Visible light promoted [3+2]-cycloaddition in the synthesis of cyclopenta[b]chromenocarbonitrile derivatives

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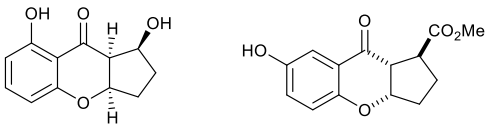
In the manuscript, a novel method for the preparation of cyclopenta[*b*]chromenocarbonitrile derivatives *via* [3+2] cycloaddition reaction of substituted 3-cyanochromones and *N*-cyclopropyloamines initiated by visible light catalysis in the presence of Eosin Y as a photocatalyst has been described. The key parameters responsible for the success of the described strategy are: visible light, small amount of photoredox catalyst, anhydrous solvent and inert atmosphere.

Cyclopentachromene is a common structural motif present in many natural products. Selected examples of bioactive derivatives, relevant for the life-science industry, are shown in the Scheme 1. For instance, the natural product Diaportheone B was isolated from the endophytic fungus *Diaporthe sp.* P133 and possess antituberculosis activity against the virulent strain of *Mycobacterium tuberculosis*.[1] Applanatumol Y was isolated by Cheng in 2016 from the fruiting body of *Ganoderma applanatum* it is wood-decaying fungi.[2] Total synthesis of this compound was performed by Ito using a Morita−Baylis−Hillman reaction as a key step.[2b] Cyclopentane structural motif constitutes relevant building block widely employed in target-oriented synthesis and presented in many bioactive natural products and pharmaceuticals, including the peramivir,[3] prostaglandins,[4] Jatrophanes,[5] and pactamycin.[6]

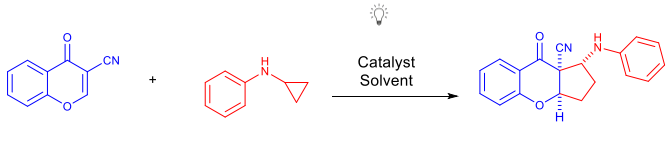


Diaportheone B Applanatumol Y

Scheme 1. Biologically relevant cyclopentane derivatives.

[3+2]-Cycloaddition reactions are a very useful tool for the synthesis of functionalized five-membered carbocycles or heterocycles.[7] 1,3-Dipolar cycloaddition involving ionic intermediates constitutes the most popular example. Recently, new approach to [3+2]-cycloadditions involving radical intermediates has been introduced.[8]

Visible-light-induced radical functionalization of organic compounds has emerged as a powerful method for the construction of C–C bonds.[9] In continuation of our interest in the development of photocatalytic reactions,[10] we turned our attention to the application of 3-cyanochromones and *N*-cyclopropyloamines as convenient staring materials for the synthesis of interesting from medicinal point of view cyclopenta[*b*]chromenocarbonitrile products (Scheme 2).

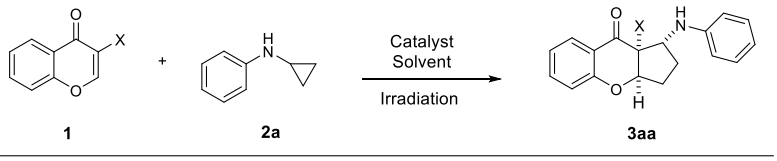


1 2 3

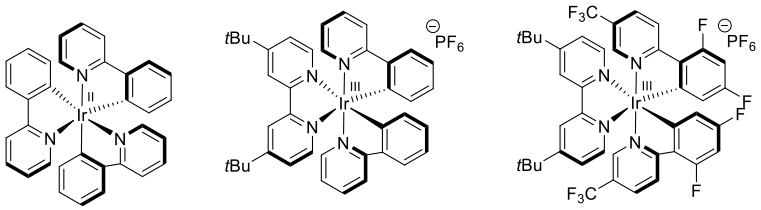
Scheme 2. Objectives of our study.

Herein we report an intermolecular [3+2]-cycloaddition of electron poor olefins with cyclopropylanilines under visible light photocatalysis. The process is initiated by the visible light leading to the formation of cyclopentan carbonitrile derivatives.

Table 1. Visible-light driven [2+3]-photocycloaddition of 3-cyanochromone **1** and *N*-cyclopropyloaniline **2a**.[a]



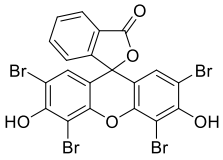
1 **2a** **3aa**



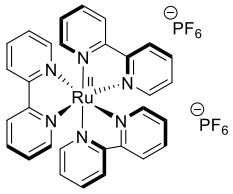
4a
fac-Ir(ppy)$_3$

4b
Ir(ppy)$_2$dtbpy

4c
Ir[dF(CF$_3$)ppy]$_2$dtbpy



4d
Eosin Y



4e
Ru(bpy$_3$)$_2$(PF$_6$)$_2$

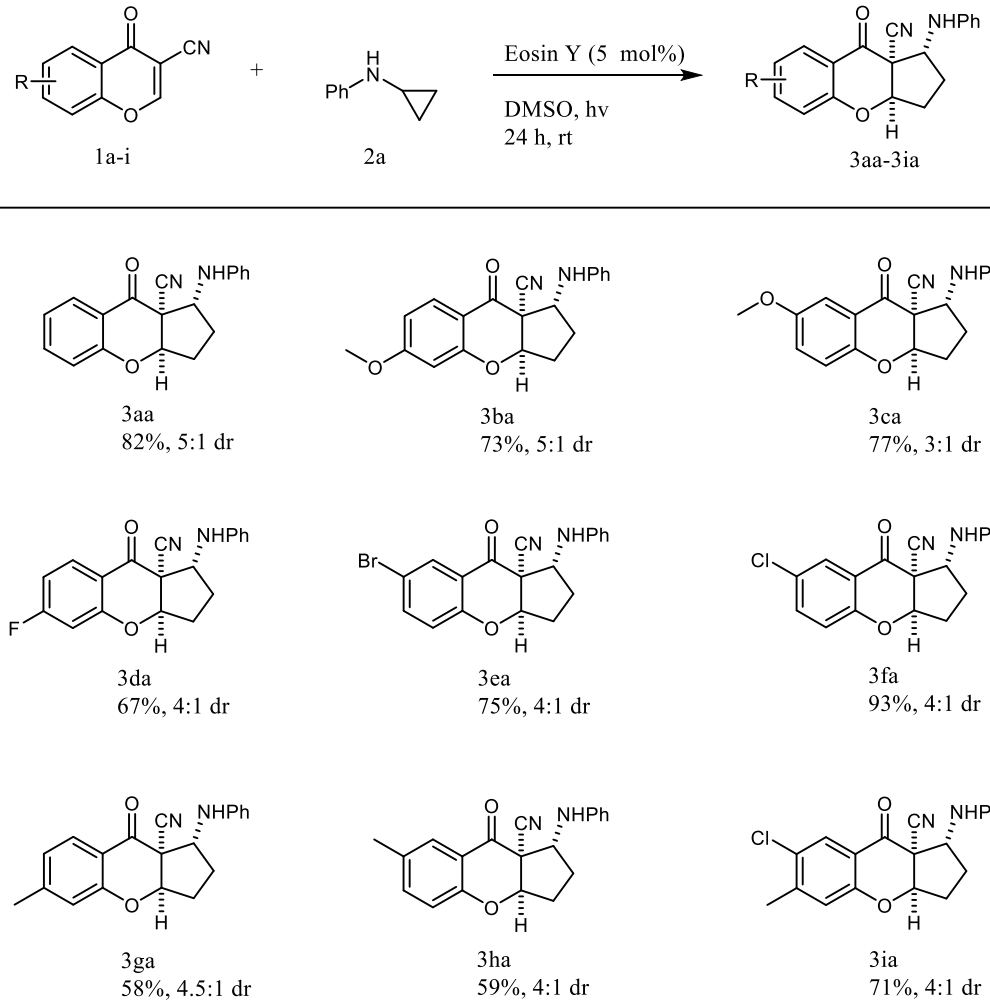
Entry	Cat./ [mol%]	Sol-vent	X	Yield [%]	dr
1[b]	**4a**/5	CH_2Cl_2	H (**5a**)	-	-
2[b]	**4a**/5	CH_2Cl_2	COOH (**5b**)	-	-
3[b]	**4a**/5	CH_2Cl_2	C(O)Me (**5c**)	-	-
4[b]	**4a**/5	CH_2Cl_2	CN (**1a**)	57	4.5:1
5[b]	**4b**/5	CH_2Cl_2	CN (**1a**)	41	5:1
6[b]	**4c**/5	CH_2Cl_2	CN (**1a**)	47	4.5:1
7[c]	**4d**/5	CH_2Cl_2	CN (**1a**)	72	4.5:1
8[b]	**4e**/5	CH_2Cl_2	CN (**1a**)	44	4.5:1
9[c]	**4d**/5	$CHCl_3$	CN (**1a**)	47	5:1
10[c]	**4d**/5	CCl_4	CN (**1a**)	-	-
11[c]	**4d**/5	MeOH	CN (**1a**)	28	5:1
12[c]	**4d**/5	MeCN	CN (**1a**)	76	4.5:1
13[c]	**4d**/5	DMSO	CN (**1a**)	82	5:1
14[c]	**4d**/10	DMSO	CN (**1a**)	78	5:1
15[c]	**4d**/3	DMSO	CN (**1a**)	74	5:1
16[c,d]	**4d**/5	DMSO	CN (**1a**)	46	4:1
17[c,e]	**4d**/5	DMSO	CN (**1a**)	72	5:1
18[c,f]	**4d**/5	DMSO	CN (**1a**)	81	5:1
19[c,g]	**4d**/5	DMSO	CN (**1a**)	75	5:1
20	-	DMSO	CN (**1a**)	-	-
21[h]	**4d**/5	DMSO	CN (**1a**)	-	-
22[c,i]	**4d**/5	DMSO	CN (**1a**)	-	-

[a] All reactions were performed in a 0.1 mmol scale using **1** (1.0 equiv.) and **2a** (2.0 equiv.) in the presence of the corresponding photoredox catalyst **4** (5 mol%) in the solvent (2 mL) for 24h. [b]Reaction performed under irradiation with the blue light. [c] Reaction performed under irradiation with the green light. [d]Reaction performed in DMSO (3 mL). [e]Reaction performed in DMSO (1 mL). [f]Reaction performed for 48h. [g]Reaction performed at a 1.0 mmol scale. [h]Reaction performed in the dark. [i]Reaction performed in the presence of TEMPO (1 equiv).

Initially, the [3+2]-photocycloaddition between chromen-4-one **5a** and *N*-cyclopropylaniline **2a** was performed in CH_2Cl_2 in the presence of *fac*-Ir(ppy)$_3$ as a photocatalyst under irradiation with blue light and an inert atmosphere (Table 1, entry 1). As expected, no reaction was observed, which indicated the crucial role of the EWG-activation of **5** in the devised methodology. As highlighted in our previous work, the incorporation of an electron-withdrawing group into the chromenone is necessary to increase its nucleophilic properties, and hence for the reaction to occur. Therefore, the activation of **5** through the introduction of various activating groups in the 3-position was attempted (Table 1, entries 2–4).

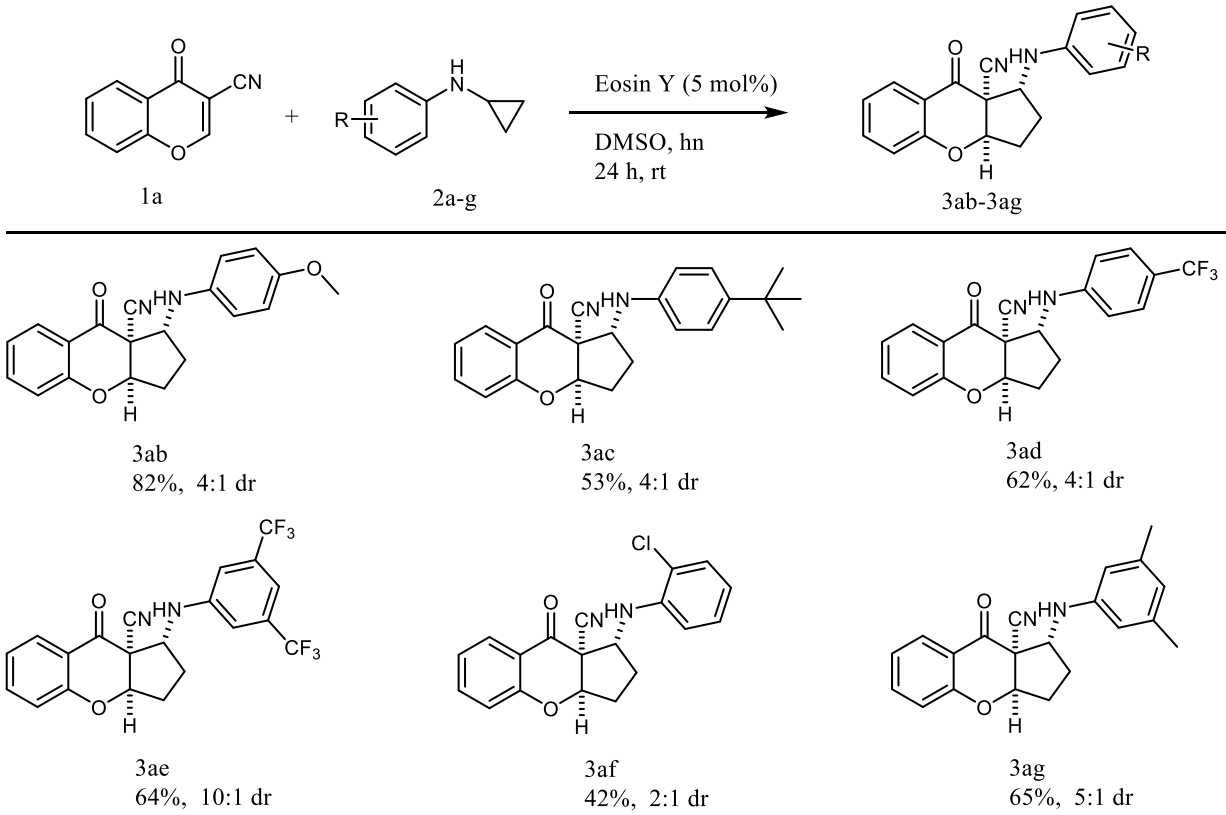
Most of the tested derivatives displayed no reactivity under these conditions, but to our delight cycloaddition between 3-cyanochromone **1a** and *N*-cyclopropylaniline **2a** resulted in the formation of the desired product (Table 1, entry 4). The corresponding cyclopenta[*b*]chromeno-carbonitrile **3aa** was obtained with 57% yield as a mixture of two diastereoisomers which differed in the configuration on the C-1 stereogenic center. Various factors such as solvent, photocatalyst and reaction concentration were tested in the course of optimization studies, while the temperature and *N*-cyclopropylaniline equivalents were held constant throughout. In the first part, the catalytic activity of five different photoredox catalysts was examined (with the irradiation with the light source of suitable wavelength) (Table 1, entries 4–8). All tested catalysts **4a-e** provided the desired reactivity with the best results obtained in the presence of Eosin Y (Table 1, entry 7). During further investigations, the effect of the solvent on the reaction outcome was evaluated (Table 1, entries 7 and 9–13). This part of the studies revealed dimethyl sulfoxide to be the best solvent, providing the target product in 82% yield and with the diastereoisomer ratio at a level of 5:1 (Table 1, entry 13). Change in the amount of catalyst negatively affected reaction efficiency (Table 1, entries 13–15). Subsequently, the effect of the reaction concentration on both the yield and diastereoselectivity was evaluated, but neither increasing, nor decreasing improved the results of the cycloaddition (Table 1, entries 13, 16 and 17). Eventually, cyclopenta[b]chromeno-carbonitrile **3aa** was formed in the presence of 5 mol% of Eosin Y in DMSO in 82% yield as a mixture of diastereoisomers in the 5:1 ratio. These results were validated on an initial scale up to 1.0 mmol providing **3aa** in 75% yield (Table 1, entry 19). A series of control experiments demonstrated that the reaction did not take place in the absence of photocatalyst or in the dark, indicating the crucial effect of photoredox catalyst and the source of light on the reaction outcome (Table 1, entries 20 and 21). Finally, the experiment in the presence of TEMPO was carried out and no reaction was observed, thus confirming the radical nature of the developed reaction (Table 1, entry 22).

With the optimized reaction conditions in hand (Table 1, entry 13), the applicability of the developed methodology with regard to both reaction partners was examined (Schemes 3 and 4). Initially, various 3-cyanochromones **1a-i** containing either electron-withdrawing or donating substituents were tested in the [3+2]-photocycloaddition with *N*-cyclopropylaniline **2a** (Scheme 3). To our delight, the reaction proceeded efficiently, and in most cases the desired products were obtained with yields in the range of 70–80%. Only for the 3-cyanochromones **1g**,**h** with a methyl substituent in the 6- and 7-position, the yield of the reaction lowered to 58% and 59%, respectively. In this context, it is worth noting that for the example with chlorine substituent on the aromatic ring of the 3-cyanochromone **1f** the cycloaddition proceeded with an excellent yield, and it was as high as 93%. Gratifyingly, the studies also indicated that the position of the substituent in 3-cyanochromone **1** had no pronounced influence on the reaction outcome, and the introduction of two substituents on the aromatic ring was also possible (Scheme 3, product **3ia**). In terms of diastereoselectivity, the cycloaddition was found to be unbiased towards the electronic properties of substituents, and it remained at a similar level to the model reaction.



Scheme 3. Photocatalytic [3+2]-cycloaddition initiated by visible light – scope of cyanochromones **2**.

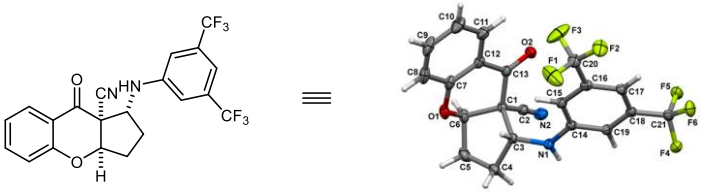
In the second part of the scope studies, the possibility of employing various *N*-arylcyclopropylamines **2a-g** in the devised strategy was tested (Scheme 4). Unfortunately, it was found that the efficiency of the cascade decreased and target products **3ab-3ag** were obtained in yields within the range of 42–82%. The lowest efficiency was obtained when *N*-cyclopropylaniline with an electron-donating chlorine substituent was applied, in addition the diastereoselectivity of the process decreased and amounted to only 2:1 dr (Scheme 4, product **3af**). In some of the cases it was required to extend the reaction time from 24 to 72 hours in order to achieve full conversion (Scheme 4, products **3ad**, **3ae**). To our delight, for the example with two trifluoromethyl groups on the aromatic ring of the *N*-cyclopropylaniline **2e** the diastereoselectivity of the cycloaddition increased to 10:1 dr. Unfortunately, for monosubstituted *N*-cyclopropylaniline **2f** the diastereomeric ratio remained at a moderate level.



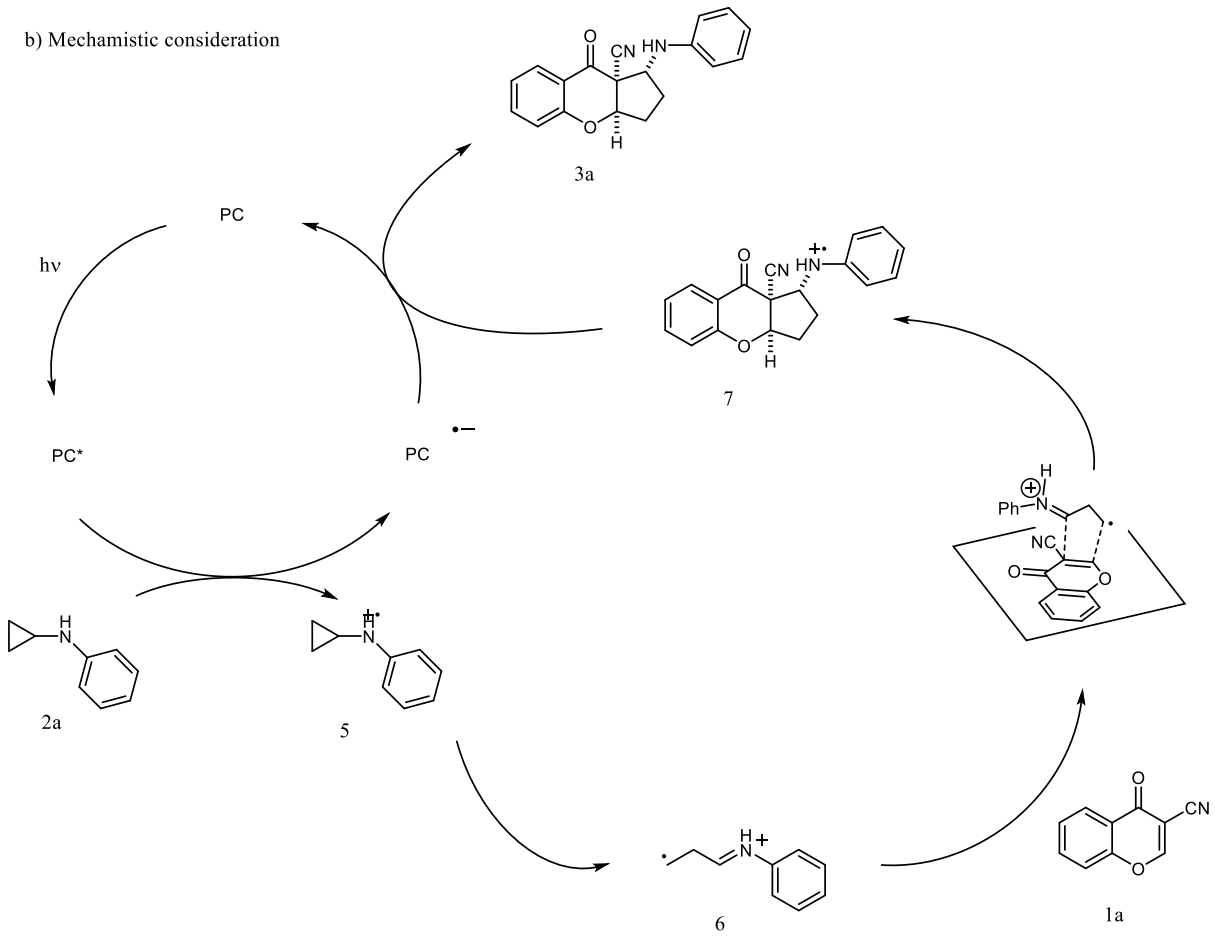
Scheme 4. Photocatalytic [3+2]-cycloaddition initiated by visible light – scope of cyanochromones **2**.– scope of *N*-cyclopropyloanilines.

In order to assign the relative configuration of target products **3**, the single crystal X-ray analysis was performed. To our delight, major diastereoisomer of **3ea** provided crystals suitable for this experiment.[11] The relative configuration of all major diastereoisomers of **3** was established by analogy. (Scheme 5a). To get insight into the reaction mechanism, a set of control experiments was performed (Table 1, entries 20-22) and demonstrated that developed protocol is radical. Consequently, the catalytic cycle of the reaction and the stereochemical model accounting for the formation of the major diastereomer were proposed (Scheme 5b).

a) X-Ray crystallography



3ea



Scheme 5. Photocatalytic [3+2]-cycloaddition initiated by visible light– mechanistic considerations and x-ray structure.

It is postulated that oxidation of *N*-cyclopropylaniline by a photoexcited catalyst initiates the reaction to form the corresponding amine radical cation **5**. Then ring-opening of **5** affords the distonic radical cation **6** and the cycloaddition leads to the annulation of the five-membered ring, yielding the amine radical **7**. The approach of **6** to **1** is governed by steric factors. The subsequent reduction of **7** leads to the target product **3** and the regeneration of catalyst-Eosin Y, which restarts the catalytic cycle.

In summary, we have developed new visible light mediated sythetic methodology leading to the formation of hybrid molecules containing chromone and cyclopentans rings. The protocol was realized in the presence of 5 mol% of Eosin Y as a catalyst in dry DMSO as a solvent. The presented methodology gives access to fifteen functionalized cyclopenta[*b*]chromeno-carbonitriles **3aa-3ag** under mild reaction conditions in good yields and diastereoselectivity.

Acknowledgment

This work was financially supported by Young Scientists' Fund at the Faculty of Chemistry, Lodz University of Technology, Grant W3-D/FMN/10G/2022. This contribution has been completed while authors (EK and MD) were the Doctoral Candidates in the Interdisciplinary Doctoral School of Lodz University of Technology, Poland.

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11 CCDC 2268189 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via https://www.ccdc.cam.ac.uk/structures.