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Conformational analysis and geometry optimization of Amlodipine Besylate (NORVASC) as a vasodilator

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Abstract: Conformational analysis and geometry optimization of amlodipine besylate, preformed according to the Hartree-Fock (HF) calculation method by ArgusLab software. The minimum potential energy is calculated by geometry convergence function by ArgusLab software and energy minimization programs. The best conformation of the molecule is present at minimum potential energy which is found to be 46.219 K.cal/mol.

Keywords: Conformation, geometry, amlodipine besylate, NORVASC, vasodilator.
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INTRODUCTION

Amlodipine besylate is chemically 3-ethyl 5-methyl 2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-1,4-dihydro-6-methyl pyridine -3,5-dicarboxylate monobenzene sulfonate. It is a calcium channel-blocking agent with vasodilator activity[1]. It is the besylate salt of amlodipine 1,4 dihydro pyridine calcium channel blocker. Within the pH range it is an ionized compound (pKa=8.6) amlodipine is a chiral calcium antagonist and in therapeutic used as a racemate [1:1mixture of (R) – (+)- and (S)-(-)amlodipine][2] . A method for the semipreperative chromatographic purification of the enentiomers(s) – (-) amlodipine and (+) amlodipine has been reported[3]. Amlodipine is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure. It may be used alone or in combination with other antihypertensive agents. With chronic once daily oral administration, antihypertensive effectiveness is maintained for at least 24 hours and is well tolerated as monotherapy and in combination with other drugs without orthostatic hypotention[4]. It has a long elimination half life making it suitable for once daily dosing confirmed by intra-arterial ambulatory blood pressure monitoring [5] .Stability studies of amlodipine besylate in two liquid dosage forms ;one in 1% methyl cellulose in syrup (1;0 and another in equal volumes of ora plus, showed 905 physical and chemical stability of its initial concentration [6].Spectrophotometric determinations of amlodipine besylate in pure forms and in pharmaceutical [7] , with combination of 2, 3, dichloro 5, 6-dicyano 1, 4-benzoquinone and ascorbic acid[8] and by charge-transfer complex formation with p-chloranilic acid[9]. Despite the availability of numerous antihypertensive agents many patients with hypertension fail to achieve the blood pressure goal, therefore require multihypertensive therapy. A patient-related factor likely to affect adherence to treatment is the convenience of the prescribed drug reg iman and was studied in antihypertensive therapy with fixed dose amlopidine besylate/benazepril HCL versus compareable component based therapy[10,11]. In another study the initial angiotensin-converting enzyme inhibitor/calcium channel blocker combination therapy achieves superior blood pressure control compared with amlodipine monotherapy in patients with stage 2 hypertension [12].Comparative safety and efficacy trials indicate that angiotensin receptor blockers like olmesartan medoxomil have superior tolerability and antihypertensive efficacy[13]. Similar investigation using olmesartan medoxomil and amlodipine besylate showed great effectiveness and tolerance in patient with hypertension[14] . Combination therapies reduced B.P to a greater extent than with amlodipine besylate alone as indicated with benazepril hydrochloride with valsartan and with perindopril[15,16].

The present work describes the computer aided conformational analysis and geometry optimization of b- blocker/vasodilatory agent amlodipine besylate similar to other drugs by Argus lab4 software[17,18].

MATERIALS AND METHODS

The three-dimensional quantitative structure activity relationship (3D.QSAR) provides the valuable information about the nature of the receptor[19-21]. 3D QSAR helps to describe new drug candidates and to improve in vitro potency[22]. Potential energy has been calculated by using kitaigorodsky function[23]. In order to determine the allowed conformation the contact distance between the atoms in the adjacent residues have to be examined using criteria for minimum vander waals contact distances. ArgusLab is the electronic structure program that is based on the quantum mechanics, it predicts the potential energies,

molecular structures; geometry optimization of structure, vibration frequencies of coordinates of atoms, bond length, bond angle and reactions pathway[24]. 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 torsional angles etc.The energy (E) of the molecule is calculated as a sum of terms as in equation:

$E = E_{\text{stretching}} + E_{\text{bending}} + E_{\text{torsion}} + E_{\text{vander Waals}} + E_{\text{electrostatic}} + E_{\text{hydrogen bond}}$ + cross term

These terms are of importance for the accurate calculation of geometric properties of molecules. The set of energy functions and the corresponding parameters are called a force field[25] . The molecular mechanics method calculates the energy as a function of the coordinates and energy minimization is an integral part of method. A molecular geometry is constructed by using computer graphics techniques and the atoms moved are iteratively 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.

The 3D (3 rotatable bonds) structure of molecule corresponding to this energy minimum is one of the stable conformations of molecule but not necessarily the most stable one[26]. Since the energy minimization methods can't move the molecule across energy barriers, the minimization of a trial molecule continues until the first local energy minimum is found. Other local energy minima including the lowest energy one, the global energy minimum, may be found by repeating the calculation with another start geometry or more efficiently. Conformation search methods random numbers are used to determine how many and which torsional angles and space to be incremented and which directions of the x, y, z, co-ordinates of each atoms are to be translated[27].

Amlodipine besylate is chemically described as 3-Ethy l-5-methyl (±)-2-[(2-aminoethoxy) methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridine dicarboxylate, monobenzenesulphonate[28]. Its empirical formula is $C_{20}H_{25}ClN_2O_5 \cdot C_6H_6O_3S$, and its structural formula as shown in figure 1.

The three dimensional quantitative structure activity relationships (3D-QSAR) describe the biological activity of molecule with pharmacological potential as a function of their structural properties [27, 28].Computational advances have generated many tools which are widely used to construct models, minimization and representations of molecular structure[29-31]. All conformational analysis (geometry optimization) study was performed on a window based computer using Arguslab 4 and ACDLabs ChemSketch 12 softwares. The chemical structure of amlodipine besylate[32] was refined by x-ray crystallography technique. The amlodipine besylate molecule is utilized to determine 3D structure of molecule[33]. Several computer programs were used to infer the shape of molecule from geometry optimization calculations.

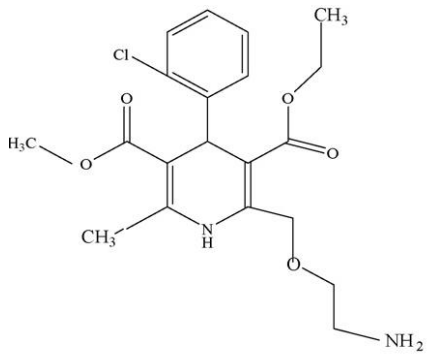


Figure 1: Prospective view of amlodipine besylate.

The amlodipine besylate structure is generated by Arguslab, and minimization was performed with the semi-empirical Austin Model 1 (AM1) parameterization[34]. The minimum potential energy is calculated by using geometry convergence function in Arguslab software. In order to determine the allowed conformation the contact distance between the atoms in adjacent residues is examined using criteria for minimum Vander Waal contact distance[35]. Surfaces created to visualize ground state properties as well as excited state properties such as orbital, electron densities, electrostatic potentials (ESP), spin densities and generated the grid data used to make molecular orbital surfaces and visualized he molecular orbital and making an electro static potential mapped and electron density surface. The minimum potential energy was calculated for drug receptor interaction through the geometry convergence map.

RESULTS AND DISCUSSION

The prospective view of amlodipine besylate, is shown in figure 1. The results give detail information about the conformation of amlodipine besylate can exist in at least two stable conformations shown figure 2. Prospective view and active conformation of amlodipine besylate are shown in figure 3. Figures 4 and 5 show the electron density mapped of

atoms of amlodipine besylate and all physical properties calculated by ACDLabs 3D viewer software respectivelly.

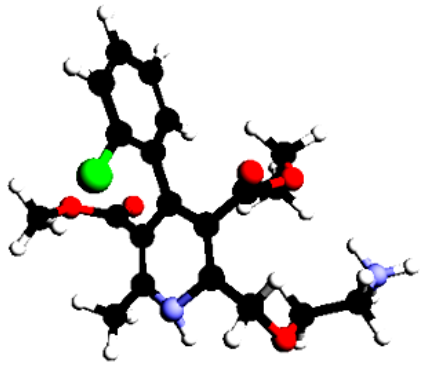


Figure 2: 3D view of amlodipine besylate.

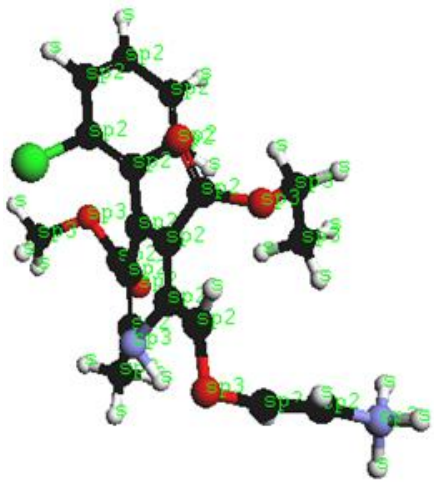


Figure 3: Prospective view and active conformation of amlodipine besylate with label atom.

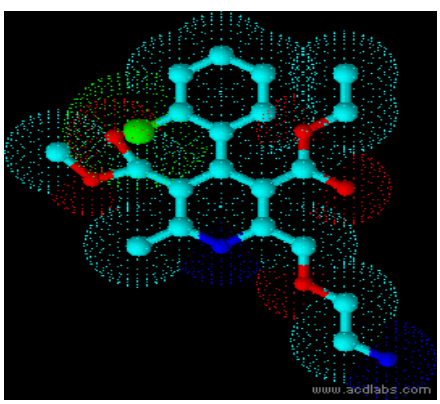
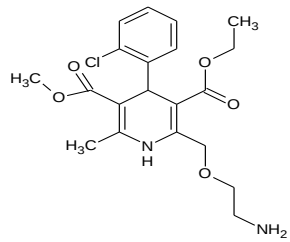


Figure 4: Electron density mapped of atoms of amlodipine besylate.

Figure 6 shows the electrostatic potential of amlodipine besylate ground state mapped on to the electron density surface for the ground state. The color map shows the ESP energy (in hartrees) for the various colors. 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. These images show that the carboxyl-end of the molecule is electron rich relative to the amino end.



Molecular Formula	= $C_{20}H_{25}ClN_2O_5$
Formula Weight	= 408.8759
Composition	= C(58.75%) H(6.16%) Cl(8.67%) N(6.85%) O(19.57%)
Molar Refractivity	= 105.41 ± 0.3 cm^3
Molar Volume	= 333.0 ± 3.0 cm^3
Parachor	= 859.8 ± 6.0 cm^3
Index of Refraction	= 1.545 ± 0.02
Surface Tension	= 44.4 ± 3.0 dyne/cm
Density	= 1.227 ± 0.06 g/cm^3
Dielectric Constant	= Not available
Polarizability	= 41.79 ± 0.5 $10^{-24}cm^3$
Monoisotopic Mass	= 408.1452 Da
Nominal Mass	= 408 Da
Average Mass	= 408.8759 Da
M+	= 408.144651 Da
M-	= 408.145748 Da
[M+H]+	= 409.152476 Da
[M+H]-	= 409.153573 Da
[M-H]+	= 407.136826 Da
[M-H]-	= 407.137923 Da

Figure 5: All properties calculated by ACD chemskatch 12.

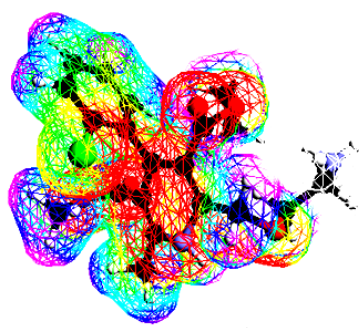


Figure 6: The electrostatic potential of amlodipine besylate.

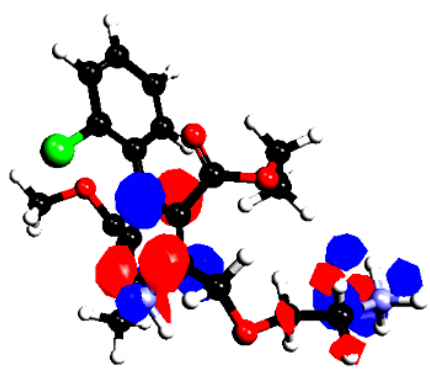


Figure 7: The occupied π-molecular orbital of amlodipine besylate.

Table 1: Rectangular co-ordinates of amlodipine besylate.

Atoms	x	y	z	Positions
C1	13.88	11.43	0.60	6
C2	13.84	12.81	0.78	6
C3	13.53	10.86	0.61	6
C4	13.48	13.66	0.26	6
C5	13.15	11.69	1.67	6
C6	13.13	13.07	1.49	6
C7	13.42	15.11	0.11	6
C8	14.36	16.00	0.64	6
C9	14.09	17.35	0.80	6
N10	12.72	17.85	0.59	7
C11	12.22	15.69	0.44	6
C12	11.88	16.98	0.21	6
C13	14.99	18.33	1.45	6
O14	15.36	19.44	0.58	8
C15	15.76	19.08	0.69	6
C16	17.31	19.18	0.78	6
N17	17.79	18.73	2.13	7
C18	10.61	17.58	0.72	6
C19	11.37	14.85	1.34	6
O20	10.23	14.20	0.95	8
C21	9.81	14.33	0.38	6
C22	15.72	15.51	1.00	6
O23	16.19	15.19	2.07	8
O24	16.76	15.54	0.05	8
C25	16.60	14.76	1.12	6
C26	15.92	15.52	2.25	6
O27	11.53	14.65	2.53	8
H28	14.16	10.78	1.44	1
H29	14.08	13.23	1.76	1
H30	13.55	9.77	0.75	1
H31	12.86	11.25	2.63	1
H32	12.79	18.73	0.12	1
H33	14.51	18.90	2.27	1
H34	15.92	17.88	1.83	1
H35	15.40	18.06	0.96	1
H36	15.29	19.82	1.36	1
H37	17.77	18.56	0.01	1
H38	17.63	20.22	0.59	1
H39	17.49	17.784	2.30	1
H40	17.40	19.32	2.84	1
H41	18.79	18.79	2.17	1
H42	9.77	16.89	0.56	1
H43	10.36	18.52	0.21	1
H44	10.66	17.78	1.80	1
H45	9.60	13.31	0.73	1
H46	10.55	14.80	1.04	1
H47	8.89	14.93	0.39	1
H48	17.65	14.52	1.36	1
H49	16.05	13.82	0.90	1
H50	14.87	15.76	2.00	1
H51	16.45	16.46	2.49	1
H52	15.92	14.91	3.16	1
Cl53	12.61	14.04	2.80	17

Figure 7 shows the occupied π-molecular orbital of amlodipine besylate, calculated with the ZINDO method and rendered as a mesh.The positive and negative phases of the orbital are represented by the two colors, the blue regions represent an increase in electron density and the red regions a decrease in electron density.

The minimum potential energy shows for drug receptor interaction through the geometry convergence map in graph 1. Input atomic coordinates of amlodipine besylate are given in table 1. Bond lengths and bond angles are given in the tables 2 and 3 respectively, which are taken after geometry optimization of amlodipine besylate molecule from Arguslabs by using molecular mechanics calculation.

Dihedral angles, improper torsions angles are given in table 4 and 5 respectively. Table 6, 7 and 8 shows bond topology, initial energy evaluation and final geometry co-ordinates respectively.

Table 2: Bond Length of atoms of amlodipine besylate.

Atoms	Bond Lengths
C1 C2	1.323
C1 C3	1.458
C2 C4	1.458
C3 C5	1.323
C4 C6	1.323
C4 C7	1.458
C5 C6	1.458
C7 C8	1.458
C7 C11	1.458
C8 C9	1.323
C8 C22	1.461
C9 N10	1.433
C9 C13	1.461
N10 C12	1.433
C11 C12	1.323
C11 C19	1.461
C12 C18	1.461
C13 O14	1.410
O14 C15	1.410
C15 C16	1.464
C16 N17	1.437
C19 O20	1.410
C19 O27	1.260
O20 C21	1.436
C22 O23	1.260
C22 O24	1.410
O24 C25	1.410
C25 C26	1.464
C6 Cl28	1.795

CONCLUSION

The result indicates that the best conformation of the molecule is present at minimum potential energy is found to be 46.219k.cal/mol. At this point amlodipine besylate will be more active as a long-acting calcium channel blocker and vasodilator agent. It is possible that drug amlodipine besylate is interacting with receptor in this conformation.

Table 3: Bond angles between atoms of amlodipine besylate.

1st atom	2nd atom	3rd atom	Bond angles	
(C2)	(C1)	(C3)	120	216
(C1)	(C2)	(C4)	120	216
(C2)	(C1)	(H28)	120	123
(C1)	(C2)	(H29)	120	123
(C1)	(C3)	(C5)	120	216
(C3)	(C1)	(H28)	120	103
(C1)	(C3)	(H30)	120	103
(C2)	(C4)	(C6)	120	216
(C2)	(C4)	(C7)	120	188
(C4)	(C2)	(H29)	120	102
(C3)	(C5)	(C6)	120	216
(C5)	(C3)	(H30)	120	123
(C3)	(C5)	(H31)	120	123
(C6)	(C4)	(C7)	120	215
(C4)	(C6)	(C5)	120	216
(C4)	(C6)	(Cl53)	120	183
(C4)	(C7)	(C8)	120	186
(C4)	(C7)	(C11)	120	186
(C5)	(C6)	(Cl53)	120	164
(C6)	(C5)	(H31)	120	102
(C8)	(C7)	(C11)	120	186
(C7)	(C8)	(C9)	120	213
(C7)	(C8)	(C22)	120	186
(C7)	(C11)	(C12)	120	213
(C7)	(C11)	(C19)	120	186
(C9)	(C8)	(C22)	120	213
(C8)	(C9)	(N10)	120	292
C8)	(C9)	(C13)	120	207
(C8)	(C22)	(O23)	120	275
(C8)	(C22)	(O24)	120	236
(N10)	(C9)	(C13)	120	247
(C9)	(N10)	(C12)	106	268
(C9)	(N10)	(H32)	106	144
(C9)	(C13)	(O14)	109	285
(C9)	(C13)	(H33)	109	120
(C9)	(C13)	(H34)	109	120
(N10)	(C12)	(C11)	120	292
(N10)	(C12)	(C18)	120	247
(C12)	(N10)	(H32)	106	144
(C12)	(C11)	(C19)	120	213
(C11)	(C12)	(C18)	120	207
(C12)	(C18)	(H42)	109	121
1(C12)	(C18)	(H43)	109	121
(C12)	(C18)	(H44)	109	121
(C13)	(O14)	(C15)	104	285
(O14)	(C13)	(H33)	109	157
(O14)	(C13)	(H34)	109	157
(O14)	(C15)	(C16)	109	279
(O14)	(C15)	(H35)	109	157
(O14)	(C15)	(H36)	109	157
(C15)	(C16)	(N17)	109	300
(C16)	(C15)	(H35)	109	117
(C16)	(C15)	(H36)	109	117
(C15)	(C16)	(H37)	109	117
(C15)	(C16)	(H38)	109	117
(N17)	(C16)	(H37)	109	167
(N17)	(C16)	(H38)	109	167
(C16)	(N17)	(H39)	107	140
(C16)	(N17)	(H40)	106	140
(C16)	(N17)	(H41)	107	140
(O20)	(C19)	(O27)	120	353
1(C19)	(O20)	(C21)	104	293
(O20)	(C21)	(H45)	109	156
(O20)	(C21)	(H46)	109	156
(O20)	(C21)	(H47)	109	156
(O23)	(C22)	(O24)	120	353
(C22)	(O24)	(C25)	105	293
(O24)	(C25)	(C26)	109	278
(O24)	(C25)	(H48)	109	156
(O24)	(C25)	(H49)	109	156
(C26)	(C25)	(H48)	109	117
(C26)	(C25)	(H49)	109	117
(C25)	(C26)	(H50)	109	117
(C25)	(C26)	(H51)	109	117
(C25)	(C26)	(H52)	109	117
(H33)	(C13)	(H34)	109	75
(H35)	(C15)	(H36)	109	75
(H37)	(C16)	(H38)	109	75
(H39)	(N17)	(H40)	107	92
(H39)	(N17)	(H41)	106	92
(H40)	(N17)	(H41)	106	92
(H42)	(C18)	(H43)	109	72
(H42)	(C18)	(H44)	109	75
(H43)	(C18)	(H44)	109	75
(H45)	(C21)	(H46)	109	75
(H45)	(C21)	(H47)	109	75
(H46)	(C21)	(H47)	109	75
(H48)	(C25)	(H49)	109	75
(H50)	(C26)	(H51)	109	75
(H50)	(C26)	(H52)	109	75
(H51)	(C26)	(H52)	109	75

Table 4: Dihedral angles between atoms of amlodipine besylate.

	Four atoms	Angle	Plain
1 term(s) in expansion	C4-C2-C1-C3	8.97	180
1 term(s) in expansion	C2-C1-C3-C5	10.00	180
1 term(s) in expansion	C1-C2-C4-C6	5.00	180
1 term(s) in expansion	C1-C2-C4-C7	5.00	180
1 term(s) in expansion	C1-C3-C5-C6	38.9	180
1 term(s) in expansion	C2-C4-C6-C5	9.74	180
1 term(s) in expansion	C2-C4-C6-Cl28	9.74	180
1 term(s) in expansion	C2-C4-C7-C8	2.5	180
1 term(s) in expansion	C2-C4-C7-C11	2.50	180
1 term(s) in expansion	C3-C5-C6-C4	5.04	180
1 term(s) in expansion	C3-C5-C6-Cl28	5.0	180
1 term(s) in expansion	C5-C6-C4-C7	9.74	180
1 term(s) in expansion	Cl28-C6-C4-C7	9.74	180
1 term(s) in expansion	C6-C4-C7-C8	2.5	180
1 term(s) in expansion	C6-C4-C7-C11	2.50	180
1 term(s) in expansion	C4-C7-C8-C9	2.5	180
1 term(s) in expansion	C4-C7-C8-C22	2.5	180
1 term(s) in expansion	C4-C7-C11-C12	2.52	180
1 term(s) in expansion	C4-C7-C11-C19	2.5	180
1 term(s) in expansion	C9- C8-C7-C11	2.5	180
1 term(s) in expansion	C22-C8-C7-C11	2.5	180
1 term(s) in expansion	C8-C7-C11-C12	2.5	180
1 term(s) in expansion	C8-C7-C11-C19	2.5	180
I term(s) in expansion	C7-C8-C9-N10	9.74	180
1 term(s) in expansion	C7-C8-C9-C13	9.74	180
1 term(s) in expansion	C7-C8-C22-O23	2.50	180
1 term(s) in expansion	C7-C8-C22-O24	2.50	180
1 term(s) in expansion	C7-C11-C12-N10	9.74	180

1 term(s) in expansion	C7-C11-C12-C18	9.74	180
1 term(s) in expansion	C7-C11-C19-O20	2.5	180
1 term(s) in expansion	C7-C11-C19-O27	2.5	180
1 term(s) in expansion	N10-C9-C8-C22	9.74	180
1 term(s) in expansion	C13-C9-C8-C22	9.74	180
1 term(s) in expansion	C9-C8-C22-O23	2.5	180
1 term(s) in expansion	C9-C8-C22-O24	2.5	180
1 term(s) in expansion	C8-C9-N10-C12	5.0	180
1 term(s) in expansion	C8-C9-C13-O14	5.0	180
1 term(s) in expansion	C8-C22-O24-C25	5.0	90.0
1 term(s) in expansion	C12-N10-C9-C13	5.0	180
1 term(s) in expansion	N10-C9-C13-O14	5.0	180
1 term(s) in expansion	C9-N10-C12-C11	5.0	180
Iterm(s) in expansion	C9-N10-C12-C18	5.0	180
1 term(s) in expansion	C9-C13-O14-C15	10	90
1 term(s) in expansion	N10-C1-C11-C19	9.7	180
1 term(s) in expansion	C18-C12-C11-C19	9.7	180
1 term(s) in expansion	C12-C11-C19-O20	2.5	180
1 term(s) in expansion	C12-C11-C19-O27	2.5	180
1 term(s) in expansion	C11-C19-O20-C21	5.0	90
1 term(s) in expansion	C13-O14-C15-C16	10	90
1 term(s) in expansion	O14-C15-C16-N17	10	180
1 term(s) in expansion	C21-O20-C19-O27	5.0	90
1 term(s) in expansion	O23-C22-O24-C25	5.0	90
1 term(s) in expansion	C22-O24-C25-C26	10	90

Table 5: Improper Torsions of bonded atoms of amlodipine besylate.

Bonded atoms	Angle 1	Angle 2
C6-C7-C4-C2	2.0	0.0
C5-Cl28-C6-C4	2.0	0.0
C8-C11-C7-C4	2.0	0.0
C9-22C-C8-C7	2.0	0.0
C12-C19-C11-C7	2.0	0.0
N10-C13-C9-C8	2.0	0.0
O23-O24-C22-C8	16.6	0.0
C11-C18-C12-N10	2.0	0.020 27 19 11
O20-O27-C1 –C2	16.6	0.000000

Table 6: Bonded topology of bonded atoms of amlodipine besylate.

Bonds	29
Bond Angles	39
Dihedral Angles	53
Imp. Torsions	9
NB Exclusion List	68
Initial NB List	222

Table 7: Initial energy evaluation of amlodipine besylate.

MM Bond	0.00642112
MM Angle	0.00300676
MM Dihedral	0.02908135
MM ImpTor	0.00013933
MM vdW	0.03500656
MM Coulomb	0.00000000
Total	0.07365512 au
Total	46.21932461 kcal/mol

Table 8: Final geometry co-ordinates of amlodipine besylate.

C1	13.6	-11.21	-0.572
C2	13.63	-12.53	0.774
C3	13.27	-10.66	0.740
C4	13.22	-13.45	0.315
C5	12.90	-11.48	1.729
C6	12.87	12.94	1.515
C7	13.21	14.90	0.060
C8	14.38	15.74	0.475
C9	14.28	17.08	0.387
N10	13.06	17.68	0.089
C11	11.95	15.56	0.423
C12	11.91	16.91	0.48
C13	15.41	17.97	0.72
O14	15.30	19.37	0.56
C15	15.83	19.65	0.71
C16	17.24	20.01	0.88
N17	17.76	20.28	2.19
C18	10.75	17.64	0.98
C19	10.77	14.74	0.80
O20	9.46	15.17	0.48
C21	9.17	14.59	0.80
C22	15.62	15.08	0.97
O23	16.26	15.58	1.94
O24	16.09	13.87	0.39
C25	16.97	14.26	0.64
C26	16.49	14.40	2.01
O27	10.92	13.66	1.44
Cl28	12.35	14.00	2.88

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