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Viewpoint

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Substituted Benzimidazole and Imidazopyridine Compounds Useful as Cyp17 Modulators

Patent Highlight

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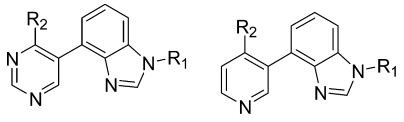
Title:	Substituted Benzimidazole and Imidazopyridine Compounds Useful as Cyp17 Modulators		
Application Number:	WO 2012044537	**Publication Date:**	April 5, 2012
Priority Application:	US 61388837	**Priority Date:**	January 10, 2010
Inventors:	Huang, Audris		
Assignee Company:	Bristol Myers Squibb Company, Princeton, New Jersey		
Disease Area:	Cancer	**Primary Target:**	Cyp17

Summary: Prostate cancer is a leading cause of cancer-related mortality. It has been previously established that androgens such as testosterone and dihydrotestosterone are intimately involved in prostate cancer progression. Androgen synthesis, in turn, is mediated by a series of cytochrome P450 (Cyp) enzymes, including Cyp17, which plays a key role in all androgen synthesis. Cyp17 inhibition would inhibit androgen synthesis and provide a treatment option for prostate cancer patients. This patent application describes a series of substituted benzimidazoles and imidazopyridines and their uses as Cyp17 inhibitors for the treatment of cancer.

Important Compound Classes:



Definitions:

R^1 is

(i) C_{1-6} alkyl substituted with 0−4 R^a;

(ii) C_{3-6} cycloalkyl substituted with 0−4 R^a;

(iii) $-S(O)_2(C_{1-4}$ alkyl), $-S(O)_2(C_{1-4}$ fluoroalkyl), or $-C(O)(C_{1-6}$ alkyl);

(iv) aryl substituted with 0−6 R^b;

(v) heterocyclyl substituted with 0−6 R^c; or

(vi) heteroaryl substituted with 0−6 R^c

R^2 is

(i) H, halo, −CN, $-OR^d$, $-NR^eR^e$, or $-C(0)OR^f$;

(ii) C_{1-6} alkyl substituted with 0−4 R^a;

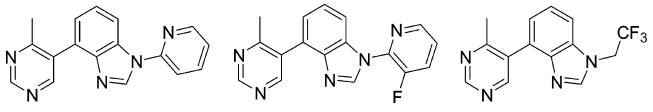
(iii) C_{3-6} cycloalkyl substituted with 0−4 R^a;

(iv) aryl substituted with 0−6 R^b;

(v) heterocyclyl substituted with 0−6 R^c; or

(vi) heteroaryl substituted with 0−6 R^c

Key Structures:



Recent Review Articles:

Vasaitis, T. S.; Bruno, R. D.; Njar, V. C. O. Cyp17 inhibitors for prostate cancer therapy. *J. Steroid Biochem. Mol. Biol.* **2011**, *125* (1−2), 23−31.

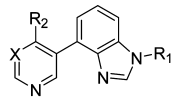
Yap, T. A.; Carden, C. P.; Attard, G.; de Bono, J. S. Targeting Cyp17: Established and novel approaches in prostate cancer. *Curr. Opin. Pharmacol.* **2008**, *8* (4), 449−457.

Biological Assay

Cyp17 Total SPA Assay employing stably transfected HEK2 cells and ^{3}H-pregnenolone.

Published: July 2, 2012

Biological Data



Cyp17 Total SPA Assay: Inhibition of Pregnenolone degradation by representative compounds of the disclosure

Entry	R^1	R^2	X	Cyp17 IC_{50} (nM)
1	2- Pyridyl	CH_3	CH	5.8
2	2-Pyrazine	CH_3	CH	37
3	2-Pyridazine	CH_3	CH	250
4	6-(trifluoromethyl)-2-pyridine	CH_3	CH	40
5	6-Fluoro-2-pyridine	CH_3	CH	11
6	3,5-Difluoro-2-pyridine	CH_3	CH	758
7	4-Pyrimidine	CH_3	CH	656
8	4- Pyridyl	CH_3	CH	405
9	CH_2CF_3	CH_3	CH	12
10	CH_2CN	CH_3	CH	330
11	cyc-Propyl	CH_3	CH	396
12	CH_2CF_3	Cl	CH	361
13	CH_2CF_3	NH_2	N	674
14	CH_2CF_3	OCH_2CH_3	N	135
15	2,4-Diflurophenyl	NH_2	N	797

AUTHOR INFORMATION

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Notes

The authors declare no competing financial interest.