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A Novel Thiolate Mediated Cyclization to OPC-15161

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Abstract—An efficient synthetic route to OPC-15161 (**1**) was developed via novel pyrazine ring closure promoted by a lithium thiolate anion. The key intermediate (**4**) was prepared in a one-pot procedure by treating the methyl ester (**2**) with a lithium arylthiolate. This protocol does not require a free acid intermediate and thus can establish the shortest route to pyrazine dioxide skeleton from tryptophan ester derivatives. In the present transformation, lithium arylthiolates could behave like aluminium arylthiolates, and not like lithium alkylthiolates that often cleave esters to the corresponding acids. One-pot reactions that involve lengthy multiple steps in a single flask are of significant importance in contemporary organic synthesis. Utilization of a catalytic or stoichiometric promoter which can facilitate several transformations is a key to the success of such reactions. In this paper, we would like to disclose an interesting one-pot transformation discovered in our process research, which offered us novel information on the reactivity of metal thiolates. Main feature of our one-pot process is a merged deprotection-cyclization sequence. © 2000 Elsevier Science Ltd. All rights reserved.

OPC-15161 (**1**) is a novel inhibitor against superoxide anion generation, isolated in our institute from the product of the culture broth of fungus Thielavia *minor* OFR-1561.[1] Previous reports have already described successful chemical syntheses of **1**, though they necessitated undesirable multiple steps with low yields.[2] These initial difficulties have been overcome in our plant-scale synthesis through the beneficial use of a protecting group.[3] We now wish to report here another practical synthetic route to **1**, which includes a novel and simple cyclization protocol for the pyrazine dioxide skeleton. This new method is notable because the cyclization can be achieved by the use of a metal thiolate anion. Furthermore, *N*,*O*-diprotected oxime ester (**2**) was employed as starting material without extra conversion to the deprotected hydroxyimino carboxylic acid precursor as depicted in Scheme 1.

Here again, we utilized 2-cyanoethyl (CE) group as a key protecting group for the N^1-position of pyrazinone, because it can be introduced and removed by a simple alkaline treatment and does not interfere with the sensitive part of the molecule (indole ring).[3]

The key intermediate *N*,*O*-diprotected ester (**2**) was prepared without event (for the detailed sequence, see Experimental). Hydrolysis of this ester (**2**) with aq. NaOH followed by the addition of boric acid and dimethyl sulfate gave the corresponding *N*-protected methyl esters (**3a**) in 65% yield. On the other hand, *N*-protected benzyl ester (**3b**) was also prepared in 44% yield in a similar manner using benzyl bromide instead of dimethyl sulfate.

Having obtained these precursors, we next investigated the transformation of the hydroxyimino esters (**3**) using various kinds of metal thiolates in an attempt to form an active thioester intermediate. While aliphatic metal thiolates gave only complex mixtures, some aromatic or heterocyclic metal thiolates were found to be an excellent promoter for the sequential transformation to the cyclized product (**4**). The pyrazine (**4**) was directly obtained from *N*,*O*-diprotected ester (**2**) in a good yield when treated with lithium 2-benzimidazolethiolate generated in situ from 2-mercaptobenzimidazole and excess lithium hydroxide in DMF. The pyrazine (**4**) was also obtained in good yields *without* the addition of excess lithium hydroxide when lithium naphthalenethiolate was used. This direct conversion of **2** to **4** did not take place in CH_3CN, while with deprotected substrates (**3a**, **3b**), reaction proceeded even in CH_3CN. The results obtained are summarized in Table 1. Fig. 1 also delineates the reaction course monitored by HPLC.

These experimental observations suggested that the steric effect of the alkoxycarbonyl group was small, because no significant difference in yields was observed between **3a** and **3b**. The resulting hydroxypyrazinone (**4**) was methylated with dimethyl sulfate to give the key intermediate (**5**) in 61% yield. To our delight, **5** was directly obtained in 37% yield from **2** in one-pot procedure by treating with *lithium 2-naphthalenethiolate* followed by subsequent methylation. Same conversion (**2** to **5**) by *lithium 2-benzimidazolethiolate* gave less satisfactory results due to the formation of by-products. This new sequence was operationally simple and useful to prepare methoxypyrazinone (**5**).

Keywords: one-pot reaction; alkylthiolates; aluminium arylthiolate.
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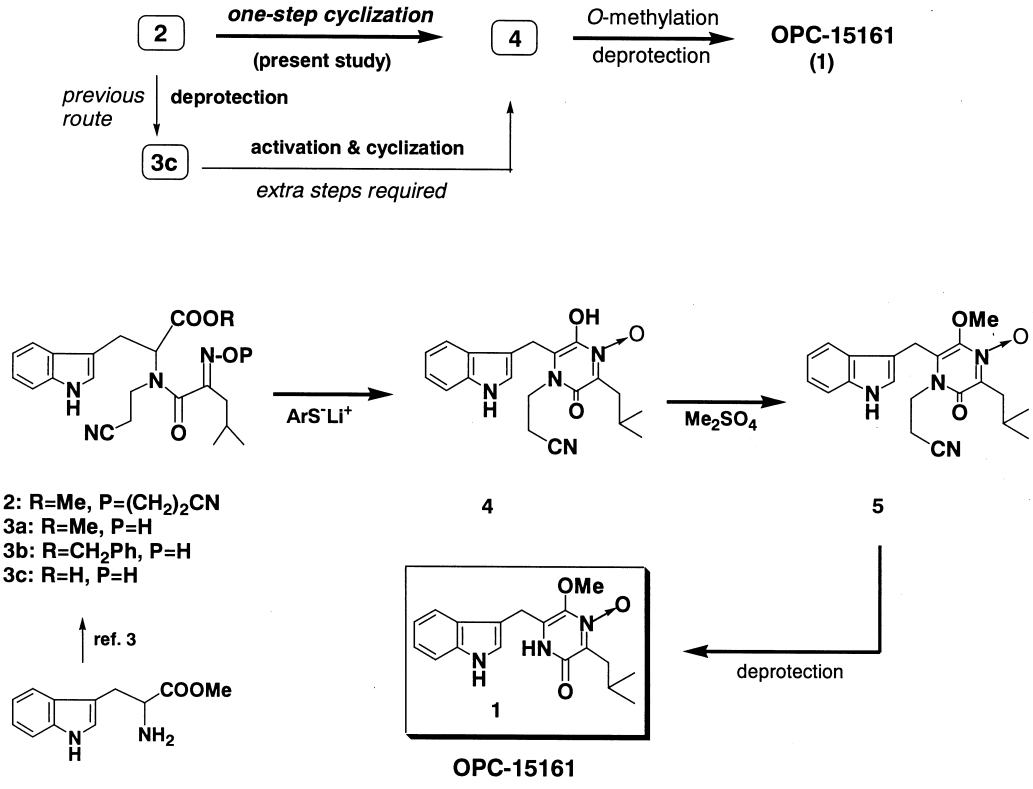


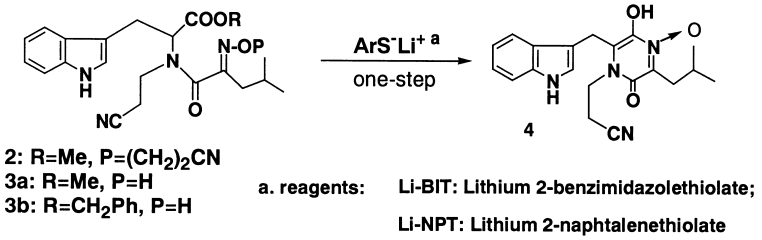
Scheme 1. Direct cyclization sequence without deprotection.

Although the partially deprotected hydroxyimino esters (**3a** and **3b**) could be used for the same purpose, the *N*,*O*-diprotected ester (**2**) was considered to be a better synthetic intermediate because of the operational simplicity (less steps required for preparation) and a higher isolated yield. It also should be noted that deprotected hydroxyimino acids were relatively unstable and more prone to isomerization at oxime. We observed that **3a** and **3b** contained *syn*-oxime isomer, which could not be cyclized into the pyrazine (**4**).

Insights into the Mechanism

The cyclization described above is notable because almost no reports have disclosed related cyclization between oxime-nitrogen and ester promoted by a metal thiolate. We initially speculated that this cyclization from **2** to **4** was brought about in the presence of a catalytic amount of thiolate (as indicated in the following Scheme 2). However, the actual reaction required more than 1.1 (and optimally 1.5–2.5) equivalents of the thiolate as shown in Table 1.

Table 1. Thiolate promoted cyclization



SM	ArS (equiv.)[a]/base (equiv.)	Solvent, time	**4** (% HPLC yield)
2	Li–BIT (2.0)/LiOH (1.0)	DMF, 2.5 h	80
2	Li–BIT (2.5)	DMF, 1.5 h	8
2	Li–NPT (1.5)	DMF, 0.8 h	55
2	Li–NPT (2.0)/LiOH (1.0)	DMF, 1.8 h	58
3a	Li–BIT (3.0)	DMF, 2.0 h	60
3a	Li–BIT (1.6)	CH_3CN, 1.5 h	53
3a	Na-NPT (1.4)	CH_3CN, 1.5 h	58
3b	Li–BIT (3.0)	DMF, 2.1 h	79
3b	Li–BIT (1.6)	CH_3CN, 1.5 h	52
3b	Li–NPT (1.3)	CH_3CN, 1.5 h	60

[a] Li–BIT: Lithium 2-benzimidazolethiolate; Li–NPT: Lithium 2-naphthalenethiolate.

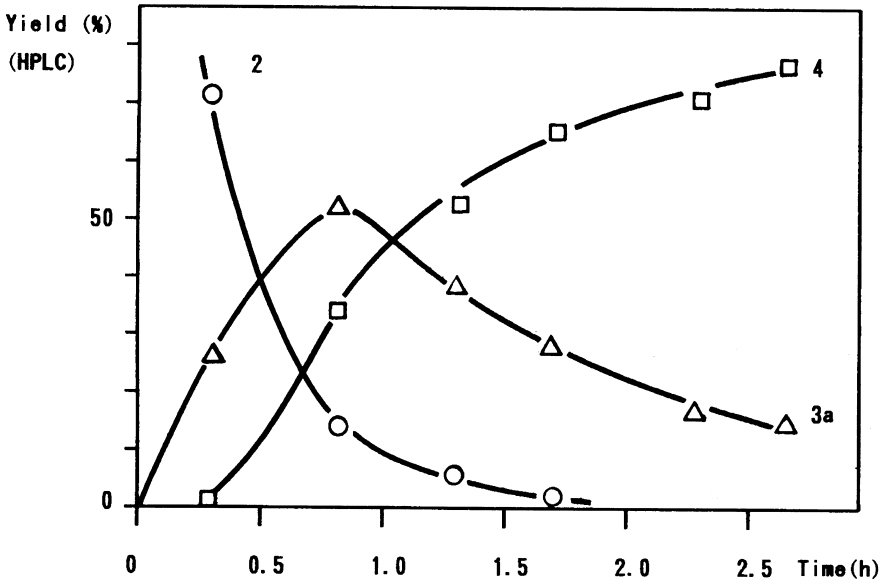
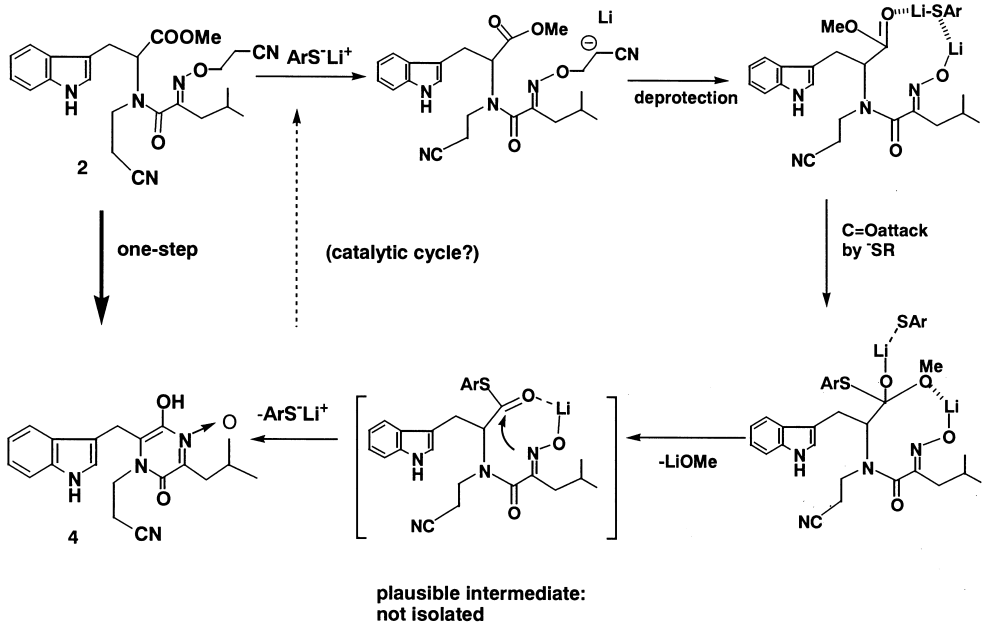


Figure 1. Cyclization of *N,O*-diprotected ester (**2**) with lithium 2-benzimidiazolethiolate (2.5 equiv.) and LiOH (1.0 equiv.) in DMF.

We then assumed that at least one equivalent of the reagent was consumed in the formation of the stable product, 2-cyanoethyl sulfide. Another possibility was some kind of complexation with the substrate (as indicated in Scheme 2). In fact, generation of the lithium thiolate for the catalytic path was not a feasible process. A plausible reaction pathway was proposed to understand the role of the lithium thiolate (as shown in Scheme 2). Thus, the reaction started with C–O bond fission in the CE group to form the oxime anion under basic conditions. This was followed by the controlled nucleophilic attack of a thiolate anion on the carbonyl carbon to reach to the key intermediate shown. Another more simple description might be possible, but we believe, the final step is most likely an intramolecular nucleophilic attack of the oxime nitrogen on the carbonyl carbon of the thiol ester. Several unsuccessful attempts have been made to isolate this intermediate thiol ester so far.

Besides these inspections, it is interesting to note here the reactivity of the thiolates towards alkyl esters. The reaction described here is not similar to the reported patterns of lithium alkylthiolates. Lithium alkylthiolates such as lithium propanethiolate are reported to cleave esters into the corresponding acids[4,5] In the present cyclization, we believe, lithium arylthiolates could behave like aluminium arylthiolates,[5] which can produce thioesters in a single step. Thus, lithium arylthiolates are different from lithium alkylthiolates in their behavior towards esters.

Additionally, we observed that sodium arylthiolates were



Scheme 2. Thiolate-mediated ring closure from **2** to **4**.

ineffective for the conversion of **2** into **4**, but did promote the cyclization from **3a** as shown in Table 1.

The subtle assistance of a lithium ion associated with the steric surroundings of **2** might be key factors involved in this cyclization reaction, which will be the subject of our further research.

Summary

In the quest for an efficient synthetic pathway to the dioxygenated pyrazines, we developed here a novel thiolate-mediated ring closure. The key cyclization is triggered by the deprotection of one CE group by a lithium arylthiolate. The subsequent cyclization to pyrazine skeleton was presumably assisted by a lithium cation. Thus, the penultimate intermediate (**5**) was prepared in a one-pot procedure by treating the precursor methyl ester (**2**) with lithium 2-naphthalenethiolate followed by methylation with dimethyl sulfate in 37% yield. The resulting pyrazinone (**5**) was successfully converted to OPC-15161 (**1**) by the treatment with sodium hydroxide in DMF–methanol. Our process research here again revealed the important and crucial assistance of a protecting group for a new type of ring closure to inaccessible pyrazinones as well as some synthetic potential of a thiolate anion for attaining one-pot process.

Experimental

All the melting points were uncorrected. Analytical determinations by HPLC were performed on a Shimadzu LC-6A liquid chromatography with a TSK gel ODS-80TM column. ^{1}H NMR spectra were taken at Varian 200 MHz spectrometer. IR spectra were recorded with a Perkin–Elmer 1600 series FTIR apparatus. Mass spectra were recorded with a Shimadzu GCMS-QP1000 spectrometer at 70 eV.

Metal thiolates

Metal thiolates used in the following experiments were prepared from the corresponding thiols by usual methods (from ArSH and LiOH).[5] They were also prepared in situ by treating thiols with one or more equivalents of anhydrous lithium hydroxide in dry DMF.

***N*-[2-(2-Cyanoethoxyimino)isohexanoyl]-*N*-(2-cyanoethyl)-L-tryptophan methyl ester (2).** 2-(2-Cyanoethoxyimino)-isohexanoyl chloride (2.14 kg, 9.88 mol) was added to a stirred solution of *N*-(2-cyanoethyl)-L-tryptophan methyl ester (1.44 kg, 4.72 mol) in dichloromethane (12 l) during 1 h at 27–28°C, and the solution was stirred further for 35 min at 22–25°C. Then aq. potassium carbonate (2.4 kg in 3 l of water) was added to the solution. The organic layer was separated, washed with aq. potassium carbonate, 20% hydrochloric acid, and saturated aq. sodium chloride, dried over $MgSO_4$, concentrated, and recrystallized from 60% aq. *i*-PrOH to give **2** (1340 g, 63%); mp 102–103°C (recrystallized from acetonitrile). IR (neat): 3398, 2961, 2250, 1728, 1634, 1435, 1266, 961, and 744 cm^{-1}. ^{1}H NMR ($CDCl_3$): 0.61 (d, *J*=6.8 Hz, 0.9H), 0.65 (d, *J*=6.8 Hz, 0.9H), 0.90 (d, *J*=6.8 Hz, 2.1H), 0.91 (d, *J*=6.8 Hz, 2.1H), 1.53–1.61 (m, 0.6H), 1.82–2.14 (m, 1H), 2.19 (dt, *J*=4.3, 1.8 Hz, 1.4H), 2.42–2.57 (m, 1.4H), 2.64 (dt, *J*=6.0, 2.2 Hz, 0.6H), 2.72 (t, *J*=6.0 Hz, 1.4H), 2.87 (dt, *J*=4.5, 2.5 Hz, 0.6H), 3.18–3.33 (m, 1H), 3.43–3.67 (m, 2.4H), 3.81–3.87 (m, 3.6H), 4.05 (dt, *J*=6.0, 2.2 Hz, 0.6H), 4.25 (t, *J*=6.0 Hz, 1.4H), 4.39 (dd, *J*=10.4, 5.0 Hz, 0.7H), 5.20 (dd, *J*=10.0, 4.7 Hz, 0.3H), 6.99–7.17 (m, 3H), and 7.34–7.39 ppm (m, 1H). Anal. Calcd for $C_{24}H_{29}N_5O_4$: C, 63.84; H, 6.47; N, 15.51. Found: C, 63.82; H, 6.41; N, 15.41.

***N*-(2-Cyanoethyl)-*N*-(2-hydroxyiminoisohexanoyl)-L-tryptophan methyl ester (3a).** A mixture of 4N-sodium hydroxide aq. solution (0.75 ml), **2** (0.45 g, 1.00 mmol), and THF (20 ml) was stirred at room temperature for 15 h. After addition of DMF (20 ml) and boric acid (124 mg, 2.01 mmol), the solution was stirred further for 30 min. Then dimethyl sulfate (0.40 ml, 4.23 mmol) was added to the solution and stirred further for 2 h. The solution was diluted with ethyl acetate, washed with saturated aq. sodium hydrogen sulfate and saturated aq. sodium chloride, dried over $MgSO_4$, and concentrated. Purification by column chromatography (silica gel, dichloromethane/methanol=99:1) gave pure **3a** (0.26 g, 65%); mp 122–124°C. ^{1}H NMR ($CDCl_3$): 0.73 (m, 1.5H), 0.91 (m, 4.5H), 3.71 (s, 0.75H), 3.76 (s, 2.25H), 4.18 (dd, *J*=10.8 Hz, 0.25H), 6.9–7.4 (m, 4H), 7.56 (d, *J*=8 Hz, 1H), 8.00 (s, 0.75H), 8.90 (s, 0.25H), and 9.41 ppm (s, 0.25H). Anal. Calcd for $C_{21}H_{26}N_4O_4 \cdot 0.3H_2O$: C, 62.44; H, 6.44; N, 13.87. Found: C, 62.43; H, 6.50, N, 13.96.

***N*-(2-Cyanoethyl)-*N*-(2-hydroxyiminoisohexanoyl)-L-tryptophan benzyl ester (3b).** Benzyl ester **3b** (2.11 g, 44%) was obtained from **2** by using benzyl bromide (2 equiv based on **2**) instead of dimethyl sulfate in the same manner as in the above experiment. ^{1}H NMR ($CDCl_3$): 0.68 (d, *J*=6.4 Hz, 2.4H), 0.85 (d, *J*=6.6 Hz, 3.6H), 1.6–2.3 (m, 5H), 2.5 (m, 1.2H), 2.7 (t, *J*=6 Hz, 0.8H), 3.1–3.8 (m, 4.4H), 4.2 (t, *J*=9 Hz, 0.6H), 5.19 (s, 2H), 7.34 (s, 5H), 6.9–7.4 (m, 4H), 7.58 (d, *J*=10 Hz, 1H), and 8.25 ppm (br, s, 1H). MS *m/z* (rel. int.): 474 (M^+, 1), 201 (20), and 130 (100). Anal. Calcd for $C_{27}H_{30}N_4O_4$: C, 68.34; H, 6.37; N, 11.81. Found: C, 68.16; H, 6.48, N, 11.64.

1-(2-Cyanoethyl)-3-isobutyl-5-hydroxy-6-(indol-3-yl)-methyl-1,2-dihydropyrazin-2-one 4-oxide (4). *Method A:* A mixture of 2-mercaptobenzimidazole (6.67 g, 44.4 mmol), anhydrous lithium hydroxide (1.60 g, 66.6 mmol), and dry DMF (150 ml) was stirred at room temperature for 30 min. After addition of **2** (10.0 g, 22.2 mmol), the mixture was stirred further for 3 h at room temperature, then diluted with ethyl acetate (500 ml), and poured into ice-cold hydrochloric acid (500 ml). The organic layer was separated, washed with water, and extracted with aq. sodium hydrogen carbonate, which was then acidified with hydrochloric acid, and extracted with ethyl acetate. The organic extract was washed with water, dried over $MgSO_4$, and concentrated in vacuo at room temperature to give crude **4** (5.03 g, 62%) as an unstable yellow amorphous solid. IR (KBr): 3310, 1600, 1174, 1099, and 746 cm^{-1}. ^{1}H NMR ($CDCl_3$): 0.97 (d, *J*=7 Hz, 6H), 2.18–2.40 (m, 1H), 2.48 (t, *J*=6 Hz, 2H), 2.89 (d, *J*=7 Hz, 2H), 3.0–4.0 (br s, 1H), 4.21 (t, *J*=6 Hz, 2H), 4.36 (s, 2H), 7.03–7.63 (m, 5H), and 8.30 ppm (br s,

1H). MS *m*/*z* (rel. int.): 366 (M^+, 3), 350 (15), and 130 (100).

Method B: A mixture of **3b** (40.9 mg, 0.0862 mmol), lithium 2-benzimidazolethiolate (40.0 mg, 0.256 mmol), and dry DMF (0.4 ml) was stirred for 2 h at room temperature. The yield of **4** (79%) was determined by HPLC analysis based on the calibration curve.

1-(2-Cyanoethyl)-3-isobutyl-5-methoxy-6-(indol-3-yl)-methyl-1,2-dihydropyrazin- 2-one 4-oxide (5). *Method A:* A mixture of 2-naphthalenethiol (8.52 g, 53.2 mmol), anhydrous lithium hydroxide (1.27 g, 53.2 mmol), and dry DMF (100 ml) was stirred for 15 min at room temperature. Then a solution of **2** (12.0 g, 22.6 mmol) in DMF (40 ml) was added and the mixture was stirred further for 2.3 h at room temperature. After addition of powdered anhydrous potassium carbonate (18.4 g, 133 mmol) and dimethyl sulfate (12.6 ml, 133 mmol), the mixture was stirred further for 1.8 h, poured into cold water, then extracted with ethyl acetate. The extract was washed with water, dried over $MgSO_4$, and concentrated to ca. 1/4 volume. The resulting precipitate was separated by filtration and dried in vacuo to give **5** (3.75 g, 37%); mp 223–225°C. IR (neat): 3320, 2251, 1659, 1614, 1259, 1614, 1259, 910, and 733 cm^{-1}. ^1H NMR ($CDCl_3$): 0.96 (d, *J*=7 Hz, 6H), 2.18–2.40 (m, 1H), 2.53 (t, *J*=7 Hz, 2H), 2.85 (d, *J*=7 Hz, 2H), 4.00 (s, 3H), 4.11 (t, *J*=7 Hz, 2H), 4.31 (s, 2H), 6.90–7.65 (m, 5H), and 8.68 ppm (br, s, 1H). Anal. Calcd for $C_{21}H_{24}N_4O_3$: C, 66.30; H, 6.36; N, 14.73. Found: C, 66.36; H, 6.55; N, 14.60.

Method B: Dimethyl sulfate (64 mg, 0.51 mmol) and powdered anhydrous potassium carbonate (70 mg, 0.51 mmol) were added to a stirred solution of **4** (93.5 mg, 0.255 mmol) in dry DMF (1.3 ml). The mixture was stirred at room temperature for 20 min, then diluted with ethyl acetate (10 ml), washed with cold water, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by TLC (silica gel, chloroform/methanol=20:1) to give **5** (58.8 mg, 61%).

6-(Indol-3-yl)methyl-3-isobutyl-5-methoxy-1,2-dihydropyrazin-2-one 4-oxide (OPC-15161) (1). A mixture of **5** (2.16 g, 5.68 mmol), sodium hydroxide (1.50 g, 37.5 mmol), DMF (10 ml), and methanol (10 ml) was stirred at room temperature for 30 min. The mixture was poured into cold water, and acidified with hydrochloric acid. The resulting crystals were collected by filtration and dried in vacuo to give **1** (1.79 g, 96%); mp 225°C. IR (KBr): 3246, 1627, 1373, 1247, 1100, 998, 744, 719, and 521 cm^{-1}. ^1H NMR (DMSO): 0.84 (d, *J*=6.6 Hz, 6H), 1.97–2.12 (m, 1H), 2.60 (d, *J*=7.1 Hz, 2H), 3.76 (s, 3H), 3.91 (s, 2H), 6.93–7.59 (m, 5H), 10.97 (br s, 1H). These spectroscopic data were identical with those of authentic sample.

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