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Fused Heterocyclic Compounds as Ion Channel Modulators

Patent Highlight

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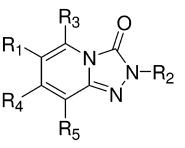
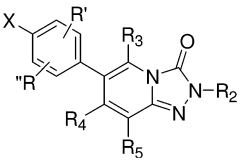
Title:	Fused Heterocyclic Compounds as Ion Channel Modulators		
Patent/Patent Application Number:	WO2012003392A1	**Publication Date:**	January 5, 2012
Priority Application:	US61/361056	**Priority Date:**	July 2, 2010
Inventors:	Kobayashi, Tetsuya; Koltun, Dmitry; Notte, Gregory; Parkhill, Eric; Zablocki, Jeff		
Assignee Company:	Gilead Science Inc.		
Disease Area:	Cardiovascular Disease	**Biological Target:**	Voltage Gated Sodium Channel $Na_v1.5$

Summary: Voltage-gated sodium channels play an important role in both cardiac myocytes and neuronal cells. The $Na_v1.5$ channel is responsible for the late sodium current (INaL), and dysfunction of this channel can contribute to the development of a variety of disease states associated with abnormally high $Na_v1.5$ activity. Ranexa, a selective INaL inhibitor, has clinical utility for the treatment of stable angina pectoris, unstable angina, and arrhythmia. This patent application discloses a series of functionalized triazolopyridin-3-ones that are useful as $Na_v1.5$ channel inhibitors for the treatment cardiovascular diseases associated with increased $Na_v1.5$ activity.

Important Compound Classes:





Definitions:

R^1 is aryl, heteroaryl.

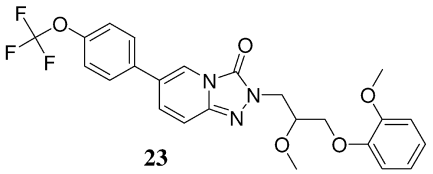
R^2 is hydrogen, C_{1-15} alkyl, C_{1-8} alkoxy, $-C(O)OR^{26}$, $-C(O)N(R^{26})(R^{28})$, $N(R^{20})SO_2R^{20}$, cycloalkyl, aryl, heteroaryl, heterocyclyl.

R^3 is hydrogen, OH, halogen, C_{1-4} alkyl, C_{1-4} alkoxy, $-R^{25}-N(R^{20})(R^{22})$, $-R^{25}-OR^{20}$, $-R^{25}C(O)OR^{20}$, $-R^{25}C(O)N(R^{20})(R^{22})$, $-R^{25}C(O)ON(R^{20})(R^{22})$, $-R^{25}N(R^{20})C(O)R^{22}$, $-R^{25}OC(O)N(R^{20})(R^{22})$.

R^4 is hydrogen, C_{1-4} alkyl, aryl, CF_3, halo, $-OR^{24}$.

R^5 is hydrogen, optionally substituted alkyl, amino, optionally substituted alkoxy, CF_3, OCF_3, CN, $-N(R^{20})C(O)R^{22}$.

Key Structures:



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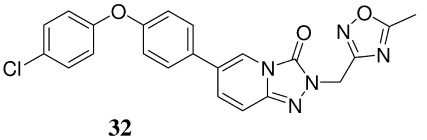

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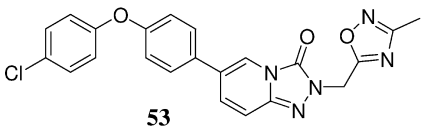

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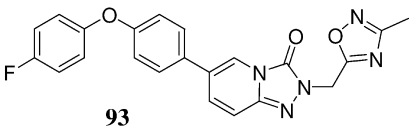

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Published: July 2, 2012

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dx.doi.org/10.1021/ml300158j | ACS Med. Chem. Lett. 2012, 3, 616–617

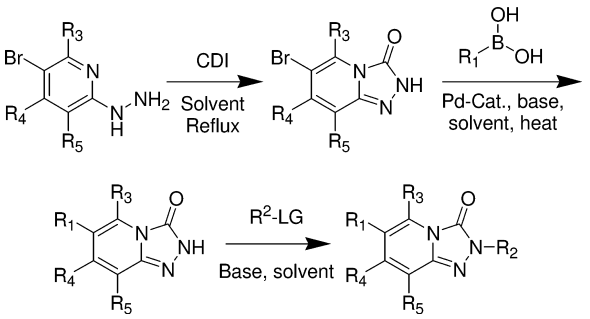
Recent Review Articles: Rook, M. B.; Evers, M. M.; Vos, M. A.; Bierhuizen, M. F. A. Biology of cardiac sodium channel $Na_v1.5$ expression. *Cardiovasc. Res.* **2012**, *93* (1), 12−23.

Biological Assay: Whole cell electrophysiological patch clamp (PatchXpress7000A MDS Analytical Technologies) using HEK293 cells expressing $hNa_v1.5$. Inhibition of $hNa_v1.5$ is reported as a percent inhibition at 1.0 μM.

Biological Data: Table 1: Exemplary $hNa_v1.5$ Inhibition Data

Example	% Inhibition @1.0 μM	Example	% Inhibition @1.0 μM
23	55.0%	93	71.2%
32	68.4%	120	73.9%
53	55.8%	140	60.6%

Synthesis:



Claims: The application claims the compounds of the disclosure and their use for the treatment of cardiovascular disease, diabetes, diabetic peripheral neuropathy, neuropathic pain, epilepsy, seizures, and paralysis.

Additional Information: The application provides methods for screening of compounds against the following additional ion channels: L-type calcium, $Na_v1.7$, $Na_v1.1$, and $Na_v1.2$.

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Notes

The authors declare no competing financial interest.