Bioorganic & Medicinal Chemistry 17 (2009) 4900–4909

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

An extended study of dimeric phenyl tropanes

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ARTICLE INFO

Article history:
Received 6 January 2009
Revised 29 May 2009
Accepted 5 June 2009
Available online 10 June 2009

Keywords:
Monoamine transporter
Inhibition
Dimeric
Phenyl tropane

ABSTRACT

A series of dimeric phenyl tropanes consisting of two molecules of 4-chloro, 4-iodo or 4-(3-thiopheno)-phenyl tropane tethered together at the carboxylic acid moiety by a diamine or diol linker were prepared. The diamines used were a variety of linear, cyclic and aromatic diamines, while the diol tethered compounds were prepared by 'click' chemistry and contained a triazole in the linker. The new compounds were tested for binding to hDAT, hSERT and hNET. Amide linked chlorophenyl tropanes with an aromatic linker was found to be potent and selective DAT inhibitors with the best K_i value for hDAT being 6 nM. The ester linked halophenyl tropanes were more potent but displayed little selectivity in inhibition of monoamine transporter binding. Among the studied compounds an ester linker of 10 atoms between the tropane moieties gave the highest affinity. One monomeric phenyl tropane was made for comparison and was found to be less potent than the dimeric counterparts towards SERT and NET but remain highly active against DAT. Dimeric thiophenophenyl tropanes were in general found to be comparatively poor monoamine transporter binders, but significant gains of affinity of up to 45-fold could be achieved with selected dimeric chlorophenyl tropanes compared to the parent monomer. This observation implies that a secondary binding site that has affinity for phenyl tropanes, most likely the putative S2 site, is located within 13 Å of the primary central S1 binding site.

1. Introduction

The three biogenic monoamine neurotransmitters dopamine (DA), serotonin (SER) and norepinephrine (NE) control a variety of functions in the central nervous system. The transporter proteins for these neurotransmitters, the dopamine, serotonin and norepinephrine transporters (DAT, SERT and NET, respectively) belong to the class of Na^+/Cl^- dependent secondary active transporters. Their role is to carry DA, SER and NE across cell membranes and they therefore serve an important role in regulating the synaptic level of these neurotransmitters.

SERT plays a key role in many psychiatric diseases such as depression,[1] Parkinson's[2] and Alzheimer's diseases.[3] Significant progress has been made in the area of monoamine transporter inhibition and this has led to selective serotonin reuptake inhibitors (SSRIs) that are now the most common pharmacological treatment of mild and moderate depression offering several advantages compared to traditional tricyclic antidepressants. Still the SSRIs suffer from some limitations which are seen by a 2–6 weeks delay in the onset of therapeutic effect, and that each SSRI currently on the marked is only efficient in 60–70% of patients.[4] Development of novel SSRIs remains a very active research area in medicinal chemistry.

Studies have both shown that SERT furthermore is also partially involved in mediating the stimulating and addictive properties of cocaine,[5] but that inhibition of DAT is pivotal[6] in connection to this widely abused drug. Although there currently exits no therapeutic treatment for cocaine addiction it has been speculated it would be possible to prepare compounds that could antagonize the effect of cocaine while still allowing for DA transport. This idea has for a number of years spawned the development of selective DAT binders with compounds of the phenyl tropane type of which chloro-derivative **1** is a prime example (Fig. 1).[7] Recent results, however, have suggested that phenyl tropanes and dopamine have partially overlapping binding sites on DAT indicating that this approach for addiction treatment may be futile.[8] Based on homology modeling and biochemical experiments, however, the vestibule connecting the central binding site and the extracellular space is large enough to accommodate small molecules.[9] Indeed, the existence of a vicinal modulatory substrate site in the homologous bacterial leucine transporter (LeuT), the S2 site,[10] that is also able to accommodate tricyclic antidepressants[11,12] implies that a similar site may be present in both hDAT and hSERT. We hypothesized that a bivalent ligand successfully utilizing both the central binding site (S1) and the putative S2 site could potentially exhibit considerable gains

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doi:10.1016/j.bmc.2009.06.007

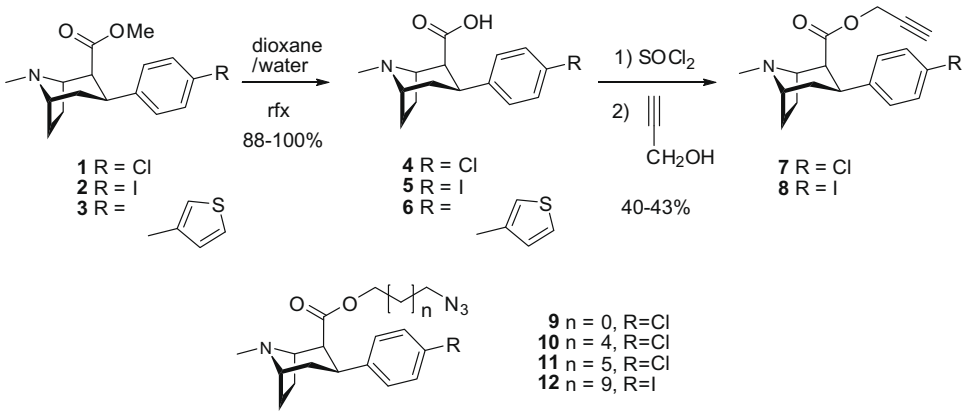

Figure 1. Synthesis of building blocks for dimeric phenyl tropanes.

in affinity and selectivity compared to the parent monovalent compounds (**1**–**3**, Fig. 1) only utilizing the central binding site. By utilizing the well known high affinity of tropanes we aim to establish a platform anchored to the central binding site from which we by linkers can probe the affinity of different attachments for the S2 site. The present study explores facile synthetic routes to linking tropanes with different moieties in order to identify novel ligands that also utilize the S2 site and by this strategy possibly create stronger and more selective ligands for DAT and/or SERT compared to the monovalent counterparts. Such compounds could be valuable as biochemical tools or potential novel medicinal candidates. To a first approximation ligands of a bivalent nature, which both has affinity for the S1 and S2 sites can be expected to show increased binding provided that the linker only has an insignificant effect. Fatty ester- or amide substituents in place of the parent methyl ester of cocaine and cocaine analogues have previously been found to be well tolerated by DAT, while SERT/NET binding was affected to a greater extent.[7]

Bivalent ligands for monoamine transporters have previously been explored with some success.[13,14]

In the present work we report a broader study of dimeric phenyl tropanes to establish the influence of (a) linker length beyond the 6 atoms used by Fandrick et al.,[13] (b) linker rigidity and (c) changes in attachment sites on binding affinity and selectivity. We here describe the synthesis of a number of these interesting dimeric molecules and a study of their binding to hDAT, hSERT and hNET.

2. Chemistry

A series of building blocks for the preparation of dimeric phenyl tropanes were prepared as outlined in Figure 1. Besides the 4-chlorophenyl tropane, the 4-iodophenyl and 4-thiophenophenyl derivatives were also included; the former was included because the 4-iodo derivatives generally are more potent than 4-chloro derivatives[7] and the latter was included because a 4-thiophene group recently has been shown to lead to strong and selective SERT binding.[15] The phenyl tropanes **1–3** were synthesized as previously described.[13,15] The hydrolysis of the methyl esters of these starting materials was carried out by the refluxing the substrates in dioxane–water[13] the basicity of the amine being the single means of hydrolysis. The corresponding acids **4–6** were obtained in 88–100% yield. These could be converted to propargyl esters **7** and **8** or azidoalkyl esters **9–12** (Fig. 1) by reaction with thionyl chloride followed by treatment with propargyl or azidoalkyl alcohol. The esters were obtained in 40–43% yield from the acids.

From these monomeric building blocks two sets of dimers could be synthesized (Fig. 2). From the acids **4–6** and selected diamines, the diamides **13**–**28** were prepared using coupling with benzotrizol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (BOP) in dichloromethane (DCM) in the presence of triethylamine (TEA).[13] A slight excess of diacid (1.1 equiv per amino-group) was used. Purification of the products was not always trivial, but chromatography in DCM containing small amounts of TEA was generally found to be an efficient method. Nevertheless, yields in these dimerizations varied widely. From 4-chlorophenyl tropane **4** the dimers **13**–**18** were obtained in yields given in Figure 3. Likewise, from the 4-thiophenyl tropane **6** dimers **19**–**28** was obtained in yields shown (Fig. 4). These yields reflect not only the different reactivity of the diamines, but also problems associated with purification of some of the products.

The azido alkyl and propargyl esters of linker type B were prepared via $CuSO_4$ and ascorbic acid catalyzed 'click' chemistry[16] in

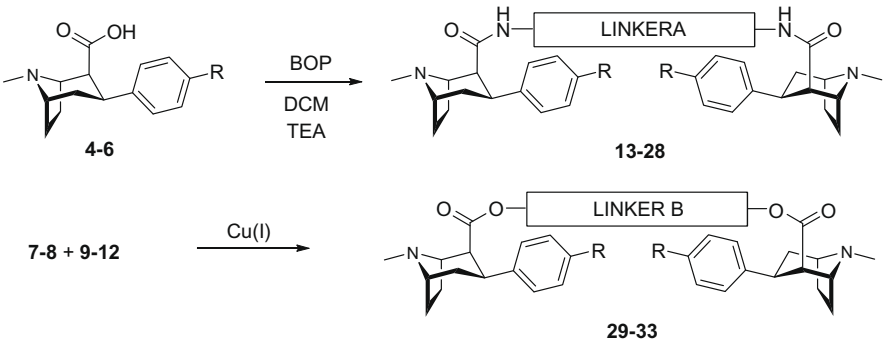

Figure 2. Synthesis of dimeric phenyl tropanes.

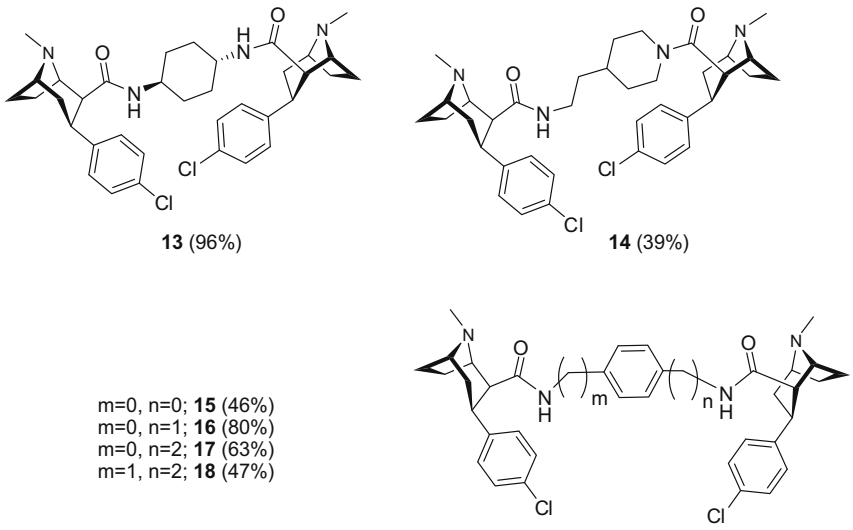

Figure 3. Diamide dimers with linker type A prepared from **4**. Values in brackets indicate isolated chemical yield for the coupling step.

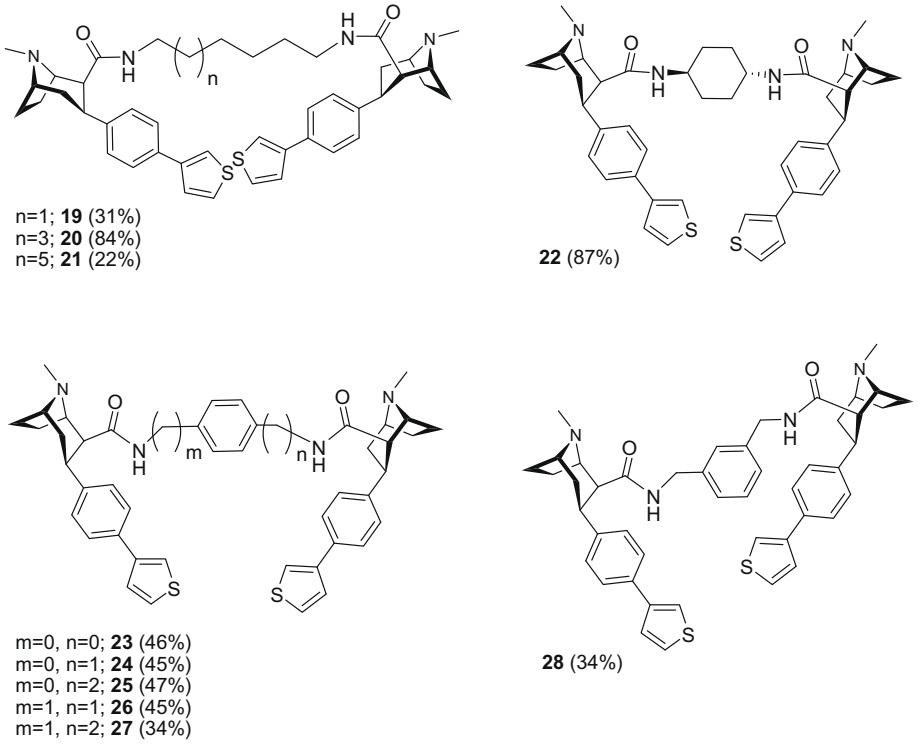

Figure 4. Diamide dimers with linker type A prepared from **6**. Values in brackets indicate isolated chemical yield for the coupling step.

water/*tert*-butanol to explore the effect of another type of linker on monoamine transporter binding. This gave the 1,4-substituted triazole-linked dimers **29**–**31** in fair to good yields as the only product (Fig. 5). The coupling of **8** and **12**, however, behaved sluggishly and was accordingly carried out at elevated temperature which resulted in the inseparable regioisomers **32** and **33** in a 69:31 ratio. Due to sterical hindrance the 1,4-triazole would be expected to be the major product, but no attempts were made to establish this.

To test the effect of having a dimeric as opposed to a monomeric presentation of the phenyl tropane skeleton and to investigate whether the linker functionality itself would have an effect on monoamine transporter binding, compound **37** was prepared (Fig. 6). Azido-alcohol was reacted with TMS–acetylene in the presence of $CuSO_4$/sodium ascorbate to yield triazole alcohol **35** in 40%. The silyl group was removed by treatment with tetrabutylammonium fluoride (TBAF) in 96% yield and the resulting alcohol **36** was reacted with the acid chloride made from carboxylic acid **4**. This gave triazole tropane ester **37** in 68% yield.

3. Biology

Data for binding of the new compounds to DAT, SERT and NET transporters were determined using competitive binding assays with a radioactive ligand. Cloned human monoamine transporters were expressed in the membrane of COS-1 cells and displacement of radioligand ^{125}I-(**2**) measured.

Compound **3** has been found to be a very potent and selective rSERT inhibitor in a binding assay employing rat brain homoge-

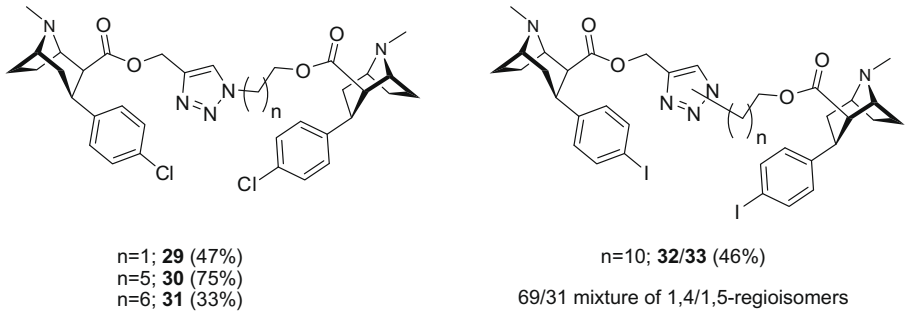

Figure 5. Triazole dimers with linker type B prepared from compounds **7**–**11**. Values in brackets indicate isolated chemical yield for the coupling step. Compound **32**/**33** was prepared as a mixture of regioisomers.

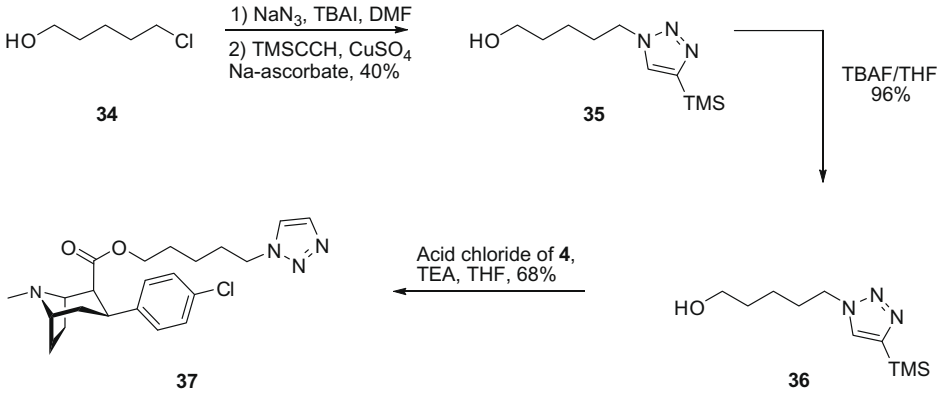

Figure 6. Synthesis of triazole tropane monomer **37**.

nates. Our assay confirmed that **3** is a potent SERT binder albeit the binding was 30 times weaker on hSERT from a heterologous expression system than previously found for rSERT from natural sources (Table 1).[15] Accordingly, the selectivity for the SERT is in our assay also much lower than previous findings. The discrepancy is presumably due to the difference in species and the source of monoamine transporters.

Table 1
K_i values for binding of hDAT, hSERT and hNET found as the mean value from at least 3 independent measurements

Substance	K_i binding (nM)			Selectivity	
	hDAT	hSERT	hNET	hSERT/ hDAT	hNET/ hDAT
1 (RTI-31)	2.7 ± 1.1	21 ± 0.5	39 ± 28	7.8	14
2 (RTI-55)	3.9 ± 1.1	4.2 ± 0.3	19 ± 2.8	1.1	4.9
3	2.5 ± 1.8	0.58 ± 0.2	26 ± 11	0.24	10
13	890 ± 570	4000 ± 2800	4900 ± 1900	4.6	5.5
14	180±100	2500 ± 130	440 ± 140	14	2.5
15	690 ± 230	3200 ± 320	5400 ± 3300	4.6	7.8
16	21 ± 9	1500 ± 400	810±350	74	39
17	6.6 ± 4	2600 ± 1100	180 ± 72	390	27
18	20 ± 16	65 ± 72	100 ± 100	3.3	5.2
19	540 ± 190	2100 ± 1100	2200 ± 650	4.0	4.0
20	690 ± 230	470 ± 220	1700 ± 400	0.68	2.4
21	350 ± 110	250 ± 9	1500 ± 700	0.72	4.4
22	1300 ± 730	810 ± 210	5000 ± 2100	0.62	3.8
23	210 ± 120	270 ± 76	1900 ± 550	1.3	9.4
24	800 ± 340	730 ± 230	2700 ± 100	0.92	3.4
25	710 ± 340	340 ± 150	3300 ± 580	0.48	4.6
26	93 ± 37	160 ± 80	620 ± 84	1.7	6.7
27	160 ± 17	62 ± 59	1300 ± 440	0.38	8.2
28	230 ± 170	860 ± 600	1200 ± 760	3.7	5.1
29	16 ± 9	27 ± 12	120 ± 36	1.6	7.3
30	1.0 ± 0.6	0.86 ± 0.79	8.5 ± 2	0.86	8.5
31	3.9 ± 2	3.5 ± 3	20 ± 8	0.89	5.1
32/33	140 ± 140	120 ± 51	220±140	0.91	1.6
37	5.5 ± 2	20 ± 18	380 ± 200	3.6	69

Inhibition was found to be competitive. Uncertainty is reported as SEM.

The dimeric analogues of **1** (Fig. 3) **13**–**18** varied considerably in binding affinity to DAT. Compounds **15–18** with an aromatic diamine tether were considerably more potent than aliphatic tethered compounds **13**–**14** consistent with favourable interactions with the aromatic residues (Y156 and F266 in hDAT) lining the short canal between the central (S1) binding site and the putative (S2) vestibular binding site.[10] The results also indicate that a relatively short tether, as in **13** and **15**, results in poor binding, which is in agreement with the previous study.[13] SERT- and NET binding are poor for all these compounds, making **16** and **17** quite selective compounds for the DAT.

The series of dimeric analogues of **3** (Fig. 4) compounds **19**–**28** are all quite poor monoamine transporter binders (Table 1). Despite the high affinity of the parent (**3**), analogues with very long tethers, **19**–**21**, are two orders of magnitude weaker against DAT and NET, while SERT affinity is affected even more. A significant decrease in binding affinity compared to monovalent **3** against all monoamine transporters is also observed for compounds **22**–**28** with benzene- or cyclohexyl containing linkers.

The triazole linked dimers **29**–**33** (Fig. 5) were, in terms of binding affinity, the most potent compounds in this study. The three compounds derived from **1**, **29**–**31** (Fig. 5), are strong DAT-binders with the analogues with long tethers (compounds **30** and **31**) being the most effective albeit not significantly outstanding compared to the parent compound (**1**) (Table 1). SERT binding is likewise strong especially for compound **30** being 24-fold more potent than the parent monomer (**1**). NET binding was found to be somewhat weaker and for the best compounds (**30** and **31**) in the range of monomeric affinity as found for DAT binding. Binding of the mixture of iodinated regioisomers **32** and **33** is considerably weaker

than **29**–**31**, which must also be true for the individual compounds even if there is a considerable difference in biological activity between them.

The selectivity of compounds **30**–**33** is essentially identical but due to their improved SERT affinity inverse that of the parent compound (**1**).

Monomeric phenyl tropane with a triazole linker (**37**) was found to be a potent hDAT binder with a low nanomolar affinity. For all three monoamine transporters the result of adding the linker as in monomeric **37** to the parent methylester (**1**) was found to be inconsequential (DAT and SERT) or deleterious (NET). However, the benchmark for the value of dimers can be found when comparing **37** with **30** and **31**. Compound **30** shows a moderate 5.5-fold tighter binding affinity for hDAT compared to monovalent **37**, whereas a more significant increase was found towards hSERT (23-fold) and even more pronounced hNET (45-fold).

Ligands selective for the putative S2 site over the S1 site of monoamine transporters may have interesting pharmaceutical prospects as well as applications in studying whether the S2 site plays the same role for the transport mechanism of monoamine transporters than what has been proposed for LeuT.[10] Even though small noncompetitive inhibitors and allosteric modulators of monoamine transporters exist there is, however, no evidence for these compounds binding selectively to S2. If such a S2 selective compound was to be developed the screening for the desired selectivity would be complicated. By using phenyl tropane as an anchor to the primary site via a linker it would be possible to screen for suitable lead compounds for S2 by determining the gain of affinity contributed by the potential lead compound to a dimer with phenyl tropane as the other subunit.

We set out to probe if a phenyl tropane in the primary binding site[8] could act as an anchor point for exploring affinity in the S2 site of different linked moieties and to identify which linker chemistries would be suitable. The considerable gains of affinity, up to 45-fold, of the dimer relative to the monomer suggest that improved affinity is certainly obtainable using this strategy and that phenyl tropane is also accepted in the juxtaposed site. We also show that attention to the chemical characteristics and length of the linker is very important to prevent that a poorly accepted linker cancels out the positive effects of the dimer approach.

The gains in affinity from homodimers of tropane analogues imply that the second tropane may be a suitable ligand also for the S2 site. The S2 site appears to be highly promiscous in LeuT[11,12,17] and may be forgiving for a phenyl tropane even though it was originally developed for high S1 site affinity. Accordingly, a second dimer subunit more optimized for the S2 site may yield even greater gains of affinity. The observations that antidepressants will bind to the S2 site of LeuT[11,12] suggests that a bivalent ligand linking a tropane analogue with an antidepressant analogue may exhibit the desired gains in affinity and selectivity should a similar site exist in the monoamine transporters. Inhibition data of the superior compound **30** (Table 1) imply that two sites are separated by 13 Å.[18] Building on the knowledge gathered in the present study linked bivalent tropane-tricyclic antidepressants are being pursued by us.

In summary, we have synthesized a diverse series of bivalent phenyl tropanes with different linkers to evaluate the effect of both linker composition and a secondary tropane on inhibition of monoamine transporters. It was found that bivalent chlorophenyl tropanes with aromatic diamine linkers are potent and selective binders of the hDAT. Chlorophenyl tropanes with intermediate length ester tethers were likewise found to be strong hDAT binders, but for these compounds inhibition of hSERT and hNET was also significant. Finally, it was observed that bivalent 3-thiophenophenyl tropanes were poor monoamine transport binders despite the high affinity of the parent monomeric 3-thiophenophenyl tropane.

4. Experimental

4.1. General

All reactions were carried out under nitrogen atmosphere and only dried glassware from the oven (~125–150 °C) was used. Evaporation on the evaporator to remove solvents was done under reduced pressure unless otherwise stated, and the temperature was kept around 40 °C. Dry solvents were used for the reactions. Dichloromethane was dried by distillation over CaH_2 and diethyl ether was dried over sodium wire. As the stationary phase for the chromatography Fluka Silica Gel 60 (230–400 mesh) were used. TLC-plates were performed on silica gel (Merck Kieselgel, 60 F_{254}). ^{1}H NMR and ^{13}C NMR spectra were recorded at a Varian Mercury 400 spectrometer. ^{1}H NMR spectra were recorded at 400 MHz in chloroform-*d* or D_2O. ^{13}C NMR spectra were recorded at 100 MHz in chloroform-*d* or D_2O. HRMS spectra were recorded at a Micromass LC-TOF instrument by using electro spray in positive ionization mode.

4.1.1. 3β-(4-Thiopheno-3-yl-phenyl) tropane-2β-carboxylic acid (6)

To a flask with 2β-carbomethoxy-3β-(4-thiopheno-3-yl-phenyl)tropane (**3**, 0.21 g, 0.62 mmol) was added 15 mL H_2O and 15 mL dioxane. The mixture was refluxed overnight. The solvent was removed under reduced pressure and lyophilized to dryness. The product, 0.201 g of a white solid, **6** (0.61 mmol, 100%) was obtained and used without further purification. ^{1}H NMR (D_2O) δ 1.88 (1H, dt, J_d = 14.6 Hz and J_t = 4.0 Hz, H4$_{endo}$), 2.09–2.21 (2H, m, H6$_{endo}$ and H7$_{endo}$), 2.31–2.49 (2H, m, H6$_{exo}$ and H7$_{exo}$), 2.74 (1H, dt, J_d = 2.8 Hz and J_t = 14.6 Hz, H4$_{exo}$), 2.80 (1H, m, H2), 2.82 (3H, s, NCH_3), 3.42 (1H, dt, J_d = 13.2 Hz and J_t = 6.1 Hz, H3), 3.99 (2H, m, H1 and H5), 7.36 (2H, dm, J_d = 8.6 Hz), 7.54–7.57 (2H, m), 7.68 (2H, dm, J_d = 8.6 Hz), 7.70 (1H, dd, J_d = 1.6 Hz and J_d = 2.8 Hz). ^{13}C NMR (D_2O) δ 23.5, 23.8, 32.2, 33.3, 38.3, 52.7, 63.5, 65.9, 120.9, 126.3, 126.4, 127.4, 128.5, 134.2, 139.5, 141.5, 179.3. HRMS(ES): calculated for **6** + Na *m*/*z* 350.1191. Found *m*/*z* 350.1196.

4.2. General synthesis of 3β-(4-halophenyl) tropane-2β-carboxylic acid prop-2-ynyl or azidoalkyl esters (7–12)[19]

To a flask containing 3β-(4-halophenyl)tropane-2β-carboxylic acid (1 equiv, halo = Cl or I) was added 4 mL thionyl chloride. The mixture was stirred for 90 min and excess of thionyl chloride was removed under reduced pressure to afford 3β-(4-halophenyl)tropane-2β-carbonyl chloride. This was dissolved in 10 mL dichloromethane. Propargyl or azidoalkyl alcohol (5 equiv) was added. Then triethylamine (5 equiv) and the mixture stirred overnight. To the solution was added 20 mL H_2O and the organic layer was separated. The aqueous layer was extracted with 3 × 20 mL dichloromethane, and the combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure.

4.2.1. 3β-(4-Chlorophenyl)tropane-2β-carboxylic acid prop-2-ynyl ester (7)

The amount of starting material, **4** used for the reaction was 0.353 g (1.27 mmol). The product was purified by flash chromatography (49.5% pentane–49.5% diethyl ether–1% triethylamine) to afford 0.172 g of a white solid of **7** (0.54 mmol, 43%). ^{1}H NMR ($CDCl_3$) δ 1.49–1.68 (3H, m, H4$_{endo}$, H6$_{endo}$ and H7$_{endo}$), 1.89–2.20 (2H, m, H6$_{exo}$ and H7$_{exo}$), 2.15 (3H, s, NCH_3), 2.32 (1H, m, –C≡C*H*), 2.48 (1H, dt, J_d = 2.4 Hz and J_t = 12.4 Hz, H4$_{exo}$), 2.84 (1H, m, H2), 2.90 (1H, dt, J_d = 12.4 Hz and J_t = 5.2 Hz, H3), 3.29 (1H, m, H5), 3.52 (1H, m, H1), 4.37 (1H, dd, J_d = 15.6 Hz and J_d = 12.8 Hz, OCH_2–C≡CH), 4.53 (1H, dd, J_d = 15.6 Hz and J_d = 2.8 Hz, OCH_2–C≡CH), 7.11 (2H, dm, J_d = 8.2 Hz), 7.15 (2H, dm, J_d = 8.2 Hz). ^{13}C NMR

($CDCl_3$) δ 25.1, 25.8, 33.2, 33.8, 41.8, 51.3, 52.4, 62.1, 65.0, 74.4, 77.8, 128.0, 128.7, 131.5, 141.2, 170.3. HRMS(ES) calculated for **7** + H *m*/*z* 318.1261. Found *m*/*z* 318.1265.

4.2.2. 3β-(4-Iodophenyl)tropane-2β-carboxylic acid prop-2-ynyl ester (8)

The amount of starting material **5** used for the reaction was 0.482 g (1.30 mmol). The product was purified by flash chromatography (49.5% pentane–49.5% diethyl ether–1% triethylamine) to afford 0.210 g of a white solid of **8** (0.51 mmol, 40%). ^{1}H NMR ($CDCl_3$) δ 1.58–1.75 (3H, m, H4$_{endo}$, H6$_{endo}$ and H7$_{endo}$), 2.05–2.26 (2H, m, H6$_{exo}$ and H7$_{exo}$), 2.23 (3H, s, NC*H*$_3$), 2.39 (1H, m, –C≡C*H*), 2.55 (1H, dt, J_d = 2.8 Hz and J_t = 12.4 Hz, H4$_{exo}$), 2.92 (1H, m, H2), 2.95 (1H, dt, J_d = 12.8 Hz and J_t = 4.8 Hz, H3), 3.36 (1H, m, H5), 3.60 (1H, m, J_d = 6.4 Hz, H1), 4.45 (1H, dd, J_d = 15.6 Hz and J_d = 2.4 Hz, OC*H*$_2$–C≡CH), 4.61 (1H, dd, J_d = 15.6 Hz and J_d = 2.4 Hz, OC*H*$_2$–C≡CH), 7.01 (2H, dm, J_d = 8.4 Hz), 7.58 (2H, dm, J_d = 8.4 Hz). ^{13}C NMR ($CDCl_3$) δ 25.1, 25.8, 33.4, 33.6, 41.9, 51.4, 52.4, 62.1, 65.0, 74.5, 77.8, 91.2, 129.5, 136.9, 142.5, 170.3. HRMS(ES) calculated for **8** + H *m*/*z* 410.0617. Found *m*/*z* 410.0619.

4.2.3. Synthesis of 3β-(4-Iodophenyl)tropane-2β-carboxylic acid 9-azido-undecyl ester (12)

The amount of 3β-(4-iodophenyl)tropane-2β-carboxylic acid used was 74 mg (0.2 mmol) leading to 108 mg of a yellow oil of **12**. ^{1}H NMR ($CDCl_3$) δ 0.93 (2H, quint, J_{quint} = 7.5 Hz, CH_2–*CH*$_2$–CH_2), 1.12–1.44 (13H, m, CH_2–C*H*$_2$–CH_2) 1.57 (2H, quint, J_{quint} = 7.5 Hz, CH_2–C*H*$_2$–CH_2) 1.76 (1H, quint, J_{quint} = 7.5 Hz, CH_2–C*H*$_2$–CH_2), 2.07 (1H, dm, J_d = 14.4 Hz, H4$_{endo}$), 2.26–2.42 (2H, m, H6$_{endo}$ and H7$_{endo}$), 2.51–2.63 (2H, m, H6$_{exo}$ and H7$_{exo}$), 2.87 (1H, dt, J_d = 2.8 Hz and J_t = 14.4 Hz, H4$_{exo}$), 3.06 (3H, s, NC*H*$_3$), 3.13 (1H, m, H2), 3.25 (1H, t, J_t = 7.0 Hz, C*H*$_2$N$_3$), 3.52 (1H, m, H3), 3.53 (1H, t, J_t = 7.0 Hz, C*H*$_2$N$_3$), 3.76 (1H, dt, J_d = 10.8 Hz and J_t = 6.8 Hz, OC*H*$_2$–), 3.89 (1H, dt, J_d = 10.8 Hz and J_t = 6.8 Hz, OC*H*$_2$–), 4.25 (1H, m, H5), 4.32 (1H, m, H1), 7.05 (2H, dm, J_d = 8.4 Hz), 7.67 (2H, dm, J_d = 8.4 Hz). ^{13}C NMR ($CDCl_3$) δ 24.2, 25.2, 25.5, 26.7, 26.9, 27.9, 28.9, 29.1, 29.3, 32.4, 32.7, 33.7, 41.3, 45.5, 49.1, 51.6, 64.6, 66.2, 67.0, 93.5, 129.8, 137.3, 138.0, 174.3. HRMS(ES) calculated for **12** + H *m*/*z* 567.2196. Found *m*/*z* 567.2192.

4.3. General synthesis of 1, *N*-di-3β-(4-chlorophenyl)tropane-2β-carboxy amide linked molecules (13–18)

To a solution of benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate, BOP (2.8 equiv) in 10 mL dichloromethane was added triethylamine (20 equiv) and the mixture was stirred at 0 °C for 20 min. 3β-(4-Chlorophenyl)tropane-2β-carboxylic acid, **4** (2.2 equiv) was added and the mixture was stirred at 0 °C for 30 min. The linker/diamine (1 equiv) was added and the mixture was stirred over night at room temperature. H_2O (10 mL) was added to the reaction mixture and the organic layer was separated. The aqueous layer was extracted with 3 × 10 mL ethyl acetate. The combined organic layers was dried over magnesium sulfate and concentrated under reduced pressure.

4.3.1. *trans*-1,4-Di[3β-(4-chlorophenyl)tropane-2β-carbonyl-amino] cyclohexane (13)

The reaction was performed with 35 mg (0.31 mmol) of *trans*-1,4-diaminocyclohexane. The residue was purified by flash chromatography (99% dichloromethane, 1% triethylamine) to afford 0.186 g. of white crystals, **13** (0.29 mmol, 96%). ^{1}H NMR ($CDCl_3$) δ 1.25 (4H, m) 1.58–1.71 (6H, m, H4$_{endo}$, H6$_{endo}$ and H7$_{endo}$), 1.85 (4H, m), 2.00–2.24 (6H, m, H4$_{exo}$, H6$_{exo}$ and H7$_{exo}$), 2.20 (6H, s, NC*H*$_3$), 2.87 (2H, m, H2), 3.05 (2H, dt, J_d = 13.6 Hz and J_t = 5.6 Hz, H3), 3.25 (2H, m, H5) 3.29 (2H, m, H1), 3.59 (2H, m), 7.07 (4H, dm, J_d = 8.4 Hz), 7.19 (4H, dm, J_d = 8.4 Hz), 9.55 (2H, d, J_d = 8.0 Hz, –C=O–N*H*–). ^{13}C NMR ($CDCl_3$) δ 24.6, 25.9, 31.0, 31.5, 34.3, 35.0, 40.7, 46.0, 54.0, 60.9, 63.8, 128.2, 129.0, 132.2, 139.7, 171.4. HRMS(ES) calculated for **13** + H *m*/*z* 637.3076. Found *m*/*z* 637.3077.

4.3.2. 1-[3β-(4-Chlorophenyl)tropane-2β-carbonyl-amino]-2-[3β-(4-chlorophenyl)tropane-2β-carbonyl-piperidine-4-yl] ethane (14)

For this experiment 43 mg (0.21 mmol) of 2-piperidin-4-yl-ethylamine was employed. The residue was purified by flash chromatography (99% dichloromethane, 1% triethylamine) to afford 54 mg. of a clear oil, **14** (0.083 mmol, 39%). ^{1}H NMR ($CDCl_3$) δ 0.77 (1H, m), 1.00 (1H, m), 1.15–1.43 (4H, m), 1.58–1.75 (7H, m, H4$_{endo}$, H4$_{endo'}$, H6$_{endo}$, H6$_{endo'}$, H7$_{endo}$, H7$_{endo'}$), 2.04–2.32 (6H, m, H4$_{exo}$, H4$_{exo'}$, H6$_{exo}$, H6$_{exo'}$, H7$_{exo}$ and H7$_{exo'}$), 2.21 (6H, s, NC*H*$_3$), 2.45 (1H, m, H2/H2′), 2.82 (1H, dt, J_d = 12.2 Hz and J_t = 2.8 Hz), 2.92 (1H, m, H2/H2′), 2.93 (1H, dt, J_d = 12.8 Hz and J_t = 4.4 Hz), 3.08 (2H, m, H3 and H3′), 3.14(2H, m), 3.25–3.32 (2H, m, H5 and H5′), 3.29 (1H, m, H1/H1′), 3.38 (1H, m, H1/H1′), 3.76 (1H, m), 4.46 (1H, m), 7.07 (2H, dm, J_d = 8.4 Hz), 7.15–7.20 (6H, m) 9.42 (1H, m, –C=O–N*H*–). ^{13}C NMR ($CDCl_3$) δ 24.9, 26.2, 34.1, 34.4, 35.4, 36.2, 36.5, 41.3, 53.1, 54.3, 61.3, 62.3, 64.0, 128.1, 128.4, 128.9, 129.0, 131.2, 132.4, 139.9, 142.5, 171.4. HRMS(ES) calculated for **14** + H *m*/*z* 651.3232. Found *m*/*z* 651.3835.

4.3.3. 1,4-Di[3β-(4-chlorophenyl)tropane-2β-carbonyl-amino] benzene (15)

For this experiment 19 mg (0.18 mmol) of 1,4-diaminobenzene was used. The product was purified by flash chromatography (99% dichloromethane, 1% triethylamine) to afford 0.186 g of a red solid of **15** (0.053 mmol, 46%). ^{1}H NMR ($CDCl_3$) δ 1.56–1.76 (6H, m, H4$_{endo}$, H6$_{endo}$ and H7$_{endo}$), 2.04–2.36 (6H, m, H4$_{exo}$, H6$_{exo}$ and H7$_{exo}$), 2.38 (6H, s, NC*H*$_3$), 2.54 (2H, m, H2), 3.17 (2H, dt, J_d = 13.6 Hz and J_t = 6.4 Hz, H3) 3.44 (4H, m, H1 and H5), 7.11 (4H, dm, J_d = 8.4 Hz), 7.21 (4H, dm, J_d = 8.4 Hz) 7.34 (4H, s), 12.0 (2H, s, –C=O–N*H*–). ^{13}C NMR ($CDCl_3$) δ 25.0, 26.3, 35.4, 35.5, 41.0, 55.0, 61.4, 63.8, 120.4, 128.5, 129.2, 132.6, 134.3, 139.7, 170.2. HRMS(ES) calculated for **15** + H *m*/*z* 630.2528. Found *m*/*z* 630.2542.

4.3.4. 1-[3β-(4-Chlorophenyl)tropane-2β-carbonyl-amino]-1-[3β-(4-chlorophenyl)tropane-2β-carbonyl-aminobenzene-4-yl] methane (16)

The reaction was performed with 40 mg (0.327 mmol) of 4-aminobenzylamine. The residue was purified by flash chromatography (99% dichloromethane, 1% triethylamine) to afford 0.168 g of a red solid **16** (0.26 mmol, 80%). ^{1}H NMR ($CDCl_3$) δ 1.56–1.84 (6H, m, H4$_{endo}$, H4$_{endo'}$, H6$_{endo}$, H6$_{endo'}$, H7$_{endo}$ and H7$_{endo'}$), 2.04–2.32(5H, m, H4$_{exo}$/H4$_{exo'}$, H6$_{exo}$, H6$_{exo'}$, H7$_{exo}$ and H7$_{exo'}$), 2.21 (3H, s, NC*H*$_3$), 2.40 (1H, m, H4$_{exo}$/H4$_{exo'}$), 2.41 (3H, s, NC*H*$_3$), 2.57 (2H, m, H2 and H2′), 3.10 (1H, dt, J_d = 14.0 Hz and J_t = 6.4 Hz, H3/H3′), 3.19 (1H, dt, J_d = 14.0 Hz and J_t = 6.4 Hz, H3/H3′), 3.30 (1H, m, H5/H5′), 3.34 (1H, m, H5/H5′), 3.45 (2H, m, H1 and H1′), 4.29 (2H, d, J_d = 6.0 Hz), 7.04 (2H, dm, J_d = 8.4 Hz), 7.12 (2H, dm, J_d = 8.8 Hz), 7.18 (4H, dm, J_d = 8.8 Hz), 7.20 (2H, dm, J_d = 8.8 Hz), 7.38 (2H, dm, J_d = 8.4 Hz) 9.86 (1H, t, J_t = 6.0 Hz, –C=O–N*H*–CH_2–), 12.08 (1H, s, –C=O–N*H*-C_6H_4–). ^{13}C NMR ($CDCl_3$): δ 24.8, 24.9, 26.0, 26.1, 34.6, 35.2, 35.2, 40.8, 41.0, 46.2, 54.1, 54.9, 61.0, 61.2, 63.6, 63.8, 119.7, 128.2, 128.2, 128.3, 129.0, 129.0, 132.1, 132.4, 134.2, 137.3, 139.5, 139.6, 170.4, 172.1. HRMS(ES) calculated for **16** + H *m*/*z* 645.2763. Found *m*/*z* 645.2753.

4.3.5. 1-[3β-(4-Chlorophenyl)tropane-2β-carbonyl-amino]-2-[3β-(4-chlorophenyl)tropane-2β-carbonyl-aminobenzene-4-yl] ethane (17)

Amount of 4-(2-amino-ethyl)phenyl amine (linker) added to the reaction was 44 mg. (0.32 mmol). The residue was purified

by flash chromatography (99% dichloromethane, 1% triethylamine) to afford 0.134 g of a red solid, **17** (0.20 mmol, 63%). ^{1}H NMR ($CDCl_3$) δ 1.45–1.82 (6H, m, H4$_{endo}$, H4$_{endo'}$, H6$_{endo}$, H6$_{endo'}$, H7$_{endo}$ and H7$_{endo'}$), 1.88–2.34 (6H, m, H4$_{exo}$, H4$_{exo'}$, H6$_{exo}$, H6$_{exo'}$, H7$_{exo}$ and H7$_{exo}$), 2.07 (3H, s, NCH_3), 2.38 (3H, s, NCH_3), 2.43 (1H, m, H2/H2′), 2.55 (1H, m, H2/H2′), 2.76 (2H, m), 3.00 (1H, dt, J_d = 13.6 Hz and J_t = 6.2 Hz, H3/H3′), 3.15 (2H, dt, J_d = 13.6 Hz and J_t = 6.2 Hz, H3/H3′), 3.19 (2H, m, H5 and H5′), 3.42 (4H, m, H1, H1′), 6.88 (2H, dm, J_d = 8.8 Hz), 7.01 (2H, dm, J_d = 8.4 Hz), 7.06 (2H, dm, J_d = 8.4 Hz), 7.15 (4H, dm, J_d = 8.4 Hz), 7.16 (2H, dm, J_d = 8.4 Hz), 7.39 (2H, dm, J_d = 8.8 Hz), 9.52 (1H, t, J_t = 5.0 Hz, –C═O–N*H*–CH$_2$–), 11.98 (1H, s, –C═O–N*H*–C$_6$H$_4$–). ^{13}C NMR ($CDCl_3$) δ 24.8, 25.0, 26.1, 26.2, 34.9, 34.9, 35.1, 35.2, 35.3, 40.4, 40.9, 41.0, 54.3, 55.0, 61.1, 61.3, 63.7, 119.8, 128.3, 128.4, 129.1, 129.1, 129.2, 132.2, 132.4, 134.7, 137.0, 139.6, 140.0, 170.3, 172.4. HRMS(ES) calculated for **17** + H *m*/*z* 659.2920. Found *m*/*z* 659.2835.

4.3.6. 1-[3β-(4-Chlorophenyl)tropane-2β-carbonyl-amino]-2-[3β-(4-chlorophenyl)tropane-2β-carbonyl-aminomethylbenzene-4-yl] ethane (18)

The reaction was performed with 39 mg (0.176 mmol) of 2-(4-aminomethylphenyl)-ethylamine. The residue was purified by flash chromatography (99% dichloromethane, 1% triethylamine) to afford 56 mg. of a red oil, **18** (0.083 mmol, 47%). ^{1}H NMR ($CDCl_3$) δ 1.48–1.74 (6H, m, H4$_{endo}$, H4$_{endo'}$, H6$_{endo}$, H6$_{endo'}$, H7$_{endo}$ and H7$_{endo'}$), 1.98-2.26 (6H, m, H4$_{exo}$, H4$_{exo'}$, H6$_{exo}$, H6$_{exo'}$, H7$_{exo}$ and H7$_{exo}$), 2.02 (3H, s, NCH_3), 2.18 (3H, s, NCH_3), 2.45 (1H, m, H2/H2′), 2.59 (1H, m, H2/H2′), 2.81 (2H, dt, J_d = 3.2 Hz and J_t = 7.0 Hz), 3.09 (1H, dt, J_d = 12.6 Hz and J_t = 6.2 Hz, H3/H3′), 3.09 (2H, dt, J_d = 12.6 Hz and J_t = 6.2 Hz, H3/H3′), 3.18 (2H, m, H5 and H5′), 3.25 (1H, m, H1/H1′), 3.33 (1H, m, H1/H1′), 3.40 (1H, dd, J_d = 6.0 Hz and J_d = 12.0 Hz), 3.47 (1H, dd, J_d = 6.0 Hz and J_d = 12.0 Hz), 4.32 (2H, t, J_d = 6.0 Hz), 6.96 (2H, dm, J_d = 8.4 Hz), 7.05 (2H, dm, J_d = 8.4 Hz), 7.17 (2H, dm, J_d = 8.4 Hz), 7.18 (2H, dm, J_d = 8.4 Hz), 7.20 (4H, s), 9.55 (1H, t, J_t = 5.6 Hz, –C═O–N*H*–CH$_2$–), 9.90 (1H, t, J_t = 5.6 Hz, –C═O–N*H*–CH$_2$–). ^{13}C NMR ($CDCl_3$) δ 24.5, 24.6, 25.8, 25.8, 34.4, 34.5, 34.9, 34.9, 35.0, 39.8, 40.7, 40.8, 42.3, 53.9, 54.0, 60.8, 60.9, 63.4, 63.6, 127.5, 128.0, 128.6, 128.7, 128.8, 132.0, 137.1, 138.1, 139.4, 139.5, 172.0, 172.1. HRMS(ES) calculated for **18** + H *m*/*z* 673.3076. Found *m*/*z* 673.3082.

4.4. General synthesis of dimers of 1,*n*-di-3β-(4-thiophene-3-yl-phenyl)tropane-2β-carboxy amide linked molecules (19–28)

To a solution of benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate, BOP (2.8 equiv) in 10 mL dichloromethane was added triethylamine (20 equiv) and the mixture was stirred at 0 °C for 20 min. 2β-Carboxylic acid-3β-(4-thiophene-3-yl-phenyl)tropane, **6** (2.2 equiv) was added and the mixture was stirred at 0 °C for 30 min. The linker/diamine (1 equiv) was added, and the mixture was stirred overnight at room temperature. H_2O (10 mL) was added to the reaction mixture, and the organic layer separated. The aqueous layer was extracted with 3 × 10 mL ethyl acetate. The combined organic layers was dried over magnesium sulfate and concentrated under reduced pressure.

4.4.1. 1,6-Di[3β-(4-thiophene-3-yl-phenyl)tropane-2β-carbonyl-amino] hexane (19)

The experiment was carried out with 19 mg (0.161 mmol) of 1,6-amino hexane. The residue was purified by flash chromatography (99% dichloromethane, 1% triethylamine) to afford 37 mg of a white solid, **19** (0.05 mmol, 31%). ^{1}H NMR ($CDCl_3$) δ 1.29–1.33 (4H, m, H21) 1.44 (4H, m, H20) 1.58–1.68 (6H, m, H4$_{endo}$, H6$_{endo}$ and H7$_{endo}$), 2.00–2.25 (6H, m, H4$_{exo}$, H6$_{exo}$ and H7$_{exo}$), 2.50 (6H, s, NCH_3), 2.50 (2H, m, H2), 3.02–3.13 (6H, m, H3), 3.25 (4H, m, H1 and H5), 7.12 (4H, dm, J_d = 8.4 Hz), 7.25 (4H, m), 7.29 (2H, m), 7.40 (2H, dm, J_d = 8.4 Hz), 9.44 (2H, t, J_t = 5.4 Hz, –C═O–N*H*–). ^{13}C NMR ($CDCl_3$) δ 24.6, 25.9, 26.7, 29.6, 34.7, 35.3, 38.5, 41.0, 54.1, 61.0, 63.9, 119.6, 125.5, 126.0, 126.1, 127.8, 133.9, 140.1, 142.1, 172.2. HRMS(ES) calculated for **19** + H *m*/*z* 735.3766. Found *m*/*z* 735.3748.

4.4.2. 1,8-Di[3β-(4-thiophene-3-yl-phenyl)tropane-2β-carbonyl-amino] octane (20)

The experiment was performed with 22 mg (0.15 mmol) of 1,8-aminooctane. The residue was purified by flash chromatography (99% dichloromethane, 1% triethylamine) to afford 98 mg of a white solid, **20** (0.05 mmol, 84%). ^{1}H NMR ($CDCl_3$) δ 1.26–1.39 (8H, m), 1.50 (4H, m), 1.62–1.78 (6H, m, H4$_{endo}$, H6$_{endo}$ and H7$_{endo}$), 2.04–2.31 (6H, m, H4$_{exo}$, H6$_{exo}$ and H7$_{exo}$), 2.26 (6H, s, NCH_3), 2.56 (2H, m, H2), 3.09–3.18 (6H, m, H3), 3.33 (4H, m, H1 and H5), 7.19 (4H, dm, J_d = 8.0 Hz), 7.33 (4H, m), 7.48 (2H, m), 7.48 (2H, dm, J_d = 8.0 Hz), 9.51 (2H, t, J_t = 5.2 Hz, –C═O–N*H*–). ^{13}C NMR ($CDCl_3$) δ 24.9, 26.3, 27.3, 29.4, 29.8, 35.1, 35.7, 38.9, 41.3, 54.4, 61.3, 64.2, 119.9, 125.9, 126.3, 126.5, 128.2, 134.2, 140.4, 142.4, 172.6. HRMS(ES) calculated for **20** + H *m*/*z* 763.4079. Found *m*/*z* 763.4120.

4.4.3. 1,10-Di[3β-(4-thiophene-3-yl-phenyl)tropane-2β-carbonyl-amino] decane (21)

The experiment was performed with 28 mg (0.161 mmol) of 1,10-aminodecane. The residue was purified by flash chromatography (99% dichloromethane, 1% triethylamine) to afford 28 mg of a white solid, **21** (0.035 mmol, 22%). ^{1}H NMR ($CDCl_3$) δ 1.24 (12H, m), 1.43 (4H, m), 1.55–1.71 (6H, m, H4$_{endo}$, H6$_{endo}$ and H7$_{endo}$), 2.00–2.28 (6H, m, H4$_{exo}$, H6$_{exo}$ and H7$_{exo}$), 2.20 (6H, s, NCH_3), 2.52 (2H, m, H2), 3.04–3.11 (6H, m, H3), 3.26 (4H, m, H1 and H5), 7.12 (4H, dm, J_d = 8.0 Hz), 7.26 (4H, m), 7.30 (2H, m) 7.40 (2H, dm, J_d = 8.0 Hz), 9.43 (2H, t, J_t = 5.2 Hz, –C═O–N*H*–). ^{13}C NMR ($CDCl_3$) δ 25.0, 26.3, 27.4, 29.4, 29.7, 29.8, 35.1, 35.7, 39.0, 41.4, 54.4, 61.5, 64.3, 120.0, 125.9, 126.4, 126.5, 128.2, 134.3, 140.4, 142.4, 172.6. HRMS(ES) calculated for **21** + H *m*/*z* 791.4392. Found *m*/*z* 791.4378.

4.4.4. *trans*-1,4-Di[3β-(4-thiophene-3-yl-phenyl)tropane-2β-carbonyl-amino] cyclohexane (22)

The reaction was performed with 17 mg (0.15 mmol) of *trans*-1,4-diamino cyclohexane. The product was purified by flash chromatography (99% dichloromethane, 1% triethylamine) to afford 95 mg of a white solid, **22** (0.13 mmol, 87%). ^{1}H NMR ($CDCl_3$) δ 1.32 (4H, m), 1.63–1.77 (6H, m, H4$_{endo}$, H6$_{endo}$ and H7$_{endo}$) 1.92 (4H, m) 2.23–2.70 (4H, m, H6$_{exo}$ and H7$_{exo}$), 2.20 (6H, s, NCH_3), 2.29 (2H, dt, J_d = 6.8 Hz and J_t = 13.0 Hz, H4$_{exo}$), 2.53 (2H, m, H2), 3.13 (2H, dt, J_d = 12.8 Hz and J_t = 6.2 Hz, H3), 3.29 (4H, m, H1 and H5), 3.67 (2H, m), 7.07 (4H, dm, J_d = 8.4 Hz) 7.34 (2H, dd, J_d = 4.8 Hz and J_d = 2.8 Hz), 7.35 (2H, dd, J_d = 4.8 Hz and J_d = 1.6 Hz), 7.39 (2H, dd, J_d = 2.8 Hz and J_d = 1.6 Hz), 7.49 (4H, dm, J_d = 8.4 Hz), 9.59 (2H, d, J_d = 8.0 Hz, –C═O–N*H*–). ^{13}C NMR ($CDCl_3$) δ 24.9, 26.2, 31.3, 31.7, 34.9, 35.4, 41.0, 46.3, 54.3, 61.2, 63.2, 119.9, 125.9, 126.2, 126.5, 128.2, 134.2, 140.3, 142.4, 171.8. HRMS(ES) calculated for **22** + H *m*/*z* 733.3610. Found *m*/*z* 733.3636.

4.4.5. 1,4-Di[3β-(4-thiophene-3-yl-phenyl)tropane-2β-carbonyl-amino] benzene (23)

The experiment was performed with 16 mg (0.15 mmol) of 1,4-diamino benzene. The residue was purified by flash chromatography (99% dichloromethane, 1% triethylamine) to afford 50 mg of a red solid, **23** (0.069 mmol, 46%). ^{1}H NMR ($CDCl_3$) δ 1.70–1.88 (6H, m, H4$_{endo}$, H6$_{endo}$ and H7$_{endo}$) 2.12–2.34 (4H, m, H6$_{exo}$ and H7$_{exo}$), 2.40 (6H, s, NCH_3), 2.43 (2H, tm, J_t = 12.8 Hz, H4$_{exo}$), 2.62 (2H, m, H2), 3.23 (2H, dt, J_d = 12.8 Hz and J_t = 6.2 Hz, H3), 3.45 (2H, dm, J_d = 5.6 Hz, H5), 3.49 (2H, dm, J_d = 5.6 Hz, H1), 7.23 (4H,

dm, J_d = 8.0 Hz), 7.33–7.41 (10H, m) 7.502 (4H, dm, J_d = 8.0 Hz), 12.0 (2H, s, -C=O–N*H*–). ^{13}C NMR ($CDCl_3$) δ 24.7, 26.0, 35.3, 40.7, 53.2, 54.8, 61.1, 63.6, 119.7, 120.1, 125.6, 126.1, 128.0, 134.0, 134.1, 139.8, 142.0, 170.2. HRMS(ES) calculated for **23** + H *m*/*z* 727.3140. Found *m*/*z* 727.3151.

4.4.6. 1-[3β-(4-Thiophene-3-yl-phenyl)tropane-2β-carbonyl-amino]-1-[3β-(4-thiophene-3-yl-phenyl)tropane-2β-carbonyl-aminobenzene-4-yl] methane (24)

The experiment was performed with 15 mg (0.13 mmol) of 4-aminobenzylamine. The residue was purified by flash chromatography (99% dichloromethane, 1% triethylamine) to afford 44 mg of an orange oil, **24** (0.057 mmol, 45%). ^{1}H NMR ($CDCl_3$) δ 1.61–1.88 (6H, m, H4$_{endo}$, H4$_{endo'}$, H6$_{endo}$, H6$_{endo'}$, H7$_{endo}$ and H7$_{endo'}$), 2.04–2.49 (6H, m, H4$_{exo}$, H4$_{exo'}$, H6$_{exo}$, H6$_{exo'}$, H7$_{exo}$ and H7$_{exo'}$), 2.21 (3H, s, NC*H*$_3$) 2.41 (3H, s, NC*H*$_3$) 2.49 (2H, m, H2 and H2′), 3.15 (1H, dt, J_d = 14.4 Hz and J_t = 6.2 Hz, H3/H3′), 3.24 (1H, dt, J_d = 14.4 Hz and J_t = 6.2 Hz, H3/H3′), 3.30 (1H, m, H5/H5′), 3.36 (1H, m, H5/H5′), 3.47 (2H, m, H1 and H1′), 4.30 (1H, dd, J_d = 5.6 Hz and J_d = 14.8 Hz) 4.36 (1H, dd, J_d = 5.6 Hz and J_d = 14.8 Hz) 7.18 (2H, dm, J_d = 8.0 Hz) 7.21 (2H, dm, J_d = 8.0 Hz), 7.22 (2H, dm, J_d = 8.0 Hz) 7.30–7.37 (4H, m), 7.40 (2H, m), 7.41 (2H, dm, J_d = 8.0 Hz), 7.48 (2H, dm, J_d = 8.0 Hz), 7.49 (2H, dm, J_d = 8.0 Hz), 9.87 (1H, t, J_t = 5.0 Hz, –C=O–N*H*–CH$_2$–), 12.07 (1H, s, –C=O–N*H*–C$_6$H$_4$–). ^{13}C NMR ($CDCl_3$) δ 24.5, 24.7, 25.8, 25.9, 34.5, 34.6, 35.1, 35.2, 40.6, 40.8, 42.3, 54.0, 54.7, 60.9, 61.0, 63.5, 63.6, 119.5, 119.6, 126.0, 126.0, 126.0, 127.8, 127.8, 127.9, 127.9, 133.8, 133.9, 134.0, 137.2, 139.6, 139.9, 142.0, 172.1. HRMS(ES) calculated for **24** + H$^+$ *m*/*z* 741.3297. Found *m*/*z* 741.3314.

4.4.7. 1-[3β-(4-Thiophene-3-yl-phenyl)tropane-2β-carbonyl-amino]-2-[3β-(4-thiophene-3-yl-phenyl)tropane-2β-carbonyl-aminobenzene-4-yl] ethane (25)

The reaction was performed with 17 mg (0.125 mmol) of 4-(2-aminoethyl)phenyl amine. The product was purified by flash chromatography (99% dichloromethane, 1% triethylamine) to afford 44 mg. of a clear oil, **25** (0.059 mmol, 47%). ^{1}H NMR ($CDCl_3$) δ 1.44–1.82 (6H, m, H4$_{endo}$, H4$_{endo'}$, H6$_{endo}$, H6$_{endo'}$, H7$_{endo}$ and H7$_{endo'}$), 1.88–2.44 (6H, m, H4$_{exo}$, H4$_{exo'}$, H6$_{exo}$, H6$_{exo'}$, H7$_{exo}$ and H7$_{exo'}$), 2.08 (3H, s, NC*H*$_3$) 2.40 (3H, s, NC*H*$_3$) 2.56 (1H, m, H2/H2′), 2.61 (1H, m, H2/H2′), 2.80 (2H, t, J_t = 6.6 Hz), 3.05 (1H, dt, J_d = 13.6 Hz and J_t = 6.2 Hz, H3/H3′), 3.21 (3H, m, H3/H3′) 3.44 (4H, m, H5, H5′, H1 and H1′), 7.04 (2H, dm, J_d = 8.0 Hz), 7.14 (2H, dm, J_d = 8.0 Hz), 7.19 (2H, dm, J_d = 8.0 Hz), 7.33 (6H, m), 7.38 (2H, m), 7.44 (2H, dm, J_d = 8.0 Hz), 7.46 (2H, dm, J_d = 8.0 Hz), 9.53 (1H, t, J_t = 4.8 Hz, –C=O–N*H*–CH$_2$–), 11.97 (1H, s, –C=O–N*H*–C$_6$H$_4$–). ^{13}C NMR ($CDCl_3$) δ 24.8, 25.0, 26.1, 26.2, 35.0, 35.1, 35.3, 35.4, 40.4, 40.9, 41.0, 54.4, 55.1, 61.2, 61.4, 63.8, 119.8, 125.7, 125.8, 126.2, 126.4, 128.1, 129.2, 132.8, 132.9, 134.6, 137.1, 139.9, 140.4, 142.2, 142.4, 170.5, 172.6. HRMS(ES) calculated for **25** + H *m*/*z* 755.3453. Found *m*/*z* 755.3429.

4.4.8. 1,4-Di[3-(4-thiophene-3-yl-phenyl)tropane-2-carbonyl-aminomethyl] benzene (26)

The reaction was performed with 20 mg (0.147 mmol) of *para*-xylylenediamine. The residue was purified by flash chromatography (99% dichloromethane, 1% triethylamine) to afford 50 mg of a white solid, **26** (0.066 mmol, 45%). ^{1}H NMR ($CDCl_3$) δ 1.65–1.81 (6H, m, H4$_{endo}$, H6$_{endo}$ and H7$_{endo}$) 2.24–2.35 (4H, m, H6$_{exo}$ and H7$_{exo}$) 2.23 (6H, s, NC*H*$_3$) 2.30 (2H, dt, J_d = 2.8 Hz, J_d = 12.8 Hz, H4$_{exo}$), 2.71 (2H, m, H2) 3.19 (2H, dt, J_d = 12.4 Hz and J_t = 6.4 Hz, H3), 3.31 (2H, m, H5), 3.40 (2H, dm, J_d = 6.4 Hz, H1), 4.38 (2H, dd, J_d = 5.6 Hz and J_d = 14.8 Hz) 4.46 (2H, dd, J_d = 5.6 Hz and J_d = 14.8 Hz), 7.22 (4H, dm, J_d = 8.4 Hz), 7.27 (4H, s) 7.39 (4H, m), 7.43 (2H, dd, J_d = 2.4 Hz and J_d = 1.2 Hz), 7.52 (4H, dm, J_d = 8.4 Hz) 9.96 (2H, t, J_t = 5.6 Hz, –C=O–N*H*–). ^{13}C NMR ($CDCl_3$) δ 25.0, 26.3, 35.0, 35.5, 41.2, 42.8, 54.4, 61.3, 64.1, 120.0, 125.9, 126.4, 126.5, 127.9, 128.2, 134.2, 138.2, 140.2, 142.4, 172.6.

4.4.9. 1-[3β-(4-Thiophene-3-yl-phenyl)tropane-2β-carbonyl-amino]-2-[3β-(4-thiophene-3-yl-phenyl)tropane-2β-carbonyl-aminomethylbenzene-4-yl] ethane (27)

The reaction was performed with 28 mg (0.126 mmol) of 2-(4-aminomethylphenyl)-ethylamine. The product was purified by flash chromatography (99% dichloromethane, 1% triethylamine) to afford 33 mg of a clear oil, **27** (0.043 mmol, 34%). ^{1}H NMR ($CDCl_3$) δ 1.53–1.77 (6H, m, H4$_{endo}$, H4$_{endo'}$, H6$_{endo}$, H6$_{endo'}$, H7$_{endo}$ and H7$_{endo'}$), 1.98–2.29 (6H, m, H4$_{exo}$, H4$_{exo'}$, H6$_{exo}$, H6$_{exo'}$, H7$_{exo}$ and H7$_{exo'}$), 2.02 (3H, s, NC*H*$_3$), 2.19 (3H, s, NC*H*$_3$), 2.52 (2H, m, H2/H2′), 2.66 (2H, m, H2/H2′), 2.84 (2H, m), 3.07 (1H, dt, J_d = 12.4 Hz and J_t = 6.2 Hz, H3/H3′), 3.15 (2H, dt, J_d = 12.4 Hz and J_t = 6.2 Hz, H3/H3′), 3.20 (2H, m, H5 and H5′), 3.28 (1H, m, H1/H1′), 3.35 (1H, m, H1/H1′), 3.40–3.60 (2H, m), 4.33 (1H, dd, J_d = 6.0 Hz and J_d = 14.8 Hz), 4.39 (1H, dd, J_d = 6.0 Hz and J_d = 14.8 Hz), 7.10 (2H, dm, J_d = 8.4 Hz), 7.18 (2H, dm, J_d = 8.4 Hz), 7.23 (4H, s), 7.34 (4H, m), 7.38 (2H, m), 7.46 (2H, dm, J_d = 8.4 Hz), 7.48 (2H, m), 9.54 (1H, t, J_t = 5.2 Hz, –C=O–N*H*–CH$_2$–), 9.86 (1H, t, J_t = 5.2 Hz, –C=O–N*H*–CH$_2$–). ^{13}C NMR ($CDCl_3$) δ 24.5, 24.5, 25.7, 25.8, 34.5, 34.7, 34.9, 34.9, 35.0, 39.7, 40.6, 40.8, 42.3, 53.9, 54.0, 60.9, 60.9, 63.5, 63.6, 119.5, 125.5, 125.5, 125.9, 126.0, 126.0, 127.4, 127.7, 127.8, 128.6, 132.5, 132.6, 137.0, 138.0, 139.8, 139.9, 141.9, 172.2, 172.3. HRMS(ES) calculated for **27** + H *m*/*z* 769.3610. Found *m*/*z* 769.3601.

4.4.10. 1,3-Di[3-(4-thiophene-3-yl-phenyl)tropane-2-carbonyl-aminomethyl] benzene (28)

The reaction was performed with 20 mg (0.147 mmol) of *meta*-xylylenediamine. The product was purified by flash chromatography (99% dichloromethane, 1% triethylamine) to afford 50 mg of a red solid, **28** (0.050 mmol, 34%). ^{1}H NMR ($CDCl_3$) δ 1.64–1.78 (6H, m, H4$_{endo}$, H6$_{endo}$ and H7$_{endo}$), 2.04–2.30 (4H, m, H6$_{exo}$ and H7$_{exo}$), 2.20 (6H, s, NC*H*$_3$), 2.27 (2H, dt, J_d = 2.4 Hz, J_d = 13.2 Hz, H4$_{exo}$), 2.68 (2H, m, H2), 3.17 (2H, dt, J_d = 13.2 Hz and J_t = 6.2 Hz, H3), 3.29 (2H, m, H5), 3.39 (2H, m, H1), 4.34 (2H, dd, J_d = 6.0 Hz and J_d = 14.8 Hz), 4.47 (2H, dd, J_d = 6.0 Hz and J_d = 14.8 Hz), 7.19 (8H, m) 7.36 (4H, m), 7.40 (2H, dd, J_d = 2.4 Hz and J_d = 1.6 Hz) 7.48 (4H, dm, J_d = 8.0 Hz) 9.95 (2H, t, J_t = 5.0 Hz, -C=O–N*H*–). ^{13}C NMR ($CDCl_3$) δ 24.9, 26.1, 34.9, 35.4, 41.1, 42.9, 54.3, 61.2, 64.0, 119.8, 125.8, 126.2, 126.3, 126.3, 126.8, 128.1, 128.7, 134.1, 139.7, 140.1, 142.3, 172.5.

4.5. General synthesis of 1-[3β-(4-chloro-phenyl)tropane-2β-carbonyl-oxy]-*n*-[4-(3β-{4-chloro-phenyl}tropane-2β-carbonyl-oxy-methyl)-(1,2,3)triazol-1-yl]alkane (29–33)

3β-(4-Halophenyl)tropane-2β-carboxylic acid prop-2-ynyl ester, **7** or **8** (1 equiv) and 3β-(4-chlorophenyl)tropane-2β-carboxylic acid ω-azidoalkyl ester (1 equiv) **9**, **10**, **11** or **12** were suspended in a 1:1 mixture of water and *tert*-butyl alcohol (4 mL). Ascorbic acid (0.1 equiv) and copper(II) sulfate pentahydrate (0.05 equiv) was added. The heterogeneous mixture was stirred for 44 h at room temperature. The reaction mixture was diluted with 5 mL water and basified to pH 9. The organic layer was separated and the aqueous layer was extracted with 3 × 5 mL dichloromethane. The combined organic layers was dried over magnesium sulfate and concentrated under reduced pressure.

4.5.1. 1-[3β-(4-Chloro-phenyl)tropane-2β-carbonyl-oxy]-2-[4-(3β-{4-chloro-phenyl}tropane-2β-carbonyl-oxy-methyl)-(1,2,3)triazol-1-yl]ethane (29)

Amount of reactants used for the reaction was; 3β-(4-chloro-phenyl)tropane-2β-carboxylic acid prop-2-ynyl ester (**7**, 35 mg,

0.11 mmol) and 3β-(4-chlorophenyl)tropane-2β-carboxylic acid 6-azidoethyl ester (**9**, 42 mg, 0.11 mmol). The residue was purified by flash chromatography (99% dichloromethane–1% triethylamine) to afford 36 mg of a clear oil, **29** (0.052 mmol, 47%). ^{1}H NMR ($CDCl_3$) δ 1.56–1.72 (6H, m, H4$_{endo}$, H4$_{endo'}$, H6$_{endo}$, H6$_{endo'}$, H7$_{endo}$ and H7$_{endo'}$), 2.05–2.27 (4H, m, H6$_{exo}$, H6$_{exo'}$, H7$_{exo}$ and H7$_{exo'}$), 2.06 (3H, s, NCH_3) 2.08 (3H, s, NCH_3) 2.37 (1H, tm, J_t = 12.0 Hz, H4$_{exo}$/H4$_{exo'}$), 2.50 (1H, dm, J_t = 12.0 Hz, H4$_{exo}$/H4$_{exo'}$), 3.81 (2H, m, H2 and H2′), 3.89 (2H, dt, J_d = 12.8 Hz and J_t = 5.6 Hz, H3 and H3′), 3.27 (2H, m, H5 and H5′), 3.39 (1H, m, H1/H1′), 3.46 (1H, m, H1/H1′), 4.18 (2H, m), 4.30 (1H, m), 4.39 (1H, m), 5.01 (2H, s), 7.06 (2H, dm, J_d = 8.4 Hz), 7.08 (2H, dm, J_d = 8.4 Hz), 7.11 (2H, dm, J_d = 8.4 Hz), 7.15 (2H, dm, J_d = 8.4 Hz), 7.28 (1H, s). ^{13}C NMR ($CDCl_3$) δ 24.6, 24.7, 25.4, 32.6, 32.7, 33.3, 33.4, 41.3, 41.3, 49.2, 52.0, 52.1, 57.1, 61.3, 61.6, 63.1, 64.5, 64.7, 123.4, 127.4, 127.6, 128.0, 128.2, 130.9, 131.1, 140.8, 141.0, 143.8, 170.6. HRMS(ES) calculated for **29** + H m/z 666.2614. Found m/z 666.2627.

4.5.2. 1-[3β-(4-Chloro-phenyl)tropane-2β-carbonyl-oxy]-6-[4-(3β-{4-chloro-phenyl}tropane-2β-carbonyl-oxy-methyl)-(1,2,3)triazol-1-yl]hexane (30)

Amount of reactants used for the reaction was; 3β-(4-chlorophenyl)tropane-2β-carboxylic acid prop-2-ynyl ester, **7** (66 mg, 0.208 mmol) and 3β-(4-chlorophenyl)tropane-2β-carboxylic acid 6-azido-hexyl ester **10** (84 mg, 0.208 mmol). The product was purified by flash chromatography (99% dichloromethane–1% triethylamine) to afford 0.112 g of a white solid, **30** (0.155 mmol, 75%). ^{1}H NMR ($CDCl_3$) δ 1.21 (4H, m), 1.42 (2H, quint, J_{quint} = 7.2 Hz), 1.54–1.74 (6H, m, H4$_{endo}$, H4$_{endo'}$, H6$_{endo}$, H6$_{endo'}$, H7$_{endo}$ and H7$_{endo'}$), 1.79 (2H, quint, J_{quint} = 7.2 Hz), 2.02–2.25 (4H, m, H6$_{exo}$, H6$_{exo'}$, H7$_{exo}$ and H7$_{exo'}$), 2.13 (3H, s, NCH_3) 2.19 (3H, s, NCH_3), 2.51 (1H, dt, J_d = 2.8 Hz and J_t = 12.8 Hz, H4$_{exo}$/H4$_{exo'}$), 2.54 (1H, dt, J_d = 2.8 Hz and J_t = 12.8 Hz, H4$_{exo}$/H4$_{exo'}$), 2.85 (1H, m, H2/H2′), 2.89 (1H, m, H2/H2′), 2.93 (1H, m, H3/H3′), 2.96 (1H, m, H3/H3′), 3.33 (1H, m, H5/H5′), 3.34 (1H, m, H5/H5′), 3.52 (dm, J_d = 6.4 Hz, H1/H1′), 3.53 (dm, J_d = 6.4 Hz, H1/H1′), 3.80 (dt, J_t = 6.4 Hz and J_d = 10.0 Hz), 3.97 (dt, J_t = 6.4 Hz and J_d = 10.0 Hz), 4.22 (2H, t, J_t = 7.2 Hz), 5.05 (1H, d, J_d = 12.8 Hz), 5.09 (1H, d, J_d = 12.8 Hz), 7.14 (2H, dm, J_d = 8.5 Hz), 7.16 (2H, dm, J_d = 8.5 Hz), 7.18 (2H, dm, J_d = 8.5 Hz), 7.20 (2H, dm, J_d = 8.5 Hz), 7.20 (1H, s). ^{13}C NMR ($CDCl_3$) δ 24.8, 24.8, 24.9, 25.5, 25.7, 28.1, 29.7, 32.8, 33.5, 33.6, 41.5, 42.6, 49.8, 52.1, 52.3, 56.8, 61.8, 63.0, 64.6, 65.0, 122.7, 127.5, 127.6, 128.3, 128.4, 131.0, 141.2, 141.4, 142.9, 170.8, 171.1. HRMS(ES) calculated for **30** + H m/z 722.3240. Found m/z 722.3214.

4.5.3. 1-[3β-(4-Chloro-phenyl)tropane-2β-carbonyl-oxy]-7-[4-(3β-{4-chloro-phenyl}tropane-2β-carbonyl-oxy-methyl)-(1,2,3)triazol-1-yl] heptane (31)

The amounts used was for 3β-(4-chlorophenyl)tropane-2β-carboxylic acid prop-2-ynyl ester, **7** (53 mg, 0.17 mmol) and for 3β-(4-chlorophenyl)tropane-2β-carboxylic acid 6-azidoheptyl ester **11** (58 mg, 0.17 mmol). The residue was purified with flash chromatography (99% dichloromethane–1% triethylamine) to afford 37 mg of a clear oil, **31** (0.056 mmol, 33%). ^{1}H NMR ($CDCl_3$) δ 1.28–1.56 (6H, m), 1.47 (2H, quint, J_{quint} = 7.2 Hz), 1.58–1.79 (6H, m, H4$_{endo}$, H4$_{endo'}$, H6$_{endo}$, H6$_{endo'}$, H7$_{endo}$ and H7$_{endo'}$), 1.86 (2H, quint, J_{quint} = 7.2 Hz), 2.08–2.29 (4H, m, H6$_{exo}$, H6$_{exo'}$, H7$_{exo}$ and H7$_{exo'}$), 2.19 (3H, s, NCH_3), 2.25 (3H, s, NCH_3), 2.57 (1H, dt, J_d = 2.4 Hz and J_t = 12.4 Hz, H4$_{exo}$/H4$_{exo'}$), 2.60 (1H, dt, J_d = 2.4 Hz and J_t = 12.4 Hz, H4$_{exo}$/H4$_{exo'}$), 2.91 (1H, m, H2/H2′), 2.94 (1H, m, H2/H2′), 2.99 (1H, m, H3/H3′), 3.01 (1H, m, H3/H3′), 3.39 (1H, m, H5/H5′), 3.40 (1H, m, H5/H5′), 3.58 (1H, m, H1/H1′), 3.60 (1H, m, H1/H1′), 3.85 (1H, dt, J_t = 6.6 Hz and J_d = 10.8 Hz), 3.93 (1H, dt, J_t = 6.6 Hz and J_d = 10.8 Hz), 4.22 (2H, t, J_t = 7.2 Hz), 5.10 (1H, d, J_d = 12.8 Hz), 5.15 (1H, d, J_d = 12.8 Hz), 7.19 (2H, dm, J_d = 8.4 Hz), 7.21 (2H, dm, J_d = 8.4 Hz), 7.24 (2H, dm, J_d = 8.4 Hz), 7.26 (2H, dm, J_d = 8.4 Hz), 7.30 (1H, s). ^{13}C NMR ($CDCl_3$) δ 25.1, 25.2, 25.6, 25.9, 26.4, 28.5, 28.6, 30.2, 33.2, 33.2, 33.9, 34.0, 41.8, 42.0, 50.2, 52.5, 52.7, 57.2, 62.1, 63.6, 65.0, 65.4, 123.1, 127.9, 127.8, 128.6, 128.7, 131.4, 141.6, 141.8, 143.3, 171.2, 171.5. HRMS(ES) calculated for **31** + H m/z 736.3396. Found m/z 736.3443.

4.5.4. Synthesis of 1-[3β-(4-iodophenyl)tropane-2β-carbonyl-oxy]-11-[4-(3β-{4-iodo-phenyl}tropane-2β-carbonyloxy-methyl)-(1,2,3)triazol-1-yl] undecane (32) and 1-[3-(4-iodophenyl)tropane-2-carbonyloxy]-11-[5-(3-{4-iodo-phenyl}tropane-2-carbonyloxy-methyl)-(1,2,3)triazol-3-yl] undecane (33)

From 3β-(4-iodophenyl)tropane-2β-carboxylic acid prop-2-ynyl ester, **8** (53 mg, 0.130 mmol) and 3β-(4-iodo-phenyl)tropane-2β-carboxylic acid 11-azido-undecyl ester, **12** (73 mg, 0.191 mmol) were obtained a product was purified by flash chromatography (99% dichloromethane–1% triethylamine) to afford 58 mg of a yellow oil consisting of **32** and **33** in a 69:31 regioisomeric ratio (0.059 mmol, 46%). The exact structure of the major product was not established. ^{1}H NMR ($CDCl_3$), **32** δ 1.07–1.30 (14H, m) 1.38 (2H, m) 1.49–1.67 (6H, m, H4$_{endo}$, H4$_{endo'}$, H6$_{endo}$, H6$_{endo'}$, H7$_{endo}$ and H7$_{endo'}$), 1.78 (2H, m), 1.98–2.16 (4H, m, H6$_{exo}$, H6$_{exo'}$, H7$_{exo}$ and H7$_{exo'}$), 2.07 (3H, s, NCH_3), 2.14 (3H, s, NCH_3), 2.46 (2H, m, H4$_{exo}$ and H4$_{exo'}$), 2.78–2.89 (2H, m, H2, H2′, H3 and H3′), 3.28 (2H, m, H5 and H5′), 3.48 (2H, m, H1 and H1′), 3.73 (1H, dt, J_t = 6.4 Hz and J_d = 10.8 Hz), 3.93 (1H, dt, J_t = 6.4 Hz and J_d = 10.8 Hz), 4.21 (2H, t, J_t = 7.4 Hz), 4.99 (1H, d, J_d = 12.8 Hz), 5.05 (1H, d, J_d = 12.8 Hz), 7.91 (2H, dm, J_d = 8.0 Hz), 7.93 (2H, dm, J_d = 8.0 Hz), 7.12 (1H, s), 7.47 (2H, dm, J_d = 8.0 Hz), 7.51 (2H, dm, J_d = 8.0 Hz). ^{13}C NMR ($CDCl_3$), **32** δ 24.6, 25.3, 25.9, 28.0, 28.4, 28.7, 28.8, 28.9, 29.8, 32.8, 32.8, 33.2, 33.3, 41.3, 41.4, 49.9, 51.9, 52.1, 56.7, 61.6, 63.3, 64.5, 64.8, 90.4, 122.6, 128.9, 129.0, 136.3, 142.6, 142.7, 170.7, 171.0. HRMS(ES) calculated for **32/33** + H m/z 976.2735. Found m/z 976.2748. ^{1}H NMR ($CDCl_3$), **33** δ 1.07–1.30 (14H, m), 1.38 (2H, m), 1.49–1.67 (6H, m, H4$_{endo}$, H4$_{endo'}$, H6$_{endo}$, H6$_{endo'}$, H7$_{endo}$ and H7$_{endo'}$), 1.78 (2H, m), 1.98–2.16 (4H, m, H6$_{exo}$, H6$_{exo}$‘, H7$_{exo}$ and H7$_{exo'}$), 2.07 (3H, s, NCH_3), 2.14 (3H, s, NCH_3), 2.46 (2H, m, H4$_{exo}$ and H4$_{exo}$‘), 2.78–2.89 (4H, m, H2, H2′, H3 and H3′), 3.28 (2H, m, H5 and H5′), 3.48 (2H, m, H1 and H1′), 3.73 (1H, dt, J_t = 6.4 Hz and J_d = 10.8 Hz), 3.93 (1H, dt, J_t = 6.4 Hz and J_d = 10.8 Hz), 4.27 (2H, t, J_t = 7.4 Hz), 4.92 (1H, d, J_d = 12.8 Hz), 4.96 (1H, d, J_d = 12.8 Hz), 7.91 (2H, dm, J_d = 8.0 Hz), 7.93 (2H, dm, J_d = 8.0 Hz), 7.20 (1H, s), 7.47 (2H, dm, J_d = 8.0 Hz), 7.51 (2H, dm, J_d = 8.0 Hz). ^{13}C NMR ($CDCl_3$), **33** δ 24.6, 25.3, 25.9, 28.0, 28.4, 28.7, 28.8, 28.9, 29.8, 32.8, 32.8, 33.2, 33.3, 41.3, 41.4, 49.9, 51.9, 52.1, 56.7, 61.6, 63.3, 64.5, 64.8, 90.4, 128.9, 129.0, 129.1, 136.3, 136.7, 142.6, 170.7, 171.0.

4.5.5. 5-(4-Trimethylsilyl-1*H*-1,2,3-triazol-1-yl)pentan-1-ol (35)

A solution of 5-chloro-1-pentanol (**34**, 0.90 mL, 7.7 mmol), sodium azide (751 mg, 11.6 mmol) and tetrabutylammonium iodide (291 mg, 0.79 mmol) in 4 mL DMF was stirred for 2 days at room temperature. The mixture was diluted with 50 mL H_2O and extracted with 5x25 mL diethyl ether. The combined organic phases were washed with 25 mL H_2O and 25 mL brine, dried over $MgSO_4$. Removal of the solvent at atmospheric pressure and room temperature afforded 766 mg of 5-azidopentan-1-ol (5.93 mmol, 77%) as a colourless oil. ^{1}H NMR ($CDCl_3$) δ 1.35 (1H, br s, OH), 1.42–1.50 (2H, m), 1.57–1.68 (4H, m), 3.29 (2H, t, J = 6.8 Hz), 3.67 (2H, t, J = 6.8 Hz, H5). The crude 5-azidopent-1-ol (600 mg, 4.65 mmol) was taken up in 10 mL H_2O/*tert*-butanol (1:1). To the solution was added trimethylsilyl acetylene (0.66 mL, 4.67 mmol), $CuSO_4$ (37 mg, 0.23 mmol) and sodium ascorbate (275 mg, 1.39 mmol). After 5 h of stirring at room temperature, additionally $CuSO_4$ (37 mg, 0.23 mmol) and sodium ascorbate (275 mg, 1.39 mmol) was

added. The mixture was stirred for 12 h, diluted with 50 mL H_2O and extracted with 3 × 25 mL EtOAc. The combined organic layers were washed with 25 mL 5% NH_4OH and 25 mL brine and dried over $MgSO_4$ before the solvents were removed at reduced pressure. Flash chromatography (60% EtOAc/40% CH_2Cl_2) afforded **35** (548 mg, 2.41 mmol, 52%) as a colourless oil. ^{1}H NMR ($CDCl_3$) δ 0.31 (9H, s), 1.38–1.46 (2H, m), 1.57–1.64 (2H, m), 1.89 (1H, br s, O*H*), 1.94 (2H, quint, *J* = 7.6 Hz), 3.64 (2H, t, *J* = 6.4 Hz), 4.37 (2H, t, *J* = 7.6 Hz), 7.49 (1H, s). ^{13}C NMR ($CDCl_3$) δ -1.0, 23.0, 30.4, 32.1, 49.8, 62.5, 128.9, 146.6. HRMS(ES) calculated for **35** + Na *m*/*z* 250.1352. Found *m*/*z* 250.1346.

4.5.6. 5-(1*H*-1,2,3-Triazol-1-yl)pentan-1-ol (36)

To a solution of 5-(4-trimethylsilyl-1*H*-123-triazol-1-yl)pentan-1-ol (**35**, 477 mg, 2.10 mmol)) in 10 mL THF was added tetrabutylammonium fluoride (1 M in THF, 2.60 mL, 2.60 mmol), and the reaction mixture was heated to 50 °C. After 18 h the crude mixture was evaporated to dryness at reduced pressure. Flash chromatography (5% methanol–95% dichloromethane) gave **36** (314 mg, 2.02 mmol, 96%) as a colourless oil. ^{1}H NMR ($CDCl_3$) δ 1.38–1.46 (2H, m), 1.55 (1H, br s, O*H*), 1.61 (2H, m), 1.96 (2H, quint, *J* = 7.2 Hz), 3.65 (2H, t, *J* = 6.4 Hz), 4.41 (2H, t, *J* = 7.2 Hz), 7.54 (1H, s), 7.70 (1H, s). ^{13}C NMR ($CDCl_3$) δ 22.9, 30.2, 32.0, 50.2, 62.3, 123.4, 133.9. HRMS(ES) calculated for **36** + Na *m*/*z* 178.0956. Found *m*/*z* 178.0948.

4.5.7. 1-[3β-(4-Chlorophenyl)tropane-2β-carbonyl-oxy]-5-[(1,2,3)triazol-1-yl]pentane (37)

3β-(4-Chlorophenyl)tropane-2β-carboxylic acid (**4**, 240 mg, 0.86 mmol) was dissolved in 3.5 mL dry dichloromethane. Oxalyl chloride (90 μL, 1.0 mmol) and dry DMF (20 μL, 0.26 mmol) and the mixture was stirred at room temperature. After 3 h the reaction mixture was evaporated to dryness at reduced pressure, and the crude residue was taken up in 3 mL dry THF. 5-(1,2,3-Trizole-1-yl)pentan-1-ol (**36**, 105 mg, 0.68 mmol) and freshly distilled triethylamine (380 μL, 3.73 mmol) in 3 mL THF was added dropwise, and the reaction mixture stirred overnight at room temperature. The solvent was removed by evaporation. To the crude residue was added 25 mL H_2O, and the aqueous phase was extracted with 5 × 25 mL EtOAc. The combined organic layers were washed with 25 mL H_2O and 25 mL brine and dried over $MgSO_4$. Flash chromatography (1% triethylamine–99% dichloromethane) afforded **37** (193 mg, 0.46 mmol, 68%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 1.10–1.16 (2H, m), 1.41 (2H, quint, *J* = 7.2 Hz), 1.50–1.68 (3H, m, $H4_{endo}$ and $H6_{endo}$ and $H7_{endo}$), 1.78 (2H, quint, *J* = 7.2 Hz), 1.97–2.18 (2H, m, $H6_{exo}$ and $H7_{exo}$), 2.12 (3H, s, N*C*H_3) 2.44 (1H, dt, J_d = 2.8 Hz and J_t = 12.8 Hz, $H4_{exo}$), 2.78–2.80 (1H, m, H2), 2.89 (1H, dt, J_t = 5.2 Hz and J_d = 12.8 Hz, H3), 3.28 (1H, m, H5), 3.46 (1H, m, H1), 3.76 (1H, dt, J_t = 6.4 Hz and J_d = 11.2 Hz), 3.91 (1H, dt, J_t = 6.4 Hz and J_d = 11.2 Hz), 4.25 (2H, t, *J* = 7.2 Hz), 7.08–7.16 (4H, m), 7.45 (1H, s), 7.62 (1H, s). ^{13}C NMR ($CDCl_3$) δ 22.9, 25.2, 25.9, 28.1, 29.9, 33.2, 34.0, 42.0, 50.0, 52.7, 62.2, 63.2, 65.4, 123.2, 128.1, 128.7, 131.4, 133.8, 141.9, 171.6. HRMS(ES) calculated for **37** + H *m*/*z* 417.2057. Found *m*/*z* 417.2058.

4.6. Binding assay

Expression of the three monoamine transporters in COS-1 cells was achieved by stable transfection with the pIRES vector (Invitrogen) carrying the cDNA of the transporters. 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, homogenizing 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). 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-(**2**). Membrane and ligands were incubated for 1 h at 20 °C. Using a Filtermate cellharvester (Packard) membranes were captured on GF/B 96-well filter plates (Packard) pre-soaked with 0.5% polyethyleneimine (Merck) and washed thrice with ice-cold water. The filter in each well was dissolved in 40 μL Microscint 20 and scintillation counts were determined with a Packard Topcounter. Precise concentration of radioligand was quantified by liquid scintillation counting on a Packard Tri-Carb.

Acknowledgements

We kindly acknowledge OChem Graduate School, Aarhus University for support and Bente Ladegaard for skilful technical assistance.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2009.06.007.

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