Supplementary Material

Synthesis of 6-Azapurines by Transformation of Toxoflavins and Reumycins (7-Azapteridines) and their Cytotoxicities.

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Fig. 1 HMQC-NMR spectra of Toxoflavin (1a) and 6-Azapurine (5a) measured in DMSO-$d_6$ (300 MHz).
Fig. 2 HMBC spectra of Toxoflavin (1a) and 6-azapurine (5a) measured in DMSO-\(d_6\)
**Fig. 3** $^{13}$C - NMR spectra of Toxoflavin (1a) and 6-Azapurine (5a) measured in DMSO-$d_6$ (300 MHz).
Fig. 4 $^1$H-NMR spectrum of 1,5-dimethyl-1-$H$-imidazo[4,5-e][1,2,4]triazin-6($5H$)-one (5a) measured in CDCl$_3$ (300 MHz)
Fig. 5 ES$^+$ - MS spectrum for 6-Azapurine (5a).
Fig. 6 UV spectra for Toxoflavin (1a) and 6-Azapurine (5a)
Fig. 7 $^1$H-NMR spectra of 3-Methylxoflavin (1b) and 6-Azapurine (5b) measured in DMSO-$d_6$ (300 MHz).
Fig. 8 $^1$H-NMR spectra of 3-Phenyltoxoflavin (1f) and 6-Azapurine (5f) measured in DMSO-$d_6$ (300 MHz).
Fig. 9 $^{13}$C-NMR spectra of 3-Methyltoxoflavin (1b) and 6-Azapurine (5b) measured in DMSO-$d_6$ (300 MHz).
Fig. 10 $^{13}$C-NMR spectra of 3-Phenyltoxoflavin (1f) and 6-Azapurine (5f) measured in DMSO-$d_6$ (300 MHz).
Fig. 11 UV spectra for 3-Methyltoxoflavín (1b) and 6-Azapurine (5b).
<table>
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<th>Compd. No.</th>
<th>$\lambda_{\text{max}}$ (nm)</th>
<th>log $\varepsilon$</th>
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<tr>
<td><strong>1f</strong></td>
<td>289 (4.50)</td>
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<td></td>
<td>435 (3.50)</td>
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<tr>
<td><strong>5f</strong></td>
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*Fig. 12* UV spectra for 3-Phenyltoxoflavin (1f) and 6-Azapurine (5f).
Fig. 13 HMBC spectra of 1-methyl-1,2,4-triazine-5,6(1H,4H)-dione (6a) measured in DMSO-d$_6$. 
Fig. 14 ¹H-NMR and ¹³C-NMR spectra of 1-methyl-1,2,4-triazine-5,6(1H,4H)-dione (6a) measured in DMSO-d₆
Fig. 15 $^1$H-NMR and $^{13}$C-NMR spectra of 1-Methyl-3-phenyl[1,2,4]triazine-5,6(1H,4H)-dione (6c) measured in DMSO-$d_6$ (300 MHz).
Fig. 16 $^1$H-NMR and $^{13}$C-NMR spectra of 1-Methyl-3-(p-tolyl)[1,2,4]triazine-5,6(1H,4H)-dione (6h) measured in DMSO-$d_6$ (300 and 75 MHz).
Fig. 17 UV spectra for 3-Phenyl- and 3-(p-tolyl)-1-Methyl-[1,2,4]triazine-5,6-(1H,4H)-dione (6c and 6h).
Fig. 18 $^{13}$C-NMR spectra of reumycin (3a) and 6-azapurine (7a) measured in DMSO-$d_6$ (75 MHz).
Fig. 19 UV spectra for reumycin (3c) and 6-azapurine (7c)
Supplementary Experiment

Synthesis of 6-azapurines 5a-t by ring contraction of toxoflavins 1a-t

1,5-Dimethyl-1H-imidazo[4,5-e][1,2,4]triazin-6(5H)-one 5a
A solution of 1,6-dimethylpyrimido[5,4-e][1,2,4]triazine-5,7(1H,6H)-dione 1a (0.5 g, 2.6 mmol) in 10% aqueous NaOH solution (10 mL) was stirred at 5-10 °C for 3 days. Then, the solution was adjusted to pH 7 with 10% HCl under cooling on ice-water and concentrated to dryness in vacuo. The residue was crystallized from a mixture of EtOH/H₂O to give the pure 6-azapurine derivative 5a[12] (380 mg, 89%) as colorless needles.

1,3,5-Trimethyl-1H-imidazo[4,5-e][1,2,4]triazin-6(5H)-one 5b
A solution of 1,3,6-trimethylpyrimido[5,4-e][1,2,4]triazine-5,7(1H,6H)-dione 1b (0.5 g, 2.4 mmol) in 10% aqueous NaOH solution (10 mL) was stirred at 5-10 °C for 3 days. Then, the solution was adjusted to pH 7 with 10% HCl under cooling on ice-water and concentrated to dryness in vacuo. The residue was crystallized from a mixture of EtOH/H₂O to give the pure 6-azapurine derivative 5b (294 mg, 68%) as colorless needles.

3-Ethyl-1,5-dimethyl-1H-imidazo[4,5-e][1,2,4]triazin-6(5H)-one 5c
A solution of 3-ethyl-1,6-dimethylpyrimido[5,4-e][1,2,4]triazine-5,7(1H,6H)-dione 1c (0.5 g, 2.3 mmol) in 10% aqueous NaOH solution (10 mL) was stirred at 5-10 °C for 3 days. Then, the solution was adjusted to pH 7 with 10% HCl under cooling on ice-water and concentrated to dryness in vacuo. The residue was crystallized from a mixture of EtOH/H₂O to give the pure 6-azapurine derivative 5c (183 mg, 42%) as colorless needles.

1,5-Dimethyl-3-(n-propyl)-1H-imidazo[4,5-e][1,2,4]triazin-6(5H)-one 5d
A solution of 1,6-dimethyl-3-(n-propyl)pyrimido[5,4-e][1,2,4]triazine-5,7(1H,6H)-dione 1d (0.5 g, 2.1 mmol) in 10% aqueous NaOH solution (10 mL) was stirred at room temperature for 1 day. Then, the solution was adjusted to pH 7 with 10% HCl under cooling on ice-water and concentrated to dryness in vacuo. The residue was crystallized from a mixture of EtOH/H₂O to give the pure 6-azapurine derivative 5d (203 mg, 46%) as colorless needles.

3-Isopropyl-1,5-dimethyl-1H-imidazo[4,5-e][1,2,4]triazin-6(5H)-one 5e
A solution of 3-isopropyl-1,6-dimethylpyrimido[5,4-e][1,2,4]triazine-5,7(1H,6H)-dione 1e (0.5 g, 2.1 mmol) in 10% aqueous NaOH solution (10 mL) was stirred at room temperature for 1 day. Then, the solution was adjusted to pH 7 with 10% HCl under cooling on ice-water and concentrated to dryness in vacuo. The residue was crystallized from a mixture of EtOH/H₂O to give the pure 6-azapurine derivative 5e (233 mg, 53%) as colorless needles.

1,5-Dimethyl-3-phenyl-1H-imidazo[4,5-e][1,2,4]triazin-6(5H)-one 5f
A solution of 1,6-dimethyl-3-phenylpyrimido[5,4-e][1,2,4]triazine-5,7(1H,6H)-dione 1f (0.5 g, 1.9 mmol) in 10% aqueous NaOH solution (10 mL) was heated with stirring at 60-70 °C for 15 min. Then, the solution was adjusted to pH 7 with 10% HCl under cooling on ice-water to afford the solid. The solid was collected by filtration and washed with H₂O and recrystallized from EtOH to give the pure 6-azapurine derivative 5f (358 mg, 80%) as colorless needles.

3-(4-Fluorophenyl)-1,5-dimethyl-1H-imidazo[4,5-e][1,2,4]triazin-6(5H)-one 5g
A solution of 3-(4-fluorophenyl)-1,6-dimethylpyrimido[5,4-e][1,2,4]triazine-5,7(1H,6H)-dione 1g (0.5 g, 1.7 mmol) in 10% aqueous NaOH solution (10 mL) was heated with stirring at 60-70 °C for 10 min. Then, the solution was adjusted to pH 7 with 10% HCl under cooling on ice-water to afford the solid. The solid was collected by filtration and washed with H₂O and recrystallized from EtOH to give the pure 6-azapurine derivative 5g (284 mg, 63%) as colorless needles.

3-(3-Chlorophenyl)-1,5-dimethyl-1H-imidazo[4,5-e][1,2,4]triazin-6(5H)-one 5h
A solution of 3-(3-chlorophenyl)-1,6-dimethylpyrimido[5,4-e][1,2,4]triazine-5,7(1H,6H)-dione 1h (0.5 g, 1.6 mmol) in 10% aqueous NaOH solution (10 mL) was heated with stirring at 60-70 °C for 15 min. Then, the solution was adjusted to pH 7 with 10% HCl under cooling on ice-water to afford the solid. The solid was collected by filtration and washed with H₂O and recrystallized from EtOH to give the pure 6-azapurine derivative 5h (209 mg, 46%) as colorless needles.

3-(4-Chlorophenyl)-1,5-dimethyl-1H-imidazo[4,5-e][1,2,4]triazin-6(5H)-one 5i
A solution of 3-(4-chlorophenyl)-1,6-dimethylpyrimido[5,4-e][1,2,4]triazine-5,7(1H,6H)-dione 1i (0.5 g, 1.6 mmol) in 10% aqueous NaOH solution (10 mL) was heated with stirring at 60-70 °C for 15 min. Then, the solution was adjusted to pH 7 with 10% HCl under cooling on ice-water to afford the solid. The solid was collected by filtration and washed with H₂O and recrystallized from EtOH to give the pure 6-azapurine derivative 5i (182 mg, 40%) as colorless needles.

3-(4-Bromophenyl)-1,5-dimethyl-1H-imidazo[4,5-e][1,2,4]triazin-6(5H)-one 5j
A solution of 3-(4-bromophenyl)-1,6-dimethylpyrimido[5,4-e][1,2,4]triazine-5,7(1H,6H)-dione 1j (0.5 g, 1.4 mmol) in 10% aqueous NaOH solution (10 mL) was heated with stirring at 60-70 °C for 20 min. Then, the solution was adjusted to pH 7 with 10% HCl under cooling on ice-water to afford the solid. The solid was collected by filtration and washed with H₂O and recrystallized from EtOH to give the pure 6-azapurine derivative 5j (267 mg, 58%) as colorless needles.

3-(4-Hydroxyphenyl)-1,5-dimethyl-1H-imidazo[4,5-e][1,2,4]triazin-6(5H)-one 5k
A solution of 3-(4-hydroxyphenyl)-1,6-dimethylpyrimido[5,4-e][1,2,4]triazine-5,7(1H,6H)-dione 1k (0.5 g, 1.8 mmol) in 10% aqueous NaOH solution (15 mL) was heated with stirring at 60-70 °C for 20 min. Then, the solution was adjusted to pH 7 with 10% HCl under cooling on ice-water to afford the solid. The solid was collected by filtration and washed with H₂O and recrystallized from EtOH to give the pure 6-azapurine derivative 5k (226 mg, 50%) as colorless needles.
1.5-Dimethyl-3-(p-tolyl)-1H-imidazo[4,5-e][1,2,4]triazin-6(5H)-one 5l

A solution of 1.6-dimethyl-3-(p-tolyl)pyrimido[5,4-e][1,2,4]triazine-5,7(1H,6H)-dione 11 (0.5 g, 1.8 mmol) in 10% aqueous NaOH solution (15 mL) was heated with stirring at 60-70 °C for 20 min. Then, the solution was adjusted to pH 7 with 10% HCl under cooling on ice-water to afford the solid. The solid was collected by filtration and washed with H₂O and recrystallized from EtOH to give the pure 6-azapurine derivative 5l (275 mg, 61%) as colorless needles.

3-(4-Isopropylphenyl)-1.5-dimethyl-1H-imidazo[4,5-e][1,2,4]triazin-6(5H)-one 5m

A solution of 3-(4-isopropylphenyl)-1.6-dimethylpyrimido[5,4-e][1,2,4]triazine-5,7(1H,6H)-dione 1m (0.5 g, 1.6 mmol) in 10% aqueous NaOH solution (15 mL) was heated with stirring at 60-70 °C for 20 min. Then, the solution was adjusted to pH 7 with 10% HCl under cooling on ice-water to afford the solid. The solid was collected by filtration and washed with H₂O and recrystallized from EtOH to give the pure 6-azapurine derivative 5m (332 mg, 73%) as colorless needles.

3-(4-Methoxyphenyl)-1.5-dimethyl-1H-imidazo[4,5-e][1,2,4]triazin-6(5H)-one 5n

A solution of 3-(4-methoxyphenyl)-1.6-dimethylpyrimido[5,4-e][1,2,4]triazine-5,7(1H,6H)-dione 1n (0.5 g, 1.7 mmol) in 10% aqueous NaOH solution (15 mL) was heated with stirring at 60-70 °C for 15 min. Then, the solution was adjusted to pH 7 with 10% HCl under cooling on ice-water to afford the solid. The solid was collected by filtration and washed with H₂O and recrystallized from EtOH to give the pure 6-azapurine derivative 5n (344 mg, 76%) as colorless needles.

3-(3,4-Dimethoxyphenyl)-1.5-dimethyl-1H-imidazo[4,5-e][1,2,4]triazin-6(5H)-one 5o

A solution of 3-(3,4-dimethoxyphenyl)-1.6-dimethylpyrimido[5,4-e][1,2,4]triazine-5,7(1H,6H)-dione 1o (0.5 g, 1.5 mmol) in 10% aqueous NaOH solution (15 mL) was heated with stirring at 60-70 °C for 20 min. Then, the solution was adjusted to pH 7 with 10% HCl under cooling on ice-water to afford the solid. The solid was collected by filtration and washed with H₂O and recrystallized from EtOH to give the pure 6-azapurine derivative 5o (352 mg, 77%) as colorless needles.

3-(3,4,5-Trimethoxyphenyl)-1.5-dimethyl-1H-imidazo[4,5-e][1,2,4]triazin-6(5H)-one 5p

A solution of 3-(3,4,5-trimethoxyphenyl)-1.6-dimethylpyrimido[5,4-e][1,2,4]triazine-5,7(1H,6H)-dione 1p (0.5 g, 1.4 mmol) in 10% aqueous NaOH solution (15 mL) was heated with stirring at 60-70 °C for 25 min. Then, the solution was adjusted to pH 7 with 10% HCl under cooling on ice-water to afford the solid. The solid was collected by filtration and washed with H₂O and recrystallized from EtOH to give the pure 6-azapurine derivative 5p (378 mg, 82%) as colorless needles.

3-(4-Acetoxyphenyl)-1.5-dimethyl-1H-imidazo[4,5-e][1,2,4]triazin-6(5H)-one 5q

A solution of 3-(4-acetoxyphenyl)-1.6-dimethylpyrimido[5,4-e][1,2,4]triazine-5,7(1H,6H)-dione 1q (0.5 g, 1.5 mmol) in 10% aqueous NaOH solution (20 mL) was heated with stirring at 60-70 °C for 30 min. Then, the solution was adjusted to
pH 7 with 10% HCl under cooling on ice-water to afford the solid. The solid was collected by filtration and washed with H₂O and recrystallized from EtOH to give the pure 6-azapurine derivative 5q (247 mg, 54%) as yellow needles.

1.5-Dimethyl-3-(4-(dimethylamino)phenyl)-1H-imidazo[4,5-e][1,2,4]triazin-6(5H)-one 5r
A solution of 1,6-dimethyl-3-(4-(dimethylamino)phenyl)pyrimido[5,4-e][1,2,4]triazine-5,7(1H,6H)-dione 1r (0.5 g, 1.6 mmol) in 10% aqueous NaOH solution (20 mL) was heated with stirring at 60-70 °C for 45 min. Then, the solution was adjusted to pH 7 with 10% HCl under cooling on ice-water to afford the solid. The solid was collected by filtration and washed with H₂O and recrystallized from EtOH to give the pure 6-azapurine derivative 5r (214 mg, 47%) as yellow needles.

3-(2-Furyl)-1.5-dimethyl-1H-imidazo[4,5-e][1,2,4]triazin-6(5H)-one 5s
A solution of 3-(2-furyl)-1,6-dimethylpyrimido[5,4-e][1,2,4]triazine-5,7(1H,6H)-dione 1s (0.5 g, 1.9 mmol) in 10% aqueous NaOH solution (20 mL) was heated with stirring at 60-70 °C for 45 min. Then, the solution was adjusted to pH 7 with 10% HCl under cooling on ice-water to afford the solid. The solid was collected by filtration and washed with H₂O and recrystallized from EtOH to give the pure 6-azapurine derivative 5s (326 mg, 73%) as colorless needles.

1.5-Dimethyl-3-(2-thienyl)-1H-imidazo[4,5-e][1,2,4]triazin-6(5H)-one 5t
A solution of 1,6-dimethyl-3-(2-thienyl)pyrimido[5,4-e][1,2,4]triazine-5,7(1H,6H)-dione 1t (0.5 g, 1.8 mmol) in 10% aqueous NaOH solution (20 mL) was heated with stirring at 60-70 °C for 1h. Then, the solution was adjusted to pH 7 with 10% HCl under cooling on ice-water to afford the solid. The solid was collected by filtration and washed with H₂O and recrystallized from EtOH to give the pure 6-azapurine derivative 5t (377 mg, 84%) as colorless needles.