such substitution in the bicyclo[3.2.1]octane series in both the 8-aza-[47] and 8-oxa series, as we shall report elsewhere.[48]

Table 2 presents an array of compounds that explored the displacement of the pyrrolidine ring along the butyl chain (**6a, b**), the introduction of different C2 side chains (**9a,b**) as well as introduction of side chain unsaturation (**9c–e**), the effects of opening the pyrrolidine ring (**9f**), as well as expanding it to the 6-membered piperidine (**9g**). Finally, reduction of the ketone to obtain both isomers (**9h** and **9j**) is presented. The stereochemistry of these two diastereomers has not yet been determined. However, neither isomer shows any potency at DAT, SERT, and NET. A comparison of **6a** with **4a**, and **6b** with **4u** showed that essentially all inhibitory potency at all three transporters was lost when the pyrrolidine ring was moved one carbon along the chain. The nature of the pyrrolidine itself appears to be important since if it was opened (**9f**), or expanded (**9g**), the inhibitory potency was again much reduced compared with the parent compound **4u**. Lancelot et al.[28] had published a similar finding in their evaluation of 2-amino-1-(2-thienyl)-1-pentanones. Reduction of the ketone **4a** to yield the diastereomeric alcohols **9h** and **9j** provided totally inactive compounds. Modification of the alkyl chain of **4a** proved interesting. While a terminal acetylene (**9e**) resulted in a very substantial loss of potency at DAT, SERT, and NET, the allyl compounds **9c** and **9d** retained potency at DAT. The 3,4-dichloro compound **9d** (DAT: K_i = 39.9 nM) was again the more potent of the two, although NET potency declined substantially (K_i = 509 nM) compared with the comparative compound **4u** (K_i = 37.8 nM). Of these chain altered compounds, the isobutyl analog **9b** proved most interesting with a DAT K_i = 13.7 nM, but DA uptake IC_{50} = 5.9 nM. This compares with data for **4a** (DAT K_i = 21.4 and DA uptake IC_{50} = 52 nM). Thus the introduction of a branching methyl in the side chain has served to increase DA inhibition about 10-fold over the parent compound **4a**. The possible significance of this is not clear at this time.

The biological selectivity within this class of compounds proved striking. Thirteen compounds (**4b,f,k–m,o,p,r–t,y**, **6a**, and **6b**) were evaluated for inhibition of $5HT_{1A}$, $5HT_{1B}$, $5HT_{1C}$, D_1, D_2, and D_3 receptors. The compounds were essentially inactive (IC_{50} > 10 μM) in these assays. Two compounds (**4o**, which was a selective DAT inhibitor, and **4t**, which had similar potency at DAT and SERT) were selected for evaluation of locomotor activity. Both manifested a time and dose dependent stimulation of locomotor activity (ED_{50} = 0.21 mg/Kg and 2.2 mg/Kg respectively) with a duration of action of > 8 hours.

Conclusion

A family of 38 analogs of a lead compound 1-(4-methylphenyl)-2-pyrrolidin-1-yl-pentan-1-one (pyrovalerone) has been prepared. The biological activity at dopamine, serotonin and norepinephrine transporters has been determined. This family has yielded compounds that provide selective inhibitors of the dopamine and norepinephrine transporters with little effect upon serotonin trafficking. Furthermore, a subset of compounds selected for evaluation of their effect upon serotonin and dopamine receptors has shown them to be inactive at these sites. The lead compound **4a** has been demonstrated to be biologically enantioselective and it remains to be determined whether this enantioselectivity extends to other members of this family of compounds. Two compounds **4o** and **4t** manifested a time and dose dependent stimulation of locomotor activity with a duration of action of > 8 hours.

The inhibitory potency, the neurotransmitter selectivity profile and the inactivity at selected receptor sites of **4 k** and **4o** have encouraged us to enter behavioral pharmacological evaluation in rat drug discrimination studies, and in vivo studies are currently ongoing.

Experimental Section

NMR spectra were recorded on a Jeol 300 NMR spectrometer (300.53 MHz for ^{1}H and 75.58 MHz for ^{13}C) with tetramethylsilane (TMS) as internal standard and DMSO-d_6 as solvent, with the exception of compounds **2** and **3**, which were measured in $CDCl_3$. Optical rotations were measured on a Jasco P1010 polarimeter at room temperature. HPLC and MS data were obtained on an Agilent Series 1100 LC/MSD system. Melting points are uncorrected and were measured on a Mel-Temp melting point apparatus. Thin layer chromatography (TLC) was carried out on Baker Si 250F plates. Visualization was accomplished with iodine vapor, UV exposure or treatment with phosphomolybdic acid (PMA). Flash chromatography was carried out on Baker Silica Gel 40 μM (Silica gel). All reactions were conducted under an atmosphere of dry nitrogen. Elemental analyses were performed by Atlantic Microlab, Norcross, GA. Chemicals obtained from commercial sources were used as received. Room temperature is 22 °C +/− 2 °C. Yields have not been optimized.

General Procedure A. Preparation of intermediate ketones, 2

The ketones **2** were prepared (except where noted) by alkylation of the analogous commercially available nitrile compounds, followed by acidic hydrolysis. The nitrile (10 mmol) was added in several portions, over 0.5 h, to a solution of the *n*-BuMgCl (12 mmol) in toluene (20 mL). The reactions were monitored by TLC and heated where necessary. Generally, after 2 h stirring at room temperature, the reaction was complete. The reaction mixture was poured onto ice and concentrated H_2SO_4 (2 mL) was added. Hydrolysis of the intermediate imine usually occurred at room temperature after several minutes. However, for some substrates, heating was necessary to effect this transformation. The organics were extracted into Et_2O, dried ($MgSO_4$), filtered, and reduced *in vacuo* to an oil.

General Procedure B. Preparation of intermediate α-bromoketones, 3

Compounds **3** were prepared by α-bromination of ketones **2**. The ketone (as a solution in Et_2O, or CH_2Cl_2 (for less soluble substrates)) was cooled in an ice bath and anhydrous $AlCl_3$ was added to the solution (1 – 5 mol%). Bromine (approximately 0.1 mol eq) was added to the solution all at once. Typically, after 10 min the solution changed from a light orange to colorless (if this change did not occur at 0 °C, then the mixture was warmed to room temperature). The remaining bromine (0.9 mol eq) was then added to the solution in a drop-wise manner over 5 min. The solution was neutralized (aqueous $NaHCO_3$), separated, dried ($MgSO_4$), filtered, and reduced to a lightly colored oil *in vacuo*. Yields were quantitative and the crude materials were sufficiently pure (^{1}H NMR) for use in the subsequent step.

General Procedure C. 1-Aryl-2-pyrrolidin-1-yl-pentan-1-ones (4)

Compounds **4** were prepared employing General Procedure C except where noted. α-Bromoketone **3** (10 mmol) was dissolved in Et_2O (10 mL) (EtOH is a suitable alternative solvent) and cooled on an ice bath. Pyrrolidine (22 mmol) was added all at once. The mixture became orange and an oil was observed to separate from the solution. After 1 – 24 h stirring at room temperature, the crude reaction mixture was partitioned between H_2O (10 mL) and Et_2O. The Et_2O layer was separated and the aqueous layer was washed with Et_2O (2 × 10 mL). The ether layer was extracted with 1 M aqueous HCl (2 × 10 mL), then backextracted into Et_2O (3 × 10 mL) by basification to pH 8–9 with 20% aqueous Na_2CO_3 or 2 M aqueous NaOH. The Et_2O extracts were dried ($MgSO_4$) and filtered. The filtrate was treated with 2 M ethereal

HCl (usually 5 – 10 mL) until precipitation of solid or oil had ceased. Solids (oils were triturated to give solids) were collected by filtration and recrystallized from EtOH/Et_2O.

1-(4-Methylphenyl)-2-pyrrolidin-1-yl-pentan-1-one hydrochloride (4a)

1-(4-Methylphenyl)pentan-1-one **2a**, prepared by Friedel-Crafts acylation of toluene: ^{1}H NMR δ 7.86 (dd, 2H), 7.25 (dd, 2H), 2.92 (m, 2H), 2.41 (s, 3H), 1.71 (m, 2H), 1.40 (m, 2H), 0.95 (t, 3H) was brominated (General Procedure B) to provide 2-bromo-1-(4-methylphenyl)-pentan-1-one **3a**: ^{1}H NMR δ 7.92 (d, 2H), 7.29 (d, 2H), 5.14 (dd, 1H), 2.43 (s, 3H), 2.25 - 2.05 (m, 2H), 1.65 - 1.35 (m, 2H), 0.98 (t, 3H). Compound **4a**, obtained as a colorless solid, was prepared from **3a** (General Procedure C). Yield 68%. Mp 180 °C (dec.); ^{1}H NMR δ 10.8 - 10.65 (br, 1H), 8.01 (d, 2H), 7.44 (d, 2H), 5.56 (m, 1H), 3.7 - 3.55 (br, 1H), 3.55 - 3.4 (br, m, 1H), 3.35 - 3.2 (br, m, 1H), 3.15 - 3.0 (br, m, 1H), 2.42 (s, 3H), 2.15 - 1.85 (br, m, 6H), 1.4 - 1.2 (m, 1H), 1.15 - 0.95 (m, 1H), 0.78 (t, 3H); ^{13}C NMR δ 196.1, 145.8, 132.1, 129.8, 129.0, 67.1, 53.5, 51.9, 31.8, 22.9, 21.3, 17.4, 13.7; APCI MS *m/z* 246 (M + 1); Anal. ($C_{16}H_{24}ClNO.1/6H_2O$) C, H, N, Cl.

(1*R*)-1-(4-Methylphenyl)-2-pyrrolidin-1-yl-pentan-1-one hydrochloride (4c) and (1*S*)-1-(4-Methylphenyl)-2-pyrrolidin-1-yl-pentan-1-one hydrochloride (4b)

1-(4-Methylphenyl)-2-pyrrolidin-1-yl-pentan-1-one hydrochloride, **4a**, (10.0 g, 35.5 mmol) was extracted into Et_2O from 20% aqueous Na_2CO_3 at pH 8–9. The ether was removed and the free base was dissolved in EtOH (50 mL) and heated to 70°C. Dibenzoyl-D-tartaric acid (12.7 g, 35.5 mmol) in hot ethanol (150 mL) was added all at once to the pale yellow solution of free base. The resulting colorless solution was refluxed for 1 min, cooled, and the solvent was removed *in vacuo*. The residue was dissolved in CH_2Cl_2 (530 mL) and hexane (700 mL) was added with swirling. After 3 d, the resulting crystalline solid (9.1 g) was collected by filtration. ^{1}H NMR ($CDCl_3$) showed a diastereomeric excess (d.e.) of 70 – 75%. Three consecutive recrystallizations from CH_2Cl_2/hexane (300 mL/400 mL) gave a single diastereoisomer (6.1 g, 61%). Mp 100 – 120 °C; ^{1}H NMR δ 8.10 (d, 4H), 7.87 (d, 2H), 7.51 (t, 2H), 7.37 (t, 4H), 7.18 (d, 2H), 5.91 (s, 2H), 5.37 (t, 1H), 3.75 (br, m, 2H), 2.32 (s, 3H), 2.0 - 1.8 (br, m, 6H), 1.4 - 1.1 (br, m, 4H), 0.71 (t, 3H). X-ray structural analysis of this compound showed it to be the dibenzoyl-D-tartaric acid salt of (1*R*)-1-(4-methylphenyl)-2-pyrrolidin-1-yl-pentan-1-one. $[\alpha]^{20}_D = +59.6°$ (c 1.06, EtOH).

The salt was dissolved in 20% aqueous Na_2CO_3 and extracted into Et_2O. The Et_2O layer was collected, dried and filtered. Ethereal 2M HCl was added to this solution to provide a white solid that was recrystallized from EtOH/Et_2O to give pure (1*R*)-1-(4-methylphenyl)-2-pyrrolidin-1-yl-pentan-1-one hydrochloride, **4c**. The physical properties of this compound were identical with those of the racemic material **4a**.

The residues from recrystallization of the dibenzoyl-D-tartaric acid (1*R*)-1-(4-methylphenyl)-2-pyrrolidin-1-yl-pentan-1-one, were combined and the free base was liberated with 20% aqueous Na_2CO_3. The ethereal extracts were washed once with 20% aqueous Na_2CO_3, dried ($MgSO_4$), filtered, and reduced *in vacuo* to an oil (5.2 g, 21 mmol). This oil was dissolved in hot EtOH (50 mL), and a solution of dibenzoyl-L-tartaric acid (7.5 g, 21 mmol) in hot EtOH (100 mL) was added with swirling. The mixture was refluxed for 1 min, cooled, and the solvent was removed *in vacuo*. Four recrystallizations, as described above, gave a single diastereoisomer (5.4 g, 50%). X-ray structural analysis confirmed the diastereomeric salt of dibenzoyl-L-tartaric acid (1*S*)-1-(4-methylphenyl)-2-pyrrolidin-1-yl-pentan-1-one. $[\alpha]^{20}_D = -61.1$ ° (c 1.07, EtOH).

The hydrochloride salt of (1*S*)-1-(4-methylphenyl)-2-pyrrolidin-1-yl-pentan-1-one, **4b** was then prepared as described above for (1*R*)-1-(4-methylphenyl)-2-pyrrolidin-1-ylpentan-1-one.

The enantiomeric purities of **4b** and **4c** were confirmed by chiral HPLC (Chiralpak AD, 0.46 × 25cm; Flow rate 1 mL/min; eluent 2–10% EtOH/hexanes + 0.1 % NEt_3). **4b**: t_R = 6.77 min, purity 99.8%; **4c**: t_R = 5.85 min, purity 100%.

Single-crystal X-ray analysis of dibenzoyl-D-tartaric acid salt of (1*R*)-1-(4-methylphenyl)-2-pyrrolidin-1-yl-pentan-1-one

Monoclinic crystals of the purified title compound were obtained from CH_2Cl_2/hexane. A representative crystal was selected and a 1.54178 Å data set was collected at 198 °K. Pertinent crystal, data collection and refinement parameters: crystal size, 0.32 × 0.12 × 0.03 mm; cell dimensions, a = 7.8458 (10) Å, b = 13.4366 (2) Å, c = 18.2054 (3) Å, α = 90°, β = 93.717 (10)°, γ = 90°; formula, $C_{40}H_{51}NO_9$; formula weight = 689.82; volume = 1915.19 (5) $Å^3$; calculated density = 1.196 g cm^{-3}; space group = $P2_1$; number of reflections = 11525 of which 5630 were considered independent (R_{int} = 0.0244). Refinement method was full-matrix least-squares on F_2. The final *R*-indices were [$I > 2\sigma$ (I)] R1 = 0.0520, wR2 = 0.1439.

Single-crystal X-ray analysis of dibenzoyl-L-tartaric acid (1*S*)-1-(4-methylphenyl)-2-pyrrolidin-1-yl-pentan-1-one

Monoclinic crystals of the purified dibenzoyl-L-tartaric acid (1*S*)-1-(4-methylphenyl)-2-pyrrolidin-1-yl-pentan-1-one were obtained from CH_2Cl_2/hexane. A representative crystal was selected and a 1.54178 Å data set was collected at 153 °K. Pertinent crystal, data collection and refinement parameters: crystal size, 0.58 × 0.16 × 0.05 mm; cell dimensions, a = 7.8456 (1) Å, b = 13.4605 (2) Å, c = 18.2956 (3) Å, α = 90°, β = 93.5910 (10)°, γ = 90°; formula, $C_{40}H_{51}NO_9$; formula weight = 689.82; volume = 1930.88 (5) $Å^3$; calculated density = 1.186 g cm^{-3}; space group = $P2_1$; number of reflections = 9774 of which 5860 were considered independent (R_{int} = 0.0317). Refinement method was full-matrix least-squares on F_2. The final *R*-indices were [$I > 2\sigma$ (I)] R1 = 0.0537, wR2 = 0.1410.

2-Pyrrolidin-1-yl-1-phenylpentan-1-one (4d)

Commercially available **2d** was brominated (General Procedure B) to give 2-bromo-1-phenylpentan-1-one **3d**: ^{1}H NMR δ 8.02 (d, 2H), 7.62 (m, 1H), 7.49 (t, 2H), 5.15 (dd, 1H), 2.25 - 2.05 (m, 2H), 1.7 - 1.4 (m, 2H), 0.99 (t, 3H). Compound **4d**, obtained as a colorless solid, was prepared from **3d** (General Procedure C) (51% yield); Mp 173 °C; ^{1}H NMR δ 10.9 - 10.6 (br, 1H), 8.11 (d, 2H), 7.78 (t, 1H), 7.64 (t, 2H), 5.62 (m, 1H), 3.64 (br, m, 1H), 3.49 (br, m, 1H), 3.26 (br, m, 1H), 3.10 (br, m, 1H), 2.15 - 1.85 (m, 6H), 1.4 - 1.2 (m, 1H), 1.2 - 0.95 (m, 1H), 0.78 (t, 3H); ^{13}C NMR 196.7, 134.9, 134.5, 129.2, 128.8, 67.3, 53.6, 51.9, 31.7, 22.9, 17.4, 13.7; APCI MS *m/z* 232 (M + 1); Anal. ($C_{15}H_{22}ClNO$) C, H, N, Cl.

1-(4-Fluorophenyl)-2-pyrrolidin-1-yl-pentan-1-one hydrochloride (4e)

Commercially available **2e** was brominated (General Procedure B) to give 2-bromo-1-(4-fluorophenyl)pentan-1-one **3e**: ^{1}H NMR δ 8.05 (dd, 2H), 7.16 (dd, 2H), 5.09 (dd, 1H), 2.25 - 2.05 (m, 2H), 1.7 - 1.35 (m, 2H), 0.99 (t, 3H). Compound **4e**, obtained as a colorless solid, was prepared from **3e** (General Procedure C) (84% yield). Mp 218 °C (dec.); ^{1}H NMR δ 10.7 - 10.5 (br, 1H), 8.19 (m, 2H), 7.49 (t, 2H), 5.6 - 5.5 (br, m, 1H), 3.7 - 3.55 (br, 1H), 3.55 - 3.4 (br, 1H), 3.3 - 3.15 (br, m, 1H), 3.15 - 3.0 (br, 1H), 2.15 - 1.8 (br, m, 6H), 1.35 - 1.15 (m, 1H), 1.15 - 0.95 (m, 1H), 0.79 (t, 3H); ^{13}C NMR δ 195.2, 132.2, 132.0, 131.3, 116.6, 116.3, 67.2, 53.5, 51.9, 31.7, 22.9, 17.4, 13.7; APCI MS *m/z* 250 (M + 1); Anal. ($C_{15}H_{21}ClFNO$) C, H, N, Cl.

1-(4-Bromophenyl)-2-pyrrolidin-1-yl-pentan-1-one hydrochloride (4f)

Commercially available **2f** was brominated (General Procedure B) to give 2-bromo-1-(4-bromophenyl)pentan-1-one **3f**: ^{1}H NMR δ 7.88 (d, 2H), 7.63 (d, 2H), 5.06 (dd, 1H), 2.25 - 2.05 (m, 2H), 1.65 - 1.35 (m, 2H), 0.99 (t, 3H). Compound **4f**, obtained as a colorless solid, was prepared from **3f** (General Procedure C) (62% yield). Mp 200 °C (dec.); ^{1}H NMR δ 10.7 - 10.5 (br, 1H), 8.03 (d, 2H), 7.87 (d, 2H), 5.56 (m, 1H), 3.7 - 3.55 (br, m, 1H), 3.55 - 3.4 (br, m, 1H), 3.35 - 3.1 (br, m, 1H), 3.1 - 3.0 (br, m, 1H), 2.1 - 1.8 (br, m, 6H), 1.4 - 1.2 (m, 1H), 1.15 - 0.95 (m, 1H), 0.78 (t, 3H); ^{13}C NMR δ 196.0, 133.4, 132.4, 130.8, 129.4, 67.4, 53.7, 51.9, 31.6, 22.9, 17.3, 13.7; APCI MS *m/z* 312, 310 (M + 1); Anal. ($C_{15}H_{21}BrClNO$) C, H, N, Cl.

1-(4-Iodophenyl)-2-pyrrolidin-1-yl-pentan-1-one hydrochloride (4g)

1-(4-Iodophenyl)pentan-1-one **2g**, prepared by Friedel-Crafts acylation of 4-iodobenzene and purified by distillation (Bp 112 °C, 0.1 mm Hg) and recrystallization from EtOH: (11% yield); ^{1}H NMR δ 7.82 (d, 2H), 7.67 (d, 2H), 2.92 (t, 2H), 1.71 (m, 2H), 1.40 (m, 2H), 0.95 (t, 3H) was brominated (General Procedure B) to give 2-bromo-1-(4-iodophenyl)pentan-1-one **3g**: ^{1}H NMR δ 7.85 (d, 2H), 7.72 (d, 2H), 5.06 (dd, 1H), 2.25 - 2.05 (m, 2H), 1.65 - 1.35 (m, 2H), 0.98 (t, 3H). Compound **4g** was prepared from **3g** (General Procedure C) (37% yield); Mp 218 °C (dec.); ^{1}H NMR δ 10.75 - 10.65 (br, 1H), 8.05 (d, 2H), 7.84 (d, 2H), 5.53 (m, 1H), 3.7 - 3.65 (br, 1H), 3.65 - 3.5 (br, m, 1H), 3.3 - 3.15 (br, m, 1H), 3.15 - 3.0 (br, m, 1H), 2.1 - 1.8 (br, m, 6H), 1.35 - 1.15 (m, 1H), 1.15 - 0.95 (m, 1H), 0.78 (t, 3H); ^{13}C NMR δ 196.3, 138.2, 133.6, 130.3, 104.6, 67.3, 53.7, 51.9, 31.6, 22.9, 17.3, 13.7; APCI MS *m/z* 358 (M + 1); Anal. ($C_{15}H_{21}ClINO$) C, H, N, Cl.

1-(3-Iodophenyl)-2-pyrrolidin-1-yl-pentan-1-one hydrochloride (4h)

1-(3-Iodophenyl)pentan-1-one **2h**, prepared in 29 % yield from 3-iodobenzonitrile (General Procedure A) and purified by column chromatography (3% EtOAc/hexane): R_f 0.25 (5% EtOAc/hexane); ^{1}H NMR δ 8.28 (t, 1H), 7.90 (m, 2H), 7.21 (t, 1H), 2.93 (t, 2H), 1.71 (m, 2H), 1.40 (m, 2H), 0.96 (t, 3H); ^{13}C NMR δ 199.1, 141.6, 138.8, 137.0, 130.3, 127.1, 94.4, 38.3, 26.2, 22.4, 13.9, was brominated (General Procedure B) to provide 2-bromo-1-(3-iodophenyl) pentan-1-one **3h**: ^{1}H NMR δ 8.33 (dd. 1H), 7.96 (ddd, 1H), 7.93 (ddd, 1H), 7.22 (d, 1H), 5.05 (dd, 1H), 2.25 - 2.05 (m, 2H), 1.7 - 1.35 (m, 2H), 0.98 (t, 3H). Compound **4h**, obtained as a colorless solid, was prepared from **3h** (General Procedure C) (20% yield); Mp 203 °C (dec.); ^{1}H NMR δ 10.6 - 10.4 (br, 1H), 8.39 (s, 1H), 8.14 (d, 1H), 8.07 (d, 1H), 7.44 (t, 1H), 5.51 (m, 1H), 3.7 - 3.55 (br, m, 1H), 3.55 - 3.4 (br, m, 1H), 3.3 - 3.15 (br, m, 1H), 3.15 - 3.0 (br, m, 1H), 2.1 - 1.8 (br, m, 6H), 1.35 - 1.15 (m, 1H), 1.1 - 0.9 (m, 1H), 0.79 (t, 3H); ^{13}C NMR δ 195.7, 143.3, 136.9, 136.1, 131.8, 131.3, 128.0, 95.7, 67.5, 53.8, 51.9, 31.5, 22.8, 17.2, 13.6; APCI MS *m/z* 358 (M + 1); Anal. ($C_{15}H_{21}ClINO$) C, H, N, Cl.

4-(2-Pyrrolidin-1-yl-pentanoyl)benzonitrile hydrochloride (4i)

4-(2-Bromopentanoyl)benzonitrile, **3i**: ^{1}H NMR δ 8.11 (d, 2H), 7.80 (d, 2H), 5.07 (dd, 1H), 2.25 - 2.05 (m, 2H), 1.7 - 1.35 (m, 2H), 1.00 (t, 3H) was prepared (General Procedure B) from 4-cyanovalerophenone **2i**[35] and converted to **4i** as described in General Procedure C (70% yield); Mp 197 – 199 °C (dec.); ^{1}H NMR δ 10.9 - 10.7 (br, 1H), 8.24 (d, 2H), 8.14 (d, 2H), 5.7 - 5.55 (br, m, 1H), 3.7 - 3.6 (br, m, 1H), 3.6 - 3.5 (br, m, 1H), 3.3 - 3.1 (br, m, 2H), 2.1 - 1.8 (m, 6H), 1.4 - 1.2 (m, 1H), 1.1 - 0.9 (m, 1H), 0.77 (t, 3H); ^{13}C NMR δ 196.2, 137.5, 133.2, 129.4, 117.9, 116.6, 67.8, 53.7, 51.9, 31.3, 22.9, 17.2, 13.7; APCI MS *m/z* 257 (M + 1); Anal. ($C_{16}H_{21}ClN_2O.1/4H_2O$) C, H, N, Cl.

1-(4-Hydroxymethylphenyl)-2-pyrrolidin-1-yl-pentan-1-one hydrochloride (4j)

2-Bromo-1-(4-hydroxymethylphenyl)-pentan-1-one **3j**: ^{1}H NMR δ 8.01 (d, 2H), 7.48 (d, 2H), 5.15 (dd, 1H), 4.79 (br, d, 2H), 2.25 - 2.05 (m, 2H), 2.05 - 1.95 (br, 1H), 1.65 - 1.4 (m, 2H), 0.99 (t, 3H) was prepared (General Procedure B) from 1-(4-hydroxymethylphenyl)pentan-1-one **2j**[35] and converted to **4j** as described in General Procedure C (79% yield); Mp 186 – 187 °C (dec.); ^{1}H NMR δ 10.6 - 10.4 (br, 1H), 8.05 (d, 2H), 7.56 (d, 2H), 5.7 - 5.4 (br, m, 2H), 4.62 (s, 2H), 3.7 - 3.55 (m, 1H), 3.55 - 3.3 (m, 1H), 3.35 - 3.15 (m, 1H), 3.1 - 3.0 (m, 1H), 2.1 - 1.8

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(m, 6H), 1.3 - 1.15 (m, 1H), 1.15 - 0.95 (m, 1H), 0.78 (t, 3H); ^{13}C NMR δ 196.2, 150.4, 132.8, 128.8, 126.7, 67.4, 62.2, 53.8, 51.9, 31.8, 22.8, 17.3, 13.7; APCI MS *m/z* 262 (M + 1); Anal. ($C_{16}H_{24}ClNO_2$.1/4H_2O) C, H, N, Cl.

1-(4-Hydroxyphenyl)-2-pyrrolidin-1-yl-pentan-1-one hydrochloride (4k)

1-(4-Methoxyphenyl)-2-pyrrolidin-1-yl-pentan-1-one **4m** (9.00 g, 30.3 mmol) was freed from its hydrochloride salt by basification to pH 8–9 with 20% aqueous Na_2CO_3 and extraction into CH_2Cl_2. The free base was dissolved in CH_2Cl_2 (50 mL) and cooled to −78 °C. BBr_3 (90 mL, 1.0 M solution in CH_2Cl_2, 90 mmol) was added to the solution over 0.5 h. The mixture was stirred for a further 1 h before warming gradually to room temperature. The gummy mixture, which became difficult to stir, was quenched after 2 h with saturated aqueous $NaHCO_3$ and the neutral organics were extracted into CH_2Cl_2. A white solid precipitated from the aqueous layer and was collected on a frit (2.8 g). This material was dissolved in Et_2O and treated with 2 M ethereal HCl. The solid obtained was collected by filtration then recrystallized from ethanol to give pure 1-(4-hydroxyphenyl)-2-pyrrolidin-1-yl-pentan-1-one as its hydrochloride **4k** (2.9 g, 34%). Mp 235 °C (dec.); ^{1}H NMR (CD_3OD) δ 7.99 (d, 2H), 6.93 (d, 2H), 5.26 (t, *J* = 5.5 Hz, 1H), 3.7 - 3.0 (br, 4H), 2.2 - 1.9 (br, m, 6H), 1.4 - 1.1 (m, 2H), 0.89 (t, 3H); ^{13}C NMR δ 195.0, 156.8, 132.9, 127.3, 117.0, 69.8, 33.9, 24.1, 18.6, 14.2; APCI MS *m/z* 248 (M + 1); Anal. ($C_{15}H_{22}ClNO_2$) C, H, N, Cl.

1-(4-Nitrophenyl)-2-pyrrolidin-1-yl-pentan-1-one hydrochloride (4l)

A 50% w/w aqueous solution of H_2O_2 (7 mL, 0.12 mol) was added to CH_2Cl_2 (50 mL) which had been cooled on an ice bath. Trifluoroacetic anhydride (23 mL, 0.14 mol) was added slowly *via* syringe. The solution was then warmed to room temperature. *N*-[4-(2-Pyrrolidin-1-ylpentanoyl)phenyl]acetamide hydrochloride **4o** (4.5 g, 18 mmol) was added over 20 min, and the mixture was heated to reflux for 1 h. The solution was cooled, then quenched cautiously with aqueous Na_2SO_3 (100 mL of a 1.6 M solution, 0.16 mol). The organics were separated and extracted into Et_2O, then back-extracted into 1 M aqueous HCl. The acidic extracts were basified with 20% aqueous Na_2CO_3 to pH 8–9 and extracted into Et_2O. The organic extracts were dried ($MgSO_4$), filtered, and then treated with 2 M ethereal HCl. The resulting white precipitate was collected on a frit, dissolved in water, and then freeze-dried to give pure 1-(4-nitrophenyl)-2-pyrrolidin-1-yl-pentan-1-one hydrochloride **4l** (290 mg, 5%). Mp 189 °C (dec.); ^{1}H NMR δ 10.8 - 10.6 (br, 1H), 8.45 (d, 2H), 8.32 (d, 2H), 5.65 (m, 1H), 3.7 - 3.3 (br, m, 2H), 3.3 - 3.1 (br, m, 2H), 2.1 - 1.8 (br, m, 6H), 1.4 - 1.2 (m, 1H), 1.1 - 0.9 (m, 1H), 0.78 (t, 3H); ^{13}C NMR δ 196.0, 150.8, 138.7, 130.4, 124.3, 68.1, 53.9, 52.0, 31.2, 22.9, 17.2, 13.7; APCI MS *m/z* 277 (M + 1); Anal. ($C_{15}H_{21}ClN_2O_3$.1/2H_2O.1/10HCl) C, H, N, Cl.

1-(4-Methoxyphenyl)-2-pyrrolidin-1-yl-pentan-1-one hydrochloride (4m)

1-(4-Methoxyphenyl)pentan-1-one **2m**, obtained by methylation of commercially available 1-(4-hydroxyphenyl)pentan-1-one, **2k**, with MeI/K_2CO_3 in refluxing acetone, was brominated (General Procedure B) to afford 2-bromo-1-(4-methoxyphenyl)pentan-1-one **3m**: ^{1}H NMR δ 8.01 (d, 2H), 6.96 (d, 2H), 5.12 (dd, 1H), 3.89 (s, 3H), 2.25 - 2.05 (m, 2H), 1.65 - 1.35 (m, 2H), 0.98 (t, 3H). Compound **4m** was obtained as a colorless solid from **3m** (General Procedure C) (68% yield); ^{1}H NMR δ 10.8 - 10.6 (br, 1H), 8.10 (d, 2H), 7.15 (d, 2H), 5.55 (m, 1H), 3.89 (s, 3H), 3.7 - 3.55 (br, m, 1H), 3.55 - 3.4 (br, m, 1H), 3.3 - 3.15 (br, m, 1H), 3.1 - 2.95 (br, m, 1H), 2.15 - 1.85 (br, m, 6H), 1.34 - 1.15 (m, 1H), 1.15 - 1.0 (m, 1H), 0.79 (t, 3H); ^{13}C NMR δ 194.7, 164.5, 131.4, 127.4, 114.5, 66.7, 55.8, 53.4, 51.8, 32.0, 22.9, 17.5, 13.7; APCI MS *m/z* 262 (M + 1); Anal. ($C_{16}H_{24}ClNO_2$.1/2H_2O.1/2HCl) C, H, N, Cl.

4-(2-Pyrrolidin-1-yl-pentanoyl)benzoic acid methyl ester hydrochloride (4n)

4-(2-Bromopentanoyl)benzoic acid methyl ester **3n**: ^{1}H NMR δ 8.14 (d, 2H), 8.06 (d, 2H), 5.13 (t, 1H), 3.96 (s, 3H), 2.2 - 2.05 (m, 2H), 1.65 - 1.35 (m, 2H), 1.00 (t, 3H) was prepared (General Procedure B) from **2n**[35] and converted to **4n** as described in General Procedure C (77% yield); Mp 202 °C (dec.); ^{1}H NMR δ 10.7 - 10.5 (br, 1H), 8.3 - 8.1 (m, 4H), 5.58 (m, 1H), 3.91 (s, 3H), 3.7 - 3.5 (br, m, 2H), 3.3 - 3.05 (br, m, 2H), 2.15 - 2.85 (br, m, 6H), 1.4 - 1.2 (m, 1H), 1.15 - 0.95 (m, 1H), 0.77 (t, 3H); ^{13}C NMR δ 196.5, 165.3, 137.6, 134.6, 129.8, 129.2, 67.9, 53.9, 52.7, 51.9, 31.4, 22.9, 17.2, 13.7; APCI MS *m/z*: 290 ((M + 1), 100%), 275; Anal. ($C_{17}H_{24}ClNO_3$) C, H, N, Cl.

N-[4-(2-Pyrrolidin-1-yl-pentanoyl)phenyl]acetamide hydrochloride (4o)

N-(4-Pentanoylphenyl)acetamide, **2o**, prepared in 60% yield by Friedel-Crafts acylation of acetanilide in CS_2, and purified by recrystallization from hot MeOH: ^{1}H NMR δ 7.94 (d, 2H), 7.61 (d, 2H), 7.41 (br, s, 1H), 2.94 (t, 2H), 2.22 (s, 3H), 1.8 - 1.65 (m, 2H), 1.45 - 1.35 (m, 2H), 0.95 (t, 3H); ^{13}C NMR δ 168.4, 142.0, 132.9, 129.5, 118.8, 38.2, 26.6, 24.8, 22.5, 14.0, was brominated (General Procedure B) to provide *N*-[4-(2-bromopentanoyl)phenyl]acetamide, **3o**: ^{1}H NMR δ 8.00 (d, 2H), 7.65 (br, m, 3H), 5.12 (dd, 1H), 2.23 (s, 3H), 2.2 - 2.05 (m, 2H), 1.7 - 1.35 (m, 2H), 0.98 (t, 3H). Compound **4o** was prepared from **3o** as described in General Procedure C (56% yield); Mp 195 °C (dec.); ^{1}H NMR δ 10.76 (s, 1H), 10.55 - 10.35 (br, 1H), 8.05 (d, 2H), 7.85 (d, 2H), 5.5 - 5.4 (br, m, 1H), 3.7 - 3.55 (br, 1H), 3.5 - 3.3 (br, 1H), 3.3 - 3.15 (br, m, 1H), 3.15 - 3.0 (br, m, 1H), 2.13 (s, 3H), 2.1 - 1.8 (br, m, 6H), 1.3 - 1.15 (m, 1H), 1.15 - 1.0 (m, 1H), 0.79 (t, 3H); ^{13}C NMR δ 194.8, 169.4, 145.4, 130.4, 128.8, 118.4, 67.0, 53.6, 51.9, 32.0, 24.2, 22.8, 17.4, 13.7; APCI MS *m/z* 289 (M + 1); Anal. ($C_{17}H_{25}ClN_2O_2.1/2H_2O$) C, H, N, Cl.

2-Pyrrolidin-1-yl-1-(4-trifluoromethylphenyl)pentan-1-one hydrochloride (4p)

1-(4-Trifluoromethylphenyl)pentan-1-one **2p**, prepared in 95% yield from 4-trifluoromethylbenzonitrile (General Procedure A): ^{1}H NMR δ 8.06 (d, 2H), 7.43 (d, 2H), 3.00 (t, 2H), 1.74 (m, 2H), 1.41 (m, 2H), 0.96 (t, 3H) was brominated (General Procedure B) to provide 2-bromo-1-(4-trifluoromethylphenyl)pentan-1-one, **3p**: ^{1}H NMR δ 8.13 (d, 2H), 7.76 (d, 2H), 5.11 (dd, 1H), 2.25 - 2.1 (m, 2H), 1.7 - 1.4 (m, 2H), 1.00 (t, 3H). Compound **4p** was prepared from **3p** as described in General Procedure C (44% yield); Mp 228 °C (dec.); ^{1}H NMR δ 10.8 - 10.6 (br, 1H), 8.28 (d, 2H), 8.03 (d, 2H), 5.62 (m, 1H), 3.7 - 3.4 (br, m, 2H), 3.3 - 3.05 (br, m, 2H), 2.1 - 1.8 (br, m, 6H), 1.4 - 1.2 (m, 1H), 1.1 - 0.9 (m, 1H), 0.78 (t, 3H); ^{13}C NMR δ 196.2, 137.4, 129.7, 126.3, 67.8, 53.8, 51.9, 31.3, 22.9, 17.2, 13.7; APCI MS *m/z* 300 (M + 1); Anal. ($C_{16}H_{21}ClF_3NO$) C, H, N, Cl.

1-(4-Propynylphenyl)-2-pyrrolidin-1-yl-pentan-1-one hydrochloride (4q)

1-(4-Iodophenyl)-2-pyrrolidin-1-yl-pentan-1-one hydrochloride (500 mg, 1.27 mmol) **4g**, was taken up in Et_2NH (10 mL) and degassed by purging with N_2. [$PdCl_2(PPh_3)_2$] (18 mg, 2.5×10^{-5} mol) and CuI (2.4 mg, 1.3×10^{-5} mol) were added to the stirring solution at room temperature. Propyne was then bubbled through the resulting yellow mixture for 7 h. The mixture was filtered and reduced to an oil *in vacuo*. The oil was taken up in Et_2O and extracted into 1M aqueous HCl, then back-extracted into Et_2O by treatment with 20% aqueous Na_2CO_3 until pH 8–9. The organic extracts were dried ($MgSO_4$), filtered, and reduced *in vacuo* to a pale yellow oil. The hydrochloride was prepared from 2M ethereal HCl and recrystallized twice from EtOH/Et_2O to give pure 1-(4-propynylphenyl)-2-pyrrolidin-1-yl-pentan-1-one **4q** as a colorless crystalline solid (260 mg, 67%). Mp 231 °C (dec.); ^{1}H NMR δ 10.6 - 10.4 (br, 1H), 8.04 (d, 2H), 7.62 (d, 2H), 5.55 - 5.4 (br, m, 1H), 3.7 - 3.55 (br, 1H), 3.55 - 3.4 (br, 1H), 3.3 - 3.1 (br, m, 1H), 3.1 - 2.95 (br, m, 1H), 2.12 (s, 3H), 2.1 - 1.8 (br, m, 6H), 1.3 - 1.15 (m, 1H), 1.15 - 0.95 (m, 1H), 0.78 (t, 3H); ^{13}C NMR δ 195.9, 133.1, 131.9, 129.9, 129.1, 92.1, 79.0, 67.5, 53.8, 51.9, 31.7, 22.8, 17.2, 13.7, 4.1; APCI MS *m/z* 270 (M + 1); Anal. ($C_{18}H_{24}ClNO$) C, H, N, Cl.

1-(2-Methylphenyl)-2-pyrrolidin-1-yl-pentan-1-one hydrochloride (4r)

1-(2-Methylphenyl)pentan-1-one **2r** obtained in 75% yield from 2-methylbenzonitrile (General Procedure A) and purified by distillation (Bp 58 – 60°C, 0.05 mm Hg): ^{1}H NMR δ 7.62 (m, 1H), 7.36 (m, 1H), 7.26 (m, 2H), 2.89 (t, 2H), 2.48 (s, 3H), 1.68 (m, 2H), 1.39 (m, 2H), 0.94 (t, 3H) was brominated (General Procedure B) to afford 2-bromo-1-(2-tolyl) pentan-1-one **3r**: ^{1}H NMR δ 7.63 (d, 1H), 7.42 (m, 1H), 7.27 (m, 2H), 5.05 (dd, 1H), 2.50 (s, 3H), 2.25 - 2.0 (m, 2H), 1.65 - 1.35 (m, 2H), 0.99 (t, 3H). Compound **4r** was prepared from **3r** as described in General Procedure C (39% yield); ^{1}H NMR δ 10.9 - 10.7 (br, 1H), 8.12 (d, 1H), 7.58 (t, 1H), 7.44 (t, 2H), 5.56 (m, 1H), 3.7 - 3.5 (br, 2H), 3.35 - 3.1 (br, m, 2H), 2.46 (s, 3H), 2.1 - 1.7 (br, m, 6H), 1.4 - 1.2 (m, 1H), 1.1 - 0.9 (m, 1H), 0.76 (t, 3H); ^{13}C NMR δ 199.1, 138.8, 134.4, 133.2, 132.3, 130.0, 126.2, 68.9, 53.5, 51.8, 31.4, 23.0, 20.7, 17.5, 13.7; APCI MS *m/z* 246 (M + 1); Anal. ($C_{16}H_{24}ClNO.H_2O$) C, H, N, Cl.

1-(3-Methylphenyl)-2-pyrrolidin-1-yl-pentan-1-one hydrochloride (4s)

1-(3-Methylphenyl)pentan-1-one **2s**, obtained in 98% yield from 3-methylbenzonitrile (General Procedure A) and purified by distillation (Bp 64 – 68°C, 0.1 mm Hg): ^{1}H NMR δ 7.86 (d, 2H), 7.26 (d, 2H), 2.94 (t, 2H), 2.41 (s, 3H), 1.71 (m, 2H), 1.41 (m, 2H), 0.95 (t, 3H), was brominated (General Procedure B) to provide 2-bromo-1-(3-methylphenyl)pentan-1-one, **3s**: ^{1}H NMR δ 7.81 (m, 2H), 7.40 (m, 2H), 5.15 (dd, 1H), 2.43 (s, 3H), 2.25 - 2.05 (m, 2H), 1.7 - 1.35 (m, 2H), 0.99 (t, 3H). Compound **4s** was prepared from **3s** as described in General Procedure C (53% yield); Mp 166 °C (dec.); ^{1}H NMR δ 10.8 - 10.6 (br, 1H), 7.90 (d, 2H), 7.65 - 7.5 (m, 2H), 5.57 (m, 1H), 3.7 - 3.55 (br, 1H), 3.55 - 3.4 (br, 1H), 3.3 - 3.15 (br, m, 1H), 3.15 - 3.0 (br, m, 1H), 2.42 (s, 3H), 2.1 - 1.8 (br, m, 6H), 1.35 - 1.15 (m, 1H), 1.15 - 0.95 (m, 1H), 0.78 (t, 3H); ^{13}C NMR δ 196.7, 138.8, 135.6, 134.5, 129.1, 126.1, 67.4, 53.6, 51.9, 31.7, 22.9, 20.8, 17.3, 13.7; APCI MS *m/z* 246 (M + 1); Anal. ($C_{16}H_{24}ClNO$) C, H, N, Cl.

1-Naphthalen-2-yl-2-pyrrolidin-1-yl-pentan-1-one hydrochloride (4t)

1-Naphthalen-2-yl-pentan-1-one **2t** prepared in 95 % yield from naphthalene-2-carbonitrile (General Procedure A): ^{1}H NMR δ 8.48 (s, 1H), 8.04 (dd, 1H), 7.97 (d, 1H), 7.90 (m, 2H), 7.57 (m, 2H), 3.11 (t, 2H), 1.79 (m, 2H), 1.44 (m, 2H), 0.98 (t, 3H) was brominated (General Procedure B) to afford 2-bromo-1-naphthalen-2-yl-pentan-1-one **3t**: ^{1}H NMR δ 8.55 (s, 1H), 8.1 - 7.85 (m, 4H), 7.60 (m, 2H), 5.33 (dd, 1H), 2.3 - 2.1 (m, 2H), 1.7 - 1.4 (m, 2H), 1.01 (t, 3H). Compound **4t** was prepared from **3t** as described in General Procedure C (51% yield); Mp 221 – 223 °C (dec.); ^{1}H NMR δ 10.8 - 10.6 (br, 1H), 8.92 (s, 1H), 8.2 - 8.0 (m, 4H), 7.75 (dt, 2H), 5.73 (m, 1H), 3.75 - 3.6 (br, 1H), 3.6 - 3.4 (br, m, 1H), 3.35 - 3.1 (br, m, 2H), 2.2 - 1.8 (m, 6H), 1.4 - 1.2 (m, 1H), 1.2 - 1.0 (m, 1H), 0.78 (t, 3H); ^{13}C NMR δ 196.6, 135.7, 132.0, 131.8, 131.7, 129.9, 129.7, 129.0, 127.8, 127.5, 123.4, 67.3, 53.6, 52.0. 31.9, 22.9, 17.4, 13.7; APCI MS *m/z* 282 (M + 1); Anal. ($C_{19}H_{24}ClNO$) C, H, N, Cl.

1-(3,4-Dichlorophenyl)-2-pyrrolidin-1-yl-pentan-1-one hydrochloride (4u)

1-(3,4-Dichlorophenyl)pentan-1-one **2 u** prepared in 93% yield from 3,4-dichlorobenzonitrile (General Procedure A) and used crude in the next step of the reaction: ^{1}H NMR δ 8.03 (d, 1H), 7.78 (dd, 1H), 7.54 (d, 1H), 2.92 (t, 2H), 1.71 (m, 2H), 1.39 (m, 2H), 0.94 (t, 3H) was brominated (General Procedure B) to afford 2-bromo-1-(3,4-dichlorophenyl)pentan-1-one **3u**: ^{1}H NMR δ 8.09 (d, 1H), 7.84 (dd, 1H), 7.55 (d, 1H), 5.02 (dd, 1H), 2.25 - 2.05 (m, 2H), 1.65 - 1.35 (m, 2H), 0.99 (t, 3H). Compound **4u** was prepared from **3u** as described in General Procedure C (32% yield); Mp 195 °C (dec.); ^{1}H NMR δ 10.8 - 10.6 (br, 1H), 8.35 (d, 1H), 8.04 (dd, 1H), 7.94 (d, 1H), 5.58 (m, 1H), 3.7 - 3.6 (br, 1H), 3.6 - 3.45 (br, m, 1H), 3.3 - 3.05 (br, m, 2H), 2.15 - 2.85 (br, m, 6H), 1.35 - 1.15 (m, 1H), 1.15 - 0.95 (m, 1H), 0.79 (t, 3H); ^{13}C NMR δ 195.0, 137.8, 134.5, 132.3, 131.6, 130.8, 128.8, 67.5, 53.7, 51.9, 31.4, 22.9, 17.2, 13.6; APCI MS *m/z* 300, 302, 304 (M + 1); Anal. ($C_{15}H_{20}Cl_3NO$) C, H, N, Cl.

1-(3,4-Dihydroxyphenyl)-2-pyrrolidin-1-yl-pentan-1-one hydrobromide (4v)

1-(3,4-Dimethoxyphenyl)-2-pyrrolidin-1-yl-pentan-1-one **4w** (1.50 g, 4.6 mmol) was freed from its hydrochloride salt by treatment with aqueous Na_2CO_3 and extraction into CH_2Cl_2. The organics were dried ($MgSO_4$), filtered, and reduced to a pale yellow oil *in vacuo*. The oil was taken up in CH_2Cl_2 (10 mL) and cooled to −78 °C, whereon BBr_3 (46 mL, 1.0 M solution in CH_2Cl_2, 46 mmol) was added dropwise over 0.5 h. The resulting yellow mixture was warmed slowly to room temperature and stirred for 3 h. The yellow solution was hydrolyzed cautiously with aq. Na_2CO_3 (20% solution) until the pH was 8, then water (50 mL) was added and the solution was allowed to stand overnight. Neutral organics were extracted from the mixture by separation of the CH_2Cl_2 layer, which was then discarded. The aqueous layer was acidified to pH 3 with 1 M HCl, most of the water was removed by rotary evaporation, and the remaining volume of ca. 10 mL was allowed to cool in the refrigerator. After 3 d, a white solid separated from the solution and was collected by filtration. Recrystallization (EtOH/Et_2O) afforded pure 1-(3,4-dihydroxyphenyl)-2-pyrrolidin-1-yl-pentan-1-one **4v** as its hydrobromide, an off-white solid (0.60 g, 44%); Mp 181 – 182 °C; ^{1}H NMR δ 10.42 (s, 1H), 10.1 - 9.9 (br, 1H), 9.59 (s, 1H), 7.51 (dd, 1H), 7.43 (d, 1H), 6.91 (d, 1H), 5.35 - 5.25 (br, 1H), 3.75 - 3.5 (br, 1H). 3.5 - 3.3 (br, 1H), 3.3 - 3.15 (br, 1H), 3.0 - 2.85 (br, 1H), 2.1 - 1.8 (m, 6H), 1.3 - 1.0 (m, 2H), 0.80 (t, 3H); ^{13}C NMR δ 194.8, 153.4, 146.4, 126.7, 123.5, 116.0, 115.9, 67.5, 54.5, 52.3, 32.8, 23.2, 17.9, 14.3; APCI MS *m/z* 264 (M + 1); Anal. ($C_{15}H_{22}BrNO_3$) C, H, N, Br.

1-(3,4-Dimethoxyphenyl)-2-pyrrolidin-1-yl-pentan-1-one hydrochloride (4w)

2-Bromo-1-(3,4-dimethoxyphenyl)pentan-1-one **3w** was obtained together with 2-bromo-1-(2-bromo-4,5-dimethoxyphenyl)pentan-1-one by General Procedure B. The compounds were separated by flash column chromatography (10% EtOAc/hexane) to provide 2-bromo-1-(3,4-dimethoxyphenyl)-pentan-1-one **3w**: ^{1}H NMR δ 7.66 (dd, 1H), 7.58 (d, 1H), 6.91 (d, 1H), 5.15 (dd, 1H), 3.97 (s, 3H), 3.95 (s, 3H), 2.25 - 2.05 (m, 2H), 1.7 - 1.35 (m, 2H), 1.01 (t, 3H), and 2-bromo-1-(2-bromo-4,5-dimethoxyphenyl)pentan-1-one: ^{1}H NMR δ 7.07 (s, 1H), 7.04 (s, 1H), 5.28 (dd, 1H), 3.92 (s, 3H), 3.90 (s, 3H), 2.3 - 2.0 (m, 2H), 1.7 - 1.4 (m, 2H), 1.00 (t, 3H). Compound **4w** was then prepared from **3w** as described in General Procedure C to provide a solid (74% yield); Mp 177 °C (dec.); ^{1}H NMR δ 10.5 - 10.3 (br, 1H), 7.78 (d, 1H), 7.53 (d, 1H), 7.18 (d, 1H), 5.55 - 5.4 (br, m, 1H), 3.90 (s, 3H), 3.86 (s, 3H), 3.7 - 3.55 (br, m, 1H), 3.5 - 3.3 (br, m, 1H), 3.3 - 3.15 (br, m, 1H), 3.05 - 2.9 (br, m, 1H), 2.1 - 1.8 (m, 6H), 1.3 - 1.0 (m, 2H), 0.80 (t, 3H); ^{13}C NMR δ 194.7, 154.7, 149.0, 127.2, 124.6, 111.2, 110.5, 66.7, 56.0, 55.7, 53.7, 51.8, 32.1, 22.8, 17.4, 13.7; APCI MS *m/z* 292 (M + 1); Anal. ($C_{17}H_{26}ClNO_3$) C, H, N, Cl.

1-(4-Furan-2-ylphenyl)-2-pyrrolidin-1-yl-pentan-1-one hydrochloride (4x)

This compound was prepared using a procedure analogous to that described later for the preparation of **4z**, except that commercially available 2-tributylstannyl furan was employed as a starting material, and chromatography was not performed on the crude free base. The crude hydrochloride was recrystallized from hot EtOH to give pure **4x** as a colorless crystalline solid: (59% yield); Mp 236 °C (dec.); ^{1}H NMR (DMSO-d_6 + 6 drops CD_3OD) δ 8.14 (d, 2H), 7.95 (d, 2H), 7.90 (d, 1H), 7.29 (d, 1H), 6.71 (dd, 1H), 5.51 (m, 1H), 3.7 - 3.6 (br, m, 1H), 3.6 - 3.45 (br, m, 1H), 3.35 - 3.2 (br, m, 1H), 3.15 - 3.0 (br, m, 1H), 2.15 - 1.85 (br, m, 6H), 1.35 - 1.15 (m, 1H), 1.15 - 1.0 (m, 1H), 0.81 (t, 3H); ^{13}C NMR δ 195.7, 151.8, 145.1, 136.0, 132.6, 130.0, 123.8, 112.9, 109.9, 67.8, 54.2, 52.0, 32.0, 22.9, 17.3, 13.7; APCI MS *m/z* 298 (M + 1); Anal. ($C_{19}H_{24}ClNO_2$) C, H, N, Cl.

2-Pyrrolidin-1-yl-1-(4-thiophen-2-yl-phenyl)pentan-1-one hydrochloride (4y)

This compound was prepared using a procedure analogous to that described later for the preparation of **4z**, except that commercially available 2-tributylstannyl thiophene was employed as a starting material, and chromatography was not performed on the crude free base. The crude hydrochloride was readily obtained by treatment of the crude free base with 2M ethereal HCl. Recrystallization from hot EtOH gave pure **4v** as a colorless crystalline solid (61% yield). Mp 220 °C (dec.); ^{1}H NMR (DMSO-d_6 + 12 drops CD_3OD) δ 8.12 (d, 2H), 7.93 (d, 2H), 7.77 (dd, 1H), 7.72 (dd, 1H), 7.23 (dd, 1H), 5.5 - 5.4 (br, 1H), 3.7 - 3.45 (br, m, 2H), 3.3 - 3.2 (br, m, 1H), 3.1 - 3.0 (br, m, 1H), 2.2 - 1.9 (br, m, 6H), 1.35 - 1.2 (m, 1H), 1.2 - 1.0 (m, 1H), 0.83 (t, 3H); ^{13}C NMR δ 195.9, 141.8, 140.3, 132.9, 130.3, 129.3, 128.6, 126.6, 126.0, 68.1, 54.5, 52.1, 32.2, 23.1, 17.4, 13.8; APCI MS *m/z* 314 (M + 1); Anal. ($C_{19}H_{24}ClNOS$) C, H, N, Cl.

1-(4-*N*-Methylpyrrolephenyl)-2-pyrrolidin-1-yl-pentan-1-one hydrochloride (4z)

To a cooled (−78 °C) solution of *N*-methylpyrrole (1.14 g, 14 mmol) in THF (10 mL), ^{t}BuLi (9.1 mL of a 1.7M solution in pentane, 15 mmol) was added drop-wise. The mixture was then warmed to room temperature for 2 h, then cooled to −78 °C. Chlorotributylstannane (5.0 g, 15 mmol) was added to the mixture dropwise. On completion of addition, the mixture was warmed to room temperature and stirred for 1 h. The mixture was filtered and reduced to an oil *in vacuo*. This oil (crude 2-tributylstannyl-(*N*-methylpyrrole)) was added to a solution of 2-pyrrolidin-1-yl-1-(4-bromophenyl)-pentan-1-one (which had been freed from its hydrochloride **4f** by treatment with 20% aqueous Na_2CO_3 and extraction into Et_2O) in dioxane (30 mL). The resulting solution was degassed by purging with N_2. [$Pd(PPh_3)_4$] (264 mg, 0.22 mmol) was added and the mixture was heated to 95 – 100 °C (oil bath temperature) for a period of 10 h. The solvent was removed *in vacuo*. The pure free base was obtained by column chromatography (5% MeOH/CH_2Cl_2) as a yellow oil. The hydrochloride was prepared by treatment with 2M ethereal HCl. Lyophilization of an aqueous solution of the salt afforded 1-(4-*N*-methylpyrrolephenyl)-2-pyrrolidin-1-yl-pentan-1-one hydrochloride as a pale green solid **4z** (1.4 g, 36%). Mp 185 °C; ^{1}H NMR δ 10.6 - 10.45 (br, 1H), 8.11 (d, 2H), 7.72 (d, 2H), 7.00 (dd, 1H), 6.45 (dd, 1H), 6.15 (dd, 1H), 5.54 (m, 1H), 3.77 (s, 3H), 3.7 - 3.55 (br, 1H), 3.55 - 3.4 (br, 1H), 3.35 - 3.15 (br, m, 1H), 3.15 - 3.0 (br, m, 1H), 2.1 - 1.85 (br, m, 6H), 1.35 - 1.2 (m, 1H), 1.2 - 1.0 (m, 1H), 0.82 (t, 3H); ^{13}C NMR δ 195.6, 139.1, 131.9, 131.5, 129.4, 127.4, 127.1, 111.1, 108.2, 67.2, 53.7, 51.9, 35.6, 31.9, 22.9, 17.4, 13.7; APCI MS *m/z* 311 (M + 1); Anal. ($C_{20}H_{27}ClN_2O.2/3H_2O$) C, H, N, Cl.

1-(4-Methylphenyl)pent-2-en-1-one (5a)

This compound was prepared as described below for **5b** employing 2-bromo-1-(4-methylphenyl)pentan-1-one **3a** as starting material (82% yield); ^{1}H NMR δ 7.85 (d, 2H), 7.25 (d, 2H), 7.10 (dt, 1H), 6.88 (dt, 1H), 2.39 (s, 3H), 2.32 (m, 2H), 1.13 (t, 3H); ^{13}C NMR δ 190.3, 150.6, 143.2, 135.3, 129.0, 128.5, 124.7, 25.7, 21.5, 12.2.

1-(3,4-Dichlorophenyl)pent-2-en-1-one (5b)

2-Bromo-1-(3,4-dichlorophenyl) pentan-1-one, **3u**, (3.36 g, 10.9 mmol) was dissolved in DMF (60 mL). Li_2CO_3 (1.28 g, 17 mmol) and LiBr (0.99 g, 11.5 mmol) were added to the solution, which was then heated with stirring to 110 – 120 °C (oil bath temperature) for 1.5 h. The mixture was diluted with H_2O (100 mL) and the organics were extracted into EtOAc (3 × 50 mL). The ethyl acetate layer was collected and washed with saturated brine (2 × 50 mL), dried ($MgSO_4$), filtered, and reduced to an oil *in vacuo.* Flash column chromatography (1% EtOAc/hexane to 2.5% EtOAc/hexane) furnished pure **5b** as a colorless solid (1.5 g, 60%). ^{1}H NMR δ 8.01 (d, 1H), 7.76 (dd, 1H), 7.55 (d, 1H), 7.15 (dt, 1H), 6.80 (dt, 1H), 2.37 (m, 2H), 1.15 (t, 3H); ^{13}C NMR δ 188.5, 152.8, 137.6, 137.1, 133.2, 130.6, 130.5, 127.5, 124.1, 26.0, 12.2.

1-(3,4-Dichlorophenyl)-3-pyrrolidin-1-yl-pentan-1-one hydrochloride (6b)

1-(3,4-Dichlorophenyl)pent-2-en-1-one **5b** (1.29 g, 5.63 mmol) was taken up in EtOH (10 mL), cooled on an ice bath, and degassed by purging with N_2. Pyrrolidine (0.80 g, 11 mmol) was added dropwise over 2 min. After 0.5 h, the ethanolic solution was separated between 1M aqueous HCl and Et_2O. The HCl extracts were collected and back-extracted into Et_2O by treatment with 20% aqueous Na_2CO_3. The ethereal extracts were dried ($MgSO_4$), filtered, and treated with 2M ethereal HCl. Trituration afforded 1-(3,4-dichlorophenyl)-2-pyrrolidin-1-yl-methylpentan-1-one hydrochloride **6b** as a white powder which was filtered and washed copiously with Et_2O (0.99 g, 50%); Mp 104 – 107 °C (dec.); ^{1}H NMR δ 11.1 - 10.9 (br, 1H), 8.27 (d, 1H), 7.98 (dd, 1H), 7.87 (d, 1H), 3.9 - 3.35 (br, m, 5H), 3.15 - 2.95 (br, 2H), 2.05 - 1.8 (br, m, 5H), 1.8 - 1.6 (m, 1H), 0.90 (t, 3H); ^{13}C NMR δ 195.0, 136.4, 136.1, 131.8, 131.1, 130.3, 128.1, 59.2, 50.7, 50.1, 38.2, 23.8, 22.9, 10.0; APCI MS *m/z* 300, 302, 304 (M + 1); Anal. ($C_{15}H_{20}Cl_3NO.1/3H_2O$) C, H, N, Cl.

1-(4-Methylphenyl)-3-pyrrolidin-1-yl-pentan-1-one hydrochloride (6a)

This compound was prepared from 1-(4-methylphenyl)-2-en-1-one **5a** using the same procedure as that described for **6b**. Mp 97 °C (dec.); ^{1}H NMR δ 11.1 - 10.9 (br, 1H), 7.94 (d, 2H), 7.38 (d, 2H), 3.9 - 3.75 (br, 1H), 3.7 - 3.6 (m, 1H), 3.6 - 3.3 (m, 3H), 3.15 - 2.95 (br, m, 2H), 1.96 (s, 3H), 2.0 - 1.8 (br, m, 5H), 1.8 - 1.6 (m, 1H), 0.88 (t, 3H); ^{13}C NMR δ 196.2, 144.3, 133.5, 129.3, 128.3, 59.7, 50.7, 50.4, 37.9, 23.8, 22.9, 22.8, 21.2, 9.9; APCI MS *m/z* 246 (M + 1); Anal. ($C_{16}H_{24}ClNO$) C, H, N, Cl.

1-(3,4-Dichlorophenyl)-2-pyrrolidin-1-yl-methylpentan-1-one hydrochloride (7b)

2-Bromo-1-(3,4-dichlorophenyl)pentan-1-one **3u** (3.5 g, 15 mmol), pyrrolidine.HCl (2.4 g, 23 mmol) and paraformaldehyde (1.35 g, 45 mmol) were taken up in ^{i}PrOH (25 mL) containing concentrated HCl (0.2 mL). The mixture was brought to reflux for 16 h. The solvent was removed by rotary evaporation and the residue was separated between 1 M aqueous HCl and Et_2O. The aqueous extracts were basified with 20% aqueous Na_2CO_3 to pH 8–9 and the organics were extracted into Et_2O. The organics were dried ($MgSO_4$), filtered, and reduced to an oil *in vacuo*. Column chromatography (10% MeOH/CH_2Cl_2) gave the pure free base. Reaction with 2 M ethereal HCl and filtration of the resulting white precipitate provided 1-(3,4-dichlorophenyl)-2-pyrrolidin-1-yl-methylpentan-1-one hydrochloride, **7b** (0.61 g, 12%). Mp 168 °C (dec.); ^{1}H NMR δ 10.7 - 10.5 (br, 1H), 8.29 (d, 1H), 8.05 (dd, 1H), 7.88 (d, 1H), 4.3 - 4.1 (br, 1H), 3.7 - 3.5 (br, m, 2H), 3.5 - 3.25 (br, m, 2H), 3.15 - 2.85 (br, m, 2H), 2.1 - 1.75 (br, m, 4H), 1.75 - 1.4 (m, 2H), 1.35 - 1.05 (m, 2H), 0.81 (t, 3H); ^{13}C NMR δ 198.9, 136.6, 135.9, 132.1, 131.4, 131.2, 130.5, 130.3, 128.7, 128.5, 54.1, 53.4, 42.3, 42.2, 33.1, 22.7, 22.4, 18.8, 13.8; APCI MS *m/z* 314, 312, 310 (M + 1); Anal. ($C_{16}H_{22}Cl_3NO$) C, H, N, Cl.

1-(4-Methylphenyl)-2-pyrrolidin-1-yl-methylpentan-1-one hydrochloride (7a)

This compound was prepared from 1-(2-methylphenyl)pentan-1-one (3.5 g, 20 mmol) using the same method as described for **7b** with the following modifications. No chromatography was performed. The hydrochloride salt of the crude free base was isolated after extraction of the crude reaction mixture into 1 M aqueous HCl, and back extraction (with 20% aqueous Na_2CO_3) into Et_2O, followed by acidification with 2M HCl in Et_2O. The product was recrystallized from EtOH/Et_2O to give pure crystalline 1-(4-methylphenyl)-2-pyrrolidin-1-yl-methylpentan-1-one hydrochloride **7a** (2.6 g, 44%). Mp 176 °C (dec.); ^{1}H NMR δ 10.8 - 10.6 (br, 1H), 7.98 (d, 2H), 7.39 (d, 2H), 4.25 - 4.15 (br, m, 1H), 3.65 - 3.5 (m, 2H), 3.5 - 3.25 (m, 2H), 3.1 - 2.95 (br, m, 1H), 2.95 - 2.8 (br, m, 1H), 2.40 (s, 3H), 2.0 - 1.75 (m, 4H), 1.7 - 1.4 (m, 2H), 1.3 - 1.1 (m, 2H), 0.81 (t, 3H); ^{13}C NMR δ 200.4, 144.4, 135.2, 129.7, 129.5, 128.7, 128.5, 54.0, 53.7, 53.3, 41.9, 33.5, 22.8, 22.3, 21.1, 19.0, 13.8; APCI MS *m/z* 260 (M + 1); Anal. ($C_{17}H_{26}ClNO$) C, H, N, Cl.

1-(3,4-Dichlorophenyl)-2-pyrrolidin-1-yl-butan-1-one hydrochloride (9a)

1-(3,4-Dichlorophenyl)butan-1-one, prepared in quantitative yield from 3,4-dichlorobenzonitrile and *n*-PrMgCl (General Procedure A); ^{1}H NMR δ 8.01 (d, 1H), 7.78 (dd, 1H), 7.54 (d, 1H), 2.91 (t, 2H), 1.77 (sextet, 2H), 1.01 (t, 3H), was brominated according to General Procedure B to give 2-bromo-1-(3,4-dichlorophenyl)butan-1-one; ^{1}H NMR δ 8.09 (d, 1H), 7.84 (dd, 1H), 7.57 (d, 1H), 4.95 (dd, 1H), 2.35 - 2.05 (m, 2H), 1.09 (t, 3H). Compound **9a** was prepared according to General Procedure C (71% yield); Mp 211 °C (dec.); ^{1}H NMR δ 10.95 - 10.75 (br, 1H), 8.35 (d, 1H), 8.06 (dd, 1H), 7.92 (d, 1H), 5.75 - 5.65 (br, m, 1H), 3.65 - 3.35 (br, m, 2H), 3.3 - 3.1 (br, m, 2H), 2.15 - 1.9 (br, m, 6H), 0.78 (t, 3H); ^{13}C NMR δ 194.7, 137.7, 134.5, 132.3, 131.6, 130.7, 128.8, 68.5, 53.7, 51.8, 23.0, 22.6, 8.4; APCI MS *m/z* 286, 288, 290 (M + 1); Anal. ($C_{14}H_{18}Cl_3NO$) C, H, N.

4-Methyl-2-pyrrolidin-1-yl-1-(4-methylphenyl)pentan-1-one hydrochloride (9b)

4-Methyl-1-(4-methylphenyl)pentan-1-one, prepared in quantitative yield by Friedel-Crafts acylation of toluene with 4-methylvaleroyl chloride: ^{1}H NMR δ 7.86 (d, 2H), 7.26 (d, 2H), 3.94 (t, 2H), 2.41 (s, 3H), 1.62 (m, 3H), 0.94 (d, 6H) was converted to 2-bromo-4-methyl-1-(4-methylphenyl)pentan-1-one, as described in General Procedure B: ^{1}H NMR δ 7.92 (d, 2H), 7.29 (d, 2H), 5.21 (dd, 1H), 2.43 (s, 3H), 2.15 - 1.95 (m, 2H), 1.95 - 1.75 (m, 1H), 0.96 (d, 6H). 4-Methyl-2-pyrrolidin-1-yl-1-(4-methylphenyl)pentan-1-one hydrochloride **9b** was then prepared as described in General Procedure C (68% yield); Mp 218 °C (dec.); ^{1}H NMR δ 10.9 - 10.75 (br, 1H), 8.06 (d, 2H), 7.45 (d, 2H), 5.46 (m, 1H), 3.75 - 3.6 (br, 1H), 3.6 - 3.4 (br, 1H), 3.3 - 3.0 (br, m, 2H), 2.42 (s, 3H), 2.1 - 1.7 (m, 6H), 1.45 - 1.3 (m, 1H), 0.82 (dd, J = 2, 6 Hz, 6H); ^{13}C NMR δ 197.2, 164.0, 132.9, 129.9, 129.0, 64.4, 52.7, 51.2, 24.2, 23.3, 22.8, 21.5, 21.3; APCI MS *m/z* 260 (M + 1); Anal. ($C_{17}H_{26}ClNO$) C, H, N, Cl.

1-(4-Methylphenyl)-2-pyrrolidin-1-yl-pent-4-ene-1-one hydrochloride (9c)

This compound was prepared as described previously.[29] Mp 196 °C (dec.); ^{1}H NMR δ 10.8 - 10.6 (br, 1H), 7.96 (d, 2H), 7.43 (d, 2H), 5.8 - 5.6 (m, 2H), 5.03 (s, 1H), 5.00 (m, 1H), 3.75 - 3.6 (br, 1H), 3.6 - 3.4 (br, 1H), 3.4 - 3.2 (br, m, 1H), 3.15 - 3.0 (br, m, 1H), 3.85 - 3.65 (br, m, 2H), 2.42 (s, 3H), 2.2 - 1.85 (br, m, 4H); ^{13}C NMR δ 195.2, 145.8, 131.8, 130.6, 129.7, 129.0, 120.1, 66.9, 53.8, 52.0, 34.2, 22.9, 21.3; APCI MS *m/z* 244 (M + 1); Anal. ($C_{16}H_{22}ClNO$) C, H, N, Cl.

1-(3,4-Dichlorophenyl)-2-pyrrolidin-1-yl-pent-4-ene-1-one hydrochloride (9d)

This compound was prepared as described for **9c** [29] Mp 176 °C (dec.); ^{1}H NMR δ 10.8 - 10.6 (br, 1H), 8.29 (d, 1H), 8.00 (dd, 1H), 7.94 (d, 1H), 5.8 - 5.6 (m, 2H), 5.07 (s, 1H), 5.02 (m, 1H), 3.75 - 3.6 (br, m, 1H), 3.6 - 3.3 (br, m, 1H), 3.3 - 3.1 (br, m, 2H), 2.77 (m, 2H), 2.2 - 1.8 (br, m, 4H); ^{13}C NMR δ 194.2, 137.8, 134.4, 132.2, 131.6, 130.8, 130.3, 128.8, 120.6, 67.2, 53.9, 52.1, 33.8, 22.9; APCI MS *m/z* 302 ((M + 1), 100%), 300, 298; Anal. ($C_{15}H_{18}Cl_3NO$) C, H, N, Cl.

1-(4-Methylphenyl)-2-pyrrolidin-1-yl-pent-4-yn-1-one hydrochloride (9e)

1-(4-Methylphenyl)-2-pyrrolidin-1-ylethanone **8**[29] (25 g, 104 mmol) was freed from its hydrochloride by treatment with aqueous Na_2CO_3 and extraction into Et_2O. The organics were dried ($MgSO_4$), filtered and reduced *in vacuo* to a yellow oil. This oil was taken up in toluene (200 mL), and $NaNH_2$ was added to the stirring solution, which was then heated to approximately 120 °C (oil bath temperature) for 0.5 h. The solution was allowed to cool to about 100 °C and propargyl bromide (13 mL, 80% w/w solution in toluene, 14 g, 115 mmol) was added to the orange mixture at such a rate that steady reflux was maintained with concomitant NH_3 evolution. Upon complete addition (0.5 h), the mixture was allowed to cool to room temperature and was then hydrolyzed cautiously by addition of water (100 mL). The toluene layer was separated and the aqueous layer was extracted with toluene (2 × 50 mL). The combined organics were dried ($MgSO_4$), filtered and reduced *in vacuo* to a brown oil that was taken up in Et_2O (50 mL). 2 M HCl in Et_2O was added to the ethereal solution of the oil. Trituration afforded a brown solid that could not be crystallized from EtOH/Et_2O. The solvents were removed *in vacuo* and the free base was prepared by addition of 2 M NaOH solution until pH 8–9. The organics were extracted into Et_2O (3 × 100 mL) to give a light brown solution. Back-extraction into 1 M HCl (3 × 50 mL) gave a light yellow solution. The water was removed by rotary evaporation; lyophilization than gave a light brown gum (5.3 g). Recrystallization from EtOH/Et_2O afforded pure 1-(4-methylphenyl)-2-pyrrolidin-1-yl-pent-4-yn-1-one hydrochloride **9e** (3.15 g, 11%): Mp 178 °C (dec.); ^{1}H NMR δ 10.6 - 10.4 (br, 1H), 7.97 (d, 2H), 7.45 (d, 2H), 5.66 (m, 1H), 3.7 - 3.2 (m, 3H), 3.2 - 2.9 (m, 4H), 2.43 (s, 3H), 2.1 - 1.8 (m, 4H); ^{13}C NMR δ 193.9, 146.0, 131.1, 129.7, 129.2, 76.8, 76.6, 65.2, 54.0, 52.0, 22,9, 22.9, 21.3, 20.0; APCI MS *m/z* 242 (M + 1); Anal. ($C_{16}H_{20}ClNO$) C, H, N, Cl.

2-Butylamin-1-yl-1-(3,4-dichlorophenyl)pentan-1-one hydrochloride (9f)

Compound **9f** (an off-white solid) was obtained from **3u** (described above) and *n*-butylamine, according to General Procedure C (71% yield); Mp 185 °C (dec.); ^{1}H NMR δ 9.8 - 9.6 (br, 1H), 9.3 - 9.1 (br, 1H), 8.35 (d, 1H), 8.04 (dd, 1H), 7.91 (d, 1H), 5.4 - 5.25 (br, 1H), 3.05 - 2.75 (br, m, 2H), 2.05 - 1.8 (br, m, 2H), 1.8 - 1.6 (br, m, 2H), 1.4 - 1.2 (m, 3H), 1.2 - 1.0 (m, 1H), 0.88 (t, 3H), 0.78 (t, 3H); ^{13}C NMR δ 194.8, 137.6, 134.3, 132.3, 131.5, 130.6, 128.7, 60.8, 45.7, 31.5, 27.4, 19.3, 17.2, 13.6, 13.5; APCI MS *m/z* 302, 304, 306 (M + 1); Anal. ($C_{15}H_{22}Cl_3NO$) C, H, N, Cl.

1-(3,4-Dichlorophenyl)-2-piperidin-1-yl-pentan-1-one hydrochloride (9g)

Compound **9g** was prepared from **3u** (described above) and piperidine, as described in General Procedure C (35% yield); Mp 202 °C (dec.); ^{1}H NMR δ 10.5 - 10.3 (br, 1H), 8.40 (d, 1H), 8.10 (dd, 1H), 7.94 (d, 1H), 5.45 - 5.35 (br, m, 1H), 3.7 - 3.55 (br, m, 1H), 3.45 - 3.3 (br, m, 1H), 3.2 - 1.95 (br, m, 2H), 2.1 - 1.65 (br, m, 7H), 1.5 - 1.3 (br, 1H), 1.2 - 1.0 (br, m, 2H), 0.81 (t, 3H); ^{13}C NMR δ 195.3, 138.0, 135.3, 132.4, 131.6, 130.7, 128.8, 65.8, 52.0, 50.2, 29.3, 22.3, 22.0, 21.5, 17.8, 13.7; APCI MS *m/z* 314, 316, 318 (M + 1); Anal. ($C_{16}H_{22}Cl_3NO$) C, H, N, Cl.

1-(4-Methylphenyl)-2-pyrrolidin-1-yl-pentan-1-ol hydrochloride (diastereoisomers 9h and 9j)

1-(4-Methylphenyl)-2-pyrrolidin-1-yl-pentan-1-one hydrochloride **4a** (1.50 g, 5.32 mmol) was suspended in THF (20 mL). $LiAlH_4$ (0.20 g, 5.3 mmol) was added in several small portions at room temperature to the stirring mixture with slight heat evolution. The resulting clear solution was hydrolyzed cautiously with H_2O, then made acidic by addition of 1M aqueous HCl. The aqueous extracts were collected and basified to pH 8–9 with 20% aqueous Na_2CO_3. The organics were extracted into Et_2O, dried ($MgSO_4$), filtered, and reduced to an oil *in vacuo*. Chromatography (5% NEt_3/15% EtOAc/80% hexane) gave the two diastereoisomers **9h** and **9j**. The hydrochlorides were prepared from 2M ethereal HCl and recrystallized from EtOH/Et_2O to afford 1-(4-methylphenyl)-2-pyrrolidin-1-yl-pentan-1-ol hydrochloride **9h**, a colorless crystalline solid (0.57 g, 37%); Mp 140 – 142 °C; ^{1}H NMR δ 10.15 - 10.0 (br, 1H), 7.32 (d, 2H), 7.19 (d, 2H), 6.20 (d, *J* = 5 Hz, 1H), 5.24 (s, 1H), 3.75 - 3.65 (br, m, 1H), 3.65 - 3.5 (br, m, 1H), 3.4 - 3.3 (br, 2H), 3.2 - 3.05 (br, m, 1H), 2.30 (s, 3H), 2.1 - 1.8 (br, m, 4H), 1.75 - 1.6 (m, 1H), 1.4 - 1.25 (br, m, 1H), 1.1 - 0.95 (m, 1H), 0.8 - 0.6 (m, 1H), 0.57 (t, 3H); ^{13}C NMR δ 138.3, 136.2, 128.6, 125.5, 69.3, 68.1, 51.5, 26.5, 22.7, 22.5, 20.7, 20.3, 13.7; APCI MS *m/z* 248 (M + 1); Anal. ($C_{16}H_{26}ClNO$) C, H, N, Cl. and 1-(4-methylphenyl)-2-pyrrolidin-1-yl-pentan-1-ol hydrochloride **9j**, a colorless microcrystalline solid (159 mg, 10%), this was the more polar material; Mp 219 °C (dec.); ^{1}H NMR δ 9.8 - 9.65 (br, 1H), 7.33 (d, 2H), 7.20 (d, 2H), 6.53 (d, *J* = 4 Hz, 1H), 4.65 (dd *J* = 4, 9 Hz, 1H), 3.55 - 3.3 (m, 3H), 3.3 - 3.15 (br, m, 1H), 3.15 - 2.95 (br, m, 1H), 2.31 (s, 3H), 2.0 - 1.85 (br, 4H), 1.55 - 1.35 (br, m, 2H), 1.05 - 0.85 (m, 1H), 1.75 - 1.6 (m, 4H); ^{13}C NMR δ 138.4, 137.3, 128.9, 127.1, 72.1, 67.0, 40.3, 40.1, 27.6, 23.3, 23.0, 20.8, 20.0, 13.6; APCI MS *m/z* 248 (M + 1); Anal. ($C_{16}H_{26}ClNO$) C, H, N, Cl.

Biological Procedures

(Provided by NIDA from Oregon Health & Science University and SRI International). Unknowns were weighed and dissolved in DMSO to make a 10 mM stock solution. An initial dilution to 50 µM in assay buffer for binding, or to 1 mM in assay buffer for uptake, was made. Subsequent dilutions were made with assay buffer supplemented with DMSO, maintaining a final concentration of 0.1% DMSO. Pipetting was conducted using a Biomek 2000 robotic workstation.

Inhibition of Radioligand Binding of [^{125}I]RTI 55 to hDAT, hSERT or hNET in Clonal Cells

Cell preparation: HEK293 cells expressing hDAT, hSERT or hNET inserts are grown to 80% confluence on 150 mm diameter tissue culture dishes and serve as the tissue source. Cell membranes are prepared as follows. Medium is poured off the plate, and the plate is washed with 10 ml of calcium- and magnesium-free phosphate-buffered saline. Lysis buffer (10 ml; 2 mM HEPES with 1 mM EDTA) is added. After 10 min, cells are scraped from plates, poured into centrifuge tubes, and centrifuged 30,000 × g for 20 min. The supernatant fluid is removed, and the pellet is resuspended in 12–32 ml of 0.32 M sucrose using a Polytron at setting 7 for 10 sec. The resuspension volume depends on the density of binding sites within a cell line and is chosen to reflect binding of 10% or less of the total radioactivity. Assay conditions: Each assay tube contains 50 µl of membrane preparation (about 10–15 µg of protein), 25 µl of unknown, compound used to define non-specific binding, or buffer (Krebs-HEPES, pH 7.4; 122 mM NaCl, 2.5 mM $CaCl_2$, 1.2 mM $MgSO_4$, 10 µM pargyline, 100 µM tropolone, 0.2% glucose and 0.02% ascorbic acid, buffered with 25 mM HEPES), 25 µl of [^{125}I]RTI-55 (40–80 pM final concentration) and additional buffer sufficient to bring up the final volume to 250 µl. Membranes are preincubated with unknowns for 10 min prior to the addition of the [^{125}I]RTI-55. The assay tubes are incubated at 25°C for 90 min. Binding is terminated by filtration over GF/C filters using a Tomtec 96-well cell harvester. Filters are washed for six seconds with ice-cold saline. Scintillation fluid is added to each square and radioactivity remaining on the filter is determined using a Wallac µ- or beta-plate reader. Specific binding is defined as the difference in binding observed in the presence and absence of 5 µM mazindol (HEK-hDAT and HEK-hNET) or 5 µM imipramine (HEKhSERT). Two or three independent competition experiments are conducted with duplicate determinations. GraphPAD Prism is used to analyze the ensuing data, with IC_{50} values converted to K_i values using the Cheng-Prusoff equation ($K_i=IC_{50}/(1+([RTI\text{-}55]/K_d\ RTI\text{-}55))$).

Filtration Assay for Inhibition of [^{3}H]Neurotransmitter Uptake in HEK293 Cells Expressing Recombinant Biogenic Amine Transporters

Cell preparation: Cells are grown to confluence as described above. The medium is removed, and cells are washed twice with phosphate buffered saline (PBS) at room temperature. Following the addition of 3 ml Krebs-HEPES buffer, the plates are warmed in a 25°C water bath for 5 min. The cells are gently scraped and then triturated with a pipette. Cells from multiple plates are combined. One plate provides enough cells for 48 wells, which is required to generate data on two complete curves for the unknowns.

Uptake inhibition assay conditions: The assay is conducted in 96 1-ml vials. Krebs- HEPES (350 µl) and unknowns, compounds used to define non-specific uptake, or buffer (50 µl) are added to vials and placed in a 25°C water bath. Specific uptake is defined as the difference in uptake observed in the presence and absence of 5 µM mazindol (HEK-hDAT and HEK-hNET) or 5 μM imipramine (HEK-hSERT). Cells (50 μl) are added and preincubated with the unknowns for 10 min The assay is initiated by the addition of [^{3}H]dopamine, [^{3}H]serotonin, or [^{3}H]norepinephrine (50 μl, 20 nM final concentration). Filtration through Whatman GF/C filters presoaked in 0.05% polyethylenimine is used to terminate uptake after 10 min. The IC_{50}S are calculated applying the GraphPAD Prism program to triplicate curves made up of 6 drug concentrations each. Two or three independent determinations of each curve are made.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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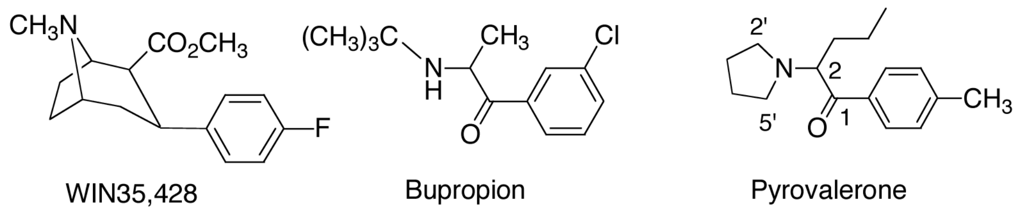
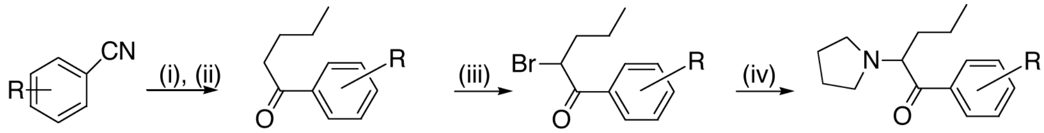

CH3N
CO2CH3
F
WIN35,428
(CH3)3C
N
H
CH3
Cl
O
Bupropion
2'
N
2
5'
O
1
CH3
Pyrovalerone

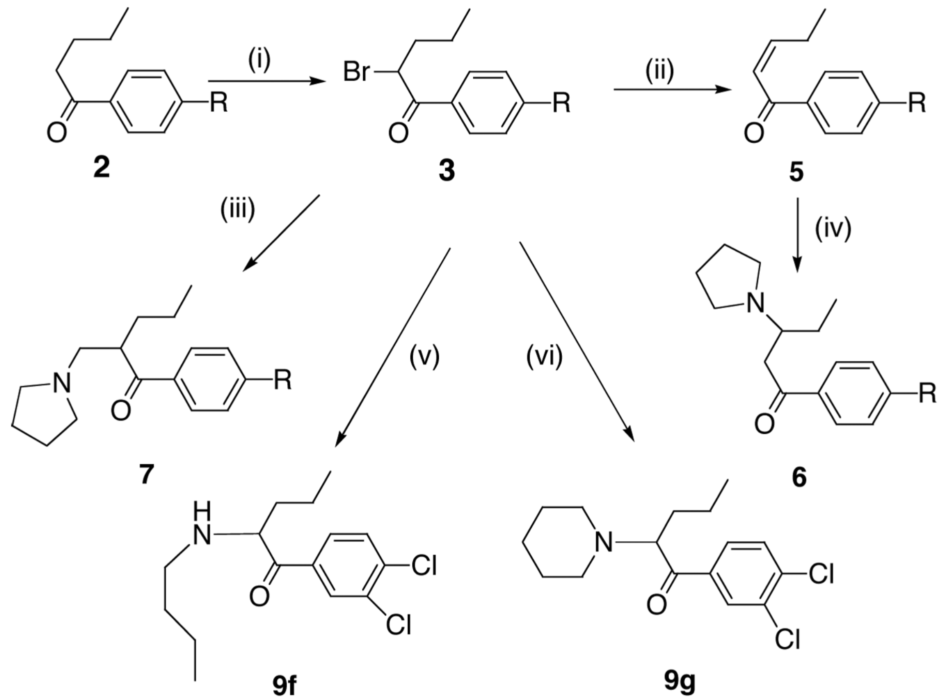
Figure 1.



1 **2** **3** **4**

a R = 4-CH_3 (R/S)
b R = 4-CH_3 (S)
c R = 4-CH_3 (R)
d R = H
e R = 4-F
f R = 4-Br
g R = 4-I
h R = 3-I
i R = 4-CN
j R = 4-CH_2OH
k R = 4-OH
l R = 4-NO_2
m R = 4-OCH_3
n R = 4-CO_2CH_3
o R = 4-$NHCOCH_3$
p R = 4-CF_3
q R = 4-$CCCH_3$
r R = 2-CH_3
s R = 3-CH_3
t R = Naphthyl
u R = 3,4-Cl_2
v R = 3,4-$(OH)_2$
w R = 3,4-$(OCH_3)_2$
x R = 4-(2-Furan)
y R = 4-(2-Thiophene)
z R = 4-(2-Methylpyrrole)

Scheme 1.
General Heffe synthesis of 1-(4-substitutedphenyl)-2-pyrrolidin-1-yl-pentan-1-ones, **4**ab
[a]Reagents and conditions: i) *n*-BuMgCl; ii) H_2SO_4; iii) $AlCl_3$, Br_2; iv) pyrrolidine
[b]The Heffe synthesis was not followed for certain compounds. Synthetic details for those compounds are presented in the Experimental Section and are discussed in the text.

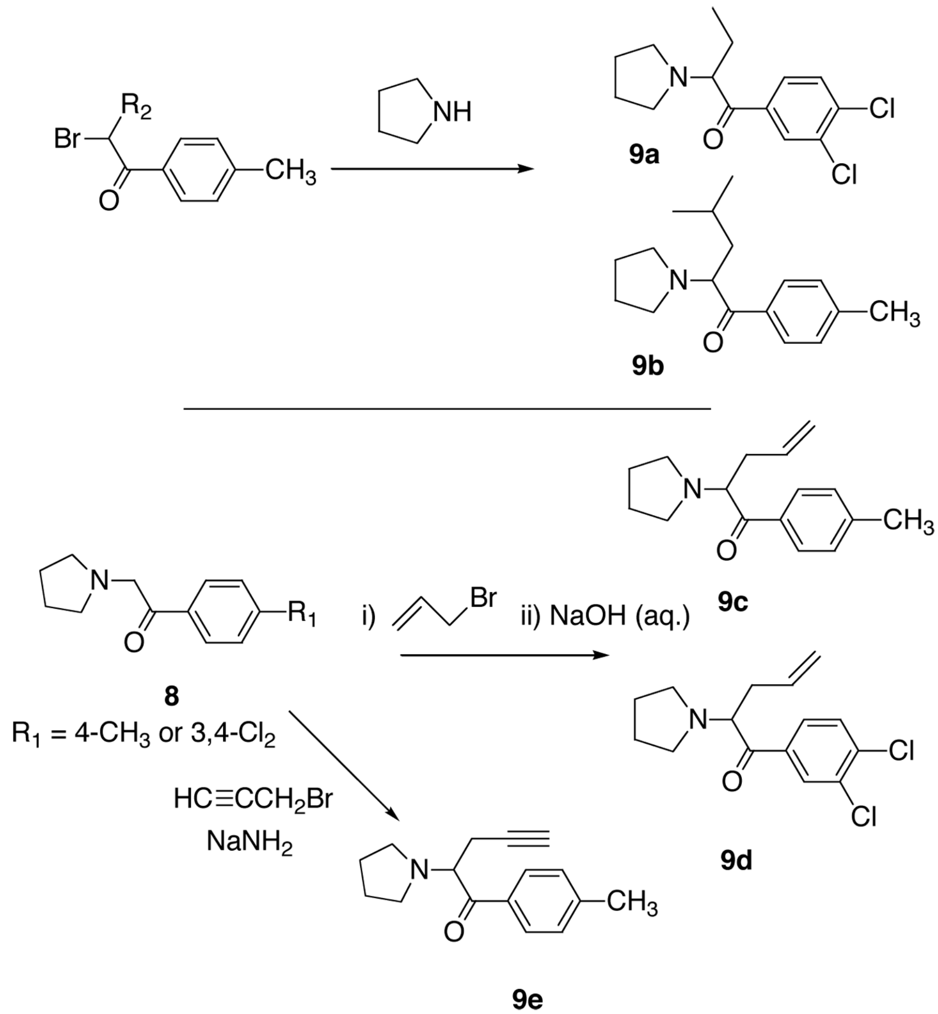


a R = CH_3 **b** R = 3,4-Cl_2

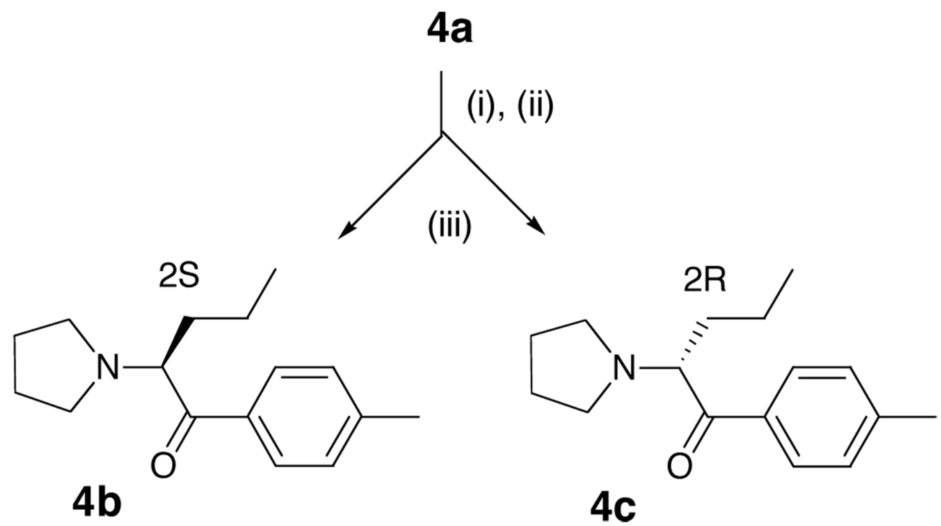
Scheme 2.

Synthesis of Analogs **6, 7**, **9f** and **9g**a

[a]Reagents and conditions: (i) $AlCl_3$,Br_2; (ii) Li_2CO_3, LiBr, DMF; (iii) pyrrolidine HCl, $(HCHO)_n$; (iv) pyrrolidine; (v) *n*-$BuNH_2$; (vi) piperidine



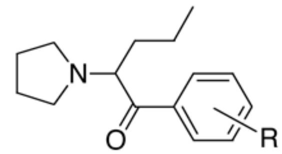
Scheme 3.
Synthesis of Compounds **9a–e**



Scheme 4.
Resolution of 1-(4-methylphenyl)-2-pyrrolidin-1-yl-pentan-1-one, **4a**a
[a]Reagents: (i) Dibenzoyl-D (or L)-tartaric acid, EtOH; (ii) Recrystallization (CH_2Cl_2/hexanes); (iii) Na_2CO_3. Et_2O

Table 1

The affinity of **4** ([^{125}I]RTI 55) and its inhibition of uptake of [^{3}H]dopamine, [^{3}H]serotonin, and [^{3}H]norepinephrine by HEK-hDAT, HEK-hSERT and HEK-hNET cells[a]



4

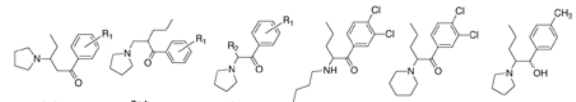
Cpd 4		R	DAT K_i (nM)	DA Uptake (IC_{50})	DR[b]	SERT K_i (nM)	SER Uptake (IC_{50})	NET K_i (nM)	NE Uptake (IC_{50})
		Cocaine	432 ± 29	461 ± 46	1.06	358 ± 24	494 ± 51	2150 ± 190	378 ± 48
a	O-2371	4-CH_3 (*R/S*)	21.4 ± 4.6	52.0 ± 20	2.43	3770 ± 560	2780 ± 590	195 ± 26	28.3 ± 8.1
b	O-2442	4-CH_3 (*S*)	18.1 ± 3.0	16.3 ± 2.3	0.91	2220 ± 550	1070 ± 230	109 ± 45	11.3 ± 2.4
c	O-2440	4-CH_3 (*R*)	1330 ± 300	1790 ± 320	1.35	>10μM		>10μM	
d	O-2387	H	33.7 ± 5.4	52.3 ± 6.2	1.55	>10μM		199 ± 45	56.0 ± 13
e	O-2370	4-F	82.0 ± 25	185 ± 62	2.26	>10μM		830±140	171 ± 35
f	O-2419	4-Br	51.0 ± 6.7	39.5 ± 7.5	0.77	830 ± 190	1050 ± 90	386 ± 53	83.0 ± 30
g	O-2493	4-I	81.4 ± 9.2	32.0 ± 11	0.39	301 ± 26	197 ± 35	310 ± 34	46.5 ± 8.4
h	O-2495	3-I	109 ± 32	52.0 ± 16	0.48	1400 ± 120	1070 ± 170	670 ± 130	81.0 ± 20
i	O-2575	4-CN	5900 ± 1100	1000 ± 170	0.17	>10μM		>10μM	
j	O-2577	4-CH_2OH	48.7 ± 2.2	44.3 ± 8.4	0.91	>10μM		150 ± 23	12.4 ± 2.8
k	O-2418	4-OH	125 ± 23	49.7 ± 3.4	0.40	>10μM		1290 ± 480	86.7 ± 7.5
l	O-2443	4-NO_2	266 ± 32	1110 ± 340	4.17	2460 ± 290	1110 ± 450	2690 ± 530	531 ± 67
m	O-2417	4-OCH_3	329 ± 33	283 ± 66	0.86	4080 ± 410	2430 ± 720	2600 ± 1000	235 ± 8.7
n	O-2558	4-CO_2CH_3	360 ± 140	154 ± 50	0.43	3950 ± 690	2350 ± 560	1140 ± 320	22.8 ± 3.3
o	O-2439	4-$NHCOCH_3$	30.2 ± 2.0	67.9 ± 8.4	2.25	>10μM		4000 ± 1100	317 ± 64
p	O-2481	4-CF_3	>10μM			959 ± 92	1030 ± 340	>10μM	
q	O-2537	4-C≡CCH_3	61.0 ± 16	11.8 ± 2.8	0.19	6700 ± 1100	3300 ± 1100	69.8 ± 5.4	19.3 ± 4.1
r	O-2479	2-CH_3	59.7 ± 9.0	63.0 ± 19	1.06	3720 ± 520	2020 ± 670	425 ± 63	19.7 ± 3.3
s	O-2480	3-CH_3	51.0 ± 14	62.9 ± 6.9	1.23	5900 ± 1600	4400 ± 1100	216 ± 38	9.4 ± 0.8
t	O-2482	Naphthyl	20.1 ± 7.1	40.0 ± 13	1.99	33.1 ± 1.1	46.0 ± 5.5	136 ± 27	11.7 ± 0.9
u	O-2390	3,4-Cl_2	11.5 ± 1.4	43.0 ± 20	3.91	199 ± 50	600 ± 63	37.8 ± 3.2	21.0 ± 0.6
v	O-2574	3,4-$(OH)_2$	84.0 ± 12	42.0 ± 11	0.50	>10μM		219 ± 71	7.6 ± 2.9
w	O-2512	3,4-$(OCH_3)_2$	>10μM			7460 ± 770	1540 ± 220	>10μM	
x	O-2441	4-Furan	105 ± 17	122 ± 18	1.16	3330 ± 1200	2180 ± 440	95 ± 20	93 ± 38
y	O-2438	4-Thiophene	460 ± 120	539 ± 69	1.17	3320 ± 280	1960 ± 720	370 ± 160	263 ± 94
z	O-2446	4-Mepyrrole	3850 ± 330	5400 ± 1600	1.40	>10μM		>10μM	

[a]Numbers represent the means ± SEM from at least three independent experiments, each conducted with duplicate (for binding assays) or triplicate (for uptake assays) determinations. When the K_i or the IC_{50} for the test compound is greater than 10 μM, only two experiments were conducted and no standard error was reported. Data from Oregon Health & Science University and VA Medical Center, Portland, OR.

[b]DR = Discrimination Ratio

Table 2

The affinity of **6, 7** and **9** ([^{125}I]RTI 55) and their inhibition of uptake of [^{3}H]dopamine, [^{3}H]serotonin, and [^{3}H]norepinephrine by HEK-hDAT, HEK-hSERT and HEK-hNET cells[a]



Cpd		R_1	R_2	DAT K_i(nM)	DA Uptake (IC_{50})	SERT K_i(nM)	SER Uptake (IC_{50})	NET K_i(nM)	NE Uptake (IC_{50})
6a	O-2525	4-CH_3		>10μM		>10μM		>10μM	
6a	O-2524	3,4-Cl_2		8440 ± 310	>10μM	3900 ± 1000	1780 ± 220	>10μM	
7a	O-2477	4-CH_3		>10μM		4100 ± 1800	4800 ± 1200	>10μM	
7a	O-2478	3,4-Cl_2		1530 ± 520	2900 ± 1300	630 ± 110	710 ± 170	>10μM	
9a	O-2384	3,4-Cl_2	CH_2CH_3	28.8 ± 2.1	55.0 ± 12	810 ± 150	441 ± 12	262 ± 36	18.5 ± 8.0
9b	O-2494	4-CH_3	$CH_2CH(CH_3)_2$	13.7 ± 3.0	5.9 ± 2.3	2870 ± 10	2040 ± 150	259 ± 80	18.0 ± 5.0
9c	O-2556	4-CH_3	$CH_2CH{=}CH_2$	90.5 ± 3.1	55 ± 17	>10μM		1400 ± 370	88.0 ± 16
9d	O-2557	3,4-Cl_2	$CH_2CH{=}CH_2$	39.9 ± 5.5	18.3 ± 3.7	1060 ± 170	440 ± 170	509 ± 100	24.9 ± 8.2
9e	O-2576	4-CH_3	$CH_2C{\equiv}CH$	2310 ± 110	231 ± 25	>10μM		4100 ± 1300	350 ± 120
9f	O-2389			520 ± 110	1190 ± 58	5080 ± 60	>10,000	4200 ± 1200	2520 ± 190
9g	O-2388			144 ± 48	666 ± 89	2460 ± 260	>10,000	2350 ± 230	800 ± 200
9h[b]	O-2529-1			>10μM		>10μM		>10μM	
9j[b]	O-2529-2			>10μM		>10μM		>10μM	

[a]Numbers represent the means ± SEM from at least three independent experiments, each conducted with duplicate (for binding assays) or triplicate (for uptake assays) determinations. When the $K_i$or the IC_{50} for the test compound is greater than 10 μM, only two experiments were conducted and no standard error was reported. Data from Oregon Health & Science University and VA Medical Center, Portland, OR.

[b]Compounds **9h** and **9j** are pure diastereomers

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