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Synthesis of a Novel Series of S-Alkyl Thiobenzoate Compounds as Farnesyltransferase Inhibitors

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Abstract: S-akyl thiobenzoate compounds were designed as farnesyltransferase (FTase) inhibitors. An effective synthetic method was explored. The structures of the target compounds were elucidated by NMR spectral and elemental analysis.

Keywords: S-Akyl thiobenzoate compounds, benzodiazepine, farnesyltransferase.

Benzodiazepines are considered and used as a "privileged structure" in drug researches[1-2]. Previously, we have reported the synthesis of CAAX-mimetic (C=cysteine, A=aliphatic amino acids, X=Ser or Met) FTase inhibitors (**Figure 1**)[3]. The feature of these compounds is the substitutent with a terminal caboxylate at N1, and another substituent at C7 with imidazole group. The substituent of imidazole is considered as an important group for binding to the zinc in FTase core[4]. Based on our reported inhibitors, another series of novel inhibitors were designed, the main difference is that S-alkyl thiobenzoates were used instead of imidazole for binding to the zinc. The designed molecules **5A**-**5C** are CAAX-mimetic, and **5D**-**5F** were anticipated to mimic the FTase products in which there is a farnesyl group (**Figure 1**)[5].

Employing general methods for the selective synthesis of two different esters, including one thioester in one molecule, is difficult, especially in the case of benzodiazepines, as they are sensitive to strongly acidic and basic conditions. This was evident from the opening of the 7 member ring on our initial attempts to synthesize such esters.

Fortunately, we found that the intermediate S-methyl thiobenzamide was easily hydrolyzed to S-methyl thiobenzoate in the synthesis of benzamidine from the corresponding aromatic nitrile[6-7]. Thus this reaction was used to prepare S-alkyl thiobenzoate with different alkyl groups as shown in **Scheme 1**.

Compound **2** was prepared from nitrazepam by the same method as previously reported[3], and then reacted with H_2S at room temperature to give thiobenzamide compound **3**. Subsequent alkylation with an appropriate alkyl halide in DMF and acetone at

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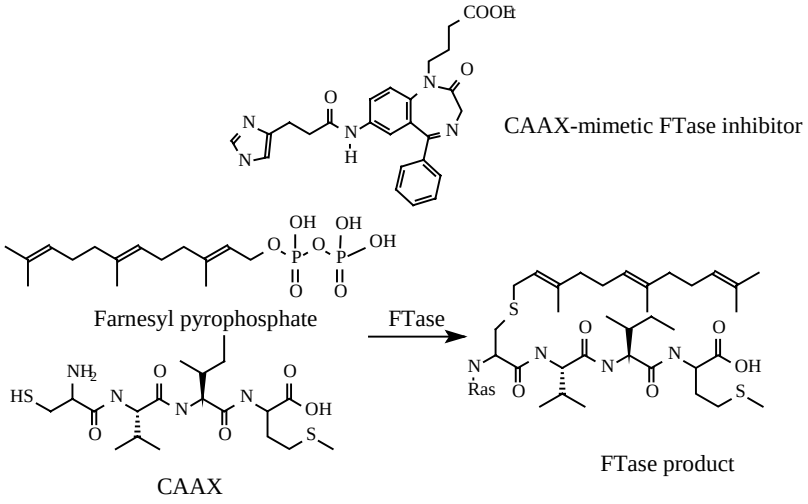
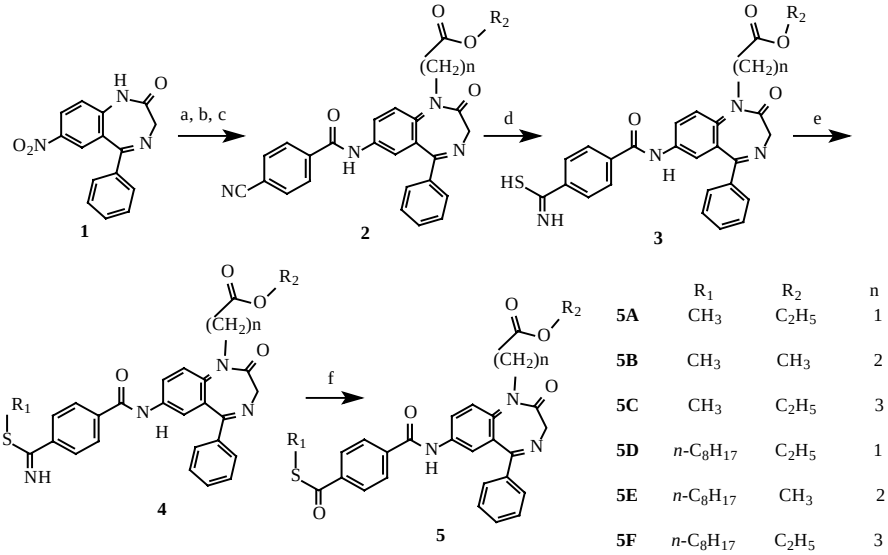
50°C furnished the desired S-alkyl thiobenzamide **4**. Treatment of **4** with H_2O in DMF afforded the desired thioesters **5A-5F.** The key feature of this step is absence of acid and basic catalysts as reported[8-9]. The effective synthesis method gave good yields (50-60% from compound **2)**. The spectral data of the compounds are listed in **Table 1**. Compound **5B** was elucidated by X-ray crystallography and shown in **Figure 2**.

Figure 1 Structure of CAAX-mimetic FTase inhibitor and FTase product



Scheme 1 Synthetic route of **5A-5F**



	R_1	R_2	n
5A	CH_3	C_2H_5	1
5B	CH_3	CH_3	2
5C	CH_3	C_2H_5	3
5D	n-C_8H_{17}	C_2H_5	1
5E	n-C_8H_{17}	CH_3	2
5F	n-C_8H_{17}	C_2H_5	3

a) $Br(CH_2)nCOOR_2$, K_2CO_3, CH_3CN, rt; b) $SnCl_2$, ethanol, 70°C; c) 4-cyanobezoyl chloride, $NaHCO_3$, CH_2Cl_2/H_2O; d) H_2S, Py/DMF; e) R_1I, DMF/acetone/H_2O, 50℃; f) DMF/H_2O, 80℃.

Figure 2 The X-ray crystallography of compound **5B**

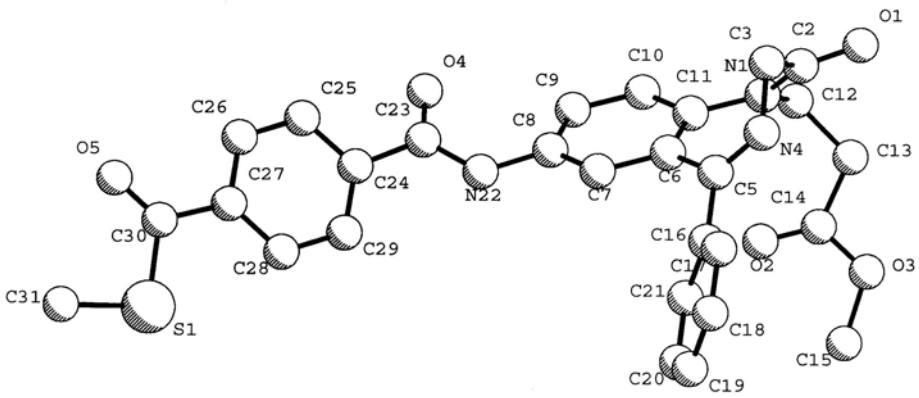


Table 1 The analytical data of the inhibitors

Comp.	^{1}HNMR (300MHz, $CDCl_3$, δ ppm)	Elemental Analysis	Calcd.	Found
5A	8.04-7.99 (m, 3H, J=8.4Hz), 7.90-7.87 (AB, 4H, J=8.4Hz), 7.67-7.33(m, 7H), 4.83 (AX, 1H, J=10.5Hz), 4.61-4.45 (m, 2H), 4.20-4.15 (m, 2H, J=7.2Hz), 3.89 (AX, 1H, J=10.5Hz), 2.49 (s, 3H), 1.21 (m, 3H, J=7.2Hz)	C H N	63.60 5.34 7.67	63.80 5.47 7.94
5B	8.31 (s, 1H), 8.06-8.03 (dd, 1H), 7.99-7.88 (AB, 4H, J=8.4Hz), 7.63-7.34 (m, 7H), 4.70 (AX, 1H, J=10.5Hz), 4.56-4.48 (m, 1H), 3.93-3.84 (m, 1H), 3.74 (AX, 1H, J=10.5Hz), 3.40 (s, 3H), 2.66-2.42 (m, 2H), 2.48(s, 3H)	X-ray		
5C	8.14 (s, 1H), 8.07-8.03 (dd, 1H), 8.01-7.88 (AB, 4H, J=8.4Hz), 7.64-7.36 (m, 7H), 4.74 (AX, 1H, J=10.2Hz), 4.34-4.29 (m, 1H), 4.05-3.97 (m, 2H), 3.76 (AX, 1H, J=10.2Hz), 3.69-3.66 (m, 1H), 2.49 (s, 2H), 2.20-2.10 (m, 2H), 1.90-1.71 (m, 2H), 1.15 (t, 3H, J=7.2Hz)	C H N	64.15 5.56 7.48	64.41 5.33 7.69
5D	8.04-8.01 (m, 3H), 7.89-7.41 (AB, 1H, J=8.4Hz), 7.68-7.33 (m, 7H), 4.82 (AX, 1H, J=10.5Hz), 4.61-4.45 (dd, 2H), 4.20-4.13 (m, 2H), 3.89 (AX, 1H, J=10.5Hz), 3.08 (t, 2H), 1.70-1.28 (m, 12H), 1.21 (t, 3H), 0.87 (t, 3H)	C H N	68.49 6.41 6.84	68.47 6.37 6.99
5E	8.07-8.02 (m, 3H), 7.90-7.87 (AB, 4H, J=8.4Hz), 7.67-7.38 (m, 7H), 4.75 (AX, 1H, J=10.5Hz), 4.58-4.54 (m, 1H), 3.95-3.90 (m, 1H), 3.77 (AX, 1H, J=10.5Hz), 3.42 (s, 3H), 3.08 (t, 3H), 2.65-2.52 (m, 2H), 1.72-1.21 (m, 12H), 0.87 (t, 3H)	C H N	68.49 6.41 6.85	68.15 6.43 6.63
5F	8.18 (s, 1H), 8.06-8.05 (m, 1H), 8.07-7.82 (AB, 4H, J=8.4Hz), 7.62-7.35 (m, 7H), 4.75 (AX, 1H, J=10.5Hz), 4.36-4.27 (m, 1H), 4.05-3.97 (m, 2H, J=7.2Hz), 3.79 (AX, 1H, J=10.5Hz), 3.72-3.63 (m, 1H), 3.07 (t, 2H, J=7.2Hz), 2.23-2.07 (m, 2H), 1.93-1.27 (m, 14H), 1.15 (t, 3H, J=7.2Hz), 0.87 (t, 3H, J=6.9Hz)	C H N	69.24 6.75 6.55	69.13 6.84 6.71

The successful exploration of the thioester synthetic method affords a simple approach to the designed inhibitors. The preliminary pharmacological results showed that the EC_{50} of compound **5B**, **5C** and **5F** on A549 (one kind of lung tumor cell lines) are 17.82 , 9.85 and 27.29 μmol/L, respectively, and the EC_{50} of compound **5B, 5C** and **5F** on HT-29 (one kind of colon tumor cell lines) are 44.86 , 26.01 and 86.23 μmol/L, respectively. Adriamycin is tested together with those compounds as control-group drug, the EC_{50} of which on A549 and HT-29 are 0.002 μmol/L and 0.032 μmol/L. The further evaluation of the biological activities is in progress.

Acknowledgments

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References

1. B. E. Evans, K. E. Rittle, M. G. Bock, *et al., J. Med. Chem.*, **1988**, *31*(12), 2235.
2. A. A. Patchett, R. P. Nargund, *Annual Reports in Medicinal Chemistry*, **2000**, *35*, 289.
3. S. B. Wan, F. M. Chu, Z. R. Guo, *Yao Xue Xue Bao (Acta Pamaceutica Sinica*, in Chinese), **2002**, *37*(7), 516.
4. M. Daniele, J. S. Leonard, *Drug of the Future*, **1999**, *24*(10), 1099.
5. S. Martin, B. Markus, S. Isabel, *et al.*, *Bioorg. Med. Chem.*, **2000**, *8*(8), 1991.
6. A. Z. Jeffery, G. R. Joseph, *et al. J. Med. Chem.*, **1995**, *38*, 2378.
7. I. O. Shin, I. Yoshihisa, *et al. Chem. Pharm. Bull.*, **1999**, *47*(12), 1685.
8. C. M. Stevens, D. S. Tarbell, *Journal of Organic Chemistry*, **1954**, *19*, 1996.
9. G. M. Coppola, M. J. Shapiro, *Journal of Heterocyclic Chemistry*, **1981**, *18*(3), 495.

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