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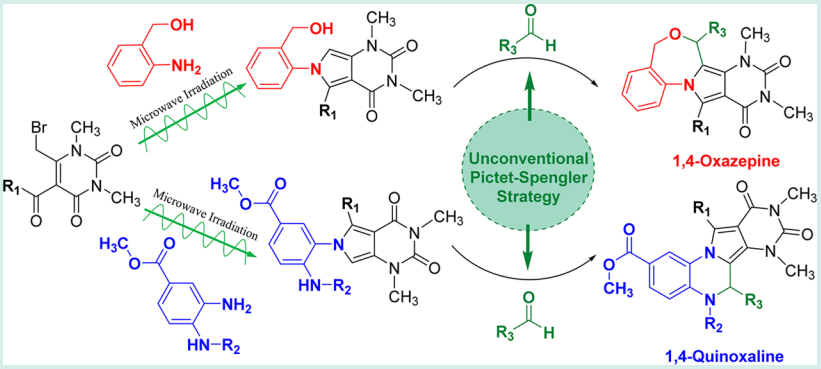
Skeletally Diverse Synthesis of Innovative [2,1-*c*]-1,4-Oxazepine and [1,4]-Quinoxaline Systems

Chia-Hsin Lee,[†,‡] Wen-Chun Wu,[†] Prasad S. Dangate,[†] Li-Ching Shen,[†] Wen-Sheng Chung,*[,†] and Chung-Ming Sun*[,†,‡]

[†]Department of Applied Chemistry, National Chiao-Tung University, 1001 Ta-Hseuh Road, Hsinchu 300-10, Taiwan

[‡]Department of Medicinal and Applied Chemistry, Kaohsiung Medical University, 100, Shih-Chuan First Road, Kaohsiung 807-08, Taiwan

Supporting Information



ABSTRACT: An efficient, innovative synthesis of [2,1-*c*]-1, 4-oxazepine and [1,4]-quinoxaline heterocycles along with the embodied pyrimido-pyrrolo motifs was established. Initially, the pyrrole ring was installed using microwave irradiation through an intramolecular base-catalyzed cyclization between acetyl bromomethyl pyrimidine dione and *o*-amino phenyl methanol or *o*-phenylenediamine methyl benzoates. Furthermore, oxazepine, and quinoxaline scaffolds were constructed by an acid-catalyzed condensation with a variety of aldehydes by an unconventional Pictet–Spengler reaction strategy. An important aspect of this work is to build novel heterocyclic ring systems with potential medicinal interest.

KEYWORDS: *oxazepine, quinoxaline, pyrimido-pyrrolo motifs, unconventional Pictet–Spengler reaction strategy*

INTRODUCTION

In the last few decades, medicinal chemists have been interested in oxazepines and pyrimido-pyrrolo-quinoxaline diones (PPQs), and these novel scaffolds are still not extensively studied. Both compounds are currently of great interest due to their therapeutic value in highly widespread diseases such as deadly cancers and AIDS. Derivatives of oxazepine were found to exhibit a vast variety of biological activities such as antibacterial, antifungal, anti-inflammatory, antiepileptic, anti-depressive, and antiviral activities.[1] For example, 5-amino oxazepine as a β-secretase inhibitor is useful for the treatment of Alzheimer's disease.[2] Pyrrolobenzoxazepine has been applied to treat tumors derived from the hemopoietic system.[3] Similarly, PPQ derivatives are known potent inhibitors of cystic fibrosis transmembrane conductance regulator (CFTR) and are also applied as treatments for polycystic kidney disease (PKD), a common human genetic disorder (Figure 1).[4,5]

Very few strategies to synthesize these scaffolds have been reported. Oxazepine is usually prepared by the pericyclic cycloaddition of Schiff bases with maleic, phthalic, and succinic anhydrides.[6] This compound can also be synthesized via intramolecular dehydration between carboxaldehyde and a substituted pyrrole with phosphorus pentaoxide,[7] or coupling between pyrrolinones and *o*-hydroxyl aniline with piperidine.[8]

PPQ has been typically prepared using 6-methyl uracil as one of the starting materials. It was first alkylated by methyl iodide with sodium hydroxide. Acylation was performed by benzoyl chloride and zinc chloride, whereas bromination at the allylic position was achieved by bromine to form benzoyl pyrimidine diones. Later, the intermediate was cyclized with *o*-phenyl-enediamine to obtain pyrimidine-pyrrolo benzoate, which was further condensed with an aldehyde under acidic conditions to afford the corresponding PPQ compounds.[9-12] In this protocol, a microwave was used as the heat source to improve the reaction rate and reduce cost and energy during the synthesis.[13] Therefore, in furthering our research interest to synthesize these fused heterocyclic systems, we developed here an efficient diversity-oriented synthesis of oxazepines and PPQ using an unconventional Pictet–Spengler strategy.

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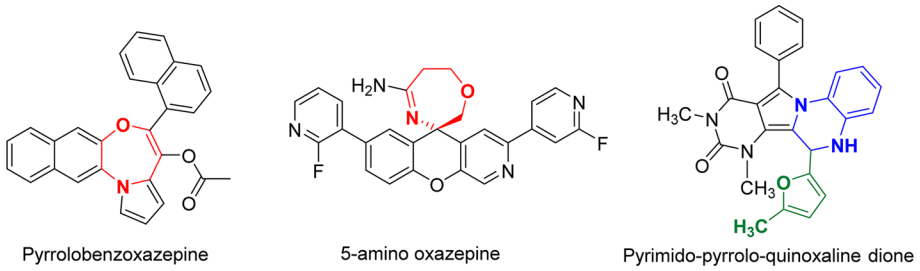
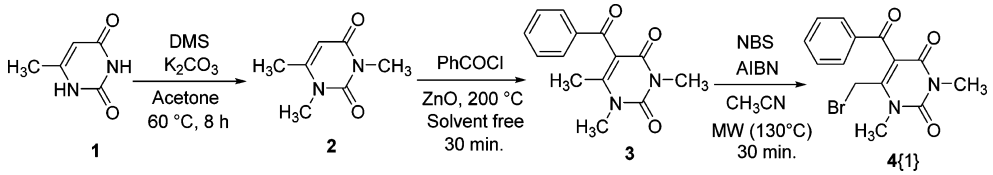


Figure 1. Biologically active oxazepines and PPQ compounds.

Scheme 1. Synthesis of Bromomethyl Benzoyl Pyrimidine Diones 4{1}



RESULTS AND DISCUSSION

Synthesis of substituted pyrimidine diones **4**{1} was achieved in three consecutive steps from 6-methyl uracil **1** (Scheme 1). In the first step, the nitrogen in uracil was methylated by dimethyl sulfate or methyl iodine to synthesize compound **2**. The most favorable reaction conditions included using acetone, potassium carbonate, and dimethyl sulfate as solvent for 8 h with 96% isolated yield (entry 6, Table 1). The reaction was found to proceed faster and produce higher yields than the reported literature procedure.[14]

Table 1. Optimization of Reaction Conditions for Methylation

entry	alkylating reagent	base	solvent	condition	time (h)	yield (%)
1	CH_3I	NaOH	DMF	rt	8	65
2	CH_3I	NaOH	DMF/EtOH = 1:1	rt	100	20
3	CH_3I	NaOH	DMF/H_2O	rt	100	0
4	CH_3I	*t*-BuOK	CH_3CN	reflux	8	72
5	dimethyl sulfate	NaOH	H_2O	rt	48	96
6	dimethyl sulfate	K_2CO_3	acetone	reflux	8	96

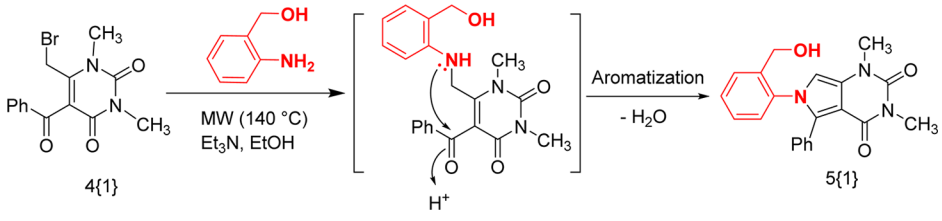
In the next step, benzoylation of pyrimidine dione **2** with benzoyl chloride was performed using zinc chloride as a catalyst; however, these reaction conditions resulted in an unsatisfactory 25% yield.[15] It has been reported that zinc oxide has been used for the *N*-formylation of amines.[16] Hence, we utilized zinc oxide as a catalyst instead of zinc chloride, and benzoyl pyrimidine dione **3** was obtained in 80% yield under solvent-free conditions at 200 °C.

In the initial procedure, bromine was used for the allylic bromination of benzoyl pyrimidine dione **3** in cosolvents (CH_2Cl_2/CCl_4 = 1:10) after refluxing for 48 h to obtain an 85% yield.[17] Although the obtained yield is quantitatively high, the corrosive and toxic effects of bromine should be avoided.[18] Therefore, we reacted *N*-bromo succinimide with AIBN to transform **3** to **4**{1} under microwave conditions at 130 °C for 15 min, which produced a high yield (85%). Next, we employed the current synthetic strategy to construct the pyrrole ring. Compound **4**{1} and *o*-amino phenyl methanol were reacted under microwave irradiation at 140 °C (Scheme 2). Pyrrole ring formation was observed after aromatization due to the nucleophilic attack of aniline of *o*-amino phenyl methanol at the carbon attached to the bromine, followed by condensation with a benzoyl group to remove water. The reaction of 1,3-dimethylpyrimidine dione **4**{1} rapidly converted to its corresponding pyrrole adduct **5**{1} in 85% yield in 15 min. A list of essential building blocks that were used to synthesize target molecules can be found in Figure 2.

The synthesis of oxazepine was performed by the reaction of 2-arylethanol attached to dimethyl pyrrolo pyrimidine dione **5**{1} with aldehydes in chloroform for 6 h under reflux conditions to afford a fused heterocyclic compound with a newly formed pyranic ring. As presented in Scheme 3, the synthesis of pyrimido pyrrolo-1,4-oxazepine dione **8** {1,12} from **5**{1} was optimized to afford a 77% yield of product (entry 7, Table 2).

The oxygen version of the Pictet–Spengler reaction was first termed the "oxa-Pictet–Spengler reaction" by Wünsch and Zott in 1992. In our current study, this rare oxa-Pictet–Spengler

Scheme 2. Synthesis of Pyrrole under Microwave Condition



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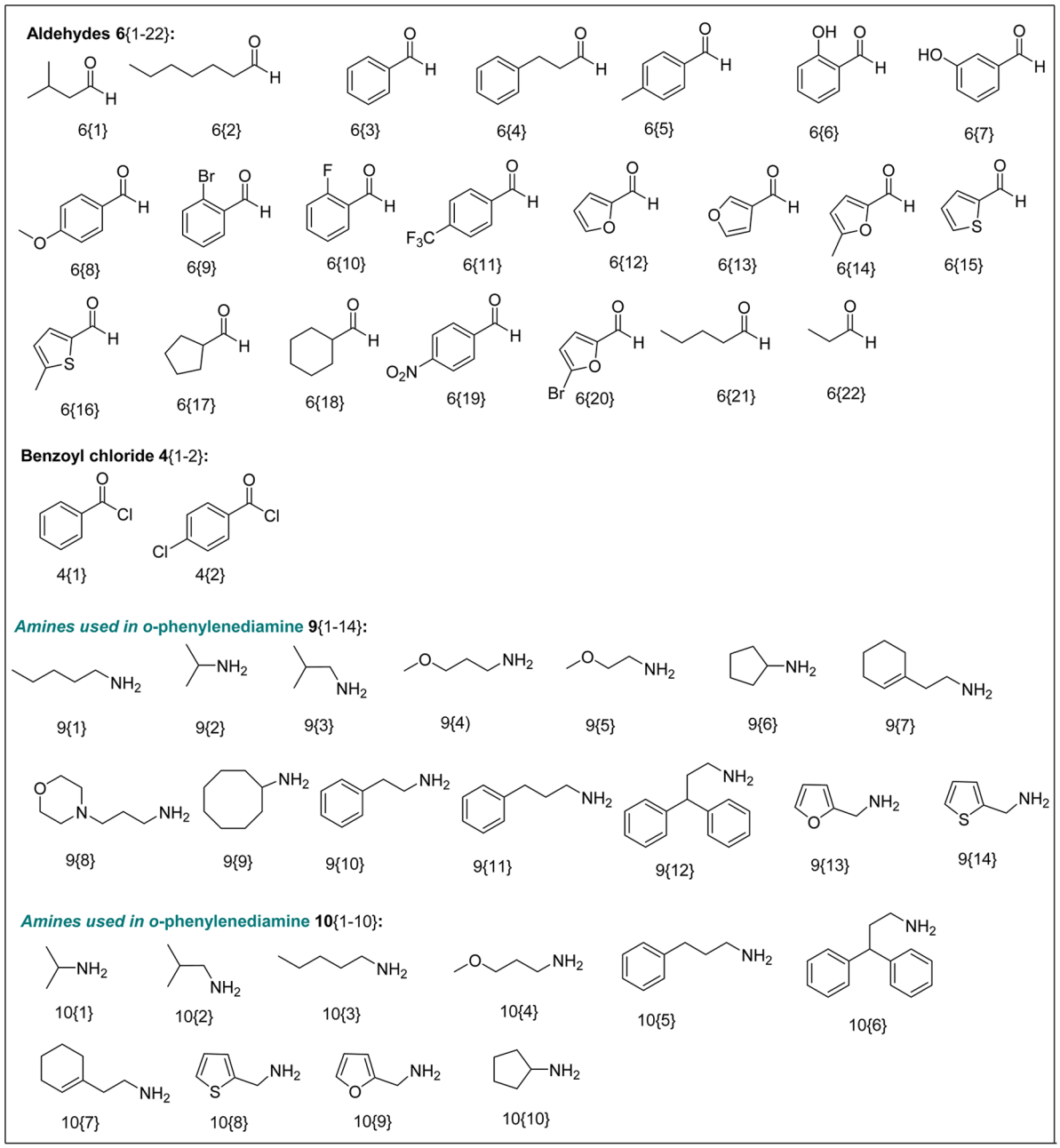
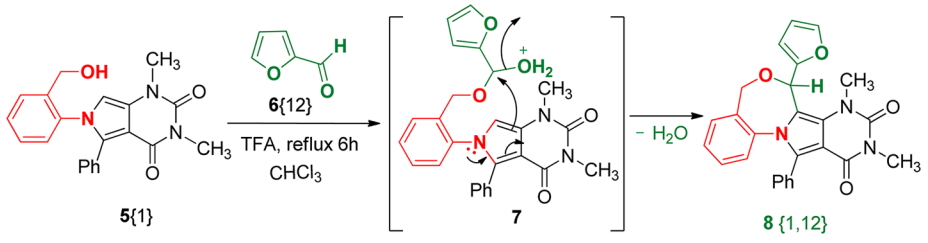


Figure 2. Essential building blocks.

Scheme 3. Synthesis of Oxazepine 8



reaction is applied so that the electron-deficient aromatic pyrrole carbon atom can close the heterocyclic ring by the lone pair electron resonance of nitrogen acting as a carbon nucleophile to attack the imine. The other possible mechanism for this uncommon reaction involves the acid-catalyzed Friedel–Crafts-type hydroxyl-alkylation with various aldehydes.

In the next stage, the 1,4-oxazine core is formed by loss of the hydroxyl group via an intramolecular electrophilic attack of the pyrrole-substituted benzyl alcohol. Next, the primary alcohol of 1, 3-dimethyl pyrrolo pyrimidine dione **5**{1} attacks the electrophilic carbon of furfuraldehyde **6**{12} to form intermediate **7**. Furthermore, water was removed by

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Table 2. Optimization of Reaction Conditions for Pictet–Spengler Reaction

entry	acid	solvent	condition	time (h)	yield (%)
1	PTSA	ACN	reflux	2	trace
2	PTSA	EDC	reflux	2	50
3	PTSA	EDC	reflux	5	trace
4	PTSA	$CHCl_3$	reflux	24	no reaction
5		$CHCl_3$	reflux	2	no reaction
6	TFA	EDC	reflux	1	trace
7	TFA	$CHCl_3$	reflux	6	77

nucleophilic attack of pyrrole ring electrons by nitrogen lone pair delocalization to the electrophilic carbon. This intramolecular cyclization led to the formation of the seven-membered oxazepine ring **8**{1,12} via an unconventional oxa-type Pictet–Spengler reaction. Formation of this compound was absolutely confirmed by X-ray crystallography (Figure 3). The pyrrole ring and oxazepine ring are fused in one plane, and furan is located above the plane.

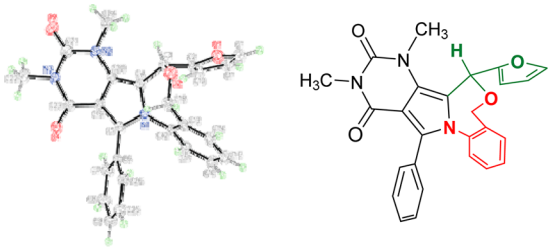
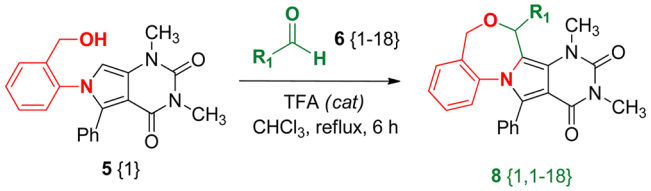


Figure 3. ORTEP diagram of compound **8**{1,12} (Table 3, entry 12).

To summarize the reaction, compound **5**{1} was treated with a variety of alkyl (entries 1–2), aromatic (entries 3–11), heterocyclic (entries 12–16), and nonaromatic (entries 17–18) aldehydes using optimized conditions to obtain the corresponding oxazepine **8**{1,1–18} in 68–82% yield (Table 3). To expand the scope of functionality, compound **5**{1} was further reacted with acetonitrile in neat MW condition, as shown in Scheme 4. Presumably, the primary alcohol in 2-aryl ethanol can attack the nitrile group to deliver the imine under acidic conditions, which may induce further reactions with the pyrrole-C2 nucleophile to produce compound **14**. However,

Table 3. Substrate Scope for Synthesis of Oxazepine 8



entry	product	yield (%)	entry	product	yield (%)
1	**8**{1,1}	68	10	**8**{1,10}	80
2	**8**{1,2}	71	11	**8**{1,11}	82
3	**8**{1.3}	73	12	**8**{1,12}	77
4	**8**{1,4}	72	13	**8**{1, 13}	75
5	**8**{1,5}	72	14	**8**{1,14}	75
6	**8**{1,6}	74	15	**8**{1,15}	75
7	**8**{1,7}	71	16	**8**{1,16}	72
8	**8**{1,8}	70	17	**8**{1,17}	74
9	**8**{1,9}	75	18	**8**{1,18}	73

the electron-deficient pyrrole was not able to attack the imine, and it was further hydrolyzed to ester **13** in 35% yield (Supporting Information, S552–S553).

Similarly, the synthesis of **10**{1,3} was achieved when benzoyl bromomethyl dimethyl pyrimidine dione **4**{1} and substituted *o*-phylene diamine ester **9**{3} were reacted under microwave conditions at 140 °C in ethanol for 15 min (Scheme 5).

The primary amine present in compound **9**{3} is more nucleophilic as the lone pair electrons on the secondary nitrogen atom is involved in resonance with the ester group at the *para* position.[19] Therefore, pyrrole ring formation occurred through aromatization after nucleophilic substitution of the primary amine, followed by acid-catalyzed condensation with the benzoyl group. The reaction was completed in 15 min as *o*-phenylenediamine methyl carboxylate **9**{3} was rapidly converted to methyl benzoates **10**{1,3} in 99% yield (entry 3, Table 4). To investigate the generality of this process, substituted pyrimidine dione **4**{1} was reacted with alkyl- (entries 1–4 and 14–16), aryl- (entries 9–13 and 19–20), cyclopentyl- (entries 5 and 17), cyclooctyl- (entry 8), morpholine- (entry 7), and cyclohexene- (entry 6 and 18) substituted *o*-phenylenediamine esters **9**{1–14} with triethylamine in ethanol, under pressure, and in microwave conditions at 140 °C.

Through intramolecular acid-catalyzed cyclization, a variety of pyrimido-pyrrolo amino methyl benzoates (**10**) were formed in 60–99% yield. For the synthesis of a new scaffold similar to compound **12**{2,19}, an unconventional Pictet–Spengler reaction strategy was applied, a model study where *p*-TSA was used as an acid catalyst for the condensation between compound **10**{2} and *p*-nitro benzaldehyde **6**{19} to generate an iminium intermediate (**11**) with the release of water (Scheme 6). The iminium ion derived from the aniline moiety is more electron-deficient and thus provides a driving force to prompt carbon–carbon bond formation with the sp^2 carbon nucleophile of the pyrrole ring. Hence, nucleophilic attack of the secondary nitrogen atom of compound **10**{2} to the *p*-nitrobenzaldehyde **6**{19} leads to the formation of adduct **12**{2,19}. Furthermore, quinoxaline ring formation was achieved as a result of delocalization of the lone pair electrons from the pyrrole nitrogen and attack of the ring π-electrons to the electrophilic imine via π-cyclization. This endocyclization to create a new carbon–carbon bond between a carbon nucleophile (C2) of an unreactive aromatic pyrrole and the electrophilic Schiff's base successfully delivered an N-heterocyclic pyrimido-pyrrolo quinoxaline ring. Reaction conditions were optimized, and compound **12**{2,19} was obtained in 95% yield (entry 7, Table 5).

The formation of a highly substituted compound was confirmed by X-ray crystallography (Figure 4).

As shown in Table 6, alkyl-, aryl,- cyclopentyl-, and benzyl-substituted compounds **10**{1–10} were condensed with electron donating and withdrawing alkyl, aryl, and phenyl aldehydes **6**{1–22} through intramolecular cyclization in the presence of acid to produce the corresponding pyrimido-pyrrolo quinoxaline methyl carboxylates **12** in 52–98% yield. Mainly, substitution patterns on the nitrogen of compound **10**{1–10} are found to affect the yield.

The yield was also dependent on the electron donating and withdrawing nature of the substitution on aldehydes. The reaction with *p*-nitro benzaldehyde produced (entry 14, Table

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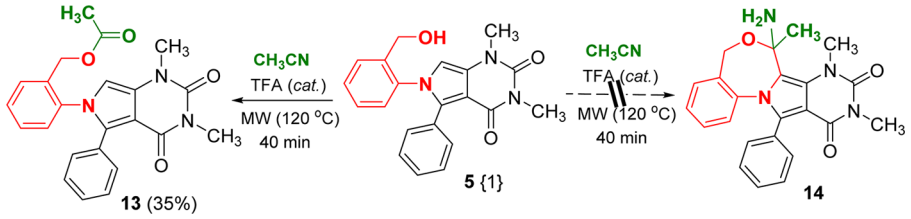
Scheme 4. Reaction of Pyrrolo Pyrimidine Dione 5{1} with Acetonitrile



Scheme 5. Synthesis of Pyrimido-Pyrrolo Amino Methyl Benzoate 10

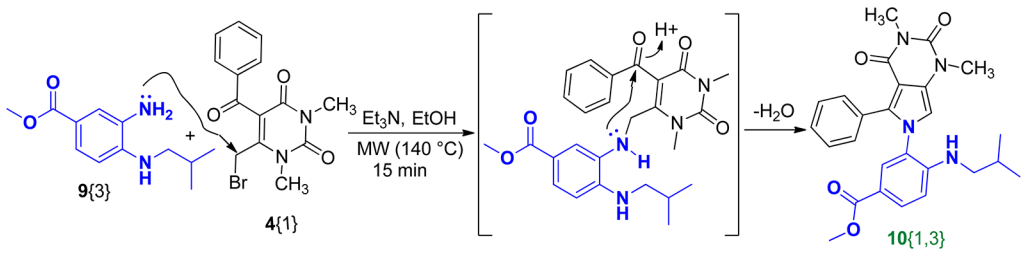
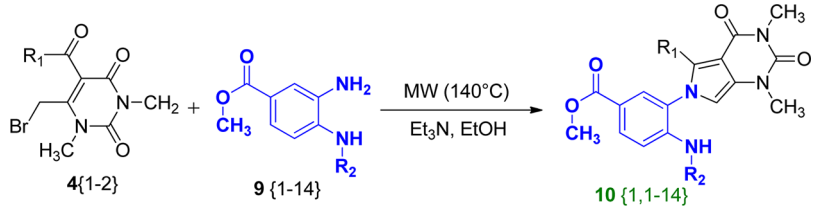
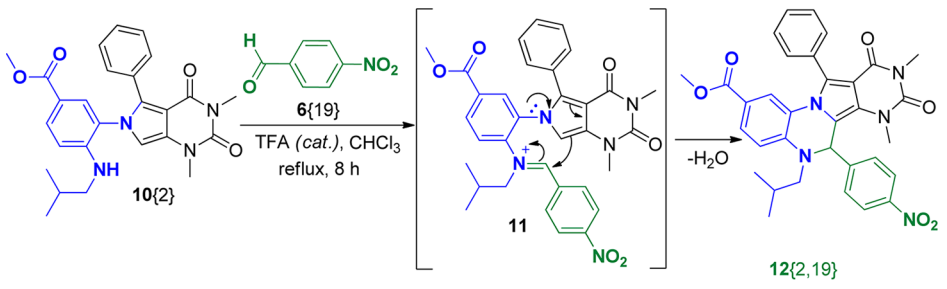


Table 4. Substrate Scope for the Synthesis of Pyrimido-Pyrrolo Amino Methyl Benzoates (10)



entry	product	isolated yield (%)	entry	product	isolated yield (%)
1	**10**{1,1}	65	11	**10**{1,11}	77
2	**10**{1,2}	82	12	**10**{1,12}	60
3	**10**{1,3}	99	13	**10**{1,13}	80
4	**10**{1,4}	94	14	**10**{1,14}	84
5	**10**{1,5}	73	15	**10**{2,1}	60
6	**10**{1,6}	70	16	**10**{2,3}	60
7	**10**{1,7}	80	17	**10**{2,6}	65
8	**10**{1,8}	60	18	**10**{2,7}	61
9	**10**{1,9}	63	19	**10**{2,13}	70
10	**10**{1,10}	80	20	**10**{2,14}	70

Scheme 6. Synthesis of Pyrimido-Pyrrolo Quinoxaline Carboxylate 12



5) a higher yield than the reaction with *p*-methoxy benzaldehyde (entry 15, Table 5).

In summary, the generalization of this approach and the expansion of skeletal diversity are achieved using various aldehydes in an unconventional Pictet–Spengler cyclization. This novel intramolecular cyclization combines the less reactive pyrrole-C2 as a nucleophile with a pyrrole-N-attached 2-aryl ethanol or aniline functionality with aldehydes in this unconventional Pictet–Spengler reaction. The work described here demonstrates the versatility of the oxa-type Pictet–Spengler cyclization in the construction of novel heterocycles. The variety of aldehydes used and the built-in pyrimido-pyrrolo scaffold produced additional diversity in the target skeleton. The use of a microwave-promoted, nontraditional Pictet–Spengler reaction opens a new route for the efficient synthesis of diversified and fused heterocycles of medicinal interest. The rapid synthesis of skeletally diverse libraries and the results

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Table 5. Optimization of Reaction Condition for Pictet–Spengler Reaction

entry	acid	solvent	condition	time (h)	yield (%)
1	PTSA	ACN	reflux	2	trace
2	PTSA	EDC	reflux	2	90
3	PTSA	EDC	reflux	5	trace
4	PTSA	$CHCl_3$	reflux	24	no reaction
5		$CHCl_3$	reflux	2	no reaction
6	TFA	EDC	reflux	1	trace
7	TFA	$CHCl_3$	reflux	8	95

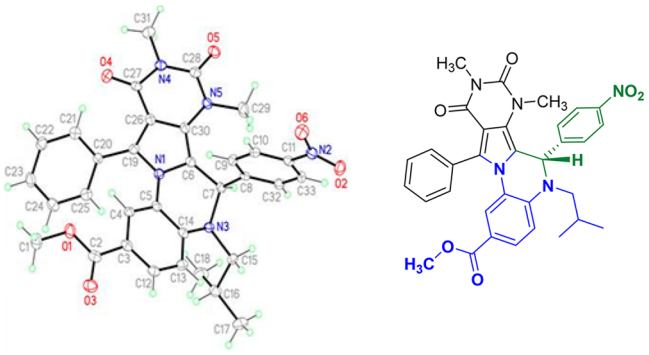


Figure 4. ORTEP Diagram of Compound **12**{2,19} (Table 3, entry 4).

from their screening to identify biologically active compounds will be reported elsewhere.

EXPERIMENTAL PROCEDURES

General Procedure for the Synthesis of Compound 2. To the solution of 6-methyluracil **1** (1 g, 7.9 mmol) in acetone (15 mL), potassium carbonate (2.72 g, 19.8 mmol, 2.5 equiv) was added and stirred for 20 min at 25 °C. To the above stirred solution, dimethyl sulfate (2.49 g, 19 mmol, 2.5 equiv) was added, and the reaction mixture was heated to 60 °C. Reaction progress was monitored by TLC. After 3 h, another lot of DMS (1 g, 7.9 mmol, 1 equiv) was added, and the reaction continued for 8 h until completion. The reaction mixture was filtered, and the solvent was concentrated under reduced pressure at 45 °C. Crude product was further recrystallized in ethyl acetate to obtain the pure 1,3,6-trimethyl pyrimidine-2,4 (1H, 3H)-dione **2** (1.17 g, 96% yield).

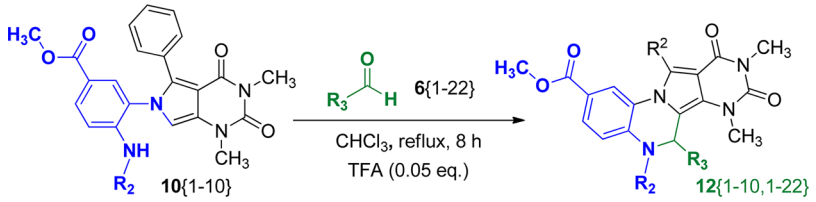
^{1}H NMR (300 MHz, $CDCl_3$) δ 5.64 (s, 1H), 3.42 (s, 3H), 3.35 (s, 3H), 2.25 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.9, 152.1, 151.9, 101.6, 32.1, 28.3, 20.6. MS (ESI-MS) *m/z*: 177 $(M+Na)^+$. HRMS: calcd for $C_7H_{10}N_2O_2$ *m/z*: 154.0742; found 177.0639 $(M+Na)^+$.

General Procedure for the Synthesis of Compound 3. To a mixture of 1,3,6-trimethyl pyrimidine-2,4 (1H, 3H)-dione **2** (1 g, 6.48 mmol) and ZnO (0.26 g, 3.2 mmol, 0.5 equiv), benzoyl chloride (1.6 g, 11.3 mmol, 1.77 equiv) was added, and the reaction mixture was heated in an oil bath at 200 °C for 30 min. Reaction progress was monitored by TLC. After the reaction was complete, dichloromethane (25 mL) was added to the reaction mixture, and ZnO was removed by filtration. The organic solvent was then washed with H_2O (2 × 10 mL), added to a saturated solution of $NaHCO_3$, and dried over anhydrous $MgSO_4$. The organic solvent was concentrated under reduced pressure at 38 °C to obtain the crude product. After removal of the solvent, the crude product was further purified by column chromatography to yield pure 5-benzoyl-1,3,6-trimethylpyrimidine-2,4 (1H, 3H)-dione **3** (1.3 g, 78% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82–7.92 (dd, J = 7.6, 1.9 Hz, 2H), 7.72–7.62 (m, 1H), 7.52 (t, J = 7.6 Hz, 2H), 3.53 (s, 3H), 3.42 (s, 3H), 2.31 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.22, 161.10, 153.12, 152.33, 138.36, 135.42, 131.19, 131.19, 129.14, 129.14, 114.25, 33.04, 28.17, 18.21. MS (ESI–MS) *m/z*: 259.3 $(M+H)^+$. HRMS: calcd for $C_{14}H_{14}N_2O_3$ *m/z*: 258.1004; found 259.1082 $(M+H)^+$.

General Procedure for the Synthesis of Compound 4{1}. The 5-benzoyl-1,3,6-trimethylpyrimidine-2,4 (1H, 3H)-dione **3** (0.5 mg, 1.9 mmol) was dissolved in 8 mL of acetonitrile with *N*-bromosuccinimide (0.7 g, 3.9 mmol, 2.05 equiv) and a catalytic amount of AIBN (0.015 g, 0.09 mmol, 0.05 equiv). The reaction mixture was exposed to microwave radiation (150 W, 130 °C) for 15 min. After completion of the reaction, the solvent was concentrated under reduced pressure at 70 °C. Crude products were further purified by column chromatography to obtain 5-benzoyl-6-(bromomethyl)-1,3-

Table 6. Substrate Scope for the Pyrimido-Pyrrolo-Quinoxaline Dione Methyl Carboxylate 12



entry	product	yield (%)	entry	product	yield (%)
1	**12**{1,1}	52	11	**12**{6,21}	54
2	**12**{1,4}	80	12	**12**{7,3}	55
3	**12**{2,12}	90	13	**12**{8,22}	65
4	**12**{2,19}	95	14	**12**{8,19}	98
5	**12**{3,3}	70	15	**12**{8,8}	60
6	**12**{3,4}	82	16	**12**{9,8}	67
7	**12**{3,20}	95	17	**12**{9,22}	96
8	**12**{4,3}	85	18	**12**{9,21}	61
9	**12**{4,8}	81	19	**12**{10,3}	93
10	**12**{5,1}	55	20	**12**{10,8}	90

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dimethylpyrimidine-2,4 (1H, 3H)-dione **4**{1} (0.55 g, 85% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, J = 7.4 Hz, 2H), 7.60 (t, J = 7.3 Hz, 1H), 7.48 (d, J = 7.4 Hz, 2H), 3.51 (s, 3H), 3.36 (s, 3H), 2.25 (S, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.7, 161.0, 152.1, 152.1, 137.8, 134.2, 129.7, 129.1, 113.5, 32.5, 28.6, 18.1. MS (ESI-MS) m/z: 259 $(M+H)^+$. HRMS: calcd for $C_{14}H_{14}N_2O_3$ m/z: 258.1004; found 259.1082 $(M+H)^+$.

General Procedure for the Synthesis of Compounds 5{1} and 10{1,1−14}. The 5-aryl carbonyl-6-(bromomethyl)-1,3-dimethylpyrimidine-2,4 (1H, 3H)-dione (0.5 g, 1 equiv) **4**{1} and *o*-amino phenyl methanol (1.2 equiv) or methyl 3-amino-4-(isobutylamino)benzoate (1.2 equiv) were added to a 15 mL high pressure glass bottle with ethanol (8 mL). Triethyl amine (1 equiv) was added to the above solution, and the reaction mixture was exposed to microwave irradiation (180 W, 140 °C) for 15 min. After completion of the reaction, the organic phase was washed with acetic acid (5 mL) and concentrated under reduced pressure at 70 °C. Crude product was further recrystallized with ethyl acetate to obtain compounds **5**{1} (0.41 g, 85% yield) and **10**{1,3} (1.01 g, 99% yield).

*Methyl-3-(1,3-dimethyl-2,4-dioxo-5-phenyl-3,4-dihydro-1H-pyrrolo[3,4-d]-pyrimidin-6(2H)-yl)-4-(isobutyl amino)-benzoate **10**{1,3}.* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, J = 8.7 Hz, 1H), 7.75 (s, 1H), 7.38−7.29 (m, 2H), 7.25−7.18 (m, 3H), 6.57 (d, J = 8.7 Hz, 1H), 6.43 (s, 1H), 3.82 (s, 3H), 3.40 (s, 3H), 3.38 (s, 3H), 2.94−2.76 (m, 2H), 1.71 (m, 1H), 0.82 (d, J = 6.8 Hz, 3H), 0.80 (d, J = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8, 160.2, 152.1, 148.1, 148.1, 135.3, 132.5, 131.0, 130.6, 129.2, 128.7, 128.1, 123.6, 118.0, 110.6, 104.3, 103.6, 52.2, 51.0, 32.0, 28.5, 28.3, 20.7, 20.6. MS (ESI−MS) m/z: 461 $(M+Na^+)$. HRMS: calcd for $C_{26}H_{28}N_4O_4$ m/z: 460.2111; found 483.2005 $(M+Na^+)$.

General Procedure for the Synthesis of Oxazepine 8{1,1−18}. To the solution of compound **5**{1} (0.5 g, 1 equiv) in chloroform (12 mL), aldehyde (1.2 equiv) and a catalytic amount of trifluoroacetic acid (0.05 equiv) were added. The reaction mixture was refluxed for 6 h, and reaction progress was monitored by TLC. After completion of the reaction, the solvent was concentrated under reduced pressure at 55 °C. Crude product was purified by column chromatography to obtain pure product **8**{1,1−18} (68−82% yield).

*7-(Furan-2-yl)-8,10-dimethyl-12-phenyl-8,10-dihydrobenzo[e]pyrimido[4′,5′:3,4]pyrrolo[2,1-c][1,4]-oxazepine-9,11(5H,7H)-dione **8**{1,12}.* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (d, J = 7.5 Hz, 1H), 7.17−7.32 (m, 5H), 7.13 (t, J = 7.5 Hz, 1H), 7.01 (s, 1H), 6.87 (t, J = 7.8 Hz, 1H), 6.65 (s, 1H), 6.40 (d, J = 8.0 Hz, 1H), 5.91 (m, 1H), 5.43 (d, J = 2.4 Hz, 1H), 4.90 (d, J = 11.9 Hz, 1H), 4.70 (d, J = 11.9 Hz, 1H), 3.74 (s, 3H), 3.39 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5, 152.9, 152.3, 141.2, 137.5, 134.6, 132.2, 131.0, 129.8, 128.9, 128.8, 128.7 127.9, 127.6, 126.2, 112.1, 110.3, 106.5, 104.5, 67.4, 66.6, 33.1, 28.1. MS (ESI−MS) m/z: 440 $(M+H^+)$. HRMS: calcd for $C_{26}H_{21}N_3O_4$ m/z 439.1532; found 440.1605 $(M+H^+)$. IR (cm^{-1}, neat): 3069, 2954, 2865, 1700, 1658.

General Procedure for the Synthesis of PPQ 12{1−10,1−22}. To the solution of compound **5**{1} (0.5 g, 1 equiv) in chloroform (12 mL), aldehyde (1.2 equiv) and a catalytic amount of trifluoroacetic acid (0.05 equiv) were added. The reaction mixture was refluxed for 8 h, and reaction progress was monitored by TLC. After completion of the reaction, the solvent was removed under reduced pressure. Crude product was purified by column chromatography to obtain pure product PPQ **12**{1−10,1−22} in 52−98% yield.

*Methyl-5-isobutyl-7,9-dimethyl-8,10-dioxo-6,11-diphenyl-5,6,7,8,9,10-hexa-hydropyrimido[4′,5′:3,4] pyrrolo[1,2-a]-quinoxaline-2-carboxylate **12**{2,19}.* ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (d, J = 8.6 Hz, 2H), 7.88 (m, 1H), 7.66 (dd, J = 8.6, 1.7 Hz, 1H), 7.50 (t, J = 7.2 Hz, 1H), 7.36 (d, J = 7.2 Hz, 2H), 7.15 (d, J = 8.6 Hz, 2H), 6.99 (d, J = 8.6 Hz, 1H), 5.97 (s, 1H), 3.65 (s, 3H), 3.57 (s, 3H), 3.43 (dd, J = 13.6, 6.1 Hz, 1H), 3.34 (s, 3H), 2.97 (dd, J = 13.6, 6.1 Hz, 1H), 2.19 (m, 1H), 1.07 (d, J = 6.4 Hz, 3H), 1.02 (d, J = 6.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9, 159.4, 152.0, 147.7, 145.6, 140.8, 131.1, 130.2, 129.3, 128.7, 128.3, 127.7, 127.7, 125.1, 124.3, 124.3, 123.0, 122.5, 115.2, 111.4, 105.9, 59.8, 58.4, 51.7, 32.6, 27.9, 26.5, 20.6, 20.1. MS (ESI−MS) m/z: 594.2 $(M+H^+)$. HRMS: calcd for $C_{33}H_{31}N_5O_6$ m/z: 593.2274; found 594.2342 $(M+H^+)$.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscombsci.5b00093.

Spectroscopic data (^{1}H and ^{13}C NMR, LRMS, HRMS, FT-IR) of oxazepines **8**{1,1−18}, pyrimido-pyrrolo amino methyl benzoates **10**{1,1−14}, and PPQ **12**{1−10,1−22} (PDF)

Single X-ray crystallographic data of compound **8**{1,12} (CIF)

Single X-ray crystallographic data of compound **12**{2,19} (CIF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: cmsun@mail.nctu.edu.tw.

*E-mail: wschung@nctu.edu.tw.

Notes

The authors declare no competing financial interest.

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