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Short Note

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8-Phenyl-13a-(Trifluoromethyl)-13a*H*-benzo[4,5]imidazo[1,2-*a*]chromeno[3,2-*e*]pyridine-6-Carbonitrile

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Posted Date: 9 February 2026

doi: 10.20944/preprints202602.0696.v1

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doi:10.20944/preprints202602.0696.v1

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Short Note

8-Phenyl-13a-(Trifluoromethyl)-13a*H*-benzo[4,5]imidazo[1,2-*a*]chromeno[3,2-*e*]pyridine-6-Carbonitrile

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Abstract

A DABCO-catalyzed one-pot synthesis of a novel pentacyclic heterocycle featuring an unprecedented benzo[4,5]imidazo[1,2-*a*]chromeno[3,2-*e*]pyridine scaffold from 2-(cyanomethyl)benzimidazole and 3-trifluoroacetyl-4-phenyl-4*H*-chromene has been developed. This hybrid architecture merges three privileged pharmacophores – benzimidazole, chromene, and pyridine – into a rigid, nearly planar π-extended system decorated with trifluoromethyl and nitrile groups. The structure of 8-phenyl-13a-(trifluoromethyl)-13a*H*-benzo[4,5]imidazo[1,2-*a*]chromeno[3,2-*e*]pyridine-6-carbonitrile was unambiguously confirmed by NMR spectroscopy and X-ray diffraction analysis. A plausible mechanism involves Michael addition, hemiaminal formation, ring opening, recyclization, and oxidation.

Keywords: chromenes; 2-(cyanomethyl)benzimidazole; benzo[4,5]imidazo[1,2-*a*]chromeno[3,2-*e*]pyridine; cyclic N,O-acetal; cascade reaction; Michael reaction; hybrid heterocycles

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1. Introduction

Fused polyheterocyclic systems, particularly those integrating multiple pharmacophoric units within a single molecular framework, have emerged as privileged scaffolds for drug discovery due to their structural complexity, conformational rigidity, and ability to engage multiple biological targets simultaneously. The strategic fusion of distinct heterocyclic cores through molecular hybridization has become a powerful approach in rational drug design, enabling the synergistic combination of complementary pharmacological properties while potentially overcoming limitations such as drug resistance, poor bioavailability, or off-target effects associated with parent compounds [1–4]. Hybrid heterocycles incorporating chromene motifs have emerged as particularly promising scaffolds [5–11].

In particular, 5*H*-chromeno[2,3-*b*]pyridine system [12–15] is known as a privileged pharmacophore due to its ability to readily interact with a wide range of biological targets, and it is often used as a scaffold for the development of new drugs. Amlexanox is approved for treatment of recurrent aphthous ulcers and exhibits anti-inflammatory, antiallergic, and immunomodulatory properties; remarkably, recent studies have revealed its efficacy in managing type 2 diabetes and obesity through inhibition of IKK-ε and TBK1 kinases [16]. Pranoprofen, a non-steroidal anti-inflammatory drug (NSAID) containing the chromeno[2,3-*b*]pyridine core, is widely used in ophthalmology for acute inflammatory conditions and postoperative ocular therapy [17]. The anti-inflammatory properties of the condensed chromone **C** are based on the inhibition of 15-Lipoxigenase

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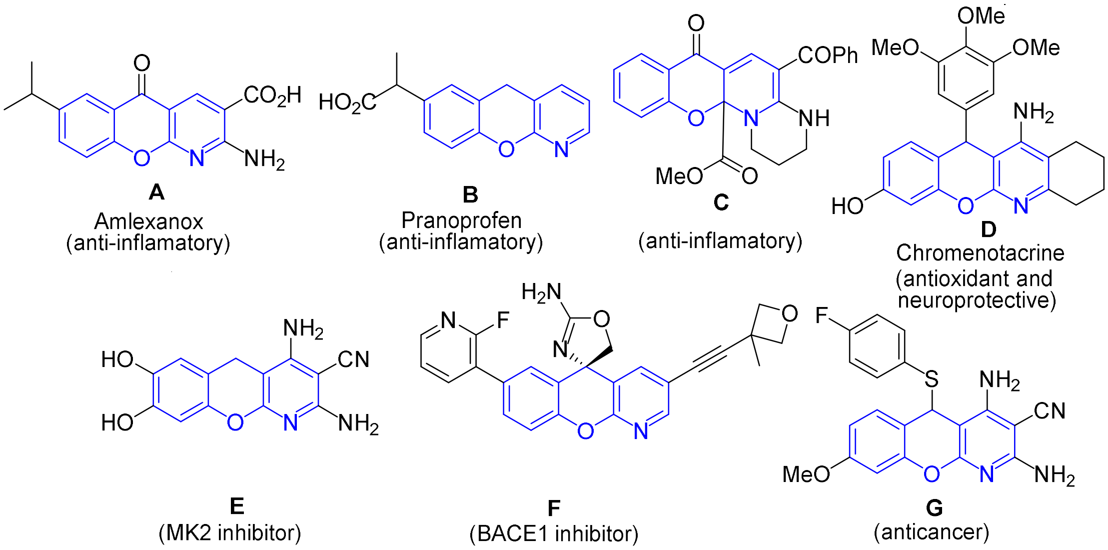
(15-LOX) [18]. Chromenotacrine (**D**), a hybrid molecule combining chromene and tacrine moieties, functions as a selective acetylcholinesterase inhibitor with antioxidant and neuroprotective properties, showing promise for Alzheimer's disease treatment [19]. Furthermore, chromeno[2,3-*b*]pyridine derivatives have demonstrated inhibition of mitogen-activated protein kinase (MK2) (compound **E**) [20] and β-site amyloid precursor protein cleaving enzyme (BACE1) (**F**) [21], as well as anticancer activity (**G**) [22] (Figure 1).


A Amlexanox (anti-inflamatory)

B Pranoprofen (anti-inflamatory)

C (anti-inflamatory)

D Chromenotacrine (antioxidant and neuroprotective)

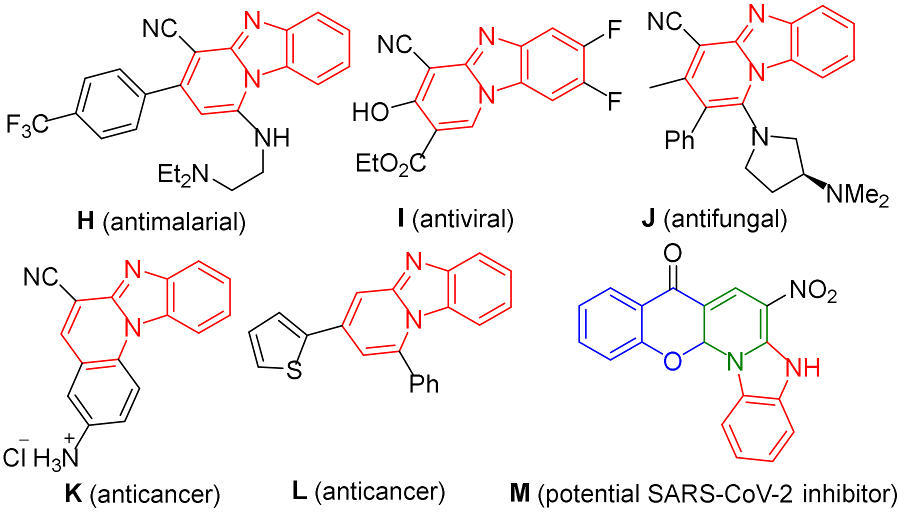
E (MK2 inhibitor)

F (BACE1 inhibitor)

G (anticancer)

Figure 1. Representative examples of pharmacologically active chromeno[2,3-*b*]pyridines.

On the other hand, benzo[4,5]imidazo[1,2-*a*]pyridines [23] represent another privileged scaffold that occurs in various derivatives exhibiting diversified biological activities such as antimalarial (compound **H**) [24], antiviral (**I**) [25], antifungal (**J**) [26], anticancer (**K**, **L**) [27, 28], and compound **M**, which combines the structural fragments of benzo[4,5]imidazo[1,2-*a*]pyridine and chromeno[2,3-*b*]pyridine, is a potential SARS-CoV 2 inhibitor [29] (Figure 2).


H (antimalarial)

I (antiviral)

J (antifungal)

K (anticancer)

L (anticancer)

M (potential SARS-CoV-2 inhibitor)

Figure 2. Representative examples of pharmacologically active benzo[4,5]imidazo[1,2-*a*]pyridines.

In this context, we hypothesized that combining 2-(cyanomethyl)benzimidazole, a bifunctional synthon bearing both a nucleophilic methylene group and a benzimidazole nitrogen atom, with 3-trifluoroacetyl-4-phenyl-4*H*-chromene would trigger a cascade sequence yielding a structurally unprecedented hybrid scaffold.

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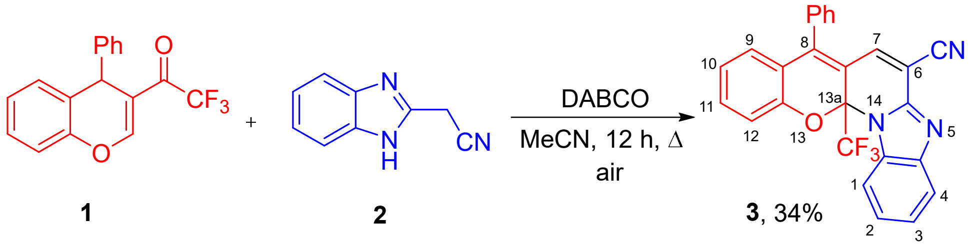
2. Results and Discussion

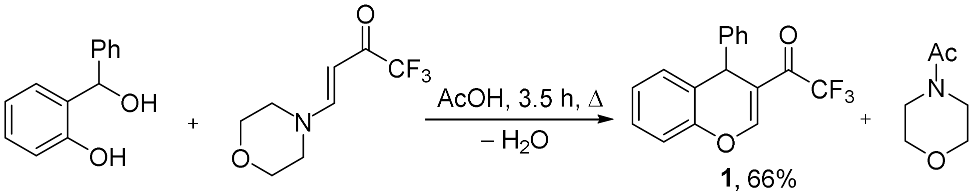
2.1. Synthesis and Spectroscopy

In continuation of our research on the chemical transformations of highly polarized 4*H*-chromenes [30, 31], we investigated the interaction of chromene **1** with 2-(cyanomethyl)benzimidazole [32]. This resulted in a complex mixture of products, from which benzo[4,5]imidazo[1,2-*a*]chromeno[3,2-*e*]pyridine **3** was isolated in pure form and identified (Scheme 1). The reaction was carried out by refluxing compounds **1** and **2** in a 1:1 ratio in acetonitrile for 12 h in the presense of DABCO (0.5 equiv). The product was isolated by column chromatography on silica gel. The moderate yield (34%) reflects the complexity of the multistep cascade involving at least five discrete transformations with potential competing pathways.



Scheme 1. Reaction of 4*H*-chromene **1** with 2-(cyanomethyl)benzimidazole **2**.

The starting chromene **1** [33], the synthesis of which has not been previously described in the literature, was obtained from 2-[hydroxy(phenyl)methyl]phenol as a precursor of *o*-quinone methide [34] and 1,1,1-trifluoro-4-morpholinobut-3-en-2-one (Scheme 2). The high degree of polarization of the double bond in the pyran ring of the chromene **1** makes it susceptible to attack by nucleophiles, ambiphilic reagents, and 1,3-dipoles. Consequently, this heterocycle could potentially serve as an excellent substrate for Michael additions and 1,3-dipolar cycloaddition reactions.



Scheme 2. Synthesis of 2,2,2-trifluoro-1-(4-phenyl-4*H*-chromen-3-yl)ethanone **1**.

The structure of the compound **3** was confirmed by a complex of spectral analysis methods. IR spectroscopy showed an absorption band at 2226 cm^{-1} characteristic of the nitrile group. The ^{1}H NMR spectrum displayed a characteristic singlet at δ 7.42 ppm assigned to H-7, along with a number of doublet and multiplet signals (δ 6.90–8.15 ppm) integrating for 13 aromatic protons consistent with the fused framework plus phenyl substituent. Notably, the absence of aliphatic proton signals confirmed the presence of 2*H*-chromene fragment. The presence of a trifluoromethyl group was detected by the characteristic quartet signal at 123.8 ppm with $^1J_{CF}$ = 298.1 Hz in the ^{13}C NMR spectrum, as well as by the signal of the carbon atom bonded with it in the region of 84.6 ppm with $^2J_{CF}$ = 31.6 Hz. In the DEPT spectra, the number of carbon atoms directly bonded to protons is consistent with the considered structure.

In addition, the structure of the compound **3** was confirmed by X-ray diffraction data (Figure 3). The molecular structure reveals a nearly planar fused pentacyclic core comprising chromene, benzimidazole, and dihydropyridine rings, indicating extensive π-conjugation. Subtle puckering occurs at the sp^3-hybridized bridgehead carbon C-13a (C-2 in CIF numbering) connected with the trifluoromethyl group. The phenyl ring at C-8 (C-18 in CIF numbering) is nearly perpendicular to the fused ring system (dihedral angles C32–C31–C18–C17 = –86.36° and C36–C31–C18–C19 = –86.68°), which minimizes steric repulsion with the H-16 and H-20 hydrogen atoms while completely

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disrupting π-conjugation. The trifluoromethyl group adopts a pseudo-axial orientation relative to the heterocyclic framework and F–C–F angles averaging 107.3°, consistent with tetrahedral geometry. The nitrile group is essentially coplanar with the dihydropyridine ring, enabling effective π-conjugation extension.

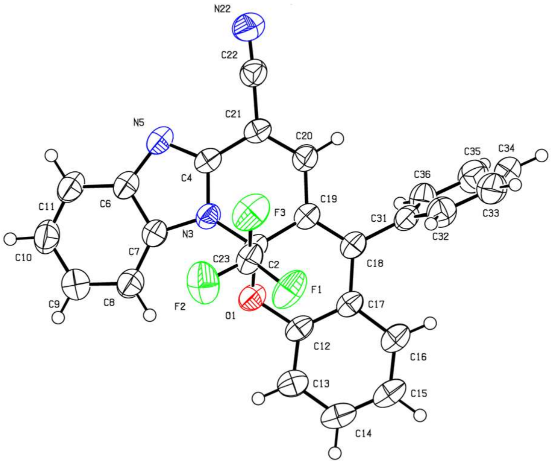
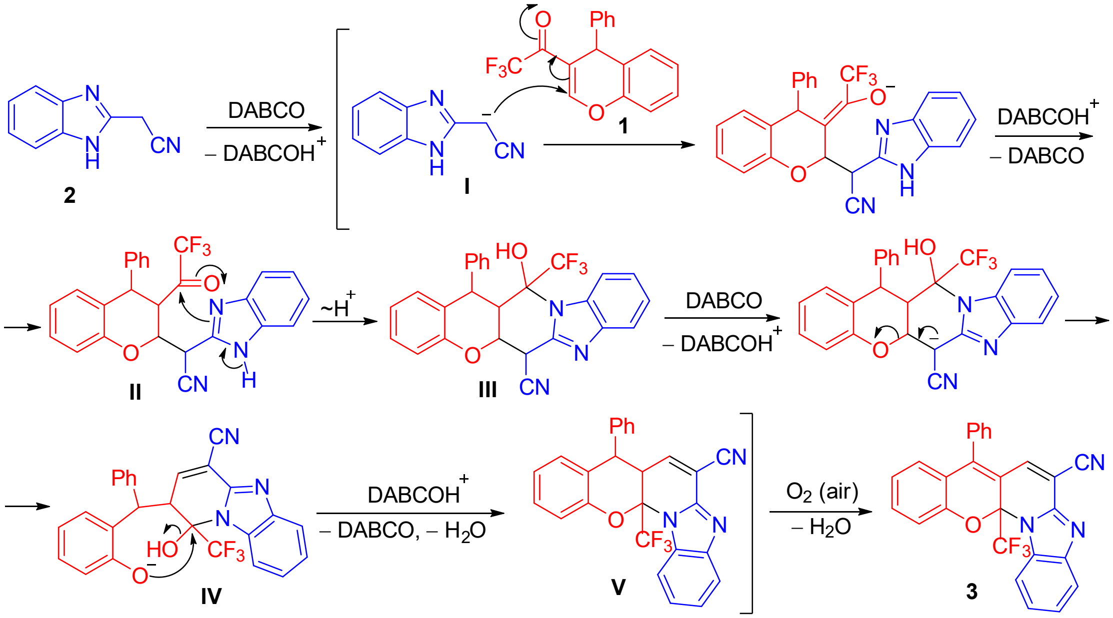


Figure 3. Molecular structure of compound **3** shown with thermal ellipsoids of atomic displacement parameters at the 50% probability level.

2.2. Proposed Mechanism

A plausible mechanism (Scheme 3) involves initial reversible deprotonation of the acidic methylene group in 2-(cyanomethyl)benzimidazole by DABCO, generating a stabilized carbanion **I**. This nucleophile undergoes regioselective Michael addition to the β-carbon (C-2) of the enone system in chromene **1**, forming adduct **II**. Intramolecular nucleophilic attack of the benzimidazole nitrogen atom on the electrophilic carbonyl carbon atom of the trifluoroacetyl group then yields hemiaminal intermediate **III**. Subsequent ring opening of the dihydropyran moiety *via* C–O bond cleavage generates open-chain species **IV**, which undergoes recyclization through attack of the phenoxide oxygen on the hemiaminal carbon atom to form cyclic N,O-acetal **V**. Finally, air-mediated oxidation of the dihydropyran ring affords the conjugated pentacyclic product **3**.



Scheme 3. Proposed mechanism for the DABCO-mediated cascade reaction.

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The resulting benzo[4,5]imidazo[1,2-*a*]chromeno[3,2-*e*]pyridine scaffold represents a structurally novel architecture merging benzimidazole, pyridine, and chromene units and decorated with a bridgehead trifluoromethyl substituent, and a nitrile functionality. The nitrile group offers versatile handles for further derivatization (e.g., hydrolysis to carboxylic acid, reduction to amine, or participation in click chemistry). The presence of both strong electron-withdrawing groups (CF_3 and CN) combined with extended π-conjugation creates a polarized electronic structure potentially favorable for interactions with biological targets containing complementary electrostatic features.

3. Materials and Methods

All synthetic manipulations were performed in air. All reagents and solvents were purchased from commercial vendors and used as received. ^{1}H and ^{13}C (proton-decoupled) NMR spectra (at 400 and 100 MHz, respectively), as well as DEPT-135 spectra, were registered on a JEOL JNM-ECX400 spectrometer (Japan) in DMSO-d_6 or $CDCl_3$. Chemical shifts were referenced internally to the residual solvent signal (DMSO-d_6: 2.50 ppm for ^{1}H nuclei, 39.5 ppm for ^{13}C nuclei; $CDCl_3$: 7.26 ppm for ^{1}H nuclei, 77.2 ppm for ^{13}C nuclei). IR spectra were registered on a Shimadzu IRAffinity-1 spectrometer (Japan) equipped with a Specac Diamond ATR GS10800-B accessory. Elemental analysis was performed on an automated Euro Vector EA-3000 CHNS analyzer (Italy) using L-cystine as a standard. Melting points were determined by the capillary method on an SRS OptiMelt MPA100 instrument (USA). Reaction progress and purity of the obtained compounds were monitored by TLC on Merck Silica gel 60 F_{254} plates (eluent – CH_2Cl_2).

*3.1. Synthesis and Characterization of 2,2,2-Trifluoro-1-(4-phenyl-4H-chromen-3-yl)ethanone (**1**)*

A mixture of 2-[hydroxy(phenyl)methyl]phenol (0.60 g, 3 mmol) and 1,1,1-trifluoro-4-morpholinobut-3-en-2-one (0.63 g, 3 mmol) in acetic acid (15 mL) was heated under reflux for 3.5 h, diluted with 15 mL of methanol and kept at –30 °C for 24 h. The precipitated solid was filtered off and purified by recrystallization from ethanol to afford **1** (0.60 g, 66%).

Colorless crystals, mp 98–100 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ, ppm: 8.02 (s, 1H), 7.27–7.06 (m, 9H), 5.06 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ, ppm: 178.6 (q, $^{2}J_{CF}$ = 35.3 Hz, C), 155.9 (q, $^{4}J_{CF}$ = 5.7 Hz, CH), 148.4 (C), 144.6 (C), 130.2 (CH), 128.8 (2CH), 128.3 (CH), 128.0 (2CH), 127.2 (CH), 126.3 (CH), 123.8 (C), 116.9 (CH), 116.5 (q, $^{1}J_{CF}$ = 289.9 Hz, C), 114.7 (C), 38.5 (CH). FTIR, ν_{max}: 1688, 1630, 1576, 1485, 1454, 1321, 1225, 1175, 1136, 1103, 1032, 964, 907, 756, 735, 696 cm^{-1}. Calc. for $C_{17}H_{11}F_3O_2$: C 67.11, H 3.64. Found: C 67.19, H 3.59.

*3.2. Synthesis and Characterization of 8-Phenyl-13a-(trifluoromethyl)-13aH-benzo[4,5]imidazo[1,2-a]chromeno[3,2-e]pyridine-6-carbonitrile (**3**)*

A mixture of 2,2,2-trifluoro-1-(4-phenyl-4*H*-chromen-3-yl)ethanone **1** (0.30 g, 1 mmol), 2-(cyanomethyl)benzimidazole **2** (0.16 g, 1 mmol) and DABCO (55 mg, 0.5 mmol) in acetonitrile (5 mL) was refluxed for 12 h, cooled to –30 °C and kept overnight. The precipitated solid was collected by filtration, purified by silica gel column chromatography (eluent – CH_2Cl_2) and recrystallized from methanol to afford **3** (0.15 g, 34%).

Orange crystals, mp 240–241 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ, ppm: 8.15 (d, *J* = 8.0 Hz, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.67–7.45 (m, 7H), 7.42 (s, 1H), 7.41–7.37 (m, 1H), 7.31–7.26 (m, 1H), 7.17–7.12 (m, 1H), 6.90 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ, ppm: 149.8 (C), 148.4 (C), 143.93 (C), 143.87 (C), 139.5 (CH), 135.0 (CH), 133.8 (C), 132.5 (C), 130.4 (CH), 130.2 (br. signal, CH), 129.7 (br. signal, 3CH), 129.4 (CH), 126.4 (CH), 125.1 (CH), 124.9 (CH), 123.8 (q, $^{1}J_{CF}$ = 298.1 Hz, C), 121.4 (C), 121.2 (CH), 116.9 (CH), 114.9 (CH, C), 114.6 (C), 102.1 (C), 84.6 (q, $^{2}J_{CF}$ = 31.6 Hz, C). FTIR, ν_{max}: 3061, 2226, 1589, 1564, 1443, 1418, 1339, 1254, 1204, 1180, 1134, 1094, 1007, 939, 889, 764, 750, 737, 702 cm^{-1}. Calc. for $C_{26}H_{14}F_3N_3O$: C 70.75; H 3.20; N 9.52. Found: C 70.69; H 3.17; N 9.46.

3.3. X-Ray Crystallography

X-ray structural analysis of the compound **3** was carried out on a Stoe STADI VARI diffractometer equipped with a Pilatus100K detector using Cu Kα radiation (λ = 1.5418 Å) at 295(2) K. Crystals suitable for X-ray diffraction were grown from ethanol by the slow evaporation of the

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solvent at room temperature. Data collection, as well as determination and refinement of unit-cell parameters, were performed using the CrysAlisPro software package [35]. The structure was solved and refined using the SHELX97 program package [36]. Molecular graphics and preparation of the manuscript were performed with the OLEX2 software package [37].

Selected crystallographic data: $C_{26}H_{14}F_{3}N_{3}O$, $M = 441.40$, monoclinic, $a = 9.2933(2)$, $b = 14.3417(4)$, $c = 15.1408(5)$ Å, $\alpha = 90°$, $\beta = 91.442(2)°$, $\gamma = 90°$, $V = 2017.35(10)$ Å^3, $T = 295$ K, space group $P2_1/n$, $Z = 4$, $d_{calc} = 1.453$ g/cm^3. An orange prismatic single crystal with dimensions of 0.200 × 0.200 × 0.200 mm was selected for data collection. A total of 21351 reflections were measured in the range $4.25° \leq \theta \leq 72.89°$, yielding 3991 independent reflections ($R_{\text{int}} = 0.0513$). Final refinement based on $I > 2\sigma(I)$ gave $R_1 = 0.0382$ and $wR_2 = 0.0770$ for 298 refined parameters, $S = 1.021$. Hydrogen atoms were placed geometrically and refined using the riding model. CCDC 1939479 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/structures.

4. Conclusions

In this work, we described the preparation of π-extended pentacyclic heterocyclic system, 8-phenyl-13a-(trifluoromethyl)-13a*H*-benzo[4,5]imidazo[1,2-*a*]chromeno[3,2-*e*]pyridine-6-carbonitrile. Structural elucidation by NMR spectroscopy and X-ray diffraction revealed a unique fused framework with N,O-acetal fragment.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org, Figure S1: ^{1}H NMR spectrum of **1**; Figure S2: ^{13}C NMR spectrum of **1;** Figure S3: DEPT-135 spectrum of **1**; Figure S4: ^{1}H NMR spectrum of **3**; Figure S5: ^{13}C NMR spectrum of **3;** Figure S6: DEPT-135 spectrum of **3**.

Author Contributions: D.V.O.—funding acquisition, supervision, writing (original draft, review and editing); P.E.K.—investigation, data analysis; V.A.O.—conceptualization, supervision, data analysis. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the Russian Science Foundation No. 25-23-00682, https: //rscf.ru/project/25-23-00682/.

Data Availability Statement: Data are contained within the article and Supplementary Materials.

Acknowledgments: This work was performed using the equipment of the Center for Collective Use «Investigation of Physicochemical Properties of Substances and Materials» of the Samara State Technical University.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

NMR	Nuclear Magnetic Resonance
DEPT	Distortionless Enhancement by Polarization Transfer
DABCO	1,4-Diazabicyclo[2.2.2]octane

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