A Computational Investigation of the Structures and Properties of Derivatives of Methylphenidate and Cocaine with Comparisons to Experimental Activity Data

Laura A. Duckworth and Gary W. Van Horn
Department of Chemistry
Humboldt State University
Arcata, California 95521-8299 U.S.A.

Faculty Advisor: Robert W. Zoellner

Abstract

Methylphenidate (Ritalin[®]) is a commonly prescribed pharmaceutical used to minimize the symptoms of attention deficit hyperactivity disorder (ADHD). The primary mode of action of this medication is thought to be through binding to an active site on the dopamine transporter. When abused, methylphenidate exhibits physiological effects similar to those of cocaine, most notably dopamine re-uptake inhibition. Because both methylphenidate and cocaine appear to bind to similar sites on the dopamine transporter, and because methylphenidate is a cocaine antagonist, it is may be feasible to use derivatives of methylphenidate to treat cocaine abuse. Semiempirical (PM3) methods have been used to calculate the structures and properties of approximately fifty derivatives of methylphenidate and fifty derivatives of cocaine in order to establish correlations between experimental binding affinities and calculated electronic and molecular orbital properties. Calculated properties that appear to correlate strongly with binding affinities will be discussed and methods to enhance binding affinity will be inferred for both methylphenidate and cocaine.

Keywords: 1. Methylphenidate. 2. Cocaine, 3. Semiempirical.

1. Introduction

Cocaine is a powerfully addictive drug, and cocaine addiction is a continuing problem in the United States. As of 1997, 20 to 30 million people in the United States were estimated to have tried cocaine, and about 4 million were addicted to the drug.[1] Cocaine is a strong central nervous system (CNS) stimulant that blocks the dopamine transporter (DAT). As a result of the blockage of the DAT by cocaine, the synaptic gap between nerves is flooded with higher than normal levels of dopamine; these higher than normal levels lead to a continuous excitation of the postsynaptic neurons. Dopamine is itself a neurotransmitter that plays a major role in drug addiction because it affects brain processes that control movement, emotion, and the ability to experience pleasure and pain. Proper regulation of dopamine is important for good mental and physical health.

Methylphenidate (Ritalin[®]) is currently the most prescribed drug for attention deficit hyperactivity disorder (ADHD). Like cocaine, methylphenidate blocks the DAT, and this phenomenon has been linked to the reinforcing effects of both cocaine and methylphenidate. Because methylphenidate binds to the DAT at a site similar to the binding site of cocaine, methylphenidate and methylphenidate analogs have been investigated as potential candidates to act as either a cocaine agonist or antagonist. Although studies have shown that methylphenidate itself is not effective as a potential therapeutic drug because users may become addicted to the pharmaceutical, analogs or derivatives of methylphenidate may show promise. [2]

Computational methods may provide additional data that may be used to investigate the properties that delineate methylphenidate or cocaine binding to the DAT. Properties difficult to determine experimentally for a large dataset of compounds, such as energies of formation, molecular orbital energies, dipole moments, and molecular areas and

volumes, can be quickly calculated using semiempirical methods. Herein are reported these calculated properties for methylphenidate, cocaine, and a large variety of derivatives of each of these molecules. Comparisons to experimental binding affinities will be made, when possible, to determine whether any correlations exist.

2. Computational Details

All calculations were carried out using the *PC SPARTAN Pro*[®] [3] software package running on *Gateway*[®] *E-4200 Pentium III*[®] 600 MHz computers with 384 Mbyte RAM and 20 Gbyte hard drives. Semiempirical (PM3) methods have been used to calculate the structures and properties of approximately fifty derivatives of methylphenidate and fifty derivatives of cocaine in an attempt to establish correlations between experimental binding affinities and calculated structural, electronic, and molecular orbital properties. Molecular areas and volumes were calculated using the options in the *PC SPARTAN Pro*[®] graphical user interface.

3. Results

Searches of the available literature using *Chemical Abstracts Online* were carried out in an effort to identify and classify the reported derivatives of methylphenidate, Figure 1. Only the mono-substituted derivatives of methylphenidate found in these searches were investigated computationally. Computational results, including energies of formation, highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) energies, the LUMO–HOMO differences, dipole moments, and molecular areas and volumes for these derivatives have been listed in Table 1. Using a search strategy similar to that used for methylphenidate, mono-substituted derivatives of cocaine (Figure 2) were also identified. Computational results for these derivatives have been listed in Table 2.
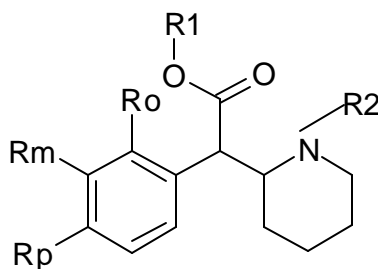

Figure 1 The methylphenidate skeleton, with potential substituent positions indicated. Methylphenidate itself has $R_2 = R_o = R_m = R_p = H$ and $R_1 = CH_3$. Only mono-substituted derivatives of methylphenidate were investigated.
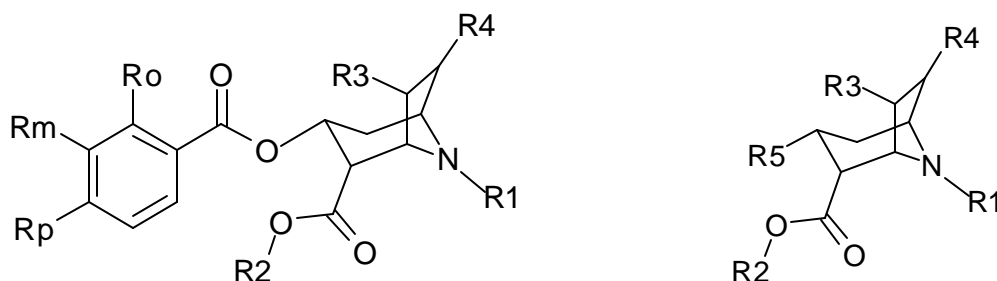

Figure 2 The cocaine skeleton. Cocaine (left) itself has $R_3 = R_4 = R_o = R_m = R_p = H$ and $R_1 = R_2 = CH_3$; when the complete benzoate substitutent is removed and replaced by another group, that group is designated R_5.

2

Table 1. Computational Results for the mono-Substituted[a] Methylphenidate Derivatives

Compound	Energy[b] (kcal/mol)	HOMO (eV)[c]	LUMO (eV)[c]	LUMO–HOMO (eV)[c]	Dipole (D)[d]	Area[b] (Å^2)	Volume[b] (Å^3)
methylphenidate[e]	−71.273	−9.6358	0.0576	9.6934	3.078	289.69	282.47
R_1 = n-pentyl	−87.701	−9.2554	0.1049	9.3603	3.056	386.03	366.19
R_1 = sec-butyl	−82.101	−9.2606	0.1458	9.4064	3.008	358.33	345.29
R_o = Br	−56.070	−9.2399	−0.1655	9.0744	2.834	309.28	304.69
R_o = Cl	−70.287	−9.2377	−0.1152	9.1225	2.902	305.65	299.70
R_o = F	−107.75	−9.2654	−0.2085	9.0569	2.737	300.11	290.10
R_o = OCH_3	−100.00	−9.0792	0.1179	9.1971	3.542	321.81	314.32
R_o = OH	−111.45	−9.1477	0.0871	9.2348	2.160	298.33	291.95
R_m = Br	−59.345	−9.3731	−0.1683	9.2048	3.485	318.96	308.18
R_m = CH_3	−76.497	−9.2693	0.1491	9.4184	3.023	317.08	304.20
R_m = Cl	−73.761	−9.3354	−0.1183	9.2171	2.770	313.79	302.01
R_m = F	−110.22	−9.3580	−0.2144	9.1436	2.373	303.38	290.88
R_m = OCH_3	−104.98	−9.1834	0.0933	9.2767	3.368	327.94	315.38
R_m = OH	−111.96	−9.2443	0.0401	9.2844	3.138	307.07	294.28
R_p = Br	−59.328	−9.3788	−0.1997	9.1791	3.021	318.96	308.16
R_p = t-butyl	−90.489	−9.2660	0.1390	9.4050	3.130	371.97	361.87
R_p = CH_3	−76.548	−9.2377	0.1057	9.3434	3.221	317.48	304.23
R_p = Cl	−73.798	−9.2904	−0.1757	9.1147	2.994	313.70	301.99
R_p = F	−110.30	−9.3601	−0.2315	9.1286	3.031	303.44	290.89
R_p = I	−45.322	−9.0775	−0.5154	8.5621	2.901	325.49	316.18
R_p = OCH_3	−103.14	−9.2945	−0.0920	9.2025	3.460	317.98	312.64
R_p = NO_2	−75.652	−9.6239	−1.2651	8.3588	5.705	326.63	315.24
R_p = OH	−112.02	−9.1535	0.1019	9.2554	2.433	307.37	294.72
R_1 = n-butyl	−82.289	−9.2542	0.1060	9.3602	3.060	363.61	345.69
R_1 = i-butyl	−82.147	−9.2553	0.1049	9.3602	2.851	356.31	345.12
R_1 = CH_2CH_2Cl	−80.190	−9.3219	0.0462	9.3681	2.445	360.37	343.92
R_1 = $CH_2CH_2OCH_3$	−112.32	−9.2972	0.0851	9.3823	3.087	374.83	357.20
R_1 = CH_2Ph	−37.654	−9.2414	0.0540	9.2954	3.099	379.99	372.35
R_1 = cyclohexyl	−54.548	−9.2633	0.1405	9.4038	2.981	381.30	371.32
R_1 = cyclopentyl	−78.101	−9.2640	0.1367	9.4007	3.082	362.70	352.49
R_1 = ethyl	−72.515	−9.2866	0.1403	9.4269	2.912	317.12	304.25
R_1 = C_2H_4O-n-butyl	−121.61	−9.2555	0.0803	9.3358	3.415	413.00	396.64
R_1 = i-propyl	−77.255	−9.2355	0.1213	9.3568	2.932	339.13	325.01
R_2 = NH_2	−105.73	−9.6070	−0.1199	9.4871	3.615	324.12	320.46
R_2 = $CH_2CH=CH_2$	−49.647	−9.0992	0.1231	9.2223	2.890	339.81	337.24
R_2 = CH_2Ph	−41.056	−9.1219	0.1481	9.2700	2.546	394.42	390.77
R_2 = CH_3	−69.152	−9.1152	0.1219	9.2371	2.971	312.28	304.26
R_2 = $C(O)CF_3$	−253.91	−9.9321	−0.1788	9.7533	4.101	350.30	346.83
R_2 = CO_2-t-butyl	−160.68	−9.6569	−0.1884	9.4685	5.659	390.53	394.96
R_2 = CO_2CH_2Ph	−116.83	−9.8485	−0.1826	9.6659	6.018	414.27	423.78
R_2 = C(O)Ph	−75.581	−9.4908	−0.1001	9.3907	4.463	394.73	394.94
R_2 = $C(O)CH_3$	−110.87	−9.5102	−0.0792	9.4310	4.296	330.49	326.73
R_2 = NO	−40.967	−9.7861	−0.0905	9.6956	4.044	314.39	304.10
R_2 = n-propyl	−77.189	−9.2752	0.1281	9.4033	3.120	340.82	325.19

[a] All derivatives are mono-substituted; the substituent is H unless otherwise stated.
[b] Energies, areas, and volumes have been arbitrarily reported to five significant digits.
[c] Molecular orbital energies have been arbitrarily reported to four decimal places.
[d] Dipole moments have been arbitrarily reported to four significant digits.
[e] R_1 = CH_3.

Table 2. Computational Results for the mono-Substituted[a] Cocaine Analogs

Compound	Energy[b] (kcal/mol)	HOMO (eV)[c]	LUMO (eV)[c]	LUMO–HOMO (eV)[c]	Dipole (D)[b]	Area[b] (Å^2)	Volume[b] (Å^3)
cocaine[d]	–137.13	–9.4505	–0.4445	9.0060	4.228	355.97	348.59
R_o = F	–178.41	–9.4806	–0.6345	8.8461	5.040	362.59	355.30
R_o = CH_3	–144.76	–9.4421	–0.2247	9.2174	4.061	377.09	368.61
R_o = Cl	–146.18	–9.4551	–0.5055	8.9496	4.430	392.08	386.32
R_o = OAc	–216.59	–9.3693	–0.5753	8.7940	6.094	418.02	405.55
R_o = OH	–184.77	–9.3854	–0.6190	8.7664	4.227	362.73	356.93
R_m = Cl	–148.32	–9.4785	–0.6341	8.8444	4.269	393.99	386.77
R_m = I	–115.22	–9.2315	–0.6848	8.5467	4.233	385.46	380.72
R_p = $(CH_2)_2NH_2$	–143.31	–9.4030	–0.3440	9.0590	5.552	415.46	404.71
R_p = CH_2Cl	–137.13	–9.4505	–0.4445	9.0060	4.228	355.97	348.59
R_p = CH_2NH_2	–140.41	–9.4870	–0.6322	8.8548	3.394	394.91	384.41
R_p = CHO	–175.35	–9.5257	–1.0688	8.4569	4.404	401.74	394.04
R_p = F	–180.41	–9.5113	–0.7467	8.7646	3.382	363.06	355.40
R_p = I	–115.38	–9.3037	–0.7210	8.5827	3.823	385.49	380.71
R_p = NH_2	–145.07	–8.9700	–0.3919	8.5781	4.374	391.55	383.84
R_p = OH	–182.81	–9.4360	–0.4344	9.0016	3.827	366.49	359.15
R_p = Ph	–112.53	–9.4405	–0.6996	8.7409	4.429	439.31	436.26
R_2 = $(CH_2)_2PhNCS$	–71.787	–8.7264	–0.7240	8.0024	7.608	512.03	503.56
R_2 = $(CH_2)_2PhNH$-$(CH_2)_2CO_2Et$	–207.37	–8.5174	–0.4356	8.0818	4.977	605.39	590.92
R_2 = $(CH_2)_5C(O)NH_2$	–194.14	–9.4601	–0.4285	9.0316	4.461	487.48	471.12
R_2 = $C(NH$-i-$Pr)_2$	–139.01	–9.5658	–0.4120	9.1538	5.239	506.34	496.71
R_2 = CH_2NH_2	–212.40	–9.5143	–0.5516	8.9627	4.914	428.43	420.24
R_2 = $(CH_2)_2PhNH$-$C(O)CH_2Br$	–148.84	–9.2527	–0.8175	8.4352	7.668	545.41	541.83
R_2 = i-propyl	–146.53	–9.4088	–0.4253	8.9835	3.846	396.13	389.07
R_2 = ethyl	–152.11	–9.4316	–0.1610	9.2706	3.775	391.76	387.76
R_5 = $CO_2(CH_2)_5CH_3$	–199.07	–9.4522	0.9145	10.3667	4.000	404.99	383.43
R_5 = CO_2-naphthyl	–119.81	–9.1592	–0.8706	8.2886	4.460	404.97	402.10
R_5 = O_2CPhCH_2NH-$C(O)CH(Ph)$-CO_2H	–238.05	–9.3959	–0.5639	8.8320	5.708	554.98	552.07
R_3 = Cl	–144.72	–9.5960	–0.3271	9.2689	4.328	384.00	384.35
R_3 = OH	–178.54	–9.5159	–0.4751	9.0408	2.743	359.32	357.05
R_3 = OCH_3	–172.62	–9.3422	–0.4986	8.8436	3.612	387.02	380.35
R_4 = OCH_3	–173.28	–9.4289	–0.4496	8.9793	3.120	379.29	377.97
R_1 = $(CH_2)_2Br$	–135.18	–9.7776	–0.5169	9.2607	4.475	400.57	393.74
R_1 = $[(CH_2)_2O]_2Et$	–222.16	–9.5195	–0.4634	9.0561	2.228	485.66	472.81
R_1 = $(CH_2)_2OH$	–182.47	–9.6063	–0.4861	9.1202	3.374	388.37	380.04
R_1 = $(CH_2)_4NH_2$	–152.24	–9.4957	–0.4657	9.0300	4.331	454.22	444.29
R_1 = $CO(CH_2)_2CO_2H$	–269.13	–9.9413	–0.5346	9.4067	7.270	438.85	429.20
R_1 = C≡CH	–79.914	–9.2484	–0.5036	8.7448	4.242	364.81	357.35
R_1 = CH_2C≡CH	–82.329	–9.5132	–0.4499	9.0633	4.282	384.92	377.53
R_1 = $CH_2CO_2CH_2Ph$	–187.28	–9.7008	–0.4470	9.2538	5.559	501.35	494.32
R_1 = CH_2NH_2	–133.15	–9.5863	–0.4859	9.1004	4.254	372.91	364.32
R_1 = $CH_2CO_2CH_3$	–216.40	–9.7561	–0.4941	9.2620	4.795	413.67	405.62
R_1 = $C(O)(CH_2)_2NH_2$	–176.98	–9.8064	–0.5350	9.2714	5.643	417.22	408.86
R_1 = CO_2CH=CH_2	–188.02	–9.8330	–0.5169	9.3161	4.142	402.29	398.48

[a] All derivatives are mono-substituted; the substituent is H unless otherwise stated.
[b] Energies, areas, and volumes are arbitrarily reported to five significant digits, dipole moments to four.
[c] Molecular orbital energies are arbitrarily reported to four decimal places.
[d] R_1 = R_2 = CH_3.

4. Discussion

The computational results for methylphenidate and the mono-substituted derivatives of methylphenidate (Table 1) and for cocaine and the mono-substituted cocaine analogs (Table 2) were compared to published data for binding affinity for those derivatives or analogs, when such data could be found. As previous studies have shown, *m*-chloro- and *m*-bromo -methylphenidate derivatives (Figure 1, R_m = Cl, Br) have demonstrated high affinities for the DAT, with low potency for reuptake inhibition.[4] Other studies have demonstrated that *ortho*-substituents (Figure 1, R_o) have less affinity for the DAT than derivatives containing electron withdrawing substituents at the *meta-* and *para*-positions (R_m and R_p). Large groups in the *para*-positions tend to decrease methylphenidates activity, [5] while substitutions on the nitrogen of methylphenidate tend to attenuate the inhibition of dopamine transport (Tables 3 and 4).[6,7]

Table 3. Inhibition of [^{3}H]-WIN-35,428 Binding of Compounds With and Without an N-methyl Group [7]

Compound	unsubstituted[a]		substituted[b]		Ratio[d]
	IC_{50} (nM)	Hill coefficient	IC_{50} (nM)	Hill coefficient	
no phenyl substituents [c]	83 ± 8	0.90 ± 0.09	500 ± 25	1.00 ± 0.01	6.0
R_m = Cl	5.1 ± 1.6	0.95 ± 0.12	161 ± 18	0.96 ± 0.04	32.
R_m = CH$_3$	21.4 ± 1.1	1.01 ± 0.12	108 ± 16	1.00 ± 0.04	5.0
R_p = CH$_3$	33 ± 1.2	1.05 ± 0.02	139 ± 13	1.03 ± 0.04	4.2
R_m = OH	98 ± 10	1.07 ± 0.12	1220 ± 140	1.06 ± 0.01	12.

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[a] Compounds in which R_2 = H.
[b] Compounds in which R_2 = CH$_3$
[c] Methylphenidate has R_1 = CH$_3$ and R_2 = H.
[d] IC_{50} of the substituted compound divided by the IC_{50} of the unsubstituted compound.

Table 4. Affinities of Methylphenidate and Other Compounds for Transporters [8]

Compound	IC_{50} Values (nM) for Binding or Uptake			
	dopamine binding	dopamine uptake	NET	5-HTT
methylphenidate	84 ± 33	153 ± 92	514 ± 74	>50000
R_o = Br	880 ± 316		20000	
R_m = Br	4 ± 1	18 ± 11	20 ± 6	3800
R_p = Br	21 ± 3	45 ± 19	31 ± 7	2600
R_p = OH	125	263 ± 74	270 ± 69	17000
R_p = OCH$_3$	42 ± 24	490 ± 270	410	10000
R_p = I	26 ± 14		32	1800
R_2 = CH$_3$	1400		2800	40000
cocaine	120	313 ± 160	2100	190

Studies using cocaine analogs have shown that a wide range of substituents at the 2β-position (Figure 2, R_2) can be tolerated with little or no loss in activity. This position does not require the presence of the carbonyl group in order for the molecule to exhibit binding to the DAT. Conversely, the size of the substituent at the nitrogen position in cocaine (Figure 2, R_1) appears to be inversely proportional to the activity of the molecule. Further, when the lone pair of electrons on the nitrogen is constrained by a substituent so as to point toward the three-carbon bridge rather than the two-carbon bridge, the cocaine analog is more selective for the DAT than for the 5-HTT.[4] Finally, however, it is important to note that IC_{50} values vary significantly depending upon the placement of substituents on the phenyl ring, and these changes also are affected by substituents at other positions on the cocaine skeleton.

Table 5. Binding Potency of Substituted Cocaine Derivatives for Rat Brain Dopamine [9]

Compound	DAT IC$_{50}$ (nM)[a]	NET IC$_{50}$ (nM)[b]	5-HTT IC$_{50}$ (nM)[c]
cocaine[d]	249 ± 37	2500 ± 70	615 ± 120
R$_o$ = OH	25 ± 4	48 ± 2	143 ± 21
R$_o$ = OAc	70 ± 1	72 ± 9	219 ± 20
R$_o$ = F	604 ± 67	1392 ± 173	1770 ± 309
R$_p$ = OH	158 ± 8	601 ± 11	3104 ± 148
R$_p$ = I	2522 ± 4	18458 ± 1073	1052 ± 23
WIN-35,428	24 ± 4	258 ± 40	690 ± 14
nisoxetine	775 ± 20	135 ± 21	762 ± 90
fluoxetine	5200 ± 1270	963 ± 158	15 ± 3

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[a] IC$_{50}$ values were determined by displacement of bound [^{3}H]-WIN-35,428.
[b] IC$_{50}$ values were determined by displacement of bound [^{3}H]-nisoxetine.
[c] IC$_{50}$ values were determined by displacement of bound [^{3}H]-paroxetine.
[d] R$_1$ = R$_2$ = CH$_3$ for cocaine.

  With the experimental data listed above, as well as additional data from other sources, comparisons could be made to the computational data reported in Tables 1 and 2. Both methylphenidate and cocaine derivatives exhibit significant potential to act as effective cocaine antagonists. However, the comparison of published IC$_{50}$ binding data to calculated energies of formation, highest occupied molecular orbital (HOMO) energies, lowest unoccupied molecular orbital (LUMO) energies, the difference (LUMO–HOMO) in these energies, the dipole moments, or the molecular areas or volumes did not yield any realistic correlations. All such plots were simply random scatters with no possibility of trends being drawn.

5. Conclusions

Computational methods are the method of choice for accurate determination of many molecular properties. However, in the instance of methylphenidate, cocaine, and derivatives of these two molecules, simple computational methods do not produce data useful in the determination or delineation of the properties that are necessary for biochemical binding. The properties investigated here (energies of formation, HOMO energies, LUMO energies, LUMO–HOMO differences, dipole moments, and molecular areas or volumes) cannot be used to predict the binding affinity of either a methylphenidate or a cocaine derivative from these calculated properties.

6. Acknowledgements

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