JOC The Journal of Organic Chemistry

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Synthesis of Purine Analogues: Photocatalyst-Free Visible-Light-Enhanced Annulation Approach to Pyrazolo[1,5-*a*][1,3,5]triazine-2,4-diamines

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Cite This: *J. Org. Chem.* 2021, 86, 8365−8380 Read Online

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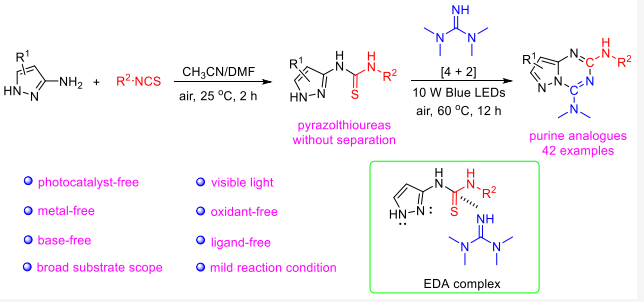
ABSTRACT: A new photocatalyst-free visible-light-enhanced strategy for the synthesis of pyrazolo[1,5-*a*][1,3,5]triazine-2,4-diamines via the formation of electron donor−acceptor (EDA) complexes is reported. The *in situ* generated pyrazolthiourea intermediates from 1*H*-pyrazol-3-amines and isothiocyanates undergo formal [4 + 2] annulation with 1,1,3,3-tetramethylguanidines (TMG) to deliver the corresponding products involved in three C−N bond formations in a one-pot protocol. The formation of EDA complex from pyrazolthiourea and TMG is confirmed by UV−vis spectroscopy and ^{1}H NMR experiments. Moreover, this mild reaction proceeds in the absence of any external transition metals, oxidants, bases, and ligands. This efficient methodology for the synthesis of purine analogues pyrazolo[1,5-*a*][1,3,5]triazine-2,4-diamines provides potential synthetic applications in the field of drug research and development.



INTRODUCTION

Pyrazolo[1,5-*a*][1,3,5]triazines and their derivatives incorporating two privileged *N*-heterocycles are one of the most prevalent purine analogues and/or bioisosteres with diverse biological activities in drug discovery.[1] Typically, BOF-4272 (I) can be used as an antihyperuricaemic agent to inhibit xanthine oxidase activity in the biosynthesis of uric acid (Figure 1).[2] Compound II is a selective corticotropin-releasing factor receptor-1 (CRF1) antagonist and may be a potential anxiolytic or antidepressant drug.[3] Compound III represents a new and selective phosphodiesterase type-4 inhibitor.[4] Furthermore, many specifically pyrazolo[1,5-*a*][1,3,5]triazine-2,4-diamines and their derivatives exhibit a broad spectrum of pharmacological properties.[5] For example, compound IV shows micromolar antiproliferative activity,[6] compound V is a threonine tyrosine kinase (TTK) inhibitor,[7] and compound VI can inhibit cyclic-dependent kinase (CDK) activities and induce cell death for various human tumor cell lines.[8]

Considering the diverse biological and pharmacological activities of pyrazolo[1,5-*a*][1,3,5]triazines, the exploration of various synthetic approaches attracts particular attention in the field of organic and medicinal chemistry.[8,9] Significant representative methodologies have been reported in previous works. For example, reaction of 5-amino-1*H*-pyrazoles with sodium cyanocarbonimidodithioate salt, *O*,*S*-diethyl heteroarylimidothiocarbonates, *S*,*S*-dimethyl 4-methylbenzoylimidodithiocarbonates, or *N*-acyl imidates can provide pyrazolo[1,5-*a*][1,3,5]triazine-4-thiol derivatives through a condensation reaction under microwave irradiation or high reaction temperature conditions.[10−12] Dolzhenko et al. explored a multicomponent reaction (MCR) of aminopyrazole-4-carboxylates with trimethyl orthoformate and cyanamide for constructing pyrazolo[1,5-*a*][1,3,5]triazines under microwave irradiation (Scheme 1, a).[13] In 2013, Insuasty's group discovered an efficient two-step strategy for the synthesis of 2-amino-substituted pyrazolo[1,5-*a*][1,3,5]triazines from 5-amino-3-hetaryl-1*H*-pyrazoles, isothiocyanates, and amines (Scheme 1, b).[14] In this case, the amination/cyclization process is promoted by the couple $HgCl_2$/TFA and DMF as solvent. Chu et al. and Kaiser et al. further reported a multistep synthesis of pyrazolo[1,5-*a*][1,3,5]triazine-2,4-diamine derivatives as potent protein kinase CK2 inhibitors and antibiotics (Scheme 1, c).[15] Although the above contributions we discuss here are useful for the construction of pyrazolo[1,5-*a*][1,3,5]triazines,[16,17] these reactions proceed under the conditions of high reaction temperature, microwave irradiation, and multistep reactions. Some starting materials and reagents are unstable, moisture-sensitive, unavailable, and even highly toxic. To solve those

Received: April 3, 2021
Published: June 7, 2021

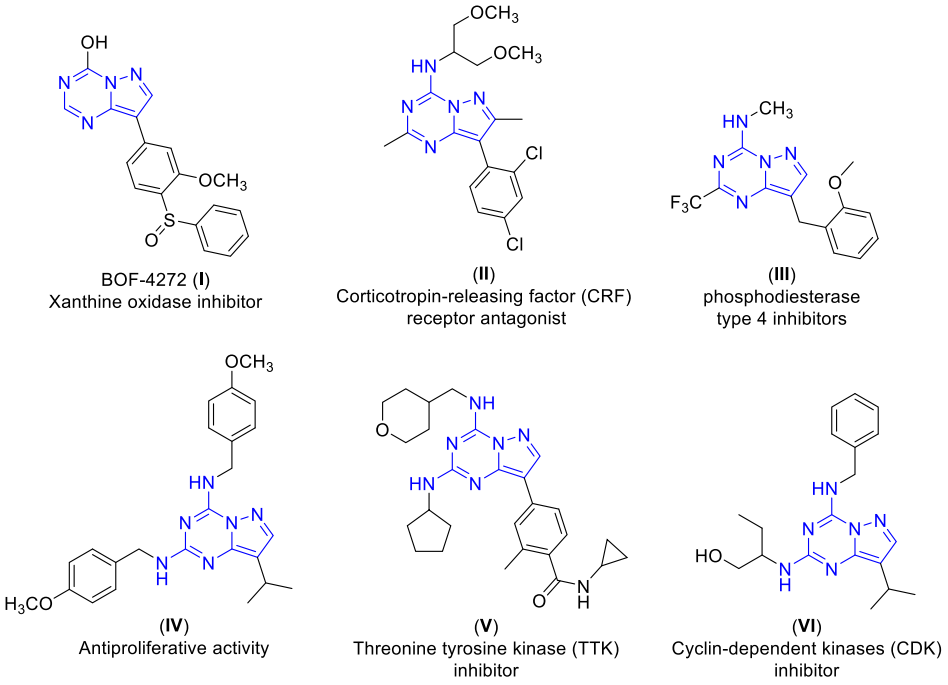
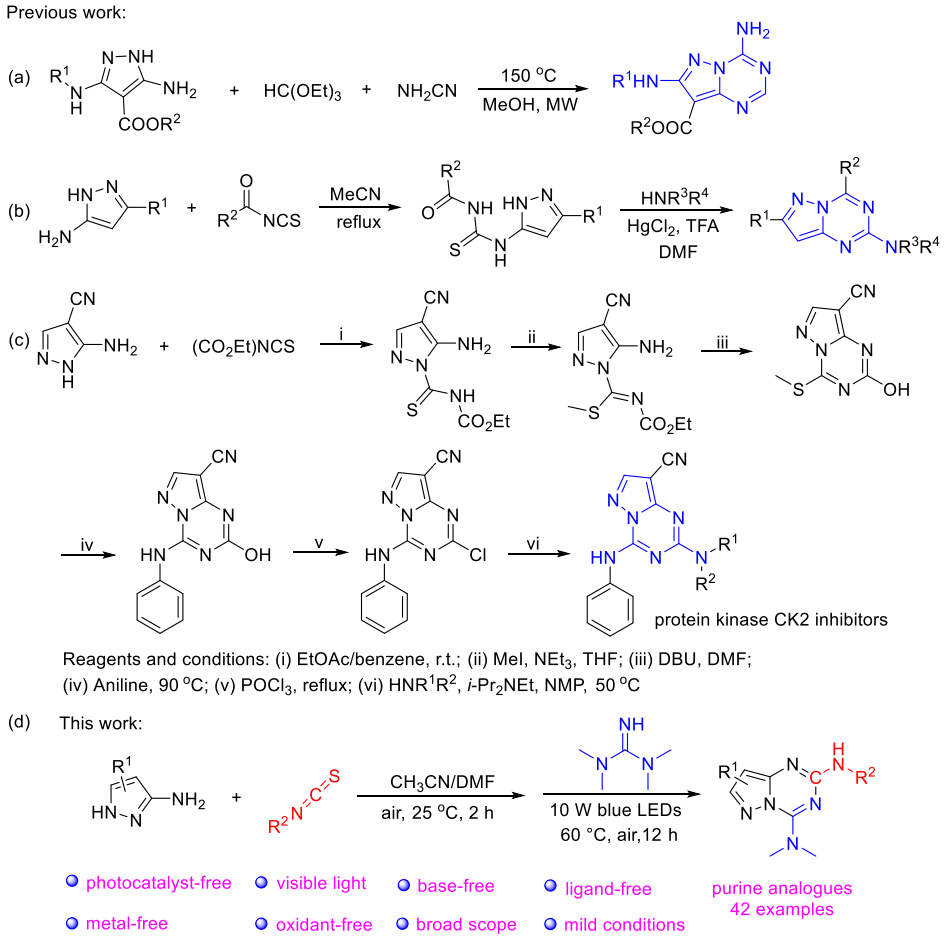


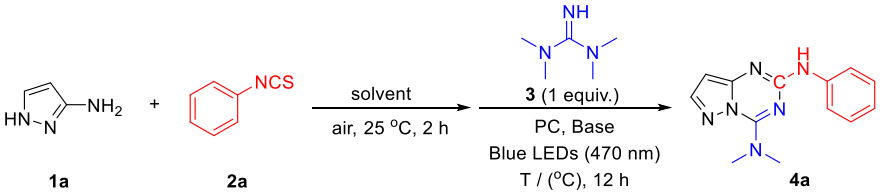
Figure 1. Important drug molecules containing pyrazolo[1,5-*a*][1,3,5]triazines, pyrazolo[1,5-*a*][1,3,5]triazine-2,4-diamines, and their derivatives.

Scheme 1. Multicomponent Synthesis of Pyrazolo[1,5-*a*][1,3,5]triazines, Pyrazolo[1,5-*a*][1,3,5]triazine-2,4-diamines, and Their Derivatives



https://doi.org/10.1021/acs.joc.1c00783
J. Org. Chem. 2021, 86, 8365−8380

Table 1. Screening of Reaction Conditions[a]



entry	photocatalyst (1 mol %)	solvent (1 mL)	base (2 equiv)	T (°C)	**4a**, yield[b] (%)
1	$Ru(bpy)_3Cl_2$	CH_3CH_2OH		25	27
2	eosin B	CH_3CH_2OH		25	20
3	eosin Y	CH_3CH_2OH		25	22
4	*fac*-$Ir(ppy)_3$	CH_3CH_2OH		25	21
5	Rose Bengal	CH_3CH_2OH		25	15
6		CH_3CH_2OH		25	26
7		CH_2Cl_2		25	20
8		$CH_3COOC_2H_5$		25	16
9		DMF		25	35
10		DMSO		25	24
11		H_2O		25	12
12		CH_3CN		25	33
13		CH_3CN/DMF (1:1)		25	38
14[c]		CH_3CN/DMF (1:1)		25	42
15[d]		CH_3CN/DMF (1:1)		25	64
16[d]		CH_3CN/DMF (1:1)	NaOH	25	40
17[d]		CH_3CN/DMF (1:1)	K_2CO_3	25	38
18[d]		CH_3CN/DMF (1:1)	$NaHCO_3$	25	53
19[d]		CH_3CN/DMF (1:1)	DABCO	25	38
20[d]		CH_3CN/DMF (1:1)	DBU	25	38
21[d]		CH_3CN/DMF (1:1)	TMEDA	25	46
22[d]		CH_3CN/DMF (1:1)		60	84
23[d,e]		CH_3CN/DMF (1:1)		60	22
24[d,f]		CH_3CN/DMF (1:1)		60	37
25[d,g]		CH_3CN/DMF (1:1)		60	76
26[d,h]		CH_3CN/DMF (1:1)		60	15
27[d,i]		CH_3CN/DMF (1:1)		60	47

[a]Reaction conditions: Unless otherwise stated, the reaction of 1*H*-pyrazol-3-amine **1a** (12.5 mg, 0.15 mmol) and isothiocyanatobenzene **2a** (13.5 mg, 0.10 mmol) was carried out in CH_3CH_2OH (1 mL) at 25 °C for 2 h under air, and then 1,1,3,3-tetramethylguanidine **3** (11.5 mg, 0.10 mmol) and photocatalyst (1 mol %) were introduced to the reaction. The reaction further proceeded under 10 W blue LED (470 nm) irradiation at 25 °C for 12 h. [b]Isolated yields based on **2a**. [c]**3** (23 mg, 0.20 mmol, 2 equiv). [d]**3** (34.5 mg, 0.30 mmol, 3 equiv). [e]In the dark at 60 °C. [f]Under N_2. [g]Under O_2. [h]Under Ar through three freeze−pump−thaw cycles. [i]Gram-scale experiment based on **2a** (675 mg, 5 mmol).

disadvantages, it is necessary to explore a green and efficient pathway to access pyrazolo[1,5-*a*][1,3,5]triazines from available materials under mild reaction conditions.

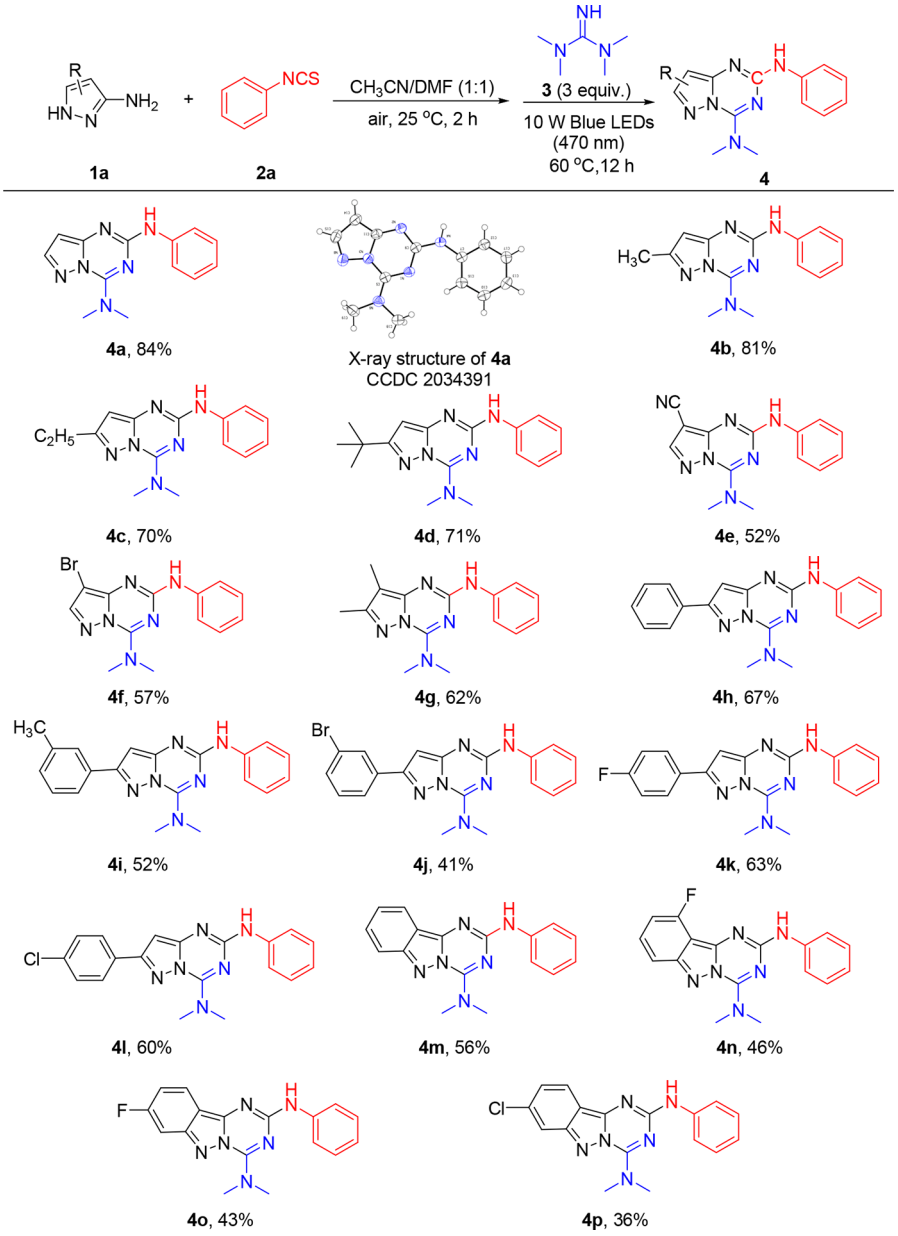
In previous reports, visible-light-catalyzed/promoted reactions have emerged as powerful synthetic platforms to prepare diverse useful organic products, which exhibit high efficiency and environmental friendliness.[18] Our group also successfully developed a series of visible-light-catalyzed/promoted coupling annulations to furnish various *N*-heterocyclic compounds from simple substrates.[19] Based on the our previous reports in the field of photochemical transformations enabled by electron donor−acceptor (EDA) complexes,[20] we further described an efficient photocatalyst-free visible-light-enhanced annulation strategy for the synthesis of pyrazolo[1,5-*a*][1,3,5]triazine-2,4-diamines via the formation of EDA complexes under mild reaction conditions (Scheme 1, d). The *in situ* generated pyrazolthiourea intermediates from 1*H*-pyrazol-3-amines and isothiocyanates undergo formal [4 + 2] annulations with 1,1,3,3-tetramethylguanidines (TMG) to deliver the corresponding products involving in three C−N bond formations. The formation of EDA complexes derived from pyrazolthiourea intermediates with TMG was characterized by UV and ^{1}H NMR experiments. Raw materials used in this reaction are economically available and air-compatible and tolerate various functional groups. Furthermore, no additional additives are required, such as catalysts, metals, bases, ligands and oxidants.

RESULTS AND DISCUSSION

We first screened the optimal conditions using 1*H*-pyrazol-3-amine **1a**, isothiocyanatobenzene **2a**, and 1,1,3,3-tetramethylguanidine **3** as starting materials through a two-step one pot reaction process. The reaction of 3-aminopyrazole **1a** (0.15 mmol) and isothiocyanatobenzene **2a** (0.10 mmol) was first carried out in CH_3CH_2OH (1 mL) at 25 °C for 2 h under air, and then 1,1,3,3-tetramethylguanidine **3** (0.10 mmol) and $Ru(bpy)_3Cl_2$ (1 mol %) were introduced into the reaction system. The reaction further proceeded under the irradiation of a 10 W blue LED (470 nm) at 25 °C for 12 h. Gratifyingly, the desired product **4a** was obtained in 27% yield (Table 1, entry 1). The structure of **4a** was characterized by X-ray crystal diffraction measurement (CCDC 2034391) (see Figure S2). However,

https://doi.org/10.1021/acs.joc.1c00783
J. Org. Chem. 2021, 86, 8365−8380

Table 2. Scope of 1*H*-Pyrazol-3-amines[a]

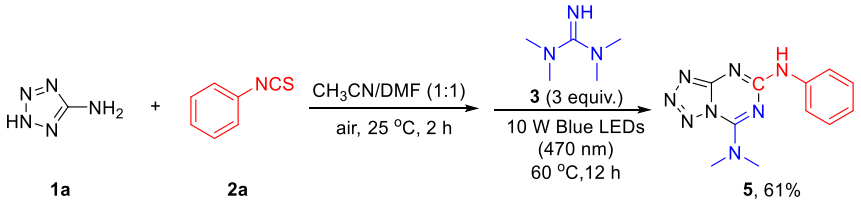


[a]Isolated yield based on **2a**.

investigating other photocatalysts did not afford a higher yield of **4a** (Table 1, entries 2−5). Subsequently, the reaction was performed in the absence of any external photocatalysts, affording the product **4a** in 26% yield (Table 1, entry 6). Next, different reaction solvents such as CH_2Cl_2, $CH_3COOC_2H_5$, DMF, DMSO, H_2O, and CH_3CN were tested for the transformations, respectively (Table 1, entries 7−12). The above results showed that the yield of **4a** improved to 35% using DMF as solvent (Table 1, entry 9). Furthermore, a combination of CH_3CN and DMF (v/v = 1:1) as a solvent system gave the compound **4a** in 38% yield (Table 1, entry 13). Increasing the amount of **3** from 0.10 to 0.30 mmol improved the yield of **4a** to 64% (Table 1, entries 14 and 15). However, utilization of NaOH, K_2CO_3, $NaHCO_3$, DABCO, DBU, and TMEDA as the base additives decreased the yield (Table 1, entries 16−21). Gratifyingly, we conducted the second-step reaction at 60 °C without the addition of any photocatalysts and bases, and the isolated yield of **4a** reached up to 84% (Table 1, entry 22). However, when the reaction was performed in the dark, the yield of **4a** reduced obviously, showing that light is crucial to promote this reaction (Table 1, entry 23). We also carried out the reaction under N_2 and O_2 atmosphere, respectively. The results suggested that O_2 in air might facilitate the transformation (Table 1, entries 24 and 25). When the reaction was performed under argon atmosphere through three freeze−pump−thaw cycles, **4a** was obtained in 15% yield (Table 1, entry 26). For this reaction, light and reaction temperature could influence the yield of **4a**. After screening of light sources, reaction time, and temperature (see Tables S1−S3), the optimal reaction conditions in entry 22 were selected as the standard conditions for subsequent investigations. Finally, a gram-scale experiment was performed on 5 mmol scale based on **2a** under the standard conditions, affording the compound **4a** in 47% yield, which shows the potential synthetic application of this

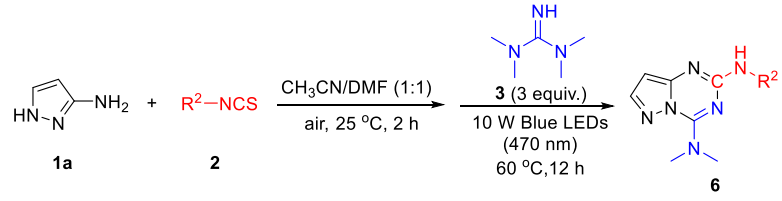
https://doi.org/10.1021/acs.joc.1c00783
J. Org. Chem. 2021, 86, 8365−8380

Scheme 2. Synthesis of 5

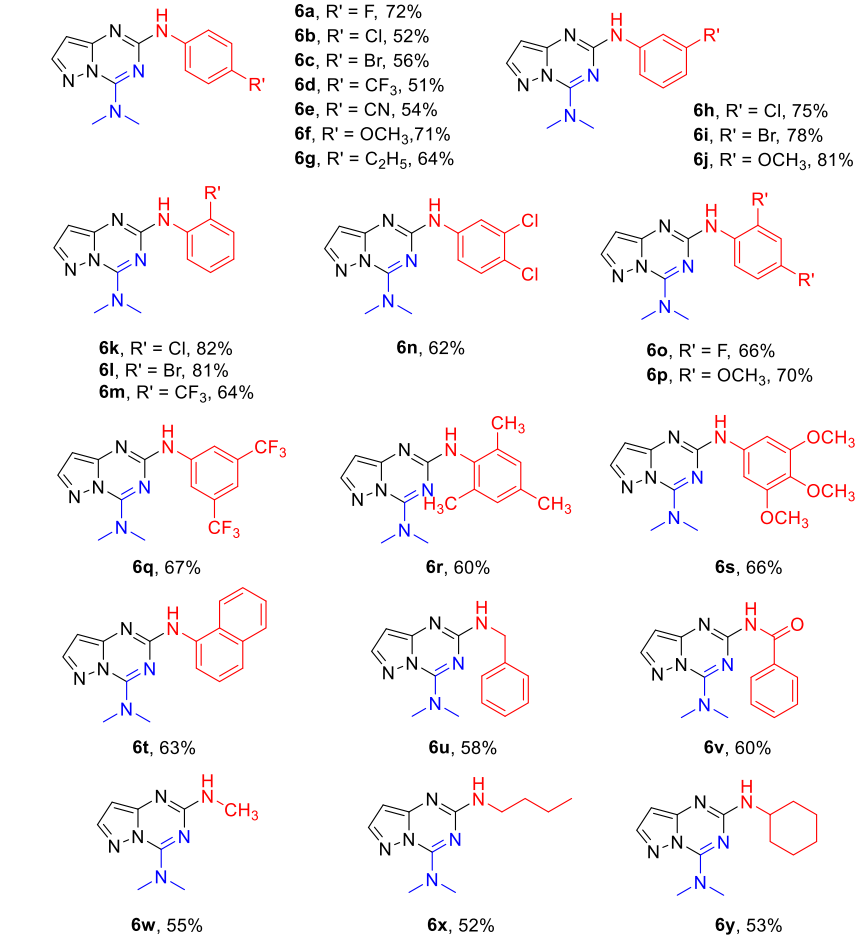


1a 2a 5, 61%

Table 3. Scope of Isothiocyanate Substrates[a]



1a 2 6



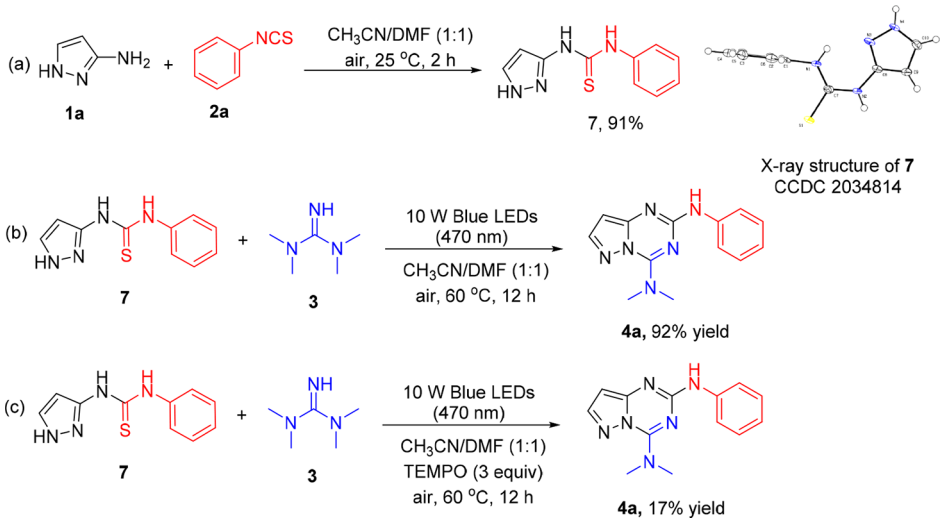
[a]Isolated yield based on **2**.

methodology in organic synthesis and medicinal chemistry (Table 1, entry 27, see the Experimental Section).

Encouraged by the above experimental results, we first probed the 1*H*-pyrazol-3-amines substrate scope under the optimal reaction conditions (Table 2). A variety of 1*H*-pyrazol-3-amines containing electron-donating (−CH_3, −C_2H_5, and −$C(CH_3)_3$) or electron-withdrawing groups (−Br and −CN) were tolerated in this transformation, delivering the corresponding products (**4b**−**4f**) with moderate to good yields. The disubstituted substrate 4,5-dimethyl-1*H*-pyrazol-3-amine also afforded the desired product (**4g**) in 62% yield. Moreover, a serial of phenyl group substituted 1*H*-pyrazol-3-amine substrates were capable of providing the corresponding products (**4h**−**4l**) in 41−67% yields. It was satisfying that when some 1*H*-indazol-3-amine derivatives were employed in the reaction the desired fused ring [1,3,5]triazino[1,2-*b*]indazole-2,4-diamine products (**4m**−**4p**), which might be applied in the field of drug screening, were obtained in moderate yields. Furthermore, 2*H*-tetrazol-5-amine

https://doi.org/10.1021/acs.joc.1c00783
J. Org. Chem. 2021, 86, 8365−8380

Scheme 3. Control Experiments



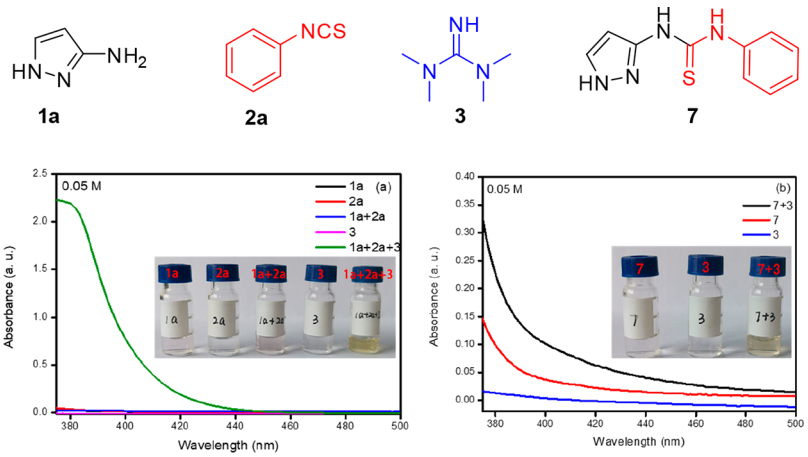


Figure 2. UV/vis absorption spectra of EDA complexes. (a) **1a**, **2a**, **3**, and the mixture of (**1a** + **2a**) and (**1a**+**2a**+**3**) in CH_3CN from 380 to 500 nm, respectively ([**1a**] = [**2a**] = [**3**] = 0.05 M). (b) **7**, **3**, and the mixture of (**7** + **3**) in CH_3CN from 380 to 500 nm, respectively ([**7**] = [**3**] = 0.05 M).

was proven to be suitable for delivering the energetic and potential biologically active molecular **5** in 61% yield (Scheme 2).

Then the substrate scope of the photocatalyzed annulation was turned to various substituted isothiocyanate compounds. As shown in Table 3, an array of isothiocyanatobenzene substrates bearing electron-deficient (−F, −Cl, −Br, $-CF_3$, and −CN) and electron-rich groups ($-OCH_3$ and $-C_2H_5$) at the *para*-position delivered the cyclization products (**6a**−**6g**) in 51−72% yields. The *meta*- and *ortho*- substituted isothiocyanatobenzenes also afforded the desired products (**6h**−**6m**) in good yields (64−82%). The influence of steric and electronic effects seems negligible. Furthermore, disubstituted (3,4-di-Cl, 2,4-di-F, 2,4-di-OCH_3, and 3,5-di-CF_3) and trisubstituted (2,4,6-tri-CH_3 and 3,4,5-tri-OCH_3) substrates also proceeded smoothly to produce the corresponding compounds (**6n**−**6s**) in 60−70% yields. Meanwhile, 2-isothiocyanatonaphthalene could be converted into the desired product (**6t**) in 63% yield. To our delight, (isothiocyanatomethyl)benzene and benzoyl isothiocyanate were suitable partners and furnished **6u** and **6v** in 58% and 60% yields, respectively. In addition, alkyl-substituted isothiocyanates also afforded the corresponding compounds (**6w**−**6y**) in moderate yields (52−55%).

Furthermore, a series of mechanistic experiments were carried out to clarify the possible reaction mechanism (Scheme 3). First, compound **1a** was reacted with **2a** in CH_3CN/DMF at 25 °C for 2 h to produce the compound **7** in 91% yield. The structure of compound **7** was confirmed by X-ray diffraction measurement (CCDC 2034814) (see Figure S3) (Scheme 3, a). Subsequently, the transformation of compound **7** with compound **3** gave the desired product **4a** in 92% yield, indicating that compound **7** is a plausible intermediate for the reaction (Scheme 3, b). However, the above reaction was suppressed by the addition of radical scavenger 2,2,6,6-teramethylpiperidinyl-1-oxy (TEMPO), and the yield of **4a** was reduced from 92% to 17%, which meant that radical process should be involved in this transformation (Scheme 3, c). Furthermore, the quantum yield (Φ) of 19.2 was obtained from the reaction of **7** and **3** (λ = 436 nm) using potassium trioxalatoferrate(III) trihydrate as a standard chemical actinometer,[21a,b] which might suggest that the transformation proceeded through radical combination or radical chain mechanism (see the Supporting Information).[21c−e]

In previous work, the *in situ* generated electron donor−acceptor (EDA) complexes have been investigated in various visible-light-promoted organic synthesis reactions.[22] In these cases, the photochemical transformations proceeded without the requirement of any photocatalysts under mild conditions.

https://doi.org/10.1021/acs.joc.1c00783
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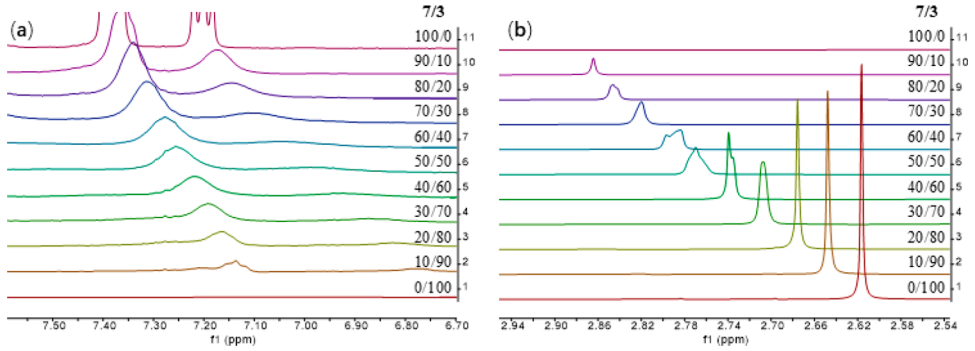
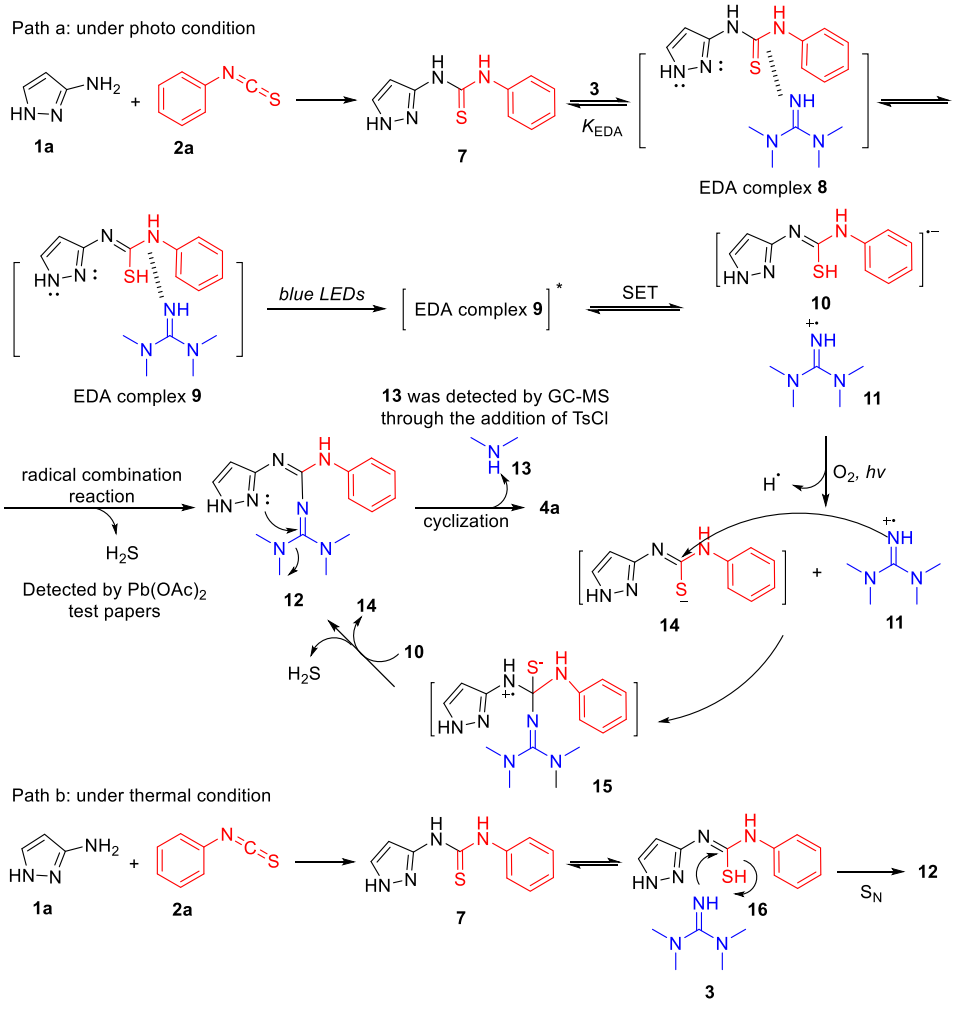


Figure 3. ^{1}H NMR titration experiments between 7 and 3.

Scheme 4. Possible Reaction Mechanism for the Visible-Light-Enhanced Annulations



Notably, assembling a colorless electron-donating compound with a colorless electron-accepting partner can form a colored complex, which means the generation of a new absorption band and/or charge transfer band.[23] The new absorption phenomenon can be detected by UV/visible absorption spectrum. Remarkably, in our experiments, when compound **1a** was mixed with **2a** and **3** in CH_3CN, the mixture solution displayed an obvious yellow color change from the three colorless starting materials (Figure 2, a). Similarly, the mixture of colorless compound **7** and **3** also exhibited a visibly color change (Figure 2, b). Furthermore, the optical absorption spectrum of the above samples showed a significant bathochromic shift in the visible spectral region, thus demonstrating the formation of an EDA complex.[21] The absorption of the mixture of compound **7** and **3** falls into the range of blue LED wavelength, which indicates that the irradiation of visible light is necessary to this transformation. Additionally, a Job's plot was recorded to assess the stoichiometry of the EDA complexes from compound **7** and **3** in CH_3CN (see Figure S6). We found that the ratio of **7**/**3** was much closer to 1:1 in the maximal absorbance, which might be determined that charge transfer occurred between **7** and **3** during the formation of EDA complex under visible light irradiation. The ^{1}H NMR titration experiments were further carried out to study the interaction between compound **7** and **3**

https://doi.org/10.1021/acs.joc.1c00783
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(Figure 3). The peaks of compound **7** in the δ 7.60−6.50 ppm range move toward high field with the increasing amount of **3**, indicating that compound **3** can be used as electron donor to provide compound **7** with higher electron density (Figure 3, a). Meanwhile, for compound **3**, the electron acceptor **7** can withdraw more electrons from **3**, thus resulting in the increase of chemical shift in the δ 2.90−2.55 ppm range (Figure 3, b).

On the basis of the above experimental results and previous reports,[24] a possible mechanism is outlined in Scheme 4. First, the *in situ* generated compound **7** from compound **1a** and **2a** is combined with **3a** to produce the EDA complex **8** or **9** (path a). The binding-constant value (K_{EDA} = 19.91 M^{-1}) was tested by Benesi−Hildebrand analysis (see Figure S7).[25] Then irradiation of EDA complex **9** provides the excited complex **9***, which further undergoes the photoinduced single electron transfer (SET) process to deliver the tight radical-ion-pair (solvent cage molecule) intermediate radical anion **10** and imine nitrogen-centered radical **11**.[21b,c,24a] In addition, the O_2 in air is considered to be beneficial for the SET process in this aerobic oxidative EDA reaction.[24,26] Subsequently, radical combination reaction of intermediate **10** and **11** provides the intermediate **12**, accompanied with the release of H_2S.[21,24] Intermediate **12** is not stable, which is further converted into the desired product **4a** and compound **13** through an intramolecular annulation process. In this case, compound **13** was detected by GC−MS through the addition of TsCl (see Figure S8). Furthermore, the generated H_2S was also confirmed by $Pb(OAc)_2$ test papers (see Figure S9). A radical-chain mechanism could be involved in this transformation according to the quantum yield test. Irradiation of radical intermediate **10** could generate intermediate anion **14**. Then imine radical **11** is trapped by intermediate **14** to produce intermediate **15**. Next, the elimination of a H_2S from intermediate **15** delivers intermediate **12**. The yield of **4a** was also affected by the reaction temperature. (Table 1, entry 23). In the dark at 60 °C (path b), compound **7** is converted into compound **16** by isomerization, which might further react with **3a** to form intermediate **12** via an S_N (nucleophilic substitution) type reaction.[24c] However, this reaction is easily affected by electronic or steric factors. Therefore, photoexcited process is important in promoting the three-component annulation.

CONCLUSIONS

In conclusion, we have demonstrated a visible-light-enhanced annulation of 1*H*-pyrazol-3-amines and isothiocyanates with 1,1,3,3-tetramethylguanidines (TMG) to give pyrazolo[1,5-*a*][1,3,5]triazine-2,4-diamines through the generation of EDA complexes. The reaction proceeds involving formation of three C−N bonds in one pot. Mechanistic exploration showed that the *in situ* formed EDA complex is the important photoactive species for the photochemical reaction. This procedure has the advantage of being photocatalyst-/metal-/base-/oxidant-/ligand-free and having broad scope and mild reaction conditions, despite the fact that the scale-up protocol might be improved. Moreover, these synthetic purine analogues have potential applications in medicinal chemistry in future work.

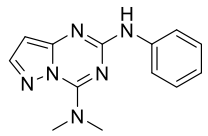
EXPERIMENTAL SECTION

General Information. The starting materials, reagents and solvents were purchased from Beijing InnoChem Science & Technology Co., Ltd. (China). All purchased products were used without further purification.

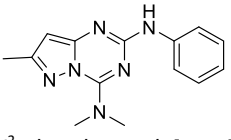
Melting points were investigated using a digital melting point apparatus and are uncorrected. IR spectra data were collected on an infrared spectrometer using KBr pellets. ^1H and ^{13}C NMR spectra were measured on a 400 MHz NMR spectrometer with $CDCl_3$ or DMSO-d_6 as solutions. Gas chromatography−mass spectrometry (GC−MS) was carried out using electron ionization. High-resolution mass spectrometry (HRMS) data were recorded on a high-resolution mass spectrometer (LCMS-ITTOF). The crystal data were collected on a diffractometer Rigaku Oxford diffraction supernova dual source, Cu at Zero equipped with an AtlasS2 CCD using Cu Kα radiation (1.54178 Å) by a scan mode. The reaction proceeded on the photoreaction instrument (WP-TEC-1020L, WATTCAS, China) with a heating mantle and a condenser system. The distance from the light source to the irradiation vessel is 5 mm. The thin-layer chromatography (TLC) and column chromatography were prepared on commercially available 100−400 mesh silica gel.

General Procedure for the Synthesis of Pyrazolo[1,5-*a*][1,3,5]triazine-2,4-diamines. 3-Aminopyrazoles (0.15 mmol), isothiocyanatobenzenes (0.10 mmol), and CH_3CN/DMF (v/v = 1/1, 1 mL) were introduced into a quartz reaction tube. The mixture was stirred at 25 °C for 2 h under air, then 1,1,3,3-tetramethylguanidine **3** (0.30 mmol) was added to the reaction system. The reaction further proceeded under the irradiation of a 10 W blue LEDs (470 nm) at 60 °C for 12 h. After completing the reaction (monitored by TLC), the reaction solvent was concentrated under reduced pressure. The obtained crude residue was purified by chromatography on a silica gel using petroleum ether/ethyl acetate (v/v = 5/1) as eluent to afford the desired product.

For the gram-scale synthesis of **4a**, the mixture of 1*H*-pyrazol-3-amine **1a** (0.622 g, 7.5 mmol), isothiocyanatobenzene **2a** (0.675 g, 5 mmol), and CH_3CN/DMF (v/v = 1/1, 4 mL) was stirred at 25 °C for 2 h under air, then 1,1,3,3-tetramethylguanidine **3** (1.725 g, 15 mmol) was added to the reaction system. The reaction was performed under the irradiation of a 10 W blue LED (470 nm) at 60 °C for 12 h. The mixture was concentrated and purified by flash column chromatography on silica gel using petroleum ether/ethyl acetate (v/v = 5/1) as eluent to provide the desired compound **4a** (0.596 g, 2.35 mmol, yield of 47%).



*N^4,N^4-Dimethyl-N^2-phenylpyrazolo[1,5-a][1,3,5]triazine-2,4-diamine (**4a**).* Eluent: petroleum ether/ethyl acetate (v/v = 5/1). Pink solid: 84% yield (21.4 mg, 0.08 mmol); mp 162−163 °C; IR (KBr, cm^{-1}) 3309, 3040, 2924, 2847, 1629, 1594, 1485, 1359, 1239, 1098, 915, 840, 798, 692, 509; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.80 (d, J = 2.0 Hz, 1H), 7.62 (d, J = 8.0 Hz, 2H), 7.32 (t, J = 8.0 Hz, 2H), 7.03 (t, J = 8.0 Hz, 1H), 6.95 (s, 1H), 6.00 (d, J = 2.0 Hz, 1H), 3.58 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm) δ 155.0, 153.2, 150.5, 144.9, 139.6, 128.8, 122.4, 119.5, 91.5, 40.4; MS (EI, 70 eV) m/z 254, 214, 144, 132, 92; HRMS (ESI) calcd $C_{13}H_{15}N_6$ $[M + H]^+$ m/z 255.1353, found m/z 255.1362.



*N^4,N^4,7-Trimethyl-N^2-phenylpyrazolo[1,5-a][1,3,5]triazine-2,4-diamine (**4b**).* Eluent: petroleum ether/ethyl acetate (v/v = 5/1). Pink solid: 81% yield (21.7 mg, 0.08 mmol); mp 132−134 °C; IR (KBr, cm^{-1}) 3233, 2920, 2824, 1595, 1484, 1353, 1253, 1098, 1005, 902, 762, 696; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.60 (d, J = 8.0 Hz, 2H), 7.31−7.28 (t, J = 8.0 Hz, 2H), 7.19 (s, 1H), 7.02−6.98 (t, J = 8.0 Hz, 1H), 5.79 (s, 1H), 3.54 (s, 6H), 2.34 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm) δ 154.9, 154.8, 153.7, 150.2, 139.7, 128.8, 122.3, 119.4, 91.6, 40.2, 14.7; MS (EI, 70 eV) m/z 268, 253, 212, 199, 92; HRMS (ESI) calcd $C_{14}H_{17}N_6$ $[M + H]^+$ m/z 269.1509, found m/z 269.1503.

https://doi.org/10.1021/acs.joc.1c00783
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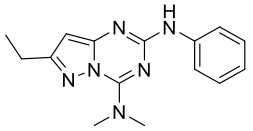
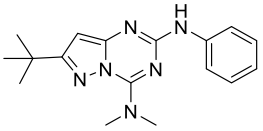
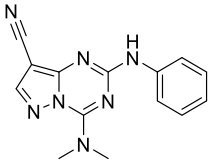


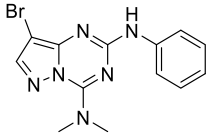
*7-Ethyl-N^4,N^4-dimethyl-N^2-phenylpyrazolo[1,5-a][1,3,5]triazine-2,4-diamine (**4c**).* Eluent: petroleum ether/ethyl acetate (v/v = 5/1). Pink solid: 70% yield (19.6 mg, 0.07 mmol); mp 112−114 °C; IR (KBr, cm^{-1}) 3240, 3044, 3969, 2605, 1254, 1171, 1007, 954, 764, 693; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.61 (d, J = 4.0 Hz, 2H), 7.29 (t, J = 8.0 Hz, 2H), 7.22 (s, 1H), 7.00 (t, J = 8.0 Hz, 1H), 5.83 (s, 1H), 3.55 (s, 6H), 2.70 (q, J = 8.0 Hz, 2H), 1.29 (t, J = 8.0 H, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm) δ 160.5, 154.9, 153.6, 150.3, 139.8, 128.8, 122.2, 119.4, 90.1, 40.2, 22.4, 13.2; MS (EI, 70 eV) m/z 282, 241, 228, 174, 132; HRMS (ESI) calcd $C_{15}H_{19}N_6$ $[M + H]^+$ m/z 283.1666, found m/z 283.1661.



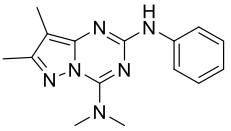
*7-tert-Butyl-N^4,N^4-dimethyl-N^2-phenylpyrazolo[1,5-a][1,3,5]-triazine-2,4-diamine (**4d**).* Eluent: petroleum ether/ethyl acetate (v/v = 5/1). Brown solid: 71% yield (22 mg, 0.07 mmol); mp 180−182 °C; IR (KBr, cm^{-1}) 3268, 3142, 2956, 1661, 1530, 1353, 1298, 1134, 1095, 978, 811, 776, 671; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.61 (d, J = 8.0 Hz, 2H), 7.29 (t, J = 8.0 Hz, 2H), 7.23 (s, 1H), 6.99 (t, J = 8.0 Hz, 1H), 5.88 (s, 1H), 3.56 (s, 6H), 1.34 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm) δ 167.3, 154.8, 153.3, 150.3, 139.8, 128.8, 122.1, 119.4, 88.4, 40.3, 32.8, 30.1; MS (EI, 70 eV) m/z 310, 295, 253, 225, 185; HRMS (ESI) calcd $C_{17}H_{23}N_6$ $[M + H]^+$ m/z 311.1979, found m/z 311.1973.



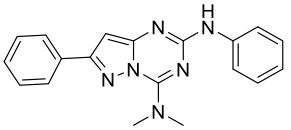
*4-(Dimethylamino)-2-(phenylamino)pyrazolo[1,5-a][1,3,5]-triazine-8-carbonitrile (**4e**).* Eluent: petroleum ether/ethyl acetate (v/v = 5/1). White solid: 52% yield (14.5 mg, 0.05 mmol); mp 151−153 °C; IR (KBr, cm^{-1}) 3328, 3299, 2922, 2219, 1619, 1556, 1468, 1412, 1325, 1246, 1193, 1057, 900, 760, 692 ; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.11 (s, 1H), 7.87 (s, 1H), 7.61 (d, J = 8.0 Hz, 2H), 7.35 (t, J = 8.0 Hz, 2H), 7.14 (t, J = 8.0 Hz, 1H), 3.19 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm) δ 158.6, 154.2, 146.6, 145.7, 136.0, 129.2, 125.2, 120.7, 113.9, 37.7, 37.2; MS (EI, 70 eV) m/z 279, 253, 214, 173, 118; HRMS (ESI) calcd $C_{14}H_{14}N_7$ $[M + H]^+$ m/z 280.1311, found m/z 280.1314.



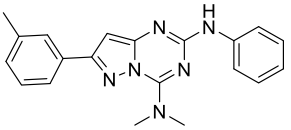
*8-Bromo-N^4,N^4-dimethyl-N^2-phenylpyrazolo[1,5-a][1,3,5]-triazine-2,4-diamine (**4f**).* Eluent: petroleum ether/ethyl acetate (v/v = 5/1). White solid: 57% yield (18.9 mg, 0.06 mmol); mp 180−182 °C; IR (KBr, cm^{-1}) 3260, 3105, 2931, 1603, 1493, 1363, 1248, 1116, 1045, 961, 870, 754, 615; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.76 (s, 1H), 7.63 (d, J = 8.0 Hz, 2H), 7.32 (t, J = 8.0 Hz, 2H), 7.10 (s, 1H), 7.04 (t, J = 8.0 Hz, 1H), 3.56 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm) δ 155.4, 154.5, 150.2, 149.9, 144.5, 139.3, 128.9, 122.7, 119.4, 40.6; MS (EI, 70 eV) m/z 332, 294, 196, 132, 118; HRMS (ESI) calcd $C_{13}H_{14}BrN_6$ $[M + H]^+$ m/z 333.0458, found m/z 333.0453.



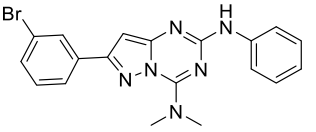
*N^4,N^4,7,8-Tetramethyl-N^2-phenylpyrazolo[1,5-a][1,3,5]triazine-2,4-diamine (**4g**).* Eluent: petroleum ether/ethyl acetate (v/v = 5/1). Pink solid: 62% yield (17.5 mg, 0.06 mmol); mp 193−195 °C; IR (KBr, cm^{-1}) 3256, 2921, 1590, 1494, 1353, 1257, 1136, 1055, 898, 745, 691, 599; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.66 (d, J = 8.0 HZ, 2H), 7.30 (t, J = 8.0 HZ, 2H), 6.99 (t, J = 8.0 HZ, 2H), 3.54 (s, 6H), 2.30 (s, 3 H), 2.08 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm) δ 154.2, 154.2, 150.2, 150.2, 140.0, 128.8, 121.9, 118.9, 98.5, 40.1, 12.8, 6.8; MS (EI, 70 eV) m/z 282, 228,214, 161, 118; HRMS (ESI) calcd $C_{15}H_{19}N_6$ $[M + H]^+$ m/z 283.1666, found m/z 283.1661.



*N^4,N^4-Dimethyl-N^2,7-diphenylpyrazolo[1,5-a][1,3,5]triazine-2,4-diamine (**4h**).* Eluent: petroleum ether/ethyl acetate (v/v = 5/1). Yellow solid: 67% yield (22 mg, 0.07 mmol); mp 170−172 °C; IR (KBr, cm^{-1}) 3235, 3133, 3032, 1598, 1479, 1354, 1294, 1104, 943, 830, 759, 695; ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ 9.29 (s, 1H), 7.96 (d, J = 8.0 Hz, 2H), 7.79 (d, J = 8.0 Hz, 2H), 7.47 (t, J = 8.0 Hz, 2H), 7.41 (t, J = 8.0 Hz, 1H), 7.29 (t, J = 8.0 Hz, 2H), 6.95 (t, J = 8.0 Hz, 1H), 6.51 (s, 1H), 3.59 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm) δ 155.6, 155.0, 154.0, 150.2, 139.6, 133.0, 128.9, 128.8, 128.6, 126.4, 122.4, 119.5, 88.7, 40.5; MS (EI, 70 eV) m/z 330, 278, 253, 200, 132; HRMS (ESI) calcd $C_{19}H_{18}N_6Na$ $[M + Na]^+$ m/z 353.1485, found m/z 353.1479.



*N^4,N^4-Dimethyl-N^2-phenyl-7-(m-tolyl)pyrazolo[1,5-a][1,3,5]-triazine-2,4-diamine (**4i**).* Eluent: petroleum ether/ethyl acetate (v/v = 5/1). White solid: 52% yield (17.9 mg, 0.05 mmol); mp 185−187 °C; IR (KBr, cm^{-1}) 3238, 3064, 2921, 2850, 1599, 1447, 1382, 1255, 1107, 1062, 962, 882, 763, 686; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.70 (d, J = 8.0 Hz, 2H), 7.63 (d, J = 8.0 Hz, 2H), 7.32 (d, J = 8.0 Hz, 3H), 7.19 (d, J = 8.0 Hz, 1H), 7.08 (s, 1H), 7.02 (t, J = 8.0 Hz, 1H), 6.31 (s, 1H), 3.62 (s, 6H), 2.42 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm) δ 155.8, 154.9, 153.9, 150.3, 139.6, 138.2, 132.9, 129.7, 128.8, 128.5, 127.0, 123.6, 122.4, 119.5, 88.8, 40.5, 21.5; MS (EI, 70 eV) m/z 344, 291, 276, 253, 211; HRMS (ESI) calcd $C_{20}H_{21}N_6$ $[M + H]^+$ m/z 345.1822, found m/z 345.1839.



*7-(3-Bromophenyl)-N^4,N^4-dimethyl-N^2-phenylpyrazolo[1,5-a]-[1,3,5]triazine-2,4-diamine (**4j**).* Eluent: petroleum ether/ethyl acetate (v/v = 5/1). Yellow solid: 41% yield (17 mg, 0.04 mmol); mp 161−163 °C; IR (KBr, cm^{-1}) 3280, 2923, 2852, 1623, 1561, 1470, 1346, 1243, 1072, 952, 899, 743, 683; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.05 (s, 1H), 7.80 (d, J = 8.0 Hz, 1H), 7.63 (d, J = 8.0 Hz, 2H), 7.50 (d, J = 8.0 Hz, 1H), 7.35−7.27 (m, 3H), 7.04 (t, J = 8.0 Hz, 1H), 6.96 (s, 1H), 6.29 (s, 1H), 3.63 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm) δ 155.0, 154.3, 154.1, 150.3, 139.5, 135.1, 131.7, 130.1, 129.3, 128.9, 125.1, 122.8, 122.6, 119.6, 88.9, 40.5; MS (EI, 70 eV) m/z 408, 329, 278, 212, 173; HRMS (ESI) calcd $C_{19}H_{18}N_6Br$ $[M + H]^+$ m/z 409.0771, found m/z 409.0791.

https://doi.org/10.1021/acs.joc.1c00783
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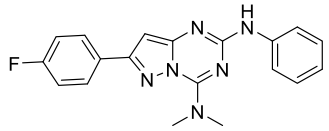
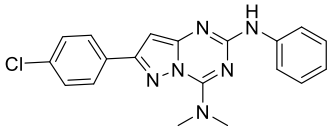
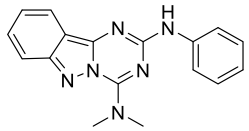


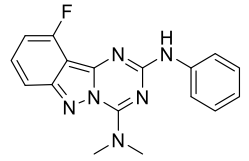
*7-(4-Fluorophenyl)-N^4,N^4-dimethyl-N^2-phenylpyrazolo[1,5-a]-[1,3,5]triazine-2,4-diamine (**4k**).* Eluent: petroleum ether/ethyl acetate (v/v = 5/1). White solid: 63% yield (22 mg, 0.06 mmol); mp 196−198 °C, IR (KBr, cm^{-1}) 3237, 3140, 2923, 2853, 1611, 1524, 1480, 1350, 1223, 1155, 1096, 943, 845, 772, 669, 580;^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.88 (t, J = 4.0 Hz, 2H), 7.63 (t, J = 8.0 Hz, 2H), 7.33 (t, J = 8.0 Hz, 2H), 7.12 (t, J = 8.0 Hz, 3H), 7.05 (J = 8.0 Hz, 1H), 6.28 (s, 1H), 3.63 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm) δ 164.6, 162.1, 154.7 (d, J = 4 Hz), 153.8, 150.2, 139.4, 129.1 (d, J = 3 Hz), 128.9, 128.2 (d, J = 8 Hz), 122.6, 119.6, 115.6 (d, J = 22 Hz), 88.5, 40.5; MS (EI, 70 eV) m/z 348, 329, 291, 252, 214; HRMS (ESI) calcd $C_{19}H_{18}N_6F$ $[M + H]^+$ m/z 349.1577, found m/z 349.1575.



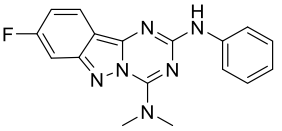
*7-(4-Chlorophenyl)-N^4,N^4-dimethyl-N^2-phenylpyrazolo[1,5-a]-[1,3,5]triazine-2,4-diamine (**4l**).* Eluent: petroleum ether/ethyl acetate (v/v = 5/1). White solid: 60% yield (21.8 mg, 0.06 mmol); mp 169−171 °C; IR (KBr, cm^{-1}) 3265, 3136, 2924, 2854, 1599, 1484, 1350, 1248, 1107, 1011, 943, 833, 765, 695; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.83 (d, J = 8.0 Hz, 2H), 7.63 (d, J = 8.0 Hz, 2H), 7.40 (d, J = 8.0 Hz, 2H), 7.33 (t, J = 8.0 Hz, 2H), 7.04 (t, J = 8.0 Hz, 2H), 6.29 (s, 1H), 3.63 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm) δ 154.9, 154.5, 154.0, 150.2, 139.4, 134.8, 131.4, 128.9, 128.8, 127.6, 122.6, 119.6, 88.7, 40.5; MS (EI, 70 eV) m/z 364, 302, 253, 132, 92; HRMS (ESI) calcd $C_{19}H_{18}N_6Cl$ $[M + H]^+$ m/z 365.1276, found m/z 365.1294.



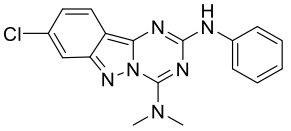
*N^4,N^4-Dimethyl-N^2-phenyl-[1,3,5]triazino[1,2-b]indazole-2,4-diamine (**4m**).* Eluent: petroleum ether/ethyl acetate (v/v = 5/1). Brown solid: 56% of yield (17 mg, 0.06 mmol); mp 172−174 °C, IR (KBr, cm^{-1}) 3253, 3159, 3041, 2924, 2842, 1684, 1597, 1496, 1338, 1248, 1157, 1029, 901, 747, 692; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8. 08 (d, J = 8.0 Hz, 1H), 7.93 (d, J = 8.0 Hz, 1H), 7. 68 (d, J = 8.0 Hz, 2H), 7.51 (d, J = 12.0 Hz, 1H), 7.40 (t, J = 8.0 Hz, 1H), 7.33 (t, J = 8.0 Hz, 2H), 7. 04 (t, J = 8.0 Hz, 1H), 6. 94 (t, J = 8.0 Hz, 1H), 3.65 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm) δ 154.8, 151.3, 150.8, 148.2, 139.5, 132.1, 129.5, 122.6, 121.8, 120.6, 118.2, 116.0, 111.1, 40.7; MS (EI, 70 eV) m/z 304, 265, 250, 208, 132; HRMS (ESI) calcd $C_{17}H_{17}N_6$ $[M + H]^+$ m/z 305.1509, found m/z 305.1503.



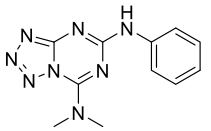
*10-Fluoro-N^4,N^4-dimethyl-N^2-phenyl-[1,3,5]triazino[1,2-b]-indazole-2,4-diamine (**4n**).* Eluent: petroleum ether/ethyl acetate (v/v = 5/1). Brown solid: 46% of yield (15 mg, 0.05 mmol); mp 192−194 °C; IR (KBr, cm^{-1}) 3404, 3145, 3089, 2922, 2851, 1614, 1547, 1498, 1351, 1218, 1153, 1064, 02, 867, 786, 691; ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ 9.78 (s, 1H), 7.85 (d, J = 8.0 Hz, 2H), 7.37−7.28 (m, 4H), 6.99 (t, J = 8.0 Hz, 1H), 6.60 (t, J = 8.0 Hz, 1H), 3.63 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm) δ 159.1, 156.6, 154.3, 152.8 (d, J = 5 Hz), 150.3, 139.0, 131.0 (d, J = 9 Hz), 128.8, 123.0, 119.5, 112.0 (d, J = 5 Hz), 102.2 (d, J = 18 Hz), 99.4, 40.8; MS (EI, 70 eV) m/z 322, 303, 265, 214, 92; HRMS (ESI) calcd $C_{17}H_{15}N_6FNa$ $[M + Na]^+$ m/z 345.1234, found m/z 345.1246.



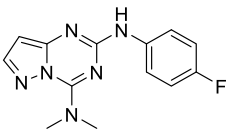
*8-Fluoro-N^4,N^4-dimethyl-N^2-phenyl[1,3,5]triazino[1,2-b]-indazole-2,4-diamine (**4o**).* Eluent: petroleum ether/ethyl acetate (v/v = 5/1). Brown solid: 43% yield (13.7 mg, 0.04 mmol); mp 154−156 °C; IR (KBr, cm^{-1}) 3369, 3268, 3143, 2923, 2850, 1618, 1564, 1495, 1349, 1204, 1159, 1052, 962, 833, 756; ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ 9.73 (s, 1H), 7.84 (t, J = 8.0 Hz, 3H), 7.31 (t, J = 8.0 Hz, 2H), 7.14 (d, J = 8.0 Hz, 1H), 6.98 (t, J = 8.0 Hz, 1H), 6.76 (t, J = 8.0 Hz, 1H), 3.60 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm) δ 164.9 (d, J = 256 Hz), 154.5, 151.7 (d, J = 14 Hz), 150.4, 149.2, 139.1, 128.9, 123.9 (d, J = 12 Hz), 122.9, 119.5, 110.3 (d. J = 28 Hz), 107.0, 99.2 (d, J = 24 Hz), 40.6; MS (EI, 70 eV) m/z 322, 278, 252, 223, 189; HRMS (ESI) calcd $C_{17}H_{16}N_6F$ $[M + H]^+$ m/z 323.1420, found m/z 323.1417.



*8-Chloro-N^4,N^4-dimethyl-N^2-phenyl-[1,3,5]triazino[1,2-b]-indazole-2,4-diamine (**4p**).* Eluent: petroleum ether/ethyl acetate (v/v = 5/1). Yellow solid: 36% yield (12 mg, 0.04 mmol); mp 171−173 °C; IR (KBr, cm^{-1}) 3277, 2923, 2851, 1741, 1609, 1565, 1446, 1347, 1233, 1152, 1042, 949, 844, 752, 694, 507; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.80 (d, J = 8.0 Hz, 1H), 7.61 (d, J = 8.0 Hz, 2H), 7.43 (s, 1H), 7.29 (t, J = 8.0 Hz, 2H), 7.11 (s, 1H), 7.00 (t, J = 8.0 Hz, 1H) 6.81 (d, J = 8.0 Hz, 1H), 3.60 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm) δ 154.5, 151.3, 150.5, 149.2, 139.1, 136.7, 129.0, 123.1, 122.9, 120.1, 119.5, 115.0, 108.2, 40.7; MS (EI, 70 eV) m/z 338, 296, 268, 239, 205; HRMS (ESI) calcd $C_{17}H_{16}N_6Cl$ $[M + H]^+$ m/z 339.1125, found m/z 339.1124.



*N^7,N^7-Dimethyl-N^5-phenyltetrazolo[1,5-a][1,3,5]triazine-5,7-diamine (**5**).* Eluent: petroleum ether/ethyl acetate (v/v = 5/1). White solid: 61% yield (15.6 mg, 0.06 mmol); mp 179−181 °C; IR (KBr, cm^{-1}) 3331, 2925, 2223, 2134, 1584, 1497, 1349, 1261, 1062, 967, 799, 685; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.59 (d, J = 8.0 Hz, 2H), 7.33 (t, J = 8.0 Hz, 2H), 7.08 (d, J = 8.0 Hz, 1H), 7.04(d, J = 4.0 Hz, 1H), 3.20−3.18 (d, J = 8.0 Hz, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm) δ 165.8, 163.4, 141.3, 128.3, 123.6, 113.2, 36.4; MS (EI, 70 eV): m/z = 256, 243, 204, 179, 164; HRMS (ESI) calcd $C_{11}H_{13}N_8$ $[M + H]^+$ m/z 257.1258, found m/z 257.1262.



*N^2-(4-Fluorophenyl)-N^4,N^4-dimethylpyrazolo[1,5-a][1,3,5]-triazine-2,4-diamine (**6a**).* Eluent: petroleum ether/ethyl acetate (v/v = 5/1). Pink solid: 72% yield (19.6 mg, 0.07 mmol); mp 161−163 °C; IR (KBr, cm^{-1}) 3266, 3114, 3052, 2999, 1613, 1569, 1499, 1340, 1209, 1158, 1097, 915, 834, 755, 687, 531, ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.79 (d, J = 4.0 Hz, 1H), 7.56−7.53 (m, 2H), 7.17 (s, 1H), 7.00 (t, J = 8.0 Hz, 2H), 5.96 (d, J = 2.0 Hz, 1H), 3.56 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm) δ 158.5 (d, J = 240 Hz), 155.0, 153.2, 150.5, 144.9, 135.6, 121.4 (d, J = 7 Hz), 115.3 (d, J = 22 Hz), 91.5, 40.4; MS (EI, 70 eV): m/z = 272, 228, 203,190, 136; HRMS (ESI) calcd $C_{13}H_{14}FN_6$ $[M + H]^+$ m/z 273.1259, found m/z 273.1251.

https://doi.org/10.1021/acs.joc.1c00783
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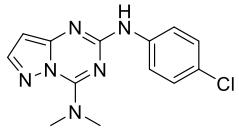
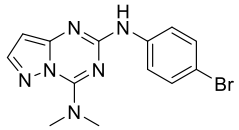
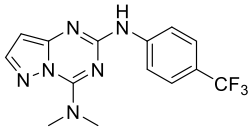


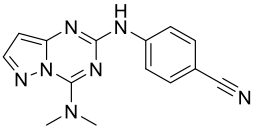
*N^2-(4-Chlorophenyl)-N^4,N^4-dimethylpyrazolo[1,5-a][1,3,5]-triazine-2,4-diamine (**6b**).* Eluent: petroleum ether/ethyl acetate (v/v = 5/1). Pink solid: 52% yield (15 mg, 0.05 mmol); mp 213-215 °C; IR (KBr, cm^{-1}) 3234, 3103, 2979, 2853, 1603, 1569, 1490, 1365, 1247, 1090, 913, 834, 762, 680; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.80 (s, 1H), 7.57 (d, J = 8.0 Hz, 2H), 7.27 (d, J = 8.0 Hz, 2H), 7.07 (s, 1H), 6.01 (d, J = 4.0 Hz, 1H), 3.58 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm) δ 154.7, 153.5, 150.6, 145.0, 138.2, 128.8, 127.3, 120.7, 91.8, 40.4; MS (EI, 70 eV): m/z = 288, 259, 244, 219, 178; HRMS (ESI) calcd $C_{13}H_{14}ClN_6$ $[M + H]^+$ m/z 289.0963, found m/z 289.0958.



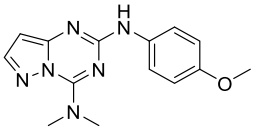
*N^2-(4-Bromophenyl)-N^4,N^4-dimethylpyrazolo[1,5-a][1,3,5]-triazine-2,4-diamine (**6c**).* Eluent: petroleum ether/ethyl acetate (v/v = 5/1). Pink solid: 56% yield (18.6 mg, 0.06 mmol); mp 165−167 °C; IR (KBr, cm^{-1}) 3273, 3021, 2931, 1627, 1584, 1489, 1362, 1241, 1096, 919, 866, 756, 671, 474; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.03 (s, 1H), 7.79 (s, 1H), 7.39 (d, J = 8.0 Hz, 1H), 7.24 (s, 1H), 7.14 (d, J = 8.0 Hz, 2H), 6.02 (d, J = 2.0 Hz,, 1H), 3.60 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm) δ 154.5, 152.7, 150.4, 145.0, 141.0, 130.0, 125.1, 122.5, 122.2, 117.7, 91.8, 40.5; MS (EI, 70 eV): m/z = 332, 281, 265, 207, 184; HRMS (ESI) calcd $C_{13}H_{14}BrN_6$ $[M + H]^+$ m/z 333.0458, found m/z 333.0453.



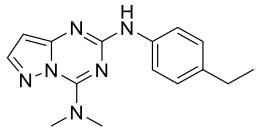
*N^4,N^4-Dimethyl-N^2-(4-(trifluoromethyl)phenyl)pyrazolo[1,5-a]-[1,3,5]triazine-2,4-diamine (**6d**).* Eluent: petroleum ether/ethyl acetate (v/v = 5/1). Brown solid: 51% yield (16.6 mg, 0.05 mmol); mp 123−125 °C; IR (KBr, cm^{-1}) 3462, 3349, 3201, 3102, 2932, 2813, 1673, 1595, 1468, 1374, 1279, 1167, 1095, 914, 837, 769, 641,523; ^1H NMR (400 MHz, DMSO-d_6, ppm) δ 9.70 (s, 1H), 7.99 (d, J = 8.0 Hz, 2H), 7.91 (s, 1H), 7.61 (d, J = 8.0 Hz, 2H), 6.04 (s, 1H), 3.53 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6, ppm) δ 154.7, 152.9, 150.7, 146.0, 144.7, 126.1 (d, J = 4 Hz), 125.2 (d, J = 268 Hz), 121.6 (d, J = 31 Hz), 118.9, 91.8, 40.4; MS (EI, 70 eV): m/z = 322, 278, 253, 212, 186; HRMS (ESI) calcd $C_{14}H_{14}F_3N_6$ $[M + H]^+$ m/z 323.1227, found m/z 323.1222.



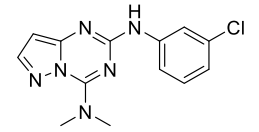
*4-((4-(Dimethylamino)pyrazolo[1,5-a][1,3,5]triazin-2-yl)amino)-benzonitrile (**6e**).* Eluent: petroleum ether/ethyl acetate (v/v = 5/1). Brown solid: 54% of yield (15 mg, 0.05 mmol); mp 211−212 °C; IR (KBr, cm^{-1}) 3314, 3177, 2923, 2216, 1591, 1406, 1371, 1257, 1177, 1097, 915, 818, 760, 679, 545; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.84 (d, J = 4.0 Hz, 1H), 7.78 (d, J = 8.0 Hz, 2H), 7.59 (d, J = 8.0 Hz, 2H), 7.21 (s, 1H), 6.08 (d, J = 3.0 Hz, 1H), 3.61 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm) δ 154.1, 152.5, 150.4, 145.1, 143.9, 133.1, 118.6, 104.6, 92.4, 40.6; MS (EI, 70 eV): m/z = 279, 227, 162, 157, 102; HRMS (ESI) calcd $C_{14}H_{14}N_7$ $[M + H]^+$ m/z 280.1305, found m/z 280.1301.



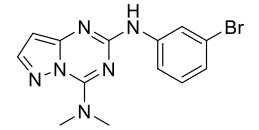
*N^2-(4-Methoxyphenyl)-N^4,N^4-dimethylpyrazolo[1,5-a][1,3,5]-triazine-2,4-diamine (**6f**).* Eluent: petroleum ether/ethyl acetate (v/v = 5/1). Brown solid: 71% yield (20.1 mg, 0.07 mmol); mp 141−143 °C; IR (KBr, cm^{-1}) 3240, 3092, 2923, 1628, 1574, 1491, 1366, 1246, 1173, 1041, 913, 809, 739, 624; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.76 (s, 1H), 7.48 (J = 8.0 Hz, 2H), 7.32 (s, 1H), 6.86 (d, J = 8.0 Hz, 2H), 5.93 (d, J = 3.0 Hz, 1H), 3.78 (s, 3H), 3.53 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm) δ 155.4, 155.4, 153.4, 150.4, 144.8, 132.7, 121.9, 114.0, 91.2, 55.5, 40.3; MS (EI, 70 eV): m/z = 284, 240, 199, 188, 122; HRMS (ESI) calcd $C_{14}H_{17}N_6O$ $[M + H]^+$ m/z 285.1458, found m/z 285.1453.



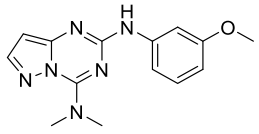
*N^2-(4-Ethylphenyl)-N^4,N^4-dimethylpyrazolo[1,5-a][1,3,5]triazine-2,4-diamine (**6g**).* Eluent: petroleum ether/ethyl acetate (v/v = 5/1). Red solid: 64% yield (18.1 mg, 0.06 mmol); mp 113−115 °C; IR (KBr, cm^{-1}) 3251, 3127, 2959, 2864, 1621, 1597, 1489, 1366, 1252, 1177, 1097, 915, 810, 759, 625, 487; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.79 (d, J = 4.0 Hz, 1H), 7.51 (d, J = 8.0 Hz, 2H), 7.15 (d, J = 8.0 Hz, 2H), 6.99 (s, 1H), 5.98 (d, J = 4.0 Hz, 1H), 3.56 (s, 6H), 2.62 (q, J = 4.0 Hz, 2H), 1.23 (t, J = 4.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm) δ 155.0, 153.3, 150.5, 144.9, 138.6, 137.1, 128.2, 119.8, 91.4, 40.4, 28.3, 15.8; MS (EI, 70 eV): m/z = 282, 238, 213, 197, 172; HRMS (ESI) calcd $C_{15}H_{19}N_6$ $[M + H]^+$ m/z 283.1666, found m/z 283.1662.



*N^2-(3-Chlorophenyl)-N^4,N^4-dimethylpyrazolo[1,5-a][1,3,5]-triazine-2,4-diamine (**6h**).* Eluent: petroleum ether/ethyl acetate (v/v = 5/1). Pink solid: 75% yield (21.6 mg, 0.08 mmol); mp 167−169 °C; IR (KBr, cm^{-1}) 3263, 3147, 3049, 2895, 1642, 1552, 1417, 1364, 1266, 1100, 967, 854, 764, 688; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.88 (t, J = 4.0 Hz, 1H), 7.81 (d, J = 4.0 Hz, 1H), 7.34 (d, J = 8.0 Hz, 1H), 7.19 (t, J = 8.0 Hz, 1H), 6.97 (d, J = 8.0 Hz, 1H), 6.01 (d, J = 3.0 Hz 1H), 3.59 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm) δ 154.6, 152.9, 150.5, 145.0, 140.9, 134.4, 129.7, 122.1, 119.3, 117.2, 91.8, 40.5; MS (EI, 70 eV): m/z = 288, 259, 178, 126, 71; HRMS (ESI) calcd $C_{13}H_{14}ClN_6$ $[M + H]^+$ m/z 289.0963, found m/z 289.0958.



*N^2-(3-Bromophenyl)-N^4,N^4-dimethylpyrazolo[1,5-a][1,3,5]-triazine-2,4-diamine (**6i**).* Eluent: petroleum ether/ethyl acetate (v/v = 5/1). Pink solid: 78% yield (26 mg, 0.08 mmol); mp 168−170 °C; IR (KBr, cm^{-1}) 3270, 3130, 2921, 1627, 1590, 1489, 1362, 1242, 1097, 919, 891, 756, 681; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.03 (s, 1H), 7.8 (d, J = 4.0 Hz, 1H), 7.39 (d, J = 8.0 Hz, 1H), 7.22 (s, 1H), 7.14−7.11 (m, 2H), 6.01 (d, J = 3.0 Hz, 1H), 3.59 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm) δ 154.5, 152.9, 150.5, 145.0, 141.0, 130.0, 125.1, 122.6, 122.2, 117.7, 91.9, 40.5; MS (EI, 70 eV): m/z = 332, 290, 224, 184, 155; HRMS (ESI) calcd $C_{13}H_{14}BrN_6$ $[M + H]^+$ m/z 333.0458, found m/z 333.0453.



*N^2-(3-Methoxyphenyl)-N^4,N^4-dimethylpyrazolo[1,5-a][1,3,5]-triazine-2,4-diamine (**6j**).* Eluent: petroleum ether/ethyl acetate (v/v = 5/1). Brown solid: 81% yield (23 mg, 0.08 mmol); mp 152−153 °C; IR (KBr, cm^{-1}) 3279, 3153, 3097, 2959, 1627, 1572, 1494, 1364, 1280, 1197, 1047, 905, 863, 756, 682; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ

https://doi.org/10.1021/acs.joc.1c00783
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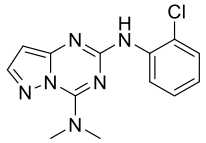
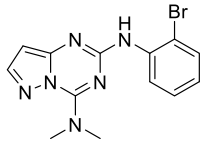
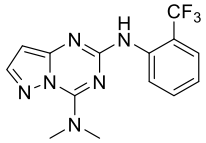
7.80 (d, J = 4.0 Hz, 1H), 7.42 (t, J = 4.0 Hz, 1H), 7.20 (t, J = 8.0 Hz, 1H), 7.13 (s, 1H), 7.09 (dd, J = 4.0 Hz, 1H), 6.58 (dd, J = 4.0 Hz, 1H), 6.00 (d, J = 2.0 Hz, 1H), 3.82 (s, 3H), 3.58 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm) δ 160.2, 154.7, 152.9, 150.5, 144.9, 140.8, 129.5, 111.9, 107.9, 105.5, 91.6, 55.3, 40.5; MS (EI, 70 eV): m/z = 284, 269, 240, 215, 185; HRMS (ESI) calcd $C_{14}H_{17}N_6O$ $[M + H]^+$ m/z 285.1458, found m/z 285.1452.



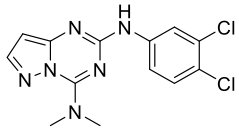
*N^2-(2-Chlorophenyl)-N^4,N^4-dimethylpyrazolo[1,5-a][1,3,5]-triazine-2,4-diamine (**6k**).* Eluent: petroleum ether/ethyl acetate (v/v = 5/1). Orange solid: 82% yield (23.6 mg, 0.08 mmol); mp 157−158 °C; IR (KBr, cm^{-1}) 3263, 3147, 3049, 2895, 1642, 1552, 1417, 1364, 1266, 1100, 967, 854, 764, 688; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.58 (dd, J = 8.0 Hz, 1H), 7.80 (d, J = 3.0 Hz, 1H), 7.35 (dd, J = 8.0 Hz, 1H), 7.29 (t, J = 8.0 Hz, 1H), 7.26−7.24 (m, 1H), 6.93 (t, J = 8.0 Hz, 1H), 6.04 (d, J = 4.0 Hz, 1H), 3.57 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm) δ 154.5, 153.0, 150.4, 144.9, 136.3, 129.1, 127.3, 122.5, 122.3, 120.6, 92.1, 40.4; MS (EI, 70 eV): m/z = 288, 231, 187, 126, 71; HRMS (ESI) calcd $C_{13}H_{14}ClN_6$ $[M + H]^+$ m/z 289.0963, found m/z 289.0959.



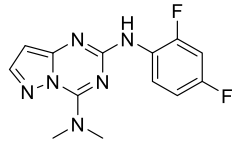
*N^2-(2-Bromophenyl)-N^4,N^4-dimethylpyrazolo[1,5-a][1,3,5]-triazine-2,4-diamine (**6l**).* Eluent: petroleum ether/ethyl acetate (v/v = 5/1). Brown solid: 81% of yield (27 mg, 0.08 mmol); mp 150−152 °C; IR (KBr, cm^{-1}) 3397, 3112, 2920, 1903, 1792, 1650, 1537, 1456, 1319, 1162, 1014, 915, 794, 686, 581;^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.55 (d, J = 8.0 Hz, 1H), δ 7.81 (d, J = 4.0 Hz, 1H), 7.52 (d, J = 8.0 Hz, 1H), 7.33−7.28 (m, 2H), 6.87 (d, J = 8.0 Hz, 1H), 6.04 (d, J = 2.0 Hz, 1H), 3.58 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm) δ 154.5, 153.0, 150.5, 145.0, 137.4, 132.3, 128.0, 123.1, 121.0, 113.2, 92.2, 40.4; MS (EI, 70 eV): m/z = 332, 277, 224, 187, 126; HRMS (ESI) calcd $C_{13}H_{14}BrN_6$ $[M + H]^+$ m/z 333.0458, found m/z 333.0453.



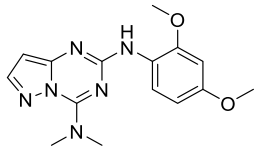
*N^4,N^4-Dimethyl-N^2-(2-(trifluoromethyl)phenyl)pyrazolo[1,5-a]-[1,3,5]triazine-2,4-diamine (**6m**).* Eluent: petroleum ether/ethyl acetate (v/v = 5/1). White solid: 64% yield (20.6 mg, 0.06 mmol); mp 200−202 °C; IR (KBr, cm^{-1}) 3276, 3147, 3091, 2934, 1625, 1599, 1491, 1328, 1294, 1109, 1068, 971, 841, 758, 624; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.42 (d, J = 8.0 Hz, 1H), 7.81 (d, J = 2.0 Hz, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.54 (t, J = 8.0 Hz, 1H), 7.12 (t, J = 8.0 Hz, 1H), 7.08 (s, 1H), 6.03 (d, J = 2.0 Hz, 1H), 3.57 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm) δ 155.4, 152.9, 150.5, 145.4, 136.4, 132.4, 126.0 (q, J = 5 Hz), 123.6, 123.0, 122.4, 119.3, 93.8, 39.3; MS (EI, 70 eV): m/z = 322, 278, 253, 210, 187; HRMS (ESI) calcd $C_{14}H_{14}F_3N_6$ $[M + H]^+$ m/z 323.1227, found m/z 323.1222.



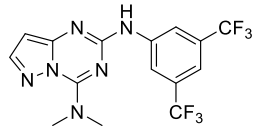
*N^2-(3,4-Dichlorophenyl)-N^4,N^4-dimethylpyrazolo[1,5-a][1,3,5]-triazine-2,4-diamine (**6n**).* Eluent: petroleum ether/ethyl acetate (v/v = 5/1). White solid: 62% yield (20 mg, 0.06 mmol); mp 218−220 °C; IR (KBr, cm^{-1}) 3267, 3136, 3060, 2931, 1627, 1583, 1487, 1362, 1241, 1156, 1097, 928, 866, 759, 656, 540; ^1H NMR (400 MHz, DMSO-d_6, ppm) δ 9.61 (s, 1H), 8.22 (d, J = 4.0 Hz, 1H), 7.92 (d, J = 4.0 Hz, 1H), 7.69 (d, J = 8.0 Hz, 1H), 7.49 (d, J = 8.0 Hz, 1H), 6.04 (d, J = 4.0 Hz, 1H), 3.53 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6, ppm) δ 155.3, 153.3, 150.3, 146.0, 141.3, 131.3, 129.5, 122.8, 120.1, 119.2, 93.6, 40.5; MS (EI, 70 eV): m/z = 322, 315, 311, 307, 299, 287; HRMS (ESI) calcd $C_{13}H_{13}Cl_2N_6$ $[M + H]^+$ m/z 323.0573, found m/z 323.0570.



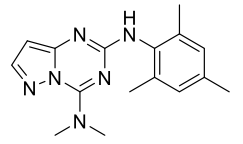
*N^2-(2,4-Difluorophenyl)-N^4,N^4-dimethylpyrazolo[1,5-a][1,3,5]-triazine-2,4-diamine (**6o**).* Eluent: petroleum ether/ethyl acetate (v/v = 5/1). Pink solid: 66% yield (19 mg, 0.07 mmol); mp 147−149 °C; IR (KBr, cm^{-1}) 3233, 3114, 3085, 2974, 1625, 1579, 1492, 1364, 1255, 1196, 1094, 963, 842, 763, 698, 595; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.45−8.38 (m, 1H), 7.80 (s, 1H), 6.90−6.88 (m, 2H), 6.87−6.83 (m, 1H), 6.02 (d, J = 2.0 Hz, 1H), 3.57 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm) δ 157.5 (q, J = 242 Hz), 154.6, 152.9, 152.5 (q, J = 233 Hz), 150.5, 144.9, 124.3 (d, J = 11 Hz), 122.1 (d, J = 11 Hz), 110.7 (d, J = 22 Hz), 103.4 (d, J = 24 Hz), 91.5, 40.4; MS (EI, 70 eV): m/z = 290, 271, 228, 221, 203; HRMS (ESI) calcd $C_{13}H_{13}F_2N_6$ $[M + H]^+$ m/z 291.1164, found m/z 291.1158.



*N^2-(2,4-Dimethoxyphenyl)-N^4,N^4-dimethylpyrazolo[1,5-a][1,3,5]-triazine-2,4-diamine (**6p**).* Eluent: petroleum ether/ethyl acetate (v/v = 5/1). Black solid: 70% yield (22 mg, 0.07 mmol); mp 171−173 °C; IR (KBr, cm^{-1}) 3435, 3229, 3108, 2922, 1734, 1630, 1535, 1342, 1277, 1155, 1096, 911, 824, 763, 625, 579; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.33−8.31 (d, J = 8.0 Hz, 1H), 7.77 (d, J = 2.0 Hz, 1H), 7.21 (s, 1H), 6.53−6.50 (m, 2H), 5.98 (d, J = 2.0 Hz, 1H), 3.87 (s, 3H), 3.80 (s, 3H), 3.57 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm) δ 155.3, 154.9, 153.3, 150.4, 149.4, 144.8, 122.7, 120.1, 103.7, 98.7, 91.3, 55.7, 55.6, 40.4; MS (EI, 70 eV): m/z = 314, 283, 268, 229, 207; HRMS (ESI) calcd $C_{15}H_{19}N_6O_2$ $[M + H]^+$ m/z 315.1564, found m/z 315.1559.



*N^2-(3,5-Bis(trifluoromethyl)phenyl)-N^4,N^4-dimethylpyrazolo[1,5-a][1,3,5]triazine-2,4-diamine (**6q**).* Eluent: petroleum ether/ethyl acetate (v/v = 5/1). Pink solid: 67% yield (26.1 mg, 0.07 mmol); mp 188−190 °C; IR (KBr, cm^{-1}) 3283, 3133, 3048, 2937, 1637, 1502, 1424, 1383, 1289, 1171, 1229, 952, 877, 758, 682, 599; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.16 (s, 3H), 7.85 (d, J = 2.0 Hz, 1H), 7.47 (s, 1H), 6.02 (d, J = 2.0 Hz, 1H), 3.63 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm) δ 154.5, 152.4, 150.5, 145.2, 141.3, 132.1 (q, J = 43 Hz), 123.5 (d, J = 271 Hz), 118.8, 115.0, 92.0, 40.7; MS (EI, 70 eV): m/z = 390, 371, 321, 294, 213; HRMS (ESI) calcd $C_{15}H_{13}F_6N_6$ $[M + H]^+$ m/z 391.1100, found m/z 391.1093.



*N^2-Mesityl-N^4,N^4-dimethylpyrazolo[1,5-a][1,3,5]triazine-2,4-diamine (**6r**).* Eluent: petroleum ether/ethyl acetate (v/v = 5/1). Pink solid: 60% yield (17.8 mg, 0.06 mmol); mp 151−153 °C; IR (KBr, cm^{-1}) 3226, 3102, 2952, 2347, 1769, 1601, 1518, 1487, 1392, 1251, 1152, 1097, 936, 847, 760, 622, 564; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.70 (d, J = 2.0 Hz, 1H), 6.90 (s, 2H), 5.78 (s, 1H), 3.44 (s, 6H),

https://doi.org/10.1021/acs.joc.1c00783
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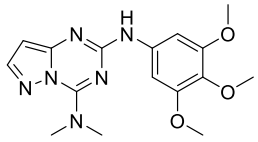
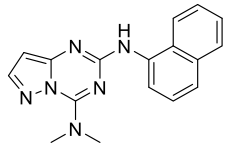
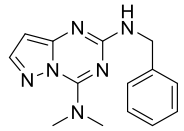
2.28 (s, 3H), 2.23 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm) δ 156.8, 154.0, 150.6, 144.7, 136.0, 133.2, 128.7, 93.2, 40.1, 21.0, 18.6; MS (EI, 70 eV): m/z = 296, 281,252, 226, 184; HRMS (ESI) calcd $C_{16}H_{21}N_6$ $[M + H]^+$ m/z 297.1822, found m/z 297.1818.



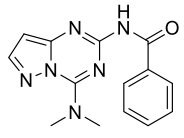
*N^4,N^4-Dimethyl-N^2-(3,4,5-trimethoxyphenyl)pyrazolo[1,5-a][1,3,5]triazine-2,4-diamine (**6s**).* Eluent: petroleum ether/ethyl acetate (v/v = 5/2). White solid: 66% yield (22.7 mg, 0.07 mmol); mp 172−173 °C; IR (KBr, cm^{-1}) 3285, 3100, 2935, 1614, 1494, 1363, 1233, 1127, 1041, 926, 822, 755, 627; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.80 (d, J = 2.0 Hz, 1H), 7.15 (s, 1H), 6.92 (s, 2H), 5.98 (d, J = 2.0 Hz, 1H), 3.86 (s, 6H), 3.82 (s, 3H), 3.59 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm) δ 154.9, 153.2, 153.1, 150.5, 144.9, 135.7, 133.5, 97.4, 91.6, 61.0, 56.1, 40.4; MS (EI, 70 eV): m/z = 344, 329, 312, 283, 271; HRMS (ESI) calcd $C_{16}H_{21}N_6O_3$ $[M + H]^+$ m/z 345.1670, found m/z 345.1662.



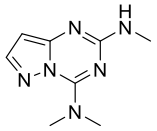
*N^4,N^4-Dimethyl-N^2-(naphthalen-2-yl)pyrazolo[1,5-a][1,3,5]-triazine-2,4-diamine (**6t**).* Eluent: petroleum ether/ethyl acetate (v/v = 5/1). Pink solid: 63% yield (19.1 mg, 0.06 mmol); mp 170−172 °C; IR (KBr, cm^{-1}) 3218, 3102, 3057, 2924, 1631, 1587, 1490, 1345, 1294, 1102, 1022, 913, 818, 785, 690; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.08 (d, J = 8.0 Hz, 1H), 8.02 (t, J = 4.0 Hz, 1H), 7.86−7.84 (m, 1H), 7.77 (d, J = 2.0 Hz, 1H), 7.64 (d, J = 8.0 Hz, 1H), 7.51−7.45 (m, 3H), 7.38 (s, 1H), 5.93 (d, J = 2.0 Hz, 1H), 3.49 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm) δ 156.1, 153.4, 150.5, 144.9, 134.4, 134.3, 128.6, 127.6, 125.9, 125.8, 125.8, 124.3, 121.4, 119.8, 91.5, 40.3; MS (EI, 70 eV): m/z = 304, 278, 262, 206, 142; HRMS (ESI) calcd $C_{17}H_{17}N_6$ $[M + H]^+$ m/z 305.1509, found m/z 305.1502.



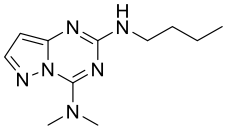
*N^2-Benzyl-N^4,N^4-dimethylpyrazolo[1,5-a][1,3,5]triazine-2,4-diamine (**6u**).* Eluent: petroleum ether/ethyl acetate (v/v = 5/1). Pink solid: 58% yield (15.5 mg, 0.06 mmol); mp 151−153 °C; IR (KBr, cm^{-1}) 3235, 3114, 2999, 1611, 1504, 1403, 1340, 1237, 1127, 1088, 962, 802, 759, 698, 508, 490; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.74 (s, 1H), 7.36−7.31 (m, 5H), 5.88 (s, 1H), 5.33 (s, 1H), 4.62 (d, J = 4.8 Hz, 2H), 3.49 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm) δ 157.5, 152.4, 150.5, 143.7, 139.4, 128.6, 127.6, 127.2, 90.8, 47.4, 41.3; MS (EI, 70 eV): m/z = 268, 224, 197, 163, 134; HRMS (ESI) calcd $C_{14}H_{17}N_6$ $[M + H]^+$ m/z 269.1509, found m/z 269.1502.



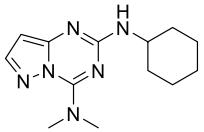
*N-(4-(Dimethylamino)pyrazolo[1,5-a][1,3,5]triazin-2-yl)-benzamide (**6v**).* Eluent: petroleum ether/ethyl acetate (v/v = 5/1). Yellow solid: 60% of yield (16.9 mg, 0.06 mmol); mp 152−154 °C; IR (KBr, cm^{-1}) 3111, 3071, 2989, 1064, 1580, 1474, 1353, 1277, 1125, 1096, 939, 827, 725, 690, 559; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.71 (s, 1H), 7.90−7.85 (m, 3H), 7.52 (t, J = 8.0 Hz, 1H), 7.43 (t, J = 8.0 Hz, 2H), 6.20 (d, J = 1.2 Hz, 1H), 3.59 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm) δ 165.4, 152.5, 152.2, 150.5, 145.1, 134.6, 132.2, 128.7, 127.5, 94.1, 40.4; MS (EI, 70 eV): m/z = 282, 253, 239, 203, 185, 172; HRMS (ESI) calcd $C_{14}H_{15}N_6O$ $[M + H]^+$ m/z 283.1302, found m/z 283.1300.



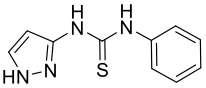
*N^2,N^4,N^4-Trimethylpyrazolo[1,5-a][1,3,5]triazine-2,4-diamine (**6w**).* Eluent: petroleum ether/ethyl acetate (v/v = 5/1). Orange solid: 55% yield (10.6 mg, 0.06 mmol); mp 179−181 °C; IR (KBr, cm^{-1}) 3267, 3130, 2994, 2824, 1813, 1729, 1670, 1565, 1451, 1297, 1167, 1092, 981, 905, 798, 680; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.73 (d, J = 1.6 Hz, 1H), 5.90 (s, 1H), 5.13 (s, 1H), 3.50 (s, 6H), 2.98 (d, J = 4.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm) δ 158.2, 153.9, 150.3, 144.6, 88.0, 40.1, 28.3; MS (EI, 70 eV): m/z = 192, 163, 123, 82, 57; HRMS (ESI) calcd $C_8H_{13}N_6$ $[M + H]^+$ m/z 193.1196, found m/z 193.1194.



*N^2-Butyl-N^4,N^4-dimethylpyrazolo[1,5-a][1,3,5]triazine-2,4-diamine (**6x**).* Eluent: petroleum ether/ethyl acetate (v/v = 5/1). Pink solid: 52% yield (12.2 mg, 0.05 mmol); mp 98−100 °C, IR (KBr, cm^{-1}) 3262, 3121, 3013, 2925, 2867, 1650, 1503, 1407, 1339, 1240, 1145, 1091, 904, 886, 760, 681, 623; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.73 (d, J = 2.0 Hz, 1H) 5.89 (s, 1H), 4.84 (s, 1H), 3.51 (s, 6H), 3.40 (q, J = 4.0 Hz, 2H), 1.62−1.55 (m, 2H), 1.46−1.37 (m, 2H), 0.95 (t, J = 8.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm) δ 157.6, 153.9, 150.4, 144.6, 60.4, 41.2, 40.1, 31.9, 20.1, 13.9; MS (EI, 70 eV): m/z = 234, 205, 192, 163, 135; HRMS (ESI) calcd $C_{11}H_{19}N_6$ $[M + H]^+$ m/z 235.1666, found m/z 235.1662.



*N^2-Cyclohexyl-N^4,N^4-dimethylpyrazolo[1,5-a][1,3,5]triazine-2,4-diamine (**6y**).* Eluent: petroleum ether/ethyl acetate (v/v = 5/1). Orange solid: 53% of yield (13.8 mg, 0.05 mmol); mp 131−133 °C; IR (KBr, cm^{-1}) 3259, 3116, 2923, 2850, 1626, 1499, 1339, 1235, 1150, 1091, 969, 883, 762, 623, 584; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.72 (d, J = 2.0 Hz, 1H), 5.86 (s, 1H), 4.83 (s, 1H), 3.82 (s, 1H), 3.50 (s, 6H), 2.07−2.02 (m, 2H), 1.75−1.72 (m, 2H), 1.64−1.61 (m, 1H), 1.45−1.36 (m, 2H), 1.25−1.19 (m, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm) δ 156.8, 154.0, 150.5, 144.6, 91.7, 50.1, 40.1, 33.4, 25.7, 24.9; MS (EI, 70 eV): m/z = 260, 231, 203, 178, 135, 109; HRMS (ESI) calcd $C_{13}H_{21}N_6$ $[M + H]^+$ m/z 261.1822, found m/z 261.1815.



*1-Phenyl-3-(1H-pyrazol-3-yl)thiourea (**7**).*[27] Eluent: petroleum ether/ethyl acetate (v/v = 1/1). White solid: 91% of yield (19.8 mg, 0.11 mmol); mp 174−176 °C; IR (KBr, cm^{-1}) 3346, 3187, 3064, 2923, 1726, 1580, 1462, 1361, 1270, 1187, 1057, 995, 898, 758, 689, 506; ^1H NMR (400 MHz, DMSO-d_6, ppm) δ 12.68 (s, 1H), 11.79 (s, 1H), 10.75 (s, 1H), 7.73 (s, 1H), 7.65 (d, J = 8 Hz, 2H), 7.37 (t, J = 8 Hz, 2H), 7.19 (t, J = 8 Hz, 1H), 6.08 (s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6, ppm) δ 176.8, 149.9, 139.5, 130.1, 129.0, 125.7, 124.6, 94.8; HRMS (ESI) calcd $C_{10}H_{10}N_4SNa$ $[M + Na]^+$ m/z 241.0518, found m/z 241.0537.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c00783.

Optimization of the reaction conditions for **4a**, Job's plot, X-ray crcstallography data (**4a** and **7**), GC−MS for the

https://doi.org/10.1021/acs.joc.1c00783
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detected intermediate, copies of ^{1}H and $^{13}C\{^{1}H\}$NMR spectra of all synthesized products (PDF)

Accession Codes

CCDC 2034391 and 2034814 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We are grateful to the National Natural Science Foundation of China (21867001, 21662002, and 21602031), the Academic & Technical Leadership Development Program of Jiangxi Province (20194BCJ22014), the Double-Thousand Talents Plan of Jiangxi Province (2019), the Jiangxi Provincial Natural Science Foundation (20202ACBL206022, 20171BAB203010), the Science Foundation of Jiangxi Provincial Department of Education (GJJ201429), and the Graduate Innovation Research Project of Gannan Normal University (YCX19A004).

REFERENCES

(1) (a) Jorda, R.; Paruch, K.; Kryštof, V. Cyclin-dependent Kinase Inhibitors Inspired by Roscovitine: Purine Bioisosteres. *Curr. Pharm. Des.* **2012**, *18*, 2974−2980. (b) Junien, J. L.; Lakatos, C.; Brohon, J.; Guillaume, M.; Sterne, J. Anti-Inflammatory Effect of LA 2851 and Reference Drugs on Some Models of Inflammation. Investigation of the Mechanism of Action. *Agents Actions* **1982**, *12*, 459−465. (c) Okamoto, K.; Nishino, T. Mechanism of Inhibition of Xanthine Oxidase with a New Tight Binding Inhibitor. *J. Biol. Chem.* **1995**, *270*, 7816−7821. (d) Senga, K.; O'Brien, D. E.; Scholten, M. B.; Novinson, T.; Miller, J. P.; Robins, R. K. Synthesis and Enzymic Activity of Various Substituted Pyrazolo[1,5-*a*]-1,3,5-triazines as Adenosine Cyclic 3′,5′-Phosphate Phosphodiesterase Inhibitors. *J. Med. Chem.* **1982**, *25*, 243−249. (e) Li, Y.-W.; Hill, G.; Wong, H.; Kelly, N.; Ward, K.; Pierdomenico, M.; Ren, S.; Gilligan, P.; Grossman, S.; Trainor, G.; Taub, R.; Mcelroy, J.; Zazcek, R. Receptor Occupancy of Nonpeptide Corticotropin-Releasing Factor 1 Antagonist DMP696: Correlation with Drug Exposure and Anxiolytic Efficacy. *J. Pharmacol. Exp. Ther.* **2003**, *305*, 86−96.

(2) (a) Naito, S.; Nishimura, M. Biotrasformation of the Xanthine Oxidase Inhibitor BOF-4272 and its Metabolites in the Liver and by the Intestinal Flora in Rat. *Xenobiotica* **2000**, *30*, 103−109. (b) Naito, S.; Nishimura, M.; Tamao, Y. Evaluation of the Pharmacological Actions and Pharmacokinetics of BOF-4272, a Xanthine Oxidase Inhibitor, in Mouse Liver. *J. Pharm. Pharmacol.* **2000**, *52*, 173−179. (c) Naito, S.; Nishimura, M.; Nogawa, H. Pharmacokinetics of BOF-4272, a Xanthine Oxidase Inhibitor, after Single Intravenous or Oral Administration to Male Mice and Rats. *J. Pharm. Pharmacol.* **1999**, *51*, 347−351. (d) Saito, S.; Ogawa, J.-I.; Minamiya, Y. Pulmonary Reexpansion Causes Xanthine Oxidase-Induced Apoptosis in Rat Lung. *Am. J. Physiol. Lung Cell Mol. Physiol.* **2005**, *289*, L400−L406. (e) Naito, S.; Nishimura, M.; Jin, Y. Biotransformation of BOF-4272, a Sulfoxide-Containing Drug, in the Cynomolgus Monkey. *Eur. J. Drug Metab. Pharmacokinet.* **1999**, *24*, 279−286. (f) Nishimura, M.; Yamaoka, K.; Yasui, H.; Naito, S.; Nakagawa, T. Effect of Temperature in Perfusate on Local Hepatic Disposition of BOF-4272, a New Xanthine Oxidase Inhibitor. *Biol. Pharm. Bull.* **1995**, *18*, 980−983. (g) Nishimura, M.; Yamaoka, K.; Naito, S.; Nakagawa, T. Influence of Albumin on Enantioselective Local Disposition of BOF-4272, a Xanthine Oxidase Inhibitor with Chiral Sulfoxide, in Rat Liver. *Biol. Pharm. Bull.* **1997**, *20*, 1285−1289. (h) Naito, S.; Nishimura, M.; Yoshitsugu, H.; Nogawa, H. Metabolic Pathways and Pharmacokinetics of BOF-4272, a Sulfoxide-Containing Drug, in the Dog: *In Vivo* and *in Vitro* Studies. *Biol. Pharm. Bull.* **1999**, *22*, 1391−1395.

(3) (a) He, L.; Gilligan, P. J.; Zaczek, R.; Fitzgerald, L. W.; McElroy, J.; Shen, H-S. L.; Saye, J. A.; Kalin, N. H.; Shelton, S.; Christ, D.; Trainor, G.; Hartig, P. 4-(1,3-Dimethoxyprop-2-ylamino)-2,7-dimethyl-8-(2,4-dichlorophenyl)- pyrazolo[1,5-*a*]-1,3,5-triazine: A Potent, Orally Bioavailable CRF1 Receptor Antagonist. *J. Med. Chem.* **2000**, *43*, 449−456. (b) Saito, T.; Obitsu, T.; Minamoto, C.; Sugiura, T.; Matsumura, N.; Ueno, S.; Kishi, A.; Katsumata, S.; Nakai, H.; Toda, M. Pyrazolo[1,5-*a*]pyrimidines, Triazolo[1,5-*a*]pyrimidines and Their Tricyclic Derivatives as Corticotropin-Releasing Factor 1 (CRF1) Receptor Antagonists. *Bioorg. Med. Chem.* **2011**, *19*, 5955−5966. (c) Nielsen, D. M.; Carey, G. J.; Gold, L. H. Antidepressant-like Activity of Corticotropin-Releasing Factor Type-1 Receptor Antagonists in Mice. *Eur. J. Pharmacol.* **2004**, *499*, 135−146. (d) Gilligan, P. J.; Clarke, T.; He, L.; Lelas, S.; Li, Y.-W.; Heman, K.; Fitzgerald, L.; Miller, K.; Zhang, G.; Marshall, A.; Krause, C.; McElroy, J. F.; Ward, K.; Zeller, K.; Wong, H.; Bai, S.; Saye, J.; Grossman, S.; Zaczek, R.; Arneric, S. P.; Hartig, P.; Robertson, D.; Trainor, G. Synthesis and Structure-Activity Relationships of 8-(Pyrid-3-yl)pyrazolo[1,5-*a*]-1,3,5-triazines: Potent, Orally Bioavailable Corticotropin Releasing Factor Receptor-1 (CRF_1)

Antagonists. *J. Med. Chem.* **2009**, *52*, 3084−3092. (e) Gilligan, P. J.; He, L.; Clarke, T.; Tivitmahaisoon, P.; Lelas, S.; Li, Y.-W.; Heman, K.; Fitzgerald, L.; Miller, K.; Zhang, G.; Marshall, A.; Krause, C.; McElroy, J.; Ward, K.; Shen, H.; Wong, H.; Grossman, S.; Nemeth, G.; Zaczek, R.; Arneric, S. P.; Hartig, P.; Robertson, D. W.; Trainor, G. 8-(4-Methoxyphenyl)pyrazolo[1,5-*a*]-1,3,5-triazines: Selective and Centrally Active Corticotropin-Releasing Factor Receptor-1 (CRF_1) Antagonists. *J. Med. Chem.* **2009**, *52*, 3073−3083. (f) Gilligan, P. J.; Folmer, B. K.; Hartz, R. A.; Koch, S.; Nanda, K. K.; Andreuski, S.; Fitzgerald, L.; Miller, K.; Marshall, W. J. Pyrazolo-[1,5-*a*]-1,3,5-triazine Corticotropin-Releasing Factor (CRF) Receptor Ligands. *Bioorg. Med. Chem.* **2003**, *11*, 4093−4102.

(4) Raboisson, P.; Schultz, D.; Muller, C.; Reimund, J.-M.; Pinna, G.; Mathieu, R.; Bernard, P.; Do, Q.-T.; DesJarlais, R. L.; Justiano, H.; Lugnier, C.; Bourguignon, J.-J. Cyclic Nucleotide Phosphodiesterase Type 4 Inhibitors: Evaluation of Pyrazolo[1,5-*a*]-1,3,5-triazine Ring System as an Adenine Bioisostere. *Eur. J. Med. Chem.* **2008**, *43*, 816−829.

(5) (a) Oudah, K. H.; Najm, M. A. A.; Samir, N.; Serya, R. A. T.; Abouzid, K. A. M. Design, Synthesis and Molecular Docking of Novel Pyrazolo[1,5-*a*][1,3,5]triazine Derivatives as CDK2 Inhibitors. *Bioorg. Chem.* **2019**, *92*, 103239. (b) Nie, Z.; Perretta, C.; Erickson, P.; Margosiak, S.; Lu, J.; Averill, A.; Almassy, R.; Chu, S. Structure-Based Design and Synthesis of Novel Macrocyclic Pyrazolo[1,5-*a*][1,3,5]-triazine Compounds as Potent Inhibitors of Protein Kinase CK2 and Their Anticancer Activities. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 619−623.

(6) Popowycz, F.; Schneider, C.; DeBonis, S.; Skoufias, D.; Kozielski, F.; Galmarini, C. M.; Joseph, B. Synthesis and Antiproliferative Evaluation of Pyrazolo[1,5-*a*]-1,3,5-triazine Myoseverin Derivatives. *Bioorg. Med. Chem.* **2009**, *17*, 3471−3478.

(7) Liu, Y.; Laufer, R.; Patel, N. K.; Ng, G.; Sampson, P. B.; Li, S.-W.; Lang, Y.; Feher, M.; Brokx, R.; Beletskaya, I.; Hodgson, R.; Plotnikova, O.; Awrey, D. E.; Qiu, W.; Chirgadze, N. Y.; Mason, J. M.; Wei, X.; Lin, D. C.-C.; Che, Y.; Kiarash, R.; Fletcher, G. C.; Mak, T. W.; Bray, M. R.; Pauls, H. W. Discovery of Pyrazolo[1,5-*a*]pyrimidine TTK Inhibitors: CFI-402257 is a Potent, Selective, Bioavailable Anticancer Agent. *ACS Med. Chem. Lett.* **2016**, *7*, 671−675.

(8) Popowycz, F.; Fournet, G.; Schneider, C.; Bettayeb, K.; Ferandin, Y.; Lamigeon, C.; Tirado, O. M.; Mateo-Lozano, S.; Notario, V.; Colas, P.; Bernard, P.; Meijer, L.; Joseph, B. Pyrazolo[1,5-*a*]-1,3,5-triazine as a Purine Bioisostere: Access to Potent Cyclin-Dependent Kinase Inhibitor (*R*)-Roscovitine Analogue. *J. Med. Chem.* **2009**, *52*, 655−663.

(9) (a) Cabon, G.; Gaucher, B.; Gegout, A.; Heulle, S.; Masquelin, T. Novel Solution- and Solid-Phase Syntheses of Heterocyclic Systems. *Chimia* **2003**, *57*, 248−254. (b) Xiang, Y.; Du, J.; Chu, C. K. Syntheses of 2',3'-Dideoxy-*D*-*C*-Nucleosides from γ-Lactone. *Nucleosides Nucleotides* **1996**, *15*, 1821−1834. (c) Lee, C. S.; Du, J.; Chu, C. K. Syntheses of 2',3'-Dideoxy-L-Glycero-Pentofuranosyl *C*-Nucleosides. *Nucleosides Nucleotides* **1996**, *15*, 1223−1236. (d) Zhang, H.-C.; Brakata, M.; Daves, G. D., Jr. Palladium-Mediated Coupling Reactions of an Aminosubstituted Heterocycle. Direct Synthesis of *C*-Nucleosides Related to Adenosine. *Nucleosides Nucleotides* **1995**, *14*, 105−116. (e) Norman, R. E.; Perkins, M. V.; Liepa, A. J.; Francis, C. L. *N,N*-Dialkyl-*N'*-Chlorosulfonyl Chloroformamidines in Heterocyclic Synthesis. Part XIII. Cleavage and Rearrangement Reactions of Pyrazolo-[1,5-*b*][1,2,4,6]thiatriazine 1,1-Dioxides. *Aust. J. Chem.* **2016**, *69*, 61−75. (f) Gudmundsson, K. S.; Johns, B. A.; Weatherhead, J. Pyrazolopyrimidines and Pyrazolotriazines with Potent Activity Against Herpesviruses. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5689−5692. (g) Raboisson, P.; Schultz, D.; Lugnier, C.; Bourguignon, J.-J. Efficient Synthesis of 8-Substituted Pyrazolo[1,5-*a*]-1,3,5-triazines by Regioselective Acylation. *Tetrahedron Lett.* **2002**, *43*, 9501−9503. (h) Raboisson, P.; Schultz, D.; Lugnier, C.; Mathieu, R.; Bourguignon, J.-J. A General Approach Toward the Synthesis of 8-Acylamidopyrazolo[1,5-*a*]-1,3,5-triazines. *Tetrahedron Lett.* **2003**, *44*, 703−705.

(10) Elgemeie, G.; Abu-Zaied, M. Purine and Guanine Thioglycoside Analogs: Novel Synthesis of a New Class of Pyrazolo[1,5-*a*][1,3,5]-Triazine-4-Thioglycoside Derivatives under Microwave Activation. *Nucleosides, Nucleotides Nucleic Acids* **2015**, *34*, 834−847.

(11) (a) Insuasty, H.; Estrada, S.; Quiroga, J.; Insuasty, B.; Abonia, R.; Nogueras, M.; Cobo, J. Solvent-Free Microwave-Assisted Synthesis of Novel 4-Hetarylpyrazolo[1,5-*a*][1,3,5]triazines. *J. Heterocyclic Chem.* **2012**, *49*, 1339−1345. (b) Insuasty, H.; Insuasty, B.; Castro, E.; Quiroga, J.; Abonía, R.; Nogueras, M.; Cobo, J. Three Practical Approaches for the Synthesis of Novel 4,7-Dihetarylpyrazolo[1,5-*a*][1,3,5]triazines. *Tetrahedron* **2012**, *68*, 9384−9390.

(12) (a) Insuasty, H.; Estrada, M.; Corteés, E.; Quiroga, J.; Insuasty, B.; Abonía, R.; Nogueras, M.; Cobo, J. Regioselective Synthesis of Novel 4-Aryl-2-ethylthio-7-methylpyrazolo[1,5-*a*]-[1,3,5]-triazines. *Tetrahedron Lett.* **2006**, *47*, 5441−5443. (b) Estrada, M. H.; Insuasty, H.; Cuca, L. E.; Marder, M.; Fierro, A.; Guerrero, M. F. Anticonvulsant Profile of 2-Ethylthio-7-methyl-4-(4-methylphenyl) pyrazolo[1,5-*a*]-[1,3,5]triazine. *Braz. J. Pharm. Sci.* **2014**, *50*, 73−81. (c) Bekircan, O.; Küxük, M.; Kahveci, B.; Kolaylı, S. Convenient Synthesis of Fused Heterocyclic 1,3,5-Triazines from Some *N*-Acyl Imidates and Heterocyclic Amines as Anticancer and Antioxidant *Agents*. *Arch. Pharm.* **2005**, *338*, 365−372.

(13) (a) Lim, F. P. L.; Halcovitch, N. R.; Tiekink, E. R. T.; Dolzhenko, A. V. A new Microwave-Assisted, Three-Component Reaction of 5-Aminopyrazole-4-Carboxylates: Selective Synthesis of Substituted 5-Aza-9-deaza-adenines. *Tetrahedron* **2018**, *74*, 1868−1879. (b) Lim, F. P. L.; Luna, G.; Dolzhenko, A. V. A New, One-pot, Multicomponent Synthesis of 5-Aza-9-deaza-adenines under Microwave Irradiation. *Tetrahedron Lett.* **2014**, *55*, 5159−5163.

(14) Insuasty, H.; Insuasty, B.; Castro, E.; Quiroga, J.; Abonia, R. An Efficient Two-Step Synthesis of Novel 2-Amino-substituted Pyrazolo-[1,5-*a*][1,3,5]triazines. *Tetrahedron Lett.* **2013**, *54*, 1722−1725.

(15) (a) Nie, Z.; Perretta, C.; Erickson, P.; Margosiak, S.; Almassy, R.; Lu, J.; Averill, A.; Yager, K. M.; Chu, S. Structure-Based Design, Synthesis, and Study of Pyrazolo[1,5-*a*][1,3,5]triazine Derivatives as Potent Inhibitors of Protein Kinase CK2. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4191−4195. (b) Bongard, J.; Schmitz, A. L.; Wolf, A.; Zischinsky, G.; Pieren, M.; Schellhorn, B.; Bravo-Rodriguez, K.; Schillinger, J.; Koch, U.; Nussbaumer, P.; Klebl, B.; Steinmann, J.; Buer, J.; Sanchez-Garcia, E.; Ehrmann, M.; Kaiser, M. Chemical Validation of DegS as a Target for the Development of Antibiotics with a Novel Mode of Action. *ChemMedChem* **2019**, *14*, 1074−1078.

(16) (a) El-Sayed, H. A. Design and Synthesis of Some Tricyclic Pyrimidines and Triazines via Cycloaddition and Intermolecular Cyclization of Cyclic Amidine. *J. Iran. Chem. Soc.* **2017**, *14*, 2239−2246. (b) Popowycz, F.; Bernard, P.; Raboisson, P.; Joseph, B. Synthesis of 8-Substituted Pyrazolo[1,5-*a*]-1,3,5-triazine Derivatives by Palladium-Catalyzed Cross-Coupling Reactions. *Synthesis* **2007**, *2007*, 367−374. (c) Zamigailo, L. L.; Petrova, O. N.; Shirobokova, M. G.; Lipson, V. V. Reactions of 4-Oxobenz[1,3-*e*]oxazinium Perchlorates with α-Aminoazoles. *Russ. J. Org. Chem.* **2013**, *49*, 288−293.

(17) (a) Lübbers, T.; Angehrn, P.; Gmünder, H.; Herzig, S.; Kulhanek, J. Design, Synthesis, and Structure-Activity Relationship Studies of ATP Analogues as DNA Gyrase Inhibitors. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 821−826. (b) Raboisson, P.; Baurand, A.; Cazenave, J.-P.; Gachet, C.; Schultz, D.; Spiess, B.; Bourguignon, J.-J. A General Approach toward the Synthesis of C-Nucleoside Pyrazolo[1,5-*a*]-1,3,5-triazines and Their 3',5'-Bisphosphate C-Nucleotide Analogues as the First Reported in Vivo Stable $P2Y_1$-Receptor Antagonists. *J. Org. Chem.* **2002**, *67*, 8063−8071. (c) Lefoix, M.; Mathis, G.; Kleinmann, T.; Truffert, J.-C.; Asseline, U. Pyrazolo[1,5-*a*]-1,3,5-triazine C-Nucleoside as Deoxyadenosine Analogue: Synthesis, Pairing, and Resistance to Hydrolysis. *J. Org. Chem.* **2014**, *79*, 3221−3227. (d) Liang, C.; Ma, T.; Cooperwood, J. S.; Du, J.; Chu, C. K. Synthesis of L-Ribofuranosyl *C*-Nucleosides. *Carbohydr. Res.* **1997**, *303*, 33−38.

(18) (a) Yu, X.-Y.; Chen, J.-R.; Xiao, W.-J. Visible Light-Driven Radical-Mediated C-C Bond Cleavage/Functionalization in Organic Synthesis. *Chem. Rev.* **2021**, *121*, 506−561. (b) Guo, W.; Tao, K.; Tan, W.; Zhao, M.; Zheng, L.; Fan, X. Recent Advances in Photocatalytic C−S/P−S Bond Formation via the Generation of Sulfur Centered Radicals and Functionalization. *Org. Chem. Front.* **2019**, *6*, 2048−2066.

https://doi.org/10.1021/acs.joc.1c00783
J. Org. Chem. 2021, 86, 8365−8380

(c) Chen, Y.; Lu, L.-Q.; Yu, D.-G.; Zhu, C.-J.; Xiao, W.-J. Visible Light-Driven Organic Photochemical Synthesis in China. *Sci. China: Chem.* **2019**, *62*, 24−57. (d) Zhang, H.-H.; Chen, H.; Zhu, C.; Yu, S. A Review of Enantioselective Dual Transition metal/photoredox Catalysis. *Sci. China: Chem.* **2020**, *63*, 637−647. (e) Guo, W.; Tan, W.; Zhao, M.; Zheng, L.; Tao, K.; Chen, D.; Fan, X. Direct Photocatalytic S−H Bond Cyanation with Green "CN" Source. *J. Org. Chem.* **2018**, *83*, 6580−6588. (f) Guo, W.; Tan, W.; Zhao, M.; Tao, K.; Zheng, L.-Y.; Wu, Y.; Chen, D.; Fan, X.-L. Photocatalytic Direct C-S Bond Formation: Facile Access to 3-Sulfenylindoles via Metal-Free C-3 Sulfenylation of Indoles with Thiophenols. *RSC Adv.* **2017**, *7*, 37739−37742. (g) Yu, X.-Y.; Zhao, Q.-Q.; Chen, J.; Xiao, W.-J.; Chen, J.-R. When Light Meets Nitrogen-Centered Radicals: From Reagents to Catalysts. *Acc. Chem. Res.* **2020**, *53*, 1066−1083. (h) Teng, Q.-H.; Yao, Y.; Wei, W.-X.; Tang, H.-T.; Li, J.-R.; Pan, Y.-M. Direct C−H Sulfenylation of Quinoxalinones with Thiols Under Visible-Light-Induced Photocatalyst-Free Conditions. *Green Chem.* **2019**, *21*, 6241−6245.

(19) (a) Zheng, L.; Tao, K.; Guo, W. Recent Developments in Photo-Catalyzed/Promoted Synthesis of Indoles and Their Functionalization: Reactions and Mechanisms. *Adv. Synth. Catal.* **2021**, *363*, 62−119. (b) Guo, W.; Tao, K.; Xie, Z.; Cai, L.; Zhao, M.; Tan, W.; Liu, G.; Mei, W.; Deng, L.; Fan, X.; Zheng, L. Photo-Driven Photocatalyst-/Metal-Free Direct C-C/C-N Bond Formation: Synthesis of Indoles via EDA Complexes. *J. Org. Chem.* **2019**, *84*, 14168−14178. (c) Guo, W.; Zhao, M.; Tan, W.; Zheng, L.; Tao, K.; Liu, L.; Wang, X.; Chen, D.; Fan, X. Visible Light-Promoted Three-Component Tandem Annulation for Synthesis of 2-Iminothiazolidin-4-ones. *J. Org. Chem.* **2018**, *83*, 1402−1413.

(20) (a) Guo, W.; Tao, K.; Zheng, L.; Zhao, M.; Tan, W.; Cai, L.; Xie, Z.; Chen, D.; Fan, X. Visible Light-Promoted Three-Component Coupling Annulation: Synthesis of 2-Iminothiazolidin-4-ones via in situ Formed Electron Donor−Acceptor Complexes. *J. Org. Chem.* **2019**, *84*, 6448−6458. (b) Guo, W.; Zhao, M.; Du, C.; Zheng, L.; Li, L.; Chen, L.; Tao, K.; Tan, W.; Xie, Z.; Cai, L.; Fan, X.; Zhang, K. Visible-Light-Catalyzed [3 + 1 + 2] Coupling Annulations for the Synthesis of Unsymmetrical Tri-substituted Amino-1,3,5-triazines. *J. Org. Chem.* **2019**, *84*, 15508−15519. (c) Zheng, L.; Cai, L.; Tao, K.; Xie, Z.; Lai, Y.-L.; Guo, W. Progress in Photoinduced Radical Reactions using Electron Donor-Acceptor Complexes. *Asian J. Org. Chem.* **2021**, *10*, 711−748.

(21) (a) Hatchard, C. G.; Parker, C. A. A New Sensitive Chemical Actinometer. II. Potassium Ferrioxalate as a Standard Chemical Actinometer. *Proc. R. Soc. (London)* **1956**, *A235*, 518−536. (b) Kuhn, H. J.; Braslavsky, S. E.; Schmidt, R. Chemical actinometry (IUPAC Technical Report). *Pure Appl. Chem.* **2004**, *76*, 2105−2146. (c) Wang, R.; Wang, L.; Xu, Q.; Ren, B.-Y.; Liang, F. Visible-Light-Promoted [5 + 1] Annulation Initiated by Electron-Donor−Acceptor Complexes: Synthesis of Perfluoroalkyl-*s*-Triazines. *Org. Lett.* **2019**, *21*, 3072−3076. (d) Cismesia, M. A.; Yoon, T. P. Characterizing Chain Processes in Visible Light Photoredox Catalysis. *Chem. Sci.* **2015**, *6*, 5426−5434. (e) Nikitas, N. F.; Triandafillidi, L.; Kokotos, C. G. Photoorganocatalytic Synthesis of Acetals from Aldehydes. *Green Chem.* **2019**, *21*, 669−674.

(22) (a) Lima, C. G. S.; Lima, T. d. M.; Duarte, M.; Jurberg, I. D.; Paixão, M. W. Organic Synthesis Enabled by Light-Irradiation of EDA Complexes: Theoretical Background and Synthetic Applications. *ACS Catal.* **2016**, *6*, 1389−1407. (b) Crisenza, G. E. M.; Mazzarella, D.; Melchiorre, P. Synthetic Methods Driven by the Photoactivity of Electron Donor−Acceptor Complexes. *J. Am. Chem. Soc.* **2020**, *142*, 5461−5476. (c) Yuan, Y.-Q.; Majumder, S.; Yang, M.-H.; Guo, S.-R. Recent Advances in Catalyst-Free Photochemical Reactions via Electron-Donor Acceptor (EDA) Complex Process. *Tetrahedron Lett.* **2020**, *61*, 151506.

(23) Chen, Z.; Jin, W.; Xia, Y.; Zhang, Y.; Xie, M.; Ma, S.; Liu, C. Aminothiolation of α-Bromocinnamaldehydes to Access Imidazo[2,1-b]thiazoles by Incorporation of Two Distinct Photoinduced Processes. *Org. Lett.* **2020**, *22*, 8261−8266.

(24) (a) Liu, S.; Wang, R.; Zhu, B.; Guan, W.; Liang, F. Photo- and Dioxygen-Enabled Radical C(sp^3)—N(sp^2) Cross-Coupling Between Guanidines and Perfluoroalkyl iodides. *Org. Biomol. Chem.* **2019**, *17*, 8695−8700. (b) Wang, R.; Guan, W.; Han, Z.-B.; Liang, F.; Suga, T.; Bi, X.; Nishide, H. Ambient-Light-Promoted Three-Component Annulation: Synthesis of Perfluoroalkylated Pyrimidines. *Org. Lett.* **2017**, *19*, 2358−2361. (c) Yadav, A. K.; Singh, K. N. Visible-Light-Induced Oxidative Difunctionalization of Styrenes: Synthesis of α-Trifluoromethylthiosubstituted Ketones. *Chem. Commun.* **2018**, *54*, 1976−1979.

(25) Benesi, H. A.; Hildebrand, J. H. A Spectrophotometric Investigation of the Interaction of Iodine with Aromatic Hydrocarbons. *J. Am. Chem. Soc.* **1949**, *71*, 2703−2707.

(26) (a) Hsu, C.-W.; Sunden, H. α-Aminoalkyl Radical Addition to Maleimides via Electron Donor−Acceptor Complexes. *Org. Lett.* **2018**, *20*, 2051−2054. (b) Li, Y.; Miao, T.; Li, P.; Wang, L. Photo-Driven Synthesis of C6-Polyfunctionalized Phenanthridines from Three-Component Reactions of Isocyanides, Alkynes, and Sulfinic Acids by Electron Donor−Acceptor Complex. *Org. Lett.* **2018**, *20*, 1735−1739.

(27) Singh, B. N. Synthesis of New Unsymmetrical 1,3-Disubstituted-thioureas. *Agric. Biol. Chem.* **1978**, *42*, 1285−1286.

https://doi.org/10.1021/acs.joc.1c00783
J. Org. Chem. 2021, 86, 8365−8380