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# 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.



Alzheimer's disease (AD) is the foremost cause of dementia among elderly persons worldwide.[1] Amyloid plaques containing aggregated Aβ peptide, and neurofibrillary tangles containing hyper-phosphorylated tau protein, within the hippocampus and the cerebral cortex, are the diagnostic pathologies of AD. Aβ 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 Aβ 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 Aβ 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-pseudopelletierine[5] (**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

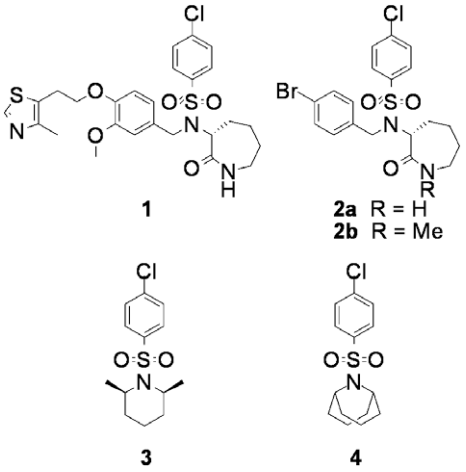


**Figure 1.** Screening hits and hit expansion compounds.

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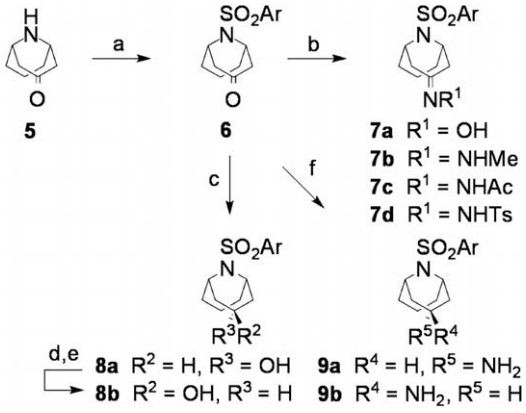
**Table 1**
Inhibition of γ-secretase by compounds not *N*–H pyrazoles

| 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 |

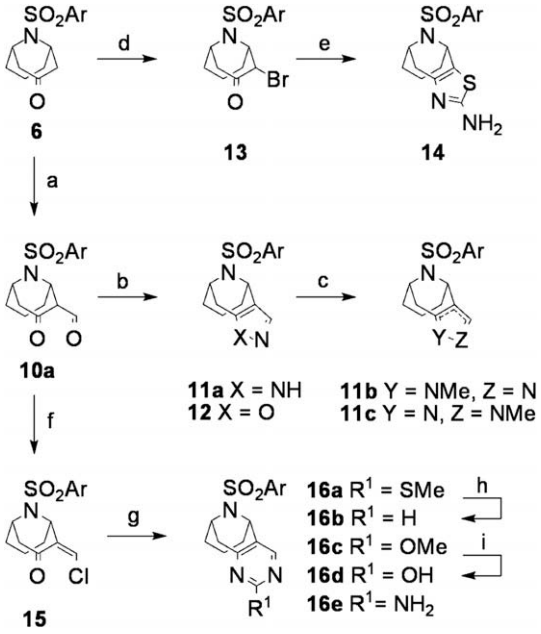


**Scheme 1.** Ar = 4-$ClC_6H_4$. All compounds *meso* or racemic. Reagents: (a) $ArSO_2Cl$, pyridine; (b) $R^1NH_2$, EtOH; (c) $NaBH_4$, EtOH; (d) $PhCO_2H$, $PPh_3$, $EtO_2CN{=}NCO_2Et$, THF; (e) NaOH, THF/$H_2O$; (f) $NH_4OAc$, $NaBH_3CN$, MeOH, and then separation of diastereomers by HPLC.

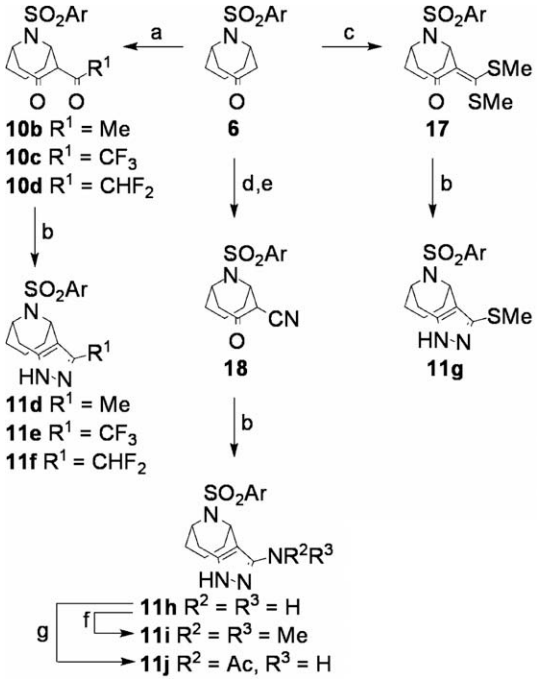
first fused heterocycle we prepared, the pyrazole **11a**, proved to be 500-fold more potent than **4**. The high potency of **11a** suggested we explore other heterocycles in the place of the pyrazole. Interestingly, the *N*-methyl pyrazoles **11b–c**, the isoxazole **12**, the 2-aminothiazole **14**, 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 $CH_2$ 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]

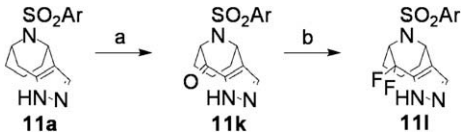
We separated the enantiomers of **11a** by chiral HPLC, and we determined only the positively rotating enantiomer is more potent than **4**. X-ray crystallography showed (+)-**11a** has the configuration illustrated in Scheme 2, and the solid-state conformation illus-



**Scheme 2.** Ar = 4-$ClC_6H_4$. All compounds *meso* or racemic. Reagents: (a) $EtO_2CH$, NaH, THF; (b) $H_2NNH_2$ or $HONH_2$, EtOH; (c) MeI, NaH, DMF; (d) $C_5H_5NHBr_3$, toluene; (e) $SC(NH_2)_2$, THF; (f) neat $SOCl_2$; (g) $R^1C(=NH)NH_2$, EtOH, to **16a**, **16c**, **16e**; (h) Raney Ni, EtOH; (i) $BBr_3$, $CH_2Cl_2$.



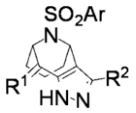
**Scheme 3.** Ar = 4-$ClC_6H_4$. All compounds *meso* or racemic. Reagents: (a) $R^1CO_2Et$, NaH, THF; (b) $N_2H_4$, EtOH; (c) KO*t*Bu, $CS_2$, MeI, THF; (d) $C_5H_5NHBr_3$, toluene; (e) KCN, THF/$H_2O$; (f) formalin, $NaBH_3CN$, AcOH, MeOH; (g) neat $Ac_2O$.



**Scheme 4.** Ar = 4-$ClC_6H_4$. All compounds *meso* or racemic. Reagents: (a) $CrO_3$, $HIO_4$, AcOH; (b) neat $F_3SN(CH_2CH_2OMe)_2$.

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 |

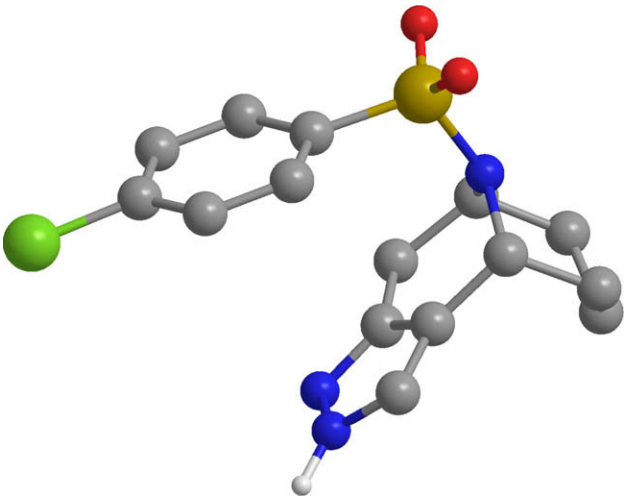


**Figure 2.** X-ray crystal structure of (+)-**11a**.

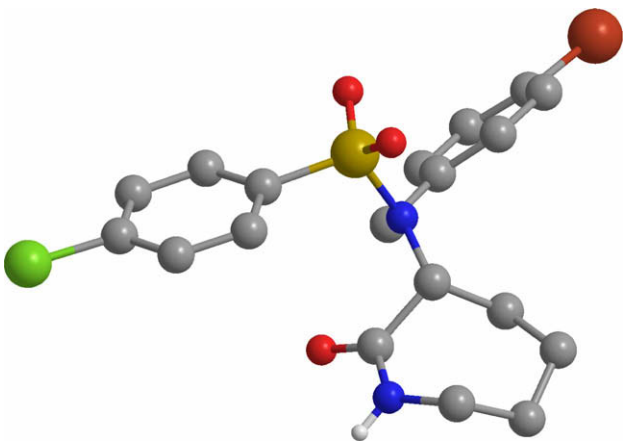


**Figure 3.** X-ray crystal structure of **2a**.

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 Aβx-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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