Efficient Synthesis of [1,3]Oxazino[3,2-*f*]phenanthridine Derivatives by a Novel 1,4-Dipolar Cycloaddition Involving a Phenanthridine–Dimethyl Acetylenedicarboxylate Zwitterion and Aromatic Aldehydes

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An efficient synthesis of [1,3]oxazino[3,2-*f*]phenanthridine derivatives *via* a three-component reaction of phenanthridine, dimethyl acetylenedicarboxylate (DMAD), and aromatic aldehydes is described. This novel method is complementary to the classical *Huisgen* 1,4-dipolar cycloaddition in that it is well-suited to the preparation of [1,3]oxazino[3,2-*f*]phenanthridines.

Introduction. – Multicomponent reactions (MCRs), an important subclass of tandem reactions, have been steadily gaining importance in synthetic organic chemistry [1]. They offer significant advantages over conventional stepwise syntheses due to their flexible, convergent, and atom-efficient nature [2]. Devising such types of MCRs that achieve the formation of multiple bonds in a single operation is one of the major challenges in modern organic synthesis [3].

Polar reactions are of great importance in C,C and C,heteroatom bond-forming reactions, which are central to organic synthesis. The monumental work of *Huisgen* has established 1,3- or 1,4-dipolar cycloaddition as the most important methodology for the construction of a wide range of heterocycles [4]. 1,4-Dipolar zwitterions resulting from the addition of nucleophiles to activated π-systems have been among the most attractive and valuable intermediates in recent years. Extensive work in this area has revealed that trapping the zwitterions derived from dimethyl acetylenedicarboxylate (DMAD) and various nucleophiles leads to a number of interesting C,C bond-forming reactions and heterocyclic constructions [5]. Recent work has been mainly focused on the chemistry of zwitterions derived from DMAD and N-heterocycles such as pyridine [6], 1-alkyl-1*H*-imidazoles [7], isoquinoline [8], and benzothiazole [9]. However, zwitterions derived from DMAD and nucleophiles with fused multicyclic compounds have received only scant attention [10]. Accordingly, we have undertaken investigations involving the phenanthridine–DMAD zwitterion.

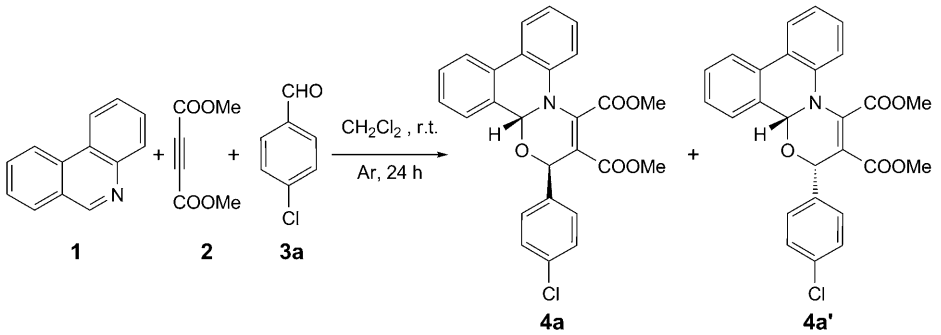
Phenanthridine derivatives have attracted considerable attention in medicinal chemistry due to their biological activities and their presence in a variety of significant natural alkaloids [11]. Therefore, to obtain molecules with pharmacological potential, we assume that synthesis of [1,3]oxazino[3,2-*f*]phenanthridines derivatives may be of great significance.

In view of the advantages of MCRs and tandem reactions, and prompted by our previous research on multicomponent reactions [12], we investigated the reactivity of the zwitterion generated from phenanthridine and DMAD with aldehydes.

To the best of our knowledge, this reaction has not been investigated previously. To expand the structural diversity accessible, we report the first results on trapping the phenanthridine–DMAD zwitterions with aromatic aldehydes, leading to novel [1,3]oxazino[3,2-*f*]phenanthridine derivatives *via* a one-pot multicomponent procedure.

Results and Discussion. – In a preliminary experiment, a solution of phenanthridine (**1**), DMAD (**2**), and 4-chlorobenzaldehyde (**3a**) in dry CH_2Cl_2 under Ar was stirred at room temperature for 24 h. Removal of the solvent, followed by column chromatography, afforded the diastereoisomeric [1,3]oxazino[3,2-*f*]phenanthridine derivatives **4a** and **4a′** as racemates in 70.5% yield, in a ratio of 4 : 1 (*Scheme 1*). The diastereoisomers were separated by column chromatography.

Scheme 1. *Reaction of Phenanthridine* (**1**)*, DMAD* (**2**)*, and 4-Chlorobenzaldehyde* (**3a**)



The reaction conditions of this transformation were optimized by varying the solvent (THF, CH_2Cl_2, toluene), the temperature (room temperature or reflux), and reaction times, to establish a versatile and high-yielding protocol. The results are compiled in *Table 1*. The reaction was found to give a lower yield in THF at room temperature or under reflux, while it led to a complex mixture in refluxing toluene as the solvent. Also, the yield of product was not improved by prolonging the reaction time. Finally, we selected CH_2Cl_2 and room temperature as the best condition for our investigation.

Table 1. *Optimization of Reaction Conditions*

Entry	Solvent	Temp.	Time [h]	Yield [%]
1	THF	r.t.	24	58.5
2	THF	reflux	24	55.3
3	CH_2Cl_2	r.t.	12	63.0
4	CH_2Cl_2	r.t.	24	70.5
5	CH_2Cl_2	r.t.	36	70.0
6	toluene	reflux	24	complex mixture

The structures of compounds **4** were deduced from their IR, ^{1}H- and ^{13}C-NMR, and high-resolution (HR) mass spectra. For example, the ^{1}H-NMR spectrum of **4c**, obtained after chromatographic separation of the mixture **4c**/**4c′**, exhibited four signals corresponding to MeO (δ(H) 3.56 and 3.76) and CH (δ(H) 5.89 and 6.01 ppm) H-atoms, along with *multiplet*s for the aromatic residues. The ^{13}C-NMR spectrum of **4c** showed 26 distinct resonances, which were also in good agreement with the assigned structure. The signals at δ(C) 164.34 and 164.93 were typical of the ester CO groups. The IR spectrum of **4c** displayed characteristic ester CO bands (1731 and 1712 cm^{-1}). In the HR mass spectrum, the $[M+H]^+$ peak appeared at m/z 446.1418 (calc. 446.1404 for $C_{26}H_{21}FNO_5$). Finally, the structure and the relative configuration of the major diastereoisomer **4c** was established by a single-crystal X-ray analysis (*Fig.*)[1]). The structures and configurations of other compounds were derived on the basis of their ^{1}H-NMR spectra in comparison with that of **4c**.

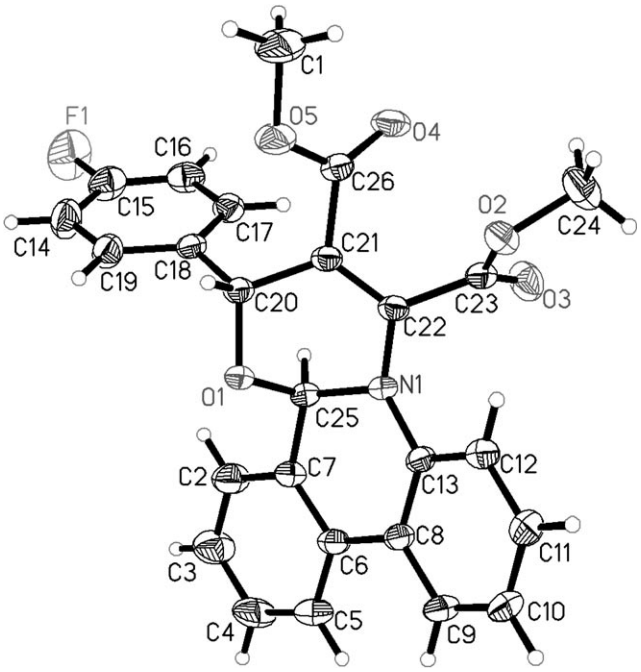


Figure. *ORTEP Diagram of compound* **4c**

As shown in *Table 2*, the methodology was applicaple to a variety of aromatic aldehydes with electronically different substituents to afford compounds **4** in moderate yields.

The feasibility of employing dipolarophiles other than aldehydes under the optimized reaction conditions mentioned above was also investigated. Unfortunately,

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[1]) CCDC-748583 (**4c**) contains the supplementary crystallographic data for this article. These data can be obtained free of charge from *The Cambridge Crystallographic Data Centre via* http://www.ccdc.cam.ac.uk/data_request/cif.

Table 2. *Reaction of Phenanthridine and Dimethyl But-2-ynedioate with Various Aldehydes*

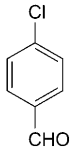
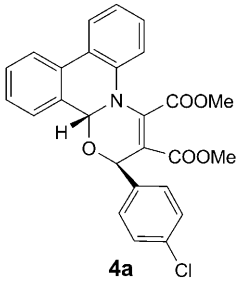
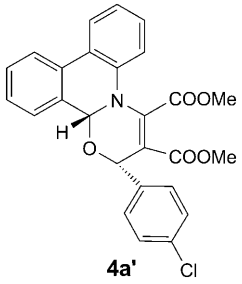
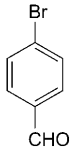
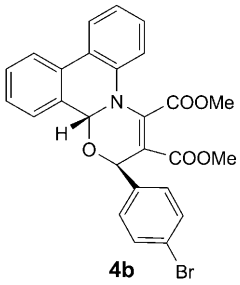
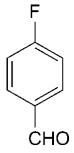
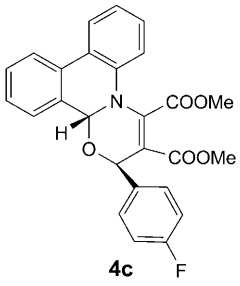
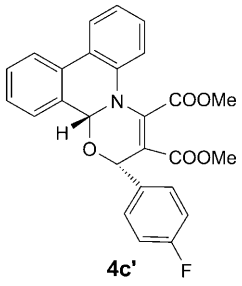
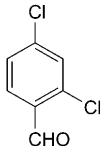
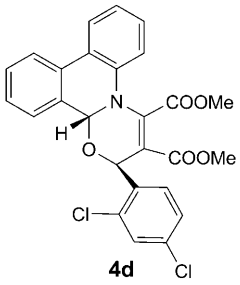
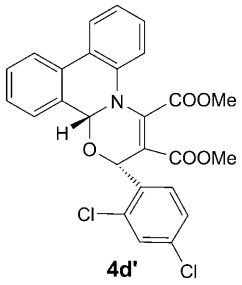
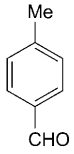
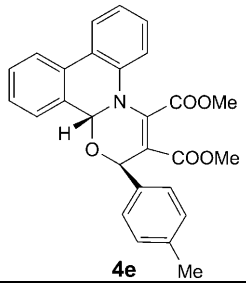
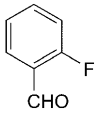
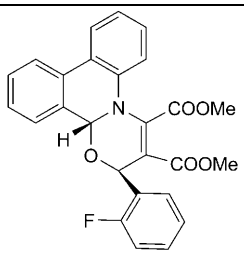
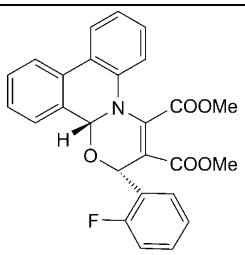
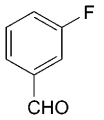
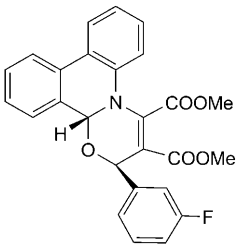
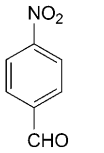
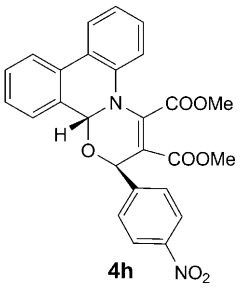
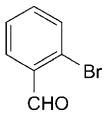
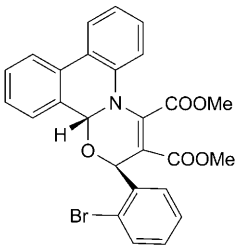
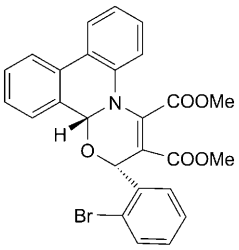
Entry	Aldehyde	Product	Yield[a]) [%] (Ratio)[b])
1		 **4a**  **4a'**	67.5 (4 : 1)
2		 **4b**	70.9
3		 **4c**  **4c'**	65.8 (4 : 1)
4		 **4d**  **4d'**	62.8 (1 : 1)
5		 **4e**	55.6

Table 2 (cont.)

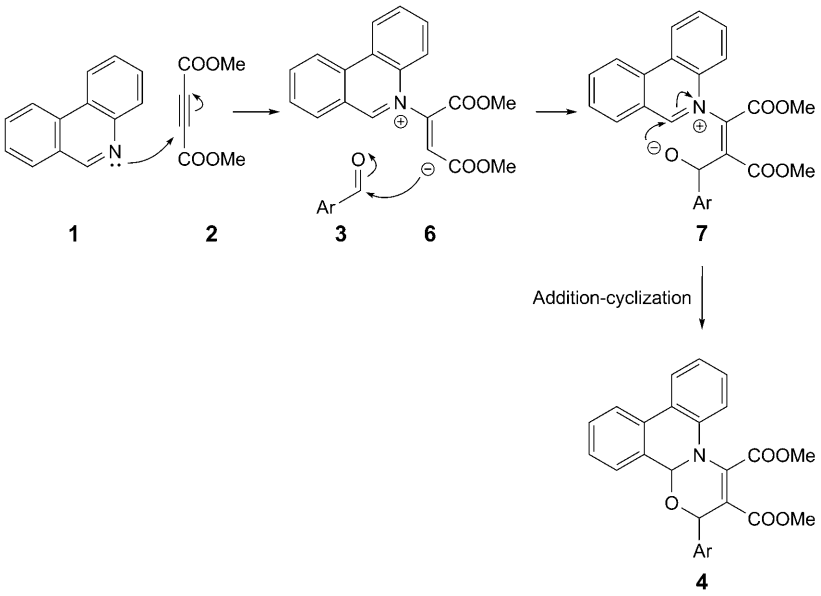
Entry	Aldehyde	Product	Yield[a]) [%] (Ratio)[b])
6		 **4f**  **4f'**	46.6 (3:1)
7		 **4g**	55.5
8		 **4h**	75.1
9		 **4i**  **4i'**	58.5 (1:1)

[a]) Combined yield of both isomers. [b]) The diastereoisomeric ratios of the products were determined by ^{1}H-NMR spectroscopy; all products are racemates.

when ketones, such as isatin and 1-phenylpyrrolidine-2,5-dione, and electrophilic styrenes like benzylidenemalononitrile were used, the reactions were usually very slow and resulted in a complex mixture of products, or no reaction occurred. These experimental results further hint at the steric hindrance of phenanthridine (**1**).

Although the mechanistic details of the reactions are not known, the formation of these heterocycles can be rationalized by initial formation of a highly reactive 1:1 zwitterionic intermediate **6**, formed by the *Michael* addition of **1** and **2**, which adds to the C=O group of aldehyde **3**, leading to a dipolar species **7** (*Scheme 2*). Cyclization of the latter affords to the corresponding [1,3]oxazino[3,2-*f*]phenanthridine derivatives **4**.

Scheme 2. *Mechanism Proposed for the Conversion of* **1**, **2**, *and* **3** *to* **4**



In conclusion, we have devised a novel three-component reaction for the regioselective synthesis of racemic [1,3]oxazino[3,2-*f*]phenanthridine derivatives *via* 1,4-dipolar cycloaddition under mild conditions. This novel method is well-suited for the preparation of oxazinophenanthridines. Further work is under way in this area.

Experimental Part

General. Phenanthridine (98%) was purchased from *ACROS*, other reagents were purchased from local suppliers, and all solvents were used after redistilling. All reactions were monitored by TLC. Chromatography refers to open column chromatography (CC) on silica gel (SiO_2; 100–200 mesh). M.p.: *RY-1* microscopic melting-point apparatus; uncorrected. IR Spectra: *Nicolet 510P FT-IR* spectrometer. ^{1}H- and ^{13}C-NMR spectra: at 500 and 125 MHz, resp., in (D_6)DMSO; *Bruker Avance 500M* spectrometer; chemical shifts δ in ppm rel. to TMS or (D_6)DMSO as internal standards. ESI-MS: *Ultima Global* spectrometer. The X-ray single-crystal diffraction was performed on *Bruker Smart APEX II*.

Preparation of Compounds **4**: *General Procedure.* To a stirred soln. of *phenanthridine* (**1**; 1.2 mmol) and *dimethyl acetylenedicarboxylate* (DMAD, **2**, 1.2 mmol) in dry CH_2Cl_2 (15 ml), was added aldehyde **3** (1 mmol), and the mixture was stirred at r.t. for 24 h. The solvent was removed under reduced pressure on a rotary evaporator. The residue was subjected to CC (SiO_2 (100–200 mesh); petroleum ether (PE)/AcOEt) to afford separated diastereoisomeric [1,3]oxazino[3,2-*f*]phenanthridine derivatives such as **4a** and **4a′**, **4c** and **4c′**, or unseparated diastereoisomeric mixtures such as **4d**/**4d′**, **4f**/**4f′**, **4i**/**4i′**, while **4b**, **4e**, **4g**, and **4h** were obtained as single diastereoisomers.

*Dimethyl 2-(4-Chlorophenyl)-2*H,*13b*H-*[1,3]oxazino[3,2-*f]*phenanthridine-3,4-dicarboxylate* (**4a**). Yellow solid. M.p. 189–190°. IR (KBr): 751, 924, 1001, 1122, 1226, 1259, 1498, 1605, 1712, 1737. ^{1}H-NMR: 3.58 (*s*, MeO); 3.77 (*s*, MeO); 5.90 (*s*, CH); 6.03 (*s*, CH); 6.85–8.09 (*m*, 12 arom. H). ^{13}C-NMR: 52.74; 53.67; 77.96; 83.12; 116.27; 121.49; 122.66; 123.04; 125.03; 128.20; 128.55; 128.77; 129.41; 129.63; 129.67; 130.02; 130.32; 130.53; 133.36; 137.57; 138.04; 140.37; 164.37; 164.92. HR-ESI-TOF-MS: 462.1124 ($[M+H]^+$, $C_{26}H_{21}ClNO_5^+$; calc. 462.1108).

Diastereoisomer **4a′**. Yellow solid. M.p. 142–144°. IR (KBr): 751, 976, 1116, 1229, 1267, 1438, 1490, 1605, 1707, 1729. ^{1}H-NMR: 3.63 (*s*, MeO); 3.82 (*s*, MeO); 5.96 (*s*, CH); 6.08 (*s*, CH); 6.91–8.14 (*m*, 12 arom. H). ^{13}C-NMR: 52.74; 53.67; 77.95; 83.10; 116.26; 121.48; 122.67; 123.04; 125.03; 128.20; 128.56; 128.77; 129.42; 129.67; 130.02; 130.32; 130.54; 133.35; 137.57; 138.03; 140.35; 164.36; 164.90. HR-ESI-TOF-MS: 462.1104 ($[M+H]^+$, $C_{26}H_{21}ClNO_5^+$; calc. 462.1108).

*Dimethyl 2-(4-Bromophenyl)-2*H,*13b*H-*[1,3]oxazino[3,2-*f]*phenanthridine-3,4-dicarboxylate* (**4b**). Yellow solid. M.p. 146–148°. IR (KBr): 748, 971, 1009, 1111, 1278, 1438, 1492, 1602, 1715, 1742. ^{1}H-NMR: 3.56 (*s*, MeO); 3.75 (*s*, MeO); 5.87 (*s*, CH); 5.99 (*s*, CH); 6.83–8.06 (*m*, 12 arom. H). ^{13}C-NMR: 52.77; 53.69; 77.98; 83.10; 116.26; 121.44; 121.95; 122.62; 123.11; 125.00; 128.12; 128.59; 129.23; 129.61; 130.33; 130.59; 131.69; 137.48; 138.44; 140.44; 164.41; 164.92. HR-ESI-TOF-MS: 506.0619 ($[M+H]^+$, $C_{26}H_{21}BrNO_5^+$; calc. 506.0603).

*Dimethyl 2-(4-Fluorophenyl)-2*H,*13b*H-*[1,3]oxazino[3,2-*f]*phenanthridine-3,4-dicarboxylate* (**4c**). Yellow solid. M.p. 168–170°. IR (KBr): 751, 842, 973, 1111, 1267, 1438, 1506, 1602, 1712, 1731. ^{1}H-NMR: 3.57 (*s*, MeO); 3.76 (*s*, MeO); 5.89 (*s*, CH); 6.02 (*s*, CH); 6.85–8.08 (*m*, 12 arom. H). ^{13}C-NMR: 52.69; 53.61; 77.91; 83.06; 115.47; 115.64; 116.22; 121.46; 122.62; 122.94; 124.98; 128.22; 128.51; 129.58; 129.65; 129.89; 130.14; 130.20; 130.27; 130.48; 135.11; 137.66; 139.97; 161.36; 164.34; 164.93. HR-ESI-TOF-MS: 446.1418 ($[M+H]^+$, $C_{26}H_{21}FNO_5^+$; calc. 446.1404).

Diastereoisomer **4c′**. Yellow solid. M.p. 168–170°. IR (KBr): 751, 842, 973, 1111, 1267, 1438, 1506, 1602, 1712, 1731. ^{1}H-NMR: 3.59 (*s*, MeO); 3.83 (*s*, MeO); 5.64 (*s*, CH); 5.82 (*s*, CH); 6.88–8.06 (*m*, 12 arom. H). ^{13}C-NMR: 52.62; 53.64; 73.71; 78.75; 116.11; 116.28; 117.73; 119.66; 123.11; 123.28; 124.04; 125.11; 127.37; 128.66; 129.90; 130.01; 130.14; 130.97; 131.04; 135.39; 136.52; 139.48; 161.66; 164.03; 165.57. HR-ESI-TOF-MS: 446.1411 ($[M+H]^+$, $C_{26}H_{21}FNO_5^+$; calc. 446.1404).

*Dimethyl 2-(2,4-Dichlorophenyl)-2*H,*13b*H-*[1,3]oxazino[3,2-*f]*phenanthridine-3,4-dicarboxylate* (**4d**/**4d′**). Yellow solid. M.p. 102–104°. IR (KBr): 751, 973, 1056, 1111, 1262, 1435, 1498, 1602, 1718, 1742. ^{1}H-NMR: 3.66 (*s*, MeO, **4d′**); 3.69 (*s*, MeO, **4d**); 3.89 (*s*, 2 MeO, **4d**/**4d′**); 5.70 (*s*, CH, **4d′**); 6.09 (*s*, CH, **4d**); 6.25 (*s*, CH, **4d′**); 6.45 (*s*, CH, **4d**); 6.97–8.18 (*m*, 22 arom. H, **4d**/**4d′**). ^{13}C-NMR: 52.69; 52.81; 53.53; 53.64; 70.88; 74.77; 79.12; 83.26; 116.11; 116.26; 116.82; 116.96; 117.88; 118.03; 121.33; 121.48; 122.45; 122.59; 123.01; 123.43; 123.58; 124.25; 124.39; 124.82; 124.97; 125.01; 127.18; 127.33; 128.08; 130.07; 131.55; 131.70; 133.99; 134.14; 134.65; 134.80; 135.10; 135.36; 135.51; 136.13; 136.28; 137.32; 137.47; 140.94; 163.82; 164.14; 164.64; 165.09. HR-ESI-TOF-MS: 496.0707 ($[M+H]^+$, $C_{26}H_{20}Cl_2NO_5^+$; calc. 496.0719).

*Dimethyl 2-(4-Methylphenyl)-2*H,*13b*H-*[1,3]oxazino[3,2-*f]*phenanthridine-3,4-dicarboxylate* (**4e**). Yellow solid. M.p. 173–174°. IR (KBr): 751, 984, 1116, 1111, 1229, 1438, 1506, 1608, 1712, 1734. ^{1}H-NMR: 2.27 (*s*, Me); 3.67 (*s*, MeO); 3.86 (*s*, MeO); 5.93 (*s*, CH); 6.09 (*s*, CH); 6.95–8.19 (*m*, 12 arom. H). ^{13}C-NMR: 21.16; 52.66; 53.59; 78.56; 83.13; 116.34; 121.53; 122.64; 122.84; 124.97; 128.12; 128.44; 128.49; 129.23; 129.60; 129.75; 130.21; 130.45; 135.85; 137.92; 138.09; 139.76; 164.43; 165.05. HR-ESI-TOF-MS: 442.1673 ($[M+H]^+$, $C_{27}H_{24}NO_5^+$; calc. 442.1654).

*Dimethyl 2-(2-Fluorophenyl)-2*H,*13b*H-*[1,3]oxazino[3,2-*f]*phenanthridine-3,4-dicarboxylate* (**4f**/**4f′**). Yellow solid. M.p. 172–174°. IR (KBr): 756, 1094, 1127, 1229, 1435, 1487, 1583, 1715, 1756. ^{1}H-NMR: 3.58 (*s*, MeO, **4f′**); 3.62 (*s*, MeO, **4f**); 3.82 (*s*, 2 MeO, **4f**/**4f′**); 5.68 (*s*, CH, **4f′**); 6.01 (*s*, CH, **4f′**);

6.12 (*s*, CH, **4f**); 6.21 (*s*, CH, **4f**); 6.90–8.14 (*m*, 12 arom. H, **4f**/**4f′**). ^{13}C-NMR: 52.75; 53.67; 53.74; 53.84; 68.76; 72.65; 79.21; 83.15; 115.96; 116.13; 116.37; 116.62; 116.75; 117.71; 121.36; 122.62; 122.93; 123.18; 123.23; 124.15; 124.79; 124.92; 125.19; 125.98; 126.07; 127.47; 128.13; 128.18; 128.54; 128.77; 129.44; 129.66; 130.02; 130.19; 130.53; 130.80; 130.87; 131.79; 136.43; 137.44; 140.29; 140.98; 160.19; 162.16; 163.98; 164.44; 164.81; 165.34. HR-ESI-TOF-MS: 446.1407 ($[M+H]^+$, $C_{26}H_{21}FNO_5^+$; calc. 446.1404).

*Dimethyl 2-(3-Fluorophenyl)-2*H,*13b*H-*[1,3]oxazino[3,2-*f*]phenanthridine-3,4-dicarboxylate* (**4g**). Yellow solid. M.p. 150–151°. IR (KBr): 754, 1020, 1226, 1262, 1438, 1498, 1602, 1723, 1745. ^{1}H-NMR: 3.64 (*s*, MeO); 3.82 (*s*, MeO); 5.95 (*s*, CH); 6.07 (*s*, CH); 6.91–8.15 (*m*, 12 arom. H). ^{13}C-NMR: 52.76; 53.68; 77.84; 83.06; 116.28; 121.53; 122.70; 123.08; 124.34; 125.08; 128.19; 128.57; 129.48; 129.63; 129.70; 130.31; 130.55; 137.63; 140.47; 141.85; 141.91;161.25; 164.32; 164.88. HR-ESI-TOF-MS: 446.1384 ($[M+H]^+$, $C_{26}H_{21}FNO_5^+$; calc. 446.1404).

*Dimethyl 2-(4-Nitrophenyl)-2*H,*13b*H-*[1,3]oxazino[3,2-*f*]phenanthridine-3,4-dicarboxylate* (**4h**). Yellow solid. M.p. 118–121°. IR (KBr): 751, 973, 1111, 1229, 1267, 1347, 1520, 1602, 1715, 1740. ^{1}H-NMR: 3.64 (*s*, MeO); 3.83 (*s*, MeO); 6.12 (*s*, CH); 6.13 (*s*, CH); 6.94–8.17 (*m*, 12 arom. H). ^{13}C-NMR: 52.83; 53.77; 77.61; 83.08; 116.29; 121.45; 122.71; 123.27; 124.00; 125.10; 127.95; 128.05; 128.64; 129.52; 129.59; 129.67; 130.44; 130.63; 137.16; 141.30; 146.66; 147.81; 164.33; 164.74. HR-ESI-TOF-MS: 473.1352 ($[M+H]^+$, $C_{26}H_{21}N_2O_7^+$; calc. 473.1349).

*Dimethyl 2-(2-Bromophenyl)-2*H,*13b*H-*[1,3]oxazino[3,2-*f*]phenanthridine-3,4-dicarboxylate* (**4i**/**4i′**). Yellow solid. M.p. 174–176°. IR (KBr): 751, 968, 1113, 1229, 1297, 1355, 1492, 1589, 1704, 1748. ^{1}H-NMR: 3.57 (*s*, MeO, **4i′**); 3.62 (*s*, MeO, **4i**); 3.82 (*s*, 2 MeO, **4i′**); 3.82 (*s*, MeO, **4i**); 5.60 (*s*, CH, **4i′**); 6.02 (*s*, CH, **4i**); 6.17 (*s*, CH, **4i′**); 6.37 (*s*, CH, **4i**); 6.90–8.03 (*m*, 24 arom. H, **4i**/**4i′**). ^{13}C-NMR: 52.79; 52.91; 53.75; 53.80; 73.80; 77.58; 78.92; 83.24; 116.34; 117.52; 118.02; 121.54; 122.67; 123.03; 123.26; 123.60; 124.44; 124.81; 125.06; 125.28; 127.29; 128.21; 128.38; 128.63; 128.86; 129.48; 129.73; 129.99; 130.04; 130.13; 130.32; 130.60; 130.80; 131.61; 133.29; 134.30; 136.35; 137.12; 137.73; 137.88; 140.55; 140.76; 164.07; 164.35; 164.85; 165.37. HR-ESI-TOF-MS: 506.0603 ($[M+H]^+$, $C_{26}H_{21}BrNO_5^+$; calc. 506.0603).

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