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Novel trifluoroacetophenone derivatives as malonyl-CoA decarboxylase inhibitors

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Abstract—A series of trifluoroacetophenone derivatives were prepared and evaluated as malonyl-CoA decarboxylase (MCD) inhibitors. Some of the 'reverse amide' analogs were found to be potent inhibitors of MCD enzyme activity. The trifluoroacetyl group may interact with the MCD active site as the hydrate in a similar fashion to the hexafluoroisopropanol analogs reported previously. Adding electron-withdrawing groups to the phenyl ring stabilizes the hydrated species and enhances this interaction.

The enzyme malonyl-CoA decarboxylase (MCD, EC 4.1.1.9; CoA, coenzyme A) catalyzes the conversion of malonyl-CoA to acetyl-CoA, thereby regulating malonyl-CoA levels in the cells. Malonyl-CoA is a key intermediate for fatty acid synthesis and a key regulator for fatty acid oxidation through carnitine palmitoyltransferase I (CPT-I). CPT-I is required for the transport of long-chain acyl-CoA molecules from the cytosol to the mitochondria where they are oxidized.[1] Different isoform distributions of CPT-1 have the potential to mediate its responsiveness to malonyl-CoA, in particular during pathophysiological changes.[2] As a metabolic fuel sensor, malonyl-CoA also regulates nutrition partitioning,[3] insulin secretion and sensitivity[4,5], and food intake.[6] MCD was first purified from uropygial glands of goose and subsequently from a number of mammalians, plants, and bacteria.[7] Identification of patients with MCD deficiency led to the cloning of a human MCD gene that is highly homologous to the goose and rat genes.[8] The highest MCD mRNA expression levels in rats are found in muscle and heart tissues, followed by liver, kidney, and pancreas, with detectable amounts found in many other tissues including brain.[9] Recent studies indicate that MCD exists in cytosolic, mitochondrial, and peroxisomal compartments.[8b,10] Targeting malonyl-CoA regulation through MCD inhibition is an attractive approach to certain diseases involving disorders of fatty acid metabolism such as diabetes, obesity, and myocardial ischemia.

We have recently described the first generation of small molecule MCD inhibitors containing a hexafluoroisopropanol moiety.[11] As expected, those MCD inhibitors significantly increased malonyl-CoA levels and decreased the fatty acid oxidation rates in ex vivo experiments with isolated working rat hearts. As a result, the glucose oxidation rates were accelerated in these working rat hearts, consistent with 'glucose-fatty acid cycle' or 'Randle cycle' hypothesis.[12] Previous SAR studies on HTS hit **1** led to the identification of several potent MCD inhibitors (**2**–**4**, Fig. 1).[11a,b,c] In the process of investigating the SAR of the hexafluoroisopropanol pharmacophore, we discovered that the trifluoroacetyl function could serve as a potential bioisostere. Herein we described the design, synthesis, and SAR of a series of trifluoroacetophenone MCD inhibitors **5**.

Synthesis of aniline-based trifluoroacetophenone MCD inhibitors is illustrated in Scheme 1. According to the

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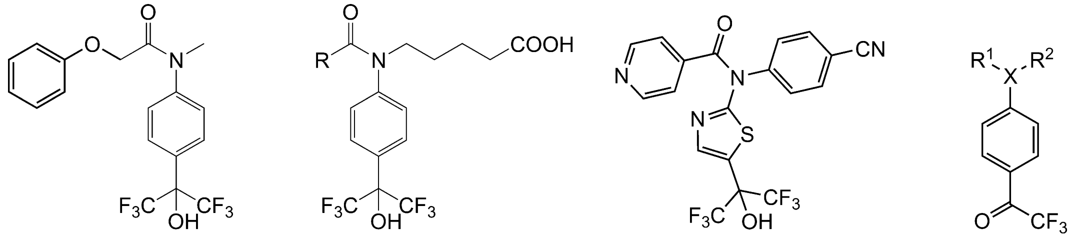


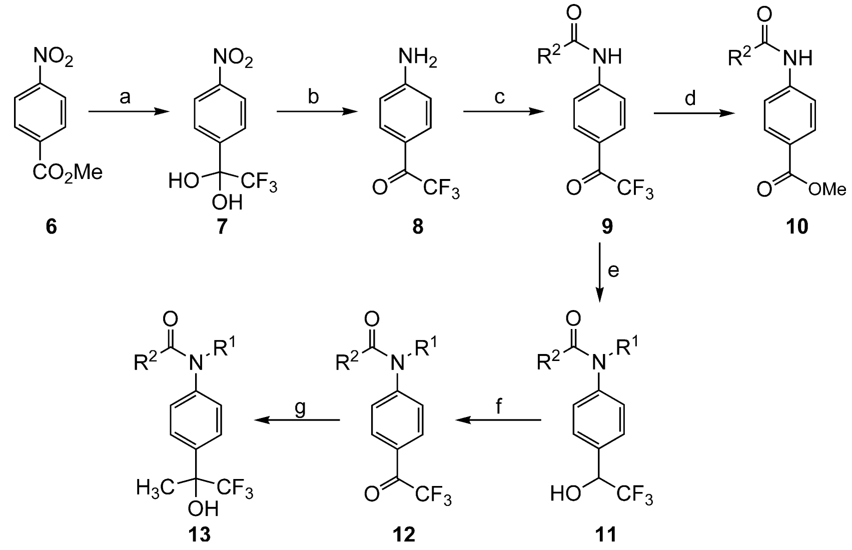
1: Initial HTS hit

2: R = 1-morpholinyl
IC_{50}: 14 nM (MBP-hMCD)
3: R = iPr
IC_{50}: 8 nM (MBP-hMCD)

4
IC_{50}: 9 nM (MBP-hMCD)

5
X = N or C

Figure 1. Representative MCD inhibitors.

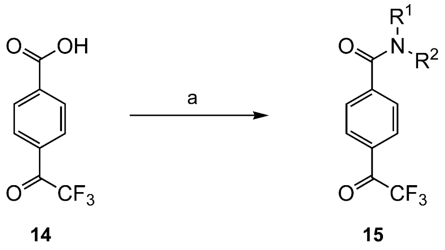


Scheme 1. Reagents and conditions: (a) i—CF_3TMS, DCM, cat. TBAF, −78 °C to rt, ii—aq HCl, acetone, 92%; (b) Fe/HOAc, EtOH, reflux, 79%; (c) R^2COCl, DCM, Et_3N, rt, 81–96%; (d) MeI, NaH, THF; (e) i—$NaBH_4$, MeOH, ii—R^1X, NaH, THF, rt, 45–65%; (f) Dess–Martin periodinane in DCM, 83%; (g) MeMgBr, THF, −30 °C, 67%.

literature procedure,[13] methyl 4-nitrobenzoate **6** was treated with (trifluoromethyl)-trimethylsilane in the presence of catalytic TBAF to afford the hydrated form of 2,2,2-trifluoro-1-(4-nitrophenyl)ethanone **7**. Reduction of the nitro group with iron provided the desired aniline compound **8**. Reaction of **8** with acyl chlorides gave the amide derivatives **9**. Attempts to alkylate the amide nitrogen at this step produced primarily the corresponding methyl ester **10**. This transformation is potentially due to methylation of the hydrate, followed by the elimination of the CF_3 function. Therefore, ketone **9** was reduced with $NaBH_4$ in MeOH, followed by alkylation of the amide with an alkyl bromide in the presence of NaH to give predominately the desired trisubstituted amide **11**. O-Alkylated products also were obtained in 10–30% yield, depending on the alkyl halide used. Amide **11** was then oxidized using Dess–Martin periodinane to afford the trifluoroacetyl derivative **12**. As part of our SAR study of the hexafluoroisopropanol compound series, ketones **12** were treated with MeMgBr at −30 °C to produce trifluoroisopropanols **13**.

The synthesis of benzoic acid-based trifluoroacetyl MCD inhibitors **15** is illustrated in Scheme 2. To distinguish these amides from the ones mentioned above, we designated these analogs as 'reverse amides'. The reverse amides were prepared efficiently by conventional peptide coupling methods in a 96-well plate format from commercially available 4-(trifluoroacetyl)benzoic acid **14**.

MCD inhibitors synthesized above were evaluated for their ability to inhibit the soluble form of recombinant

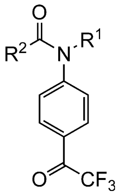


Scheme 2. Reagents and conditions: (a) R^1R^2NH, EDC, DMAP, DCM.

MBP fusion protein (MBP-hMCD) as described previously.[11b,14] The IC_{50} values for some selected compounds are tabulated in Tables 1 and 2.

Compounds **11** and **13** (R^1 = Me; R^2 = $–CH_2OPh$) were evaluated as part of a SAR study on the hexafluoroisopropanol series. Both compounds were found to be significantly less active than the corresponding hexafluoroisopropanol compound **1** against MBP-hMCD (IC_{50}: **1**: 0.93 μM vs. **11**: 32.4 μM; **13**: 19.8 μM). The weak activity of mono trifluoromethyl substituted compounds **11** or **13** indicates how sensitive the MCD active site is to the acidity of the hydroxyl group.[11a,11b,11c] The trifluoroacetophenone analogs **12** were found to be the most active of the modifications made to the hexafluoroisopropanol moiety, but they were still weaker than the corresponding hexafluoroisopropanol analogs (IC_{50}: **1**: 0.93 μM vs. **12d**: 4.51 μM). The fact that trifluoromethyl ketone compounds showed higher activity than the corresponding alcohol compound may be due to the presence of the hydrated form (ketal), which mimics the acidic hydroxyl moiety of the hexafluoroisopropanol group. It is therefore reasonable to hypothesize that improving the stability of the hydrate could increase the activity of the trifluoroacetophenone derivatives.

Table 1. Amide MCD inhibitors

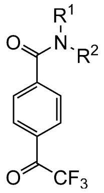


Compound	R^1	R^2	IC_{50}[a] (μM)
12a	H	*i*-Pr	5.45
12b	H	4-CNPh	4.9
12c	H	$–CH_2OPh$	1.5
12d	Me	$–CH_2OPh$	4.5
12e	H	1-Morpholinyl	17.2
12f	*n*-Pr	–N(*i*-Bu)$_2$	2.8

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

Accordingly, the 4-(trifluoroacetyl)benzamide analogs or reverse amide analogs were found to have increased potency against MBP-hMCD (Table 2) when compared to the 'normal amide' analogs. ^1H NMR of these reverse

Table 2. Reverse amide MCD inhibitors



Compound	R^1	R^2	IC_{50}[a] (nM)
15a	*i*-Pr	Ph	1731
15b	*n*-Pr	*n*-Pr	153
15c	*n*-Pr	Cyclopropylmethyl	68
15d	*i*-Bu	3-Nitrophenyl$CO_2CH_2CH_2$–	80
15e	*i*-Bu	*i*-Bu	73
15f	H	*i*-Bu	1531
15g	H	*i*-Pr	3361
15h	H	2-Furanylmethyl	2034
15i	H	*n*-Hexyl	679
15j	H	$–CH(CH_3)(CH_2)_4CH_3$	115
15k	H	$–CH(CH_3)CH_2CH(CH_3)_2$	242
15l	H	$–CH_2CH_2C(CH_3)_3$	2753
15m	H	2-Methylcyclohexyl	304
15n	H	Cyclohexylmethyl	2298
15o	H	2-MeOphenyl	5011
15p	H	3-CF_3benzyl	507
15q	H	3,5-$(CF_3)_2$benzyl	654
15r	H	$–CH_2(CH_2)_2CH_2Ph$	1739
15s	H	$–CH_2CH_2CH_2Ph$	1351
15t	H	$–CH_2CH_2Ph$	566
15u	Me	$–CH_2CH_2Ph$	953
15v	Ph	$–CH_2CH_2CN$	155
15w	Et	$–CH_2CH_2CN$	214
15x	Et	$–CH_2C(CH_3)_2OH$	399
15y	Et	$–CH_2CH_2OMe$	1105
15z	Et	Et	1619
15aa	$–CH_2CH_2CH_2CH_2–$		3280

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

amide compounds showed the hydrated form is the primary form in a $CDCl_3$ solution, while the normal amide showed very little of the hydrated species. This improved activity is most likely due to the electron-withdrawing effects of the reverse amide affecting the formation of the hydrate. Two of the three most active compounds **15c–e** were found to be substituted on the nitrogen with two aliphatic substituents, one of which is a branched aliphatic chain. The third active compound **15d** also possesses a branched aliphatic chain along with an aliphatic alcohol as its 3-nitrophenylcarboxylic ester. Similar activity trends were observed in the reverse amide hexafluoroisopropanol series (data not shown).[11b] In fact, when **15e** or **15u** is compared with its corresponding hexafluoroisopropanol analog, the trifluoroacetophenone analogs are of similar or enhanced potency (IC_{50}: **15e**: 73 nM vs. 70 nM; **15u**: 953 nM vs. 1990 nM). A notable exception was those compounds substituted with a single aliphatic chain containing an α-methyl (e.g., **15j**, IC_{50}: 115 nM).

In summary, a series of trifluoroacetophenone MCD inhibitors were designed to replace the hexafluoroisopropanol moiety found in the original HTS hit. Some of the reverse amide analogs were found to be potent inhibitors of MCD enzyme activity in the in vitro MCD enzyme assay. The trifluoroacetyl group may interact with the MCD active site as the hydrate in a similar fashion to the hexafluoroisopropanol analogs reported previously. Adding electron-withdrawing groups to the phenyl ring, thereby stabilizing the hydrated species, can enhance this interaction.

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