The Last Decade of Deuterium in Drug Discovery and Development

D. G. Dennis, October19, 2018

Introduction

deuterium
kinetic isotope effect
deuterium in the universe
deuterium in drugs

Methods of D/H Exchange

acid / base reactions
heterogenous catalysis
homogeneous catalysis
non-exchange methods (misc.)

Reviews:

Angew. Chem. Int. Ed. **2018**, *57*, 3022; *J. Med. Chem.* **2011**, *54*, 2529; *Biochemistry* **2018**, *57*, *472*; *J. Med. Chem.* **2014**, *57*, 3595; *Med. Chem. News* **2014**, *2*, 8.

Examples

telaprivir
tramadol
deutetrabenazine
apalutamide
plinabulin
BMT-052
paroxetine

Conclusion

deuterium:

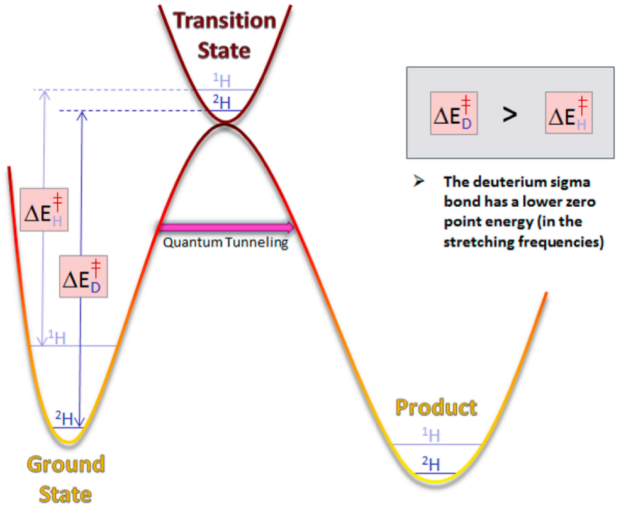
A Hydrogen Isotope of Mass 2

The proton-electron plot of known atomic nuclei shows some rather marked regularities among atoms of lower atomic number.[1] Up with well-established experimental evidence. We find that the vapor pressures for these three molecules in equilibrium with their sol-

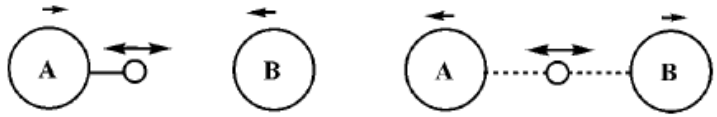
Deuterium was first discovered by Harold Urey in 1931, about a year before the identification of the neutron.

symbol		*name*	*natural abundance*	*stability*	*physical properties of $^{x}H_2O$*
$^{1}_{1}$H	H	Hydrogen	99.98%	stable	mp = 0 °C bp = 100 °C d = 1.000 g/cm^3
$^{2}_{1}$H	D	Deuterium	0.0156%	stable	mp = 3.79 °C bp = 101.4 °C d = 1.105 g/cm^3
$^{3}_{1}$H	T	Tritium	trace	radioactive, β-decay $T_{1/2}$ = 12.3 years	mp = 4.49 °C bp = 101.5 °C d = 1.215 g/cm^3

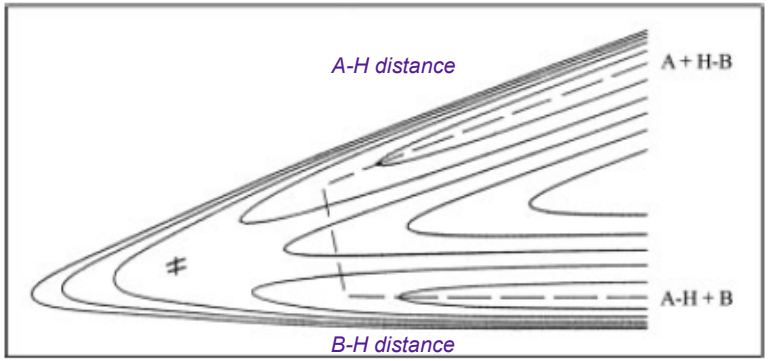
kinetic isotope effect (KIE):



Standard explanation for the KIE is due to the differing zero point energies of the isotopic nuclei.

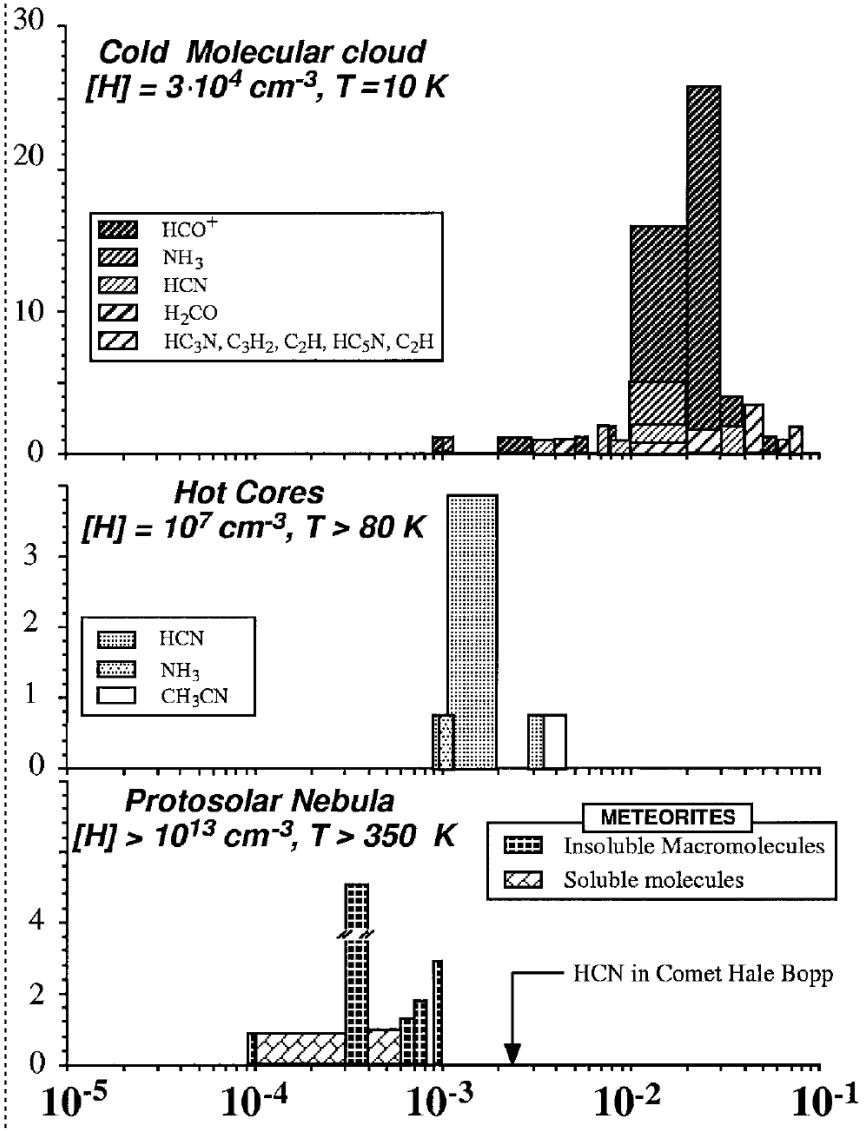


The bond which is present in the transition state, and which contributes to its zero-point energy is one which does not exist in either the reactants or the products; it is a vibration peculiar to the activated complex.



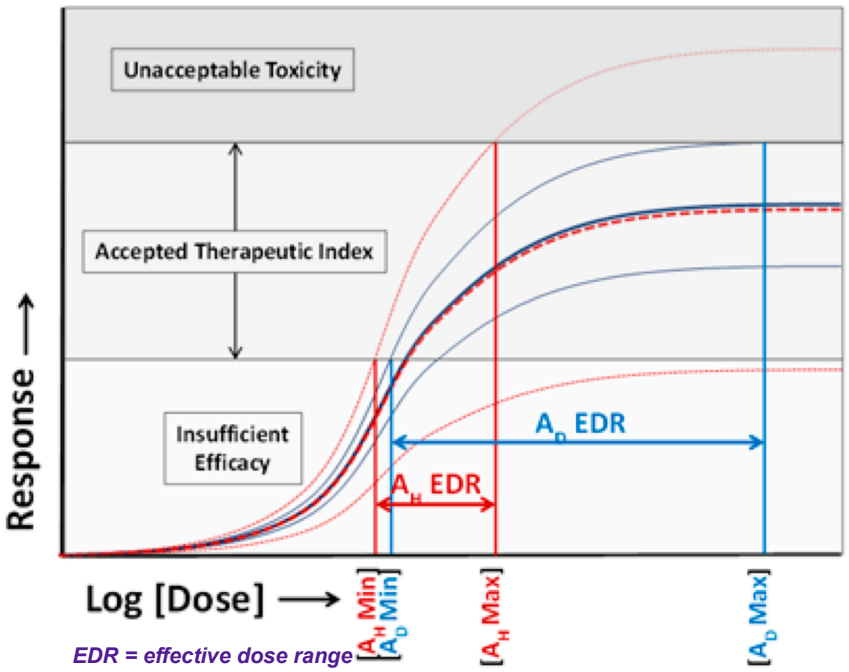
Deuterium Occurrence and Use

D/H ratios in organic species outside the solar system



"The prevalence of deuterium appears to be fairly consistent throughout the universe, the majority of the universe extending far beyond the influence of the pharmaceutical industry." - Thomas Gant

"...we are certain that expression levels of CYP3A4 can vary tremendously, within even one individual over time and not merely between individuals. This way of viewing the world of metabolism causes all oxidative clearance mechanisms to become opportunities for reducing variability of response." -Thomas Gant



EDR = effective dose range

Targets for deuterium incorperation:

decreasing racial and gender differences in drug efficacy and toxicity

reducing interpatient variability

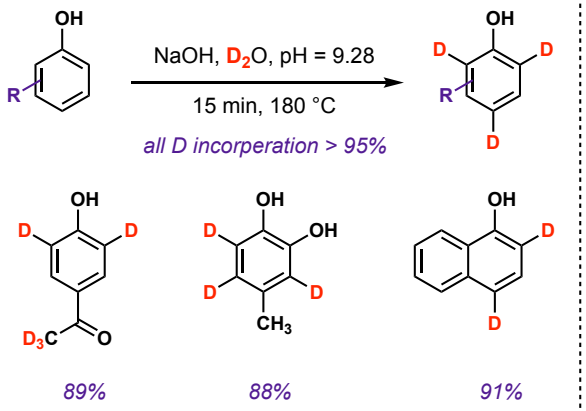
reduction of unwanted metabolites may lead to direct reduction of adverse events (AE's)

reducing genotoxicity

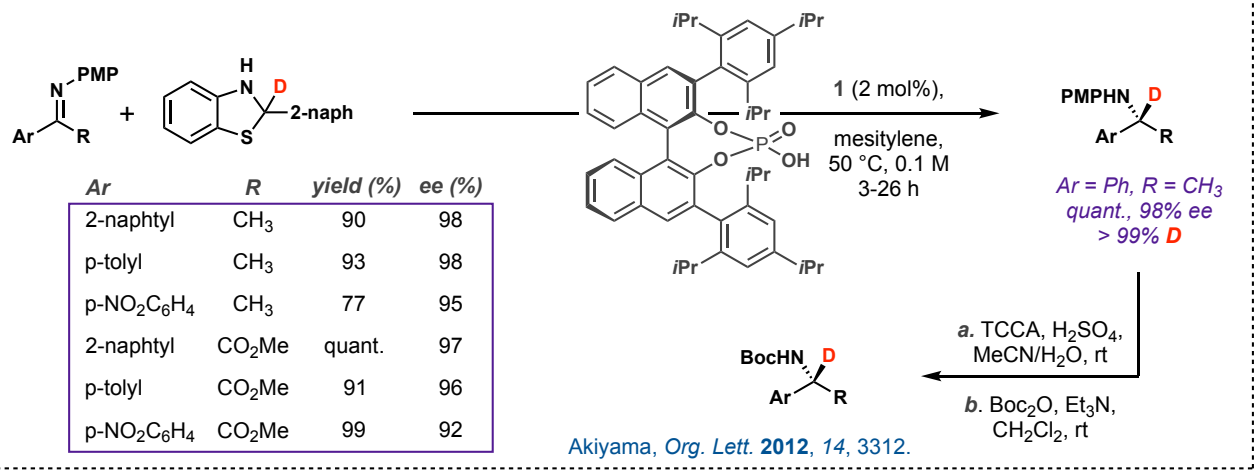
Space Sci. Rev. **2000**, *92*, 201.

Gant, *J. Med. Chem.* **2014**, 57, 3595.,

Acid / Base Mediated H / D Exhange

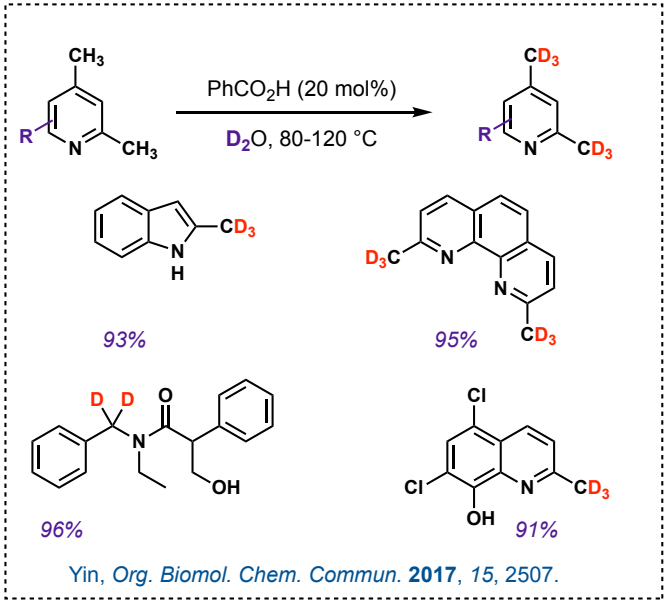


Xie and Chen, *Eur. J. Org. Chem.* **2015**, 3370.

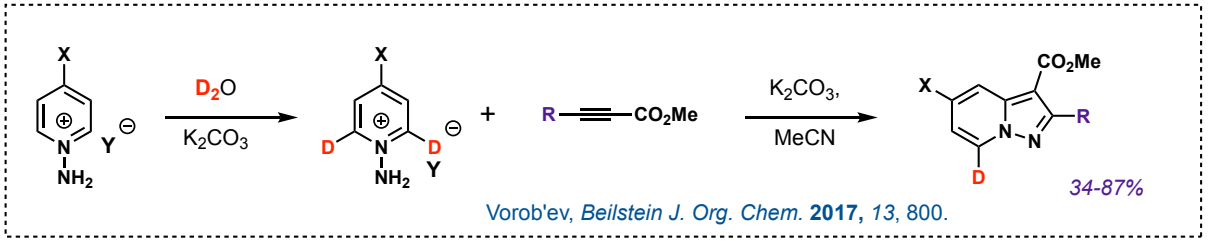


Ar	R	yield (%)	ee (%)
2-naphtyl	CH_3	90	98
p-tolyl	CH_3	93	98
p-$NO_2C_6H_4$	CH_3	77	95
2-naphtyl	CO_2Me	quant.	97
p-tolyl	CO_2Me	91	96
p-$NO_2C_6H_4$	CO_2Me	99	92

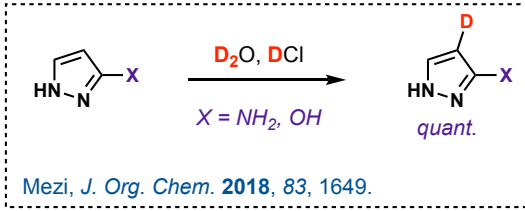
Akiyama, *Org. Lett.* **2012**, *14*, 3312.



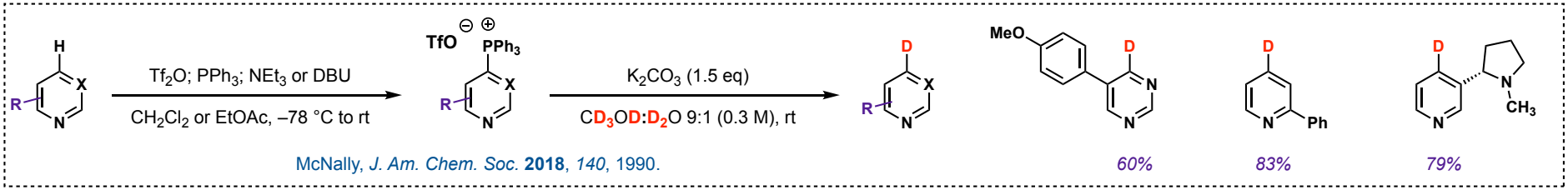
Yin, *Org. Biomol. Chem. Commun.* **2017**, *15*, 2507.



Vorob'ev, *Beilstein J. Org. Chem.* **2017**, *13*, 800.

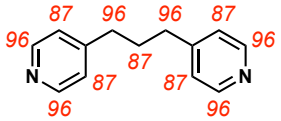
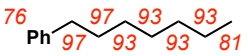
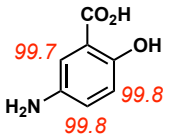
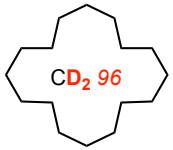
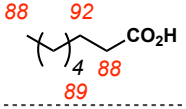
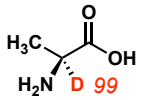
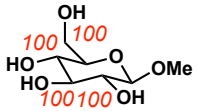
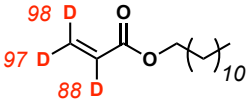


Mezi, *J. Org. Chem.* **2018**, *83*, 1649.

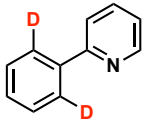
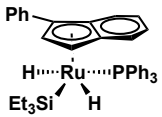
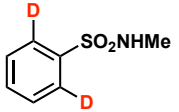
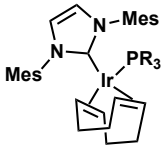
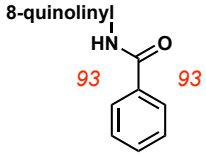
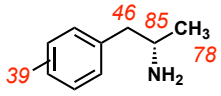
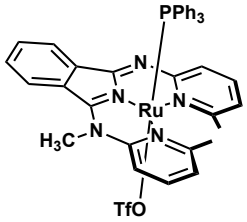
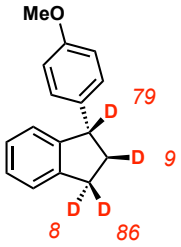
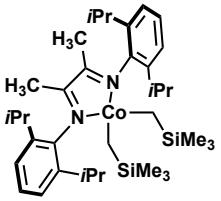
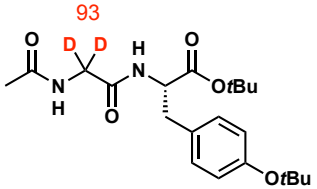
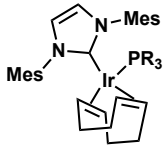


McNally, *J. Am. Chem. Soc.* **2018**, *140*, 1990.

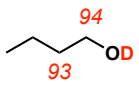
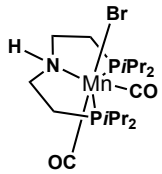
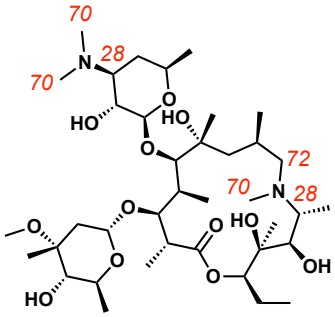
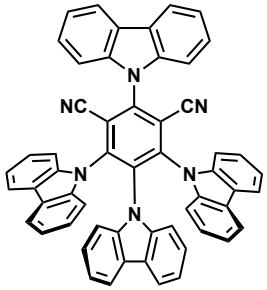
H / D Exhange by Heterogeneous Catalysis

gereralization	example product(s)	conditions	method summary	reference
Sp^2 and Sp^3 C-H / C-D exchange		Pd/C (10 mol%), H_2, D_2O, 24 h, 110-180 °C	*36 examples, 80-99% yield*	Sajiki, *Tetrahedron* **2006**, *62*, 10954.
		Pd/C (10 mol%), H_2, D_2O 110-160 °C, 24 h	*18 examples, 51-100% yield*	Sajki, *Chem. Eur. J.* **2007,** *13*, 4052.
		[Pd/C+Pt/C] (10 mol% each), H_2, D_2O, 24 h, 145 °C	*6 examples, 90-96% yield*	Shah, *Tet. Lett.* **2015**, *56*, 1211.
		Rh/C+Pt/C (15 mol% each) *i*PrO**D-d_8** / D_2O 120 °C, 24 h	*9 examples, 69-100% yield*	Sajki, *RSC Adv.* **2015**, 13727.
		Pt/C (8 mol%) iPrOH/D_2O 120 °C, 24 h	*11 examples, 95-100% yield*	Sajki, *Adv. Synth. Catal.* **2016,** *358*, 3277.
Sp^3 α–heteroatom C-H / C-D exchange		Ru/ACC, 22.2 A/m^2 D_2O, 60 °C, 2-15 h	*17 examples, 16-87% yield*	Jackson, *Eur. J. Org. Chem.* **2016**, 4230.
		Ru/C (10 mol%), NaOH, D_2O, H_2 70-90 °C, 12 h	*12 examples, 90-96% yield*	Roche, *Org. Process. Res. Dev.* **2017**, 1741.
		Ru/C (10 mol%), H_2, D_2O, 24 h, 80 °C	*11 examples, 96-100% yield*	Sajiki, *Chem. Pharm. Bull.* **2018**, *66*, 21.
Sp^2 C-H / C-D exchange		Pt/C (10 mol%), hydroquinone (10 mol%) *i*PrOH/D_2O, 120 °C, 24 h	*13 examples, 30-91% yield*	Sajki, *Adv. Synth. Catal.* **2018,** *360*, 2303.

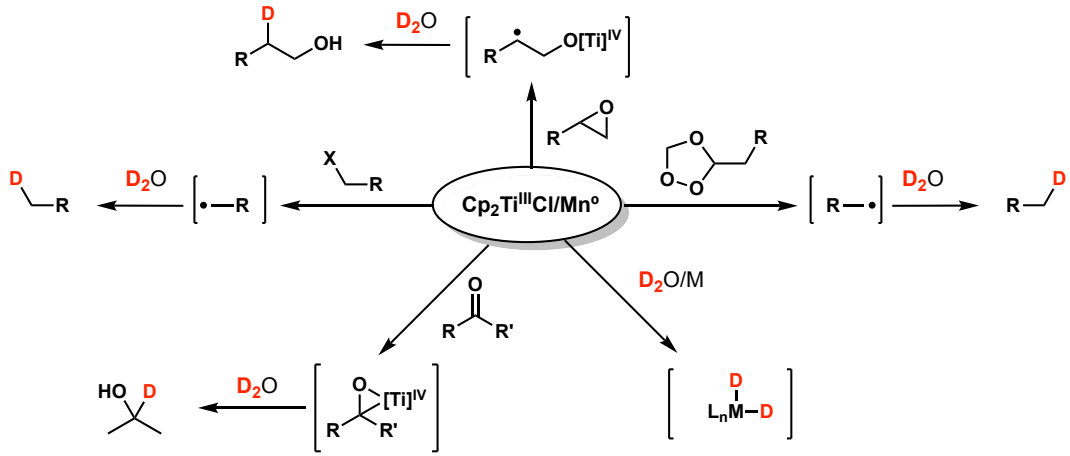
H / D Exhange by Homogeneous Catalysis

	example product	catalyst	conditions	method summary	reference
aryl C–H/C–D exchange			*catalyst* (2 mol%), D_2O 110 °C, 16 h	*9 examples* *50-100% yield*	Nolan, *Org. Biomol. Chem.* **2014**, *12*, 8683.
			catalyst (10 mol%) PhCl, D_2, 120 °C, 1 h	*25 examples* *70-96% yield*	Derdau and Atzrodt, *Eur. J. Org. Chem.* **2017**, 1418.
		Pd(OAc)$_2$	D_2O, 140 °C, 48 h	*8 aromatic examples* *8 aliphatic examples* *80-99% yield*	Yu, *J. Org. Chem.* **2018,** *83,* 7860.
aliphatic C–H/C–D exchange			*catalyst* (2 mol%), D_2O MeTHF, 110 °C, 20 h	*14 examples* *38-78% yield* ***enantioretentive***	Szymczak, *J. Am. Chem. Soc.* **2016**, *138*, 13489.
			*catalyst* (10 mol%), D_2 heptane or dodecane 50 °C, 24 h	*27 examples* *23-90% yield* ***enantioretentive***	Chirik, *ACS Catal.* **2017**, 7, 5674.
			*catalyst* (10 mol%), D_2 isopropyl acetate 80 °C, 8 h	*28 examples* *up to 99%*	Derdau and Atzrodt, *Angew. Chem. Int. Ed.* **2018**, *57*, 8159.

H / D Exhange by Homogeneous Catalysis

example product	catalyst	conditions	method summary	reference
aliphatic C–H/C–D exchange 		catalyst (1 mol%), NaOH (5 mol%), D_2O, 120 °C, 12 h	*12 examples* *89-94% yield*	Prakash *Green Chem.* **2018**, *20*, 2706
		*catalyst* (2 mol%), iPr_3SiSH (30 mol%) D_2O (50 eq), NMP, rt blue LED, 24 h; HCl	*12 examples* *59-88% yield*	MacMillan *Science*, **2017**, *358*, 1182.

Cp_2TiCl/Mn



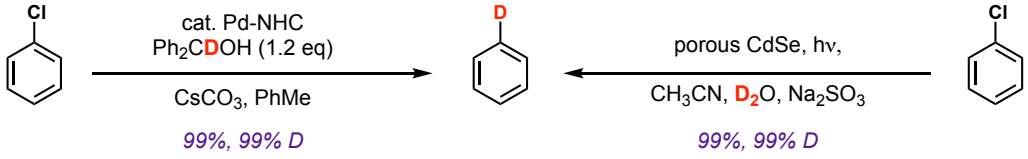
11 examples
30-98% yield

Rosales,
Beilstein J. Org. Chem.
2016, *12*, 1585.

minireview

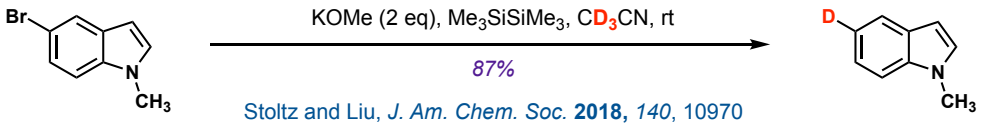
D incorporation by Miscellaneous Means

from aryl halides:



99%, 99% D — *99%, 99% D*

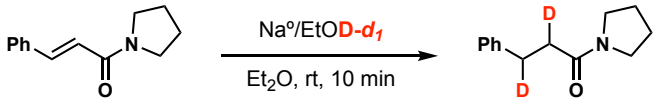
Kuriyama, *J. Org. Chem.* **2016**, *81*, 8934 — Zhang, *Angew. Chem. Int. Ed.* **2018**, *57*, 5590.



87%

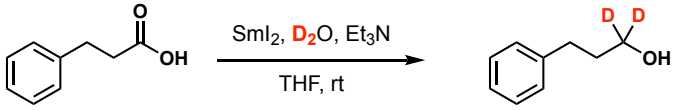
Stoltz and Liu, *J. Am. Chem. Soc.* **2018,** *140*, 10970

***via* reduction:**



81%

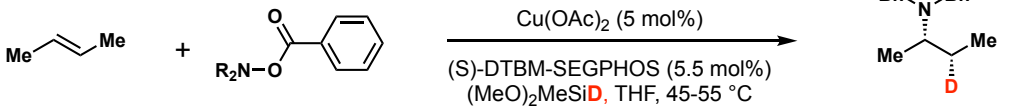
An, *Tet. Lett.* **2017**, *58*, 2757.; *Org. Lett.* **2018**, *20*, 3010.



94%, 91.5% D

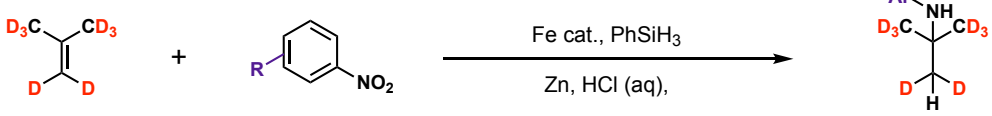
Procter, *Org. Lett.* **2014,** *16*, 5052.

from unactivated alkenes:



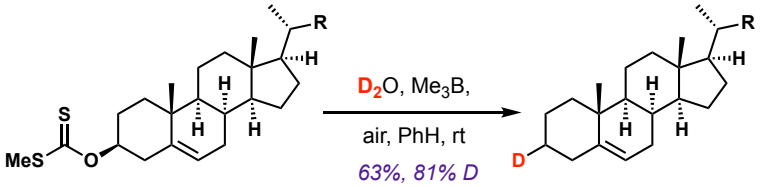
Buchwald, *Science* **2015,** *349*, 6243., *J. Am. Chem. Soc.* **2014**, *136*, 15913.

38%
dr > 95:5 98% ee



Baran, *Science* **2015**, *248*, 6237.

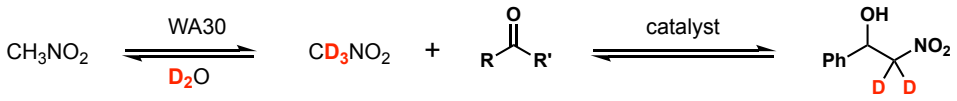
27%



63%, 81% D

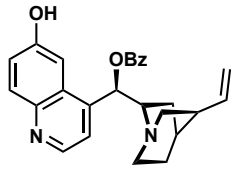
Renaud, *J. Am. Chem. Soc.* **2018**, *140*, 155.

organocatalysis:

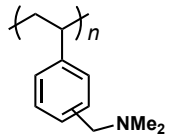


90%

Sajiki, *Adv. Synth. Catal.* **2018,** *360*, 637.



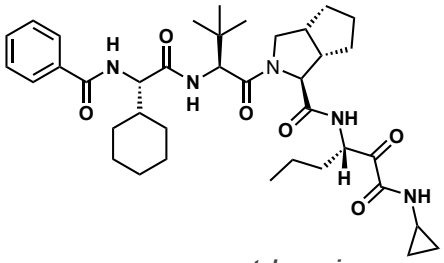
quinine derivative catalyst



WA30 (basic resin)

Telaprevir

background:

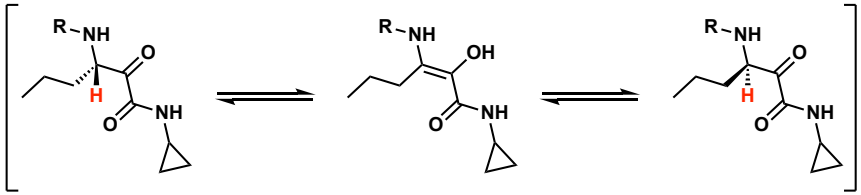


telaprevir

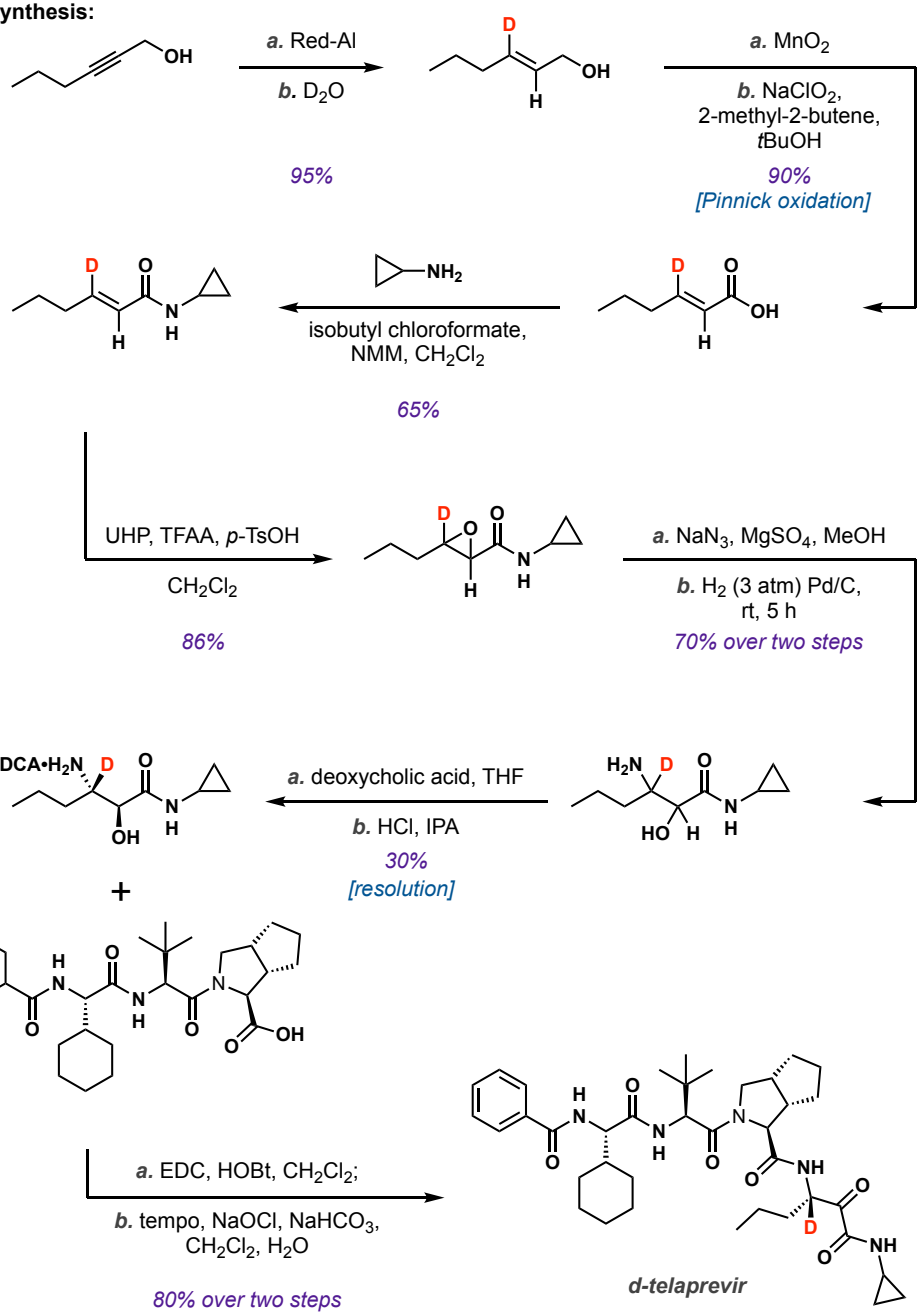
Johnson & Johnson

originally developed by Johnson & Johnson and Vertex for the treatment of hepatitis C. Deuterium studies conducted by Vertex and Sirtris, a GSK company.

VERTEX



synthesis:

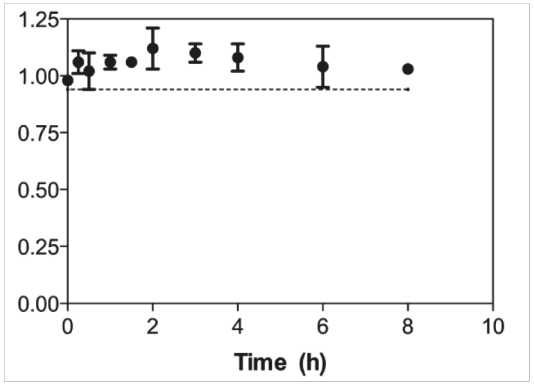


biological studies:

effect of plasma on the epimerization of d-telaprevir and telaprevir

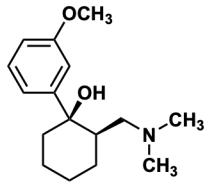
medium	relative rate[a]	kinetic isotope effect[b] (k_H/k_D) @ 1 μM	kinetic isotope effect[b] (k_H/k_D) @ 10 μM
buffer (pH 7.4)	1	5	6
rat plasma	1.0 – 1.5	7	7
dog plasma	1.4 – 3.4	4	6
human plasma	> 8	> 5	> 5

ratio of d-telaprevir to telaprevir in blood samples after administering a 10mg/kg dose of 50:50 d-telaprevir:telaprevir to six Sprague–Dawley rats



Tramadol

background:



tramadol (Ultram®)

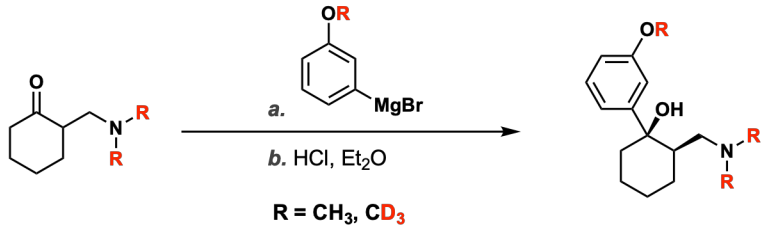
opiod pain medication used for moderate to moderately severe pain

metabolite 1 (M_1) believed to be responsible for opiod-like side effects

first launched in 1977 by Grunenthal

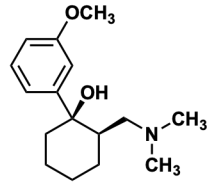
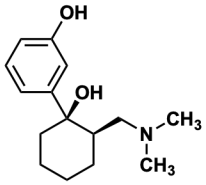
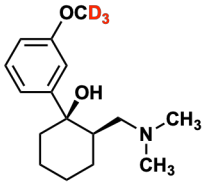
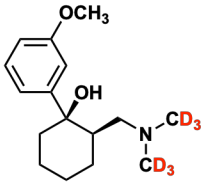
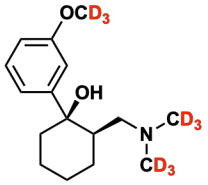
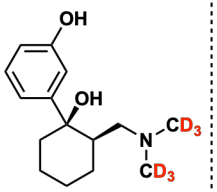
higher incidence of nausea, dizziness, and loss of appetite thought to deter it's recreational use

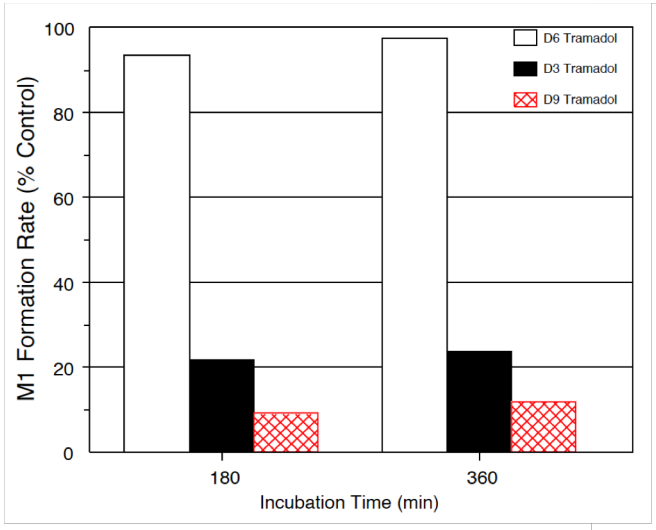
synthesis:

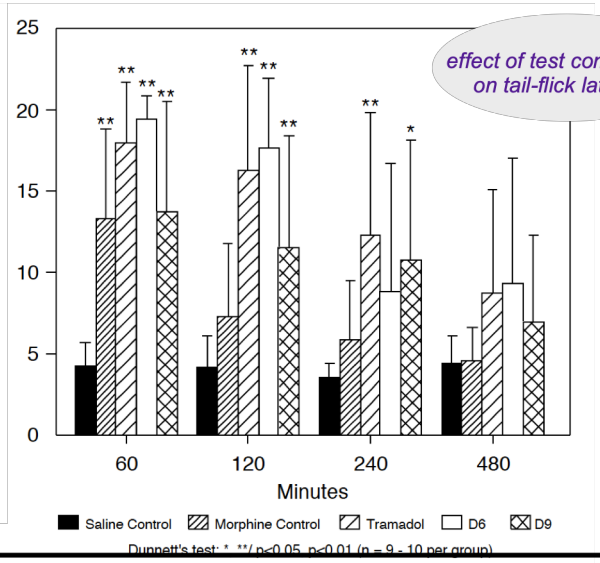


biological evaluation:

μ = μ-opiod receptors, 5-HT = 5-hydroxytryptamine, NE = norepinephrine

IC_{50} (nM)	*tramadol*	*metabolite 1 (M_1)*	*D_3*	*D_6*	*D_9*	*M_1 (D_6)*
						
μ	7600	47	>10,000	>10,000	5300	43
5-HT	4300	4600	1900	3100	1100	9900
NE	790	>10,000	3600	3200	2000	6700





effect of test compounds on tail-flick latency:

Tramadol: The Opioid Crisis for the Rest of the World

An addictive synthetic painkiller that some studies say is as powerful as morphine remains unregulated on the recommendation of the World Health Organization, helping spread abuse and addiction in the developing world

By Justin Scheck Updated Oct. 19, 2016 11:59 p.m. ET

Hussein, 28 years old, quit taking tramadol himself after his older brother died of an overdose. "My body was broken," he says.

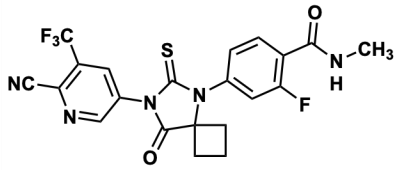
Mackenzie Knowles-Coursin for The Wall Street Journal

https://www.wsj.com/articles/tramadol-the-opioid-crisis-for-the-rest-of-the-world-1476887401

Bioorg. Med. Chem. Lett. **2006**, *16*, 691.

Apalutamide

background:

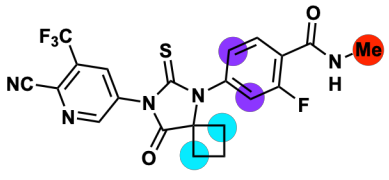


apalutamide

treatment for prostate cancer by AR antagonism- inhibiting gene transcription overexpressing prostate cancer cells

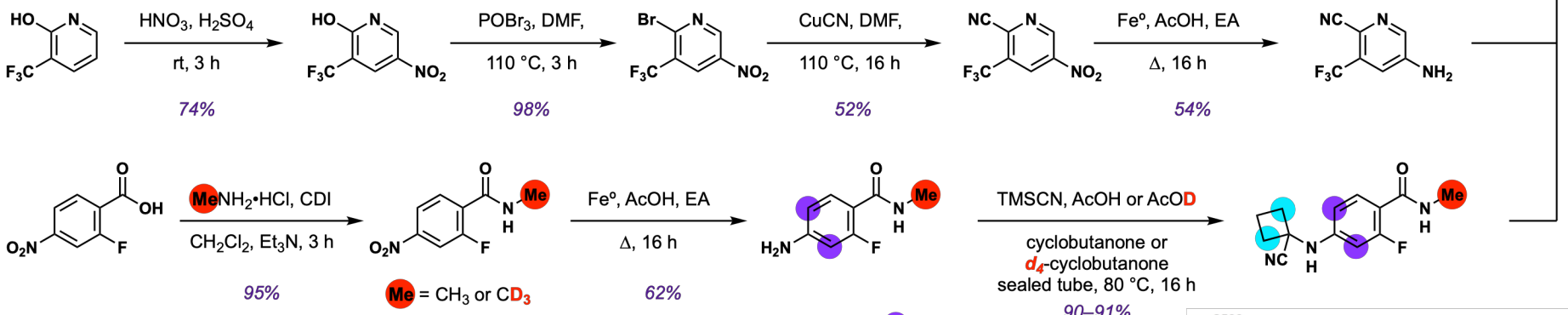
specifically used in conjuction with castration in the treatment of non-metastic castration-resist prostate cancer

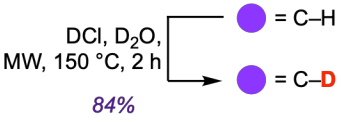
side effects: fatigue, nausea, abdominal pain, hypertension, bone fractures, underactive thyroid, and seizures



apalutamide-d_n (A-D

synthesis:





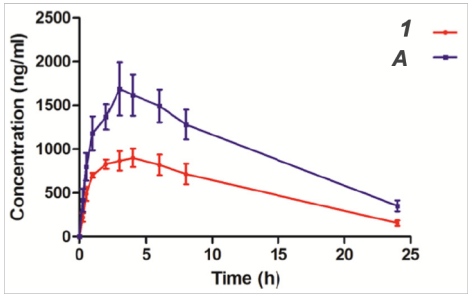
Erleada™ (apalutamide) 60 mg tablets

trade name of apalutamide, discovered by Janssen in 2007 and approved in 2018

janssen

PHARMACEUTICAL COMPANIES OF Johnson & Johnson

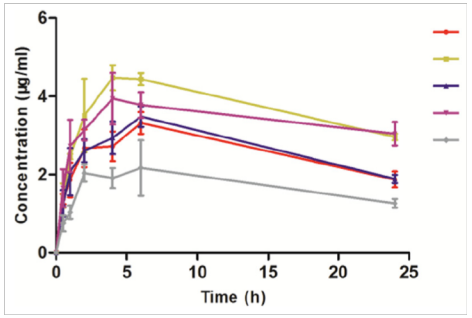
competition study between 1 and A, 10 mg/kg orally administered to Sprague-Dawley rats



PK studies:

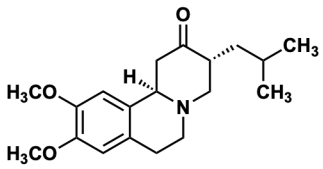
pharmacokenetic profiles of compounds 1-D after a 10 mg/kg oral dose in Balb/c mice.

compound	●	●	●	T_{max} (h)	C_{max} (μg/ml)	$AUC_{0\text{-}24\ h}$ (h•μg/ml)	$T_{1/2}$ (h)
apalutamide (1)	CH_3	H	H	6	3.32	61.56	5.9
A	CD_3	H	H	4	4.48	87.84	32.3
B	CH_3	H	D	6	3.48	63.79	6.6
C	CD_3	H	D	4	3.94	80.62	54.9
D	CH_3	D	H	6	2.17	41.08	32.3

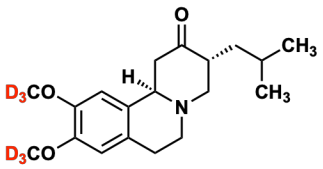


Deutetrabenazine

background:



tetrabenazine



deu *do®)*

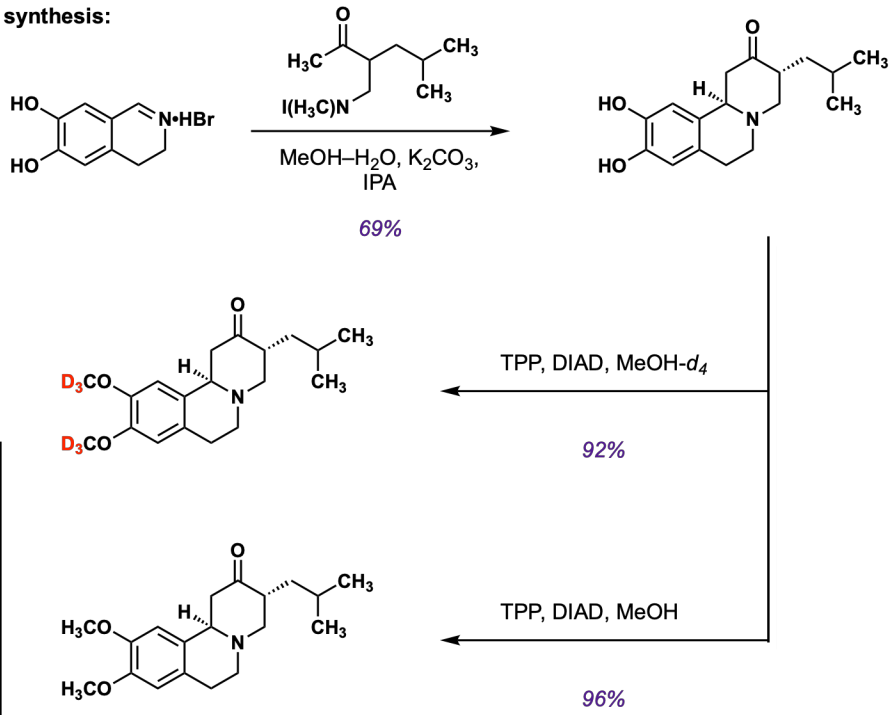
used for the treatment of hyperkinetic movement disorders

approved for the treatment of chorea associated with huntington's disease in 2008

AUSPEX PHARMACEUTICALS

teva Pharmaceutical Industries Ltd.

synthesis:



indirect tolerability comparison:

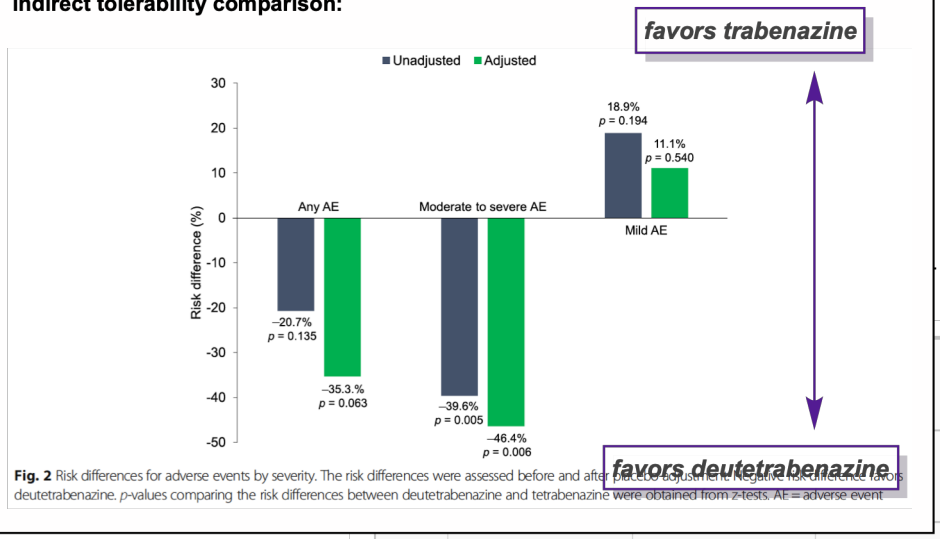


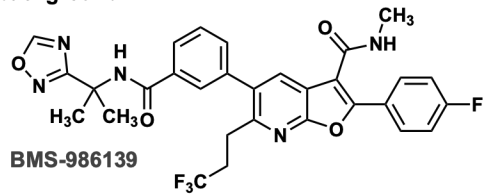
Fig. 2 Risk differences for adverse events by severity. The risk differences were assessed before and after placebo adjustment. Negative risk difference favors deutetrabenazine. *p*-values comparing the risk differences between deutetrabenazine and tetrabenazine were obtained from *z*-tests. AE = adverse event

Auspex Pharma stock prices
March 2014 - May 2015
amigobulls.com

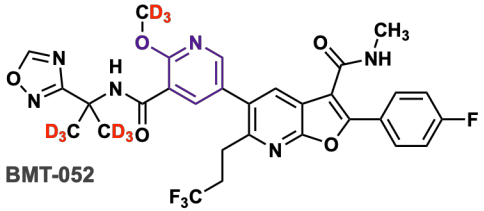
Background and Clinical Data: J. of Clin. Movement Dis. **2017,** *4,* 3. **Synthesis:** *Org. Process Res. Dev.* **2018**, *22*, 520.

BMT-052

background:



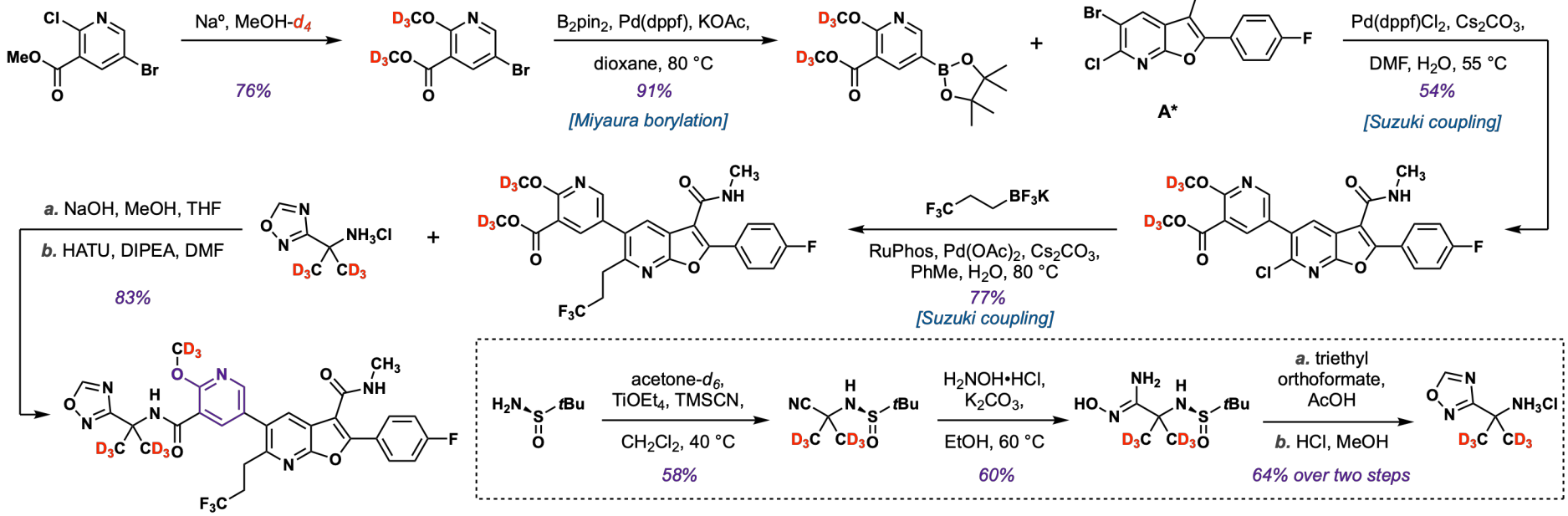
iterative
SAR studies



Bristol-Myers Squibb
Together we can prevail.

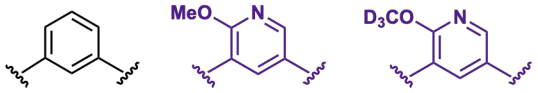
development of a treatment for the hepatitis C virus (HCV)

synthesis:



SAR studies:

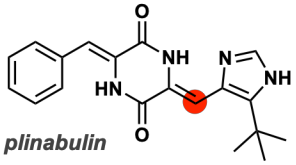
increased solubility



EC_{50} (nM) GT 1a HS	52	33	34	**EC_{50} (nM) GT 1a HS**	23	33	31
CC_{50} (mM)	51	>100	76	**CC_{50} (mM)**	>100	>100	>100
$t_{1/2}$ (min)	>120	14	24	**$t_{1/2}$ (min)**	26	33	31

Plinabulin

background:



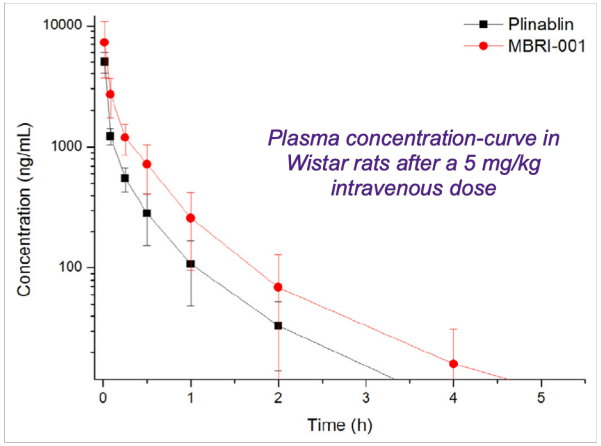
In development by BeyondSpring Pharmaceuticals

In phase III clinical trials for non-small cell lung cancer

compound		IC$_{50}$ (μM)				
		CYP1A2	CYP2C9	CYP2C19	CYP2D6	CYP3A4-M
plinabulin	C–H	1.24	0.53	4.23	>50	>50
MBRI-001	C–D	1.02	0.56	3.81	18.4	>50

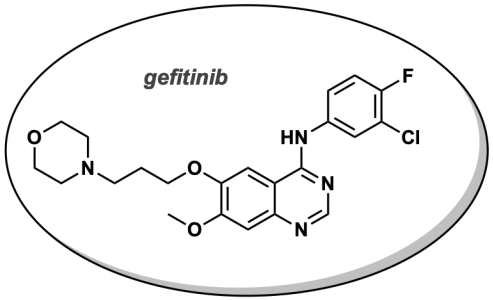
CYP's enzymes inhibitory activity evaluation of plinabulin and MBRI-001 in human liver microsomes

biological evaluation:



Plasma concentration-curve in Wistar rats after a 5 mg/kg intravenous dose

Antitumor activity against NCI-H460 in nude mice xenograft models reveals combinatory strategy with gefitinib to be better than treatment with MBRI-001 and gefitinib alone



control

MBRI-001 3 mg/kg

MBRI-001 6 mg/kg

MBRI-001 9 mg/kg

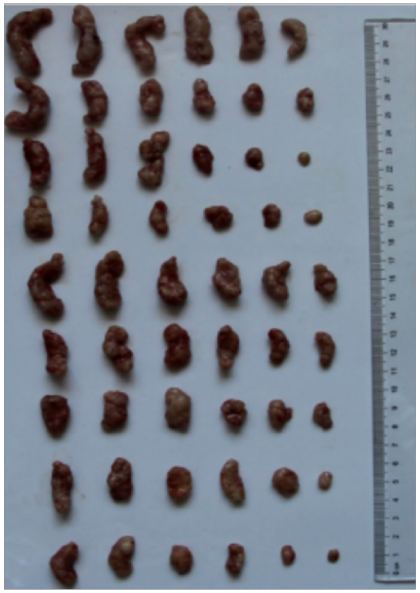
gefitinib 25 mg/kg

gefitinib 50 mg/kg

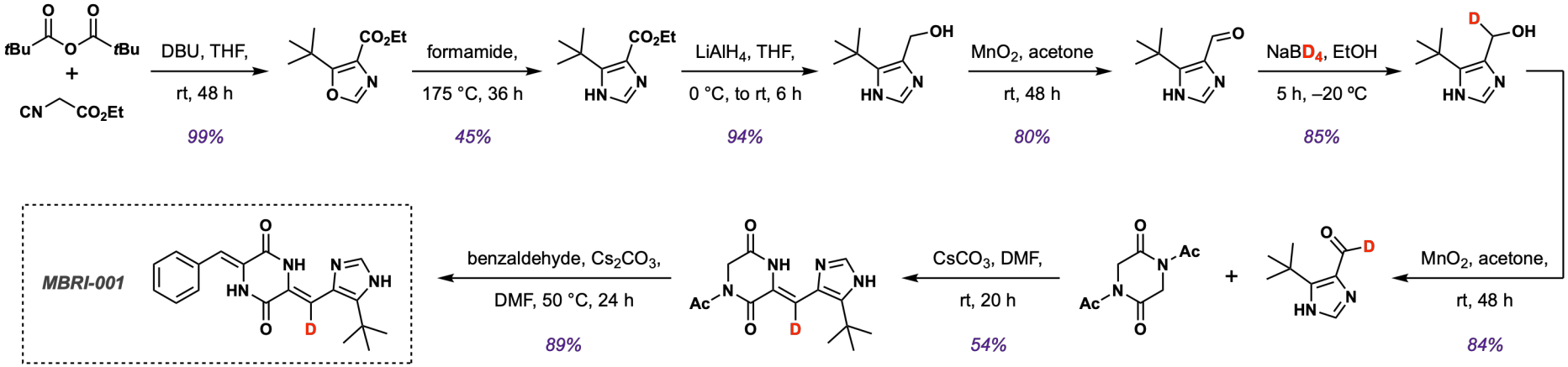
gefitinib 100 mg/kg

MBRI-001 3 mg/kg + gefitinib 25 mg/kg

MBRI-001 6 mg/kg + gefitinib 50 mg/kg



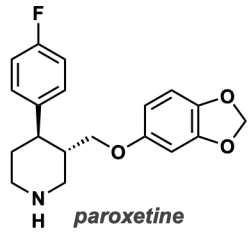
synthesis:



Bioorg. Med. Chem. Lett. **2017**, *27*,**1416**.; *Bioorg. Med. Chem.* **2018,** *26*, 4687.

Paroxetine

background:

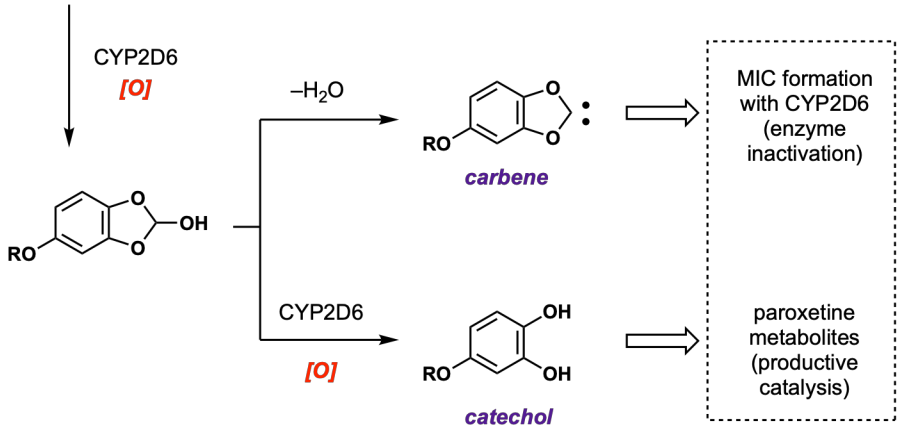


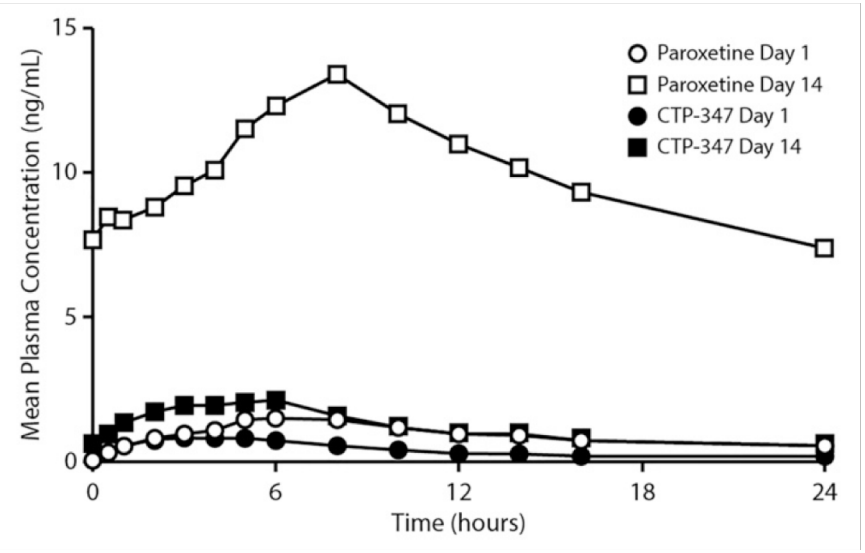
paroxetine

SSRI (selective serotonin reuptake inhibitor) used to treat depression, anxiety disorders, obsessive-compulsive disorder, and premenstrual dysphoric disorder.

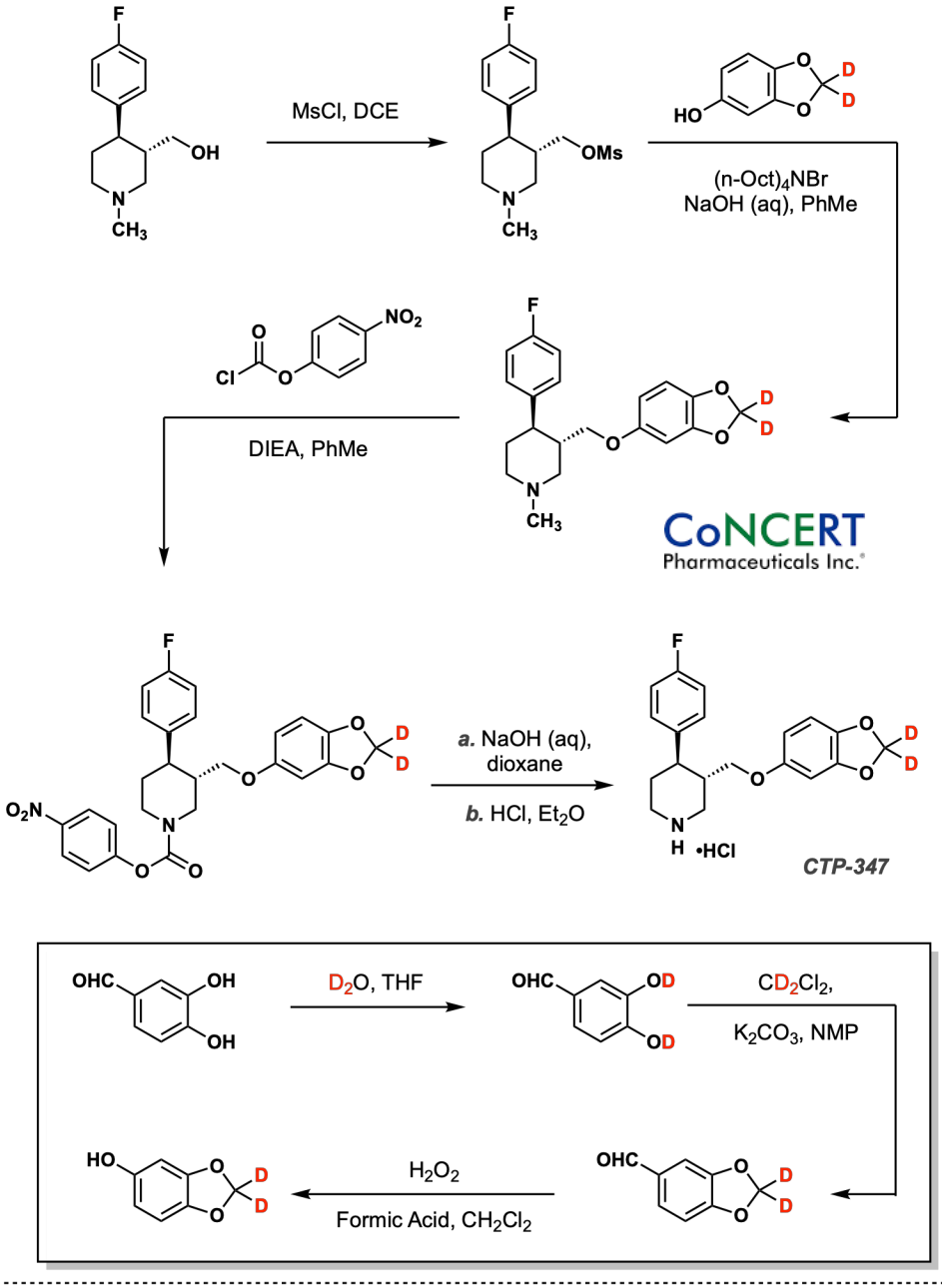
First brought to market by SmithKline Beecham, now GlaxoSmithKline

Drawbacks: many common side-effects and withdrawl symptoms

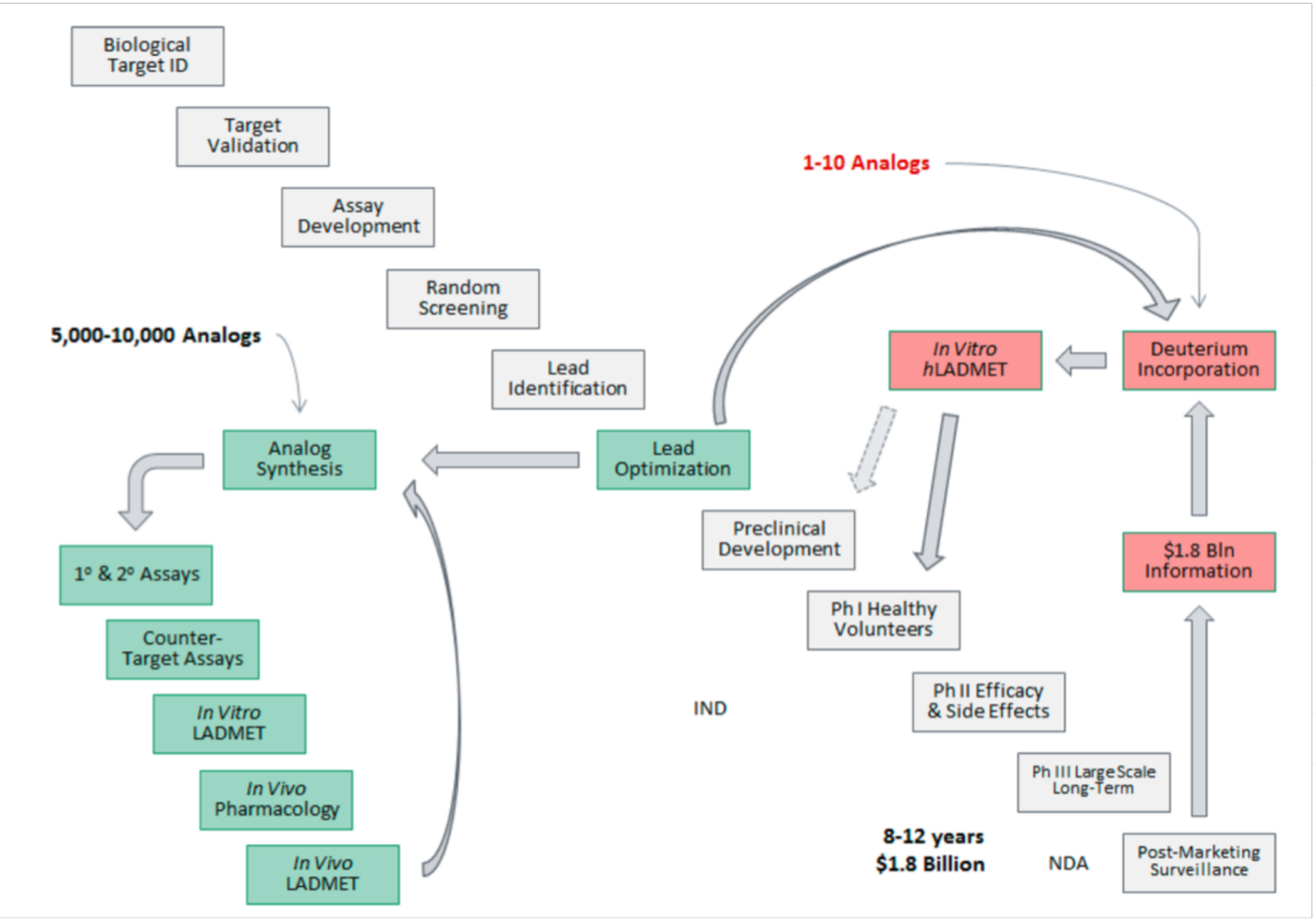




synthesis:



Conclusion



"The chemical properties of two isotopes are in general very similar... The differences in physical and chemical properties of... compounds of hydrogen and deuterium are much greater than in teh case of any other two isotopes which have been investigated thus far.... The velocities of chemical reactions in which deuterium replaces hydrogen differ more markedly than do the equilibrium properties. Hydrogen reacts with chlorine 13.4 times more rapidly at 0 ºC than deuterium, and similar differences are observed in the case of other chemical reactions... perhaps more interesting than the gross effects of life and death of living organisms in deuterium oxide can be secured by using deuterium as an indicator in the study of metabolic processes within living things. It often is of interest to trace a variety of atoms or compounds through living organisms. Deuterium makes possible such studies for if given to an animal in its food the particular compounds of the food can again be identified in teh excretory products, in the blood, in teh fat deposits of the body, or other tissues, and hence the course of the foods through the animal body can be traced. Studies of this kind will probably prove to be among the most interesting applications of deuterium" -Harold Urey, 1936