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Ultraviolet Spectroscopy of Anticonvulsant Enaminones

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Abstract—The ultraviolet (UV) spectra of selected enaminones were determined in acidic, alkaline and neutral media and compared to their anticonvulsant activities. The wavelength of maximum absorption and molar absorptivity were compared with the anticonvulsant activity of the selected secondary and tertiary enaminones, and general inferences were made. The UV spectra of the enaminones had hypsochromic shifts in acidic media in comparison with neutral media. Generally, a small hypsochromic shift occurred in alkaline media when compared to the neutral solutions of the enaminones. The tertiary enaminones absorbed UV light at longer wavelength than the secondary enaminones in acidic, neutral and alkaline media. In particular, the tertiary enaminones displayed absorption at the higher end and secondary enaminones towards the lower end of the UV wavelength range 292–315 nm in aqueous media. Tertiary enaminones (**30**–**33**) which were devoid of the NH proton were found to be uniformly inactive in a mouse model of electroshock seizures, while some secondary enaminones (**1**, **5**–**8**, **12**, **16**, **18**, **20**, **23**–**25**, **28** and **29**) had anticonvulsant activity. Thus the NH group of secondary enaminones is very important for anticonvulsant activity, and this agrees with an already established trend in proton NMR spectroscopy. In addition, the *para*-substitution on the phenyl group in some enaminones result in higher molar absorptivity (ε) values that enhance anticonvulsant activity. These results indicate that the anticonvulsant activity of enaminones is not due to electronic effect alone, but is probably due to a combination of factors including electronic and steric effects, lipophilicity, and hydrogen bonding.

Introduction

Several series of enaminones have been synthesized and screened for pharmacological activities.[1–8] Enaminones are chemical compounds consisting of an amino group linked through a carbon–carbon double bond to a keto group.[9] Enaminones are very stable and the cyclic enaminones are more stable than acyclic enaminones.[10] Due to the conjugation existing in the enaminone system, enaminones absorb ultraviolet (UV) radiation.[11]

The objective of this study was to determine the wavelength of maximum absorption (λ_{max}) and absorptivity (ε) values for selected enaminones and attempt to establish a correlation between UV data and anticonvulsant activity. Anticonvulsant activity of a compound is the ability of the compound to protect against seizures. Established procedures exist for screening compounds for anticonvulsant activity.[12–14]

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Results and Discussion

Generally, the enaminones can be prepared from reactions between beta hydroxyketo compounds and primary or secondary amines (Scheme 1); and the enaminones described in this paper were synthesized according to the methods of Edafiogho, Scott and coworkers.[2,11]

Nuclear magnetic resonance (NMR) studies had confirmed the general conformation of the enaminones to be *trans-S-trans* conformation, and that the enaminone system was present in all the compounds.[5,15] The enaminone compounds produced intense peaks under UV spectroscopy, and where a compound exhibited more than one peak, the most intense peak was reported. These peaks had ε values greater than 15,000. Generally, the UV data of enaminones **1**–**33** in water indicated their absorption in neutral medium. However, in acidic medium (1 M HCl), the enaminones were protonated; while in alkaline medium (1 M NaOH) they were deprotonated. One common feature among the enaminones evaluated in this study was that most of them had similar data in neutral and alkaline solutions

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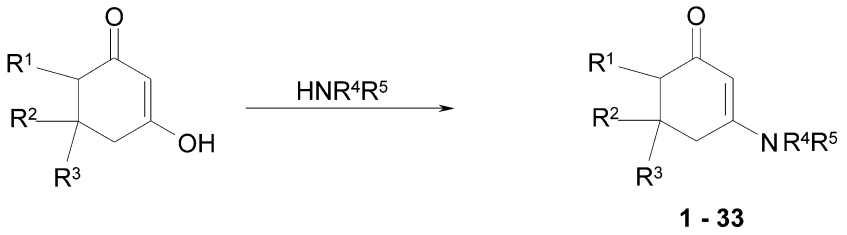
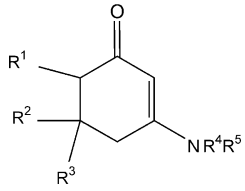


Scheme 1. General scheme for the synthesis of cyclic enaminones.

indicating that most of them were basic in nature. Deprotonation of these enaminones in alkaline solutions had small hypsochromic or no significant effect on their λ_{max} values when compared to neutral solutions. The enaminones that normally behave as weak bases exhibited hypsochromic shift (from longer to shorter wavelength) on moving from neutral to acidic media (see Tables 1 and 2).

In comparing UV data with anticonvulsant activity (Tables 1 and 2), it was found that the secondary enaminones **1**, **28** and **29** (with phenyl amino side chain), which absorbed above 282 nm in acidic medium, showed anticonvulsant activity while the secondary enaminones **2** and **3** which absorbed below 282 nm in acidic medium were inactive, irrespective of the number of methylene groups between the unsubstituted phenyl group and the NH group. In addition, enaminone **5** (Scheme 2) was anticonvulsant and displayed hypsochromic shift from neutral (311 nm) to acidic medium (301 nm). The hypsochromic shift in alkaline medium was not significant. The UV data for enaminone **6**

Table 1. Anticonvulsant screening project (ASP): phase 1 test results



Compound	Mp (°C)	R^1	R^2	R^3	R^4	R^5	ASP classification[a]
1	118–119	$-CO_2CH_3$	$-CH_3$	–H	–H	$-(CH_2)_2Ph$	1
2	163–164	$-CO_2CH_3$	$-CH_3$	–H	–H	$-(CH_2)_3Ph$	3
3	90–92	$-CO_2CH_3$	$-CH_3$	–H	–H	$-(CH_2)_4Ph$	3
4[16]	208–210	–H	$-CH_3$	$-CH_3$	–H	4-Chlorophenyl	3
5	178–180	$-CO_2CH_3$	$-CH_3$	–H	–H	4-Chlorophenyl	1
6	198–199.5	–H	$-CH_3$	–H	–H	4-Chlorophenyl	1
7	161–164	$-CO_2CH_3$	$-CH_3$	–H	–H	4-Fluorophenyl	1
8	188–190	$-CO_2CH_3$	$-CH_3$	–H	–H	4-Bromophenyl	1
9	221–222	$-CO_2CH_3$	$-CH_3$	–H	–H	4-*t*–Butylphenyl	3
10	178–179	$-CO_2CH_3$	$-CH_3$	$-CH_3$	–H	4-Nitrophenyl	2
11	168–169	$-CO_2CH_3$	$-CH_3$	$-CH_3$	–H	Phenyl	3
12	137–138	$-CO_2CH_3$	$-CH_3$	–H	–H	3-Chlorophenyl	1
13	175–177	$-CO_2CH_3$	$-CH_3$	–H	–H	3-Chloro-4-methoxyphenyl	3
14	178–181	$-CO_2CH_3$	$-CH_3$	–H	–H	3-Methoxyphenyl	3
15	166.5–168	$-CO_2CH_3$	$-CH_3$	–H	–H	3-Nitrophenyl	3
16	165–166	$-CO_2CH_3$	$-CH_3$	–H	–H	3-Methylphenyl	1
17	159–163	$-CO_2CH_3$	$-CH_3$	–H	–H	3-Bromophenyl	3
18	173–176	$-CO_2CH_3$	$-CH_3$	–H	–H	3-Trifluoromethoxyphenyl	1
19	177–178	$-CO_2CH_3$	$-CH_3$	–H	–H	4-Methoxyphenyl	3
20	151–155	$-CO_2CH_3$	$-CH_3$	–H	–H	3-Fluorophenyl	1
21	163–166	$-CO_2CH_3$	$-CH_3$	–H	–H	3-Iodophenyl	3
22	167–169	$-CO_2CH_3$	$-CH_3$	–H	–H	3-Trifluoromethylphenyl	3
23	146–149	$-CO_2CH_3$	$-CH_3$	–H	–H	3-Ethylphenyl	1
24	169–170	$-CO_2CH_3$	$-CH_3$	–H	–H	4-Trifluoromethylphenyl	1
25	206–208	$-CO_2CH_3$	$-CH_3$	–H	–H	4-Chloro-2-pyridinyl	1
26[16]		–H	$-CH_3$	$-CH_3$	–H	$-CH_3$	–
27[17]		–H	$-CH_3$	$-CH_3$		$-[CH_2]_4-$	–
28	154–155	$-CO_2CH_3$	$-CH_3$	–H	–H	$-CH_2Ph$	1
29	139–140	$-CO_2CH_3$	$-CH_3$	$-CH_3$	–H	$-CH_2Ph$	2
30	138–139	$-CO_2CH_3$	$-CH_3$	–H		$-[CH_2]_4-$	3
31	112–113	$-CO_2CH_3$	$-CH_3$	$-CH_3$		$-[CH_2]_4-$	3
32	168–169	$-CO_2C_2H_5$	$-CH_3$	–H		$-[CH_2]_4-$	3
33	194–195	$-CO_2CH_3$	–Ph	–H		$-(CH_2)_2-O-(CH_2)_2-$	3

[a]Anticonvulsant activity at 100 mg/kg or less = 1; at 300 mg/kg = 2; at > 300 mg/kg = 3 (inactive).

Table 2. Ultraviolet data of enaminones

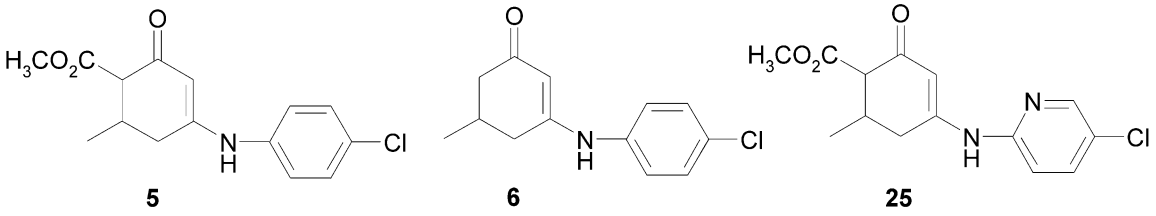
Compound	Molecular formula	MW	1 M HCl		H_2O		1 M NaOH	
			λ_{max}	ε	λ_{max}	ε	λ_{max}	ε
1	$C_{17}H_{21}NO_3$	287.39	284	22,000	295	32,600	294	33,500
2	$C_{18}H_{23}NO_3$	301.42	280	21,800	292	30,300	292	29,000
3	$C_{19}H_{25}NO_3$	315.45	278	23,400	292	31,200	292	30,000
4[16]	$C_{14}H_{16}NOCl$	249.80	301	21,900	312	23,800	311	23,300
5	$C_{15}H_{16}NO_3Cl$	293.81	301	18,400	311	28,200	307	24,100
6	$C_{13}H_{14}NOCl$	235.77	297	19,300	310	27,400	305	20,500
7	$C_{15}H_{16}NO_3F$	277.32	297	23,800	302	30,900	303	28,700
8	$C_{15}H_{16}NO_3Br$	338.22	302	21,600	310	29,100	308	27,200
9	$C_{19}H_{25}NO_3$	315.45	302	22,000	308	29,300	306	27,100
10	$C_{16}H_{18}N_2O_5$	318.36	350	15,100	365	20,500	299	20,500
11	$C_{16}H_{19}NO_3$	273.36	301	22,100	310	26,500	305	24,200
12	$C_{15}H_{16}NO_3Cl$	293.72	301	19,700	309	27,600	306	25,600
13	$C_{16}H_{19}NO_4Cl$	324.81	302	17,200	303	25,600	307	23,700
14	$C_{16}H_{19}NO_4$	289.36	297	18,000	309	25,200	304	23,300
15	$C_{15}H_{16}N_2O_5$	304.33	302	19,700	309	27,600	303	24,900
16	$C_{16}H_{19}NO_3$	273.36	298	20,400	307	27,900	304	25,700
17	$C_{15}H_{16}NO_3Br$	338.22	301	17,500	309	25,700	306	23,700
18	$C_{16}H_{16}NO_4F_3$	343.33	302	16,100	309	25,800	305	23,600
19	$C_{16}H_{19}NO_4$	289.36	300	17,400	307	26,900	305	29,300
20	$C_{15}H_{16}NO_3F$	277.32	301	18,900	309	26,600	304	24,200
21	$C_{15}H_{16}NO_3I$	385.22	301	19,800	309	27,300	308	25,800
22	$C_{16}H_{16}NO_3F_3$	327.33	301	19,400	308	26,200	307	24,500
23	$C_{17}H_{21}NO_3$	287.39	299	21,500	307	28,100	304	26,400
24	$C_{16}H_{16}NO_3F_3$	327.33	306	13,300	315	23,000	308	18,700
25	$C_{14}H_{15}N_2O_3$	271.41	335	17,400	328	29,300	309	20,700
26[16]			280	23,500	291	29,000	292	29,600
27[17]			288	24,600	304	35,600	304	35,600
28[11]	$C_{16}H_{19}NO_3$	273.35	286	26,700	294	33,900	295	33,400
29[11]	$C_{17}H_{21}NO_3$	287.38	288	25,700	299	31,800	298	31,800
30[11]	$C_{13}H_{19}NO_3$	237.32	284	24,900	303	35,800	304	36,000
31[11]	$C_{14}H_{21}NO_3$	251.35	288	23,200	308	33,200	309	33,900
32[11]	$C_{19}H_{23}NO_3$	313.42	286	24,200	305	35,200	305	35,500
33[11]	$C_{18}H_{21}NO_4$	315.39	296	23,600	308	33,300	308	33,000

(Scheme 2) compared well with the UV data for compound **5**.

When the UV data for enaminones **7**, **8** and **9** were examined, there was a hypsochromic shift on protonation in acidic medium but the shift was larger for **8** (8 nm) than for enaminone **7** (5 nm) or for enaminone **9** (6 nm). The λ_{max} for **7** and **8** were different in all media even though they were both halogenated enaminones. Substitution with different halogens resulted in different UV characteristics due to different electronic effects. Although the UV data for **8** and **9** were close, enaminone **8** was anticonvulsant while enaminone **9** was inactive. This probably indicates that both steric and electronic factors affect the anticonvulsant property of enaminones.

Comparing the effects of *para*- and *meta*-substitutions on the phenyl groups in some of the enaminones, it was observed that *para*-substitution resulted in higher molar absorptivity (ε) values that correlated with anticonvulsant activity. For instance, the *para*-bromo enaminone **8** was anticonvulsant whereas the *meta*-bromo enaminone **17** had lower ε value and was inactive. In moving from neutral to alkaline media, the *para*-substituted enaminone **7**, and unsubstituted **10** showed bathochromic shifts, while some *para*-substituted compounds (**4**–**6**, **8**–**10**, **19**, **24**) and *meta*-substituted enaminones (**12**–**18**, **20**–**23**) displayed hypsochromic shifts. However, this property could not be used to predict anticonvulsant activity of the enaminones. The bulky size of the *para* substituent (as in **9** and **19**) tended to prevent anticonvulsant activity.

Enaminones **10** (λ_{max} 350 nm) and **25** (λ_{max} 335 nm) were unique in displaying λ_{max} values higher than 315 nm in acidic solutions. They possessed anticonvulsant activity.



Scheme 2. Structures of potent anticonvulsant enaminones **5**, **6**, and **25**.

Enaminone **25** (Scheme 2) did not behave like a typical enaminone (weak base). Instead, it exhibited the properties of a weak acid in aqueous solutions. The λ_{max} for enaminone **25** showed bathochromic shift from 328 to 335 nm in acidic medium, and a hypsochromic shift from 328 to 309 nm in alkaline medium.

As shown in Table 2, the tertiary enaminones **27**, **30**–**33** absorbed at the higher end and secondary enaminones (**1**–**26**) generally towards the lower end of the UV wavelength range 292–315 nm. In water, and alkaline solution, tertiary enaminones had intense molar absorptivity values (ε 33,000–36,000) whereas the secondary enaminones had lower values (ε 18,700–33,500). The tertiary enaminones **30**–**33** which were devoid of the NH proton were uniformly inactive while some secondary enaminones (**1**, **5**–**8**, **12**, **16**, **18**, **20**, **23**–**25**, **28** and **29**) were anticonvulsant in mice. These data validate the trend that was previously established in the proton NMR spectroscopy of enaminones.[5,11] Thus, the NH of secondary enaminones was found to be very important for anticonvulsant activity, and hydrogen bonding may contribute significantly to this activity. Although a straight-line correlation could not be established between the UV data and anticonvulsant activity of the enaminones, the following general rules are suggested.

General Rules

i. Relationship Between Secondary and Tertiary Enaminones, and Anticonvulsant Activity: Certain secondary enaminones have lower λ_{max} and ε values than the tertiary enaminones. Delocalization of electrons is easier in the planar secondary enaminones and consequently secondary enaminones may show anticonvulsant activity while the tertiary enaminones are inactive.

ii. Effect of Alkene Side Chain Between the Amino and Cyclohexenone Groups: Ethylene bridge, rather than propylene or butylene bridge between the amino and cylohexenone groups facilitates anticonvulsant activity of the secondary enaminones. Hence, compound **1** is active while compounds **2** and **3** are inactive. The λ_{max} values for **1** are longer in acid (284 nm), neutral (295 nm), and alkaline (294 nm) media than for compounds **2** and **3**.

iii. Effects of Lipophilicity (π) and Electron-withdrawing (σ) Ability of Substituents on Aromatic Ring: Employing the Craig Plot[4] to determine the quadrant which has more anticonvulsant analogues when comparing substitution on the aromatic ring with lipophilicity (π) and electron-withdrawing (σ) characteristics, it is found that electron-withdrawing halogens (F, Cl, Br) in the $+\pi, +\sigma$ quadrant for *para*-substitution result in anticonvulsant activity. Accordingly, compounds **5**, **7**, and **8** are anticonvulsant, and they exhibit hypsochromic shifts of at least 5 nm on protonation (in moving from neutral to acidic solution). They absorb UV radiation between 303 and 308 nm in alkaline solution in comparison to the inactive compound **4**, which absorbs at higher wavelength (311 nm) in alkaline solution.

iv. Effect of Steric Hindrance: The positioning of the substituents on the aromatic ring plays an important role in the activity of the analogues as the *p*-bromo (**8**) is anticonvulsant, but the meta analogue (**17**) is inactive. The ε values for **8** in acid, neutral and alkaline media are consistently higher than those of **17**. This isomeric change in position is also observed with the active *p*-nitro **10**, compared to the inactive *m*-nitro **15**; and active *p*-trifluoromethyl (**24**) compared to the inactive *m*-trifluoromethyl (**22**). Furthermore, the chloro- (*para*, **5**; *meta*, **12**) and fluoro-substituted compounds (*para* **7**, *meta* **20**) are anticonvulsant. These data suggest that the *meta*-substituted enaminones are generally restricted by steric constraints, but the overall effects of π and σ make some of them (**12** and **20**) to be active. Hence, lipophilicity (π) is considered a predominant factor in determining the anticonvulsant effect of enaminones.

v. Effect of *meta*-Substitution on Aromatic Ring: *meta*-Substitution with CH_3 group as in **16** results in lower λ_{max} values in all three solutions than *meta*-substitution with CF_3 group (**22**). Compound **16** is anticonvulsant while **22** is inactive. On the other hand, the protonation of enaminone **18** which has a *meta*-substitution with a trifluoromethoxy group showed a hypsochromic shift of 7 nm, compared to the *meta*-methoxy **14** which shows a hypsochromic shift of 12 nm on protonation. Compound **18** which exhibits a smaller shift is anticonvulsant, while compound **14** which exhibits a larger shift is inactive.

vi. Effect of Mono Methyl Versus Geminal Methyl Substitutions on Cyclohexenone Ring: Comparing enaminones **4** and **6**, substitution of only one CH_3 group on the cyclohexenone ring as in enaminone **6** results in lower λ_{max} values in all three media (acidic, neutral, and alkaline), and anticonvulsant activity. Geminal methyl groups in enaminone **4** result in decreased λ_{max} values in all solutions, and loss of anticonvulsant activity. Similarly, compound **28** possessing one CH_3 group exhibits a lower λ_{max} in acidic solution than compound **29** which has geminal CH_3 groups. Compound **28** is active while **29** is inactive.

Conclusion

On the whole, the results from the UV data of enaminones could not be used to establish a definite correlation with anticonvulsant activity of the enaminones since active and inactive compounds had similar λ_{max} and ε values. However, the UV data gave very useful information from which we could draw general inferences. First, tertiary enaminones which absorbed at higher wavelength were inactive while secondary enaminones which absorbed at lower wavelength were generally anticonvulsant. Secondly, *para*-substitution of the

phenyl group of the enaminones with a variety of moieties enhanced anticonvulsant activity. The general conclusion of this study was that anticonvulsant activity of enaminones was not due to electronic effect alone as shown by UV data, but probably due to a combination of factors including electronic and steric effects, and hydrogen bonding.

Experimental

UV spectroscopy

UV spectra of the enaminones were determined on a Milton Roy Spectronic 1201 UV spectrophotometer equipped with computerized programs to plot the spectrum as the sample was being run, and to print out the λ_{max} value for each enaminone. Absorptivity (ε) was then calculated for each enaminone using Beer–Lambert law according to the method of Greenhill.[16] The most intense peak was selected for each compound, and the ε value rounded to the nearest one hundred.

Anticonvulsant evaluation

Anticonvulsant activity of the enaminones was determined by the Antiepileptic Drug Development (ADD) Protocol, Epilepsy Branch, Neurological Disorder Program, National Institute of Neurological Disorders and Stroke (NINDS) with testing procedures that have been previously described.[12–14]

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