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A Potent Analgesic Drug 3-(4-Amino-1-Oxo-1, 3-Dihydro-2*h*-Isoindol-2-Yl)Piperidine-2,6-Dione (Anileridine) And Its Basic Conformational Analysis Using Computational Tools

Amaku Friday James[1], Otuokere Ifeanyi Edozie[2] and Igwe Kalu Kalu[3]

[1] Department of Chemistry, Michael Okpara University of Agriculture, Umudike, Abia ,+234 / Nigeria
[2] Department of Chemistry, Michael Okpara University of Agriculture, Umudike, Abia ,+234 / Nigeria
[3] Department of Vet. Biochemistry and Pharmacology,Michael Okpara University of Agriculture, Umudike, Abia +234 / Nigeria

Abstract

3-(4-amino-1-oxo-1,3-dihydro-2*H*-isoindol-2-yl)piperidine-2,6-dione (Anileridine) is a chemotherapy agent used mainly in the treatment of multiple myeloma. Conformational analysis and geometry optimization of Anileridine was performed according to the Hartree-Fock (HF) calculation method by ArgusLab 4.0.1 software. The minimum heat of formation was found to be 2177.8692 kcal/mol as calculated by geometry convergence function by ArgusLab software. The most feasible position for the drug to interact with the receptor was found to be -135.9487528822 au (-85309.2074 kcal/mol).

Keywords: *Anileridine, Molecular mechanics, Arguslab software.*

1. Introduction

For treatment and management of pain (systemic) and for use as an anaesthesia adjunct. Anileridine, a potent analgesic, is an analog of pethidine. Anileridine is useful for the relief of moderate to severe pain [1]. It may also be used as an analgesic adjunct in general anaesthesia in the same manner as meperidine to reduce the amount of anesthetic needed, to facilitate relaxation, and to reduce laryngospasm. In addition, anileridine exerts mild antihistaminic, spasmolytic and antitussive effects. Anileridine's main pharmacologic action is exerted on the CNS. Respiratory depression, when it occurs, is of shorter duration than that seen with morphine or meperidine when equipotent analgesic doses are used [2]. Opiate receptors are coupled with G-protein receptors and function as both positive and negative regulators of synaptic transmission via G-proteins that activate effector proteins [3]. Binding of the opiate stimulates the exchange of GTP for GDP on the G-protein complex. As the effector system is adenylate cyclase and cAMP located at the inner surface of the plasma membrane, opioids decrease intracellular cAMP by inhibiting adenylate cyclase. Subsequently, the release of nociceptive neurotransmitters such as substance dopamine, acetylcholine and noradrenaline is inhibited. Opioids also inhibit the release of vasopressin, somatostatin, insulin and glucagon. Opioids such as anileridine close N-type voltage-operated calcium channels (OP2-receptor agonist) and open calcium-dependent inwardly rectifying potassium channels (OP3 and OP1 receptor agonist). This results in hyperpolarization and reduced neuronal excitability Conformational analysis of molecule is based on molecular mechanics, it is method for the calculation of molecular structures, conformational energies and other molecular properties using concept from classical mechanics. A molecule is considered as a collection of atoms held together by classical forces. These forces are described by potential energy function of structural features like bond lengths, bond angles and torsion angles, these set of energy functions and the corresponding parameters are called a force field [4]. The molecular mechanics method calculates the energy as a function of the coordinates and energy minimization is an integral part of method [5]. A molecular geometry is constructed by using computer graphics techniques and the atoms are interactively moved (without breaking bonds) using an energy minimization technique until the net forces on all atoms vanish and the total energy of the molecule reaches a minimum.

We hereby present Anileridine (3-(4-amino-1-oxo-1,3-dihydro-2*h*-isoindol-2-yl)piperidine-2,6-dione) a potent anaesthesia adjunct and its basic conformational analysis using computational tools by arguslab 4.0.1 software.

2 . MATERIALS AND METHODS

Computational conformational analysis and geometry optimization study of 3-(4-amino-1-oxo-1,3-dihydro-2*H*-isoindol-2-yl)piperidine-2,6-dione (Anileridine)was performed on a window based computer using Argus lab and ACD Lab ChemSketch software. The structure was generated by ArgusLab 4.0.1 and geometric optimization was performed with the semi-empirical RHF/ (AM1). The minimum potential energy was calculated by using geometry convergence function in Argus lab software [6]. In order to determine the allowed conformation, the contact

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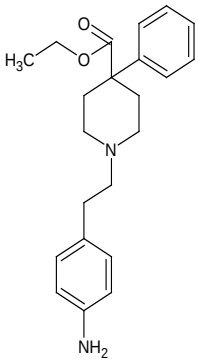
distance between the atoms in adjacent residues was examined using criteria for minimum Vander Waal contact distance [7]. Surfaces created to visualize ground state properties as well as excited state properties such as orbital, electron densities, electrostatic potentials (ESP), and spin densities were used to generate the grid data used to make molecular orbital surfaces and visualize the molecular orbital, making an electro static potential mapped and electron density surface [8]. The final geometrical energy and SCF energy was calculated by RHF/AM1 method, as performed by ArgusLab 4.0.1 suite, which shows the degree of drug-receptor interaction.



Molecular Formula	= $C_{22}H_{28}N_2O_2$
Formula Weight	= 352.46992
Composition	= C(74.97%) H(8.01%) N(7.95%) O(9.08%)
Molar Refractivity	= 104.60 ± 0.3 cm^3
Molar Volume	= 314.8 ± 3.0 cm^3
Parachor	= 824.7 ± 6.0 cm^3
Index of Refraction	= 1.578 ± 0.02
Surface Tension	= 47.1 ± 3.0 dyne/cm
Density	= 1.119 ± 0.06 g/cm^3
Dielectric Constant	= Not available
Polarizability	= 41.46 ± 0.5 $10^{-24}cm^3$
Monoisotopic Mass	= 352.215078 Da
Nominal Mass	= 352 Da
Average Mass	= 352.4699 Da

Figure 1: Prospective view of Anileridine by ACD/ChemSketch

3. RESULTS AND DISCUSSION

Heat of Formation of Anileridine was 2177.8692 kcal/mol, The steric energy calculated for Anileridine was 0.08308313 a.u. (52.13549834 kcal/mol) and SCF energy was found to be -135.9487528822 au (-85309.2074 kcal/mol) as calculated by RHF/ PM3 method, as performed by ArgusLab 4.0.1 suite**.**

Prospective view and calculated properties of Anileridine molecule is shown in figure 1. The active conformation and electron density mapped of Anileridine by ACDLABS-3D viewer software are shown in figure 3 and 2 respectively. Figure 6 shows Electrostatic potential of molecular ground state mapped onto the electron density surface for the ground state. The colour map shows the ESP energy (in hartrees) for the various colours. The red end of the spectrum shows regions of highest stability for a positive test charge, magenta/ blue show the regions of least stability for a positive test charge. Figure 4 and 5 shows the highest occupied molecular orbital of molecule (HOMO) and the lowest unoccupied molecular orbital (LUMO) respectively of Anileridine molecule , The positive and negative phases of the orbital are represented by two colors, the blue regions represent an increase in electron density and the red regions shows a decrease in electron density.

Fractional coordination of Anileridine molecule is given in Table1. Bond length and bond angles are given in table 2 and 3 respectively, which are calculated after geometry optimization of molecule from ARGUS LAB by using molecular mechanics calculation. Tables 4 and 5 show the Mulliken Atomic Charges, ZDO Atomic Charges of Anileridine and the calculated steric energy of Anileridine respectively.

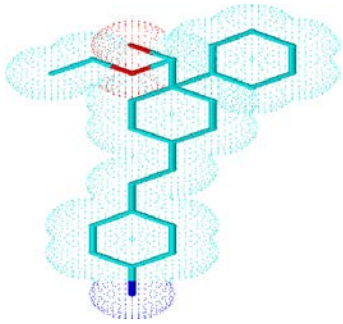


Figure 2: Electro density cloud of Anileridine by ACDLab 3D Viewer

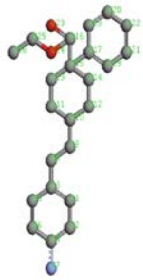


Figure 3: Prospective view of active comformation of Anileridine by Arguslab

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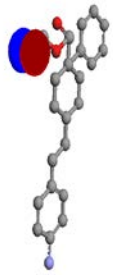

Figure 4 : Highest occupied molecular orbital's (HOMO) of Anileridine

Figure 5 : Lowest unoccupied molecular orbital's (LUMO) of Anileridine

Figure 6: Electrostatic potential mapped density of Anileridine

Table 1: Atomic Coordinate of Anileridine

S.No	Atoms	X	Y	Z
1	C	21.406300	-42.231500	0.000000
2	C	21.406300	-43.561500	0.000000
3	C	20.254400	-41.566500	0.000000
4	C	20.254400	-44.226500	0.000000
5	C	19.102600	-42.231500	0.000000
6	C	19.102600	-43.561500	0.000000
7	N	20.254400	-45.556500	0.000000
8	C	20.254400	-40.236500	0.000000
9	C	21.406200	-39.571500	0.000000
10	C	21.406100	-38.241500	-0.168017
11	C	20.254300	-37.576500	0.168017
12	C	22.558000	-37.576400	-0.168017
13	C	20.254400	-36.246400	0.168017
14	C	22.558000	-36.246400	-0.168017
15	C	21.406200	-35.581400	0.168017
16	C	21.406200	-34.251400	0.000000
17	C	22.558000	-34.916400	0.000000
18	C	22.558000	-33.586400	0.000000
19	C	23.709900	-35.581500	0.000000
20	C	23.709900	-32.921500	0.000000
21	C	24.861700	-34.916500	0.000000
22	C	24.861700	-33.586500	0.000000
23	O	20.254400	-33.586400	0.000000
24	O	20.254300	-34.916400	0.000000
25	C	19.102500	-34.251400	0.000000
26	C	17.950700	-34.916400	0.000000

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Table 2: Bond length of Anileridine

Atoms	Bond length
(C1)-(C2)	1.458000
(C1)-(C3)	1.323387
(C2)-(C4)	1.323387
(C3)-(C5)	1.458000
(C3)-(C8)	1.461000
(C4)-(C6)	1.458000
(C4)-(N7)	1.343384
(C5)-(C6)	1.323387
(C8)-(C8)	1.464000
(C9)-(C9)	1.464000
(C10)-(C10)	1.464000
(C10)-(C10)	1.464000
(C11)-(C11)	1.464000
(C12)-(C12)	1.464000
(C13)-(C13)	1.489000
(C14)-(C14)	1.489000
(C15)-(C15)	1.514000
(C15)-(C15)	1.486000
(C16)-(O16)	1.305512
(C16)-(O16)	1.436155
(C17)-(C17)	1.458000
(C17)-(C17)	1.323387
(C18)-(C18)	1.323387
(C19)-(C21)	1.458000
(C20)-(C22)	1.458000
(C21)-(C22)	1.323387
(O24)-(C25)	1.410739
(C25)-(C26)	1.464000

Table 3: Bond angles of Anileridine

Atoms	Bond angles	Alternate angles
(C2)-(C1)-(C3)	120.000000	216.488007
(C1)-(C2)-(C4)	120.000000	216.488007
(C1)-(C3)-(C5)	120.000000	216.488007
(C1)-(C3)-(C8)	120.000000	215.760874
(C2)-(C4)-(C6)	120.000000	216.488007
(C2)-(C4)-(N7)	120.000000	327.778708
(C5)-(C3)-(C8)	120.000000	187.861407
(C3)-(C5)-(C6)	120.000000	216.488007
(C3)-(C8)-(C9)	120.000000	186.707708
(C6)-(C4)-(N7)	120.000000	282.167276
(C4)-(C6)-(C5)	120.000000	216.488007
(C8)-(C9)-(C10)	120.000000	186.134654
(C9)-(C10)-(C11)	120.000000	186.134654
(C9)-(C10)-(C12)	120.000000	186.134654
(C11)-(C10)-(C12)	120.000000	186.134654
(C10)-(C11)-(C13)	120.000000	186.134654
(C10)-(C12)-(C14)	120.000000	186.134654
(C11)-(C13)-(C15)	120.000000	181.430228
(C12)-(C14)-(C15)	120.000000	181.430228
(C13)-(C15)-(C14)	109.470000	225.183707
(C13)-(C15)-(C16)	109.470000	219.577891
(C13)-(C15)-(C17)	109.470000	225.865192
(C14)-(C15)-(C16)	109.470000	219.577891
(C14)-(C15)-(C17)	109.470000	225.865192
(C16)-(C15)-(C17)	109.470000	220.229931
(C15)-(C16)-(O23)	109.470000	315.920606
(C15)-(C16)-(O24)	109.470000	278.259153
(C15)-(C17)-(C18)	120.000000	183.094781
(C15)-(C17)-(C19)	120.000000	209.804299
(O23)-(C16)-(O24)	109.470000	415.812844
(C16)-(O24)-(C25)	104.510000	292.510719
(C18)-(C17)-(C19)	120.000000	216.488007
(C17)-(C18)-(C20)	120.000000	216.488007
(C17)-(C19)-(C21)	120.000000	216.488007
(C18)-(C20)-(C22)	120.000000	216.488007
(C19)-(C21)-(C22)	120.000000	216.488007
(C20)-(C22)-(C21)	120.000000	216.488007
(O24)-(C25)-(C26)	120.000000	236.478255

Tables 4: ZDO atomic charges and Mulliken atomic charges of Anileridine

S.NO	Atoms	ZDO atomic charges	Mulliken atomic charges
1	C	-0.2525	-0.2223
2	C	-0.3818	-0.3637
3	C	0.2776	0.2465
4	C	0.2364	0.2167
5	C	-0.2268	-0.1969
6	C	-0.3821	-0.3710
7	N	0.1743	0.1426
8	C	0.0034	-0.0060
9	C	0.2692	0.2787
10	C	-0.0750	-0.1265
11	C	-0.1101	-0.0373
12	C	-0.0354	0.0313
13	C	-0.2120	-0.2045
14	C	0.0096	-0.0034
15	C	0.0287	0.0153
16	C	0.4935	0.5285

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17	C	-0.5356	-0.6909
18	C	0.1175	0.1557
19	C	0.0443	0.1002
20	C	-0.2211	-0.2296
21	C	-0.1977	-0.1355
22	C	0.1006	0.0680
23	O	-0.1133	-0.1696
24	O	0.0561	-0.0134
25	C	-0.3597	-0.3988
26	C	0.2919	0.3862

Table 5: Final energyevaluation. Of anileridine

S.No.	Force field	Energy components (au)
1	Molecularmechanics bond (Estr)	0.00717727
2	Molecular mechanics angle (Ebend)+ (Estr-bend)	0.01002180
3	Molecularmechanicsdihedral (Etor)	0.01543957
4	MolecularmechanicsImpTor (Eoop)	0.00005676
5	MolecularmechanicsvdW (EVdW)	0.05038773
6	Molecularmechanics coulomb (Eqq)	0.00000000
Total		0.08308313 a.u. (52.13549834 kcal/mol)

4. CONCLUSIONS

Conclusively, the lowest energy and most stable conformation of anileridine was 0.08308313 a.u. (52.13549834 kcal/mol). The most energetically favourable conformation of anileridine was found to have a heat of formation of 2177.8692 kcal/mol. The self-consistent field (SCF) energy was calculated by geometry convergence function using ArgusLab software. The most feasible position for the drug to interact with the receptor was found to be -135.9487528822 au (-85309.2074 kcal/mol). At this point anileridine will be more active as a chemotherapy agent.

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First Author : Amaku James Friday is a specialist in adsorption and computational chemistry. He is a menber of the Chemical Society of Nigeria. He is a lecturer in the department of Chemistry, Michael Okpara University of Agriculture, Umudike, Nigeria.

Second Author Otuokere Ifeanyi Edozie (Ph.D). He bagged his Ph.D degree in 2008 in the field of Inorganic Chemistry. He is a menber of Chemical Society of Nigeria. He is a lecturer in the department of Chemistry, Michael Okpara University of Agriculture, Umudike, Nigeria. He is a menber of the Chemical Society of Nigeria.

Third Author : Igwe Kalu Kalu bagged the degree of Doctor of Vet.
Medicine in 1990, M.Sc in Biochemistry (2008) and a Ph.D degree in Biochemistry (2015). He is a lecturer in the department of Vet. Biochemistry and Pharmacology in Michael Okpara University of Agriculture, Umudike, Nigeria..