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Addressing hERG activity while maintaining favorable potency, selectivity and pharmacokinetic properties of PPARδ Modulators

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ABSTRACT: One of the most commonly used strategies to reduce hERG (human ether-a-go-go) activity in the drug candidates is incorporating a carboxylic acid group. During the optimization of PPARδ modulators some of the compounds containing a carboxylic acid were found to inhibit the hERG channel in a patch clamp assay. By modifying the basicity of the imidazole core, potent and selective PPARδ modulators that do not inhibit the hERG channel were identified. Some of the modulators have excellent pharmacokinetic profiles in mice.

We have recently disclosed a series ("benzamide series") of PPARδ modulators such as **1a-b** that show good selectivity for PPARδ over PPARα and PPARγ (**Figure 1**).[1,2] By replacing the *cis* amide conformer found in the x-ray structure of benzamides in the ligand binding domain of PPARδ receptor, a second series ("imidazole series") of PPARδ modulators was designed (**Figure 1**).[3] The compounds in the imidazole series such as **2a** were found to be more potent and selective modulators of PPARδ receptor. Modifications to the hexanoic acid moiety in both series significantly improves plasma exposures after oral dosing as compared to their unsubstituted counterparts.[1,3] We have shown that MA-0204 (**2c**), a derivative in the imidazole series, may be an effective therapeutic for Duchene Muscular Dystrophy (DMD).[3]

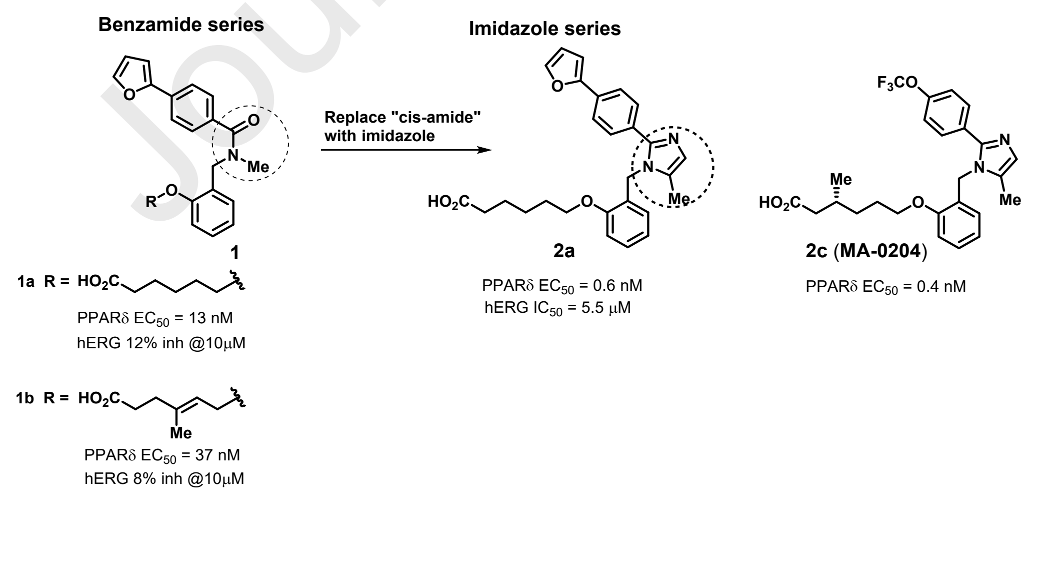


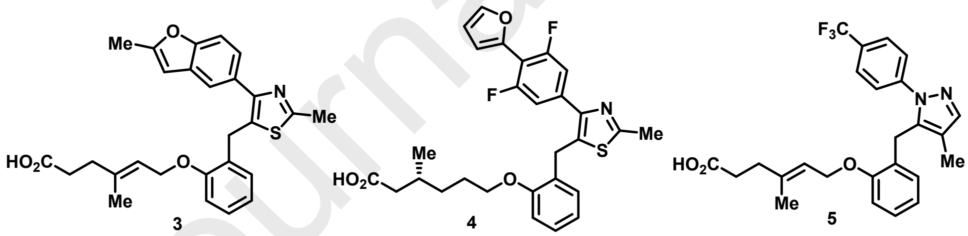
Figure 1.

Medicinal chemists routinely screen lead compounds for hERG channel binding in order to assess their potential to cause QT prolongation, which could lead to Torsades de pointes arrythmias.[4] Several drugs have been withdrawn from market or given “black box” labels due to risks related to hERG channel-related QT prolongation.[5] Such measures are necessary if the concentration of drug required for its therapeutic activity nears the concentration where the hERG channel is inhibited.[6]

In order to address this potential safety concern, medicinal chemists optimize lead compounds for minimal hERG inhibition (typically IC_{50} >10 μM), while maintaining or improving activity for the molecular target (typically IC_{50} or EC_{50}<100 nM). Although not an absolute requirement, a vast majority of the hERG active molecules possess basic amines in their structures. In order to understand the interaction of molecules with the channel, structural information regarding the hERG K-channel is used.[7-8] It is known that hERG channel binding pocket interactions occur *via* the hydrophobic central cavity and two amino acid residues Y652 and F656.[9] The interactions of the hERG inhibitors with the phenylalanine moiety are more hydrophobic in nature whereas the interactions with the tyrosine moiety are hypothesized to be π-cationic in nature.[9,10] Therefore, modulating lipophilicity of compounds (TPSA, LogD or LogP) or the basicity (pKa) of nitrogens in the molecules is a commonly used tactic to reduce hERG activity[4, 11-13] A carboxyl group in the structure of a molecule can help lower the lipophilicity and minimize hydrophobic interactions. There are several examples in the literature where a carboxylic acid moiety was introduced into a compound structure to reduce the hERG activity.[14-15] In certain cases, adding a carboxylic acid moiety can result in a zwitterionic compound.[16] Zwitterionic molecules typically have low permeability, which reduces the probability of hERG binding.[11]

When lead compounds in the benzamide series,**1a** and **1b**, were screened for hERG activity in an automated patch clamp assay, little or no activity (<15% inhibition at 10 μM) was observed.[17] Such results were consistent with our expectations as **1a** and **1b** lack basic nitrogen atoms and possess a carboxylic acid. Therefore, when imidazole **2a**, was found to inhibit hERG channel activity (IC_{50} = 5 μM), the result was unexpected because: (1) the compound contains a carboxylic acid and (2) even if the imidazole nitrogen is basic, the compound still would exist in a zwitterionic form.

In order to further understand whether the change in the shape of the molecule resulting from replacing an amide group in **1a** and **1b** with an imidazole(**2a)** led to the hERG acivity, two thiazoles (**3** and **4**) and one pyrazole (**5**) were synthesized and screened for hERG activity (**Figure 2**). All three compounds lack hERG inhibitory activity (<15% inhibition at 10 μM).



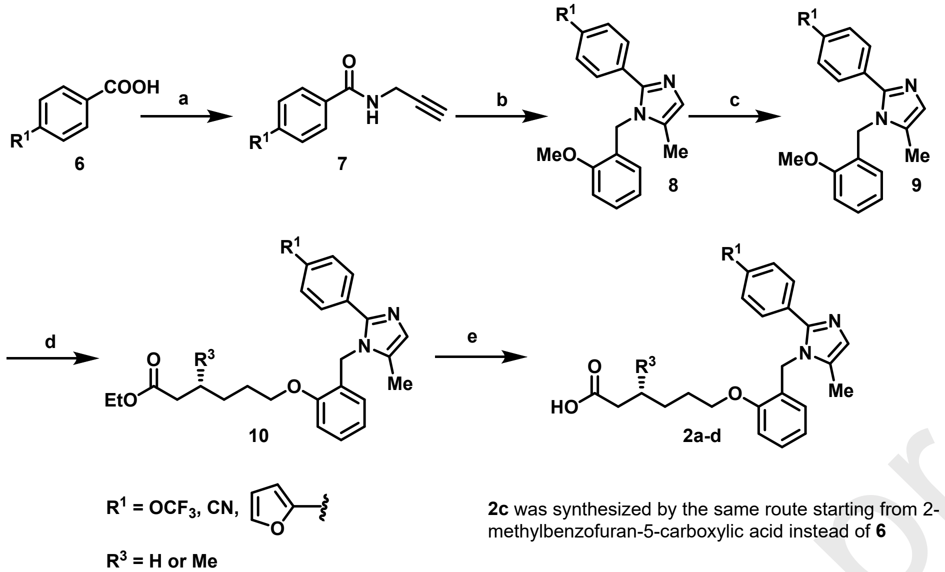
3 | 4 | 5

PPARδ EC_{50} = 29.7 nM, hERG 14% inh @10μM | PPARδ EC_{50} = 11.2 nM, hERG 4% inh @10μM | PPARδ EC_{50} = 2.0 nM, hERG 4% inh @10μM

Figure 2.

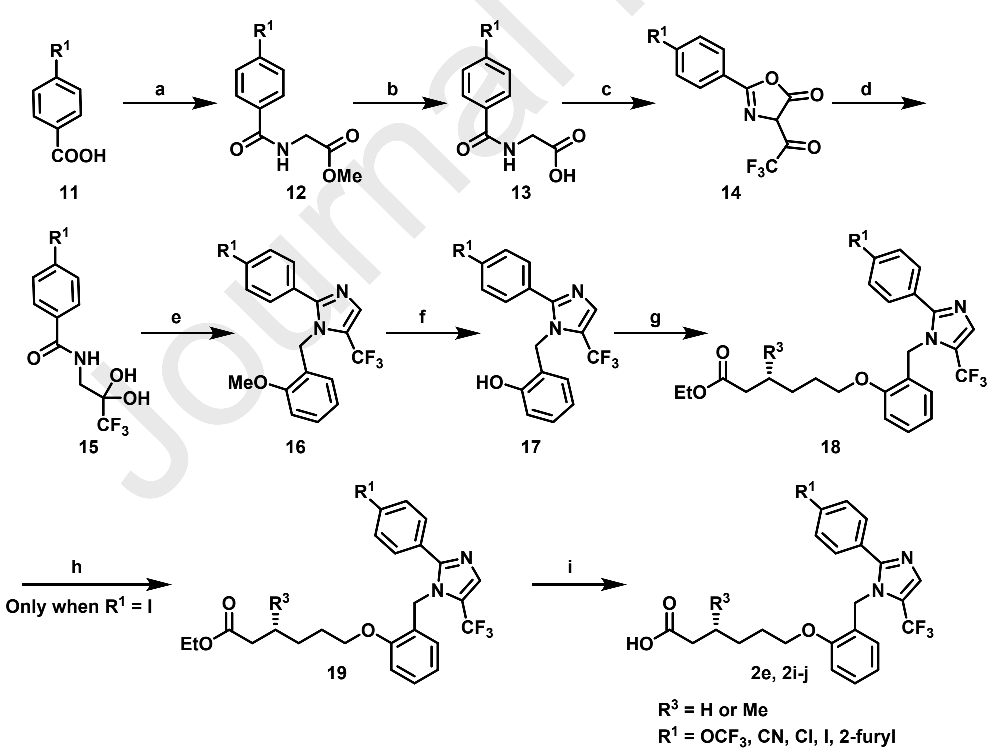
Based on these results, it is unlikely that the hERG activity observed for imidazole **2a** results from the three dimensional shape of the molecule. We assessed whether lipophilicity (as characterized by cLogP or TPSA (topological polar surface area) impacts the hERG inhibition.[11-12] Calculated logP for **2a** (cLogP = 5.1)[18] is lower than those for **3**, **4** and **5** (cLogP = 6.1-7.5). TPSA for all four compounds are between 71A° and 78A°. Therefore, lipophilicity parameters do not seem to correlate with the differences in the hERG activity of these compounds. We then examined if the basicity of the nitrogen atoms in the heterocyclic rings could explain the difference in the hERG inhibitory properties of these compounds. In order to test this hypothesis, imidazoles **2b-2l** with either electron withdrawing or electron donating groups on the imidazole ring or on the phenyl ring that is directly attached to the imidazole ring (**Table 1**) were synthesized and tested. The imidazole compounds bearing a methyl group on the imidazole ring, were synthesized using **Scheme 1**.[1,3] For the synthesis of compounds **2e** and **2i-j**, the central imidazole rings bearing a trifluoromethyl group were constructed *via* 2-(4-substituted-phenyl)-4-(2,2,2-trifluoroacetyl)oxazol-5(4*H*)-one as shown in **Scheme 2**.[19] Compounds with a trifluoromethyl (**2f**), a chloro (**2h**) or a cyano (**2g**) substituent on the imidazole ring were synthesized *via* a common intermediate **23** as shown in Scheme 3.[19]

Scheme 1. Synthesis of Compounds **2a-d**



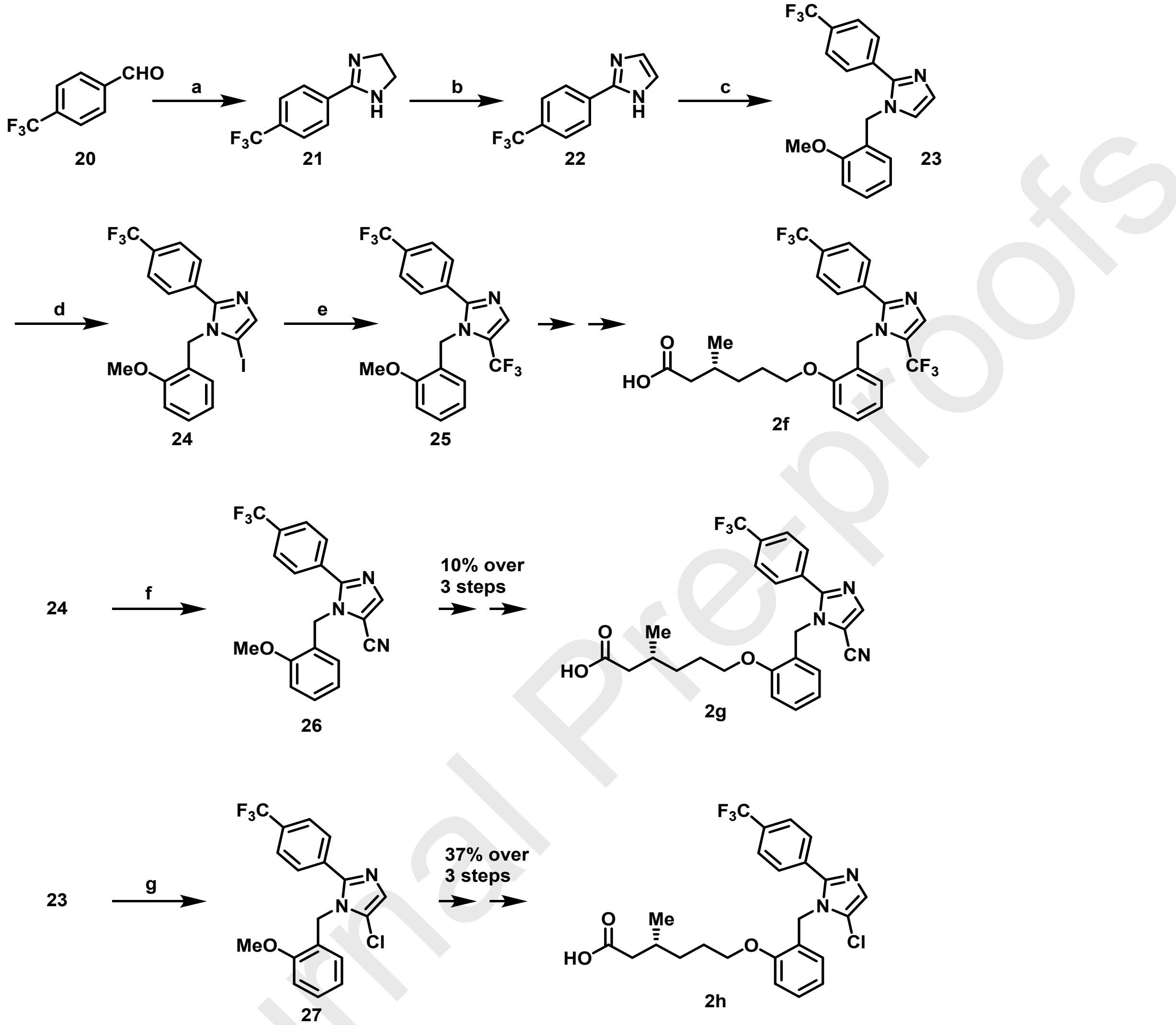
Reagents and conditions: a) Prop-2-yn-1-amine, EDCI.HCl, HOBt, Et_3N, DMF, RT, 12h; b) 2-Methoxybenzyl amine, $Zn(OTf)_2$, toluene, 110°C, 12h; c) BBr_3, DCM, 0°C-RT, 4h; d) Ethyl (*3R*)-6-bromo-3-methylhexanoate or ethyl-6-bromohexanoate, K_2CO_3, DMF, RT, 12h; e) $LiOH.H_2O$, THF, EtOH, H_2O, RT, 12h.

Scheme 2. Synthesis of Compounds **2e, 2i-j**



Reagents and conditions: a) Methyl glycinate hydrochloride, EDCI.HCl, HOBt, Et_3N, DMF, 12h, RT; b) $LiOH.H_2O$, THF, EtOH, H_2O, RT, 12h; c) 2,2,2-Trifluoroacetic anhydride, acetone, 0°C-RT, 12h; d) 1,4-Dioxane, H_2O, 100°C, 3h; e) 2-Methoxyl benzyl amine, AcOH, toluene, 120°C, 12h; f) BBr_3, DCM, -78°C-RT; g) Ethyl 6-bromohexanoate, K_2CO_3, DMF, RT, 12h; h) In the case where R^1 = I, furan-2-boronic acid, $Pd(PPh_3)_4$, Na_2CO_3, DME, EtOH, H_2O, 90°C, 12h; i) $LiOH.H_2O$, THF, EtOH, H_2O, RT, 12h.

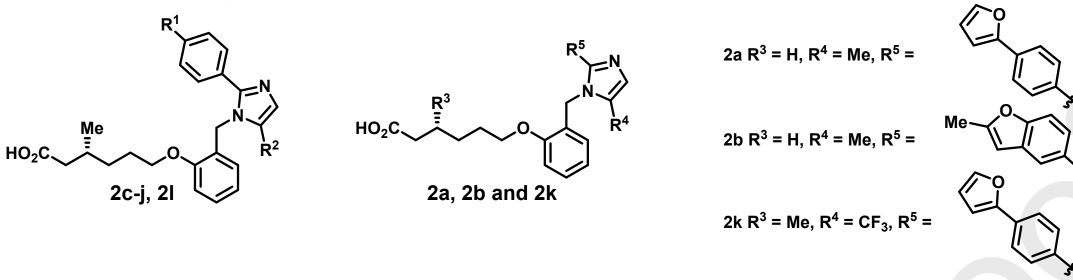
Scheme 3. Synthesis of **2f, 2g** and **2h**



Reagents and conditions: a) Ethane-1,2-diamine, I_2, K_2CO_3, t-BuOH, 85°C, 5h, 85% yield; b) (Diacetoxyiodo)benzene, K_2CO_3, DMSO, RT, 12h, 55% yield; c) 2-Methoxybenzyl bromide, NaH (60% dispersion), DMF 0°C-RT, 4h, 83% yield; d) NIS, DMF, 80°C, 12h, 36% yield; e) $TMSCF_3$, Ag_2CO_3, 1,10-phenanthroline, KF, CuI, DMF, 100°C, 12h, 59% yield; f) CuCN, $Pd(PPh_3)_4$, DMF, microwave, 150°C, 2h, 45% yield; g) NCS, CH_3CN, 70°C, 12h, 40% yield.

All the compounds in **Table 1** show excellent PPARδ activity (EC_{50} = 0.4 - 30 nM). The comparison of hERG activity and cLogP or TPSA for a set of compounds (**Table 1**) revealed no correlation between the hERG activity and physicochemical properties. However, a clear relationship was observed between nitrogen basicity in the heteroaromatic ring and the hERG activity with an infliction point around pKa = 6.0 (**Figure 3**).[20] Decreasing electron-donation to the phenyl ring that is attached to the imidazole **(2c)** lowered hERG activity. Adding a stronger electron withdrawing (cyano) group at the same position (**2d),** reduced hERG inhibition below 50% at 10 μM. When electron withdrawing groups were placed directly on the imidazole ring (**2e - 2l**), hERG activity was diminished substantially, for example, when comparing **2a** (hERG IC_{50} = 5.5 μM) to **2k** and **2l** (<10% inhibition of hERG @ 10μM)or **2c** to **2e**.

Table 1. pKa, cLogP, TPSA and PPARδ activity for compounds **2a-2l** and **3-5.**



Cpd	R^1	R^2	PPARδ EC_{50} nM[a]	hERG (EC_{50})[b], %inh@10μM	Calculated parameters[c]		
					pKa	cLogP	TPSA
3	---	---	29.7±3.4	14	2.8	6.7	72.6
4	---	---	2.0±0.1	4	1.8	6.1	64.4
5	---	---	11.2±3.9	4	2.8	7.5	72.6
2a	---	---	0.6±0.3	5.5 μM	6.3	5.1	77.5
2b	---	---	3.9±1.3	51	6.3	5.1	77.5
2c	OCF_3	Me	0.4±0.1	10 μM	6.3	5.8	73.6
2d	CN	Me	4.6	15	6.3	4.2	88.1
2e	OCF_3	CF_3	2.6 ± 1.1	2.0	4.7	5.9	73.6
2f	CF_3	CF_3	2.9 ±0.2	5.7	4.7	5.6	64.4
2g	CF_3	CN	2.7	2.5	3.4	4.5	88.1
2h	CF_3	Cl	1.5±0.8	3	4.7	5.7	64.4
2i	CN	CF_3	8.2 ± 2.6	4	4.7	4.3	88.1
2j	Cl	CF_3	8.0±0.4	5.0	4.7	5.4	64.4
2k	2-Furyl	CF_3	0.7±0.2	2.3	4.7	5.2	77.5
2l	---	---	1.2±0.9	7.0	ND	ND	ND

[a]Transactivation assay[24] EC_{50} values are an average of at least two experiments (SEM shown unless single determination). % Activation of compound at each concentration was calculated considering activity of GW501516 at 10 uM as 100%. The Emax was between 81-103% except for compound **3** (Emax = 61%). Please see reference 3 or WO2016057660 for the details of the assay system; [b]See reference 17; [c]For the calculation of cLogP, TPSA and pKa, commercially available ACD software was used.[18, 21]; ND = Not Determined;

The observed differences in the hERG activity of imidazole **2a** versus other heteroaromatic ring containing compounds (**3-5**) tracks the differences in the basicity of nitrogens (pKa = 6.3 versus 1.8-2.8). Compound **2b** where the basicity of nitrogen is similar to the nitrogen in **2a**, also has hERG activity (50% inhibition at 10 μM). With the increased basicity of nitrogen in the heteroaromatic ring, it's more likely that molecule exists in zwitterionic form, which could increase hERG activity. This may contradict some reports where zwitterionic character was introduced in the molecules as a strategy to decrease hERG activity including the well-known example of transforming terfenadine into zwitterionic fexofenadine with reduce hERG activity.[21] However, there are a few publications where zwitterionic compounds that inhibit the hERG channel were reported.[22]

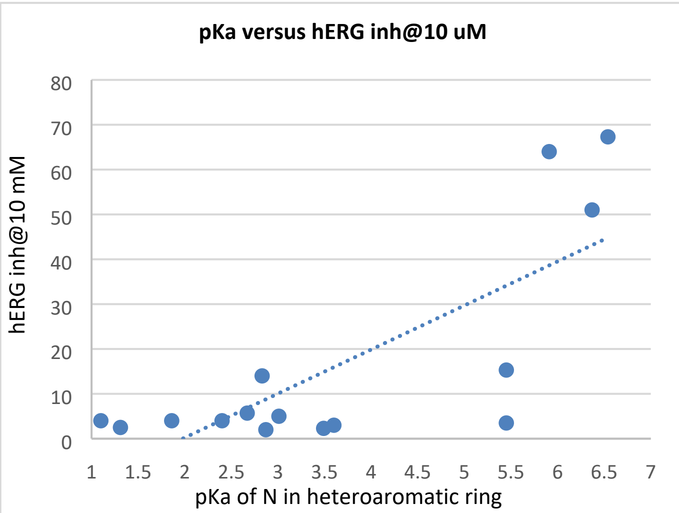


Figure 3: Correlation between pKa and hERG activity for compounds in **Table 1**. The graph was generated in MS Excel. The dotted line represented trendline generated by the software based on the data.

While reviewing the hERG activity of compounds, it's important to consider many points, for example, differences in assays. The data shown here was generated using an automated patch clamp assay. For an accurate measurement of hERG activity, especially for compounds with low aqueous solubility, a manual patch clamp assay should be performed.[23] It is important to point out that most of the the imidazole compounds described in **Table 1** exhibit low aqueous solubility (thermodynamic solubility <25 mM). Compounds such as **2c** could be a viable clinical candidate because of the large window between the PPARδ potency (EC_{50} = 0.4 nM) and the observed hERG activity (IC_{50} = 10 μM, in the automated patch clamp assay).[3] Typically cardiac safety is then measured in telemetrized animals before a compound enters clinical trials in human. Therefore, it was important to assess oral bioavailability of these new compounds in addition to their profile for activating PPAR isoforms. Potency, selectivity and the pharmacokinetic (PK) profiles for **2f**, **2h** and **2i** are shown in **Table 2**.

All the compounds are potent PPARδ modulators (EC_{50} <10 nM) and selective over PPARα and PPARγ receptors (EC_{50} >100,000 nM)) in transactivation assays.[24] Compounds **2f**, **2h** and **2i** show good oral bioavailability (F = 70 - 100%) in mice, have low to moderate clearance (5-16 mL/min/kg) and reasonable elimination half-lives (3.5-4.1 h). The observed PK profile in mice is better than that observed for **2c** and some previously reported imidazole compounds.[3]

Table 2. PPAR isoform selectivity and mouse PK data for compounds **2f**, **2h** and **2i**.

Compound	**2f**	**2h**	**2i**
EC_{50} PPARδ nM[a]	2.9 ±0.2	1.5±0.8	8.2 ± 2.6
EC_{50} PPARα nM[a]	>100,000	>100,000	>100,000
EC_{50} PPARγ nM[a]	>100,000	>100,000	>100,000
$AUC_{(0\text{-}inf)}$ (ng*h/mL)[b]	6962	3881	14735

CL (mL/min/kg)[b]	5.0	16	2.5
$t_{1/2}$ (h)[b]	5.8	3.5	4.1
%F[b]	70	100	73

[a]Transactivation assay[24] EC_{50} values are an average of at least two experiments (SEM shown unless single determination); [b]Exposure data for compounds dosed i.v. at 1 mg/kg and orally at 3 mg/kg in CD-1 mice[25]

In summary, we have demonstrated that the hERG activity of the imidazole PPARδ modulators can be attenuated by tuning the basicity of the nitrogen in the imidazole ring. We effectively decreased the hERG activity while maintaining favorable PPARδ potency, selectivity and oral bioavailability. This study serves as another reminder for the medicinal chemists not to be overconfident that hERG activity can be ameliorated by adding a carboxylic acid moiety to a structure.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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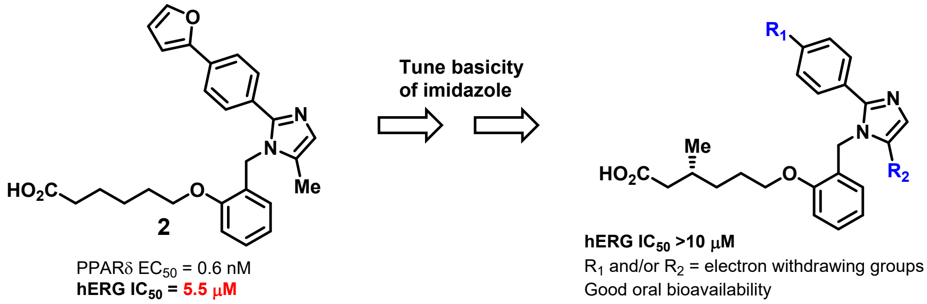
ABBREVIATIONS

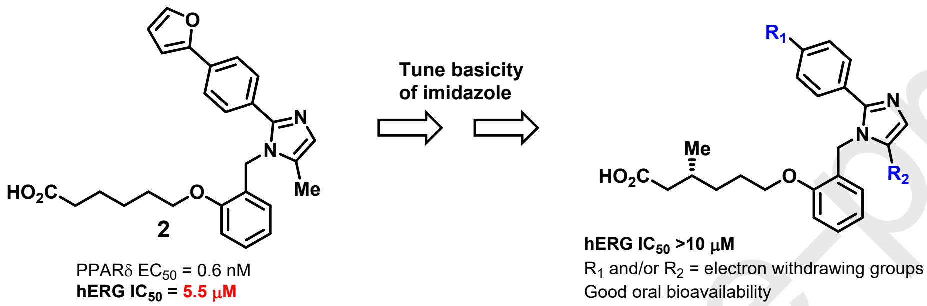
DMSO, Dimethyl Sulfoxide; BBr_3, boron tribromide; DCM, dichloromethane; RT, room temperature; h, hour; $Pd(PPh_3)_4$, Tetrakis(triphenylphosphine)palladium(0); Na_2CO_3, sodium carbonate; DME, 1,2-dimethoxyethane; EtOH, ethyl alcohol; $LiOH.H_2O$, lithium hydroxide monohydrate; THF, tetrahydrofuran; EDCI.HCl, ethylcarbodiimide hydrochloride; HOBt, 1-hydroxy benzotriazole; Et_3N, triethylamine; DMF, N,N-dimethyl formamide; $Zn(OTf)_2$, zinc trifluoromethanesulfonate.

REFERENCES

1. Lagu, B.; Kluge, A. F.; Fredenburg, R. A.; Tozzo, E.; Senaiar, R. S.; Jaleel, M.; Panigrahi, S. K.; Tiwari, N. K.; Krishnamurthy, N. R.; Takahashi, T.; Patane, M. A. "Novel highly selective peroxisome proliferator-activated receptor δ (PPARδ) modulators with pharmacokinetic properties suitable for once-daily oral dosing" *Bioorg. Med. Chem. Lett.* **2017**, *27*, 5230-5234.
2. Lagu, B.; Kluge, A. F.; Fredenburg, R. A.; Goddeeris, M. M.; Tozzo, E.; Senaiar, R. S.; Jaleel, M.; Chellur, S.; Babu, R. K.; Tiwari, N. K.; Takahashi, T.; Patane, M. A. "Highly selective peroxisome proliferator-activated receptor δ (PPARδ) modulator demonstrates improved safety profile compared to GW501516" *Bioorg. Med. Chem. Lett.* **2018**, *28,* 533-536.
3. Lagu, B.; Kluge, A. F.; Tozzo, E.; Fredenburg, R.; Bell, E. L.; Goddeeris, M. M.; Dwyer, P.; Basinski, A.; Senaiar, R. S.; Jaleel, M.; Tiwari, N. K.; Panigrahi, S. K.; Krishnamurthy, N. R.; Takahashi, T.; Patane, M. A. "Selective PPARδ Modulators Improve Mitochondrial Function: Potential Treatment for Duchenne Muscular Dystrophy (DMD)" *ACS Med. Chem. Lett.* **2018**, *9*, 935-940.
4. Kalyaanamoorthy, S.; Barakat, K. H. "Development of Safe Drugs: The hERG Challenge" *Medicinal Research Reviews*, **2018**, *38* (2), 525–555.

5. Yap, Y. G.; Camm, A. J. "Drug induced QT prolongation and torsades de pointes" *Heart* **2003**, *89*, 363–1372.
6. Pearlstein, R.; Vaz, R.; Rampe, D. "Understanding the Structure-Activity Relationship of the Human Ether-a-go-go-Related Gene Cardiac K+ Channel. A Model for Bad Behavior" *J.Med. Chem.* **2003**, *46*, 2017-2022.
7. Cabral, J. H. M.; Lee, A.; Cohen, S. L.; Chait, B. T.; Li, M.; MacKinnon, R. "Crystal Structure and Functional Analysis of the HERG Potassium Channel N Terminus:A Eukaryotic PAS Domain" *Cell*, **1998**, *95*, 649-655.
8. Wang, W.; MacKinnon, R. "Cryo-EM Structure of the Open Human Ether-a`-go-go-Related K+ Channel hERG" *Cell*, **2017**, *169*, 422-430.
9. Sanguinetti, M. C.; Tristani-Firouzi, M. "hERG potassium channels and cardiac arrhythmia" *Nature* **2006**, *440*, 463–469.
10. Durdagi, S.; Subbotina, J.; Lees-Miller, J.; Guo, J.; Duff, H. J.; Noskov, S.Y. "Insights into the molecular mechanism of hERG1 channel activation and blockade by drugs" *Curr Med Chem* **2010**; *17*, 3514–3532.
11. Jamieson, C.; Moir, E. M.; Rankovic, Z.; Wishart, G. "Medicinal Chemistry of hERG Optimizations: Highlights and Hang-Ups" *J. Med. Chem.* **2006**, *49*, 5029-5046.
12. Jamieson, C.; Moir, E. M.; Rankovic, Z.; Wishart, G. "Strategy and Tactics for hERG Optimizations" Antitargets (Edited by R. J. Vaz and T. Klabunde Copyright **2008** WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim).
13. Didziapetris, R.; Lanevskij, K. "Compilation and physicochemical classification analysis of a diverse hERG inhibition database" *J Comput Aided Mol Des* **2016**, *30*, 1175–1188.
14. Vaz, R. J.; Gao, Z.; Pribish, J.; Chen, X.; Levell, J.; Davis, L.; Albert, E.; Brollo, M.; Ugolini, A.; Cramer, D. M.; Cairns, J.; Sides, K.; Liu, F.; Kwong, J.; Kang, J.; Rebello, S.; Elliot, M.; Lim, H.; Chellaraj, V.; Singleton, R. W.; Li, Y. "Design of bivalent ligands using hydrogen bond linkers: synthesis and evaluation of inhibitors for human β-tryptase" *Bioorg. Med. Chem. Lett.* **2004**, *14*, 6053-6056.
15. Xu, J.; Mathvink, R.; He, J.; Park, Y. J.; He, H.; Leiting, B.; Lyons, K. A.; Marsilio, F.; Patel, R. A.; Wu, J. K.; Thornberry, N. A.; Weber, A. E. Discovery of potent and selective phenylalanine based dipeptidyl peptidase IV inhibitors. *Bioorg. Med. Chem. Lett.* **2005**, *15,* 2533-2536.
16. Choi, Y. J.; Seo, J.; Shin, K. J. "Successful reduction of off-target hERG toxicity by structural modification of a T-type calcium channel blocker" *Bioorg. Med. Chem. Lett.* 2014, 24, 880–883.
17. Semi-automatic patch clamp method was used using Port-A- Patch (from Nanion technologies, Germany). HEK293 cells stably expressing hERG potassium channels. 0.1% DMSO in extracellular HEPES buffer was used as the vehicle. Assay conditions were room temperature and the compound addition was done manually. Aspirin at 10μM concentration was used as a negative control. Cisapride or verapamil at 1μM concentration were used as positive controls.
18. TPSA and cLogP were calculated using ACD/ToxSuite 2.95 ACD/Labs. (http://www.acdlabs.com/products/admet/tox).
19. The description of the synthesis and the spectroscopic data has been described in WO2017180818.
20. pKa were calculated using ACD/ToxSuite 2.95 ACD/Labs. Comparable pKa numbers were obtained using Marvin suite (https://chemaxon.com/products/marvin).
21. Rampe, D.; Wibble, B.; Brown, A. M.; Dage, R. C. Effects of terfenadine and its metabolites on a delayed rectifier K+ channel cloned from human heart. *Mol. Pharmacol.* **1993**, *44*, 1240-1245.
22. Nikolov, N. G.; Dybdahl, M.; Jónsdóttir, S. Ó.; Wedebye, E. B. "hERG blocking potential of acids and zwitterions characterized by three thresholds for acidity, size and reactivity" *Bioorg. Med. Chem.* **2014**, *22*, 6004-6013.
23. Yajuan, X.; Xin, L.; Zhiyuan, L. "A Comparison of the Performance and Application Differences between Manual and Automated Patch-Clamp Techniques" *Current Chemical Genomics,* **2012**, *6,* 87-92.
24. In the transactivation assay CV-1 cells are transfected with a PPAR ligand binding domain fused to a GAL4 promoter to generate a hormone-inducible activator. A test ligand is added and activity is measured in a luciferase assay. See WO2016057660 for further details.
25. All the animal experiments were carried out as per the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Government of India and approved by the Institutional Animal Ethics Committee (IAEC), Aurigene Discovery Technologies Ltd,, Bengaluru, India.


HO2C
O
N
N
Me
2
PPARδ EC50 = 0.6 nM
hERG IC50 = 5.5 μM
Tune basicity of imidazole
R1
N
N
R2
Me
HO2C
O
hERG IC50 >10 μM
R1 and/or R2 = electron withdrawing groups
Good oral bioavailability


HO2C
O
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PPARδ EC50 = 0.6 nM
hERG IC50 = 5.5 μM
Tune basicity of imidazole
R1
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R2
Me
HO2C
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hERG IC50 >10 μM
R1 and/or R2 = electron withdrawing groups
Good oral bioavailability