

Journal of
Medicinal Chemistry

J. Med. Chem., 1996, 39(12), 2339-2346, DOI:[10.1021/jm950712d](https://doi.org/10.1021/jm950712d)

Terms & Conditions

Electronic Supporting Information files are available without a subscription to ACS Web Editions. The American Chemical Society holds a copyright ownership interest in any copyrightable Supporting Information. Files available from the ACS website may be downloaded for personal use only. Users are not otherwise permitted to reproduce, republish, redistribute, or sell any Supporting Information from the ACS website, either in whole or in part, in either machine-readable form or any other form without permission from the American Chemical Society. For permission to reproduce, republish and redistribute this material, requesters must process their own requests via the RightsLink permission system. Information about how to use the RightsLink permission system can be found at <http://pubs.acs.org/page/copyright/permissions.html>



ACS Publications

MOST TRUSTED. MOST CITED. MOST READ.

Copyright © 1996 American Chemical Society

M-2346-1

Table I. Modifications of the 10-Hydroxyl Substituent of Ryanodine and the Cyclohexane Ring of Dehydroryanodine in Relation to Action at Calcium Release Channels

no.	10-substituent or modification of cyclohexane ring	activity relative to ryanodine ^a			rat ventricular strip assay
		ryanodine receptor		canine ventricle	
		rabbit muscle	mouse brain		
1	ryanodine	100	100	100	100
<u>Modifications of the 10-Hydroxyl Substituent of 1</u>					
3	oxo	30			
4	10-epi-hydroxy	97	69	78	34
5	oxime	26			
6	methoxime	13	13	17	34
7	benzyloxime	13			
8	hydrazone	18			
9	epi-hydroxyamine	32			
10	epi-benzoyloxyamine	8.5	11		
11	epi-methoxyamine	68		36	31
12	epi-benzyloxyamine	14	6.3		
13	epi-amine	68	65		
14	epi-benzamide	9.5			
15	epi-4-azidobenzoylhydrazide	67			
16	lactam	42		7.4	11
<u>Modifications of the Cyclohexane Ring of 2</u>					
17	10-benzoyloxy	3.9	17		
18	Δ^8 (10-hydroxy)	26		27	11
19	Δ^8 -10-oxo	12			
20	10-oxo-2	4.2	1.3		

^a Values for 1 are: IC₅₀s of 3.5 and 3.3 nM for rabbit muscle and mouse brain; K_i of 1.8 nM for cardiac ventricle preparation; and IC₅₀ of 34 nM for rat ventricular muscle strip assay.

M-2346-2

Table II. Defunctionalization of the Cyclohexane Ring of Dehydroryanodine in Relation to Action at Calcium Release Channels

no.	modifications of cyclohexane ring	activity relative to ryanodine ^a =100			
		ryanodine receptor			rat ventricular strip assay
		rabbit muscle	mouse brain	canine ventricle	
21	21- <i>nor</i> -9-oxo(EtB)	13	8.3		
22	21- <i>nor</i> -9 _{ax} -hydroxy(EtB)	0.82	2.1		
23	21- <i>nor</i> -9-oxo	10	7.1	6.5	5.9
24	21- <i>nor</i> -9 _{ax} -hydroxy	0.62	0.50	2.7	26
25	21- <i>nor</i> -9 _{eq} -hydroxy	1.2	0.90	0.66	<3.5
26	21- <i>nor</i> -9-oxo-10-acetoxy	8.3	8.3		
27	21- <i>nor</i> -10-deoxy-9-oxo	1.0	0.20	0.79	4.7
28	21- <i>nor</i> -10-deoxy-9 _{ax} -hydroxy	0.20	0.40	0.42	28
29	21- <i>nor</i> -10-deoxy-9 _{eq} -hydroxy	2.4	4.3	1.6	<3.5
30	10-deoxydehydro	37	77	45	121
31	21- <i>nor</i> -10-deoxy	6.5	78		
32	21- <i>nor</i> -10-deoxy-6,9-oxido	0.16	<0.10	0.13	<3.5
33	21- <i>nor</i> -10-deoxy- Δ^8/Δ^9	0.57 ^b	1.3 ^b		

^a Values for 1 are: IC₅₀s of 3.5 and 3.3 nM for rabbit muscle and mouse brain preparations; K_i of 1.8 nM for cardiac ventricle preparation; and IC₅₀ of 34 nM for rat ventricular muscle strip assay.

^b Single assay of Δ^8/Δ^9 mixture.