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Enaminones 10. Molecular modeling aspects of the 5-methylcyclohexenone derivatives

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ABSTRACT

This article expands upon our original submission to the Eddington, N. D.; Cox, D. S.; Khurana, M.; Salama, N. N.; Stables, J. P.; Harrison, S. J.; Negussie, A.; Taylor, R. S.; Tran, U. Q.; Moore, J. A.; Barrow, J. C.; Scott, K. R. *Eur. J. Med. Chem.* **2003**, *38*, 49 on a series of twenty (20) compounds, all 5-methyl-3-[(substituted)-phenylamino]-cyclohex-2-enone derivatives. This article provides the reasons why the compounds are active/inactive. By use of computational methods, the reasons for activity/inactivity are explained.

1. Introduction

Epilepsy is a common neurological condition, affecting 0.5–1% of the population worldwide (45–100 million people).[1,2] Despite optimal use of available antiepileptic agents, many patients with the disease fail to experience seizure control and others do so only at the expense of significant side effects. Estimates suggest that available medication controls the seizures in only 50% of patients or decreases the incidence in only 75% of patients.[3] During our investigation of enaminones, we uncovered a group of compounds that had excellent anticonvulsant properties.[4,5] We had modeled our compounds using the Unverferth analysis,[6,7] and included those compounds in the series that were active in the maximal electroshock seizure (MES) mode. In a related occurrence, Edafiogho and co-workers investigated the enaminone, methyl 4-(4′-bromo-phenyl)amino-6-methyl-2-oxocyclohex-3-en-1-oate,[8] and determined that the compound exhibited two independent molecules, with an absolute configuration C11(*S*), C12(*R*), and the inverse (Fig. 1). Ab initio calculations with the 6-31G, 3-21G and STO-3G basis sets confirmed that the C11(*S*), C12(*R*) enantiomer with both substituents in the equatorial position had the lowest energy. Further, the amino tautomer[9] was confirmed by NMR spectroscopy. Using the putative binding site theory proposed by Dimmock et al.[10] and utilized by Pandeya et al.[11] in postulating the interaction of anticonvulsant compounds at a specific binding site, the molecule would appear to interact with the protein receptor as shown in Figure 2.[2]

In our current series, which appeared in the European Journal of Medicinal Chemistry, we did not attempt to provide an explanation as to why some compounds were active and some were inactive in that series, but now we do so with this article. The N–H binding site was confirmed early in our work when it was found that no compound was active with the N–H proton missing.[4] Further, all of the active compounds were those that were *para*-substituted with an electron-withdrawing group. We have not reported on the vinyl proton substitution as yet.

2. Chemistry and pharmacology

The compounds in the series were based on the structure above. Chirality was not addressed in the synthesis, but is so now. The

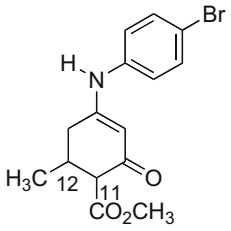

Figure 1. After Edafiogho et al. Ref. 8.

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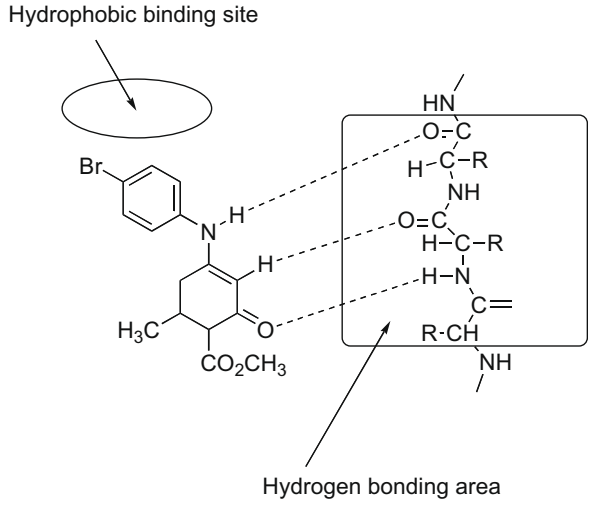

Figure 2. After Ref. 8.

structures as shown in Table 1 and Figure 3 were synthesized according to the procedure as noted previously.[5]

3. Molecular modeling

The compounds were computationally examined using GAUSSIAN 03 system at the DFT-B3LYP level of theory with the 3-21G** basis set. HH-the amine proton is next to the vinyl proton; H2H-the amine proton is next to the methylene protons; E-the methyl group is equatorial to the cyclohexenone ring; X-the methyl group is axial to the cyclohexenone ring. This is shown in Table 2. Also, the variation of average Mulliken charge on the nitrogen with the X group is shown in Figure 4.

In addition, we analyzed a subset (X = *para* Cl, *para* Br, *para* F, and *para* I) by means of the DFT with the B3LYP functional and the LanL2MB Basis set, in the neutral and protonated states. The output structures showed that the substituted methyl group of the cyclohexene ring was positioned out-of-plane to the remaining carbons in the ring. The out-of-plane angles this carbon makes with each side of the ring, the Mulliken charges of the nitrogen and halogen atoms in the protonated and neutral states, and the dipole moment of the molecules were noted (Tables 3–7). The proton affinities of the molecules were calculated as the difference between the total energies of its neutral and protonated forms.

In this series, all H2H compounds in Tables 3–7 have the amine proton facing the two alkyl protons of the cyclohexenone ring with the methyl group either axial (Ax) or equatorial (Eq) position, and all HH compounds have the amine proton facing the vinyl proton of the cyclohexenone ring with the methyl group either axial (Ax) or equatorial (Eq). This is shown in the depiction above (Fig. 4).

Table 1
5-Methyl-3-[(substituted)-phenylamino]-cyclohex-2-enone, **2** derivatives

Compound	X	Activity[a,b]
2a	4-Cl	Phase II: ED_{50} 16.7, TD_{50} 110.7, PI 6.6, TPE 0.25 Phase VIB: ED_{50} 14.7, TD_{50} > 186 PI > 83.3, TPE 1.0
2b	4-Br	Phase VIB: ED_{50} 7.6, TD_{50} > 500, PI > 65.8, TPE 0.5
2c	4-I	Phase II: ED_{50} 77.0, TD_{50} 343.6, PI 4.5, TPE 0.25 Phase VIB: ED_{50} 17.6, TD_{50} > 500, PI > 28.3, TPE 2.0
2d	4-F	Not active
2e	4-CF_3	Phase VIB: ED_{50} 10.3, TD_{50} > 500, PI > 48.4 TPE 1.0
2f	4-OCF_3	Phase VIB: ED_{50} 6.5, TD_{50} > 400, PI > 62.0, TPE 0.5
2g	4-CN	Not active
2h	4-NO_2	Phase VIB: ED_{50} 18.4, TD_{50} > 500, PI > 27.4, TPE 4.0
2i	4-CH_3	Not active
2j	4-H	Not active
2k	3-Cl	Not active
2l	3-Br	Not active
2m	3-I	Not active
2n	3-F	Not active
2o	3-CF_3	Not active
2p	3-OCF_3	Not active
2q	3-CN	Not active
2r	3-NO_2	Not active
2s	3-CH_3	Not active
2t	3-OCH_3	Phase VIB: ED_{50} 39.4, TD_{50} > 500, PI > 12,7, TPE 0.5

[a] Activity taken from Ref. 5.
[b] All results versus maximal electroshock (MES), Phase II in mice, Phase VIB in rats; ED_{50}, median effective dose in mg kg^{-1}; TD_{50}, median toxic dose in mg kg^{-1}; TPE, time of peak effect in hours.

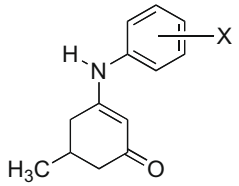

Figure 3. After Eddington et al. Ref. 5.

Table 2
Computational data on compounds **2a–t**

Compound	Molar volume (cm^3/mol)	Energy (a.u.)	Comment
2a	178.4125	1088.4842172	Active
2b	182.0502	3192.4154694	Active
2c	171.8143	7521.0070663	Active
2d	164.6640	729.67258926	Not active
2e	172.3517	966.18730154	Active
2f	182.7197	1040.9900879	Active
2g	176.5065	722.70702929	Not active
2h	171.7318	834.31711709	Active
2i	185.4710	670.08938845	Not active
2j	163.7658	630.97896136	Not active
2k	168.7308	1088.4857028	Not active
2l	163.3708	3192.4162979	Not active
2m	187.8483	729.67359942	Not active
2n	164.8848	729.67367502	Not active
2o	173.2935	966.18826477	Not active
2p	181.2430	1040.9913672	Not active
2q	172.0415	722.70602840	Not active
2r	171.8135	834.31509991	Not active
2s	169.6250	670.09055084	Not active
2t	177.2780	744.88401955	Active

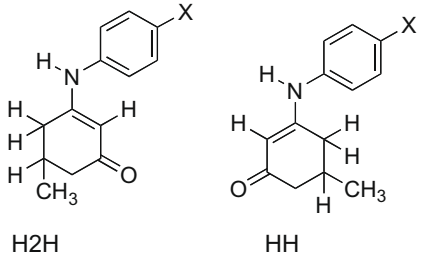

Figure 4. Possible configurations of the *para* derivatives as noted in Tables 3–7.

4. Results and discussion

The variation of the average Mulliken charge on the nitrogen with the X group is found in Figure 5. Data is found in Table 1. Compounds

Table 3
Bond angles, Mulliken charges, dipole moment of the neutral compounds

Compound	<ABC	<AFE	Mulliken N	Mulliken X	Dipole	<BAF
2a-HHeq	111.64972	110.96712	−0.282007	−0.258876	1.9340	109.58946
2a-HHAx	112.13643	111.46354	−0.282112	−0.258829	1.9307	109.36363
2a-H2Heq	111.41465	111.95604	−0.283960	−0.259381	6.0656	109.33116
2a-H2HAx	111.41419	111.95285	−0.283950	−0.259398	6.0652	109.32565
2b-HHEq	111.67383	110.92330	−0.282039	−0.213889	1.8913	109.57978
2b-HHAx	112.14646	111.44968	−0.282064	−0.213830	1.8738	109.35166
2b-H2HEq	111.42376	111.97159	−0.283971	−0.214527	5.9994	109.32717
2b-H2HAx	111.40422	111.97400	−0.283969	−0.214516	5.9986	109.32293
2c-HHEq	111.68896	110.88300	−0.282033	−0.167126	1.9406	109.55445
2c-HHAx	112.14104	111.44763	−0.282037	−0.166956	1.8928	109.33927
2c-H2HEq	111.42069	111.97737	−0.283922	−0.167915	5.9990	109.31918
2c-H2HAx	111.94275	112.38052	−0.283841	−0.167616	5.9562	109.06474
2d-HHEq	111.56629	111.09637	−0.285679	−0.061894	2.8307	109.56774
2d-HHAx	112.11503	111.60224	−0.285729	−0.061953	2.8085	109.34670
2d-H2HEq	111.50225	111.90586	−0.286834	−0.062249	3.7380	109.2488
2d-H2HAx	111.98465	112.39042	−0.286799	−0.062270	3.7267	109.02033

Table 4
Proton affinity calculations

Compound	Energy neutral (a.u.)	Energy charged (a.u.)	Proton affinity (a.u.)	Proton affinity (−) (kJ/mol)
2a-HHEq	−640.83807662	−641.24271473	−0.40463811	1062.37743873
2a-H2HEq	−640.83898440	−642.24180140	−0.4028170	1057.596114
2a-HHAx	−640.83674072	−641.24143282	−0.4046921	1062.5191895
2a-H2HAx	−640.83898438	−641.24048682	−0.40150244	1054.14473652
2b-HHEq	−639.05739136	−639.46283893	−0.40544757	1064.50267612
2b-H2HEq	−639.05829614	−639.46196977	−0.40367363	1059.8451963
2b-HHAx	−639.05605952	−639.46155049	−0.40549097	1064.61662283
2b-H2HAx	−639.05829613	−639.46067188	−0.40237575	1056.4376121
2c-H2HEq	−637.27512205	−637.68131310	−0.40619105	1066.45468301
2c-H2HEq	−637.27602710	−637.68035865	−0.40433155	1061.57256539
2c-HHAx	−637.27378493	−637.68001058	−0.40622565	1066.54552532
2c-H2HAx	−637.27477006	−637.67910497	−0.40433491	1061.58138707
2d-HHEq	−724.27396306	−724.69567388	−0.42171082	1107.20184225
2d-H2HEq	−724.27481402	−724.69500292	−0.42018890	1103.2060410
2d-HHAx	−724.27263825	−724.69441443	−0.42177618	1107.3734495
2d-H2HAx	−724.27357557	−724.6937044	−0.42012883	1103.04832719

Table 5
Bond angles, Mulliken charges, dipole moment of the charged compounds

Compound	<ABC	<AFE	Mulliken N	Mulliken X	Dipole D	<BAF
2a-H2HEq	112.13714	110.00836	−0.257117	−0.170603	8.7538	110.33654
2a-H2HAx	112.38463	110.30303	−0.257201	−0.170546	15.6415	110.04841
2a-HHEq	112.21685	109.91113	−0.256895	−0.171582	7.2617	110.33901
2a-HHAx	112.49575	110.18214	−0.256953	−0.171502	6.6412	110.08147
2b-H2HEq	112.14955	109.97805	−0.257105	−0.107158	10.9178	110.32625
2b-H2HAx	112.38999	110.31384	−0.257205	−0.107121	11.2273	110.08185
2b-HHEq	112.19712	109.91141	−0.256937	−0.108351	9.2880	110.34265
2b-HHAx	112.45336	110.22986	−0.256992	−0.108174	8.7736	110.09223
2c-H2HEq	112.13189	109.96195	−0.257136	−0.039815	12.9675	110.30901
2c-H2HAx	112.41726	110.23951	−0.257207	−0.039705	13.2932	110.04884
2c-HHEq	112.27150	109.84852	−0.256981	−0.041192	11.3058	110.32983
2d-HHAx	112.40933	110.23232	−0.257050	−0.040908	10.8601	110.07884
2d-H2HEq	112.12457	110.08510	−0.256925	−0.016667	6.2476	110.29355
2d-H2HAx	112.37605	110.34793	−0.256950	−0.016625	6.4969	109.99274
2d-HHEq	112.20307	110.04330	−0.256826	−0.017324	6.2756	110.36194
2d-HHAx	112.39627	110.43822	−0.257187	−0.017141	5.8755	110.11168

that are active have the (−) energy is above 1000 atomic units. Note the values for the inactive 4-fluoro derivative (**2d**) (average value: 729.8408626775), 4-nitrilo (**2g**) (average value: 722.707042045), 4-tolyl (**2i**) (average value: 670.2866236525), unsubstituted (**2j**) (average value: 630.97896136), 3-iodo (**2m**) (average value: 729.67367502), 3-fluoro (**2n**), (average value: 729.672869130967), 3-trifluoromethyl (**2o**), (average value: 966.1884147675), 3-nitrilo (**2q**), (average value: 722.7060284) 3-nitro (**2r**), (average value: 834.321906267) and 3-tolyl (**2s**), (average value: 670.090550835).

The 3-chloro (**2k**) the molar volume (168.7308) of this compound, when compared to active 4-chloro **4a** (178.4125) isomer, while the 4-bromo **4b** (182.0503) while the inactive 3-Br (**4l)** was 163.3708. The inactive 3-trifluoromethyl (**2o**) (168.680) and active 4-trifluoromethyl (**2e**) (571.927) Note that the active derivatives are larger than the inactive molecules.

The inactive 3-trifluoromethoxy (**2p**) (181.243), and the active 4-trifluoromethoxy (**2f**) (182.7197) was the similar. So, with this exception, it would seem that either the molecular volume or the

Table 6
Atomic distances for charged compounds

Compound	O–N	N–Me	X–Me	O–Me	X–O
2a-H2HEq	4.95769	5.14869	10.45900	5.00742	7.57732
2a-H2HAx	4.95781	4. 44588	9.71977	4.03646	7.97666
2a-HHEq	4.92670	5.16106	8.82477	5.01111	9.80406
2a-HHAx	4.92610	4.44105	9.61987	4.04787	9.82421
2b-H2HEq	4.95730	5.14659	11.06717	5.00930	8.06244
2b-H2HAx	4.95759	4.45015	9.81301	4.03705	8.08275
2b-HHEq	4.92629	5.6114	8.98166	5.01038	9.92397
2b-HHAx	4.92598	4.44550	9.76030	4.04384	9.96090
2c-H2HEq	4.95720	5.14667	11.23060	5.00928	8.20172
2c-H2HAx	4.95650	4.44103	9.84344	4.04282	8.19426
2c-HHEq	4.92610	5.15990	9.17632	9.01310	10.04722
2c-HHAx	4.92618	4.44934	9.94232	4.03880	10.10500
2d-H2HEq	4.95368	5.14869	10.45900	5.00742	7.57732
2d-H2HAx	4.95377	4.44612	9.15865	4.03730	7.57494
2d-HHEq	4.92566	5.15935	8.39568	5.00936	9.40317
2d-HHAx	4.92557	4.45270	6.77557	4.03269	9.23009

Table 7
Proton affinity calculations

Compound	O–N	N–Me	X–Me	O–Me	X–O
2a-HHEq	4.83779	5.09675	8.97997	5.00827	10.86936
2a-HHAx	4.83658	4.24842	8.98439	4.09037	10.86971
2a-H2HEq	4.90902	5.03580	11.09452	4.99476	8.92362
2a-H2HAx	4.90901	5.03578	11.09471	4.99473	8.92427
2b-HHEq	4.83725	5.09540	9.12898	5.00926	9.12898
2b-HHAx	4.83625	4.24650	9.13850	4.09173	11.01959
2b-H2HEq	4.90909	5.03521	11.24516	4.99514	9.06172
2b-H2HAx	4.90916	5.03531	11.24534	4.99461	9.06198
2c-HHEq	4.83714	5.09349	9.30948	5.01000	11.18647
2c-HHAx	4.83625	4.24551	9.31925	4.09175	11.19313
2c-H2HEq	4.90913	5.03476	11.42091	4.99525	9.22499
2c-H2HAx	4.90967	4.31264	10.34498	4.04256	9.22499
2d-HHEq	4.84235	5.09721	8.39435	5.00515	10.38005
2d-HHAx	4.84081	4.27397	8.31204	4.08281	10.38202
2d-H2HEq	4.91005	5.03361	10.60019	4.99589	8.40530
2d-H2HAx	4.90972	4.31766	9.44074	4.04541	8.42130

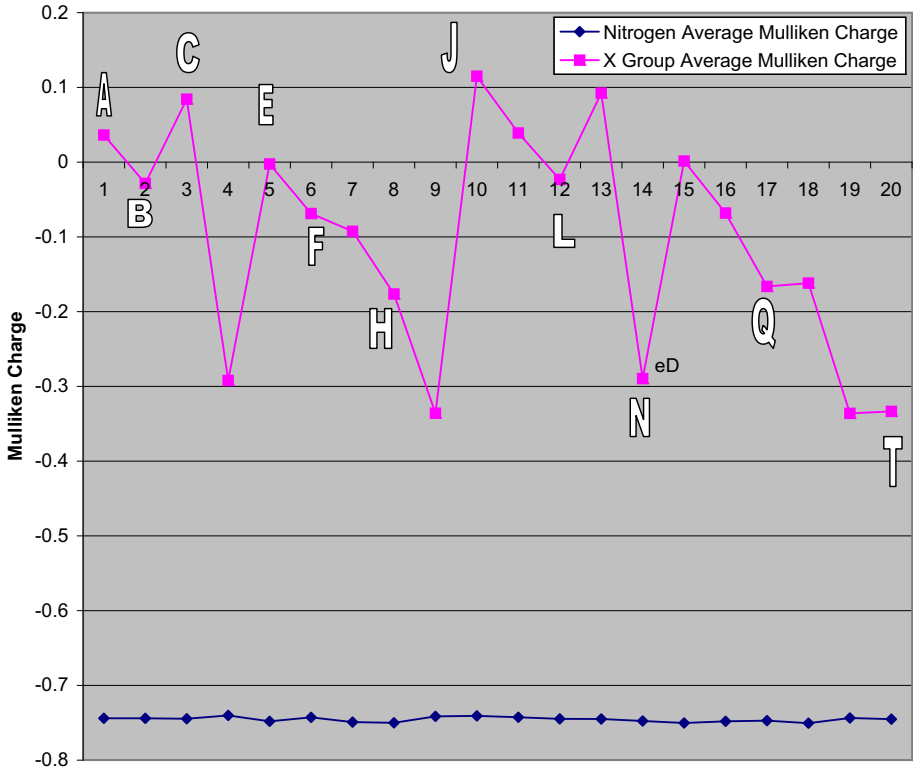

Figure 5. Variation of average Mulliken charge on the nitrogen with the X Group.

(−) energy would be different for the compounds to be either active or inactive. It is quite apparent that in this latter series resonance and inductive effects plays a critical role in their activity, as the *meta* substitution provides little in terms of inductive effect as opposed to the same substituent in the *para* position. Figure 5 shows the variation of the average Mulliken charge on the nitrogen with the X group.

In the second series, Tables 2 and 3, the Mulliken X is quite different for the *para* F (**2d**) than for the others; in Table 4, the energy is quite different with para F being quite high in the neutral state or the protonated form, and, as would be expected its proton affinity would be highest. In Table 5, Mulliken X is highest in the *para* F. In Tables 6 and 7 there were no notable differences in the atomic distances for the charged compounds or the proton affinity calculations.

It is clear that the lowest energy enantiomer is the one in which the methyl group is in the equatorial configuration, consistent with Edafiagho's initial results with the *p*-Br derivative.[8]

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