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Drug Discovery Based on the Structure of FKBPs: Design, Synthesis and Evaluation of L-1, 4-Thiazane-3-carboxylic Acid Derivatives as Neuroimmunophilin Ligands

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Abstract: Based on the structure of FK506, FKBP12 and calcineurin complex and the interactive characteristics of small molecular ligands with FKBPs, a series of L-1,4-thiazane-3-carboxylic acid derivatives as neuroimmunophilin ligands was designed and synthesized. The results of evaluation show that compound N308 has a great promise as a candidate of neuroprotective and neuroregenerative agent.

Keywords: FKBPs, neuroimmunophilin ligands, design, synthesis.

Neuroimmunophilin ligands are a class of compounds that hold great promise for the treatment of nerve injuries and neurology disease[1]. In contrast to neurotrophins (*e.g.*, nerve growth factor), these compounds readily cross the blood–brain barrier, being orally effective in a variety of animal models of ischemia, traumatic nerve injury and human neurodegenerative disorders. A further distinction is that neuroimmunophilin ligands act *via* unique receptors, that is, FK506-binding proteins (FKBPs), to produce neuroprotective and neuroregenerative properties[2]. A major breakthrough for the development of this class of compounds for the treatment of human neurology disorders was the ability to separate the neuroregenerative property of FK506 from its immunosuppressant action *via* the development of non-immunosuppressant (non-calcineurin inhibitting) derivates[3].

Design and synthesis of target compounds

Based on the structure of FK–506, FKBP12 and calcineurin compolex (**Figure 1**) and the interactive characteristics of small molecular ligands with FKBPs, novel scaffolds (**Scheme 2**, R: see notes of **Table 1**, R': *p*-toluenesulfonyl) of FKBPs ligands were screened and obtained by DOCK. These scaffolds included the key hydrogen bonds and dipolar interactions of FKBP12 ligands with FKBP12 (**Scheme 3, Figure 2**). After determination of the scaffolds, a virtual library (included 50 compounds) was constructed by the method of project library. Twenty-seven compounds (**Table 1**) of the virtual library were synthesized by parallel synthesis. Their structures were determined by MS and NMR. In contrast to the structure of FK506, these compounds were remained the

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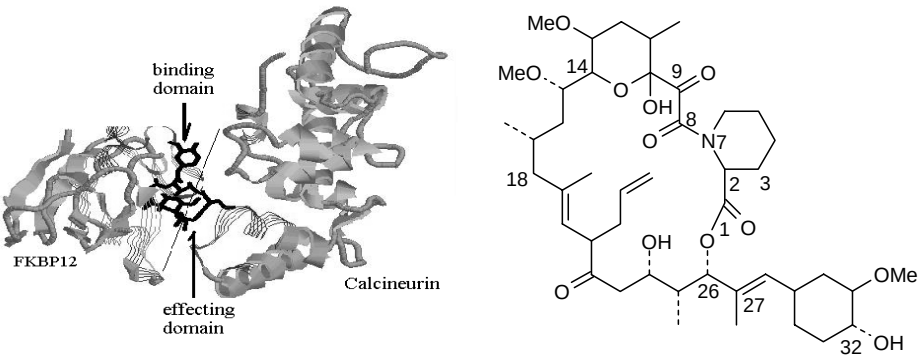
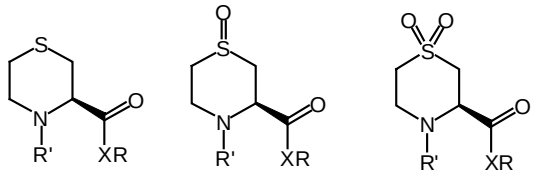
FKBP–binding domain and removed the effecting domain of FK506. The synthetic route of these compounds was described in **Scheme 4**.

Figure 1 Structures of FK–506, FKBP12 and calcineurin compolex (left) and (right)



Scheme 2 Novel scaffolds based on the structure of FKBP12



Scheme 3 The key interactions of FKBPs ligands with FKBPs

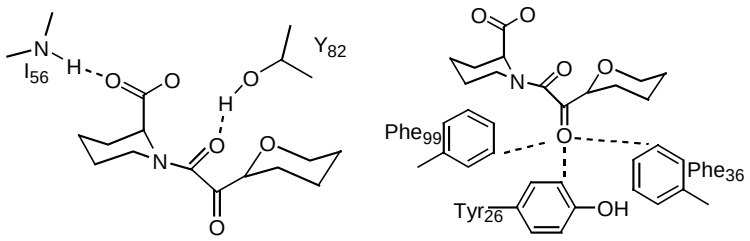


Figure 2 Interaction of novel scaffolds with active sites of FKBP12

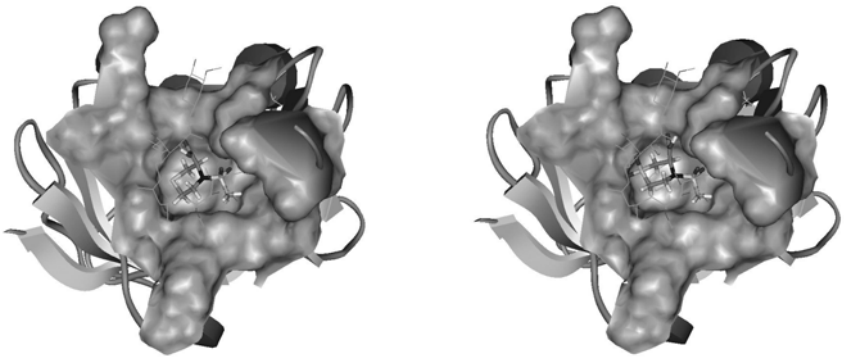
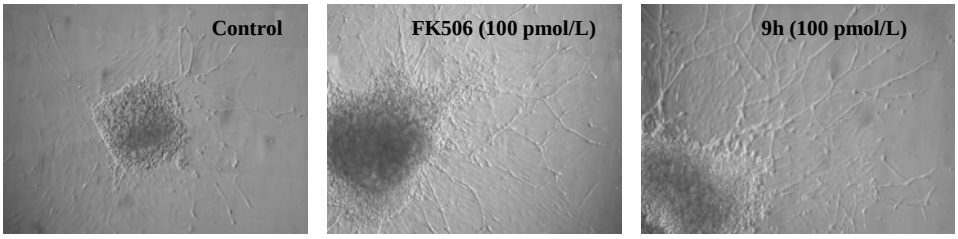
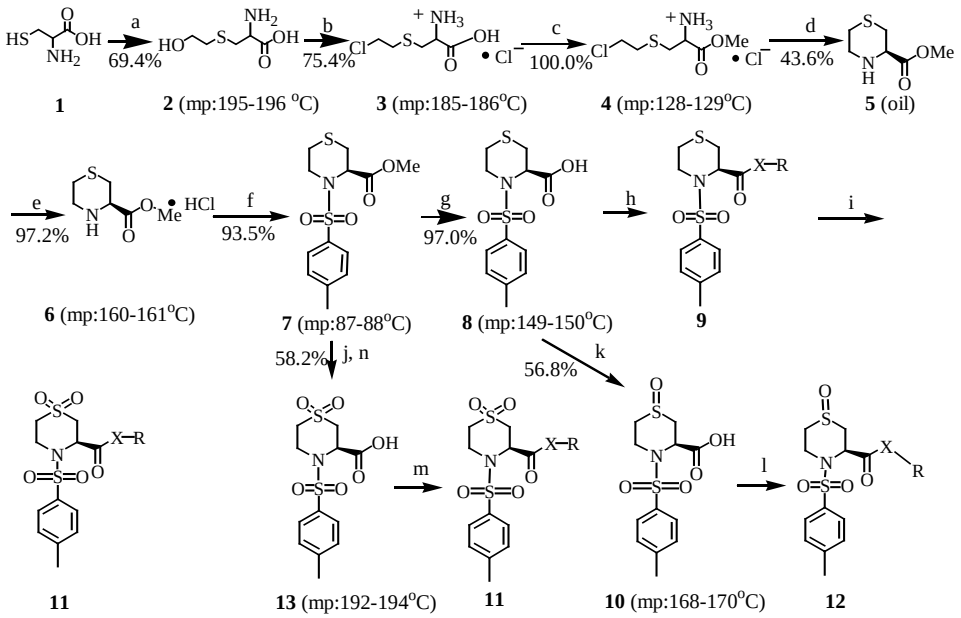


Figure 3 Compound **9h (N308)** enhancing the development of axon outgrowth in DRG



Scheme 4 Synthesis of L-1,4-thiazane-3-carboxylic acid derivates (X=O, NH)



a) C_2H_4O, 0℃; b) HCl(H_2O), 90～95℃; c) CH_3OH, 0℃; d) DMF, Et_3N, 90～95℃; e) HCl(EtOH), 0℃; f) *p*-toluenesulfonyl chloride, Et_3N, 0～5℃; g, n) LiOH(1 mol/L), CH_3OH, HCl(1 mol/L), pH=2; h, l, m) D-(+)-camphorsulfonic acid, 4-dimethylaminopyridine, ROH or RNH_2, r.t; i, j) *m*-chloroperoxybenzoic acid, CH_2Cl_2; k) H_2O_2.

In accordance with the absolute configuration (relative position of $ArSO_2$- and RXOC-group is *trans*–configuration and chiral center C-3 is R-configuration) of the target compounds, L-leucine was used as starting material. All reaction conditions of each step were carefully chosen in order to avoid racemization. X-ray diffraction of the typical target compounds demonstrated that their structures are in the desired absolute configuration[5].

Evaluation of the target compounds

Six methods, including binding assays[4, 5], PC12 cells survival and neurite outgrowth model, chick dorsal root ganglion cultures (DRG), 6-OHDA lesioned mice model and

sciatic nerve crash lesioned rats were applied to evaluate neuroprotective and neuroregenerative properties of these target compounds. The DRG evaluation result of the typical compound **9h** (**N308**) was shown in **Figure 3**.

In conclusion, twenty-eight target compounds were synthesized. The evaluation results of these compounds show that compound **9h (N308)** has a great promise as a candidate of neuroprotective and neuroregenerative agent.

Table 1 Target compounds* synthesized *via* Scheme 4**

Entry	Formula	Yield(%)#	HRMS	Entry	Formula	Yield(%)#	HRMS
9a	$C_{22}H_{28}N_2O_4S_2$	80.4	449.0525	**9o**	$C_{20}H_{24}N_2O_4S_2$	92.9	420.1179
9b	$C_{21}H_{23}NO_4S_2$	50.4	417.1067	**9p**	$C_{20}H_{25}N_3O_4S_2$	73.6	435.1309
9c	$C_{21}H_{31}NO_4S_2$	77.6	425.1754	**9q**	$C_{28}H_{31}NO_5S_2$	38.1	525.1678
9d	$C_{27}H_{29}NO_4S_2$	30.3	495.1565	**9r**	$C_{27}H_{28}FNO_4S_2$	76.0	513.3334
9e	$C_{21}H_{25}NO_5S_2$	89.7	435.1172	**9s**	$C_{25}H_{27}NO_4S_3$	73.8	501.1100
9f	$C_{21}H_{26}N_2O_4S_2$	53.0	434.1320	**9t**	$C_{21}H_{25}NO_4S_2$	64.4	419.1156
9g	$C_{23}H_{30}N_2O_4S_2$	56.3	462.1608	**9u**	$C_{21}H_{22}F_3NO_4S_2$	93.0	473.0860
9h	$C_{29}H_{33}NO_6S_2$	90.1	556.1820	**9v**	$C_{21}H_{22}F_3NO_4S_2$	45.8	473.0914
9i	$C_{18}H_{21}NO_4S_3$	68.1	411.0671	**9w**	$C_{19}H_{20}N_2O_6S_2$	66.5	436.0759
9j	$C_{26}H_{27}NO_4S_2$	83.2	481.1426	**9x**	$C_{25}H_{25}NO_4S_2$	62.1	467.1224
9k	$C_{28}H_{30}N_2O_5S_2$	74.3	539.1603	**9y**	$C_{20}H_{23}NO_5S_2$	75.1	421.1080
9l	$C_{24}H_{30}N_2O_5S_2$	40.8	491.1662	**9z**	$C_{22}H_{27}NO_6S_2$	68.1	465.1254
9m	$C_{25}H_{32}N_2O_5S_2$	90.2	505.1839	**11**	$C_{20}H_{30}N_2O_7S_2$	84.4	473.3462
9n	$C_{20}H_{30}N_2O_5S_2$	81.4	443.1673				

*All of the target compounds are oil; **RNH_2 or ROH: **9a**, N-Benzyl-N-methylethanolamine; **9b**, Cinnamyl alcohol; **9c**, 3-Cyclohexyl-1-propanol; **9d**, 1,3-Diphenyl-1-propanol; **9e**, 3-Phenoxy-propanol; **9f**, 6-Methyl-2-pyridinepropanol; **9g**, 2-(N-Ethyl-*m*-toluidino)ethanol; **9h**, 1,3-Di-benzyloxy-2-propanol; **9i**, 2-(2-Thienyl)ethanol; **9j**, 4-Methylbenzhydrol; **9k**, L-Phenylalanine benzyl ester; **9l**, L-Valine benzyl ester; **9m**, L-Leucine benzyl ester; **9n**, L-Leucine ethyl ester; **9o**, 3-(3-Pyridyl)-1-propanol; **9p**, N-Ethyl-N-(2-pyridyl)ethanoamine; **9q**, 1-(4-Methoxylphenyl)-3-phenylpropanol; **9r**, 1-(4-Fluorophenyl)-3-phenylpropanol; **9s**, 1-(2- Thienyl)-3-phenylpropanol; **9t**, 3-Phenyl-1-propanol; **9u**, 2-(Trifluoromethyl)phenyl ethanol; **9v**, α-Methyl-3-(trifluoromethyl) benzyl alcohol; **9w**, 4-Nitrobenzyl alcohol; **9x**, 4-Phenyl- benzyl alcohol; **9y**, 2-Methoxybenzyl alcohol; **9z**, 4-Ethyl-3-methoxybenzyl alcohol; **11**, L-Leucine ethyl ester. # Isolated yield (of final step).

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