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Design, synthesis and evaluation of novel hydroxyamides as orally available anticonvulsants

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Abstract—Themisone, also known as Atrolactamide, was found, in the 1950s, to be a very potent anticonvulsant. It was hypothesized that the -CF_3 substitution would maintain the anticonvulsant activity. Anticonvulsant testing of our novel compounds by the National Institute of Health's Anticonvulsant Screening Project of the Antiepileptic Drug Discovery Program identified analogue **1**, 3,3,3-trifluoro-2-hydroxy-2-phenyl-propionamide, to have potent anticonvulsant activity (MES ED_{50} of 9.9 mg/kg, ScMET ED_{50} of 34 mg/kg and TD_{50} of 100 mg/kg). Therefore, a diverse range of analogues were synthesized utilizing multiple synthetic pathways to explore the structure–activity relationship. Patch clamp electrophysiology experiments demonstrate that compound **1** is an effective T-type calcium channel blocker. Altogether, these results suggest these compounds as a class of orally available anticonvulsants.

1. Introduction

Epilepsy is a neurological disorder of brain function seen by the periodic and unpredictable occurrence of seizures. There have already been 40 types of epilepsy characterized in patients. Numerous types of epileptic seizures occur, with frequency and type differing in each patient, often making it difficult for one drug to help all patients. Approximately 30% of the medicated epileptic patients do not have complete control of their seizures and may require medication for the duration of their life. There are also numerous side effects associated with even the most common anticonvulsant drugs available.[1] Specifically, there is a need for new medications that are devoid of side effects.

The drug treatment of epilepsy is accomplished with the use of anticonvulsants. Common mechanisms, which can be exploited in the treatment of epilepsy, include neuronal voltage-dependent sodium channels (NVSC),[2] γ-aminobutyric acid (GABA),[3] voltage-dependent calcium channels (VDCC), especially the T-type current,[1] and *N*-methyl-D-aspartate (NMDA) receptors. Recent evidence has also lead to the application of ligands competing with glutamate binding on alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) and kianic acid (KA) to minimize symptoms of epilepsy.[4]

Calcium channels are the primary route for translating electrical signals into the biochemical events underlying key processes such as neurotransmitter release, cell excitability, and gene expression. In addition to the neuronal voltage gated sodium channel, T-type or low voltage activated (LVA) calcium channels such as $Ca_v3.2$ are thought to contribute to neuronal excitability and are important targets for the treatment of epilepsy.[5] These channels are thought to contribute to the oscillatory firing of neurons in the thalamus and dysrhythmias in this region can lead to epilepsy.[6] Furthermore, calcium channels enhance postsynaptic responses in somatodendrites and re-excitation following periods of bursting which is believed to be related to epilepsy.[7,8] There has also been evidence of activation of VDCC's triggering changes in gene expression.[9] Thus,

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Keywords: Amides; Alcohols; Ion channel; Calcium channel.

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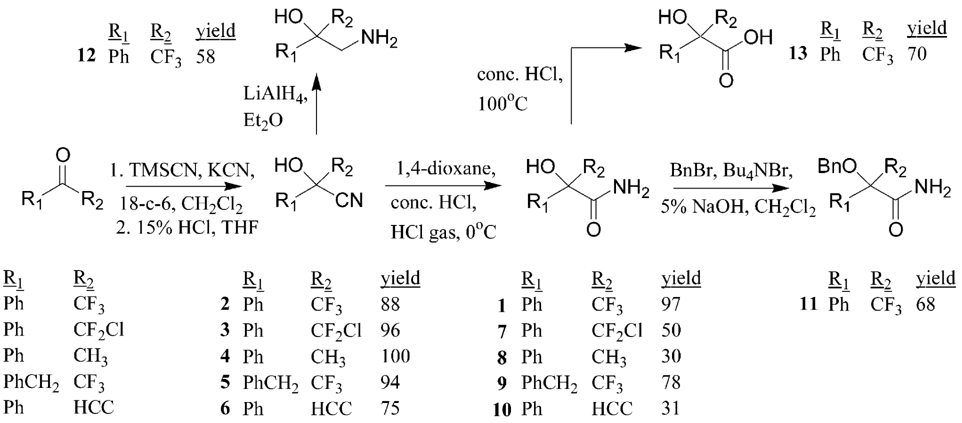


Scheme 1.

we sought to examine the ability of these novel anticonvulsants to block T-type calcium channels.

The development of our lead compound **1** was based upon the toxicity found in Themisone. Fluorination of this compound was originally designed by us in an effort to avoid the potential formation of the toxin phenylacylamide.[10,11] Utilizing traditional medicinal chemistry transformations, we designed a series of compounds to explore the SAR of stepwise changes in electronic and conformational properties of **1** on anticonvulsant activity.

2. Results

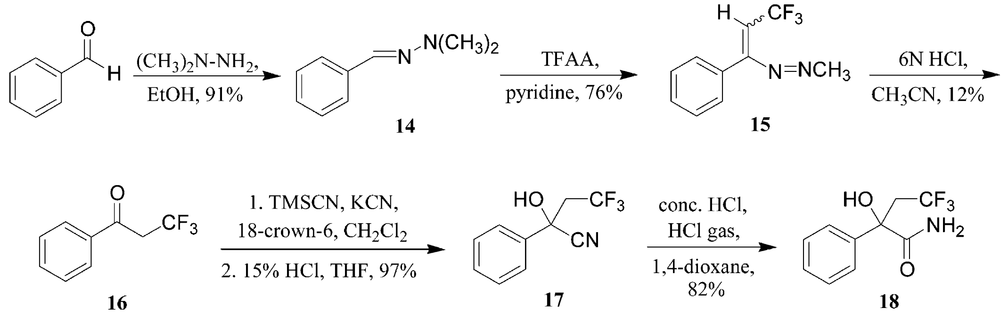
All compounds were synthesized and 300 mg of each were sent to the National Institute of Health's Anticonvulsant Screening Project of the Antiepileptic Drug Discovery Program (NINDS ADD program). NIH performs anticonvulsant testing (oral and intraperitoneal, ip) on both mice and rats in phase I trials. The grand mal model was conducted with a maximal electroshock (MES) test, where corneal electrode implants are primed with a drop of electrolyte solution and an electrical stimulus was delivered for 0.2 s to elicit a psychomotor seizure. Typically, a seizure was noted when a minimal clonic phase was observed, followed by stereotyped, automatistic behavior. The model examines the compounds' ability to stop the spread of seizures. The petite mal model was conducted with a subcutaneous pentylenetetrazol seizure threshold (scMet) test. The animals were injected with a convulsant dose of pentylenetetrazol at the peak effect time of the compound. This model measured the compounds' threshold for seizures. Results were expressed as the number of animals protected out of the number of animals tested at different time intervals. A neuronal toxicity test (TOX) was performed where the animals walk on a spinning rod (6 rpm) for varying lengths of time to check for the loss of righting reflex or other toxic effects. Normal mice can remain on a rod rotating at this speed indefinitely. Neurotoxicity was noted when the animal failed to remain on the rod for one min. Phase I of each compound occurs at 30, 100 and 300 mg/kg of the test compounds when challenged by each model at 15 to 30 min intervals up to 4 h. Compounds which demonstrated profound activity were evaluated in Phase II for ED_{50} and TD_{50} quantification in mice, which required an additional 1000 mg of the compound.[12]

Anticonvulsant evaluation of compound **1** administered intraperitoneally in mice demonstrated complete (3/3

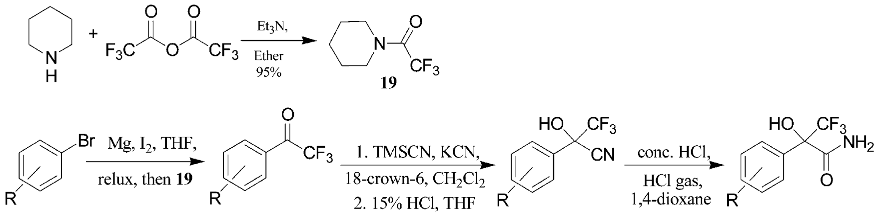
Table 1. Phase I rat anticonvulsant activity (po.)

	MES 30 mg/kg drug					Rotorod 30 mg/kg drug				
Compd	0.25 h	0.50 h	1.0 h	2 h	4 h	0.25 h	0.50 h	1 h	2 h	4.0 h
1	4/4	4/4	4/4	4/4	4/4	0/4	0/4	0/4	0/4	0/4
8	3/4	0/4	3/4	1/4	0/4	0/4	0/4	0/4	0/4	0/4
10	0/4	1/4	0/4	2/4	2/4	0/4	0/4	0/4	0/4	0/4
12	1/4	2/4	3/4	1/4	1/4	0/4	0/4	0/4	0/4	0/4
40	0/4	1/4	1/4	1/4	1/4	0/4	0/4	0/4	0/4	0/4
44	0/4	0/4	0/4	1/4	0/4	0/4	0/4	0/4	0/4	0/4
45	1/4	1/4	1/4	1/4	1/4	0/4	0/4	0/4	0/4	0/4
46	0/3	2/3	2/3	2/3	3/3	0/3	0/3	0/3	0/3	0/3
47	1/4	2/4	1/4	4/4	3/4	0/4	0/4	0/4	0/4	0/4
48	4/4	3/4	3/4	3/4	4/4	0/4	0/4	0/4	0/4	0/4
53	1/4	1/4	0/4	0/4	2/4	0/4	0/4	0/4	0/4	0/4
54	2/4	2/4	3/4	2/4	4/4	0/4	0/4	2/4[a]	0/4	0/4
55	2/4	1/4	2/4	2/4	2/4	0/4	0/4	0/4	0/4	0/4

[a] Wild running.



Scheme 2.



	R	yield		R	yield		R	yield
20	m-Cl	58	**27**	m-Cl	100	**38**	m-Cl	97
21	o-OCH_3	58	**28**	o-OCH_3	95	**39**	o-OCH_3	78
22	m-OCH_3	66	**29**	m-OCH_3	87	**40**	m-OCH_3	75
23	p-OCH_3	81	**30**	p-OCH_3	96	**41**	p-OCH_3	99
24	m-CH_3	63	**31**	m-CH_3	96	**42**	m-CH_3	94
25	p-CH_3	71	**32**	p-CH_3	100	**43**	p-CH_3	97
26	m,p-di-Cl	72	**33**	m,p-di-Cl	95	**44**	m,p-di-Cl	89
*	p-Cl		**34**	p-Cl	100	**45**	p-Cl	93
*	m-F		**35**	m-F	100	**46**	m-F	98
*	p-F		**36**	p-F	94	**47**	p-F	93
*	m-CF_3		**37**	m-CF_3	100	**48**	m-CF_3	76

* commerically available ketones

Scheme 3.

mice) protection at a dose of 100 mg/kg up to 4 h when challenged with MES (Table 2). Compound **1** also demonstrated effectiveness against scMet (5/5 mice protected) for 0.5 h at the same dose. At a 100 mg/kg dose, 50% of the mice were unable to grasp the rotating rod and exhibited the loss of the righting reflex upon falling off the rod. Phase II trials evaluated the compound for the ED_{50}'s in both models and the TD_{50} with the compound administrated orally (po). The MES ED_{50} was found to be 9.9 mg/kg, the ScMET ED_{50} was 34 mg/kg and the TD_{50} noted at 100 mg/kg, yielding a therapeutic index of 10 for the MES model and 2.6 for the ScMET model (Table 4). Analogue **53**'s MES ED_{50} was also determined to be 62.4 mg/kg but has notably longer lasting effects (up to 6 h, see Table 3) and a TD_{50} over 100 mg/kg. Analogue **1** was notably able to provide protection of up to 4 h at 100 mg/kg. Comparisons with phenytoin demonstrated significantly improved broad spectrum coverage in the model with little change in MES protection.[13] Serendipitously, anesthesia was noted as a toxicity at the 300 mg/kg dose at 4 h in 2 out of 2 animals. Compound **1** was then tested independently for general anesthesic activity and was found to lower the minimum alveolar concentration of isoflurane by 33% at 60 mg/kg.[13]

With the emergent anticonvulsant activity of compound **1** other analogues were designed, synthesized and evaluated for their anticonvulsant activity. The general synthetic methods are shown in Schemes 1–7. Final products **1**, **7–10**, **18**, **38–48**, **50**, and **58** were synthesized by converting the corresponding ketones to the trimethylsilyl ether with trimethylsilyl cyanide (TMSCN). Subsequent hydrolysis with 15% HCl generated the cyanohydrin. Conversion of the corresponding cyanohydrin to the hydroxyamide was accomplished under acidic conditions, by saturating with HCl gas and allowing the mixtures to stand at room temperature for 16 h.[14] The trifluoromethyl ketones **20–26** were obtained from formation of the corresponding Grignard reagent from their aromatic bromide and adding 2,2,2-Trifluro-1-piperidin-1-yl-ethanone **19** to introduce the fluorine (Scheme 3).[15] Analogue **1** was heated at 100 °C for 24 h in concentrated HCl to obtain **13**, the acid of the lead compound (Scheme 1). Analogue **12** was synthesized from the reduction of compound **2** with $LiAlH_4$.[16] Compound **18** was synthesized by reacting dimethylhydrazine with benzaldehyde to give the *N*′-Benzylidene-*N*,*N*-dimethyl-hydrazone **14**. Addition of the anhydride generated the methyl-(3,3,3-trifluoro-1-phenyl-propenyl)-diazene **15**. Intermediate **15** was converted to the 3,3,3-Trifluoro-1-phenyl-propan-1-one **16** under acidic conditions (Scheme 2).[17] TMSCN was added to the ketone **16** to produce the cyanohydrin and finally to the hydroxyamide using the method discussed above. Compound **50** was synthesized using the

Table 2. Phase I mouse anticonvulsant activity (*ip*)

		MES 30 mg/kg drug		ScMET 30 mg/kg drug		Rotorod 30 mg/kg drug	
Compd	Dosage (mg/kg)	0.50 h	4 h	0.50 h	4 h	0.5 h	4 h
1	30	0/1	0/1	0/1	0/1	0/4	0/2
	100	3/3	3/3	5/5	0/1	4/8	2/4^{a}
	300	1/1	1/1	1/1	1/1	4/4^{b}	2/2^{c}
7	30	0/1	0/1	0/1	2/5	0/4	0/2
	100	1/1	0/0	n/a	n/a	8/8	n/a
	300	n/a	n/a	n/a	n/a	4/4^{d}	n/a
8	30	0/1	0/1	0/1	0/1	0/4	0/2
	100	0/3	0/3	0/1	0/1	2/8	0/4
	300	1/1	0/1	1/1	0/1	4/4^{a}	0/2
9	30	0/1	0/1	0/1	0/1	0/4	0/2
	100	0/3	0/3	0/1	0/1	5/8	0/4
	300	0/1	0/0	1/1	0/0	4/4	1/1^{d}
10	30	0/1	0/1	0/1	0/1	0/4	0/2
	100	1/3	0/3	0/1	0/1	0/8	0/4
	300	1/1	0/1	1/1	0/1	2/4	0/2
11	30	0/1	0/1	0/1	0/1	0/4	0/2
	100	1/3	0/3	4/5	0/1	4/8	0/4
	300	1/1	0/0	1/1	1/1	4/4^{b}	2/2^{d}
12	30	0/1	0/1	0/1	0/1	0/4	0/2
	100	3/3	0/3	0/1	0/1	1/8	0/4
	300	1/1	1/1	1/1	0/1	4/4^{a}	0/2
13	30	0/1	0/1	0/1	0/1	0/4	0/2
	100	0/3	0/3	0/1	0/1	0/8	0/4
	300	0/1	0/1	0/1	0/1	0/4	1/2
18	30	0/1	0/1	0/1	0/1	0/4	0/2
	100	1/3	1/3	0/1	0/1	2/8	0/4
	300	1/1	1/1	1/1	1/1	4/4^{a}	2/2
38	30	0/1	0/1	0/1	0/1	1/4	0/2
	100	3/3	3/3	1/1	3/5	6/8^{a}	2/4
	300	n/a	n/a	n/a	n/a	4/4^{d}	n/a
39	30	0/1	0/1	0/1	0/1	0/4	0/2
	100	0/3	0/3	0/1	0/1	0/8	0/4
	300	1/1	0/1	0/1	0/1	4/4	0/2
40	30	0/1	0/1	0/1	0/1	0/4	0/2
	100	1/3	0/3	0/1	0/1	0/8	0/4
	300	1/1	0/1	1/1	0/1	4/4^{b}	0/2
41	30	0/1	0/1	0/1	0/1	0/4	0/2
	100	0/3	0/3	0/1	0/1	0/8	0/4
	300	n/a	n/a	n/a	n/a	4/4^{d}	n/a
42	30	0/1	0/1	0/1	0/1	0/4	0/2
	100	0/3	0/3	0/1	0/1	0/8	0/4
	300	n/a	n/a	0/1	n/a	4/4	n/a
43	30	0/1	0/1	0/1	0/1	0/4	0/2
	100	1/3	0/3	0/1	0/1	1/8	0/4
	300	n/a	n/a	n/a	n/a	4/4^{d}	n/a
44	30	0/1	0/1	0/1	0/1	0/4	0/2
	100	0/3	2/3	0/1	1/1	4/8	1/4
	300	1/1	1/1	1/1	1/1	4/4^{a}	2/2^{a}
45	30	0/1	0/1	0/1	0/1	0/4	0/2
	100	0/3	1/3	4/4^{e}	1/1	6/8	3/4
	300	n/a	n/a	0/0	1/1	4/4^{d}	1/1^{a}
46	30	0/1	0/1	2/5	0/1	0/4	0/2
	100	3/3	3/3	1/1	1/1	6/8	0/4
	300	0/0	1/1	n/a	n/a	4/4	1/1^{a}
47	30	0/1	0/2	0/1	0/1	0/4	0/2
	100	0/3	0/3	5/5	1/1	7/8^{a}	3/4^{a}
	300	1/1	n/a	n/a	n/a	4/4	n/a
48	30	0/1	0/1	0/1	0/1	0/4	0/2
	100	3/3	2/3	0/1	0/1	4/8^{a}	1/4
	300	1/1	1/1	1/1	1/1	4/4^{a}	2/2^{b}
50	30	0/1	0/1	0/1	0/1	0/4	0/2
	100	2/3	1/3	1/1	0/1	6/8	0/4
	300	n/a	n/a	n/a	n/a	4/4	n/a
53	30	0/1	0/1	0/1	0/1	0/4	0/2
	100	2/3	3/3	0/1	0/1	0/8	0/4
	300	1/1	1/1	1/1	1/1	4/4^{a}	2/2^{a}
54	30	0/1	0/1	2/5	0/1	0/4	0/2

(*continued on next page*)

Table 2 (*continued*)

Compd	Dosage (mg/kg)	MES 30 mg/kg drug 0.50 h	MES 30 mg/kg drug 4 h	ScMET 30 mg/kg drug 0.50 h	ScMET 30 mg/kg drug 4 h	Rotorod 30 mg/kg drug 0.5 h	Rotorod 30 mg/kg drug 4 h
	100	3/3	2/3	1/1	0/1	8/8[a]	0/4
	300	1/1	1/1	1/1	1/1	4/4[b]	2/2[b]
55	30	0/1	0/1	1/5	0/1	0/4	0/2
	100	3/3	0/3	0/1	0/1	1/8	0/4
	300	1/1	1/1	1/1	1/1	4/4[a]	1/2
58	30	0/1	0/1	0/1	0/1	0/4	0/2
	100	0/3	0/3	0/1	0/1	0/8	0/4
	300	0/1	0/1	0/1	0/1	0/4	0/2

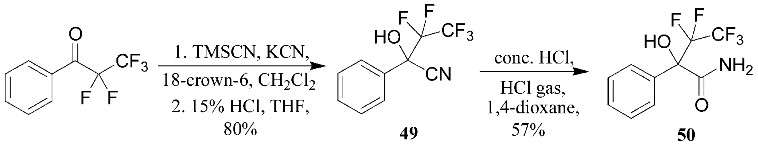
[a] Unable to grasp rotorod.

[b] Loss of righting reflex.

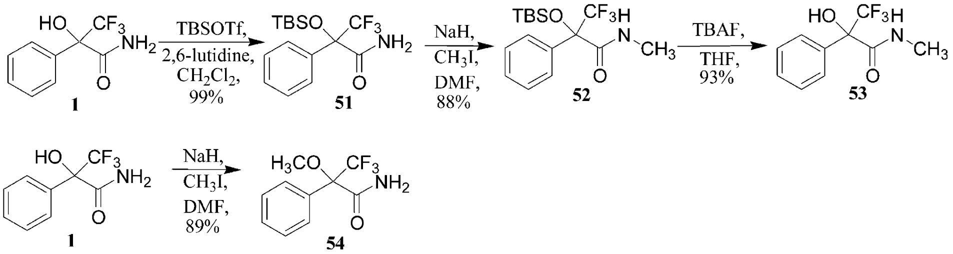
[c] Anesthesia.

[d] Death.

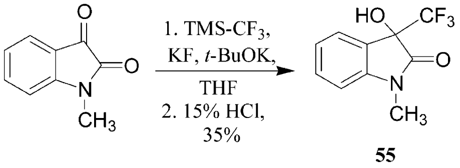
[e] 1/5 died during test without having a seizure.



Scheme 4.



Scheme 5.



Scheme 6.

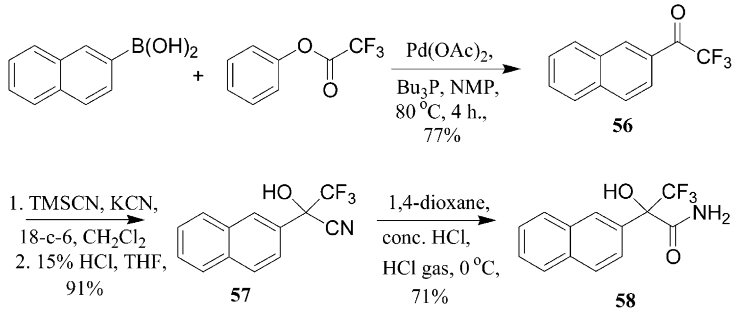
standard conditions for formation of an α-hydroxyamide from the commercially available ketone (Scheme 4).

Compound **1**'s tertiary alcohol was silylated to allow for methylation of the amide with NaH and methyl iodide. Removal of the silyl protecting group with TBAF resulted in analogue **53** (Scheme 5). Compound **54** was obtained from the direct methylation of **1** with NaH and methyl iodide.[18] The synthesis of analogue **55** was accomplished by treating methyl-isatin with trimethyl (trifluoromethyl)silane ($TMSCF_3$) to generate the TMS ether (Scheme 6) and the TMS ethers were hydrolyzed with acid to obtain the final products.[19] Ketone **56** resulted from the palladium-catalyzed cross coupling of phenyl trifluoroacetate and 2-Naphthaleneboronic acid,[20] followed by formation of the cyanohydrin and finally the hydroxyamide (Scheme 7).

Our previous demonstration that phenylhydroxyamides bind to the hydantoin-anesthetic binding site in the NVSC,[21] led us to evaluate this mechanism for these similar compounds. We evaluated the effects of 10 and 100 μM of analogue **1** on rNa_V 1.3 expressed in *xenopus* oocytes. The results of this study suggested that analogue **1** did not block voltage gated Na^+ channels. The specific binding of labeled batrachotoxinin-A 20-α-benzoate ($[^3H]$BTX-B)[22] to voltage-sensitive sodium channels was also tested and it was found that compound **1** inhibited BTX at 6.78% at 40 μM.

Other mechanisms of action thus far include several subtypes of K^+ channels. Compound **1** did not activate or inhibit rat TASK-1 and TASK-3 leak K^+ channels expressed in HEK293 cells at 100 μM.

Several anticonvulsant agents enhance $GABA_A$ receptor currents. It was therefore important to evaluate effects of compound **1** on $GABA_A$ receptors in rat hippocampal neurons. Hippocampal neurons in culture for 10–14 days were studied with whole-cell patch clamp recording technique. Application of 1 mM of compound **1** was found to accentuate the GABA current elicited by GABA at 10 μM.[23]



Scheme 7.

Table 3. Phase I administration of compound **53** in rats at 100 mg/kg (po)

	4.0 h	6.0 h
MES	4/4	4/4
TOX	0/4	0/4

Table 4. Phase II administration of drugs in rats (*p.o.*)

Compd	MES ED_{50}	ScMET ED_{50}	Rotorod TD_{50}	T.I.[b]
1	9.92 mg/kg (6.9–13.4)[a]	38.57 mg/kg (24.6–51.9)	100 mg/kg	MES 10.0 ScMET 2.6
53	62.39 mg/kg (44.56–80.62)[a]	N/A	> 100 mg/kg	MES > 1.6

[a] ( )95% confidence level.

[b] T.I. = therapeutic index.

In order to examine the effects of compounds **1**, **53** and **54** on T-type calcium channels, a use dependent protocol was utilized as described in the biology section. In the absence of compound, there was a 33.8 ± 3.4% decrease in current as a result of the protocol. This decrease in current amplitude stabilized within 10 s under control conditions. Upon application of compound **1** or compound **53**, a further decrease in current was observed. In the presence of 200 μM and 1 mM of compound **1**, an additional 20.0 ± 9.0% and 34.3 ± 7.4% decrease in current was observed by the last pulse in the protocol respectively in comparison to control (Fig. 1). This use dependent block could be partially removed upon washout, with 84.1 ± 4.0% of the blocked current returning. In the presence of 200 μM and 1 mM of compound **53**, an additional 5.1 ± 6.5% and 11.1 ± 1.1% decrease in current was observed by the last pulse in the protocol respectively in comparison to control. However, compound **1** induced significantly more block at both 200 μM and 1 mM in comparison to compound **53** ($P = 0.002$ and $P = 0.01$, respectively). Upon application of 1mM of compound **54**, no further decrease in current amplitude was observed in comparison to control (Fig. 1). To examine tonic block, the first pulse recorded during the use dependent protocol was compared in the absence and in the presence of compound. At 1 mM compounds **1**, **53** and **54** decreased current amplitudes by 44.2 ± 2.7%, 61.1 ± 8.2% and 43.5 ± 3.5% respectively and were not significantly different from each other.

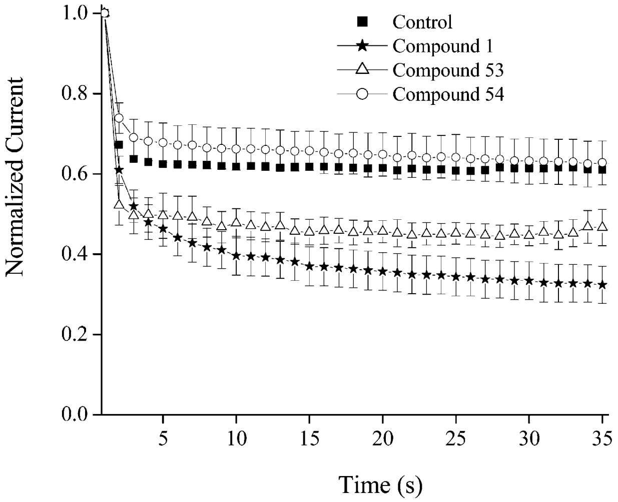


Figure 1. Use dependent blockade of $hCa_V3.2$ channels by compounds **1**, **53** and **54**. Cells were held at −110 mV and a step to −20 mV for 150 ms was applied, this was repeated at a 1 Hz stimulation frequency. Under control conditions, there is a distinctive use dependent decrease in calcium current that reached steady state within the first 10 seconds. In the presence 1 mM of compounds **1** or **53** the inactivation fails to stabilize, and current continues to decrease with subsequent stimulations due to channel blockade. This blockade was partially reversible on washout (data not shown). Compound **54** did not induce a significant use dependent blockade.

3. Discussion

The compounds presented here provide a first generation structure–activity relationship (SAR) of compound **1** analogues. Below we provide a brief summary of the medicinal chemistry transformations. Analogue **7** represents other haloform saturation and analogue **11** introduces steric bulk into the hydroxy functionality. Analogues **9** and **18** represent methylene inserted analogues of compound **1** and begin to explore the steric tolerance of the amide, hydroxy group, aromatic and aliphatic binding regions. Analogue **10** does not contain an alpha hydrogen (instead contains an alkyne functionality), to determine if the trifluoromethyl group or absence of the alpha hydrogen increases activity. Analogue **12** and **13** represent homologous transformations introducing charge into the amide region. Analogues **38**–**48** explore the electron donating and withdrawing effects at the *ortho*, *meta*, and *para* positions of the phenyl ring. Analogue **50** fluorinates the methylene insertion of analogue **18**. Compounds **53** and **54** are methylated versions of compound **1** at the amide and alcohol, respectively. Analogue **55** is a closed ring analogue of the lead compound and allow us to evaluate ring conformation and activity. Finally, analogue **58** introduces an additional phenyl ring fused to compound **1** to explore the steric bulk of the phenyl region.

Tables 1 and 2 summarize Phase I rat and mouse anticonvulsant evaluation, respectively. Saturation of the trifluoromethyl group with a chlorine (compound **7**) decreased activity and the only protection was noted at 100 mg/kg for 0.5 h. The methylene inserted analogues **9** and **18** showed reduced activity, indicating that the triflurομethyl and phenyl regions do not tolerate a probe depth greater than a methylene group in this region. The alkyne substitution in compound **10** also reduced activity and toxicity, therefore acknowledging the trifluoromethyl group is responsible for activity, instead of the absence of an alpha hydrogen. Obviously steric bulk is not tolerated as seen by the protection of 1/3 animals at 100 mg/kg in the MES model for compound **11**. The primary amine (compound **12**) offered protection of all 3 animals at 100 mg/kg in the MES model but its duration of action was only 0.5 h. The acid **13** of the lead compound did not protect any animals in either model as well as in a 6 Hz mouse evaluation. Compounds in the 6 Hz test are evaluated for their ability to block seizures induced by a low frequency (6 Hz) long-duration (3 s) stimulus delivered through corneal electrodes.[12]

The *meta*-substituted chlorine **38** provided protection up to 4 h at 100 mg/kg but resulted in increased toxicity and even death of the mice at 300 mg/kg. The para-substituted chlorine **45** was inactive against both seizure models, as well as the *para*-methoxy **41**. The 3,4-dichloro analogue **44** only protected at a dose of 300 mg/kg, where toxicity was also prevalent. The *ortho*- and *meta*-substituted methoxy groups (compounds **39** and **40**, respectively) offered little protection and activity was only seen at 100 mg/kg in 1/3 animals in the MES model for compound **39**. The same pattern was noticed for the methyl substituted analogues. The *meta*-fluoro analogue **46** offered protection of all the animals at 100 mg/kg in both models and similar toxicity to compound **1** with the animals unable to grasp the rotorod. The *para*-fluoro analogue **47** is selective against the ScMET model protecting 5/5 animals at 100 mg/kg with a duration of up to 4 h. Although, there was no separation between activity and toxicity noted. The *meta*-substituted trifluoromethyl **48** was found to protect at 100 mg/kg in the MES model in mice. In rats, it offered protection in 4 of the 4 animals tested up to 4 h at 30 mg/kg, with no noted toxicity at that dosage. All together, no substantial SAR was noted for the aromatic substitutions.

Compound **50** showed protection against seizures in both models. Phase I mouse data revealed that compound **54** was similarily active to compound **1**. Protection at 100 mg/kg was observed for 3/3 mice at 0.5 h in the MES model and 1/1 mice were protected at the same dose and time interval in the ScMET model. The rat evaluation revealed that 4 out of 4 animals were protected at 4 h. Toxicity of wild running was only noted at the 1 h time point in 2 out of the 4 animals. Compound **53** also noted protection in the MES model at 100 mg/kg, with no toxicity reported at that dose. Interestingly, this compound was also tested at the 4 and 6 h-intervals in rats and it was found to protect 4/4 animals as both time intervals in the MES model at 100 mg/kg, thus noting its protection at later time points. There was also no toxicity noted in any of the animals. Therefore, the methylated alcohol and amide will represent new leads from this class and will allow for future development. Although already noted steric bulk is not tolerated in the alcohol region. The closed ring analogue **55** protected 3/3 animals at 100 mg/kg in the MES model where no protection was seen in the ScMET model, as well as minimal toxicity noted (1/8 animals). Analogue **58** did not possess any anticonvulsant activity, thus displaying the steric tolerance of compound **1′s** aromatic region.

Phase I rat data showed that several compounds were selective for the two seizure models. As noted, complete protection was noted for compound **1** in MES at 30 mg/kg. No protection was noted for any of the compounds in the ScMET model in the rats. Compounds **10** and **47** had increased activity at 2 and 4 h intervals, whereas **12** offered protection but only up to 2 h.

Patch clamp electrophysiology studies demonstrated significant tonic blockade of T-type calcium current by compounds **1**, **53** and **54** at 1 mM. Furthermore, compounds **1** and **53** induced a significant use dependent blockade of T-type calcium currents. These results suggest that the mechanism of anticonvulsant activity may include blockade of T-type calcium currents.

4. Conclusion

A series of hydroxyamides were synthesized and submitted to the NINDS ADD Program for anticonvulsant screening. We have demonstrated that compound **1** is an active orally available anticonvulsant with similar activity to phenytoin. Compounds **53** and **54**, which are the methylated alcohol and amide, showed similar activity. However, compound **53** offered increased duration of action (up to 6 h) with no observed toxicity. This study provides evidence for the first time that the anticonvulsant activity of these compounds may be due to use dependent blockade of T-type calcium channels.

5. Experimental

5.1. Chemistry

All reactions requiring anhydrous conditions were performed in flame-dried glassware under an atmosphere of argon or nitrogen. Melting points were determined with an Electrothermal Mel-Temp melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were measured on a General Electric 300 MHz or Varian 300 or 500 MHz. Chemical shifts are reported in ppm relative to resonances of the solvent, $CDCl_3$ (unless specified otherwise): 7.25 ppm (s) in the ^1H spectra and 77.08 ppm (t) in the ^{13}C spectra. ^{19}F NMR spectra were measured on a Varian 300 MHz instrument, externally referenced with TFA (−76.6 ppm). IR spectra were recorded on either a Perkin–Elmer 1310 or FT-IR Impact 400D. High-resolution mass spectrometry was performed at the University of Illinois at Urbana-Champaign School of Chemical Science. Elemental analyses were performed by Atlantic Microlabs. Concentration in vacuo refers to high vacuum (0.35 mmHg). Concentration refers to a rotary evaporator with a water aspirator. Anhydrous THF, diethyl ether, and dichloromethane were purified by pressure filtration through activated alumina. Flash chromoatography was performed on silica gel (Merck grade 9385, 230–400 mesh, 60 Å). Hydrogen chloride gas was purchased from Aldrich or produced by dropwise addition of sulfuric acid to ammonium chloride.

5.1.1. General Procedure A: preparation of ketones from 2,2,2-trifluoro-1-piperidin-1-yl-ethanone. Crushed Mg (1.4 equiv), 2-3 I_2 crystals and a small portion of the ketone was heated until the reaction began to occur. The remaining ketone (1.2 equiv) in dry THF (25 mL) was added dropwise over 30 min. The mixture was refluxed for 2 h and then allowed to cool to room temperature. The mixture was cooled to 0 °C and 2,2,2-Trifluoro-1-piperidin-1-yl-ethanone (**19**, 1.0 equiv) in dry THF (5 mL) was added dropwise over 30 min. The mixture was brought to room temperature and allowed to stir for 2 h. The reaction was quenched with saturated NH_4Cl (5 mL), filtered, dried over $MgSO_4$, filtered, and concentrated to yield the crude product. Purification was performed on a flash column (8:1 hexanes–EtOAc), collecting all fractions with a component of $R_f = 0.38$ to yield the pure ketone.

5.1.2. General Procedure B: preparation of cyanohydrins from ketones.[14] The ketone (1.0 equiv) was dissolved in a minimal amount of dry CH_2Cl_2. Trimethylsilyl cyanide (TMSCN, 2.2 equiv) and ZnI_2 (1.0 equiv), (or KCN and 18-crown-6, 10 mg each for every 1.0 mmole of ketone) were added. The mixture was stirred at room temperature overnight (16 h). The CH_2Cl_2 was evaporated in vacuo and a minimal amount of dry THF was added. The mixture was cooled to 0 °C and 15% HCl (5 mL) was added and then stirred at room temperature for 2 h. The solution was combined with H_2O and extracted with Et_2O (3×25 mL), dried over $MgSO_4$, filtered, and concentrated to yield the cyanohydrin. The cyanohydrins were used in General Procedure C without further purification.

5.1.3. General Procedure C: preparation of α-hydroxyamides from cyanohydrins. The cyanohydrin was dissolved in 1,4-dioxane (2 mL). The mixture was cooled to 0 °C, and previously cooled concd HCl (0.2 mL for every 1 mmole of cyanohydrin) was added. HCl gas was then passed through the reaction mixture for 45 min at 0 °C. The mixture was allowed to stand at room temperature overnight (16 h). The mixture was extracted with EtOAc (3×25 mL), dried over $MgSO_4$, filtered, and concentrated to yield the crude α-hydroxyamide. Purification was performed on a flash column (1:1 hexanes–EtOAc), collecting all fractions with a component of $R_{f=}0.28$ to yield the pure α-hydroxyamide.

5.1.4. 3,3,3-Trifluoro-2-hydroxy-2-phenyl-propionamide (1).[24] General Procedure C was employed with **2** (8.0 g, 40 mmol) and concd HCl (8.0 mL). The hydroxyamide was obtained as a white solid (8.6 g, 99%): mp = 83–85 °C. ^1H NMR: δ ($CDCl_3$, 300 MHz) 7.65–7.68 (m, 2H), 7.41–7.46 (m, 3H), 6.17 (s, 2H), 4.78 (s, 1H). ^{13}C NMR: δ (CD_3OD, 125 MHz) 173.0, 136.5, 130.1, 129.2, 127.7, 125.5 (q, $^1J_{CF} = 473$ Hz), 79.4 (q, $^2J_{CF} = 46$ Hz). ^{19}F NMR: δ −73.14. IR (KBr): 3360, 1697 cm^{-1}. APCI MS m/z: 219.9 ($M + H^+$). HRMS (EI): calcd for $C_9H_8F_3NO_2$, 219.0507; found, 219.0507. Anal. calcd for $C_9H_8F_3NO_2$: C, 49.32; H, 3.68; N, 6.39. Found: C, 49.62; H, 3.63; N, 6.45.

5.1.5. 3,3,3-Trifluoro-2-hydroxy-2-phenyl-propionitrile (2). 2,2,2-Trifluoro-1-phenyl-ethanone (7.0 g, 40.0 mmol) in a minimal amount of dry CH_2Cl_2 was cooled to 0 °C and $TiCl_4$ (5.3 mL, 48.0 mmol) was added dropwise. After 30 min, TMSCN (5.4 mL, 40.0 mmol) was added. The mixture was brought to room temperature and allowed to stir for 6 h. The reaction was quenched with water (30 mL) and the organic layer was washed with saturated $NaHCO_3$ (30 mL), dried over $MgSO_4$, filtered, and concentrated to yield a colorless oil (8.0 g, 99%). IR (neat): 3389, 3071, 2358 cm^{-1}.

5.1.6. 3-Chloro-3,3-difluoro-2-hydroxy-2-phenyl-propionitrile (3). General Procedure B was employed with 2 chloro-2,2-difluoro-1-phenyl-ethanone (3.0 g, 15.7 mmol), TMSCN (3.1 g, 31.2 mmol), KCN (100 mg) and 18-crown-6 (100 mg). The cyanohydrin was obtained as a yellow oil (3.3 g, 96%). IR (neat): 3383, 2246 cm^{-1}.

5.1.7. 2-Hydroxy-2-phenyl-propionitrile (4). General Procedure B was employed with acetophenone (5.0 g, 41.6 mmol), TMSCN (12.2 mL, 91.6 mmol), KCN (400 mg) and 18-crown-6 (400 mg). The hydroxyamide was obtained as a colorless oil (6.2 g, 100%). IR (neat): 3400, 2220 cm^{-1}.

5.1.8. 2-Benzyl-3,3,3-trifluoro-2-hydroxy-propionitrile (5). General Procedure B was employed with 1,1,1-trifluoro-3-phenyl-propan-2-one (1.0 g, 5.3 mmol), TMSCN (1.6 mL, 11.7 mmol), KCN (60 mg) and 18-crown-6 (60 mg). The cyanohydrin was obtained as an orange oil (1.0 g, 91%). IR (neat): 3627, 2963, 2217 cm^{-1}.

5.1.9. 2-Hydroxy-2-phenyl-but-3-yne nitrile (6).[25] General Procedure B was employed with 1-phenyl-propynone (2.2 g, 16.9 mmol), TMSCN (3.3 g, 33.3 mmol), KCN (80 mg) and 18-crown-6 (80 mg). The cyanohydrin was obtained as a dark brown oil (2.0 g, 75%). IR (neat): 3400, 2246 cm^{-1}.

5.1.10. 3-Chloro-3,3-difluoro-2-hydroxy-2-phenyl-propionamide (7). General Procedure C was employed with **3** (3.3 g, 15.2 mmol) and concd HCl (3.0 mL). The hydroxyamide was obtained as a white solid (1.8 g, 50%): mp 79–81 °C. ^{1}H NMR (CD_3OD, 300 MHz) δ 7.31–7.76 (m, 5H). ^{13}C NMR (CD_3OD, 125 MHz) δ 173.0, 136.4, 134.7, 134.7, 130.7, 130.0, 129.0, 127.8, 126.7 (q, $^1J_{CF}=450$ Hz), 82.4 (q, $^2J_{CF}=50$ Hz). IR (KBr): 3510, 3340, 3224, 1700 cm^{-1}. APCI MS *m*/*z*: 236.0 ($M+H^+$). HRMS (EI): calcd for $C_9H_8ClF_2NO_2$, 235.0212; found, 235.0214. Anal. calcd for $C_9H_8ClF_2NO_2$: C, 45.88; H, 3.42; N, 5.94. Found: C, 45.88; H, 3.44; N, 6.01.

5.1.11. 2-Hydroxy-2-phenyl-propionamide (8).[26] General Procedure C was employed with 4 (850 mg, 5.8 mmol) and conc HCl (2.0 mL). The hydroxyamide was obtained as a white solid (290 mg, 30%): mp 97–99 °C. ^{1}H NMR: δ ($CDCl_3$, 300 MHz) 7.10–7.71 (m, 5H), 6.61 (d, $J=7.7$ Hz, 2H), 2.15 (s, 1H). ^{13}C NMR: δ ($CDCl_3$, 75 MHz) 173.7, 141.3, 129.9, 128.5, 128.4, 72.0, 29.8. IR (KBr): 3371, 3193, 1733 cm^{-1}. APCI MS *m*/*z*: 148.1, loss of H_2O, ($M+H^+$).

5.1.12. 2-Benzyl-3,3,3-trifluoro-2-hydroxy-propionamide (9). General Procedure C was employed with **5** (1.0 g, 4.8 mmol) and concd HCl (1.0 mL). The hydroxyamide was obtained as a white solid (1.0 g, 89%): mp = 115–116 °C. ^{1}H NMR: δ ($CDCl_3$, 300 MHz) 7.25–7.34 (m, 5H), 6.02 (d, $J=171.3$, 2H), 3.59 (s, 1H), 3.36 (d, $J=13.8$ Hz, 1H), 2.94 (d, $J=13.5$ Hz, 1H). ^{13}C NMR: δ (CD_3OD, 125 MHz) 171.4, 134.5, 131.2, 128.5, 128.2, 127.6, 127.4, 127.3, 125.9 (q, $^1J_{CF}=285$ Hz), 123.5, 110.3, 79.4 (q, $^2J_{CF}=27$ Hz), 38.4; ^{19}F NMR: δ −76.60. IR (KBr): 3503, 3385, 3210, 1700 cm^{-1}. ESI MS *m*/*z*: 232.2 ($M-H^-$). HRMS (EI): calcd for $C_{10}H_{10}F_3NO_2$, 233.0664; found, 233.0665. Anal. calcd for $C_{10}H_{10}F_3NO_2$: C, 51.51; H, 4.32; N, 6.01. Found: C, 51.27; H, 4.36; N, 5.99.

5.1.13. 2-Hydroxy-2-phenyl-but-3-ynoic acid amide (10). General Procedure C was employed with **6** (2.0 g, 12.7 mmol) and concd HCl (2.5 mL). The hydroxyamide was obtained as a white solid (0.7 g, 31%): mp 79–81 °C. ^{1}H NMR: δ ($CDCl_3$, 300 MHz) 7.70–7.35 (m, 5H), 6.07 (d, 2H), 4.60 (s, 1H), 2.81 (s, 1H). ^{13}C NMR: δ ($CDCl_3$, 75 MHz) 173.7, 140.1, 129.5, 129.2, 126.4, 82.8, 76.3, 73.6. IR (KBr): 3453, 3409, 3274, 3170, 2100, 1696 cm^{-1}. CI MS *m*/*z*: 175.15 ($M-H^-$). HRMS (FAB $M+H^+$): calcd for $C_{10}H_{10}NO_2$, 176.1919; found 176.0718. HPLC μBondapak C18 column (A: 0.1% TFA in H_2O, B: 0.1% TFA in 1:1 CH_3CN:H_2O, B increased from 5 to 10% over 30 min, one peak at 10.54 mins.) (B: 0.1% TFA in H_2O, B: 0.1% TFA in MeOH, B increased from 5 to 10% over 30 mins, one peak at 2.79 mins.)

5.1.14. 2-Benzyloxy-3,3,3-trifluoro-2-phenyl-propionamide (11).[27] Compound **1** (0.63 g, 2.9 mmol) was dissolved in dry CH_2Cl_2 (14 mL) and 5% NaOH (7 mL) was added. Benzyl bromide (0.5 g, 2.9 mmol) was added and the mixture was allowed to stir for 10 min. Bu_4NBr (0.1 g, 0.3 mmol) was added to the reaction mixture and stirred for 16 h at room temperature. The organic layer was washed with H_2O (3×10 mL), dried over Na_2SO_4, filtered, and concentrated. Purification was performed on a flash column (3:1 hexanes–EtOAc), collecting all fractions with a component of $R_f=0.35$. The product was recrystallized from hot toluene to yield a white solid (605 mg, 68%): mp 70–72°C. ^{1}H NMR: δ ($CDCl_3$, 300 MHz) 7.64–7.34 (m, 10H), 6.68 (d, 2H), 4.61 (m, 2H). ^{13}C NMR: δ (CD_3OD, 125 MHz) 169.4, 136.7, 132.4, 129.7, 129.0, 128.9, 128.7, 128.2, 127.7, 126.7, 125.4 (q, $^1J_{CF}=287$ Hz), 109.3, 85.5 (q, $^2J_{CF}=26$ Hz), 69.3. ^{19}F: δ −67.92. IR (KBr): 3227, 1700 cm^{-1}. ESI MS *m*/*z*: 308.5 (M-H$^-$). HRMS (EI): calcd for $C_{16}H_{14}F_3NO_2$, 309.0977; found, 309.0979. Anal. calcd for $C_{16}H_{14}F_3NO_2$: C, 62.13; H, 4.56; N, 4.53. Found: C, 62.20; H, 4.63; N, 4.59.

5.1.15. 3-Amino-1,1,1-trifluoro-2-phenyl-propan-2-ol (12).[16] Compound **2** (2.0 g, 10.0 mmol) was dissolved in dry Et_2O (5 mL) and added to cold (0 °C) $LiAlH_4$ (0.4 g, 10.9 mmol) dissolved in dry Et_2O (10 mL). The reaction mixture was stirred at room temperature for 2 h, then cooled to 0 °C. After allowing the reaction mixture to warm to room temperature, H_2O (2.0 mL) and 15% NaOH (1.0 mL) were added dropwise. The precipitate was filtered, washed with Et_2O, and concentrated. Purification was performed on a flash column (3:2 hexanes–EtOAc), collecting all fractions with a component of $R_f=0.14$. The product was recrystallized from 1:1 hexanes–EtOAc to yield a white solid (1.6 g, 78%): mp 57–59 °C. ^{1}H NMR: δ ($CDCl_3$, 500 MHz) 7.60–7.38 (m, 5H), 3.52 (d, $J=13.2$ Hz, 1H), 3.04 (d, $J=13.5$ Hz, 1H). ^{13}C NMR: δ ($CDCl_3$, 125 MHz) 36.9, 128.4, 128.3, 126.2, 125.7 (q, $^1J_{CF}=284$ Hz), 74.5 (q, $^2J_{CF}=27$ Hz), 45.4;. ^{19}F NMR: δ −77.52. IR (KBr): 2973, 3349 cm^{-1}. APCI MS *m*/*z*: 206.1 ($M+H^+$). HRMS (EI): calcd for $C_9H_{10}F_3NO$, 206.0793; found, 206.0789. Anal. calcd for $C_9H_{10}F_3NO$: C, 52.68; H, 4.91; N, 6.83. Found: C, 52.87; H, 5.02; N, 6.78.

5.1.16. 3,3,3-Trifluoro-2-hydroxy-2-phenyl-propionic acid (13). Compound **1** (1.0 g, 4.6 mmol) was dissolved in 1,4-dioxane (1.5 mL). Conc. HCl (2.5 mL) was added to the reaction mixture dropwise at 0 °C. The mixture was heated at 100 °C for 24 h. After cooling, the solution was washed with H_2O (4×20 mL) and concentrated. Purification was performed on a flash column (1:1 hexanes–EtOAc), collecting all fractions with a component of $R_f=0.20$ to yield a white solid (700 mg, 70%): mp 96–97 °C. ^{1}H NMR: δ (CD_3OD, 300 MHz) 7.69–7.32 (m, 5H). ^{13}C NMR: δ (CD_3OD, 75 MHz) 170.2, 134.9, 129.7, 129.3, 128.3, 126.8, 126.0, 122.3 (q, $^1J_{CF}=465$ Hz), 109.9, 78.4 (q, $^2J_{CF}=45$ Hz). ^{19}F NMR: δ −75.45. IR (KBr): 3403, 1735 cm^{-1}. EI MS *m*/*z*: 220.0. HRMS (EI): calcd for $C_9H_7F_3O_3$, 220.0344; found, 220.0343. Anal. calcd for $C_9H_7F_3O_3$: C, 49.10; H, 3.20. Found: C, 48.99; H, 3.21.

5.1.17. *N*′-Benzylidene-*N*,*N*-dimethyl-hydrazine (14).[28] Benzaldehyde (0.5 g, 4.7 mmol) and ethanol (24 mL) were cooled to 10 °C and a solution containing *N*,*N*-dimethylhydrazine (0.54 mL, 7.1 mmol) and ethanol (5 mL) were added dropwise. The resulting mixture was allowed to warm to room temperature, followed by stirring for 30 min, and then heated to reflux for 24 h. After cooling, the reaction mixture was concentrated in vacuo and the resulting mixture diluted with H_2O and extracted with Et_2O (3×20 mL). The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated to yield a colorless oil (636 mg, 91%). ^1H NMR: δ ($CDCl_3$, 300 MHz) 7.16–7.86 (m, 5H), 3.02 (s, 6H). ^{13}C NMR: δ ($CDCl_3$, 75 MHz) 137.6, 133.2, 129.1, 128.8, 127.9, 126.2, 43.4. The product was used without further purification.

5.1.18. Methyl-(3,3,3-trifluoro-1-phenyl-propenyl)-diazene (15). To a solution of **14** (2.0 g, 13.5 mmol) in pyridine (40 mL) at 0 °C was added trifluoroacetic anhydride (18 mL, 130 mmol) dropwise with stirring. After stirring for 5 h at room temperature, the solution was concentrated in vacuo and CH_2Cl_2 was added to the residue. The mixture was washed with 1 N HCl (100 mL), H_2O (100 mL) and saturated Na_2CO_3 (100 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated to yield a colorless oil (2.1 g, 76%). The product was used without further purification. All spectral data matched the literature.[17]

5.1.19. Preparation of 3,3,3-trifluoro-1-phenyl-propan-1-one (16). A solution of **15** (2.1 g, 9.8 mmol) in CH_3CN (20 mL) and 6N HCl (20 mL) was allowed to stir for 24 h at room temperature. The mixture was concentrated in vacuo, extracted with CH_2Cl_2 (4×20 mL), dried over Na_2SO_4, filtered, and concentrated to yield an oil (450 mg, 13%). ^1H NMR: δ ($CDCl_3$, 300 MHz) 8.05–7.20 (m, 5H), 3.79 (q, J = 9.9 Hz, 2H). ^{13}C NMR: δ ($CDCl_3$, 75 MHz) 190.2, 136.3, 134.7, 129.4, 128.8, 124.6 (q, $^1J_{CF}$ = 274 Hz), 42.6 (q, $^2J_{CF}$ = 28.2 Hz). IR (neat): 3200, 1700 cm^{-1}.

5.1.20. 4,4,4-Trifluoro-2-hydroxy-2-phenyl-butyronitrile (17). General Procedure B was employed with **16** (1.5 g, 8.0 mmol), TMSCN (2.3 mL, 17.6 mmol), KCN (80 mg) and 18-crown-6 (80 mg). The cyanohydrin was obtained as a brown oil (1.8 g, 97%). IR (neat): 3403, 2248 cm^{-1}.

5.1.21. 4,4,4-Trifluoro-2-hydroxy-2-phenyl-butyramide (18). General Procedure C was employed with **17** (1.8 g, 8.4 mmol) and concd HCl (2.5 mL). The hydroxyamide was obtained as white solid (1.6 g, 82%): mp 75–76 °C. ^1H NMR: δ ($CDCl_3$, 300 MHz) 7.48–7.33 (m, 5H), 6.77 (s, 1H), 5.62 (s, 1H), 4.02 (bs, 1H), 3.30 (m, 1H), 2.70 (m, 1H). ^{13}C NMR: δ (CD_3OD, 125 MHz) 174.9, 140.8, 128.6, 128.4, 124.7, 123.6 (q, $^1J_{CF}$ = 370 Hz), 109.3, 41.8 (q, $^2J_{CF}$ = 26 Hz). ^{19}F NMR: δ −59.12. IR (KBr): 3426, 1675 cm^{-1}. ESI MS m/z: 232.3 ($M-H^-$). HRMS (EI): calcd for $C_{10}H_{10}F_3NO_2$, 233.0664; found, 233.0665. Anal. calcd for $C_{10}H_{10}F_3NO_2$: C, 51.51; H, 4.32; N, 6.01. Found: C, 51.62; H, 4.27; N, 6.03.

5.1.22. 2,2,2-Trifluoro-1-piperidin-1-yl-ethanone (19).[18] Trifluoroacetic anhydride (14.8 mL, 105 mmol) was added via an additional funnel over 3 h to triethylamine (14.6 mL, 105 mmol), piperdine (12.5 mL, 126 mmol) and ethyl ether (6 mL). The mixture was cooled to 0 °C and allowed to stir for 30 min. The mixture was brought to room temperature and allowed to stir vigorously for 1 h. The mixture was washed with 1M HCl (20 mL). The ether layer was concentrated and distilled in vacuo (53 °C, 2.6 torr) to obtain a colorless oil (18.0 g, 95%). ^1H NMR: δ ($CDCl_3$, 500 MHz) 3.20 (d, J = 17.7 Hz, 4H), 1.26 (m, 5H). ^{13}C NMR: δ ($CDCl_3$, 125 MHz) 155.0 (q, $^2J_{CF}$ = 35.0 Hz), 116.9 (q, $^1J_{CF}$ = 286 Hz), 46.7, 44.4, 26.3, 25.4, 24.0. ^{19}F NMR: δ −68.02. IR (neat): 2946, 2864, 1695 cm^{-1}. APCI MS m/z: 182.2 ($M+H^+$).

5.1.23. 1-(3-Chloro-phenyl)-2,2,2-trifluoro-ethanone (20). General Procedure A was employed with magnesium (0.75 g, 31 mmol), 1-bromo-3-chloro-benzene (3.1 mL, 27 mmol), and **19** (4.0 g, 22 mmol) in dry THF (25 mL). The ketone was obtained as a colorless oil (2.65 g, 58%) purified by vacuum distillation (74 °C, 15 torr). ^1H NMR: δ ($CDCl_3$, 300 MHz) 7.96 (s, 1H), 7.90 (d, J = 6.9 Hz, 1H), 7.62 (d, J = 6.9 Hz, 1H), 7.46 (t, J = 7.3 Hz, 1H). ^{13}C NMR: δ ($CDCl_3$, 75 MHz) 179.8 (q, $^2J_{CF}$ = 36 Hz), 136.0, 135.8, 131.8, 130.8, 130.2, 128.5, 116.9 (q, $^1J_{CF}$ = 289 Hz). IR (neat): 3074, 1726 cm^{-1}. EI MS m/z: 206.1.

5.1.24. 2,2,2-Trifluoro-1-(2-methoxy-phenyl)-ethanone (21). General Procedure A was employed with magnesium (0.7 g, 29 mmol), 1-bromo-2-methoxy-benzene (3.1 mL, 25 mmol), and **19** (3.8 g, 21 mmol) in dry THF (30 mL). The ketone was obtained as a colorless oil (2.5 g, 58%). ^1H NMR: δ ($CDCl_3$, 300 MHz) 7.53–7.65 (m, 2H), 6.99–7.04 (m, 2H), 3.87 (s, 3H). ^{13}C NMR: δ ($CDCl_3$, 75 MHz) 183.5 (q, $^2J_{CF}$ = 36.8 Hz), 160.3, 136.4, 131.7, 122.2, 121.2, 116.7 (q, $^1J_{CF}$ = 289.2 Hz), 112.6, 56.2. IR (neat): 2949, 2845, 1713 cm^{-1}. APCI MS m/z: 205.1 ($M+H^+$).

5.1.25. 2,2,2-Trifluoro-1-(3-methoxy-phenyl)-ethanone (22). General Procedure A was employed with magnesium (0.7 g, 29 mmol), 1-bromo-3-methoxy-benzene (3.2 mL, 25 mmol), and **19** (3.8 g, 21 mmol) in dry THF (25 mL). The ketone was obtained as a colorless oil (2.8 g, 66%) purified by vacuum distillation (93 °C, 15 torr). ^1H NMR: δ ($CDCl_3$, 300 MHz) 7.17–7.56 (m, 4H), 3.78 (s, 3H). ^{13}C NMR: δ ($CDCl_3$, 75 MHz) 180.6 (q, $^2J_{CF}$ = 34.7 Hz), 160.5, 131.5, 130.4, 122.9, 122.3, 117.2 (q, $^1J_{CF}$ = 289.2 Hz), 114.5, 55.5. IR (neat): 3012, 2947, 2841, 1721 cm^{-1}. EI MS m/z: 204.1.

5.1.26. 2,2,2-Trifluoro-1-(4-methoxy-phenyl)-ethanone (23). General Procedure A was employed with magnesium (0.7 g, 29 mmol), 1-bromo-4-methoxy-benzene (3.1 mL, 25 mmol) and **19** (3.8 g, 21 mmol) in dry THF (25 mL). The ketone was obtained as a colorless oil (3.4 g, 81%). ^1H NMR: δ ($CDCl_3$, 300 MHz) 8.03–8.06 (m, 2H), 6.97–7.02 (m, 2H), 3.90 (s, 3H). ^{13}C NMR: δ ($CDCl_3$, 75 MHz) 179.4 (q, $^2J_{CF}$ = 34.7 Hz), 165.9, 133.2, 128.2, 123.3, 117.4 (q, $^1J_{CF}$ = 289.2 Hz), 114.9, 114.7, 56.2. IR (neat): 3392, 2941, 2845, 1707 cm^{-1}. APCI MS m/z: 205.1 ($M+H^+$).

5.1.27. 2,2,2-Trifluoro-1-m-tolyl-ethanone (24). General Procedure A was employed with magnesium (0.75 g, 31 mmol), 1-bromo-3-methyl-benzene (3.2 mL, 26.5 mmol) and **19** (3.5 g, 19.3 mmol) in dry THF (25 mL). The ketone was obtained as a yellow oil (2.3 g, 63%), purified by vacuum distillation (75–77 °C, 15 torr). ^1H

NMR: δ ($CDCl_3$, 300 MHz) 7.81 (s, 2H), 7.32–7.44 (m, 2H), 2.36 (s, 3H). ^{13}C NMR: δ ($CDCl_3$, 75 MHz) 180.2 (q, $^2J_{CF} = 30.3$ Hz), 139.0, 136.0, 130.1, 129.8, 128.7, 127.0, 116.8 (q, $^1J_{CF} = 290.1$ Hz), 20.5. IR (neat): 2929, 1719 cm^{-1}. EI MS *m*/*z*: 188.1.

5.1.28. 2,2,2-Trifluoro-1-p-tolyl-ethanone (25). General Procedure A was employed with magnesium (0.75 g, 31 mmol), 1-bromo-4-methyl-benzene (3.3 mL, 26.5 mmol) and **19** (4.0 g, 22 mmol) in dry THF (30 mL). The ketone was obtained as a yellow oil (2.9 g, 71%), purified by vacuum distillation (70–71 °C, 15 torr). ^{1}H NMR: δ ($CDCl_3$, 300 MHz) 7.87 (t, *J* = 6.5 Hz, 2H), 7.22 (t, *J* = 7.3 Hz, 2H), 2.36 (s, 3H). ^{13}C NMR: δ ($CDCl_3$, 75 MHz) 180.2 (q, $^2J_{CF} = 31.4$ Hz), 147.5, 130.4, 130.1, 127.8, 117.3 (q, $^1J_{CF} = 290.3$ Hz), 21.6. IR (neat): 2927, 1716 cm^{-1}. APCI MS *m*/*z*: 189.0 ($M + H^+$).

5.1.29. 1-(3,4-Dichloro-phenyl)-2,2,2-trifluoro-ethanone (26). General Procedure A was employed with magnesium (0.75 g, 31 mmol), 4-bromo-1,2-dichloro-benzene (3.4 mL, 26.5 mmol) and **19** (4.0 g, 22 mmol) in dry THF (30 mL). The ketone was obtained as a orange oil (3.84 g, 72%). ^{1}H NMR: δ ($CDCl_3$, 300 MHz) 7.98 (s, 1H), 7.79 (dd, *J* = 1.2 Hz, *J* = 7.3 Hz, 1H), 7.53 (d, *J* = 8.5 Hz, 1H). ^{13}C NMR: δ ($CDCl_3$, 75 MHz) 178.7 (q, $^2J_{CF} = 35.8$ Hz), 140.9, 134.4, 131.9, 131.5, 129.7, 129.1, 116.7 (q, $^1J_{CF} = 289.2$ Hz). IR (neat): 3098, 2769, 1725 cm^{-1}. EI MS *m*/*z*: 242.0.

5.1.30. 2-(3-Chloro-phenyl)-3,3,3-trifluoro-2-hydroxy-propionitrile (27). General Procedure B was employed with **20** (1.1 g, 5.3 mmol), TMSCN (1.6 mL, 11.6 mmol), KCN (60 mg) and 18-crown-6 (60 mg). The cyanohydrin was obtained as a brown oil (1.25 g, 100%). IR (neat): 3398, 3075, 2964, 2247 cm^{-1}.

5.1.31. 3,3,3-Trifluoro-2-hydroxy-2-(2-methoxy-phenyl)-propionitrile (28). General Procedure B was employed with **21** (2.5 g, 12.2 mmol), TMSCN (3.6 mL, 27 mmol), KCN (120 mg) and 18-crown-6 (120 mg). The cyanohydrin was obtained as a brown oil (2.70 g, 95%). IR (neat): 3379, 3082, 2964, 2843, 2244 cm^{-1}.

5.1.32. 3,3,3-Trifluoro-2-hydroxy-2-(3-methoxy-phenyl)-propionitrile (29). General Procedure B was employed with **22** (2.8 g, 13.7 mmol), TMSCN (4.0 mL, 30.2 mmol), KCN (140 mg) and 18-crown-6 (140 mg). The cyanohydrin was obtained as a brown oil (2.75 g, 87%). IR (neat): 3377, 2965, 2840, 2219 cm^{-1}.

5.1.33. 3,3,3-Trifluoro-2-hydroxy-2-(4-methoxy-phenyl)-propionitrile (30). General Procedure B was employed with **23** (3.4 g, 16.7 mmol), TMSCN (4.9 mL, 36.6 mmol), KCN (170 mg) and 18-crown-6 (170 mg). The cyanohydrin was obtained as a brown oil (3.70 g, 96%). IR (neat): 3402, 2966, 2842, 2245 cm^{-1}.

5.1.34. 3,3,3-Trifluoro-2-hydroxy-2-m-tolyl-propionitrile (31). General Procedure B was employed with **24** (2.0 g, 10.6 mmol), TMSCN (3.2 mL, 23.3 mmol), KCN (110 mg) and 18-crown-6 (110 mg). The cyanohydrin was obtained as a yellow oil (2.2 g, 96%). IR (neat): 3386, 2981, 2883, 2246 cm^{-1}.

5.1.35. 3,3,3-Trifluoro-2-hydroxy-2-p-tolyl-propionitrile (32). General Procedure B was employed with **25** (2.2 g, 11.7 mmol), TMSCN (3.4 mL, 25.7 mmol), KCN (120 mg) and 18-crown-6 (120 mg). The cyanohydrin was obtained as a yellow oil (2.5 g, 100%). IR (neat): 3407, 3037, 2964, 2928, 2246 cm^{-1}.

5.1.36. 2-(3,4-Dichloro-phenyl)-3,3,3-trifluoro-2-hydroxy-propionitrile (33). General Procedure B was employed with **26** (2.0 g, 8.2 mmol), TMSCN (2.4 mL, 18.1 mmol), KCN (90 mg) and 18-crown-6 (90 mg). The cyanohydrin was obtained as a orange oil (2.1 g, 95%). IR (neat): 3378, 3099, 2982, 2883, 2247 cm^{-1}.

5.1.37. 2-(4-Chloro-phenyl)-3,3,3-trifluoro-2-hydroxy-propionitrile (34). General Procedure B was employed with 1-(4-chloro-phenyl)-2,2,2-trifluoro-ethanone (3.0 g, 14.4 mmol), TMSCN (4.2 mL, 32 mmol), KCN (140 mg) and 18-crown-6 (140 mg). The cyanohydrin was obtained as a dark oil (3.4 g, 100%). IR (neat): 3383, 2884, 2216 cm^{-1}.

5.1.38. 3,3,3-Trifluoro-2-(3-fluoro-phenyl)-2-hydroxy-propionitrile (35). General Procedure B was employed with 2,2,2-trifluoro-1-(3-fluoro-phenyl)-ethanone (650 mg, 3.4 mmol), TMSCN (0.5 mL, 4.1 mmol), KCN (30 mg) and 18-crown-6 (30 mg). The cyanohydrin was obtained as a dark oil (0.74 g, 100%). IR (neat): 3383, 3087, 2981, 2884, 2247, 2884 cm^{-1}.

5.1.39. 3,3,3-Trifluoro-2-(4-fluoro-phenyl)-2-hydroxy-propionitrile (36). General Procedure B was employed with 2,2,2-trifluoro-1-(4-fluoro-phenyl)-ethanone (3.0 g, 15.6 mmol), TMSCN (4.6 mL, 34.3 mmol), KCN (160 mg) and 18-crown-6 (160 mg). The cyanohydrin was obtained as a yellow oil (3.2 g, 94%). IR (neat): 3379, 3124, 2968, 2882, 2247 cm^{-1}.

5.1.40. 3,3,3-Trifluoro-2-hydroxy-2-(3-trifluoromethyl-phenyl)-propionitrile (37). General Procedure B was employed with 2,2,2-trifluoro-1-(3-trifluoromethyl-phenyl)-ethanone (1.0 g, 4.1 mmol), TMSCN (1.2 mL, 9.1 mmol), KCN (50 mg) and 18-crown-6 (50 mg). The cyanohydrin was obtained as a yellow oil (1.11 g, 100%). IR (neat): 3389, 2967, 2248 cm^{-1}.

5.1.41. 2-(3-Chloro-phenyl)-3,3,3-trifluoro-2-hydroxy-propionamide (38). General Procedure C was employed with **27** (1.25 g, 5.3 mmol) and concd HCl (1.0 mL). The hydroxyamide was obtained as a white solid (1.30 g, 97%): mp = 61–64 °C. ^{1}H NMR: δ ($CDCl_3$, 300 MHz) 7.68 (s, 1H), 7.57 (d, *J* = 6.9 Hz, 1H), 7.36–7.40 (m, 2H), 6.32 (d, *J* = 19.6 Hz, 2H) 4.90 (s, 1H). ^{13}C NMR: δ (CD_3OD, 125 MHz) 169.4, 136.3, 135.5, 130.7, 130.5, 127.2, 125.8, 125.2 (q, $^1J_{CF} = 282$ Hz), 125.0, 122.0, 79.1 (q, $^2J_{CF} = 27$ Hz). ^{19}F NMR: δ −73.33. IR (KBr): 3385, 1676 cm^{-1}. APCI MS *m*/*z*: 236.1 (M-OH). HRMS (EI): calcd for $C_9H_7ClF_3NO_2$, 253.0117; found, 253.0123. Anal. calcd for $C_9H_7ClF_3NO_2$: C, 42.62; H, 2.78; N, 5.52. Found: C, 42.70; H, 2.71; N, 5.57.

5.1.42. 3,3,3-Trifluoro-2-hydroxy-2-(2-methoxy-phenyl)-propionamide (39). General Procedure C was employed with **28** (1.5 g, 6.5 mmol) and concd HCl (3.0 mL). The hydroxyamide was obtained as a white solid (1.25 g, 78%): mp = 101–102 °C. ^{1}H NMR: δ ($CDCl_3$, 300 MHz) 7.77 (d, *J* = 7.8 Hz, 1H), 7.37–7.44 (m, 1H), 6.99–7.06 (m, 2H), 6.67 (s, 1H), 6.34 (s, 1H), 6.03 (s, 1H), 3.92 (s, 3H). ^{13}C NMR: δ (CD_3OD, 125 MHz) 172.5, 158.6, 130.9, 128.7, 126.6, 125.7 (q, $^1J_{CF}$ = 287 Hz), 124.1, 122.8, 120.6, 112.8, 79.4 (q, $^2J_{CF}$ = 22 Hz), 55.2. ^{19}F NMR: δ −74.22. IR (KBr): 3342, 2359, 1700 cm^{-1}. APCI MS *m/z*: 249.9 (M + H$^+$). HRMS (EI): calcd for $C_{10}H_{10}F_3NO_3$, 249.0613; found, 249.0608. Anal. calcd for $C_{10}H_{10}F_3NO_3$: C, 48.20; H, 4.04; N, 5.62. Found: C, 48.47; H, 4.13; N, 5.47.

5.1.43. 3,3,3-Trifluoro-2-hydroxy-2-(3-methoxy-phenyl)-propionamide (40). General Procedure C was employed with **29** (2.0 g, 8.7 mmol) and concd HCl (2.8 mL). The hydroxyamide was obtained as a white solid (1.60 g, 75%): mp = 148–149 °C. ^{1}H NMR: δ ($CDCl_3$, 300 MHz) 7.22–7.38 (m, 3H), 6.94–6.98 (m, 1H), 5.92 (d, *J* = 98 Hz, 2H), 4.74 (s, 1H), 3.83 (s, 3H). ^{13}C NMR: δ (CD_3OD, 125 MHz), 171.9, 160.0, 136.9, 129.2, 126.4, 125.4 (q, $^1J_{CF}$ = 284 Hz), 122.6, 118.9, 114.5, 112.7, 79.3 (q, $^2J_{CF=}$27 Hz), 54.8. ^{19}F NMR: δ −73.12. IR (KBr): 3440, 1690 cm^{-1}. APCI MS *m/z*: 248.4 (M−H$^+$). HRMS (EI): calcd for $C_{10}H_{10}F_3NO_3$, 249.0613; found, 249.0614. Anal. calcd for $C_{10}H_{10}F_3NO_3$: C, 48.20; H, 4.04; N, 5.62. Found: C, 48.05; H, 4.10; N, 5.61.

5.1.44. 3,3,3-Trifluoro-2-hydroxy-2-(4-methoxy-phenyl)-propionamide (41). General Procedure C was employed with **30** (1.0 g, 4.3 mmol) and concd HCl (3.5 mL). The hydroxyamide was obtained as a white solid (1.10 g, 99%): mp = 77–79 °C. ^{1}H NMR: δ ($CDCl_3$, 300 MHz) 7.59 (d, *J* = 8.0 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 4.79 (s, 1H), 3.73 (s, 3H). ^{13}C NMR: δ (CD_3OD, 125 MHz) 172.3, 160.7, 128.1, 127.4, 126.5, 125.6 (q, $^1J_{CF}$ = 285 Hz), 122.6, 113.6, 79.2 (q, $^2J_{CF}$ = 29 Hz), 54.8. IR (KBr): 3446, 1684 cm^{-1}. APCI MS *m/z*: 248.0 (M−H$^+$). HRMS (EI): calcd for $C_{10}H_{10}F_3NO_3$, 249.0613; found, 249.0615. Anal. calcd for $C_{10}H_{10}F_3NO_3$: C, 48.20; H, 4.04; N, 5.62. Found: C, 48.20; H, 4.12; N, 5.56.

5.1.45. 3,3,3-Trifluoro-2-hydroxy-2-m-tolyl-propionamide (42). General Procedure C was employed with **31** (2.2 g, 10.2 mmol) and concd HCl (2.0 mL). The hydroxyamide was obtained as a white solid (2.25 g, 94%): mp = 71–74 °C. ^{1}H NMR: δ ($CDCl_3$, 300 MHz) 7.22–7.46 (m, 4H), 6.16 (s, 2H), 4.76 (s, 1H), 2.38 (s, 3H). ^{13}C NMR: δ (CD_3OD, 125 MHz) 170.0, 139.4, 134.5, 130.9, 129.3, 127.4, 125.5 (q, $^1J_{CF}$ = 284 Hz), 123.6, 79.4 (q, $^2J_{CF}$ = 27 Hz), 22.0. ^{19}F NMR: δ −73.10. IR (KBr): 3401, 1651 cm^{-1}. APCI MS *m/z*: 216.1 (M-OH). HRMS (EI): calcd for $C_{10}H_{10}F_3NO_2$, 233.0664; found. 233.0673. Anal. calcd for $C_{10}H_{10}F_3NO_2$: C, 51.51; H, 4.32; N, 6.01. Found: C, 51.90; H, 4.20; N, 6.06.

5.1.46. 3,3,3-Trifluoro-2-hydroxy-2-p-tolyl-propionamide (43). General Procedure C was employed with **32** (2.0 g, 9.3 mmol) and concd HCl (2.0 mL). The hydroxyamide was obtained as a white solid (2.1 g, 97%): mp = 102–104 °C. ^{1}H NMR: δ ($CDCl_3$, 300 MHz) 7.54 (d, *J* = 7.7 Hz, 2H), 7.24 (d, *J* = 8.1 Hz, 2H), 6.05 (d, *J* = 29.3 Hz, 2H), 4.68 (s, 1H), 2.37 (s, 3H). ^{13}C NMR: δ (CD_3OD, 125 MHz) 170.0, 139.4, 134.5, 130.9, 129.3, 127.4, 125.5 (q, $^1J_{CF}$ = 284 Hz), 123.6, 79.4 (q, $^2J_{CF}$ = 27 Hz), 22.0. ^{19}F NMR: δ −73.25. IR (KBr): 3275, 1683 cm^{-1}. APCI MS *m/z*: 216.1 (M-OH). HRMS (EI): calcd for $C_{10}H_{10}F_3NO_2$, 233.0664; found, 233.0668. Anal. calcd for $C_{10}H_{10}F_3NO_2$: C, 51.51; H, 4.32; N, 6.01. Found: C, 51.62; H, 4.24; N, 6.10.

5.1.47. 2-(3,4-Dichloro-phenyl)-3,3,3-trifluoro-2-hydroxy-propionamide (44). General Procedure C was employed with **33** (2.1 g, 7.8 mmol) and concd HCl (1.6 mL). The hydroxyamide was obtained as a white solid (2.0 g, 89%): mp = 105–106 °C. ^{1}H NMR: δ ($CDCl_3$, 300 MHz) 7.78 (s, 1H), 7.50 (d, *J* = 2.1 Hz, 2H), 6.01 (d, *J* = 81.6 Hz, 2H), 4.65 (s, 1H). ^{13}C NMR: δ (CD_3OD, 125 MHz) 168.3, 133.9, 130.8, 128.6, 125.7, 125.1,125.0 (q, $^1J_{CF}$ = 271 Hz), 121.3, 78.5 (q, $^2J_{CF}$ = 27 Hz). ^{19}F NMR: δ −73.46. IR (KBr): 3331, 2963, 1717 cm^{-1}. APCI MS *m/z*: 270.1 (M-OH). HRMS (EI): calcd for $C_9H_6Cl_2F_3NO_2$, 286.9728; found, 286.9731. Anal. calcd for $C_9H_6Cl_2F_3NO_2$: C, 37.53; H, 2.10; N, 4.86. Found: C, 37.77; H, 2.10; N, 4.81.

5.1.48. 2-(4-Chloro-phenyl)-3,3,3-trifluoro-2-hydroxy-propionamide (45). General Procedure C was employed with **34** (3.4 g, 14.4 mmol) and concd HCl (5.2 mL). The hydroxyamide was obtained as a white solid (3.4 g, 93%): mp = 65–68 °C. ^{1}H NMR: δ ($CDCl_3$, 300 MHz) 7.60 (d, *J* = 8.1 Hz, 2H), 7.39 (d, *J* = 8.5 Hz, 2H), 6.35 (d, *J* = 27.7 Hz, 2H), 4.88 (s, 1H). ^{13}C NMR: δ (CD_3OD, 125 MHz) 172.6, 136.2, 135.2, 129.5, 129.3, 129.2, 125.3 (q, $^1J_{CF}$ = 285 Hz), 79.0 (q, $^2J_{CF}$ = 27 Hz). ^{19}F NMR: −73.40. IR (KBr): 3457, 1654 cm^{-1}. APCI MS *m/z*: 253.9 (M + H$^+$). HRMS (EI): calcd for $C_9H_7ClF_3NO_2$, 253.0117; found, 253.0119. Anal. calcd for: $C_9H_7ClF_3NO_2$: C, 42.62; H, 2.78; N, 5.52. Found: C, 42.57; H, 2.64; N, 5.60.

5.1.49. 3,3,3-Trifluoro-2-(3-fluoro-phenyl)-2-hydroxy-propionamide (46). General Procedure C was employed with **35** (740 mg, 3.4 mmol) and concd HCl (1.5 mL). The hydroxyamide was obtained as a white solid (0.85 g, 98%): mp = 101–103 °C. ^{1}H NMR: δ ($CDCl_3$, 300 MHz) 7.11–7.48 (m, 4H), 6.06 (d, *J* = 49 Hz, 2H), 4.75 (s, 1H). ^{13}C NMR: δ (CD_3OD, 75 MHz) 170.1, 162.7 (d, $^1J_{CF}$ = 242 Hz), 138.8 (d, $^4J_{CF}$ = 6.4 Hz), 131.0 (d, $^3J_{CF}$ = 7.6 Hz), 124.9, (q, $^1J_{CF}$ = 285 Hz), 123.5, 116.7 (d, $^2J_{CF}$ = 20.5 Hz), 114.4 (d, $^2J_{CF}$ = 23.8 Hz), 78.1 (q, $^2J_{CF}$ = 27.1 Hz). ^{19}F NMR: δ −73.42, −109.72. IR (KBr): 3501, 3270, 1699 cm^{-1}. APCI MS *m/z*: 220.3 (M + H$^+$). HRMS (EI): calcd for $C_9H_7F_4NO_2$, 237.0413; found, 237.0417. Anal. calcd for $C_9H_7F_4NO_2$: C, 45.58; H, 2.98; N, 5.91. Found: C, 45.43; H, 3.00; N, 5.91.

5.1.50. 3,3,3-Trifluoro-2-(4-fluoro-phenyl)-2-hydroxy-propionamide (47). General Procedure C was employed with **36** (3.2 g, 14.6 mmol) and concd HCl (2.0 mL). The hydroxyamide was obtained as a white solid (3.2 g, 93%): mp = 83–84 °C. ^{1}H NMR: δ ($CDCl_3$, 300 MHz)

7.63–7.67 (m, 2H), 7.08–7.13 (m, 2H), 5.95 (d, $J = 88.5$ Hz, 2H), 4.64 (s, 1H). ^{13}C NMR: δ ($CDCl_3$, 75 MHz) 169.1, 163.3 (d, $^{1}J_{CF} = 248$ Hz), 143.2, 128.5, 128.3 (d, $^{2}J_{CF} = 223$ Hz), 123.5 (q, $^{1}J_{CF} = 284$ Hz), 115.9 (d, $^{3}J_{CF} = 116$ Hz), 79.1 (q, $^{2}J_{CF} = 23$ Hz). ^{19}F NMR: δ −73.64, −110.37. IR (KBr): 3409, 1710 cm^{-1}. APCI MS *m/z*: 236.0 (M-H$^-$). HRMS (FAB M + H$^+$): calcd for $C_9H_8F_4NO_2$, 238.1519; found, 238.0503. Anal. calcd for $C_9H_7F_4NO_2$: C, 45.58; H, 2.98; N, 5.91. Found: C, 45.73; H, 2.98; N, 6.01.

5.1.51. 3,3,3-Trifluoro-2-hydroxy-2-(3-trifluoromethyl-phenyl)-propionamide (48). General Procedure C was employed with **37** (1.11 g, 4.1 mmol) and concd HCl (0.8 mL). The hydroxyamide was obtained as a white solid (.90 g, 76%): mp = 56–59 °C. ^{1}H NMR: δ ($CDCl_3$, 300 MHz) 7.96 (s, 1H), 7.90 (d, $J = 8.1$ Hz, 1H), 7.69 (d, $J = 7.5$ Hz, 1H), 7.55 (t, $J = 7.5$ Hz, 1H), 6.43 (s, 2H), 5.06 (s, 1H). ^{13}C NMR: δ ($CDCl_3$, 75 MHz) 169.8, 160.4 (q, $^{2}J_{CF} = 164$ Hz), 134.6, 131.4 (q, $^{3}J_{CF} = 132$ Hz), 129.6 (q, $^{4}J_{CF} = 28$ Hz), 126.7, 123.6 (q, $^{1}J_{CF} = 271$ Hz), 123.3, 123.2 (q, $^{1}J_{CF} = 285$ Hz), 81.1 (q, $^{2}J_{CF} = 24$ Hz). ^{19}F NMR: δ −61.63, −73.44. IR (KBr): 3491, 3335, 1699 cm^{-1}. APCI MS *m/z*: 288.0 (M + H$^+$). HRMS (EI): calcd for $C_{10}H_8F_6NO_3$, 288.0459; found, 288.0460. Anal. calcd for $C_{10}H_7F_6NO_2$: C, 41.83; H, 2.46; N, 4.88. Found: C, 41.92; H, 2.35; N, 4.95.

5.1.52. 3,3,4,4,4-Pentafluoro-2-hydroxy-2-phenyl-butyronitrile (49). 2,2,2-,2,3,3,3-Pentafluoro-1-phenyl propan-1-one (2.0 g, 8.9 mmol) in a minimal amount of dry CH_2Cl_2 was cooled to 0 °C and $TiCl_4$ (1.2 mL, 10.7 mmol) was added dropwise. After 30 min, TMSCN (1.2 mL, 8.9 mmol) was added. The mixture was brought to room temperature and allowed to stir for 6 h. The reaction was quenched with water (30 mL) and the organic layer was washed with saturated $NaHCO_3$ (30 mL), dried over $MgSO_4$, filtered, and concentrated to yield a yellow oil (1.8 g, 80%). IR (neat): 3363, 2965, 2883, 2220 cm^{-1}.

5.1.53. 3,3,4,4,4-Pentafluoro-2-hydroxy-2-phenyl-butyramide (50). General Procedure C was employed with **49** (1.8 g, 7.2 mmol) and concd HCl (3.0 mL). The hydroxyamide was obtained as a white solid (1.1 g, 57%): mp = 98–99 °C. ^{1}H NMR: δ ($CDCl_3$, 300 MHz) 7.71–7.73 (m, 2H), 7.41–7.45 (m, 3H), 6.15 (d, $J = 39.3$ Hz, 2H), 5.00 (s, 1H). ^{13}C NMR: δ (CD_3OD, 125 MHz) 172.9, 136.5, 130.7, 130.0, 129.1, 127.7, 120.7 (q of t, $^{1}J_{CF} = 60$ and 477 Hz), 115.2 (t of q, $^{1}J_{CF} = 57$ and 444 Hz), 78.3 (t, $^{2}J_{CF} = 37$ Hz). ^{19}F NMR: δ −76.84, −115.26 (dd, $J = 281$ and 543 Hz). IR (KBr): 3373, 1683 cm^{-1}. EI$^+$ MS *m/z*: 270.1 (M + H$^+$). HRMS (EI): calcd for $C_{10}H_8F_5NO_2$, 269.0475; found, 269.0469. HPLC μBondapak C18 column (A: 0.1% TFA in H_2O, B: 0.1% TFA in 1:1 CH_3CN:H_2O, B increased from 5 to 10% over 30 min, one peak at 10.59 min) (B: 0.1% TFA in H_2O, B: 0.1% TFA in MeOH, B increased from 5 to 10% over 30 min, one peak at 12.39 min).

5.1.54. 2-(*tert*-Butyl-dimethyl-silanyloxy)-3,3,3-trifluoro-2-phenyl-propionamide (51). A 0.1M solution of **1** (2.4g, 11.0 mmole) in dry CH_2Cl_2 was cooled to 0 °C. After 30 min, 2,6-lutidine (1.9 mL, 16.5 mmol) was added. After 10 min, *tert*-butyldimethylsilyltrifluoromethanesulfonate (2.8 mL, 12.0 mmol) was added dropwise. The reaction mixture was allowed to stir at room temperature for 2 h and then quenched with saturated NH_4Cl. The mixture was extracted with CH_2Cl_2, dried over $MgSO_4$, filtered, and concentrated. Purification was performed on a flash column (4:1 hexanes–EtOAc), collecting all fractions with a component of $R_f = 0.71$ to yield the product as a white solid (3.6 g, 99%): mp = 91–93 °C. ^{1}H NMR: δ ($CDCl_3$, 300 MHz) 7.55–7.56 (m, 2H), 7.39–7.41 (m, 3H), 7.17 (s, 1H), 6.76 (s, 1H), 0.94 (s, 9H), −0.74 (d, $J = 32$ Hz, 6H). ^{13}C NMR: δ (CD_3OD, 125 MHz) 171.5, 135.3, 129.5, 128.5, 127.4, 125.5, 125.1 (q, $^{1}J_{CF} = 285$ Hz), 121.6, 83.0 (q, $^{2}J_{CF} = 33$ Hz), 25.8, 18.6, −3.8, −4.1. IR (KBr): 3438, 3285, 2956, 2931, 2860, 2887, 1708 cm^{-1}. APCI MS *m/z*: 334.1 (M + H$^+$).

5.1.55. 2-(*tert*-Butyl-dimethyl-silanyloxy)-3,3,3-trifluoro-N-methyl-2-phenyl-propionamide (52).[18] To a solution of **51** (3.0 g, 9.0 mmol) in dry DMF (60 mL) was added NaH (432 mg, 10.8 mmol, 60% dispersion in mineral oil). The mixture was allowed to stir for 20 min or the conclusion of the evolution of H_2 gas. The reaction mixture was cooled to 0 °C and methyl iodide (0.56 mL, 9.0 mmol) was added dropwise. The mixture was allowed to slowly warm to room temperature and stir for 4 h. The mixture was diluted with Et_2O, washed with H_2O, dried over $MgSO_4$, filtered, and concentrated. Purification was performed on a flash column (3:1 hexanes–EtOAc), collecting all fractions with a component of $R_f = 0.40$ to yield the product as a white solid (2.75 g, 88%): mp = 71–74 °C. ^{1}H NMR: δ ($CDCl_3$, 300 MHz) 7.49–7.52 (m, 2H), 7.35–7.40 (m, 3H), 6.69 (s, 1H), 2.90 (d, $J = 5.1$ Hz, 3H), 0.96 (s, 9H), 0.05 (d, $J = 25.5$ Hz, 6H). ^{13}C NMR: δ ($CDCl_3$, 125 MHz) 168.5, 135.6, 129.3, 128.4, 127.3, 123.6 ($^{1}J_{CF} = 287$ Hz), 81.7 ($^{2}J_{CF} = 27$ Hz), 26.2, 25.8, 18.6, −3.9, −4.2. IR (KBr): 3445, 2956, 2859, 1683 cm^{-1}. APCI MS *m/z*: 348.0 (M + H$^+$).

5.1.56. 3,3,3-Trifluoro-2-hydroxy-N-methyl-2-phenyl-propionamide (53). A solution of **52** (2.75 g, 7.9 mmol) in dry THF (80 mL) was cooled to 0 °C, followed by the addition of tetrabutylammonium fluoride (1.0M in THF, 9.5 mL, 9.5 mmol). The reaction mixture was allowed to warm to room temperature and stir for 16 h. The reaction was quenched with saturated NH_4Cl, extracted with Et_2O, dried over $MgSO_4$, filtered, and concentrated. Purification was performed on a flash column (1:1 hexanes–EtOAc), collecting all fractions with a component of $R_f = 0.50$ to yield the product as a white solid (1.7 g, 93%). mp = 139–140 °C. ^{1}H NMR: δ ($CDCl_3$, 300 MHz) 7.60–7.63 (m, 2H), 7.40–7.43 (m, 3H), 6.05 (s, 1H), 4.85 (s, 1H), 2.88 (d, $J = 2.7$ Hz, 3H). ^{13}C NMR: δ (CD_3OD, 125 MHz) 167.8, 134.4, 129.5, 128.9, 126.3, 125.6 (q, $^{1}J_{CF} = 284$ Hz), 79.4 (q, $^{2}J_{CF} = 27$ Hz), 27.3. ^{19}F NMR: δ −73.05. IR (KBr): 3436, 2357, 1675 cm^{-1} APCI MS *m/z*: 234.0 (M + H$^+$). HRMS (EI): calcd for $C_{10}H_{10}F_3NO_2$, 233.0664; found, 233.0667. Anal. calcd for $C_{10}H_{10}F_3NO_2$: C, 51.51; H, 4.32; N, 6.01. Found: C, 51.77; H, 4.48; N, 5.94.

5.1.57. 3,3,3-Trifluoro-2-methoxy-2-phenyl-propionamide (54).[18] To a solution of **1** (500 mg, 2.28 mmol) in dry DMF (20 mL) was added NaH (110 mg, 2.74 mmol, 60% dispersion in mineral oil). The mixture was allowed to stir for 20 min or the conclusion of the evolution of H_2 gas. The reaction mixture was cooled to 0 °C and methyl iodide (0.14 mL, 2.28 mmol) was added dropwise. The mixture was allowed to slowly warm to room temperature and stir for 2 h. The mixture was diluted with Et_2O, washed with H_2O, dried over $MgSO_4$, filtered, and concentrated. Purification was performed on a flash column (1:1 hexanes–EtOAc), collecting all fractions with a component of $R_f = 0.40$ to yield the product as a white solid (470 mg, 89%): mp = 67–69 °C. ^{1}H NMR: δ ($CDCl_3$, 300 MHz) 7.55–7.56 (m, 2H), 7.38–7.40 (m, 3H), 6.53 (d, $J = 87.3$ Hz, 2H), 3.42 (s, 3H). ^{13}C NMR: δ (CD_3OD, 125 MHz) 169.2, 129.6, 128.6, 127.6, 125.6, 125.4 (q, $^1J_{CF} = 288$ Hz), 85.4 (q, $^2J_{CF} = 26$ Hz) 55.0. ^{19}F NMR: δ −67.94. IR (KBr): 3477, 2953, 2849, 1699 cm^{-1}. APCI MS *m/z*: 234.1 ($M + H^+$). HRMS (EI): calcd for $C_{10}H_{10}F_3NO_2$, 234.0742; found, 234.0736. Anal. calcd for $C_{10}H_{10}F_3NO_2$: C, 51.51; H, 4.32; N, 6.01. Found: C, 51.63; H, 4.25; N, 6.04.

5.1.58. 3-Hydroxy-1-methyl-3-trifluoromethyl-1,3-dihydro-indol-2-one (55).[19] Anhydrous KF (0.47 g, 5.0 mmol) and a solution of methyl-isatin (4.0 g, 24.8 mmol) in dry THF (100 mL) was added dropwise via syringe, followed by trimethyl(trifluoromethyl)silyl ($TMSCF_3$, 5.5 mL, 37.2 mmol). A saturated solution of *t*-BuOK in dry THF (30 mL) was added until the reaction began to reflux. The mixture was brought to room temperature and allowed to stir for 2 h. The mixture was extracted with hexanes (3×40 mL), dried over $MgSO_4$, filtered and concentrated. The crude product was dissolved in dry THF (5 mL), cooled to 0 °C, and 15% HCl (6 mL) was added and allowed to stir for 15 min. The mixture was extracted with hexanes (3×40 mL), dried over $MgSO_4$, filtered, and concentrated. Purification was performed on a flash column (10:1 CH_2Cl_2–acetone), collecting all fractions containing a component of $R_f = 0.81$ to yield the product as a yellow solid (2.0 g, 35%): mp = 168–170 °C. ^{1}H NMR: δ ($CDCl_3$, 300 MHz) 7.0–7.5 (m, 5H), 4.75 (s, 1H), 3.18 (s, 3H). ^{13}C NMR: δ (CD_3OD, 125 MHz) 171.8, 144.8, 131.8, 125.8, 125.7, 124.8 (q, $^1J_{CF} = 284$ Hz), 124.5, 123.6, 123.5, 109.4, 76.3 (q, $^2J_{CF} = 30$ Hz), 25.8. ^{19}F NMR: δ −78.55. IR (KBr): 3302, 1717 cm^{-1}. APCI MS *m/z*: 232.0 ($M + H^+$). HRMS (EI): calcd for $C_{10}H_8F_3NO_2$, 231.0507; found, 231.0509. Anal. calcd for $C_{10}H_8F_3NO_2$: C, 51.96; H, 3.49; N, 6.06. Found: C, 52.22; H, 3.45; N, 6.01.

5.1.59. 2,2,2-Trifluoro-1-naphthalen-2-yl-ethanone (56).[20] NMP (85 mL) and phenyl trifluoroacetate (distilled under reduced pressure, 15 mmHg, 51 °C, 2.17 mL, 14.53 mmol) were degassed overnight with argon. 2-Naphthaleneboronic acid (3.0 g, 17.44 mmol), tributylphosphine (distilled under reduced pressure, 15 mmHg, 115 °C, 0.54 mL, 2.18 mmol) and $Pd(OAc)_2$ (166 mg, 0.74 mmol) were added and the reaction mixture was heated at 80 °C for 4 h. After cooling the reaction mixture, Et_2O and H_2O were added and the aqueous layer was extracted with Et_2O. The combined Et_2O layers were dried over $MgSO_4$, filtered, and concentrated. Purification was performed on a flash column (9:1 hexanes–Et_2O), collecting all fractions with a component of $R_f = 0.80$ to yield the product as a yellow solid. (2.0 g, 77%): mp = 35–37 °C. ^{1}H NMR: δ ($CDCl_3$, 300 MHz) 8.59 (s, 1H), 8.04 (d, $J = 8.4$ Hz, 1H), 7.96 (d, $J = 8.1$ Hz, 1H), 7.88 (t, $J = 8.4$ Hz, 2H), 7.67 (t, $J = 7.8$ Hz, 1H), 7.58 (t, $J = 7.2$ Hz, 1H). ^{13}C NMR: δ ($CDCl_3$, 125 MHz) 180.2 (q, $^2J_{CF} = 35$ Hz), 136.3, 132.9, 132.0, 129.9, 129.8, 128.8, 127.7, 127.2, 123.9, 116.9 (q, $^1J_{CF} = 290$ Hz). IR (KBr): 3052, 2958, 2929, 2872 cm^{-1}. EI MS *m/z*: 228.2.

5.1.60. 3,3,3-Trifluoro-2-hydroxy-2-naphthalen-2-yl-propionitrile (57). General Procedure B was employed with **56** (610 mg, 2.7 mmol), TMSCN (4.0 mL, 30 mmol), KCN (30 mg) and 18-crown-6 (30 mg). The cyanohydrin was obtained as a white solid (620 mg, 91%). IR (neat): 3370, 2960, 2875, 2141 cm^{-1}.

5.1.61. 3,3,3-Trifluoro-2-hydroxy-2-naphthalen-2-yl-propionamide (58). General Procedure C was employed with **57** (620 mg, 2.5 mmol) and concd HCl (3.0 mL). The hydroxyamide was obtained as a white solid (470 mg, 71%): mp = 94–96 °C. ^{1}H NMR: δ ($CDCl_3$, 300 MHz) 8.15 (s, 1H), 7.83–7.91 (m, 3H), 7.67 (d, $J = 8.7$ Hz, 1H), 7.50–7.55 (m, 2H), 5.99 (d, $J = 72.3$ Hz, 2H), 4.86 (s, 1H). ^{13}C NMR: δ ($CDCl_3$, 125 MHz) 169.0, 133.1, 132.4, 130.9, 128.6, 128.2, 127.3, 127.0, 126.5, 125.7, 123.4 (q, $^1J_{CF} = 280$ Hz), 122.9, 78.2 (q, $^2J_{CF} = 28$ Hz). ^{19}F NMR: δ −73.04. IR (KBr): 3387, 2961, 2359, 1695 cm^{-1}. APCI MS *m/z*: 252.2 (M-OH$^-$). HRMS (EI): calcd for $C_{13}H_{10}F_3NO_2$, 269.0664; found, 269.0658. HPLC μBondapak C18 column (A: 0.1% TFA in H_2O, B: 0.1% TFA in 1:1 CH_3CN:H_2O, B increased from 5 to 10% over 30 min, one peak at 27.06 min) (B: 0.1% TFA in H_2O, B: 0.1% TFA in MeOH, B increased from 5 to 10% over 30 min, one peak at 29.95 min).

6. Biology

6.1. Cell culture

HEK-293 cells stably expressing a human T-type calcium channel, ($hCa_v3.2$) α1H,[29] were a kind gift from Dr. Edward Perez-Reyes, at the University of Virginia. Cells were maintained in DMEM containing 10% fetal bovine serum with 1mg/mL G418. Cells were enzymatically dissociated with 0.05% trypsin plus 1mM EDTA for 1 min. Cells were then diluted with DMEM and plated on glass coverslips or poly-L-lysine coated coverslips and were incubated for 1–4 h prior to electrophysiological studies.

6.2. Patch clamp electrophysiology

Calcium currents were recorded from HEK-293 cells stably expressing the $Ca_v3.2$α1H channels using the whole-cell configuration of the patch clamp recording technique with an Axopatch 200B amplifier (Axon

Instruments, Foster City, CA). All voltage protocols were applied using pCLAMP 8 software (Axon, USA) and a Digidata 1322A (Axon). Currents were amplified and low pass filtered (2 kHz) and sampled at 10 kHz. Borosilicate glass pipettes were pulled using a Brown-Flaming puller (model -P87, Sutter Instruments Co, Novato, CA) and heat polished to produce electrode resistances of 0.7–1.7 MΩ when filled with the following electrode solution (in mM) CsCl 135, MgATP 4, Na_3GTP 0.3, EGTA 10, HEPES 10 (pH adjusted to 7.3 with CsOH). Cells were superfused at 1 mL/min with the following solution (in mM) $CaCl_2$ 5, tetraethylammonium (TEA) chloride 155, HEPES 10, (pH adjusted to 7.4 with TEA-OH). The compound was prepared as 100 mM stock solution in DMSO and diluted to desired concentrations in perfusion solution. All experiments were performed at room temperature (20–22 °C) with continuous perfusion. Cells were held at −110 mV and a step to −20 mV for 150 ms was applied, this was repeated a total of 100 times at a frequency of 1 Hz. Compound was applied at increasing concentrations followed by washout and use dependent blocking data were acquired in this manner.

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