Synthesis of SF2809-V, Chymase Inhibitor, and Its Analogs by Three Component Reaction: Model Study for High Throughput Synthesis of a Chymase Inhibitor Library

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SF2809-V, chymase inhibitor, was synthesized by a three component reaction and its sixteen analogs were also synthesized to establish a method for preparation of a chymase inhibitor library.

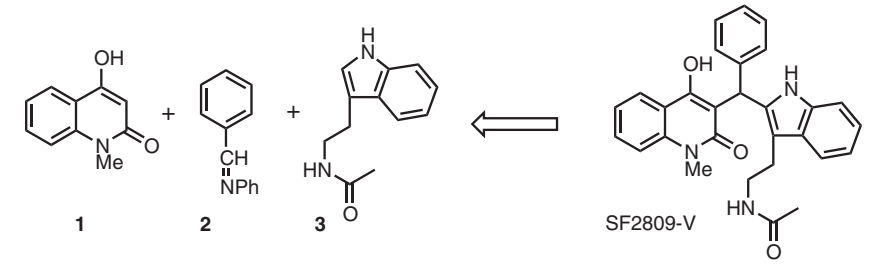
SF2809-V, a new class of chymase inhibitor, was isolated as a racemate from fermentation broth of an actinomycete (*Dactylosporangium* sp. SF2809) and its structure was determined as shown in Scheme 1.[1] Chymase is dominant to angiotensin converting enzyme (ACE) to generate angiotensin II from angiotensin I in the heart.[2] ACE inhibitors are widely used in the treatment of hypertention and congestive heart failure. Therefore, it is considered that a chymase inhibitor could be a promising drug for treatment of cardiovascular diseases.

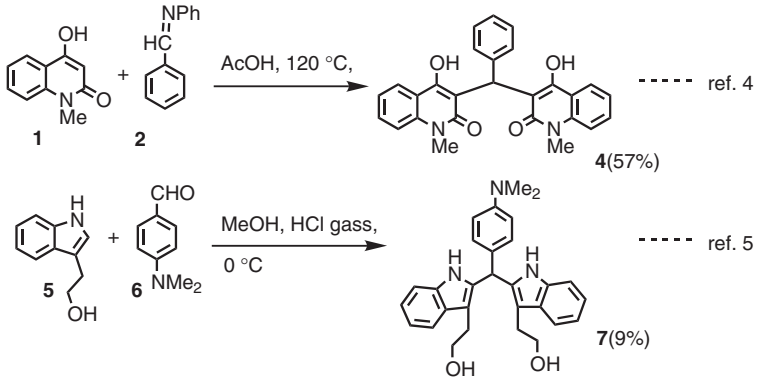
To increase chymase inhibitory activity, we need a method for preparation of a huge number of SF2809-V analogs (chymase inhibitor library) by high throughput synthesis which is a powerful tool for accelerating lead optimization in drug discovery. In liquid phase synthesis, multiple component reaction is a suitable method for high throughput synthesis, for example, Ugi, Biginelli, and Mannich reactions are widely established.[3]

Herein, we describe the synthesis of SF2809-V by a three component reaction and optimization of the reaction. In addition, sixteen analogs of SF2809-V were prepared to establish a method for preparation of a chymase inhibitor library.

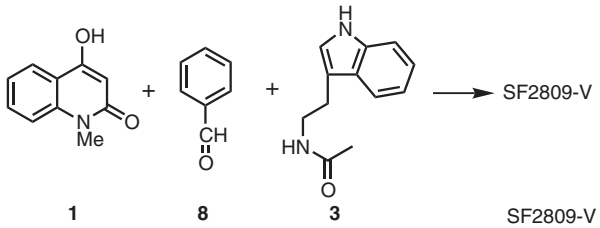
Based on Refs. 4 and 5, we planned to synthesize SF2809-V from 4-hydroxy-1-methyl-2-quinolone (**1**), *N*-benzylideneaniline (**2**), and *N*-acetyltryptamine (**3**) by a three component reaction (Scheme 1). SF2809-V was successfully synthesized from **1**, **2**, and **3** in acetic acid at 120 °C for 4.5 h. The yield of SF2809-V was 16% and ^{1}H NMR and mass spectral data of synthetic SF2809-V were in accord with those of naturally occurring SF2809-V isolated from the actinomycete. In this reaction, formation of the undesired compound **4** took precedence over that of SF2809-V. To improve the yield of SF2809-V, we optimized the reaction using **1**, **8**, and **3** in various acids and solvents.

SF2809-V was obtained in 50% yield in acetic acid at 60 °C for 20 h (Scheme 2). By the use of excess benzaldehyde (1.5 equiv.) for suppression of formation of **4**, SF2809-V was synthesized in 80% yield at 70 °C for 20 h (Scheme 2).[6] We have also examined other protocols (trifluoroacetic acid, sulfuric acid, hydrochloric acid, *p*-toluenesulfonic acid, pyridinium *p*-toluenesulfonate, and Nafion® NR50 in various solvents, titanium(IV) chloride in dichloromethane, and boron trifluoride diethyl etherate in dichloromethane). Unfortunately, these procedures were not as effective as the method using acetic acid. In most cases, compound **1** showed poor solubility against reaction solvent, un-



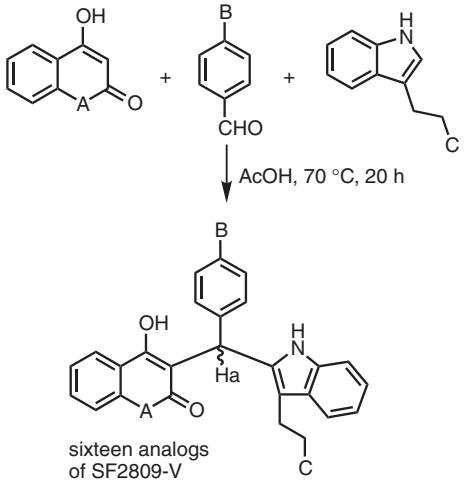


Scheme 1.



1	8	3		SF2809-V
0.20 mmol	0.20 mmol	0.20 mmol	60 °C, 20 h	50%
0.20 mmol	0.30 mmol	0.20 mmol	70 °C, 20 h	80%

Scheme 2.



	A	B	C	yield	MS(*m/z*)
9	NMe	CF_3	–OCOPh	90%	595(M-H)$^-$/ 596 [a]
10	O	CF_3	–OCOPh	92%	582(M-H)$^-$/ 583
11	NMe	Me	–OCOPh	57%	543(M+H)$^+$/ 542
12	O	Me	–OCOPh	88%	528(M-H)$^-$/ 529
13	NMe	CF_3	–NNCONMePh	84%	623(M-H)$^-$/ 624
14	O	CF_3	–NNCONMePh	78%	610(M-H)$^-$/ 611
15	NMe	Me	–NNCONMePh	71%	571(M+H)$^+$/ 570
16	O	Me	–NNCONMePh	66%	556(M-H)$^-$/ 557
17	NMe	CF_3	–NHCOPh	82%	594(M-H)$^-$/ 595
18	O	CF_3	–NHCOPh	93%	581(M-H)$^-$/ 582
19	NMe	Me	–NHCOPh	68%	542(M+H)$^+$/ 541
20	O	Me	–NHCOPh	84%	527(M-H)$^-$/ 528
21	NMe	CF_3	–$NHSO_2Ph$	89%	630(M-H)$^-$/ 631
22	O	CF_3	–$NHSO_2Ph$	85%	617(M-H)$^-$/ 618
23	NMe	Me	–$NHSO_2Ph$	77%	578(M+H)$^+$/ 577
24	O	Me	–$NHSO_2Ph$	90%	563(M-H)$^-$/ 564

a) Found / calcd

Scheme 3.

desired compound **4** was mainly obtained, or separation of SF2809 was difficult from complex reaction mixtures, and so SF2809-V was not efficiently synthesized. We decided to use the procedure described in reference 6 to prepare a model library.

We designed and prepared sixteen analogs of SF2809-V containing various components to confirm the usefulness of the optimized reaction condition. All compounds were successfully synthesized in a good to an excellent yield by the reaction condition mentioned above (Scheme 3). In Scheme 3, mass spectral data of sixteen analogs are shown. In ^{1}H NMR spectra of **9**–**24**, a peak (1H, s) of a characteristic Ha proton was observed at 6.0–6.4 ppm in all analogs of SF2809-V.

In conclusion, SF2809-V was successfully synthesized in 80% yield by a three component reaction and sixteen analogs of SF2809-V were rapidly prepared. We have been able to establish a method for high throughput synthesis of a chymase inhibitor library.

References and Notes

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