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ortho Substituent effects on the anticonvulsant properties of *4*-hydroxy-trifluoroethyl phenols

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ABSTRACT

2,6-Dialkylphenols with isopropyl and sec-butyl substituent are well known anesthetic compounds. The 4-substitution with 1-hydroxy-2,2,2-trifluoroethyl (4-HTFE) group in these compounds led to the discovery of compounds with anticonvulsant activity in the 6 Hz (32 mA) model of partial epilepsy. In the present study a series of 2-alkyl-4-HTFE phenols with the 6-position being replaced with either hydrogen and bromine were designed, synthesized and tested to evaluate the effect of *ortho*-substitution on the anticonvulsant property. The studies show that 2-substituted branched alkyl chain (iso-propyl and sec-butyl) is necessary for the anti-seizure effect. Phenols with 2-substituted linear alkyl groups (methyl, ethyl and *n*-propyl) having no substitution at 6-position were found to be devoid of antiseizure effects. The 6-substitution with bromine moderately reduces the anticonvulsant effect in the compounds with branched alkyl chains, but led to enhanced anticonvulsant effect in the compound with a linear alkyl chain. This study shows that 4-HTFE phenols having isopropyl or sec-butyl *ortho* groups produce good antiseizure protection in the 6 Hz therapy-resistant mouse model.

2,6-Dialkylphenols having isopropyl and *sec*-butyl substituents are potent anesthetic/sedative compounds.[1,2] Accompanying these CNS depressant effects are anticonvulsant properties that can occur at sub-anesthetic doses. The only currently marketed anesthetic in this class of compounds, propofol (2,6-diisopropylphenol), is sufficiently effective as an anticonvulsant that it is recommended for the acute treatment of status epilepticus in humans.[3,4] The anticonvulsant effects of propofol and of the related compound, 2,6-di-*sec*-butylphenol, have been confirmed in animal seizure models.[5–7] 2,6-Di-*sec*-butylphenol (*R,R*) is currently undergoing development as an anesthetic due to its anesthetic potency and low cardiovascular side effects.[8]

It was previously demonstrated that the addition of a 4-(1-hydroxy-2,2,2-trifluoroethyl) group (4-HTFE) to propofol (MB003) and 2,6-di-*sec*-butylphenol (MB050) (Fig. 1) results in compounds that are also anticonvulsant.[7] Anticonvulsant screening revealed that these two 4-HTFE phenols are protective in the mouse 6 Hz (32 mA) model of partial epilepsy, whereas they have little to no protective effects in the mouse maximal electroshock (MES) and subcutaneous Metrazol (scMET) models. The 6 Hz model is considered an important animal model for therapy-resistant epilepsy.[9,10] Therapy-resistant epilepsy is defined as cases of epilepsy that are not satisfactorily treated with available agents. This anticonvulsant profile, effectiveness in the 6 Hz model, but not in MES and scMET models, is similar to the profile of the successful anticonvulsant levetiracetam.[11]

Another feature of 4-HTFE-substituted phenols is that this ring addition reduces the sedative effects of these compounds. That is, anticonvulsant effects occur at doses where animals can maintain a gait on the rotorod. This is reflected in wider protective indices (TD_{50}/ED_{50}). Propofol and 2,6-di-*sec*-butylphenol's potent sedative effects, properties considered toxic for anticonvulsant compounds,[12] limit their usefulness in the more widespread treatment of seizures. However, the lower toxicity of the 4-HTFE-substituted phenols suggests that such compounds may be useful as anticonvulsants outside the clinical setting where sedation is less well tolerated. Furthermore, it suggests that the anticonvulsant effects of alkyl phenols are not inherently linked to sedative effects of these compounds.

Even though the anesthetic 2,6-dialkylphenols, when substituted, yielded compounds having anticonvulsant properties, 4-HTFE substitution of a non-anesthetic 2,6-dialkyl phenol, 2,6-dimethylphenol,[2] yielded a compound that likewise did not have anticonvulsant activity in the MES, scMET or 6 Hz models. These results suggest that the 2,6-di-isopropyl and 2,6-di-*sec*-butyl groups play important roles in protection in the 6 Hz seizure model.

In an effort to clarify the role of the *ortho* alkyl groups in seizure protection by 4-HTFE-substituted phenols, this study evaluated the effects of modifications to the active 2,6-diisopropyl and 2,6-di-*sec*-butyl 4-HTFE pharmacophores. These modifications include

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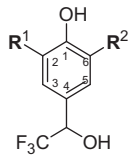


Compound	R^1	R^2
MB003	- $CH(CH_3)_2$	- $CH(CH_3)_2$
MB050	- $CH(CH_3)CH_2CH_3$	- $CH(CH_3)CH_2CH_3$
DMPF	- CH_3	- CH_3
3d	- $CH(CH_3)_2$	Br
3e	- $CH(CH_3)CH_2CH_3$	Br
3c	- $CH_2CH_2CH_3$	Br
4d	- $CH(CH_3)_2$	H
4e	- $CH(CH_3)CH_2CH_3$	H
4a	- CH_3	H
4b	- CH_2CH_3	H
4c	- $CH_2CH_2CH_3$	H

Figure 1. Structures of alkyl 4-HTFE phenol compounds.

substitution of an alkyl group with bromine (an isostere of isopropyl),[13] removal of an *ortho* group and varying the structure of the alkyl group.[13] Each compound was tested by the NINDS anticonvulsant screening program (ASP) for toxicity and seizure protection in the MES, scMET and 6 Hz mouse models.

All compounds (Fig. 1) were screened in three whole mouse models: the maximal electroshock model (MES), the scMET test (pentylenetetrazole, Metrazol),[14] and the 6 Hz psychomotor seizure model of partial epilepsy (32 mA).[9] Adult male CF No 1 albino mice (26–30 g) were used for the 6 Hz test and 18–25 g mice were used in the MES and scMet tests. The animals are housed, fed, and handled in a manner consistent with the recommendations in the National Council Publication, 'Guide for the Care and Use of Laboratory animals'. The animal studies were performed by the NINDS Anticonvulsant Screening Program under IACUC number 09-12014. All compounds were administered ip in polyethylene glycol, 30%.

The MES model, which generates generalized tonic-clonic seizures, involved pre-treating mice with experimental compound, and administering 60 Hz of alternating current (50 mA) for 0.2 s via corneal electrodes. Prior to current administration, the animal's corneas were treated topically with 1% tetracaine. Animals are considered protected if the hindlimb tonic extensor component is absent.[15] The scMET test was done by pretreating mice with experimental compound and administering 85 mg/kg Metrazol into the loose folds of the skin in the midline of the neck. Eighty-five milligram per kilogram Metrazol is the dose that causes seizures in 97% (CD97) of control animals. The animals were observed for 30 min for progression or absence of seizure which consists of clonic spasms of 3–5 s of the forelimbs, hindlimbs, jaws or vibrasse.[16]

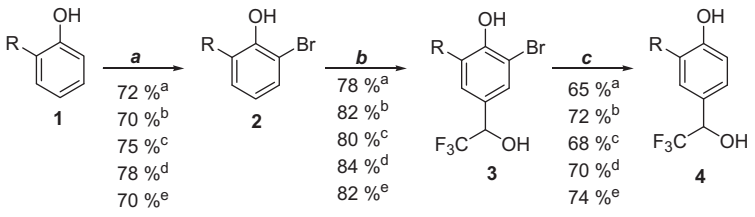
The 6 Hz test (also known as the minimal clonic seizure, or psychomotor test) involved delivering a corneal stimulus of 32 mA for 3 s. This current elicits psychomotor seizures in 97% of untreated animals.[9] Seizures consist of a minimal clonic phase followed by stereotyped automatistic behaviors. Animals not showing such behaviors were considered protected. Toxicity was determined by the rotorod test. For this test the animal are placed on a rotorod at 6 rpm following dosing. The animal is considered toxic if it falls off the rotorod three times in a 1 min period. The ED_{50}, TD_{50} and confidence intervals were determined by probit analysis.

The compounds (Fig. 1) were synthesized as described in Scheme 1. The 2-substituted alkyl phenols **1**, were regiospecifically brominated[17] at 6-position using *N*-bromosuccinimide in carbon disulfide to obtain 2-alkyl-6-bromo phenols **2**. The 2-alklyl-6-bromo phenols **2**, were treated with trifluoroacetaldehyde ethyl hemiacetal and catalytic amount of potassium carbonate at 60–70 °C[18] to get **3**, the 2-alkyl-6-bromo-4-HTFE substituted phenols. The bromine was removed by catalytic hydrogenation using Pd/C and a hydrogen balloon to get **4**, the 2-alkyl-4-HTFE substituted phenols.[19]

All compounds were administered in a PEG solvent (30%) in order to allow the best comparison between molecules. The protective effects of each compound in the MES test are shown in Table 1. All compounds showed poor to no protective effects in this model. Compounds **4a**, **4c**, **4d**, **4e**, and **3e** provided some protection, but only at the 300 mg/kg dose. Compounds **4a, 4c**, and **4d** exhibited protection at both 0.5 and 4 h, whereas **4e** and **3e** protected only at 0.5 h following this dosing. Compounds **4b**, **3c**, and **3d** showed no MES protection at any dose. The protective effects of each compound in the scMET test are shown in Table 2. No protective effects in the scMET model were seen with any compound except **4d** and **4c**. Compound **4d** exhibited protection at the highest 300 mg/kg dose at 0.5 and 4 h following dosing, and **4c** at 0.5 h only.

The protective effects of each compound in the 6 Hz test are shown in Tables 3 and 4. Compound **4b** showed no protective effects at 100 mg/kg at any time point from 0.25 to 4 h following dosing. **4a** inhibited seizures in no more than 2 of 4 animals at 100 mg/kg at any time point from 0.25 to 4 h. **3c** showed complete protection (4/4) at 0.25 and 0.5 h and partial protection at 1 h. Neither **4a** nor **4b** showed any evidence of toxicity at doses up to 300 mg/kg. Compound **3c** showed only low toxicity.

Compounds **4d**, **4e**, **3d**, and **3e**, provided complete protection (4 of 4 animals) at 100 mg/kg at one or more time points from 0.25 or 1 h. Because of their protective activities in the 6 Hz model, their toxic (TD_{50}) as well as protective effects (ED_{50}) were quantitated (Table 4). These compounds exhibited a time-to-peak effect of 0.5 h except for **4d** for which it was 0.25 h. Dose-response determinations showed that **4e** exhibited the greatest potency (ED_{50} = 53.8 mg/kg), whereas **3d** showed the weakest protection (ED_{50} = 112 mg/kg) of these compounds. **4e** was the most toxic, having a TD_{50} of 86 mg/kg, whereas **3d** was the least toxic with a TD_{50} of 403 mg/kg. The protective indices (TD_{50}/ED_{50}) ranged from a low of 1.6 for **4e** to a high of 3.6 for **3d**. No deaths occurred following the administration of any of these compounds.



[a]: R = Me; [b]: R = Et; [c]: R = *n*-Pr; [d]: R = *i*-Pr; [e]: R = *sec*-Bu

a. NBS, CS_2, rt, 6 h; ***b***. K_2CO_3, $CF_3CH(OH)OEt$, 60-70 °C, 12 h; ***c***.H_2, Pd/C, MeOH, rt, 12 h.

Scheme 1. Synthesis of 4-HTFE phenols.

Table 1
Substituted phenol effects in the maximal electroshock (MES) model[a]

Compound	Dose, mg/kg, ip	Time (h)					
		0.25	0.5	1	2	4	6
4a	30		0/1				
	100	0/3	0/3	0/3	0/3	0/3	0/3
	300		1/1			1/1	
4b	30		0/1			0/1	
	100		0/3			0/3	
	300		0/1			0/1	
4c	30	0/2	0/1	0/3	0/3	0/1	0/3
	100		0/3			0/3	
	300		1/1			1/1	
4d	30		0/1			0/1	
	100	0/3	0/3	1/3	1/3	0/3	0/1
	300		1/1			1/1	
4e	30		0/1			0/1	
	100		0/3			0/3	
	300		1/1			0/1	
3d	30		0/1			0/1	
	100		0/3			0/3	
	300		0/1			0/1	
3e	30		0/1			0/1	
	100	0/3	0/3	0/3		0/3	
	300		1/1			0/1	
3c	30		0/1			0/1	
	100		0/3			0/3	
	300		0/1			0/1	

[a] Data represent number of animals protected/number of animals tested.

Table 2
Protective effects of substituted phenols in the scMET model[a]

Compound	Dose, mg/kg, ip	Time (h)		Compound	Dose mg/kg, ip	Time (h)	
		0.5	4			0.5	4
4a	30	0/1	0/1	**4e**	30	0/1	0/1
	100	0/1	0/1		100	0/1	0/1
	300	0/1	0/1		300	1/1	0/1
4b	30	0/1	0/1	**3d**	30	0/1	0/1
	100	0/1	0/1		100	0/1	0/1
	300	0/1	0/1		300	0/1	0/1
4c	30	0/1	0/1	**3e**	30	0/1	0/1
	100	0/1	0/1		100	0/1	0/1
	300	1/1	0/1		300	0/1	0/1
4d	30	0/1	0/1	**3c**	30	0/1	0/1
	100	0/1	0/1		100	0/1	0/1
	300	1/1	1/1		300	0/1	0/1

[a] Data represent number of animals protected/number of animals tested.

Table 3
Toxicity and protective effects of RM170, RM166, RM1204 and RM1208 in the 6 Hz (32 mA) model[a]

Compound	Dose, ip	Time (h) Toxicity					
		0.25	0.5	1	2	4	6
4a	30		0/4			0/2	
	100	0/3	0/8	0/3	0/3	0/4	0/3
	300		0/4			0/2	
4b	30		0/4			0/2	
	100		0/8			0/4	
	300		0/4			0/2	
4c	30		0/4			0/2	
	100	0/2	0/8	0/3	0/3	0/4	0/3
	300		3/4			0/2	
3c	100	1/4	0/4	1/4	0/4	0/4	
		Protective effects					
4a	100	0/4	0/4	2/4	1/4	1/4	
4b	100	0/4	0/4	0/4	0/4	1/4	
3c	100	4/4	4/4	2/4	0/4	0/4	

[a] Data represent the number of animals protected/number of animals tested.

Table 4
Protective effects of substituted phenols in the 6 Hz (32 mA) model

Compound	Time to peak effect (h)	ED_{50}, mg/kg (95% CI)	TD_{50}, mg/kg (95% CI)	PI
4d	0.25	84.12 (52.93–147.82)	161.12 (128.83–191.36)	1.9
4e	0.5	53.85 (30.02–66.14)	86.04 (72.37–97.2)[a]	1.6
3d	0.5	112.45 (72.99–177.16)	403.12 (286.08–531.42)	3.6
3e	0.5	87.6 (50.35–166.64)	144.4 (109.47–192.79)	1.7

[a] Anesthesia occurred in 4 of 4 animals at 300 mg/kg dose.

This study demonstrates that a number of alkyl-substituted phenols can act as anticonvulsants in acute whole animal seizure models. Of the three initial screening models used by ASP, these small molecular weight phenols were predominately active against seizures in the 6 Hz model (a model of partial or psychomotor epilepsy), but not in the MES and scMET models.[7] This profile suggests that such compounds may have novel mechanisms of action. In brief, compounds effective in the MES model, such as phenytoin, are thought to be sodium channel blockers and block seizure spread. Those effective in the scMET model are often $GABA_A$ agonists and are thought to raise seizure threshold. The 6 Hz model is an animal model of therapy-resistant epilepsy. To date, compound effectiveness in this model is not reflective of any specific anticonvulsant mechanism of action.[9] For example, one compound protective in the 6 Hz model is levetiracetam. This compound is believed to act by stabilizing SV2A vesicles.[20] Another 6 Hz active compound is ganaxolone. It is thought to act as an allosteric $GABA_A$ agonist.[21] It is recognized, however, that most anticonvulsant act by multiple mechanisms.[22]

It has previously been shown that 4-HTFE phenols having 2,6-di-isopropyl or *sec*-butyl groups (MB003, MB050) possess good anticonvulsant activity in the 6 Hz model.[7] This investigation of 4-HTFE phenols that are further modified about the *ortho* positions reveals some of the molecular features that are important to anti-seizure activity. Firstly, replacement of an alkyl group (6-position) of MB003 and MB050 with bromine (**3d** and **3e**, respectively), creates compounds that also have antiseizure activity. The comparative effect of bromine is to cause a moderate lessening of seizure protection (84.12 [mg/kg] vs 112.45; 53.85 vs 87.6), but not elimination of seizure protection. Taken alone it could be reasoned that this halogen is serving in part as an isostere of the isopropyl group where it maintains important molecular target interactions. However, the relatively good antiseizure activity of the analogous compounds having no 6-substituent (**4d** and **4e**) indicates that bromine is not serving a vital function in these compounds. Indeed the data indicate that a second *ortho* substituent is not required for anticonvulsant activity in the 2-isopropyl and 2-*sec*-butyl compounds, and 6-substituents may be redundant.

The effect of varying the single *ortho* alkyl group on 4-HTFE phenols having no 6-substituent shows that the nature of the alkyl group is important to activity. Compounds having the 2-methyl, 2-ethyl or 2-*n*-propyl group were poorly protective in contrast to those possessing isopropyl and *sec*-butyl groups. The inactivity of the 2-methyl compound is similar to the lack of activity of DMPF, the 2,6-dimethyl analog.[7] It is noteworthy that the apparent requirement for isopropyl and sec-butyl groups for optimal activity in these compounds is similar to the groups needed for good anesthetic activity among the alkyl phenols.[2] A difference is that potent anesthetics require placement of the isopropyl or sec-butyl groups in both the 2- and 6- positions with the 4- position being free.[1] Whereas, in the anticonvulsant 4-HTFE phenols, only a single *ortho* substituent is required. It appears that alkyl groups having

increased spatial properties via branching, provide both optimal anesthetic (2,6-dialkyl phenols)[1] and antiseizure (2-alkyl-4-HTFE phenols) activity. The anticonvulsant effects of compounds having branched or linear groups greater than 4 carbons have not been determined.

An exception to the need for a branched alkyl group is compound **3c**. It contains the 2-*n*-propyl group which as the lone ortho substituent (**4c**) was not an active compound. However, the addition of bromine as the second ortho substituent (**3c**) created a compound exerting complete protection at two time periods after dosing of 100 mg/kg, 0.25 and 0.5 h. The ED_{50} of this compound was not determined. The reason for this improved activity is not known. This bromine being in an equivalent *ortho* position to the *n*-propyl, may act in this molecule as an isostere of isopropyl by providing important target interactions not provided by *n*-propyl. As a whole, the data suggest that the 6-substitution may be viewed not as redundant, but as modulatory. This is reflected by the differing effects of alkyl group removal. MB003 has an ED_{50} of 38.6 mg/kg,[7] whereas **4d** (removal of an isopropyl) is less effective with an ED_{50} of 84. MB050 has an ED_{50} of 73 mg/kg, but **4e** (removal of a *sec*-butyl group) is more effective with an ED_{50} of 53.85.

Compound effectiveness determined by the ED_{50}s in this study should be interpreted with some caution. Compounds were administered ip. Although all were given in 30% polyethylene glycol, there could be differences in absorption into the systemic circulation. Plasma or CNS levels of compound causing anticonvulsant activity were not determined. It is not likely that the alterations of the alkyl groups alone, for example isopropyl versus *n*-propyl, had major effects on plasma or CNS concentrations of these compounds.

The protective indices of the present compounds ranged from 1.6 to 3.6. Prior studies of propofol and 2,6-di-*sec*-butylphenol showed that these two compounds had protective indices of only 1.1 and 1.3, respectively. Therefore, similar to the effect of 4-HTFE substitution on 2,6-dialkyphenols, protective indices were also broad with the 4-HTFE phenols reported here. It is not apparent why 6-bromination of 2-isopropy-4-HTFE phenol (**4d**) but not 2-*sec*-butyl-4-HTFE phenol (**4e**) caused a multi-fold widening of the PI.

The specific role of 4-HTFE in anticonvulsant activity remains to be determined. It is hypothesized that 4-HTFE substitution diminishes the binding of alkyl phenols to sites that cause anesthesia and sedation while not substantially disrupting binding to targets that prevent seizures in the 6 Hz mouse model. Ample evidence indicates that the anesthetic/sedative effects of 2,6-dialkyphenols result from stimulation of the inhibitory $GABA_A$ receptors.[23] Consequently, the anticonvulsant effects of 4-HTFE phenols may not be primarily mediated by $GABA_A$ receptors.

In summary, 4-HTFE phenols having isopropyl or *sec*-butyl *ortho* groups produce good antiseizure protection in the 6 Hz therapy-resistant mouse model. Such compounds may be useful for the treatment of seizures.

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19. *Spectral data for selected compounds: 2-Bromo-6-isopropyl-4-(2,2,2-trifluoro-1-hydroxy-ethyl)-phenol (**3d**)*: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.47 (d, J = 2 Hz, 1H), 7.24 (d, J = 2 Hz, 1H), 5.73 (s, 1H), 4.98–4.92 (m, 1H), 3.33 (sep, J = 7.2 Hz, 1H), 2.6 (d, J = 4.4 Hz, 1H), and 1.26 (dd, J = 7.2 Hz, 0.8 Hz, 6H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 151.67, 137.99, 129.66, 129.40, 125.69 (q, J^2_{CF} = 282 Hz), 125.49, 111.75, 70.32 (q, J^2_{CF} = 30 Hz), 27.75, 23.28, and 23.23. ^{19}F NMR-^{1}H Decoupled (DMSO-d_6, 282 MHz) δ −77.36. *2-Bromo-6-sec-Butyl-4-(2,2,2-trifluoro-1-hydroxy-ethyl)-phenol (**3e**)*: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.45 (t, J = 2.4 Hz, 1H), 7.17 (t, J = 2.4 Hz, 1H), 5.67 (s, 1H), 4.96–4.90 (m, 1H), 3.14–3.05 (m, 1H), 2.56 (d, J = 4.4 Hz, 1H) 1.71–1.54 (m, 1H), 1.21 (dd, J = 7.2 Hz, 1.2 Hz, 3H), and 0.85 (dt, J = 7.6 Hz, 1.2 Hz, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 152.01, 136.70, 129.55, 129.33, 126.16, 125.65 (q, J^1_{CF} = 280 Hz), 111.77, 71.23 (q, J^2_{CF} = 280 Hz), 34.42, 29.86, 21.18 and 12.49. ^{19}F NMR-^{1}H Decoupled ((DMSO-d_6, 282 MHz) δ −77.45. *2-Bromo-6-n-propyl-4-(2,2,2-trifluoro-1-hydroxy-ethyl)-phenol (**3c**)*: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.46 (s, 1H), 7.17 (s, 1H), 5.67 (s, 1H), 4.96–4.90 (m, 1H), 2.66 (t, J = 7.2 Hz, 2H), 2.55 (d, J = 4.0 Hz, 1H), 1.7–1.61 (m, 2H), and 0.97 (t, J = 7.2 Hz, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 152.40, 131.71, 130.04, 129.30, 128.98, 128.60 (q, J^1_{CF} = 280 Hz) 111.42, 70.15 (q, J^2_{CF} = 30 Hz), 33.10, 23.2, and 14.4. ^{19}F NMR-^{1}H Decoupled ((DMSO-d_6, 282 MHz) δ −77.36. *2-Methyl-4-(2,2,2-trifluoro-1-hydroxy-ethyl)-phenol (**4a**)*: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.25 (s, 1H), 7.20 (d, J = 8.0 Hz, 1H), 6.80 (d, J = 8.0 Hz, 1H), 4.97–4.91 (m, 1H), 4.95 (s, 1H), 2.54 (d, J = 4.4 Hz, 1H), and (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 156.53, 130.54, 126.82, 126.59, 125.90 (q, J^1_{CF} = 280 Hz), 124.21, 114.81, 71.5 (q, J^2_{CF} = 30 Hz), and 16.69. ^{19}F NMR-^{1}H Decoupled ($CDCl_3$, 282 MHz) δ −77.20. *2-Ethyl-4-(2,2,2-trifluoro-1-hydroxy-ethyl)-phenol (**4b**)*: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.24 (d, J = 2.0 Hz, 1H), 7.18 (dd, J = 6.4 Hz, 2.0 Hz, 1H), 6.78 (d, J = 7.2 Hz, 1H), 4.96–4.91 (m, 1H), 4.92 (s, 1H), 2.65 (q, J = 7.2 Hz, 2H), 2.52 (d, J = 4.4 Hz, 1H), and 1.24 (t, J = 7.6 Hz, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 156.12, 130.22, 129.00, 126.77,125.94 (q, J^1_{CF} = 284 Hz), 115.05, 71.11 (q, J^2_{CF} = 30 Hz), 23.47 and 14.82. ^{19}F NMR-^{1}H Decoupled ($CDCl_3$, 282 MHz) δ −77.21. *2-n-Propyl-4-(2,2,2-trifluoro-1-hydroxy-ethyl)-phenol (**4c**)*: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.21 (d, J = 3.0 Hz, 1H), 7.17 (dd, J = 6.4 Hz, 3.0 Hz, 1H), 6.77 (d, J = 9 Hz), 4.96–4.87 (m, 1H), 4.80 (s, 1H), 2.57 (t, J = 9 Hz, 2H), 2.42 (d, J = 6.0 Hz, 1H), 1.69–1.57 (m, 1H), and 0.95 (t, J = 9.0 Hz, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 156.23, 129.90, 128.56, 126.79, 126.55, 125.96 (q, J^1_{CF} = 282 Hz), 151.10, 71.06 (q, J^2_{CF} = 30 Hz), 32.42, 23.15, and 14.55. ^{19}F NMR-^{1}H Decoupled ((DMSO-d_6, 282 MHz) δ −77.32. *2-sec-Butyl-4-(2,2,2-trifluoro-1-hydroxy-ethyl)-phenol (**4e**)*: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.25 (t, J = 2.8 Hz, 1H), 7.19 (td, J = 6.4 Hz, 2.8 Hz, 1H), 6.79 (d, J = 8.4 Hz, 1H), 4.99–4.92 (m, 1H), 4.90 (s, 1H), 3.02–2.94 (m, 1H), 2.50 (d, J = 4.4 Hz, 1H), 1.72–1.24 (m, 1H), 1.25 (dd, J = 6.8 Hz, 2.0 Hz, 3H), and 0.88 (dt, J = 7.2 Hz, 1.2 Hz, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 155.82, 133.23, 126.83, 126.75, 126.33, 125.92 (q, J^1_{CF} = 284 Hz), 115.21, 71.5 (q, J^2_{CF} = 30 Hz), 33.78, 29.71, 20.99, and 12.67. ^{19}F NMR-^{1}H Decoupled ((DMSO-d_6, 282 MHz) δ −77.38. *2-iso-Propyl-4-(2,2,2-trifluoro-1-hydroxy-ethyl)-phenol (**4d**)*: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.28 (s, 1H), 7.18 (d, J = 8.0 Hz, 1H), 6.77 (d, J = 8.0 Hz, 1H), 4.97–4.92 (m, 1H), 3.26–3.15 (m, 1H), and 1.26 (dd, J = 7.2 Hz, 0.8 Hz, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 155.52, 134.49, 126.81, 126.47, 126.10, 125.94 (q, J^1_{CF} = 282 Hz), 115.16, 71.24 (q, J^2_{CF} = 30 Hz), 27.02, 23.14, and 23.11. ^{19}F NMR-^{1}H Decoupled ((DMSO-d_6, 282 MHz) δ −77.36.
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