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Short Note

2,4-Diamino-5-(5-hydroxy-1-phenyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl)-5*H*-chromeno[2,3-*b*]pyridine-3-carbonitrile

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Abstract: 5*H*-Chromeno[2,3-*b*]pyridines are important compounds with industrial, biological, and medicinal properties. In this short note, the multicomponent reaction of salicylaldehyde, malononitrile dimer, and 2-phenyl-5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrazol-3-one in dimethyl sulfoxide at ambient temperature was investigated to give 2,4-diamino-5-(5-hydroxy-1-phenyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl)-5*H*-chromeno[2,3-*b*]pyridine-3-carbonitrile with good yield. The structure of the previously unknown chromeno[2,3-*b*]pyridine derivative was confirmed by elemental analysis, mass, nuclear magnetic resonance, and infrared spectroscopy data. The ADME (absorption, distribution, metabolism, and excretion) properties were also assessed.

Keywords: multicomponent reaction; salicylaldehyde; malononitrile dimer; 2-phenyl-5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrazol-3-one; chromeno[2,3-*b*]pyridines; ADME properties

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1. Introduction

The assessment of absorption, distribution, metabolism, and excretion (ADME) properties is a necessary and responsible approach to drug discovery and design that aids in optimizing the safety of the hit compound [1]. Early estimation of ADME in the discovery phase drastically reduces the fraction of pharmacokinetics-related failures in clinical phases [2]. The high-throughput and low-cost nature of ADME prediction models allow for a more streamlined drug development process [3].

Chromeno[2,3-*b*]pyridine fragment is known as a privileged medicinal scaffold [4]. Its derivatives are important compounds with industrial, biological, and medicinal properties [5]. Chromeno[2,3-*b*]pyridines have a wide spectrum of pharmacological activity, and this moiety was found in two commercial anti-inflammatory drugs: Amlexanox [6] and Pranoprofen [7] (Figure 1).

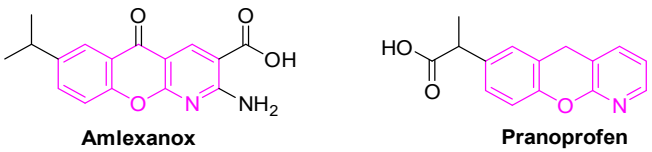


Figure 1. Bioactive chromeno[2,3-*b*]pyridines.

The trifluoromethyl pyrazole fragment is a privileged medicinal scaffold as well. Many examples of bioactive fluorinated pyrazoles have emerged in recent years, including the non-steroidal anti-inflammatory drug celecoxib (Celebrex) [8] and the herbicide fluazolate [9] (Figure 2).

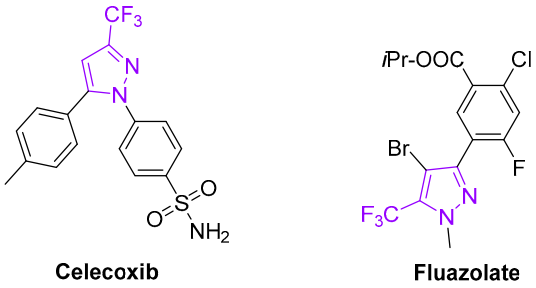


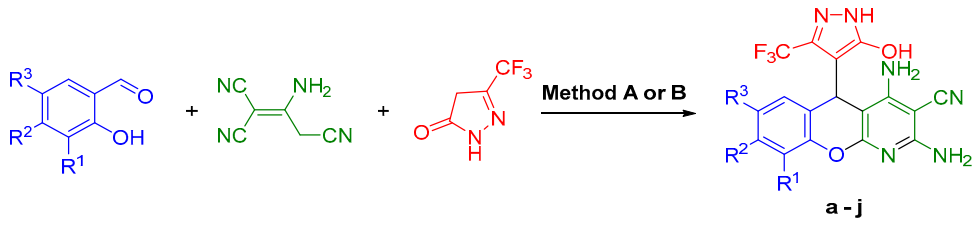
Figure 2. Bioactive trifluoromethyl pyrazole derivatives.

The incorporation of both of these fragments may lead to new properties. Thus, the synthesis of a compound containing both of these fragments is of prominent interest.

2. Results and Discussion

2.1. Multicomponent Synthesis of 2,4-Diamino-5-(5-hydroxy-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-5H-chromeno[2,3-b]pyridine-3-carbonitrile 4

We previously carried out a multicomponent transformation of salicylaldehydes, 2-aminoprop-1-ene-1,1,3-tricarbonitrile (malononitrile dimer), and 5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrazol-3-one into 2,4-diamino-5-(5-hydroxy-3-(trifluoromethyl)-1*H*-pyrazol-4-yl)-5*H*-chromeno[2,3-*b*]pyridine-3-carbonitriles by two different methods [10] (Scheme 1). However, the use of these reaction systems did not allow for the introduction of the *N*-phenyl-substituted C-H acid derivative into the reaction.



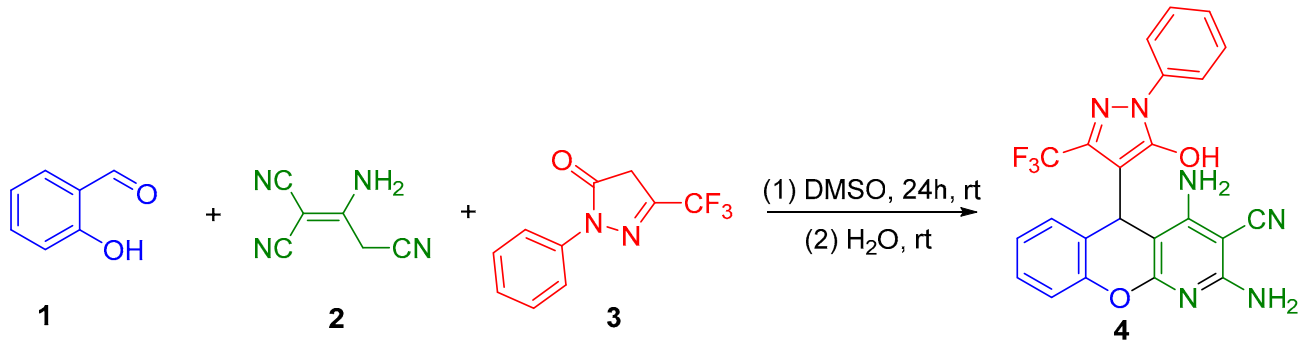
Method A: Py, 2h, Δ
Method B: Et_3N (10mol%), *n*-PrOH, 4h, Δ

a $R^1 = R^2 = R^3 = H$ (A=90%, B=92%)
b $R^1 = R^2 = H$, $R^3 = Me$ (A=73%, B=89%)
c $R^1 = OMe$, $R^2 = R^3 = H$ (A=67%, B=90%)
d $R^1 = R^3 = H$, $R^2 = OMe$ (A=65%, B=85%)
e $R^1 = R^2 = H$, $R^3 = Cl$ (A=69%, B=83%)
f $R^1 = R^2 = H$, $R^3 = Br$ (A=72%, B=85%)
g $R^1 = OMe$, $R^2 = H$, $R^3 = Br$ (A=53%, B=87%)
h $R^1 = R^2 = H$, $R^3 = NO_2$ (A=48%, B=62%)
i $R^1 = R^3 = Cl$, $R^2 = H$ (A=46%, B=58%)
j $R^1 = R^3 = I$, $R^2 = H$ (A=51%, B=78%)

Scheme 1. Multicomponent reaction of salicylaldehydes, malononitrile dimer, and 5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrazol-3-one.

We developed the multicomponent synthesis of chromeno[2,3-*b*]pyridines in dimethyl sulfoxide (DMSO) [11–13]. This method produced chromeno[2,3-*b*]pyridines, which were previously unknown and unavailable via other methods (methods A and B [10]). Salicylaldehydes, malononitrile dimer, and malonic acid or dimethyl malonate were then transformed into 2-(2,4-diamino-3-cyano-5*H*-chromeno[2,3-*b*]-pyridin-5-yl)malonic acids or dimethyl 2-(2,4-diamino-3-cyano-5*H*-chromeno[2,3-*b*]-pyridin-5-yl)malonate [11,12]. Then, similarly, 2,4-Diamino-5-(nitromethyl)5*H*-chromeno[2,3-*b*]pyridine3-carbonitrile was also synthesized [13].

Now, we wish to report our results in the facile multicomponent transformation of salicylaldehyde (**1**), 2-aminoprop-1-ene-1,1,3-tricarbonitrile (**2**), and 2-phenyl-5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrazol-3-one (**3**) into the previously unknown 2,4-diamino-5-(5-hydroxy-1-phenyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl)-5*H*-chromeno[2,3-*b*]pyridine-3-carbonitrile (**4**) in DMSO at ambient temperature (23 °C, 24 h), as shown in Scheme 2.



Scheme 2. Reaction of salicylaldehyde (**1**), malononitrile dimer (**2**), and 2-phenyl-5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrazol-3-one (**3**).

After the reaction was completed, water was poured into the DMSO solution, and the pure chromeno[2,3-*b*]pyridine (**4**) was precipitated. The yield of compound **4** was 84%.

The BFI (bond-forming index) [14] of the process is as high as four, as four new non-hydrogen bonds were formed in one synthetic transformation, namely two C-C bonds, one C-N bond, and one C-O bond.

The structure of the new chromeno[2,3-*b*]pyridine (**4**) was confirmed by spectral methods such as ^{1}H and ^{13}C NMR, IR spectroscopy and mass spectrometry data, and elemental analysis data (see Supplementary Materials). The NMR spectrum corresponds to similar known structures [10]. There is also a 2D NMR assignment for chromeno[2,3-*b*]pyridine aromatics [15].

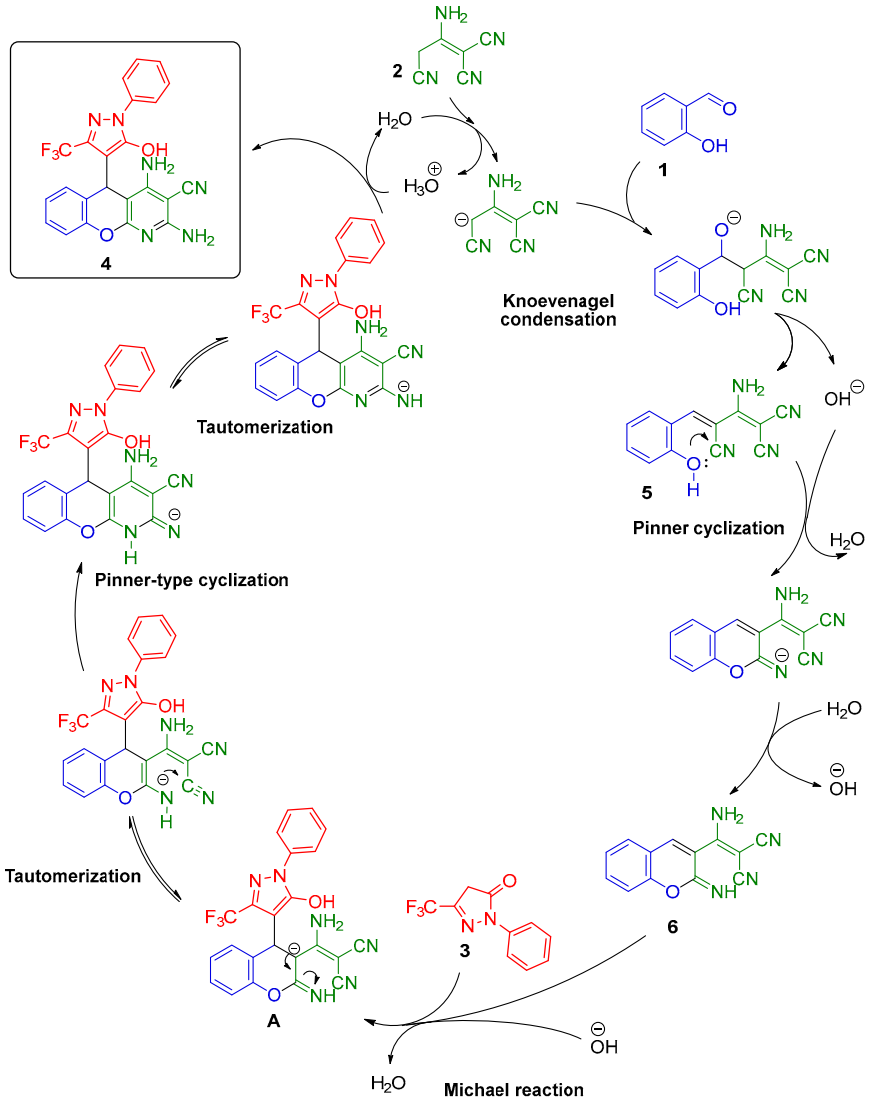
Taking into consideration our previous results on the determination of intermediates [16] and ^{1}H NMR monitoring data of similar multicomponent processes [11,17], the following mechanism for the transformation of salicylaldehyde (**1**), malononitrile dimer (**2**), and 2-phenyl-5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrazol-3-one (**3**) was proposed, as shown in Scheme 3.

The first stage of the multicomponent transformation was a Knoevenagel condensation with the formation of unsaturated adduct **5** and the release of a hydroxide anion [18]. This hydroxide anion catalyzed a Pinner cyclization of adduct **5** into intermediate **6**. The Michael addition of 2-phenyl-5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrazol-3-one (**3**) then led to the formation of anion **A**. In the last stage, tautomerization, Pinner-type cyclization, and another tautomerization with protonation led to the final 2,4-diamino-5-(5-hydroxy-1-phenyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl)-5*H*-chromeno[2,3-*b*]pyridine-3-carbonitrile (**4**).

2.2. ADME Prediction

The ADME of the synthesized chromeno[2,3-*b*]pyridine (**4**) was predicted using an online resource [19,20].

The bioavailability radar of chromeno[2,3-*b*]pyridine (**4**) is shown in Figure 3. Bioavailability radar allows for rapid assessment of drug similarity parameters [21]. Six physicochemical properties are taken into account: lipophilicity, size, polarity, solubility, flexibility, and saturation [22]. The pink area is the optimal range for each property. The synthesized compound (**4**) has a low boundary value of polarity but within the normal range of flexibility, as well as low saturation (Figure 3). Thus, compound **4** corresponds to Lipinski's rule (Table 1) but has limited oral bioavailability.



Scheme 3. Simplified mechanism of salicylaldehyde (**1**), malononitrile dimer (**2**), and 2-phenyl-5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrazol-3-one (**3**) transformation into chromeno[2,3-*b*]pyridine (**4**).

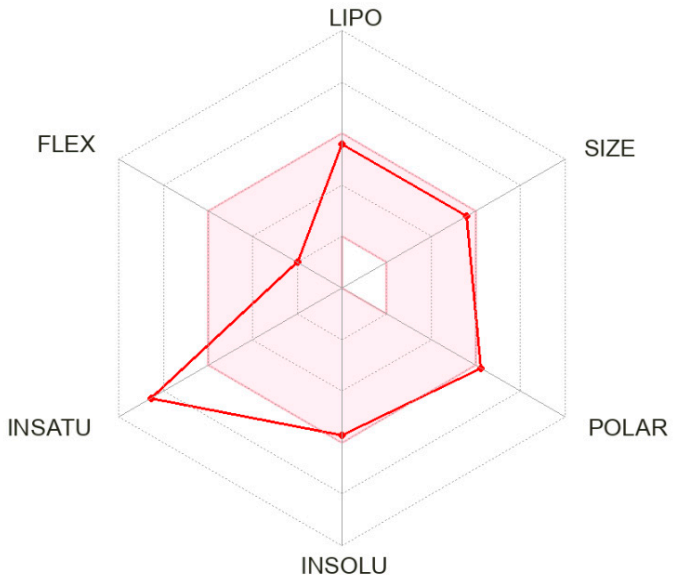


Figure 3. The bioavailability radar of chromeno[2,3-*b*]pyridine (**4**).

The BOILED-Egg is a graphical display of two important parameters, i.e., passive gastrointestinal absorption (HIA) and brain access (BBB) [23]. The yolk is the physicochemical space for highly probable BBB permeation, and the white is the physicochemical space for highly probable HIA absorption. The two spaces are not mutually exclusive; the outside gray region stands for low absorption and limited brain penetration of the molecule. The point is supposed to be blue if the molecule is actively effluxed by P-glycoprotein (PGP+) and red (in this case) if it is a non-substrate of P-glycoprotein (PGP−) [24]. Figure 4 shows that the synthesized compound (**4**) is predicted not to be absorbed and not brain penetrant (outside the Egg), as well as not subject to active efflux (red dot).

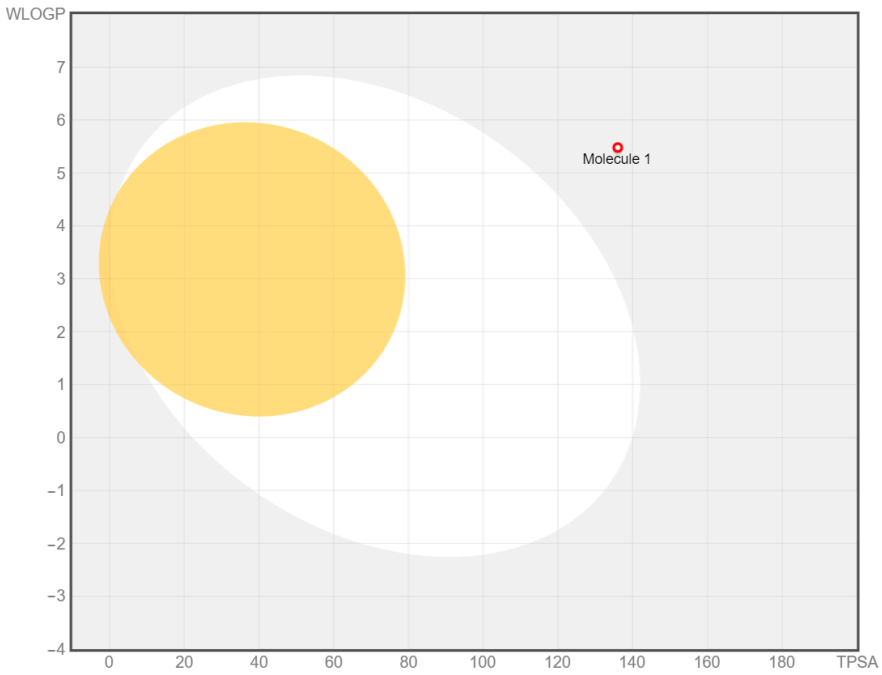


Figure 4. The 'BOILED-Egg' diagram for chromeno[2,3-*b*]pyridine (**4**).

Some of the calculated ADME parameters are presented in Table 1. It also follows from the calculations that compound **4** complies with the Lipinski [25], Ghose [26], Veber [27], and Muegge [28] rules.

Table 1. Calculated ADME parameters of synthesized chromeno[2,3-*b*]pyridine (**4**).

Parameter	Value
Fraction Csp^3	0.09
Num. rotatable bonds	3
Topological polar surface area	136.00 $Å^2$
Consensus Log $P_{o/w}$ (Lipophilicity)	3.55
Log S (ESOL) [29]	−5.72
Water solubility	8.88×10^{-4} mg/mL; 1.91×10^{-6} mol/L
Class	Moderately soluble
Gastrointestinal absorption	Low
BBB permeant	No
P-gp substrate	No
Log K_p (skin permeation)	−6.09 cm/s
Bioavailability score	0.55

Based on the above data, it can be concluded that pyridine may be a potential drug.

3. Materials and Methods

3.1. General Methods

All solvents and reagents were used as received from commercial sources without further purification (except the reagents described below). 2-Aminoprop-1-ene-1,1,3-tricarbonitrile (**2**) (malononitrile dimer) was synthesized by dimerization of malononitrile in an alkaline medium [30]. 2-Phenyl-5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrazol-3-one (**3**) was obtained from phenylhydrazine and ethyl 4,4,4-trifluoroacetoacetate according to the literature [31].

The melting point was measured with a Gallenkamp melting-point apparatus (Gallenkamp & Co., Ltd., London, UK). ^{1}H and ^{13}C NMR spectra were registered in DMSO-d_6 with a Bruker AM300 spectrometer (Bruker Corporation, Billerica, MA, USA) at ambient temperature. The IR spectrum was recorded with a Bruker ALPHA-T FT-IR spectrometer (Bruker Corporation, Billerica, MA, USA) in KBr pellets. The MS spectrum (EI = 70 eV) was recorded with a Kratos MS-30 spectrometer (Kratos Analytical Ltd., Manchester, UK). For elemental analysis, a 2400 elemental analyzer (Perkin Elmer Inc., Waltham, MA, USA) was applied.

The ADME prediction of the synthesized molecule (**4**) was carried out using online resources [19,20].

3.2. Multicomponent Synthesis of 2,4-Diamino-5-(5-hydroxy-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-5H-chromeno[2,3-b]pyridine-3-carbonitrile 4

Salicylic aldehyde (**1**) (0.122 g, 1 mmol), 2-aminoprop-1-ene-1,1,3-tricarbonitrile (**2**) (0.132 g, 1 mmol), and 2-phenyl-5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrazol-3-one (**3**) (0.228 g, 1 mmol) were stirred in 5 mL of DMSO for 24 h at ambient temperature (23 °C). After the process was finished, 10 mL of water was added to the reaction mixture. The precipitate was filtered, washed with well-chilled ethanol (3 mL × 2), and dried to isolate pure 2,4-diamino-5-(5-hydroxy-1-phenyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl)-5*H*-chromeno[2,3-*b*]pyridine-3-carbonitrile (**4**).

2,4-Diamino-5-(5-hydroxy-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-5H-chromeno[2,3-b]pyridine-3-carbonitrile (4). Yellowish powder; yield 84% (0.390 g); mp = 202–203 °C (decomp.) (from DMSO-H_2O); FTIR (KBr) cm^{-1}: 3557 (NH_2), 3437 (NH_2), 3342 (NH_2), 3207 (NH_2), 3069 (O-H), 2219 (C≡N), 1691 (C=N), 1647 (C=C Ar), 1600 (C-C Ar), 1536 (C=C Ar), 1494 (C=C Ar), 1473 (C=C Ar), 1454 (C=C Ar), 1280 (C-F), 1146 (C-F), 1120 (C-F). ^{1}H NMR (300 MHz, DMSO-d_6): δ 5.36 (s, 1H, CH), 6.02 (br s, 2H, NH_2), 6.51 (br s, 2H, NH_2), 7.07 (t, ^{3}J = 8.1 Hz, 2H, 2 CH Ar s.ald.), 7.19-7.30 (m, 2H, 2 CH Ph), 7.43 (t, ^{3}J = 7.2 Hz, 1H, CH Ph), 7.55 (t, ^{3}J = 7.2 Hz, 2H, 2 CH Ph), 7.74 (d, ^{3}J = 8.1 Hz, 2H, 2 CH Ar s.ald.), 11.52-12.78 (br s, 1H, OH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 27.8 (C(5)H), 71.2 (C(3)-CN), 88.0 (C(4a)), 106.8 (C(4')), 116.7 (C(9)H Ar), 116.8 (CN), 121.2 (q, ^{1}J = 269.5 Hz, 1C, CF_3), 122.9 (C(7)H Ar), 123.1 (2C, *o*-CH from Ph), 124.3 (*p*-CH from Ph), 128.0 (C(6)H Ar), 128.8 (C(8)H Ar), 129.7 (2C, *m*-CH from Ph), 137.2 (q, ^{2}J = 37.1 Hz, 1C, C(3')-CF_3), 138.0 (2C, C(5a) and N(1')-C), 149.8 (C(9a)), 150.9 (C(4)-NH_2), 157.4 (C(2)-NH_2), 158.9 (C(5')-OH), 159.9 (C(1a)) ppm; MS (*m/z*, relative intensity %): 464 $[M]^+$ (3), 444 $[M - HF]^+$ (43), 277 $[M - C_8H_6F_3N_2]^+$ (5), 237 $[M - C_{10}H_6F_3N_2O]^+$ (100), 228 $[C_{10}H_7F_3N_2O]^+$ (47), 77 $[C_6H_5]^+$ (31); Anal. calcd. for $C_{23}H_{15}F_3N_6O_2$: C, 59.48; H, 3.26; N, 18.10%; found: C, 59.40; H, 3.36; N, 18.05%.

^{1}H and ^{13}C NMR, IR and MS spectra for compound **4** are presented in the Supplementary Materials.

4. Conclusions

In conclusion, the title compound, 2,4-diamino-5-(5-hydroxy-1-phenyl-3-(trifluo-romethyl)-1*H*-pyrazol-4-yl)-5*H*-chromeno[2,3-*b*]pyridine-3-carbonitrile, was synthesized in good yield using a facile and efficient multicomponent reaction. During the study, we used simple equipment and available starting materials. The newly synthesized compound was characterized by spectroscopic techniques (NMR, IR, and MS-EI) and elemental analy-

sis. According to ADME parameters, the resulting chromo[2,3-*b*]pyridine contains two pharmacologically promising fragments and has a chance of being useful as a drug.

Supplementary Materials: The following are available online: compound **4** spectra: ^{1}H NMR (Figure S1), ^{13}C NMR (Figure S2), IR (Figure S3), and MS (EI) (Figure S4).

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