The Identification of a Novel Highly Condensed Pentacyclic Heteroaromatic Ring System 1,3,5,5b,6,8,10,10b-Octaazacyclopenta[h,i] Aceanthrylene and its Application in the Synthesis of 5,7-Substituted Pyrazolo[4,3-*d*]Pyrimidines

Libor Havlíček,[a] Daniela Moravcová,[a] Vladimír Kryštof,[b] and Miroslav Strnad[b]*

[a]Isotope Laboratory, Institute of Experimental Botany ASCR, Videnska 1083, 142 20 Prague, Czech Republic
[b]Laboratory of Growth Regulators, Faculty of Science, Palacký University & Institute of Experimental Botany ASCR, Šlechtitelů 11, 78371 Olomouc, Czech Republic
*E-mail:miroslav.strnad@upol.cz

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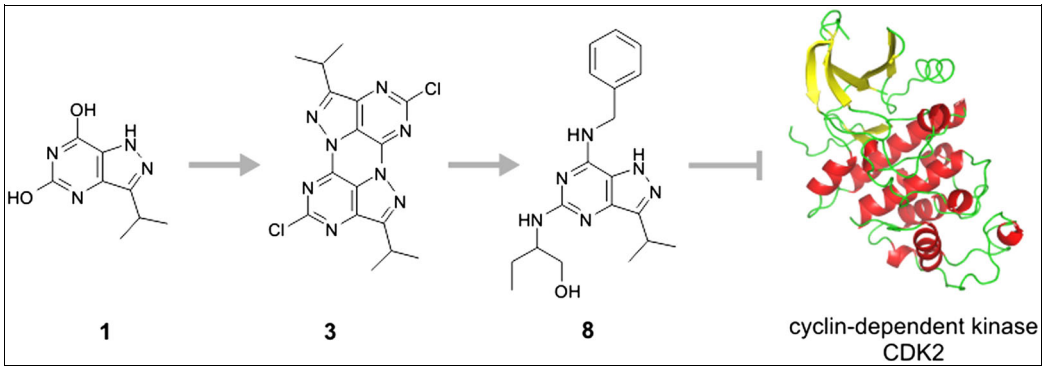

Pyrazolo[4,3-d]pyrimidines are of interest as potential kinase inhibitors. This article describes the formation of a novel highly conjugated, condensed, centrosymmetric heteroaromatic compound, **4,9-dichloro-2,7-diisopropyl-1,3,5,5b,6,8,10,10b-octaazacyclopenta[h,i]aceanthrylene** (**3**), during the chlorination of 5,7-dihydroxypyrazolo[4,3-*d*]pyrimidine (**1**) with phenylphosphonic dichloride. The nucleophilic attack of benzylamine on 3 afforded **N-benzyl-5-chloro-3-isopropyl-1H-pyrazolo[4,3-d]pyrimidin-7-amine** (**6**), which was further substituted to yield a pyrazolo[4,3-*d*]pyrimidine analogue of roscovitine, a well-known cyclin-dependent kinase inhibitor.

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INTRODUCTION

Protein kinases have become important targets in the development of drugs for the treatment of various cancers [1]. In recent years, 15 new small molecule drugs targeting kinases such as the oncogenic Bcr–Abl fusion kinase, In recent years, 15 new small molecule drugs targeting kinases such as the oncogenic Bcr-Abl fusion kinase, the EGFR (epidermal growth factor receptor) and VEGFR (vascular endothelial growth factor receptor) receptor kinases, and the JAKs (Janus kinases) and B-raf cytoplasmic kinases have been approved for sale and come onto the market. and B-raf cytoplasmic kinases have been approved for sale and come onto the market [1b]. Many more kinase-targeting compounds are currently undergoing clinical trials, including various cyclin-dependent kinase (CDK) inhibitors [2]. The CDKs are a family of enzymes that are regarded as attractive targets for the treatment of proliferative diseases because they regulate processes that are essential for cellular proliferation and survival such as cell cycling (e.g., CDKs 1, 2, 4, and 6), transcription (CDKs 7, 8, and 9), and apoptosis (CDKs 2 and 9) [3]. Our research group has identified several potent purine-based CDK inhibitors, including roscovitine [4]. Roscovitine (Fig. 1) was one of the first CDK inhibitors to enter clinical trials, and partly because of this, its structure has been explored by many groups and optimized in different ways.

With the increasing number of articles describing kinase inhibitors, it is becoming increasingly difficult to identify new chemotypes that could be used to develop new adenosine triphosphate competitive inhibitors. One potential way of overcoming this hurdle involves modifying the heterocyclic skeleton that forms the core of the inhibitor. To this end, we analyzed the binding of roscovitine to various CDKs and used structure-based reasoning to identify modifications of the purine core that could potentially yield new bioisosteric inhibitors. Investigations of compounds based on such modified core structures have led to the discovery of several groups of purine bioisosteres; the progress made in this area has recently been reviewed [5]. Notably, the bioisosteric approach was applied in the discovery and development of dinaciclib, a CDK inhibitor that is currently undergoing clinical trials (Fig. 1). Dinaciclib binds to the active site of CDK2 in the same orientation as roscovitine but is a more potent inhibitor because it has substituents that facilitate its binding [6].

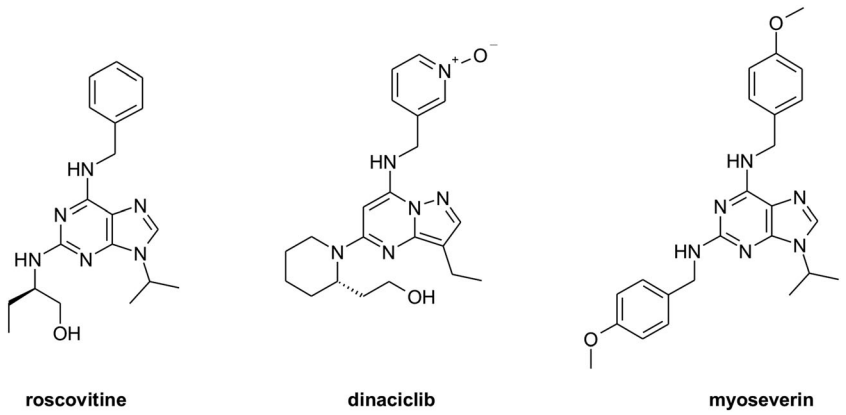


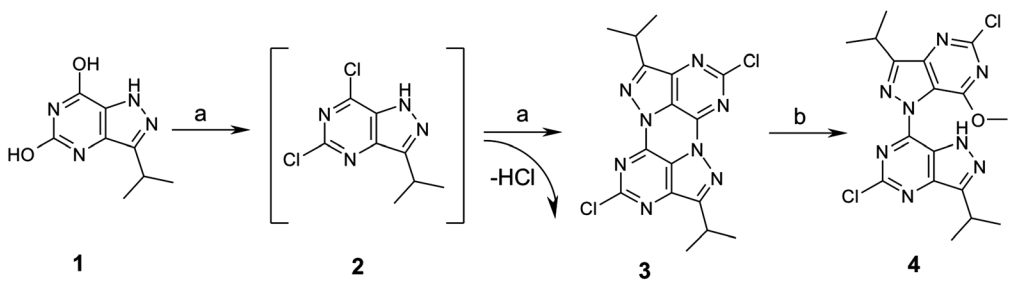
Figure 1. Structures of roscovitine, dinaciclib, and myoseverin.

One of our early attempts at modifying the purine core of roscovitine focused on the synthesis of isomeric pyrazolo[4,3-*d*]pyrimidine derivatives. A synthetic approach to this skeleton was used to prepare 5,7-bis-[(4-methoxybenzyl)amino]-3-isopropyl-1(2)*H*-pyrazolo[4,3-*d*]pyrimidine (Fig. 1), an isomer of the microtubule-interfering agent myoseverin [7]. The starting material for this synthesis was 3-isopropyl-1(2)*H*-pyrazolo[4,3-*d*]pyrimidine-5,7-diol (**1**), which was chlorinated with phenylphosphonic dichloride ($PhPOCl_2$) or pyrophosphoryl dichloride [$Cl_2(O{=})P{-}O{-}P({=}O)Cl_2$] using a protocol developed for use with isomeric xanthine derivatives [8]. This reaction is assumed to produce the 5,7-dichlorinated derivative **2** (Scheme 1), although this compound was not purified and thoroughly characterized. Instead, the initial reaction mixture was subjected to a simple extraction and immediately reacted with a large excess of 4-methoxybenzylamine to yield the desired product via an S_N process. This procedure provided a 20% yield of 5,7-bis-[(4-methoxybenzyl)amino]-3-isopropyl-1(2)*H*-pyrazolo[4,3-*d*]pyrimidine after chromatography [7].

RESULTS AND DISCUSSION

In order to adapt this synthesis for the preparation of the pyrazolo[4,3-*d*]pyrimidine analogue of roscovitine, which has two different substituents on the pyrimidines rings, it was necessary to isolate the presumed intermediate **2** [9]. To this end, the reaction mixture obtained after the completion of the chlorination step was mixed with water, and the product was extracted with benzene. The organic phase was dried, the benzene was removed by evaporation, and the residue was dissolved in a minimal volume of toluene. Cyclohexane was then added, and the first fraction of the final product was crystallized. Another fraction was obtained by chromatography of the mother liquor on silica gel using 1% MeOH in toluene. However, it was found that the methanol reacted with the product at room temperature and so in subsequent runs, the methanol was replaced with the more sterically hindered *tert*-butanol, which did not react with the product even at elevated temperatures (80°C). The crystalline product (mp > 300°C) is light yellow-green and exhibits fluorescence (peaks at 402, 423, and 448 nm); its fluorescent spectrum is a mirror image of its UV absorption spectrum. The UV spectrum (measured in *tert*-butanol) contains strong and sharp peaks at 364, 382, and 400 nm (with the latter being the strongest peak) and clearly indicates the formation of a more extensive conjugated system of double bonds than would be expected for the expected dichlorinated compound **2**. On the basis of the ^1H NMR spectrum of the isolated material (which did not contain any peaks that could reasonably be assigned to the HN^1 proton when acquired in $CDCl_3$ or abs. DMSO), CHN analysis, and EI-MS data, we conclude that rather than the expected product **2**, we in fact obtained

Scheme 1. Reagents and conditions: (a) 1. $PhPOCl_2$, 145°C, ampoule, 3 h; 2. evaporation 110°C/0.5 Torr; 3. H_2O, benzene, 0°C, 24%; (b) MeOH, rt, 1 h, 95%.



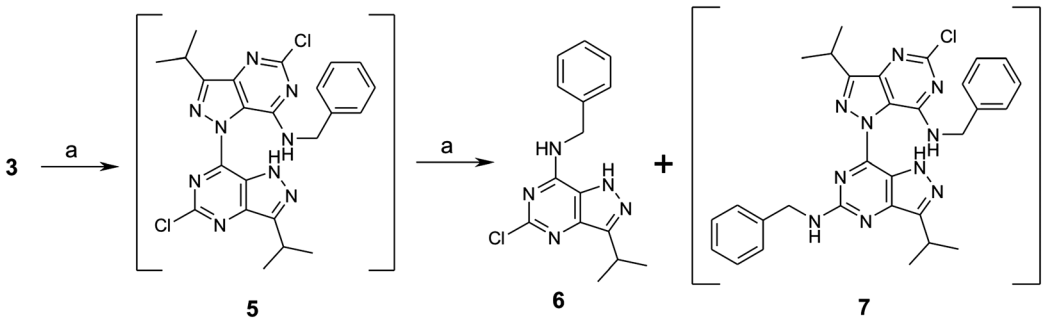
4,9-dichloro-2,7-diisopropyl-1,3,5,5b,6,8,10,10b-octaazacyclopenta[h,i]aceanthrylene (**3**) (Scheme 1). This compound is presumably formed via some sort of condensation process involving two molecules of **2**. Unfortunately, attempts to determine the structure of this compound directly by X-ray crystallography were unsuccessful; whereas crystals of adequate size were prepared via multiple methods, and they tended to form flat and mutually adherent plates that were unsuitable for X-ray diffraction analysis. However, inspection of the product's IR (KBr tablet) and Raman (powder sample) spectra indicated that it has a center of symmetry, which is consistent with the proposed dimeric structure; the bands observed in the IR spectrum were not apparent in the Raman spectrum and vice versa. This implies that the molecule has a center of symmetry and is rigid. However, the methyl groups of the isopropyl unit can obviously rotate freely and so the exclusion principle does not hold for their bands.

Compound **3** is rather reactive, and the central heterocycle opens readily at room temperature in MeOH undergoing near-complete solvolysis (>95%) within 60 min. An analogous reaction occurs in n-BuOH. The course of the reaction can be readily observed by monitoring the UV spectrum of the reaction mixture: the absorption peaks of compound **3** disappear gradually and are replaced by new maxima at 341 and 355 nm. The mass spectra of methanolic solutions of compound **3** acquired using ESI (desolvation temperature 120°C, coin voltage 20 V) in negative ion mode contain only one peak, at *m/z* 419 $[M-H]^-$. No detectable signal was observed in positive mode ESI spectra. However, a positively charged ion at *m/z* 421 $[M+H]^+$ was observed in the atmospheric pressure chemical ionization mass spectrum of the reaction mixture. The isotopic patterns observed in both the positive and negative mass spectra of the undesired product of solvolysis **4** are consistent with the suggested structure **4**.

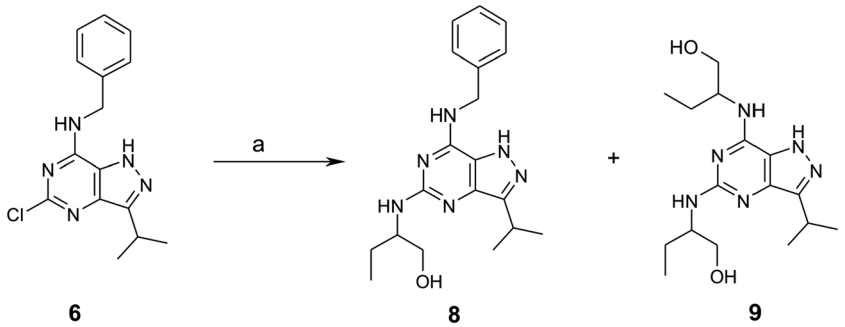
Unfortunately, we were unable to isolate and fully characterize compound **4**. The second putative bond between the two pyrazolo[4,3-*d*]pyrimidine ring systems is substantially more resistant to nucleophilic attack than the first and is not cleaved in MeOH even at an elevated temperature of 55°C. However, it is rapidly cleaved even at 25°C if a drop of 1 M CH_3ONa is added to the reaction mixture.

In order to prepare the desired roscovitine analogue, compound **3** was reacted with benzylamine (Scheme 2) in *tert*-butanol, a solvent that does not attack **3**. The progress of this reaction is readily monitored by studying the UV spectrum of the reaction mixture (in *tert*-butanol): the peaks arising from compound **3** disappear gradually and are initially replaced by those corresponding to intermediate **5**, which occur at 372 and 357 nm. The formation of the desired product is reflected by the subsequent appearance of a peak at 300 nm with shoulders at 311 and 324 nm. Unfortunately, this reaction yields a fairly complex mixture of products. The main contaminant is believed to be compound **7** on the basis of the observation of a positive ion of *m/z*

Scheme 2. Reagents and conditions: (a) 1. benzylamine, t-BuOH, 60°C, 6 h; 2. LC, silica gel, 0–3% MeOH in $CHCl_3$, 35%.



Scheme 3. Reagents and conditions: (a) 1. 2-amino-1-butanol, 150°C, 6 h; 2. LC 0–3% MeOH in $CHCl_3$, 40%.



567.4 and a negative ion of *m/z* 565.3 in the ESI-MS spectrum of the crude material. This compound was not isolated. The isotopic patterns seen in the positive and negative mass spectra of the side product **7** are consistent with the suggested structure **7**. The formation of this side product, which may in fact be a positional isomer or a mixture of such isomers, results from the small difference in reactivity between positions 5 and 7 of intermediate **5**. The desired product **6** does not crystallize and was therefore isolated chromatographically. The final transformation (Scheme 3) in the synthesis of roscovitine analogue **8** was achieved by dissolving compound **6** in neat 2-amino-1-butanol and heating the resulting mixture to 150°C. The chlorine in position 5 of the heterocycle is not readily substituted by amines, and the difference between the electrophilic reactivities of positions 5 and 7 of the pyrazolo[4,3-*d*]pyrimidine ring system seems to be less pronounced than is the case in the analogous 5,7-dichlorinated purines. In addition to the desired product **8**, the reaction mixture also contained the undesired derivative **9** and the unconverted starting material **6**.

CONCLUSIONS

As demonstrated by molecular modeling and its performance in biochemical and cellular assays, compound **8** is a potent CDK inhibitor with interesting anticancer activity and lower IC_{50} values than its bioisostere roscovitine [9]. The CDK-inhibiting activity of related substituted pyrazolo [4,3-*d*]pyrimidines has been also investigated in some detail [10]. On the basis of our knowledge of the structure-activity relationships for the analogous trisubstituted purines, we are currently aiming to synthesize 3,5,7-trisubstituted pyrazolo [4,3-*d*]pyrimidine derivatives, which are expected to have nanomolar potency.

EXPERIMENTAL

Melting points were determined on a Kofler block and are uncorrected. NMR spectra were acquired using a Varian UNITY Inova-400 spectrometer (Varian Inc., Palo Alto, CA, USA) in $CDCl_3$ at 303 K. The residual signal of the solvent was used as an internal standard ($CHCl_3$, δ_H 7.265 ppm, δ_C 77.00 ppm). ^{1}H NMR spectra were zero-filled to fourfold data points and multiplied by a window function (two-parameter double-exponential Lorentz–Gauss function) prior to Fourier transformation to improve resolution. Protons were assigned by COSY and TOCSY, and assignments were transferred to carbons by HMQC. Chemical shifts are given in δ-scale (ppm), coupling constants in Hertz. Carbon chemical shifts were read out from HMQC (protonated carbons) and HMBC spectra. ESI or atmospheric pressure chemical ionization mass spectra were acquired using a Waters Micromass ZMD (Micromass UK Ltd., Manchester, UK) mass spectrometer (direct inlet, coin voltage 20 V). Standard electron ionization EI mass spectra were acquired using a Jeol D100 (Jeol Ltd., Tokyo, Japan) double-focusing mass spectrometer (ionization energy 75 eV, chamber temperature 200°C, ionizing current 300 mA, and accelerating voltage 3 kV). IR spectra were recorded on a Nicolet 200 FT-IR instrument (Nicolet Analytical Instrument, Madison, WI, USA); Raman spectra were acquired on a Labram HR instrument (Yobin Yvon Ltd., Tokyo, Japan). Merck silica gel (Merck, Darmstad, Germany) Kieselgel 60 (230–400 mesh) was used for column chromatography. 3-Isopropyl-1(2)*H*-pyrazolo [4,3-*d*]pyrimidin-5,7-diol (1) was prepared according to the published synthesis [7].

4,9-dichloro-2,7-diisopropyl-1,3,5,5b,6,8,10,10b-octaazacyclopenta[h,i]ace-anthrylene (3). 5,7-Dihydroxy-3-isopropylpyrazolo [4,3-*d*]pyrimidine **1** (5.1 g; 26.3 mmol) was dissolved in $PhPOCl_2$ (32 mL) and the mixture was heated at 145°C in sealed ampoule for 3 h. The solution was evaporated in 0.5 Torr vacuum (bath temperature up to 110°C), and the residue was cooled and poured in the mixture of crushed ice and benzene. The benzene extract was once washed by water and immediately dried over Na_2SO_4. The extract was evaporated, and the residue was dissolved in minimum toluene; the first portion of product was crystallized by adding cyclohexane (0.7 g). The rest of the product (0.5 g) was isolated from the mother liquor by column chromatography in toluene–*tert*-butanol (99:1); yield 1.2 g (43%), mp (December) > 300°C. UV, λ_{max} (ε): 364 nm (16700), 382 nm (40700) 402 nm (59000). ^{1}H NMR (400 MHz, $CDCl_3$): 1.54 (d, J = 7.0 Hz, 6H, $C\underline{H}_3CH$-), 3.53 (September, J = 7.0 Hz, 1H, $CH_3C\underline{H}-$). ^{13}C NMR (100 MHz, $CDCl_3$): 21.2 (11, 12); 28.1 (10); 127.0; 145.5; 147.2 (9); 157.9; 161.5 (3). IR (cm^{-1}): 2984 (sh), 2970, 2932, 2876, 1635, 1580 (vs), 1524 (vs), 1475, 1456 (vw), 1397, 1386, 1368 (sh), 1341 (w-m), 1290 (sh), 1277 s, 1254, 1214 (vs), 1182, 1134, 1110, 1080, 1010, 892, 864, 817, 785, 725, 712. Raman (cm^{-1}): 2987 (vw), 2971 (vw), 2931, 2873, 1643, 1573, 1479, 1454, 1407, 1381, 1369 (sh), 1343 (vw), 1333, 1319, 1307, 1292 (sh), 1284, 1230, 1151, 1120, 1093, 982, 966, 910, 835, 790, 760, 716, 702, 631, 622 (sh). EI-MS: 388 (M^+, 35), 373 ($M - CH_3^+$ 30), 331 (25), 186 (20), 43($C_3H_7^+$, 100). HRMS: Calcd for $C_{16}H_{14}^{35}Cl_2N_8$: 388.07185, found: 388.07095. CHNCl analyses: Calcd for $C_{16}H_{14}\ Cl_2N_8$: C, 49.37; H, 3.63; Cl, 18.22; N, 28.79. Found: C, 49.52; H, 3.61; Cl, 18.40; N, 28.47.

N-benzyl-5-chloro-3-isopropyl-1H-pyrazolo[4,3-d]pyrimidin-7-amine (6). A mixture of **3** (1 g, 2.58 mmol), 25 mL t-butanol and 4 mL benzylamine was stirred at 60°C for 6 h. The reaction mixture was evaporated to dryness. Column chromatography (stepwise 0%, 1%, 2%, and 3% MeOH in toluene) afforded product **6**, after evaporation noncrystallizable amorphous yellowish glass, 0.54 g (36%), mp 69–72°C, light green crystals. MS ESI$^+$: $[M+H]^+$ = 302.3 (100); MS ESI$^-$: $[M-H]^-$ = 300.2 (100). Isotope pattern corresponds to a single chlorine atom. EI-MS: 301 (M^+, 43), 286 ($M - CH_3^+$ 33), 106 ($C_7H_8N^+$, 39), 91 ($C_7H_7^+$, 70) 36 (100). HRMS: 301.10769 error + 1.7 mmu. ^{1}H NMR (300 MHz, $CDCl_3$): 1.37 (d, J = 7.1 Hz, 6H, CH_3CH–); 3.39 (September, J = 7.1 Hz, 1H, CH_3CH–), 6.72 (bs, 1H, –NH), 4.82 (s, 2H, –CH_2–NH–), 7.28 (m, 5H, Ar H). ^{13}C NMR (75 MHz, $CDCl_3$): 22.3 (19); 26.7 (18); 44.9 (11); 127.1 (15); 127.9 (13 + 17); 128.8 (14 + 16); 140.3 (12); 143.5; 154.4; 155.2; 156.4; 171.0. HRMS: Calcd for $C_{15}H_{16}^{35}ClN_5$: 301.109423, found: 301.10769. CHClN analyses: Calcd for $C_{15}H_{16}ClN_5$: C, 59.70; H, 5.34; Cl, 11.75; N, 23.21. Found: C, 59.56; H, 5.39; Cl, 11.62; N, 23.02.

2-{[7-(benzylamino)-3-isopropyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl]amino}-1-butanol (8). A mixture of (0.5 g, mmol) compound **6** and 5 mL of 2-amino-1-butanol was heated at 150°C in a sealed ampoule for 6 h. After cooling, the reaction mixture was partitioned between water and $CHCl_3$. The organic phase was dried by Na_2SO_4 and evaporated. Column chromatography (stepwise 0%, 1%, 2%, and 3% MeOH in $CHCl_3$) afforded product **8** (after evaporation,

noncrystallizable amorphous colorless glass), 0.15 g (36 %), amorphous. MS ESI$^+$: $[M+H]^+ = 355.4$ (100), MS ESI$^-$: $[M-H]^- = 353.3$ (100). ^{1}H NMR (300 MHz, DMSO-d*6*): 0.85 (t, $J = 7.5$ Hz, 3H, 23), 1.32 (d, $J = 7.0$ Hz, 6H, 19), 1.39–1.68 (m, 2H, 22a, 22b), 3.16 (September, $J = 7.0$ Hz, 1H, 18), 3.37–3.51 (m, 2H, 24a, 24b), 3.78 (m, 1H, 21), 4.68 (t, $J = 4.8$ Hz, 2H, 11), 5.74 (bs, 1H, 20), 7.26 (t, 1H, 15), 7.34 (t, 2H, 14 + 16), 7.39 (d, 2H, 13 + 17), 11.79 (bs, 1H, 10), 13.28 (bs, 1/2H, 1). ^{13}C NMR (75 MHz, DMSO-d*6*): 10.6 (23); 21.5 (19); 21.6 (19); 23.8 (22); 25.9 (18); 43.0 (11); 54.2 (21); 63.4 (24); 126.9 (15); 127.5 (13 + 17); 128.3 (14 + 16); 130.7; 130.4; 139.3 (12); 158.8; 158.9; 161.4. CHN analyses: Calcd for $C_{19}H_{26}N_6O$: C, 64.38; H,7.39; N, 23.71; Found: C, 64.51, H, 7.57, N, 23.48.

2,2'-[(3-isopropyl-1H-pyrazolo[4,3-d]pyrimidine-5,7-diyl)diimino]di(1-butanol) (9). Yield 12%, amorphous. MS ESI$^+$: $[M+H]^+ = 337.4$ (100), MS ESI$^-$: $[M-H]^- = 353.3$ (100). ^{1}H NMR (300 MHz, CD_3OD): 0.86 (t, $J = 7.5$ Hz, 3H, 21), 0.89 (t, $J = 7.5$ Hz, 3H, 15) 1.32 (d, $J = 7.0$ Hz, 6H, 23), 1.38–1.52 (m, 2H, 20), 1.63–1.79 (m, 2H, 14), 3.16 (September, $J = 7.0$ Hz, 1H, 22), 3.29–3.43 (m, 2H, 18), 3.51–3.64 (m, 2H, 12), 3.78 (m, 1H, 17), 3.83 (m, 1H, 11), 5.69 (bs, 1H, 16), 5.72 (bs, 1H, 10), 12.29 (bs, 1H, 1). ^{13}C NMR (75 MHz, CD_3OD): 10.5 (21), 10.9 (15), 21.6 (23), 23.9 (20), 24.2 (14), 25.6 (22), 53.9 (17), 54.2 (11), 63.4 (18), 64.6 (12), 139.9, 149.7, 157.2, 157.8, 160.4. CHN analyses: Calcd for $C_{18}H_{31}N_5O_2$: C, 57.12; H, 8.39; N, 24.98. Found: C, 57.37; H, 8.50; N, 24.71.

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