Supplemental Material

Online Methods

Drug-hERG interaction function scale model

The wild-type drug-free hERG Markov model (Online Table I) previously described in [77] is shown in main text Figure 3B. To simulate drug interactions with hERG, we used ***simulated affinities***, (i.e. drug dissociation constants) K_{Do}, and drug diffusion rates, D, both computed from the umbrella sampling (US) molecular dynamics (MD) simulations (Main text Figure 2) used to constrain the drug "on" (k_{o_d}, k_{od}, and k_{od_zw}) and "off" (r_{o_d}, r_{od}, and r_{od_zw}) model transition rates for open state (Online Table II). Based on available literature data [44], K_{DI} was assumed to be 70-fold less than K_{Do} in the dofetilide model. Then, using the relation, $k_{off} = k_{on} * K_{Do}$, we optimized k_{i_d} *and* k_{id} for open-inactivated state of neutral and cationic forms of dofetilide (Online Table III).

There are two modes of drug bound channel states – neutral (cyan) and cationic (red) for dofetilide (Main text Figure 3B). The cationic and neutral drug fractions, f_1 and f_0, are calculated using the following equations:

$$f_1 = \frac{1}{(1+10^{(pH-pKa)})}; \quad f_0 = 1 - f_1 \qquad [1]$$

Where pH = 7.2 and pK_a = 7.0 .[39]

For moxifloxacin, there are three modes of drug bound channel states – neutral (cyan), cationic (red), and zwitterionic (purple) as shown in Main text Figure 3D. The drug fractions at pH = 7.2 based on [40] are shown in Online Table IV.

Online Table I: Transition rates in the I_{Kr} model

Transition rates (ms^{-1})

Drug free Kr channel

C3→C2 $$ae = \frac{T}{T_{base}} e^{(24.335+\frac{T_{base}}{T}(0.0112\times V-25.914))}$$

C2→C3 $$be = \frac{T}{T_{base}} e^{(13.688+\frac{T_{base}}{T}(-0.0603\times V-15.707))}$$

C2→C1 $$ain = \frac{T}{T_{base}} e^{(22.746+\frac{T_{base}}{T}(-25.914))}$$

C1→C2 $$bin = \frac{T}{T_{base}} e^{(13.193+\frac{T_{base}}{T}(-15.707))}$$

C1→O $$aa = \frac{T}{T_{base}} e^{(22.098+\frac{T_{base}}{T}(0.0365\times V-25.914))}$$

O→C1 $$bb = \frac{T}{T_{base}} e^{(7.313+\frac{T_{base}}{T}(-0.0399\times V-15.707))}$$

O→I $$\beta i = \frac{T}{T_{base}} e^{(30.016+\frac{T_{base}}{T}(0.0223\times V-30.88)} \times \left(\frac{5.4}{[K]^o}\right)^{0.4}$$

I→O $$\alpha i = \frac{T}{T_{base}} e^{(30.061+\frac{T_{base}}{T}(-0.0312\times V-33.243))}$$

Online Table II: Transition rates for Moxifoxacin model (see main text Figures 2E and 3D)

	Open
Transition rates	***Neutral Drug***
k_{on} (k_{o_d})	6.6E+02 ($\mu M^{-1}s^{-1}$) * [drug]
k_{off} (r_{o_d})	4.9E+02 (s^{-1})
	Cationic Drug
k_{on} (k_{od})	4.2E+02 ($\mu M^{-1}s^{-1}$) * [drug]
k_{off} (r_{od})	2.8E+06 (s^{-1})
	Zwitterionic Drug
k_{on} (k_{od_zw})	3.4E+02 ($\mu M^{-1}s^{-1}$) * [drug]
k_{off} (r_{od_zw})	2.9E+06 (s^{-1})

Online Table III: Transition rates for Dofetilide model (see main text Figures 2E and 3B)

	Open	**Inactivated**
Transition rates	***Neutral Drug***	
k_{on} (k_{o_d}, k_{i_d})	6.7E+02 ($\mu M^{-1}s^{-1}$) * [drug]	1.7E+03 ($\mu M^{-1}s^{-1}$) * [drug]
k_{off} (r_{o_d}, r_{i_d})	1.1E+02 (s^{-1})	3.9 (s^{-1})
	Cationic Drug	
k_{on} (k_{od}, k_{id})	5.3E+02 ($\mu M^{-1}s^{-1}$) * [drug]	1.5E+06 ($\mu M^{-1}s^{-1}$) * [drug]
k_{off} (r_{od}, r_{id})	3.5E+04 (s^{-1})	1.4E+06 (s^{-1})

Online Table IV: Drug fraction for cationic, zwitterionic and neutral states in moxifloxacin model (Main text Figures 2E and 3D)

States	**Fractions**
Moxifloxacin (±), zwitterionic	83.99%
Moxifloxacin (+), cationic	10.33%
Moxifloxacin (0), neutral	5.68%

Computed dofetilide concentrations

We used the population C_{max} (maximum plasma concentration) of dofetilide: 2.72 ng/mL [56], and converted it to nanomolar (nM) concentration ($\frac{2.72\ ng/ml}{441.567\ g/mol} \times 1000 \cong 6.16\ nM$) in the models, where 441.567 g/mol is dofetilide molar mass.

Computed moxifloxacin concentrations

We used the population C_{max} (maximum plasma concentration) of moxifloxacin: 2.5 mg/L [58], and converted it to micromolar (μM) concentration ($\frac{2.5\ \mu g/l}{401.431\ g/mol} \times 1000 \cong 6.23\ \mu M$) in the models, where 401.431 g/mol is moxifloxacin molar mass.

Simulation of TRIaD in dofetilide and control case in O'Hara-Rudy Human model

First, action potential duration (APD) *Triangulation* was calculated as the repolarization time from APD_{30} to APD_{90} from 1000 simulated cells with application of noise current. The noise current was calculated using the equation from [67],

$$V_{t+\Delta t} = V_t - \frac{I(V_t)\Delta t}{C_m} + \xi n\sqrt{\Delta t} \qquad [2]$$

where n is a random number between 0 and 1 from a Gaussian distribution, and Δt is the time step. ξ (= 0.3) is the diffusion coefficient, which defines the amplitude of noise [67]. The noise current was generated and applied to the membrane potential V_t throughout the simulated time course. *Reverse-use-dependence* was measured as APD_{90} at steady state for each pacing cycle length (from 2 Hz to 0.5 Hz), and APD adaptation curves were constructed. *Beat-to-beat* (*bTb) Instability* was simulated by applying small amplitude inward currents randomly between -0.1 to -0.2 pA/pF for 50 ms over the course of the action potential plateau between 10 to 700 ms at 1 Hz for 1000 beats.

Fiber simulations

We simulated a transmural fiber composed of 165 O'Hara-Rudy human ventricular cells [57] (Δx = Δy = 100 μm) connected by resistances to simulate gap junctions [93]. The fiber contains an endocardial region (cells 1 to 80) and epicardial region (cells 81 to 165), which showed a linear decrease in APDs [70, 71]. G_{Kr} was monotonically increased from 0.04 to 0.05. The heart was paced at 1 Hz to match the clinically observed QT intervals ~400 ms [94-96]. AP simulations were carried out in epi/endocardial cells by changing various ion channel conductances [57]. The stimulus is applied to the first cell.

The fiber was paced at varying cycle length from 800 to 1400 ms for 200 beats (mean heart rates = 61 bpm) in order to match the clinical data (56.8$\pm$6.4 bpm) [56]. Pseudo ECGs were computed from the transmembrane potential V_m using the integral

expression as in Gima and Rudy [97]. Heart rate corrected QT (QTc) was computed using Fridericia formula using the cubic root of RR interval [98].

$$QT_C = \frac{QT}{\sqrt[3]{RR}} \qquad [3]$$

Spatial APD dispersion was measured using the T-wave area indicator, which was calculated as the T-wave amplitude on the computed pseudo-ECGs. For this purpose, a 1-dimensional model of the transmural wedge preparation, as described in [82], was stimulated by applying a standard short-long protocol as follows: The transmural wedge preparation was stimulated by a train of pulses (S1) at 1 Hz pacing rate until the steady-state was reached followed by a premature beat (S1-S2 interval = 800 ms) and then a delayed beat (S3) was delivered after a long pause (S2-S3 interval = 5000 ms). T-wave area calculations were computed as follows:

$$\sum_{t=t_1}^{t_2} |ecg(\mathrm{mV})| \cdot \Delta t \qquad [4]$$

where $\Delta t = 1$ ms, t_1 is the time where ECG equals to $T_{peak} - 0.9*(T_{peak}$ = minimum of left side of T wave), and t_2 is the time where ECG equals to $T_{peak} - 0.9*(T_{peak}$ = minimum of right side of T wave).

Frequency-dependent QT prolongation

The fiber was paced at 1Hz for 1000 beats (S1) and then a second stimulus (S2) was applied after a varying RR interval (between 550 and 1200 ms). The QT interval, in response to S2, was recorded. The same simulations were carried out 6 times for both control, 2.5 mg/L moxifloxacin, and 2.72 ng/mL dofetilide with noise currents, and the relative changes in slope of relationship of QT and preceding RR intervals were calculated.

Two-dimensional simulations

2D simulations were performed to determine if proarrhythmic phenomena observed in lower dimensions cause reentrant arrhythmias. Current flow is described by the following equation:

$$\frac{\partial V(x,y,t)}{\partial t} = D_x \frac{\partial^2 V(x,y,t)}{\partial x^2} + D_y \frac{\partial^2 V(x,y,t)}{\partial y^2} - \frac{I_{ion} - I_{stim}}{C_m} \qquad [5]$$

where V is the membrane potential, x and y are distances in the longitudinal and transverse directions, respectively, D_x and D_y are diffusion coefficients in the x and y directions. We simulated a *heterogeneous* and a *homogenous* cardiac tissue on a 500 by 500 pixel grid with $\Delta x = \Delta y = 100$ μm. The heterogeneous tissue contains an endocardial region (fibers 1 to 180) and epicardial region (fibers 181 to 500). We also incorporated anisotropic effects by setting D_x and D_y such that the ratio of conduction velocities is 1:2 [99]. A typical S1-S2 protocol was used for Main Text Figure 7. The tissue was first paced (S1) in a 0.5 cm × 1.1 cm area on the left edge of the endocardial region, and a premature stimulus (S2) was then applied in a 1.8 cm × 1.5 cm area on the top left corner of the endocardial region. Small amplitude inward currents were randomly applied between -0.1 to -0.45 pA/pF on *each cell* in both *heterogeneous* and *homogenous* tissues after 0.5 ms.

Action potential duration (APD) mapping

We reconstructed the "human transmural myocardial wedge" based on data describing transmural action potential heterogeneity mapped from normal human left ventricle [71] (Main Text Figure 8). First, the O'Hara-Rudy human model [57] was used to generate a G_{Kr} lookup table corresponding to APD_{80}. Next, experimental 2D APD_{80} map (100 x 100 – Main Text Figure 8) was used to create a 2D G_{Kr} map using the G_{Kr} lookup table. Then the two-dimensional G_{kr} values (100x100) were used to simulate APD_{80} at pacing rate of 0.5 Hz. We then constructed ***3D wedge*** of 100 by 100 by 1 cells with $\Delta x = \Delta y = 200$ μm and $\Delta z = 500$ μm using this APD mapping data. Current flow is described by the following equation:

$$\frac{\partial V(x,y,z,t)}{\partial t} = D_x \frac{\partial^2 V(x,y,z,t)}{\partial x^2} + D_y \frac{\partial^2 V(x,y,z,t)}{\partial y^2} + D_z \frac{\partial^2 V(x,y,z,t)}{\partial z^2} - \frac{I_{ion} - I_{stim}}{C_m} \qquad [6]$$

Where V is the membrane potential. D_x, D_y and D_z are diffusion coefficients in the x, y and z directions. Stimulus current I_{stim} is 150 mA/cm^2 for 0.5 ms. We also incorporated anisotropic effects by setting D_x, D_y and D_z such that the ratio of conduction velocities is 2:4:1 [99].

Local sensitivity analysis

We calculated elasticity coefficients (sensitivities) for arrhythmia vulnerability parameters from the TRIaD based simulations. The protocol for arrhythmia vulnerability parameters from the TRIaD based simulations is the same as in Online Figure II in the presence of 2.72 ng/mL dofetilide and in Online Figure III with 2.5 mg/L moxifloxacin. The relative change in each arrhythmia vulnerability parameter in response to a parameter perturbation (local sensitivity) was calculated by following equation:

x-elasticity of y: $\varepsilon = \frac{\partial \ln y}{\partial \ln x} \cong \frac{\ln(y_2) - \ln(y_1)}{\ln(x_2) - \ln(x_1)} = \frac{\ln\left(\frac{y_2}{y_1}\right)}{\ln\left(\frac{x_2}{x_1}\right)} = \frac{ln\left(\frac{outputs\ at+20\%}{outputs\ at-20\%}\right)}{ln\left(\frac{rate\ at+20\%}{rate\ at-20\%}\right)}$ [7]

In each case, the model rate constants were increased and decreased by 20%. If $|\varepsilon| > 1$ (sensitive), y (model output) changes more than changes in x (the model rate). In contrast, $|\varepsilon| < 1$ (insensitive) indicates that y (model output) changes less than changes in x (the model rate) [100, 101].

Simulated data of the arrhythmia vulnerability parameters from TRIaD for random forest machine learning application

1) APD TRI: APD triangulations were calculated from APD_{30} to APD_{90} from 1000 simulated cells with noise currents. The protocol is same as in **Simulation of TRIaD**. *2) bTb instability*: 1000 simulated $APDs_{90}$ were recorded by adding noise currents into membrane potential calculations. The protocol is same as in **Simulation of TRIaD**. *3) RUD:* $APDs_{90}$ were recorded from 1000 cells at slow pacing rate (BCL = 2000 ms) with noise currents. *4) T-wave area:* The transmural fibers were stimulated by a standard short-long protocol, and T-wave areas were calculated (as described in **Fiber simulations)** from 1000 cases with noise currents.

Random forest machine learning algorithm

We applied a multivariate correlation-based filter selection (CFS) technique using a random forest machine learning algorithm for multiclass classification [102] to indicate the importance of each arrhythmia vulnerability parameter from **TRIaD** (*APD TRI, bTb instability, T-wave area and RUD*) towards the target (classification of control, different moxifloxacin doses and different dofetilide doses) (Online Figure IV). We calculated the existing correlation coefficients using Pearson's correlation coefficient Eq. [8] to explore the linear dependence of arrhythmia vulnerability parameters from **TRIaD**. Pearson's coefficient values vary between -1 and 1, where 1 is highly correlated (changes in x_1 are correlated with changes in x_2) and -1 is highly anticorrelated (changes in x_1 are negatively correlated with changes in x_2) [103].

$$\rho(\vec{x}_1, \vec{x}_2) = \frac{cov(\vec{x}_1, \vec{x}_2)}{\sigma_{x_1}\sigma_{x_2}} \qquad [8]$$

where $\bar{x}_i$ is a vector consisting of each **TRIaD** parameter's observations, cov is covariance between two **TRIaD** parameters and σ is standard deviation of each **TRIaD** parameter observed in the simulations.

Random forest is an ensemble decision tree, which contains a collection of single decision trees. Each tree is built over random extraction of the observations from the dataset and the random extraction of the features (arrhythmia vulnerability parameters

in this case) [104]. For each feature a series of questions are formulated so that the answer to those questions lead to the best possible separation of classes into groups that contain only one class or the majority of one class at each node. Therefore, the importance of each feature is indicated by purity in each branched out node, and impurity within a node for a particular feature indicates reduced importance in Eq. [10]. The importance of each feature is averaged across all the trees in random forest classifier to determine the final importance of the features [105] in Eq. [11].

$$n_{i_j} = w_j E_j - w_{L_j} E_{L_j} - w_{R_j} E_{R_j} \qquad [9]$$

$$norm\left(f_{i_i}\right) = \frac{\Sigma_j n_{i_j} / \Sigma_k n_{i_k}}{\Sigma_m f_{i_m}} \qquad [10]$$

$$RF\left(f_{i_n}\right) = \frac{\sum_n norm\left(f_{i_{i_n}}\right)}{T} \qquad [11]$$

Where n_{i_j} is the importance of node *j* splits on feature *i*, w_j is the weighted number of samples in node *j*, E_j is the impurity value of node *j*, *L* and *R* represents child node from left and right split on node *j*, f_{i_i} is the importance of feature *i*, *k* and *m* belong to nodes and features sets, $RF\left(f_{i_n}\right)$ is the importance of feature *i* calculated from all trees in the RF model, $norm\left(f_{i_{i_n}}\right)$ is the normalized feature importance *i* in tree *n*, and *T* is total number of trees.

In order to train the random forest classifier, we first performed feature scaling using Eq. [12] to assure that each feature in the dataset has zero-mean and unit-variance [106]

$$\frac{\vec{x}_i - \bar{x}_i}{\sigma_{x_i}} \qquad [12]$$

After feature scaling, we split our dataset into random training and testing subsets (using 80% of data for training and 20% of data for testing the performance of the trained classifier). Then we trained the random forest multiclass classifier using the training subset and set 20 trees and entropy at the same time as the measure of

impurity for the random forest classifier. Entropy (*E*) is a measure that controls how the decision tree decides which feature to choose first and where to split the data (Eq. [13]).

$$E = \sum_i -P_i log_2(P_i) \quad [13]$$

Where the P_i is the fraction of examples in class *i*. After training the classifier, we used test dataset to evaluate the performance of the classifier, where classifier will classify test data; which has not seen them before, into specified classes and reported the percentage of correct responses as accuracy of the classifier.

Atomistic structural modeling

hERG open-state atomistic model generation

The 3D coordinates of hERG (PDB: 5VA2) obtained via cryogenic electron microscopy (cryo-EM) were used as a template[81] for our wild-type open state model of voltage sensing and pore domains (residues 405-668) . This structure is mostly complete except for some missing extracellular loops; namely, residues 434-451 (between helices S1 and S2), 512-519 (between helices S3 and S4), and 578-582, 598-602 (in the outer vestibule pore loop region) are unresolved. ROSETTA symmetry methods [107], and *de novo* loop modeling protocols[107-109] were used to generate the missing loop regions.

General molecular dynamics (MD) simulation protocols

The CHARMM-GUI online toolkit [110], CHARMM [111, 112], NAMD [113], and Anton 2 [114] software programs were used to build and simulate the molecular systems in this study. In all atomistic simulations in this study all-atom biomolecular CHARMM force fields were used including CHARMM36 protein[115] and lipid models,[116] standard ion parameters [117] and TIP3P water model.[118] Dofetilide and moxifloxacin force field models were optimized based on CHARMM general force field (CGENFF) parameters [119] as described below.

hERG – dofetilide and moxifloxacin as well as dofetilide – membrane simulations contained 1-palmitoyl-2-oleoylphosphatidylcholine (POPC) lipid bilayer hydrated by a 0.15 M aqueous KCl solution. Moxifloxacin – membrane simulations contained a 1,2-dimyristoylphosphatidylcholine (DMPC) lipid bilayer hydrated by a 0.15 M aqueous KCl solution. The membrane normal axis was aligned along the *z*-axis in all cases. The hERG channel was placed in the bilayer center with its aqueous pore aligned with the membrane normal. All membrane – drug and hERG – drug MD simulations were carried out in an *NPT* ensemble with 1 atm pressure maintained by Langevin piston barostat [120], and 310 K, controlled by Nosé-Hoover thermostat [121, 122]. MD simulations with applied voltage used to study ion conduction were carried out in the constant volume *NVT* ensemble. Tetragonal cells with periodic boundary conditions (PBC) were used in all the simulations, and the SHAKE algorithm [123] was employed to fix the bonds to all hydrogen atoms, allowing for the use of a 2 fs time step. Electrostatic interactions were computed via Particle Mesh Ewald [124], with a mesh grid of 1 Å.

For all hERG simulations in this study we used an extended staged MD equilibration protocol. For drug-free and drug "flooding" simulations we gradually reduced harmonic restraints on the backbone atoms of the whole protein, then pore domain and finally selectivity filter from 1.0 to 0.1 kcal/mol/Å^2 over the first 40 ns and then continued equilibration simulations for additional 50 ns without restraints. For enhanced sampling hERG – drug binding simulations we kept 1.0 kcal/mol/ Å^2 harmonic restraints on the selectivity filter backbone non-hydrogen and pore domain C_α atoms throughout initial 50 ns long equilibration with drug in bulk solvent and 90 ns long steered MD simulations for drug pulling into the channel pore. To avoid bias related to initial drug orientation and conformation, five independent steered MD runs with different starting points were used to randomly "seed" structures for umbrella sampling simulations. We gradually reduced restraints to 0.2 kcal/mol/Å^2 over the course of initial 5 ns for each umbrella sampling run and kept them throughout production simulations to prevent a random channel transition to a different conformational state.

hERG open-state atomistic model validation

Our hERG open state channel pore was found to be stable in a ~1 μs long unbiased MD simulations, and potassium ion permeation was measured by applying transmembrane voltage during multi-microsecond simulations on Anton 2 [114]. To do so, a uniform electric field was applied in *z* direction, and it can be computed as:

$$E_z = \frac{V}{L_z \cdot 43.5} \qquad [14],$$

Where *V* is the voltage in mV, E_z is the *z* component of the electric field vector in kcal/(mol·Å·e), and L_z is the length of the unit cell in *z* direction in Å. A factor of 43.5 was used to convert from mV/Å to kcal/(mol·Å·e). Seven instances of outward K^+ conduction were observed (depicted in Online Figure V) during 0.3 μs of a ~5 μs long unrestrained hERG MD simulation under 750 mV applied voltage, with similar findings for a K_V1.2/2.1 chimera (PDB ID: 2R9R) [125] MD run under the same conditions. This confirmed that our hERG model represent an open conducting state of the channel.

Atomistic force field parameterization of drug models

Atomistic models for cationic and neutral dofetilide and moxifloxacin as well as zwitterionic moxifloxacin were optimized using initial guesses from generalized CHARMM force field (CGENFF) program[126, 127] and the ffTK plugin[128] for the Visual Molecular Dynamics program (VMD)[129]. Gas-phase quantum mechanical (QM) calculations utilizing Møller–Plesset (MP2) and Hartree-Fock (HF) perturbation theory and the 6-31(d) basis set in Gaussian 09 [130] program were used to compute target data for molecular mechanical (MM) parameter optimization. Optimized charges (*Data Supplement* Tables DSI &DSII) provide a good agreement with QM target dipole values. The optimized MM dipole moments are larger in magnitude compared to QM MP2/6-31G(d) dipole moments by 19% (9.7 vs. 8.1 Debye) for neutral dofetilide, 17% (10.8 vs. 9.2 Debye) for cationic dofetilide, 12% (41.3 vs. 37.0 Debye) for zwitterionic moxifloxacin, 20% (24.6 vs. 20.3 Debye) for cationic moxifloxacin, and 17% (9.9 vs 8.6 Debye) for neutral moxifloxacin, which are all close to the 20% threshold suggested for

CGENFF. The water interaction distances and energies were also in good agreement with QM values (*Data Supplement* Tables DSIII-DSVII). Dihedral angle parameter optimizations resulted in substantial improvement over CGENFF initial guesses, with optimized torsional energy minima within ~1 kcal/mol of QM values for dofetilide (*Data Supplement* Figure DSII) and within ~2 kcal/mol for moxifloxacin (*Data Supplement* Figures DSIII & DSIV). Final topology and parameters for dofetilide and moxifloxacin are provided at the end of this document in *Data Supplement* Tables DSVIII – DSXII.

Atomistic drug model validation

To validate developed drug force field parameters, all-atom umbrella sampling (US) MD simulations[131] of drug partitioning across a hydrated lipid bilayers (POPC for dofetilide, and DMPC for moxifloxacin) were performed. For each drug model, 81 independent simulation windows were created, in which the center of mass (COM) of a randomly oriented drug molecule was placed at 1 Å intervals from z=–40 Å to z=40 Å with respect to COM of the membrane. In addition, for the membrane-spanning central windows, z=–20 Å to z=20 Å, additional simulations were performed, in which the drug was flipped about its z-axis in order to enhance sampling, and hence reduce asymmetries in the computed potential of mean force (PMF) profiles (Online Figure VI). For all US MD simulations, the COM of the drug was restrained along the z-axis with a force constant of 2.5 kcal/mol/Å^2, and an additional 5 kcal/mol/Å^2 cylindrical restraint was applied in order to prevent its drift in the xy plane. The PMF profiles were computed using the weighted histogram analysis method (WHAM)[132] with error bars representing standard errors of mean computed from profile asymmetries with respect to z = 0 (error($W(z)$) = $|W(z) - W(-z)| / 2$). See Online Figure VI for convergence of unsymmetrized PMF profiles.

Symmetrized diffusion coefficient profiles (–40 Å to 0 Å shown in Main Text Figure 1D &1H) were obtained using Laplace transform of drug position autocorrelation function [133] as was described in our recent studies [42, 43]. Water-membrane distribution coefficients logD_{MW} were computed as was done previously [43, 134, 135], resulting in 0.32±0.15 for

dofetilide and 0.13±0.11 for moxifloxacin. The values for dofetilide were in reasonable agreement with experimental water-octanol (0.84 [136] , 0.96 [137]) and water-artificial membrane (2.08 [136]) values. The values for moxifloxacin agreed less favorably with an experimental value for DMPC membrane (2.4 [138]), but in a good agreement with water-octanol and water-artificial membrane values (1.12 and 1.57, respectively [136]). To compute the translocation rates of both drugs across lipid membranes we used Kramer's transition rate approximation, as was done previously [139, 140] using Laplace transform of position autocorrelation function [133] for computing diffusion coefficients at the *z* positions of the PMF profile peaks, and also computing PMF barrier heights and profile curvatures at the peaks and wells.

Drug binding to the hERG pore

Both drugs in each ionization state were found to spontaneously access through an intracellular gate and bind in the hERG channel pore during 2.5 μs long unbiased "flooding" MD simulations with multiple (11) drug molecules corresponding to ~25 mM initial aqueous concentration. However, in most cases we did not observe any drug unbinding events, and had to use enhanced sampling simulations to compute affinities and rates as described below. The only exception is cationic moxifloxacin, for which we only observed transient drug binding and unbinding events at the intracellular end of the pore. We also did not observe any drug binding through lipid-facing fenestrations as in the case of Na_V channels,[42, 135] justifying enhanced sampling simulations for drug binding through an intracellular channel gate. To do this, US MD simulations were run for 40 ns for each US window for dofetilide, and 70 ns per US window for moxifloxacin. US windows corresponded to harmonically restrained drug center of mass *z* positions, in 0.5 Å increments from –50 to –5 Å with respect to hERG selectivity filter (SF) C_α atoms. The first 10 ns of each run was considered equilibration, and the rest was used to compute free energy, or potential of mean force (PMF) profiles (see Online Figure VII for convergence) using the weighted histogram analysis method (WHAM), [132] and diffusion coefficient profiles via Laplace transform of drug position autocorrelation function[133]. Error bars for PMF profiles in ain text Figure 2 B & D were computed as

standard errors of mean from block averaging analysis. For that we separated US simulation data into three blocks of 5 ns for dofetilide or 20 ns for moxifloxacin and computed PMF profiles from each of them.

Dissociation constants, K_D, were computed from PMF profiles using established methods[141] and are shown in main text Figure 2E. For open state hERG binding, cationic and neutral dofetilide K_D were computed to be 65 μM and 0.16 μM, respectively, and 8600 μM, 6700 μM, and 0.74 μM for zwitterionic, cationic, and neutral moxifloxacin, respectively. For both drugs, there was much stronger binding of the neutral form.

To compute the drug-channel association or ingress "on" rate (k_{on}) for each drug binding to hERG, we assumed that the binding process is a purely diffusion-limited reaction (barrier-free), and that the reaction is fast once a drug molecule enters the reactive region. Diffusion coefficient, $\mathcal{D}(z)$, profiles for each drug going from the intracellular bulk aqueous solution region into the hERG pore were obtained using Laplace transform of drug position autocorrelation function [133] as was done in our recent studies on drug - membrane partitioning [42, 43]. The rates, k_{on}, were computed from $\mathcal{D}(z)$ and free energy, $W(z)$, profiles using a formulation of the Debye-Smoluchowski equation [49, 50]:

$$k_{\mathrm{on}}{}^{-1} = \frac{1}{\pi R^2}\int_{z_{\mathrm{out}}}^{z_{\mathrm{bind}}} e^{\frac{W(z)}{k_{\mathrm{B}}T}}\,\mathcal{D}(z)^{-1}dz \quad [15]$$

where R is the radius of a cylinder (10 Å) encompassing the channel pore and used as a flat-bottomed restraint for US MD simulations, k_B is Boltzmann constant, T is absolute temperature, and z is the reaction coordinate. Using computed K_D and k_{on} values, we can estimate drug – channel dissociation rate constant, k_{off}, as:

$$k_{off} = k_{on} \cdot K_D \quad [16].$$

Computed K_D, k_{on} and k_{off} values are listed in main text Figure 2E and were used as parameters for drug-hERG interaction function scale models (see sections above and main text).

We also compared computed drug ingress rates at maximum physiological plasma concentrations (C_{max}) of dofetilide (~6.16 nM, see above) and moxifloxacin (~6.23 μM, see above) using $x \cdot C_{max} \cdot k_{on}$, where x is each drug ionization species fraction at pH = 7.2. For dofetilide, ingress rates at maximal plasma concentration were computed to be equal to 2.5 and 1.2 s^{-1} for cationic and neutral dofetilide, respectively, and 1,800, 270, and 230 s^{-1} for zwitterionic, cationic, and neutral moxifloxacin, respectively. Drug-membrane translocation rates, in comparison, were 8,000 s^{-1} for neutral dofetilide, 43,000 s^{-1} for cationic moxifloxacin, and $1.1 \cdot 10^6$ s^{-1} for neutral moxifloxacin. For either drug, channel ingress rates are 2–3 orders of magnitude slower than membrane translocation rates, indicating that kinetics associated with open hERG – drug interactions will be rate-determining.

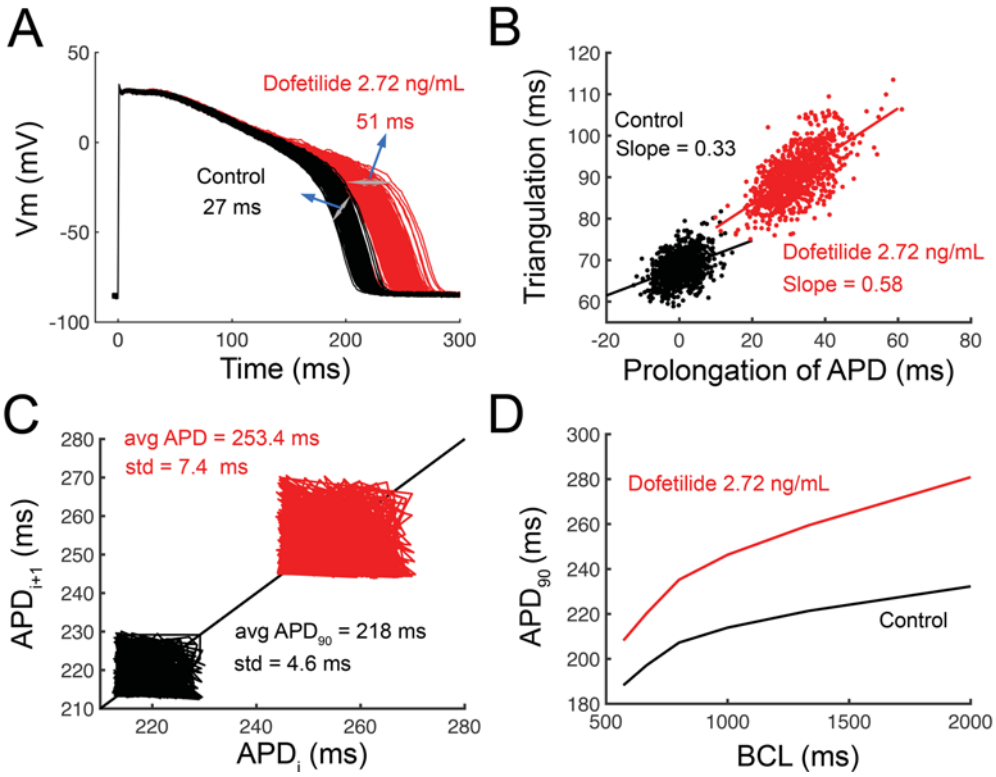
Drug binding pocket topologies within the hERG pore

The topologies of the binding pockets for the neutral and cationic forms of dofetilide in representative poses from US MD simulations are shown in Online Figure VIII A and VIII B, respectively. Neutral dofetilide binds at z=–15.5 Å with one end pointing up toward polar residues in the SF, stabilized by interactions near its base (S624) as well as a cluster of residues from S6 helix including S660, Y652 and F656 from multiple chains, which are all the residues that have been implicated in experimental drug binding studies[142]. Cationic dofetilide was observed to bind below the Y652 ring at z=–20 Å and is also coordinated by hydrophobic residues F656 and Y652 from multiple chains, with both terminal methanesulfonamide groups coordinated via hydrogen bonds with S660 residues (near the intracellular ends of S6 helices) from two chains (see Online Figure VIII B). In other words, both ends of the molecule point down toward the bulk aqueous solvent, whereas its cationic ammonium group in the middle points up towards the SF and forms a hydrogen bond with Y652. Zwitterionic moxifloxacin was found to bind at the intracellular end of the pore at z=-22.5 Å and coordinate with S6

residues Y652, F656, S660 as well as Q664 (see Online Figure IX A). Neutral moxifloxacin most tightly binds in the hERG pore at *z*=-20 Å and engages in the interactions with S6 helix residues F656, G657, and S660 from two chains (Online Figure IX B). Cationic moxifloxacin was found to bind hERG at *z*=-21.5 Å interacting with S6 residues N658, S660 and Q664 (Online Figure XI C).

Online Figures I - IX

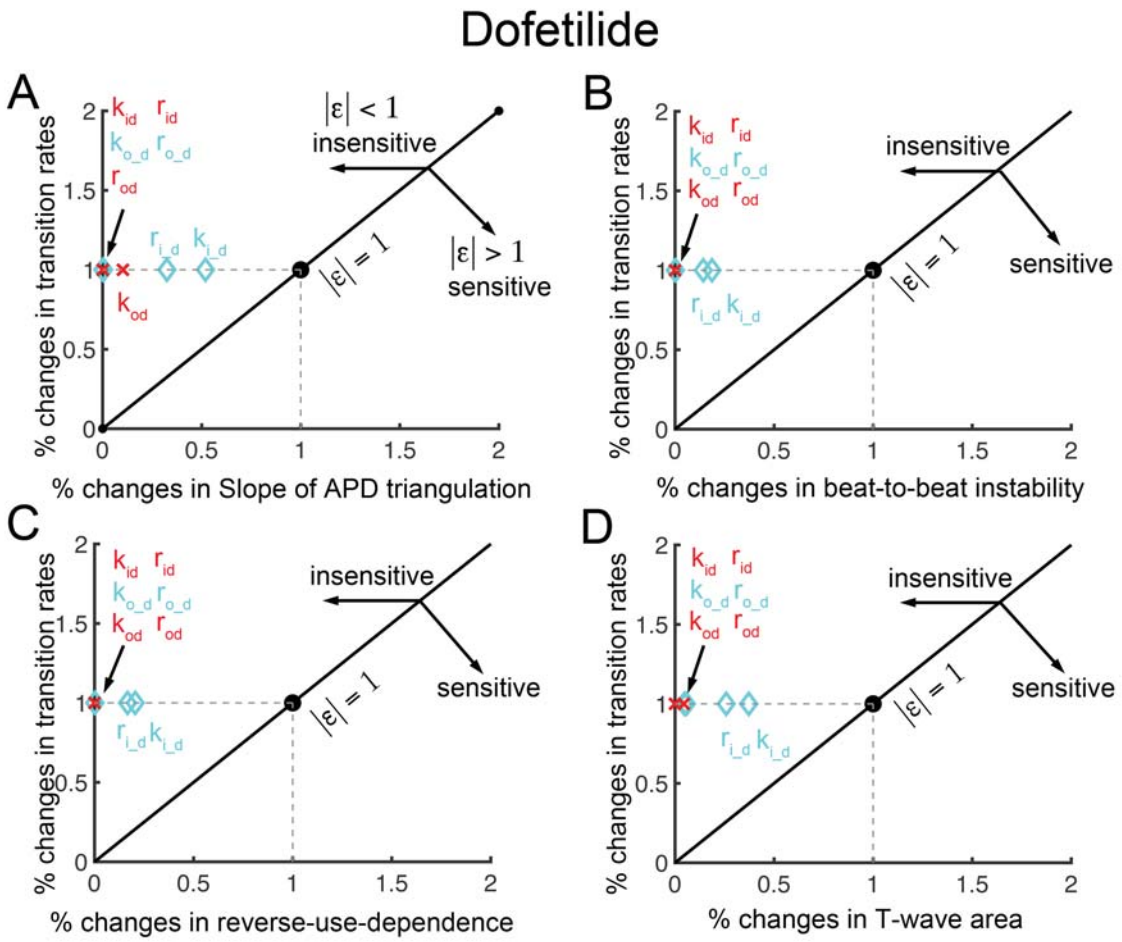
Online Figure I



Computational screen of arrhythmia vulnerability in rabbit model. In panel A, ***temporal action potential duration dispersion*** was quantified in a cell population of

1000 individual simulated cardiac myocyte action potentials constructed by incorporating physiological noise [67, 68]. *Dispersion* of APD was quantified as the difference between the maximum and minimum action potential duration. Dofetilide within the clinical dosing range has a clear effect to promote temporal action potential duration variability in the presence of the drug (Control – 27 ms; Dofetilide 2.72 ng/mL = 51 ms). Panel B illustrates the effect of dofetilide to promote ***triangulation*** of the action potential as a function of APD prolongation. In the absence of drug, control cells had a slope = 0.33, while Dofetilide 2.72 ng/mL increased the slope = 0.58. Panel C shows Poincaré plots of sequential APD pairs indicating beat-to-beat ***instability*** following the application of small electrical perturbations in the absence of drug or with 2.72 ng/mL dofetilide. Instability was assessed by applying small amplitude inward currents randomly between -0.1 to -0.2 pA/pF for 50 ms over the course of the action potential plateau at a pacing cycle length = 1000 ms. Finally, in panel D, ***reverse use dependence*** induced by dofetilide was evaluated. The action potential adaptation curves were generated using APD_{90} values from human computational ventricular myocytes at steady-state at the indicated pacing frequencies. When dofetilide (red) was applied, there was a clear steepening of the APD adaptation curve compared to the baseline drug-free case (black).

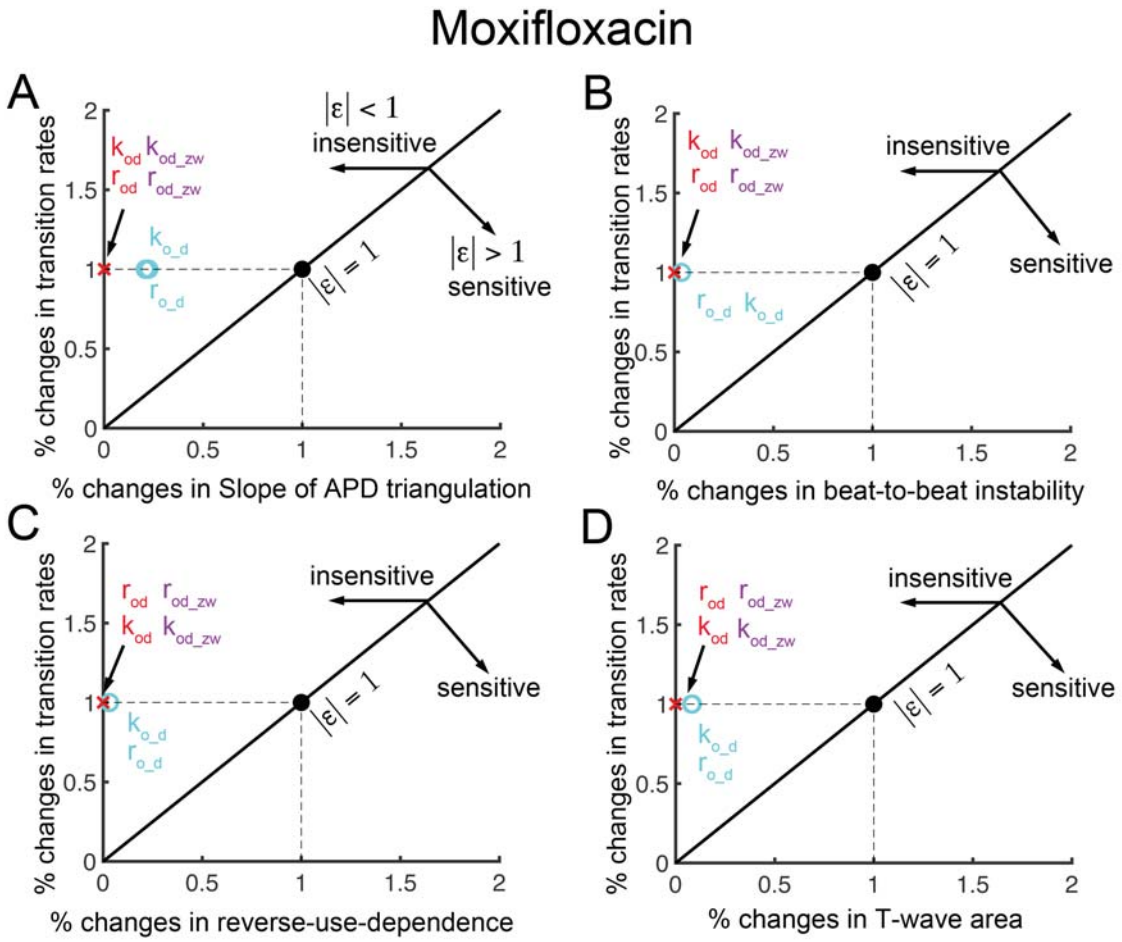
Online Figure II



Local sensitivity analysis of arrhythmia vulnerability parameters from the TRIaD for Dofetilide

In order to assess the specific drug-channel interactions comprising the dofetilide structure-activity relationship and the link to proarrhythmia, we undertook sensitivity analysis to determine how sensitive the arrhythmia vulnerability parameters from the TRIaD based simulations are to our underlying model parameters. As shown in panel A, we first carried out an *in silico* test of the local sensitivity of the slope of the relationship between action potential *triangulation* and APD prolongation in O'Hara-Rudy computational myocytes plotted for a range of drug "on" (k_{o_d}, k_{od}, k_{i_d}, and k_{id}) and "off" (r_{o_d}, r_{od}, r_{i_d} and r_{id}) model transition rates for open and open-inactivated states by increasing and decreasing each rate at ±20% for neutral (cyan) and cationic (red), and calculated elasticity coefficients. The local sensitivity analysis showed that perturbation to the rate constant k_{i_d} (open-inactivated state binding) of neutral drug results in the greatest effect on the slope of APD triangulation. The elasticity value of k_{i_d} shown in panel A is 0.52, which suggests that if the rate constant k_{i_d} is increased by 1% then the slope of APD triangulation increases by approximately 0.52%, indicating relative insensitivity to even the most sensitive model parameter. Perturbation to all other rate constants also results in less than 1% changes in the slope of APD triangulation. Similarly, in panel B, simulated beat-to-beat *instability* of action potentials (average and standard deviation of APD_{90} for each rate perturbation are shown) with respect to transition rate changes are demonstrated. And panel C shows relative changes in transition rates with respect to the APD_{90} at a slow pacing rate, which reflect maximal reverse use dependence (BCL = 2000 ms). Again, binding and unbinding rate parameters of neutral drug (cyan) for inactivated channel state caused more changes in the model outputs compared to other parameters, but the model outputs are still relatively insensitive. Finally, panel D, shows higher elasticity values of the T-wave area to neutral drug (cyan) binding and unbinding rates for inactivated state. However, the analysis showed that the model was robust to perturbations (elasticity value < 1).

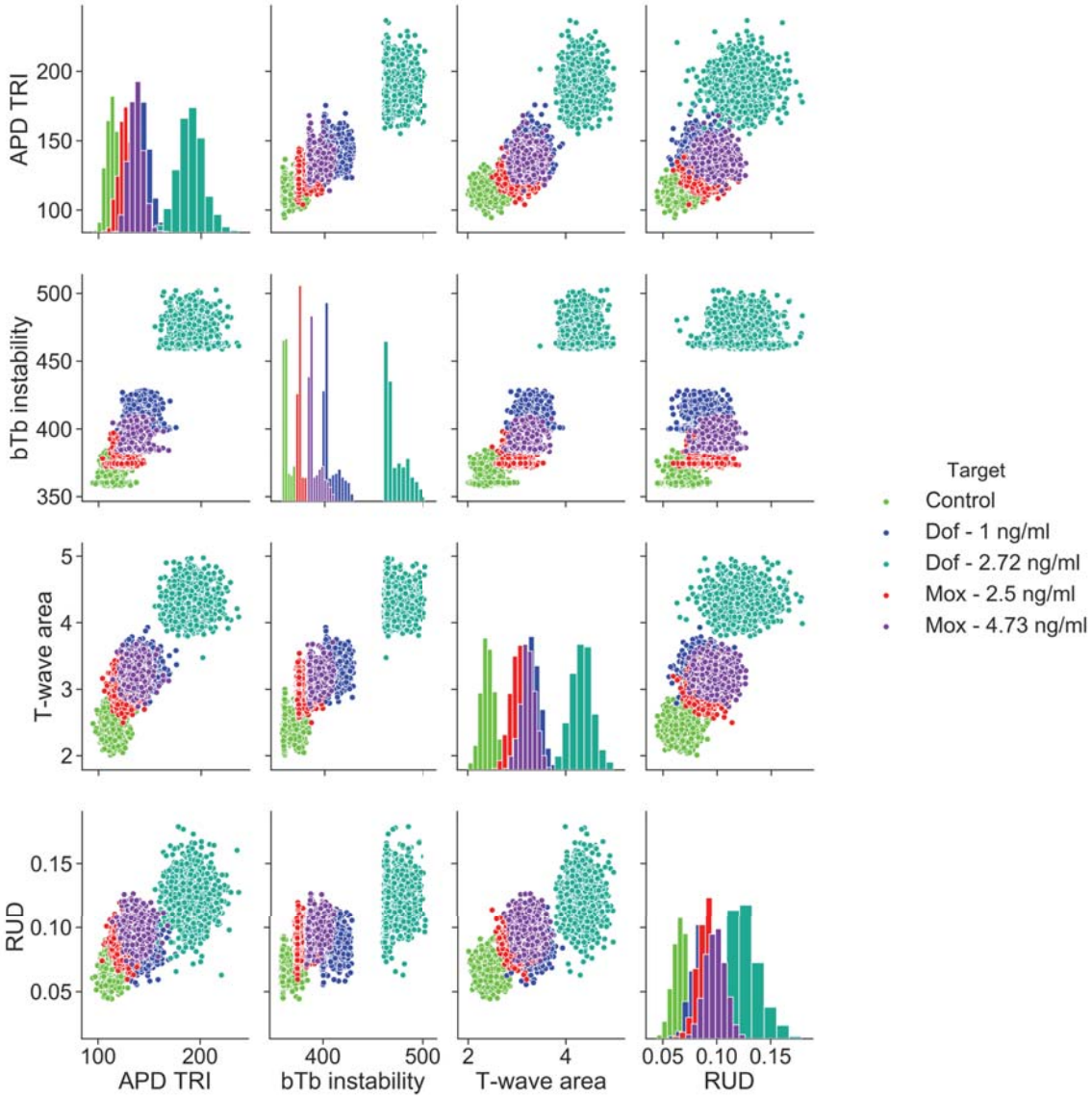
Online Figure III



Local sensitivity analysis of arrhythmia vulnerability parameters from the TRIaD for Moxifloxacin

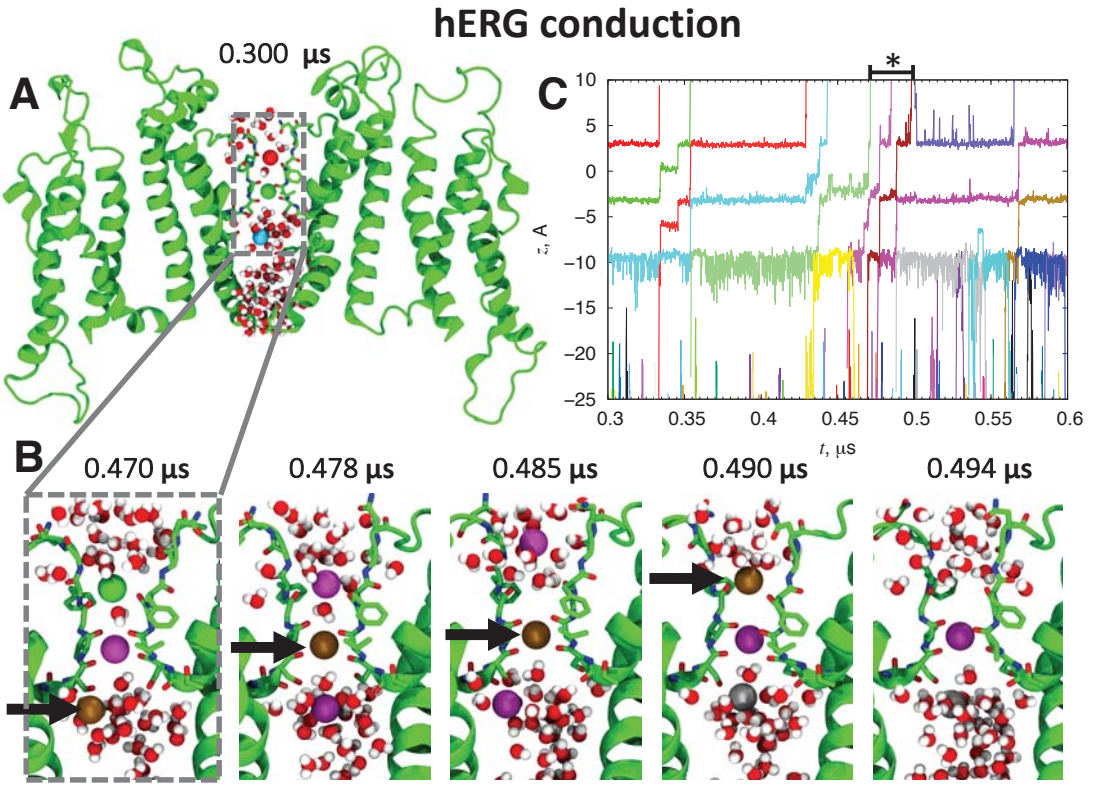
A) The sensitivity of the slope of the relationship between action potential *triangulation* in O'Hara-Rudy computational myocytes plotted for a range of drug "on" (k_{o_d}, k_{od}, and k_{od_zw}) and "off" (r_{o_d}, r_{od}, and r_{od_zw}) model transition rates for open and inactivated states by increasing and decreasing each rate at ±20% for neutral (cyan), cationic (red), and zwitterionic (purple). B) Sensitivity of simulated beat-to-beat *instability* of action potentials for a range of rate constants. C) The sensitivity to changes in drug transition rates of the recorded APD_{90} at BCL of 2000 ms. D) Sensitivity of the T-wave area to model transition rates.

Online Figure IV



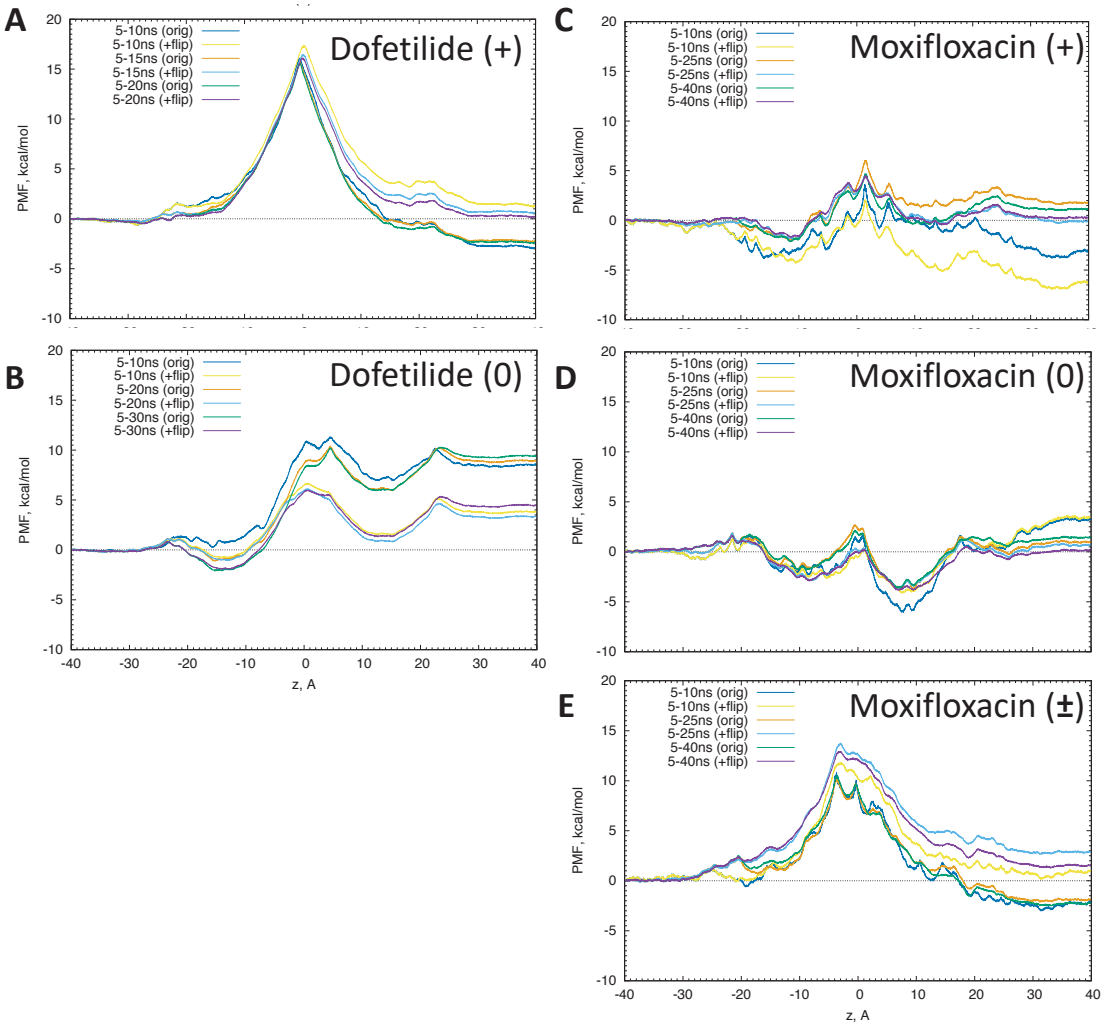
The scatter plots show the distribution of the arrhythmia vulnerability parameter from TRIaD (*APD TRI, bTb instability, T-wave area and RUD*) and relationship between the target (classification of control, different moxifloxacin doses and different dofetilide doses).

Online Figure V



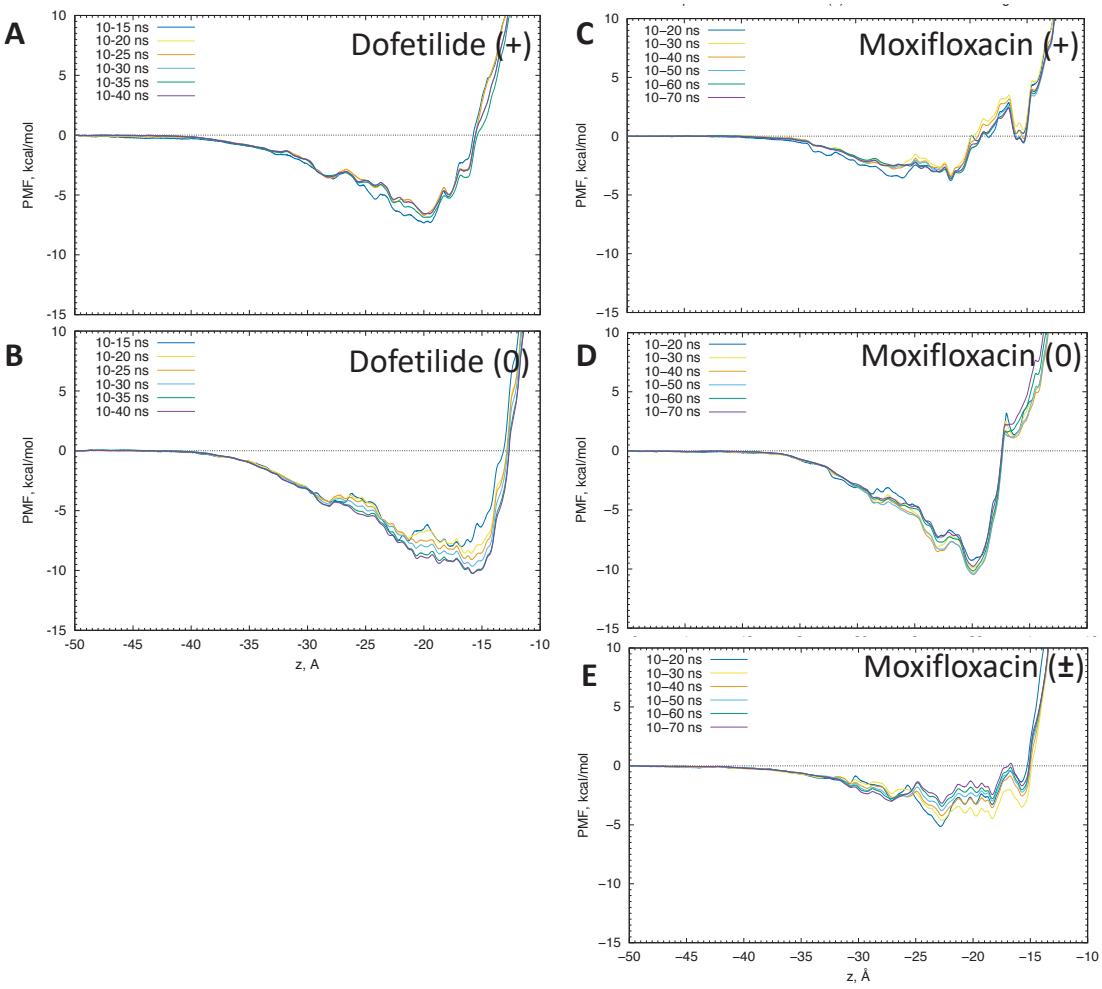
K^+ conduction of atomistic open state hERG model under an applied 750 mV voltage. A 0.3 μs slice of a 5 μs trajectory, where most conduction events took place, is shown. (**A**) Initial frame in this time slice (*t* = 0.300 μs) showing two opposite protein chains (green ribbons with SF residues S624-G628, S6 helix Y652 and F656 residues shown as sticks with red O and blue N), pore ions (colored balls) and waters (red/white). (**B**) Close-up views of the channel SF in the same representation at different time points, showing a complete translocation of one ion (brown ball), indicated by an arrow. (**C**) Time series of ion *z*-positions (with respect to the SF backbone center of mass). Colors of the *z* profiles match those of the ions in panels **A**, **B**. Portion of the profiles corresponding to snapshots in panel **B** is indicated with an asterisk.

Online Figure VI



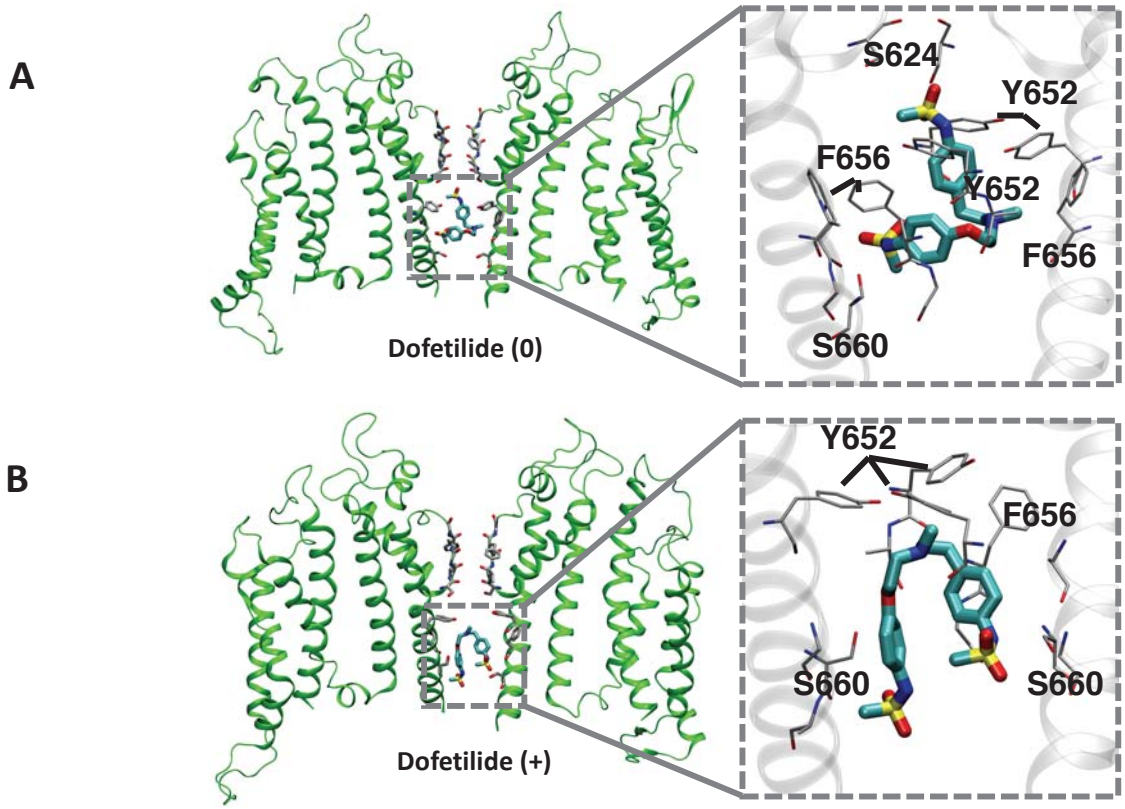
Non-symmetrized free energy or potential of mean force (PMF) profiles for drug models crossing a lipid bilayer computed from umbrella sampling MD simulations. Cationic (**A**) and neutral (**B**) dofetilide across a POPC bilayer, and cationic (**C**) neutral (**D**) and zwitterionic (**E**) moxifloxacin across a DMPC bilayer They were computed using weighted histogram analysis method (WHAM) discarding first 5 ns for each umbrella sampling window. In some cases, additional simulations with initial drug orientation rotated around the *z*-axis (indicated as +flip) were performed to improve drug re-orientation sampling.

Online Figure VII



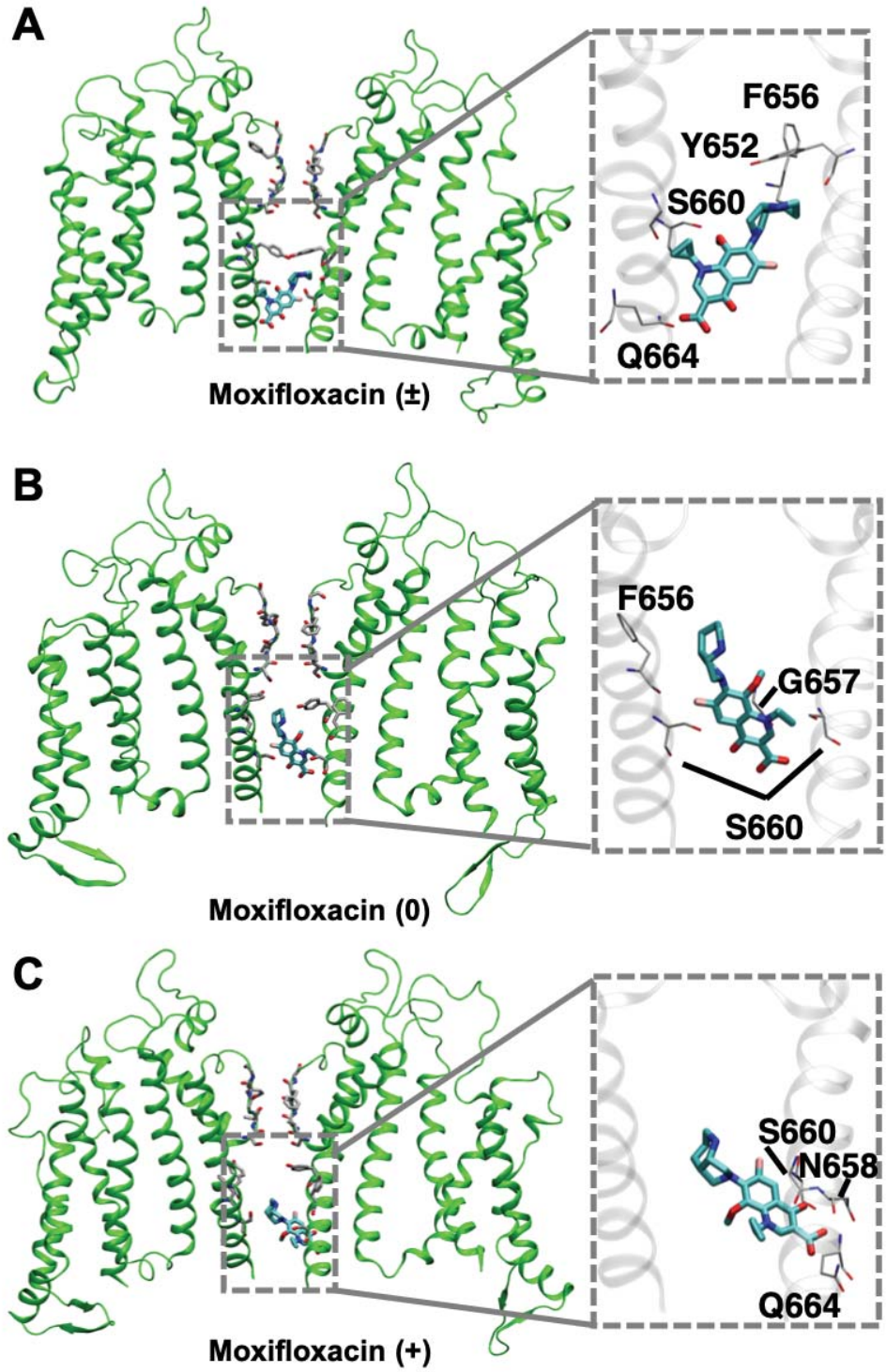
Convergence of free energy or potential of mean force (PMF) profiles for dofetilide and moxifloxacin binding to an open hERG channel model computed from umbrella sampling MD simulations. Cationic (**A**) and neutral (**B**) dofetilide profiles, and cationic (**C**) neutral (**D**) and zwitterionic (**E**) moxifloxacin profiles computed using weighted histogram analysis method (WHAM) discarding first 10 ns for each umbrella sampling window, and incrementally including data from additional 5 ns blocks up to 40 ns for dofetilide and 10 ns blocks up to 70 ns for moxifloxacin.

Online Figure VIII



Cationic and neutral dofetilide hERG binding from umbrella sampling MD simulations. Representative lowest free energy drug binding configurations for neutral (**A**) and cationic (**B**) dofetilide in the hERG pore. Two opposite hERG chains with a drug bound are shown on the left, whereas insets on the right show close-up views of hERG residues interacting with dofetilide (within 3.5 Å counting non-H atoms only). hERG is shown as ribbons (green or gray), interacting residues as thin sticks and dofetilide as thick sticks (C – cyan, O – red, N – blue, S – yellow, F – pink).

Online Figure IX



Zwitterionic (±), neutral (0) and cationic (+) moxifloxacin hERG binding from umbrella sampling MD simulations. See Online Fig. VIII for more details.

Data Supplement: Atomistic force field models for different ionization states of dofetilide and moxifloxacin

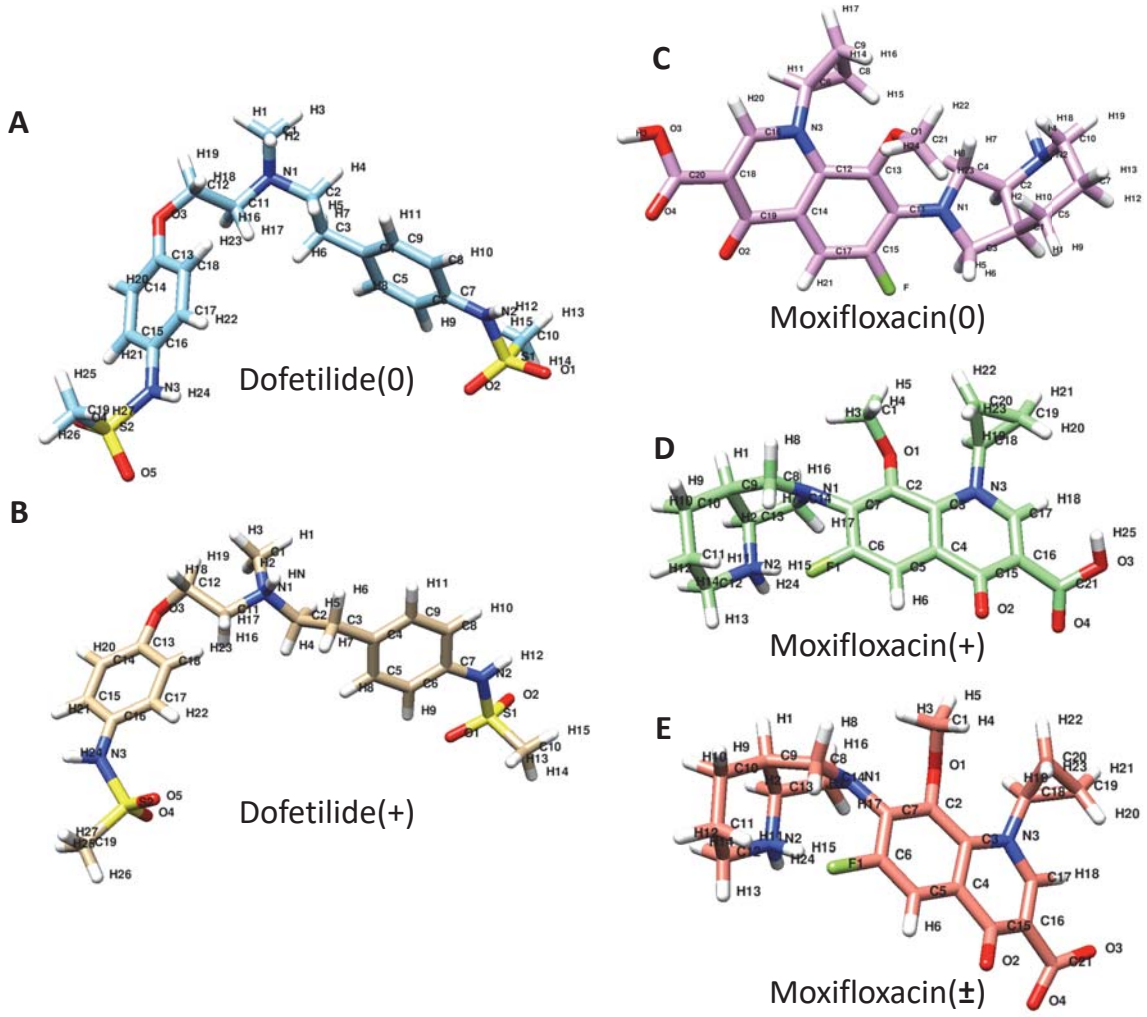


Figure DSI. Atom naming for different ionization states of dofetilide and moxifloxacin atomistic force field models. (**A**) Neutral dofetilide (DOFN or Dofetilide(0)). (**B**) Cationic dofetilide - DOFC or Dofetilide(+) (**C**) Neutral moxifloxacin - MOX0 or Moxifloxacin (0) (**D**) Cationic moxifloxacin - MOXC or Moxifloxacin (+), and (**E**) Zwitterionic moxifloxacin - MOXZ or Moxifloxacin (±)

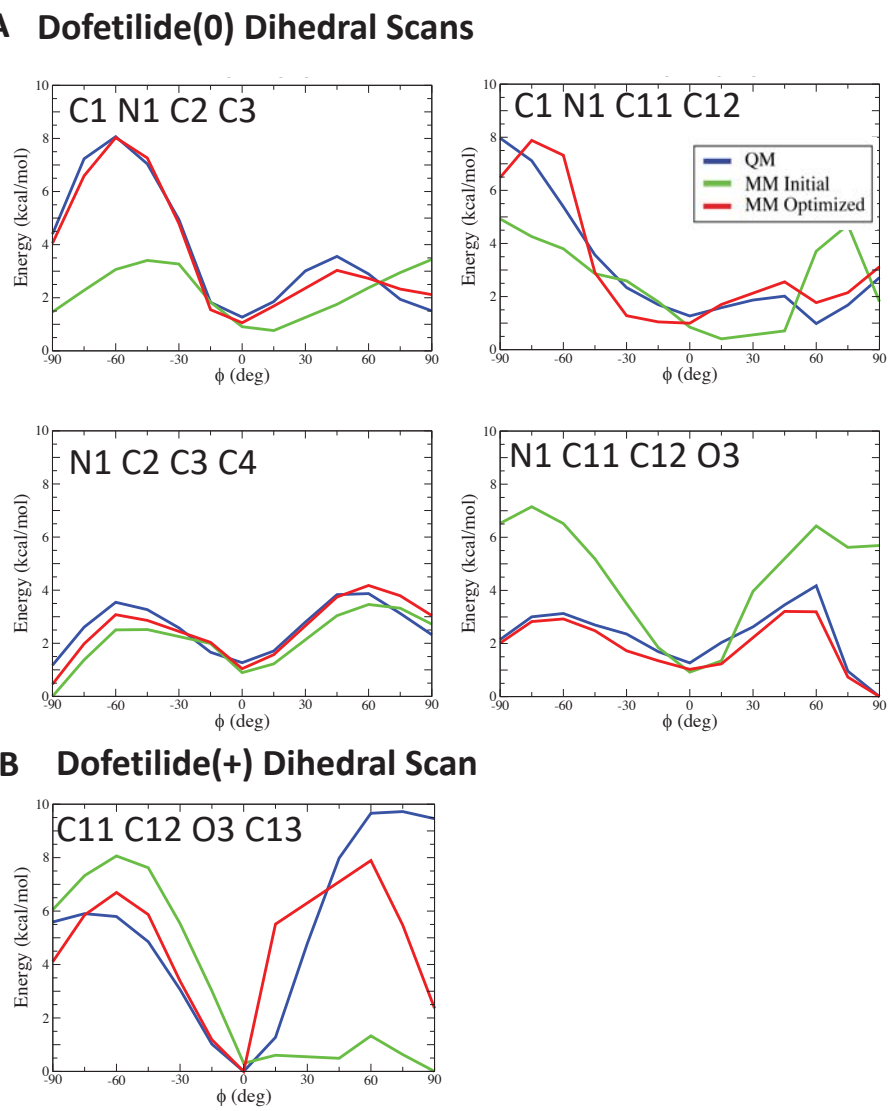


Figure DSII. Gas-phase torsional energy profiles for neutral and cationic dofetilide models from quantum mechanical (QM), initial and optimized molecular mechanics (MM) calculations. Atom names corresponding to the ones in *Data Supplement* Fig. DSIA and Fig.DSIB for (**A**) Dofetilide (0) or DOFN, and (**B**) Dofetilide (+) or DOFC, respectively, with corresponding topology and parameter files in the *Data Supplement* Tables DSVIII and DSIX.

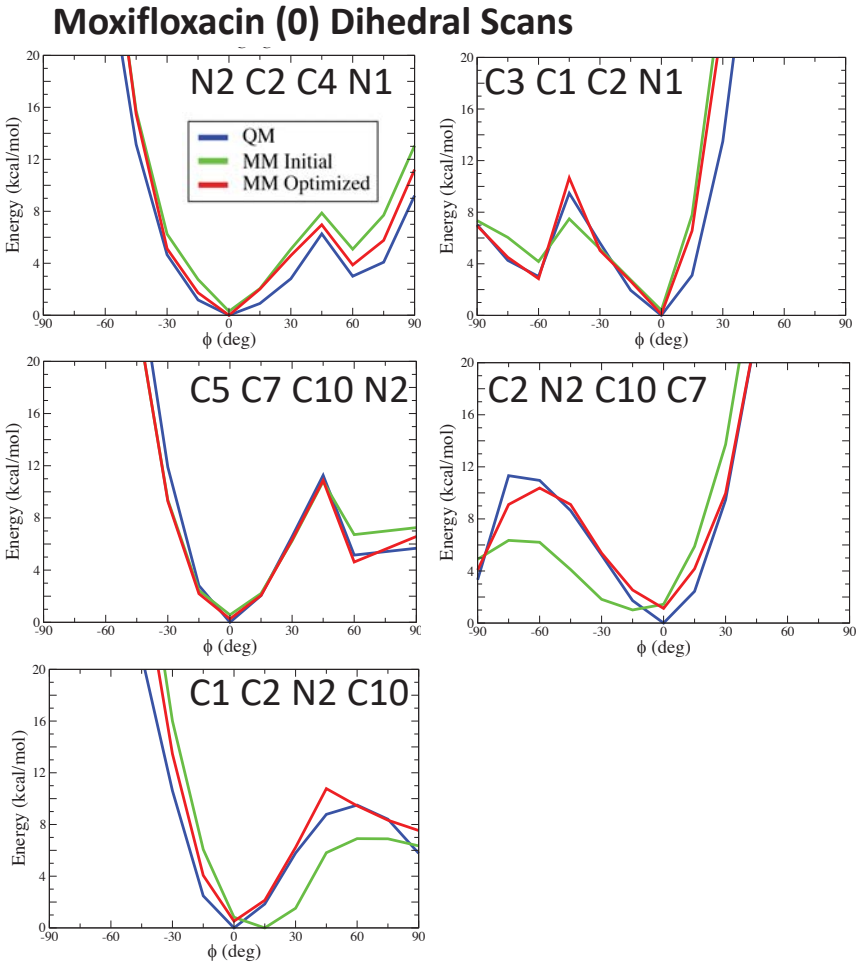


Figure DSIII. Gas-phase torsional energy profiles for neutral moxifloxacin drug model from quantum mechanical (QM), initial and optimized molecular mechanics (MM) calculations. Atom names corresponding to the ones in *Data Supplement* Fig. DSIC for Moxifloxacin (0) with corresponding topology and parameter files in the *Data Supplement* Table DSXII.

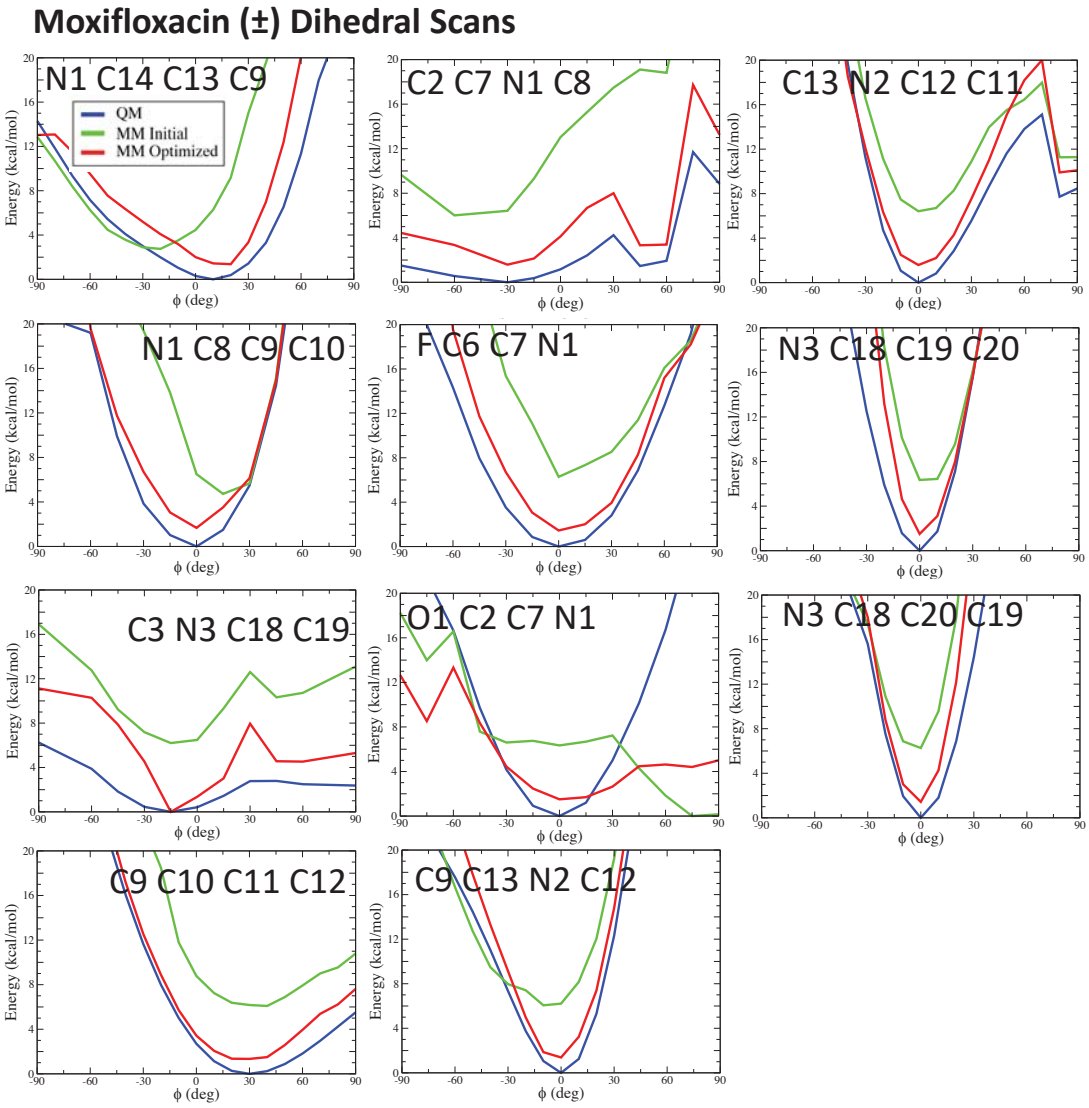


Figure DSIV. Gas-phase torsional energy profiles for zwitterionic moxifloxacin drug model from quantum mechanical (QM), initial and optimized molecular mechanics (MM) calculations. Atom names corresponding to the ones in Fig. DSIE for Moxifloxacin (±), with corresponding topology and parameter files in the *Data Supplement* Table DSX.

Drug	Total Charge	Drug	Total Charge
DOFC	1	**DOFN**	0
C1	0.149	C1*	-0.392
N1*	-0.006	N1*	-0.401
C2*	-0.495	C2*	0.24
C3*	-0.25	C3*	-0.559
C4*	0.31	C4*	0.296
C5	-0.115	C5	-0.115
C6	-0.111	C6	-0.111
C7	0.219	C7	0.219
C8	-0.111	C8	-0.111
C9	-0.115	C9	-0.115
N2	-0.466	N2	-0.466
S1	0.439	S1	0.439
O1	-0.384	O1	-0.384
O2	-0.384	O2	-0.384
C10	-0.019	C10	-0.019
C11	0.162	C11*	0.01
C12	-0.014	C12	-0.021
O3	-0.391	O3	-0.39
C13	0.219	C13	0.219
C14	-0.113	C14	-0.113
C15	-0.115	C15	-0.115
C16	0.219	C16	0.219
C17	-0.115	C17	-0.115
C18	-0.113	C18	-0.113
N3	-0.466	N3	-0.466
S2	0.439	S2	0.439
O4	-0.384	O4	-0.384
O5	-0.384	O5	-0.384
C19	-0.019	C19	-0.019
H1	0.09	H1	0.09
H2	0.09	H2	0.09
H3	0.09	H3	0.09
H4	0.09	H4	0.09
H5	0.09	H5	0.09
H6	0.09	H6	0.09
H7	0.09	H7	0.09
H8	0.115	H8	0.115
H9	0.115	H9	0.115
H10	0.115	H10	0.115
H11	0.115	H11	0.115
H12	0.323	H12	0.323
H13	0.09	H13	0.09
H14	0.09	H14	0.09
H15	0.09	H15	0.09
H16	0.09	H16	0.09
H17	0.09	H17	0.09
H18	0.09	H18	0.09
H19	0.09	H19	0.09
H20	0.115	H20	0.115
H21	0.115	H21	0.115
H22	0.115	H22	0.115
H23	0.115	H23	0.115
H24	0.323	H24	0.323
H25	0.09	H25	0.09
H26	0.09	H26	0.09
H27	0.09	H27	0.09
HN	0.318		

Table DSI. Partial atomic charges for cationic (DOFC) and neutral (DOFN) dofetilide models.

(Optimized charge values are shown by asterisk)

Drug	Total Charge	Drug	Total Charge	Drug	Total Charge
MOXC	1.00	MOXZ	0.00	MOX0	0.00
C1	-0.1	C1	-0.1	F *	-0.145
O1	-0.391	O1	-0.391	O1	-0.391
C2*	0.297	C2*	0.275	O2*	-0.425
C3*	0.395	C3*	0.296	O3	-0.513
C4	-0.234	C4*	-0.386	O4	-0.437
C5	0.021	C5	0.04	N1*	-0.094
C6*	0.006	C6*	0.061	N2*	-0.761
C7*	0.118	C7*	0.278	N3*	-0.177
N1*	-0.507	N1*	-0.69	C1*	-0.086
C8*	0.169	C8*	0.222	C2*	0.018
C9*	-0.114	C9*	-0.216	C3*	-0.019
H1	0.09	H1	0.09	C4*	0.096
C10	-0.19	C10	-0.19	C5	-0.178
C11	-0.161	C11	-0.177	C6*	0.094
C12*	0.17	C12*	0.127	C7*	-0.171
N2*	-0.344	N2*	-0.409	C8	-0.18
C13*	0.245	C13*	0.342	C9	-0.18
H2	0.09	H2	0.09	C10*	0.078
C14*	-0.026	C14*	-0.045	C11*	-0.15
F1*	-0.282	F1*	-0.258	C12*	0.027
C15*	0.304	C15*	0.469	C13*	0.216
O2*	-0.449	O2*	-0.609	C14*	0.097
C16*	0.118	C16*	-0.203	C15*	-0.135
C17	0.095	C17*	0.187	C16	0.016
N3*	-0.402	N3*	-0.41	C17	0.04
C18*	0.099	C18*	0.092	C18*	0.261
C19	-0.18	C19	-0.18	C19*	0.026
C20	-0.18	C20	-0.18	C20*	0.314
C21*	0.32	C21*	0.805	C21	-0.1
O3	-0.513	O3	-0.76	H1	0.09
O4	-0.437	O4	-0.76	H2	0.09
H3	0.09	H3	0.09	H3	0.429
H4	0.09	H4	0.09	H4	0.342
H5	0.09	H5	0.09	H5	0.09
H6	0.161	H6	0.177	H6	0.09
H7	0.09	H7	0.09	H7	0.09
H8	0.09	H8	0.09	H8	0.09
H9	0.09	H9	0.09	H9	0.09
H10	0.09	H10	0.09	H10	0.09
H11	0.09	H11	0.09	H11	0.09
H12	0.09	H12	0.09	H12	0.09
H13	0.09	H13	0.09	H13	0.09
H14	0.09	H14	0.09	H14	0.09
H15	0.329	H15*	0.341	H15	0.09
H16	0.09	H16	0.09	H16	0.09
H17	0.09	H17	0.09	H17	0.09
H18	0.105	H18	0.111	H18	0.09
H19	0.09	H19	0.09	H19	0.09
H20	0.09	H20	0.09	H20	0.111
H21	0.09	H21	0.09	H21	0.177
H22	0.09	H22	0.09	H22	0.09
H23	0.09	H23	0.09	H23	0.09
H24	0.329	H24	0.341	H24	0.09
H25	0.429				

Table DSII. Partial atomic charges for cationic (MOXC), zwitterionic (MOXZ), and neutral (MOX0) moxifloxacin models.

(Optimized charge values are shown by asterisk)

Table DSIII. Gas-phase neutral dofetilide (DOFN) – water interactions.

	Water interaction distance (A)			Water interaction energy (kcal/mol)		
	QM	MM	*Difference*	QM	MM	*Difference*
N1	3.077	3.13	*0.05*	-5.839	-6.017	*-0.178*
N2	3.205	3.31	*0.10*	-3.572	-2.582	*0.990*
N3	3.26	3.21	*-0.05*	-4.137	-5.059	*-0.922*
O1	3.003	2.95	*-0.05*	-6.363	-6.377	*-0.014*
O1	2.986	2.94	*-0.05*	-6.34	-6.396	*-0.056*
O1	3.049	2.95	*-0.10*	-5.384	-5.409	*-0.025*
O2	3.053	2.95	*-0.10*	-6.019	-6.677	*-0.658*
O2	2.977	2.93	*-0.05*	-6.822	-7.164	*-0.342*
O2	3.065	2.97	*-0.10*	-5.515	-5.753	*-0.238*
O3	3.01	2.91	*-0.10*	-4.847	-5.452	*-0.605*
O4	3.039	2.99	*-0.05*	-5.764	-6.268	*-0.504*
O4	2.987	2.94	*-0.05*	-6.254	-6.867	*-0.613*
O4	3.018	2.97	*-0.05*	-5.721	-6.023	*-0.302*
O5	3.045	3.00	*-0.05*	-5.844	-6.039	*-0.195*
O5	2.974	2.92	*-0.05*	-6.761	-6.833	*-0.072*
O5	3.044	2.94	*-0.10*	-5.713	-5.814	*-0.101*
H8	2.515	2.82	*0.30*	-2.324	-2.02	*0.304*
H9	3.28	3.68	*0.40*	-3.321	-2.796	*0.525*
H10	2.375	2.78	*0.40*	-3.877	-3.12	*0.757*
H11	2.504	2.80	*0.30*	-3.24	-2.828	*0.412*
H12	1.989	2.04	*0.05*	-7.541	-6.935	*0.606*
H20	2.512	2.86	*0.35*	-1.634	-0.797	*0.837*
H21	2.538	2.94	*0.40*	-0.309	0.884	*1.193*
H22	2.43	2.78	*0.35*	-4.092	-3.323	*0.769*
H24	2.012	2.01	*0.00*	-7.342	-6.946	*0.396*
RMSE			***0.211***			***0.527***

Table DSIV. Gas-phase cationic dofetilide (DOFC) – water interactions.

	Water interaction distance (A)			Water interaction energy (kcal/mol)		
	QM	MM	*Difference*	QM	MM	*Difference*
N2	3.237	3.29	*0.05*	-2.26	-1.975	*0.285*
N3	3.148	3.20	*0.05*	-3.155	-2.233	*0.922*
O1	3.086	2.99	*-0.10*	-8.934	-9.013	*-0.079*
O1	2.973	2.92	*-0.05*	-6.092	-6.75	*-0.658*
O1	3.067	2.97	*-0.10*	-7.698	-7.875	*-0.177*
O2	3.037	2.99	*-0.05*	-6.907	-7.176	*-0.269*
O2	3.006	2.96	*-0.05*	-5.22	-5.922	*-0.702*
O2	3.081	2.98	*-0.10*	-4.433	-5.068	*-0.635*
O3	3.114	2.91	*-0.20*	-1.865	-3.155	*-1.290*
O4	7.296	7.30	*0.00*	-0.851	-0.618	*0.233*
O5	4.481	4.88	*0.40*	-3.364	-1.704	*1.660*
O5	3.04	2.94	*-0.10*	-3.51	-4.124	*-0.614*
O5	3.092	2.94	*-0.15*	-3.383	-4.898	*-1.515*
H8	2.529	2.83	*0.30*	-5.074	-4.223	*0.851*
H9	2.839	3.24	*0.40*	-5.555	-3.318	*2.237*
H10	2.356	2.76	*0.40*	-5.84	-4.289	*1.551*
H12	1.981	2.03	*0.05*	-9.487	-7.887	*1.600*
H20	2.331	2.73	*0.40*	-6.588	-4.648	*1.940*
H21	2.356	2.76	*0.40*	-6.025	-3.831	*2.194*
H22	2.207	2.61	*0.40*	-7.815	-5.072	*2.743*
H23	2.298	2.70	*0.40*	-7.732	-5.814	*1.918*
H24	1.943	1.99	*0.05*	-12.94	-10.529	*2.411*
RMSE			***0.246***			***1.443***

Table DSV. Gas-phase zwitterionic moxifloxacin (MOXZ) – water interactions.

	Water interaction distance (A)			Water interaction energy (kcal/mol)		
	QM	MM	Delta	QM	MM	Delta
N3	3.451	3.30	*-0.150*	-6.045	-7.362	*-1.317*
O1	3.013	2.91	*-0.100*	-6.199	-6.409	*-0.21*
O2	2.913	2.86	*-0.050*	-11.398	-13.53	*-2.132*
O3	2.797	2.80	*0.000*	-15.015	-14.01	*1.005*
O4	2.829	2.83	*0.000*	-14.72	-14.64	*0.08*
H1	2.433	2.78	*0.350*	-5.325	-4.465	*0.86*
H2	2.318	2.67	*0.350*	-7.508	-7.329	*0.179*
H3	6.061	6.26	*0.200*	-3.634	-3.073	*0.561*
H4	3.266	3.47	*0.200*	-3.118	-2.912	*0.206*
H5	2.569	2.87	*0.300*	-2.865	-1.924	*0.941*
H6	2.219	2.57	*0.350*	-2.191	-1.147	*1.044*
H7	3.021	3.42	*0.400*	-4.813	-3.817	*0.996*
H8	2.524	2.77	*0.250*	-4.191	-4.296	*-0.105*
H9	2.467	2.82	*0.350*	-4.823	-3.801	*1.022*
H10	2.541	2.84	*0.300*	-4.946	-4.429	*0.517*
H11	3.713	4.11	*0.400*	-4.112	-3.784	*0.328*
H12	2.426	2.78	*0.350*	-5.159	-4.063	*1.096*
H13	2.252	2.65	*0.400*	-8.578	-7.249	*1.329*
H14	2.33	2.73	*0.400*	-7.392	-6.804	*0.588*
H16	2.477	2.78	*0.300*	-4.51	-3.864	*0.646*
H17	2.331	2.73	*0.400*	-9.584	-8.85	*0.734*
H18	0.282	0.68	*0.400*	0.587	1.797	*1.21*
H19	2.936	3.04	*0.100*	-0.2	-0.037	*0.163*
H21	2.613	2.91	*0.300*	-1.411	-0.59	*0.821*
H22	2.784	2.93	*0.150*	-2.16	-1.418	*0.742*
H23	2.504	2.85	*0.350*	-2.829	-2.334	*0.495*
H24	1.871	1.97	*0.100*	-17.35	-17.13	*0.22*
RMSE			***0.290***			***0.864***

Table DSVI. Gas-phase cationic moxifloxacin (MOXC) – water interactions.

	Water interaction distance (A)			Water interaction energy (kcal/mol)		
	QM	MM	Delta	QM	MM	Delta
N3	3.811	3.41	*-0.400*	-1.131	-2.43	*-1.296*
O1	3.087	3.09	*0.000*	-2.324	-2.64	*-0.315*
O2	4.746	4.35	*-0.400*	-2.647	-3.07	*-0.418*
O2	3.723	3.52	*-0.200*	-5.188	-6.24	*-1.053*
O2	3.023	2.92	*-0.100*	-6.031	-7.03	*-0.994*
O3	3.133	3.08	*-0.050*	-4.107	-4.92	*-0.813*
O4	3.091	2.99	*-0.100*	-9.64	-9.60	*0.037*
O4	3.09	2.99	*-0.100*	-5.311	-5.88	*-0.564*
O4	3.074	2.92	*-0.150*	-5.62	-6.89	*-1.273*
H1	2.39	2.74	*0.350*	-7.217	-6.61	*0.608*
H2	2.266	2.67	*0.400*	-9.652	-8.86	*0.796*
H4	2.647	2.85	*0.200*	-6.009	-5.27	*0.742*
H5	2.454	2.80	*0.350*	-5.801	-3.81	*1.987*
H6	2.196	2.55	*0.350*	-4.854	-3.32	*1.536*
H7	2.91	3.31	*0.400*	-6.713	-4.76	*1.949*
H8	2.499	2.75	*0.250*	-6.254	-6.30	*-0.048*
H9	2.418	2.77	*0.350*	-6.332	-5.37	*0.958*
H10	2.468	2.77	*0.300*	-6.686	-6.15	*0.541*
H11	3.267	3.67	*0.400*	-4.74	-3.21	*1.531*
H12	2.36	2.76	*0.400*	-6.914	-5.60	*1.314*
H13	2.238	2.64	*0.400*	-9.438	-8.12	*1.321*
H14	2.285	2.69	*0.400*	-9.318	-8.51	*0.805*
H16	2.436	2.74	*0.300*	-6.831	-6.08	*0.755*
H17	2.325	2.73	*0.400*	-9.275	-8.39	*0.883*
H18	2.213	2.56	*0.350*	-7.808	-6.02	*1.792*
H19	2.443	2.84	*0.400*	-3.756	-2.358	*1.398*
H21	2.437	2.84	*0.400*	-4.805	-2.951	*1.854*
H22	2.634	2.93	*0.300*	-5.4	-3.401	*1.999*
H23	2.488	2.89	*0.400*	-4.997	-4.293	*0.704*
H24	1.87	1.97	*0.100*	-18.08	-17.68	*0.400*
H25	1.999	1.95	*-0.050*	-7.705	-8.912	*-1.207*
RMSE			***0.312***			***1.165***

Table DSVII. Gas-phase neutral moxifloxacin (MOX0) – water interactions.

	Water interaction distance (A)			Water interaction energy (kcal/mol)		
	QM	MM	Delta	QM	MM	Delta
N3	5.521	5.271	*-0.25*	-0.197	-0.79	*-0.595*
O1	5.114	5.014	*-0.1*	-1.026	-1.23	*-0.203*
O2	4.489	4.889	*0.4*	-1.315	-0.85	*0.466*
O2	4.481	4.481	*0*	-6.081	-5.58	*0.501*
O2	2.972	2.922	*-0.05*	-7.7	-7.78	*-0.075*
O3	5.118	4.718	*-0.4*	-1.264	-1.61	*-0.346*
O4	2.914	2.864	*-0.05*	-7.85	-7.29	*0.563*
O4	4.218	4.268	*0.05*	-7.061	-6.27	*0.787*
O4	3.011	2.911	*-0.1*	-7.089	-7.37	*-0.284*
H1	2.686	2.936	*0.25*	-1.424	-0.77	*0.658*
H2	2.662	2.862	*0.2*	-1.862	-1.41	*0.454*
H3	1.852	1.952	*0.1*	-8.475	-8.02	*0.453*
H4	2.255	2.305	*0.05*	-3.717	-3.67	*0.052*
H5	2.604	2.854	*0.25*	-1.395	-0.97	*0.428*
H6	2.649	2.849	*0.2*	-1.719	-1.25	*0.465*
H7	3.884	4.134	*0.25*	-2.494	-1.88	*0.614*
H8	2.812	2.862	*0.05*	-2.287	-2.35	*-0.061*
H9	2.788	2.888	*0.1*	-1.467	-1.34	*0.130*
H11	2.394	2.794	*0.4*	-3.805	-3.16	*0.641*
H12	2.783	2.983	*0.2*	-0.842	-0.35	*0.494*
H13	2.846	2.896	*0.05*	-1.231	-1.47	*-0.239*
H14	2.615	2.915	*0.3*	-2.14	-1.60	*0.545*
H17	2.644	2.894	*0.250*	-2.027	-1.544	*0.483*
H19	2.766	2.916	*0.15*	-1.304	-1.354	*-0.050*
H20	2.36	2.71	*0.35*	-2.321	-1.977	*0.344*
H21	2.24	2.54	*0.3*	-1.66	-1.432	*0.228*
H22	2.553	2.903	*0.35*	-2.51	-1.555	*0.955*
H24	2.593	2.943	*0.35*	-3.35	-2.661	*0.689*
RMSE			***0.225***			***0.475***

Table DSVIII. Optimized force field topology and parameters for cationic **dofetilide**

Topology file: top_dof1.rtf

```
* Initial topologies generated by
* CHARMM General Force Field (CGenFF) program version 1.0.0
* For use with CGenFF version 3.0.1
36 1

! "penalty" is the highest penalty score of the associated parameters.
! Penalties lower than 10 indicate the analogy is fair; penalties between 10
! and 50 mean some basic validation is recommended; penalties higher than
! 50 indicate poor analogy and mandate extensive validation/optimization.

!============================================================
! Dofetilide(+)
!============================================================


RESI DOF1       1.000
GROUP             ! CHARGE   CH_PENALTY
ATOM C1     CG334   0.149
ATOM N1     NG3P1  -0.006
ATOM C2     CG324  -0.495
ATOM C3     CG321  -0.250
ATOM C4     CG2R61  0.310
ATOM C5     CG2R61 -0.115 !    8.929
ATOM C6     CG2R61 -0.111 !    0.000
ATOM C7     CG2R61  0.219 !    0.000
ATOM C8     CG2R61 -0.111 !    0.000
ATOM C9     CG2R61 -0.115 !    8.929
ATOM N2     NG311  -0.466 !    0.000
ATOM S1     SG3O2   0.439 !    0.000
ATOM O1     OG2P1  -0.384 !    0.000
ATOM O2     OG2P1  -0.384 !    0.000
ATOM C10    CG331  -0.019 !    0.000
ATOM C11    CG324   0.162 !    1.152
ATOM C12    CG321  -0.014 !    1.152
ATOM O3     OG301  -0.391 !    0.861
ATOM C13    CG2R61  0.219 !    0.850
ATOM C14    CG2R61 -0.113 !    0.000
ATOM C15    CG2R61 -0.115 !    0.000
ATOM C16    CG2R61  0.219 !    0.000
ATOM C17    CG2R61 -0.115 !    0.000
ATOM C18    CG2R61 -0.113 !    0.000
ATOM N3     NG311  -0.466 !    0.000
ATOM S2     SG3O2   0.439 !    0.000
ATOM O4     OG2P1  -0.384 !    0.000
```

```
ATOM O5     OG2P1  -0.384 !    0.000
ATOM C19    CG331  -0.019 !    0.000
ATOM H1     HGA3    0.090 !    0.000
ATOM H2     HGA3    0.090 !    0.000
ATOM H3     HGA3    0.090 !    0.000
ATOM H4     HGA2    0.090 !    2.455
ATOM H5     HGA2    0.090 !    2.455
ATOM H6     HGA2    0.090 !    0.000
ATOM H7     HGA2    0.090 !    0.000
ATOM H8     HGR61   0.115 !    0.000
ATOM H9     HGR61   0.115 !    0.000
ATOM H10    HGR61   0.115 !    0.000
ATOM H11    HGR61   0.115 !    0.000
ATOM H12    HGP1    0.323 !    0.000
ATOM H13    HGA3    0.090 !    0.000
ATOM H14    HGA3    0.090 !    0.000
ATOM H15    HGA3    0.090 !    0.000
ATOM H16    HGA2    0.090 !    0.075
ATOM H17    HGA2    0.090 !    0.075
ATOM H18    HGA2    0.090 !    0.000
ATOM H19    HGA2    0.090 !    0.000
ATOM H20    HGR61   0.115 !    0.000
ATOM H21    HGR61   0.115 !    0.000
ATOM H22    HGR61   0.115 !    0.000
ATOM H23    HGR61   0.115 !    0.000
ATOM H24    HGP1    0.323 !    0.000
ATOM H25    HGA3    0.090 !    0.000
ATOM H26    HGA3    0.090 !    0.000
ATOM H27    HGA3    0.090 !    0.000
ATOM HN     HGP2    0.318 !    0.000

BOND C1   N1
BOND C1   H1
BOND C1   H2
BOND C1   H3
BOND N1   C2
BOND N1   C11
BOND N1   HN
BOND C2   C3
BOND C2   H4
BOND C2   H5
BOND C3   C4
BOND C3   H6
BOND C3   H7
BOND C4   C9
BOND C4   C5
BOND C5   C6
BOND C5   H8
BOND C6   C7
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```
BOND C6   H9
BOND C7   C8
BOND C7   N2
BOND C8   C9
BOND C8   H10
BOND C9   H11
BOND N2   S1
BOND N2   H12
BOND S1   O1
BOND S1   O2
BOND S1   C10
BOND C10  H13
BOND C10  H14
BOND C10  H15
BOND C11  C12
BOND C11  H16
BOND C11  H17
BOND C12  O3
BOND C12  H18
BOND C12  H19
BOND O3   C13
BOND C13  C18
BOND C13  C14
BOND C14  C15
BOND C14  H20
BOND C15  C16
BOND C15  H21
BOND C16  C17
BOND C16  N3
BOND C17  C18
BOND C17  H22
BOND C18  H23
BOND N3   S2
BOND N3   H24
BOND S2   O4
BOND S2   O5
BOND S2   C19
BOND C19  H25
BOND C19  H26
BOND C19  H27

END
```

Parameter file: par_dof1.prm

```
* Initial parameters generated by analogy by
```

```
* CHARMM General Force Field (CGenFF) program version 1.0.0
* For use with CGenFF version 3.0.1

! Penalties lower than 10 indicate the analogy is fair; penalties between 10
! and 50 mean some basic validation is recommended; penalties higher than
! 50 indicate poor analogy and mandate extensive validation/optimization.

!============================================================
! Dofetilide(+)
!============================================================

BONDS

ANGLES
CG2R61 CG321  CG324    51.80    107.50 ! ZINC00 , from CG2R61 CG321 CG314, penalty= 0.6
CG324  CG321  OG301    75.70    110.10 ! ZINC00 , from CG324 CG321 OG302, penalty= 0.5

DIHEDRALS
CG2R61 CG2R61 CG321   CG324        0.2300   2    180.00 ! ZINC00 , from CG2R61 CG2R61 CG321 CG314,
penalty= 0.6
CG2R61 CG321   CG324   NG3P1       0.2000   3      0.00 ! ZINC00 , from NG3P3 CG314 CG321 CG2R61,
penalty= 5.5
CG2R61 CG321   CG324   HGA2         0.0400   3      0.00 ! ZINC00 , from CG2R61 CG321 CG321 HGA2,
penalty= 1
OG301   CG321   CG324   NG3P1        3.3000   1    180.00 ! ZINC00 , from OG302 CG321 CG324 NG3P0,
penalty= 1.7
OG301   CG321   CG324   NG3P1       -0.4000   3    180.00 ! ZINC00 , from OG302 CG321 CG324 NG3P0,
penalty= 1.7
OG301   CG321   CG324   HGA2         0.1900   3      0.00 ! ZINC00 , from OG301 CG321 CG321 HGA2,
penalty= 1
CG324  CG321  OG301  CG2R61     2.9990  1   180.00
CG324  CG321  OG301  CG2R61     2.4130  2   180.00
CG324  CG321  OG301  CG2R61     2.3380  3     0.00
```

Table DSIX. Optimized force field topology and parameters for neutral dofetilide

Topology file: top_dof0.rtf

```
* Initial topologies generated by
* CHARMM General Force Field (CGenFF) program version 1.0.0
* For use with CGenFF version 3.0.1
36 1

! "penalty" is the highest penalty score of the associated parameters.
! Penalties lower than 10 indicate the analogy is fair; penalties between 10
! and 50 mean some basic validation is recommended; penalties higher than
! 50 indicate poor analogy and mandate extensive validation/optimization.

!============================================================
! Dofetilide(0)
!============================================================


RESI DOF0       0.000
GROUP             ! CHARGE   CH_PENALTY
ATOM C1     CG331  -0.392
ATOM N1     NG301  -0.401
ATOM C2     CG321   0.240
ATOM C3     CG321  -0.559
ATOM C4     CG2R61  0.296
ATOM C5     CG2R61 -0.115 !    0.000
ATOM C6     CG2R61 -0.111 !    0.000
ATOM C7     CG2R61  0.219 !    0.000
ATOM C8     CG2R61 -0.111 !    0.000
ATOM C9     CG2R61 -0.115 !    0.000
ATOM N2     NG311  -0.466 !    0.000
ATOM S1     SG3O2   0.439 !    0.000
ATOM O1     OG2P1  -0.384 !    0.000
ATOM O2     OG2P1  -0.384 !    0.000
ATOM C10    CG331  -0.019 !    0.000
ATOM C11    CG321   0.010
ATOM C12    CG321  -0.021 !    6.242
ATOM O3     OG301  -0.390 !    1.650
ATOM C13    CG2R61  0.219 !    0.000
ATOM C14    CG2R61 -0.113 !    0.000
ATOM C15    CG2R61 -0.115 !    0.000
ATOM C16    CG2R61  0.219 !    0.000
ATOM C17    CG2R61 -0.115 !    0.000
ATOM C18    CG2R61 -0.113 !    0.000
ATOM N3     NG311  -0.466 !    0.000
```

```
ATOM S2     SG3O2   0.439 !    0.000
ATOM O4     OG2P1  -0.384 !    0.000
ATOM O5     OG2P1  -0.384 !    0.000
ATOM C19    CG331  -0.019 !    0.000
ATOM H1     HGA3    0.090 !    3.536
ATOM H2     HGA3    0.090 !    3.536
ATOM H3     HGA3    0.090 !    3.536
ATOM H4     HGA2    0.090 !    3.536
ATOM H5     HGA2    0.090 !    3.536
ATOM H6     HGA2    0.090 !    0.480
ATOM H7     HGA2    0.090 !    0.480
ATOM H8     HGR61   0.115 !    0.000
ATOM H9     HGR61   0.115 !    0.000
ATOM H10    HGR61   0.115 !    0.000
ATOM H11    HGR61   0.115 !    0.000
ATOM H12    HGP1    0.323 !    0.000
ATOM H13    HGA3    0.090 !    0.000
ATOM H14    HGA3    0.090 !    0.000
ATOM H15    HGA3    0.090 !    0.000
ATOM H16    HGA2    0.090 !    3.536
ATOM H17    HGA2    0.090 !    3.536
ATOM H18    HGA2    0.090 !    0.480
ATOM H19    HGA2    0.090 !    0.480
ATOM H20    HGR61   0.115 !    0.000
ATOM H21    HGR61   0.115 !    0.000
ATOM H22    HGR61   0.115 !    0.000
ATOM H23    HGR61   0.115 !    0.000
ATOM H24    HGP1    0.323 !    0.000
ATOM H25    HGA3    0.090 !    0.000
ATOM H26    HGA3    0.090 !    0.000
ATOM H27    HGA3    0.090 !    0.000

BOND C1   N1
BOND C1   H1
BOND C1   H2
BOND C1   H3
BOND N1   C2
BOND N1   C11
BOND C2   C3
BOND C2   H4
BOND C2   H5
BOND C3   C4
BOND C3   H6
BOND C3   H7
BOND C4   C9
BOND C4   C5
BOND C5   C6
BOND C5   H8
BOND C6   C7
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BOND C6   H9
BOND C7   C8
BOND C7   N2
BOND C8   C9
BOND C8   H10
BOND C9   H11
BOND N2   S1
BOND N2   H12
BOND S1   O1
BOND S1   O2
BOND S1   C10
BOND C10  H13
BOND C10  H14
BOND C10  H15
BOND C11  C12
BOND C11  H16
BOND C11  H17
BOND C12  O3
BOND C12  H18
BOND C12  H19
BOND O3   C13
BOND C13  C18
BOND C13  C14
BOND C14  C15
BOND C14  H20
BOND C15  C16
BOND C15  H21
BOND C16  C17
BOND C16  N3
BOND C17  C18
BOND C17  H22
BOND C18  H23
BOND N3   S2
BOND N3   H24
BOND S2   O4
BOND S2   O5
BOND S2   C19
BOND C19  H25
BOND C19  H26
BOND C19  H27

END
```

Parameter file: par_dof0.prm

```
* Initial parameters generated by analogy by
* CHARMM General Force Field (CGenFF) program version 1.0.0
* For use with CGenFF version 3.0.1

! Penalties lower than 10 indicate the analogy is fair; penalties between 10
! and 50 mean some basic validation is recommended; penalties higher than
! 50 indicate poor analogy and mandate extensive validation/optimization.

BONDS
CG321  NG301   263.00     1.4740 ! ZINC00 , from CG321 NG311, penalty= 5
CG331  NG301   255.00     1.4630 ! ZINC00 , from CG331 NG311, penalty= 5

ANGLES
CG321  CG321  NG301    43.70    112.20 ! ZINC00 , from CG331 CG321 NG311, penalty= 1.5
NG301   CG321   HGA2       32.40     109.50    50.00    2.13000 ! ZINC00 , from NG311 CG321 HGA2,
penalty= 0.6
NG301   CG331   HGA3       30.50     109.70    50.00    2.14000 ! ZINC00 , from NG311 CG331 HGA3,
penalty= 0.6
CG321  NG301  CG321    42.452   104.717
CG321  NG301  CG331    59.281   106.264

DIHEDRALS
CG2R61 CG321  CG321  NG301      0.3650  3     0.00
NG301  CG321  CG321  OG301      3.0000  1   180.00
NG301  CG321  CG321  OG301      0.9850  2     0.00
NG301   CG321   CG321   HGA2         0.1600   3       0.00 ! ZINC00 , from NG311 CG321 CG331 HGA3,
penalty= 6.6
CG321  CG321  NG301  CG321      1.7910  1     0.00
CG321  CG321  NG301  CG321      0.7430  2     0.00
CG321  CG321  NG301  CG321      0.1570  3     0.00
CG321  CG321  NG301  CG331      0.5940  1     0.00
CG321  CG321  NG301  CG331      0.1350  2     0.00
CG321  CG321  NG301  CG331      1.0280  3     0.00
HGA2   CG321  NG301  CG321      0.3570  3   180.00
HGA2   CG321  NG301  CG331      0.7040  3     0.00
HGA3   CG331  NG301  CG321      0.8520  3   180.00
```

Table DSX. Optimized force field topology and parameters for zwitterionic moxifloxacin (CHARMM stream including CGENFF parameters)

```
* Toppar stream file generated by
*

read rtf card append
* Initial topologies generated by
* CHARMM General Force Field (CGenFF) program version 1.0.0
* For use with CGenFF version 3.0.1
*
36 1

!============================================================
! Moxifloxacin - Zwitterionic
!============================================================

RESI MOX            0.000
GROUP             ! CHARGE   CH_PENALTY
ATOM C1     CG331  -0.100 !    0.025
ATOM O1     OG301  -0.391 !    2.180
ATOM C2     CG2R61  0.275
ATOM C3     CG2R62  0.296
ATOM C4     CG2R62 -0.386
ATOM C5     CG2R61  0.040 !    6.996
ATOM C6     CG2R66  0.061
ATOM C7     CG2R61  0.278
ATOM N1     NG3C51 -0.690
ATOM C8     CG3C52  0.222
ATOM C9     CG3RC1 -0.216
ATOM H1     HGA1    0.090 !    2.316
ATOM C10    CG321  -0.190 !    5.785
ATOM C11    CG321  -0.177 !    5.331
ATOM C12    CG324   0.127
ATOM N2     NG3P2  -0.409
ATOM C13    CG3RC1  0.342
ATOM H2     HGA1    0.090
ATOM C14    CG3C52 -0.045
ATOM F1     FGR1   -0.258
ATOM C15    CG2R63  0.469
ATOM O2     OG2D4  -0.609
ATOM C16    CG2R62 -0.203
ATOM C17    CG2R62  0.187
ATOM N3     NG2R61 -0.410
ATOM C18    CG3C31  0.092
ATOM C19    CG3C31 -0.180 !    7.029
ATOM C20    CG3C31 -0.180 !    7.029
ATOM C21    CG2O3   0.805
ATOM O3     OG2D2  -0.760 !    0.528
ATOM O4     OG2D2  -0.760 !    0.528
ATOM H3     HGA3    0.090 !    0.000
ATOM H4     HGA3    0.090 !    0.000
ATOM H5     HGA3    0.090 !    0.000
ATOM H6     HGR62   0.177 !    0.253
ATOM H7     HGA2    0.090 !    1.375
```

```
ATOM H8     HGA2    0.090 !    1.375
ATOM H9     HGA2    0.090 !    0.000
ATOM H10    HGA2    0.090 !    0.000
ATOM H11    HGA2    0.090 !    0.000
ATOM H12    HGA2    0.090 !    0.000
ATOM H13    HGA2    0.090 !    0.975
ATOM H14    HGA2    0.090 !    0.975
ATOM H15    HGP2    0.341
ATOM H16    HGA2    0.090 !    2.637
ATOM H17    HGA2    0.090 !    2.637
ATOM H18    HGR62   0.111 !    6.687
ATOM H19    HGA1    0.090 !    4.940
ATOM H20    HGA2    0.090 !    2.500
ATOM H21    HGA2    0.090 !    2.500
ATOM H22    HGA2    0.090 !    2.500
ATOM H23    HGA2    0.090 !    2.500
ATOM H24    HGP2    0.341

BOND C1   O1
BOND C1   H3
BOND C1   H4
BOND C1   H5
BOND O1   C2
BOND C2   C7
BOND C2   C3
BOND C3   N3
BOND C3   C4
BOND C4   C5
BOND C4   C15
BOND C5   C6
BOND C5   H6
BOND C6   C7
BOND C6   F1
BOND C7   N1
BOND N1   C14
BOND N1   C8
BOND C8   C9
BOND C8   H7
BOND C8   H8
BOND C9   H1
BOND C9   C13
BOND C9   C10
BOND C10  C11
BOND C10  H9
BOND C10  H10
BOND C11  C12
BOND C11  H11
BOND C11  H12
BOND C12  N2
BOND C12  H13
BOND C12  H14
BOND N2   C13
BOND N2   H15
BOND N2   H24
BOND C13  H2
BOND C13  C14
```

```
BOND C14  H16
BOND C14  H17
BOND C15  O2
BOND C15  C16
BOND C16  C17
BOND C16  C21
BOND C17  N3
BOND C17  H18
BOND N3   C18
BOND C18  C20
BOND C18  C19
BOND C18  H19
BOND C19  C20
BOND C19  H20
BOND C19  H21
BOND C20  H22
BOND C20  H23
BOND C21  O3
BOND C21  O4
IMPR C15    C4     C16    O2
IMPR C21    O4     O3     C16

END

read param card flex append
* Parameters generated by analogy by
* CHARMM General Force Field (CGenFF) program version 2.2.0
*

! Penalties lower than 10 indicate the analogy is fair; penalties between 10
! and 50 mean some basic validation is recommended; penalties higher than
! 50 indicate poor analogy and mandate extensive validation/optimization.

BONDS
CG2O3  CG2R62  200.00     1.5000 ! ****** , from CG2O3 CG2R61, PENALTY= 5
CG2O3  OG2D2   525.00     1.2600 ! PROT adm jr. 7/23/91, acetic acid
CG2R61 CG2R61  305.00     1.3750 ! PROT benzene, JES 8/25/89
CG2R61 CG2R62  394.00     1.3750 ! YTHY, 2,4(1H,3H)-quinazolinedione, isg
CG2R61 CG2R66  305.00     1.3700 ! NAMODEL difluorotoluene
CG2R61 NG3C51  406.429    1.370
CG2R61 OG301   230.00     1.3820 ! COMPDS peml
CG2R61 HGR62   340.00     1.0800 ! NA, DFT
CG2R62 CG2R62  420.00     1.3500 ! NA nad/ppi, jjp1/adm jr. 7/95
CG2R62 CG2R63  302.00     1.4030 ! NA T, adm jr. 11/97
CG2R62 NG2R61  302.00     1.3430 ! NA C, adm jr. 11/97
CG2R62 HGR62   350.00     1.0900 ! NA C,U, JWK
CG2R63 OG2D4   660.00     1.2340 ! NA U,A,G par_a4 adm jr. 10/2/91
CG2R66 FGR1    400.00     1.3580 ! NAMODEL difluorotoluene
CG321  CG321   222.50     1.5300 ! PROT alkane update, adm jr., 3/2/92
CG321  CG324   222.50     1.5300 ! FLAVOP PIP1,2,3
CG321  CG3RC1  222.50     1.5240 ! CARBOCY carbocyclic sugars
CG321  HGA2    309.00     1.1110 ! PROT alkane update, adm jr., 3/2/92
CG324  NG3P2   200.00     1.4900 ! PIP, piperidine
CG324  HGA2    284.50     1.1000 ! FLAVOP PIP1,2,3
CG331  OG301   360.00     1.4150 ! diethylether, alex
CG331  HGA3    322.00     1.1110 ! PROT alkane update, adm jr., 3/2/92
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CG3C31 CG3C31  240.00     1.5010 ! PROTMOD cyclopropane
CG3C31 NG2R61  352.828    1.448
CG3C31 HGA1    340.00     1.0830 ! PROTMOD cyclopropane
CG3C31 HGA2    340.00     1.0830 ! PROTMOD cyclopropane
CG3C52 CG3RC1  222.50     1.5240 ! CARBOCY carbocyclic sugars
CG3C52 NG3C51  400.00     1.4780 ! PRLD, pyrrolidine; 2PRL, 2-pyrroline, kevo
CG3C52 HGA2    307.00     1.1000 ! THF, THF neutron diffr., 5/30/06, viv
CG3RC1 CG3RC1  222.50     1.5230 ! CARBOCY carbocyclic sugars
CG3RC1 NG3P2   164.854    1.497
CG3RC1 HGA1    309.00     1.1110 ! CARBOCY carbocyclic sugars
NG3P2  HGP2    460.00     1.0060 ! PROT AcProNH2, ProNH2, AcProNHCH3 RLD 4/23/93

ANGLES
CG2R62 CG2O3  OG2D2    40.00    116.00   50.00   2.35300 ! ****** , from CG2R61 CG2O3 OG2D2, PENALTY= 0.5
OG2D2  CG2O3  OG2D2   100.00    128.00   70.00   2.25870 ! PROT adm jr. 7/23/91, correction, ACETATE (KK)
CG2R61 CG2R61 CG2R62   40.00    119.00   35.00   2.41620 ! YTHY, 2,4(1H,3H)-quinazolinedione, isg
CG2R61 CG2R61 CG2R66   40.00    119.00   35.00   2.41620 ! NAMODEL difluorotoluene
CG2R61 CG2R61 NG3C51   40.00    120.00 ! ****** , from CG2R61 CG2R61 NG311, PENALTY= 3
CG2R61 CG2R61 OG301   110.00    120.00 ! BIPHENYL ANALOGS, peml
CG2R62 CG2R61 CG2R66   40.00    119.00   35.00   2.41620 ! ****** , from CG2R61 CG2R61 CG2R66, PENALTY= 0.5
CG2R62 CG2R61 OG301   110.00    120.00 ! ****** , from CG2R61 CG2R61 OG301, PENALTY= 0.5
CG2R62 CG2R61 HGR62    30.00    120.00   22.00   2.15250 ! ****** , from CG2R61 CG2R61 HGR62, PENALTY= 0.5
CG2R66 CG2R61 NG3C51   40.00    120.00 ! ****** , from CG2R61 CG2R61 NG311, PENALTY= 4.5
CG2R66 CG2R61 HGR62    30.00    121.50   22.00   2.15250 ! NAMODEL difluorotoluene
CG2O3  CG2R62 CG2R62   45.00    119.00 ! ****** , from CG2O3 CG2R61 CG2R61, PENALTY= 5.5
CG2O3  CG2R62 CG2R63   45.00    119.00 ! ****** , from CG2O3 CG2R61 CG2R61, PENALTY= 8
CG2R61 CG2R62 CG2R62   40.00    121.00 ! RIN, coumarin, isg
CG2R61 CG2R62 CG2R63  120.00    122.30 ! YTHY, 2,4(1H,3H)-quinazolinedione, isg
CG2R61 CG2R62 NG2R61   23.00    116.10 ! YTHY, 2,4(1H,3H)-quinazolinedione, isg
CG2R62 CG2R62 CG2R63  120.00    116.70 ! NA T
CG2R62 CG2R62 NG2R61   85.00    122.90 ! NA C
CG2R62 CG2R62 HGR62    42.00    119.00 ! NA nadh/ppi, jjp1/adm jr. 7/95
NG2R61 CG2R62 HGR62    44.00    115.00 ! NA C, h6
CG2R62 CG2R63 CG2R62   10.00    120.80 ! 4PYO, 4(1H)-pyridinone; from CG2R62 CG2R62 CG2R62; isg
CG2R62 CG2R63 OG2D4   100.00    124.60 ! NA T, o4
CG2R61 CG2R66 CG2R61   40.00    122.50   35.00   2.41620 ! NAMODEL difluorotoluene
CG2R61 CG2R66 FGR1     60.00    118.75 ! NAMODEL difluorotoluene
CG321  CG321  CG324    58.35    110.50   11.16   2.56100 ! FLAVOP PIP1,2,3
CG321  CG321  CG3RC1   53.35    111.00    8.00   2.56100 ! CARBOCY carbocyclic sugars
CG321  CG321  HGA2     26.50    110.10   22.53   2.17900 ! PROT alkane update, adm jr., 3/2/92
CG324  CG321  HGA2     26.50    110.10   22.53   2.17900 ! FLAVOP PIP1,2,3
CG3RC1 CG321  HGA2     34.50    110.10   22.53   2.17900 ! CARBOCY carbocyclic sugars
HGA2   CG321  HGA2     35.50    109.00    5.40   1.80200 ! PROT alkane update, adm jr., 3/2/92
CG321  CG324  NG3P2    40.00    110.00 ! PIP, piperidine
CG321  CG324  HGA2     26.50    111.80   22.53   2.17900 ! FLAVOP PIP1,2,3
NG3P2  CG324  HGA2     45.00    102.30   35.00   2.10100 ! PIP, piperidine
HGA2   CG324  HGA2     35.50    109.00    5.40   1.80200 ! PIP1,2,3
OG301  CG331  HGA3     45.90    108.89 ! MEOB, Methoxybenzene, cacha
HGA3   CG331  HGA3     35.50    108.40    5.40   1.80200 ! PROT alkane update, adm jr., 3/2/92
CG3C31 CG3C31 CG3C31   77.35    111.00    8.00   2.56100 ! PROTMOD cyclopropane
CG3C31 CG3C31 NG2R61   30.184   117.044
CG3C31 CG3C31 HGA1     23.00    117.10   22.53   2.17900 ! PROTMOD cyclopropane
CG3C31 CG3C31 HGA2     23.00    117.10   22.53   2.17900 ! PROTMOD cyclopropane
NG2R61 CG3C31 HGA1     75.892   114.188
HGA2   CG3C31 HGA2     23.00    117.00    5.40   1.80200 ! PROTMOD cyclopropane
CG3RC1 CG3C52 NG3C51   84.00    107.60 ! ****** , from CG3C52 CG3C52 NG3C51, PENALTY= 1.1
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CG3RC1 CG3C52 HGA2     34.50    110.10   22.53   2.17900 ! CARBOCY carbocyclic sugars
NG3C51 CG3C52 HGA2       54.00     109.00 !v 107.7 PRLD, pyrrolidine; 110.8 2PRL, 2-pyrroline; 110.4 3PRL, 3-
pyrroline; 111.4 2IMI, 2-imidazoline; 111.7 2PRZ, 2-pyrazoline, kevo
HGA2   CG3C52 HGA2     38.50    106.80    5.40   1.80200 ! THF, 10/17/05 viv
CG321  CG3RC1 CG3C52   58.35    113.50   11.16   2.56100 ! BAM1, bile acid steroidal C-D ring, cacha, 02/08
CG321  CG3RC1 CG3RC1   53.35    111.00    8.00   2.56100 ! CARBOCY carbocyclic sugars
CG321  CG3RC1 HGA1     34.50    110.10   22.53   2.17900 ! CARBOCY carbocyclic sugars
CG3C52 CG3RC1 CG3RC1   53.35    111.00    8.00   2.56100 ! CARBOCY carbocyclic sugars
CG3C52 CG3RC1 NG3P2   162.274   108.021
CG3C52 CG3RC1 HGA1     34.50    110.10   22.53   2.17900 ! CARBOCY carbocyclic sugars
CG3RC1 CG3RC1 NG3P2    97.279   109.977  8.00     2.5610
CG3RC1 CG3RC1 HGA1     34.50    110.10   22.53   2.17900 ! CARBOCY carbocyclic sugars
NG3P2  CG3RC1 HGA1    105.536   105.525
CG2R62 NG2R61 CG2R62   30.00    120.00 ! NA nad/ppi, jjp1/adm jr. 7/95
CG2R62 NG2R61 CG3C31   45.00    118.40 ! ****** , from CG2R62 NG2R61 CG3C51, PENALTY= 6.9
CG2R61 NG3C51 CG3C52   93.282   116.898
CG3C52 NG3C51 CG3C52  140.00    103.70 !v 102.9 PRLD, pyrrolidine; 105.4 3PRL, 3-pyrroline, kevo
CG324  NG3P2  CG3RC1   26.558   115.625
CG324  NG3P2  HGP2     30.00    110.80   27.00   2.07400 ! PIP, piperidine
CG3RC1 NG3P2  HGP2     97.752   110.057  27.00    2.0740
HGP2   NG3P2  HGP2     51.00    107.50 ! PROT AcProNH2, ProNH2, AcProNHCH3 RLD 4/23/93
CG2R61 OG301  CG331    65.00    108.00 ! MEOB, Methoxybenzene, cacha

DIHEDRALS
OG2D2  CG2O3  CG2R62 CG2R62     3.1000  2   180.00 ! ****** , from OG2D2 CG2O3 CG2R61 CG2R61, PENALTY= 5.5
OG2D2  CG2O3  CG2R62 CG2R63     3.1000  2   180.00 ! ****** , from OG2D2 CG2O3 CG2R61 CG2R61, PENALTY= 8
CG2R62 CG2R61 CG2R61 CG2R66     3.1000  2   180.00 ! ****** , from CG2R61 CG2R61 CG2R61 CG2R66, PENALTY= 0.5
CG2R62 CG2R61 CG2R61 NG3C51     3.1000  2   180.00 ! ****** , from CG2R61 CG2R61 CG2R61 NG311, PENALTY= 3.5
CG2R66 CG2R61 CG2R61 OG301      3.1000  2   180.00 ! ****** , from CG2R61 CG2R61 CG2R61 OG301, PENALTY= 1.5
NG3C51 CG2R61 CG2R61 OG301      2.4440  2   180.00
CG2R61 CG2R61 CG2R62 CG2R62     0.5000  2   180.00 ! RIN, coumarin, isg
CG2R61 CG2R61 CG2R62 NG2R61     7.0000  2   180.00 ! YTHY, 2,4(1H,3H)-quinazolinedione, isg
CG2R66 CG2R61 CG2R62 CG2R62     0.5000  2   180.00 ! ****** , from CG2R61 CG2R61 CG2R62 CG2R62, PENALTY= 1.5
CG2R66 CG2R61 CG2R62 CG2R63     3.1000  2   180.00 ! ****** , from CG2R61 CG2R61 CG2R62 CG2R63, PENALTY= 1.5
OG301  CG2R61 CG2R62 CG2R62     3.1000  2   180.00 ! ****** , from CG2R61 CG2R61 CG2R61 OG301, PENALTY= 5.5
OG301  CG2R61 CG2R62 NG2R61     2.4000  2   180.00
HGR62  CG2R61 CG2R62 CG2R62     3.1000  2   180.00 ! ****** , from HGR61 CG2R61 CG2R62 CG2R62, PENALTY= 1
HGR62  CG2R61 CG2R62 CG2R63     1.0000  2   180.00 ! ****** , from HGR61 CG2R61 CG2R62 CG2R63, PENALTY= 1
CG2R61 CG2R61 CG2R66 CG2R61     3.1000  2   180.00 ! NAMODEL difluorotoluene
CG2R61 CG2R61 CG2R66 FGR1       4.5000  2   180.00 ! NAMODEL difluorotoluene
CG2R62 CG2R61 CG2R66 CG2R61     3.1000  2   180.00 ! ****** , from CG2R61 CG2R61 CG2R66 CG2R61, PENALTY= 0.5
CG2R62 CG2R61 CG2R66 FGR1       4.5000  2   180.00 ! ****** , from CG2R61 CG2R61 CG2R66 FGR1, PENALTY= 0.5
NG3C51 CG2R61 CG2R66 CG2R61     3.1000  2   180.00 ! ****** , from CG2R61 CG2R61 CG2R61 NG311, PENALTY= 8
NG3C51 CG2R61 CG2R66 FGR1       2.4970  2   180.00
HGR62  CG2R61 CG2R66 CG2R61     4.2000  2   180.00 ! NAMODEL difluorotoluene
HGR62  CG2R61 CG2R66 FGR1       2.4000  2   180.00 ! NAMODEL difluorotoluene
CG2R61 CG2R61 NG3C51 CG3C52     1.3590  2     0.00
CG2R61 CG2R61 NG3C51 CG3C52     2.4490  4     0.00
CG2R66 CG2R61 NG3C51 CG3C52     0.3300  2   180.00
CG2R66 CG2R61 NG3C51 CG3C52     0.2440  4     0.00
CG2R61 CG2R61 OG301  CG331      1.5800  2   180.00 ! MEOB, Methoxybenzene update, yxu
CG2R61 CG2R61 OG301  CG331      0.2000  4   180.00 ! MEOB, Methoxybenzene update, yxu
CG2R62 CG2R61 OG301  CG331      1.5800  2   180.00 ! ****** , from CG2R61 CG2R61 OG301 CG331, PENALTY= 0.5
CG2R62 CG2R61 OG301  CG331      0.2000  4   180.00 ! ****** , from CG2R61 CG2R61 OG301 CG331, PENALTY= 0.5
CG2O3  CG2R62 CG2R62 NG2R61     2.5000  2   180.00 ! ****** , from CG2O1 CG2R62 CG2R62 NG2R61, PENALTY= 7.5
CG2O3  CG2R62 CG2R62 HGR62      1.0000  2   180.00 ! ****** , from CG2O1 CG2R62 CG2R62 HGR63, PENALTY= 9.5
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```
CG2R61 CG2R62 CG2R62 CG2R61     2.5000  2   180.00 ! RIN, coumarin, isg
CG2R61 CG2R62 CG2R62 CG2R63     3.7000  2   180.00 ! YTHY, 2,4(1H,3H)-quinazolinedione, isg
CG2R61 CG2R62 CG2R62 NG2R61     3.5000  2   180.00 ! YTHY, 2,4(1H,3H)-quinazolinedione, isg
CG2R63 CG2R62 CG2R62 NG2R61     3.0000  2   180.00 ! NA T
CG2R63 CG2R62 CG2R62 HGR62      1.0000  2   180.00 ! NA bases
CG2O3  CG2R62 CG2R63 CG2R62     3.0000  2   180.00
CG2O3  CG2R62 CG2R63 OG2D4      2.4980  2   180.00
CG2R61 CG2R62 CG2R63 CG2R62     1.6000  2   180.00 ! ****** , from CG2R62 CG2R62 CG2R63 CG2R62, PENALTY= 1.5
CG2R61 CG2R62 CG2R63 OG2D4      1.0000  2   180.00 ! YTHY, 2,4(1H,3H)-quinazolinedione, isg
CG2R62 CG2R62 CG2R63 CG2R62     1.6000  2   180.00 ! 4PYO, 4(1H)-pyridinone, isg
CG2R62 CG2R62 CG2R63 OG2D4      1.0000  2   180.00 ! NA bases
CG2R61 CG2R62 NG2R61 CG2R62     4.0000  2   180.00 ! ****** , from CG2R67 CG2R62 NG2R61 CG2R62, PENALTY= 0.5
CG2R61 CG2R62 NG2R61 CG3C31    11.0000  2   180.00 ! ****** , from CG2R62 CG2R62 NG2R61 CG3C51, PENALTY= 8.4
CG2R62 CG2R62 NG2R61 CG2R62     4.0000  2   180.00 ! NA nad/ppi, jjp1/adm jr. 7/95
CG2R62 CG2R62 NG2R61 CG3C31    11.0000  2   180.00 ! ****** , from CG2R62 CG2R62 NG2R61 CG3C51, PENALTY= 6.9
HGR62  CG2R62 NG2R61 CG2R62     5.6000  2   180.00 ! 4PYO, 4(1H)-pyridinone, isg
HGR62  CG2R62 NG2R61 CG3C31     0.3000  2   180.00 ! ****** , from HGR62 CG2R62 NG2R61 CG3C51, PENALTY= 6.9
CG324  CG321  CG321  CG3RC1     0.4520  3     0.00
CG324  CG321  CG321  HGA2       0.1950  3     0.00 ! FLAVOP PIP1,2,3
CG3RC1 CG321  CG321  HGA2       0.1950  3     0.00 ! LIPID alkanes
HGA2   CG321  CG321  HGA2       0.2200  3     0.00 ! LIPID alkanes
CG321  CG321  CG324  NG3P2      1.0000  3     0.00 ! PIP, piperidine ! @@@ Kenno: 0.1950 -> 1.0000
CG321  CG321  CG324  HGA2       0.1950  3     0.00 ! FLAVOP PIP1,2,3
HGA2   CG321  CG324  NG3P2      0.1950  3     0.00 ! PIP, piperidine
HGA2   CG321  CG324  HGA2       0.1950  3     0.00 ! FLAVOP PIP1,2,3
CG321  CG321  CG3RC1 CG3C52     0.2000  3     0.00 ! BAM1, bile acid steroidal C-D ring, cacha, 02/08
CG321  CG321  CG3RC1 CG3RC1     0.1500  3     0.00 ! CARBOCY carbocyclic sugars
CG321  CG321  CG3RC1 HGA1       0.1500  3     0.00 ! CARBOCY carbocyclic sugars
HGA2   CG321  CG3RC1 CG3C52     0.1950  1     0.00 ! BAM1, bile acid steroidal C-D ring, cacha, 02/08
HGA2   CG321  CG3RC1 CG3RC1     0.1500  3     0.00 ! CARBOCY carbocyclic sugars
HGA2   CG321  CG3RC1 HGA1       0.1500  3     0.00 ! CARBOCY carbocyclic sugars
CG321  CG324  NG3P2  CG3RC1     0.3190  1   180.00
CG321  CG324  NG3P2  CG3RC1     2.2270  2     0.00
CG321  CG324  NG3P2  CG3RC1     1.4290  3   180.00
CG321  CG324  NG3P2  HGP2       0.1000  3     0.00 ! PIP, piperidine
HGA2   CG324  NG3P2  CG3RC1     1.1970  3     0.00
HGA2   CG324  NG3P2  HGP2       0.1000  3     0.00 ! PIP, piperidine
HGA3   CG331  OG301  CG2R61     0.0850  3     0.00 ! MEOB, Methoxybenzene, cacha
CG3C31 CG3C31 CG3C31 NG2R61     1.2340  3   180.00
CG3C31  CG3C31  CG3C31  HGA1          0.1000   6        0.00  !  AMCP,  aminomethyl  cyclopropane;  from  PROTMOD
hf/cyclopropane; jhs
CG3C31 CG3C31 CG3C31 HGA2       0.1000  6     0.00 ! PROTMOD hf/cyclopropane
NG2R61 CG3C31 CG3C31 HGA2       2.2320  3   180.00
HGA1     CG3C31  CG3C31  HGA2          0.2000   5     180.00  !  AMCP,  aminomethyl  cyclopropane;  from  PROTMOD
hf/cyclopropane; jhs
HGA2   CG3C31 CG3C31 HGA2       0.2000  5   180.00 ! PROTMOD hf/cyclopropane
CG3C31 CG3C31 NG2R61 CG2R62     2.3350  3     0.00
HGA1   CG3C31 NG2R61 CG2R62     2.4770  3     0.00
NG3C51 CG3C52 CG3RC1 CG321      1.5720  3   180.0
NG3C51 CG3C52 CG3RC1 CG3RC1     0.9650  3     0.002
NG3C51 CG3C52 CG3RC1 NG3P2      1.4040  3     0.00
NG3C51 CG3C52 CG3RC1 HGA1       1.0890  3     0.00
HGA2   CG3C52 CG3RC1 CG321      0.1950  1     0.00 ! BAM1, bile acid steroidal C-D ring, cacha, 02/08
HGA2   CG3C52 CG3RC1 CG3RC1     0.1500  3     0.00 ! CARBOCY carbocyclic sugars
HGA2   CG3C52 CG3RC1 NG3P2      2.4440  3     0.00
HGA2   CG3C52 CG3RC1 HGA1       0.1500  3     0.00 ! CARBOCY carbocyclic sugars
```

```
CG3RC1 CG3C52 NG3C51 CG2R61     1.2050  3   180.00
CG3RC1 CG3C52 NG3C51 CG3C52     0.1800  3     0.00 ! ****** , from CG3C52 CG3C52 NG3C51 CG3C52, PENALTY= 1.1
HGA2   CG3C52 NG3C51 CG2R61     1.6800  3     0.00
HGA2   CG3C52 NG3C51 CG3C52     0.0000  3     0.00 ! 3PRL, 3-pyrroline, kevo
CG321  CG3RC1 CG3RC1 CG3C52     0.1500  3     0.00 ! CARBOCY carbocyclic sugars
CG321  CG3RC1 CG3RC1 NG3P2      0.3810  3   180.00
CG321  CG3RC1 CG3RC1 HGA1       0.1500  3     0.00 ! CARBOCY carbocyclic sugars
CG3C52 CG3RC1 CG3RC1 CG3C52     0.1500  3     0.00 ! CARBOCY carbocyclic sugars
CG3C52 CG3RC1 CG3RC1 NG3P2      0.8780  3   180.0
CG3C52 CG3RC1 CG3RC1 HGA1       0.1500  3     0.00 ! CARBOCY carbocyclic sugars
NG3P2  CG3RC1 CG3RC1 HGA1       2.0850  3   180.00
HGA1   CG3RC1 CG3RC1 HGA1       0.1500  3     0.00 ! CARBOCY carbocyclic sugars
CG3C52 CG3RC1 NG3P2  CG324      1.8470  3   180.00
CG3C52 CG3RC1 NG3P2  HGP2       1.3210  3     0.00
CG3RC1 CG3RC1 NG3P2  CG324      0.2800  3   180.00
CG3RC1 CG3RC1 NG3P2  HGP2       1.3090  3     0.00
HGA1   CG3RC1 NG3P2  CG324      0.7100  3     0.00
HGA1   CG3RC1 NG3P2  HGP2       2.4770  3   180.00

IMPROPERS
CG2O3  OG2D2  OG2D2  CG2R62    96.0000  0     0.00 ! ****** , from CG2O3 OG2D2 OG2D2 CG2R61, PENALTY= 0.5
CG2R63 CG2R62 CG2R62 OG2D4     15.0000  0     0.00 ! 4PYO, 4(1H)-pyridinone, isg

END
RETURN
```

Table DSXI. Optimized force field topology and parameters for cationic moxifloxacin (CHARMM stream including CGENFF parameters)

```
* Toppar stream file generated by
*

read rtf card append
* Topologies generated by
* CHARMM General Force Field (CGenFF) program version 2.2.0
*
36 1

!============================================================
! Moxifloxacin - Cationic
!============================================================

RESI MOXC           1.000 !
GROUP             ! CHARGE   CH_PENALTY
ATOM C1     CG331  -0.100 !    0.025
ATOM O1     OG301  -0.391 !    2.180
ATOM C2     CG2R61  0.297
ATOM C3     CG2R62  0.395
ATOM C4     CG2R62 -0.234 !    9.831
ATOM C5     CG2R61  0.021 !    6.574
ATOM C6     CG2R66  0.006
ATOM C7     CG2R61  0.118
ATOM N1     NG3C51 -0.507
ATOM C8     CG3C52  0.169
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ATOM C9     CG3RC1 -0.114
ATOM H1     HGA1    0.090 !    2.316
ATOM C10    CG321  -0.190 !    7.285
ATOM C11    CG321  -0.161
ATOM C12    CG324   0.170
ATOM N2     NG3P2  -0.344
ATOM C13    CG3RC1  0.245
ATOM H2     HGA1    0.090 !    4.911
ATOM C14    CG3C52 -0.026
ATOM F1     FGR1   -0.282
ATOM C15    CG2R63  0.304
ATOM O2     OG2D4  -0.449
ATOM C16    CG2R62  0.118
ATOM C17    CG2R62  0.095 !    8.365
ATOM N3     NG2R61 -0.402
ATOM C18    CG3C31  0.099
ATOM C19    CG3C31 -0.180 !    7.029
ATOM C20    CG3C31 -0.180 !    7.029
ATOM C21    CG2O2   0.320
ATOM O3     OG311  -0.513 !    4.026
ATOM O4     OG2D1  -0.437 !    3.884
ATOM H3     HGA3    0.090 !    0.000
ATOM H4     HGA3    0.090 !    0.000
ATOM H5     HGA3    0.090 !    0.000
ATOM H6     HGR62   0.161 !    0.075
ATOM H7     HGA2    0.090 !    1.375
ATOM H8     HGA2    0.090 !    1.375
ATOM H9     HGA2    0.090 !    0.000
ATOM H10    HGA2    0.090 !    0.000
ATOM H11    HGA2    0.090 !    0.000
ATOM H12    HGA2    0.090 !    0.000
ATOM H13    HGA2    0.090 !    0.975
ATOM H14    HGA2    0.090 !    0.975
ATOM H15    HGP2    0.329
ATOM H16    HGA2    0.090 !    2.637
ATOM H17    HGA2    0.090 !    2.637
ATOM H18    HGR62   0.105 !    4.797
ATOM H19    HGA1    0.090 !    4.940
ATOM H20    HGA2    0.090 !    2.500
ATOM H21    HGA2    0.090 !    2.500
ATOM H22    HGA2    0.090 !    2.500
ATOM H23    HGA2    0.090 !    2.500
ATOM H24    HGP2    0.329
ATOM H25    HGP1    0.429 !    0.219

BOND H23  C20
BOND H7   C8
BOND H8   C8
BOND H9   C10
BOND H4   C1
BOND H6   C5
BOND O2   C15
BOND H11  C11
BOND F1   C6
BOND C5   C6
BOND C5   C4
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```
BOND C8   N1
BOND C8   C9
BOND C20  H22
BOND C20  C19
BOND C20  C18
BOND C6   C7
BOND H12  C11
BOND H20  C19
BOND C15  C4
BOND C15  C16
BOND C4   C3
BOND H3   C1
BOND C11  C10
BOND C11  C12
BOND C10  C9
BOND C10  H10
BOND C7   N1
BOND C7   C2
BOND C1   H5
BOND C1   O1
BOND C19  C18
BOND C19  H21
BOND C3   C2
BOND C3   N3
BOND N1   C14
BOND C2   O1
BOND C9   H1
BOND C9   C13
BOND C16  C17
BOND C16  C21
BOND N3   C18
BOND N3   C17
BOND C18  H19
BOND C17  H18
BOND H15  N2
BOND H25  O3
BOND C21  O3
BOND C21  O4
BOND C12  H13
BOND C12  N2
BOND C12  H14
BOND N2   C13
BOND N2   H24
BOND C14  C13
BOND C14  H16
BOND C14  H17
BOND C13  H2
IMPR C15    C4     C16    O2
IMPR C21    C16    O4     O3

END

read param card flex append
* Parameters generated by analogy by
* CHARMM General Force Field (CGenFF) program version 2.2.0
*
```

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! Penalties lower than 10 indicate the analogy is fair; penalties between 10
! and 50 mean some basic validation is recommended; penalties higher than
! 50 indicate poor analogy and mandate extensive validation/optimization.

BONDS
CG2O2  CG2R62  254.00     1.4800 ! ****** , from CG2O2 CG2R61, PENALTY= 5
CG2O2  OG2D1   750.00     1.2200 ! PROT adm jr. 5/02/91, acetic acid pure solvent; LIPID methyl acetate
CG2O2  OG311   230.00     1.4000 ! PROT adm jr. 5/02/91, acetic acid pure solvent
CG2R61 CG2R61  305.00     1.3750 ! PROT benzene, JES 8/25/89
CG2R61 CG2R62  394.00     1.3750 ! YTHY, 2,4(1H,3H)-quinazolinedione, isg
CG2R61 CG2R66  305.00     1.3700 ! NAMODEL difluorotoluene
CG2R61 NG3C51  406.429    1.370
CG2R61 OG301   230.00     1.3820 ! COMPDS peml
CG2R61 HGR62   340.00     1.0800 ! NA, DFT
CG2R62 CG2R62  420.00     1.3500 ! NA nad/ppi, jjp1/adm jr. 7/95
CG2R62 CG2R63  302.00     1.4030 ! NA T, adm jr. 11/97
CG2R62 NG2R61  302.00     1.3430 ! NA C, adm jr. 11/97
CG2R62 HGR62   350.00     1.0900 ! NA C,U, JWK
CG2R63 OG2D4   660.00     1.2340 ! NA U,A,G par_a4 adm jr. 10/2/91
CG2R66 FGR1    400.00     1.3580 ! NAMODEL difluorotoluene
CG321  CG321   222.50     1.5300 ! PROT alkane update, adm jr., 3/2/92
CG321  CG324   222.50     1.5300 ! FLAVOP PIP1,2,3
CG321  CG3RC1  222.50     1.5240 ! CARBOCY carbocyclic sugars
CG321  HGA2    309.00     1.1110 ! PROT alkane update, adm jr., 3/2/92
CG324  NG3P2   200.00     1.4900 ! PIP, piperidine
CG324  HGA2    284.50     1.1000 ! FLAVOP PIP1,2,3
CG331  OG301   360.00     1.4150 ! diethylether, alex
CG331  HGA3    322.00     1.1110 ! PROT alkane update, adm jr., 3/2/92
CG3C31 CG3C31  240.00     1.5010 ! PROTMOD cyclopropane
CG3C31 NG2R61  352.828    1.448
CG3C31 HGA1    340.00     1.0830 ! PROTMOD cyclopropane
CG3C31 HGA2    340.00     1.0830 ! PROTMOD cyclopropane
CG3C52 CG3RC1  222.50     1.5240 ! CARBOCY carbocyclic sugars
CG3C52 NG3C51  400.00     1.4780 ! PRLD, pyrrolidine; 2PRL, 2-pyrroline, kevo
CG3C52 HGA2    307.00     1.1000 ! THF, THF neutron diffr., 5/30/06, viv
CG3RC1 CG3RC1  222.50     1.5230 ! CARBOCY carbocyclic sugars
CG3RC1 NG3P2   164.854    1.497
CG3RC1 HGA1    309.00     1.1110 ! CARBOCY carbocyclic sugars
NG3P2  HGP2    460.00     1.0060 ! PROT AcProNH2, ProNH2, AcProNHCH3 RLD 4/23/93
OG311  HGP1    545.00     0.9600 ! PROT EMB 11/21/89 methanol vib fit; og tested on MeOH EtOH,...

ANGLES
CG2R62 CG2O2  OG2D1    70.00    123.10   20.00   2.44200 ! ****** , from CG2R61 CG2O2 OG2D1, PENALTY= 0.5
CG2R62 CG2O2  OG311    40.00    113.90   30.00   2.37000 ! ****** , from CG2R61 CG2O2 OG311, PENALTY= 0.5
OG2D1  CG2O2  OG311    50.00    123.00  210.00   2.26200 ! PROT adm jr, 10/17/90, acetic acid vibrations
CG2R61 CG2R61 CG2R62   40.00    119.00   35.00   2.41620 ! YTHY, 2,4(1H,3H)-quinazolinedione, isg
CG2R61 CG2R61 CG2R66   40.00    119.00   35.00   2.41620 ! NAMODEL difluorotoluene
CG2R61 CG2R61 NG3C51   40.00    120.00 ! ****** , from CG2R61 CG2R61 NG311, PENALTY= 3
CG2R61 CG2R61 OG301   110.00    120.00 ! BIPHENYL ANALOGS, peml
CG2R62 CG2R61 CG2R66   40.00    119.00   35.00   2.41620 ! ****** , from CG2R61 CG2R61 CG2R66, PENALTY= 0.5
CG2R62 CG2R61 OG301   110.00    120.00 ! ****** , from CG2R61 CG2R61 OG301, PENALTY= 0.5
CG2R62 CG2R61 HGR62    30.00    120.00   22.00   2.15250 ! ****** , from CG2R61 CG2R61 HGR62, PENALTY= 0.5
CG2R66 CG2R61 NG3C51   40.00    120.00 ! ****** , from CG2R61 CG2R61 NG311, PENALTY= 4.5
CG2R66 CG2R61 HGR62    30.00    121.50   22.00   2.15250 ! NAMODEL difluorotoluene
CG2O2  CG2R62 CG2R62   10.00    131.80 ! ****** , from CG2O1 CG2R62 CG2R62, PENALTY= 2.5
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CG2O2  CG2R62 CG2R63   10.00    131.80 ! ****** , from CG2O1 CG2R62 CG2R62, PENALTY= 4
CG2R61 CG2R62 CG2R62   40.00    121.00 ! RIN, coumarin, isg
CG2R61 CG2R62 CG2R63  120.00    122.30 ! YTHY, 2,4(1H,3H)-quinazolinedione, isg
CG2R61 CG2R62 NG2R61   23.00    116.10 ! YTHY, 2,4(1H,3H)-quinazolinedione, isg
CG2R62 CG2R62 CG2R63  120.00    116.70 ! NA T
CG2R62 CG2R62 NG2R61   85.00    122.90 ! NA C
CG2R62 CG2R62 HGR62    42.00    119.00 ! NA nadh/ppi, jjp1/adm jr. 7/95
NG2R61 CG2R62 HGR62    44.00    115.00 ! NA C, h6
CG2R62 CG2R63 CG2R62   10.00    120.80 ! 4PYO, 4(1H)-pyridinone; from CG2R62 CG2R62 CG2R62; isg
CG2R62 CG2R63 OG2D4   100.00    124.60 ! NA T, o4
CG2R61 CG2R66 CG2R61   40.00    122.50   35.00   2.41620 ! NAMODEL difluorotoluene
CG2R61 CG2R66 FGR1     60.00    118.75 ! NAMODEL difluorotoluene
CG321  CG321  CG324    58.35    110.50   11.16   2.56100 ! FLAVOP PIP1,2,3
CG321  CG321  CG3RC1   53.35    111.00    8.00   2.56100 ! CARBOCY carbocyclic sugars
CG321  CG321  HGA2     26.50    110.10   22.53   2.17900 ! PROT alkane update, adm jr., 3/2/92
CG324  CG321  HGA2     26.50    110.10   22.53   2.17900 ! FLAVOP PIP1,2,3
CG3RC1 CG321  HGA2     34.50    110.10   22.53   2.17900 ! CARBOCY carbocyclic sugars
HGA2   CG321  HGA2     35.50    109.00    5.40   1.80200 ! PROT alkane update, adm jr., 3/2/92
CG321  CG324  NG3P2    40.00    110.00 ! PIP, piperidine
CG321  CG324  HGA2     26.50    111.80   22.53   2.17900 ! FLAVOP PIP1,2,3
NG3P2  CG324  HGA2     45.00    102.30   35.00   2.10100 ! PIP, piperidine
HGA2   CG324  HGA2     35.50    109.00    5.40   1.80200 ! PIP1,2,3
OG301  CG331  HGA3     45.90    108.89 ! MEOB, Methoxybenzene, cacha
HGA3   CG331  HGA3     35.50    108.40    5.40   1.80200 ! PROT alkane update, adm jr., 3/2/92
CG3C31 CG3C31 CG3C31   77.35    111.00    8.00   2.56100 ! PROTMOD cyclopropane
CG3C31 CG3C31 NG2R61   30.184   117.044
CG3C31 CG3C31 HGA1     23.00    117.10   22.53   2.17900 ! PROTMOD cyclopropane
CG3C31 CG3C31 HGA2     23.00    117.10   22.53   2.17900 ! PROTMOD cyclopropane
NG2R61 CG3C31 HGA1     75.892   114.188
HGA2   CG3C31 HGA2     23.00    117.00    5.40   1.80200 ! PROTMOD cyclopropane
CG3RC1 CG3C52 NG3C51   84.00    107.60 ! ****** , from CG3C52 CG3C52 NG3C51, PENALTY= 1.1
CG3RC1 CG3C52 HGA2     34.50    110.10   22.53   2.17900 ! CARBOCY carbocyclic sugars
NG3C51 CG3C52 HGA2       54.00     109.00 !v 107.7 PRLD, pyrrolidine; 110.8 2PRL, 2-pyrroline; 110.4 3PRL, 3-
pyrroline; 111.4 2IMI, 2-imidazoline; 111.7 2PRZ, 2-pyrazoline, kevo
HGA2   CG3C52 HGA2     38.50    106.80    5.40   1.80200 ! THF, 10/17/05 viv
CG321  CG3RC1 CG3C52   58.35    113.50   11.16   2.56100 ! BAM1, bile acid steroidal C-D ring, cacha, 02/08
CG321  CG3RC1 CG3RC1   53.35    111.00    8.00   2.56100 ! CARBOCY carbocyclic sugars
CG321  CG3RC1 HGA1     34.50    110.10   22.53   2.17900 ! CARBOCY carbocyclic sugars
CG3C52 CG3RC1 CG3RC1   53.35    111.00    8.00   2.56100 ! CARBOCY carbocyclic sugars
CG3C52 CG3RC1 NG3P2   162.274   108.021
CG3C52 CG3RC1 HGA1     34.50    110.10   22.53   2.17900 ! CARBOCY carbocyclic sugars
CG3RC1 CG3RC1 NG3P2    97.279   109.977  8.00     2.5610
CG3RC1 CG3RC1 HGA1     34.50    110.10   22.53   2.17900 ! CARBOCY carbocyclic sugars
NG3P2  CG3RC1 HGA1     105.536  105.525
CG2R62 NG2R61 CG2R62   30.00    120.00 ! NA nad/ppi, jjp1/adm jr. 7/95
CG2R62 NG2R61 CG3C31   45.00    118.40 ! ****** , from CG2R62 NG2R61 CG3C51, PENALTY= 6.9
CG2R61 NG3C51 CG3C52   48.288   107.844
CG3C52 NG3C51 CG3C52  140.00    103.70 !v 102.9 PRLD, pyrrolidine; 105.4 3PRL, 3-pyrroline, kevo
CG324  NG3P2  CG3RC1   26.558   115.625
CG324  NG3P2  HGP2     30.00    110.80   27.00   2.07400 ! PIP, piperidine
CG3RC1 NG3P2  HGP2     97.752   110.057  27.00    2.0740
HGP2   NG3P2  HGP2     51.00    107.50 ! PROT AcProNH2, ProNH2, AcProNHCH3 RLD 4/23/93
CG2R61 OG301  CG331    65.00    108.00 ! MEOB, Methoxybenzene, cacha
CG2O2  OG311  HGP1     55.00    115.00 ! PROT adm jr. 5/02/91, acetic acid pure solvent

DIHEDRALS
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OG2D1  CG2O2  CG2R62 CG2R62     1.0250  2   180.00 ! ****** , from OG2D1 CG2O2 CG2R61 CG2R61, PENALTY= 5.5
OG2D1  CG2O2  CG2R62 CG2R63     1.0250  2   180.00 ! ****** , from OG2D1 CG2O2 CG2R61 CG2R61, PENALTY= 8
OG311  CG2O2  CG2R62 CG2R62     1.0250  2   180.00 ! ****** , from OG311 CG2O2 CG2R61 CG2R61, PENALTY= 5.5
OG311  CG2O2  CG2R62 CG2R63     1.0250  2   180.00 ! ****** , from OG311 CG2O2 CG2R61 CG2R61, PENALTY= 8
CG2R62 CG2O2  OG311  HGP1       0.9750  1   180.00 ! ****** , from CG2R61 CG2O2 OG311 HGP1, PENALTY= 0.5
CG2R62 CG2O2  OG311  HGP1       2.7000  2   180.00 ! ****** , from CG2R61 CG2O2 OG311 HGP1, PENALTY= 0.5
CG2R62 CG2O2  OG311  HGP1       0.0500  3   180.00 ! ****** , from CG2R61 CG2O2 OG311 HGP1, PENALTY= 0.5
CG2R62 CG2O2  OG311  HGP1       0.2500  6   180.00 ! ****** , from CG2R61 CG2O2 OG311 HGP1, PENALTY= 0.5
OG2D1  CG2O2  OG311  HGP1       2.0500  2   180.00 ! PROT adm jr, 10/17/90, acetic Acid C-Oh rotation barrier
CG2R62 CG2R61 CG2R61 CG2R66     3.1000  2   180.00 ! ****** , from CG2R61 CG2R61 CG2R61 CG2R66, PENALTY= 0.5
CG2R62 CG2R61 CG2R61 NG3C51     3.1000  2   180.00 ! ****** , from CG2R61 CG2R61 CG2R61 NG311, PENALTY= 3.5
CG2R66 CG2R61 CG2R61 OG301      3.1000  2   180.00 ! ****** , from CG2R61 CG2R61 CG2R61 OG301, PENALTY= 1.5
NG3C51 CG2R61 CG2R61 OG301      2.4440  2   180.00
CG2R61 CG2R61 CG2R62 CG2R62     0.5000  2   180.00 ! RIN, coumarin, isg
CG2R61 CG2R61 CG2R62 NG2R61     7.0000  2   180.00 ! YTHY, 2,4(1H,3H)-quinazolinedione, isg
CG2R66 CG2R61 CG2R62 CG2R62     0.5000  2   180.00 ! ****** , from CG2R61 CG2R61 CG2R62 CG2R62, PENALTY= 1.5
CG2R66 CG2R61 CG2R62 CG2R63     3.1000  2   180.00 ! ****** , from CG2R61 CG2R61 CG2R62 CG2R63, PENALTY= 1.5
OG301  CG2R61 CG2R62 CG2R62     3.1000  2   180.00 ! ****** , from CG2R61 CG2R61 CG2R61 OG301, PENALTY= 5.5
OG301  CG2R61 CG2R62 NG2R61     2.4000  2   180.00
HGR62  CG2R61 CG2R62 CG2R62     3.1000  2   180.00 ! ****** , from HGR61 CG2R61 CG2R62 CG2R62, PENALTY= 1
HGR62  CG2R61 CG2R62 CG2R63     1.0000  2   180.00 ! ****** , from HGR61 CG2R61 CG2R62 CG2R63, PENALTY= 1
CG2R61 CG2R61 CG2R66 CG2R61     3.1000  2   180.00 ! NAMODEL difluorotoluene
CG2R61 CG2R61 CG2R66 FGR1       4.5000  2   180.00 ! NAMODEL difluorotoluene
CG2R62 CG2R61 CG2R66 CG2R61     3.1000  2   180.00 ! ****** , from CG2R61 CG2R61 CG2R66 CG2R61, PENALTY= 0.5
CG2R62 CG2R61 CG2R66 FGR1       4.5000  2   180.00 ! ****** , from CG2R61 CG2R61 CG2R66 FGR1, PENALTY= 0.5
NG3C51 CG2R61 CG2R66 CG2R61     3.1000  2   180.00 ! ****** , from CG2R61 CG2R61 CG2R61 NG311, PENALTY= 8
NG3C51 CG2R61 CG2R66 FGR1       2.5800  2   180.00 ! ****** , from NG311 CG2R61 CG2R61 OG3R60, PENALTY= 36.2
HGR62  CG2R61 CG2R66 CG2R61     4.2000  2   180.00 ! NAMODEL difluorotoluene
HGR62  CG2R61 CG2R66 FGR1       2.4000  2   180.00 ! NAMODEL difluorotoluene
CG2R61 CG2R61 NG3C51 CG3C52     1.3590  2     0.00
CG2R61 CG2R61 NG3C51 CG3C52     2.4490  4     0.00
CG2R66 CG2R61 NG3C51 CG3C52     0.3300  2   180.00
CG2R66 CG2R61 NG3C51 CG3C52     0.2440  4     0.00
CG2R61 CG2R61 OG301  CG331      1.5800  2   180.00 ! MEOB, Methoxybenzene update, yxu
CG2R61 CG2R61 OG301  CG331      0.2000  4   180.00 ! MEOB, Methoxybenzene update, yxu
CG2R62 CG2R61 OG301  CG331      1.5800  2   180.00 ! ****** , from CG2R61 CG2R61 OG301 CG331, PENALTY= 0.5
CG2R62 CG2R61 OG301  CG331      0.2000  4   180.00 ! ****** , from CG2R61 CG2R61 OG301 CG331, PENALTY= 0.5
CG2O2  CG2R62 CG2R62 NG2R61     2.5000  2   180.00 ! ****** , from CG2O1 CG2R62 CG2R62 NG2R61, PENALTY= 2.5
CG2O2  CG2R62 CG2R62 HGR62      1.0000  2   180.00 ! ****** , from CG2O1 CG2R62 CG2R62 HGR63, PENALTY= 4.5
CG2R61 CG2R62 CG2R62 CG2R61     2.5000  2   180.00 ! RIN, coumarin, isg
CG2R61 CG2R62 CG2R62 CG2R63     3.7000  2   180.00 ! YTHY, 2,4(1H,3H)-quinazolinedione, isg
CG2R61 CG2R62 CG2R62 NG2R61     3.5000  2   180.00 ! YTHY, 2,4(1H,3H)-quinazolinedione, isg
CG2R63 CG2R62 CG2R62 NG2R61     3.0000  2   180.00 ! NA T
CG2R63 CG2R62 CG2R62 HGR62      1.0000  2   180.00 ! NA bases
CG2O2  CG2R62 CG2R63 CG2R62     3.0000  2   180.00
CG2O2  CG2R62 CG2R63 OG2D4      2.4980  2   180.00
CG2R61 CG2R62 CG2R63 CG2R62     1.6000  2   180.00 ! ****** , from CG2R62 CG2R62 CG2R63 CG2R62, PENALTY= 1.5
CG2R61 CG2R62 CG2R63 OG2D4      1.0000  2   180.00 ! YTHY, 2,4(1H,3H)-quinazolinedione, isg
CG2R62 CG2R62 CG2R63 CG2R62     1.6000  2   180.00 ! 4PYO, 4(1H)-pyridinone, isg
CG2R62 CG2R62 CG2R63 OG2D4      1.0000  2   180.00 ! NA bases
CG2R61 CG2R62 NG2R61 CG2R62     4.0000  2   180.00 ! ****** , from CG2R67 CG2R62 NG2R61 CG2R62, PENALTY= 0.5
CG2R61 CG2R62 NG2R61 CG3C31    11.0000  2   180.00 ! ****** , from CG2R62 CG2R62 NG2R61 CG3C51, PENALTY= 8.4
CG2R62 CG2R62 NG2R61 CG2R62     4.0000  2   180.00 ! NA nad/ppi, jjp1/adm jr. 7/95
CG2R62 CG2R62 NG2R61 CG3C31    11.0000  2   180.00 ! ****** , from CG2R62 CG2R62 NG2R61 CG3C51, PENALTY= 6.9
HGR62  CG2R62 NG2R61 CG2R62     5.6000  2   180.00 ! 4PYO, 4(1H)-pyridinone, isg
HGR62  CG2R62 NG2R61 CG3C31     0.3000  2   180.00 ! ****** , from HGR62 CG2R62 NG2R61 CG3C51, PENALTY= 6.9
```

```
CG324  CG321  CG321  CG3RC1     0.4520  3     0.00
CG324  CG321  CG321  HGA2       0.1950  3     0.00 ! FLAVOP PIP1,2,3
CG3RC1 CG321  CG321  HGA2       0.1950  3     0.00 ! LIPID alkanes
HGA2   CG321  CG321  HGA2       0.2200  3     0.00 ! LIPID alkanes
CG321  CG321  CG324  NG3P2      1.0000  3     0.00 ! PIP, piperidine ! @@@ Kenno: 0.1950 -> 1.0000
CG321  CG321  CG324  HGA2       0.1950  3     0.00 ! FLAVOP PIP1,2,3
HGA2   CG321  CG324  NG3P2      0.1950  3     0.00 ! PIP, piperidine
HGA2   CG321  CG324  HGA2       0.1950  3     0.00 ! FLAVOP PIP1,2,3
CG321  CG321  CG3RC1 CG3C52     0.2000  3     0.00 ! BAM1, bile acid steroidal C-D ring, cacha, 02/08
CG321  CG321  CG3RC1 CG3RC1     0.1500  3     0.00 ! CARBOCY carbocyclic sugars
CG321  CG321  CG3RC1 HGA1       0.1500  3     0.00 ! CARBOCY carbocyclic sugars
HGA2   CG321  CG3RC1 CG3C52     0.1950  1     0.00 ! BAM1, bile acid steroidal C-D ring, cacha, 02/08
HGA2   CG321  CG3RC1 CG3RC1     0.1500  3     0.00 ! CARBOCY carbocyclic sugars
HGA2   CG321  CG3RC1 HGA1       0.1500  3     0.00 ! CARBOCY carbocyclic sugars
CG321  CG324  NG3P2  CG3RC1     0.3190  1   180.00
CG321  CG324  NG3P2  CG3RC1     2.2270  2     0.00
CG321  CG324  NG3P2  CG3RC1     1.4290  3   180.00
CG321  CG324  NG3P2  HGP2       0.1000  3     0.00 ! PIP, piperidine
HGA2   CG324  NG3P2  CG3RC1     1.1970  3     0.00
HGA2   CG324  NG3P2  HGP2       0.1000  3     0.00 ! PIP, piperidine
HGA3   CG331  OG301  CG2R61     0.0850  3     0.00 ! MEOB, Methoxybenzene, cacha
CG3C31 CG3C31 CG3C31 NG2R61     1.2340  3   180.00
CG3C31  CG3C31  CG3C31  HGA1           0.1000   6        0.00  !  AMCP,  aminomethyl  cyclopropane;  from  PROTMOD
hf/cyclopropane; jhs
CG3C31 CG3C31 CG3C31 HGA2       0.1000  6     0.00 ! PROTMOD hf/cyclopropane
NG2R61 CG3C31 CG3C31 HGA2       2.2320  3   180.00
HGA1     CG3C31  CG3C31  HGA2          0.2000   5     180.00  !  AMCP,  aminomethyl  cyclopropane;  from  PROTMOD
hf/cyclopropane; jhs
HGA2   CG3C31 CG3C31 HGA2       0.2000  5   180.00 ! PROTMOD hf/cyclopropane
CG3C31 CG3C31 NG2R61 CG2R62     2.3350  3     0.00
HGA1   CG3C31 NG2R61 CG2R62     2.4770  3     0.00
NG3C51 CG3C52 CG3RC1 CG321      1.5720  3   180.00
NG3C51 CG3C52 CG3RC1 CG3RC1     0.9650  3     0.00
NG3C51 CG3C52 CG3RC1 NG3P2      1.4040  3     0.00
NG3C51 CG3C52 CG3RC1 HGA1       1.0890  3     0.00
HGA2   CG3C52 CG3RC1 CG321      0.1950  1     0.00 ! BAM1, bile acid steroidal C-D ring, cacha, 02/08
HGA2   CG3C52 CG3RC1 CG3RC1     0.1500  3     0.00 ! CARBOCY carbocyclic sugars
HGA2   CG3C52 CG3RC1 NG3P2      2.4440  3     0.00
HGA2   CG3C52 CG3RC1 HGA1       0.1500  3     0.00 ! CARBOCY carbocyclic sugars
CG3RC1 CG3C52 NG3C51 CG2R61     1.2050  3   180.00
CG3RC1 CG3C52 NG3C51 CG3C52     0.1800  3     0.00 ! ****** , from CG3C52 CG3C52 NG3C51 CG3C52, PENALTY= 1.1
HGA2   CG3C52 NG3C51 CG2R61     1.6800  3     0.00
HGA2   CG3C52 NG3C51 CG3C52     0.0000  3     0.00 ! 3PRL, 3-pyrroline, kevo
CG321  CG3RC1 CG3RC1 CG3C52     0.1500  3     0.00 ! CARBOCY carbocyclic sugars
CG321  CG3RC1 CG3RC1 NG3P2      0.3810  3   180.00
CG321  CG3RC1 CG3RC1 HGA1       0.1500  3     0.00 ! CARBOCY carbocyclic sugars
CG3C52 CG3RC1 CG3RC1 CG3C52     0.1500  3     0.00 ! CARBOCY carbocyclic sugars
CG3C52 CG3RC1 CG3RC1 NG3P2      0.8780  3   180.00
CG3C52 CG3RC1 CG3RC1 HGA1       0.1500  3     0.00 ! CARBOCY carbocyclic sugars
NG3P2  CG3RC1 CG3RC1 HGA1       2.0850  3   180.00
HGA1   CG3RC1 CG3RC1 HGA1       0.1500  3     0.00 ! CARBOCY carbocyclic sugars
CG3C52 CG3RC1 NG3P2  CG324      1.8470  3   180.00
CG3C52 CG3RC1 NG3P2  HGP2       1.3210  3     0.00
CG3RC1 CG3RC1 NG3P2  CG324      0.2800  3   180.00
CG3RC1 CG3RC1 NG3P2  HGP2       1.3090  3     0.00
HGA1   CG3RC1 NG3P2  CG324      0.7100  3     0.00
```

```
HGA1   CG3RC1 NG3P2  HGP2       2.4770  3   180.00

IMPROPERS
CG2O2  CG2R62 OG2D1  OG311     53.0000  0     0.00 ! ****** , from CG2O2 CG2R61 OG2D1 OG311, PENALTY= 0.5
CG2R63 CG2R62 CG2R62 OG2D4     15.0000  0     0.00 ! 4PYO, 4(1H)-pyridinone, isg

END
RETURN
```

Table DSXII. Optimized force field topology and parameters for neutral moxifloxacin (CHARMM stream including CGENFF parameters)

```
* Toppar stream file generated by
*

read rtf card append
* Initial topologies generated by
* CHARMM General Force Field (CGenFF) program version 1.0.0
* For use with CGenFF version 3.0.1
*
36 1

!============================================================
! Moxifloxacin - Neutral
!============================================================
```

```
RESI MOX0         0.000
GROUP            ! CHARGE   CH_PENALTY
ATOM F      FGR1   -0.145
ATOM O1     OG301  -0.391 !    2.180
ATOM O2     OG2D4  -0.425
ATOM O3     OG311  -0.513 !    4.025
ATOM O4     OG2D1  -0.437 !    3.884
ATOM N1     NG3C51 -0.094
ATOM N2     NG311  -0.761
ATOM N3     NG2R61 -0.177
ATOM C1     CG3RC1 -0.086
ATOM C2     CG3RC1  0.018
ATOM C3     CG3C52 -0.019
ATOM C4     CG3C52  0.096
ATOM C5     CG321  -0.178 !    3.307
ATOM C6     CG3C31  0.094
ATOM C7     CG321  -0.171
ATOM C8     CG3C31 -0.180 !    7.029
ATOM C9     CG3C31 -0.180 !    7.029
ATOM C10    CG321   0.078
ATOM C11    CG2R61 -0.150
ATOM C12    CG2R62  0.027
ATOM C13    CG2R61  0.216
ATOM C14    CG2R62  0.097
ATOM C15    CG2R66 -0.135
ATOM C16    CG2R62  0.016 !    8.806
ATOM C17    CG2R61  0.040 !    6.996
ATOM C18    CG2R62  0.261
ATOM C19    CG2R63  0.026
ATOM C20    CG2O2   0.314
ATOM C21    CG331  -0.100 !    0.025
ATOM H1     HGA1    0.090 !    2.026
ATOM H2     HGA1    0.090 !    3.009
ATOM H3     HGP1    0.429 !    0.219
ATOM H4     HGPAM1  0.342 !    3.537
ATOM H5     HGA2    0.090 !    1.375
ATOM H6     HGA2    0.090 !    1.375
ATOM H7     HGA2    0.090 !    1.596
ATOM H8     HGA2    0.090 !    1.596
ATOM H9     HGA2    0.090 !    0.000
ATOM H10    HGA2    0.090 !    0.000
ATOM H11    HGA1    0.090 !    4.940
ATOM H12    HGA2    0.090 !    0.450
ATOM H13    HGA2    0.090 !    0.450
ATOM H14    HGA2    0.090 !    2.500
ATOM H15    HGA2    0.090 !    2.500
ATOM H16    HGA2    0.090 !    2.500
ATOM H17    HGA2    0.090 !    2.500
ATOM H18    HGA2    0.090 !    2.500
ATOM H19    HGA2    0.090 !    2.500
ATOM H20    HGR62   0.111 !    4.793
ATOM H21    HGR62   0.177 !    0.253
ATOM H22    HGA3    0.090 !    0.000
ATOM H23    HGA3    0.090 !    0.000
ATOM H24    HGA3    0.090 !    0.000
```

```
BOND F    C15
BOND O1   C13
BOND O1   C21
BOND O2   C19
BOND O3   C20
BOND O4   C20
BOND N1   C3
BOND N1   C4
BOND N1   C11
BOND N2   C2
BOND N2   C10
BOND N3   C6
BOND N3   C12
BOND N3   C16
BOND C1   C2
BOND C1   C3
BOND C1   C5
BOND C1   H1
BOND C2   C4
BOND C2   H2
BOND C5   C7
BOND C6   C8
BOND C6   C9
BOND C7   C10
BOND C8   C9
BOND C11  C13
BOND C11  C15
BOND C12  C13
BOND C12  C14
BOND C14  C17
BOND C14  C19
BOND C15  C17
BOND C16  C18
BOND C18  C19
BOND C18  C20
BOND O3   H3
BOND N2   H4
BOND C3   H5
BOND C3   H6
BOND C4   H7
BOND C4   H8
BOND C5   H9
BOND C5   H10
BOND C6   H11
BOND C7   H12
BOND C7   H13
BOND C8   H14
BOND C8   H15
BOND C9   H16
BOND C9   H17
BOND C10  H18
BOND C10  H19
BOND C16  H20
BOND C17  H21
BOND C21  H22
```

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BOND C21  H23
BOND C21  H24
IMPR C19    C14    C18    O2
IMPR C20    C18    O4     O3

END

read param card flex append
* Parameters generated by analogy by
* CHARMM General Force Field (CGenFF) program version 2.2.0
*

! Penalties lower than 10 indicate the analogy is fair; penalties between 10
! and 50 mean some basic validation is recommended; penalties higher than
! 50 indicate poor analogy and mandate extensive validation/optimization.

BONDS
CG2O2  CG2R62  254.00     1.4800 ! ****** , from CG2O2 CG2R61, PENALTY= 5
CG2O2  OG2D1   750.00     1.2200 ! PROT adm jr. 5/02/91, acetic acid pure solvent; LIPID methyl acetate
CG2O2  OG311   230.00     1.4000 ! PROT adm jr. 5/02/91, acetic acid pure solvent
CG2R61 CG2R61  305.00     1.3750 ! PROT benzene, JES 8/25/89
CG2R61 CG2R62  394.00     1.3750 ! YTHY, 2,4(1H,3H)-quinazolinedione, isg
CG2R61 CG2R66  305.00     1.3700 ! NAMODEL difluorotoluene
CG2R61 NG3C51  433.937    1.330
CG2R61 OG301   230.00     1.3820 ! COMPDS peml
CG2R61 HGR62   340.00     1.0800 ! NA, DFT
CG2R62 CG2R62  420.00     1.3500 ! NA nad/ppi, jjp1/adm jr. 7/95
CG2R62 CG2R63  302.00     1.4030 ! NA T, adm jr. 11/97
CG2R62 NG2R61  302.00     1.3430 ! NA C, adm jr. 11/97
CG2R62 HGR62   350.00     1.0900 ! NA C,U, JWK
CG2R63 OG2D4   660.00     1.2340 ! NA U,A,G par_a4 adm jr. 10/2/91
CG2R66 FGR1    400.00     1.3580 ! NAMODEL difluorotoluene
CG321  CG321   222.50     1.5300 ! PROT alkane update, adm jr., 3/2/92
CG321  CG3RC1  222.50     1.5240 ! CARBOCY carbocyclic sugars
CG321  NG311   263.00     1.4740 ! AMINE aliphatic amines
CG321  HGA2    309.00     1.1110 ! PROT alkane update, adm jr., 3/2/92
CG331  OG301   360.00     1.4150 ! diethylether, alex
CG331  HGA3    322.00     1.1110 ! PROT alkane update, adm jr., 3/2/92
CG3C31 CG3C31  240.00     1.5010 ! PROTMOD cyclopropane
CG3C31 NG2R61  259.453    1.372
CG3C31 HGA1    340.00     1.0830 ! PROTMOD cyclopropane
CG3C31 HGA2    340.00     1.0830 ! PROTMOD cyclopropane
CG3C52 CG3RC1  222.50     1.5240 ! CARBOCY carbocyclic sugars
CG3C52 NG3C51  400.00     1.4780 ! PRLD, pyrrolidine; 2PRL, 2-pyrroline, kevo
CG3C52 HGA2    307.00     1.1000 ! THF, THF neutron diffr., 5/30/06, viv
CG3RC1 CG3RC1  222.50     1.5230 ! CARBOCY carbocyclic sugars
CG3RC1 NG311   248.581    1.399
CG3RC1 HGA1    309.00     1.1110 ! CARBOCY carbocyclic sugars
NG311  HGPAM1  447.80     1.0190 ! AMINE aliphatic amines
OG311  HGP1    545.00     0.9600 ! PROT EMB 11/21/89 methanol vib fit; og tested on MeOH EtOH,...

ANGLES
CG2R62 CG2O2  OG2D1    70.00    123.10   20.00   2.44200 ! ****** , from CG2R61 CG2O2 OG2D1, PENALTY= 0.5
CG2R62 CG2O2  OG311    40.00    113.90   30.00   2.37000 ! ****** , from CG2R61 CG2O2 OG311, PENALTY= 0.5
OG2D1  CG2O2  OG311    50.00    123.00  210.00   2.26200 ! PROT adm jr, 10/17/90, acetic acid vibrations
CG2R61 CG2R61 CG2R62   40.00    119.00   35.00   2.41620 ! YTHY, 2,4(1H,3H)-quinazolinedione, isg
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CG2R61 CG2R61 CG2R66   40.00    119.00   35.00   2.41620 ! NAMODEL difluorotoluene
CG2R61 CG2R61 NG3C51   40.00    120.00 ! ****** , from CG2R61 CG2R61 NG311, PENALTY= 3
CG2R61 CG2R61 OG301   110.00    120.00 ! BIPHENYL ANALOGS, peml
CG2R62 CG2R61 CG2R66   40.00    119.00   35.00   2.41620 ! ****** , from CG2R61 CG2R61 CG2R66, PENALTY= 0.5
CG2R62 CG2R61 OG301   110.00    120.00 ! ****** , from CG2R61 CG2R61 OG301, PENALTY= 0.5
CG2R62 CG2R61 HGR62    30.00    120.00   22.00   2.15250 ! ****** , from CG2R61 CG2R61 HGR62, PENALTY= 0.5
CG2R66 CG2R61 NG3C51   40.00    120.00 ! ****** , from CG2R61 CG2R61 NG311, PENALTY= 4.5
CG2R66 CG2R61 HGR62    30.00    121.50   22.00   2.15250 ! NAMODEL difluorotoluene
CG2O2  CG2R62 CG2R62   10.00    131.80 ! ****** , from CG2O1 CG2R62 CG2R62, PENALTY= 2.5
CG2O2  CG2R62 CG2R63   10.00    131.80 ! ****** , from CG2O1 CG2R62 CG2R62, PENALTY= 4
CG2R61 CG2R62 CG2R62   40.00    121.00 ! RIN, coumarin, isg
CG2R61 CG2R62 CG2R63  120.00    122.30 ! YTHY, 2,4(1H,3H)-quinazolinedione, isg
CG2R61 CG2R62 NG2R61   23.00    116.10 ! YTHY, 2,4(1H,3H)-quinazolinedione, isg
CG2R62 CG2R62 CG2R63  120.00    116.70 ! NA T
CG2R62 CG2R62 NG2R61   85.00    122.90 ! NA C
CG2R62 CG2R62 HGR62    42.00    119.00 ! NA nadh/ppi, jjp1/adm jr. 7/95
NG2R61 CG2R62 HGR62    44.00    115.00 ! NA C, h6
CG2R62 CG2R63 CG2R62   10.00    120.80 ! 4PYO, 4(1H)-pyridinone; from CG2R62 CG2R62 CG2R62; isg
CG2R62 CG2R63 OG2D4   100.00    124.60 ! NA T, o4
CG2R61 CG2R66 CG2R61   40.00    122.50   35.00   2.41620 ! NAMODEL difluorotoluene
CG2R61 CG2R66 FGR1     60.00    118.75 ! NAMODEL difluorotoluene
CG321  CG321  CG321    58.35    113.60   11.16   2.56100 ! PROT alkane update, adm jr., 3/2/92
CG321  CG321  CG3RC1   53.35    111.00    8.00   2.56100 ! CARBOCY carbocyclic sugars
CG321  CG321  NG311    43.70    110.00 ! K2Cn, cgenff_compromise, kevo
CG321  CG321  HGA2     26.50    110.10   22.53   2.17900 ! PROT alkane update, adm jr., 3/2/92
CG3RC1 CG321  HGA2     34.50    110.10   22.53   2.17900 ! CARBOCY carbocyclic sugars
NG311  CG321  HGA2     32.40    109.50   50.00   2.13000 ! PEI polymers, kevo
HGA2   CG321  HGA2     35.50    109.00    5.40   1.80200 ! PROT alkane update, adm jr., 3/2/92
OG301  CG331  HGA3     45.90    108.89 ! MEOB, Methoxybenzene, cacha
HGA3   CG331  HGA3     35.50    108.40    5.40   1.80200 ! PROT alkane update, adm jr., 3/2/92
CG3C31 CG3C31 CG3C31   77.35    111.00    8.00   2.56100 ! PROTMOD cyclopropane
CG3C31 CG3C31 NG2R61   89.072   120.511
CG3C31 CG3C31 HGA1     23.00    117.10   22.53   2.17900 ! PROTMOD cyclopropane
CG3C31 CG3C31 HGA2     23.00    117.10   22.53   2.17900 ! PROTMOD cyclopropane
NG2R61 CG3C31 HGA1     12.460   104.276
HGA2   CG3C31 HGA2     23.00    117.00    5.40   1.80200 ! PROTMOD cyclopropane
CG3RC1 CG3C52 NG3C51   84.00    107.60 ! ****** , from CG3C52 CG3C52 NG3C51, PENALTY= 1.1
CG3RC1 CG3C52 HGA2     34.50    110.10   22.53   2.17900 ! CARBOCY carbocyclic sugars
NG3C51 CG3C52 HGA2      54.00     109.00 !v 107.7 PRLD, pyrrolidine; 110.8 2PRL, 2-pyrroline; 110.4 3PRL, 3-
pyrroline; 111.4 2IMI, 2-imidazoline; 111.7 2PRZ, 2-pyrazoline, kevo
HGA2   CG3C52 HGA2     38.50    106.80    5.40   1.80200 ! THF, 10/17/05 viv
CG321  CG3RC1 CG3C52   58.35    113.50   11.16   2.56100 ! BAM1, bile acid steroidal C-D ring, cacha, 02/08
CG321  CG3RC1 CG3RC1   53.35    111.00    8.00   2.56100 ! CARBOCY carbocyclic sugars
CG321  CG3RC1 HGA1     34.50    110.10   22.53   2.17900 ! CARBOCY carbocyclic sugars
CG3C52 CG3RC1 CG3RC1   53.35    111.00    8.00   2.56100 ! CARBOCY carbocyclic sugars
CG3C52 CG3RC1 NG311    82.560   114.667
CG3C52 CG3RC1 HGA1     34.50    110.10   22.53   2.17900 ! CARBOCY carbocyclic sugars
CG3RC1 CG3RC1 NG311    77.024   111.797  8.00     2.5610
CG3RC1 CG3RC1 HGA1     34.50    110.10   22.53   2.17900 ! CARBOCY carbocyclic sugars
NG311  G3RC1  HGA1     42.880   109.227
CG2R62 NG2R61 CG2R62   30.00    120.00 ! NA nad/ppi, jjp1/adm jr. 7/95
CG2R62 NG2R61 CG3C31   45.00    118.40 ! ****** , from CG2R62 NG2R61 CG3C51, PENALTY= 6.9
CG321  NG311  CG3RC1   107.450  114.812  5.00     2.4217
CG321  NG311  HGPAM1    35.00     111.00 ! compromise between PEI0 on the one hand and OBTZ AOBT on the other
hand, kevo & xxwy
CG3RC1 NG311  HGPAM1   89.535   107.894
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CG2R61 NG3C51 CG3C52   48.288   107.844
CG3C52 NG3C51 CG3C52  140.00    103.70 !v 102.9 PRLD, pyrrolidine; 105.4 3PRL, 3-pyrroline, kevo
CG2R61 OG301  CG331    65.00    108.00 ! MEOB, Methoxybenzene, cacha
CG2O2  OG311  HGP1     55.00    115.00 ! PROT adm jr. 5/02/91, acetic acid pure solvent

DIHEDRALS
OG2D1  CG2O2  CG2R62 CG2R62     1.0250  2   180.00 ! ****** , from OG2D1 CG2O2 CG2R61 CG2R61, PENALTY= 5.5
OG2D1  CG2O2  CG2R62 CG2R63     1.0250  2   180.00 ! ****** , from OG2D1 CG2O2 CG2R61 CG2R61, PENALTY= 8
OG311  CG2O2  CG2R62 CG2R62     1.0250  2   180.00 ! ****** , from OG311 CG2O2 CG2R61 CG2R61, PENALTY= 5.5
OG311  CG2O2  CG2R62 CG2R63     1.0250  2   180.00 ! ****** , from OG311 CG2O2 CG2R61 CG2R61, PENALTY= 8
CG2R62 CG2O2  OG311  HGP1       0.9750  1   180.00 ! ****** , from CG2R61 CG2O2 OG311 HGP1, PENALTY= 0.5
CG2R62 CG2O2  OG311  HGP1       2.7000  2   180.00 ! ****** , from CG2R61 CG2O2 OG311 HGP1, PENALTY= 0.5
CG2R62 CG2O2  OG311  HGP1       0.0500  3   180.00 ! ****** , from CG2R61 CG2O2 OG311 HGP1, PENALTY= 0.5
CG2R62 CG2O2  OG311  HGP1       0.2500  6   180.00 ! ****** , from CG2R61 CG2O2 OG311 HGP1, PENALTY= 0.5
OG2D1  CG2O2  OG311  HGP1       2.0500  2   180.00 ! PROT adm jr, 10/17/90, acetic Acid C-Oh rotation barrier
CG2R62 CG2R61 CG2R61 CG2R66     3.1000  2   180.00 ! ****** , from CG2R61 CG2R61 CG2R61 CG2R66, PENALTY= 0.5
CG2R62 CG2R61 CG2R61 NG3C51     3.1000  2   180.00 ! ****** , from CG2R61 CG2R61 CG2R61 NG311, PENALTY= 3.5
CG2R66 CG2R61 CG2R61 OG301      3.1000  2   180.00 ! ****** , from CG2R61 CG2R61 CG2R61 OG301, PENALTY= 1.5
NG3C51 CG2R61 CG2R61 OG301      2.4440  2   180.00
CG2R61 CG2R61 CG2R62 CG2R62     0.5000  2   180.00 ! RIN, coumarin, isg
CG2R61 CG2R61 CG2R62 NG2R61     7.0000  2   180.00 ! YTHY, 2,4(1H,3H)-quinazolinedione, isg
CG2R66 CG2R61 CG2R62 CG2R62     0.5000  2   180.00 ! ****** , from CG2R61 CG2R61 CG2R62 CG2R62, PENALTY= 1.5
CG2R66 CG2R61 CG2R62 CG2R63     3.1000  2   180.00 ! ****** , from CG2R61 CG2R61 CG2R62 CG2R63, PENALTY= 1.5
OG301  CG2R61 CG2R62 CG2R62     3.1000  2   180.00 ! ****** , from CG2R61 CG2R61 CG2R61 OG301, PENALTY= 5.5
OG301  CG2R61 CG2R62 NG2R61     2.4000  2   180.00
HGR62  CG2R61 CG2R62 CG2R62     3.1000  2   180.00 ! ****** , from HGR61 CG2R61 CG2R62 CG2R62, PENALTY= 1
HGR62  CG2R61 CG2R62 CG2R63     1.0000  2   180.00 ! ****** , from HGR61 CG2R61 CG2R62 CG2R63, PENALTY= 1
CG2R61 CG2R61 CG2R66 CG2R61     3.1000  2   180.00 ! NAMODEL difluorotoluene
CG2R61 CG2R61 CG2R66 FGR1       4.5000  2   180.00 ! NAMODEL difluorotoluene
CG2R62 CG2R61 CG2R66 CG2R61     3.1000  2   180.00 ! ****** , from CG2R61 CG2R61 CG2R66 CG2R61, PENALTY= 0.5
CG2R62 CG2R61 CG2R66 FGR1       4.5000  2   180.00 ! ****** , from CG2R61 CG2R61 CG2R66 FGR1, PENALTY= 0.5
NG3C51 CG2R61 CG2R66 CG2R61     3.1000  2   180.00 ! ****** , from CG2R61 CG2R61 CG2R61 NG311, PENALTY= 8
NG3C51 CG2R61 CG2R66 FGR1       2.5800  2   180.00 ! ****** , from NG311 CG2R61 CG2R61 OG3R60, PENALTY= 36.2
HGR62  CG2R61 CG2R66 CG2R61     4.2000  2   180.00 ! NAMODEL difluorotoluene
HGR62  CG2R61 CG2R66 FGR1       2.4000  2   180.00 ! NAMODEL difluorotoluene
CG2R61 CG2R61 NG3C51 CG3C52     1.3590  2     0.00
CG2R61 G2R61  NG3C51 CG3C52     2.4490  4     0.00
CG2R66 CG2R61 NG3C51 CG3C52     0.3300  2   180.00
CG2R66 CG2R61 NG3C51 CG3C52     0.2440  4     0.00
CG2R61 CG2R61 OG301  CG331      1.5800  2   180.00 ! MEOB, Methoxybenzene update, yxu
CG2R61 CG2R61 OG301  CG331      0.2000  4   180.00 ! MEOB, Methoxybenzene update, yxu
CG2R62 CG2R61 OG301  CG331      1.5800  2   180.00 ! ****** , from CG2R61 CG2R61 OG301 CG331, PENALTY= 0.5
CG2R62 CG2R61 OG301  CG331      0.2000  4   180.00 ! ****** , from CG2R61 CG2R61 OG301 CG331, PENALTY= 0.5
CG2O2  CG2R62 CG2R62 NG2R61     2.5000  2   180.00 ! ****** , from CG2O1 CG2R62 CG2R62 NG2R61, PENALTY= 2.5
CG2O2  CG2R62 CG2R62 HGR62      1.0000  2   180.00 ! ****** , from CG2O1 CG2R62 CG2R62 HGR63, PENALTY= 4.5
CG2R61 CG2R62 CG2R62 CG2R61     2.5000  2   180.00 ! RIN, coumarin, isg
CG2R61 CG2R62 CG2R62 CG2R63     3.7000  2   180.00 ! YTHY, 2,4(1H,3H)-quinazolinedione, isg
CG2R61 CG2R62 CG2R62 NG2R61     3.5000  2   180.00 ! YTHY, 2,4(1H,3H)-quinazolinedione, isg
CG2R63 CG2R62 CG2R62 NG2R61     3.0000  2   180.00 ! NA T
CG2R63 CG2R62 CG2R62 HGR62      1.0000  2   180.00 ! NA bases
CG2O2  CG2R62 CG2R63 CG2R62     3.0000  2   180.00
CG2O2  CG2R62 CG2R63 OG2D4      2.4980  2   180.00
CG2R61 CG2R62 CG2R63 CG2R62     1.6000  2   180.00 ! ****** , from CG2R62 CG2R62 CG2R63 CG2R62, PENALTY= 1.5
CG2R61 CG2R62 CG2R63 OG2D4      1.0000  2   180.00 ! YTHY, 2,4(1H,3H)-quinazolinedione, isg
CG2R62 CG2R62 CG2R63 CG2R62     1.6000  2   180.00 ! 4PYO, 4(1H)-pyridinone, isg
CG2R62 CG2R62 CG2R63 OG2D4      1.0000  2   180.00 ! NA bases
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CG2R61 CG2R62 NG2R61 CG2R62     4.0000  2   180.00 ! ****** , from CG2R67 CG2R62 NG2R61 CG2R62, PENALTY= 0.5
CG2R61 CG2R62 NG2R61 CG3C31    11.0000  2   180.00 ! ****** , from CG2R62 CG2R62 NG2R61 CG3C51, PENALTY= 8.4
CG2R62 CG2R62 NG2R61 CG2R62     4.0000  2   180.00 ! NA nad/ppi, jjp1/adm jr. 7/95
CG2R62 CG2R62 NG2R61 CG3C31    11.0000  2   180.00 ! ****** , from CG2R62 CG2R62 NG2R61 CG3C51, PENALTY= 6.9
HGR62  CG2R62 NG2R61 CG2R62     5.6000  2   180.00 ! 4PYO, 4(1H)-pyridinone, isg
HGR62  CG2R62 NG2R61 CG3C31     0.3000  2   180.00 ! ****** , from HGR62 CG2R62 NG2R61 CG3C51, PENALTY= 6.9
CG321  CG321  CG321  CG3RC1     0.1500  3     0.00 ! CARBOCY carbocyclic sugars
CG321  CG321  CG321  NG311      3.0000  1   180.00
CG321  CG321  CG321  NG311      0.5000  2     0.00
CG321  CG321  CG321  HGA2       0.1950  3     0.00 ! LIPID alkanes
CG3RC1 CG321  CG321  HGA2       0.1950  3     0.00 ! LIPID alkanes
NG311  CG321  CG321  HGA2       0.1950  3     0.00 ! K2Cn, cgenff_compromise, kevo
HGA2   CG321  CG321  HGA2       0.2200  3     0.00 ! LIPID alkanes
CG321  CG321  CG3RC1 CG3C52     0.2000  3     0.00 ! BAM1, bile acid steroidal C-D ring, cacha, 02/08
CG321  CG321  CG3RC1 CG3RC1     0.1500  3     0.00 ! CARBOCY carbocyclic sugars
CG321  CG321  CG3RC1 HGA1       0.1500  3     0.00 ! CARBOCY carbocyclic sugars
HGA2   CG321  CG3RC1 CG3C52     0.1950  1     0.00 ! BAM1, bile acid steroidal C-D ring, cacha, 02/08
HGA2   CG321  CG3RC1 CG3RC1     0.1500  3     0.00 ! CARBOCY carbocyclic sugars
HGA2   CG321  CG3RC1 HGA1       0.1500  3     0.00 ! CARBOCY carbocyclic sugars
CG321  CG321  NG311  CG3RC1     2.1190  1     0.00
CG321  CG321  NG311  CG3RC1     2.9060  2     0.00
CG321  CG321  NG311  CG3RC1     0.0660  3     0.00
CG321  CG321  NG311  HGPAM1     0.3000  3     0.00 ! K2Cn, cgenff_compromise, kevo
HGA2   CG321  NG311  CG3RC1     0.9290  3   180.00
HGA2   CG321  NG311  HGPAM1     0.0500  3     0.00 ! PEI0, OBTZ, AOBT, kevo & xxwy
HGA3   CG331  OG301  CG2R61     0.0850  3     0.00 ! MEOB, Methoxybenzene, cacha
CG3C31 CG3C31 CG3C31 NG2R61     1.2340  3   180.00
CG3C31  CG3C31  CG3C31  HGA1           0.1000   6        0.00  !  AMCP,  aminomethyl  cyclopropane;  from  PROTMOD
hf/cyclopropane; jhs
CG3C31 CG3C31 CG3C31 HGA2       0.1000  6     0.00 ! PROTMOD hf/cyclopropane
NG2R61 CG3C31 CG3C31 HGA2       2.2320  3   180.00
HGA1     CG3C31  CG3C31  HGA2           0.2000   5     180.00  !  AMCP,  aminomethyl  cyclopropane;  from  PROTMOD
hf/cyclopropane; jhs
HGA2   CG3C31 CG3C31 HGA2       0.2000  5   180.00 ! PROTMOD hf/cyclopropane
CG3C31 CG3C31 NG2R61 CG2R62     2.3350  3     0.00
HGA1   CG3C31 NG2R61 CG2R62     2.4770  3     0.00
NG3C51 CG3C52 CG3RC1 CG321      1.5720  3   180.00
NG3C51 CG3C52 CG3RC1 CG3RC1     0.9650  3     0.00
NG3C51 CG3C52 CG3RC1 NG311      2.9350  3     0.00
NG3C51 CG3C52 CG3RC1 HGA1       1.0890  3     0.00
HGA2   CG3C52 CG3RC1 CG321      0.1950  1     0.00 ! BAM1, bile acid steroidal C-D ring, cacha, 02/08
HGA2   CG3C52 CG3RC1 CG3RC1     0.1500  3     0.00 ! CARBOCY carbocyclic sugars
HGA2   CG3C52 CG3RC1 NG311      0.8650  3   180.00
HGA2   CG3C52 CG3RC1 HGA1       0.1500  3     0.00 ! CARBOCY carbocyclic sugars
CG3RC1 CG3C52 NG3C51 CG2R61     1.2050  3   180.00
CG3RC1 CG3C52 NG3C51 CG3C52     0.1800  3     0.00 ! ****** , from CG3C52 CG3C52 NG3C51 CG3C52, PENALTY= 1.1
CG3RC1 CG3C52 NG3C51 CG2R61     1.2050  3   180.00
HGA2   CG3C52 NG3C51 CG3C52     0.0000  3     0.00 ! 3PRL, 3-pyrroline, kevo
CG321  CG3RC1 CG3RC1 CG3C52     0.1500  3     0.00 ! CARBOCY carbocyclic sugars
CG321  CG3RC1 CG3RC1 NG311      1.6840  3     0.00
CG321  CG3RC1 CG3RC1 HGA1       0.1500  3     0.00 ! CARBOCY carbocyclic sugars
CG3C52 CG3RC1 CG3RC1 CG3C52     0.1500  3     0.00 ! CARBOCY carbocyclic sugars
CG321  CG3RC1 CG3RC1 NG311      1.6840  3     0.00
CG3C52 CG3RC1 CG3RC1 HGA1       0.1500  3     0.00 ! CARBOCY carbocyclic sugars
NG311  CG3RC1 CG3RC1 HGA1       0.5290  3     0.00
HGA1   CG3RC1 CG3RC1 HGA1       0.1500  3     0.00 ! CARBOCY carbocyclic sugars
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CG3C52 CG3RC1 NG311  CG321      0.5830  3     0.00
CG3C52 CG3RC1 NG311  HGPAM1     0.7110  3   180.00
CG3RC1 CG3RC1 NG311  CG321      0.6760  3     0.00
CG3RC1 CG3RC1 NG311  HGPAM1     2.9830  3   180.00
HGA1   CG3RC1 NG311  CG321      2.6450  3     0.00
HGA1   CG3RC1 NG311  HGPAM1     0.7990  3     0.00

IMPROPERS
CG2O2  CG2R62 OG2D1  OG311     53.0000  0     0.00 ! ****** , from CG2O2 CG2R61 OG2D1 OG311, PENALTY= 0.5
CG2R63 CG2R62 CG2R62 OG2D4     15.0000  0     0.00 ! 4PYO, 4(1H)-pyridinone, isg

END
RETURN
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