



Discovery of sulfonamide-pyrazole γ -secretase inhibitors

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ABSTRACT

Utilizing a pharmacophore hypothesis, previously described γ -secretase inhibiting HTS hits were evolved into novel tricyclic sulfonamide-pyrazoles, with high in vitro potency, good brain penetration, low metabolic stability, and high clearance.

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Alzheimer's disease (AD) is the foremost cause of dementia among elderly persons worldwide.¹ Amyloid plaques containing aggregated A β peptide, and neurofibrillary tangles containing hyper-phosphorylated tau protein, within the hippocampus and the cerebral cortex, are the diagnostic pathologies of AD. A β peptide is a 40–42 aminoacid peptide, formed by sequential cleavage of Amyloid precursor protein (APP) by the proteases β -secretase (BACE) and γ -secretase. Although deposition of A β peptide in the brain has not been proven to cause AD, inhibitors of BACE and γ -secretase are the subject of much drug discovery research. Several γ -secretase inhibitors (GSIs) are in clinical trials, as are agents targeting A β peptide by different mechanisms.² This Letter describes the discovery of a new class of GSIs.

High throughput screening (HTS) of circa 500 K small molecules revealed **1** to be a moderately potent GSI (Fig. 1 and Table 1).^{3,4} Hit expansion based on **1** provided many compounds with comparable or increased potencies, including **2a** and **3**. Two aspects of SAR were clear following hit expansion. First, the 4-chlorobenzenesulfonamide is nearly optimal for potency. Second, the *N*-H caprolactam **2a** is much more potent than its *N*-methyl analog **2b**. We hypothesized the *N*-H group in **2a** may donate a hydrogen bond to γ -secretase. Modeling of **3** revealed a global minimum, in which the piperidine ring is a slightly flattened chair, and the methyl groups and the arylsulfonyl group all are nearly axial. This conformation suggested preparing the bicycle **4**, which proved to be as potent as **3**. We hypothesized, adding a hydrogen-bond donor to **4** might increase its potency. Modeling of **2a** revealed multiple

low energy conformations, preventing the definition of a specific three-dimensional pharmacophore, but the symmetry of **4** permitted empirical exploration of hydrogen-bond donors in many positions relative to the essential 4-chlorobenzenesulfonamide.

Initially, we converted nor-pseudopelletierine⁵ (**5**) into a group of hydrazones, alcohols, and amines, as illustrated in Scheme 1.⁶ None of the compounds in Scheme 1 have potencies superior to **4**, and therefore we redirected our efforts to fusing **4** with protic heterocycles, as illustrated in Scheme 2. Quite remarkably, the very

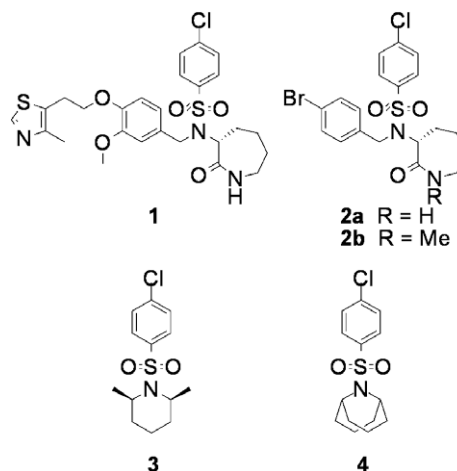


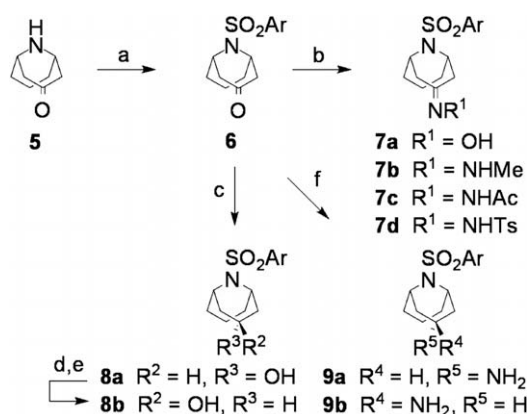
Figure 1. Screening hits and hit expansion compounds.

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Table 1
Inhibition of γ -secretase by compounds not *N*-H pyrazoles

Compound	IC ₅₀ (nM)
1	650
2a	25
2b	1700
3	1700
4	1300
7a	3300
7b	>10,000
7c	>10,000
7d	8000
8a	3000
8b	600
9a	>10,000
9b	>10,000
11b	>10,000
11c	>10,000
12	3500
14	>10,000
16a	>10,000
16b	4700
16c	9000
16d	>10,000
16e	5500

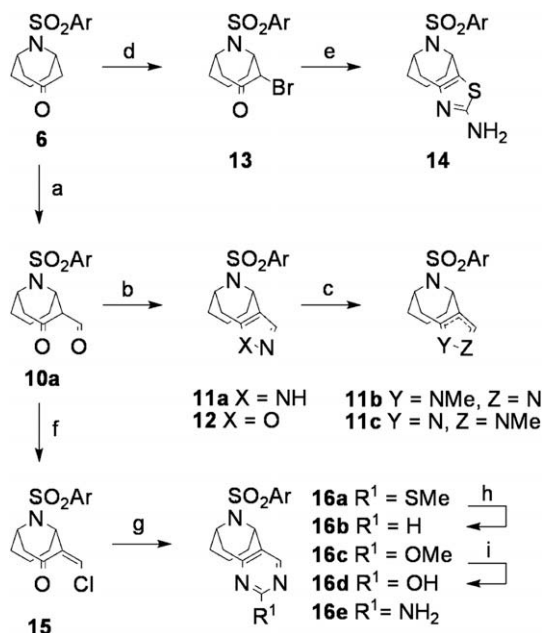


Scheme 1. Ar = 4-ClC₆H₄. All compounds *meso* or racemic. Reagents: (a) ArSO₂Cl, pyridine; (b) R¹NH₂, EtOH; (c) NaBH₄, EtOH; (d) PhCO₂H, PPh₃, EtO₂CN=NCO₂Et, THF; (e) NaOH, THF/H₂O; (f) NH₄OAc, NaBH₃CN, MeOH, and then separation of diastereomers by HPLC.

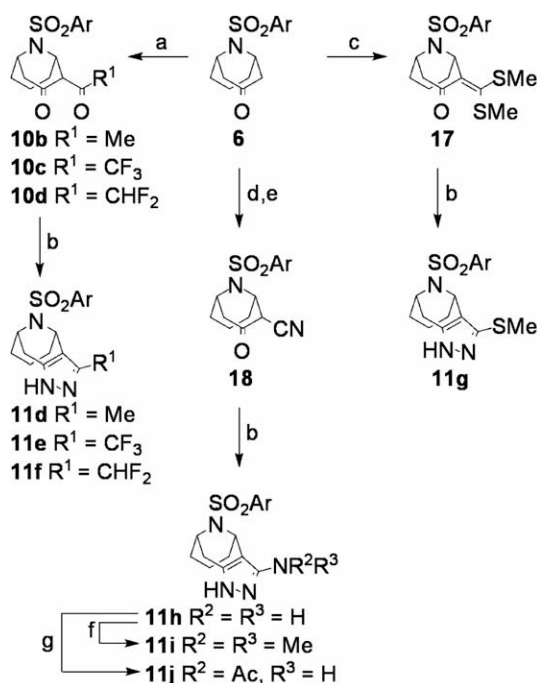
first fused heterocycle we prepared, the pyrazole **11a**, proved to be 500-fold more potent than **4**. The high potency of **11a** suggested we explore other heterocycles in the place of the pyrazole. Interestingly, the *N*-methyl pyrazoles **11b–c**, the isoxazole **12**, the 2-aminothiazole **14**, and several pyrimidines **16a–e** are not more potent than **4**.

Next, we prepared a group of substituted *N*-H pyrazoles, as illustrated in Schemes 3 and 4. The *in vitro* potencies of several substituted *N*-H pyrazoles are indicated in Table 2. Substituents larger than H on the un-fused carbon atom within the pyrazole diminish potency (**11a** vs **11d–j**). Oxygen or fluorine substituents on the CH₂ adjacent to the pyrazole have minor effects on potency (**11a** vs **11k–l**). The very high potency of **11a**, relative to the other heteroaromatics in Scheme 2, suggests the *N*-H pyrazole in **11a** may form two hydrogen bonds with γ -secretase, similar to the known interaction of some *N*-H pyrazoles with backbone carboxamides in the ATP-binding sites of kinases.⁷

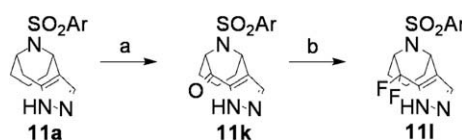
We separated the enantiomers of **11a** by chiral HPLC, and we determined only the positively rotating enantiomer is more potent than **4**. X-ray crystallography showed (+)-**11a** has the configuration illustrated in Scheme 2, and the solid-state conformation illus-



Scheme 2. Ar = 4-ClC₆H₄. All compounds *meso* or racemic. Reagents: (a) EtO₂CH, NaH, THF; (b) H₂NNH₂ or HONH₂, EtOH; (c) MeI, NaH, DMF; (d) C₅H₅NHBr₃, toluene; (e) SC(NH₂)₂, THF; (f) neat SOCl₂; (g) R¹C(=NH)NH₂, EtOH, to **16a**, **16c**, **16e**; (h) Raney Ni, EtOH; (i) BBr₃, CH₂Cl₂.



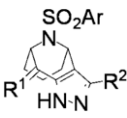
Scheme 3. Ar = 4-ClC₆H₄. All compounds *meso* or racemic. Reagents: (a) R¹CO₂Et, NaH, THF; (b) N₂H₄, EtOH; (c) KOtBu, CS₂, MeI, THF; (d) C₅H₅NHBr₃, toluene; (e) KCN, THF/H₂O; (f) formalin, NaBH₃CN, AcOH, MeOH; (g) neat Ac₂O.



Scheme 4. Ar = 4-ClC₆H₄. All compounds *meso* or racemic. Reagents: (a) CrO₃, HIO₄, AcOH; (b) neat F₃SN(CH₂CH₂OMe)₂.

trated in Figure 2.⁸ X-ray crystallography showed **2a** has the solid-state conformation illustrated in Figure 3.⁸ In the solid-state conformations of (+)-**11a** and **2a**, the respective pyrazole and carboxamide occupy similar positions relative to the 4-chlorobenzenesulfonamide, consistent with these groups hydrogen-bonding to γ -secretase.

Table 2
Inhibition of γ -secretase by *N*-H pyrazoles



Compound	R ¹	R ²	IC ₅₀ (nM)
11a	H,H	H	4
11d	H,H	Me	65
11e	H,H	CF ₃	70
11f	H,H	CHF ₂	85
11g	H,H	SMe	390
11h	H,H	NH ₂	105
11i	H,H	NMe ₂	>10,000
11j	H,H	NHAc	70
11k	O	H	8
11l	F,F	H	3

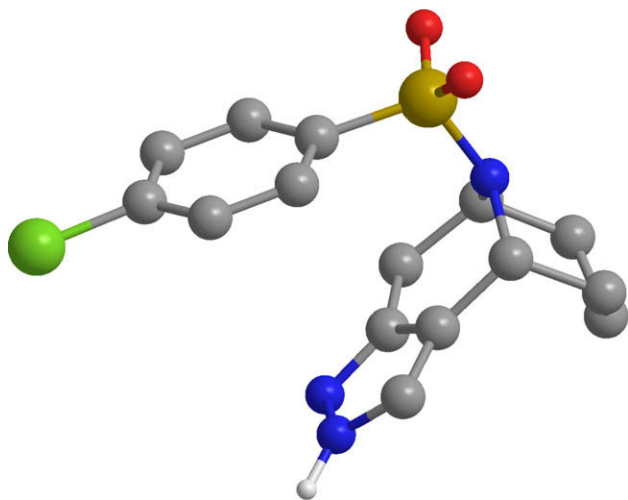


Figure 2. X-ray crystal structure of (+)-**11a**.

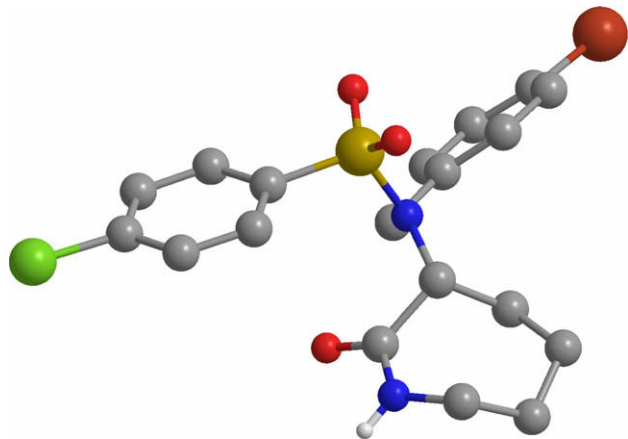


Figure 3. X-ray crystal structure of **2a**.

In Sprague-Dawley rats, (+)-**11a** exhibits low oral availability ($F = 2\%$) and high clearance ($CL = 2200$ mL/kg/h). However, 3 h after a 100 mg/kg oral dose in FVB mice, (+)-**11a** achieves a 194 nM concentration in plasma, an 86 nM concentration in cortex, and a 36% reduction of A β x-40 in cortex.⁹ Experiments utilizing rat and human liver microsomes revealed (+)-**11a** suffers efficient metabolic oxidation and glucuronidation, the latter generating isomers from glucuronyl transfer to either pyrazole nitrogen atom in the unoxidized parent molecule.⁴ Given the high in vitro potency and excellent brain penetration of (+)-**11a**, several related series of sulfonamide-pyrazole GSIs have been investigated, in pursuit of compounds with superior metabolic stability.¹⁰

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