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A Regioselective Synthesis of the Dephospho Ditholene Protected Molybdopterin

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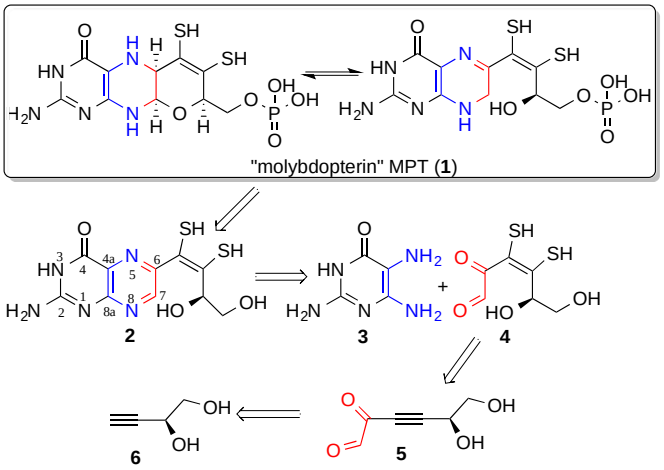
The molybdopterin (MPT) is a complex molecule, made out of three distinctly different components. A retrosynthetic analysis provides a possible route for its synthesis that utilizes the coupling of a diamine with an osone analog. A regioselective condensation of the diamine with an osone affords the dephospho MPT, which has been characterized by NMR and IR spectroscopies, as well as high-resolution mass spectrometry.

Introduction

The molybdopterin (MPT, 1) lies at the heart of more than fifty enzymes that catalyse important chemical transformations in all forms of life. [1-3] These reactions play important roles in global cycling of C, S, N, As and Se to prodrug metabolism. In humans, failures to biosynthesize MPT cofactor due to genetic predispositions lead to severe physiological disorders and even death.[4] The molybdopterin itself is a metal chelating ligand, that is known to bind molybdenum as well as tungsten in biology. When coordinated to molybdenum, it is called molybdenum cofactor.[5] During the biosynthesis molybdenum cofactor, MPT binds to copper, which subsequently is replaced by molybdebun.[4] Structurally MPT is comprised of three distinct components,[6] and they are: a pterin moiety, a pyran ring fused to the pyrazine ring of the pterin and an ene-dithiolate unit that binds to metal ions.[7] The pyran ring, however, opens up at times through C7—O bond scission resulting in a 6-substituted pterin with an alcohol functionality connected to the dithiolene moeity. [8] In prokaryotic enzymes, the phosphate moiety is often modified by a dinucleotide.

The MPT molecule is redox active, and in the reduced state it is unstable in the absence of a protein environment. The MPT molecule was originally characterized by degradative studies, and it was proposed to coordinate molybdenum via its dithiolene moiety.[6, 9] Subsequently, both the open and the closed forms of the MPT have been confirmed by protein crystallography.[10] Despite the biochemical interest, complete synthesis of this MPT remains a challenge that has compromised in-depth analyses of it properties, although progress has been made through years of efforts.[11-15] In recent years progress has been made particularly towards the syntheses of the precursor of the MPT cofactor[14, 16] and Mo coordinated MPT.[13] A general strategy to prepare the MPT is to functionalize a pterin molecule at the C-6 position to introduce a dithiolene functionality leading to a fully protected pterin moiety.[11] For past several years we have been engaged in developing robust synthetic methodologies for making molecules directed towards understanding the effect of different components of the cofactors with[17] or without metal, [18, 19] including the topological[20, 21] and hydrogen bonding[22] aspects. Herein we report our approach in meeting the synthetic challenge by constructing the pterin unit while carrying the dithiolene moiety. This approach originates from a retrosynthetic analysis of the cofactor (Scheme 1) and provides a versatile route for unprotected pterin functionality.

Scheme 1. The retrosynthetic analysis of molybdopterin cofactor



Results and Discussion.

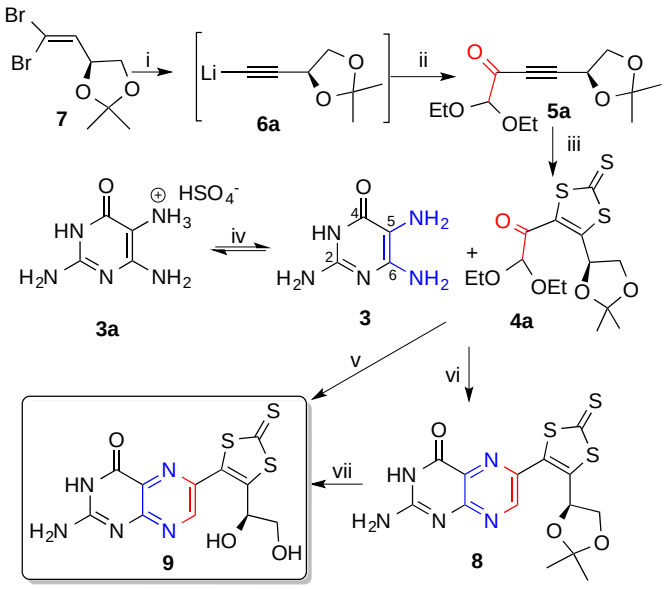
The retrosynthetic analysis, shown in Scheme 1, of the MPT provides a conceptual frame work for this investigation. The fragile N8-C7-O moiety of the MPT can be oxidatively cleaved under acidic conditions,[11, 16] yielding a fully oxidized pyrazine ring, concomitantly opening the pyran ring by breaking the C7-O bond as in compound

2. It is possible to reconstruct the N8-C7-O moiety by nucleophilic addition of the alcohol to an N-acetylated pyrazine ring, which can be formed by treating the pterin with chloroformate reagents e.g., benzyl chloroformate, 9H-fluoren-9-ylmethyl chloroformate (FMOC-Cl) that can subsequently be reduced by $NaBH_3CN$.[11] It has been proposed that both the open and the closed forms exist in equilibrium, and the open form can be oxidized to fully oxidized pterin as in **2**.[8, 23] The retrosynthetic analysis also shows compound **2** as the core MPT, without the phosphate group, as has the dithiolene and pterin functionalities. We envision that the pyrazine ring of the oxidized molybdopterin can be constructed via the condensation of an α-keto aldehyde (**4**), with 2,5,6-triamino-3,4-dihydropyrimidin-4-one (**3**). The retrosynthetic analysis highlights **4** as a key precursor to MPT, which is an 'osone' harboring a dithiolene moiety. A protected form of **4** could be achieved from an activated acetylene derivative (**5**) to which a dithiolene moiety can be introduced. [24, 25] In **5**, the adjacent keto group activates the acetylene. Compound **5** could be prepared from an acetylene e.g., compound **6**, through a nucleophilic addition reaction via an acetylide formation.[17]

The synthesis of dithiolene protected dephospho MPT has been realized by using dibromoalkene[26] **(7)** as a key building block (Scheme 2). Compound **7** is expected to afford the same stereochemistry as the MPT, whose absolute configuration has been crystallographically described.[10] Compound **7** was prepared in 68% yield, from 2,3-O-isopropylidene-D-glyceraldehyde[27] with modification of the Corey-Fuchs reaction.[28, 29] Compound **7** was reacted with ^{n}BuLi resulting in first a lithiated intermediate, **6a**, from which compound **5a** was prepared via an electrophilic substitution reaction with ethyl 2,2-diethoxyacetate. From this one-pot reaction, **5a** was isolated by radial chromatography in a 31% yield. Structurally, compounds **6a** and **5a** are very similar to **6** and **5**, respectively, with the exception of alcohol and aldehyde groups being protected. Compound **5a** contains an acetylene moiety next to an electron withdrawing keto group which makes it suitable for the introduction of a protected dithiolene unit[24, 25] with phenyl-1,3-dithiolane-2-thione[30] resulting in compound **4a** in a 58% yield. Compound **4a** is a protected form of precursor **4** and contains a protected aldehyde moiety as an acetal, a keto group, a protected dithiolene, and protected alcohol moieties.

The reaction of the compound containing a keto group next to the acetal with diamines follows that of the Isay-Gabriel-Coleman condensation[31, 32] for synthesizing pteridines.[33] The regioselective potential of this reaction is realized by exploiting the higher reactivity of the keto group relative to the acetal towards condensation with a diamine. This type of condensation reactions often lead to stereoselective formation of the undesired 7-isomer, although, a microwave assisted synthesis has afforded the 6-substituted pterin preferentially.[34] Earlier work on regiospecific synthesis of biopterin and anapterin involved condensation of the same pyrimidine with a sugar derivative.[35, 36] A similar methodology has been applied in synthesizing a pyranopterin.[37] In the present case, **4a** was successfully connected with **3a** in the presence of sodium sulfite as an additive. In the condensation reaction with the amine functionality in **3**, the keto group in **4a** serves as an electrophile. The free 5-NH_2 in **3** is the most nucleophilic among the three amine moieties[38], and is protonated forming a salt in **3a**. To obtain the desired regioisomer, the 5-NH_2 group in **3a** was deprotonated with a base (i.e., Na_2SO_3) forming **3** which then reacts with **4a** resulting in **8** in the desired regioisomer. No appreciable amount of the 7-isomer was detected in the ^{1}H NMR spectra of the reaction mixtures suggesting the regioselective nature of the condensation reaction (supplementary information). Additive assisted regioselective syntheses of pterins, like the one reported in here, have been reported before.[39] Yellow-orange **8** has been isolated in 31% yields from reactions conducted at 120 °C in the presence of 2-mercaptoethanol. At a slightly elevated temperature, the ketal protection of **8** can be removed in acidic conditions e.g., with trifluroacetic acid, resulting in the target compound, **9** in 82% yields. The ketal protection in **8** can be removed at room temperature, however, the reaction proceeds slowly.

Scheme 2



(i) ^{n}BuLi, Et_2O at -78 °C, room temperature; (ii) ethyl 2,2-diethoxyacetate at -78 °C, room temperature (31%); (iii) phenyl-1,3-dithiolane-2-thione at 130 °C (58%); (iv) Na_2SO_3, DMSO; (v) 150 °C, Na_2SO_3, DMSO (24%); (vi) 120 °C, 2-mercaptoethanol, DMSO (31%) (vii) CF_3COOH, DMF at 60 °C (82%).

Compound **9** can also be prepared directly by reacting **3** and **4a** in a 24% yield, optimally at 150 °C. During the reaction, the formation and decay of **8** can be observed by ^{1}H NMR spectroscopy (supplementary information). Here also only the desired isomer (i.e., **9)** is obtained in one step reaction in a similar overall yield. Condensation reactions of **3** with **4a,** but with unprotected acetal and ketal functionality, resulted in both the 6- and 7-isomers, and this route was not pursued further. Similar condensation reaction of **3** and **4a** bearing only the acetal protection, results in intractable products. Therefore, the protection of the aldehyde and the alcohol is important for regioselective condensation in this case.

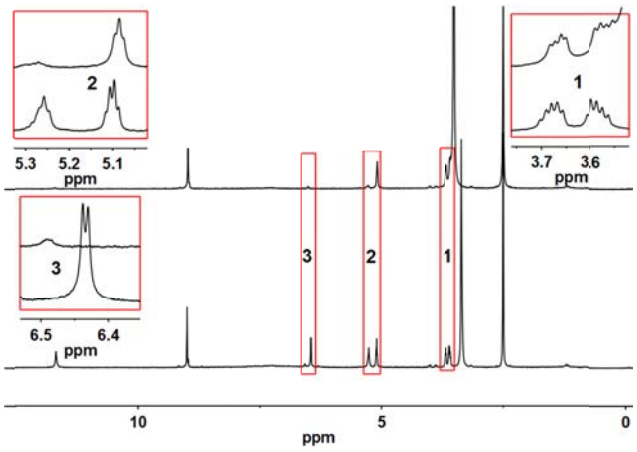


Figure 1. Room temperature ^{1}H NMR of **9**: bottom, in DMSO-d_6; top, same solution as bottom with added D_2O.

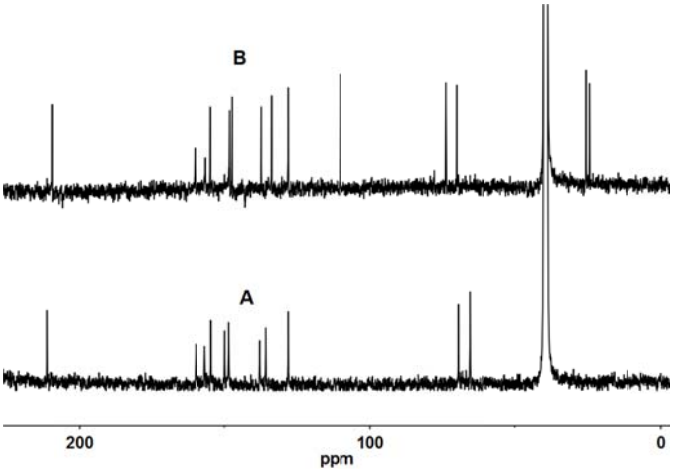


Figure 2. Room temperature ^{13}C NMR spectra of (A) 9 and (B) 8 taken in DMSO-d6.

Compound **9** has been characterized by IR, ^{1}H and ^{13}C NMR spectroscopies as well as high-resolution mass spectrometry (supplementary information). The ^{1}H NMR spectra of **9** are shown in Figure 1. Consistent with the literature[11, 40] a peak at 8.97 ppm corresponding to one proton is assigned to the proton at C7 in the pterin ring. Resonances due to the NH and NH_2 groups appear at 11.87 and 7.31 ppm, respectively, and the signals disappear in the presence of D_2O. The two alcohol protons appear at 6.43 and 5.26 ppm, respectively for the secondary and primary alcohols, and both alcohol protons are exchanged in D_2O. The CH and CH_2 protons appear at 5.11 (q), 3.67 (ddd) and 3.59 (ddd) ppm respectively. The latter two signals in equivalency of the two CH_2 protons. In the presence of D_2O these reduced splitting is observed.

The ^{13}C NMR spectroscopy has been used in characterizing the synthesized compounds. The trithiocarbonate carbon resonates almost at same place, in **4a**, **8** and **9,** at ~210 ppm. In addition to the thiocarbonyl group, a major difference between **5a** and **4a** is the conversion of acetylene to ene-dithiolate moiety. Two new peaks at ~167 and 129 ppm appeared in **4a** at the expense of peaks at 111 and 93 ppm present in **5a**. When the pterin heterocycle is attached to the dithiolene moiety, the situation becomes complicated due to the presence of several electron deficient carbon centres in the ring, making unambiguous assignment from 1D spectrum difficult. The protection of the alcohol group present in **8** is absent in **9** and consequently peaks at ~25 ppm and ~110 ppm observed in the spectrum of **8** are absent in **9** (Figure 2).

Conclusion

In conclusion, we disclose here a new approach to synthesize the core structure of the MPT, compound **9**, in a regioselective condensation reaction.[31, 32] The condensation reaction of oxo-aldehyde (**4a**) with the triaminohydroxy pyrimidine to obtain the desired 6-substituted regioisomer. The pterin functionality bears no protection, the only protection is in the dithiolene unit, which can be modified to introduce metal ions following the procedures developed by others[8, 25] and us[17]. Molecule **9** has all the components of the dephospho MPT and can serve as a spectroscopic benchmark for future studies. Results from our on going investigations to introduce metal ion, and reduction of the pterin moiety as well as introduction of a phosphate group will be reported in due course.

Experimental

General. Starting materials were purchased either from Aldrich Chemical Company or Acros Chemical Company and were used without further purification. Silica gel for column chromatography was purchased from Sorbent Technologies, and that for radial chromatography was purchased from EMD Chemicals. Ether was dried either by distillation over sodium-benzophenone or using a column (LC Technology). DMSO and DMF were dried by passing using solvent purification systems (Pure Solv, Innovative Technology) and LC Technology, respectively. All other solvents were used as received. NMR spectra were collected on a Bruker Avance 400 or a Bruker Avance 500 spectrometer operating at 400 MHz and 500 MHz for ^{1}H spectra, respectively. IR spectra were recorded using a Nicolet 380 FT spectrometer. High-resolution mass spectra were recorded on a Agilent 6200 time of flight LC MS system using a nano ESI and APCI -TOF interface.

Synthesis of 4-(2,2-dimethyl-1,3-dioxolan-4-yl)-1,1-diethoxybut-3-yn-2-one (5a).

1.7 g (5.7 mmol) of 4-(2,2-dibromovinyl)-2,2-dimethyl-1,3-dioxolane **(7)** was dissolved in 8.0 mL of dry diethyl ether and kept under N_2 for the duration of the reaction. The solution was then cooled to -78 °C before 4.16 mL (10.4 mmol) of 2.5 M *n*-butyllithium

in hexanes was added. The reaction continued for 1 hour at -78 °C, then warmed to room temperature for an additional hour. The solution was then cooled to -78 °C before 2.0 g (11.3 mmol) of ethyl 2,2-diethoxyacetate was added. The reaction mixture was stirred for 10 min at -78 °C, then for another 30 minutes at ambient temperature before it was transferred to a flask containing 30 mL of an ice-cold aqueous saturated solution of ammonium chloride and stirred vigorously. The organic layer was extracted with ethyl acetate (3 x 20 mL), and dried with anhydrous sodium sulfate and filtered, and the solvent was removed under vacuum. Crude product was purified by radial chromatography (4 mm silica gel, $60PF_{254}$) using a mixture of 9:1 hexanes and ethyl acetate yielding pure product as an oil. Yield, 31.5 % (0.463 g, 1.8 mmol). ^{1}H NMR in $CDCl_3$ (δ, ppm): 4.89 (1H, dd, J=3.6, 4.4 Hz, CH), 4.74 (1H, s, acetal), 4.21 (1H, dd, J=5.6, 9.2 Hz, CH_2), 4.07 (1H, dd, J= 5.2, 8.0 Hz, CH_2), 3.75-3.67 (2H, m, acetal), 3.66-3.59 (2H, m, acetal), 1.51 (3H, s, CH_3, ketal), 1.40 (3H, s, CH_3, ketal), 1.27 (6H, t, J=7.2 Hz, CH_3, acetal). ^{13}C NMR in $CDCl_3$ (δ, ppm): 182.58, 111.40, 92.90, 82.28, 69.44, 65.36, 63.25, 26.17, 25.96, 15.24. IR (neat, cm^{-1}): 2974, 2943, 2876, 2214, 1687, 1376, 1151, 1067, 837. HR ESIMS$^+$ with acetonitrile as the mobile phase, (m/z): 257.1379 [$C_{13}H_{20}O_5$ $(M+H)^+$, 257.1384], 279.1200 [$C_{13}H_{20}O_5$ $(M+Na)^+$, 279.1203], 295.0938 [$C_{13}H_{20}O_5$ $(M+K)^+$, 295.0942].

Synthesis of 1-(5-(2,2-dimethyl-1,3-dioxolan-4-yl)-2-thioxo-1,3-dithiol-4-yl)-2,2-diethoxyethan-1-one (4a).

0.34 g (1.32 mmol) of 4-(2,2-dimethyl-1,3-dioxolan-4-yl)-1,1-diethoxybut-3-yn-2-one **(5a)** and 3.0 g (14.12 mmol) of 4-phenyl-1,3-dithiolane-2-thione were dissolved in 5 mL of dichloromethane placed in a 100 mL round bottom flask. Addition of dichloromethane makes the reaction mixture more homogeneous, but it was removed under low pressure, before the reaction mixture was heated to 130 °C for 60 min under N_2. The reaction mixture was cooled to room temperature yielding a yellow-brown solid, which was purified by column chromatography on silica gel (65-250 mesh, 60A) using dichloromethane-*n*-hexanes (1:1) followed by dichloromethane which elutes the target compound as the second fraction. The solvent was evaporated under vacuum as a yellow liquid, which solidifies upon cooling. Yield, 58% (0.28 g, 0.768 mmol). ^{1}H NMR in $CDCl_3$ (δ, ppm): 5.55 (1H, dd, J=7.2, 7.2 Hz, CH), 4.75 (1H, s, acetal), 4.60 (1H, dd, J=8.8, 9.2 Hz, CH_2), 3.86 (1H, dd, J= 8.8, 9.2 Hz, CH_2), 3.79-3.76 (2H, m, acetal), 3.65-3.56 (2H, m, acetal), 1.53 (3H, s, CH_3, ketal), 1.38 (3H, t, CH_3, ketal), 1.29 (3H, t, J=6.8 Hz, CH_3, acetal), 1.28 (3H, t, J=6.8 Hz, CH_3, acetal). ^{13}C NMR in $CDCl_3$ (δ, ppm): 211.91, 184.83, 167.04, 129.82, 111.65, 102.04, 75.67, 70.75, 64.13, 26.04, 24.60, 15.17. IR (neat, cm^{-1}): 2978, 2925, 2884, 1679, 1053, 863. HR ESIMS$^+$ with acetonitrile as the mobile phase, (m/z): 365.0547 [$C_{13}H_{20}O_5S_3$ $(M+H)^+$, 365.0546], 387.0365 [$C_{13}H_{20}O_5S_3$ $(M+Na)^+$, 387.0386], 403.0127 [$C_{13}H_{20}O_5S_3$ $(M+K)^+$, 403.0103]

Synthesis of 2-amino-6-(5-(2,2-dimethyl-1,3-dioxolan-4-yl)-2-thioxo-1,3-dithiol-4-yl)pteridin-4(3H)-one (8).

100 mg (0.27 mmol) of 1-(5-(2,2-dimethyl-1,3-dioxolan-4-yl)-2-thioxo-1,3-dithiol-4-yl)-2,2-diethoxyethan-1-one (**4a**), 180 mg (0.75 mmol) of 4-hydroxy-2,5,6-triaminopyrimidine sulfate, 330 mg (1.30 mmol) of $Na_2SO_3.7H_2O$ and 1.1 g (~50 drops) of 2-mercaptoethanol, were taken in 10 mL dry DMSO. The mixture was warmed to 120 °C for 30 min and then cooled to room temperature. The reaction mixture turned dark brown, which was diluted with 10 mL DCM. The reaction mixture was purified by radial chromatography (4 mm silica, $60PF_{254}$) using a mixture of 1:2 DMF:DCM, only a yellow fraction was collected, and the organic solvent was evaporated under vacuum. The yellow solid was dissolved in 3 mL DMF, then diluted with 3 mL DCM. This mixture was purified again by radial chromatography using the same solvent mixture. The organic solvent was evaporated under reduced pressure. The dark orange solid was washed with water (3 × 5 mL), and then dried under vacuum yielding an orange solid. Yield, 33 mg (0.083 mmol, 31%). ^{1}H-NMR in DMSO (δ, ppm): 11.66 (1H, s, =NH) 8.75 (1H, s, H-C7), 7.22 (2H, s, $-NH_2$), 5.56(1H, dd, J=7.2, 6.0 Hz, CH), 4.88 (1H, dd, J=7.2, 9.2 Hz, CH), 4.01 (1H, dd, J=6.0, 9.2 Hz, CH), 1.48 (6H, s, CH_3), 1.34 (6H, s, CH_3). ^{13}C NMR in $CDCl_3$ (δ, ppm): 209.87, 160.69, 156.53, 154.80, 148.24, 147.38, 137.48, 133.93, 128.32, 110.49, 73.99, 70.26, 25.78, 24.60. IR (neat, cm^{-1}): 3129, 2982, 2757, 1691, 1679, 1606, 1368, 1049, 812, 502. HR ESIMS$^+$ with acetonitrile as the mobile phase, (m/z): 396.0251 [$C_{14}H_{13}N_5O_3S_3$ $(M+H)^+$, 396.0253], 418.0067 [$C_{14}H_{13}N_5O_3S_3$ $(M+Na)^+$, 418.0072], 433.9822 [$C_{14}H_{13}N_5O_3S_3$ $(M+K)^+$, 433.9812]

Synthesis of 2-amino-6-(5-(1,2-dihydroxyethyl)-2-thioxo-1,3-dithiol-4-yl)pteridin-4(3H)-one (9).

This compound was synthesized in two methods.

Method a. 100 mg (0.27 mmol) of 1-(5-(2,2-dimethyl-1,3-dioxolan-4-yl)-2-thioxo-1,3-dithiol-4-yl)-2,2-diethoxyethan-1-one **(4a)**, 262 mg (1.09 mmol) of 4-hydroxy-2,5,6-triaminopyrimidine sulfate, and 552 mg (2.19 mmol) of $Na_2SO_3.7H_2O$ were suspended in 3 mL DMSO. The mixture was warmed for 35 min at 150 °C. The mixture was extracted with DMF (6 × 3 mL), and the supernatant was separated after centrifugation. The DMF-DMSO solution was evaporated under vacuum, the ensuing solid was dissolved in 3 mL DMF, and purified by radial chromatography (2 mm silica, $60PF_{254}$,) using DMF:DCM 1:2 then DMF as eluent. The second yellow fraction was collected, evaporated yielding orange solid. The solid was recrystallized from hot water (15 mL), and dried under vacuum. Yield, 23 mg (0.064 mmol, 24%).

Method b. 20 mg (0.050 mmol) of 2-amino-6-(5-(2,2-dimethyl-1,3-dioxolan-4-yl)-2-thioxo-1,3-dithiol-4-yl)pteridin-4(3H)-one **(8)** was dissolved in 3 mL of dry DMF, and to this reaction mixture 1 mL of trifluoroacetic acid was added. The mixture was stirred for 3 h at 60 °C. The solvent was evaporated under low pressure at 60 °C. The mixture was recrystallized from boiling water. The yellow precipitate was separated by centrifugation, then dried under reduced pressure. Yield, 14.7 mg (0.041 mmol, 81%).

Characterization. ^{1}H-NMR in DMSO (δ, ppm): 11.87 (1H, s, =NH) 8.97 (1H, s, H-C7), 7.31 (2H, s, $-NH_2$), 6.43 (1H, J=5.0, Hz, -OH), 5.26 (1H, t, J= 5.0 Hz, -OH), 5.11 (1H, q, J=5.0 Hz, CH), 3.67 (1H, ddd, J= 5.0, 5.0, 5.0 Hz, CH), 3.59 (1H, ddd, J= 5.0, 5.0, 5.0 Hz, CH).^{13}C NMR in $CDCl_3$ (δ, ppm): 211.62, 160.40, 156.80, 154.65, 149.95, 148.58, 138.01, 135.94, 128.32, 69.69, 65.71. IR (neat, cm^{-1}): 3313, 3129, 2925, 1617, 1466, 1339, 1067, 1037, 988, 812, 506. HR ESIMS$^+$ with acetonitrile as the mobile phase, (m/z): 355.9973 [$C_{11}H_9N_5O_3S_3$ $(M+H)^+$, 355.9940],

377.9793 [$C_{11}H_9N_5O_3S_3$ $(M+Na)^+$, 377.9759], 393.9553 [$C_{11}H_9N_5O_3S_3$ $(M+K)^+$, 393.9499]

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Notes and references

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1. R. Hille, *Chem. Rev.* , 1996, **96**, 2757-2816.
2. C. Sparacino-Watkins, J. F. Stolz and P. Basu, *Chem. Soc. Rev.*, 2014, **43**, 676-706.
3. R. Hille, J. Hall and P. Basu, *Chem. Rev.* , 2014, Ahead of Print.
4. G. Schwarz, R. R. Mendel and M. W. Ribbe, *Nature*, 2009, **460**, 839-847.
5. B. Fischer, J. H. Enemark and P. Basu, *J. Inorg. Biochem.*, 1998, **72**, 13-21.
6. J. L. Johnson, B. E. Hainline, K. V. Rajagopalan and B. H. Arison, *J. Biol. Chem.* , 1984, **259**, 5414-5422.
7. P. Basu and S. J. N. Burgmayer, *Coord. Chem. Rev.*, 2011, **255**, 1016-1038.
8. F. J. Hine, A. J. Taylor and C. D. Garner, *Coord. Chem. Rev.* , 2010, **254**, 1570-1579.
9. J. L. Johnson and K. V. Rajagopalan, *Proc. Natl. Acad. Sci. U. S. A.* , 1982, **79**, 6856-6860.
10. M. J. Romao, *Dalton Trans.* , 2009, 4053-4068.
11. B. Bradshaw, A. Dinsmore, W. Ajana, D. Collison, C. D. Garner and J. A. Joule, *J. Chem.Soc., Perkin Trans. 1*, 2001, 3239-3244.
12. E. C. Taylor and R. Doetzer, *J. Org. Chem.* , 1991, **56**, 1816-1822.
13. B. R. Williams, Y. Fu, G. P. A. Yap and S. J. N. Burgmayer, *J. Am. Chem. Soc.*, 2012, **134**, 19584-19587.
14. K. Clinch, D. K. Watt, R. A. Dixon, S. M. Baars, G. J. Gainsford, A. Tiwari, G. Schwarz, Y. Saotome, M. Storek, A. A. Belaidi and J. A. Santamaria-Araujo, *J. Med. Chem.*, 2013, **56**, 1730-1738.
15. R. S. Pilato, K. A. Eriksen, M. A. Greaney, E. I. Stiefel, S. Goswami, L. Kilpatrick, T. G. Spiro, E. C. Taylor and A. L. Rheingold, *J. Am. Chem. Soc.*, 1991, **113**, 9372-9374.
16. S. Hilken, F. Kaletta, A. Heinsch, J.-M. Neudoerfl and A. Berkessel, *Eur. J. Org. Chem.*, 2014, Ahead of Print.
17. L. Marbella, B. Serli-Mitasev and P. Basu, *Angewandte Chemie, International Edition*, 2009, **48**, 3996-3998.
18. I. V. Pimkov, A. Nigam, K. Venna, F. F. Fleming, P. V. Solntsev, V. N. Nemykin and P. Basu, *J. Heterocycl. Chem.*, 2013, **50**, 879-886.
19. R. S. Sengar, V. N. Nemykin and P. Basu, *New J. Chem.*, 2003, **27**, 1115-1123.
20. P. Basu, V. N. Nemykin and R. S. Sengar, *Inorg. Chem.*, 2003, **42**, 7489-7501.
21. R. S. Sengar and P. Basu, *Inorg. Chim. Acta*, 2007, **360**, 2092-2099.
22. R. S. Sengar, J. J. Miller and P. Basu, *Dalton Trans.* , 2008, 2569-2577.
23. B. Fischer, J. H. Enemark and P. Basu, *J Inorg Biochem*, 1998, **72**, 13-21.
24. B. R. O'Connor and F. N. Jones, *J. Org. Chem.*, 1970, **35**, 2002-2005.
25. B. Bradshaw, A. Dinsmore, D. Collison, C. D. Garner and J. A. Joule, *J. Chem. Soc., Perkin Trans. 1*, 2001, 3232-3238.
26. B. W. Gung and G. Kumi, *J. Org. Chem.*, 2003, **68**, 5956-5960.
27. C. R. Schmid, J. D. Bryant, M. Dowlatzedah, J. L. Phillips, D. E. Prather, R. D. Schantz, N. L. Sear and C. S. Vianco, *J. Org. Chem.*, 1991, **56**, 4056-4058.
28. E. J. Corey and P. L. Fuchs, *Tetrahedron Lett.*, 1972, 3769-3772.
29. D. Habrant, V. Rauhala and A. M. P. Koskinen, *Chem Soc Rev*, **39**, 2007-2017.
30. C. C. J. Culvenor, W. Davies and K. H. Pausacker, *Journal of the Chemical Society*, 1946, 1050-1052.
31. O. Isay, *Berichte der deutschen Chemischen Gesellschaft.*, 1906, **39**, 250-265.
32. S. Gabriel and J. Coleman, *Chem. Ber.*, 1901, **34**, 1234-1257.
33. R. B. Angier, *J. Org. Chem.*, 1963, **28**, 1398-1401.
34. S. Goswami and A. K. Adak, *Tetrahedron Letters*, 2002, **43**, 8371-8373.
35. B. Schircks, J. H. Bieri and M. Viscontini, *Helv. Chim. Acta*, 1985, **68**, 1639-1643.
36. M. Viscontini and R. Bosshard, de Gruyter, 1990, pp. 73-76.
37. R. Soyka, W. Pfleiderer and R. Prewo, *Helv. Chim. Acta*, 1990, **73**, 808-826.
38. S. Murata, H. Ichinose and F. Urano, *Top. Heterocycl. Chem.*, 2007, **8**, 127-171.
39. M. T. G. Ivery and J. E. Gready, *Biol. Chem. Hoppe-Seyler*, 1992, **373**, 1125-1137.
40. T. Hanaya, H. Baba, H. Toyota and H. Yamamoto, *Tetrahedron*, 2009, **65**, 7989-7997.