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PII: S0960-894X(16)30331-6
DOI: http://dx.doi.org/10.1016/j.bmcl.2016.03.101
Reference: BMCL 23744

To appear in: *Bioorganic & Medicinal Chemistry Letters*

Received Date: 4 February 2016
Revised Date: 25 March 2016
Accepted Date: 26 March 2016

Please cite this article as: Koltun, D.O., Parkhill, E.Q., Elzein, E., Kobayashi, T., Notte, G.T., Jiang, R.H., Li, X., Perry, T.D., Avila, B., Wang, W-Q., Smith-Maxwell, C., Dhalla, A.K., Rajamani, S., Stafford, B., Tang, J., Mollova, N., Belardinelli, L., Zablocki, J.A., Discovery of triazolopyridine GS-458967, a Late Sodium Current Inhibitor (Late $I_{Na}i$) of the Cardiac Na_V 1.5 Channel with Improved Efficacy and Potency Relative to Ranolazine, *Bioorganic & Medicinal Chemistry Letters* (2016), doi: http://dx.doi.org/10.1016/j.bmcl.2016.03.101

Bioorganic & Medicinal Chemistry Letters
journal homepage: www.elsevier.com

Discovery of triazolopyridine GS-458967, a Late Sodium Current Inhibitor (Late I_{Na}i) of the Cardiac Na_V 1.5 Channel with Improved Efficacy and Potency Relative to Ranolazine

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ARTICLE INFO

Article history:
Received
Revised
Accepted
Available online

Keywords: Late I_{Na} current inhibitor; GS-458967; anti-arrhythmic; ranolazine; ventyricular arrhythmia.

ABSTRACT

We started with a medium throughput screen of heterocyclic compounds without basic amine groups to avoid hERG and β-blocker activity and identified [1,2,4]triazolo[4,3-a]pyridine as an early lead. Optimization of substituents for Late I_{Na} current inhibition and lack of Peak I_{Na} inhibition led to the discovery of **4h** (GS-458967) with improved anti-arrhythmic activity relative to ranolazine. Unfortunately, **4h** demonstrated use dependent block across the sodium isoforms including the central and peripheral nervous system isoforms that is consistent with its low therapeutic index (approximately 5-fold in rat, 3-fold in dog). Compound **4h** represents our initial foray into a 2nd generation Late I_{Na} inhibitor program and is an important proof-of-concept compound. We will provide additional reports on addressing the CNS challenge in a follow-up communication.

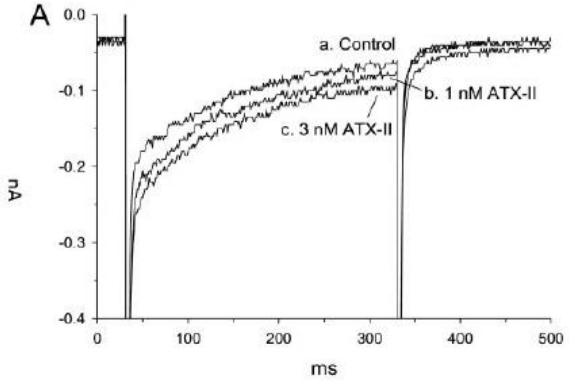
Introduction

Ischemic heart disease (IHD) is a result of atherosclerotic narrowing of coronary vessels and has a high prevalence (7%) within the United States.[1] IHD progresses from silent ischemia that often goes undetected to more severe ischemia that causes chest pain (angina), a condition that affects 9 million people in the US.[2] Ranolazine **1** is approved for the treatment of chronic angina.[3] Although the mechanism of ranolazine's antianginal effect has not been determined, it inhibits cardiac late (also known as persistent) sodium channel current (Late I_{Na} current, or simply Late I_{Na}) at therapeutic levels. Late I_{Na} (Figure 1) is enhanced in an ischemic state due to reactive oxygen species (ROS) that chemically modify the α-subunit protein (SCN5A) resulting in incomplete inactivation that occurs late in the action potential.[4] Late I_{Na} leads to intracellular Na^+ overload and subsequent Ca^{+2} overload through activity of Na-Ca^{+2} exchanger operating in the reverse mode. Ranolazine inhibits this process by lowering the ischemic burden (calcium imbalance and sequelae).[5] At its therapeutic range (2 – 8 μM in plasma), ranolazine inhibits a number of cardiac ion currents (e.g. I_{Kr}).[6] Ranolazine provides its antianginal benefit without causing bradycardia (slowing of heart rate) and/or lowering systemic blood pressure.[6] Ranolazine has been shown to eliminate early after depolarizations (EADs) and reduce the increase in transmural dispersion of repolarization (TDR), thus lowering the potential for arrhythmias to occur.[6] Late I_{Na} current is enhanced in patients with genetic mutations in SCN5A leading to a Long QT-3 syndrome (LQT-3) that can lead to sudden cardiac death by potentially fatal *Torsades des Pointes*.[7]

Late I_{Na} current (Figure 1) can be generated *in vitro* by the addition of toxins ATX-II or tefluthrin that bind to an external binding site that does not overlap with the lidocaine binding site.[8] In a manual single-patch clamp experiment, ranolazine (**1**, Figure 2) displayed inhibition of ATX-II enhanced Late I_{Na} with IC_{50} 6.9 μM.[6]

Unlike Late I_{Na} that is strictly pathological, Peak I_{Na} current's physiological role is essential to the propagation of the action potential from the pacemaker sinoatrial (SA) node through the atria and ventricles. Peak I_{Na} is triggered by change of extracellular voltage during each heartbeat. Ranolazine does not inhibit Peak I_{Na} current at therapeutic levels with a selectivity index of >50 fold.[6]

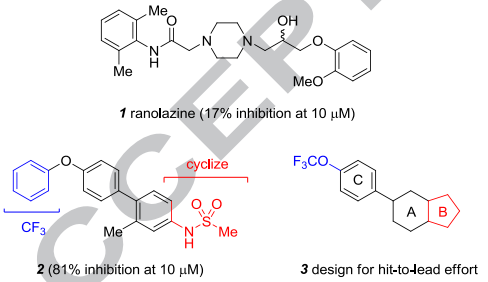
Figure 1. Late sodium channel current (Late I_{Na}) in a control experiment (a), or enhanced with aid of 1 nM (b) or 3 nM (c) ATX-II.



Herein, we describe our initial efforts to discover a potent Late I_{Na} current blocker selective against peak current, and demonstrate the anti-ischemic and anti-arrhythmic effects of our lead molecule **4h** in isolated heart and *in vivo* models, respectively. Rather than starting with ranolazine (**1**), we screened a number of in-house heterocyclic compounds without a basic group, to decrease the likelihood of hERG and β-blockade, for their Late I_{Na} inhibitory activity using automatic patch clamp system (hNav 1.5 α-subunit HEK-293).[9] We discovered a more potent compound **2** (81% inhibition at 10 μM), and used it as a starting point for our hit-to-lead effort.[9]

In our initial design, we relied on CF_3O-phenyl group as a bioisostere for the phenoxyphenyl group to enhance metabolic stability. We were seeking to eliminate the *para*-amino-biphenyl motif as well, fearing the potential oxidation into a quinone methide. We envisioned a [6,5] system being a potential bioisostere for *para*-amino-biphenyl group by virtue of cyclizing the sulfonamide group into a fused 5-member ring.[10] The proposed changes are summarized as **3** in Figure 2.

Figure 2. Ranolazine (**1**), in-house compound (**2**), and the design for hit-to-lead effort (**3**).



Chemistry

In general, the compounds were prepared via Suzuki coupling using a palladium catalyst, a bromo-core molecule, and an appropriately substituted boronic acid or ester in the presence of a mild base (e.g. $NaHCO_3$) at a temperature of 120 – 170°C for 10 min to 1 h (Figure 3).[10] Cores **4**, **6**, **7**, and **10** were prepared from the corresponding hydrazine through reaction with the appropriate substituted anhydride followed by in situ condensation to form the core (Figure 4). Core **8** was prepared from the corresponding pyridylmethylamine through reaction with the appropriate substituted anhydride followed by phosphorous oxychloride induced condensation to form the core (Figure 4).[10] Core **5** was prepared by taking the corresponding core **4** and treating with cesium carbonate at high temperature to invoke a Dimroth rearrangement as shown in Figure 5.

Figure 3. Synthesis of analogs via Suzuki coupling.

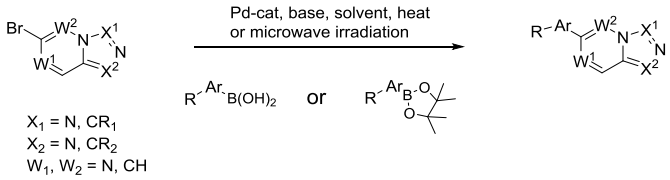


Figure 4. General core synthesis.

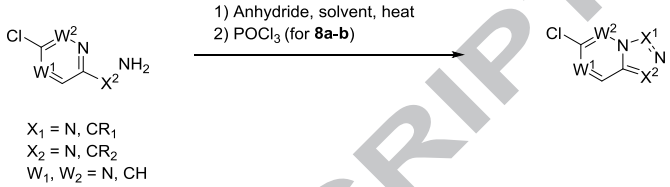
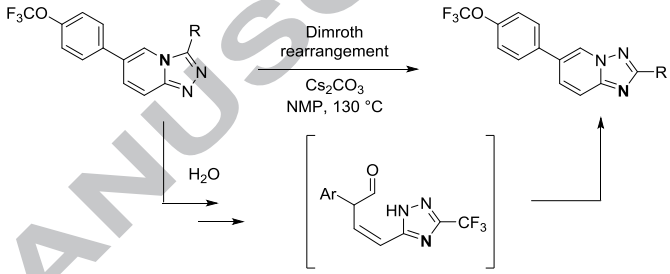


Figure 5. Dimroth rearrangement.



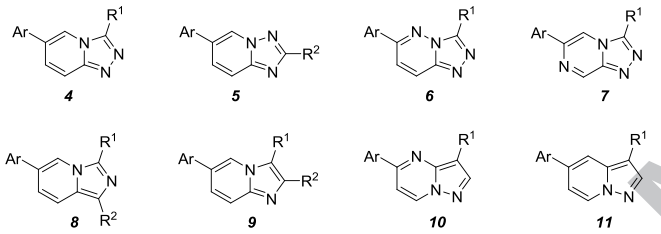
Results and Discussion

To begin our hit-to-lead effort, we performed initial screening of our synthetic analogs for Late I_{Na} inhibition at 10 μM concentration. With a few exceptions, compounds exhibiting 70% or greater inhibition at 10 μM were subsequently tested to determine an IC_{50} value. Selected compounds were then counter-screened against Peak I_{Na} inhibition at concentration close to their 50% block of Late I_{Na} – typically 1 μM or 0.1 μM. The screening for Peak I_{Na} inhibition was performed at physiologically relevant pacing frequencies of 1 Hz and 3 Hz, corresponding to 60 and 180 beats per minute, respectively.

Initially, we evaluated a number of fused bicyclic bridge-head nitrogen [6,5] systems for their effectiveness as *para*-amino-biphenyl group bioisosteres keeping the *para*-trifluoromethoxyphenyl substituent constant. The results of our study are shown in Table 1. As a first example of generic structure **3**, we evaluated [1, 2, 4]triazolo[4,3-a]pyridine system **4** for its ability to replace *para*-amino-biphenyl group while retaining Late I_{Na} inhibition properties of **2**.[10] We examined a number of groups ranging from polar (NH_2, **4a**) to lipophilic (CF_3, **4h**) at the 3-position, the lone position on ring B available for substitution. Lipophilicity is clearly preferred as seen from relatively high activity of **4e-h** (Me, *i*-Pr, CHF_2, CF_3) relative to polar groups **4a-b**. The most potent compound from this series, CF_3 analog **4h,** was found to have an IC_{50} of 333 nM for Late I_{Na} inhibition while exhibiting < 15% block of Peak I_{Na} at the same concentration under 1 and 3 Hz pacing frequencies. Next, we examined isomeric [1,2,4]triazolo[1,5-a]pyridine scaffold **5**. Unsubstituted analog **5a** had an IC_{50} of 941 nM and was less active than **4h**. Substitution at the position 2 with a CF_3 group proved detrimental to activity, especially in **5b** compared to **4h**. In subsequent series **6** and **7,** we explored the introduction of an additional nitrogen atom in ring A of the bicyclic fused system, while keeping optimal CF_3 substituent in the 3-position. In the case of **6a**, the compound retained Late I_{Na} inhibition, but had unacceptable Peak I_{Na} inhibition, more than **4h**. Compound **7a** proved inferior to **4h**, supporting the conclusion that ring A does

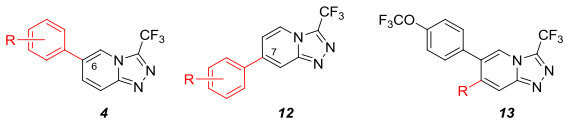
not tolerate nitrogen in this position. Having examined a number of systems with 3-nitrogen in ring B, we switched to a 2-nitrogen imidazo[1,5-a]pyridine scaffold **8**. Keeping CF_3 substituent in the position 3, we explored the additional position 1 available for substitution. Unsubstituted analog **8a** exhibited an IC_{50} of 102 nM. Unfortunately, the inhibition of Peak I_{Na} by **8a** was high (41.1% at 1 μM, 1 Hz). 1-Methyl-substituted analog **8b** was much less active. In the next 2-nitrogen scaffold **9**, positions 3 (R^1) and 2 (R^2) are available for substitution. In a head-to-head comparison, position 3 has once again proven to be advantageous for substitution (**9b**, $R^1 = CF_3$, R^2 = H, IC_{50} of 353 nM vs. **9c**, R^1 = H, $R^2 = CF_3$, IC_{50} of 3345 nM). For **9b**, the inhibition of Peak I_{Na} was high (49.0% at 1 μM, 1 Hz). Finally, we explored scaffolds **10** and **11** that represent an alternative position of the bridge-head nitrogen with respect to 4-trifluoromethoxyphenyl substituent (para vs. meta in **4**-**9**). Based on the SAR across all scaffolds the bulk at the 3-position did not yield improvement over the hydrogen substituent. Between the two scaffolds, compound **11b** was the most potent, but inhibition of Peak I_{Na} was high (40.4% at 1 μM, 1 Hz).

Table 1. Sodium channel blocking properties of fused [6,5] heterobiaryl compounds [Ar = 4-(trifluoromethoxy)phenyl] and the Structure-Activity Relationships in the central core.



			Late $Na_v1.5$ block		Peak $Na_v1.5$ block, % (μM)	
4	R^1	R^2	at 10 μM	IC_{50} nM	1 Hz	3 Hz
a	NH_2		8.4%			
b	$NHSO_2Me$		2.0%			
c	NMe_2			7541		
d	H			8935		
e	Me		57.2%			
f	^{i}Pr		48.5%			
g	CHF_2			351	25.7 (1)	22.5 (1)
h	CF_3			333	13.7 (0.1)	11.1 (0.1)
5						
a		H		941		
b		CF_3	27.1%			
6						
	CF_3			223	18.3 (1)	30.8 (1)
7						
	CF_3		52.5%			
8						
a	CF_3	H		102	41.1 (1)	13.0 (1)
b	CF_3	Me	42.5%			
9						
a	H	H	67.9%			
b	CF_3	H		353	49.0 (1)	20.3 (1)
c	H	CF_3		3345		
10						
a	H			1512	41.4 (10)	1.4 (10)
b	Me			5052		
c	CF_3			901	22.5 (1)	5.0 (1)
11						
a	H			425	34.9 (1)	4.6 (10)
b	CF_3			417	40.4 (1)	8.1 (1)

Table 2. Sodium channel blocking properties of 3-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridines.



		Late Na IC_{50} block		Peak $Na_v1.5$ block, % (μM)	
4	R	at 10 μM	IC_{50}, nM	1 Hz	3 Hz
h	4-OCF_3		333	13.7 (0.1)	11.1 (0.1)
i	3-OCF_3	52.9%			
j	4-CF_3		211	46.0 (1)	33.3 (1)
k	4-F		7915		
l	4-$OCHF_2$		887		
m	4-OCH_2CF_3		281		
n	4-$NHCH_2CF_3$	23.5%			
o	4-O^{t}Bu	49.8%			
p	4-OEt	56.8%			
q	4-OMe		2221		
r	4-^{t}Bu		182	64.4 (1)	57.2 (1)
s	4-$SiMe_3$		59	30.6 (0.1)	24.0 (0.1)
t	4-SF_5		397	52.0 (1)	76.0 (1)
u	4-CN	28.5%			
v	4-NO_2	22.5%			
w	2-Me-4-OCF_3		123	37.9 (1)	49.6 (1)
x	3-Me-4-OCF_3		166	30.8 (1)	36.8 (1)
y	2,4-Cl_2	53.5%			
12	4-OCF_3	1.9%			
13					
a	Me	67.5%		20.4 (1)	13.9 (1)
b	OMe		1647		

Having performed a "nitrogen scan" among scaffolds **4**-**11**, we settled on scaffold **4** and its most potent 3-trifluoromethyl analog **4h** as a starting point for the SAR studies in rings A and C. We synthesized analogs **4i-y** with the goal of evaluating steric and electronic effects of substituents on ring C (Table 2). We found that the substituent in 4-position is essential, while 2- or 3-substited C rings retain potency, but reduce the selectivity against peak current. Potency of substituents in 4-position correlates more with steric than electronic effects with the best compounds containing bulky, mildly electron-donating groups like OCF_3, *t*-Bu, Me_3Si, as well as electron-withdrawing CF_3 analog with a number of these having Late I_{Na} IC_{50}'s <500 nM. However, none of the analogs in this follow-on study matched the combination of potency and selectivity that initial OCF_3 analog (**4h**) provides.

Next, we evaluated the effect of the substituents in 7-position of ring A on Late I_{Na} inhibition. We hypothesized that relocating the (4-trifluoromethoxy)phenyl group from 6- to 7-position will retain the molecule's overall linear topology and allow binding in a similar fashion, but analog **12** was completely inactive. Inserting a substituent in 7-position along with 6-(4-trifluoromethoxy)phenyl group (Me, **13a**; and OMe, **13b**) was intended to force the C ring out of plane of ring A. We learned that this conformational change reduces both activity and selectivity.

Table 3. In vitro ADME and in vivo pharmacokinetic properties of compound **4h**.

In vitro	
MW	347.22
Measured LogD	3.38
Aqueous solubility, μM (HCl, pH 2.2 / PBS, pH 7.6)	6.0 / 4.7
Microsomal stability, $t_{1/2}$, min (human/dog/rat)	>395 / 70 / 229
Caco-2 permeabilty, A → B, $\times 10^{-6}$ cm/s (1 / 10 μM)	41.25 / 27.85
B → A, $\times 10^{-6}$ cm/s (1 / 10 μM)	43.95 / 35.20
In vivo, PO	
$AUC_{(0\rightarrow\infty)}$, nM·h (rat/cyno. monkey)	5703 / 76094
C_{max}, nM (rat/cyno. monkey)	397 / 1480
t_{max}, h (rat/cyno. monkey)	2.7 / 6.0
In vivo, PO	
V_{ss}, L (rat/cyno. monkey)	3.4 / 0.6
CL, L/h/kg (rat/cyno. monkey)	0.193 / 0.013
t_{max}, h (rat/cyno. monkey)	14.1 / 32.9
F, % (rat/cyno. monkey)	105 / 83

We proceeded to study *in vitro* and *in vivo* pharmacokinetic properties of **4h** (Table 3). Compound **4h** has proven to be highly metabolically stable in rat and human liver microsomes (dog was an outlier species) which translated into low *in vivo* clearance in both rat and cynomolgus monkeys. Its low molecular weight and moderate LogD values along with high Caco-2 permeability and the absence of net efflux translated into high oral bioavailability and exposure in both species.

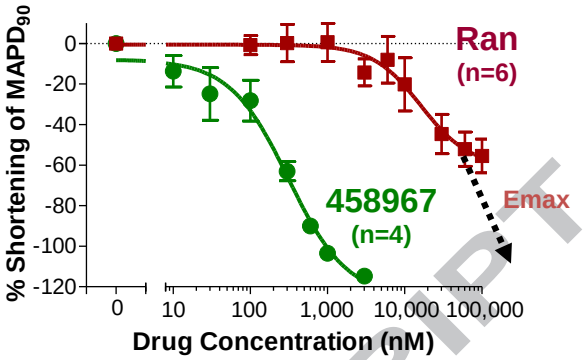
We also tested the activity of **4h** in manual patch clamp assays determining the IC_{50} for Late I_{Na} inhibition, the peak sodium inhibition against sodium isoforms, use dependent block at 10 Hz, and the hERG inhibition.[2] The IC_{50} for Late I_{Na} inhibition by **4h** was found to be 130 nM affording a good separation (≥10x) from peak sodium inhibition against the various isoforms (Table 4) based on % inhibition at 1 uM. Unfortunately, **4h** demonstrated high use dependent block at 10 Hz across the various sodium channel isoforms. Our plan in identifying leads without basic groups paid off with regards to low hERG inhibition for **4h** with 17% inhibition at 10 uM.

Next, we proceeded to study the efficacy of **4h** in Langendorff isolated heart model (Figure 5). We added ATX-II (3 nM) to prolong the mean action potential duration ($MAPD_{90}$) by 68 ± 11% from 181 ± 7 (control) to 306 ± 28 ms (n = 6). Compound **4h** completely reversed the ATX-II increase in $MAPD_{90}$ with an IC_{50} of 0.21 uM consistent with its cellular inhibition of Late I_{Na}. Ranolazine only partially (60%) reversed the effects of ATX-II increase in $MAPD_{90}$ with an IC_{50} of 16 uM (Figure 4).

Table 4. Peak and use dependent block across sodium channel isoforms for **4h**.

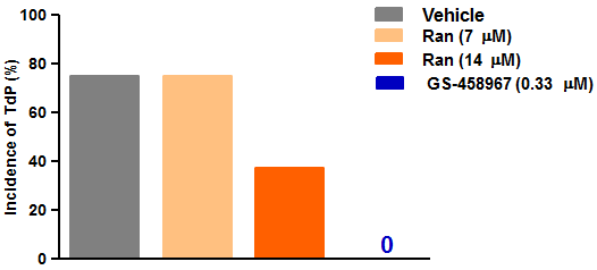
Peak INa Block	**% Block (0.1 Hz)**		**% Block (10 Hz)**	
	1 μM	0.1 μM	1 uM	0.1 uM
hNav1.1	4.7	4.8	68	34.1
hNav1.2	14.8	7.8	72	38.8
hNav1.3	19.0	0.4	60.3	44.1
hNav1.4	27.9	3.1	69.3	43.7
hNav1.5	24.3	3.4	35.6	11.1
hNav1.6	26.8	5.2	57.8	25
hNav1.7	30.0	10.5	88.7	53.5
hNav1.8	47.2	11.1	64.2	29.3

Figure 5. Reversal of ATX-II increase in $MAPD_{90}$ by **4h** and ranolazine.



Then, we determined the anti-arrhythmic effect of **4h** in an *in vivo* model of chemically induced ventricular arrhythmia (Figure 6). In anesthitized rabbits we slowed the heart rate through the addition of an α-blocker (methoxyamine) followed by the addition of a hERG blocker (clofilium) that induced 80% of the control animals to have torsade des pointes (TdP). Compound **4h** completely protected against Tdp at 300 nM concentration. Ranolazine was only partially protective at much higher concentrations (14 uM) with 40% of the animals having Tdp.

Figure 6. Protection from hERG induced ventricular arrhythmias by **4h** in anesthetized rabbits.



Conclusion

We started the Late I_{Na} program with a medium throughput screen that afforded **2** as our initial hit that was subsequently modified to a fused [6,5] heterocyclic system. We settled on a [1,2,4]triazolo[4,3-a]pyridine system that was further optimized to obtain **4h** as a potent Late I_{Na} inhibitor that had a good separation of Late I_{Na} inhibition from Peak I_{Na} and hERG. Compound **4h** was found to reverse the effects of ATX-II in isolated hearts, and it was found to protect against chemically induced ventricular arrhythmias *in vivo* at concentrations consistent with its IC_{50} for Late I_{Na} inhibition. Unfortunately, **4h** demonstrated use dependent block across the sodium isoforms including the brain and peripheral nervous system isoforms that is consistent with its low therapeutic index (approximately 5-fold in rat and 3-fold in dog). Compound **4h** represents our initial foray into a 2nd generation Late I_{Na} inhibitor program that we will provide additional reports on addressing specifically the CNS challenges in due course.

Acknowledgments

We would like to thank Manoj Desai and Gerry Rhodes for their suggestions on executing the Late I_{Na} program.

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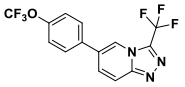

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IC_{50} = 130 nM