Pergamon

SCIENCE DIRECT®

Bioorganic & Medicinal Chemistry 11 (2003) 663–673

BIOORGANIC & MEDICINAL CHEMISTRY

Dantrolene Analogues Revisited: General Synthesis and Specific Functions Capable of Discriminating Two Kinds of Ca^{2+} Release from Sarcoplasmic Reticulum of Mouse Skeletal Muscle

Takamitsu Hosoya,[a,b] Hiroshi Aoyama,[b] Takaaki Ikemoto,[c] Yasutaka Kihara,[c] Toshiyuki Hiramatsu,[b] Makoto Endo[c] and Masaaki Suzuki[a,b,*]

[a]*Division of Regeneration and Advanced Medical Science, Gifu University Graduate School of Medicine, Gifu University, Yanagido 1-1, Gifu 501-1193, Japan*

[b]*Department of Biomolecular Science, Faculty of Engineering, Gifu University, Yanagido 1-1, Gifu 501-1193, Japan*

[c]*Department of Pharmacology, Saitama Medical School, Moro-hongo 38, Moroyama-machi, Iruma-gun, Saitama 350-0495, Japan*

Received 15 October 2002; accepted 13 November 2002

Abstract—The general synthesis of dantrolene analogues with various substituents on its phenyl ring has been developed via palladium-catalyzed cross-coupling reactions, the Stille or Suzuki reaction, as the key step. The effects of synthesized analogues have been evaluated by two kinds of Ca^{2+} release modes from sarcoplasmic reticulum (SR) of mouse skeletal muscle fibers based on: (1) the measurement of twitch contraction caused by the physiological Ca^{2+} release (PCR) of intact skeletal muscle and (2) the rate of Ca^{2+}-induced Ca^{2+} release (CICR) in saponin-treated skinned muscle fibers. Although dantrolene, a lead compound, inhibits both twitch contraction and CICR, some structurally modified analogues exhibit one or the other of these effects. The methoxy congener, GIF-0185, potently inhibits the twitch contraction without affecting the CICR, while GIF-0166 and GIF-0248, the *ortho*-nitro regioisomer and *ortho*, *ortho*-dinitro substituted analogues, respectively, doubly potentiate the CICR exclusively.

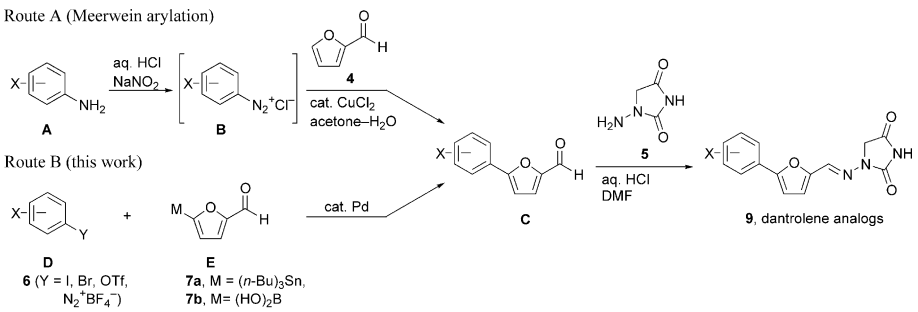
Introduction

Muscle contraction and relaxation are superbly controlled by changes in the cytoplasmic concentration of Ca^{2+} and are regulated by its release and uptake within the sarcoplasmic reticulum (SR), a Ca^{2+} store in muscle cells.[1] In skeletal muscle, the release of Ca^{2+} from SR is physiologically provoked by: (1) depolarization of a transverse tubular (T-tubule) membrane, (2) sensing the induced voltage by the dihydropyridine (DHP) receptor located on T-tubule membrane, (3) signal transmission from the DHP receptor to the ryanodine receptor (skeletal type, RyR1), a Ca^{2+}-releasing channel on the SR membrane, and (4) opening of the RyR1 channel.[1–3] However, the molecular mechanism of these sequential processes during the excitation–contraction (E–C) coupling remains to be clarified, especially whether the signal from the DHP receptor is transmitted to RyR1 directly or through some regulatory proteins.[4–6] Furthermore, although RyR1 possesses dual functions as channels for both the physiological Ca^{2+} release (PCR) in the E–C coupling and Ca^{2+}-induced Ca^{2+} release (CICR), the significance of the latter process remains unclear.[2,3a,4] The CICR of cardiac type RyR (RyR2) working as the physiological Ca^{2+}-releasing process in the cardiac muscle is also responsible for this issue.[4,7] In order to solve the existing problems concerning the Ca^{2+} regulatory systems of muscle cells, we consider that it is necessary to design, at the molecular level, a biochemical probe that acts selectively on PCR or CICR.

Dantrolene (**1**) is known as an efficient Ca^{2+}-regulating agent.[4,8] Some analogues including **1** were synthesized as a new class of muscle relaxants in 1967 by Snyder et al., and their pharmacological effects were evaluated based on their ability to alter the flexor reflex in the hind limb of anesthetized cats.[9] Since then, compound **1**, which shows great activity, has been widely used as an analytical agent for the E–C coupling of skeletal muscle

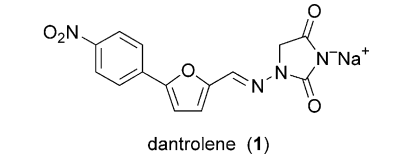
*Corresponding author. Tel.: +81-58-293-2635; fax: +81-58-293-2635; e-mail: suzukims@biomol.gifu-u.ac.jp

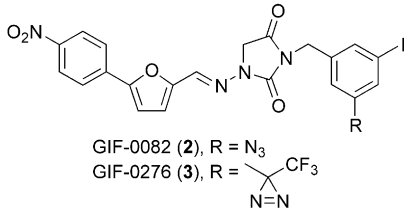
0968-0896/03/$ - see front matter © 2002 Elsevier Science Ltd. All rights reserved.
PII: S0968-0896(02)00600-4



Scheme 1. Methods for the synthesis of dantrolene and its analogues.

to inhibit the Ca^{2+} release[10] and as an efficient drug for the treatment of porcine and human malignant hyperthermia, a genetic disease triggered by excessive Ca^{2+} release when RyR1 has been activated by inhalation anesthetics.[11] Later, however, it was demonstrated that compound **1** is a dual inhibitor for both PCR and CICR of RyR1.[12,13] This non-selective agent has continued to be used for many biological and pharmacological studies due to the lack of appropriate selective agents. In view of the importance of both PCR and CICR as representative Ca^{2+}-related signal transduction mechanisms, it is important to differentiate between their intrinsic roles. Therefore, we have been attempting to develop an efficient ligand which has specificity for either of these two kinds of Ca^{2+}-releasing processes.[4,13] We recently succeeded in developing specific photoaffinity probes, GIF-0082 (**2**) and GIF-0276 (**3**), by substituting the hydantoin moiety of **1** with an azido- or diazirinyl-functionalized unit.[13,14] These compounds selectively inhibit PCR without affecting CICR. These biological findings were evaluated precisely by advanced methods capable of discriminating between the functions of PCR and CICR.[13,15] Next, we directed our attention to structural modification around the phenyl ring of **1** by introducing diverse substituents including both electron-withdrawing and electron-donating functional groups. This paper describes a general synthesis of dantrolene and its analogues based on highly effective Pd(0)-mediated cross-coupling reactions and the precise biological evaluation of synthesized analogues with selective effects on Ca^{2+} release.



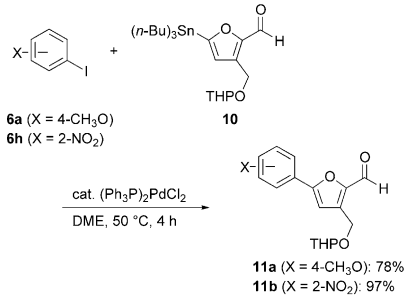


Results and Discussion

General synthesis of dantrolene analogues

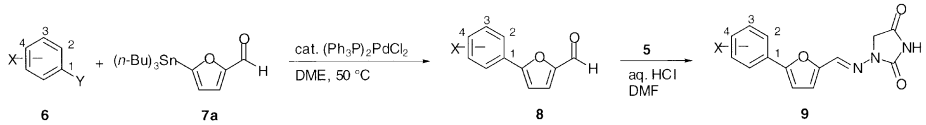
Snyder et al.[9] employed the Meerwein arylation reaction[16] as a key step in the synthesis of dantrolene and related compounds (Route A in Scheme 1); the coupling of arenediazonium salts **B**, prepared from anilines **A**, with 2-furaldehyde (**4**) in the presence of Cu(II) catalyst, followed by condensation of 5-aryl-2-furaldehydes **C** with 1-aminohydantoin (**5**). This method is particularly useful for the synthesis of some dantrolene analogues with electron-withdrawing substituents, such as NO_2 and CN, on the phenyl ring owing to the character of the Meerwein arylation reaction.[17,18] Our aim is to define an extensive structure–activity relationship for a wide variety of dantrolene analogues possessing both electron-withdrawing and electron-donating substituents on a phenyl ring. Thus, we herein describe another way to construct 5-aryl-2-furaldehydes **C**[19] by palladium-catalyzed cross-coupling reactions of aryl derivatives **D**, consisting of diverse substituents, and a stannylated or boronated 2-furaldehyde **E** (Route B in Scheme 1).

Table 1 summarizes the results of the Stille reaction[20] using organostannanes. Reactions were carried out at 50 °C in 1,2-dimethoxyethane (DME) using 4–5% of $(Ph_3P)_2PdCl_2$ and a 1.3-fold amount of 5-(tri-*n*-butylstannyl)-2-furaldehyde (**7a**)[21] for aryl substrates **6**. In most cases, the reaction proceeded smoothly within 2 h to afford 5-aryl-2-furaldehydes **8** in high yields, and was applicable to a wide variety of aryl substrates including both electron-withdrawing and electron-donating groups in a phenyl ring as well as any substitution pattern, *ortho*, *meta*, and *para* (e.g., runs 1–3 and 6–8). In addition, aryl iodides (runs 1–10), aryl bromides (runs



Scheme 2. Synthesis of **11** by the Stille reaction.

Table 1. Synthesis of dantrolene analogues by the Stille reaction[a]



6 7a 8 9

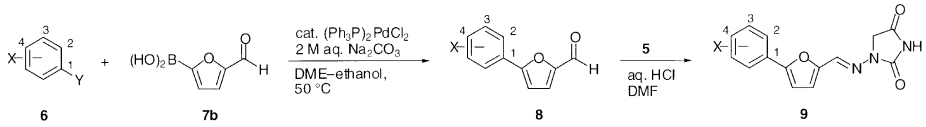
Run	6	X	Y	Time	8		9	
				(h)	Yield[b] (%)		Yield[b] (%)	
1	**6a**	4-CH_3O	I	2	**8a**[c]	79	**9a**[c]	89
2	**6b**	3-CH_3O	I	2	**8b**[c]	97	**9b**	88
3	**6c**	2-CH_3O	I	2	**8c**[c]	87	**9c**	89
4	**6d**	H	I	6	**8d**[c]	93	**9d**[c]	95
5	**6e**	4-CH_3	I	2	**8e**[c]	90	**9e**	95
6	**6f**	4-NO_2	I	2	**8f**[c]	75	**9f**[c]	94
7	**6g**	3-NO_2	I	18	**8g**[c]	90	**9g**[c]	93
8	**6h**	2-NO_2	I	1	**8h**[c]	85	**9h**[c]	96
9	**6i**	4-CF_3	I	6	**8i**[c]	93	**9i**	90
10	**6j**	2,3,4,5,6-F_5	I	2	**8j**	74	**9j**	93
11	**6k**	4-F	Br	12	**8k**[c]	81[d]	**9k**[c]	99
12	**6l**	4-C_6H_5	Br	6	**8l**[c]	48	**9l**	99
13	**6m**	2,6-$(NO_2)_2$	Br	24	**8m**	87[e]	**9m**	94
14	**6n**	2,3-Benzo	OSO_2CF_3	1.5	**8n**[c]	94[f]	**9n**	86
15	**6o**	4-Br	$N_2^+ BF_4^-$	0.5	**8o**[c]	48[g]	**9o**[c]	90
16	**6p**	4-CH_3O	$N_2^+ BF_4^-$	0.5	**8a**[c]	82[g]		

[a]Unless otherwise noted, the reactions were carried out according to the standard procedure described in the Experimental.
[b]Isolated yield.
[c]Known compound.
[d]Reaction in the presence of additional CuBr (5%) at 90 °C.
[e]Reaction at 60 °C.
[f]A 7-fold amount of LiCl was added.
[g]The reaction was carried out at room temperature using CH_3CN as a solvent.

11–13), aryl triflate (run 14), and arenediazonium salts (runs 15 and 16) can be used as reactive substrates. The reaction of 1-bromo-4-fluorobenzene (**6k**) gave rather low yields under standard conditions (2 h, 47%) as well as at higher temperature (90 °C, 12 h, 67%), but the addition of 5% CuBr increased the coupling product yield to 81% (run 11). A sterically hindered 2,6-disubstituted substrate also underwent the reaction smoothly (run 13). LiCl was necessary to promote the reaction for aryl triflate (run 14).[20b,c] Arenediazonium salts showed the highest reactivity (runs 15 and 16). The reaction was also applicable to the stannylated furaldehyde **10**,[22] a derivative with an additional substituent on the furan ring, giving coupled products **11a** and **11b** in high yields (Scheme 2).

Table 2 summarizes the synthesis by the Suzuki reaction[23] in which 5-formyl-2-furanboronic acid (**7b**)[24] was used as a counter furaldehyde. The reaction was carried out at 50 °C in DME–ethanol in the presence of aqueous Na_2CO_3 using 5% $(Ph_3P)_2PdCl_2$ and a 1.3-fold amount of **7b** for an aryl substrate **6**. The reaction proceeded smoothly within a few h to give the desired 5-aryl-2-furaldehydes **8** in high yields.[25] Like the Stille

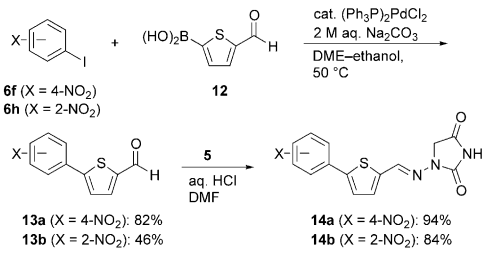
Table 2. Synthesis of dantrolene analogues by the Suzuki reaction[a]



6 7b 8 9

Run	6	X	Y	Time	8		9	
				(h)	Yield[b] (%)		Yield[b] (%)	
1	**6a**	4-CH_3O	I	1	**8a**[c]	99		
2	**6g**	3-NO_2	I	1	**8g**[c]	92		
3	**6h**	2-NO_2	I	3	**8h**[c]	100		
4	**6k**	4-F	Br	3	**8k**[c]	79		
5	**6q**	4-OH	I	1	**8q**[c]	87	**9q**	88
6	**6r**	4-CF_3SO_2	I	1	**8r**	97	**9r**	98
7	**6s**	4-CN	Br	1	**8s**[c]	89	**9s**[c]	99

[a]Unless otherwise noted, the reactions were carried out according to the standard procedure described in the Experimental.
[b]Isolated yield.
[c]Known compound.



Scheme 3. Synthesis of thiophene analogues by the Suzuki reaction.

reaction, neither the electronic character nor the substituted position of the substituents on the phenyl ring influenced the reaction to any extent. An analogue with a phenolic hydroxy group was also usable without hydroxy protection (run 5). In addition, 5-formyl-2-thiopheneboronic acid (**12**), a sulfur analogue, could be used for the reaction, giving **13a** and **13b** in high yields (Scheme 3).

Finally, 5-aryl-2-furaldehydes **8a**–**s** and thiophene analogues **13a**,**b**, thus prepared by the Stille and Suzuki reactions, were condensed with 1-aminohydantoin (**5**)[26] under acidic conditions to furnish the desired dantrolene structures, **9a**–**s** and **14a**,**b**, respectively, in high yields (Tables 1 and 2, and Scheme 3).

Evaluation of effects on Ca^{2+} release

With a wide variety of dantrolene analogues in hand, we examined their effects on two kinds of Ca^{2+} release from SR of mouse skeletal muscle: PCR and CICR. The effects on PCR were estimated by comparing the tension of twitch contraction of intact mouse skeletal muscle at room temperature before and after treatment with the analogues.[13,15] The effects on CICR were evaluated at room temperature by measuring the rates of CICR in saponin-treated skinned muscle fibers of mouse skeletal muscle by using Fura-2[27] as a Ca^{2+} indicator under Mg^{2+}-free conditions at 1 μM Ca^{2+}.[13,15] The final concentration of each analogue in both experiments was fixed at 50 μM to simplify the comparison of efficacy between the analogues, except for dantrolene at 20 μM owing to its low solubility.[28] The results are shown in Table 3 with normalized values.

Table 3. Effects of dantrolene analogues (50 μM) on twitch contraction and the rate of CICR from SR of mouse skeletal muscle[a]

Compd	X[b]	Normalized twitch contraction[c] (%)	Normalized CICR rate[c] (%)
Dantrolene (**1**)[d,e]	4-NO_2	19.2±2.5 (n=13)	51.2±6.5 (n=6)
GIF-0185 (**9a**)	4-CH_3O	18.3±2.1 (n=6)	126.2±12.1 (n=4)
9b	3-CH_3O	44.3±4.8 (n=3)	100.5±6.2 (n=3)
9c	2-CH_3O	92.0±1.7 (n=3)	117.3±5.5 (n=3)
9d	H	37.4±6.8 (n=3)	115.3±18.4 (n=3)
9e	4-CH_3	48.5±6.2 (n=3)	116.3±3.6 (n=3)
9g	3-NO_2	40.5±10.4 (n=3)	101.6±9.4 (n=3)
GIF-0166 (**9h**)	2-NO_2	98.3±1.7 (n=3)	197.0±15.3 (n=4)
9i	4-CF_3	38.2±2.1 (n=3)	96.2±8.7 (n=6)
9j	2,3,4,5,6-F_5	82.6±2.5 (n=3)	107.1±8.3 (n=3)
9k	4-F	31.3±8.4 (n=3)	93.8±8.9 (n=3)
9l	4-C_6H_5	94.8±2.9 (n=3)	104.6±4.4 (n=3)
GIF-0248 (**9m**)[e]	2,6-$(NO_2)_2$	84.6±2.3 (n=4)	180.4±2.4 (n=4)
9n	2,3-benzo	85.3±4.1 (n=3)	108.2±14.0 (n=3)
9o	4-Br	39.3±10.0 (n=3)	81.0±5.2 (n=3)
9q	4-OH	64.0±4.7 (n=3)	84.6±8.7 (n=3)
9r	4-CF_3SO_2	87.8±0.9 (n=3)	115.8±8.1 (n=3)
9s	4-CN	33.6±5.8 (n=3)	81.7±8.8 (n=3)
14a	4-NO_2	82.6±3.6 (n=3)	95.6±5.9 (n=5)
14b	2-NO_2	89.0±4.2 (n=3)	110.1±5.0 (n=3)

[a]The evaluation was carried out as described in refs 13 and 15.
[b]Substituent on the phenyl ring.
[c]The values (mean±SE mean) in comparison with that of control (100%) experiment.
[d]20 μM dose.
[e]The corresponding sodium salt was used.

As reported previously,[13,14] dantrolene (**1**) inhibits the twitch contraction of intact skeletal muscle in a dose-dependent manner by about 80% at 20 μM dose, and, at the same time, **1** decreases the rate of CICR by approximately 50% at the same dose under the conditions mentioned above. For comparison, these results are referred to as standard values in Table 3. There was no significant difference in the inhibitory effects between the sodium salt **1** and salt-free form **9f** (data not shown). Here, the effects of methoxy congener referred to as GIF-0185 (**9a**) and *ortho*-nitro congeners referred to as GIF-0166 (**9h**) and GIF-0248 (**9m**) showed remarkable selectivity. Thus, **9a** at 50 μM reduced the twitch contraction similarly as **1** did, but showed no inhibitory effect on CICR. On the other hand, **9h**, the *ortho*-nitro regioisomer of dantrolene, doubled the rate of CICR without affecting the twitch contraction. It should be noted that **9h** is the compound reported by Snyder et al. as an inert compound[9] but a specific function for CICR was now revealed in our study. GIF-0248 (**9m**) with an additional *ortho*-nitro group showed similar enhancing effect on CICR, suggesting that the nitro group at the *ortho* position is important for CICR potentiation.

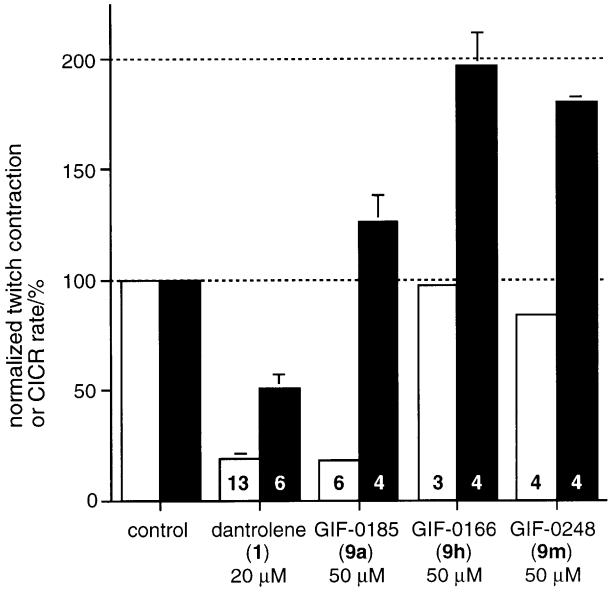


Figure 1. Effects of dantrolene (**1**), GIF-0185 (**9a**), GIF-0166 (**9h**), and GIF-0248 (**9m**) on twitch contraction (open column) and CICR rate (filled column) of mouse skeletal muscle. The number of experiments (n) is indicated in the column.

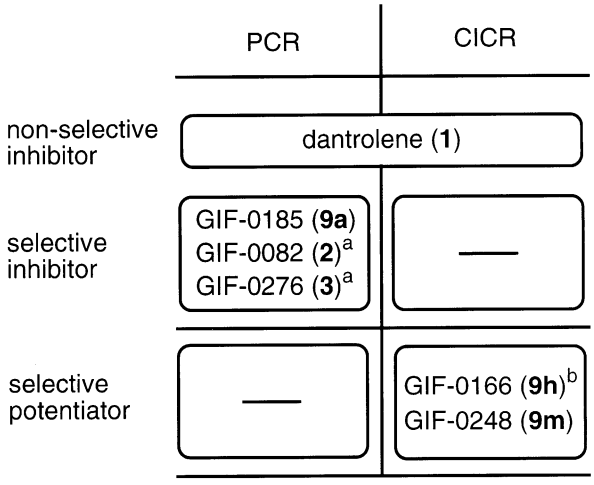


Figure 2. Classification of dantrolene analogues with selective effects on PCR or CICR of skeletal muscle. [a]See ref 14. [b]Known compound, see ref 9.

These selective effects are also illustrated in a bar graph (Fig. 1).

The trend of characteristic features for other compounds are summarized as follows:

A. Effect on twitch contraction: (1) the analogues with a substituent such as H, CH_3, CF_3, F, Br, and CN at the 4-position inhibit the twitch contraction by about 50∼70%, although not as much as **1** and **9a**, (2) the inhibitory activity on twitch contraction by *meta*-regioisomers of **1** and **9a**, which correspond to **9g** and **9b**, respectively, is retained to about 60%, (3) the presence of a polar group such as phenolic hydroxy group in **9q** does not favor expression of the effect, (4) the analogues with a large substituent at the 4-position, such as **9l** which has a phenyl group and **9r** which has a trifluoromethanesulfonyl group, are almost ineffective,[29] (5) the absence of a substituent at the 2-position is important for the activity because all of the analogues with an *ortho*-substituent failed to inhibit twitch contraction, (6) thiophene analogues, **14a** and **14b**, had almost no effect on twitch contraction, indicating the indispensability of the furan ring for PCR inhibition, and (7) in consequence, the presence of a non-polar substituent with a suitable size at the 4- or 3-position on the phenyl ring is effective at expressing an inhibitory effect on twitch contraction;
B. Effect on the rate of CICR: analogues other than **9h** and **9m** have little effect on the rate of CICR, except for **9o**, **9q**, and **9s**, which have a slight inhibitory effect (15∼20%).

Figure 2 shows the classification of selective dantrolene analogues for PCR and CICR of skeletal muscle. Here, several selective PCR inhibitors and CICR potentiators thus evaluated in our study are placed in two columns. Further study will be done to fill the remaining blanks by selective agents based on the structural modification of dantrolene (**1**).

Conclusion

We elaborated on the general synthesis of dantrolene and its analogues based on the Pd(0)-mediated cross-coupling reactions. The extensive structure–activity relationship led us to find compounds, **9a**, **9h**, and **9m**, with highly selective functions for one of two kinds of Ca^{2+} release, PCR and CICR, of mouse skeletal muscle. Thus, **9a** inhibits the twitch contraction without affecting CICR, while **9h** and **9m** act as selective potentiators of CICR. These specific biochemical compounds can be used to elucidate the precise molecular mechanisms of PCR and CICR in skeletal muscle. In addition, the CICR potentiators may be efficient probes to study physiological Ca^{2+} release in cardiac E–C coupling. Furthermore, these agents may be lead compounds for the development of a new inotropic agent since it is a physiologically important step in cardiac muscle that Ca^{2+} influx activates the RyR-Ca^{2+} release channel via the CICR mechanism.

Experimental

General

1,2-Dimethoxyethane (DME) was distilled over sodium benzophenone ketyl under Ar. Dantrolene (**1**) was donated from Yamanouchi Pharmaceutical or purchased from Nacalai Tesque. All other chemical reagents used were commercial grade. Column chromatography was conducted using silica gel (Merck 9385-5B, 70–230 mesh). Melting points (mp) were measured on a Yanaco MP-500D instrument. ^1H, ^{13}C, and ^{19}F NMR spectra were obtained with JEOL JNM α-400 or AL-400 spectrometers. $CDCl_3$ (Isotec), DMSO-d_6 (Isotec, Acros) or acetone-d_6 (Isotec) was used as solvent for obtaining NMR spectra. Chemical shifts (δ) are given in parts per million (ppm) downfield from $(CH_3)_4Si$ (for ^1H NMR in $CDCl_3$), CF_3COOH (for ^{19}F NMR), or solvents (for ^1H NMR in DMSO-d_6 and ^{13}C NMR) as internal references with coupling constants (*J*) in Hz. The abbreviations s, d, t, q, and m signify singlet, doublet, triplet, quartet, and multiplet, respectively. IR spectra were recorded on a Shimadzu FTIR-8100A spectrophotometer with the absorption band given in cm^{-1}. Elemental analyses were performed with a Yanako CHN Corder MT-6 at the Instrumental Analysis Center, Gifu University or a Perkin-Elmer Series II CHNS/O Analyzer 2400 at the Microanalytical Laboratory, Department of Chemistry, Tokyo Institute of Technology.

Palladium-catalyzed cross-coupling reactions

Standard procedures are shown in the synthesis of **8a**.

Synthesis by the Stille reaction (Table 1, run 1): A solution of 4-iodoanisole (**6a**) (233 mg, 996 μmol), 5-(tri-*n*-

butylstannyl)-2-furaldehyde (**7a**)[21] (499 mg, 1.30 mmol), and $(Ph_3P)_2PdCl_2$ (27.4 mg, 39.0 μmol) in DME (4 mL) was heated at 50 °C for 2 h. After cooling the reaction mixture to room temperature, saturated aqueous KF solution (10 mL) was added and followed by the addition of KF powder (500 mg). The resulting mixture was stirred overnight and filtered through a pad of Celite. The filtrate was extracted with EtOAc (10 mL × 3). The combined organic extracts were washed successively with a saturated aqueous KF solution, saturated aqueous $NaHCO_3$ solution, and brine. The resulting solution was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by silica-gel column chromatography (*n*-hexane/EtOAc = 5:1) to give **8a** (159 mg, 79.0%).

Synthesis by the Suzuki reaction (Table 2, run 1): A solution of 4-iodoanisole (**6a**) (234 mg, 1.00 mmol), 5-formyl-2-furanboronic acid (**7b**)[24] (183 mg, 1.31 mmol), and $(Ph_3P)_2PdCl_2$ (35.1 mg, 50.0 μmol) in DME (3 mL), ethanol (2 mL), and 2 M aqueous Na_2CO_3 (3 mL) was heated at 50 °C for 1 h. After being cooled to room temperature, the reaction mixture was extracted with EtOAc (10 mL × 3). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by silica-gel column chromatography (*n*-hexane/EtOAc = 7:1) to give **8a** (201 mg, 99.4%).

5-(4-Methoxyphenyl)-2-furaldehyde (8a). Yellow solid; mp 42–42.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.86 (s, 3H), 6.72 (d, 1H, J = 3.8 Hz), 6.94–7.00 (AA′BB′, 2H), 7.31 (d, 1H, J = 3.8 Hz), 7.75–7.79 (AA′BB′, 2H), 9.60 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.4, 106.3, 114.4 (2C), 121.8, 124.1, 126.9 (2C), 151.6, 159.8, 160.9, 176.8; IR (KBr, cm^{-1}) 768, 794, 835, 967, 1028, 1177, 1258, 1298, 1389, 1428, 1441, 1485, 1611, 1671. Anal. calcd for $C_{12}H_{10}O_3$: C, 71.28; H, 4.98. Found: C, 70.99; H, 5.21.

5-(3-Methoxyphenyl)-2-furaldehyde (8b). Yellow solid; mp 70.5–71.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.88 (s, 3H), 6.84 (d, 1H, J = 3.6 Hz), 6.94–6.97 (m, 1H), 7.32 (d, 1H, J = 3.6 Hz), 7.34–7.42 (m, 3H), 9.66 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.4, 108.0, 110.3, 115.7, 117.9, 123.5, 130.0, 130.2, 152.0, 159.3, 160.0, 177.2; IR (KBr, cm^{-1}) 769, 783, 1032, 1219, 1474, 1487, 1520, 1674. Anal. calcd for $C_{12}H_{10}O_3$: C, 71.28; H, 4.98. Found: C, 71.21; H, 5.20.

5-(2-Methoxyphenyl)-2-furaldehyde (8c). Red solid; mp 54.5–55.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.97 (s, 3H), 6.99–7.01 (m, 1H), 7.07 (dt, 1H, J = 1.3, 7.6 Hz), 7.14 (d, 1H, J = 3.8 Hz), 7.34 (d, 1H, J = 3.8 Hz), 7.35–7.39 (m, 1H), 8.05 (dd, 1H, J = 1.3, 7.6 Hz), 9.65 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.4, 111.1, 112.5, 118.0, 120.9, 123.9, 127.4, 130.6, 150.9, 156.1, 156.8, 177.1; IR (KBr, cm^{-1}) 756, 766, 1024, 1244, 1279, 1489, 1516, 1673. Anal. calcd for $C_{12}H_{10}O_3$: C, 71.28; H, 4.98. Found: C, 71.40; H, 5.23.

5-Phenyl-2-furaldehyde (8d). Orange oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83 (d, 1H, J = 3.6 Hz), 7.33 (d, 1H, J = 3.6 Hz), 7.34–7.47 (m, 3H), 7.81–7.84 (m, 2H), 9.66 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$ + acetone-d_6) δ 107.3, 123.2, 124.7 (2C), 128.36 (2C), 128.43, 129.1, 151.4, 158.6, 176.4,; IR (KBr, cm^{-1}) 691, 709, 968, 1032, 1256, 1451, 1476, 1522, 1674. Anal. calcd for $C_{11}H_8O_3$: C, 76.73; H, 4.68. Found: C, 76.65; H, 4.93.

5-(4-Methylphenyl)-2-furaldehyde (8e). Yellow solid; mp 55–56 °C (lit.[19c] 55–56 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.40 (s, 3H), 6.80 (d, 1H, J = 3.6 Hz), 7.24–7.27 (AA′BB′, 2H), 7.32 (d, 1H, J = 3.6 Hz), 7.71–7.74 (AA′BB′, 2H), 9.63 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 107.4, 123.8, 125.3 (2C), 126.2, 129.6 (2C), 140.0, 151.8, 159.8, 177.0; IR (KBr, cm^{-1}) 502, 768, 795, 822, 922, 967, 1030, 1258, 1416, 1450, 1487, 1530, 1667. Anal. calcd for $C_{12}H_{10}O_2$: C, 77.40; H, 5.41. Found: C, 77.27; H, 5.52.

5-(4-Nitrophenyl)-2-furaldehyde (8f). Yellow solid; mp 199–202 °C (lit.[19c] 199–200 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (d, 1H, J = 3.6 Hz), 7.38 (d, 1H, J = 3.6 Hz), 7.97–8.00 (AA′BB′, 2H), 8.31–8.34 (AA′BB′, 2H), 9.74 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 112.2, 124.5 (2C), 124.9, 125.9 (2C), 134.3, 147.3, 152.7, 155.5, 178.6; IR (KBr, cm^{-1}) 754, 810, 855, 967, 1044, 1264, 1329, 1345, 1474, 1520, 1601, 1669, 1690, 2361. Anal. calcd for $C_{11}H_7NO_4$: C, 60.83; H, 3.25; N, 6.45. Found: C, 60.61; H, 3.45; N, 6.24.

5-(3-Nitrophenyl)-2-furaldehyde (8g). Light yellow solid; mp 159.5–160.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (d, 1H, J = 3.9 Hz), 7.37 (d, 1H, J = 3.9 Hz), 7.65 (dd, 1H, J = 8.0, 8.2 Hz), 8.15 (ddd, 1H, J = 1.0, 1.7, 8.0 Hz), 8.25 (ddd, 1H, J = 1.0, 2.0, 8.2 Hz), 8.63 (dd, 1H, J = 1.7, 2.0 Hz), 9.73 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ 109.0, 118.8, 122.7, 122.8, 129.3, 129.6, 129.8, 147.6, 151.4, 155.1, 176.4; IR (KBr, cm^{-1}) 743, 785, 801, 1260, 1364, 1509, 1536, 1684. Anal. calcd for $C_{11}H_7NO_4$: C, 60.83; H, 3.25; N, 6.45. Found: C, 60.75; H, 3.61; N, 6.19.

5-(2-Nitrophenyl)-2-furaldehyde (8h). Yellow solid; mp 92.5–94 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.80 (d, 1H, J = 3.8 Hz), 7.33 (d, 1H, J = 3.8 Hz), 7.57 (dt, 1H, J = 1.2, 8.0 Hz), 7.68 (dt, 1H, J = 1.2, 8.0 Hz), 7.82–7.86 (m, 2H), 9.69 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 112.0, 121.9, 123.0, 124.3, 130.1, 130.3, 132.4, 148.0, 152.9, 153.4, 177.7; IR (KBr, cm^{-1}) 744, 783, 855, 974, 1053, 1248, 1360, 1474, 1514, 1526, 1684. Anal. calcd for $C_{11}H_7NO_4$: C, 60.83; H, 3.25; N, 6.45. Found: C, 60.57; H, 3.59; N, 6.29.

5-(4-Trifluoromethylphenyl)-2-furaldehyde (8i). Light yellow solid; mp 111–113.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96 (d, 1H, J = 3.9 Hz), 7.35 (d, 1H, J = 3.9 Hz), 7.71 (d, 2H, J = 8.3 Hz), 7.94 (d, 2H, J = 8.3 Hz), 9.71 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 109.1, 122.8, 123.7 (q, $^1J_{C-F}$ = 271.5 Hz), 125.3 (2C), 125.9 (q, 2C, $^3J_{C-F}$ = 3.3 Hz), 131.1 (q, $^2J_{C-F}$ = 32.9 Hz), 132.0, 152.4, 157.2, 177.2; ^{19}F NMR (372 MHz, $CDCl_3$) δ;14.77 (s, 3F); IR (KBr, cm^{-1}) 803, 843, 967, 1040, 1059, 1076, 1113, 1179, 1264, 1325, 1489, 1669. Anal. calcd for $C_{12}H_7O_2F_3$: C, 60.01; H, 2.94. Found: C, 60.23; H, 3.30.

5-(2,3,4,5,6-Pentafluorophenyl)-2-furaldehyde (8j). Yellow solid; mp 74.5–75.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 ($d_{H-H}t_{H-F}$, 1H, $^3J_{H-H}$ = 3.7, $^5J_{H-F}$ = 3.7 Hz), 7.39 (d, 1H, J = 3.7 Hz), 9.76 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 105.4 (dd, $^2J_{C-F}$ = 14.9, $^3J_{C-F}$ = 4.9 Hz), 115.4 (d, $^4J_{C-F}$ = 6.6 Hz), 120.5, 137.9 (ddddd, $^1J_{C-F}$ = 253.4, $^2J_{C-F}$ = 13.2, $^2J_{C-F}$ = 13.2, $^3J_{C-F}$ = 4.9, $^4J_{C-F}$ = 1.6 Hz), 141.3 (ddd, 2C, $^1J_{C-F}$ = 256.6, $^2J_{C-F}$ = 14.8, $^3J_{C-F}$ = 4.9 Hz), 144.0 (dddddd, 2C, $^1J_{C-F}$ = 259.9, $^2J_{C-F}$ = 14.8, $^2J_{C-F}$ = 14.8, $^3J_{C-F}$ = 3.3, $^3J_{C-F}$ = 3.3, $^4J_{C-F}$ = 1.6 Hz), 145.9 (dd, $^3J_{C-F}$ = 3.3, $^4J_{C-F}$ = 1.6 Hz), 152.8, 177.6; ^{19}F NMR (372 MHz, $CDCl_3$) δ −83.2 (dddd, 2F, $^3J_{F-F}$ = 24.4, $^3J_{F-F}$ = 21.4, $^4J_{F-F}$ = 5.3, $^5J_{F-F}$ = 3.1 Hz), −73.9 (tt, 1F, $^3J_{F-F}$ = 21.4, $^4J_{F-F}$ = 3.1 Hz), −61.3 (dddd, 2F, $^3J_{F-F}$ = 24.4, $^4J_{F-F}$ = 6.1, $^5J_{F-F}$ = 3.1, $^5J_{F-H}$ = 3.1 Hz); IR (KBr, cm^{-1}) 787, 833, 968, 1038, 1159, 1229, 1287, 1487. Anal. calcd for $C_{11}H_3O_2F_5$: C, 50.40; H, 1.15. Found: C, 50.07; H, 1.53.

5-(4-Fluorophenyl)-2-furaldehyde (8k). Yellow solid; mp 79–80 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.79 (d, 1H, J = 3.4 Hz), 7.11–7.18 (AA′BB′ with H–F coupling, 2H), 7.32 (d, 1H, J = 3.4 Hz), 7.79–7.85 (AA′BB′ with H–F coupling, 2H), 9.65 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 107.4, 116.2 (d, 2C, $^2J_{C-F}$ = 21.5 Hz), 123.6, 125.3 (d, $^4J_{C-F}$ = 3.3 Hz), 127.3 (d, 2C, $^3J_{C-F}$ = 9.1 Hz), 152.0, 158.5, 163.5 (d, $^1J_{C-F}$ = 250.6 Hz), 177.1; ^{19}F NMR (372 MHz, $CDCl_3$) δ −32.52 (tt, 1F, $^3J_{F-H}$ = 8.4, $^4J_{F-H}$ = 5.3 Hz); IR (KBr, cm^{-1}) 810, 968, 1003, 1082, 1273, 1354, 1507, 1536, 1674. Anal. calcd for $C_{11}H_7O_2F$: C, 69.47; H, 3.71. Found: C, 69.22; H, 4.06.

5-(4-Phenylphenyl)-2-furaldehyde (8l). Yellow solid; mp 137–140 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 (d, 1H, J = 3.9 Hz), 7.35 (d, 1H, J = 3.9 Hz), 7.36–7.41 (m, 1H), 7.44–7.50 (m, 2H), 7.62–7.66 (m, 2H), 7.67–7.71 (AA′BB′, 2H), 7.89–7.93 (AA′BB′, 2H), 9.67 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 107.7, 123.4, 125.6 (2C), 126.9 (2C), 127.5 (2C), 127.72, 127.74, 128.8 (2C), 139.9, 142.2, 151.9, 159.0, 176.9; IR (KBr, cm^{-1}) 689, 764, 799, 1028, 1480, 1671. Anal. calcd for $C_{17}H_{12}O_2$: C, 82.24; H, 4.87. Found: C, 82.22; H, 5.15.

5-(2,6-Dinitrophenyl)-2-furaldehyde (8m). Yellow solid; mp 120.5–122 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78 (d, 1H, J = 3.9 Hz), 7.34 (d, 1H, J = 3.9 Hz), 7.85 (t, 1H, J = 3.9 Hz), 8.21 (d, 2H, J = 3.9 Hz), 9.70 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 114.3, 118.8, 121.3, 127.9 (2C), 131.9, 146.8 (2C), 150.0, 153.9, 177.7; IR (KBr, cm^{-1}) 708, 743, 772, 824, 912, 968, 1026, 1354, 1391, 1443, 1537, 1545, 1682, 3092. Anal. calcd for $C_{11}H_6N_2O_6$: C,50.39; H, 2.31; N, 10.69. Found: C, 50.49; H, 2.52; N, 10.56.

5-(1-Naphthyl)-2-furaldehyde (8n). Orange solid; mp 51.5–52.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 (d, 1H, J = 3.6 Hz), 7.43 (d, 1H, J = 3.6 Hz), 7.51 (m, 3H), 7.87 (d, 1H, J = 6.8 Hz), 7.92 (t, 2H, J = 6.8 Hz), 8.40 (d, 1H, J = 8.4 Hz), 9.74 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 111.9, 122.7, 124.9, 125.1, 126.3, 126.6, 127.4, 127.6, 128.7, 130.2, 130.5, 133.8, 152.4, 159.3, 177.4; IR (KBr, cm^{-1}) 774, 799, 968, 1028, 1269, 1387, 1501, 1516, 1674. Anal. calcd for $C_{15}H_{10}O_2$: C, 81.07; H, 4.54. Found: C, 80.77; H, 4.68.

5-(4-Bromophenyl)-2-furaldehyde (8o). Yellow solid; mp 145–148 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.86 (d, 1H, J = 3.8 Hz), 7.33 (d, 1H, J = 3.8 Hz), 7.57–7.60 (AA′BB′, 2H), 7.68–7.71 (AA′BB′, 2H), 9.66 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 108.0, 123.5, 123.9, 126.7 (2C), 127.8, 132.2 (2C), 152.1, 158.2, 177.2; IR (KBr, cm^{-1}) 793, 831, 968, 1044, 1262, 1412, 1476, 1663, 1684, 2361. Anal. calcd for $C_{11}H_7O_2Br$: C, 52.62; H, 2.81. Found: C, 52.71; H, 3.17.

5-(4-Hydroxyphenyl)-2-furaldehyde (8q). Brown solid; mp 178–180 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.22 (s, 1H), 6.72 (d, 1H, J = 3.9 Hz), 6.90–6.95 (AA′BB′, 2H), 7.32 (d, 1H, J = 3.9 Hz), 7.71–7.76 (AA′BB′, 2H), 9.60 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 106.6, 116.0 (2C), 119.7, 126.1, 126.9 (2C), 150.9, 159.0, 159.1, 176.8; IR (KBr, cm^{-1}) 525, 756, 801, 830, 965, 1026, 1258, 1287, 1387, 1436, 1476, 1495, 1593, 1611, 1638, 1647, 3142. Anal. calcd for $C_{11}H_8O_3$: C, 70.21; H, 4.29. Found: C, 70.14; H, 4.65.

5 - [4 - (Trifluoromethanesulfonyl)phenyl] - 2 - furaldehyde (8r). Yellow solid; mp 129–129.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (d, 1H, J = 3.9 Hz), 7.39 (d, 1H, J = 3.9 Hz), 8.07–8.14 (m, 4H), 9.60 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 111.3, 119.6 (q, $^1J_{C-F}$ = 324.1 Hz), 122.3, 125.9 (2C), 131.0, 131.4 (2C), 136.2, 153.1, 155.4, 177.4; ^{19}F NMR (372 MHz, $CDCl_3$) δ −0.56 (s, 3F); IR (KBr, cm^{-1}) 581, 625, 777, 801, 967, 1036, 1076, 1138, 1186, 1221, 1260, 1293, 1368, 1418, 1522, 1599, 1663, 1676. Anal. calcd for $C_{12}H_7O_4SF_3$: C, 47.37; H, 2.32. Found: C, 47.72; H, 2.63.

5-(4-Cyanophenyl)-2-furaldehyde (8s). Colorless solid; mp 166–169 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (d, 1H, J = 3.9 Hz), 7.36 (d, 1H, J = 3.9 Hz), 7.72–7.76 (AA′BB′, 2H), 7.90–7.94 (AA′BB′, 2H), 9.72 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 110.0, 112.7, 118.2, 122.7, 125.4 (2C), 132.6 (2C), 132.7, 152.6, 156.4, 177.2; IR (KBr, cm^{-1}) 546, 808, 841, 972, 1040, 1482, 1667, 1688, 2224. Anal. calcd for $C_{12}H_7NO_2$: C, 73.09; H, 3.58; N, 7.10. Found: C, 73.08; H, 3.87; N, 6.93.

5-(4-Methoxyphenyl)-3-(tetrahydropyranyloxymethyl)-2-furaldehyde (11a). Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.53–1.72 (m, 3H), 1.73–1.92 (m, 2H), 3.54–3.60 (m, 1H), 3.86 (s, 3H), 3.86–3.93 (m, 1H), 4.78 (d, 1H, J = 14.0 Hz), 4.98 (d, 1H, J = 14.0 Hz), 6.77 (s, 1H), 6.93–6.98 (AA′BB′, 2H), 7.72–7.77 (AA′BB′, 2H), 9.82 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.5, 25.5, 30.6, 55.4, 60.5, 62.4, 98.4, 106.8, 114.3 (2C), 121.7, 126.8 (2C), 137.0, 146.9, 158.5, 160.6, 177.3; IR (KBr, cm^{-1}) 816, 837, 1030, 1063, 1078, 1125, 1177, 1256, 1304, 1435, 1466, 1483, 1611, 1667, 2869, 2942. Anal. calcd for $C_{18}H_{20}O_5$: C, 68.34; H, 6.37. Found: C, 68.10; H, 6.43.

5-(2-Nitrophenyl)-3-(tetrahydropyranyloxymethyl)-2-furaldehyde (11b). Brown oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.52–1.72 (m, 4H), 1.73–1.92 (m, 2H), 3.53–3.62 (m, 1H), 3.89 (ddd, 1H, J = 3.4, 8.0, 11.6 Hz), 4.76 (t, 1H, J = 3.6 Hz), 4.79 (d, 1H, J = 14.3 Hz), 5.00 (d, 1H,

J = 14.3 Hz), 6.86 (s, 1H), 7.56 (ddd, 1H, J = 1.5, 8.0, 8.0 Hz), 7.66 (ddd, 1H, J = 1.5, 8.0, 8.0 Hz), 7.82 (ddd, 2H, J = 1.5, 1.5, 8.0 Hz), 9.86 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.5, 25.4, 30.5, 60.6, 62.4, 98.6, 112.4, 122.9, 124.2, 129.9, 130.1, 132.2, 135.5, 147.9, 148.1, 152.2, 178.5; IR (KBr, cm^{-1}) 1034, 1059, 1078, 1125, 1354, 1443, 1458, 1534, 1676, 2869, 2944. Anal. calcd for $C_{17}H_{17}NO_6$: C, 61.63; H, 5.17; N, 4.23. Found: C, 61.29; H, 5.21; N, 3.92.

5-(4-Nitrophenyl)-2-thiophenecarboxaldehyde (13a). Yellow solid; mp 176–178.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, 1H, J = 3.9 Hz), 7.81 (d, 1H, J = 3.9 Hz), 7.82–7.85 (AA′BB′, 2H), 8.29–8.33 (AA′BB′, 2H), 9.95 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 124.4 (2C), 126.2, 126.9 (2C), 136.8, 138.9, 144.4, 147.7, 150.2, 182.4; IR (KBr, cm^{-1}) 749, 806, 844, 855, 1219, 1343, 1449, 1509, 1601, 1674. Anal. calcd for $C_{11}H_7NO_3S$: C, 56.64; H, 3.02; N, 6.01. Found: C, 56.53; H, 3.41; N, 5.66.

5-(2-Nitrophenyl)-2-thiophenecarboxaldehyde (13b). Yellow solid; mp 108–111 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (d, 1H, J = 3.9 Hz), 7.58 (ddd, 1H, J = 1.7, 7.7, 7.7 Hz), 7.60 (dd, 1H, J = 1.7, 7.7 Hz), 7.66 (ddd, 1H, J = 1.5, 7.7, 7.7 Hz), 7.73 (d, 1H, J = 3.9 Hz), 7.88 (dd, 1H, J = 1.5, 7.7 Hz), 9.93 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 124.3, 127.4, 128.0, 129.9, 132.0, 132.3, 136.2, 144.5, 146.9, 148.9, 182.5; IR (KBr, cm^{-1}) 747, 764, 781, 812, 1230, 1360, 1441, 1455, 1485, 1514, 1532, 1671. Anal. calcd for $C_{11}H_7NO_3S$: C, 56.64; H, 3.02; N, 6.01. Found: C, 57.03; H, 3.32; N, 5.88.

Condensation of arylfuraldehyde with 1-aminohydantoin. A solution of 1-aminohydantoin (**5**)[26] (25.3 mg, 220 μmol) in 0.67 M HCl (0.3 mL) was added to a solution of **8a** (40.4 mg, 200 μmol) in DMF (1.0 mL) at 0 °C and the mixture was stirred for 1 h at room temperature. Water (ca. 5 mL) was added and the precipitate was filtered and washed well with water (30 mL) on a funnel. The collected solid was dried under reduced pressure to give **9a** (53.2 mg, 89.0%).

1-{[5-(4-Methoxyphenyl)furfurylidene]amino}imidazolidine-2,4-dione (9a). Yellow solid (ethanol); mp 265–266.5 °C (lit.[9a] 266–269 °C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.79 (s, 3H), 4.33 (s, 2H), 6.91 (d, 1H, J = 3.8 Hz), 6.96 (d, 1H, J = 3.8 Hz), 7.01–7.04 (AA′BB′, 2H), 7.68–7.72 (m, 3H), 11.24 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 48.9, 55.3, 106.6, 114.5 (2C), 115.7, 122.4, 125.5 (2C), 133.2, 148.4, 153.3, 154.7, 159.4, 169.0; IR (KBr, cm^{-1}) 745, 791, 824, 936, 974, 1024, 1117, 1177, 1213, 1231, 1256, 1275, 1290, 1360, 1408, 1433, 1493, 1611, 1721, 1763, 3117. Anal. calcd for $C_{15}H_{13}N_3O_4$: C, 60.20; H, 4.38; N, 14.04. Found: C, 60.02; H, 4.45; N, 13.84.

1-{[5-(3-Methoxyphenyl)furfurylidene]amino}imidazolidine-2,4-dione (9b). Light yellow solid (ethanol); mp 249–252.5 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.81 (s, 3H), 4.34 (s, 2H), 6.91–6.94 (m, 1H), 6.94 (d, 1H, J = 3.8 Hz), 7.15 (d, 1H, J = 3.8 Hz), 7.28 (s, 1H), 7.34–7.39 (m, 2H), 7.72 (s, 1H), 11.26 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 49.0, 55.3, 108.7, 109.1, 114.1, 115.2, 116.3, 130.3, 130.8, 133.1, 149.2, 153.3, 154.3, 159.7, 169.0; IR (KBr, cm^{-1}) 774, 789, 932, 1030, 1123, 1217, 1227, 1364, 1387, 1410, 1429, 1478, 1593, 1719, 1763, 3052. Anal. calcd for $C_{15}H_{13}N_3O_4$: C, 60.20; H, 4.38; N, 14.04. Found: C, 60.04; H, 4.55; N, 13.88.

1-{[5-(2-Methoxyphenyl)furfurylidene]amino}imidazolidine-2,4-dione (9c). Light yellow solid (ethanol); mp 236 °C (sublim); ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.92 (s, 3H), 4.34 (s, 2H), 6.94 (d, 1H, J = 3.8 Hz), 7.04 (d, 1H, J = 3.8 Hz), 7.07 (t, 1H, J = 7.5 Hz), 7.15 (d, 1H, J = 7.5 Hz), 7.34 (dt, 1H, J = 0.8, 7.6 Hz), 7.72 (s, 1H), 7.80 (dd, 1H, J = 0.8, 7.6 Hz), 11.26 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 48.9, 55.6, 111.8, 112.3, 115.4, 118.1, 120.8, 125.4, 129.4, 133.1, 148.1, 151.0, 153.3, 155.5, 169.0; IR (KBr, cm^{-1}) 606, 745, 754, 905, 924, 984, 1024, 1109, 1119, 1210, 1237, 1250, 1273, 1345, 1358, 1371, 1402, 1433, 1522, 1721, 1771, 3073. Anal. calcd for $C_{15}H_{13}N_3O_4$: C, 60.20; H, 4.38; N, 14.04. Found: C, 60.07; H, 4.46; N, 13.86.

1-[(5-Phenylfurfurylidene)amino]imidazolidine-2,4-dione (9d). White solid (ethanol); mp 249–250 °C (lit.[9a] 258–260 °C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.35 (s, 2H), 6.95 (d, 1H, J = 3.6 Hz), 7.13 (d, 1H, J = 3.6 Hz), 7.35 (t, 1H, J = 7.4 Hz), 7.46 (t, 2H, J = 7.4 Hz), 7.72 (s, 1H), 7.77 (d, 2H, J = 7.4 Hz), 11.27 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 49.0, 108.3, 115.4, 123.9 (2C), 128.3, 129.1 (2C), 129.5, 133.1, 149.2, 153.3, 154.4, 169.0; IR (KBr, cm^{-1}) 600, 702, 747, 795, 1117, 1213, 1221, 1236, 1345, 1358, 1395, 1453, 1732, 1767, 1775, 2361, 3289. Anal. calcd for $C_{14}H_{11}N_3O_3$: C, 62.45; H, 4.12; N, 15.61. Found: C, 62.25; H, 4.23; N, 15.44.

1-{[5-(4-Methylphenyl)furfurylidene]amino}imidazolidine-2,4-dione (9e). Light yellow solid (ethanol); mp 255 °C (sublim); ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.32 (s, 3H), 4.34 (s, 2H), 6.93 (d, 1H, J = 3.4 Hz), 7.05 (d, 1H, J = 3.4 Hz), 7.27 (d, 2H, J = 8.2 Hz), 7.66 (d, 2H, J = 8.2 Hz), 7.71 (s, 1H), 11.25 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 20.9, 48.9, 107.5, 115.6, 123.9 (2C), 126.9, 129.6 (2C), 133.1, 137.8, 148.8, 153.3, 154.7, 169.0; IR (KBr, cm^{-1}) 795, 820, 1117, 1121, 1221, 1237, 1345, 1360, 1395, 1447, 1493, 1730, 1767, 1775. Anal. calcd for $C_{15}H_{13}N_3O_3$: C, 63.60; H, 4.63; N, 14.83. Found: C, 63.48; H, 4.67; N, 14.73.

1-{[5-(4-Nitrophenyl)furfurylidene]amino}imidazolidine-2,4-dione (9f). Yellow solid (ethanol); mp 272–273 °C (lit.[9a] 279–280 °C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.35 (s, 2H), 7.04 (d, 1H, J = 3.6 Hz), 7.46 (d, 1H, J = 3.6 Hz), 7.76 (s, 1H), 7.99–8.02 (AA′BB′, 2H), 8.29–8.32 (AA′BB′, 2H), 11.31 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 49.0, 112.5, 115.6, 124.5 (2C), 124.6 (2C), 132.6, 135.2, 146.3, 151.1, 152.1, 153.3, 168.9; IR (KBr, cm^{-1}) 608, 692, 752, 798, 855, 1109, 1126, 1211, 1235, 1339, 1352, 1388, 1435, 1480, 1518, 1539, 1599, 1736, 1773, 3076. Anal. calcd for $C_{14}H_{10}N_4O_5$: C, 53.51; H, 3.21; N, 17.83. Found: C, 53.14; H, 3.50; N, 17.54.

1-{[5-(3-Nitrophenyl)furfurylidene]amino}imidazolidine-2,4-dione (9g). Yellow solid (ethanol); mp 251–253 °C (lit.[9a] 246–247 °C); ^{1}H NMR (400 MHz, DMSO-d_6) δ

4.33 (s, 2H), 6.97–6.99 (m, 2H), 7.63 (t, 1H, $J=7.8$ Hz), 7.67 (s, 1H), 7.78 (t, 1H, $J=7.8$ Hz), 7.87 (d, 1H, $J=7.8$ Hz), 7.96 (d, 1H, $J=7.8$ Hz), 11.28 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 48.9, 112.1, 114.5, 122.6, 124.3, 129.5, 129.9, 132.5, 132.9, 147.0, 149.3, 150.8, 153.2, 168.9; IR (KBr, cm^{-1}) 743, 808, 818, 1125, 1213, 1347, 1385, 1437, 1522, 1538, 1732, 1786. Anal. calcd for $C_{14}H_{10}N_4O_5$: C, 53.51; H, 3.21; N, 17.83. Found: C, 53.24; H, 3.55; N, 17.67.

1-{[5-(2-Nitrophenyl)furfurylidene]amino}imidazolidine-2,4-dione (9h). Yellow solid (ethanol); mp 224–226 °C (lit.[9a] 224–226 °C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.33 (s, 2H), 6.97–6.99 (m, 2H), 7.63 (t, 1H, $J=7.8$ Hz), 7.67 (s, 1H), 7.78 (t, 1H, $J=7.8$ Hz), 7.87 (d, 1H, $J=7.8$ Hz), 7.96 (d, 1H, $J=7.8$ Hz), 11.28 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 48.9, 112.1, 114.5, 122.6, 124.3, 129.5, 129.9, 132.5, 132.9, 147.0, 149.3, 150.8, 153.2, 168.9; IR (KBr, cm^{-1}) 608, 696, 746, 787, 926, 980, 1022, 1136, 1210, 1244, 1348, 1402, 1437, 1464, 1518, 1701, 1755, 1803, 3071. Anal. calcd for $C_{14}H_{10}N_4O_5$: C, 53.51; H, 3.21; N, 17.83. Found: C, 53.42; H, 3.31; N, 17.65.

1-{[5-(4-Trifluoromethylphenyl)furfurylidene]amino}imidazolidine-2,4-dione (9i). Light yellow solid (ethanol); mp 254 °C (sublim); ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.35 (s, 2H), 7.01 (d, 1H, $J=3.7$ Hz), 7.34 (d, 1H, $J=3.7$ Hz), 7.75 (s, 1H), 7.82 (d, 2H, $J=8.3$ Hz), 7.98 (d, 2H, $J=8.3$ Hz), 11.30 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 49.1, 110.6, 115.3, 124.1 (q, $^1J_{C-F}=271.5$ Hz), 124.3 (2C), 125.9 (q, 2C, $^3J_{C-F}=3.3$ Hz), 127.8 (q, $^2J_{C-F}=31.3$ Hz), 132.7, 133.0, 150.1, 152.5, 153.2, 168.7; ^{19}F NMR (372 MHz, DMSO-d_6) δ 17.30 (s, 3F); IR (KBr, cm^{-1}) 602, 795, 843, 1075, 1111, 1123, 1148, 1179, 1190, 1221, 1333, 1447, 1717, 1730, 1777. Anal. calcd for $C_{15}H_{10}N_3O_3F_3$: C, 53.42; H, 2.99; N, 12.46. Found: C, 53.66; H, 3.31; N, 12.48.

1-{[5-(2,3,4,5,6-Pentafluorophenyl)furfurylidene]amino}-imidazolidine-2,4-dione (9j). Light yellow solid (ethanol); mp 220 °C (sublim); ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.34 (s, 2H), 7.07 (d, 1H, $J=3.7$ Hz), 7.13 ($d_{H-H}t_{H-F}$, 1H, $^3J_{H-H}=3.7$, $^5J_{H-F}=3.7$ Hz), 7.75 (s, 1H), 11.31 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 49.1, 105.7 (dd, $^2J_{C-F}=14.8$, $^3J_{C-F}=4.9$ Hz), 114.0, 116.1 (dd, $^3J_{C-F}=1.6$, $^4J_{C-F}=4.9$ Hz), 132.3, 137.5 (ddd, $^1J_{C-F}=248.4$, $^2J_{C-F}=13.2$, $^3J_{C-F}=3.3$ Hz), 139.9 (ddddd, 2C, $^1J_{C-F}=251.7$, $^2J_{C-F}=14.8$, $^3J_{C-F}=4.9$, $^3J_{C-F}=3.3$, $^4J_{C-F}=9.3$ Hz), 140.9 (d, $^3J_{C-F}=3.3$ Hz), 143.0 (ddddd, 2C, $^1J_{C-F}=255.0$, $^2J_{C-F}=11.5$, $^2J_{C-F}=11.5$, $^3J_{C-F}=3.3$, $^4J_{C-F}=8.2$ Hz), 151.0, 153.1, 168.6; ^{19}F NMR (372 MHz, DMSO-d_6) δ −83.88 (ddd, 2F, $^3J_{F-F}=22.1$, $^3J_{F-F}=22.1$, $^4J_{F-F}=6.1$ Hz), −76.64 (t, 1F, $^3J_{F-F}=22.1$ Hz), −62.70 (dd, 2F, $^3J_{F-F}=22.1$, $^4J_{F-F}=6.1$ Hz); IR (KBr, cm^{-1}) 444, 612, 745, 789, 818, 903, 978, 1005, 1084, 1127, 1213, 1244, 1356, 1385, 1435, 1495, 1510, 1532, 1728, 1782. Anal. calcd for $C_{14}H_6N_3O_3F_5$: C, 46.81; H, 1.68; N, 11.70. Found: C, 46.85; H, 1.92; N, 11.67.

1-{[5-(4-Fluorophenyl)furfurylidene]amino}imidazolidine-2,4-dione (9k). Light yellow solid (ethanol); mp 261 °C (sublim) (lit.[9a] 264–265 °C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.34 (s, 2H), 6.95 (d, 1H, $J=3.4$ Hz), 7.10 (d, 1H, $J=3.4$ Hz), 7.27–7.34 (AA′BB′ with H–F coupling, 2H), 7.71 (s, 1H), 7.78–7.84 (AA′BB′ with H–F coupling, 2H), 11.27 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 48.9, 108.1, 115.4, 116.1 (d, 2C, $^2J_{C-F}=22.3$ Hz,), 126.1 (d, 2C, $^3J_{C-F}=8.3$ Hz), 126.2 (d, $^4J_{C-F}=3.3$ Hz), 133.0, 149.2, 153.3, 153.5, 161.9 (d, $^1J_{C-F}=245.6$ Hz), 168.9; ^{19}F NMR (372 MHz, DMSO-d_6) δ −34.7 (tt, 1F, $^3J_{F-H}=9.2$, $^4J_{F-H}=5.3$ Hz); IR (KBr, cm^{-1}) 426, 612, 741, 791, 851, 924, 978, 1115, 1127, 1228, 1352, 1410, 1435, 1455, 1493, 1719, 1775, 1808. Anal. calcd for $C_{14}H_{10}N_3O_3F$: C, 58.54; H, 3.51; N, 14.63. Found: C, 58.42; H, 3.63; N, 14.51.

1-{[5-(4-Phenylphenyl)furfurylidene]amino}imidazolidine-2,4-dione (9l). Yellow solid (ethanol–DMF); mp 276–278 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.35 (s, 2H), 6.98 (d, 1H, $J=3.6$ Hz), 7.18 (d, 1H, $J=3.6$ Hz), 7.38 (tt, 1H, $J=1.2$, 7.5 Hz), 7.48 (ddd, 2H, $J=1.9$, 7.3, 7.5 Hz), 7.71 (ddd, 2H, $J=1.2$, 1.9, 7.3 Hz), 7.74 (s, 1H), 7.75–7.80 (AA′BB′, 2H), 7.84–7.88 (AA′BB′, 2H), 11.25 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 49.1, 108.6, 115.5, 124.4 (2C), 126.5 (2C), 127.2 (2C), 127.7, 128.5, 129.0 (2C), 133.0, 139.2, 139.6, 149.2, 153.2, 154.0, 168.8; IR (KBr, cm^{-1}) 600, 687, 762, 795, 839, 1117, 1213, 1228, 1348, 1397, 1447, 1472, 1732, 1767, 1777. Anal. calcd for $C_{20}H_{15}N_3O_3$: C, 69.56; H, 4.38; N, 12.17. Found: C, 69.43; H, 4.31; N, 12.06.

1-{[5-(2,6-Dinitrophenyl)furfurylidene]amino}imidazolidine-2,4-dione (9m). Yellow solid (ethanol); mp 287–290 °C (decomp); ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.32 (s, 2H), 6.84 (d, 1H, $J=3.7$ Hz), 6.96 (d, 1H, $J=3.7$ Hz), 7.67 (s, 1H), 8.01 (t, 1H, $J=8.1$ Hz), 8.43 (d, 2H, $J=8.1$ Hz), 11.26 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 48.9, 114.1, 114.6, 117.7, 128.3 (2C), 132.3, 132.5, 142.7, 149.3 (2C), 151.5, 153.2, 168.9; IR (KBr, cm^{-1}) 440, 608, 693, 708, 731, 752, 797, 826, 876, 899, 927, 978, 1018, 1132, 1213, 1254, 1353, 1360, 1402, 1433, 1538, 1732, 1788, 3083. Anal. calcd for $C_{14}H_9N_5O_7$: C, 46.81; H, 2.53; N, 19.49. Found: C, 46.86; H, 2.64; N, 19.22. Synthesis of **9m** sodium salt: To a solution of **9m** (470 mg, 1.31 mmol) in methanol (20 mL) was added sodium methoxide (580 mM methanol solution, 2.50 mL, 1.44 mmol) and the mixture was stirred for 8 h at room temperature. The solvent was removed under reduced pressure and the crude product was washed successively with acetone (5 mL × 5), ether (5 mL × 2), and hexane (5 mL × 2). The resulting solid was dissolved with water (100 mL), filtered to remove insolubles, and lyophilized to give sodium salt of **9m** (484 mg, 86.7%); yellow solid; mp 251 °C (decomp); ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.64 (s, 2H), 6.72 (d, 1H, $J=3.4$ Hz), 6.76 (d, 1H, $J=3.4$ Hz), 7.32 (s, 1H), 7.95 (t, 1H, $J=8.0$ Hz), 8.38 (d, 2H, $J=8.0$ Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 49.5, 111.3, 114.2, 117.7, 126.8, 128.1 (2C), 132.1, 141.2, 149.2 (2C), 153.4, 166.3, 180.4; IR (KBr, cm^{-1}) 627, 708, 750, 779, 797, 823, 835, 878, 914, 976, 1021, 1161, 1223, 1256, 1364, 1435, 1538, 1603, 1716, 3085. Anal. calcd for $C_{14}H_8N_5O_7\cdot 2.5H_2O$: C, 39.45; H, 3.07; N, 16.43. Found: C, 39.40; H, 2.74; N, 16.16.

1-{[5-(1-Naphthyl)furfurylidene]amino}imidazolidine-2,4-dione (9n). Orange solid (ethanol); mp 248–251 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.37 (s, 2H), 7.07 (d, 1H, J = 4.0 Hz), 7.10 (d, 1H, J = 4.0 Hz), 7.57–7.65 (m, 3H), 7.80 (s, 1H), 7.84 (d, 1H, J = 7.6 Hz), 8.01 (t, 2H, J = 8.8 Hz), 8.39 (d, 1H, J = 7.6 Hz), 11.27 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 49.0, 112.1, 115.0, 124.9, 125.6, 126.3, 126.5, 126.9, 127.2, 128.8, 129.29, 129.32, 133.1, 133.6, 149.6, 153.3, 154.0, 169.0; IR (KBr, cm^{-1}) 758, 785, 801, 1130, 1215, 1244, 1362, 1383, 1406, 1445, 1499, 1518, 1709, 1742, 1781, 1796, 3069. Anal. calcd for $C_{18}H_{13}N_3O_3$: C, 67.71; H, 4.10; N, 13.16. Found: C, 67.67; H, 4.27; N, 13.08.

1-{[5-(4-Bromophenyl)furfurylidene]amino}imidazolidine-2,4-dione (9o). Brown solid (ethanol); mp 271 °C (sublim) (lit.[9a] 284–285 °C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.34 (s, 2H), 6.96 (d, 1H, J = 3.8 Hz), 7.19 (d, 1H, J = 3.8 Hz), 7.64–7.66 (m, 2H), 7.70–7.73 (m, 3H), 11.27 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6 + acetone-d_6) δ 48.9, 108.9, 115.3, 121.2, 125.8 (2C), 128.8, 132.0 (2C), 132.9, 149.6, 153.3, 168.8, 206.4; IR (KBr, cm^{-1}) 602, 702, 795, 826, 976, 1026, 1117, 1213, 1221, 1345, 1394, 1410, 1447, 1478, 1730, 1775. Anal. calcd for $C_{14}H_{10}N_3O_3Br$: C, 48.30; H, 2.90; N, 12.07. Found: C, 48.23; H, 3.02; N, 11.81.

1-{[5-(4-Hydroxyphenyl)furfurylidene]amino}imidazolidine-2,4-dione (9q). Yellow solid (ethanol); mp 264–266 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.33 (s, 2H), 6.84 (d, 2H, J = 8.8 Hz), 6.86 (d, 1H, J = 3.4 Hz), 6.89 (d, 1H, J = 3.4 Hz), 7.59 (d, 2H, J = 8.8 Hz), 7.68 (s, 1H), 9.77 (s, 1H), 11.22 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 49.1, 105.8, 115.7, 115.8 (2C), 120.8, 125.6 (2C), 133.1, 148.0, 153.2, 155.1, 157.7, 168.8; IR (KBr, cm^{-1}) 430, 561, 698, 743, 772, 841, 901, 924, 974, 1030, 1129, 1171, 1213, 1231, 1285, 1360, 1416, 1455, 1489, 1609, 1711, 1777, 2786, 3044. Anal. calcd for $C_{14}H_{11}N_3O_4$: C, 58.95; H, 3.89; N, 14.73. Found: C, 58.65; H, 3.96; N, 14.74.

1-{[5-(4-Trifluoromethanesufonylphenyl)furfurylidene]-amino}imidazolidine-2,4-dione (9r). Light yellow solid (ethanol); mp 249–251 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.36 (s, 2H), 7.07 (d, 1H, J = 3.9 Hz), 7.39 (d, 1H, J = 3.9 Hz), 7.77 (s, 1H), 8.14–8.21 (m, 4H), 11.33 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 49.2, 113.7, 115.5, 119.4 (q, $^1J_{C-F}$ = 325.7 Hz), 125.1 (2C), 127.2, 131.7 (2C), 132.4, 137.2, 151.4, 151.5, 153.1, 168.7; ^{19}F NMR (372 MHz, DMSO-d_6) δ −0.17 (s, 3F); IR (KBr, cm^{-1}) 579, 608, 633, 743, 772, 801, 1078, 1136, 1192, 1219, 1238, 1354, 1370, 1435, 1595, 1717, 1730, 1773. Anal. calcd for $C_{15}H_{10}N_3O_5SF_3$: C, 44.89; H, 2.51; N, 10.47. Found: C, 44.89; H, 2.72; N, 10.37.

1-{[5-(4-Cyanophenyl)furfurylidene]amino}imidazolidine-2,4-dione (9s). Light yellow solid (ethanol); mp 273–275.5 °C (decomp) [lit.[9a] 281–285 °C (decomp)]; ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.34 (s, 2H), 7.01 (d, 1H, J = 3.6 Hz), 7.38 (d, 1H, J = 3.6 Hz), 7.74 (s, 1H), 7.88–7.95 (m, 4H), 11.29 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 49.1, 109.9, 111.5, 115.4, 118.7, 124.2 (2C), 132.6, 133.0 (2C), 133.3, 150.5, 152.3, 153.2, 168.7; IR (KBr, cm^{-1}) 444, 608, 743, 810, 837, 872, 920, 976, 1028, 1123, 1229, 1242, 1368, 1406, 1449, 1485, 1605, 1721, 1779, 2226, 3073, 3600. Anal. calcd for $C_{15}H_{10}N_4O_3$: C, 61.22; H, 3.43; N, 19.04. Found: C, 61.11; H, 3.74; N, 18.92.

1-{[5-(4-Nitrophenyl)-2-thenylidene]amino}imidazolidine-2,4-dione (14a). Yellow solid (ethanol–DMF); mp 283–285 °C (lit.[9a] 295–298 °C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.36 (s, 2H), 7.48 (d, 1H, J = 3.9 Hz), 7.80 (d, 1H, J = 3.9 Hz), 7.97–8.01 (AA′BB′, 2H), 8.04 (s, 1H), 8.24–8.28 (AA′BB′, 2H), 11.26 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 49.3, 124.4 (2C), 126.2 (2C), 127.4, 131.7, 137.6, 139.3, 141.1, 141.8, 146.3, 153.0, 168.7; IR (KBr, cm^{-1}) 590, 692, 720, 750, 803, 857, 934, 1121, 1221, 1231, 1337, 1350, 1404, 1433, 1460, 1524, 1592, 1725, 1755, 1769, 3272. Anal. calcd for $C_{14}H_{10}N_4O_4S$: C, 50.91; H, 3.05; N, 16.96. Found: C, 50.71; H, 3.13; N, 16.60.

1-{[5-(2-Nitrophenyl)-2-thenylidene]amino}imidazolidine-2,4-dione (14b). Yellow solid (ethanol); mp 247–249.5 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.34 (s, 2H), 7.16 (dd, 1H, J = 2.2, 3.9 Hz), 7.40 (dd, 1H, J = 1.9, 3.9 Hz), 7.64 (dddd, 1H, J = 2.2, 2.2, 7.0, 7.0 Hz), 7.72 (dddd, 1H, J = 1.9, 1.9, 7.7, 7.7 Hz), 7.74 (ddd, 1H, J = 1.2, 2.2, 7.0 Hz), 7.95 (ddd, 1H, J = 1.2, 1.9, 7.7 Hz), 8.02 (s, 1H), 11.2 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 49.3, 124.1, 126.4, 128.0, 129.8, 130.8, 131.7, 132.7, 132.8, 138.0, 140.7, 148.7, 153.1, 168.7; IR (KBr, cm^{-1}) 642, 706, 749, 783, 820, 864, 897, 922, 1125, 1208, 1237, 1362, 1399, 1435, 1456, 1493, 1522, 1732, 1742, 1771, 3007. Anal. calcd for $C_{14}H_{10}N_4O_4S$: C, 50.91; H, 3.05; N, 16.96. Found: C, 50.76; H, 3.34; N, 16.60.

Biological evaluation

See refs 13 and 15 and references cited therein.

Acknowledgements

This work was supported in part by a Grant-in-Aid for Creative Scientific Research (No. 13NP0401) of the Ministry of Education, Culture, Sports, Science and Technology (MEXT) of Japan.

References and Notes

1. Simmons, R. M., Ed. *Muscular Contraction*; Cambridge University Press: New York, 1992.
2. Endo, M. *Curr. Top. Membr. Transp.* **1985**, *25*, 181.
3. (a) Schneider, M. F. *Annu. Rev. Physiol.* **1994**, *56*, 463. (b) Ríos, E.; Pizarro, G. *Physiol. Rev.* **1991**, *71*, 849. (c) Sitsapesan, R., Williams, A. J., Eds. *The Structure and Function of Ryanodine Receptors*; Imperial College: London, 1998.
4. Endo, M.; Ikemoto, T. In *Pharmacology of Ionic Channel Function. Activators and Inhibitors*; Endo, M., Kurachi, Y., Mishina, M., Eds.; Springer: Berlin, 2000; p 583.
5. Iino, M. *Japan. J. Physiol.* **1999**, *49*, 325.
6. Kasai, M.; Kawasaki, T.; Yamaguchi, N. *Biophys. Chem.* **1999**, *82*, 173, and references cited therein.
7. (a) Näbauer, M.; Callewaert, G.; Cleemann, L.; Morad, M.

Science **1989**, *244*, 800. (b) Bers, D. M.; Perez-Reyes, E. *Cardiovasc. Res.* **1999**, *42*, 339.
8. Ward, A.; Chaffman, M. O.; Sorkin, E. M. *Drugs* **1986**, *32*, 130.
9. (a) Snyder, H. R., Jr.; Davis, C. S.; Bickerton, R. K.; Halliday, R. P. *J. Med. Chem.* **1967**, *10*, 807. (b) Davis, C. S.; Snyder, H. R., Jr. US Patent 3,415,821, 1968.
10. (a) Ellis, K. O.; Bryant, S. H. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1972**, *274*, 107. (b) Ellis, K. O.; Carpenter, J. F. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1972**, *275*, 83.
11. (a) Endo, M.; Yagi, S.; Ishizuka, T.; Horiuti, K.; Koga, Y.; Amaha, K. *Biomed. Res.* **1983**, *4*, 83. (b) Harrison, G. G. *Br. J. Anesth.* **1975**, *47*, 62. (c) Kolb, M. E.; Horne, M. L.; Martz, R. *Anesthesiology* **1982**, *56*, 254. (d) MacLennan, D. H.; Phillips, M. S. *Science* **1992**, *256*, 789. (e) Louis, C. F.; Balog, E. M.; Fruen, B. R. *Biosci. Rep.* **2001**, *21*, 155.
12. (a) Ohta, T.; Endo, M. *Proc. Jpn. Acad.* **1986**, *62*, 329. (b) Ohta, T.; Endo, M.; Nakano, T.; Morohoshi, Y.; Wanikawa, K.; Ohga, A. *Am. J. Physiol.* **1989**, *256*, C358.
13. Ikemoto, T.; Hosoya, T.; Aoyama, H.; Kihara, Y.; Suzuki, M.; Endo, M. *Br. J. Pharmacol.* **2001**, *134*, 729.
14. Hosoya, T.; Aoyama, H.; Ikemoto, T.; Hiramatsu, T.; Kihara, Y.; Endo, M.; Suzuki, M. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3263.
15. Ikemoto, T.; Endo, M. *Br. J. Pharmacol.* **2001**, *134*, 719.
16. (a) Akashi, H.; Oda, R. *J. Chem. Soc. Japan* **1950**, *53*, 81; *Chem. Abstr.* **1953**, *47*, 2164e. (b) Rondestvedt, C. S., Jr. *Org. React.* **1960**, *11*, 189. (c) Rondestvedt, C. S., Jr. *Org. React.* **1976**, *24*, 225.
17. The low reproducibility for preparation of 5-phenyl-2-furaldehyde was reported: Davis, C. S.; Lougheed, G. S. *J. Heterocycl. Chem.* **1967**, *4*, 153. We also failed to prepare methoxy- or methyl-substituted dantrolene congeners by this method.
18. Palnitkar, S. S.; Bin, B.; Jimenez, L. S.; Morimoto, H.; Williams, P. G.; Paul-Pletzer, K.; Parness, J. *J. Med. Chem.* **1999**, *42*, 1872.
19. (a) Other methods for the synthesis of 5-aryl-2-furaldehyde: Stille reaction using **7a** protected with ethylene acetal: Balachari, D.; Quinn, L.; O'Doherty, G. A. *Tetrahedron Lett.* **1999**, *40*, 4769. (b) Suzuki reaction using **7b** protected with ethylene acetal: McClure, M. S.; Roschangar, F.; Hodson, S. J.; Millar, A.; Osterhout, M. H. *Synthesis* **2001**, 1681. (c) Heck reaction: McClure, M. S.; Glover, B.; McSorley, E.; Millar, A.; Osterhout, M. H.; Roschangar, F. *Org. Lett.* **2001**, *3*, 1677. (d) Coupling of aryl halides and triorganozincates: Gauthier, D. R., Jr.; Szumigala, R. H., Jr.; Dormer, P. G.; Armstrong, J. D., III; Volante, R. P.; Reider, P. J. *Org. Lett.* **2002**, *4*, 375.
20. (a) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508. (b) Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1. (c) Echavarren, A. M.; Stille, J. K. *J. Am. Chem. Soc.* **1987**, *109*, 5478.
21. Denat, F.; Gaspard-Iloughmane, H.; Dubac, J. *Synthesis* **1992**, 954.
22. The stannylated furaldehyde **10** was prepared from 3-furanmethanol tetrahydropyranyl ether as follows: (i) *n*-BuLi, ether, 0 °C to room temperature, 30 min; then DMF, THF, 0 °C to room temperature, 20 h, 68% (ii) lithium *N*-methylpiperazide, THF, −78 °C, 15 min; then *n*-BuLi, −78 °C to room temperature, 3 h; then $(n\text{-Bu})_3\text{SnCl}$, −20 °C to room temperature, 17 h, 91%. See also: Han, Y.; Roy, A.; Giroux, A. *Tetrahedron Lett.* **2000**, *41*, 5447.
23. (a) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147. (b) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.
24. Florentin, D.; Roques, B. P.; Fournie-Zaluski, M. C. *Bull. Soc. Chim. Fr.* **1976**, 1999.
25. For inversed cross-coupling by the Suzuki reaction, namely, the combination of aryl boronic acids and 5-bromo-2-furaldehyde, see: Bussolari, J. C.; Rehborn, D. C. *Org. Lett.* **1999**, *1*, 965. Our method is favorable in terms of the ready availability of aryl substrates.
26. (a) Traube, W.; Hoffa, E. *Chem. Ber.* **1898**, *31*, 162. (b) Gut, J.; Novácek, A.; Fiedler, P. *Collect. Czech. Chem. Commun.* **1968**, *33*, 2087.
27. Grynkiewicz, G.; Poenie, M.; Tsien, R. Y. *J. Biol. Chem.* **1985**, *260*, 3440.
28. (a) Parness, J.; Palnitkar, S. S. *J. Biol. Chem.* **1995**, *270*, 18465. (b) Salata, J. J.; Jalife, J. *J. Pharmacol. Exp. Ther.* **1982**, *220*, 157.
29. For the inhibitory effect of 4-iodo congener of dantrolene (GIF-0146) on twitch contraction (35.6%), see ref 13.