

# One-Pot Three-Component Synthesis of Pyrano [3,2-*b*]pyrazolo[4,3-*e*]pyridin-8(1*H*)-ones

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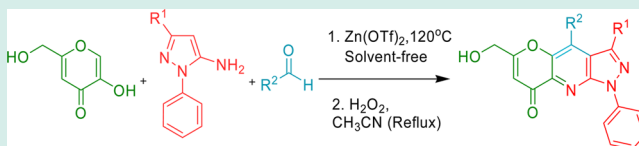
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## S Supporting Information

**ABSTRACT:** An efficient one-pot synthesis of novel pyrano [3,2-*b*]pyrazolo[4,3-*e*]pyridin-8(1*H*)-ones via three-component condensation of kojic acid, 1-*H*-pyrazol-5-amines and aldehydes in the presence of a catalytic amount of Zn(OTf)<sub>2</sub> followed by H<sub>2</sub>O<sub>2</sub>-mediated oxidation is reported. Furthermore, the synthesis of 1'*H*-spiro[indoline-3,4'-pyrano[2,3-*b*]pyrazolo[3,4-*e*]pyridine]-2,8'(9'*H*)-diones were chosen for the library validation.

**KEYWORDS:** three-component, Zn(OTf)<sub>2</sub>, H<sub>2</sub>O<sub>2</sub>, kojic acid, 1-*H*-pyrazol-5-amines



## INTRODUCTION

Recently, multicomponent reactions (MCRs) have shown to afford efficient access to highly complex final products in a single step. They have proven to be fast, convergent, atom efficient reactions often avoiding complicated purifications.<sup>1</sup> These reactions have emerged as a valuable tool in the synthesis of drug libraries because they have significant advantages over conventional reaction strategies to generate biologically active scaffolds with significant structural diversity.<sup>2</sup> Consequently, designing novel MCRs for the synthesis of diverse drug-like molecules has been the focus of many researchers.

Multiheterocyclic compounds have shown a wide spectrum of biological activities for access to the pharmaceutical and medicinal products.<sup>3</sup> In particular, pyrazolo[3,4-*b*]pyridines have emerged as a potentially interesting scaffold for biologically active compounds because of their structural analogy to purine bases, an important constituent of DNA and RNA nucleosides.<sup>4</sup> These heterocycles have been identified as anti-inflammatory,<sup>5</sup> antibacterial,<sup>6</sup> antiherpetic,<sup>7</sup> and selective inhibitors of A1 adenosine receptors.<sup>8</sup> They have also been reported as a potent treatment of Alzheimer's and gastrointestinal diseases as well as drug addiction and infertility.<sup>4,9</sup> Moreover, the existence of pyranopyridines in the framework of several biologically active compounds as well as natural alkaloids of plant origin<sup>10</sup> has encouraged researchers to synthesize and investigate their potential biological activities. For instance, pyrano[2,3-*b*]pyridines are known to exhibit antiallergic,<sup>11</sup> anti-inflammatory,<sup>12</sup> antiproliferative,<sup>13</sup> antihypertensive,<sup>14</sup> anti-antimicrobial,<sup>15</sup> and antiasthmatic activities.<sup>16</sup>

Kojic acid, is a natural substance produced by various fungal or bacterial strains, such as *Aspergillus oryzae*, *Penicillium* or *acetobacter* species. This compound acts as a natural antioxidant and scavenger of reactive oxygen species.<sup>17</sup> Also, its manganese complex showed potent radio-protective activity,<sup>18</sup> lipid

peroxidation inhibitory and protective effects against neurodegenerative diseases induced by free radicals activators.<sup>19</sup> Furthermore, Kojic acid derivatives have shown effective bioactivities as anti-HIV,<sup>20</sup> antibacterial,<sup>21</sup> antidiabetes,<sup>22</sup> hepatitis C virus inhibitory<sup>23</sup> and tyrosinase inhibitors.<sup>24</sup> Therefore, the synthesis of kojic acid derivatives has been received with great attention in bioorganic and medicinal chemistry.

Similarly, spiro-oxindole substructures received much attention from the synthetic community,<sup>25</sup> prompted by their appearance in the core structure of many pharmacological agents and neutral alkaloids.<sup>26</sup> Considering the above reports, designing a new synthetic pathway to generate diverse fused-complex structural compounds, which are a multicomination of these highly bioactive heterocycles, is a great challenge in the modern drug discovery.

As a consequence of our interest in heterocyclic synthesis,<sup>27</sup> herein we wish to report a three component synthesis of pyrano[3,2-*b*]pyrazolo[4,3-*e*]pyridin-8(1*H*)-one derivatives in the presence of Zn(OTf)<sub>2</sub> followed by H<sub>2</sub>O<sub>2</sub>-mediated oxidation.

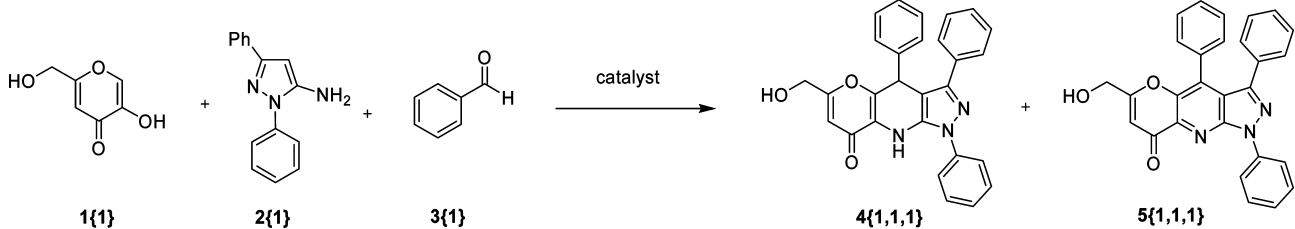
## RESULTS AND DISCUSSION

At the outset, the reaction of kojic acid (1 mmol), 1,3-diphenyl-1*H*-pyrazol-5-amine (1 mmol), and benzaldehyde (1 mmol) was selected as a template reaction to investigate the catalyst effect at 120 °C under solvent-free conditions (Table 1, entries 1–8). A comparison of catalytic activity between Brønsted and Lewis acids showed highest catalytic activity of Zn(OTf)<sub>2</sub> under solvent-free conditions at 120 °C (Table 1, entry 1). Moreover,

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Table 1. Optimization of the Reaction Conditions for Three-Component Synthesis of 4{1,1,1}<sup>a</sup>


entry	catalyst (mol %)	time (h)	yield (%) <sup>b</sup>	4:5 <sup>b</sup>
1	Zn(OTf) <sub>2</sub> (10)	1	92	65:35
2	no catalyst	10		
3	<i>p</i> -TSA (10)	1	57	75:25
4	sulfamic acid (10)	1	55	75:25
5	ZnCl <sub>2</sub> (10)	1	43	70:30
6	InCl <sub>3</sub> (10)	1	80	65:35
7	ZrOCl <sub>4</sub> (10)	1	52	70:30
8	Bi(OTf) <sub>3</sub> (10)	1	78	70:30
9 <sup>c</sup>	Zn(OTf) <sub>2</sub> (10)	1	93	65:35
10 <sup>d</sup>	Zn(OTf) <sub>2</sub> (10)	1	75	65:35
11	Zn(OTf) <sub>2</sub> (12)	1	92	65:35
12	Zn(OTf) <sub>2</sub> (8)	1	85	65:35

<sup>a</sup>Kojic acid (1 mmol), 1,3-diphenyl-1*H*-pyrazol-5-amine (1 mmol), benzaldehyde (1 mmol), catalyst (10 mol %), under solvent-free condition, at 120 °C. <sup>b</sup>Isolated yield. <sup>c</sup>Reaction was performed at 130 °C. <sup>d</sup>Reaction was performed at 110 °C.

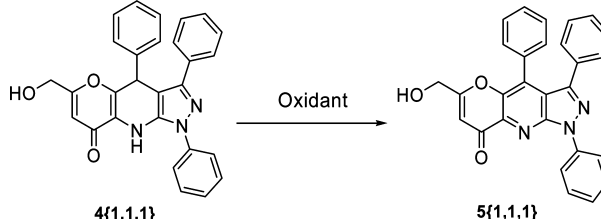
no reaction occurred in the absence of the catalyst even after 10 h (Table 1, entry 2). A higher reaction temperature (130 °C) does not make an obvious difference in the yield of product (93%, Table 1, entry 9), but a lower reaction temperature of 110 °C decreased the conversion to 75% (Table 1, entry 10). The catalyst amount is another crucial factor, as lower yields were obtained when the same reaction was carried out using a lower amount of the catalyst (Table 1, entries 11, 12). Accordingly, performing the reaction solvent free in the presence of 10 mol % of Zn(OTf)<sub>2</sub> at 120 °C was chosen as the optimal conditions.

To optimize the aromatization of 4{1,1,1}, the model reaction was performed in the presence of different oxidants and solvents (Table 2, entries 1–9). As illustrated, H<sub>2</sub>O<sub>2</sub> (2 equiv) in acetonitrile is sufficient for this transformation, and the desired product was obtained in excellent yield (Table 2, entry 5).

It is noteworthy that the effect of oxygen is negligible on improving the yield of the final product. So, with the optimized reaction conditions in hand, we considered to introduce more diversities in the pyrano[3,2-*b*]pyrazolo[4,3-*e*]pyridin-8(1*H*)-one scaffold via the novel one-pot reaction of kojic acid, 1-*H*-pyrazol-5-amines, and aryl aldehydes (Figure 1). We found that Zn(OTf)<sub>2</sub> is an efficient catalyst for the synthesis of a large spectrum of pyrano[3,2-*b*]pyrazolo[4,3-*e*]pyridin-8(1*H*)-ones by this reaction (Table 3).

It was generally observed that high to excellent yields of the products were obtained in all cases. The aryl aldehydes carrying electron-donating groups could be smoothly converted to the desired products (87–92% yields, Table 3, entries 4–6, 12 and 13). The coupling of aryl aldehydes containing electron-withdrawing groups also afforded the corresponding products in high to excellent yields.

Moreover, this reaction works well with aliphatic aldehydes and heteroaromatic carbaldehydes such as thiophene-2-carbaldehyde (Table 3, entries 9, 10). The successful production of pyrano[3,2-*b*]pyrazolo[4,3-*e*]pyridin-8(1*H*)-one

Table 2. Evaluation of Potential Oxidants<sup>a</sup>


entry	oxidant (equiv)	time (min)	yield (%) <sup>b</sup>
1	CAN (2) <sup>c</sup>	30	45
2	NaIO <sub>4</sub> (2)	30	55
3	MnO <sub>2</sub> (2)	30	50
4	<i>t</i> -BuOOH (2)	30	87
5	H <sub>2</sub> O <sub>2</sub> (2)	30	94
6	H <sub>2</sub> O <sub>2</sub> (1.5)	30	81
7	H <sub>2</sub> O <sub>2</sub> (2.5)	30	94
8 <sup>d</sup>	H <sub>2</sub> O <sub>2</sub> (2)	30	80
9 <sup>e</sup>	H <sub>2</sub> O <sub>2</sub> (2)	30	88

<sup>a</sup>The reaction was carried out with oxidant (2 equiv) in CH<sub>3</sub>CN (3 mL) at reflux temperature. <sup>b</sup>Isolated yield. <sup>c</sup>CAN: ceric (IV) ammonium nitrate. <sup>d</sup>The reaction was performed in 3 mL of methanol. <sup>e</sup>The reaction was performed in 3 mL of ethanol.

derivatives indicated that this one-pot reaction is general for such transformations. Based on these considerations, we explored a new and facile reaction for the synthesis of pyrano[3,2-*b*]pyrazolo[4,3-*e*]pyridin-8(1*H*)-one derivatives by a straightforward process.

To further expand the scope of this new MCR and because of extensive applications of spiro-oxindole heterocycles in medicinal chemistry, the synthesis of 1'*H*-spiro[indoline-3,4'-pyrano[3,2-*b*]pyrazolo[4,3-*e*]pyridine]-2,8'(9'*H*)-diones were also examined. As shown in Scheme 1, the reaction of isatin with 1*H*-pyrazol-5-amines and kojic acid in the presence of

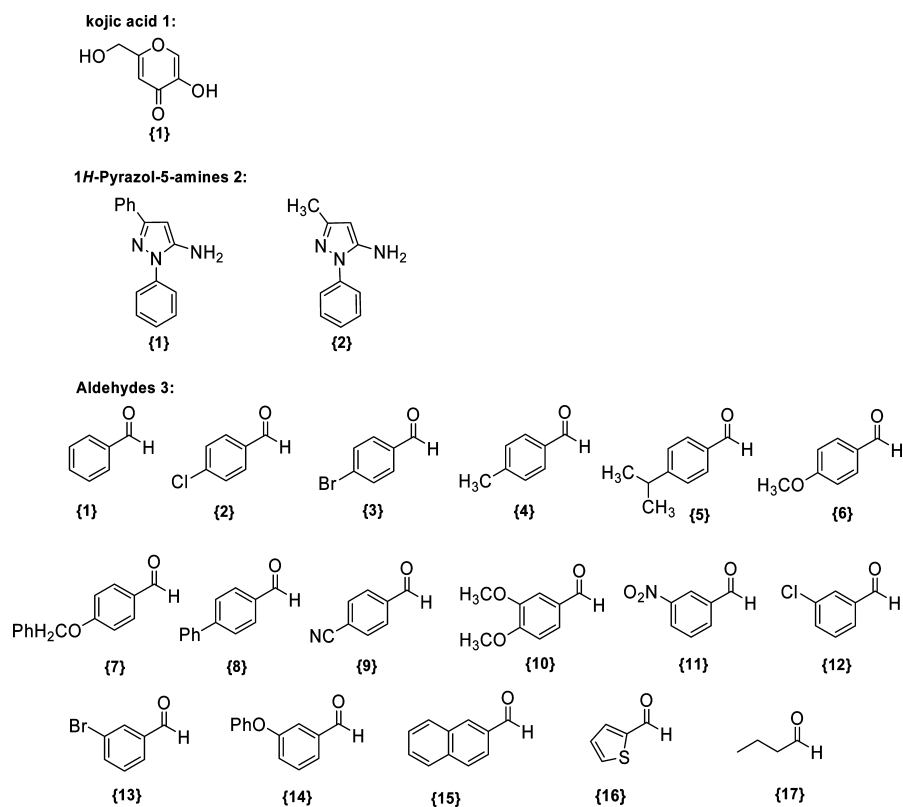
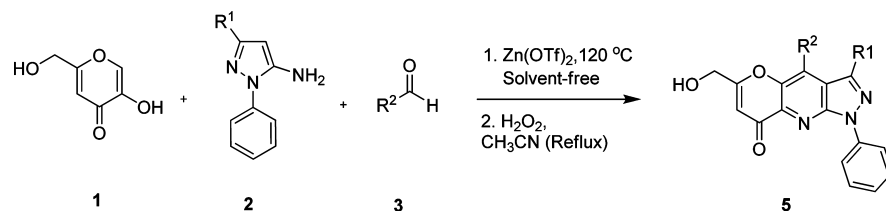


Figure 1. Diversity of reagents.

Table 3. Synthesis of Pyrano[3,2-*b*]pyrazolo[4,3-*e*]pyridin-8(1*H*)-one Derivatives 5

entry	product	yield (%) <sup>a</sup>
1	5{1,1,1}	89
2	5{1,1,2}	86
3	5{1,1,3}	90
4	5{1,1,4}	92
5	5{1,1,5}	90
6	5{1,1,7}	87
7	5{1,1,10}	94
8	5{1,1,11}	95
9	5{1,1,16}	82
10	5{1,1,17}	86
11	5{1,2,2}	93
12	5{1,2,6}	90
13	5{1,2,7}	89
14	5{1,2,8}	96
15	5{1,2,9}	96
16	5{1,2,10}	91
17	5{1,2,12}	90
18	5{1,2,13}	93
19	5{1,2,14}	88
20	5{1,2,15}	89

<sup>a</sup>Isolated yield.

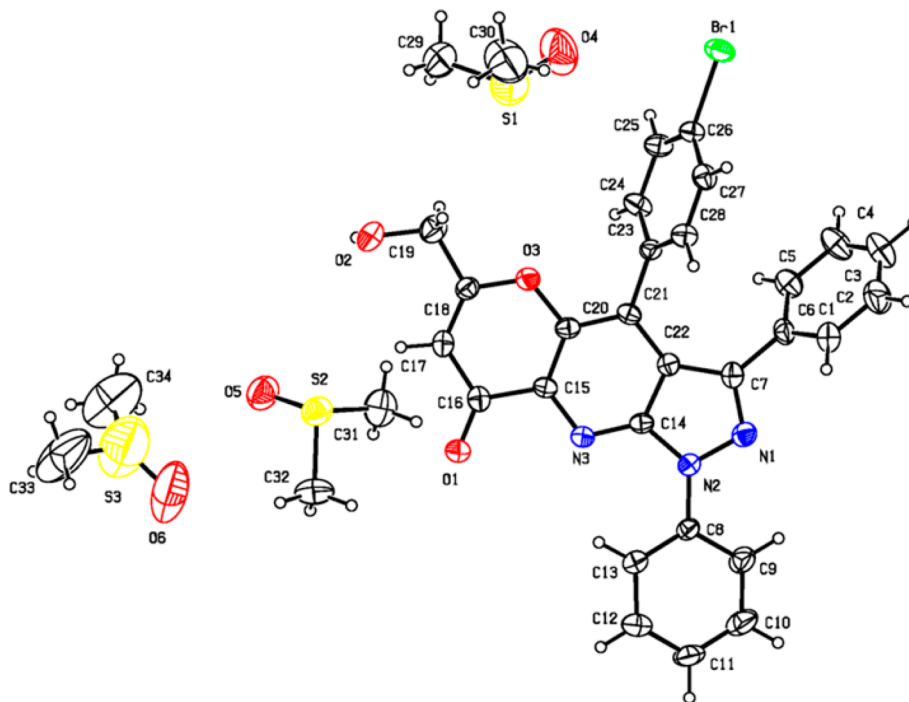
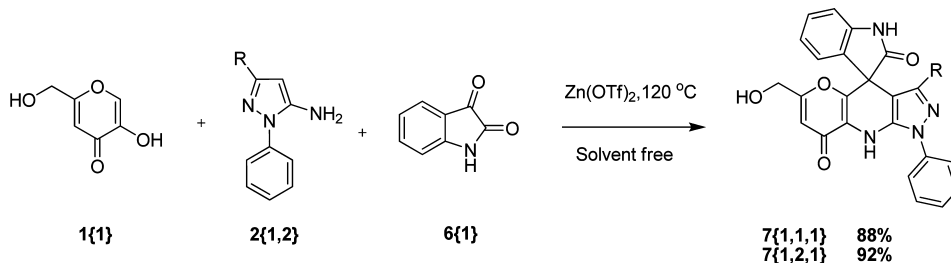
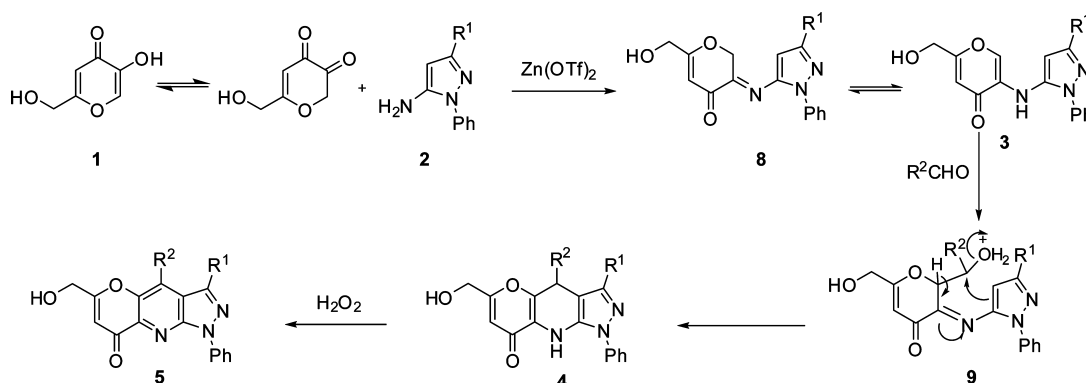
Scheme 1. Synthesis of 1'*H*-Spiro[indoline-3,4'-pyrano[3,2-*b*]pyrazolo[4,3-*e*]pyridine]-2,8'(9'*H*)-diones 7

Figure 2. X-ray Crystallography structure of compound 5{1,1,3}.

Scheme 2. Possible Mechanism for the Synthesis of Pyrano[3,2-*b*]pyrazolo[4,3-*e*]pyridin-8(1*H*)-ones

catalytic amounts of  $\text{Zn}(\text{OTf})_2$  proceeded efficiently to furnish the corresponding spiro products 7 in high yields.

To the best of our knowledge, there is no report on the synthesis of pyrano[3,2-*b*]pyrazolo[4,3-*e*]pyridin-8(1*H*)-ones through the MCR of aldehydes, 1*H*-pyrazol-5-amines, and kojic acid. Therefore, such a synthesis can be considered as a powerful and practical method for the preparation of a new class of kojic acid fused heterocyclic derivatives.

The structures of the products were identified by their FTIR,  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR, mass spectroscopy, and elemental analysis. Furthermore, the structure of 5{1,1,3} was confirmed by X-ray crystallographic analysis (CCDC 894834, Figure 2).

A plausible mechanism for the formation of pyrano[3,2-*b*]pyrazolo[4,3-*e*]pyridin-8(1*H*)-one is proposed in Scheme 2. The condensation of 1*H*-pyrazol-5-amine 2 with the keto form of kojic acid in the presence of the catalyst gave the intermediate 8. Nucleophilic attack of 8 to the aldehyde 3

furnished the intermediate **9**, which upon intramolecular cyclization and dehydration gave **4**. In the last step, the intermediate **4**, by further oxidation and subsequent aromatization, was converted to the desired product **5**.

## CONCLUSION

We have demonstrated a simple and efficient route for the one-pot, three-component synthesis of pyrano[3,2-*b*]pyrazolo[4,3-*e*]pyridin-8(1*H*)-ones and 1'*H*-spiro[indoline-3,4'-pyrano[3,2-*b*]pyrazolo[4,3-*e*]pyridine]-2,8'(9'*H*)-diones using readily available starting materials. The significant features of this method are short reaction times, high yields of the products, operational simplicity, and easy workup procedure, which make it an applicable method for the synthesis of diverse libraries.

## EXPERIMENTAL PROCEDURES

**General Information.** The chemicals used in this work were purchased from Fluka and Merck chemical companies. The progress of the reaction was monitored by TLC using 0.25  $\mu\text{m}$  precoated silica gel plates. Melting points were determined using Stuart Scientific SMP2 apparatus and are uncorrected.  $^1\text{H}$  and  $^{13}\text{C}$  NMR (400 and 100 MHz) spectra were recorded on a Bruker-AC 400 spectrometer. FT-IR spectra were recorded on a Nicolet-Impact 400D instrument in the range of 400–4000  $\text{cm}^{-1}$ . Mass spectra were recorded on a Platform II spectrometer from Micromass; EI mode at 70 eV. Elemental analysis was done on LECO, CHNS-932 analyzer.

**Typical Procedure for the Synthesis of 6-(Hydroxymethyl)-4-(4-isopropylphenyl)-1,3-diphenylpyrano[3,2-*b*]pyrazolo[4,3-*e*]pyridin-8(1*H*)-one **5**{1,1,5}.** A mixture of kojic acid (0.140 g, 1 mmol), 1,3-diphenyl-1*H*-pyrazol-5-amine (0.235 g, 1 mmol), 3-nitrobenzaldehyde (0.151 g, 1 mmol), and  $\text{Zn}(\text{OTf})_2$  (0.036 g, 0.1 mmol) was stirred at 120  $^\circ\text{C}$  for 1 h. After consumption of precursors as indicated by TLC,  $\text{H}_2\text{O}_2$  (30 mol %, 0.2 mL) and  $\text{CH}_3\text{CN}$  (3 mL) were added, and the mixture was stirred under reflux conditions for 30 min. The progress of the reaction was monitored by TLC (eluent: *n*-hexane/ethyl acetate: 2/1). After completion of the reaction, the mixture was cooled to room temperature, and the precipitated product was filtered and washed with water (2  $\times$  5 mL) and ethanol (5 mL) to afford the pure product **5**{1,1,5} as a yellow powder. Mp >180  $^\circ\text{C}$  decomposes. IR (KBr):  $\nu_{\text{max}}$  = 3373, 3060, 2959, 1636, 1455, 1352, 1103, 840, 755  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  = 1.21 (d,  $J$  = 6.8 Hz, 6H, 2 $\text{CH}_3$ ), 2.87 (m, 1H, CH), 4.34 (d,  $J$  = 5.2 Hz, 2H,  $\text{CH}_2\text{OH}$ ), 5.82 (t,  $J$  = 5.6 Hz, 1H, OH), 6.50 (s, 1H, CH), 7.05–7.11 (m, 5H, ArH), 7.24 (d,  $J$  = 8.0 Hz, 4H, ArH), 7.24 (t,  $J$  = 7.4 Hz, 1H, ArH), 7.65 (t,  $J$  = 8.0 Hz, 2H, ArH), 8.44 (d,  $J$  = 7.6 Hz, 2H, ArH).  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  = 23.77, 33.28, 59.58, 108.17, 116.48, 120.64, 125.61, 126.29, 127.37, 127.48, 127.82, 128.71, 129.31, 130.35, 131.47, 135.63, 138.59, 138.72, 145.81, 145.98, 147.63, 149.53, 170.31, 176.31. MS:  $m/z$  = 487.25 ( $\text{M}^+$ ). Anal. Calcd for  $\text{C}_{31}\text{H}_{25}\text{N}_3\text{O}_3$  (487.55): C, 76.37; H, 5.17; N, 8.62. Found: C, 76.33; H, 5.21; N, 8.57.

## ASSOCIATED CONTENT

### Supporting Information

$^1\text{H}$  and  $^{13}\text{C}$  NMR spectra for all products and crystallographic data for compound **5**{1,1,3}. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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### Notes

The authors declare no competing financial interest.

## REFERENCES

- (1) (a) Zhu, J.; Bienayme, H., Eds.; *Multicomponent reactions*; Wiley-VCH: Weinheim, Germany, 2005. (b) Bienayme, H.; Hulme, C.; Odon, G.; Schmitt, P. Maximizing Synthetic Efficiency: Multicomponent Transformations Lead the Way. *Chem. Eur. J.* **2000**, *6*, 3321–3329. (c) Dömling, A.; Ugi, I. Multicomponent Reactions with Isocyanides. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168–3210.
- (2) (a) Huang, Z.; Hu, Y.; Zhou, Y.; Shi, D. Efficient One-Pot Three-Component Synthesis of Fused Pyridine Derivatives in Ionic Liquid. *ACS Comb. Sci.* **2011**, *13*, 45–49. (b) Zou, Y.; Hu, Y.; Liu, H.; Shi, D. Rapid and Efficient Ultrasound-Assisted Method for the Combinatorial Synthesis of Spiro[indoline-3,4'-pyrano[2,3-*c*]pyrazole] Derivatives. *ACS Comb. Sci.* **2012**, *14*, 38–43.
- (3) Ghahremanzadeh, R.; Sayyafi, M.; Ahadi, S.; Bazgir, A. Novel One-Pot Three-Component Synthesis of Spiro[indoline-pyrazolo[4',3':5,6]pyrido[2,3-*d*]pyrimidine]trione Library. *J. Comb. Chem.* **2009**, *11*, 393–396.
- (4) Chen, Y. L. Pyrazolo- and Pyrazolopyridines Useful as CRF Antagonists, WO 9534563 A1. *Chem. Abstr.* **1995**, *124*, 232447.
- (5) (a) Ochiai, H.; Ishida, A.; Ohtani, T.; Kusumi, K.; Kishikawa, K.; Yamamoto, S.; Takeda, H.; Obata, T.; Makai, H.; Toda, M. New Orally Active PDE4 Inhibitors with Therapeutic Potential. *Bioorg. Med. Chem.* **2004**, *12*, 4089–4100. (b) Revesz, L.; Blum, E.; Di Padova, F. E.; Buhl, T.; Feifel, R.; Gram, H.; Hiestand, P.; Manning, U.; Neumann, U.; Rucklin, G. Pyrazoloheteroaryls: Novel p38 $\alpha$  MAP Kinase Inhibiting Scaffolds with Oral Activity. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 262–266. (c) Chioua, M.; Samadi, A.; Soriano, E.; Lozach, O.; Meijer, L.; Marco-Contelles, J. Synthesis and Biological Evaluation of 3,6-Diamino-1*H*-pyrazolo[3,4-*b*]pyridine Derivatives as Protein Kinase Inhibitors. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4566–4569.
- (6) (a) Goda, F. E.; Abdel-Aziz, A. A.-M.; Attef, O. A. Synthesis, Antimicrobial Activity and Conformational Analysis of Novel Substituted Pyridines: BF<sub>3</sub>-Promoted Reaction of Hydrazine with 2-Alkoxy Pyridines. *Bioorg. Med. Chem.* **2004**, *12*, 1845–1852. (b) Frolova, L. V.; Malik, I.; Uglinskii, P. Y.; Rogelj, S.; Kornienko, A.; Magedov, I. V. Multicomponent Synthesis of 2,3-Dihydrochromeno[4,3-*d*]pyrazolo[3,4-*b*]pyridine-1,6-diones: A Novel Heterocyclic Scaffold with Antibacterial Activity. *Tetrahedron Lett.* **2011**, *52*, 6643–6645.
- (7) Johns, B. A.; Gudmundsson, K. S.; Turner, E. M.; Allen, S. H.; Jung, D. K.; Sexton, C. J.; Boyd, F. L., Jr.; Peel, M. R. Pyrazolo[1,5-*a*]pyridines: Synthetic Approaches to A Novel Class of Antiherpetics. *Tetrahedron* **2003**, *59*, 9001–9011.
- (8) Kuroda, S.; Akahane, A.; Itani, H.; Nishimura, S.; Durkin, K.; Kinoshita, T.; Tenda, Y.; Sakane, K. Discovery of FR166124, A Novel Water-Soluble Pyrazolo[1,5- $\alpha$ ]pyridine Adenosine A<sub>1</sub> Receptor Antagonist. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1979–1984.
- (9) Barreiro, E. J.; Camara, C. A.; Verli, H.; Brazil-Más, L.; Castro, N. G.; Cintra, W. M.; Aracava, Y.; Rodrigues, C. R.; Fraga, C. A. M. Design, Synthesis, and Pharmacological Profile of Novel Fused Pyrazolo[4,3-*d*]pyridine and Pyrazolo[3,4-*b*][1,8]naphthyridine Isosteres: A New Class of Potent and Selective Acetylcholinesterase Inhibitors. *J. Med. Chem.* **2003**, *46*, 1144–1152.
- (10) (a) Mitaka, S.; Skaltsounis, A.-L.; Tillequin, F.; Koch, M.; Pusset, J.; Chauviere, G. Plantes de nouvelle-calédonie, XCVI.

Alcaloides de Geijera Balansae. *J. Nat. Prod.* **1985**, *48*, 772–777. (b) Tantivatana, P.; Ruangrunsi, N.; Vaisiroiroj, V.; Lankin, D. C.; Bhacca, N. S.; Borris, R. P.; Cordell, G. A.; Johnson, L. F. Microminutin, A Novel Cytotoxic Coumarin from *Micromelum Minutum* (Rutaceae). *J. Org. Chem.* **1983**, *48*, 268–270.

(11) (a) Yamada, N.; Kadowaki, S.; Takahashi, K.; Umeza, K. MY-1250, A Major Metabolite of the Anti-allergic Drug Repirinast, Induces Phosphorylation of a 78-kDa Protein in Rat Mast Cells. *Biochem. Pharmacol.* **1992**, *44*, 1211–1213.

(12) Madsen-Duggan, C. B.; Debenham, J. S.; Walsh, T. F.; Yan, L.; Huo, P.; Wang, J.; Tong, X.; Lao, J.; Fong, T. M.; Xiao, J. C.; Huang, C. R.-R.C.; Shen, J. C.-P.; Stribling, D. S.; Shearman, L. P.; Strack, A. M.; Goulet, M. T.; Hale, J. J. Dihydro-pyrano[2,3-*b*]pyridines and Tetrahydro-1,8-naphthyridines as CB1 Receptor Inverse Agonists: Synthesis, SAR and Biological Evaluation. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 3750–3754.

(13) Magedov, I. V.; Manpadi, M.; Ogasawara, M. A., M. A.; Dhawan, A. S.; Rogelj, S.; slambrouck, S. V.; Steelant, W. F. A.; Evdokimov, N. M.; Uglinskii, P. Y.; Elias, E. M.; Knee, E. J.; Tongwa, P.; Antipin, M. Y.; Kornienko, A. Structural Simplification of Bioactive Natural Products with Multicomponent Synthesis. 2. Antiproliferative and Antitubulin Activities of Pyrano[3,2-*c*]pyridones and Pyrano[3,2-*c*]quinolones. *J. Med. Chem.* **2008**, *51*, 2561–2570.

(14) (a) Evans, J. M.; Geoffrey, R. S.; Frederick, C. Anti-hypertensive Pyranopyridine Compounds. US Patent 4812459, 1989. (b) Girgis, A. S.; Ismail, N. S. M.; Farag, H. Facile Synthesis, Vasorelaxant Properties and Molecular Modeling Studies of 2-Amino-8a-methoxy-4H-pyrano[3,2-*c*]pyridine-3-carbonitriles. *Eur. J. Med. Chem.* **2011**, *49*, 2397–2407.

(15) (a) Kumar, R. R.; Perumal, S.; Menéndez, J. C.; Yogeewari, P.; Sriram, D. Antimycobacterial Activity of Novel 1,2,4-Oxadiazole-pyrano[2,3-*b*]pyridine/Chromene Hybrids Generated by Chemoselective 1,3-Dipolar Cycloadditions of Nitrile Oxides. *Bioorg. Med. Chem.* **2011**, *19*, 3444–3450. (b) Zhuravel', I. O.; Kovalenko, S. M.; Ivachtchenko, A. V.; Balakin, K. V.; Kazmirchuk, V. V. Synthesis and Antimicrobial Activity of 5-Hydroxymethyl-8-methyl-2-(*N*-arylimino)-pyrano[2,3-*c*]pyridine-3-(*N*-aryl)-carboxamides. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5483–5487.

(16) Ukawa, K.; Ishiguro, T.; Kuriki, H.; Nohara, A. Synthesis of the Metabolites and Degradation Products of 2-Amino-7-isopropyl-5-oxo-5H-[1]benzopyrano[2,3-*b*]pyridine-3-carboxylic Acid (Amoxanox). *Chem. Pharm. Bull.* **1985**, *33*, 4432–4437.

(17) Kobayashi, Y.; Kayahara, H.; Tadasa, K.; Tanaka, H. Synthesis of *N*-Kojic-Amino Acid and *N*-Kojic-Amino Acidkojiate and Their Tyrosinase Inhibitory Activity. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1303–1308.

(18) Emami, S.; Hosseinimehr, S. J.; Taghdisi, S. M.; Akhlaghpour, S. Kojic Acid and its Manganese and Zinc Complexes as potential radioprotective agents. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 45–48.

(19) Vajragupta, O.; Boonchoong, P.; Sumanont, Y.; Watanabe, H.; Wongkrajang, Y.; Kammasud, N. Manganese-Based Complexes of Radical Scavengers as Neuroprotective Agents. *Bioorg. Med. Chem.* **2003**, *11*, 2329–2337.

(20) Tanaka, R.; Tsujii, H.; Yamada, T.; Kajimoto, T.; Amano, F.; Hasegawa, J.; Hamashima, Y.; Node, M.; Katoh, K.; Takebe, Y. Novel 3a-Methoxyserrat-14-en-21b-ol (PJ-1) and 3b-Methoxyserrat-14-en-21b-ol (PJ-2)-curcumin, Kojic Acid, Quercetin, and Baicalein Conjugates as HIV Agents. *Bioorg. Med. Chem.* **2009**, *17*, 5238–5246.

(21) (a) Reddy, B. V. S.; Reddy, M. R.; Madan, C.; Kumar, K. P.; Rao, M. S. Indium(III) Chloride Catalyzed Three-Component Coupling Reaction: A Novel Synthesis of 2-Substituted Aryl(indolyl)-kojic Acid Derivatives as Potent Antifungal and Antibacterial Agents. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 7507–7511. (b) Aytemir, M. D.; Özçelik, B. A Study of Cytotoxicity of Novel Chlorokojic Acid Derivatives with Their Antimicrobial and Antiviral Activities. *Eur. J. Med. Chem.* **2010**, *45*, 4089–4095.

(22) Xiong, X.; Pirrung, M. C. Modular Synthesis of Candidate Indole-based Insulin Mimics by Claisen Rearrangement. *Org. Lett.* **2008**, *10*, 1151–1154.

(23) Pace, P.; Nizi, E.; Pacini, B.; Pesci, S.; Matassa, V.; Francesco, R. D.; Altamura, S.; Summa, V. The Monoethyl Ester of Meconic Acid is an Active Site Inhibitor of HCV NS5B RNA-Dependent RNA Polymerase. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3257–3261.

(24) Ahn, S. M.; Rho, H. S.; Baek, H. S.; Joo, Y. H.; Hong, Y. D.; Song Seok Shin, S. S.; Park, Y.-H.; Park, S. N. Inhibitory Activity of Novel Kojic Acid Derivative Containing Trolox Moiety on Melanogenesis. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 7466–7469.

(25) Houlihan, W. J.; Remers, W. A.; Brown, R. K. *Indoles: Part I*; Wiley: New York, 1992.

(26) (a) Joshi, K. C.; Chand, P. Biologically Active Indole Derivatives. *Pharmazie* **1982**, *37*, 1–12. (b) Abdel-Rahman, A. H.; Keshk, E. M.; Hanna, M. A.; El-Bady, S. M. Synthesis and Evaluation of Some New Spiro Indoline-based Heterocycles as Potentially Active Antimicrobial Agents. *Bioorg. Med. Chem.* **2004**, *12*, 2483–2488. (c) Joshi, K. C.; Jain, R.; Sharma, K.; Bhattacharya, S. K.; Goel, R. K. Studies in Spiro-heterocycles. Part-XII. Synthesis of Some Fluorine Containing Spiro[3H-indole-3,4(4H)-pyrano[2,3-*d*]pyrimidine]-2,5,7(1H)-triones as CNS Agents. *J. Indian Chem. Soc.* **1988**, *115*, 202–204.

(27) (a) Safaei, S.; Mohammadpour-Baltork, I.; Khosropour, A. R.; Moghadam, M.; Tangestaninejad, S.; Mirkhani, V. Regioselective Multicomponent Synthesis of Fully Substituted Pyrazoles and Bispypyrazoles Catalyzed by Zinc Triflate. *Synlett* **2011**, 2214–2222. (b) M. Rostami, M.; Khosropour, A. R.; Mirkhani, V.; Mohammadpour-Baltork, I.; Moghadam, M.; Tangestaninejad, S. An Efficient, Simple, and Scalable Domino Reaction to Diverse *N*-(1-Oxo-1H-inden-2-yl)benzamides Catalyzed by HPW@nano-SiO<sub>2</sub> under Microwave Irradiation. *Synlett* **2011**, 1677–1682. (c) Khorsandi, Z.; Khosropour, A. R.; Mirkhani, V.; Mohammadpour-Baltork, I.; Moghadam, M.; Tangestaninejad, S. A Simple and Efficient Large-Scale Synthesis of 3-Hydroxyphthalans via Oxa-Pictet-Spengler Reaction Catalyzed by Nanosilica Sulfuric Acid. *Tetrahedron Lett.* **2011**, *52*, 1213–1216. (d) Mohammadpour-Baltork, I.; Moghadam, M.; Tangestaninejad, S.; Mirkhani, V.; Eskandari, Z. Ultrasound Promoted Selective Synthesis of 2-Aryl-5,6-dihydro-4H-1,3-oxazines Catalyzed by K-10 and KSF Montmorillonite Clays: A Practical Procedure Under Mild and Solvent-Free Conditions. *Ultrason. Sonochem.* **2010**, *17*, 857–862. (e) Safaei, S.; Mohammadpour-Baltork, I.; Khosropour, A. R.; Moghadam, M.; Tangestaninejad, S.; Mirkhani, V. Diastereoselective Synthesis of Pyrazolines Using A Bifunctional Brønsted Acidic Ionic Liquid under Solvent-Free Conditions. *Adv. Synth. Catal.* **2012**, *354*, 3095–3104.