

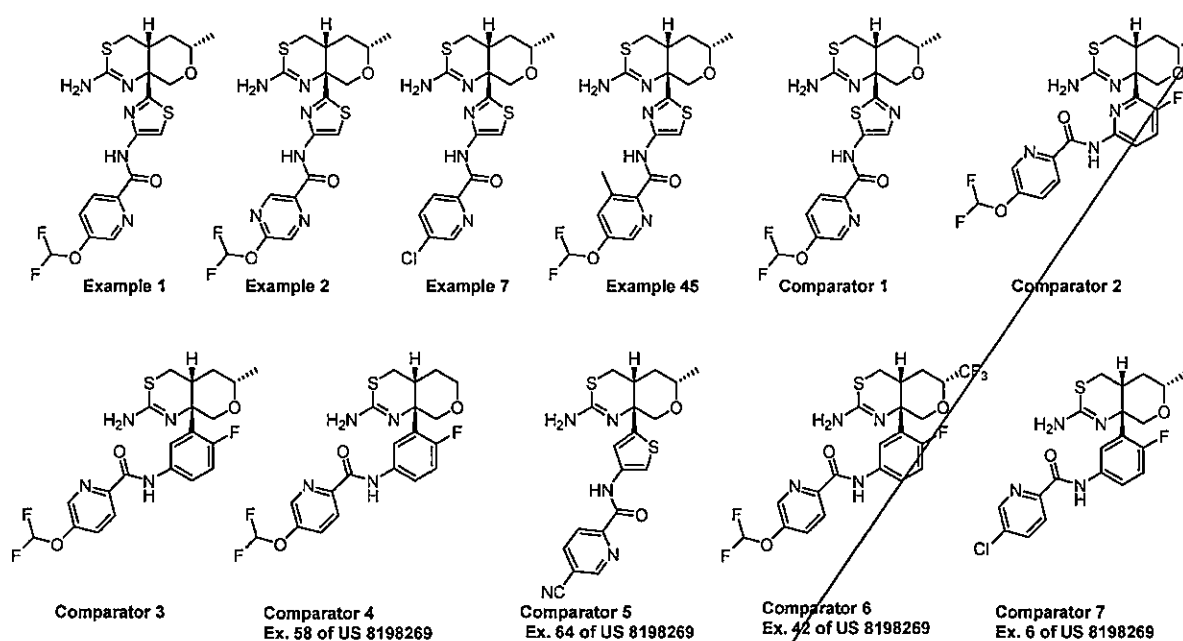


Table 4

Compound	BACE1 Cell Free IC ₅₀	sAPPβ Whole Cell IC ₅₀	BACE2/BACE1 Binding Ratio
Example 1	41 nM	5 nM	27.9
Example 2	73 nM	7 nM	25.8
Example 7	33 nM	4 nM	3.8
Example 45	23 nM	3 nM	6.4
Comparator 1	> 100 μM	13.6 μM	0.5
Comparator 2	43 nM	1 nM	2.9
Comparator 3	3 nM	< 1 nM	ND
Comparator 4 (Ex. 58 of US 8198269)	9 nM	< 1 nM	2.1
Comparator 5 (Ex. 64 of US 8198269)	19 nM	2 nM	3.1
Comparator 6 (Ex. 42 of US 8198269)	6 nM	< 1 nM	1.0
Comparator 7 (Ex. 6 of US 8198269)	1 nM	< 1 nM	1.0

US Patent No. 8,198,269. Those skilled in the art will appreciate the potential impact of selectivity over BACE2 with respect to skin pigmentation changes in human clinical trials.

5 Table 5, below, provides HLM Clint, CYP2D6 IC₅₀ and observed glutathione (GSH) adduct data for the compounds of examples 1, 2, 7 and 45 and comparators 1-7, whose structures are provided below. The data was obtained using the General Multi-Point Cocktail DDI IC₅₀ and GSH incubation assays as described hereinabove.

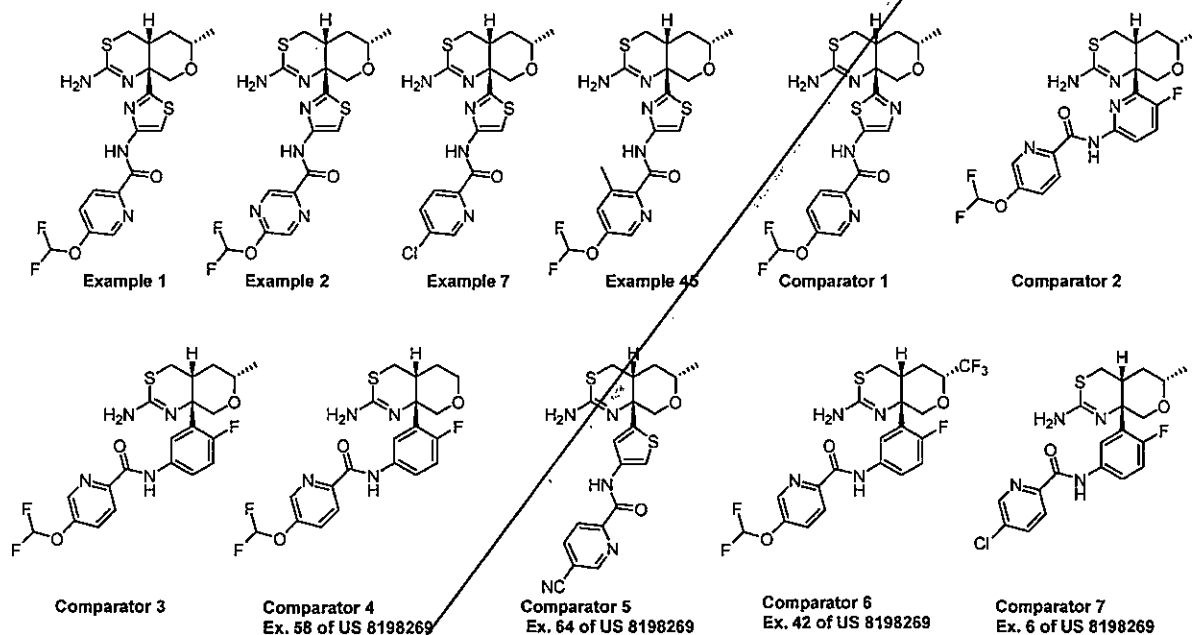
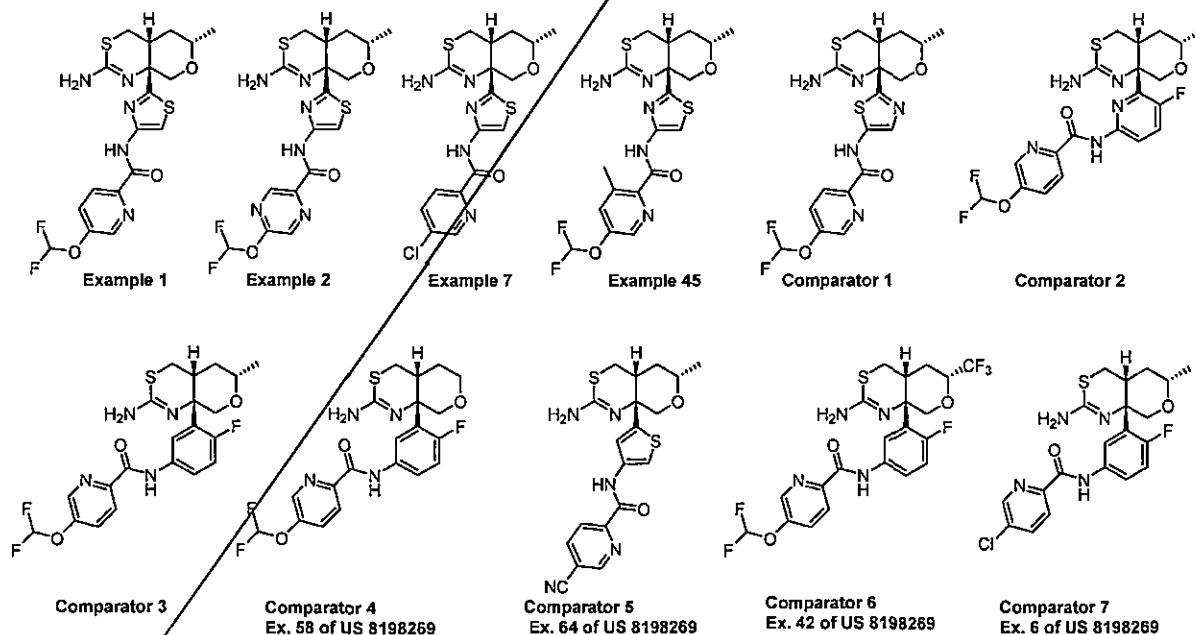


Table 5

Compound	HLM CLint	CYP2D6 IC ₅₀ ^a	Observed GSH adducts ^b
Example 1	<8 mL/min/kg	>30 μM	Negative
Example 2	<8 mL/min/kg	>30 μM	Negative
Example 7	<8 mL/min/kg	>30 μM	Negative
Example 45	<8.7 mL/min/kg	>30 μM	Negative
Comparator 1	<8 mL/min/kg	14% inh @ 3 μM	Not Determined
Comparator 2	22.9 mL/min/kg	< 30 nM	Not Determined
Comparator 3	19.8 mL/min/kg	< 30 nM	Not Determined
Comparator 4	8.3 mL/min/kg	65 nM	Not Determined

The potential clinical hepatotoxicity or drug induced liver injury (DILI) is one of the major reasons for the withdrawal of compounds from the market.⁹ Those skilled in the art will appreciate that bioactivation or covalent binding of compounds to proteins is a potential mechanism for hepatotoxicity. A common assay for understanding the impact of covalent binding is to monitor for the formation of glutathione (GSH) adducts. For examples 1, 2, 7, and 45 in Table 5, the formation of GSH adducts was not detected following metabolite identification in human hepatocytes. This is advantageous as it indicates that the compounds of examples 1, 2, 7 and 45 are not compounds which would lead to the potential for a glutathione-adduct induced mechanism of hepatotoxicity. However, incubation of comparator 5 (example 64 from US 8,198,269) in human liver microsomes in the presence of GSH showed the formation of chemical adducts which has the potential to lead to DILI.

Table 6, below, provides hERG IC₅₀, Pgp substrate MDR1 Er and pKa data as well as an indication of an aniline structural alert and for the compounds of examples 1, 2, 7 and 45 and comparators 1-7, whose structures are provided below. The hERG IC₅₀ and Pgp substrate MDR1 Er data was obtained using the hERG and Pgp substrate MDR1 Er assays as described hereinabove.



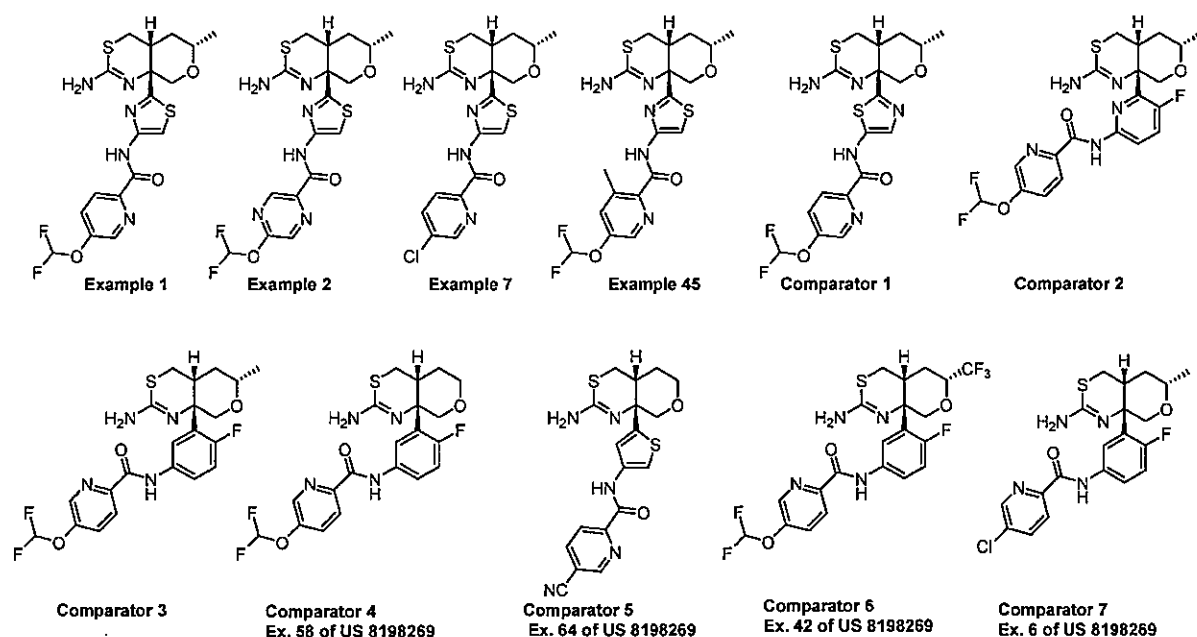
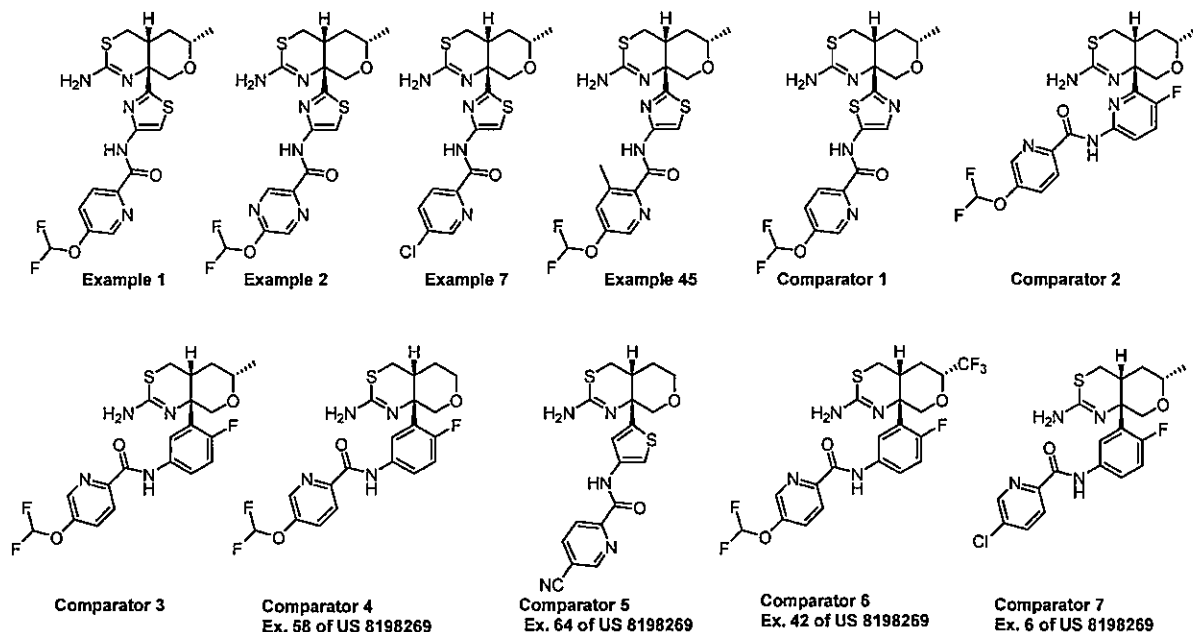


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