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Crystal structure and identification of a pyrimido[6,1-*b*][1,3]oxazin-6-one derivative from the reaction of acrolein with 5-(phenoxymethyl)-2-amino-2-oxazoline

*Structure cristalline et identification d'un dérivé de la pyrimido[6,1-*b*][1,3]oxazin-6-one par réaction de l'acroléine avec la 5-(phénoxyméthyl)-2-amino-2-oxazoline*

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ABSTRACT

The X-ray crystal structure of 2-(4,5-dihydro-5-phenoxymethyl-1,3-oxazol-2-ylamino)-7-(2-hydroxy-3-phenoxypropyl)hexahydro-2*H*,6*H*-pyrimido[6,1-*b*][1,3]oxazin-6-one (**1**), a structure of adduct formed by the reaction of 5-(phenoxymethyl)-2-amino-2-oxazoline and acrolein, has been established. The present work deals with the structural identification of the adduct **1** and presents a plausible mechanism for its formation. It crystallizes in the monoclinic space group $P2_1/c$ with cell parameters $a = 21.3337\ (10)$ Å, $b = 11.3712\ (7)$ Å, $c = 10.4936\ (7)$ Å, $\beta = 103.041\ (3)$, $V = 2480.0\ (3)$ Å^3, $Z = 4$. $C_{26}H_{32}N_4O_6$, $D_c = 1.330$ g/cm^3, μ (Cu Kα) = 1.5418 Å, $S = 1.188$, $F\ (000) = 1056$, $R = 0.0501$, and $wR = 0.1584$.

Mots-clés:
Pyrimido[6,1-*b*][1,3]oxazin-6-one
2-Amino-2-oxazoline
Réaction de Michael
Structure cristalline déterminée aux rayons X

RESUME

La structure complète de la 2-(4,5-dihydro-5-phénoxymethyl-1,3-oxazol-2-ylamino)-7-(2-hydroxy-3-phénoxypropyl)hexahydro-2*H*,6*H*-pyrimido[6,1-*b*][1,3]oxazin-6-one **1**, une structure d'adduit formée lors de la réaction de la 5-(phénoxyméthyl)-2-amino-2-oxazoline et de l'acroléine, a été établie sans équivoque par une analyse cristallographique aux rayons X. Le présent travail porte sur l'identification structurale de l'adduit **1** et présente un mécanisme plausible pour sa formation. La molécule cristallise dans le système monoclinique, dans le groupe spatial $P2_1/c$ avec $a = 21.3337\ (10)$ Å, $b = 11.3712\ (7)$ Å,

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$c = 10.4936\,(7)$ Å, $\beta = 103.041\,(3)$, $V = 2480.0\,(3)$ Å^3, $Z = 4$. $C_{26}H_{32}N_4O_6$, $D_c = 1.330$ g/cm^3, μ (Cu Kα) = 1.5418 Å, $S = 1.188$, $F(000) = 1056$, $R = 0.0501$ et $wR = 0.1584$.

1. Introduction

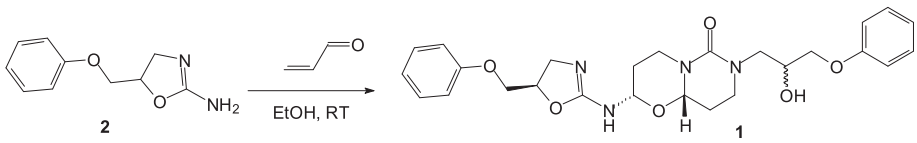
For the past few decades, we have focused our attention on the (bio)chemistry and reactivity of 2-amino-2-oxazolines developed either as synthons or potential bioactive heterocyclic derivatives. We have previously described the design and synthesis of biologically active derivatives based on the reactivity of the amidine group of 2-amino-2-oxazolines with various bis-electrophiles [1–4]. As with other amidines, the 2-amino-2-oxazoline moiety possesses two competing sites for potential ring annulation, leading to regioselectivity considerations. An empirical observation has emerged from our previous investigations, which indicates that, in such reactions, the endocyclic nitrogen is considered generally as the most nucleophilic and attacks the most electrophilic carbon of the bis-electrophile. A ring closure between the exocyclic nitrogen and the second electrophilic function generally concludes the synthesis [5,6].

As a continuation of our research for pharmaceutical tools, we herein report the structural characterization of the 2-(4,5-dihydro-5-phenoxymethyl-1,3-oxazol-2-ylamino)-7-(2-hydroxy-3-phenoxypropyl)hexahydro-2*H*,6*H*-pyrimido[6,1-*b*][1,3]oxazin-6-one (**1**), a serendipity structure of an adduct formed by a reaction of 5-(phenoxymethyl)-2-amino-2-oxazoline (**2**) with acrolein (Scheme 1). Pyrimido[6,1-*b*][1,3]oxazine derivatives are heterocyclic building blocks showing potential biological utilities, such as anti-human immunodeficiency virus (HIV), antibacterial, antifungal, antiamoebic, and anthelmintic properties [7–9].

2. Results and discussion

As a part of our research program on crystal structure analysis, the three-dimensional structure of this pyrimido[6,1-*b*][1,3]oxazin-6-one **1** has been achieved. Hence, after crystallization in a mixture of chloroform and methanol (4/1 v/v) at room temperature, the 2-(4,5-dihydro-5-phenoxymethyl-1,3-oxazol-2-ylamino)-7-(2-hydroxy-3-phenoxypropyl)hexahydro-2*H*,6*H*-pyrimido[6,1-*b*][1,3]oxazin-6-one (**1**) was surprisingly isolated as colorless needles. Title derivative was then submitted to spectroscopic analysis to confirm its molecular structure. The structure of **1** is depicted in Fig. 1. The proposed mechanism to access pyrimido[6,1-*b*][1,3]oxazin-6-one **1** is described in Scheme 2. Thus, the reaction proceeds via adduct formation first at the endocyclic nitrogen of 2-amino-2-oxazoline **1** [10,11] via a Michael reaction leading to intermediate **I**, and subsequently a ring closure takes place at the carbonyl carbon by the exocyclic nitrogen atom of **I** to form the ring-fused monoadduct **II** through a Dimroth-like rearrangement (Scheme 2). This first Michael addition is then followed by a second Michael reaction of acrolein at the exocyclic nitrogen atom of the oxazolopyrimidine **II** to give the intermediate **III**, which is then probably hydrolyzed into the pyrimidine **IV** in equilibrium with its tautomeric form **V**. We have previously described such hydrolysis in the opening of the oxazoline ring [4]. Condensation of the amino function of a second molecule of 2-amino-2-oxazoline **2** with the carbonyl of **V** led to the formation of the imine intermediate **VI**. Compound **1** is finally obtained through a second cyclization by addition of the hydroxyl of the initially formed ring onto the imine group of **VI** to complete the reaction sequence. Similar reactivity of a hydroxyl function has been previously described by a reaction of acrolein with adenosine/cytidine and adenine/cytosine, leading to the formation of diastereoisomers of the adducts, made up from two fused rings [12,13]. According to the X-ray data, compound **1** appears only as a mixture of 2*S**-(4,5-dihydro-5*R**-phenoxymethyl-1,3-oxazol-2-ylamino)-7-(2*S**-hydroxy-3-phenoxypropyl)hexahydro-2*H*,6*H*-(9a*S**)-pyrimido[6,1-*b*][1,3]oxazin-6-one and 2*S**-(4,5-dihydro-5*R**-phenoxymethyl-1,3-oxazol-2-ylamino)-7-(2*R**-hydroxy-3-phenoxypropyl)hexahydro-2*H*,6*H*-(9a*S**)-pyrimido[6,1-*b*][1,3]oxazin-6-one diastereoisomers and their respective enantiomers. Both diastereoisomers correspond, respectively, to the *SRSS* and *SRRS* absolute configurations in the order of the nomenclature or the corresponding *RSRR* or *RSSR* enantiomers. The only difference between the two stereoisomers is found for the hydroxyl function at position 2 of the 7-propyl side chain. From these crystallographic data, the diastereomers were formed in unequal amounts, that is, 75% and 25%, respectively, but they could not be separated (see Fig. 2).

Title compound **1** crystallized at 183 K in the monoclinic system, space group $P2_1/c$ with the unit cell parameters: a = 21.3337 (10) Å, b = 11.3712 (7) Å, c = 10.4936 (7) Å, β = 103.041 (3), and V = 2480.0 (3) Å^3. Each asymmetric unit is constituted of one molecule corresponding to the formula $C_{26}H_{32}N_4O_6$ with four molecules



Scheme 1. Synthesis of 2-(4,5-dihydro-5-phenoxymethyl-1,3-oxazol-2-ylamino)-7-(2-hydroxy-3-phenoxypropyl)hexahydro-2*H*,6*H*-pyrimido[6,1-*b*][1,3]oxazin-6-one (**1**).

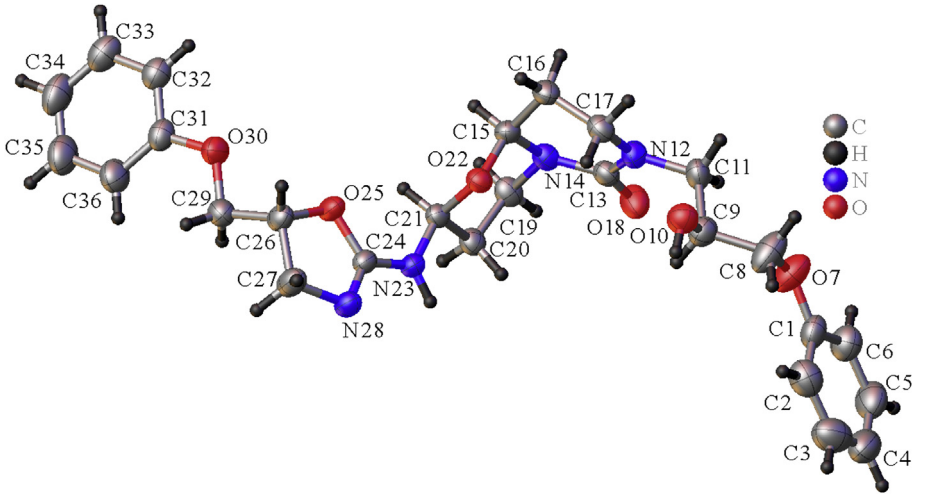


Fig. 1. View of the asymmetric unit of **1**, with the labeling scheme. The thermal ellipsoids are represented at 50% probability. The disordered OH group on C9 is not represented for clarity, and only the major diastereoisomer is represented here.

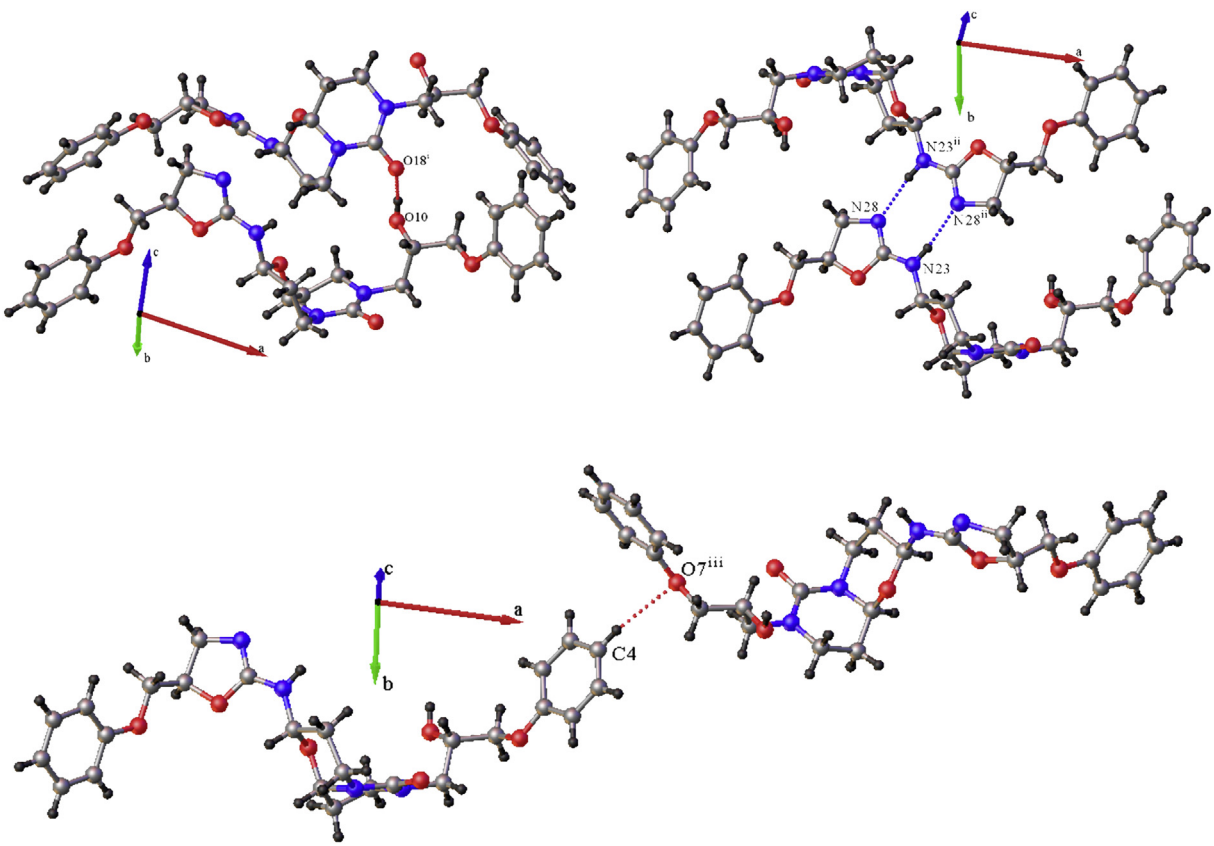
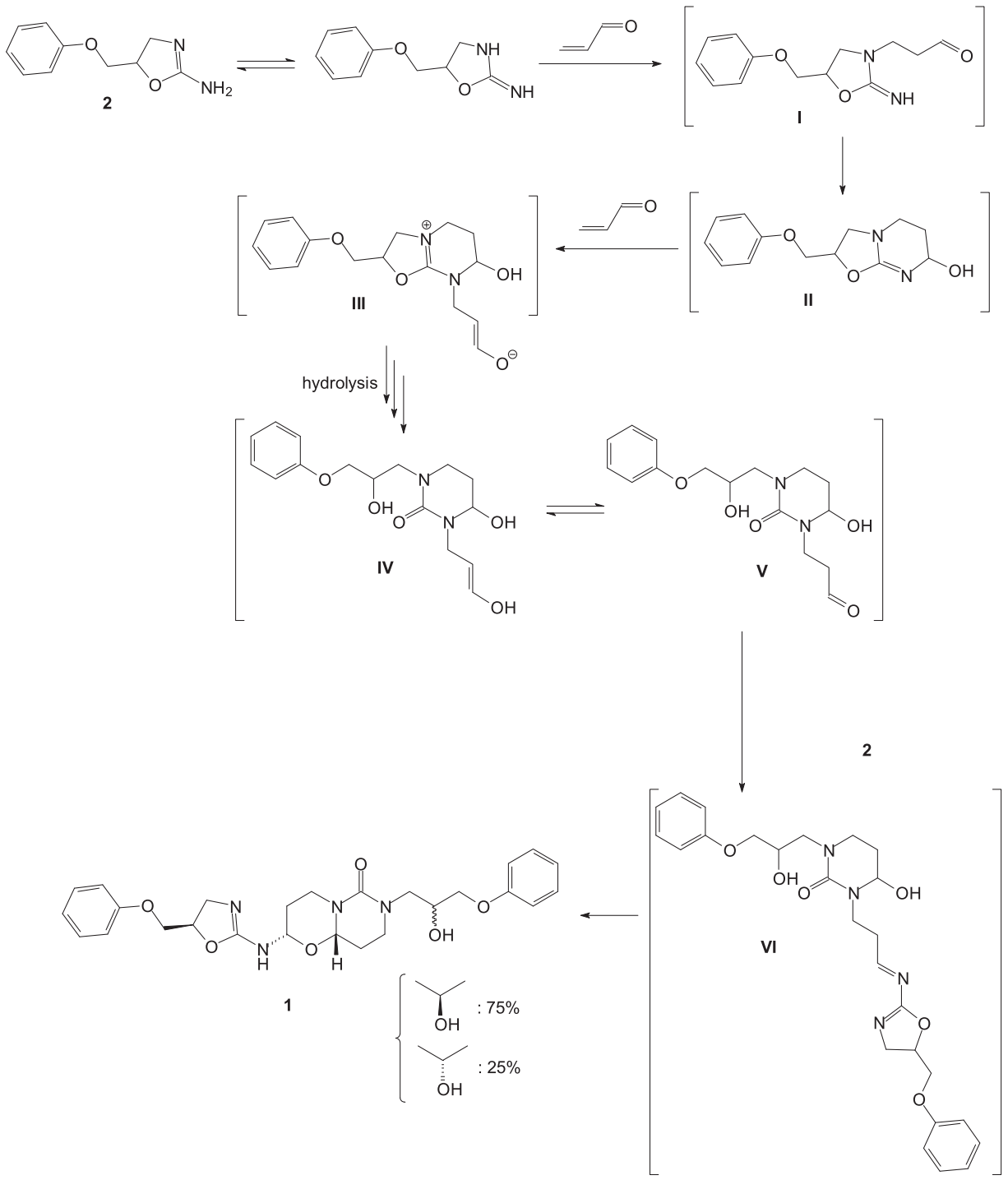


Fig. 2. View of the principal intermolecular interactions in the crystal of pyrimido[6,1-*b*][1,3]oxazin-6-one **1** that ensure the crystal cohesion in (a) the *c* direction, (b) the *b* direction, and (c) the *a* direction. Symmetry codes: (i) *x*, ½ − *y*, ½ + *z*; (ii) −*x*, −*y*, 1 − *z*; (iii) 1 − *x*, −½ + *y*; 3/2 − *z*.

in the unit cell ($Z = 4$) leading to a calculated density (D_c) of 1.330 g/cm^3. The molecular structure of pyrimido[6,1-*b*] hydroxy-3-phenoxypropyl[1,3]oxazin-6-one **1** is depicted in Fig. 1.

The double bond C13═O18 of the urea group is found at 1.242(2) Å, whereas the two C–N bonds (C13–N14 = 1.379 (2) Å and C13–N12 = 1.356 (2) Å) of this same function were in agreement with the C(sp^2)–N distance [14]. The



Scheme 2. Hypothetical mechanism for the formation of 2-(4,5-dihydro-5-phenoxymethyl-1,3-oxazol-2-ylamino)-7-(2-hydroxy-3-phenoxypropyl)hexahydro-2*H*,6*H*-pyrimido[6,1-*b*][1,3]oxazin-6-one (**1**).

C_{sp^3}–O bonds (C15–O22 and C21–O22) of the oxazine ring were noticed at 1.434 (2) and 1.456 (2) Å, respectively, whereas the other C_{sp^3}–O bonds (C8–O7, C29–O30, C9–O10, C9–O10′, and C26–O25) range from 1.425 (2) to 1.516 (6) Å. The intracyclic double bond C24–N28 of the oxazoline is measured at 1.282 (2) Å, slightly smaller than those observed for C(sp^2)=N double bonds [14]. In addition, the C24–N23 bond of this amidine function is found at 1.349 (2) Å due to the delocalization of the double bond in the amidine moiety of 2-amino-2-oxazoline. The C–C bond lengths in the two phenyl rings lie in the range 1.361 (4)–1.391 (4) Å.

Table 1
Selected bond lengths (Å) and angles (°).

Bond lengths			
O(7)–C(8)	1.429 (3)	C(15)–O(22)	1.434 (2)
C(9)–O(10)	1.434 (3)	C(21)–O(22)	1.456 (2)
C(9)–O(10′)	1.516 (6)	N(23)–C(24)	1.349 (2)
N(12)–C(13)	1.356 (2)	C(24)–N(28)	1.282 (2)
C(13)–O(18)	1.242 (2)	O(25)–C(26)	1.461 (2)
C(13)–N(14)	1.379 (2)	C(29)–O(30)	1.425 (2)
Bond angles			
O(22)–C(21)–C(20)–C(19)	−51.55 (18)	C(1)–O(7)–C(8)	119.7 (2)
O(22)–C(15)–N(14)–C(19)	62.96 (18)	C(31)–O(30)–C(29)	117.22 (15)

Table 2
Hydrogen bonds for **1**.

D–H···A	*d*(D–H) (Å)	*d*(H–A) (Å)	*d*(D–A) (Å)	D–H–A (°)
O10–H10···O18^{i}	0.84	1.937	2.714 (3)	153.3
O10′–H10′···O18^{i}	0.83	2.069	2.748 (4)	139.2
N23–H23···N28^{ii}	0.88	2.064	2.931 (3)	168.1
C4–H4···O7^{iii}	0.95	2.583	3.514 (3)	166.5

Symmetry codes: (i) $x, ½ - y, ½ + z$; (ii) $-x, -y, 1 - z$; (iii) $1 - x, -½ + y; 3/2 - z$.

Compound **1** adopts a half-chair conformation for the pyrimidine ring while oxazine ring is a chair conformation. The torsion angles of this oxazine moiety O22–C21–C20–C19 and O22–C15–N14–C19 are −51.55 (18)° and 62.96 (18)°, respectively. In addition, the C1–O7–C8 and C31–O30–C29 of the phenoxy side chains are found at 119.7 (2)° and 117.22 (15)° (see Table 1).

The crystal-structure cohesion is essentially ensured by intermolecular hydrogen bond between the OH group on C9 and the oxygen O18 from the carbonyl function propagating in the direction *c*, and between one amino and one imine group (N23 and N28, respectively) leading to a cyclic double hydrogen bond propagating in the *b* direction (Table 2). It is worth noting that both diastereoisomers, which correspond to two different conformations of the OH group on C9, lead nevertheless to a very similar H-bond between the hydroxyl and the carbonyl functions. This can explain why both diastereoisomers can accommodate in the same crystal lattice. The slightly weaker H-bond obtained for the *SRRS* diastereoisomer may explain why its proportion is smaller in the crystal leading to the 75/25 M ratio for the *SRSS* and *SRRS* diastereoisomers, respectively (Table 2). A weaker hydrogen-like interaction between an aromatic C–H of the phenyl group (C4–H4) with the oxygen O7 of another symmetrical equivalent O-phenyl group ensures the crystal cohesion in the *c* direction.

3. Experimental section

3.1. Preparation

The title compound **1** was prepared in moderate yield (55%) by a direct reaction of 1 equiv of 5-(phenoxymethyl)-2-amino-2-oxazoline **2** with 1 equiv of acrolein in ethanol at room temperature for 2 days. The precipitate formed during the reaction was then filtered and suitable crystals for X-ray diffraction analysis were obtained from a chloroform–methanol (4:1 v/v) solution by slow evaporation of the solvent at +20 °C.

Table 3
Crystallographic data and structure refinement details.

CCDC deposit number	891807
Chemical formula	$C_{26}H_{32}N_4O_6$
Formula weight	496.56
Temperature (K)	183 (2)
Wavelength (Å)	1.54180
Crystal size (mm)	0.20 × 0.20 × 0.15
Crystal system	Monoclinic
Space group	$P2_1/c$
a (Å)	21.3337 (10)
b (Å)	11.3712 (7)
c (Å)	10.4936 (7)
α (°)	90.00
β (°)	103.041 (3)
γ (°)	90.00
V (Å^3)	2480.0 (3)
Z	4
D_c (g/cm^3)	1.330
F (000)	1056
Absorption coefficient (mm^{-1})	0.786
2θ range (°)	4.26–144.62
Index ranges	$-26 \le h \le 26$; $-13 \le k \le 13$; $-12 \le l \le 12$
Reflection collected	32,457
Independent reflections	4802 [$R_{int} = 0.0428$]
Data/restraints/parameters	4802/2/335
Goodness-of-fit on F^2	1.189
R, *wR* indices [$I > 2\sigma(I)$]	0.0501, 0.1584
R, *wR* indices (all data)	0.0569, 0.1878
Largest differential peak and hole (eÅ^{-3})	0.24, −0.30

3.2. X-ray crystallography

A single crystal of the title compound with dimensions 0.20 × 0.20 × 0.15 mm^3 was chosen for X-ray diffraction study. The data were collected using a Rigaku *R*-axis rapid diffractometer equipped with micro-focus rotating anode Cu Kα radiation (λ = 1.5418 Å) mode at 183 (2) K. In the range of 2.13° < θ <72.31°, a total of 32,457 reflections were collected, of which 4802 were independent ($R_{int} = 0.0501$) and 4497 were observed with $I > 2\sigma(I)$. The crystal structure was solved by direct methods and successive Fourier difference syntheses with the SHELXS program [15]. Refinement of the crystal structure was performed on F^2 by weighted anisotropic full-matrix least-squares methods using the SHELXL program [15]. An absorption correction was performed by semiempirical methods using the SADABS program [15]. All

parts of the program were used within the OLEX2 package [16]. All non-H atoms were refined anisotropically, and the positions of the H atoms were deduced from the coordinates of the non-H atoms to which they are linked, confirmed by Fourier synthesis and treated according to the riding model during refinement. H atoms were included for structure factor calculations, but not refined. The final full-matrix least-squares refinement gave $R = 0.0501$ and $wR = 0.1584$ for 4497 reflections with $I > 2\sigma(I)$. The maximum and minimum difference peaks and holes were 0.239 and -0.302 eÅ^{-3}, respectively. $S = 1.188$ and $(\Delta/\sigma)_{max} = 0.000$. The crystal data and refinement details are listed in Table 3.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.crci.2018.09.013.

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