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Synthesis, inhibition and binding of simple non-nitrogen inhibitors of monoamine transporters

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Abstract—A series of simple truncated analogues of phenyl tropanes, 2-arylcycloalk-1-enyl carboxylic acid methylesters, were prepared and investigated for their activity towards the dopamine, serotonin and norepinephrine transporters. The compounds were prepared from cyclic ketoesters, which were converted to enolic triflates and reacted with arylboronates using the Suzuki coupling. For comparison the corresponding piperidines were also made and investigated. The new compounds inhibit monoamine-transporters with K_i values ranging from 0.1 to 1000 μM.

1. Introduction

The three classical monoamine neurotransmitters dopamine (DA), serotonin (5-HT) and norepinephrine (NE) control a variety of functions such as appetite, sleep, mood and locomotor activity in the central nervous system. NE is also the major neurotransmitter in the postganglionic synapses in the sympathetic nervous system. The transporters for these three neurotransmitters, the dopamine, serotonin and norepinephrine transporters (DAT, SERT and NET, respectively) have an important role in terminating the signals from neurons releasing these neurotransmitters, and also serve as targets for antidepressants and several addictive drugs.

In the early 1990s the genes coding for the three transporters were cloned, which led to a significant increase in our knowledge about the precise location of these transporters (e.g., in situ hybridisation)[1] and the role of these transporters in addiction by the construction of knockout mice.[2]

Later, PET (Positron Emission Tomography) studies with DAT, SERT or NET selective PET ligands were used to examine the activities of these transporters in vivo in various physiologic and pathologic conditions such as psychiatric diseases and addiction.[3]

Cocaine is a psychomotor stimulant, abuse of which is a growing problem in the western world. Cocaine exerts its effect by acting as an inhibitor of the monoamine transporters, thereby increasing the concentration of the monoamines in their respective synapses. It is mainly the inhibition of DAT in the mesolimbic dopamine system that is thought to be responsible for cocaine's stimulating and addictive properties,[4] although SERT inhibition probably also plays a role in the addictive properties. The mesolimbic dopamine system is comprised of dopamine neurons that have their cell bodies in the ventral tegmental area (VTA) of the midbrain and these neurons projections to the limbic forebrain. Especially the projection to the nucleus accumbens (NAc) in the limbic forebrain is thought to be important. The VTA-NAc is a key detector of rewarding stimulus, and it is generally thought that NAc is the key target for all substances of abuse, resulting in a change in the biochemistry of the reward circuits.[5] The importance of DAT in the rewarding effect of cocaine has been confirmed in many experiments.[6]

Despite extensive research no pharmacologic treatment for cocaine abuse currently exists. Several strategies interfering with the dopamine system are currently under investigation.[7] One interesting strategy is the use

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of a partial cocaine agonist: compounds that bind to DAT and inhibit the uptake of dopamine, though less effective than cocaine. Such a compound should have a significantly better binding affinity for DAT than cocaine, and ideally have long duration of action and a slow absorption to the brain. To select such a compound the discrimination ratio[8] (DR) has been defined as the compounds' K_i for inhibition of dopamine uptake, divided by the corresponding K_i for DAT binding. Although the validity of the DR has been questioned[9], and some compounds with DR values more than 10 have shown in vivo pharmacological activity very similar to that of cocaine,[10,11] a DR above 10 is still a useful criterion for selecting a cocaine antagonist or partial agonist.

PET studies have shown that the level of the monoamine transporters in many psychiatric and neurological conditions such as Parkinson disease, depression and Attention-Deficit Hyperactivity Disorder (ADHD) is altered.[12] Polymorphisms in the genes coding for monoamine transporters are thought to be associated with increased vulnerability to diseases such as depression and ADHD.[13]

Because of the variety of roles the monoamine transporters play in neurophysiology, many different classes of inhibitors have been developed.[14] One potent class of inhibitors is the phenyl tropanes such as RTI-55[15] and WIN 35065-2[16] (Fig. 1). These compounds, structurally based on cocaine, show an improved binding to the monoamine transporters compared to cocaine and display a varied selectivity for DAT.[13] A great number of compounds have been synthesized based on the phenyl tropanes. Most of this research has focused on variation on either the nitrogen substituent, the ester group or on substituents on the phenyl ring. These studies have resulted in compounds with a high affinity and high selectivity for each of the individual transporters.

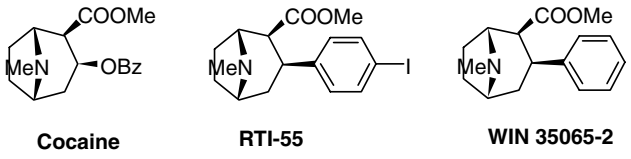


Figure 1. Cocaine and phenyltropanes.

Meltzer et al. have shown that the basic nitrogen in the tropane skeleton is not essential for binding. Oxa and carba analogues **1b** and **1c** (Fig. 2) were only four and eight-fold less potent than **1a** for binding to DAT.[17–19] They also found that the unsaturated analogues **2a–c** had similar potency as **1a–c** on DAT.[17–19] Kozikowski et al. have shown that the bicyclic system of the tropane ring is not essential for binding. In one study they tested compounds without the C6–C7 bridge, giving the monocyclic piperidine analogue **3a**,[20] these compounds were only slightly less potent than their tropane analogues. Meltzer et al. have even shown that very simple biaryls such as **4** (Fig. 2), which have no nitrogen and a monocyclic core, bind to DAT and SERT from brain tissues of cynomolgus monkey.[18] They found this compound to have an IC_{50} value for DAT binding that was 1.5 times higher than that of cocaine, which is surprisingly potent.

These findings led us to speculate as to the significance of the bicyclic system and the significance of the nitrogen atom. We therefore decided to investigate a series of simplified analogues **6**, **7** and **8** (Fig. 2 and Table 1) that more resemble tropane or piperidines than **4**, but nevertheless do not have the bicyclic system or the nitrogen. Compound **7** is a carba analogue of the piperidine **3** (with an additional unsaturation), while **8** can be seen as an analogue of the phenyl tropane **2a** with the nitrogen bridge deleted. We have also prepared piperidine analogues to **3** and unsaturated piperidines such as **5d** (Table 1), to see the effect of unsaturation and to gauge the behaviour of these compounds in our assays. This is likely to have only a marginal effect because studies have shown this substitution does not affect binding in the tropane family.[14a] Previous experience has shown us that we often obtain higher K_i values than that obtained in work with brain homogenates.[21]

In the present work, we report the synthesis of these three types of very simplified phenyl tropane analogues and their binding and inhibition on DAT, SERT and

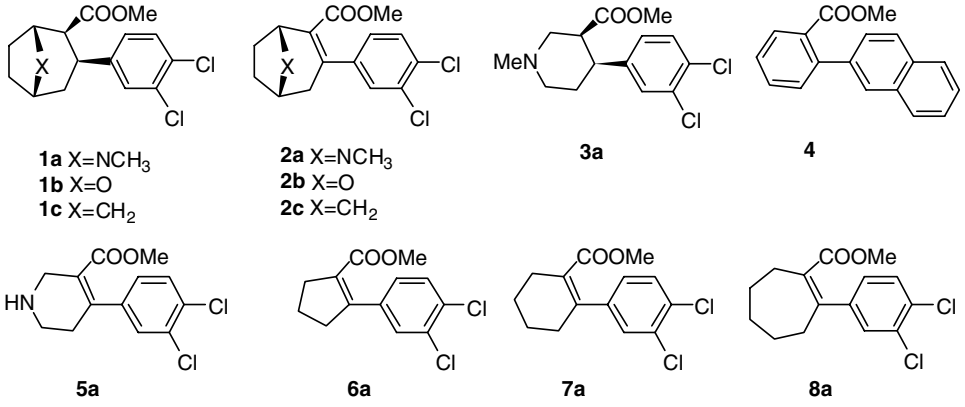


Figure 2. Analogues of phenyltropanes and target compounds.

Table 1. Binding of piperidine derivatives **3**, **5**, **10** to monoamine transporters[a]

	Binding[^{125}I]RTI-55 K_i (μM)		
	DAT	SERT	NET
Cocaine	0.630 ± 0.125	0.965 ± 0.138	0.887 ± 0.162
RTI-55	0.004 ± 0.001	0.006 ± 0.003	0.034 ± 0.020
3a	0.322 ± 0.021	1.85 ± 0.08	3.91 ± 0.54
ent-**3a**	59.4 ± 1.9	13.8 ± 0.7	41.6 ± 14.7
(±)-**3b**	8.51 ± 0.33	27.0 ± 1.0	35.2 ± 5.0
(±)-**10b**	17.4 ± 1.1	46.7 ± 3.2	36.3 ± 5.2
(±)-**3c**	0.323 ± 0.194	0.287 ± 0.202	0.855 ± 0.793
(±)-**10c**	1.25 ± 0.681	2.81 ± 0.21	2.3 ± 1.94
5d	0.079 ± 0.017	0.440 ± 0.155	0.268 ± 0.096
5a[b]	0.922	0.217	2.5
5q	20.6 ± 4.2	3.00 ± 0.94	10.0 ± 2.2

ent-**3a** is the enantiomer of **3a**.

[a] Values are expressed as means ± SEM from at least three independent experiments each conducted with duplicate determinations.

[b] The value is the result of a single experiment conducted with duplicate determinations.

NET. Although these compounds only bind with moderate potency to the transporters, the manner in which they bind is probably similar to cocaine.

2. Chemistry

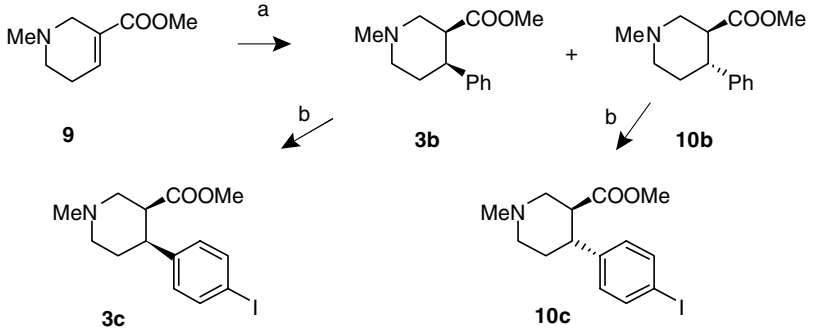
As control compounds for our assay we prepared Kozikowsky's saturated piperidines **3a** and *ent*-**3a** according to published methods.[20] We also made the racemic phenyl analogues **3b** and **10b** using this method (Scheme 1): Arecholine was reacted with phenylmagnesium bromide at −10 °C giving after separation 20% *cis*-isomer **3b** and 12% *trans*-isomer **10b**. These compounds were iodinated with iodine and silver triflate giving 58% and 44%, respectively, of the *para*-iodinated compounds **3c** and **10c** of which **3c** is a monocyclic analogue of RTI-55.

We then synthesized α,β-unsaturated analogues of Kozikowski's piperidine **3** (Scheme 2). The Boc protected piperidone **11**[22] was converted to the triflate **12** using triflic anhydride/NaH,[23] this triflate was used in a Suzuki reaction to give **13a,d,q**. Deprotection of **13a,d,q** with trifluoroacetic acid gave the products **5a,d,q**. As seen from Scheme 1 these compounds were synthesized as the ethyl esters (unlike most of the compounds in this study which were methyl esters), but this is likely to have only a marginal effect, because studies have shown that this substitution does not affect binding in the tropane family.[24]

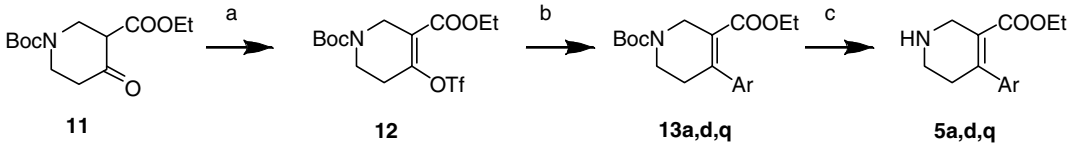
Synthesis of the carba-analogues **6**–**8** is outlined in Scheme 3. This synthesis follows the same steps as the synthesis of **5a**–**q**. The commercially available ketoesters **14**–**16** were converted to the enoltriflates **17**–**19** using triflic anhydride/NaH. This gave the triflates in 95–99% yield.[25,26] The triflates were used in a Suzuki coupling with various aryl boronic acids, using $Pd(OAc)_2$ as the palladium source and triphenylphosphine as the ligand, to give the compounds **6**–**8**. For comparison compound **4** was prepared by published methods.[19]

Some of the coupling products were hydrogenated giving the saturated derivatives **21**–**22** (Scheme 4), that are comparable to **3b**. Attempts to saturate some of the chlorinated compounds failed because dehalogenation competed with hydrogenation of the double bond.

It is known that the presence of an *n*-propyl group in the 2-position instead of the normal methylester group can increase the DAT binding 25-fold for the piperidine

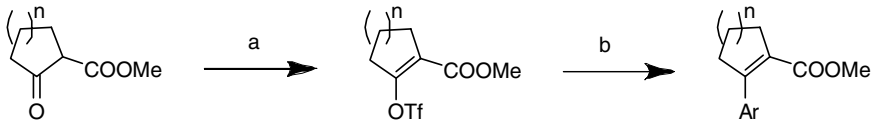


Scheme 1. Synthesis of saturated piperidines. Reagents and conditions: (a) PhMgBr, −10 °C; (b) I_2, $Ag(OTf)_2$, 25 °C.



a: Ar = 3,4-di-chlorophenyl, **d:** Ar = 2-naphthyl, **q:** Ar = 3-nitro-phenyl

Scheme 2. Synthesis of α,β-unsaturated piperidines. Reagents and conditions: (a) NaH, Tf_2O, Et_2O, 0 °C; (b) $ArB(OH)_2$, $Pd(OAc)_2$, PPh_3, Na_2CO_3, EtOH/Benzene, 65 °C; (c) TFA, DCM.

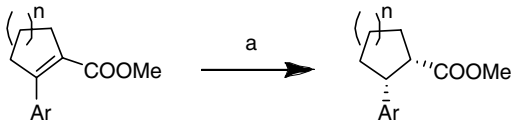


14: n=1
15: n=2
16: n=3

17: n=1
18: n=2
19: n=3

6: n=1
7: n=2
8: n=3

Scheme 3. Synthesis of α,β-unsaturated β-arylesters. Reagents and conditions: (a) NaH, Tf_2O, Et_2O, 0 °C; (b) ArB(OH)2, $Pd(OAc)_2$, PPh_3, Na_2CO_3, EtOH/benzene, 65 °C.



7: n=2
8: n=3

21: n=2
22: n=3

Scheme 4. Preparation of saturated β-arylester. Reagents: (a) Pd/C, H_2, EtOH.

analogues **3**,[20] a trend not observed in the phenyl tropanes[27]. To test this modification of our compounds, **25** was synthesized (Scheme 3) as a mixture of *cis* and *trans* isomers (1:1). First the ester group in **7a** was reduced with $LiAlH_4$. The resulting primary alcohol **23** was converted to the aldehyde **24** by a Swern oxidation, and **24** was finally converted to **25** by a Wittig reaction. We chose not to reduce the double bond on the propyl side chain, because of the risk of dehalogenation, so **25** was a 1:1 mixture of *cis* and *trans* isomers (Scheme 5).

3. Biology

3.1. Cell culture

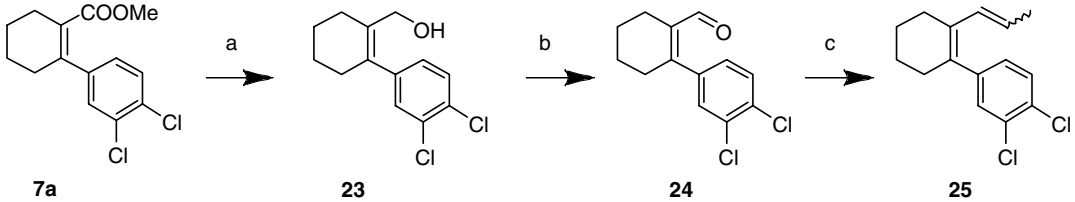
Cell lines stably expressing hSERT, hDAT or hNET were established by transfecting COS-1 cells with hSERT/hDAT/hNET inserted in the pIRES vector (BD Biosciences Clontech) also carrying a Blasticidin resistance gene. Cells were cultured in DMEM (BioWhitaker) supplemented with 10% FCS (Gibco Life Technologies), 1% Penicillin/Streptomycin (BioWhitaker) and 10 μg/mL of Blasticidin (Cayla) selection of transfected cells. After 14 days of selection Blasticidin was adjusted to 2 μg/mL in the culture medium and cells were subcultured under this selection regime and grown at 37 °C, 5% CO_2, 95% humidity.

3.2. Uptake assay

For the uptake assay stably transfected cells were seeded in 96 well microplates (Nunc) and grown at 37 °C, 5% CO_2, 95% humidity for two days. Prior to the IC_{50} assay the medium was aspired and the cells were washed in PBSCM (137 mM NaCl, 2.7 mM KCl, 4.3 mM Na_2HPO_4, 1.4 mM KH_2PO_4, 0.1 mM $CaCl_2$ and 1 mM $MgCl_2$,, pH 7.4) on an automatic microplate washer. The dilution series of the drug in PBSCM were added to the adhering cells for 30 min of preincubation to allow equilibration of binding before the uptake was initiated by the addition of 30–100 nM tritiated 5-HT (Perkin–Elmer Life Sciences) or DA (Amersham Biscience) mixed with the dilution series of the drug. Accumulation of 5-HT or DA was allowed to proceed for 10 min at 20 °C and the assay was terminated by aspiration of the uptake media and washing with PBSCM. Scintillant (MicroScint 20 from Packard) was used to solubilize cells and accumulated radioactivity was quantified on a Packard Topcounter. Concentration of substrate was quantified by liquid scintillation counting on a Packard Tri-Carb.

3.3. Binding assay

Membrane preparations for the binding assay were produced by scraping the stably transfected cells from cell culture dishes (Nunc), pelleting the cells in ice-cold PBSCM by centrifugation and homogenising the cells in ice cold Harvest Buffer I (150 mM NaCl, 50 mM Tris, 20 mM EDTA) using a Ultra-Turrax (Janke & Kunkel AG) for 60 s. Membrane was pelleted by centrifugation at 12,000*g* for 10 min at 4 °C and washed in ice-cold Harvest Buffer I. The membranes were pelleted again and finally resuspended in PBSCM using the Ultraturrax briefly. Membrane preparations were aliquoted into 2 mL portions and stored at −80 °C until use. The concentration of total protein in the membrane preparation was determined with the MicroBCA kit (Pierce).



7a **23** **24** **25**

Scheme 5. Synthesis of **25**. Reagents and conditions: (a) $LiAlH_4$, ether, reflux; (b) DMSO, oxalylchloride, NEt_3, −78 °C; (c) $EtPPh_3Br$, BuLi, 0 °C.

A concentration of 5 μg/well of membrane preparation was used with the nominated concentration of drug of interest in combination with 0.1–0.25 nM ^{125}I-RTI-55. Membrane and ligands were incubated for 1 h at 20 °C. Using a Filtermate cellharvester (Packard) membranes were captured on GF/B 96-well filterplates (Packard) presoaked with 0.5% polyethyleneimine (Merck) and washed twice with ice cold water. The filter in each well was dissolved in 40 μL Microscint 20 and scintillationcounts were determined with a Packard Topcounter. Precise concentration of radioligand was quantified by liquid scintillation counting on a Packard Tri-Carb.

3.4. Data analysis

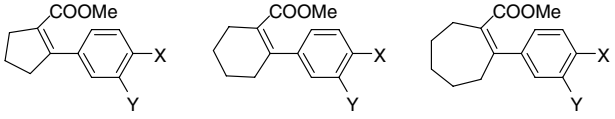
Counts from the Packard Topcounter were fitted to a sigmoidal dose–response curve using the built-in non-linear regression tool in the Graphpad Prism 3 software. From at least three independent experiments the resulting IC_{50} values were transformed to K_i values using the equation described by Cheng and Prusoff.[28]

4. Results and discussion

The new compounds and the controls **3a**, *ent*-**3a**, **4** were screened for inhibition of RTI-55 binding, and in some cases inhibition of uptake, on hDAT, hNET and hSERT. The results of this are shown in Table 1 (piperidines), Table 2 (unsaturated compounds) and Table 3 (saturated compounds).

First it is noted that the K_i values for hDAT of **3a** and *ent*-**3a** are over 10 times higher than the IC_{50} values reported for binding to rat striatal membrane, which

Table 2. Binding and uptake of the non-nitrogen containing compounds **6**–**8** to monoamine transporters[a]



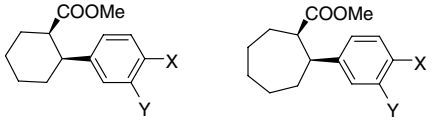
	X	Y	Binding[^{125}I]RTI-55 K_i (μM)			Uptake K_i (μM)		
			DAT	SERT	NET	[^{3}H]DA	[^{3}H]SER	[^{3}H]DA (NET)
Co-caine			0.630 ± 0.125	0.965 ± 0.138	0.887 ± 0.162	0.347 ± 0.150	0.524 ± 0.223	0.182 ± 0.058
RTI-55			0.004 ± 0.001	0.006 ± 0.003	0.034 ± 0.020	0.009 ± 0.006	0.004 ± 0.003	0.010 ± 0.008
4[b]			4.06	620	46.7	—	—	—
6a	Cl	Cl	1.9 ± 0.3	785 ± 268	11 ± 11	5.5 ± 0.4	—	28 ± 5
6b	Cl	H	18 ± 9	2840 ± 912	420 ± 28	2.1 ± 0.8	—	178 ± 70
6c	H	Cl	34 ± 8	2240 ± 443	470 ± 215	3.3 ± 1.2	—	285 ± 138
6d	–(CH)$_4$–		4.1 ± 0.4	417 ± 188	39 ± 52	7.0 ± 0.7	—	26 ± 4
6f	OMe	H	140 ± 52	2690 ± 920	550 ± 57	6.3 ± 3.9	—	1390 ± 45
6g	*t*-Bu	H	302 ± 87	1460 ± 380	789 ± 122	—	—	—
6h	OCF_3	H	2649 ± 765	3800 ± 175	2884 ± 749	—	—	—
6i	SO_2Me	H	—	3388 ± 315	—	—	—	—
6j	COMe	H	335 ± 33	296 ± 62	240 ± 30	49 ± 17	1161 ± 40	646 ± 99
6k	H	NH_2	875 ± 96	1950 ± 197	1318 ± 211	121 ± 29	2904 ± 826	247 ± 32
6p	NO_2	H	6.54± 7.72	1141 ± 400	111 ± 45	—	—	—
7a	Cl	Cl	2.1 ± 0.3	228 ± 34	14 ± 5	0.625 ± 0.245	—	4.9 ± 28
7b	Cl	H	85 ± 23	1860 ± 858	993 ± 278	0.589 ± 0.021	—	314 ± 82
7c	H	Cl	22 ± 5	1180 ± 629	339 ± 146	26 ± 7	—	871 ± 524
7d	–(CH=CH)$_2$–		12 ± 0.7	109 ± 29	81 ± 19	1.5 ± 0.8	—	10 ± 7
7e	Ph	H	264 ± 151	841 ± 304	215 ± 78	—	—	—
7g	*t*-Bu	H	605 ± 272	2250 ± 1320	1100 ± 759	—	—	—
7h	OCF_3	H	1660 ± 270	4680 ± 702	2540 ± 451	—	—	—
7l	H	H	630 ± 186	668 ± 177	2500 ± 422	—	—	—
7m	H	CF_3	1050 ± 136	5020 ± 586	2110 ± 270	—	—	—
7n	CF_3	H	590 ± 114	4710 ± 657	2020 ± 346	—	—	—
7o	OH	H	231 ± 42	573 ± 49	675 ± 144	—	—	499 ± 3
7q	H	NO_2	239 ± 30	28.7 ± 10.9	121 ± 27	—	—	—
8a	Cl	Cl	1.36 ± 0.33	149 ± 35	15 ± 3.7	0.515 ± 0.246	—	4.72 ± 2.21
8b	Cl	H	15 ± 1.7	706 ± 59	84 ± 24	2.2 ± 1.0	—	20 ± 11
8c	H	Cl	22 ± 5	463 ± 89	85 ± 23	3.78 ± 1.41	—	—
8d	–(CH=CH)$_2$–		392 ± 57	532 ± 48	68 ± 0.2	—	—	—
8e	Ph	H	2.0 ± 0.1	32 ± 3	13 ± 1.3	0.81 ± 0.35	—	3.9 ± 2.3
8g	*t*-Bu	H	884 ± 140	1040 ± 69	62 ± 12	—	—	—
25			11 ± 5	381 ± 85	255 ± 137	42 ± 70	—	—

—, Not determined.

[a] Values are expressed as mean ± SEM from at least three independent experiments each conducted with duplicate determinations.

[b] The value is the result of two independent experiments each conducted with duplicate determinations.

Table 3. Binding and uptake of the saturated compounds **21**–**22** to monoamine transporters



21 **22**

	Structure		Binding[^{125}I]RTI-55 K_i (μM)		
	X	**Y**	DAT	SERT	NET
21e	Ph	H	830 ± 813	390 ± 78	658 ± 76
21g	*t*-Bu	H	766 ± 483	9120 ± 1670	675 ± 356
21h	OCF_3	H	1180 ± 297	605 ± 168	719 ± 317
21l	H	H	975 ± 323	1510 ± 670	1360 ± 108
21m	H	CF_3	569 ± 140	1910 ± 399	991 ± 361
21n	CF_3	H	222 ± 58	185 ± 40	439 ± 175
22e	Ph	H	313 ± 103	73 ± 21	51 ± 19
22g	*t*-Bu	H	1140 ± 30	1800 ± 320	94 ± 33

Values are expressed as mean ± SEM from at least three independent experiments each conducted with duplicate determinations.

were 0.024 μM and 1.4 μM, respectively.[20] This somewhat confirms our observation that many compounds (but not all) frequently are less potent in the hDAT assay.[21] Cocaine and RTI-55 are also 5–6 times less potent in this study than values obtained with brain homogenates,[20,14] suggesting that the relative values of the different inhibitors remained constant. The unsubstituted phenyl piperidines **3b** and **10b** give values in the low micromolar range which is 25 times higher than the 4-chlorophenyl derivative. The new iodophenylpiperidines **3c** and **10c** bind to the DAT with a potency equal to **3a**, but **3c** is about 40 times weaker (bearing in mind that **3c** is racemic) than the tropane equivalent RTI-55. Thus, our finding is that the piperidines are significantly weaker than the tropanes. The difference in binding between *cis* and *trans* isomers (**3b** versus **10b**, **3c** versus **10c**) is comparatively small (2–10-fold) reflecting the greater flexibility of these small molecules relative to the phenyl tropanes.

The unsaturated piperidines (**5a,d,q**) were found to have roughly a similar potency to the monoamine transporters as saturated piperidines (Table 1). Though the study did not include identical aromatic groups we can nevertheless compare compounds with strong-binding aromatic groups such as the saturated piperidine with iodophenyl **3c** and the unsaturated dichlorophenyl and naphthyl piperidines **5a** and **5d**. These compounds bind to DAT with K_i values varying with less than 1 order of magnitude, which reveals that the double bond in the 2-position does not influence activity much. Modifications in the aromatic moiety are obviously much more crucial than introduction of this double bond, since unsaturated 3-nitrophenyl piperidine **5q** is 50–300 times weaker than **5d** and **5a**.

The importance of the nitrogen in the monocyclic compounds in binding and uptake to the monoamine transporters is addressed in the data for **6**–**8** (Table 2a and b). The cyclohexenes **7** are direct analogues of **5** without the nitrogen. Comparing **7a**, **7d** and **7q** with the corresponding piperidines **5a**, **5d** and **5q**, we see that the unsaturated piperidines bind with 20–30 times better potency to the monoamine transporters than the cyclohexene analogues, showing that the nitrogen has a larger effect on these monocyclic compounds than seen on the tropane analogues.

Another interesting comparison is to compare **6**–**8** with Meltzers 2-arylbenzoates since this reflects the influence of saturation/unsaturation in the ring system. At first sight compounds **6**–**8** appear weaker since a value of 150 nM has been reported for **4** on DAT binding, when assayed on rat homogenates, and we obtained 4 and 12 μM for **6d** and **7d**. However, the necessity to compare with data obtained under identical condition was once more evident when we find that compound **4** in our assay had a K_i for DAT binding of 4.06 μM (Table 2b). This value is close to what we find for **6d** and **7d** meaning that there is little difference between a partially saturated or aromatic ring in the binding to the DAT.

Confirming this is the observation that the change in ring-size between 5-, 6- and 7-membered ring appears unimportant. In general, the three series of compounds **6**–**8** display largely similar activity profiles, when substituents are kept constant, with just a few exceptions.

It is a general characteristic about the carba analogues **6**–**8** that the SERT binding is poor, so that the loss of the nitrogen has introduced a degree of DAT and NET selectivity. Compound **4** resembles **6**–**8** in this respect.

Another characteristic for the compounds **6**–**8** is that the aromatic substituent is extremely important for binding and that 3,4-dichloro (**6a**, **7a** and **8a**) is 10–50-fold more potent towards DAT than 3- or 4-chloro (**6b**, **6c**, **7b**, **7c**, **8b** and **8c**), which is 10–50-fold better than the unsubstituted phenyl **7l**. This general trend is more drastic than is observed in the phenyl tropanes:[14a] in those compounds halogenation of the phenyl group is also advantageous, but introduction of one chlorine only increases DAT binding 20-fold, and the 3,4-dichloro is only slightly more active than the 4-chloro. This indicates

that the binding mode of the aromatic group is not identical in the two series of compounds.

Many different phenyl substituents were investigated and some specific details can be noted: a trifluoromethyl group is in general considered as a bioisostere of a chlorine atom, the two compounds with a trifluoromethyl group on the aromatic ring, **7m** and **7n**, bind worse than their chlorine analogues **7b** and **7c**. The same effect has however been observed in phenyltropanes, where the 4-CF_3 substituted derivative was 10-fold less potent than the 4-chlorine.[14a] It suggests that the function of chloride is related to its ability of electron donation through conjugation; the only quality the CF_3 group does not possess.

The compounds **6k** and **7o** were made in order to test the effect of having a hydroxyl or an amino group on the phenyl ring. An amino and hydroxyl group can function as a hydrogen bond donor/acceptor, but both compounds show a poor binding. This indicates that polar substituents on the phenyl are unfavourable.

The compounds **6f–j**, **7g–l** and **8g** were made in order to test some new substituents on the phenyl ring, all of these modifications resulted in poor binding with K_i values higher than 100 μM.

The effect of saturation of the double bond is still unclear because most of the compounds that were saturated have a weak binding in both their saturated and unsaturated state. The exception to this is the biphenyl **8e**. As can be seen from Table 3 the saturation of **8e–22e** (Scheme 1) decreases the K_i for binding to the DAT more than 150-fold, while the binding to SERT and NET was only decreased 2–4-fold. Although the binding of **8e** to the three transporters was decreased by saturation, the effect was largest for binding to DAT. Meltzer et al. have previously reported that for the phenyl tropanes and the oxa and carba analogues of these **1a–c**, the saturation of the double bond results in only a small decrease in DAT binding, but in a substantial improvement in SERT binding especially for the oxa analogues.

Many of the compounds show considerably higher potency for inhibition of dopamine uptake than binding on DAT. The most extreme compound **7b** shows around 150-fold lower K_i towards dopamine uptake inhibition than inhibition of RTI-55 binding. This should be compared to the almost equal K_i values for binding and uptake for cocaine and RTI-55. Compound **7b** seems in fact to be very selective for DAT uptake inhibition since it is much weaker towards SERT and NET. An explanation for this potency is that **7b** has multiple binding sites or modes on DAT. One of these binding sites is probably capable of inhibiting uptake, but RTI-55 only has low affinity (or no affinity at all) for this binding site, and can therefore not displace **7b** during the binding studies, giving the high K_i value.

Finally it is noted that compound **25** (Table 2b), where the ester group has been substituted with a propene chain, has a slightly decreased potency (DAT and SERT) compared to the parent compound **7a**.

In summary, this study confirms previous findings that very simple truncated versions of phenyl tropanes can inhibit monoamine transporters albeit with low to moderate potency. It was observed that a decrease of 40-fold in binding occurs when the bicyclic tropane-structure is transformed into a piperidine and another loss of 20–30-fold when the piperidine nitrogen is replaced with carbon. While these decreases appear drastic they are nevertheless much smaller than the loss observed when the aromatic group of a phenyltropane is replaced with alkyl.[29] The fact that the compounds share the ester and aromatic group with the phenyl tropanes implies the possibility of a similarity in the mode of binding. However, in these non-nitrogen containing compounds the importance of the substituents in the aromatic group is greatly enhanced, which suggests an altered or increased binding towards this group. The same phenomenon was observed by Meltzer for non-nitrogenous tropanes. We propose that the non-nitrogen containing compounds obtain compensation for the loss of binding to nitrogen by sliding into a position with a more tightly bound aromatic group. This implies that phenyltropanes do not have optimal binding to the aromatic group, and indeed this is supported by the observation that 3-phenethyltropane is a stronger DAT inhibitor than the 3-phenyltropane.[14a]

5. Experimental

5.1. General

5.1.1. Apparatus. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Gemini 2000 Spectrometer (400 and 100 MHz, respectively), using $CDCl_3$ as solvent and reference point (δ 7.26 ppm and δ 77.16 ppm, respectively). Mass spectra were recorded on a Micromass LC-TOF spectrometer. Melting points were measured on a Stuart Scientific Melting Point Apparatus SMP3 and are not corrected.

5.1.2. Solvents. DCM was dried by distillation over CaH_2. Et_2O was dried over sodium. Benzene was dried over molecular sieves (4 Å).

5.1.3. Chromatography. Flash column chromatography was performed with a Merck silica gel (230–400 mesh). TLC was performed on silica gel (Merck Kieselgel 60 F_{254}) and for visualization of the spots either UV light (254 nm), Ce-Mol solution ($Ce(SO_4)_2$ (10 g) and $(NH_4)_2MoO_4$ (15 g) dissolved in 10% H_2SO_4) or $KMnO_4$ dissolved in ethanol were used. After application of the solutions, the TLC-plates were heated to dryness.

5.1.4. Evaporation. Evaporation was done at reduced pressure at 40 °C.

5.1.5. Methyl 3,4-*cis*-*N*-methyl-4-phenylpiperidine-3-carboxylate (3b) and methyl 3,4-*trans*-*N*-methyl-4-phenylpiperidine-3-carboxylate (10b). A stirred solution of phenylmagnesium bromide (36 mL, 1.35 M in Et_2O) in

dry Et_2O (219 mL) was cooled to −10 °C. A solution of arecoline (**9**) (4.02 g, 25.9 mmol) in dry Et_2O (94 mL) was added dropwise and stirred at −10 °C for 11/2 h (followed by TLC). The mixture was then poured onto crushed ice and slowly treated with 10% HCl (62 mL). The aqueous phase was separated, washed with Et_2O (62 mL), then while cooling in an ice bath slowly treated with 50% Na_2CO_3 until pH 10–11, and then extracted with Et_2O (3 × 50 mL). The combined organic phases were washed with brine (62 mL), dried over $MgSO_4$ and concentrated in vacuo to give a crude mixture of (±)-**3b** and (±)-**10b**. Flash chromatography (diethyl ether–pentane; 3:1 with Et_3N in 1%) afforded the *cis*-isomer (±)-**3b** (1.19 g, 20%) as a white solid, and the *trans*-isomer (±)-**10b** (0.72 g, 12%) as colourless oil.

5.1.5.1. Compound (±)-3b. ^{1}H NMR ($CDCl_3$) δ: 7.27–7.09 (5H, m); 3.43 (3H, s); 3.11 (1H, br d, J = 11.2 Hz); 2.98–2.87 (2H, m); 2.80 (1H, dt, J_1 = 4.0 Hz, J_2 = 11.6 Hz); 2.61 (1H, dq, J_1 = 4.0 Hz, J_2 = 11.6 Hz); 2.31 (1H, dd, J_1 = 3.6 Hz, J_2 = 11.6 Hz); 2.22 (3H, s); 2.03 (1H, dt, J_1 = 2.8 Hz, J_2 = 11.2 Hz); 1.79–1.73 (1H, m).

^{13}C NMR ($CDCl_3$) δ: 172.4; 144.5; 128.2; 127.9; 126.4; 59.0; 56.2; 51.5; 47.0; 46.2; 42.3; 26.0.

5.1.5.2. Compound (±)-10b. ^{1}H NMR ($CDCl_3$) δ: 7.40–7.11 (5H, m); 3.35 (3H, s); 3.02 (1H, br d, J = 11.6 Hz); 2.96–2.82 (2H, m); 2.70 (1H, dt, J_1 = 3.6 Hz, J_2 = 11.2 Hz); 2.46 (1H, dq, J_1 = 4.0 Hz, J_2 = 11.6 Hz); 2.23 (1H, dd, J_1 = 3.6 Hz, J_2 = 12.0 Hz); 2.28 (3H, s), 2.12 (1H, dt, J_1 = 3.2 Hz, J_2 = 11.2 Hz); 1.82–1.74 (1H, m).

5.1.6. Methyl 3,4-*cis*-*N*-methyl-4-(4-iodophenyl)piperidine-3-carboxylate (3c). To a dry round-bottom flask were added (±)-**3b** (673 mg, 2.88 mmol), I_2 (1.48 g, 5.84 mmol), CF_3SO_3Ag (1.49 g, 5.79 mmol), 20 mL CH_2Cl_2 and 5 drops of CH_3CO_2H. The mixture was stirred in room temperature overnight in darkness, and then AgI was removed by filtration and washed with CH_2Cl_2 (4 × 3 mL). The combined organic phases were washed with diluted NH_4OH, 5% $Na_2S_2O_3$, and water, dried over Na_2SO_4 and concentrated in vacuo. Flash chromatography (diethyl ether–pentane; 2:1 with Et_3N in 0.4%) afforded the desired product (±)-**3c** (603 mg, 58%) as oil.

^{1}H NMR ($CDCl_3$) δ: 7.58 (2H, d, J = 8.0 Hz); 7.01 (2H, d, J = 8.4 Hz); 3.45 (3H, s); 3.25 (1H, br d, J = 11.2); 3.08–2.97 (2H, m); 2.89 (1H, dt, J_1 = 4.0 Hz, J_2 = 11.2 Hz); 2.58 (1H, dq, J_1 = 3.6 Hz, J_2 = 11.6 Hz); 2.30 (1H, dd, J_1 = 3.2 Hz, J_2 = 11.2 Hz); 2.23 (3H, s); 2.03 (1H, dt, J_1 = 2.8 Hz, J_2 = 11.2 Hz); 1.72 (1H, dd, J_1 = 2.8 Hz, J_2 = 12.4 Hz).

^{13}C NMR ($CDCl_3$) δ: 171.5; 142.0; 136.0; 128.3; 90.6; 57.5; 54.8; 50.8; 46.3; 45.1; 40.2; 25.1.

HR-MS(ES): Calcd for $C_{14}H_{18}NO_2 + H^+$: m/z 360.0461. Found: m/z 360.0452.

5.1.7. Methyl 3,4-*trans*-*N*-methyl-4-(4-iodophenyl)piperidine-3-carboxylate (10c). To a dry round-bottomed-flask were added (±)-**10b** (448 mg, 1.92 mmol), I_2 (977 mg, 3.85 mmol), CF_3SO_3Ag (988 mg, 3.85 mmol), 20 mL CH_2Cl_2 and 5 drops of CH_3CO_2H. The mixture was stirred at room temperature overnight in darkness, and then AgI was removed by filtration and washed with CH_2Cl_2 (4 × 3 mL). The combined organic phases were washed with diluted NH_4OH, a 5% $Na_2S_2O_3$ solution and water, dried over Na_2SO_4 and concentrated in vacuo. Flash chromatography (diethyl ether–pentane; 1.7:1 with Et_3N in 0.4%) afforded the desired product (±)-**10c** (306 mg, 44%) as yellow oil.

^{1}H NMR ($CDCl_3$) δ: 7.52 (2H, d, J = 8.4 Hz); 7.01 (2H, d, J = 8.4 Hz); 3.39 (3H, s); 3.25 (1H, br d, J = 10.8 Hz); 2.89–2.84 (2H, m); 2.80 (1H, dt, J_2 = 4.0 Hz, J_1 = 11.2 Hz); 2.65 (1H, dq, J_1 = 2.8 Hz, J_2 = 11.6 Hz); 2.27 (3H, s); 2.10 (1H, t, J = 12.0 Hz); 2.04–1.98 (1H, m); 1.76–1.68 (1H, m).

^{13}C NMR ($CDCl_3$) δ: 171.5; 142.0; 136.0; 128.3; 90.6; 57.5; 54.8; 50.8; 46.3; 45.1; 40.2; 25.1.

HR-MS(ES): Calcd for $C_{14}H_{18}NO_2 + H^+$: m/z 360.0461. Found m/z 360.0452.

5.2. General method for triflation

NaH (60% w/w), 1 g, 25 mmol was washed with pentane (3 × 20 mL) under a nitrogen atmosphere, then 20 mL of ether was added and the slurry was cooled to 0 °C. The ketoester (5 mmol) dissolved in 15 mL ether was added dropwise, and the reaction mixture was stirred at 0 °C for 30 min. Then Tf_2O (1.70 mL, 10 mmol) was added dropwise, and the reaction mixture was stirred for 60 min at 0 °C after which 25 mL of H_2O was added slowly. The layers were separated the aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were dried with $MgSO_4$ and concentrated in vacuo. Purification by Flash chromatography (diethyl ether–pentane; 1:30) afforded the triflate as colourless oil.

5.2.1. Methyl 2-(trifluoromethylsulfonyloxy)cyclopent-1-enecarboxylate (17). The general method for triflation with ketoester **14** afforded the triflate **17** as colourless oil in 99% yield.

^{1}H NMR ($CDCl_3$) δ: 3.80 (s, 3H); 2.73 (m, 4H); 2.02 (k, 2H, J = 7.8 Hz).

^{13}C NMR ($CDCl_3$) δ: 162.6; 154.0; 123.0; 118.3 (q, J = 318 Hz); 51.6; 32.6; 29.1; 18.7.

5.2.2. Methyl 2-(trifluoromethylsulfonyloxy)cyclohex-1-enecarboxylate (18). The general method for triflation with ketoester **15** afforded the triflate **18** as colourless oil in 99% yield.

^{1}H NMR ($CDCl_3$) δ: 3.76 (s, 3H); 2.47–2.35 (m, 4H); 1.79–1.61 (m, 4H).

^{13}C NMR ($CDCl_3$) δ: 165.2; 152.0; 122.9; 118.4; 52.2; 28.7; 26.2; 22.4; 21.2.

5.2.3. Methyl 2-(trifluoromethylsulfonyloxy)cyclohept-1-enecarboxylate (19). The general method for triflation with ketoester **16** afforded the triflate **19** as colourless oil in 95% yield.

^{1}H NMR ($CDCl_3$) δ: 3.79 (s, 3H); 2.61–2.51 (m, 4H); 1.80–1.63 (m, 6H).

^{13}C NMR ($CDCl_3$) δ: 165.8; 154.8; 127.6; 118.5; 51.8; 33.7; 30.4; 27.7; 25.0; 23.5.

5.2.4. 1-*tert*-Butyl 3-ethyl 4-(trifluoromethylsulfonyloxy)-5,6-dihydropyridine-1,3(2H)-dicarboxylate (12). NaH (60% (w/w), 60 mg, 1.5 mmol) was washed with pentane (3×5 mL) under a nitrogen atmosphere, 5 mL of ether was added and the slurry was cooled to 0 °C. Compound **11** (200 mg, 0.74 mmol)[22] in 3 mL ether was added dropwise and the reaction mixture was stirred for 90 min at room temperature. Then the mixture was cooled to 0 °C and Tf_2O (0.14 mL, 0.83 mmol) in 3 mL anhyd Et_2O was added dropwise followed by removal of the cooling bath. The reaction mixture was stirred for 40 min at 25 °C after which 10 mL of satd NH_4Cl was added. The layers were separated, the aqueous phase extracted with 3×10 mL CH_2Cl_2, and the combined organic phases were dried over $MgSO_4$. Concentration under reduced pressure afforded **12** as a slight yellow oil in 90% yield (266 mg). Compound **12** was used in the following reactions without further purification.

^{1}H NMR ($CDCl_3$) δ: 4.33–4.27 (m, 4H); 3.64–3.60 (m, 2H); 2.53–2.49 (m, 2H), 1.48 (s, 9H), 1.34 (t, 3H, J = 7.2 Hz).

^{13}C NMR ($CDCl_3$) δ: 165.8; 154.8; 127.6; 118.5; 51.8; 33.7; 30.4; 27.7; 25.0; 23.5.

HR-MS(ES): Calcd for $C_{14}H_{20}F_3NO_7S + Na^+$: m/z 426.0810. Found m/z 426.0812.

5.3. General method for Suzuki couplings

One equivalent of **17**, **18**, **19** or **12** (0.3 mmol) was added to a tube (5–10 mL) with Na_2CO_3 (2 equiv), $Pd(OAc)_2$ (0.05 equiv), the boronic acid (1.5 equiv) and dissolved in ethanol–benzene (1:3). Finally PPh_3 (0.1 equiv) was added and the resulting mixture was flushed with nitrogen, and the tube sealed. The reaction mixture was stirred at 65 °C for 20 h.

5.3.1. Methyl 2-(3,4-dichlorophenyl)cyclopent-1-enecarboxylate (6a). Purification by Flash chromatography (diethyl ether–pentane; 1:30) afforded **6a** as colourless oil in 96% yield.

^{1}H NMR ($CDCl_3$) δ: 7.42 (d, 1H, J = 2.1 Hz); 7.38 (d, 1H, J = 8.4 Hz); 7.17 (dd, 1H, J_1 = 2.1 Hz, J_2 = 8.4 Hz); 3.64 (s, 3H); 2.81 (m, 4H);1.99 (p, 2H, J = 7.6 Hz).

^{13}C NMR ($CDCl_3$) δ: 165.9; 150.8; 136.8; 131.8; 131.7; 130.5; 129.6; 127.3; 51.3; 39.9; 35.1; 21.8.

HR-MS(ES): Calcd for $C_{13}H_{12}Cl_2O_2 + Na^+$: m/z 293.0112. Found m/z 293.0118.

5.3.2. Methyl 2-(4-chlorophenyl)cyclopent-1-enecarboxylate (6b). Purification by Flash chromatography (diethyl ether–pentane; 1:30) afforded **6b** as colourless oil in 91% yield.

^{1}H NMR ($CDCl_3$) δ: 7.28 (m, 4H); 3.63 (s, 3H); 2.82 (t, 4H, J = 7.6 Hz); 1.98 (p, 2H, J = 7.6 Hz).

^{13}C NMR ($CDCl_3$) δ: 166.3; 152.3; 135.3; 133.7; 129.4; 129.1; 127.9; 51.1; 40.0; 35.1; 21.8.

HR-MS(ES): Calcd for $C_{13}H_{13}ClO_2 + Na^+$: m/z 259.0502. Found m/z 259.0497.

5.3.3. Methyl 2-(3-chlorophenyl)cyclopent-1-enecarboxylate (6c). Purification by Flash chromatography (diethyl ether–pentane; 1:30) afforded **6c** as colourless oil in 94% yield.

^{1}H NMR ($CDCl_3$) δ: 7.30 (s, 1H); 7.26 (d, 2H, J = 4.8 Hz); 7.20 (q, 1H, J = 4.8 Hz); 3.63 (s, 3H); 2.83 (t, 4H, J = 7.6 Hz); 1.99 (p, 2H, J = 7.6 Hz).

^{13}C NMR ($CDCl_3$) δ: 166.1; 151.8; 138.7; 133.6; 130.0; 129.0; 127.8; 127.7; 125.9; 51.2; 40.2; 35.0; 21.9.

HR-MS(ES): Calcd for $C_{13}H_{13}ClO_2 + Na^+$: m/z 259.0502. Found m/z 259.0494.

5.3.4. Methyl 2-(naphthalen-2-yl)cyclopent-1-enecarboxylate (6d). Purification by Flash chromatography (diethyl ether–pentane; 1:30) afforded **6d** as colourless oil in 85% yield.

^{1}H NMR ($CDCl_3$) δ: 7.81 (m, 4H); 7.47 (m, 3H); 3.63 (s, 3H); 2.97 (t, 2H, J = 7.7 Hz); 2.90 (t, 2H, J = 7.7 Hz); 2.05 (p, 2H, J = 7.7 Hz).

^{13}C NMR ($CDCl_3$) δ: 166.7; 153.3; 134.5; 133.0; 132.9; 129.2; 128.2; 127.6; 127.1; 126.6; 126.2; 126.1; 126.0; 51.2; 40.2; 35.3; 22.0.

HR-MS(ES): Calcd for $C_{17}H_{16}O_2 + Na^+$: m/z 275.1048. Found m/z 275.1048.

5.3.5. Methyl 2-(4-methoxyphenyl)cyclopent-1-enecarboxylate (6f). Purification by Flash chromatography (diethyl ether–pentane; 1:20) afforded **6f** as colourless oil in 98% yield.

^{1}H NMR ($CDCl_3$) δ: 7.33 (d, 2H, J = 8.8 Hz); 6.86 (d, 2H, J = 8.8 Hz); 3.81 (s, 3H); 3.65 (s, 3H); 2.83 (dq, 4H, J_1 = 2.0 Hz, J_2 = 7.4 Hz); 1.96 (p, 2H, J = 7.7 Hz).

^{13}C NMR ($CDCl_3$) δ: 166.8; 159.4; 153.1; 129.3; 129.0; 127.3; 113.1; 55.2; 51.0; 39.9; 35.2; 21.8.

HR-MS(ES): Calcd for $C_{14}H_{16}O_3 + Na^+$: m/z 255.0997. Found m/z 255.0995.

5.3.6. Methyl 2-(4-*tert*-butylphenyl)cyclopent-1-enecarboxylate (6g). Purification by Flash chromatography (diethyl ether–pentane; 1:30) afforded **6g** as colourless oil in 88% yield.

^{1}H NMR ($CDCl_3$) δ: 7.37 (d, 2 H, J = 8.6 Hz); 7.32 (d, 2H, J = 8.6 Hz); 3.66 (s, 3H); 2.85 (m, 4 H); 1.98 (p, 2H, J = 7.3 Hz);1.34 (s, 9H).

^{13}C NMR ($CDCl_3$) δ: 166.7; 153.5; 150.9; 133.6; 128.0; 127.6; 124.6; 51.1; 39.9; 35.2; 34.6; 31.2; 21.9.

HR-MS(ES): Calcd for $C_{17}H_{22}O_2 + Na^+$: *m*/*z* 281.1517. Found *m*/*z* 281.1516.

5.3.7. Methyl 2-(4-(trifluoromethoxy)phenyl)cyclopent-1-enecarboxylate (6h). Purification by Flash chromatography (diethyl ether–pentane; 1:30) afforded **6h** as colourless oil in 89% yield.

^{1}H NMR ($CDCl_3$) δ: 7.37 (d, 2H, J = 8.6 Hz); 7.17 (d, 2H, J = 8.6 Hz); 3.64 (s, 3H); 2.84 (t, 4H, J = 7.6 Hz); 2.00 (p, 2H, J = 7.6 Hz).

^{13}C NMR ($CDCl_3$) δ: 166.2; 152.2; 148.7; 135.5; 129.6; 129.3; 120.4 (q, J = 257 Hz); 120.1; 51.2; 40.1; 35.1; 21.9.

HR-MS(ES): Calcd for $C_{14}H_{13}F_3O_3 + Na^+$: *m*/*z* 309.0714. Found *m*/*z* 309.0718.

5.3.8. Methyl 2-(4-(methylsulfonyl)phenyl)cyclopent-1-enecarboxylate (6i). Purification by Flash chromatography (diethyl ether–pentane; 1:30) afforded **6i** as colourless oil in 89% yield.

^{1}H NMR ($CDCl_3$) δ: 7.89 (d, 2H, J = 8.5 Hz); 7.49 (d, 2H, J = 8.5 Hz); 3.62 (s, 3H); 3.05 (s, 3H); 2.85 (t, 4H, J = 7.6 Hz); 2.02 (p, 2H, J = 7.6 Hz).

^{13}C NMR ($CDCl_3$) δ: 165.8; 151.7; 142.9; 139.4; 131.3; 128.6; 126.8; 51.3; 44.5; 40.2; 35.0; 21.9.

HR-MS(ES): Calcd for $C_{14}H_{16}O_4S + Na^+$: *m*/*z* 303.0667. Found *m*/*z* 303.0669.

5.3.9. Methyl 2-(4-acetylphenyl)cyclopent-1-enecarboxylate (6j). Purification by Flash chromatography (diethyl ether–pentane; 1:1) afforded **6j** as colourless oil in 79% yield.

^{1}H NMR ($CDCl_3$) δ: 7.92 (d, 2H, J = 8.5 Hz); 7.39 (d, 2H, 8.5 Hz); 3.62 (s, 3H); 2.85 (m, 4H); 2.59 (s, 3H); 2.01 (p, 2H, J = 7.7 Hz).

^{13}C NMR ($CDCl_3$) δ: 197.6; 166.1; 152.5; 142.0; 136.2; 130.5; 127.9; 127.8; 51.3; 40.0; 35.1; 26.6; 22.0.

5.3.10. Methyl 2-(3-aminophenyl)cyclopent-1-enecarboxylate (6k). Purification by Flash chromatography (diethyl ether–pentane; 1:1) afforded **6k** as colourless oil in 86% yield.

^{1}H NMR ($CDCl_3$) δ: 7.11 (t, 1H, J = 7.8 Hz); 6.70 (d, 1H, J = 7.6); 6.65 (s, 1H); 6.62 (d, 1H, J = 7.9 Hz); 3.63 (s, 3H); 2.81 (t, 4H, J = 7.7 Hz); 1.97 (p, 2H, J = 7.7 Hz).

^{13}C NMR ($CDCl_3$) δ: 166.8; 153.5; 145.9; 138.0; 128.7; 118.1; 114.8; 114.3; 51.1; 40.1; 35.1; 21.9.

HR-MS(ES): Calcd for $C_{13}H_{15}NO_2 + H^+$: *m*/*z* 218.1181. Found *m*/*z* 218.1179.

5.3.11. Methyl 2-(4-nitrophenyl)cyclopent-1-enecarboxylate (6p). This reaction was performed using 4-nitrobenzeneboronic ester (1.5 equiv) synthesized by the method of Fürstner and Günter[30] Purification by Flash chromatography (EtOAc–pentane; 1:8) afforded **6p** as a yellow solid in 85% yield.

^{1}H NMR ($CDCl_3$) δ: 8.19 (dd, 2H, J_1 = 2.0 Hz, J_2 = 9.0 Hz); 7.46 (dd, 2H, J_1 = 2.0 Hz, J_2 = 9.0 Hz); 3.63 (s, 3H); 2.87 (m, 4H); 2.04 (m, 2H).

^{13}C NMR ($CDCl_3$) δ: 165.8; 151.4; 147.2; 144.0; 128.7; 128.4; 123.1; 51.4; 40.2; 35.1; 22.0.

HR-MS(ES): Calcd for $C_{13}H_{13}NO_4 + Na^+$: *m*/*z* 270.0742. Found *m*/*z* 270.0749.

5.3.12. Methyl 2-(3,4-dichlorophenyl)cyclohex-1-enecarboxylate (7a). Purification by Flash chromatography (diethyl ether–pentane; 1:20) afforded **7a** as colourless oil in 95% yield.

^{1}H NMR ($CDCl_3$) δ: 7.36 (d, 1H, J = 8.2 Hz); 7.22 (d, 1H, J = 2.0 Hz); 6.96 (dd, 1H, J_1 = 8.2 Hz, J_2 = 2.0 Hz); 3.48 (s, 3H); 2.44–2.37 (m, 2H); 2.34–2.28 (m, 2H); 1.76.1.68 (m, 4H).

^{13}C NMR ($CDCl_3$) δ: 169.3; 143.8; 143.3; 132.0; 130.8; 129.9; 128.8; 128.7; 126.3; 51.3; 32.6; 26.5; 22.2; 21.7.

HR-MS(ES): Calcd for $C_{14}H_{14}Cl_2O_2 + Na^+$: *m*/*z* 307.0269. Found *m*/*z* 307.0285.

5.3.13. Methyl 2-(4-chlorophenyl)cyclohex-1-enecarboxylate (7b). Purification by Flash chromatography (diethyl ether–pentane; 1:20) afforded **7b** as colourless oil in 99% yield.

^{1}H NMR ($CDCl_3$) δ: 7.27 (d, 2H, J = 8.4 Hz); 7.06 (d, 2H, J = 8.4 Hz); 3.45 (s, 3 H); 2.44–2.32 (m, 4 H); 1.78–1.65 (m, 4 H).

^{13}C NMR ($CDCl_3$) δ: 169.8; 144.8; 141.8; 132.8; 128.2; 128.1; 51.3; 32.7; 26.6; 22.4 21.8.

HR-MS(ES): Calcd for $C_{14}H_{15}ClO_2 + Na^+$: *m*/*z* 273.0658. Found *m*/*z* 273.0657.

5.3.14. Methyl 2-(3-chlorophenyl)cyclohex-1-enecarboxylate (7c). Purification by Flash chromatography (diethyl ether–pentane; 1:20) afforded **7c** as colourless oil in 98% yield.

^{1}H NMR ($CDCl_3$) δ: 7.24–7.21 (m, 2H); 7.14–7.12 (m, 1H); 7.02–6.98 (m, 1H); 3.45 (s, 3H); 2.45–2.40 (m, 2H); 2.38–2.32 (m, 2H); 1.78–1.70 (m, 4H).

^{13}C NMR ($CDCl_3$) δ: 169.7; 145.2; 144.6; 133.8; 129.2; 128.4; 127.0; 126.9; 125.0; 51.2; 32.6; 26.6; 22.3; 21.8.

HR-MS(ES): Calcd for $C_{14}H_{15}ClO_2 + Na^+$: *m*/*z* 273.0658. Found *m*/*z* 273.0660.

5.3.15. Methyl 2-(naphthalen-2-yl)cyclohex-1-enecarboxylate (7d). Purification by Flash chromatography (diethyl ether–pentane; 1:20) afforded **7d** as colourless oil in 80% yield.

^{1}H NMR ($CDCl_3$) δ: 7.83–7.78 (m, 3H); 7.61 (s, 1H); 7.48–7.43 (m, 2H); 7.29 (d, 1H, J = 8.5 Hz); 3.38 (s, 3H); 2.50–2.48 (m, 4H); 1.84–1.78 (m, 4H).

^{13}C NMR ($CDCl_3$) δ: 170.3; 145.7; 140.8; 133.2; 132.4; 128.1; 127.9; 127.6; 127.5; 126.0; 125.7; 125.7; 125.1; 51.4; 32.9; 27.0; 22.7; 22.1.

HR-MS(ES): Calcd for $C_{18}H_{18}O_2 + Na^+$: *m*/*z* 289.1204. Found *m*/*z* 289.1204.

5.3.16. Methyl 2-(biphenyl-4-yl)cyclohex-1-enecarboxylate (7e). Purification by Flash chromatography (diethyl ether–pentane; 1:20) afforded **7e** as colourless oil in 83% yield.

^{1}H NMR ($CDCl_3$) δ: 7.62 (d, 2H, J = 7.5 Hz); 7.56 (d, 2H, J = 8.0 Hz); 7.44 (t, 2H, J = 7.5 Hz); 7.34 (t, 1H, 7.5 Hz); 7.23 (d, 2H, 8.0 Hz); 3.47 (s, 3H); 2.48–2.42 (m, 4H); 1.81.1.74 (m, 4H).

^{13}C NMR ($CDCl_3$) δ: 170.4; 145.3; 142.3; 140.7; 139.7; 128.7; 127.8; 127.2; 127.0; 126.6; 51.2; 32.5; 26.8; 22.5; 21.9.

HR-MS(ES): Calcd for $C_{20}H_{20}O_2 + Na^+$: *m*/*z* 315.1361. Found *m*/*z* 315.1366.

5.3.17. Methyl 2-(4-*tert*-butylphenyl)cyclohex-1-enecarboxylate (7g). Purification by Flash chromatography (diethyl ether–pentane; 1:20) afforded **7g** as colourless oil in 88% yield.

^{1}H NMR ($CDCl_3$) δ: 7.32 (d, 2H, J = 8.3 Hz); 7.07 (d, 2H, J = 8.3 Hz); 3.42 (s, 3H); 2.44–2.37 (m, 4H); 1.77–1.70 (m, 4H); 1.32 (s, 9H).

^{13}C NMR ($CDCl_3$) δ: 170.6; 149.8; 145.3; 140.1; 127.4; 126.4; 124.8; 51.1; 34.4; 32.3; 31.3; 26.8; 22.5; 21.9.

HR-MS(ES): Calcd for $C_{18}H_{24}O_2 + Na^+$: *m*/*z* 295.1674. Found *m*/*z* 295.1669.

5.3.18. Methyl 2-(4-(trifluoromethoxy)phenyl)cyclohex-1-enecarboxylate (7h). Purification by Flash chromatography (diethyl ether–pentane; 1:20) afforded **7h** as colourless oil in 83% yield.

^{1}H NMR ($CDCl_3$) δ: 7.14 (s, 4H); 3.42 (s, 3H); 2.45–2.40 (m, 2H); 2.38–2.33 (m, 2H); 1.79–1.72 (m, 4H).

^{13}C NMR ($CDCl_3$) δ: 169.8; 148.1; 144.7; 142.1; 128.4; 128.2; 120.5 (q, J = 257 Hz); 120.4; 51.1; 32.7; 26.6; 22.4; 21.8.

HR-MS(ES): Calcd for $C_{15}H_{15}F_3O_3 + Na^+$: *m*/*z* 323.0871. Found *m*/*z* 323.0876.

5.3.19. Methyl 2-phenylcyclohex-1-enecarboxylate (7l). Purification by Flash chromatography (diethyl ether–pentane; 1:20) afforded **7l** as yellow oil in 85% yield.

^{1}H NMR ($CDCl_3$) δ: 8.11 (d, 1H, J = 7.6 Hz); 8.01 (s, 1H); 7.48 (m, 1H); 7.44 (dd, 1H, J = 1.4 Hz, J = 7.6 Hz); 3.46 (s, 3H); 2.45 (m, 2H); 2.38 (m, 2H); 1.77 (m, 4H).

^{13}C NMR ($CDCl_3$) δ: 170.39; 145.90; 143.44; 128.07; 127.79; 127.08; 126.80; 51.23; 32.68; 26.79; 22.58; 22.04.

5.3.20. Methyl 2-(3-(trifluoromethyl)phenyl)cyclohex-1-enecarboxylate (7m). Purification by Flash chromatography (diethyl ether–pentane; 1:20) afforded **7m** as colourless oil in 95% yield.

^{1}H NMR ($CDCl_3$) δ: 7.51 (d, 1H, J = 7.5 Hz); 7.42 (dd, 1H, J_1 = 7.5 Hz, J_2 = 7.7 Hz); 7.39 (s, 1H); 7.31 (d, 1H, J = 7.7 Hz); 3.42 (s, 3H); 2.46–2.41 (m, 2H); 2.40–2.35 (m, 2H); 1.80–1.70 (m, 4H).

^{13}C NMR ($CDCl_3$) δ: 169.5; 144.6; 144.1; 130.1; 128.8; 128.4; 124.1 (q, J = 272 Hz); 123.7; 123.7 123.6; 51.2; 32.6; 26.6; 22.3; 21.8.

HR-MS(ES): Calcd for $C_{15}H_{15}F_3O_2 + Na^+$: *m*/*z* 307.0922. Found *m*/*z* 307.0927.

5.3.21. Methyl 2-(4-(trifluoromethyl)phenyl)cyclohex-1-enecarboxylate (7n). Purification by Flash chromatography (diethyl ether–pentane; 1:20) afforded **7n** as colourless oil in 96% yield.

^{1}H NMR ($CDCl_3$) δ: 7.56 (d, 2H, J = 8.1 Hz); 7.23 (d, 2H, J = 8.1 Hz); 3.43 (s, 3H); 2.46–2.42 (m, 2H); 2.38–2.34 (m, 2H); 1.79–1.72 (m, 4H).

^{13}C NMR ($CDCl_3$) δ: 169.4; 147.2; 145.2; 128.5; 127.1; 125.0; 124.9; 124.2 (q, J = 272 Hz); 51.2; 32.8; 26.5; 22.3; 21.8.

HR-MS(ES): Calcd for $C_{15}H_{15}F_3O_2 + Na^+$: *m*/*z* 307.0922. Found *m*/*z* 307.0919.

5.3.22. Methyl 2-(4-hydroxyphenyl)cyclohex-1-enecarboxylate (7o). Purification by Flash chromatography (diethyl ether–pentane; 1:1) afforded **7o** as colourless oil in 93% yield.

^{1}H NMR ($CDCl_3$) δ: 6.99 (d, 2H, J = 8.5 Hz); 6.70 (d, 2H, J = 8.5 Hz); 6.09 (s, 1H); 3.50 (s, 3H); 2.42–2.33 (m, 4H); 1.76–1.68 (m, 4H).

^{13}C NMR ($CDCl_3$) δ: 171.4; 155.2; 145.8; 135.1; 128.0; 127.0; 115.0; 51.5; 32.5; 26.8; 22.5; 21.9.

HR-MS(ES): Calcd for $C_{14}H_{16}O_3 + Na^+$: *m*/*z* 255.0997. Found *m*/*z* 255.0991.

5.3.23. Methyl 2-phenylcyclohex-1-enecarboxylate (7q). Purification by Flash chromatography (EtOAc–pentane; 1:10) afforded **7q** as yellow oil in 53% yield.

^{1}H NMR ($CDCl_3$) δ: 8.11 (d, 1H, J = 7.6 Hz); 8.01 (s, 1H); 7.48 (m, 1H); 7.44 (dd, 1H, J = 1.4 Hz, J = 7.6 Hz); 3.46 (s, 3H); 2.45 (m, 2H); 2.38 (m, 2H); 1.77 (m, 4H).

^{13}C NMR ($CDCl_3$) δ: 168.9; 148.1; 145.3; 144.7; 133.2; 129.2; 129.0; 122.0; 121.9; 51.5; 33.1; 26.6; 22.3; 21.9.

HR-MS(ES): Calcd for $C_{14}H_{15}NO_4 + Na^+$: *m/z* 284.0899. Found *m/z* 284.0902.

5.3.24. Methyl 2-(3,4-dichlorophenyl)cyclohept-1-enecarboxylate (8a). Purification by Flash chromatography (CH_2Cl_2-pentane; 1:3) afforded **8a** as colourless oil in 90% yield.

^{1}H NMR ($CDCl_3$) δ: 7.35 (d, 1H, J = 8.2 Hz); 7.22 (d, 1H, J = 2.0 Hz); 6.95 (dd, 1H, J = 2.0 Hz, J = 8.2 Hz); 3.46 (s, 3H); 2.58–2.55 (m, 4H); 1.89–1.83 (m, 2H); 1.67–1.62 (m, 4H).

^{13}C NMR ($CDCl_3$) δ: 170.6; 148.6; 144.5; 134.8; 132.1; 130.8; 130.0; 128.6; 126.2; 51.5; 36.9; 32.2; 30.8; 26.2; 25.6.

HR-MS(ES): Calcd for $C_{15}H_{16}Cl_2O_2 + Na^+$: *m/z* 321.0425. Found *m/z* 321.0435.

5.3.25. Methyl 2-(4-chlorophenyl)cyclohept-1-enecarboxylate (8b). Purification by Flash chromatography (CH_2Cl_2–pentane; 1:2) afforded **8b** as colourless oil in 90% yield.

^{1}H NMR ($CDCl_3$) δ: 7.26 (d, 1H, J = 8.4 Hz); 7.06 (d, 2H, J = 8.4 Hz); 3.42 (s, 3H); 2.59–2.55 (m, 4H); 1.88–1.82 (m, 2H); 1.68–1.62 (m, 4H).

^{13}C NMR ($CDCl_3$) δ: 170.9; 149.6; 142.8; 133.8; 132.5; 128.0; 127.9; 51.1; 36.9; 32.1; 30.7; 26.2; 25.5.

HR-MS(ES): Calcd for $C_{15}H_{17}ClO_2 + Na^+$: *m/z* 287.0815. Found *m/z* 287.0812.

5.3.26. Methyl 2-(3-chlorophenyl)cyclohept-1-enecarboxylate (8c). Purification by Flash chromatography (CH_2Cl_2-pentane; 1:3) afforded **8c** as colourless oil in 95% yield.

^{1}H NMR ($CDCl_3$) δ: 7.21 (m, 2H); 7.12 (dd, 1H, J = 1.3 Hz, J = 2.2 Hz); 7.00 (ddd, 1H, J = 1.6 Hz, J = 2.7 Hz, J = 6.0 Hz); 3.42 (s, 3H); 2.60–2.56 (m, 4H); 1.89–1.83 (m, 2H); 1.69–1.62 (m, 4H).

^{13}C NMR ($CDCl_3$) δ: 171.0; 149.6; 146.3; 134.4; 133.9; 129.3; 127.0; 126.7; 124.9; 51.4; 37.0; 32.3; 30.9; 26.3; 25.7.

HR-MS(ES): Calcd for $C_{15}H_{17}ClO_2 + Na^+$: *m/z* 287.0815. Found *m/z* 287.0806.

5.3.27. Methyl 2-(naphthalen-2-yl)cyclohept-1-enecarboxylate (8d). Purification by Flash chromatography (CH_2Cl_2–pentane; 1:2) afforded **8d** as colourless oil in 96% yield.

^{1}H NMR ($CDCl_3$) δ: 7.79 (m, 3H); 7.58 (s, 1H); 7.45 (m, 2H); 7.29 (m, 1H); 3.32 (s, 3H); 2.72–2.62 (m, 4H); 1.93–1.87 (m, 2H); 1.75–1.68 (m, 4H).

^{13}C NMR ($CDCl_3$) δ: 171.6; 150.8; 142.0; 133.9; 133.2; 132.4; 128.0; 127.6; 126.1; 125.8; 125.4; 125.0; 51.3; 37.2; 32.4; 31.1; 26.5; 25.9.

HR-MS(ES): Calcd for $C_{19}H_{26}O_2 + Na^+$: *m/z* 303.1361. Found *m/z* 303.1357.

5.3.28. Methyl 2-(biphenyl-4-yl)cyclohept-1-enecarboxylate (8e). Purification by Flash chromatography (CH_2Cl_2–pentane; 1:2) afforded **8e** as colourless oil in 75% yield.

^{1}H NMR ($CDCl_3$) δ: 7.60 (d, 2H, J = 7.1 Hz); 7.54 (dd, 2H, J_1 = 2.0 Hz, J_2 = 8.4 Hz); 7.44 (t, 2H, J = 7.6 Hz); 7.34 (t, 1H, J = 7.3 Hz); 7.22 (dd, 2H, J_1 = 2.0 Hz, J_2 = 8.4 Hz); 3.43 (s, 3H); 2.69–2.58 (m, 4H), 1.91–1.85 (m, 2H); 1.73–1.65 (m, 4H).

^{13}C NMR ($CDCl_3$) δ: 171.6; 150.5; 143.4; 140.8; 139.7; 133.6; 128.8; 127.3; 127.2; 127.0; 126.7; 51.3; 37.1; 32.4; 31.1; 26.5; 25.8.

HR-MS(ES): Calcd for $C_{21}H_{22}O_2 + Na^+$: *m/z* 329,1517. Found *m/z* 329.1521.

5.3.29. Methyl 2-(4-*tert*-butylphenyl)cyclohept-1-enecarboxylate (8g). Purification by Flash chromatography (CH_2Cl_2–pentane; 1:2) afforded **8g** as colourless oil in 74% yield.

^{1}H NMR ($CDCl_3$) δ: 7.30 (d, 2H, J = 8.4 Hz); 7.07 (d, 2H, J = 8.4 Hz); 3.38 (s, 3H); 1.88–1.82 (m, 2H); 1.69–1.62 (m, 4H); 1.63–1.55 (m, 4H); 3.38 (s, 3H); 1.31 (s, 9H).

^{13}C NMR ($CDCl_3$) δ: 171.9; 150.7; 149.8; 141.3; 133.1; 126.4; 124.8; 51.1; 37.0; 34.5; 32.4; 31.3; 31.1; 26.6; 25.9.

HR-MS(ES): Calcd for $C_{19}H_{26}O_2 + Na^+$: *m/z* 309.1830. Found *m/z* 309.1823.

5.3.30. 1-*tert*-Butyl 3-ethyl 4-(naphthalen-2-yl)-5,6-dihydropyridine-1,3(2H)-dicarboxylate (13d). Purification by Flash chromatography (CH_2Cl_2-EtOAc; 20:1) afforded **13d** as colourless oil in 76% yield.

^{1}H NMR ($CDCl_3$) δ: 7.83–7.77 (m, 3H); 7.60 (s, 1H); 7.49–7.44 (m, 2H); 7.29–7.26 (m, 1H); 4.31 (m, 2H); 3.90 (q, 2H, J = 7.1 Hz); 3.66 (dd, 2H, J = 5.7 Hz); 2.60 (m, 2H); 1.52 (s, 9H); 0.78 (m, 3H).

^{13}C NMR ($CDCl_3$) δ: 167.0; 154.7; 146.0; 139.4; 133.2; 132.7; 127.9; 127.7; 127.7; 126.2; 126.0; 125.5; 125.4; 80.2; 60.4; 44.0; 39.6; 32.9; 28.5; 13.6.

HR-MS(ES): Calcd for $C_{23}H_{27}NO_4 + Na^+$: *m/z* 404.1838. Found *m/z* 404.1840.

5.3.31. 1-*tert*-Butyl 3-ethyl 4-(3,4-dichlorophenyl)-5,6-dihydropyridine-1,3(2H)-dicarboxylate (13a). Purification by Flash chromatography (CH_2Cl_2–EtOAc; 6:1) afforded **13a** as colourless oil in 96% yield.

^{1}H NMR ($CDCl_3$) δ: 7.40 (d, 1H, J = 8.4 Hz); 7.24 (d, 1H, J = 2.0 Hz); 6.97 (dd, 1H, J_1 = 2.0 Hz, J_2 = 8.4 Hz); 4.25 (m, 2H); 4.00 (q, 2H, J = 7.2 Hz); 3.60 (m, 2H); 2.45 (m, 2H); 1.50 (s, 9H); 1.01 (t, 3H, J = 7.2 Hz).

^{13}C NMR ($CDCl_3$) δ: 166.1; 154.5; 144.0; 141.9; 132.3; 131.5; 130.2; 129.0; 126.4; 80.4; 60.7; 43.8; 39.5; 32.8; 28.5; 13.8.

HR-MS(ES): Calcd for $C_{19}H_{23}C_{l2}NO_4 + Na^+$: *m/z* 422.0902. Found *m/z*422.0902.

5.3.32. 1-*tert*-butyl 3-ethyl 4-(3-nitrophenyl)-5,6-dihydropyridine-1,3(2H)-dicarboxylate (13q). Purification by Flash chromatography (CH_2Cl_2–EtOAc; 6:1) afforded **13q** as colourless oil in 87% yield.

^{1}H NMR ($CDCl_3$) δ: 8.16 (dd, 1H, J = 8.0 Hz); 8.02 (d, 1H, J = 2.0 Hz); 7.52–7.45 (m, 2H); 4.29 (m, 2H), 3.97 (q, 2H, J = 7.2 Hz); 3.64 (dd, 2H, J = 5.6 Hz); 2.51 (m, 2H); 1.51 (s, 9H); 0.97 (t, 3H, 7.2 Hz).

^{13}C NMR ($CDCl_3$) δ: 165.7; 154.5; 148.1; 144.5; 143.7; 133.1; 129.2; 122.3; 122.1; 80.4; 60.7; 43.8; 39.3; 33.1; 28.5; 13.8.

HR-MS(ES): Calcd for $C_{19}H_{24}N_2O_6 + Na^+$: *m/z* 399.1532. Found *m/z* 399.1527.

5.4. General method for reductive hydrogenation

The unsaturated compounds were stirred for 24 h in methanol with 10% Pd/C (10 wt%) at atmospheric pressure under H_2. After filtration through Celite and concentration in vacuo the products were purified by Flash chromatography.

5.4.1. Methyl 2-(biphenyl-4-yl)cyclohexanecarboxylate (21e). Purification by Flash chromatography (diethyl ether–pentane; 1:20) afforded **21e** as colourless oil in 70% yield.

^{1}H NMR ($CDCl_3$) δ: 7.58 (d, 2H, J = 8.0 Hz); 7.51 (d, 2H, J = 8.1 Hz); 7.42 (t, 2H, J = 7.2 Hz); 7.34–7.28 (m, 3H); 3.45 (s, 3H); 3.01 (dd, 1H, J_1 = 7.8 Hz, J_2 = 4.2 Hz); 2.93 (dt, 1H, J_1 = 11.8 Hz, J_2 = 4.2 Hz); 2.40 (dq, 1H, J_1 = 12.0 Hz, J_2 = 2.8 Hz); 2.10–2.05 (m, 1H); 1.97–1.90 (m, 1H); 1.84–1.73 (m, 3H); 1.62–1.56 (m, 1H); 1.50–1.40 (m, 1H).

^{13}C NMR ($CDCl_3$) δ: 174.5; 143.6; 141.0; 138.9; 128.7; 127.9; 127.0; 127.0 126.8; 50.9; 46.0; 44.3; 29.0; 26.7; 25.8; 21.7.

HR-MS(ES): Calcd for $C_{20}H_{22}O_2 + Na^+$: *m/z* 317.1517. Found *m/z* 317.1518.

5.4.2. Methyl 2-(4-*tert*-butylphenyl)cyclohexanecarboxylate (21g). Purification by Flash chromatography (diethyl ether–pentane; 1:20) afforded **21g** as colourless oil in 94% yield.

^{1}H NMR ($CDCl_3$) δ: 7.29 (d, 2H, J = 8.3 Hz); 7.16 (d, 2H, J = 8.3 Hz); 3.43 (s, 3H); 2.96 (dd, 1H, J_1 = 7.7 Hz, J_2 = 4.1 Hz); 2.87 (dt, 1H, J_1 = 11.7 Hz, J_2 = 4.1 Hz); 2.36 (dq, 1H, J_1 = 12.6 Hz, J_2 = 3.5 Hz); 2.07–2.02 (m, 1H); 1.95–1.87 (m, 1H); 1.80–1.70 (m, 3H); 1.61–1.54 (m, 1H); 1.46–1.35 (m, 1H); 1.30 (s, 9H).

^{13}C NMR ($CDCl_3$) δ: 174.6; 148.8; 141.3; 127.1; 124.9; 50.8; 46.0; 44.1; 34.3; 31.4; 29.0; 26.7; 25.9; 21.8.

HR-MS(ES): Calcd for $C_{18}H_{26}O_2 + Na^+$: *m/z* 297.1830. Found *m/z* 297.1833.

5.4.3. Methyl 2-(4-(trifluoromethoxy)phenyl)cyclohexanecarboxylate (21h). Purification by Flash chromatography (diethyl ether–pentane; 1:20) afforded **21h** as colourless oil in 94% yield.

^{1}H NMR ($CDCl_3$) δ: 7.27 (d, 2H, J = 8.8 Hz); 7.14 (d, 2H, J = 8.8 Hz); 3.44 (s, 3H); 2.97 (dd, 1H, J_1 = 7.9 Hz, J_2 = 3.9 Hz); 2.91 (dt, 1H, J_1 = 12.0 Hz, J_2 = 4.2 Hz); 2.37 (dq, 1H, J_1 = 13.0 Hz, J_2 = 3.7 Hz); 2.12–2.05 (m, 1H); 1.98–1.90 (m, 1H); 1.82–1.72 (m, 3H); 1.63–1.56 (m, 1H); 1.50–1.35 (m, 1H).

^{13}C NMR ($CDCl_3$) δ: 174.5; 147.7; 143.4; 129.1; 120.8 (q, J = 256 Hz); 120.8; 51.1; 46.2; 44.2; 29.2; 26.8; 26.0; 21.8.

HR-MS(ES): Calcd for $C_{15}H_{17}F_3O_3 + Na^+$: *m/z* 325.1027. Found *m/z* 325.1025.

5.4.4. Methyl 2-phenylcyclohexanecarboxylate (21l). Purification by Flash chromatography (diethyl ether–pentane; 1:20) afforded **21l** as colourless oil in 91% yield.

^{1}H NMR ($CDCl_3$) δ: 7.30–7.15 (m, 5H); 3.42 (s, 3H); 3.00–2.85 (m, 2H); 2.37 (q, 1H, J = 11.6 Hz); 2.08–2.02 (m, 1H); 1.96–1.88 (m, 1H); 1.80–1.70 (m, 3H); 1.62–1.54 (m, 1H); 1.46–1.36 (m, 1H).

^{13}C NMR ($CDCl_3$) δ: 175.0; 144.6; 128.3; 127.7; 126.3; 51.0; 46.2; 44.8; 29.1; 26.7; 26.0; 21.8.

HR-MS(ES): Calcd for $C_{14}H_{18}O_2 + Na^+$: *m/z* 241.1204. Found *m/z* 241.1197.

5.4.5. Methyl 2-(3-(trifluoromethyl)phenyl)cyclohexanecarboxylate (21m). Purification by Flash chromatography (diethyl ether–pentane; 1:20) afforded **21m** as colourless oil in 74% yield.

^{1}H NMR ($CDCl_3$) δ: 7.47–7.35 (m, 5H); 3.42 (s, 3H); 3.00–2.90 (m, 2H); 2.37 (dq, 1H, J_1 = 12.0 Hz, J_2 = 3.7 Hz); 2.12–2.04 (m, 1H); 1.98–1.89 (m, 1H); 1.81–1.72 (m, 3H); 1.63–1.56 (m, 1H); 1.48–1.36 (m, 1H).

^{13}C NMR ($CDCl_3$) δ: 174.3; 145.5 131.2; 128.6; 124.5; 123.8; 51.1; 46.1; 44.6; 29.2; 26.6; 25.9; 21.7.

HR-MS(ES): Calcd for $C_{15}H_{17}F_3O_2 + Na^+$: *m*/*z* 309.1078. Found *m*/*z* 309.1071.

5.4.6. Methyl 2-(4-(trifluoromethyl)phenyl)cyclohexanecarboxylate (21n). Purification by Flash chromatography (diethyl ether–pentane; 1:20) afforded **21m** as colourless oil in 70% yield.

^{1}H NMR ($CDCl_3$) δ: 7.53 (d, 2H, J = 8.3 Hz); 7.35 (d, 2H, J = 8.3 Hz); 3.43 (s, 3H); 3.00–2.90 (m, 2H); 2.38 (dq, 1H, J_1 = 12.0 Hz, J_2 = 3.7); 2.12–2.05 (m, 1H); 1.96–1.88 (m, 3H); 1.82–1.60 (m, 2H); 1.43–1.35 (m, 1H).

^{13}C NMR ($CDCl_3$) δ: 174.2; 148.7; 128.1; 125.1; 51.1; 46.0; 44.5; 29.2; 26.5; 25.8; 21.8.

HR-MS(ES): Calcd for $C_{15}H_{17}F_3O_2 + Na^+$: *m*/*z* 309.1078. Found *m*/*z* 309.1071.

5.4.7. Methyl 2-(biphenyl-4-yl)cycloheptanecarboxylate (22e). Purification by Flash chromatography (CH_2Cl_2–pentane; 1:1) afforded **22e** as colourless oil in 80% yield.

^{1}H NMR ($CDCl_3$) δ: 7.48 (d, 2H, J = 7.6 Hz); 7.40 (d, 2H, J = 8.2 Hz); 7.33 (t, 2H, J = 7.7 Hz); 7.23 (t, 1H, J = 7.3 Hz); 7.18 (d, 2H, J = 7.8 Hz); 3.26 (s, 3H); 3.18 (ddd, 1H, J = 4.2 Hz, J = 6.5 Hz, J = 10.4 Hz); 2.92 (ddd, 1H, J = 4.2 Hz, J = 6.5 Hz, J = 10.4 Hz); 2.15–1.82 (m, 8H); 1.39 (m, 2H).

^{13}C NMR ($CDCl_3$) δ: 175.6; 144.4; 141.1; 139.1; 128.8; 128.4; 127.1; 127.0; 126.8; 51.1; 50.2; 47.0; 32.2; 30.5; 28.6; 28.1; 27.5.

HR-MS(ES): Calcd for $C_{21}H_{24}O_2 + Na^+$: *m*/*z* 331.1674. Found *m*/*z* 331.1661.

5.4.8. Methyl 2-(4-*tert*-butylphenyl)cycloheptanecarboxylate (22g). Purification by Flash chromatography (CH_2Cl_2–pentane; 1:2) afforded **22g** as colourless oil in 78% yield.

^{1}H NMR ($CDCl_3$) δ: 7.27 (d, 2H, J = 8.2 Hz); 7.11 (d, 2H, J = 8.2 Hz); 3.29 (s, 3H); 3.18 (ddd, 1H, J = 4.2 Hz, J = 6.5 Hz, J = 10.6 Hz); 2.94 (ddd, 1H, J = 4.2 Hz, J = 6.5 Hz, J = 10.6 Hz); 2.19–1.81 (m, 8H); 1.45 (m, 2H), 1.29 (s, 9H).

^{13}C NMR ($CDCl_3$) δ: 175.7; 149.0; 142.1; 127.6; 124.9; 51.0; 50.3; 46.8; 34.4; 32.1; 31.5; 30.5; 28.6; 28.2; 27.4.

HR-MS(ES): Calcd for $C_{19}H_{28}O_2 + Na^+$: *m*/*z* 311.1987. Found *m*/*z* 331.1982.

5.4.9. Ethyl 4-(naphthalen-2-yl)-1,2,5,6-tetrahydropyridine-3-carboxylate (5d). To a solution of **13d** (49 mg, 0.13 mmol) in 5 mL CH_2Cl_2 was added 1 mL TFA (13.4 mmol) and the reaction mixture was stirred for 30 min at room temperature. The mixture was concentrated in vacuo and 10 mL of 1 M NaOH was added. The aqueous phase was extracted with 3×10 mL CH_2Cl_2 and the combined organic phases dried over $MgSO_4$ and concentrated in vacuo. Purification by Flash chromatography (CH_2Cl_2–MeOH; 6:1) afforded **5d** as a yellowish oil in 72% yield (26 mg).

^{1}H NMR ($CDCl_3$) δ: 7.83–7.78 (m, 3H); 7.61 (s, 1H); 7.48–7.43 (m, 2H); 7.30–7.28 (m, 1H); 3.87 (q, 2H, J = 7.1 Hz); 3.77 (m, 2H); 3.14 (t, 2H, J = 5.5 Hz); 2.54 (m, 2H); 2.42 (br. s, 1H); (t, 3H, J = 7.1 Hz).

^{13}C NMR ($CDCl_3$) δ: 167.8; 145.8; 139.9; 133.2; 132.6; 128.0; 127.8; 127.7; 127.6; 126.2; 126.0; 125.6; 125.4; 60.2; 45.9; 42.9; 32.8; 13.6.

HR-MS(ES): Calcd for $C_{18}H_{19}NO_2 + Na^+$: *m*/*z* 304.1313. Found *m*/*z* 304.1328.

5.4.10. Ethyl 4-(3,4-dichlorophenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (5a). To a solution of **13a** (60 mg, 0.15 mmol) in 5 mL CH_2Cl_2 was added 1 mL TFA (13.4 mmol) and the reaction mixture was stirred for 17 h at room temperature. The mixture was concentrated in vacuo and 10 mL of 1 M NaOH was added. The aqueous phase was extracted with 3×10 mL CH_2Cl_2 and the combined organic phases dried over $MgSO_4$ and concentrated in vacuo. Purification by Flash chromatography (CH_2Cl_2–MeOH; 6:1) afforded **5a** as a yellowish oil in 63% yield (28 mg).

^{1}H NMR ($CDCl_3$) δ: 7.39 (d, 1H, J = 8.2 Hz); 7.25 (d, 1H, J = 1.8 Hz); 6.99 (d, 1H, J = 8.3 Hz); 3.97 (q, 2H, J = 7.1 Hz); 3.74 (m, 2H); 3.26 (b. s, 1H); 3.12 (m, 2H); 2.44 (m, 2H); 0.98 (t, 3H, J = 7.1 Hz).

^{13}C NMR ($CDCl_3$) δ: 166.6; 144.0; 142.2; 132.3; 131.5; 130.2; 129.0; 127.7; 126.5; 60.6; 45.3; 42.4; 32.4; 13.8.

HR-MS(ES): Calcd for $C_{14}H_{15}Cl_2NO_2 + H^+$: *m*/*z* 300.0558. Found *m*/*z* 300.0552.

5.4.11. Ethyl 4-(3-nitrophenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (5q). To a solution of **13c** (48 mg, 0.13 mmol) in 5 mL CH_2Cl_2 was added 1 mL TFA (13.4 mmol) and the reaction mixture was stirred for 17 h at room temperature. The mixture was concentrated in vacuo and 10 mL of 1 M NaOH was added. The aqueous phase was extracted with 3×10 mL CH_2Cl_2 and the combined organic phases dried over $MgSO_4$ and concentrated in vacuo. Purification by Flash chromatography (CH_2Cl_2–MeOH; 6:1) afforded **5q** as a yellowish oil in 82% yield (27 mg).

^{1}H NMR ($CDCl_3$) δ: 8.15 (ddd, 1H, J = 1.9 Hz, J = 1.9 Hz, J = 7.3 Hz); 8.03 (m, 1H); 7.52–7.46 (m, 2H); 3.94 (q, 2H, J = 7.1 Hz); 3.77 (m, 2H); 3.20 (br. s, 1H); 3.14 (m, 2H); 2.49 (m, 2H); 0.93 (t, 3H, J = 7.1 Hz).

^{13}C NMR ($CDCl_3$) δ: 166.2; 148.2; 144.5; 144.1; 133.3; 129.1; 128.3; 122.3; 122.1; 60.6; 45.3; 42.4; 32.8; 13.8.

HR-MS(ES): Calcd for $C_{14}H_{16}N_2O_4 + H^+$: *m/z* 277.1188. Found *m/z* 277.1183.

5.4.12. (2-(3,4-Dichlorophenyl)cyclohex-1-enyl)methanol (23). 7a (250 mg, 0.88 mmol) dissolved in ether (5 mL) was added to a suspension of $LiAlH_4$ (250 mg, 6.58 mmol) in dry ether (10 mL). The mixture was refluxed for 1 h and after cooling to 0 °C quenched with water. The water phase was made acidic by 2 M HCl and the ether phase was isolated. The water phase was extracted with ether (10 mL), and the combined ether phases were dried ($MgSO_4$). Removal of the solvent under reduced pressure afforded **23** as a slightly yellow oil in 99% yield (224 mg). Compound **23** was used without further purification.

^{1}H NMR ($CDCl_3$) δ: 7.37 (d, 1H, J = 8.2 Hz); 7.26 (d, 1H, J = 2.0 Hz); 7.00 (dd, 1H, J_1 = 8.2 Hz, J_2 = 2.0 Hz); 3.92 (s, 2H); 2.27–2.21 (m, 4H); 1.74–1.69 (m, 4H).

^{13}C NMR ($CDCl_3$) δ: 143.0; 134.7; 134.1; 132.2; 130.6; 130.2; 127.8; 63.8; 32.0; 27.1; 23.1; 22.6.

HR-MS(ES): Calcd for $C_{13}H_{14}Cl_2O + Na^+$: *m/z* 279.0319. Found *m/z* 279.0325.

5.4.13. 2-(3,4-Dichlorophenyl)cyclohex-1-enecarbaldehyde (24). Oxalylchloride (0.1 mL, 1.18 mmol) was dissolved in dry dichloromethane (5 mL) and, after cooling to −78 °C, DMSO was added (1 mL). The mixture was stirred for 5 min at −78 °C followed by addition of **23** (207 mg, 0.80 mmol) in dry DCM (3 mL). The mixture was stirred for further 1 h at −78 °C followed by addition of Et_3N (3 mL). The mixture was stirred at rt. for 1 h and thereafter diluted with dichloromethane (10 mL). The organic solution was washed with satd aq solution of Na_2CO_3 (3 × 10 mL) and dried ($MgSO_4$). The solvent was removed in vacuo and purification by Flash chromatography (ether–pentane; 1:5) afforded **24** as colourless oil in 69% yield (142 mg).

^{1}H NMR ($CDCl_3$) δ: 9.49 (s, 1H); 7.46 (d, 1H, J = 8.2 Hz); 7.35 (d, 1H, J = 2.1 Hz); 7.08 (dd, 1H, J_1 = 8.2 Hz, J_2 = 2.1 Hz); 2.52–2.46 (m, 2H); 2.36–2.31 (m, 2H); 1.82–1.68 (m, 4H).

^{13}C NMR ($CDCl_3$) δ: 192.6; 156.2; 139.5; 136.9; 132.7; 132.6; 130.4; 130.3; 128.1; 33.8; 22.4; 22.4; 21.3.

HR-MS(ES): Calcd for $C_{13}H_{12}Cl_2O + Na^+$: *m/z* 277.0163. Found *m/z* 277.0164.

5.4.14. 1,2-Dichloro-4-(2-(prop-1-enyl)cyclohex-1-enyl) benzene (25). Ethyltriphenylphosphonium bromide (610 mg, 1.65 mmol) was added slowly to *n*-BuLi (1.6 M, 1.25 mL, 2.00 mmol) in dry THF (10 mL) at 0 °C. The mixture was stirred for 30 min at 0 °C, followed by addition of **24** (140 mg, 0.55 mmol) in dry THF (2 mL). The reaction mixture was warmed to rt. and stirred for further 14 h. Water (10 mL) and ether (15 mL) were added and the organic phase was isolated. The water phase was extracted with ether (10 mL) and the combined ether phases were dried ($MgSO_4$). The solvent was removed in vacuo and purification by Flash chromatography (pentane) afforded **25** as colourless oil in 76% yield (111 mg).

^{1}H NMR ($CDCl_3$) δ: 7.31 (d, 0.5H, J = 8.2 Hz); 7.23 (d, 0.5H, J = 8.3 Hz); 7.21–7.17 (m, 1H); 6.92 (dt, 1H, J_1 = 8.3 Hz, J_2 = 2.1 Hz); 5.94 (d, 0.5H, J = 15.5 Hz); 5.70 (d, 0.5H, J = 11.5 Hz); 5.61 (dq, 0.5H, J_1 = 15.6 Hz, J_2 = 6.6 Hz); 5.18 (dq, 0.5H, J_1 = 11.6 Hz, J_2 = 7.0 Hz); 2.25–2.12 (m, 4H); 1.70–1.58 (m, 7H).

^{13}C NMR ($CDCl_3$) δ: 144.5; 144.0; 133.8; 133.4; 133.1; 132.1; 131.8; 131.7; 130.9; 130.8; 130.7; 130.5; 130.3; 130.1; 129.8; 128.6; 128.1; 125.2; 123.9; 32.8; 31.5; 30.4; 25.7; 23.2; 23.2; 22.9; 22.7; 18.7; 15.1.

HR-MS(ES): Calcd for $C_{15}H_{16}Cl_2 + Na^+$: *m/z* 289.0527. Found *m/z* 289.0533.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2007.03.069.

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