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Design and synthesis of heterocyclic malonyl-CoA decarboxylase inhibitors

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Abstract—We have previously reported the discovery of small molecule inhibitors of malonyl-CoA decarboxylase (MCD) as novel metabolic modulators, which inhibited fatty acid oxidation and consequently increased the glucose oxidation rates in the isolated working rat hearts. MCD inhibitors were also shown to improve cardiac efficiency in rat and pig demand-induced ischemic models through the mechanism-based modulation of energy metabolism. Herein, we describe the design and synthesis of a series of novel heterocyclic MCD inhibitors with a preference for substituted imidazole and isoxazole.

The enzyme malonyl-CoA decarboxylase (MCD, EC 4.1.1.9) catalyzes the conversion of malonyl-CoA to acetyl-CoA and thereby regulates malonyl-CoA levels. MCD was first purified from the uropygial glands of waterfowl and subsequently from a number of mammals and bacteria.[1a–g] Identification of patients with MCD deficiency led to the cloning of a human MCD gene that is highly homologous to goose and rat.[1h–k] A single human MCD mRNA is observed by Northern blot analysis. The highest mRNA expression levels are found in muscle and heart tissues, followed by liver, kidney, and pancreas, with detectable amounts in all other tissues examined. Recent work indicates that MCD exists in both cytosolic and mitochondrial forms.[1l]

Malonyl-CoA is not only a key intermediate for fatty acid synthesis, but also an endogenous inhibitor of carnitine palmytoyltransferase-1 (CPT-I)[2] and a key metabolic sensor.[3] Through the regulation of malonyl-CoA and acetyl-CoA levels in the system and therefore the fatty acid synthesis and fatty acid oxidation process, MCD plays a key role in the balance of energy intake and expenditure. Despite the important processes MCD is involved, the physiological role of MCD is not clear. Recently, we developed for the first time a series of small molecule MCD inhibitors and demonstrated their ability in regulation of cardiac energy metabolism in rat and pig hearts.[4a,4c]

Through high throughput screen on the Chugai compound archive, we identified an initial hit compound **1a** (CBP-33502) with moderate MCD inhibitory activities (IC_{50}, 0.93 μM). Early structure–activity relationship studies revealed that *N*-alkyl group played a key role in the MCD inhibition. For example, compound **1b**, which lacks a *N*-methyl group, showed significant lower MCD inhibitory activity (IC_{50}, 6.6 μM). It is well known that the stable conformation of an aniline amide (anilide) in solution as well as in crystal form is highly dependent on the nature of substituents on the amide nitrogen atom; with the *cis*-conformation being preferred in *N*-alkylanilides and *trans*-conformation in non-substituted acetanilides.[5] It is therefore reasonably assumed that the active conformation of the initial hit compound **1a** is *cis* (as shown in **1a**). Based on the hypothesis that the conformation difference between **1a** and **1b** resulted in the activity difference, we designed a series of new MCD inhibitors **1c** with a heterocycle moiety in an attempt to mimic the amide conformation of **1a** (Fig. 1). Conformation overlap of **1a** with substituted imidazole or isoxazole is shown in Figure 2. 1,2-Disubstituted imidazoles and 3,4-disubstituted isoxazoles seem to best fit the original conformation of **1a**.

Two different strategies have been employed to synthesize 3,4,5-trisubstituted isoxazole-based MCD inhibitors (Schemes 1 and 2). Bromination of commercially

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Keywords: Malonyl-CoA; Acetyl-CoA; Malonyl-CoA decarboxylase; MCD.

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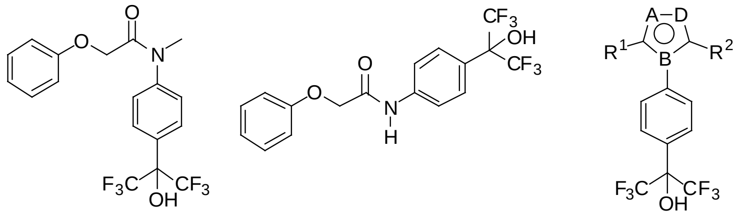


1a
(IC_{50}: 0.93 μM)

1b
(IC_{50}: 6.6μM)

1c
A,B, D: N, O or C

Figure 1. Five-membered heterocycles as bioisosteres of *N*-alkylanilide.

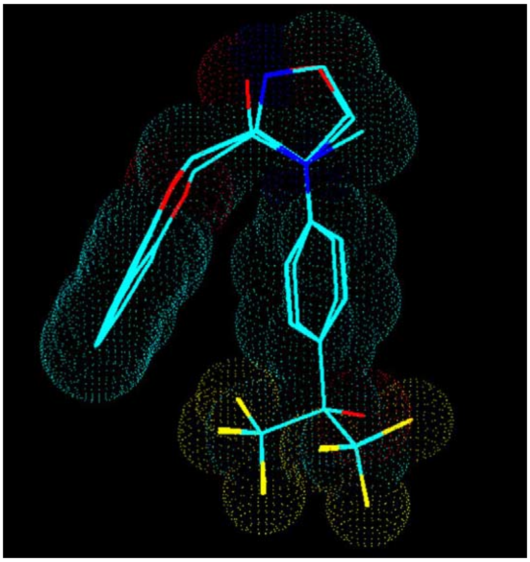
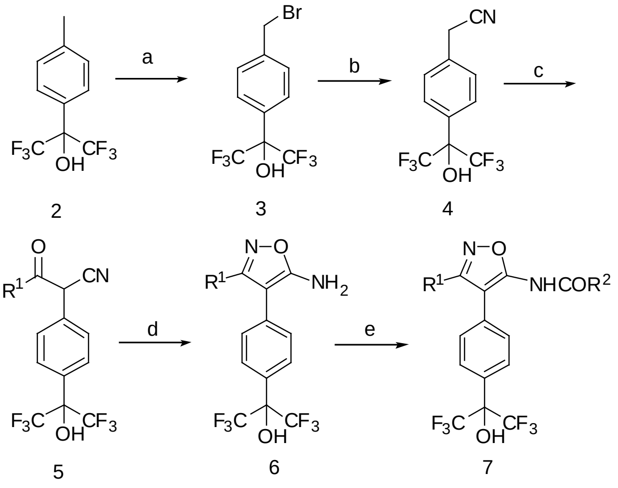


Figure 2. Overlap of **1a** with 1,2-disubstituted imidazole and 3,4-disubstituted isoxazole.



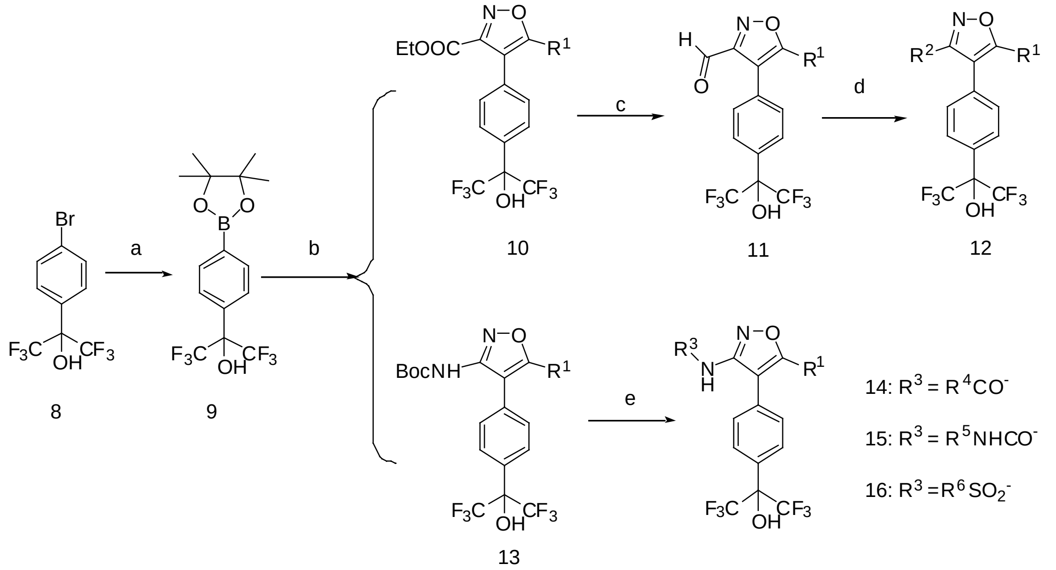
Scheme 1. Reagents and conditions: (a) NBS, CCl_4, 85%; (b) KCN, DMSO/H_2O, 100 °C, 78%; (c) LHDMS, THF, rt, then R^1COOEt, 76–90%; (d) NH_2OH, heat, 82–90%; (e) R^2COCl or $(R^2CO)_2O$, DCM, pyridine, >90%.

available 1,1,1,3,3,3-hexafluoro-2-*p*-tolyl-propan-2-ol **2** with NBS in CCl_4 provided predominantly the monobrominated derivative **3** in excellent yield. Treatment of this benzylbromide **3** with KCN in aqueous DMSO under heating condition[6] yielded the corresponding benzonitrile **4**, which upon treatment with LHMDS followed by reaction of the resultant anion intermediate with an ester provided the β-cyanoketone intermediate **5**. 5-Aminoisoxazole compounds **6** were obtained through cyclization of β-cyanoketones (**5**) with hydroxylamine.[7] Amide formation was accomplished by treating **6** with acyl chlorides or anhydrides.

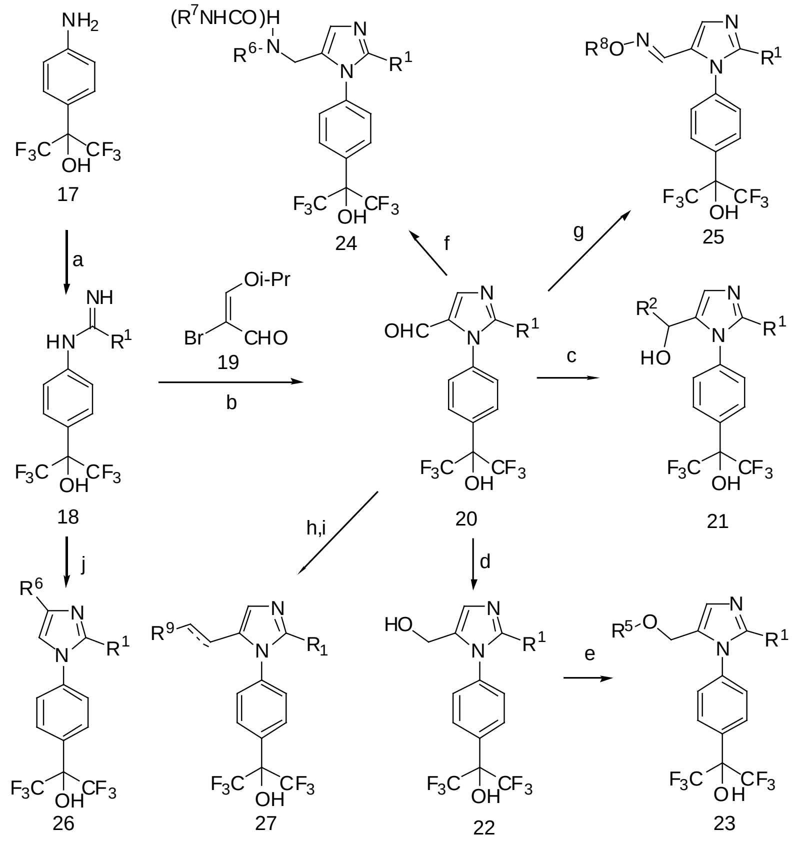
An alternative method employing Suzuki reaction to prepare similar isoxazole derivatives is illustrated in Scheme 2. The commercially available 2-(4-bromophenyl)-1,1,1,3,3,3-hexafluoro-propan-2-ol **8** was converted into its corresponding boronate **9**, which coupled with 4-bromoisoxazole afforded the 3,4,5-trisubstituted isoxazole derivatives **10**, **13** or **12** directly. Compounds **10** and **13** possess protected ester or amino functional groups at the 3-position of the isoxazole ring. Hydrolysis of ester **10** afforded the free acid, which was converted into the corresponding aldehyde intermediate **11** via Weinreb amide. Similarly, removal of Boc-protecting groups in **13** followed by conventional amide, urea or sulfonamide formation provided the isoxazole derivatives **14**–**16**.

Scheme 3 illustrates the strategy toward synthesis of 1,2,5- or 1,2,4-trisubstituted imidazole derivatives. Synthesis of key imidazole intermediate **20** was achieved by reacting 2-bromo-3-(1-methylethoxy)-2-propenal **19**[8] with amidine compound **18**, which was in turn prepared from aniline **17** and a nitrile in the presence of $AlCl_3$ at high temperature or in the presence of a strong base (e.g., NaHMDS) at room temperature depending on the nature of nitriles.[9] It was found that the latter method was useful for aromatic nitriles, especially for heteroaryl nitriles, while the aliphatic substituted amidines could be prepared in high yield just by simply dissolving aniline in the nitrile compound under refluxing conditions in the presence of $AlCl_3$. Alternatively, reaction of amidine **18** with α-haloketone provided directly 1,2,4-trisubstituted imidazoles **26**.

With imidazole aldehyde intermediate **20** in hand; a number of transformations were performed. For example, the aldehyde **20** was reacted with organolithium compounds or Grignard reagent to afford the secondary alcohol compounds **21**. Reduction of aldehyde **20** provided the corresponding alcohols **22**, which was further converted into ether derivatives (**23**). Reductive



Scheme 2. Reagents and conditions. (a) Bis(pinacolato)diborane, Pd(dppf)Cl_2, DMF, KOAc; 78%; (b) 3,5-disubstituted-4-bromoisoxazole, Pd(dppf)Cl_2, THF/H_2O, $NaHCO_3$, 39%; (c) (i) NaOH; (ii) EDAC, DMAP, MeNH(OMe); (iii) DIBAL, toluene, −78 to 0 °C, 30–40% overall yield; (d) RMgX, THF, 0 °C to rt quantitative; or (i) Wittig reagent, benzene, reflux; (ii) Pd–C/H_2, EtOH, rt; (iii) $NaOH_{aq}$, dioxane, rt, 78–92%; (e) (i) TFA, DCM, rt; (ii) R^4COCl or $(R^4CO)_2O$; or, R^5NCO, or R^6SO_2Cl, DCM, heating, 63–78%.



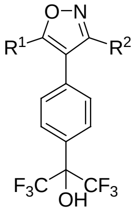
Scheme 3. Reagents and conditions: (a) R^1CN, $AlCl_3$, 180 °C; or R^1CN, NaHMDS, THF, rt, 85–90%; (b) K_2CO_3, $CHCl_3$, H_2O; 40–60%; (c) R^2MgX, THF, 0 °C, >90%; (d) $NaBH_4$, MeOH; quantitative; (e) R^5Br, *t*-BuOK, THF, 0 °C, 85–90%; (f) (i) R^6NH_2, $NaBH_3CN$, MeOH, 75–85%; (ii) R^7NCO, DCM, rt, >90%; (g) R^8ONH_2, EtOH, quantitative, overall yield. (h) $R^9CH_2PPh_3Br$, toluene, 80–90%; (i) H_2, Pd/C, EtOH; (j) $BrCH_2COR^6$, 58–72%.

amination of **20** provided secondary amines (**24**) or their corresponding tertiary amide derivatives after further acylation. Finally, reaction with hydroxylamine afforded the corresponding oxime or *O*-alkylated oximes (**25**). The aldehyde intermediate could be also converted into the alkylated derivatives **27** via Wittig reaction followed by further transformations (hydrogenation, hydrolysis etc.).

All the compounds prepared above were tested for their ability to inhibit the soluble form of recombinant human MCD MBP fusion protein (MBP–hMCD).[4b,10] Previous SAR studies on initial hit compound **1a** revealed that removal of *N*-methyl group (i.e., **1b**) dramatically decreased the activity. Amide derivatives of **1a** with a small aliphatic chain up to five carbons on the nitrogen atom or an α,α-disubstituted small aliphatic acyl group were shown to be excellent MCD inhibitors (unpublished results). The SAR for isoxazole derivative is parallel to the original amide, although no significant activity improvement was observed (Table 1). When R^1 at C-5 position equals a NH_2 group, the small aliphatic (**6c**, **6d**, **6e**, **6f**, and **6k**) shows a modest improvement in MCD inhibition over compounds with a phenyl or furanyl group such as **6b**, **6g**, **6i**, **6j**, and **6n**. 4-Pyridinyl group again gave better results than the other aryl group as seen in the amide series.[4a] Acylation of the amino group at C-5 position of the isoxazole ring either improved or exhibited similar activity. The best combination is a small R^2 group with a small aliphatic amide at C-5 position of the isoxazole ring (**7b**).

On the other hand, MCD inhibitory activity for C-5 methyl isoxazole derivatives (**12**–**15**) was generally weak. Only a handful of compounds with a methyl group (**12a**), a *trans* cyanovinyl group (**12b**), or a 4-pyridine-

Table 1. MCD inhibitory activity of isoxazole derivatives[a]



Compound	R^1	R^2	IC_{50} (μM)
6a	NH_2–	4-Pyridinyl	0.19
6b	NH_2–	–Ph	2.54
6c	NH_2–	–Et	0.68
6d	NH_2–	–*i*-Pr	0.46
6e	NH_2–	–*n*-Bu	0.67
6f	NH_2–	–CH_2OEt	0.63
6g	NH_2–	–4-MeOPh	2.77
6h	NH_2–	–CH_2CH_2COOH	1.16
6i	NH_2–	–4-Hydroxylphenyl	1.17
6j	NH_2–	–CH_2Ph	5.32
6k	NH_2–	–$CH_2CH_2CH_2OH$	0.65
6l	NH_2–	–CF_3	3.33
6m	NH_2–	–$CH_2CH{=}CHCH_3$ (*trans*)	1.13
6n	NH_2–	–3-Furanyl	1.78
7a	(4-CN–Ph)CONH–	–*i*-Pr	0.39
7b	*n*-BuCONH–	–*i*-Pr	0.14
7c	PhCH(Et)CONH–	–*i*-Pr	0.42
7d	*n*-BuCH(Et)CONH–	–*i*-Pr	0.20
7e	*i*-PrCONH–	–Ph	0.73
7f	*i*-PrCONH–	–4-Pyridinyl	0.25
7g	4-PyCONH–	–*i*-Pr	0.34
10	Me–	–COOEt	0.96
12a	Me–	–Me	0.41
12b	Me–	–*trans*-CH=CH–CN	0.29
12c	Me–	–$COCH_2CH_2CH_3$	0.93
12d	Me–	–*trans*-CH=CH–COOEt	3.16
14a	Me–	–$NHCOCH_3$	1.99
14b	Me–	–$NHCONHCH_2COOEt$	3.73
14c	Me–	–NHCONHPh	1.48
14d	Me–	–$NHCONHCH_2COOH$	1.3
14e	Me–	–NHCONH-(*c*-hexane)	4.98
14f	Me–	–$NHCONHCH_2CH_2Ph$	2.97
14g	Me–	–$NHCOCH_2CH_2Ph$	2.55
14h	Me–	–NHCO(*i*-Pr)	0.99
14i	Me–	–NHCO(4-Py)	0.39
14j	Me–	–$NHCO(CH_2)_4CH_3$	1.2
15	Me–	–$NHSO_2$–(*m*-CF_3–Ph)	N/A

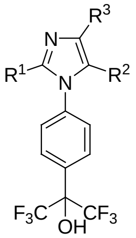
[a] Data are reported as means of $n \geqslant 3$ determinations. SD was generally ±20% of the average.

carboxylamido group (**14i**) at C-3 position showed IC_{50}s less than 0.5 μM or better activity than the initial hit **1a**. Other bulky groups at this position were not tolerated (**15**).

Similarly, a small branched aliphatic group or 4-pyridine group at C-2 position (R^1) of the imidazole ring seems to be well tolerated (Table 2). Interestingly, no significant activity difference was observed for C-4 (**26a**–**26d**) or C-5 (**22a**–**22d**) substituted imidazoles. Activity improvement was clearly observed when the substitution pattern at C-5 position changes. For example, introduction of an extra isopropyl substitution at C-5 hydroxylmethyl group (compound **21c**) caused a 5-fold activity (**21c**, 59 nM; **22a**, 321 nM) increase. An extra methyl group at this position also increased the activity slightly (**21a**), while an *n*-propyl (**21b**) is equally effective as an isopropyl group (**21c**). A phenyl group (**21d**), however, did not add any benefit to the activity.

The effect of a long chain at C-5 position of the imidazole ring (**23a** and **23b**) is not as profound as that observed in the amide or urea series.[4a] Even compounds with a terminal tetrazole group (**23c** and **23d**) only showed similar activity to a simple C-5 hydroxylmethyl group, indicating the slight different steric requirement for imidazole

Table 2. MCD inhibitory activity of imidazole derivatives[a]



Compound	R^1	R^2	R^3	IC_{50} (nM)
21a	*s*-Bu–	–CH(OH)CH_3	H	149
21b	*s*-Bu–	–CH(OH)(*n*-Pr)	H	74
21c	*s*-Bu–	–CH(OH)(*i*-Pr)	H	59
21d	*s*-Bu–	–CH(OH)Ph	H	465
22a	*s*-Bu–	–CH_2OH	H	321
22b	*i*-Pr–	–CH_2OH	H	274
22c	4-Pyridinyl–	–CH_2OH	H	114
22d	2-Pyridinyl–	–CH_2OH	H	791
23a	*i*-Pr–	–$CH_2O(CH_2)_4CN$	H	107
23b	*i*-Pr–	–$CH_2O(CH_2)_5CN$	H	168
23c	*i*-Pr–	$CH_2O(CH_2)_5$–(5-tetrazole)	H	155
23d	*i*-Pr–	–$CH_2O(CH_2)_4$–(5-tetrazole)	H	116
24a	*s*-Bu–	–CH_2NH(*i*-Pr)	H	341
24b	*s*-Bu–	–$CH_2NHCH_2CH_2OMe$	H	340
24c	*s*-Bu–	–CH_2NH–(*n*-Bu)	H	303
24d	*i*-Pr–	–CH_2NH–(*n*-Bu)	H	482
24e	*i*-Pr–	–CH_2N(2-morpholinylethyl)CONH (*i*-Pr)	H	1080
25a	*i*-Pr–	=N–OH	H	152
25b	*i*-Pr–	=N–OMe	H	63
25c	*i*-Pr–	=N–OEt	H	118
25d	*i*-Pr–	=N–OPh	H	209
25e	*i*-Pr–	=N–O(*i*-Bu)	H	350
25f	*i*-Pr–	=N–O(*t*-Bu)	H	44
26a	4-Pyridinyl–	–H	–COOEt	191
26b	*s*-Bu–	–H	–COOEt	318
26c	*i*-Pr–	–H	–CF_3	567
26d	*i*-Pr–	–H	CH_2OH	243
27a	*i*-Pr–	–*trans*-CH=CH–CN	H	140
27b	*i*-Pr–	–*cis*-CH=CH–CN	H	20
27c	*i*-Pr–	–*trans*-CH=CH–COOMe	H	55
27d	*i*-Pr–	–CH_2CH_2COOMe	H	65
27e	*i*-Pr–	–$CH_2CH(Me)COOEt$	H	37
27f	*i*-Pr–	–CH_2CH_2COOH	H	239
27g	*i*-Pr–	–$CH_2CH(Me)COOH$	H	225
27h	*s*-Bu–	–CH_2CH_2COOH	H	163
27i	*s*-Bu–	–*trans*-CH=CH–COOMe	H	88
27j	*s*-Bu–	–CH_2CH_2COOMe	H	41
27k	*s*-Bu–	–*trans*-CH=CH–COOH	H	523

[a] Data are reported as means of $n \geqslant 3$ determinations. SD was generally ±20% of the average.

compounds from amides. Amine-based derivatives **24a**–**24e** also showed similar results. A large substitution at C-5 position (R^2) is not tolerated (e.g., **24e**).

Most dramatic results were observed for oximes and Wittig products of the intermediary aldehyde **20**. *O*-Methylhydroxylamine oxime (**25b**) and *O*-(*t*-butyl)-hydroxylamine oxime (**25f**) both gave excellent MCD inhibitory activities.[11] Wittig reaction of **20** with (triphenyl phosphanylidene)-acetonitrile gave rise to two products that were stable and separable by silica gel chromatography. The *cis*-product **27b** is seven times more potent than its *trans* counterpart **27c** and is one of the most potent compounds in the imidazole series. Other Wittig products (**27c**, **27i**) also exhibited potent MCD inhibitory activities. Similarly, the terminal carboxylic acid group is tolerated, but those compounds with terminal carboxylic acid functionality tended to show lower activity as compared to their corresponding esters.

In conclusion, based on the initial HTS hit **1a**, a rational design using a five-membered heterocycle to mimic the possible active conformation of the amide moiety was performed. As a result, a series of isoxazole and imidazole-based MCD inhibitors were synthesized and structure–activity relationship was established. Although the isoxazole derivatives did not significantly improve the MCD inhibitory activity over **1a**, imidazole-based derivatives generally showed good activities. Most potent compounds were found to be those with small-branched aliphatic group (*i*-Pr, *s*-Bu, etc.) at C-2 position of the imidazole ring. These compounds are anticipated to have more favorable in vitro and in vivo ADME properties.

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10. In vitro MCD inhibition assay: The decarboxylase activity of MCD was measured spectrophotometrically by monitoring acetyl-CoA formation using the malate dehydrogenase (MD)/citrate synthase (CS) coupling system. The establishment of the kinetic equilibrium between malate/NAD and oxaloacetate/NADH was catalyzed by malate dehydrogenase. The enzymatic reaction product of MCD, acetyl-CoA, shifted the equilibrium by condensing with oxaloacetate in the presence of citrate synthase, which resulted in a continuous generation of NADH from NAD. The accumulation of NADH was measured by the fluorescence emission at 465 nm. Typically, the assay system (50 μL) contains 10 mM phosphate-buffered saline (Sigma), pH 7.4, 0.05% Tween 20, 25 mM K_2HPO_4–KH_2PO_4 (Sigma), 2 mM malate (Sigma), 2 mM NAD (Boehringer Mannheim), 0.786 units MD (Roche Chemicals), 0.028 unit CS (Roche Chemicals), 5–10 nM MBP–hMCD, and varying amounts of malonyl-CoA substrate. Assays were initiated by the addition of malonyl-CoA, and the rates were corrected for the background rate determined in the absence of hMCD.
11. Two products could be detected and purified for all *O*-substituted oximes. The predominant isomers were tested and are reported in Table 2. They are presumably the *trans* products. The minor isomers (<10% yield) showed a slightly lower activity as compared to the major products.