First Example of Friedel-Craft Acylation of Cyclopenta[*d*][1,2]oxazines and Further Reaction to Their Oxime and Hydrazone Derivatives

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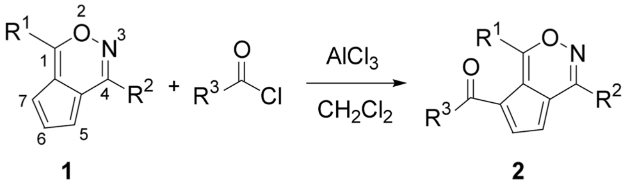
1,2-Oxazines have been gained increasing interest in organic synthesis as useful intermediates,[1] and key building blocks in the synthesis of natural products,[2] and unnatural cyclic amino acids.[3] 1,2-Oxazines also play an important role as pharmacological entities exhibiting a broad spectrum of biological activities.[4]

However, there have been only a few reports on the reaction of cyclopenta[*d*][1,2]oxazine and its derivatives. Linn and Sharkey[5] reported that the treatment of benzoylated cyclopentadiene with hydroxylamine afforded cyclopenta[*d*][1,2]oxazine with no substituents. Lloyd and co-workers[6] reported the synthesis of cyclopenta[*d*][1,2]oxazine by reaction of diaroylcyclopentadienes with hydroxylamine. They had failed to get the corresponding aldehydes by treatment of cyclopenta[*d*][1,2]oxazines with ethyl orthoformate in the presence of boron trifluoride-ether complex. On the other hand, they could synthesize only 7-bromocyclopenta[*d*][1,2]oxazine with *N*-bromosuccinimide. Previously, we reported Suzuki reaction of 7-iodocyclopenta[*d*][1,2]oxazines to afford the corresponding 7-arylated cyclopenta[*d*][1,2]oxazines.[7] Since Lloyd and co-workers reported reactions of cyclopenta[*d*][1,2]oxazine, there have been paid little attention to the chemistry of cyclopenta[*d*][1,2]oxazine and the application of cyclopenta[*d*][1,2]-oxazines as a synthetically useful starting material presumably due to the limited chemical stability of cyclopenta[*d*][1,2]oxazine skeletons.

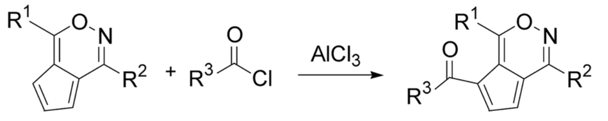
Herein, we report a facile Friedel-Craft acylation of cyclopenta[*d*][1,2]-oxazines to afford the synthetically useful 7-acyl derivatives. This is the first example of Friedel-Craft reaction of cyclopenta[*d*][1,2]-oxazine as given in Table 1.

Various functional groups can be tolerated, such as phenyl esters, lactones, and acetyl groups, and yields of reaction were moderate to excellent. The substituent position of 7-acylcyclopenta[*d*][1,2]oxazines could be unequivocally determined by the coupling constant of cyclopentadiene from spectral data. In reference, the coupling constant of

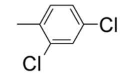
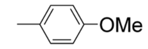
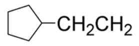
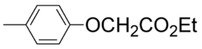
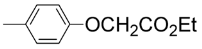
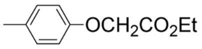
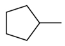
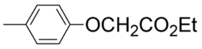
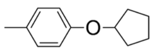
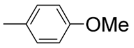
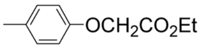
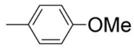
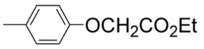
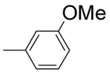
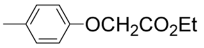
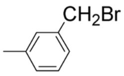
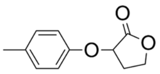
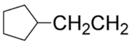
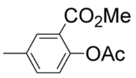
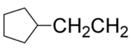
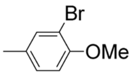
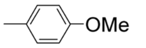
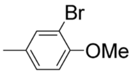
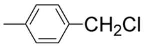
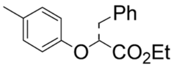
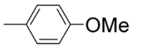
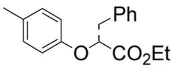


Scheme 1

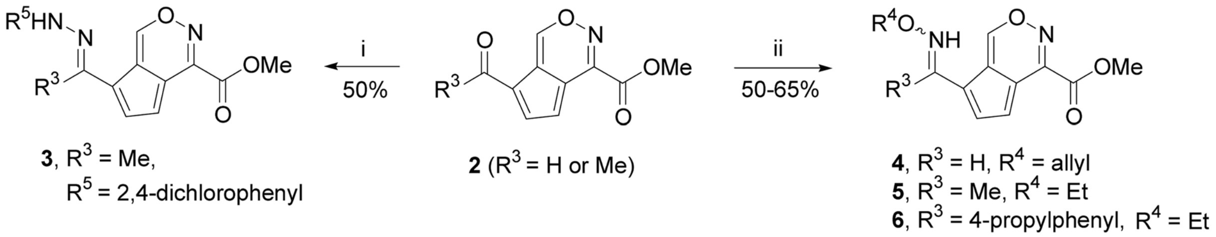
Table 1. Friedel-Craft acylation of cyclopenta[*d*][1,2]oxazines



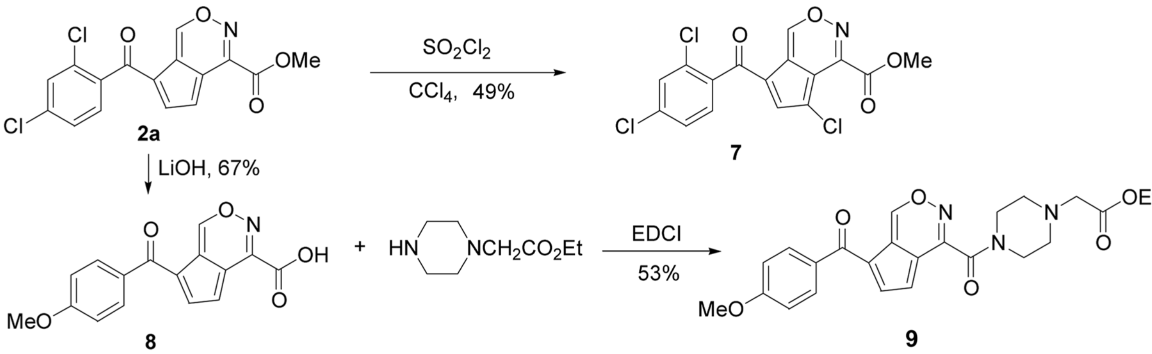
2a - 2q

No	R[1]	R[2]	R[3]	Yield (%)
2a	H	-CO_2Me		46
2b	H	-CO_2Me		39
2c	H	-CO_2Me		47
2d	H		n-C_3H_7	88
2e	H		n-$C_{12}H_{25}$	54
2f	H			72
2g	H			58
2h	H		$HO_2CCH_2CH_2$[a]	86
2i	H			77
2j	H			65
2k	H			62
2l	H			39
2m	H			68
2n	Me			64
2o	Me			61
2p	H			54
2q	H		n-$C_{12}H_{25}$	85

[a]Succinic anhydride was used in place of acid chloride.



Scheme 2. *Reagents and condition*: i) $ArNHNH_2$, Na_2CO_3, EtOH; ii) NH_2OR^4, Na_2CO_3, EtOH.



Scheme 3

cyclopentadiene are as follows as cited in the literature[8]: $J_{H1\text{-}H5} = J_{H5\text{-}H7} = 1.2$ Hz, $J_{H5\text{-}H6} = 2.9$ Hz, $J_{H6\text{-}H7} = 4.6$ Hz. For instance, the spectral data of **2c** show a typical coupling constant of $J_{H5\text{-}H6} = 3.2$ Hz at δ 7.94 (d, $J = 3.2$ Hz, 1H, H_6) and 7.38 (dd, $J = 3.2$, 1.2 Hz, 1H, H_5). Moreover, the splitting pattern of H_1 at 9.81 (d, $J = 1.2$ Hz, 1H) strongly supports that Friedel-Craft acylation occurs at 7-position of the cyclopenta[*d*][1,2]oxazine. The low yields of Friedel-Craft acylation (**2a-2c**) were presumably due to the stability of reactants in acid catalyzed reaction condition. Carboxylic acid functionality could easily be introduced to the cyclopenta[*d*][1,2]oxazine skeletons by the reaction of succinic anhydride in excellent yield.

As additional examples, oximes **4-6** and hydrazone **3** of cyclopenta[*d*][1,2]oxazines can be synthesized from the corresponding aldehyde and ketone as shown in Scheme 2. **2** (R^3 = H) was obtained from cyclopenta[*d*][1,2]oxazine-4-carboxylic acid methyl ester by treatment with dichloromethoxymethane in the presence of titanium chloride (IV).[9]

As shown in Scheme 3, chlorination of **2a** afforded **7** in moderate yield. The cross coupling reaction of **8** generated from **2a** by hydrolysis with lithium hydroxide afforded **9** in moderate yield and cyclopenta[*d*][1,2]oxazines were amenable to base treatment and coupling reaction condition. In summary, we achieved the successful Friedel-Craft reaction of cyclopenta[*d*][1,2]oxazines and this reaction leads a convenient extension for the utilization of the parent cyclopenta[*d*][1,2]oxazines.

Experimental Section

7-(2,4-Dichlorobenzoyl)cyclopenta[*d*][1,2]oxazine-4-carboxylic acid methyl ester (2a). To a stirred solution of cyclopenta[*d*][1,2]oxazine-4-carboxylic acid methyl ester[7] (1 g, 5.7 mmol) and 2,4-dichlorobenzoyl chloride (1.6 mL, 1.3 mmol) in dichloromethane (20 mL) was added aluminum chloride (1.5 g, 11.3 mmol) at 0 °C. The reaction mixture was stirred for 3 h at room temperature. The resulting mixture was poured into ice water (20 mL), and extracted with ethyl acetate (30 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography to afford **2a** as yellow solid (0.93 g, 46%): ^{1}H NMR ($CDCl_3$) δ 9.89 (d, J = 1.1 Hz, 1H), 7.58 (m, 2H), 7.39 (m, 3H), 4.11 (s, 3H); MS *m/e* (relative intensity) 349 (M^+, 66), 290 (26), 226 (18).

Likewise the following compounds were prepared.

7-(4-Methoxybenzoyl)cyclopenta[*d*][1,2]oxazine-4-carboxylic acid methyl ester (2b). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.81 (s, 1H), 7.98-7.85 (m, 3H), 7.44-7.36 (m, 1H), 7.02 (d, J = 8.6 Hz, 2H), 4.11 (s, 3H), 3.90 (s, 3H); MS *m/e* (relative intensity) 311 (M^+, 67), 252 (41), 144 (66), 135 (52), 77 (37), 59 (100).

7-(3-Cyclopentylpropionyl)cyclopenta[*d*][1,2]oxazine-4-carboxylic acid methyl ester (2c). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.81 (d, J = 1.2 Hz, 1H), 7.94 (d, J = 3.2 Hz, 1H), 7.38 (dd, J = 3.2, 1.2 Hz, 1H), 4.09 (s, 3H), 2.95 (t, 1H), 1.81-1.78 (m, 4H), 1.56 (m, 4H), 1.18 (m, 3H); MS *m/e* (relative intensity) 301 (M^+, 14), 242 (35), 219 (100), 160 (36), 144 (43), 132 (56), 59 (55), 41 (55).

[4-(7-Butyrylcyclopenta[*d*][1,2]oxazin-4-yl)phenoxy]-acetic acid ethyl ester (2d). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.86 (d, J = 1.0 Hz, 1H), 7.84 (m, 3H), 7.10 (d, J = 8.9 Hz, 2H), 6.87 (dd, J = 3.2, 1.2 Hz, 1H), 4.72 (s, 2H), 4.30 (q, J = 7.1 Hz, 2H), 2.92 (t, J = 7.1 Hz, 2H), 1.81 (q, J = 7.1 Hz, 2H), 1.33 (t, J = 7.1 Hz, 3H), 1.03 (t, J = 7.1 Hz, 3H); MS *m/e* (relative intensity) 367 (82), 338 (33), 323 (80), 296 (100).

{4-[7-(11-Bromoundecanoyl)cyclopenta[*d*][1,2]oxazin-4-yl]phenoxy}acetic acid ethyl ester (2e). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.86 (s, 1H), 7.84 (m, 3H), 7.08 (d, J = 8.4 Hz, 2H), 6.87 (m, 1H), 4.71 (s, 2H), 4.31 (q, J = 7.2 Hz, 2H), 3.40 (t, J = 7.2 Hz, 2H), 1.79 (m, 2H), 1.29 (m, 19H), 1.26 (m, 3H).

[4-(7-Cyclopentanecarbonylcyclopenta[*d*][1,2]oxazin-4-yl)phenoxy] acetic acid ethyl ester (2f). ^{1}H NMR (300 MHz, CDCl$_3$) δ9.84 (d, J = 1.1 Hz, 1H), 8.00 (d, J = 3.2 Hz, 1H), 7.84 (d, J = 8.9 Hz, 2H), 7.08 (d, J = 8.9 Hz, 2H), 6.96 (dd, J = 3.2, 1.1 Hz, 1H), 471 (s, 2H), 4.30 (q, J = 7 Hz, 2H), 2.64 (m, 1H), 1.36-1.21 (m, 6H), 1.00 (t, J = 7.8 Hz, 3H); MS *m/e* (relative intensity) 365 (M$^+$- 29), 337 (52), 324 (29), 250 (25), 222 (13), 131 (25).

{4-[7-(4-Cyclopentyloxybenzoyl)cyclopenta[*d*][1,2]oxazin-4-yl]phenoxy}acetic acid ethyl ester (2g). ^{1}H NMR (300 MHz, CDCl$_3$) δ9.86 (d, J = 1.1 Hz, 1H), 7.91 (m, 4H), 7.76 (d, J = 3.2 Hz, 1H), 7.12 (d, J = 8.9 Hz, 2H), 6.94 (m, 1H), 4.88 (m, 1H), 4.72 (s, 2H), 4.33 (q, J = 7.1 Hz, 2H), 1.66 (m, 8H), 1.33 (t, J = 7.1 Hz, 3H); MS *m/e* (relative intensity) 304 (20), 302 (22), 195 (22), 149 (55), 129 (100).

4-[4-(4-Methoxyphenyl)cyclopenta[*d*][1,2]oxazin-7-yl]-4-oxo-butyric acid (2h). ^{1}H NMR (300 MHz, CDCl$_3$) δ 12.0 (s, 1H), 10.02 (s, 1H), 8.15 (m, 1H), 7.62 (m, 1H), 7.21 (m, 2H), 6.62 (m, 1H), 2.51 (m, 2H), 2.10 (m, 2H); MS *m/e* (relative intensity) 325 (2), 300 (17), 286 (45), 258 (86).

{4-[7-(2-Methoxybenzoyl)cyclopenta[*d*][1,2]oxazin-4-yl]-phenoxy}acetic acid ethyl ester (2i). ^{1}H NMR (300 MHz, CDCl$_3$) δ9.89 (d, J = 1.1 Hz, 1H), 7.83 (d, J = 8.6 Hz, 2H), 7.54 (d, J = 3.2 Hz, 1H), 7.44 (m, 2H), 7.25 (m, 4H), 6.85 (d, J = 3.2 Hz, 1H), 4.72 (s, 2H), 4.32 (q, J = 7.2 Hz, 2H), 3.81 (s, 3H), 1.35 (t, J = 7.2 Hz, 3H); MS *m/e* (relative intensity) 431 (M$^+$, 18), 416 (100), 400 (52), 387 (11), 207 (51).

{4-[7-(3-Methoxybenzoyl)cyclopenta[*d*][1,2]oxazin-4-yl]-phenoxy}acetic acid ethyl ester (2j). ^{1}H NMR (300 MHz, CDCl$_3$) δ 9.90 (s, 1H), 7.84 (m, 2H), 7.43 (d, J = 6.8 Hz, 2H), 7.27 (m, 3H), 7.10 (m, 2H), 6.93 (d, J = 3.2 Hz, 1H), 4.72 (s, 2H), 4.31 (q, J = 6.8 Hz, 2H), 3.88 (s, 3H), 1.32 (t, J = 6.8 Hz, 3H); MS *m/e* (relative intensity) 416 (M$^+$- 15, 81), 386 (52), 316 (27), 226 (53), 193 (100).

{4-[7-(3-Bromomethylbenzoyl)cyclopenta[*d*][1,2]oxazin-4-yl]phenoxy}acetic acid ethyl ester (2k). ^{1}H NMR (300 MHz, CDCl$_3$) δ9.92 (d, J = 1.2 Hz, 1H), 7.84 (m, 4H), 7.76 (d, J = 3.2 Hz, 1H), 7.57 (d, J = 8.9 Hz, 2H), 7.12 (d, J = 8.9 Hz, 2H), 6.94 (dd, J = 3.2, 1.2 Hz, 1H), 4.73 (s, 2H), 4.54 (s, 2H), 4.32 (q, J = 7.2 Hz, 2H), 1.33 (t, J = 7.2 Hz, 3H); MS *m/e* (relative intensity) 495 (M$^+$, 18), 415 (81), 221 (91), 108 (62), 44 (100).

3-{4-[7-(3-Cyclopentylpropionyl)cyclopenta[*d*][1,2]oxazin-4-yl]phenoxy}dihydro-furan-2-one (2l). ^{1}H NMR (300 MHz, CDCl$_3$) δ9.01 (d, J = 1.2 Hz, 1H), 7.83 (m, 5H), 6.88 (dd, J = 3.2, 1.2 Hz, 1H), 5.07 (t, J = 7.7 Hz, 1H), 4.44 (m, 2H), 2.95 (t, J = 7.7 Hz, 1H), 2.73 (m, 2H), 2.53 (t, J = 5.3 Hz, 2H), 1.79 (t, J = 5.3 Hz, 2H), 1.63 (m, 6H), 1.13 (m, 2H); MS *m/e* (relative intensity) 418 (10), 204 (29), 148 (18), 108 (100), 80 (18).

2-Acetoxy-5-[7-(3-cyclopentylpropionyl)cyclopenta[*d*]-[1,2]oxazin-4-yl]benzoic acid methyl ester (2m). ^{1}H NMR (300 MHz, CDCl$_3$) δ9.86 (d, J = 1.0 Hz, 1H), 8.42 (d, J = 2.2 Hz, 1H), 8.01 (dd, J = 8.9, 2.2 Hz, 1H), 7.86 (d, J = 3.2 Hz, 1H), 7.16 (d, J = 8.9 Hz, 1H), 6.88 (dd, J = 3.2, 1.0 Hz, 1H), 4.00 (s, 3H), 2.96 (t, J = 7.1 Hz, 2H), 2.20 (s, 3H), 1.83 (m, 4H), 1.78 (m, 4H), 1.18 (m, 3H); MS *m/e* (relative intensity) 394 (M$^+$, 28), 361 (17), 323 (31), 310 (100), 295 (33).

[4-(3-Bromo-4-methoxyphenyl)-1-methylcyclopenta[*d*]-[1,2]oxazin-7-yl](4-methoxy-phenyl)methanone (2n). ^{1}H NMR (300 MHz, CDCl$_3$) δ7.56 (m, 9H), 4.00 (s, 3H), 3.90 (s, 3H), 3.09 (s, 3H); MS *m/e* (relative intensity) 453 (M$^+$, 78), 214 (51), 135 (100), 77 (69), 62 (68).

[4-(3-Bromo-4-methoxyphenyl)-1-methylcyclopenta[*d*]-[1,2]oxazin-7-yl](4-chloromethylphenyl)methanone (2o). ^{1}H NMR (300 MHz, CDCl$_3$) δ8.10 (m, 1H), 7.90 (d, J = 7.9 Hz, 1H), 7.81 (m, 1H), 7.57 (m, 4H), 7.05 (d, J = 8.5 Hz, 1H), 6.84 (d, J = 3.2 Hz, 1H), 4.66 (s, 2H), 4.00 (s, 3H), 3.16 (s, 3H); MS *m/e* (relative intensity) 472 (M$^+$, 39), 471 (100), 34(41), 153 (94), 124 (34).

2-{4-[7-(4-Methoxy-benzoyl)cyclopenta[*d*][1,2]oxazin-4-yl]phenoxy}-3-phenylpropionic acid methyl ester (2p). ^{1}H NMR (300 MHz, CDCl$_3$) δ9.86 (s, 1H), 7.90 (d, J = 8.6 Hz, 2H), 7.72 (d, J = 3.2 Hz, 1H), 7.42 (d, J = 8.6 Hz, 2H), 7.28-7.26 (m, 5H), 7.03-6.98 (m, 4H), 6.55 (d, J = 3.2 Hz, 1H), 4.82 (t, J = 6.2 Hz, 1H), 3.90 (s, 3H), 3.72 (s, 3H), 3.26 (d, J = 6.2 Hz, 2H).

3-Phenyl-2-[4-(7-tetradecanoylcyclopenta[*d*][1,2]oxazin-4-yl)phenoxy]propionic acid methyl ester (2q). ^{1}H NMR (300 MHz, CDCl$_3$) δ9.86 (s, 1H), 7.80 (m, 1H), 7.4 (m, 1H), 7.26 (m, 6H), 6.95 (m, 2H), 6.42 (m, 1H), 4.8 (t, 1H), 3.72 (s, 3H), 3.23 (d, J = 6.6 Hz, 2H). 2.88 (t, J = 7.2 Hz, 2H), 1.29-1.22 (m, 20H); MS *m/e* (relative intensity) 493 (M$^+$, 18), 478 (6), 450 (20), 436 (23), 380 (66).

7-Formylcyclopenta[*d*][1,2]oxazine-4-carboxylic acid methyl ester (**2**, R^3 = H). To a stirred solution of cyclopenta[*d*][1,2]oxazine-4-carboxylic acid methyl ester (0.7 g, 2.3 mmol) in dichloromethane (30 mL) was added titanium chloride (IV) (1.5 g, 8 mmol), and dichloromethoxymethane (0.91 g, 8 mmol). The reaction mixture was stirred for 12 h at room temperature. The resulting mixture was poured into ice water (20 mL), and extracted with ethyl acetate (30 mL). The organic layer was dried over MgSO$_4$, and concentrated under reduced pressure. The residue was purified by column chromatography to afford **2** (300 mg, 37%): mp = 166 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 10.24 (s, 1H), 9.86 (d, J = 1.2 Hz, 1H), 8.10 (d, J = 3.2 Hz, 1H), 7.52 (dd, J = 3.2, 1.2 Hz, 1H), 4.15 (s, 3H).

7-[(2,6-Dichlorophenyl)hydrazonomethyl]cyclopenta[*d*]-[1,2]oxazine-4-carboxylic acid methyl ester (3). To a solution of 7-formylcyclopenta[*d*][1,2]oxazine-4-carboxylic acid methyl ester (0.22 g, 1 mmol), Na$_2$CO$_3$ (0.11 g, 1 mmol) in ethanol (3 mL) was added 2,6-dichlorophenylhydrazine hydrochloride (0.21 g, 1 mmol). The reaction mixture was stirred for 24 h at room temperature. The resulting mixture was poured into ice water (20 mL) and extracted with ethyl acetate (30 mL). The organic layer was dried over MgSO$_4$ and concentrated under reduced pressure. The residue was purified by column chromatography to afford **3** (190 mg, 50%): mp = 171 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ9.81 (d, J = 1.2 Hz, 1H), 6.89-7.49 (m, 5H), 4.07 (s, 3H), 2.37 (s, 3H).

7-(Allyloxyiminomethyl)cyclopenta[*d*][1,2]oxazine-4-carboxylic acid methyl ester (4). To a solution of methyl-7-formylcyclopenta[*d*][1,2]-oxazine-4-carboxylate (0.2 g, 1 mmol), Na$_2$CO$_3$ (0.11 g, 1 mmol) in EtOH (3 mL) was added allylhydroxylamine hydrochloride (0.11 g, 1 mmol). The reaction mixture was stirred for 24 h at room temperature. The resulting mixture was poured into ice water (20 mL) and extracted with ethyl acetate (30 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography to afford **4** (170 mg, 64%): mp = 83 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.48 (d, J = 1.2 Hz, 1H), 8.33 (s, 1H), 7.30-7.47 (m, 2H), 5.80-6.48 (m, 1H), 5.17-5.56 (m, 2H), 4.70 (d, J = 5.6 Hz, 1H), 4.09 (s, 3H); MS *m/e* (relative intensity) 274 (M^+, 100), 256 (16), 244 (12), 196 (49), 168 (42), 104 (83).

7-(1-Ethoxyiminoethyl)cyclopenta[*d*][1,2]oxazine-4-carboxylic acid methyl ester (5). To a solution of 7-acetylcyclopenta[*d*][1,2]oxazine-4-carboxylic acid methyl ester (0.23 g, 1 mmol), Na_2CO_3 (0.1 g, 1 mmol) in EtOH (3 mL) was added *O*-ethylhydroxylamine hydrochloride (0.1 g, 1 mmol). The reaction mixture was stirred for 24 h at room temperature. The resulting mixture was poured into ice water (20 mL), and extracted with ethyl acetate (30 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography to afford **5** (180 mg, 65%): mp = 103 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.48 (d, J = 1.2 Hz, 1H), 8.33 (s, 1H), 7.30-7.47 (m, 2H), 5.80-6.48 (m, 1H), 5.17-5.56 (m, 2H), 4.70 (d, J = 5.6 Hz, 1H), 4.09 (s, 3H); MS *m/e* (relative intensity) 262 (M^+, 17), 247 (6), 205 (42), 191 (6), 165 (15).

7-[Ethoxyimino(4-propylphenyl)methyl]cyclopenta[*d*]-[1,2]oxazine-4-carboxylic acid methyl ester (6). To a solution of 7-(4-propylbenzoyl) cyclopenta[*d*][1,2]oxazine-4-carboxylic acid methyl ester (0.32 g, 1 mmol), Na_2CO_3 (0.11 g, 1 mmol) in EtOH (3 mL) was added *O*-ethylhydroxylamine hydrochloride (0.1 g, 1 mmol). The reaction mixture was stirred for 24 h at room temperature. The resulting mixture was poured into ice water (20 mL) and extracted with ethyl acetate (30 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography to afford **6** (180 mg, 50%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.50 (d, J = 1.2 Hz, 1H), 7.02-7.60 (m, 6H), 4.22 (q, J = 6.7 Hz, 2H), 4.05 (s, 3H), 2.65 (t, J = 8.4 Hz, 2H), 1.33-1.90 (m, 2H), 1.31 (t, J = 6.7 Hz, 3H), 0.97 (t, J = 6.7 Hz, 3H); MS *m/e* (relative intensity) 366 (M^+, 83), 352 (7), 338 (34), 324 (80), 296 (100).

5-Chloro-7-(2,4-dichlorobenzoyl)cyclopenta[*d*][1,2]oxazine-4-carboxylic acid methyl ester (7). To a stirred solution of 7-(2,4-dichlorobenzoyl)cyclopenta[*d*][1,2]oxazine-4-carboxylic acid methyl ester (117 mg, 0.35 mmol) in chloroform (2 mL) was added sulfuryl chloride (27 μL, 0.36 mmol) at 0 °C. The reaction mixture was stirred for 3 h at room temperature. The resulting mixture was poured into ice water (10 mL), and extracted with dichloromethane (15 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography to afford **7** as yellow solid (65 mg, 49%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.81 (s, 1H), 7.57 (s, 1H), 7.39 (s, 2H), 7.22 (s, 1H), 4.19 (s, 3H); MS *m/e* (relative intensity) 384 (M^+, 8), 326 (16), 304 (5.9), 178 (17).

7-(4-Methoxybenzoyl)cyclopenta[*d*][1,2]oxazine-4-carboxylic acid (8). To a solution of 7-(4-methoxybenzoyl)-cyclopenta[*d*][1,2]oxazine-4-carboxylic acid methyl ester (40 mg, 0.13 mmol) in THF/MeOH/H_2O (1 : 1 : 1, 2 mL) was added LiOH (10 mg, 0.26 mmol) at room temperature. The resulting mixture was stirred for 30 min at room temperature and poured into water, and extracted with ethyl acetate. The water layer was neutralized with 0.1 N HCl to pH 5 and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography to afford **8** as yellow solid (26 mg, 67%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.95 (s, 1H), 7.78 (d, J = 8 Hz, 2H), 6.98 (d, J = 8.6 Hz, 2H), 6.25 (d, J = 3.2 Hz, 1H), 6.10 (d, J = 8.8 Hz, 1H), 3.81 (s, 3H); MS *m/e* (relative intensity) 297 (M^+, 47), 268 (4), 224 (5), 210 (100), 182 (6).

{4-[7-(4-Methoxybenzoyl)cyclopenta[*d*][1,2]oxazine-4-carbonyl]piperazin-1-yl}acetic acid ethyl ester (9). To a stirred solution of 7-(4-methoxy-benzoyl)cyclopenta[*d*]-[1,2]oxazine-4-carboxylic acid (150 mg, 0.5 mmol), 1,1'-carbonyldiimidazole (327 mg, 2.0 mmol) in THF (5 mL) was added piperazin-1-yl acetic acid ethyl ester (173 mg, 1.0 mmol) and stirred for 24 h at room temperature. The resulting mixture was poured into water (20 mL) and extracted with ethyl acetate (30 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography to afford **9** as yellow solid (128 mg, 53%): ^{1}NMR (300 MHz, $CDCl_3$) δ 8.48 (s, 1H), 7.83 (d, J = 8.8 Hz, 2H), 6.94 (d, J = 8.6 Hz, 2H), 6.8 (d, J = 3.4 Hz, 1H), 6.68 (d, J = 3.6 Hz, 1H), 4.25-4.10 (m, 6H), 3.88 (s, 3H), 3.31 (s, 2H), 2.8 (brs, 4H), 1.28 (t, J = 7.2 Hz, 3H); MS *m/e* (relative intensity) 407 (M^+-44, 11), 378 (2), 334 (5), 320 (3), 272 (14), 236 (30), 142 (86).

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