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Conformationally restricted homotryptamines 3. Indole tetrahydropyridines and cyclohexenylamines as selective serotonin reuptake inhibitors

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Abstract—A series of indole tetrahydropyridine and indole cyclohexenylamines was prepared, and their binding affinities at the human serotonin transporter (SERT) were determined. In particular, a nitrile substituent at the C5 position of the indole ring gave potent SERT activity. The stereochemistry of the *N*,*N*-dimethylamine substituent was determined for the most potent indole cyclohexenylamine, **6a**. The enantiomers of **6a** were energy minimized and compared to other conformationally restricted SSRIs. Compound **6a** was found to give a dose–response similar to the SSRI fluoxetine in microdialysis studies in rats.

5-Hydroxytryptamine (5-HT, serotonin) is a neurotransmitter that plays an important role in a variety of physiological functions in the central nervous system and peripheral tissues. Consequently, the modulation of serotonin function via therapeutic agents continues to be an active and promising area of drug discovery research.

The selective serotonin reuptake inhibitors (SSRIs) are effective antidepressants, and are relatively safe despite some recognized issues.[1] Recent SSRI research has focused on compounds with added properties that may result in a more rapid onset of antidepressant action such as serotonin transporter (SERT) inhibition combined with 5-HT_{1A}, 5-HT_{1B}, or NK1 antagonism.[2]

The conformational restriction of serotonergic ligands is a precedented way to improve the binding and selectivity of these agents. One of the earliest conformationally restricted homo-serotonin analogs was the selective 5-HT_{1B} agonist RU 24969, in which the amino ethylene side chain of 5-methoxy serotonin was replaced with a tetrahydropyridin-4-yl moiety.[3] Similar analogs have been examined at various 5-HT receptor subtypes.[4] We have previously reported SERT binding results with homotryptamines **1**,[5] and conformationally restricted analogs **2**,[5a] **3**,[6] and **4**[6] (Fig. 1). Based on SAR studies, we have hypothesized that modifying the RU 24969 side chain to an *N*-methyl tetrahydropyrid-4-yl moiety (**5**) might yield analogs with high affinity for SERT. Also of interest was the impact of extending the nitrogen one more carbon away from the indole as in dimethylamino cyclohexen-4-yl analogs (**6**). We now report the

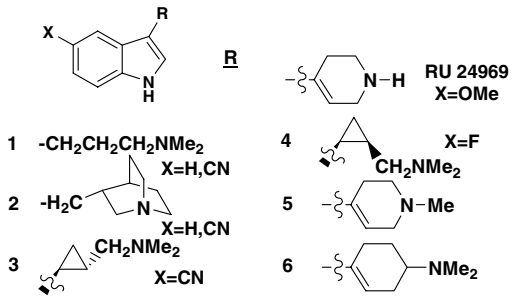

Figure 1.

Keywords: SSRI; Serotonin transporter; Homotryptamine.
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SERT activity of *N*-methyl tetrahydropyrid-4-yl indoles, **5a**–**h**, and *N*,*N*-dimethylamino cyclohexen-4-yl indoles, **6a**–**h** (Fig. 1).

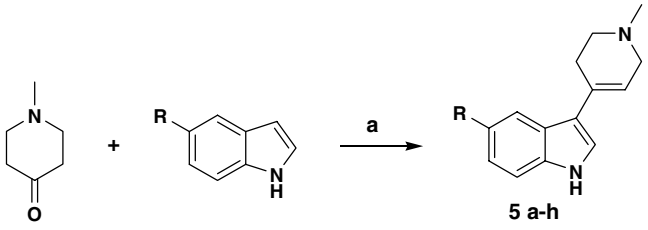
N-Methyl tetrahydropyrid-4-yl indoles **5a**–**h** were prepared by the reaction of commercially available 5-substituted indoles with *N*-methyl piperidone, as is shown in Scheme 1.

N,*N*-Dimethylamino cyclohexen-4-yl indoles **6a**–**h** were prepared by reductive amination of commercially available 1,4-cyclohexanedione mono-ethylene ketal with dimethylamine, then ketal hydrolysis, and coupling with the analogous indoles,[7] as shown in Scheme 2.

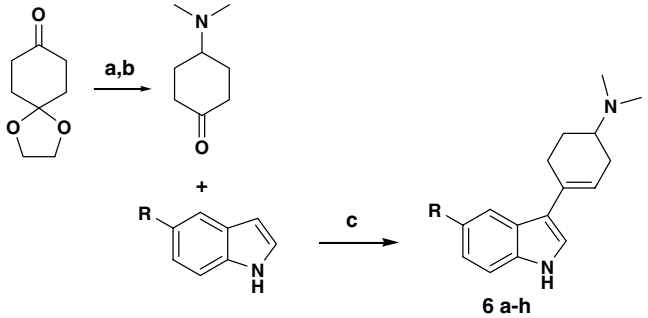
Since our previous work on indole SSRIs demonstrated high eudesmic ratios for the enantiomers of compounds **3** and **4**[6] (similar to the case of (*S*)- and (*R*)-citalopram[8]), **6a** was resolved by chiral supercritical fluid chromatography (SFC).[9] One enantiomer, *R*-**6a**, was then converted to its *N*-tosyl derivative (*p*-TsCl, NaHMDS, DMF, 0 °C, 30 min.) to determine its absolute stereochemistry by X-ray crystallography (Fig. 2).[10]

The SERT binding affinities[11] of compounds **5a**–**h** are shown in Table 1. Results for compounds **6a**–**h** and the enantiomers of **6a** are shown in Table 2.

N-Methyl tetrahydropyrid-4-yl compound **5f** is less potent than **1** (X = H, SERT IC_{50} 58 ± 6 nM),[5a] with the same carbon linker length on the side chain. This loss of binding affinity may be in part due to the lack of flexibility present in the tetrahydropyrid-4-yl ring system. By moving the nitrogen outside of the ring system and incorporating the *N*,*N*-dimethylamine moiety, cyclohexen-4-yl compound **6f** was found to have much improved

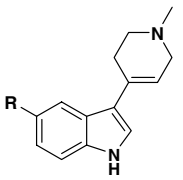


Scheme 1. Reagents and condition: (a) pyrrolidine in ethanol/reflux.



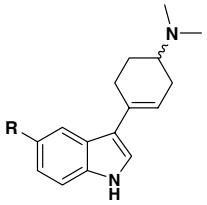
Scheme 2. Reagents and conditions: (a) Me_2NH, $NaBH(OAc)_3$; (b) aq HCl; (c) pyrrolidine/reflux.

Table 1. SERT binding affinities[11] of tetrahydropyrid-4-yl indoles



Compound	R	SERT IC_{50} (nM)[11]
5a	CN	19 ± 3
5b	NO_2	40 ± 6
5c	F	160 ± 50
5d	Br	210 ± 50
5e	Cl	240 ± 50
5f	H	690 ± 270
5g	OMe	730 ± 270
5h	Me	910 ± 90

Table 2. SERT binding affinities[11] of *N*,*N*-dimethylamino cyclohexen-4-yl indoles, and of the enantiomers of **6a**



Compound	R	SERT IC_{50} (nM)[11]
6a	CN	1.6 ± 0.3
S-**6a**	CN	1.1 ± 0.2
R-**6a**	CN	0.72 ± 0.11
6b	NO_2	1 ± 0.3
6c	F	14 ± 6
6d	Br	5.3 ± 0.9
6e	Cl	19 ± 5
6f	H	3.1 ± 0.5
6g	OMe	150 ± 30
6h	Me	770 ± 230

SERT potency. Compound **6f** is greater than 200-fold more potent than **5f**. The difference in the two bridging ring systems is consistent throughout the series, as the *N*,*N*-dimethylamino cyclohexen-4-yl analogs are generally 10- to 40-fold more active than their *N*-methyl tetrahydropyrid-4-yl counterparts. The combination of carbon chain length extension and the preferred amino functionality contributes to the SERT binding differences between these two groups of compounds.

In terms of SAR trends for the indole substituent, the potency in both series is markedly influenced by the 5-substituent on the indole. The nitro (**5b** and **6b**) and cyano (**5a** and **6a**) analog, were the most potent compounds, suggesting that electron withdrawing substituents on the indole ring might be favored for SERT binding. The same was true for the previously reported 5-cyano compounds **1** (X = CN, SERT IC_{50} 2.0 ± 0.4 nM)[5a] and **2** (X = CN, SERT IC_{50} 2.0 ± 0.3 nM),[5a] as they were also the most potent analogs in that series.

As for the effect of chirality, the *R*-enantiomer[12] of **6a** was found to be nearly equipotent to the corresponding

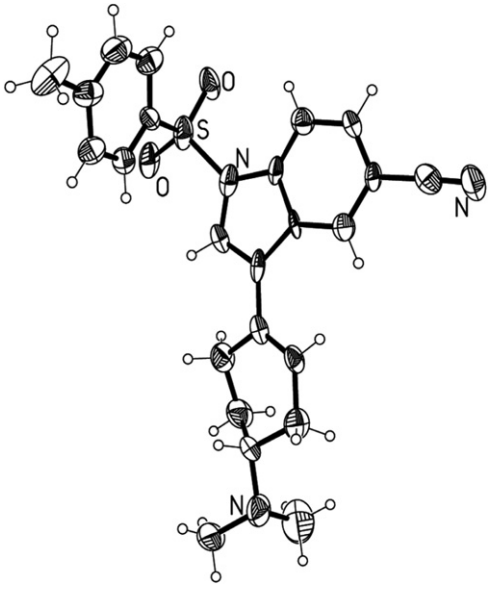


Figure 2. ORTEP drawing of *N*-1-tosyl derivative of *R*-**6a** with ellipsoids drawn at 30% probability level for non H-atoms and arbitrary scaled open circles for H-atoms. Carbon and hydrogen atoms are not labeled.

S-enantiomer. **6a** and its enantiomers are not as potent as **3** (SERT K_i 0.18 ± 0.02 nM),[6] which might suggest that the constraint of the cyclohexen-4-yl ring system gives a somewhat less favorable interaction with the serotonin transporter as compared to the *trans* cyclopropane moiety of **3**.

To examine selectivity, the most active compounds at SERT from this study were evaluated for binding affinity at the human dopamine (DAT) and norepinephrine (NET) transporters. The results are shown in Table 3, where percent inhibition was determined at a single concentration of 1 μM.

Many of the compounds were weak to moderate inhibitors at either DAT, NET or both of these transporters. Compound **6d** was the only strong inhibitor of both DAT and NET transporters while having single digit nanomolar affinity at SERT. Compound **6a** showed moderate affinity at DAT and a higher percent inhibition at NET. This compound and its enantiomers, *S*-**6a** and *R*-**6a**, were then compared directly in a single, 20-point concentration experiment to determine their binding affinities at SERT, DAT, and NET.[13] The results of this selectivity study are shown in Table 4.

Both the racemate **6a** and *S*-enantiomer *S*-**6a** showed similar levels of selectivity for SERT over DAT (>140-fold) and NET (>60-fold). Interestingly, the *R*-enantiomer *R*-**6a** gave much higher selectivity ratios for SERT, >700-fold over DAT, and >900-fold over NET. For comparison, the SSRI fluoxetine (SERT K_i 0.72 nM, DAT K_i 1900 nM, and NET K_i 440 nM)[6] has SERT selectivity over DAT (>2600-fold) and NET (>600-fold). Our previously reported SSRI compound **3** demonstrated very high selectivity for the serotonin transporter over DAT and NET (SERT K_i 0.18 nM, DAT K_i 2100 nM, and NET K_i 4600 nM).[6]

In vivo studies with the racemate **6a** were performed due to the limited availability of the single enantiomers. In microdialysis studies,[14] **6a** robustly increased extracellular serotonin concentrations in the frontal cortex of awake, freely moving rats. The maximal response was achieved at 1 mg/kg (ip) as shown in Figure 3. In oral studies, **6a** increased serotonin levels to 150–200 percent above baseline. This effect was similar to that produced by fluoxetine, both given at 10 mg/kg po (Fig. 4).

In order to relate the potency of **6a** to other potent SSRIs, low-energy conformations of the individual enantiomers were examined.[15] Figure 5 shows the predicted lowest-energy conformation of *R*-**6a** and second lowest-energy conformation of *S*-**6a** superimposed with low-energy conformations of the SSRIs (1*S*,4*S*)-sertraline and (*S*)-citalopram (av SERT IC_{50} 0.73 nM (n = 2) and 1.45 nM (n = 2), respectively,[16] Fig. 6). The predicted energy of the conformation of *S*-**6a** shown in

Table 3. Inhibition of dopamine and norepinephrine transporters

Compound	SERT IC_{50} (nM)[a]	DAT, % inhibition[b]	NET, % inhibition[b]
5a	19 ± 3	56	15
5b	40 ± 6	73	27
6a	1.6 ± 0.3	71	90
6b	1 ± 0.3	74	81
6c	14 ± 6	23	35
6d	5.3 ± 0.9	95	99
6e	19 ± 5	16	34
6f	3.1 ± 0.5	67	70

[a] From Tables 1 and 2.
[b] Test concentration 1 μM.

Table 4. SERT, DAT, and NET binding affinities[13] of **6a** and its enantiomers

Compound	SERT IC_{50} (nM)[13]	DAT IC_{50} (nM)[13]	NET IC_{50} (nM)[13]
6a	0.34	97	57
S-**6a**	0.56	80	37
R-**6a**	0.40	290	390

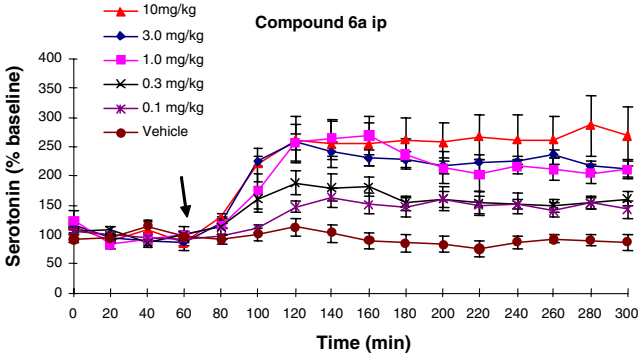


Figure 3. Dose–response curves for compound **6a** given ip.

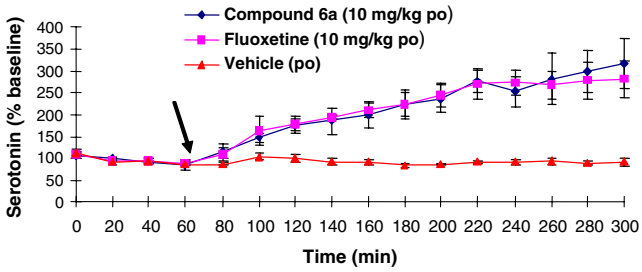


Figure 4. Compound **6a** versus fluoxetine and vehicle given po.

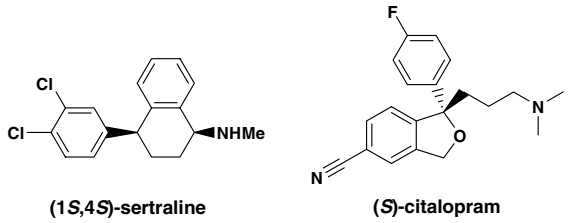


Figure 6.

the figure is 0.1 kcal/mol above that of the putative global minimum. The conformations of sertraline and (*S*)-citalopram shown in Figure 5 have energies within 1.5 kcal/mol of their respective predicted global minima. The overlay shows good correspondence between two key elements of the SSRI pharmacophore in each molecule, namely a substituted aromatic ring and a basic amine moiety.

This overlay also suggests that each enantiomer of compound **6a** may share common SERT binding interactions with sertraline and (*S*)-citalopram. Of particular note is the overall three-dimensional shape similarity of the low-energy conformers of both enantiomers of compound **6a**, as shown in Figure 5. This suggests that they can bind to the serotonin transporter in an analogous manner, forming similar intermolecular interactions with the protein. The high degree of similarity is consistent with the nearly equal IC_{50} values determined for the enantiomers.

In Figure 7, the same predicted low-energy conformers of both enantiomers of compound **6a** described above are shown overlaid with putative global energy minimum conformers of the potent SSRIs **3** (SERT K_i 0.18 ± 0.02 nM) and **4** (SERT K_i 14 ± 1.9 nM).[6] In this case as well, the correspondence between the aromatic rings is quite good, and the close grouping of the putative hydrogen bond acceptor site points suggests that the compounds should be able to interact with the same H-bond acceptor in the serotonin transporter.

Overall, the results of the molecular modeling analysis suggest that the enantiomers of compound **6a** are capable of adopting similarly shaped low-energy conformations which match key elements of the SSRI pharmacophore. Even with such a good fit in terms of energy minimized conformations, it is the differences in the conformations of the respective enantiomer pairs that are reflected in their eudesmic ratios. The SERT affinity ratio of the enantiomers of **6a** is only 1.5, while that of **3** and its enantiomer is nearly 50-fold.[6] Compound **4** and its enantiomer also show a significant difference, here about 7-fold.[6]

In conclusion, extending the basic nitrogen out of the ring system and increasing the carbon side-chain length, as with cyclohexen-4-yl compound **6a**, gave a 10-fold increase in affinity for the serotonin transporter over that of tetrahydropyridine **5a**. Compound **6a** and especially its *R*-enantiomer *R*-**6a** demonstrate selectivity for the serotonin transporter over dopamine and norepinephrine transporters, but not to the same extent as the ratios reported for **3**. In vivo, **6a** demonstrated a robust dose–response in the microdialysis experiment, increasing serotonin levels to a similar extent as fluoxetine (10 mg/kg for both compounds given po). *R*-**6a** and *S*-**6a** demonstrated nearly equal affinity for SERT. Modeling studies suggest that both enantiomers can adopt similar conformations which overlap well with our potent and highly selective compounds, **3** and **4**. This

Figure 5. Superimposition of *R*-**6a** (gray carbon atoms, ball and stick representation) and *S*-**6a** (gray carbon atoms, stick representation) with the SSRIs sertraline ((1*S*,4*S*)-stereochemistry, orange carbon atoms, stick representation) and (*S*)-citalopram (yellow carbon atoms, stick representation). Magenta spheres are putative hydrogen bond acceptor site points utilized in the RMS fitting procedure. The image was created with DS Viewer Pro™ 6.0 (Accelrys, Inc., San Diego, CA, 2005).

Figure 7. Superimposition of *R*-**6a** (gray carbon atoms, ball and stick representation) and *S*-**6a** (gray carbon atoms, stick representation) with compounds **3** (orange carbon atoms, stick representation) and **4** (yellow carbon atoms, stick representation). Magenta spheres are putative hydrogen bond acceptor site points utilized in the RMS fitting procedure. The image was created with DS Viewer Pro™ 6.0 (Accelrys, Inc., San Diego, CA, 2005).

work helps to further define the SAR and stereochemical requirements of the indole alkyl amine SSRI series.

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7. Preparation of **6a**: 1,4-cyclohexanedione mono-ethylene ketal and *N*,*N*-dimethylamine were dissolved in dichloromethane at room temperature with magnetic stirring. Sodium triacetoxyborohydride was added and the reaction mixture was stirred for 16 h. A 2 N sodium hydroxide solution was added, and the mixture was extracted with dichloromethane, dried over magnesium sulfate, filtered, and concentrated under vacuum to an oil. The crude oil was dissolved in diethyl ether at room temperature with stirring. A 3 M solution of hydrochloric acid was added and stirring continued for 2 h. The mixture was neutralized, extracted into ethyl acetate, dried over magnesium sulfate, filtered, and then concentrated under vacuum to an oil that was used without further purification. This ketone (1.9 g, 13.5 mmol, 1.2 equiv) and 5-cyanoindole (1.75 g, 11.2 mmol) were dissolved in 10 mL of ethanol at room temperature with stirring. Pyrrolidine (2.8 mL, 33.7 mmol, 3 equiv) was added and the reaction mixture was heated to reflux with stirring for 24 h. The mixture was cooled to room temperature, diluted with ethanol and ether, and extracted with 3 M HCl solution. The aqueous layer was neutralized, extracted with ethyl acetate, dried over magnesium sulfate, filtered, and concentrated under vacuum to an oil. The oil was purified by silica gel flash column chromatography, eluting with 50% ethyl acetate in hexane, then 5% methanol in dichloromethane. Compound **6a** (1.3 g, 44% yield) was recovered and converted to an HCl salt. TOF HRMS m/e 266.1667 $(M+H)^+$; ^1H NMR (400 MHz, acetone-d_6): δ 8.26 (s, 1H), 7.56 (d, J = 8.4, 1H), 7.50 (s, 1H), 7.38 (m, 1H), 6.22 (m, 1H), 2.60 (m, 1H), 2.27 (s, 6H), 2.46 (m, 3H), 2.21 (m, 1H), 2.05 (m, 1H), and 1.55 (m, 1H).
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9. Preparative SFC separation: Chiralpak AS-H, 30 × 250 mm, 5 μm, 88% CO_2/12% ethanol with 0.1% diethylamine, 50 mL/min @ 150 bar, peak 2 corresponds to *R*-**6a**.
10. Full crystallographic data have been deposited to the Cambridge Crystallographic Data Center (CCDC reference number 615920). Copies of the data can be obtained free of charge via the internet at http://www.ccdc.cam.ac.uk.
11. The SERT binding affinities were determined using membrane homogenates from HEK-293 cells that stably expressed human serotonin transporters (HEK-hSERT cells). Membrane homogenates were incubated with 2 nM [^{3}H]citalopram (specific activity = 85 C_i/mmol) and increasing concentrations of test compounds for 1 h at 25 °C in a total volume of 250 μL. Amount of radioligand bound in the presence and absence of a competitor was analyzed by plotting (−)log drug concentration versus the amount of radioligand specifically bound. Non-specific binding was defined with 10 μM fluoxetine. The midpoint of the displacement curve (IC_{50} nM) signified the potency. n = 3 for each reported IC_{50}; each n represents a duplicate measurement taken at five different concentrations and reported as the average ± SEM (standard error measurement). n = 2 for compounds with an IC_{50} > 500. n = 5 for compound **6a**.
12. Analytical data for (*R*)-3-(4-(dimethylamino)cyclohex-1-enyl)-1*H*-indole-5-carbonitrile, compound *R*-**6a**: HPLC purity: >98%; >99%ee; Optical rotation: +51.9 (methanol, c = 3.0 mg/mL).
13. SERT, DAT, and NET binding affinities were determined using membrane homogenates from stably transfected HEK-293 cell lines expressing the human form of the transporters. Membrane homogenates were incubated with ^{125}I labeled ligands. RTI-55 (Perkin-Elmer) was used for SERT (260 pM) and DAT (125 pM). A custom labeled ^{125}I Nisoxetine (Perkin-Elmer) was used for NET (300 pM). The reactions were carried out in a 384-well format and harvested in 384-well filter plates. The IC_{50} data was determined from a 20-point curve. Non-specific binding was defined using 10 μM Fluoxetine for SERT, 100 μM Desipramine for NET, and 10 μM GBR-12935 for DAT.
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15. The conformations of the *R*- and *S*-enantiomers of compound **6a** were identified as follows: conformational searches for the *N*-protonated states of each enantiomer were performed using MacroModel® 9.1 (Schrödinger, LLC, New York, NY, 2005),[a] the OPLS2001 force-field,[b] GB/SA water solvation model,[c] and PRCG minimization algorithm.[d] The geometry of each conformer of enantiomers *S*-**6a** and *R*-**6a** was then optimized using density functional theory (DFT) at the RB3LYP/6-31+G* level[e,f] with solvation effects approximated by a self-consistent reaction field (SCRF) water solvation model. Jaguar 6.5 (Schrödinger, LLC, New York, NY, 2005) was used to perform the DFT calculations. The above computational protocol is the same as described in reference 6 except for

the version of the Jaguar program used. The conformations of (1*S*,4*S*)-sertraline, (*S*)-citalopram (Fig. 6), **3**, and **4** used in this study are those shown in Figure 5a of reference 6, and were identified as described therein. Compounds **3** and **4** correspond to (+)-**12a** and (−)-**16e**, respectively, within reference 6. The DFT-optimized lowest-energy conformer of *R*-**6a** and second lowest-energy conformer of *S*-**6a** were found to superimpose well with the DFT-optimized low-energy conformer of sertraline shown in Figure 5 using a three-point RMS fitting procedure. The points used for the superposition with sertraline are phenyl ring centroids (the dichlorophenyl ring in sertraline was used), basic nitrogen atoms, and putative hydrogen bond acceptor site points located 2.8 Å from each basic nitrogen atom along the N-H vectors.[g] The RMS fitting of (*S*)-citalopram to sertraline included a fourth pair of points corresponding to the centroids of the fluorophenyl ring in (*S*)-citalopram, and the non-chlorinated phenyl ring in sertraline. The superposition shown in Figure 7 was generated by RMS fitting the low-energy conformers of *R*-**6a**, *S*-**6a,** **3**, and **4** to the sertraline reference conformer as described above for *R*-**6a** and *S*-**6a**. In both figures, all other compounds were fit to sertraline, even though it is not shown explicitly in Figure 7; (a) Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440; (b) Jorgensen, W. L.; Maxwell, D. S.; Tirado-Rives, J. *J. Am. Chem. Soc.* **1996**, *118*, 11225; (c) Still, W. C.; Tempczyk, A.; Hawley, R. C.; Hendrickson, T. A. *J. Am. Chem. Soc.* **1990**, *112*, 6127; (d) Polak, E.; Ribiere, G. *Rev. Fr. Inf. Rech. Oper.* **1969**, *16*, 35; (e) See: *Jaguar 6.5 Operating Manual*; Schrodinger, LLC: New York, NY, 2005, and references therein; (f) Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; John Wiley: New York, 1986, Chapter 4; (g) Gundertofte, K.; Bøgesø, K. P.; Liljefors, T. A Stereoselective Pharmacophoric Model of the Serotonin Re-Uptake Site. In *Computer-Assisted Lead Finding and Optimization: Current Tools for Medicinal Chemistry*; van de Waterbeemd, H., Testa, B., Folkers, G., Eds.; Verlag Helvetica Chimica Acta: Basel, Switzerland, 1997; pp 443–459.

16. In–house results.