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Computer-Aided Design, Synthesis and Biological Assay of *p*-Methylsulfonamido Phenylethylamine Analogues

Hong Liu,[a,b] Min Ji,[b] Hualiang Jiang,[a,*] Ligang Liu,[b] Weiyi Hua,[b,*] Kaixian Chen[a] and Ruyun Ji[a]

[a]*Shanghai Institute of Materia Medica, Chinese Academy of Sciences, 294 Taiyuan Road, Shanghai 200031, China*
[b]*Department of Medicinal Chemistry, China Pharmaceutical University, Nanjing 210009, China*

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Abstract—Class III antiarrhythmic agents selectively delay the effective refractory period (ERP) and increase the transmembrance action potential duration (APD). Based on our previous studies, a set of 17 methylsulfonamido phenylethylamine analogues were investigated by 3D-QSAR techniques of CoMFA and CoMSIA. The 3D-QSAR models proved a good predictive ability, and could describe the steric, electrostatic and hydrophobic requirements for recognition forces of the receptor site. According to the clues provided by this 3D-QSAR analysis, we designed and synthesized a series of new analogues of methanesulfonamido phenylethylamine ($\mathbf{VI_{a-i}}$). Pharmacological assay indicated that the effective concentrations of delaying the functional refractory period (FRP) 10 ms of these new compounds have a good correlation with the 3D-QSAR predicted values. It is remarkable that the maximal percent change of delaying FRP in μM of compound $\mathbf{VI_c}$ is much higher than that of dofetilide. The results showed that the 3D-QSAR models are reliable.

Introduction

The high incidence of sudden cardiac death (SCD) is of continuing medical concern. SCD results from electrical instability of the heart muscle leading to a loss of regular cardiac rhythm, and it is accepted that ventricular arrhythmia such as sustained tachycardia (VT) and fibrillation (VF) plays the major role in these deaths.[1,2] The Vanghan Williams classification of antiarrhythmic drugs recognizes four distinct categories. Class I is the sodium channel blockade, its mechanism being of interference with the fast sodium channels in cell membranes. Class II is β-blocking agents. Class IV is calcium channel blocking agents. Class III agents act by delaying repolarization of cardiac myocytes, lengthening action potential duration (APD) of the cell and a concomitantly increasing ERP.[3] The outward delayed rectifier potassium current, I_K, that contributes to repolarization, consists of two kinetically distinct and identifiable currents, a rapidly activating, I_{Kr}, and a slowly activating component, I_{Ks}. Selective blockade of either I_{Kr} or I_{Ks} would lead to a prolongation of the refractory period and be, by definition, a class III effect.[4,5] In our previous publication,[6,7] we reported 17 methylsulfonamido phenylethylamine analogues designed and synthesized according to the pharmacophore of class III antiarrhythmic agents and the structural feature of dofetilide, which is currently used in clinical tests. The biological activities of these compounds for increasing the functional refractory period (FRP) were also determined in isolated animal atrium (Table 1). In order to find more potent analogues of dofetilide, 3D-QSAR analyses have been performed on these 17 compounds by use of Comparative Molecular Field Analysis (CoMFA)[8] and Comparative Molecular Similarity Index Analysis (CoMSIA)[9] methods. The 3D-QSAR models proved to have a good predictive ability, and could describe the steric, electrostatic and hydrophobic requirements for recognition forces of the receptor site. According to the clues provided by the 3D-QSAR analyses, we designed and synthesized a series of new analogues of methanesulfonamido phenylethylamine ($\mathbf{VI_{a-i}}$). Pharmacological assay indicated that the effective concentrations of delaying FRP 10 ms of these new compounds have a good correlation with the 3D-QSAR predicted values. It is remarkable that the maximal percent change of delaying FRP in μM of compound $\mathbf{VI_c}$ is much higher than that of dofetilide. In this paper, we report the results of the 3D-QSAR of known compounds,[6,7] and design, synthesis and pharmacological assay of new compounds.

*Corresponding authors.

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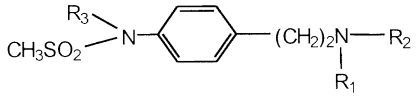
Table 1. Chemical structures of methanesulfonamido phenylethylamine compounds, their activities and CoMFA prediction



Compound	R_1	R_2	R_3	C[a]	EA[b]	PA[c]	Residue[d]
1	CH_3	$-CH_2CH_2OC_6H_4NHSO_2CH_3$-*p*	H	0.012	7.92	7.87	0.05
2	$-CH_2C_6H_5$	$-CH_2CH_2OC_6H_4NHSO_2CH_3$-*p*	H	0.016	7.80	7.89	−0.09
3	$-COCH_3$	$-CH_2CH_2OC_6H_4NHSO_2CH_3$-*p*	H	0.021	7.67	7.65	0.02
4	H	$-CH_2CH_2OC_6H_4NHSO_2CH_3$-*p*	H	0.023	7.63	7.60	0.03
5	$-CH_2C_6H_4Cl$-*p*	$-CH_2CH_2OC_6H_4NHSO_2CH_3$-*p*	H	0.037	7.44	7.47	−0.03
6	$-CH_3$	$-CH_2C_6H_5$	H	0.372	6.34	6.31	0.03
7	$-CH_3$	$-CH_2C_6H_4CH_3$-*p*	$-SO_2CH_3$	0.953	6.02	6.16	−0.14
8	$-CH_3$	$-CH_2C_6H_4Cl$-*p*	-H	2.239	5.65	5.76	−0.11
9	$-CH_3$	$-CH_2C_6H_4OCH_3$-*p*	$-SO_2CH_3$	1.170	5.93	5.79	0.14
10	$-CH_3$	$-C_6H_{11}$	-H	4.789	5.32	5.33	−0.01
11	$-CH_3$	$-CH_2C_6H_3OCH_2O$-3,4	-H	0.890	6.15	6.16	−0.01
12	$-CH_2C_6H_5$	$-CH_2C_6H_4OCH_3$-*o*	-H	0.141	6.85	6.88	−0.03
13	$-CH_2C_6H_5$	$-CH_2C_6H_5$	-H	0.270	6.57	6.41	0.16
14	$-CH_2C_6H_5$	$-CH_2C_6H_4CH_3$-*p*	$-SO_2CH_3$	0.620	6.21	6.12	0.09
15	$-CH_2C_6H_5$	$-CH_2C_6H_4Cl$-*p*	-H	1.050	5.98	6.10	−0.12
16	$-CH_2C_6H_5$	$-CH_2C_6H_4OCH_3$-*p*	$-SO_2CH_3$	0.790	6.10	6.08	0.02
17	$-CH_2C_6H_5$	$-CH_2C_6H_3OCH_2O$-3,4	$-SO_2CH_3$	0.380	6.41	6.42	−0.01

[a]C = the effective concentration of delaying FRP 10 ms (μM).
[b]EA = −log C.
[c]PA = predictive activity.
[d]Residue = EA−PA.

CoMFA and CoMSIA

Molecular 3D structure building. 3D-QSAR analyses were performed using CoMFA and CoMSIA for the 17 compounds listed in Table 1. The 3D structures of the entire set of these compounds were built using the SKETCH option in Sybyl 6.5[10] and fully geometry optimized using the standard Tripos force field, with a 0.001 kcal/mol energy gradient convergence criterion and a distance-dependent dielectric constant. The search routine of Sybyl was then employed for the systematic conformational search to find out the local energy-minimum conformations.

Alignment rule. While it is recognized that the global energy-minimum conformation may not necessarily be adopted in the drug–receptor complex, the use of a reasonably low energy conformation in the alignment is a useful starting point for statistical comparisons of flexible structures within the CoMFA and CoMSIA models. In this study, we took dofetilide as the reference molecule due to its scaffold involved in the 17 compounds and its high activity. We selected all the low-energy conformations of this scaffold as template structure and the pairs between the molecules for alignment during CoMFA and CoMSIA analyses, and took the conformations corresponding to the maximum cross-validation R^2 as the bioactive conformation to subject the final CoMFA and CoMSIA analyses. The alignment of the bioactive conformations for these 17 compounds is shown in Figure 1.

CoMFA analysis. The CoMFA analysis was carried out using the standard options of Sybyl. The analysis results are presented in Tables 1 and 2 and Figures 1 and 2. The optimized CoMFA of 17 compounds gave a good

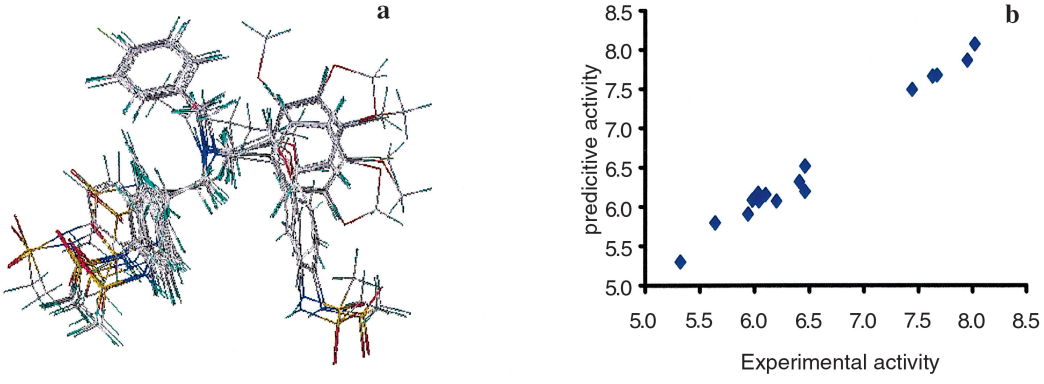


Figure 1. (a) Superposition of 17 methanesulfonamido phenylethylamine compounds (cf. Table 1) for 3D-QSAR studies; (b) experimental activities versus predictive values for the CoMFA model.

Table 2. Summary of 3D-QSAR analysis results obtained using CoMFA and CoMSIA

Method	PLS	R^2	Optimal component	Contributions		
				Steric	Electrostatic	Hydrophobic
CoMFA	Cross-validation	0.695	5	—	—	—
	Conventional	0.984	5	0.551	0.449	—
CoMSIA	Cross-validation	0.640	4	—	—	—
	Conventional	0.975	4	0.271	0.465	0.264

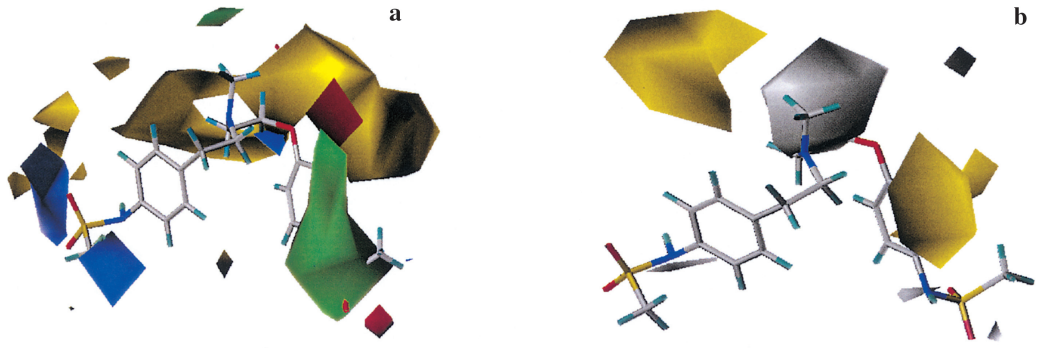
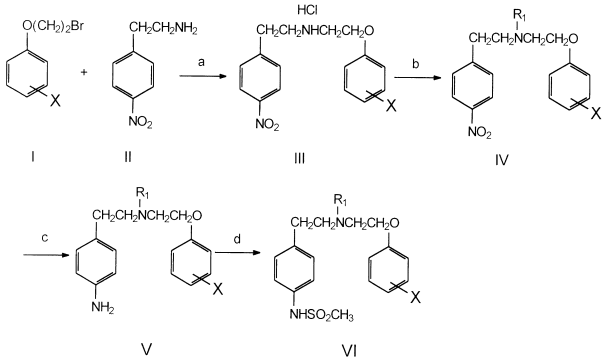


Figure 2. (a) Contour maps from the final CoMFA analysis with 2 Å grid spacing in combination with dofetilide. Steric std*coeff contour map. Green contours (>80% contribution) refer to sterically favored regions; yellow contours (>20% contribution) indicate disfavored areas. Electrostatic std*coeff contour map. Blue contours (>80% contribution) refer to regions where negatively charged substituents are disfavored; red contours (>20% contribution) indicate regions where negatively charged substituents are favoured; (b) contour maps from the final CoMSIA analysis with 2 Å grid spacing in combination with dofetilide. Hydrophobic std*coeff contour map. White contours (>80% contribution) refer to regions where hydrophilic substituents are favored; yellow contours (>20% contribution) indicate regions where hydrophobic substituents are favored.

cross-validated value of 0.695 with an optimized component of 5, the conventional correlation coefficient is $R^2 = 0.984$, $F = 132.515$, and the estimated standard error is 0.130. These predictive results have been obtained, indicating a good statistical correlation, and we also find that the resultant CoMFA model had a fair predictive ability (Fig. 1b).

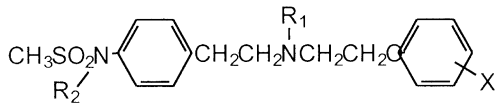
The QSAR produced by CoMFA, with its hundreds of thousands of terms, is usually represented as a 3D 'coefficient contour' map. The CoMFA steric and electrostatic fields for the analysis are presented as contour plots in Figure 2(a). To aid in visualization, the potent biological activity is displayed in the map. In general, the color polyhedra in the map surrounded all lattice points where the QSAR strongly associated changes in the compounds' field values with changes in biological potency. Green polyhedra surrounded regions where more bulk is 'good' for increasing potency, while yellow polyhedra surrounded regions where less bulk is 'good'. Red and blue contours show regions of desirable negative and positive electrostatic interactions, respectively. A large region of green contour near the phenyl moiety of phenoxyethane suggests that more potent analogues may be obtained by introducing bulky substituents to this region of dofetilide. Two red polyhedra near the sulfonyl of methanesulfonamido phenoxyethylamine and the O atom of the phenoxyethyl moiety indicate that electron rich groups are beneficial to the activity. Two blue contours near the methanesulfonyl group of methanesulfonamido phenylethylamine suggest that positive charged substituents are favorable to increase the activity.

CoMSIA analysis. To estimate the hydrophobic contributions to these antiarrhythmic agents, hydrophobic similarity index fields were constructed by use of CoMSIA, which cannot be completely treated by Lennard–Jones and Coulombic fields encoded in CoMFA. The CoMSIA analysis was performed employing the standard options of Sybyl.[11,12] The results of CoMSIA are shown in Table 2 and Figure 2b. CoMSIA fields can also be represented by color contour plots. In general, yellow polyhedra indicate that hydrophobic substituents are 'good' for increasing the potency, while hydrophilic substituents are beneficial to the activity at the regions of white contours.



Scheme 1. Synthesis of compounds $\mathbf{VI_{a-i}}$ Reagents and conditions: (a) K_2CO_3, CH_3CN, reflux, 81.5%; (b) i = HCHO, HCOOH, reflux, 87.2%; ii = R_1X, CH_3CN, reflux, 61%; iii = Ac_2O, CH_3CN, rt, 91%; (c) Fe, HCl, EtOH, reflux, 75%; (d) CH_3SO_2Cl, Et_3N, CH_2Cl_2, 0 °C, 92.3%.

Table 3. The structures and biological activities of the designed new compounds



Compound	R_1	R_2	X	n[a]	MaxΔFRP[b]	MaxΔHR[c]	MaxΔFC[d]
Dofetilide	$-CH_3$	-H	$-NHSO_2CH_3$-4	5	24.02	−30.03	17.05
VI_a	$-CH_3$	-H	-X	3	20.2	−28.51	20.25
VI_b	$-CH_2C_6H_5$	-H	-X	3	N[e]	−31.8	25
VI_c	$-COCH_3$	-H	-X	3	58.36	−46.17	−37.87
VI_d	$-CH_2CH=CH_2$	-H	-X	2	9.77	−15.18	16.67
VI_e	$-CH_2CH=CH_2$	$-SO_2CH_3$	-X	2	N[e]	−8.33	16.67
VI_f	$-COC_6H_5$	-H	-X	2	5.33	−20	33.33
VI_g	$-CH_2C_6H_5$	$-SO_2CH_3$	-X	2	N[e]	−17.86	25
VI_h	$-COCH_3$	$-SO_2CH_3$	-X	2	N[e]	−20.51	N[e]
VI_i	$-CH_3$	$-SO_2CH_3$	-X	2	12.02	−20.69	N[e]

[a]n = the sample number.
[b]MaxΔFRP = the maximal percent change of delaying FRP in μM (%).
[c]MaxΔHR = the maximal percent change of heart rate in μM (%).
[d]MaxΔFC = the maximal percent change of force of constriction in μM (%).
[e]N = No effect in μM.

New analogues design, synthesis and bioassay. According to CoMFA and CoMSIA analyses (Fig. 2), we can see that adding bulky and hydrophobic groups to the phenyl moiety of phenoxyethane of dofetilide may increase the bioactivity. Following this clue, we designed nine new analogues (compounds **$VI_{a–i}$**, Table 3). Scheme 1 depicts the synthetic sequence of these compounds. Compound **I** was substituted by using *p*-nitrophenethylamine hydrobromide (**II**), giving the key intermediates **III**. *N*-Methylation was performed with satisfactory yields in formate with formaldehyde, giving compound **IV_a**. The analogues were prepared as described in step b. *N*-Alkylation of compound **III** with benzyl chloride, *p*-chlorobenzyl chloride, allyl bromide, benzoyl chloride and acetic anhydride was conducted by refluxing with K_2CO_3 in acetone and afforded compounds **$IV_{b–i}$**, respectively, which were then reduced with Fe in hydrochloric acid. Finally, the analogues of general structure **VI** were furnished by methylsulfonation with triethylamine. Compounds of this class are thermally unstable and should be handled in an ice bath.

With completion of the synthesis, the in vitro K^+ channel inhibitory activity of these nine target compounds as compared with dofetilide was measured. According to the method of Wettwer et al.,[13] the effective concentrations of nine methanesulfonamido phenylethylamine analogues upon increasing FRP in isolated animal atrium were evaluated utilizing a pair-electric stimulus technique. The results are summarized in Table 3. It showed that compound **VI_a** prolonged FRP, reduced heart rate and strengthened cardiac muscle constriction. The level of prolonging FRP is equivalent to that of dofetilide in μM, MaxΔFRP = 24.02%. It is remarkable that the maximal percent change of delaying FRP in μM of compound **VI_c** is 58%, which is higher than that of dofetilide (Table 3), but it reduced cardiac muscle constriction, which may be due to blocking of complex K^+/Ca^{2+} channel. Further investigations are currently in progress.

Conclusion

In summary, 3D-QSAR analyses have been performed on 17 methylsulfonamido phenylethylamine analogues[6,7] by use of CoMFA and CoMSIA methods. The 3D-QSAR models proved a good predictive ability. According to the clues provided by 3D-QSAR analyses, we designed and synthesized a series of new analogues of methanesulfonamido phenylethylamine (**$VI_{a–i}$**). Pharmacological assay indicated that the effective concentrations of delaying FRP 10 ms of these new compounds have a good correlation to the 3D-QSAR predicted data. It is remarkable that the maximal percent change of delaying FRP in μM of compound **VI_c** is much higher than that of dofetilide, but it reduced cardiac muscle constriction, which may be due to blocking of complex K^+/Ca^{2+} channel. The results showed that experimental data correlates well with predicted activity, indicating that the 3D-QSAR models are reliable.

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