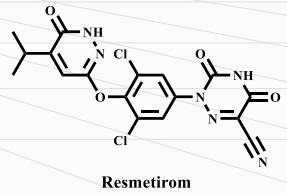
Resmetirom: the first drug for treatment of nonalcoholic steatohepatitis (NASH)

Zhang Guoqi

2025.01.18



Resmetirom

Contents

1. Introduction

1.1 Definition

NAFLD: Nonalcoholic fatty liver disease. (**MASLD**: metabolic dysfunction-associated steatotic liver disease)

NAFL: nonalcoholic fatty liver. (**MASL**: metabolic dysfunction-associated steatotic liver)

NASH: nonalcoholic steatohepatitis. (**MASH**: metabolic dysfunction-associated steatohepatitis)

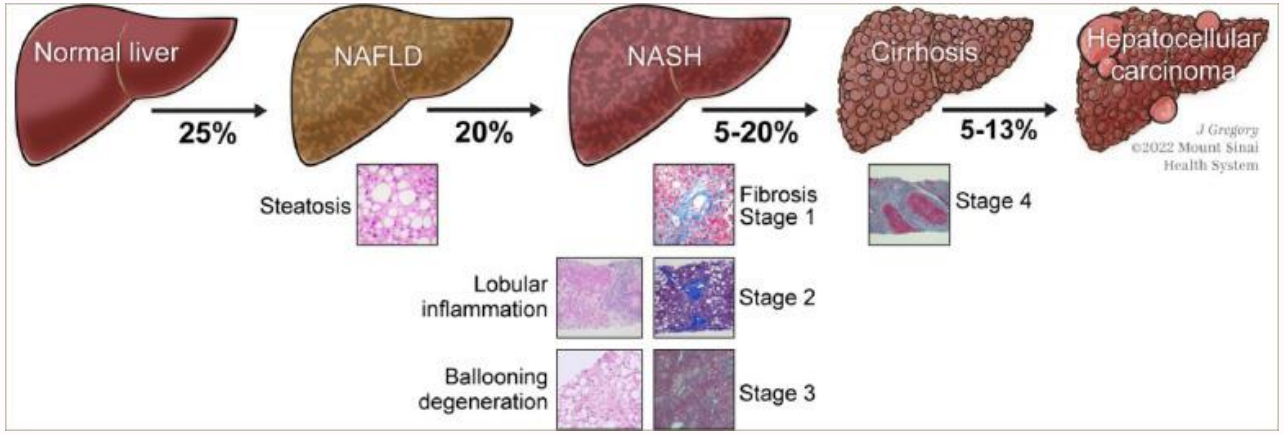


Figure 1. Schematic of the progression of non-alcoholic fatty liver disease to cirrhosis and hepatocellular carcinoma.

1.2 Challenges

(1) Up to 10% of hypercholesterolemic patients do not tolerate statins, and roughly 70% of high risk cardiovascular patients do not achieve low density lipoprotein cholesterin (LDL-C) goals.

(2) Diabetes can cause a particular form of dyslipidemia, characterized by elevated triglycerides (TG), low HDL cholesterol (HDL-C), and nonalcoholic fatty liver disease (NAFLD).

(3) As of February 2024, there are no drugs for the treatment of NASH.

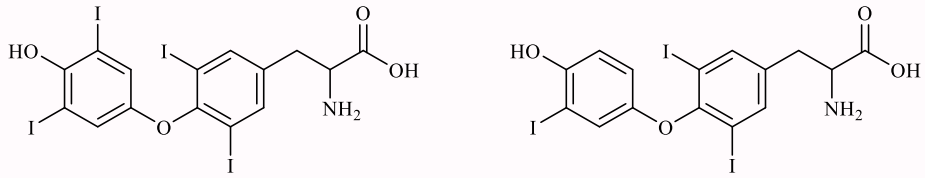


Figure 2. The structures of **T4** and **T3**.

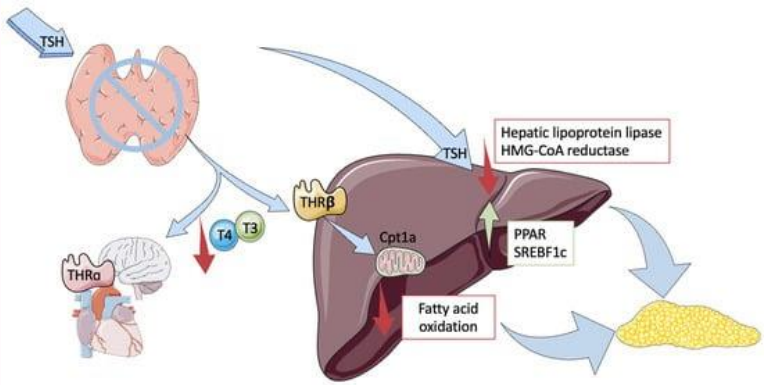


Figure 3. The physiological relationship between the thyroid and liver.

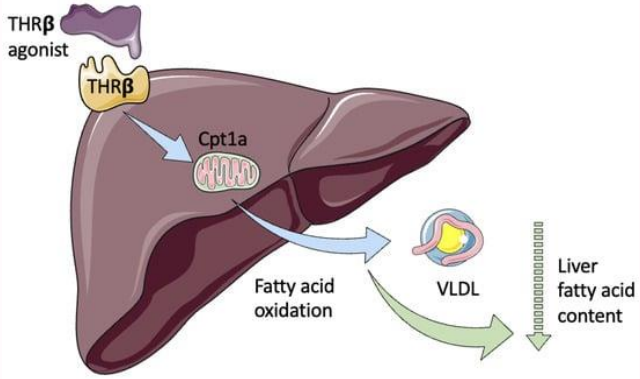


Figure 4. Effect of THR-β agonists in fatty liver content.

1.2 Challenges

(4) The ligand binding domains of the THR-α and -β receptors differ by only a single amino acid, Ser277 (THR-α)/Asn331 (THR-β).

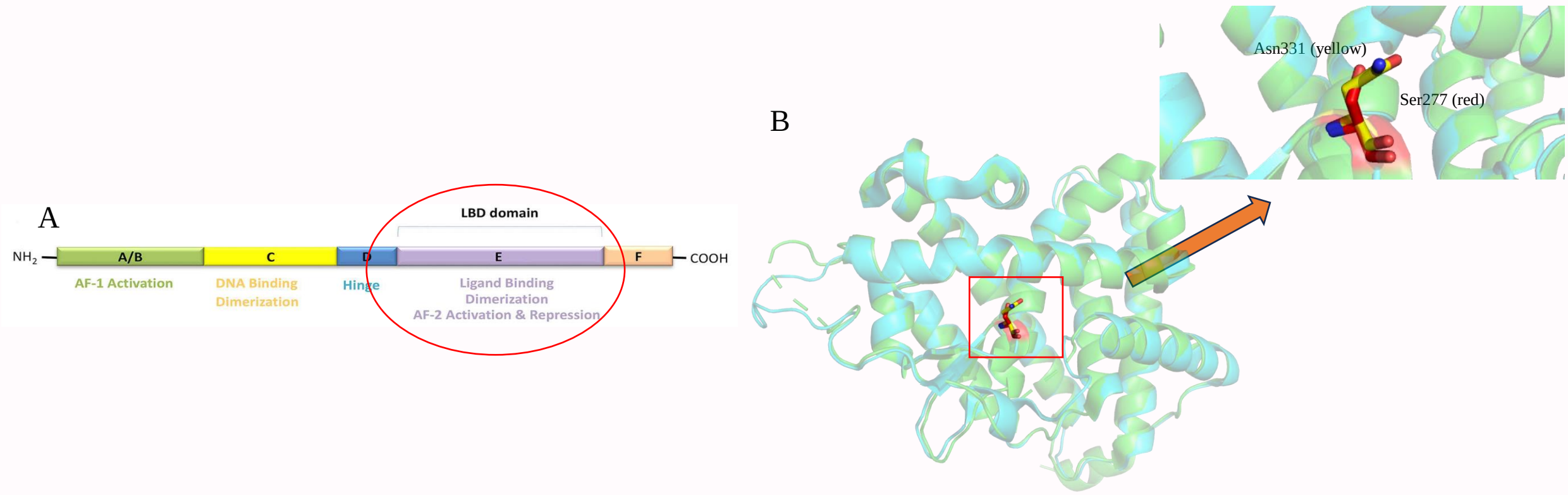
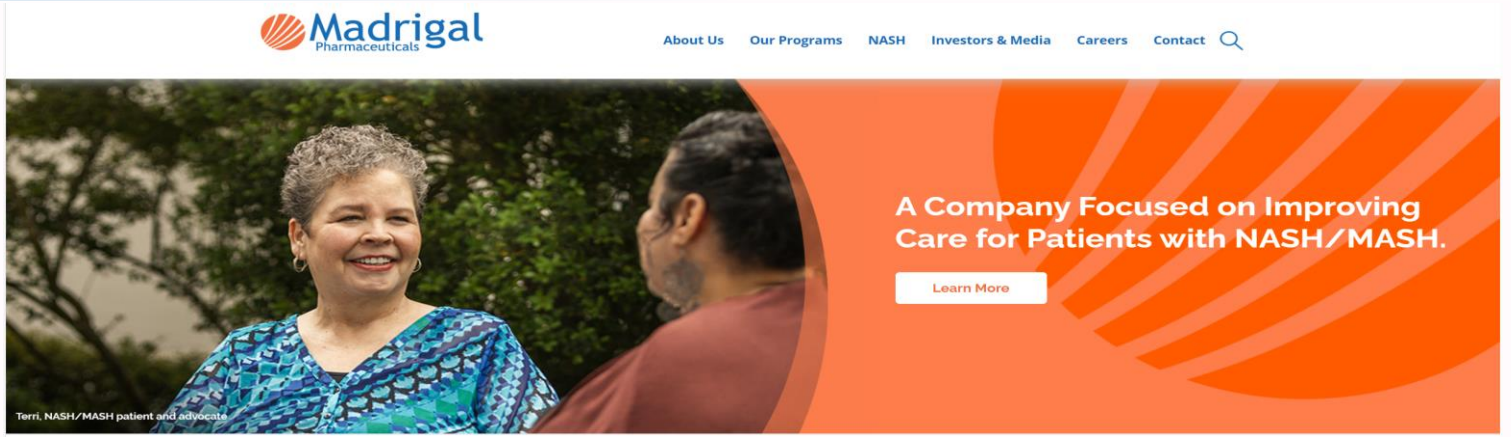


Figure 5. (A) Domain organization of Thyroid Hormone Receptors (THRs) and functional regions; (B) The ligand binding domains of the THR-α and -β receptors differ by only a single amino acid, Ser277 (THR-α)(PDB: 1NAV)/ Asn331 (THR-β)(PDB: 1NAX).

1.3 Madrigal Pharmaceuticals (新泰制药)



药物(靶点)	适应症	国家/地区	最高研发状态	机构	日期
瑞司美替罗 (THR-β) 授权	肝纤维化	美国	批准上市	Madrigal Pharmaceuticals, Inc.	2024-03-14
	非酒精性脂肪性肝炎 查看所有临床 >>	美国	批准上市	Madrigal Pharmaceuticals, Inc.	2024-03-14
		波多黎各	临床3期	Madrigal Pharmaceuticals, Inc.	2022-08-26
	肝硬化 查看所有临床 >>	美国	临床3期	Madrigal Pharmaceuticals, Inc.	2022-08-26
		波多黎各	临床3期	Madrigal Pharmaceuticals, Inc.	2022-08-26
	杂合子家族性高胆固醇血症 查看所有临床 >>	丹麦	临床2期	Madrigal Pharmaceuticals, Inc.	2017-02-09
	注意力 查看所有临床 >>	美国	临床1期	Madrigal Pharmaceuticals, Inc.	2024-03-05
	-	美国	临床1期	Madrigal Pharmaceuticals, Inc.	2011-06-01
PRCL-02 (CRAC)	银屑病	未知	临床2期	Madrigal Pharmaceuticals, Inc.	-
MGL-3745 (THR-β)	II a型高脂蛋白血症	美国	临床前	Madrigal Pharmaceuticals, Inc.	-
	非酒精性脂肪性肝炎	美国	临床前	Madrigal Pharmaceuticals, Inc.	-
STA-9183 (HSP90)	肿瘤	未知	临床前	Madrigal Pharmaceuticals, Inc.	-
Apilimod (IL-12 x IL-23 x PIKFYVE)	克罗恩病 查看所有临床 >>	美国	临床2期	Synta Pharmaceuticals Corp.	2004-02-01
	葡萄膜炎	美国	临床前	Synta Pharmaceuticals Corp.	2008-05-01

Figure 6. The website and R&D pipeline of Madrigal Pharmaceuticals.

https://www.madrigalpharma.com/
https://synapse.zhihuiya.com/

2. Design and optimization of compounds

2.1 Hit to lead

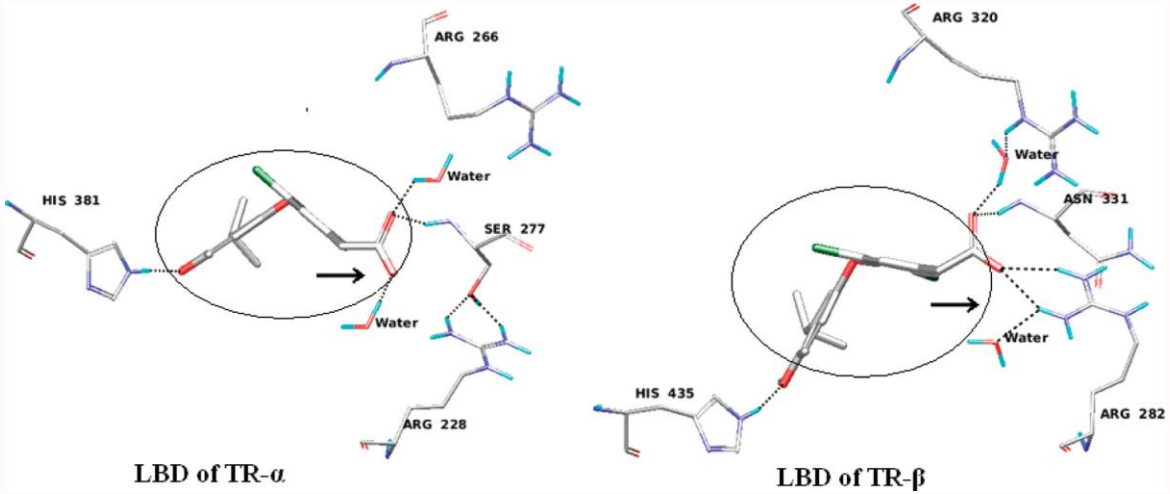


Figure 7. T3 bound into the ligand-binding pocket.

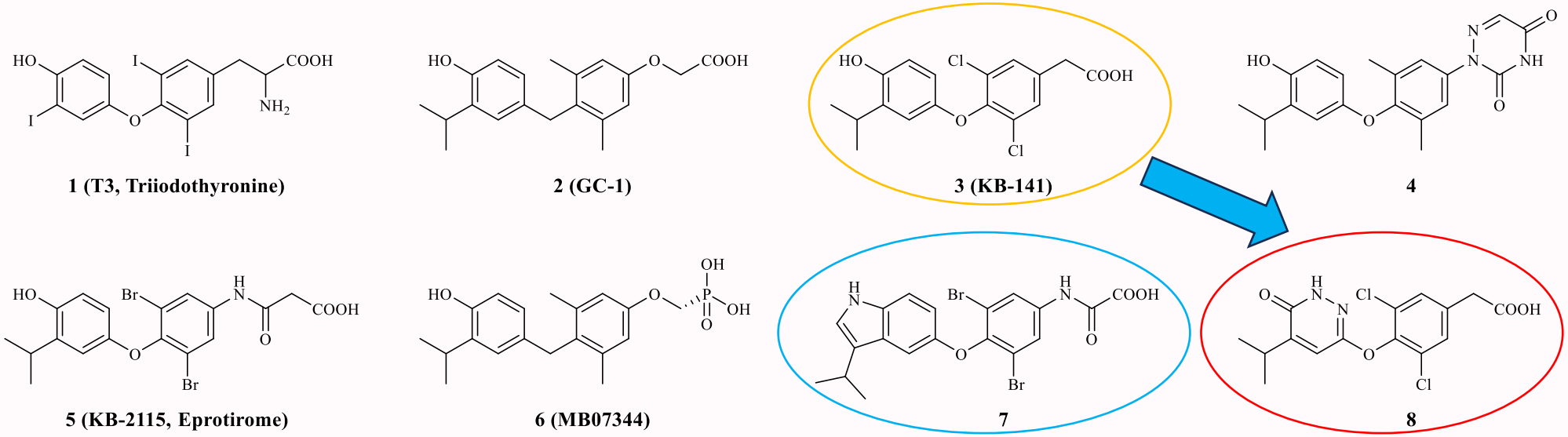
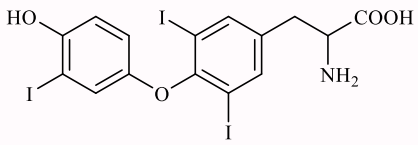


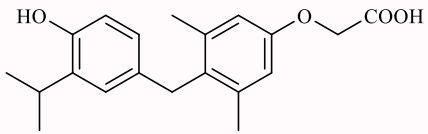
Figure 8. A number of compounds illustrating the range of TH mimetic structures.

J Med Chem, 2014, 22;57(10):3912-23.

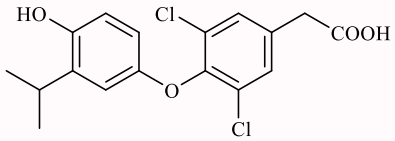
2.2 Structure-activity relationship



1 (T3, Triiodothyronine)



2 (GC-1)



3 (KB-141)

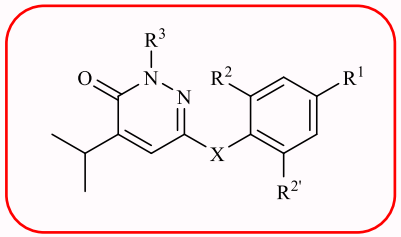


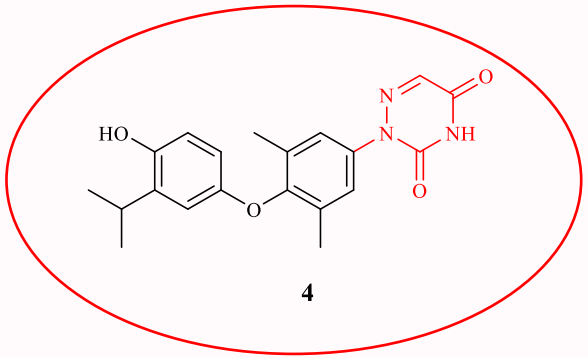
Table 1. Structure-activity relationship of pyridazinone based THR agonists[a]

Compd.	R^1	R^2, $R^{2'}$	X	R^3	THR-β EC_{50} μM[b]	THR-β Rel % Activity of T3	THR-α EC_{50} μM[b]	THR-α Rel % Activity of T3	Relative Selectivity[c]	NMT
1					0.015[d]	100%	0.01[d]	100%	1	+
2					0.018	126.8%	0.003	83.70%	0.71	-
3					0.023	116.0%	0.005	86.3%	1.02	+
8	$-CH_2CO_2H$	Cl, Cl	O	H	2.38	58.2%	7.01	50.0%	10.23	
9	$-CH_2CO_2H$	CH_3, CH_3	O	H	7.75	24.5%	15.64	19.0%	7.01	+
10	$-CH_2CO_2H$	CH_3, Cl	O	H	7.01	45.6%	12.00	38.4%	5.90	+
11	$-CH_2CO_2H$	Br, Br	O	H	0.46	80.5%	3.28	54.0%	11.65	+
12	$-CH_2CO_2H$	Cl, Cl	CH_2	H	2.99	57.6%	4.29	59.4%	7.80	
13	$-CH_2CO_2H$	Br, Br	CH_2	H	0.60	74.4%	0.75	72.0%	6.77	
14	$-CH_2CO_2H$	Cl, Cl	S	H	2.04	70.4%	8.88	30.2%	7.03	
15	$-CH_2CO_2H$	Cl, Cl	SO	H	9.17	9.9%	N/D	N/D	-	
16	$-CH_2CO_2H$	Cl, Cl	SO_2	H	6.98	62.1%	14.39	13.1%	4.15	
17	$-CH_2CO_2H$	Cl, Cl	O	CH_3	0.77	64.5%	0.78	64.3%	5.51	
18	$-(CH_2)_2CO_2H$	Br, Br	O	H	0.70	89.1%	0.39	97.7%	1.94	
19	$-NHCH_2CO_2H$	Cl, Cl	O	H	0.67	74.0%	0.70	81.0%	3.66	
20	$-NHCO_2H$	Cl, Cl	O	H	0.12	86.9%	0.21	84.4%	6.09	

[a]N/D is not determined. MNT is in vitro micronucleus test. Superscript b indicates average of triplicate determinations. Superscript c indicates that selectivity is normalized for the selectivity of **T3** in the same assay. Superscript d indicates that **T3** was run in every assay; the values for THR-β range from 0.12 to 0.024 μM, and the values for THR-α range from 0.003 to 0.10 μM.

2.2 Structure-activity relationship

A



B

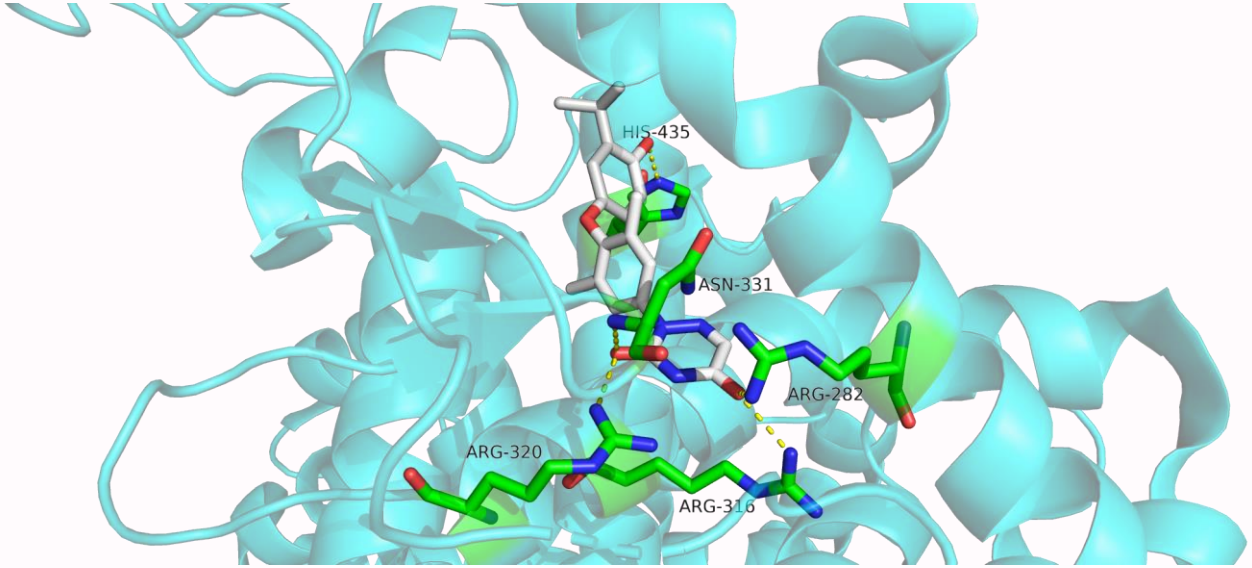


Figure 9. (A) The structure of **4**. (B) The binding model of **4** in THR-β receptor (PDB: 1N46).

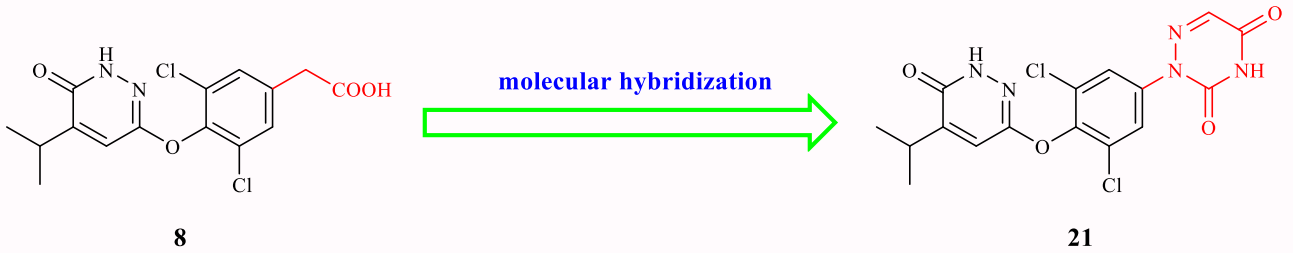


Figure 10. The molecular hybridization strategy was used to improve the selectivity of the compound to THR-β receptor.

Bioorg Med Chem Lett. 2003;13(3):379-82.

J Med Chem, 2014, 22;57(10):3912-23.

2.2 Structure-activity relationship

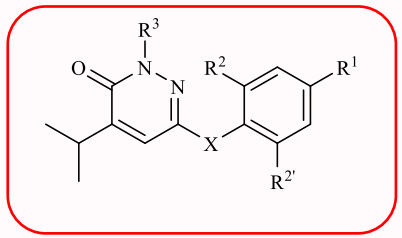
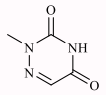
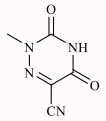
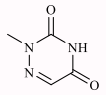
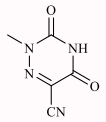
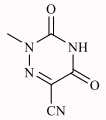
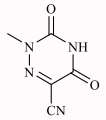


Table 2. Structure-activity relationship of pyridazinone based THR agonists[a]

Compd.	R^1	R^2, $R^{2'}$	X	R^3	THR-β EC_{50} μM[b]	THR-β Rel % Activity of T3	THR-α EC_{50} μM[b]	THR-α Rel % Activity of T3	Relative Selectivity[c]	NMT[a]
8	$-CH_2CO_2H$	Cl, Cl	O	H	2.38[d]	58.2%	7.01[d]	50.0%	10.23	
21		Cl, Cl	O	H	0.12	81.3%	0.41	78.4%	12.26	
22		Cl, Cl	O	H	0.21	83.8%	3.74	48.6%	28.29	-
23		Cl, Cl	CH_2	H	0.09	91.7%	0.82	67.6%	12.64	
24		Cl, Cl	CH_2	H	0.22	87.3%	2.75	46.0%	20.28	-
25		Cl, Cl	CH_2	CH_3	0.14	90.6%	1.25	64.0%	14.71	
26		Cl, Cl	O	CH_3	0.04	93.0%	0.33	64.9%	16.42	

Superscript a is in vitro micronucleus test. Superscript b indicates average of triplicate determinations. Superscript c indicates that selectivity is normalized for the selectivity of **T3** in the same assay. Superscript d indicates that **T3** was run in every assay; the values for THR-β range from 0.12 to 0.024 μM, and the values for THR-α range from 0.003 to 0.10 μM.

J Med Chem, 2014, 22;57(10):3912-23.

2.3 Molecular docking

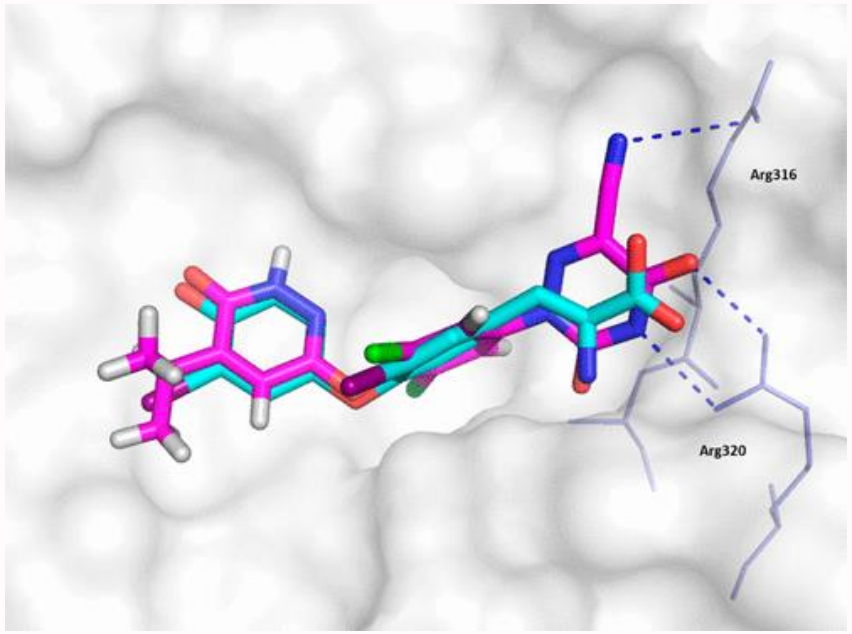


Figure 11. Model of **22** (magenta) bound to THR-β (1N46) with the **T3** geometry (cyan) from 3GWS superimposed. Polar interactions of **22** in the anion binding site are highlighted.

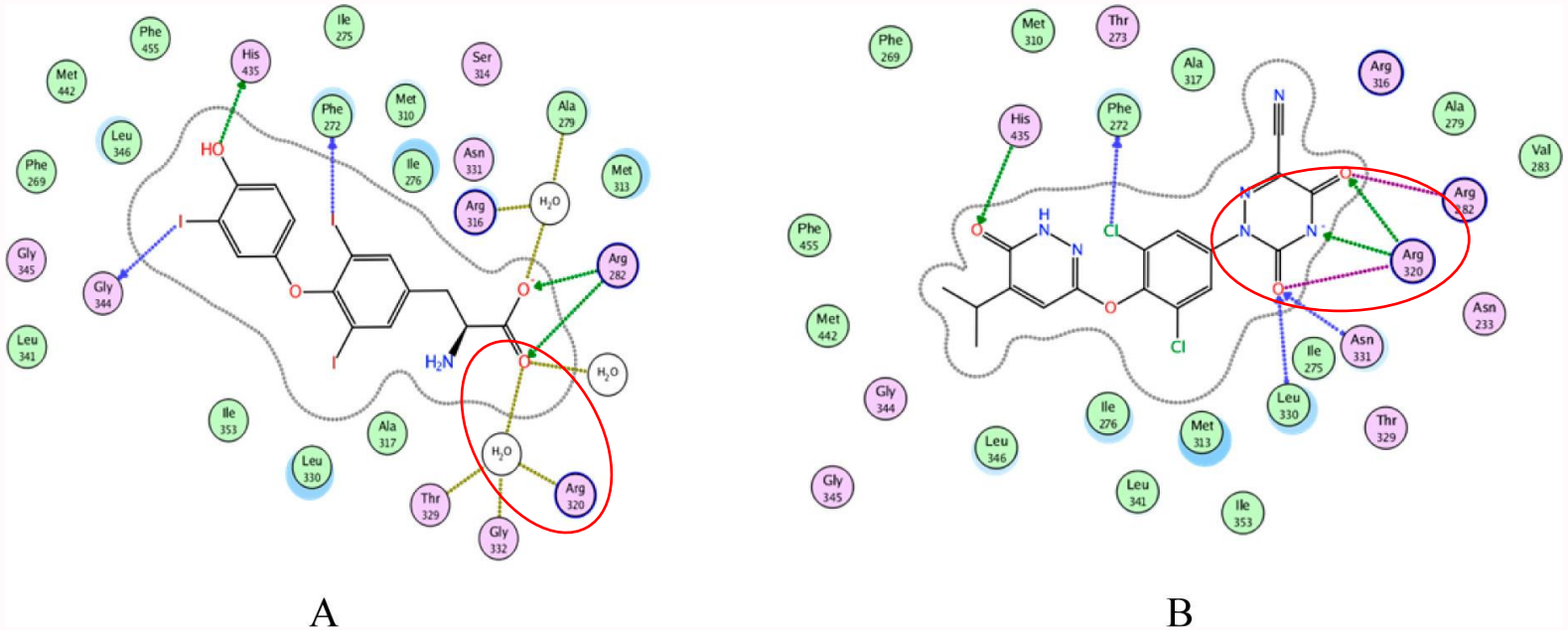


Figure 12. (A) 2D description of the binding site for **T3** (PDB code 3GWS). (B) 2D description of the binding site for the **22** model (MOE).

2.4 Cardiac-specific effects evaluation

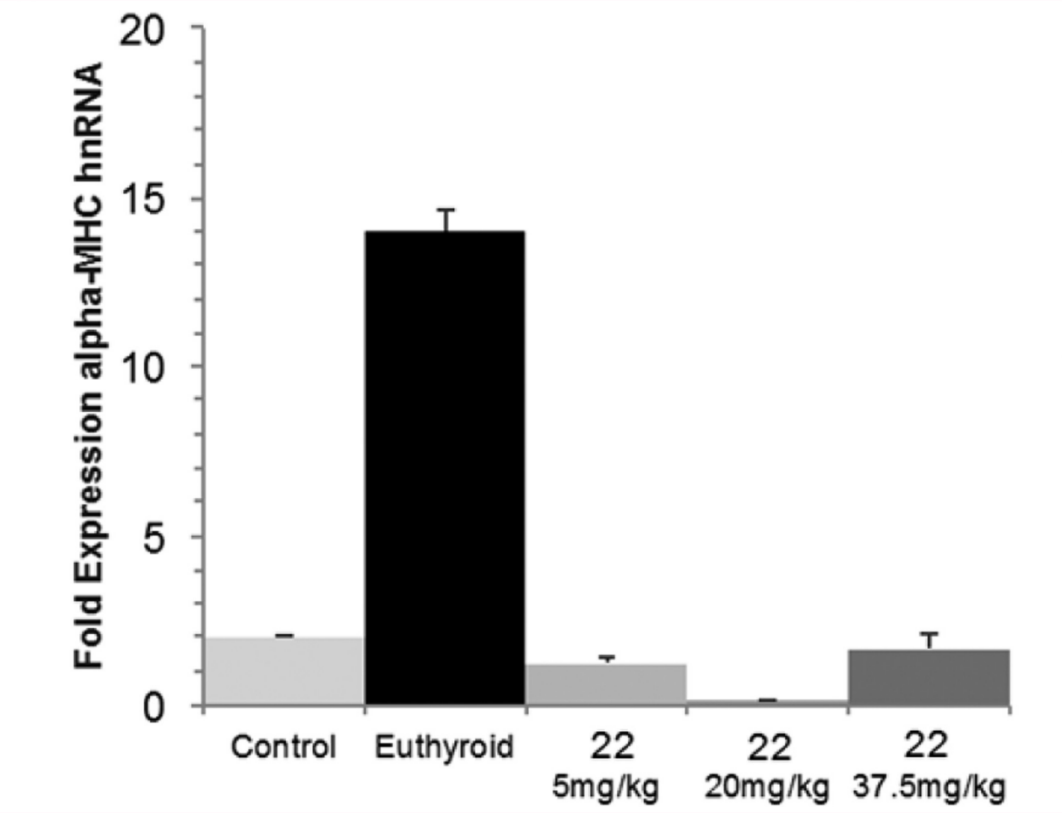


Figure 13. Cardiac α-MHC hnRNA relative levels (arbitrary units) in untreated thyroidectomized rats (control), euthyroid rats, and thyroidectomized rats 6 h after exposure to **22** dosed intraperitoneally at the specified doses.

J Med Chem, 2014, 22;57(10):3912-23.

2.5 *In vitro* and *in vivo* profiling

Table 3. Selected property data for **22**

% free (human)	human hepatocyte, CL_{int}((μL/min)/10^6 cells)	hERG, IC_{20} (μM)	CYP inhibition, IC_{50} (μM)	CYP TDI 3A4/5, 2C9/2C19	solubility, pH 7.04 (μM)	Caco-2 A-B (1×10^{-6} cm/s)	Caco-2 efflux ratio
0.6	1.04	~30	3A4/5: > 50 2C19: > 50 2C9: ~22	none detected	1.0	1.37	18.4

Table 4. Pharmacokinetic parameters of **22** after iv and po administration to rats (mean values, *N* = 3, SD in parenthes

route	rat	
	iv	po
Dose (mg/kg)	5	5
AUC (μg·h/mL)	38.1 (11.4)	17.4 (8.6)
T_{max} (h)		6 (0)
C_{max} (μg/h)		1.71 (0.85)
CL (mL min^{-1} kg^{-1})	2.35 (0.85)	
Vss (L/kg)	0.422 (0.057)	
$T_{1/2}$ (h)	3.4 (0.26)	4.08 (1.16)
***F* (%)**		45 (22.5)

3. Approval for market launch

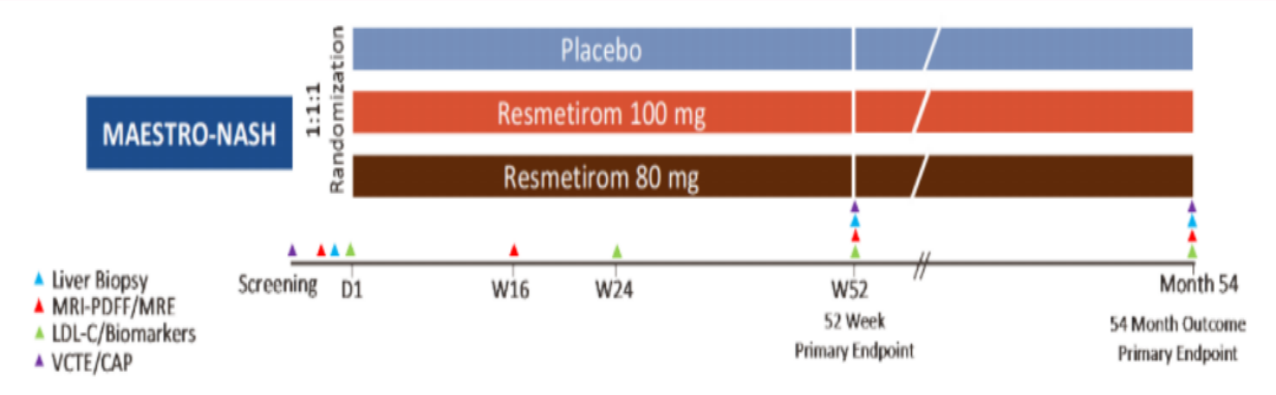
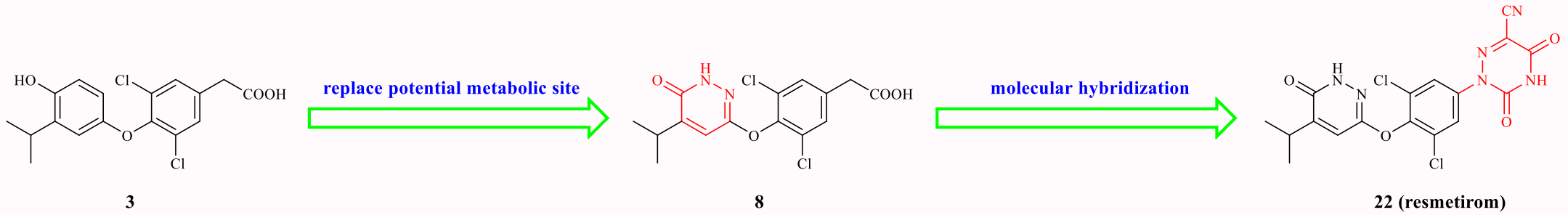


Figure 14. Resmetirom memorabilia.

https://synapse.zhihuiya.com/
https://www.madrigalpharma.com/
N Engl J Med, 2024 Feb 8;390(6):497-509
https://www.fda.gov/

4. Summary



3

THR-β EC50 = 0.023 μM
THR-β Rel % activity of T3 = 116%
THR-α EC50 = 0.005 μM
THR-α Rel % activity of T3 = 86.3%
relative selectivity = 1.02

8

THR-β EC50 = 2.38 μM
THR-β Rel % activity of T3 = 58.2%
THR-α EC50 = 7.01 μM
THR-α Rel % activity of T3 = 50.0%
relative selectivity = 10.23

22 (resmetirom)

THR-β EC50 = 0.21 μM
THR-β Rel % activity of T3 = 83.8%
THR-α EC50 = 3.74 μM
THR-α Rel % activity of T3 = 48.6%
relative selectivity = 28.29

Figure 15. Summary of drug design ideas of resmetirom.

Thanks for your listening !