Highly Chemoselective Multicomponent Biginelli-Type Condensations of Cycloalkanones, Urea or Thiourea and Aldehydes

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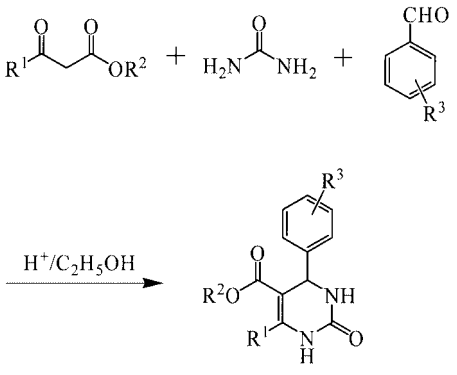
The classical Biginelli reaction is considerably extended by use of cycloalkanones instead of 1,3-dicarbonyl compounds. Use of TMSCl as a Lewis acid allowed one-pot chemoselective multicomponent Biginelli reactions between cycloalkanones, urea or thiourea, and aldehydes. Under similar reaction conditions, thiourea exhibited different behavior to urea, and aliphatic aldehydes showed lower reactivity than aromatic aldehydes. A possible mechanism to account for the reaction is proposed.

Introduction

Multicomponent reactions (MCRs) are of considerable importance in organic and medicinal chemistry.[1–4] Biginelli reactions are ranked as one of the most powerful tools for the facile synthesis of complex heterocyclic scaffolds for therapeutic and pharmacological properties.[5–7]

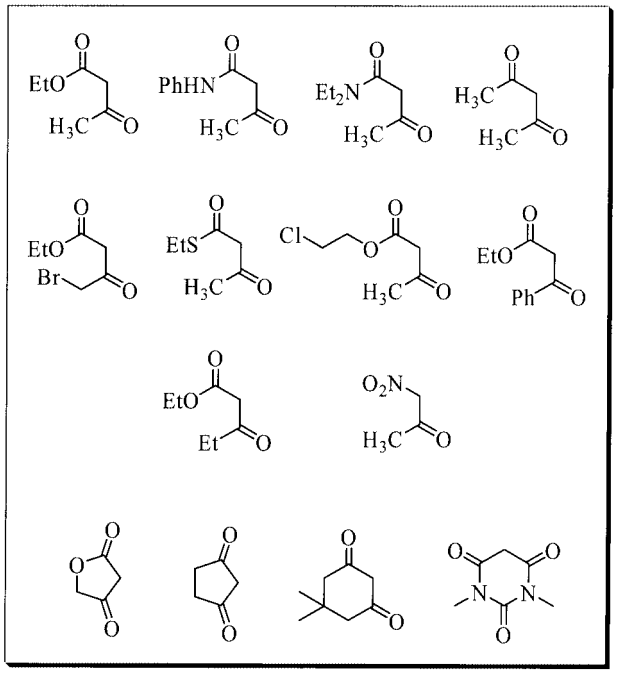
Classical Biginelli reactions involve one-pot condensations of an aldehyde, a β-ketoester, and urea under strongly acidic conditions (Scheme 1).[8]



Scheme 1.

In recent decades, the scope of the original Biginelli reaction shown in Scheme 1 was extended by variation of the 1,3-dicarbonyl compound building blocks (Table 1). Many groups have elegantly demonstrated the synthetic versatility of numerous 1,3-dicarbonyl compounds, including β-keto esters and cyclic β-diketones.[9–27]

Table 1. Ketone building blocks.



The initial aim of our work was to discover and develop novel reactions to extend the scope of the well known Biginelli reaction through the use of cycloalkanones instead of 1,3-dicarbonyl compounds.

Results and Discussion

In order to confirm our hypothesis, we began to explore the reaction between cyclopentanone (**1a**, 10 mmol), urea (**2a**, 12 mmol), and benzaldehyde (**3a**, 10 mmol) to deter-

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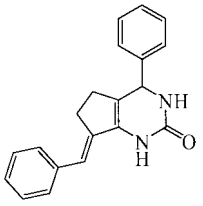
mine the best promoter. Many catalysts or promoters such as HCl,[8] $BF_3{\cdot}OEt_2$,[9] polyphosphate ester,[10] $LaCl_3$,[11] $InCl_3$,[12] $ZrCl_4$,[13] $BiCl_3$,[14] NH_2SO_3H,[22] and $Cu(OTf)_2$[23] were applied under Biginelli-type reaction conditions, but no reactions were observed. However, a satisfactory result was obtained when the reaction was carried out in the presence of TMSCl (10 mmol) in DMF/CH_3CN (6 mL/3 mL).[28–30] Curiously, the product, 7-benzylidene-4-phenyl-1,3,4,5,6,7-hexahydro-cyclopentapyrimidin-2-one (**5a**), shown in Figure 1 and confirmed by NMR measurements (including two-dimensional NMR) and mass spectrometry, was obtained in 93% yield (yield based on benzaldehyde), while in contrast, the desired classical Biginelli product (**4**, Scheme 2, below) was not obtained at all.

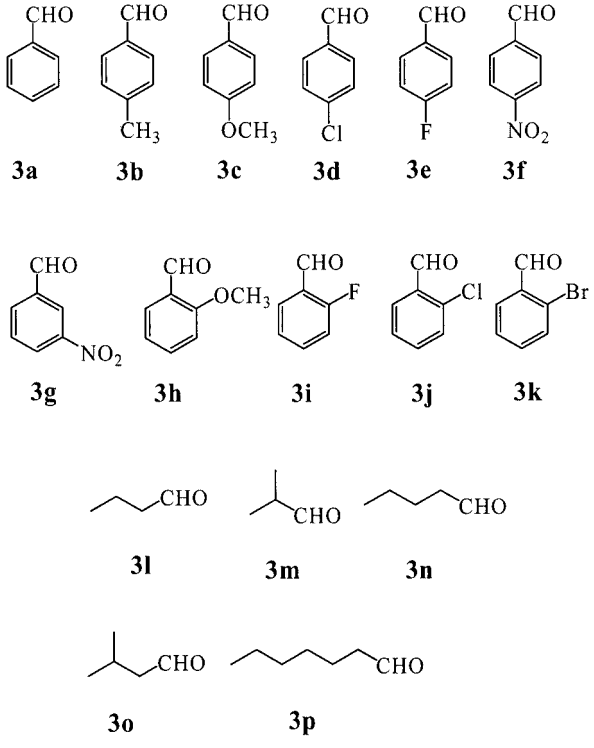


5a

Figure 1. Benzylidene heterobicyclic product **5a**.

We similarly extended this procedure to various cycloalkanones by use of parallel organic synthesis arrays. Cycloalkanones such as cyclopentanone (**1a**), cyclohexanone (**1b**), cycloheptanone (**1c**), cyclooctanone (**1d**), and cyclododecanone (**1e**) reacted cleanly with urea (**2a**) or thiourea (**2b**)

Table 2. Aldehyde building blocks **3a**–**h** used in Biginelli-type reactions.



3a **3b** **3c** **3d** **3e** **3f**

3g **3h** **3i** **3j** **3k**

3l **3m** **3n**

3o **3p**

and aldehydes **3a**–**h** to give three families of fused heterobicyclic, benzylidene heterobicyclic, and spiro heterotricyclic pyrimidines **4**, **5**, **6** as key intermediates for preparations of many biologically active compounds in the presence of TMSCl.[31–39] The aldehyde building blocks **3a**–**h** used in the Biginelli-type reactions are shown in Table 2.

Biginelli-Type Reactions of Cycloalkanones 1a–e, Urea or Thiourea, and Aromatic Aldehydes 3a–k in the Presence of TMSCl

For aromatic aldehydes, the reactions were generally run by an established procedure in which we used a 1.0:1.2:1.0:1.0 molar ratio of cycloalkanones **1a**–**e**, urea or thiourea, aromatic aldehydes **3a**–**k**, and TMSCl. The reactions took place and were complete in 2–3 h at room temperature. The products were precipitated from the medium and were isolated simply by filtration and washing with acetone. The total yields of isolated products were between 71% and 97%, with high purities by HLPC. The results are shown in Scheme 2 and Table 3–7.

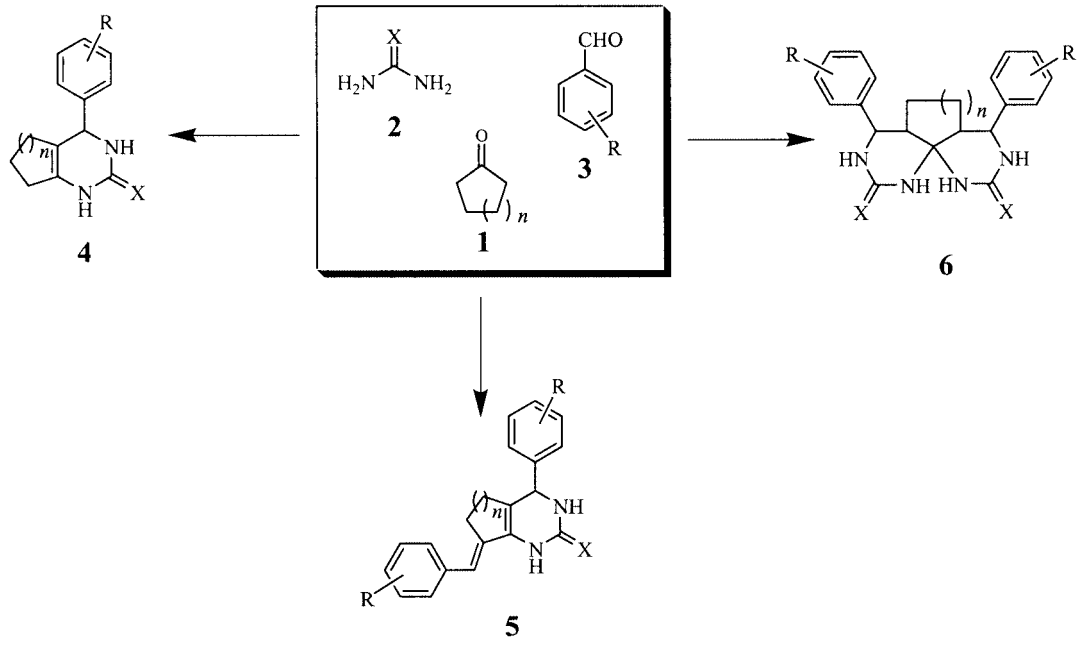
Cyclopentanone reacted with urea and aromatic aldehydes **3a**–**d**, **3f**–**k** to furnish mainly benzylidene heterobicyclic pyrimidines (Table 3, Entries 1–8, **5a**–**h**) in yields ranging from 78% to 95%.

The products were affected by the substituent groups: aromatic aldehydes bearing functional groups (such as –H, –Cl, –Br, $–CH_3$, $–OCH_3$) in the *ortho* or *para* positions reacted smoothly to give benzylidene heterobicyclic products (Table 3, compounds **5a**–**d**, **5g**–**h**) without the occurrence of side products (Scheme 3), whilst aromatic aldehydes bearing electron-withdrawing substituents (–F, $–NO_2$) in the *para* positions reacted to give mixtures of benzylidene heterobicyclic products **5i, 5j** and spiro-fused heterotricyclic products **6a, 6b**. The isolated ratio of **5i** and **6a** was 87:13 (Entry 9) and the ratio of **5j** and **6b** determined by ^1H NMR was 48:52 (Entry 10).

Cyclopentanone reacted with thiourea and aromatic aldehydes such as benzaldehyde, 4-chlorobenzaldehyde (**3d**), 4-nitrobenzaldehyde (**3f**), and 2-methoxybenzaldehyde (**3h**) to furnish mainly benzylidene heterobicyclic pyrimidines (Entries 11–14, **5k**–**n**; Scheme 3), but the reactions between cyclopentanone, thiourea, and 4-fluorobenzaldehyde (**3e**), 3-nitrobenzaldehyde (**3g**), 2-fluorobenzaldehyde (**3i**), and 2-chlorobenzaldehyde (**3j**) proceeded smoothly to give spiro-fused heterotricyclic compounds (Entries 15–18, **6c**–**f**; Scheme 4) in high yields and with high HLPC purities.

The case of cyclohexanone (**1b**) was different. Interestingly, two series of heterocyclic scaffolds, shown in Scheme 5 and Scheme 6, were formed.

For urea, the reaction provided one-pot access to spiro-fused heteropolycyclic compounds (Table 4, Entries 1–8; Scheme 5, **6g**–**n**) through formation of three new cycles and six novel bonds. The molecular structure, based on ^1H NMR spectroscopic data, was asymmetric. The corresponding coupling constants of ca. <4 Hz and ca. >11 Hz in the two pyrimidine rings (for example, **6g**) were charac-

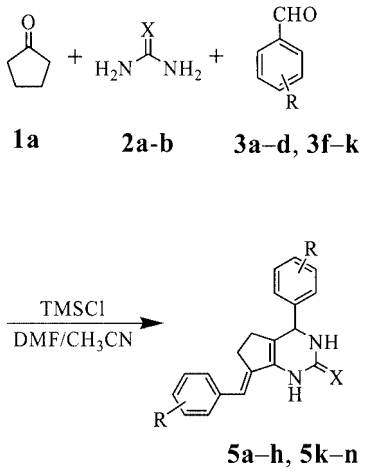


Scheme 2.

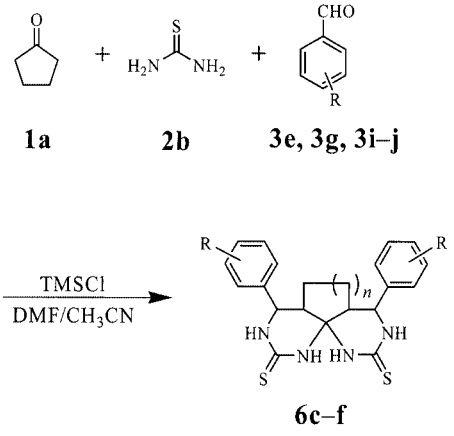
Table 3. Cyclopentanone products.

Entry	X	R	Product[a]		Yield %[b]	Ratio **5**:**6**
1	O	**3a**: H	**5a**		93	
2	O	**3b**: 4-CH_3	**5b**		95	
3	O	**3c**: 4-OCH_3	**5c**		86	
4	O	**3d**: 4-Cl	**5d**		82	
5	O	**3g**: 3-NO_2	**5e**		78	
6	O	**3i**: 2-F	**5f**		82	
7	O	**3j**: 2-Cl	**5g**		87	
8	O	**3k**: 2-Br	**5h**		85	
9	O	**3e**: 4-F	**5i**	**6a**		87:13[c]
10	O	**3f**: 4-NO_2	**5j**	**6b**		48:52[d]
11	S	**3a**: H	**5k**		96	
12	S	**3d**: 4-Cl	**5l**		92	
13	S	**3f**: 4-NO_2	**5m**		89	
14	S	**3h**: 2-OCH_3	**5n**		81	
15	S	**3e**: 4-F		**6c**	79	
16	S	**3g**: 3-NO_2		**6d**	86	
17	S	**3i**: 2-F		**6e**	80	
18	S	**3j**: 2-Cl		**6f**	95	

[a] All compounds were characterized by ^{1}H NMR, ^{13}C NMR, and mass spectrometry. [b] Isolated yield (yield based on aromatic aldehyde). [c] Ratio based on isolated yield. [d] Ratio based on ^{1}H NMR.



Scheme 3.

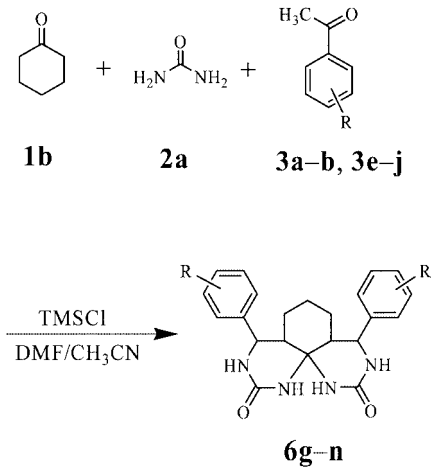


Scheme 4.

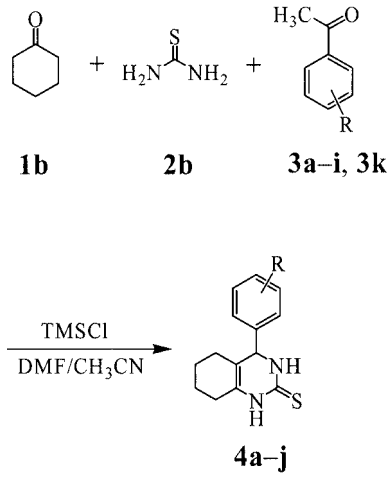
teristic of equatorial hydrogen and axial hydrogen, respectively.

Unlike those of urea, reactions of thiourea proceeded smoothly to give fused heterobicyclic products (Entries 9–18; Scheme 6, **4a**–**j**) in yields ranging from 80% to 91% with high purities, and no side products were detected. The mechanism was in agreement with the classical Biginelli reaction.

The products obtained from cycloheptanone with urea and aromatic aldehydes were affected by the substituent groups: aromatic aldehydes bearing functional groups



Scheme 5.



Scheme 6.

Table 4. Cyclohexanone products.

Entry	X	R	Product[a]	Yield [%] [b]
1	O	**3a**: H	**6g**	96
2	O	**3b**: 4-CH_3	**6h**	90
3	O	**3e**: 4-F	**6i**	83
4	O	**3f**: 4-NO_2	**6j**	81
5	O	**3g**: 3-NO_2	**6k**	88
6	O	**3h**: 2-OCH_3	**6l**	85
7	O	**3i**: 2-F	**6m**	85
8	O	**3j**: 2-Cl	**6n**	84
9	S	**3a**: H	**4a**	83
10	S	**3b**: 4-CH_3	**4b**	91
11	S	**3c**: 4-OCH_3	**4c**	97
12	S	**3d**: 4-Cl	**4d**	92
13	S	**3e**: 4-F	**4e**	82
14	S	**3f**: 4-NO_2	**4f**	80
15	S	**3g**: 3-NO_2	**4g**	89
16	S	**3h**: 2-OCH_3	**4h**	87
17	S	**3i**: 2-F	**4i**	85
18	S	**3k**: 2-Br	**4j**	97

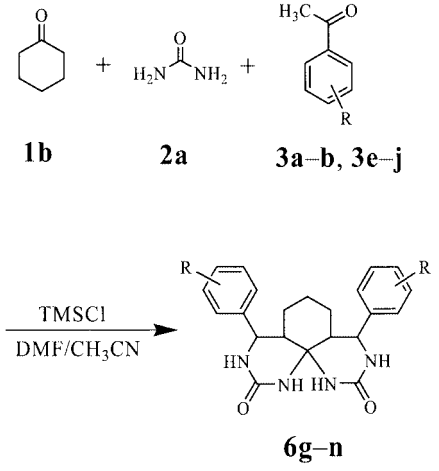
[a] All compounds were characterized by ^{1}H NMR, ^{13}C NMR, and mass spectrometry. [b] Isolated yield (yield based on aromatic aldehyde).

(–OCH_3, –Br) reacted smoothly to form spiro-fused pyrimidines (Table 5, below, Entries 5–6, **6p**–**q**; Scheme 8) while aromatic aldehydes bearing functional groups (–F, –NO_2) in the *meta*, *ortho*, or *para* positions proceeded to give benzylidene heterobicyclic products (Entries 1–3, **5o**–**q**; Scheme 7). The products from the reaction between 4-chlorobenzaldehyde (**3d**), cycloheptanone (**1c**), and urea, however, were a mixture of **5r** and **6o** at a ratio of 31:69 based on ^{1}H NMR (Entry 4).

Table 5. Cycloheptanone products.

Entry	X	Ar	Product[a]		Yield %[b]	Ratio[c] **5**:**6**
1	O	**3f**: 4-NO_2	**5o**		85	
2	O	**3g**: 3-NO_2	**5p**		81	
3	O	**3i**: 2-F	**5q**		81	
4	O	**3d**: 4-Cl	**5r**	**6o**		31:69
5	O	**3c**: 4-OCH_3		**6p**	83	
6	O	**3k**: 2-Br		**6q**	89	
7	S	**3a**: H		**6r**	90	
8	S	**3c**: 4-OCH_3		**6s**	85	
9	S	**3d**: 4-Cl		**6t**	90	
10	S	**3e**: 4-F		**6u**	92	
11	S	**3i**: 2-F		**6v**	74	
12	S	**3j**: 2-Cl		**6w**	93	
13	S	**3k**: 2-Br		**6x**	83	

[a] All compounds were characterized by ^{1}H NMR, ^{13}C NMR, and mass spectrometry. [b] Isolated yield (yield based on aromatic aldehyde). [c] Ratio based on ^{1}H NMR.

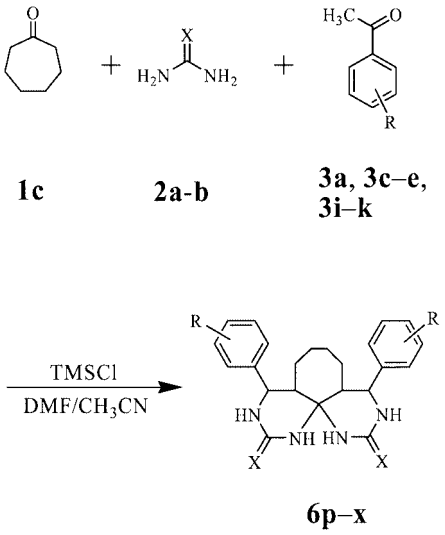


Scheme 7.

The reactions of thiourea (**2b**) proceeded smoothly to form spiro-fused heterotricyclic products (**6r**–**x**) in high yields without the occurrence of benzylidene heterobicyclic products (**5**) (Table 5, Entries 7–13; Scheme 8).

When cyclooctanone (**1d**) was treated with urea or thiourea and 2-chlorobenzaldehyde (**3j**) or 2-bromobenzaldehyde (**3k**), benzylidene heterobicyclic pyrimidines were formed in excellent yields (Table 6, **5s**–**v**; Scheme 9).

The reactions of cyclooctanone (**1d**) with thiourea and aromatic aldehydes **3a**–**f**, **3i**, however, proceeded to yield fused heterobicyclic products (Entries 5–11, **4k**–**q**; Scheme 10) in yields between 71 and 91% and with high purities.

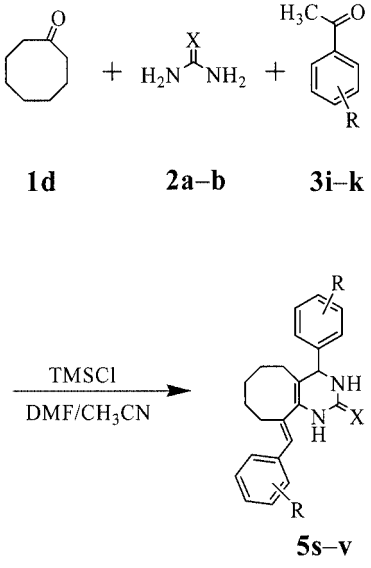


Scheme 8.

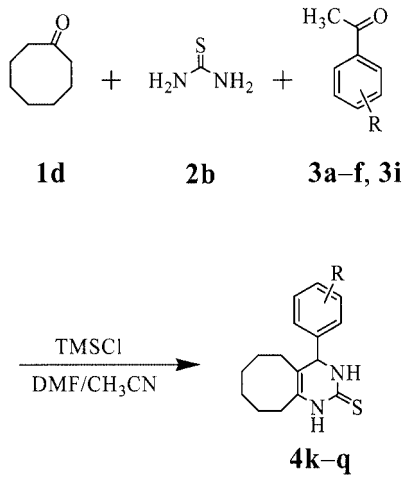
Table 6. Cyclooctanone products.

Entry	X	Ar	Product[a]	Yield [%][b]
1	O	**3j**: 2-Cl	**5s**	93
2	O	**3k**: 2-Br	**5t**	96
3	S	**3j**: 2-Cl	**5u**	92
4	S	**3k**: 2-Br	**5v**	86
5	S	**3a**: H	**4k**	90
6	S	**3b**: 4-CH_3	**4l**	87
7	S	**3c**: 4-OCH_3	**4m**	91
8	S	**3d**: 4-Cl	**4n**	89
9	S	**3e**: 4-F	**4o**	78
10	S	**3f**: 4-NO_2	**4p**	71
11	S	**3i**: 2-F	**4q**	82

[a] All compounds were characterized by ^{1}H NMR, ^{13}C NMR, and mass spectrometry. [b] Isolated yield (yield based on aromatic aldehyde).



Scheme 9.



Scheme 10.

4-(4-Fluorophenyl)-3,4,5,6,7,8,9,10-octahydro-1*H*-cyclooctapyrimidine-2-thione (Table 6, Entry 9, **4o**) was obtained from DMF as colorless, block-shaped crystals. The structural features were established by X-ray crystal structure analysis (Figure 2).[40]

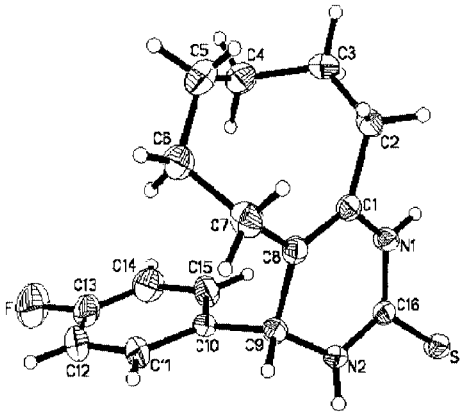


Figure 2. Crystal structure of 4-(4-fluorophenyl)-3,4,5,6,7,8,9,10-octahydro-1*H*-cyclooctapyrimidine-2-thione (**4o**).

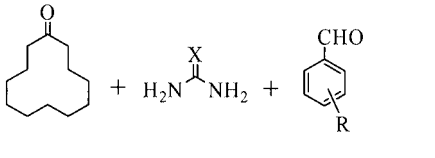
No reaction of cyclododecanone (**1e**) occurred even after 24 h, except when it was heated at reflux, when the products were precipitated directly from the reaction mixture after

Table 7. Cyclododecanone products.

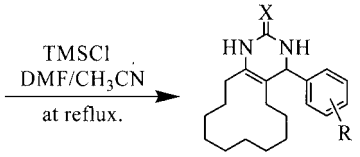
Entry	X	R	Product[a]	Yield (%)[b]
1	O	**3a**: 4-Cl	**4r**	87
2	O	**3h**: 2-OCH_3	**4s**	96
3	O	**3i**: 2-F	**4t**	93
4	O	**3j**: 2-Cl	**4u**	90
5	O	**3k**: 2-Br	**4v**	85
6	S	**3c**: 4-CH_3O	**4w**	89
7	S	**3i**: 2-F	**4x**	83

[a] All compounds were characterized by ^{1}H NMR, ^{13}C NMR, and mass spectrometry. [b] Isolated yield (yield based on aromatic aldehyde).

5–6 h. It gave only fused heterobicyclic compounds **4r–x** with either urea or thiourea in yields between 83–96% and in high purities, with no other side products being observed (Table 7; Scheme 11). Cyclododecanone showed lower reaction reactivity than cyclopentanone, cyclohexanone, cycloheptanone, and cyclooctanone.



1e **2a-b** **3a, 3c, 3h–k**



4r–x

Scheme 11.

Biginelli-Type Reactions of Cycloalkanones 1a–e, Urea or Thiourea, and Aliphatic Aldehydes 3l–p in the Presence of TMSCl

Our interest in the preparation of novel scaffolds prompted us to attempt the extension of this versatile reaction to condensations of cycloalkanones and/or aliphatic aldehydes in the Biginelli-type reaction. The same experiment conditions were applied to reactions between cycloalkanones **1a**–**e**, urea or thiourea, and aliphatic aldehydes **3l**–**p** such as *n*-butyraldehyde (**3l**), isobutyraldehyde (**3m**), *n*-valeraldehyde (**3n**), isovaleraldehyde (**3o**), and *n*-heptaldehyde (**3p**).

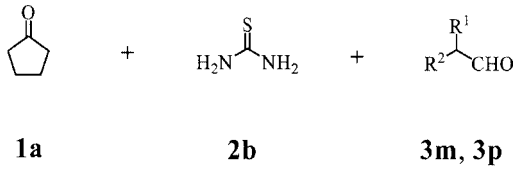
Table 8 shows that aliphatic aldehydes displayed lower reactivity than aromatic aldehydes, all reactions having to be carried out at reflux. Two series of pyrimidine products were formed (Scheme 12).

Table 8. Cross condensation of cycloalkanones and aliphatic aldehydes.

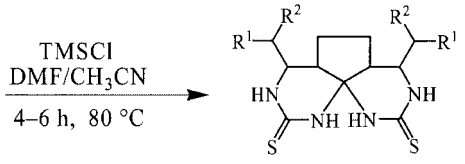
Entry	*n*	X	R^1	R^2	Product 4[a]	Yield[b]
1	3	S	CH_3	CH_3	**4A**	69
2	4	S	H	C_2H_5	**4B**	70
3	4	S	CH_3	CH_3	**4C**	78
4	4	S	H	*n*-C_3H_7	**4D**	72
5	4	S	H	*n*-C_5H_{11}	**4E**	68
6	8	S	CH_3	CH_3	**4F**	80
7	8	S	H	*i*-C_3H_7	**4G**	85
8	8	O	CH_3	CH_3	**4H**	75
9	8	O	H	*n*-C_5H_{11}	**4I**	80

[a] All compounds were characterized by ^{1}H NMR, ^{13}C NMR, and mass spectrometry. [b] Isolated yield (yield based on aliphatic aldehyde).

As shown in Scheme 13, the reactions between cyclopentanone, thiourea, and isobutyraldehyde (**3m**) or *n*-heptaldehyde (**3p**) proceeded to give only spiro-fused heterotricyclic products **6y**, **6z** in moderate yields (68% and 45%, respectively).



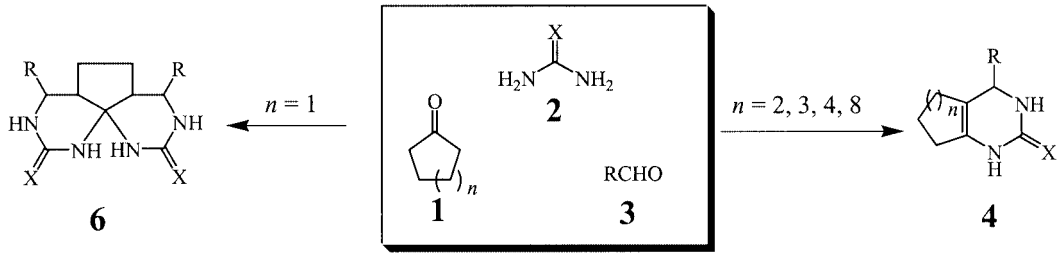
1a **2b** **3m, 3p**



6y: $R^1 = R^2 = CH_3$, 68%
6z: R^1 = H, R^2 = *n*-C_5H_{11}, 45%

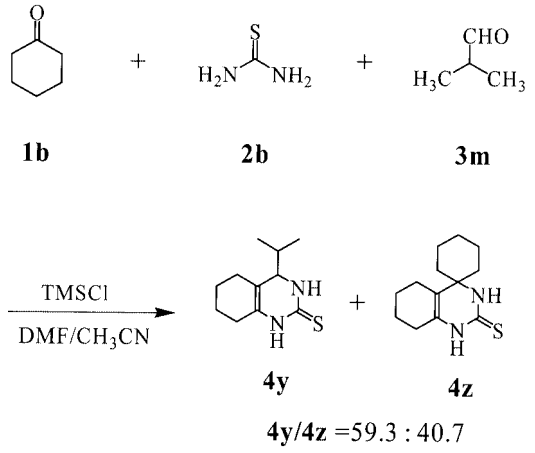
Scheme 13.

The products of treatment of cyclohexanone (**1b**) with thiourea and isobutyraldehyde (**3m**) were a mixture of fused pyrimidines **4y** and spiro-fused pyrimidine **4z** in a ratio of 59.3:40.7 as determined by HPLC (Scheme 14).



6 **1** **2** **3** **4**

Scheme 12.

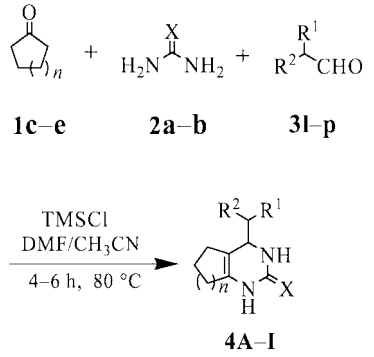


1b 2b 3m 4y 4z

Scheme 14.

The reaction between cycloheptanone (**1c**), isobutyraldehyde (**3m**), and thiourea proceeded cleanly to give the fused heterobicyclic product (Table 8, Entry 1, **4A**) in yield 69%, no side products being observed, but we completely failed to obtain the fused heterobicyclic products **4** of cyclohexanone (**1b**) or cycloheptanone (**1c**) on treatment with thiourea (**2b**) and primary aldehydes such as *n*-butyraldehyde (**3l**), *n*-valeraldehyde (**3n**), isovaleraldehyde (**3o**), or *n*-heptaldehyde (**3p**). Cyclooctanone (**1d**) and cyclododecanone (**1e**) reacted with aliphatic aldehydes **3l**–**p** and thiourea to yield the corresponding compounds (Entries 2–7, **4B**–**G**) in yields ranging from 70% to 85% and in high purities. The reaction outcomes were consistent regardless of whether α-unbranched or α-branched secondary aldehydes were used as starting materials. There was no observed self-condensation reaction of aliphatic aldehydes.

Urea showed lower reactivities than thiourea. No products were detected on treatment of aliphatic aldehydes **3l**–**p** with urea and cyclopentanone (**1a**), cyclohexanone (**1b**), cycloheptanone (**1c**), or cyclooctanone (**1d**), but cyclododecanone (**1e**) reacted with isobutyraldehyde (**3m**), *n*-heptaldehyde (**3p**), and urea to furnish the corresponding products (Entries 8 and 9, **4H** and **4I**; Scheme 15) in moderate yields of 75% and 80%, respectively, with HPLC purities higher than 84%.

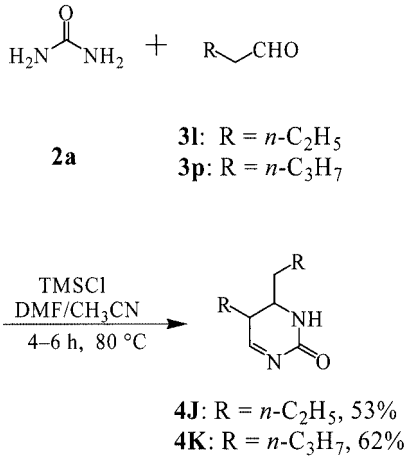


1c–e 2a–b 3l–p 4A–I

Scheme 15.

Self-Condensation Reactions of Cycloalkanones 1 or Aliphatic Aldehydes 3l–o and Urea or Thiourea in the Presence of TMSCl

The self-condensation reactions of aliphatic aldehydes, such as *n*-butyraldehyde (**3l**), isobutyraldehyde (**3m**), *n*-valeraldehyde (**3n**), and isovaleraldehyde (**3o**) on treatment with urea or thiourea were also investigated. The reactions were conducted by a procedure in which we used 1.0:1.2:1.0 molar ratios of aliphatic aldehydes **3l**–**p**, urea or thiourea, and TMSCl, and all reactions were complete after 4–6 h at 80 °C. We found that two molecules of aliphatic aldehydes **3l**–**p** proceeded to react smoothly with one molecule of urea or thiourea (Scheme 16, Scheme 18). As confirmed by NMR measurements and mass spectrometry, the corresponding heterocyclic pyrimidines were formed in moderate yields.



2a

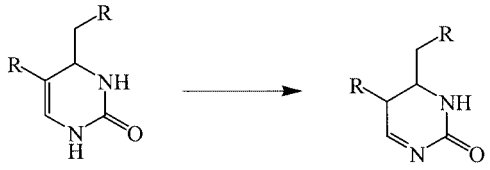
3l: R = *n*-C_2H_5
3p: R = *n*-C_3H_7

4J: R = *n*-C_2H_5, 53%
4K: R = *n*-C_3H_7, 62%

Scheme 16.

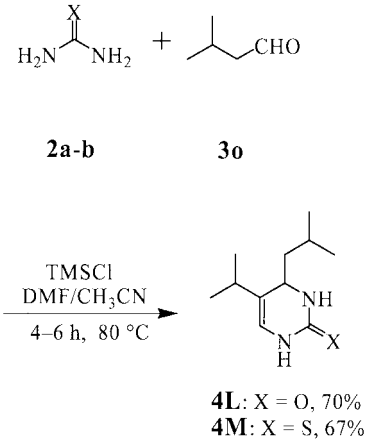
In the course of our experiments, we found that the self-condensation reactions of *n*-butyraldehyde (**3i**) and *n*-valeraldehyde (**3n**) in the presence of urea proceeded in yields of 53% and 62%, respectively (Scheme 16). The ^1H and ^{13}C NMR analysis of products revealed the formation of 5-ethyl-6-propyl-5,6-dihydro-1*H*-pyrimidin-2-one (**4J**) and 6-*n*-butyl-5-propyl-5,6-dihydro-1*H*-pyrimidin-2-one (**4K**).

We envisaged that the rearrangement between 3,4-dihydropyrimidinones and 5,6-dihydropyrimidinones might take place (Scheme 17).

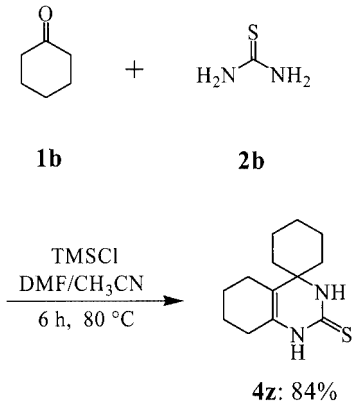


Scheme 17.

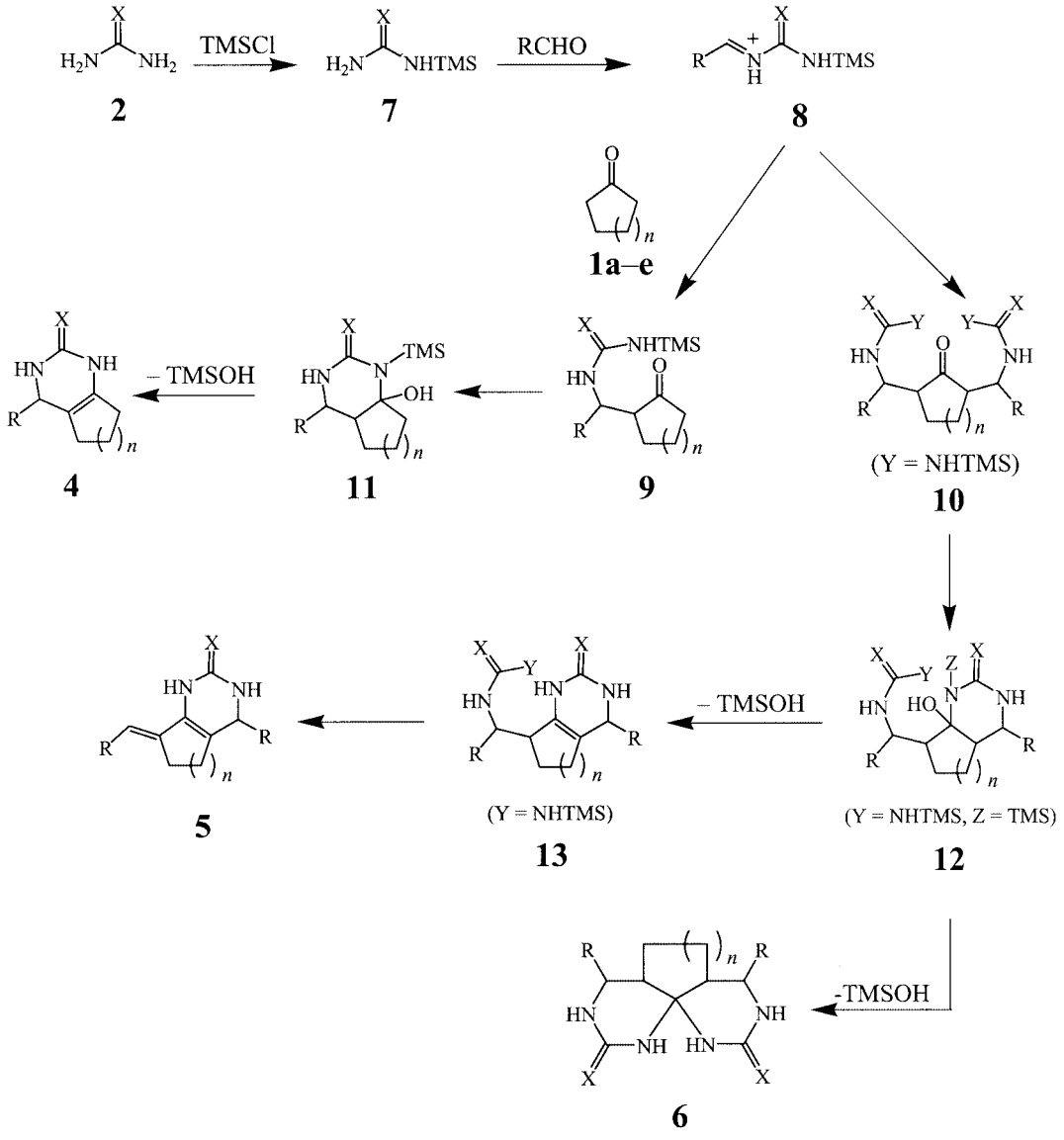
The products obtained from isovaleraldehyde (**3o**) and urea or thiourea, however, were 3,4-dihydropyrimidinones **4L**[41] and **4M**, in 70% and 67% yields, respectively (Scheme 18). We tried to promote the condensation reaction by heating mixtures of α-branched aldehyde such as



Scheme 18.



Scheme 19.



Scheme 20.

isobutyraldehyde (**3m**) with urea or thiourea, but unfortunately no reaction was observed even after 24 h at reflux.

Self-condensation of cyclohexanone with thiourea proceeded to furnish the spiro heterotricyclic product **4z** (Scheme 19) in a yield of 78%,[42] but no reaction was observed for cyclopentanone, cycloheptanone, cyclooctanone, or cyclododecanone.

Proposed Possible Mechanism

Trimethylsilyl chloride showed remarkable reactivity as a "hard-soft" reagent and considerably accelerated the reactions. On the basis of all our experimental results, together with literature reports,[42] we have proposed the mechanistic pathway shown in Scheme 20 to account for the process. The key step involves the formation of an *N*-acyliminium ion intermediate **8** from urea or thiourea and aldehyde **3** precursors through two equilibrium steps[43] in the presence of TMSCl as Lewis acid. For products **4**, the nucleophilic addition of intermediate **8** with only one α-carbon to form intermediate **9** is facilitated, and this cyclizes to hexahydropyrimidine **11** and undergoes acid-catalyzed elimination to afford the fused heterobicyclic pyrimidines **4**. For the benzylidene heterobicyclic pyrimidine **5** and spiro heterotricyclic pyrimidine **6** products, nucleophilic additions with two α-carbons tend to form **10** and this then cyclizes to give the key intermediate **12**. Two trends were observed in the competitive nucleophilic substitution/elimination reaction: one forming the elimination products, and another forming nucleophilic substitution products. For elimination products it was difficult for the attacking $-NH_2$ group to approach the substrate from a position 180° away from the –OH leaving group. Acid-catalyzed elimination occurred easily to form benzylidene heterobicyclic scaffold products **5**. For the nucleophilic substitution products, backside attack was more inclined to occur and inversion of configuration gave access to spiro heterotricyclic scaffold products **6**.

Conclusions

We have demonstrated novel multicomponent reactions of cycloalkanones, urea or thiourea, and aromatic aldehydes in the presence of TMSCl and have also studied the self- and cross-condensations of cycloalkanones and/or aliphatic aldehydes under similar conditions. Thiourea exhibited different behavior under such reaction conditions, showing lower reactivity than urea, whilst aliphatic aldehydes exhibited different behavior to aromatic aldehydes. To the best of our knowledge, cycloalkanones, unlike 1,3-keto compounds, have not been used as suitable starting materials for the Biginelli reaction. Undoubtedly, these reactions should be useful to give the designer a simple route to synthesize biologically active pyrimidinone scaffolds.

Experimental Section

General: Reagents and all solvents were analytically pure grade and were used without further purification. Anhydrous conditions were not required for the reactions. Melting points were determined with an XT-4 apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded in DMSO on a Bruker AVANCE DMX 500 spectrometer at 500 MHz and 125 MHz, respectively, chemical shifts are given in ppm (δ), TMS was used as internal standard, and coupling constants (J) are given in Hz.

General Procedures for the Synthesis of Heterobicyclic, Benzylidene Heterobicyclic, and Spiro Heterotricyclic Products (Table 3–6): The cycloalkanone (**1a**–**d**, 10 mmol), urea (12 mmol) or thiourea (12 mmol), the aromatic aldehyde (10 mmol), and DMF/CH_3CN (3 mL/6 mL) were mixed in a flask, and TMSCl (10 mmol) was added dropwise at room temperature. The reaction mixture was stirred at room temperature for 2–3 h and precipitation was observed. The products were isolated by filtered through a Büchner funnel and washed with water followed by ethanol, and then dried to give the crystalline powder products.

Compound 5a: M.p. 236–239 °C. ^1H NMR: δ = 8.79 (s, 1 H), 7.38–7.15 (m, 9 H), 6.63 (s, 1 H), 5.15 (s, 1 H), 2.85–2.75 (m, 2 H), 2.49 (m, 1 H), 2.02–1.97 (m, 1 H) ppm. ^{13}C NMR: δ = 154.5, 144.4, 140.3, 138.8, 137.0, 129.7, 129.6, 129.0, 128.6, 127.6, 127.2, 119.7, 117.9, 58.6, 29.5 ppm. MS (ESI) $[M + H]^+$ 303.

Compound 5b: M.p. 238–241 °C. ^1H NMR: δ = 8.73 (s, 1 H), 7.23–7.14 (m, 9 H), 6.58 (s, 1 H), 5.09 (s, 1 H), 2.82–2.71 (m, 2 H), 2.38–2.33 (m, 1 H), 2.28 (s, 6 H), 2.00–1.96 (m, 1 H) ppm. ^{13}C NMR: δ = 154.2, 141.4, 139.1, 137.5, 136.7, 136.2, 135.9, 130.0, 128.8, 127.4, 119.1, 117.5, 58.1, 29.3, 29.2, 21.7, 21.6 ppm. MS (ESI) $[M + H]^+$ 331.

Compound 5c: M.p. 250–252 °C. ^1H NMR: δ = 8.78 (s, 1 H), 7.33–7.15 (m, 4 H), 7.01–7.88 (m, 5 H), 6.69 (s, 1 H), 5.49 (s, 1 H), 3.79 (s, 3 H), 3.78 (s, 3 H), 2.71–2.66 (m, 2 H), 2.35–2.30 (m, 1 H), 1.99–1.95 (m, 1 H) ppm. ^{13}C NMR: δ = 157.3, 156.7, 154.7, 139.9, 137.0, 132.2, 129.4, 128.9, 128.4, 128.0, 127.5, 121.7, 121.0, 118.8, 112.3, 111.9, 111.8, 56.4, 56.2, 51.7, 29.0 ppm. MS (ESI) $[M + H]^+$ 363.

Compound 5d: M.p. 252–255 °C. ^1H NMR: δ = 8.81 (s, 1 H), 7.44–7.25 (m, 9 H), 6.62 (s, 1 H), 5.18 (s, 1 H), 2.85–2.73 (m, 2 H), 2.41–2.36 (m, 1 H), 2.01–1.96 (m, 1 H) ppm. ^{13}C NMR: δ = 154.0, 143.1, 140.8, 137.5, 137.0, 132.9, 131.2, 130.4, 129.5, 129.4, 129.3, 119.6, 116.6, 57.6, 29.2, 29.1 ppm. MS (ESI) $[M + H]^+$ 371.

Compound 5e: M.p. 235–239 °C. ^1H NMR: δ = 8.89 (s, 1 H), 8.23–8.02 (m, 4 H), 7.83–7.45 (m, 5 H), 6.81 (s, 1 H), 5.45 (s, 1 H), 2.97–2.83 (m, 2 H), 2.53–2.48 (m, 1 H), 2.06–2.03 (m, 1 H) ppm. ^{13}C NMR: δ = 153.9, 149.0, 148.9, 146.2, 143.0, 140.1, 137.3, 134.9, 134.3, 131.3, 131.0, 123.5, 122.6, 122.0, 121.5, 120.3, 116.1, 57.5, 29.3, 29.1 ppm. MS (ESI) $[M + H]^+$ 393.

Compound 5f: M.p. 241–244 °C. ^1H NMR: δ = 9.05 (s, 1 H), 7.50–7.47 (t, J = 7.4 Hz, 1 H), 7.36–7.33 (m, 2 H), 7.25–7.14 (m, 6 H), 6.72 (s, 1 H), 5.45 (s, 1 H), 2.83–2.71 (m, 2 H), 2.41–2.37 (m, 1 H), 2.06–1.98 (m, 1 H) ppm. ^{13}C NMR: δ = 161.4, 161.2, 159.4, 159.3, 154.3, 142.2, 137.3, 130.9, 130.8, 130.5, 130.4, 129.6, 129.0, 128.9, 126.3, 126.2, 125.9, 125.2, 119.0, 116.5, 116.3, 116.1, 109.4, 109.3, 52.3, 29.1, 28.8 ppm. MS (ESI) $[M + H]^+$ 339.

Compound 5g: M.p. 232–234 °C. ^1H NMR: δ = 9.15 (s, 1 H), 7.53–7.20 (m, 9 H), 6.78 (s, 1 H), 5.62 (s, 1 H), 2.77–2.67 (m, 2 H), 2.44–2.40 (m, 1 H), 1.99–1.94 (m, 1 H) ppm. ^{13}C NMR: δ = 154.3, 142.3, 141.3, 137.2, 136.5, 133.4, 131.9, 130.3, 130.2, 130.1, 130.0, 129.0, 128.8, 127.9, 119.4, 114.4, 55.3, 28.8 ppm. MS (ESI) $[M + H]^+$ 371.

Compound 5h: M.p. 242–246 °C. ^1H NMR: δ = 9.17 (s, 1 H), 7.61–7.21 (m, 9 H), 6.70 (s, 1 H), 5.58 (s, 1 H), 2.72–2.62 (m, 2 H), 2.44–2.39 (m, 1 H), 1.96–1.91 (m, 1 H) ppm. ^{13}C NMR: δ = 161.9, 156.4, 154.3, 142.9, 142.1, 139.8, 138.2, 137.0, 133.6, 130.3, 129.6, 129.4,

129.2, 128.5, 124.4, 122.1, 119.4, 117.1, 57.7, 28.9 ppm. MS (ESI) $[M + H]^+$ 458.

Compound 5i: M.p. 203–205 °C. ^{1}H NMR: δ = 10.07 (s, 1 H), 8.98 (s, 1 H), 7.41–7.17 (m, 10 H), 6.91 (s, 1 H), 5.19 (s, 1 H), 2.84–2.80 (m, 2 H), 2.46–2.41 (m, 1 H), 2.09–2.04 (m, 1 H) ppm. ^{13}C NMR: δ = 175.2, 143.1, 138.8, 138.5, 134.8, 129.6, 129.4, 128.9, 128.7, 127.5, 127.1, 122.0, 118.7, 58.8, 29.3, 28.8 ppm. MS (ESI) $[M + H]^+$ 319.

Compound 5j: ^{1}H NMR: δ = 10.10 (s, 1 H), 9.05 (s, 1 H), 7.48–7.26 (m, 8 H), 6.92 (s, 1 H), 5.25 (s, 1 H), 2.87–2.74 (m, 2 H), 2.46–2.40 (m, 1 H), 2.09–2.05 (m, 1 H) ppm. ^{13}C NMR: δ = 175.2, 141.9, 139.5, 137.3, 134.9, 133.2, 131.4, 130.9, 130.4, 129.6, 129.4, 129.0, 122.1, 117.5, 58.0, 29.2, 28.7 ppm. MS (ESI) $[M + H]^+$ 387.

Compound 5k: M.p. 219–223 °C. ^{1}H NMR: δ = 10.30 (s, 1 H), 9.18 (s, 1 H), 8.29–8.27 (d, J = 8.7 Hz, 2 H), 8.19–8.17 (d, J = 8.8 Hz, 2 H), 7.54 (m, 4 H), 7.09 (s, 1 H), 2.93–2.86 (m, 2 H), 2.52–2.49 (m, 1 H), 2.13–2.08 (m, 1 H) ppm. ^{13}C NMR: δ = 175.4, 149.7, 147.8, 145.6, 145.1, 143.5, 135.2, 129.3, 128.6, 124.8, 124.6, 123.9, 117.3, 58.0, 29.2, 29.0 ppm. MS (ESI) $[M + H]^+$ 409.

Compound 5l: M.p. 226–228 °C. ^{1}H NMR: δ = 10.2 (s, 1 H), 8.69 (s, 1 H), 7.32–6.88 (m, 9 H), 5.49 (s, 1 H), 3.80 (s, 3 H), 3.77 (s, 3 H), 2.73–2.68 (m, 2 H), 2.40–2.36 (m, 1 H), 2.07–2.05 (m, 1 H) ppm. ^{13}C NMR: δ = 175.9, 157.5, 156.5, 138.7, 134.9, 131.5, 129.8, 128.9, 128.6, 128.2, 127.4, 121.8, 121.7, 121.0, 113.5, 112.0, 111.8, 56.5, 56.3, 52.8, 29.3, 28.6 ppm. MS (ESI) $[M + H]^+$ 379.

Compound 5m: M.p. 203–207 °C. ^{1}H NMR: δ = 8.80 (s, 1 H), 7.37–7.30 (m, 4 H), 7.23–7.16 (m, 5 H), 6.64 (s, 1 H), 5.19 (s, 1 H), 2.86–2.74 (m, 2 H), 2.41–2.36 (m, 1 H), 2.02–1.97 (m, 1 H) ppm. ^{13}C NMR: δ = 163.4 and 161.4 (split), 162.3 and 160.4 (split), 154.0, 140.5, 139.7, 136.8, 135.1, 130.6, 130.5, 129.4, 129.4, 119.1, 116.6, 116.4, 116.3, 116.2, 116.1, 57.5, 29.1 ppm. MS (ESI) $[M + H]^+$ 339.

Compound 5o: M.p. 256–258 °C. ^{1}H NMR: δ = 8.31 (s, 1 H), 8.27–8.24 (m, 4 H), 7.65–7.62 (m, 4 H), 7.39 (s, 1 H), 6.93 (s, 1 H), 4.93 (s, 1 H), 2.34–2.12 (m, 2 H), 1.91–1.86 (m, 1 H), 1.75–1.59 (m, 3 H), 1.44 (m, 2 H),. ^{13}C NMR: δ = 153.9, 152.7, 147.9, 146.9, 144.6, 139.7, 134.9, 130.8, 130.7, 129.2, 129.1, 127.9, 124.9, 124.7, 124.4, 124.1, 111.6, 61.0, 30.1, 29.8, 28.0, 26.3 ppm. MS (ESI) $[M + H]^+$ 421.

Compound 5p: M.p. 239–242 °C. ^{1}H NMR: δ = 8.28–8.13 (m, 5 H), 7.86–7.79 (m, 2 H), 7.72–7.68 (m, 2 H), 7.37 (s, 1 H), 6.95 (s, 1 H), 4.97 (s, 1 H), 2.32–2.20 (m, 2 H), 1.93–1.88 (m, 1 H), 1.76–1.62 (m, 3 H), 1.47–1.45 (m, 2 H) ppm. ^{13}C NMR: δ = 153.8, 148.9, 148.7, 147.5, 139.2, 138.5, 135.9, 134.9, 134.6, 131.3, 130.8, 127.6, 124.4, 123.5, 123.0, 122.7, 122.5, 111.4, 60.8, 30.0, 29.8, 28.2, 26.4 ppm. MS (ESI) $[M + H]^+$ 421.

Compound 5q: M.p. 248–250 °C. ^{1}H NMR: δ = 8.03 (s, 1 H), 7.40–7.17 (m, 9 H), 6.69 (s, 1 H), 5.04 (s, 1 H), 2.40–2.37 (m, 1 H), 2.20–2.07 (m, 2 H), 1.79–1.66 (m, 1 H), 1.54 (m, 3 H), 1.28 (m, 1 H) ppm. ^{13}C NMR: δ = 161.5 and 159.6 (split), 161.3 and 159.4 (split), 154.0, 139.6, 134.5, 132.0, 131.9, 131.6, 130.5, 130.2, 125.8, 125.3, 122.2, 116.5, 109.8, 55.4, 30.2, 29.6, 27.7, 26.4 ppm. MS (ESI) $[M + H]^+$ 367.

Compound 5s: M.p. 247–249 °C. ^{1}H NMR: δ = 8.50 (s, 1 H), 7.64–7.63 (t, J = 0.9 Hz, 1 H), 7.38–7.26 (m, 4 H), 7.22–7.17 (m, 2 H), 7.05–7.02 (m, 2 H), 6.62 (s, 1 H), 5.21 (d, J = 1.8 Hz, 1 H), 2.49–2.40 (m, 2 H), 1.74–1.61 (m, 4 H), 1.39–1.37 (m, 4 H) ppm. ^{13}C NMR: δ = 153.6, 142.5, 139.9, 135.6, 132.9, 132.1, 130.8, 130.7, 130.6, 130.0, 129.9, 129.8, 129.7, 128.5, 127.9, 127.2, 106.5, 29.4, 27.9, 27.2 ppm. MS (ESI) $[M + H]^+$ 413.

Compound 5t: M.p. 251–257 °C. ^{1}H NMR: δ = 8.54 (s, 1 H), 7.63–7.62 (d, J = 7.6 Hz, 1 H), 7.55–7.53 (d, J = 7.9 Hz, 1 H), 7.47–7.41 (m, 2 H), 7.21–7.05 (m, 5 H), 6.55 (s, 1 H), 5.17 (s, 1 H), 2.48–2.37 (m, 2 H), 1.72–7.62 (m, 4 H), 1.40–1.30 (m, 4 H) ppm. ^{13}C NMR: δ = 153.5, 144.3, 139.6, 137.4, 133.1, 133.0, 130.9, 130.6, 130.3, 129.9, 129.8, 129.2, 128.4, 123.6, 122.6, 106.9, 57.7, 39.6, 30.0, 29.8, 27.9, 27.2 ppm. MS (ESI) $[M + H]^+$ 501.

Compound 5u: M.p. 245–246 °C. ^{1}H NMR: δ = 9.98 (s, 1 H), 8.74 (s, 1 H), 7.55–7.23 (m, 7 H), 7.05 (s, 1 H), 6.65 (s, 1 H), 5.23–5.22 (d, J = 1.8 Hz, 1 H), 2.44 (s, 2 H), 1.72–1.38 (m, 8 H) ppm. ^{13}C NMR: δ = 174.1, 141.4, 138.6, 135.3, 132.7, 131.7, 130.6, 130.4, 130.1, 129.6, 129.7, 129.5, 129.1, 128.5, 127.7, 127.7, 109.7, 29.0, 27.7, 27.3, 26.8 ppm. MS (ESI) $[M + H]^+$ 429.

Compound 5v: M.p. 240–244 °C. ^{1}H NMR: δ = 10.02 (s, 1 H), 9.54 (s, 1 H), 7.57–7.03 (m, 8 H), 6.58 (s, 1 H), 5.20 (s, 1 H), 2.43 (m, 2 H), 1.73–1.34 (m, 8 H) ppm. ^{13}C NMR: δ = 174.1, 143.6, 143.5, 138.5, 137.2, 133.2, 133.1, 131.0, 130.8, 130.6, 130.5, 130.0, 129.3, 129.1, 128.5, 123.7, 122.4, 110.2, 57.4, 39.6, 29.4, 27.9, 27.3, 27.1 ppm. MS (ESI) $[M + H]^+$ 517.

Compound 6a: ^{1}H NMR: δ = 7.38–7.14 (m, 9 H), 6.81 (s, 1 H), 6.69 (s, 1 H), 6.56 (s, 1 H), 4.85 (d, J = 3.1 Hz, 1 H), 4.08 (d, J = 11.2 Hz, 1 H), 2.43 (m, 1 H), 2.17 (m, 1 H), 1.48 (m, 2 H), 1.10 (m, 2 H) ppm. ^{13}C NMR: δ = 163.4 and 161.5 (split), 163.0 and 161.1 (split), 137.9, 137.7, 130.7, 130.5, 129.6, 129.4, 116.5, 116.1, 115.6, 74.8, 57.2, 51.3, 50.2, 49.7, 23.2, 21.3 ppm. MS (m/z) $[M + H]^+$ 399.

Compound 6c: M.p. 301–304 °C. ^{1}H NMR: δ = 9.12 (s, 1 H), 8.62 (s, 1 H), 8.52 (s, 1 H), 8.43 (s, 1 H), 7.34–7.16 (m, 8 H), 4.96 (s, 1 H), 4.14–4.12 (d, J = 11.3 Hz, 1 H), 1.45–1.41 (m, 1 H), 1.32–1.28 (m, 1 H), 1.10–1.08 (m, 2 H) ppm. ^{13}C NMR: δ = 175.2, 141.9, 139.5, 137.3, 134.9, 133.2, 131.4, 130.9, 130.4, 129.6, 129.4, 129.0, 122.1, 117.5, 58.0, 29.2, 28.7 ppm. MS (ESI) $[M + H]^+$ 431.

Compound 6d: M.p. 313–317 °C. ^{1}H NMR: δ = 10.27 (s, 1 H), 9.20 (s, 1 H), 8.24–8.20 (m, 4 H), 7.82–7.63 (m, 5 H), 5.52 (s, 1 H), 2.97–2.88 (m, 2 H), 2.57–2.51 (m, 1 H), 2.16–2.09 (m, 1 H) ppm. ^{13}C NMR: δ = 175.6, 148.9, 145.0, 143.6, 141.7, 140.0, 135.2, 134.9, 134.7, 134.3, 131.5, 131.1, 123.8, 123.7, 123.0, 122.9, 122.2, 117.1, 58.0, 29.4, 28.9 ppm. MS (ESI) $[M + H]^+$ 485.

Compound 6e: M.p. 287–289 °C. ^{1}H NMR: δ = 10.4 (s, 1 H), 8.94 (s, 1 H), 7.51–7.10 (m, 9 H), 6.99 (s, 1 H), 5.47 (s, 1 H), 2.83–2.74 (m, 2 H), 2.49–2.41 (m, 1 H), 2.08 (m, 1 H) ppm. ^{13}C NMR: δ = 161.5 and 159.5 (split), 161.1 and 159.1 (split), 141.0, 135.2, 130.9, 130.8, 130.1, 130.0, 129.8, 129.6, 129.2, 129.1, 126.2, 126.0, 125.2, 121.9, 116.6, 116.4, 116.2, 110.6, 53.0, 29.0, 28.7 ppm. MS (ESI) $[M + H]^+$ 431.

Compound 6f: M.p. 296–299 °C. ^{1}H NMR: δ = 9.34 (s, 1 H), 8.63 (s, 1 H), 8.60 (s, 1 H), 8.51 (s, 1 H), 7.49–7.30 (m, 8 H), 5.39 (d, J = 3.6 Hz, 1 H), 4.08 (d, J = 11.3 Hz, 1 H), 2.71–2.67 (m, 2 H), 1.56–1.52 (m, 1 H), 1.41–1.36 (m, 1 H), 1.15–1.09 (m, 1 H), 1.09–1.02 (m, 1 H) ppm. ^{13}C NMR: δ = 177.6, 136.9, 136.6, 134.1, 131.8, 130.4, 130.0, 129.7, 129.4, 128.5, 127.7, 74.4, 49.9, 45.1, 23.1, 21.5 ppm. MS (ESI) $[M + H]^+$ 463.

Compound 6g: M.p. 330–332 °C (ref.[36] 335 °C). ^{1}H NMR: δ = 7.37–7.25 (m, 10 H), 7.22 (s, 1 H), 6.84 (s, 1 H), 6.53 (s, 1 H), 6.47 (s, 1 H), 4.98 (d, J = 2.3 Hz, 1 H), 4.86–4.83 (d, J = 11.2 Hz, 1 H), 2.02–1.93 (m, 2 H), 1.44–1.40 (m, 2 H), 1.23–1.15 (m, 2 H), 0.89–0.87 (t, J = 14.2 Hz, 2 H) ppm. ^{13}C NMR: δ = 156.4, 155.0, 142.6, 140.9, 129.3, 128.9, 128.6, 128.3, 127.8, 127.7, 68.3, 54.0, 53.6, 43.9, 43.3, 22.8, 22.3, 19.1 ppm. MS (ESI) $[M + H]^+$ 377.

Compound 6h: M.p. 350–353 °C. ^{1}H NMR: δ = 7.15 (m, 9 H), 6.84 (s, 1 H), 6.49 (s, 1 H), 6.40 (s, 1 H), 4.93 (s, 1 H), 4.49 (d, J =

11.1 Hz, 1 H), 2.29 (s, 6 H), 2.07–1.90 (m, 2 H), 1.51–1.36 (m, 2 H), 1.21–1.12 (m, 2 H), 0.89 (m, 2 H) ppm. MS (ESI) $[M + H]^+$ 405.

Compound 6i: M.p. 302–303 °C. ^{1}H NMR: δ = 7.96 (s, 1 H), 7.83–6.88 (m, 11 H), 5.28 (d, J = 1.5 Hz, 1 H), 4.86 (d, J = 11.3 Hz, 1 H), 2.20–2.02 (m, 2 H), 1.71–1.16 (m, 4 H), 0.94–0.87 (m, 2 H), 1.43–1.36 (m, 2 H), 1.09 (m, 2 H), 0.85 (m, 1 H) ppm. ^{13}C NMR: δ = 162.3 and 160.3 (split), 161.1 and 159.1 (split), 156.5, 155.1, 130.6, 130.1, 129.9, 129.7, 129.1, 128.9, 127.4, 125.7, 124.8, 116.4, 68.3, 48.0, 47.6, 42.4, 22.9, 22.6, 19.8, 19.1 ppm. MS (ESI) $[M + H]^+$ 413.

Compound 6j: M.p. 341–344 °C (ref.[35] 330 °C, decomp.) ^{1}H NMR: δ = 7.72–7.44 (m, 9 H), 7.34 (s, 1 H), 7.00 (s, 1 H), 6.90 (s, 1 H), 5.74 (d, J = 2.7 Hz, 1 H), 4.86 (d, J = 11.3 Hz, 1 H), 2.19 (m, 1 H), 1.99 (m, 1 H), 1.90 (m, 1 H), 1.43–1.36 (m, 2 H), 1.09 (m, 2 H), 0.85 (m, 1 H) ppm. ^{13}C NMR: δ = 157.7, 140.6, 137.7, 134.3, 132.2, 130.4, 130.2, 130.0, 129.8, 128.7, 127.7, 67.9, 51.6, 51.3, 48.3, 42.2, 41.2, 27.4, 24.4, 23.5 ppm. MS (ESI) $[M + H]^+$ 445.

Compound 6k: M.p. 335–336 °C. ^{1}H NMR: δ = 7.31–7.17 (m, 9 H), 6.88 (s, 1 H), 6.62 (s, 1 H), 6.54 (s, 1 H), 4.97 (s, 1 H), 4.58 (d, J = 11.2 Hz, 1 H), 2.02–1.93 (m, 2 H), 1.44–1.40 (m, 2 H), 1.23–1.15 (m, 2 H), 0.89–0.87 (m, 2 H) ppm. ^{13}C NMR: δ = 156.4, 155.0, 142.6, 140.9, 129.3, 128.9, 128.6, 128.3, 127.8, 127.7, 68.3, 54.0, 53.6, 43.9, 43.3, 22.8, 22.3, 19.1 ppm. MS (ESI) $[M + H]^+$ 413.

Compound 6l: M.p. 348–350 °C. ^{1}H NMR: δ = 8.25 (m, 4 H), 7.58 (m, 4 H), 7.49 (s, 1 H), 7.00 (s, 1 H), 6.90 (s, 1 H), 6.83 (s, 1 H), 5.09 (s, 1 H), 4.77 (d, J = 11.4 Hz, 1 H), 2.11–2.06 (m, 2 H), 1.46–1.42 (m, 2 H), 1.25–1.17 (m, 2 H), 0.85–0.78 (m, 2 H) ppm. MS (ESI) $[M + H]^+$ 467.

Compound 6m: M.p. 331–335 °C. ^{1}H NMR: δ = 8.19–8.15 (m, 5 H), 7.78–7.66 (m, 6 H), 7.14 (s, 1 H), 5.11 (d, J = 2.8 Hz, 1 H), 4.86 (d, J = 11.3 Hz, 1 H), 2.20–2.13 (m, 2 H), 1.49–1.47 (m, 2 H), 1.26–1.16 (m, 2 H), 0.88–0.80 (m, 2 H) ppm. ^{13}C NMR: δ = 156.7, 155.6, 148.9, 148.6, 144.0, 142.9, 135.5, 134.7, 131.3, 130.8, 124.1, 123.2, 123.1, 122.6, 122.3, 68.6, 53.5, 53.4, 43.2, 42.2, 23.1, 22.4, 19.0 ppm. MS (ESI) $[M + H]^+$ 467.

Compound 6n: M.p. 324–347 °C. ^{1}H NMR: δ = 7.31 (s, 1 H), 7.28–6.87 (m, 9 H), 6.80 (s, 1 H), 5.17 (s, 1 H), 3.80 (m, 3 H), 3.78 (m, 3 H), 2.46–2.28 (m, 2 H), 2.05–2.00 (m, 2 H), 1.83–1.79 (m, 1 H), 1.51–1.42 (m, 1 H), 1.28 (m, 1 H), 0.91–0.80 (m, 1 H) ppm. ^{13}C NMR: δ = 157.9, 157.1, 156.7, 154.7, 132.6, 131.1, 131.0, 129.9, 129.6, 129.1, 128.8, 128.3, 126.8, 121.7, 120.7, 119.1, 112.1,,111.8,,56.6, 56.1, 53.3, 27.6, 26.9, 23.4 ppm. MS (ESI) $[M + H]^+$ 437.

Compound 6o: M.p. ^{1}H NMR: δ = 7.55–7.29 (m, 11 H), 6.76 (s, 1 H), 5.01(s, 1 H), 4.45(d, J = 8.3 Hz, 1 H), 1.82–1.79 (m, 2 H), 1.57–1.10 (m, 8 H) ppm. ^{13}C NMR: δ = 156.5, 154.8, 142.4, 140.1, 133.1, 132.3, 130.1, 129.9, 129.7, 129.5, 129.3, 129.1, 129.0, 108.6, 71.8, 56.4, 53.9, 50.0, 47.8, 26.9, 24.4, 20.9 ppm. MS (ESI) $[M + H]^+$ 459.

Compound 6p: M.p. 310–313 °C. ^{1}H NMR: δ = 7.57 (s, 1 H), 7.34–7.23 (m, 4 H), 7.07–6.92 (m, 5 H), 6.59 (s, 1 H), 6.06 (s, 1 H), 5.24 (s, 1 H), 4.73 (d, J = 8.0 Hz, 1 H), 3.82 (s, 3 H), 3.78 (s, 3 H), 2.06–2.03 (m, 1 H), 1.75–1.73 (m, 1 H), 1.59–1.50 (m, 2 H), 1.28–1.03 (m, 6 H) ppm. ^{13}C NMR: δ = 157.6, 156.9, 155.5, 130.1, 129.1, 128.8, 128.0, 121.7, 120.9, 112.5, 111.8, 72.0, 56.7, 56.6, 49.4, 45.6, 27.4, 21.8 ppm. MS (ESI) $[M + H]^+$ 451.

Compound 6q: M.p. 299–301 °C. ^{1}H NMR: δ = 7.65–7.23 (m, 9 H), 6.67 (s, 2 H), 6.29 (s, 1 H), 5.28 (d, J = 2.3 Hz, 1 H), 4.75 (d, J = 9.5 Hz, 1 H), 5.04 (s, 1 H), 2.61–2.54 (m, 1 H), 2.20 (d, J = 8.4 Hz, 2 H), 1.87–1.82 (m, 1 H), 1.64–1.62 (m, 1 H), 1.40–1.13 (m, 6 H) ppm. ^{13}C NMR: δ = 156.5, 153.5, 140.1, 138.1, 133.0, 129.6, 129.0, 128.2, 122.1, 121.0, 120.7, 70.5, 54.0, 53.5, 44.9, 44.6, 30.5, 25.8, 22.6, 22.6, 20.1 ppm. MS (ESI) $[M + H]^+$ 547.

Compound 6r: M.p. 307–310 °C. ^{1}H NMR: δ = 8.95 (s, 1 H), 8.45 (s, 1 H), 7.95 (s, 1 H), 7.50–7.31 (m, 10 H), 7.05 (s, 1 H), 4.75 (d, J = 11.8 Hz, 1 H), 4.55 (s, 1 H), 2.72–2.70 (m, 1 H), 2.16–2.12 (m, 1 H), 1.83–1.34 (m, 6 H), 1.03–1.01 (m, 1 H), 0.85–0.82 (m, 1 H) ppm. ^{13}C NMR: δ = 179.0, 175.3, 140.9, 130.1, 129.9, 129.4, 129.3, 129.0, 128.9, 128.3, 127.6, 126.9, 70.8, 59.4, 56.8, 48.5, 44.4, 28.3, 26.4, 23.6, 23.3 ppm. MS (ESI) $[M + H]^+$ 423.

Compound 6s: M.p. 317–321 °C. ^{1}H NMR: δ = 8.85 (s, 1 H), 8.31 (s, 1 H), 7.75 (s, 1 H), 7.40 (d, J = 8.5 Hz, 2 H), 7.28 (s, 1 H), 7.24 (d, J = 8.5 Hz, 2 H), 6.99 (d, J = 8.5 Hz, 2 H), 6.94–6.91 (d, J = 8.4 Hz, 2 H), 4.66 (d, J = 12.0 Hz, 1 H), 4.48 (s, 1 H), 3.76 (s, 3 H), 3.74 (s, 3 H), 2.72–2.66 (m, 1 H), 2.11–2.07 (m, 1 H), 1.79–1.29 (m, 6 H), 1.02–1.00 (d, J = 14.6 Hz, 1 H), 0.87–0.84 (m, 1 H) ppm. ^{13}C NMR: δ = 179.2, 175.3, 159.9, 159.8, 132.8, 132.5, 130.5, 128.9, 115.3, 114.7, 71.0, 58.7, 56.3, 56.1, 56.0, 48.5, 44.8, 27.8, 26.8, 23.5 ppm. MS (ESI) $[M + H]^+$ 483.

Compound 6t: M.p. 314–317 °C. ^{1}H NMR: δ = 8.97 (s, 1 H), 8.52 (s, 1 H), 7.84 (s, 1 H), 7.51–7.39 (m, 8 H), 7.27 (s, 1 H), 4.77 (d, J = 11.9 Hz, 1 H), 4.58 (d, J = 4.0 Hz, 1 H), 2.73 (m, 1 H), 2.16–2.12 (m, 1 H), 1.81–1.23 (m, 6 H), 0.98 (d, J = 13.6 Hz, 1 H), 0.85 (m, 1 H) ppm. MS (ESI) $[M + H]^+$ 491.

Compound 6u: M.p. 290–293 °C. ^{1}H NMR: δ = 8.95 (s, 1 H), 8.49 (s, 1 H), 7.83 (s, 1 H), 7.55–7.53 (m, 2 H), 7.38–7.35 (m, 2 H), 7.29–7.17 (m, 5 H), 4.77 (d, J = 12.0 Hz, 1 H), 4.57 (d, J = 4.2 Hz, 1 H), 2.72 (t, J = 5.8 Hz, 1 H), 2.17–2.13 (m, 1 H), 1.81–1.78 (m, 1 H), 1.66–1.26 (m, 5 H), 0.99–0.96 (d, J = 14.6 Hz, 1 H), 0.86 (m, 1 H) ppm. ^{13}C NMR: δ = 179.5, 145.4, 163.7, 161.7, 137.1, 136.9, 131.5, 1314, 130.0, 129.9, 116.8, 116.6, 116.2, 116.0, 71.0, 58.4, 56.1, 48.5, 44.7, 31.6, 27.6, 26.8, 23.5, 23.4 ppm. MS (ESI) $[M + H]^+$ 459.

Compound 6v: M.p. 300–304 °C. ^{1}H NMR: δ = 8.94 (s, 1 H), 8.64 (s, 1 H), 8.40 (s, 1 H), 7.54–7.16 (m, 8 H), 7.08 (s, 1 H), 5.11 (d, J = 11.9 Hz, 1 H), 4.69 (s, 1 H), 2.72–2.69 (m, 1 H), 2.30–2.26 (m, 1 H), 1.82–1.77 (m, 1 H), 1.62–1.40 (m, 5 H), 1.00–0.85 (m, 2 H) ppm. ^{13}C NMR: δ = 179.5, 175.5, 162.7, 160.7, 131.6, 159.7, 131.4, 131.3, 131.0, 130.8, 128.6, 127.8, 127.7, 126.3, 125.5, 117.0, 116.8, 116.5, 116.3, 70.7, 53.7, 47.3, 43.5, 28.6, 26.4, 23.6, 23.5 ppm. MS (ESI) $[M + H]^+$ 459.

Compound 6w: M.p. 313–315 °C. ^{1}H NMR: δ = 8.95 (s, 1 H), 8.72 (s, 1 H), 8.60 (s, 1 H), 7.58–7.33 (m, 8 H), 6.68 (s, 1 H), 5.27 (d, J = 6.9 Hz, 1 H), 4.64 (s, 1 H), 2.72–2.70 (m, 1 H), 2.30 (m, 1 H), 1.83–1.36 (m, 6 H), 1.02–0.84 (m, 2 H) ppm. MS (ESI) $[M + H]^+$ 491.

Compound 6x: M.p. 328–333 °C. ^{1}H NMR: δ = 8.98 (s, 1 H), 8.62 (s, 1 H), 7.74 (s, 1 H), 7.59–7.52 (m, 4 H), 7.44–7.34 (m, 4 H), 6.75 (s, 1 H), 5.11 (d, J = 11.5 Hz, 1 H), 4.59 (s, 1 H), 2.77–2.69 (m, 1 H), 2.32–2.28 (m, 1 H), 1.61–1.60 (m, 1 H), 1.54–1.24 (m, 5 H), 1.07–1.05 (m, 1 H), 0.85–0.81 (m, 1 H) ppm. ^{13}C NMR: δ = 178.9, 175.1, 140.5, 139.5, 134.7, 133.4, 131.4, 130.9, 130.8, 129.8, 129.2, 129.0, 125.9, 123.7, 70.5, 60.0, 55.8, 46.3, 44.8, 29.4, 25.9, 23.8, 22.9 ppm. MS (ESI) $[M + H]^+$ 578.

Compound 4a: M.p. 221–224 °C. ^{1}H NMR: δ = 9.41 (s, 1 H), 8.68 (s, 1 H), 7.16–7.11 (m, 5 H), 4.65 (s, 1 H), 2.07–2.03 (m, 2 H), 1.80 (d, J = 16.3 Hz, 1 H), 1.60–1.47 (m, 5 H) ppm. ^{13}C NMR: δ = 173.7, 144.3, 130.0, 129.3, 127.9, 107.9, 60.0, 25.7, 23.5, 22.9 ppm. MS (ESI) $[M + H]^+$ 245.

Compound 4b: M.p. 230–232 °C. ^{1}H NMR: δ = 9.41 (s, 1 H), 8.66 (s, 1 H), 7.16 (d, J = 7.5 Hz, 2 H), 7.11 (d, J = 7.7 Hz, 2 H), 4.60 (s, 1 H), 2.28 (s, 3 H), 2.04–2.02 (m, 2 H), 1.78 (d, J = 21.3 Hz, 1 H), 1.62–1.47 (m, 5 H) ppm. ^{13}C NMR: δ = 173.7, 141.5, 137.9, 130.1, 128.6, 127.8, 107.9, 99.7, 25.7, 25.7, 22.9, 22.7, 21.8 ppm. MS (ESI) [M + H]$^+$ 259.

Compound 4c: M.p. 226–229 °C. ^{1}H NMR: δ = 9.40 (s, 1 H), 8.65 (s, 1 H), 7.13 (d, J = 8.5 Hz, 2 H), 7.11 (d, J = 8.5 Hz, 2 H), 4.58 (s, 1 H), 3.74 (s, 3 H), 2.04–2.01 (m, 2 H), 1.79 (d, J = 16.3 Hz, 1 H), 1.60–1.46 (m, 5 H) ppm. ^{13}C NMR: δ = 173.3, 159.7, 136.3, 129.0, 128.4, 114.8, 107.8, 59.1, 56.0, 25.5, 25.5, 22.8, 22.5 ppm. MS (ESI) [M + H]$^+$ 275.

Compound 4d: M.p. 218–220 °C. ^{1}H NMR: δ = 9.50 (s, 1 H), 8.75 (s, 1 H), 7.43 (d, J = 8.4 Hz, 2 H), 7.24 (d, J = 8.4 Hz, 2 H), 4.68 (s, 1 H), 2.04–2.02 (m, 2 H), 1.81 (d, J = 16.0 Hz, 1 H), 1.55–1.43 (m, 5 H) ppm. ^{13}C NMR: δ = 173.7, 143.1, 133.1, 129.6, 129.5, 128.8, 107.2, 59.0, 25.5, 25.4, 22.7, 22.4 ppm. MS (ESI) [M + H]$^+$ 279.

Compound 4e: M.p. 211–214 °C. ^{1}H NMR: δ = 9.47 (s, 1 H), 8.73 (s, 1 H), 7.26 –7.16 (m, 2 H), 4.67 (s, 1 H), 2.04–2.01 (m, 2 H), 1.77 (d, 1 H), 1.55–1.46 (m, 5 H) ppm. ^{13}C NMR: δ = 173.6, 163.5, 161.5, 140.4, 129.8, 129.7, 128.7, 116.3, 116.1, 107.5, 59.0, 25.6, 25.5, 22.7, 22.5 ppm. MS (ESI) [M + H]$^+$ 263.

Compound 4f: M.p. 217–220 °C. ^{1}H NMR: δ = 9.60 (s, 1 H), 8.86 (s, 1 H), 8.27 (d, J = 8.0 Hz, 2 H), 7.49 (d, J = 8.0 Hz, 2 H), 4.85 (s, 1 H), 2.04–2.01 (m, 2 H), 1.87 (d, J = 15.7 Hz, 1 H), 1.67–1.46 (m, 5 H) ppm. ^{13}C NMR: δ = 174.0, 151.4, 147.9, 129.3, 129.0, 124.9, 106.7, 59.1, 31.6, 25.6, 25.4, 22.7, 22.4 ppm. MS (ESI) [M + H]$^+$ 290.

Compound 4g: M.p. 223–224 °C. ^{1}H NMR: δ = 9.61 (s, 1 H), 8.87 (s, 1 H), 8.18–8.06 (m, 2 H), 7.71 (m, 2 H), 4.90 (s, 1 H), 2.10–2.04 (m, 2 H), 1.85 (d, J = 16.2 Hz, 1 H), 1.51–1.46 (m, 5 H) ppm. MS (ESI) [M + H]$^+$ 290.

Compound 4h: M.p. 224–226 °C. ^{1}H NMR: δ = 9.39 (s, 1 H), 8.34 (s, 1 H), 7.26–6.94 (m, 4 H), 5.07 (s, 1 H), 3.80 (s, 3 H), 2.02–2.00 (m, 2 H), 1.81 (d, J = 17.0 Hz, 1 H), 1.60–1.42 (m, 5 H) ppm. ^{13}C NMR: δ = 173.9, 156.7, 132.1, 129.4, 128.3, 121.5, 111.8, 107.5, 56.2, 52.8, 25.4, 25.2, 22.6, 22.3 ppm. MS (ESI) [M + H]$^+$ 275.

Compound 4i: M.p. 207–209 °C. ^{1}H NMR: δ = 9.53 (s, 1 H), 8.69 (s, 1 H), 7.34–7.15 (m, 4 H), 4.99 (s, 1 H), 2.08–2.02 (m, 2 H), 1.83 (d, J = 16.0 Hz, 1 H), 1.61–1.43 (m, 5 H) ppm. ^{13}C NMR: δ = 174.1, 161.1 and 159.1 (split), 131.3, 131.1, 130.5, 129.9, 128.8, 125.9, 116.4, 116.2, 106.6, 53.5, 25.5, 25.2, 22.7, 22.4 ppm. MS (ESI) [M + H]$^+$ 263.

Compound 4j: M.p. 210–211 °C. ^{1}H NMR: δ = 9.56 (s, 1 H), 8.72 (s, 1 H), 7.57–7.20 (m, 4 H), 5.17 (s, 1 H), 2.08–2.04 (m, 2 H), 1.83 (m, 1 H), 1.59–1.43 (m, 5 H) ppm. ^{13}C NMR: δ = 173.9, 143.5, 133.4, 130.7, 130.6, 129.7, 128.7, 122.5, 107.5, 59.0, 25.6, 25.2, 22.7, 22.4 ppm. MS (ESI) [M + H]$^+$ 323.

Compound 4k: M.p. 230–232 °C (ref.[34] 230 °C). ^{1}H NMR: δ = 9.41 (s, 1 H), 8.67 (s, 1 H), 7.36–7.24 (m, 5 H), 4.68 (s, 1 H), 2.23 (s, 2 H), 1.97–1.83 (m, 2 H), 1.57–1.34 (m, 7 H), 1.02 (m, 1 H) ppm. ^{13}C NMR: δ = 174.1, 145.1, 130.7, 129.4, 128.7, 128.1, 109.9, 59.6, 29.8, 29.2, 28.2, 27.3, 27.1, 26.4 ppm. MS (ESI) [M + H]$^+$ 273.

Compound 4l: M.p. 234–237 °C (ref.[34] 230 °C). ^{1}H NMR: δ = 9.39 (s, 1 H), 8.63 (s, 1 H), 7.17–7.12 (m, 4 H), 4.64 (d, J = 2.3 Hz, 1 H), 3.73 (s, 3 H), 2.22 (m, 2 H), 1.95–1.82 (m, 2 H), 1.58–1.34 (m, 7 H), 1.00 (m, 1 H) ppm. ^{13}C NMR: δ = 174.0, 142.2, 137.7, 130.5, 129.9, 127.9, 109.9, 59.2, 29.8, 29.1, 28.1, 27.2, 27.0, 26.3, 21.6 ppm. MS (ESI) [M + H]$^+$ 287.

Compound 4m: M.p. 208–211 °C (ref.[34] 204 °C). ^{1}H NMR: δ = 9.38 (s, 1 H), 8.62 (s, 1 H), 7.17 (d, J = 8.3 Hz, 2 H), 6.91–6.89 (d, J = 8.3 Hz, 2 H), 4.63 (s, 1 H), 3.73 (s, 3 H), 2.23 (m, 2 H), 1.93–1.84 (m, 2 H), 1.56–1.35 (m, 7 H), 1.03 (m, 1 H) ppm. ^{13}C NMR: δ = 173.8, 159.7, 159.2, 137.2, 130.4, 130.2, 130.0, 129.2, 114.7, 114.5, 110.0, 58.9, 56.0, 29.6, 29.1, 28.2, 27.2, 27.0, 26.3 ppm. MS (ESI) [M + H]$^+$ 303.

Compound 4n: M.p. 215–216 °C (ref.[34] 215 °C). ^{1}H NMR: δ = 9.48 (s, 1 H), 8.72 (s, 1 H), 7.43 (d, J = 8.0 Hz, 2 H), 6.91–6.89 (d, J = 8.0 Hz, 2 H), 4.72 (s, 1 H), 2.23 (m, 2 H), 1.98–1.81 (m, 2 H), 1.56–1.34 (m, 7 H), 1.01 (m, 1 H) ppm. ^{13}C NMR: δ = 174.2, 144.0, 133.1, 131.0, 129.9, 129.4, 109.4, 58.7, 29.8, 29.1, 28.0, 27.2, 27.0, 26.3 ppm. MS (ESI) [M + H]$^+$ 307.

Compound 4o: M.p. 217–220 °C. ^{1}H NMR: δ = 9.46 (s, 1 H), 8.71 (s, 1 H), 7.30–7.16 (m, 4 H), 4.72 (s, 1 H), 2.23 (m, 2 H), 1.96–1.82 (m, 2 H), 1.57–1.34 (m, 7 H), 1.01 (m, 1 H) ppm. ^{13}C NMR: δ = 174.0, 163.5 and 161.6 (split), 141.4, 141.3, 130.8, 130.0, 129.9, 116.2, 116.0, 109.6, 59.6, 29.8, 29.1, 28.0, 27.2, 27.0, 26.3 ppm. MS (ESI) [M + H]$^+$ 291.

Compound 4p: M.p. 226–229 °C. ^{1}H NMR: δ = 9.58 (s, 1 H), 8.83 (s, 1 H), 8.23 (d, J = 8.6 Hz, 2 H), 7.54 (d, J = 8.6 Hz, 2 H), 4.90 (d, J = 2.3 Hz, 1 H), 2.24 (m, 2 H), 1.98–1.80 (m, 2 H), 1.48–1.25 (m, 7 H), 1.03 (m, 1 H) ppm. ^{13}C NMR: δ = 174.5, 152.2, 147.9, 131.7, 129.7, 129.2, 127.9, 124.8, 124.3, 108.8, 58.7, 29.8, 29.1, 27.9, 27.3, 27.0, 26.1 ppm. MS (ESI) [M + H]$^+$ 318.

Compound 4q: M.p. 215–217 °C. ^{1}H NMR: δ = 9.53 (s, 1 H), 8.65 (s, 1 H), 7.35–7.15 (m, 4 H), 5.02 (s, 1 H), 2.26–2.17 (m, 2 H), 1.96–1.86 (m, 2 H), 1.56–1.32 (m, 7 H), 0.94 (m, 1 H) ppm. ^{13}C NMR: δ = 174.5, 161.2 and 159.2 (split), 132.0, 131.9, 131.2, 130.7, 130.6, 130.5, 130.5, 125.8, 116.5, 116.3, 108.4, 53.4, 29.9, 29.1, 28.0, 27.2, 27.0, 26.3 ppm. MS (ESI) [M + H]$^+$ 291.

General Procedures for Synthesis of Pyrimidinone Scaffolds from Table 7: Cyclododecanone (**1e**, 10 mmol), urea (12 mmol) or thiourea (12 mmol), the aromatic aldehyde (10 mmol), and DMF/CH_3CN (3 mL/6 mL) were mixed in a flask and TMSCl (10 mmol) was added dropwise at room temperature. After 30 minutes, the reaction mixture was stirred at reflux for 5–6 h and precipitation was observed. The product was isolated by filtered through a Buechner funnel and washed with water followed by ethanol, and then dried to give the crystalline powder products.

Compound 4r: M.p. 210–213 °C. ^{1}H NMR: δ = 7.97 (s, 1 H), 7.40 (d, J = 7.6 Hz, 2 H), 7.27 (d, J = 7.6 Hz, 2 H), 7.02 (s, 1 H), 4.68 (s, 1 H), 2.33–2.30 (m, 1 H), 2.16–2.14 (m, 1 H), 1.90–1.87 (m, 1 H), 1.57–1.25 (m, 17 H) ppm. ^{13}C NMR: δ = 154.1, 144.6, 132.9, 132.7, 129.6, 129.3, 107.4, 57.2, 35.2, 26.0, 25.9, 25.8, 25.4, 25.3, 25.2, 24.8, 22.9, 22.6 ppm. MS (ESI) [M + H]$^+$ 347.

Compound 4s: M.p. 237–241 °C. ^{1}H NMR: δ = 7.90 (s, 1 H), 7.23–7.18 (m, 2 H), 6.98–6.90 (m, 2 H), 6.61 (s, 1 H), 5.13 (d, J = 1.8 Hz, 1 H), 3.77 (s, 3 H), 2.35–2.32 (m, 1 H), 2.15–2.13 (m, 1 H), 1.87–1.85 (m, 1 H), 1.57–1.19 (m, 17 H) ppm. ^{13}C NMR: δ = 157.0, 154.8, 133.3, 132.8, 129.4, 128.4, 121.6, 111.9, 10.7, 55.6, 45.0, 42.6, 125.9, 25.9, 25.5, 25.4, 25.3, 25.1, 24.9, 22.9, 22.7 ppm. MS (ESI) [M + H]$^+$ 343.

Compound 4t: M.p. 220–222 °C. ^{1}H NMR: δ = 8.03 (s, 1 H), 7.45–7.02 (m, 4 H), 6.77 (s, 1 H), 5.05 (s, 1 H), 2.33–2.30 (m, 1 H), 2.16–2.15 (m, 1 H), 1.89–1.87 (m, 1 H), 1.45–1.05 (m, 17 H) ppm. ^{13}C NMR: δ = 161.1 and 159.2 (split), 133.1, 132.6, 132.5, 130.3, 130.2, 129.8, 125.9, 116.3, 116.2, 106.6, 51.0, 31.7, 26.1, 25.9, 25.5, 25.4, 25.2, 24.8, 24.6, 23.0, 22.6 ppm. MS (ESI) [M + H]$^+$ 331.

Compound 4u: M.p. 183–185 °C. ^{1}H NMR: δ = 8.04 (s, 1 H), 7.42–7.26 (m, 1 H), 7.04 (s, 1 H), 5.20 (d, J = 1.9 Hz, 1 H), 2.33–2.30

(m, 1 H), 2.16–2.13 (m, 1 H), 1.91–1.88 (m, 1 H), 1.59–1.18 (m, 17 H) ppm. MS (ESI) $[M + H]^+$ 347.

Compound 4v: M.p. 257–260 °C. ^{1}H NMR: δ = 8.03 (s, 1 H), 7.55 (d, J = 7.9 Hz, 1 H), 7.43–7.38 (m, 2 H), 7.20–7.17 (t, J = 7.5 Hz, 1 H), 7.04 (s, 1 H), 5.17 (s, 1 H), 2.33–2.30 (m, 1 H), 2.15–2.12 (m, 1 H), 1.91–1.88 (m, 1 H), 1.61–1.18 (m, 17 H) ppm. ^{13}C NMR: δ = 174.3, 163.2, 144.0, 133.4, 131.9, 130.7, 130.5, 129.7, 122.6, 110.8, 56.6, 31.7, 26.2, 26.1, 25.7, 25.5, 25.4, 25.2, 24.9, 22.9, 22.5 ppm. MS (ESI) $[M + H]^+$ 391.

Compound 4w: M.p. 168–170 °C. ^{1}H NMR: δ = 9.36 (s, 1 H), 8.75 (s, 1 H), 7.15 (d, J = 8.5 Hz, 2 H), 6.91 (d, J = 8.5 Hz, 2 H), 4.66 (s, 1 H), 2.33–2.30 (m, 1 H), 2.16–2.14 (m, 1 H), 1.90–1.87 (m, 1 H), 1.57–1.25 (m, 17 H) ppm. ^{13}C NMR: δ = 163.3, 159.8, 136.3, 131.3, 129.1, 114.7, 111.3, 56.8, 55.7, 36.8, 26.3, 25.7, 25.6, 25.5, 25.2, 24.5, 24.1, 23.1, 22.4 ppm. MS (ESI) $[M + H]^+$ 359.

Compound 4x: M.p. 159–163 °C. ^{1}H NMR: δ = 9.46 (s, 1 H), 8.76 (s, 1 H), 7.35–7.09 (m, 4 H), 5.07 (d, J = 2.1 Hz, 1 H), 2.33–2.29 (m, 1 H), 2.20–2.17 (m, 1 H), 2.01–1.98 (m, 1 H), 1.63–0.99 (m, 17 H) ppm. ^{13}C NMR: δ = 174.6, 160.9, 158.9, 131.7, 131.4, 130.7, 129.9, 116.4, 109.9, 50.7, 31.6, 26.2, 25.6, 25.5, 25.3, 25.2, 25.1, 24.5, 23.7, 23.1, 22.4, 22.1 ppm. MS (ESI) $[M + H]^+$ 347.

General Procedures for Synthesis of Pyrimidinone Scaffolds (Scheme 13, Schemes 15–16, and Schemes 18–19): Urea (12.0 mmol) or thiourea (12.0 mmol), the cycloalkanones and/or the aliphatic aldehyde (10.0 mmol), DMF (3.0 mL), and CH_3CN (6.0 mL) were mixed in a flask and TMSCl (10.0 mmol) was added dropwise at room temperature. The resulting reaction mixture was stirred at reflux for 4–6 h and then poured into crashed ice with stirring. The precipitation was isolated by filtered through a Buechner funnel and washed with water followed by ethanol, and then dried to give the crystalline powder.

Compound 6y (Scheme 13): M.p. 285–288 °C. ^{1}H NMR: δ = 8.61 (s, 1 H), 8.29 (s, 1 H), 7.61 (s, 1 H), 7.56 (s, 1 H), 3.00 (d, J = 11.2 Hz, 1 H), 2.15 (s, 2 H), 1.89 (t, J = 6.8 Hz, 1 H), 1.74 (m, 1 H), 1.63–1.56 (m, 2 H), 1.49–1.47 (m, 1 H), 1.23–1.21 (m, 1 H), 1.18–0.92 (m, 6 H), 0.83–0.82 (d, J = 6.6 Hz, 6 H) ppm. ^{13}C NMR: δ = 177.7, 176.8, 75.8, 59.4, 55.3, 44.5, 41.3, 30.1, 28.6, 25.1, 20.9, 20.8, 20.1, 19.6, 15.8 ppm. MS (ESI) $[M + H]^+$ 327.

Compound 6z (Scheme 13): M.p. 284–286 °C. ^{1}H NMR: δ = 8.48 (s, 1 H), 8.18 (s, 1 H), 7.99 (s, 1 H), 7.93 (s, 1 H), 3.58–3.57 (m, 1 H), 3.04–3.02 (m, 1 H), 2.26–2.15 (m, 3 H), 1.63–1.49 (m, 6 H), 1.44–1.41 (m, 1 H), 1.44–1.16 (m, 16 H), 0.88–0.84 (m, 6 H) ppm. ^{13}C NMR: δ = 175.7, 175.6, 74.5, 53.7, 48.4, 44.3, 42.6, 31.7, 31.6, 31.3, 30.6, 29.2, 29.1, 28.5, 25.1, 23.9, 23.6, 22.4, 19.8, 14.4 ppm. MS (ESI) $[M + H]^+$ 411.

Compound 4z (Scheme 19): M.p. 228–233 °C. ^{1}H NMR: δ = 9.47 (s, 1 H), 7.60 (s, 1 H), 3.46 (s, 1 H), 1.97 (d, J = 18.0 Hz, 4 H), 1.67–1.62 (m, 2 H), 1.55–1.39 (m, 10 H), 1.11–1.09 (m, 1 H) ppm. ^{13}C NMR: δ = 174.6, 128.6, 113.1, 56.8, 34.4, 25.9, 25.6, 23.3, 23.0, 22.3, 20.6 ppm. MS (ESI) $[M + H]^+$ 237.

Compound 4A: M.p. 190–193 °C. ^{1}H NMR: δ = 9.09 (s, 1 H), 8.23 (s, 1 H), 3.44 (s, 1 H), 2.22 (s, 2 H), 2.04–1.90 (m, 2 H), 1.68–1.35 (m, 7 H), 0.84–0.76 (m, 6 H) ppm. ^{13}C NMR: δ = 175.1, 135.1, 111.0, 62.6, 34.2, 32.4, 31.2, 31.0, 27.7, 26.4, 19.1, 16.9 ppm. MS (ESI) $[M + H]^+$ 225.

Compound 4B: M.p. 128–132 °C. ^{1}H NMR: δ = 9.15 (s, 1 H), 8.24 (s, 1 H), 3.67 (s, 1 H), 2.16–1.96 (m, 4 H), 1.45–1.25 (m, 12 H), 0.95–0.84 (m, 3 H) ppm. ^{13}C NMR: δ = 175.1, 131.4, 109.7, 54.8, 38.4, 30.2, 28.9, 27.9, 27.3, 27.0, 26.5, 17.6, 14.9 ppm. MS (ESI) $[M + H]^+$ 239.

Compound 4C: M.p. 178–183 °C. ^{1}H NMR: δ = 9.18 (s, 1 H), 8.21 (s, 1 H), 3.45 (s, 1 H), 2.22–1.93 (m, 4 H), 1.67–1.65 (m, 1 H), 1.53–1.42 (m, 8 H), 0.86–0.76 (m, 6 H) ppm. ^{13}C NMR: δ = 175.9, 132.1, 109.2, 60.2, 34.2, 30.3, 29.0, 28.4, 27.4, 27.0, 26.6, 19.5, 17.1 ppm. MS (ESI) $[M + H]^+$ 239.

Compound 4D: M.p. 143–146 °C. ^{1}H NMR: δ = 9.15 (s, 1 H), 8.24 (s, 1 H), 3.69 (d, J = 2.6 Hz, 1 H), 2.16–1.96 (m, 4 H), 1.52–1.23 (m, 14 H), 0.85 (t, J = 4.6 Hz, 3 H) ppm. ^{13}C NMR: δ = 175.1, 131.4, 109.6, 54.8, 35.8, 30.2, 28.9, 27.9, 27.3, 27.0, 26.5, 26.4, 23.1, 15.0 ppm. MS (ESI) $[M + H]^+$ 253.

Compound 4E: M.p. 154–157 °C. ^{1}H NMR: δ = 9.15 (s, 1 H), 8.24 (s, 1 H), 3.68 (d, J = 2.7 Hz, 1 H), 2.16–1.97 (m, 4 H), 1.52–1.23 (m, 18 H), 0.85 (t, J = 6.3 Hz, 3 H) ppm. ^{13}C NMR: δ = 175.1, 131.4, 109.6, 54.9, 36.0, 32.3, 30.2, 29.6, 28.9, 27.9, 27.3, 27.0, 26.5, 24.1, 23.0, 14.9 ppm. MS (ESI) $[M + H]^+$ 281.

Compound 4F: M.p. 180–182 °C. ^{1}H NMR: δ = 9.07 (s, 1 H), 8.23 (s, 1 H), 3.54 (s, 1 H), 2.49–2.41 (m, 2 H), 2.38–2.20 (m, 2 H), 1.76–1.72 (m, 1 H), 1.81–1.13 (m, 16 H), 0.86–0.74 (m, 6 H) ppm. ^{13}C NMR: δ = 175.6, 131.9, 110.5, 58.3, 33.4, 26.2, 25.8, 25.8, 25.6, 25.3, 25.2, 25.1, 24.7, 24.2, 23.3, 22.9, 22.4, 19.6, 16.8 ppm. MS (ESI) $[M + H]^+$ 295.

Compound 4G: M.p. 150–153 °C. ^{1}H NMR: δ = 9.14 (s, 1 H), 8.43 (s, 1 H), 3.63 (q, J = 3.5 Hz, 1 H), 2.30–2.24 (m, 2 H), 1.92–1.73 (m, 3 H), 1.52–1.49 (m, 1 H), 1.38–1.19 (m, 14 H), 1.10–1.08 (m, 1 H), 0.85 (t, J = 5.2 Hz, 6 H) ppm. ^{13}C NMR: δ = 175.1, 131.5, 112.5, 51.1, 44.0, 26.2, 25.8, 25.6, 25.3, 25.1, 24.7, 24.4, 23.7, 23.1, 22.7, 22.5 ppm. MS (ESI) $[M + H]^+$ 309.

Compound 4H: M.p. 167–169 °C. ^{1}H NMR: δ = 7.60 (s, 1 H), 6.47 (s, 1 H), 3.53 (s, 1 H), 2.43–2.41 (m, 1 H), 2.36–2.22 (m, 2 H), 1.78–1.50 (m, 8 H), 1.32–1.13 (m, 10 H), 0.89–0.73 (m, 6 H) ppm. ^{13}C NMR: δ = 157.4, 134.5, 108.9, 60.2, 34.6, 27.9, 27.7, 27.5, 27.0, 26.9, 26.5, 26.3, 25.0, 24.8, 24.4, 21.8, 18.1 ppm. MS (ESI) $[M + H]^+$ 279.

Compound 4I: M.p. 155–156 °C. ^{1}H NMR: δ = 7.58 (s, 1 H), 6.47 (s, 1 H), 3.68 (s, 1 H), 2.36–2.20 (m, 2 H), 1.82–1.722 (m, 2 H), 1.54 (m, 4 H), 1.43–1.25 (m, 22 H), 0.88–0.73 (t, J = 6.1 Hz, 3 H) ppm. ^{13}C NMR: δ = 153.3, 129.5, 106.0, 50.7, 33.2, 30.0, 29.8, 27.8, 23.7, 23.5, 23.4, 23.2, 23.1, 23.0, 22.8, 22.7, 22.2, 20.7, 20.4, 20.3, 12.5 ppm. MS (ESI) $[M + H]^+$ 321.

Compound 4J: M.p. 178–180 °C. ^{1}H NMR: δ = 9.92 (s, 1 H), 7.65 (s, 1 H), 3.14 (s, 1 H), 2.16 (m, 1 H), 1.60–1.55 (m, 2 H), 1.37–1.26 (m, 4 H), 0.98–0.86 (m, 6 H) ppm. ^{13}C NMR: δ = 174.1, 153.5, 51.0, 47.1, 37.6, 23.8, 19.1, 14.7, 12.3 ppm. MS (ESI) (m/z) $[M + H]^+$ 169.

Compound 4K: M.p. 182–185 °C. ^{1}H NMR: δ = 9.89 (s, 1 H), 7.63 (s, 1 H), 3.08 (d, J = 2.7 Hz, 1 H), 2.23 (m, 1 H), 1.53–1.48 (m, 2 H), 1.37–1.24 (m, 8 H), 0.89–0.86 (m, 6 H) ppm. ^{13}C NMR: δ = 174.2, 153.4, 51.6, 45.4, 35.2, 32.9, 28.1, 22.9, 20.5, 14.9, 14.7 ppm. MS (ESI) $[M + H]^+$ 197.

Compound 4L:[41] M.p. 186–189 °C. ^{1}H NMR: δ = 7.77 (s, 1 H), 6.75 (s, 1 H), 5.72 (d, J = 4.8 Hz, 1 H), 3.67 (d, J = 9.3 Hz, 1 H), 2.15–2.13 (m, 1 H), 1.79–1.76 (m, 1 H), 1.40–1.35 (m, 1 H), 1.10–1.08 (m, 1 H), 1.12–0.85 (m, 12 H) ppm. ^{13}C NMR: δ = 155.1, 120.3, 119.4, 51.2, 45.6, 28.8, 24.9, 23.7, 23.6, 22.5, 21.7 ppm. MS (ESI) $[M + H]^+$ 197.

Compound 4M: M.p. 232–235 °C. ^{1}H NMR: δ = 9.38 (s, 1 H), 8.54 (s, 1 H), 5.76 (d, J = 3.8 Hz, 1 H), 3.75 (q, J = 3.0 Hz, 1 H), 2.21–2.18 (m, 1 H), 1.77 (m, 1 H), 1.42–1.38 (m, 1 H), 1.14–1.08 (m, 1 H), 1.02–0.87 (m, 12 H) ppm. ^{13}C NMR: δ = 174.7, 123.2, 118.5,

51.3, 45.0, 29.0, 24.8, 23.7, 23.1, 22.7, 21.4 ppm. MS (ESI) [M + H]$^+$ 213.

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[1] C. O. Kappe, *Acc. Chem. Res.* **2000**, *33*, 879–888.
[2] R. W. Armstrong, A. P. Combs, P. A. Tempest, S. D. Brown, T. A. Keating, *Acc. Chem. Res.* **1996**, *29*, 123–131.
[3] A. Domling, I. Ugi, *Angew. Chem. Int. Ed.* **2000**, *39*, 3168–3210.
[4] C. Simon, T. Constantieux, J. Rodriguez, *Eur. J. Org. Chem.* **2004**, 4957–4980.
[5] C. O. Kappe, *Tetrahedron* **1993**, *49*, 6937–6963.
[6] G. C. Rovnyak, S. D. Kimball, B. Beyer, G. Cucinotta, J. D. Dimarco, J. Gougoutas, A. Hedberg, M. Malley, J. P. Mccarthy, R. Zhang, S. Moreland, *J. Med. Chem.* **1995**, *38*, 119–129.
[7] K. S. Atwal, G. C. Rovnyak, S. D. Kimball, D. M. Floyd, S. Moreland, B. N. Swanson, J. Z. Gougoutas, J. Schwartz, K. M. Smillie, M. F. Malley, *J. Med. Chem.* **1990**, *33*, 2629–2635.
[8] P. Biginelli, *Gazz. Chim. Ital.* **1893**, *23*, 360–413.
[9] E. H. Hu, D. R. Sidler, U. H. Dolling, *J. Org. Chem.* **1998**, *63*, 3454–3457.
[10] C. O. Kappe, S. F. Falsone, *Synlett* **1998**, 718–720.
[11] J. Lu, Y. Bai, Z. Wang, B. Yang, H. Ma, *Tetrahedron Lett.* **2000**, *41*, 9075–9078.
[12] B. C. Ranu, A. Hajra, U. Jana, *J. Org. Chem.* **2000**, *65*, 6270–6272.
[13] C. V. Reddy, M. Mahesh, K. Raju, T. R. Babu, V. V. N. Reddy, *Tetrahedron Lett.* **2002**, *43*, 2657–2659.
[14] K. Ramalinga, P. Vijayalaxmi, T. N. B. Kaimal, *Synlett* **2001**, 863–865.
[15] K. A. Kumar, M. Kasthuraiah, C. S. Reddy, C. D. Reddy, *Tetrahedron Lett.* **2001**, *42*, 7873–7875.
[16] A. Stadler, C. O. Kappe, *J. Chem. Soc. Perkin. Trans. 1* **2000**, 1363–1368.
[17] P. Wipf, A. Cunningham, *Tetrahedron Lett.* **1995**, *36*, 7819–7822.
[18] A. Studer, P. Jeger, P. Wipf, D. P. Curran, *J. Org. Chem.* **1997**, *62*, 2917–2924.
[19] R. Varala, M. Alam, S. R. Adapa, *Synlett* **2003**, 67–70.
[20] A. Shaabani, A. Bazgir, F. Teimouri, *Tetrahedron Lett.* **2003**, *44*, 857–859.
[21] G. Maiti, P. Kundu, C. Guin, *Tetrahedron Lett.* **2003**, *44*, 2757–2758.
[22] J. T. Li, J. F. Hu, T. S. Liu, *Ultrason. Sonochem.* **2003**, *10*, 119–122.
[23] A. S. Paraskar, G. K. Dewkar, A. Sudalai, *Tetrahedron Lett.* **2003**, *44*, 3305–3308.
[24] G. Byk, H. Gottlieb, J. Herscovici, F. Mirkin, *J. Comb. Chem.* **2000**, *2*, 732–735.
[25] M. Abelman, S. Smith, D. James, *Tetrahedron Lett.* **2003**, *44*, 4559–4562.
[26] A. Shaabani, A. Bazgir, *Tetrahedron Lett.* **2004**, *45*, 2575–2577.
[27] M. Yarim, S. Sarac, F. S. Kilic, K. Erol, *Farmaco* **2002**, *58*, 17–24.
[28] S. I. Zavyalov, L. B. Kulikova, *Khim.-Farm. Zh.* **1992**, *26*, 116–117.
[29] G. Sabitha, G. S. Kiran Kumar Reddy, C. Srinivas Reddy, J. S. Yadav, *Synlett* **2003**, 858–860.
[30] Y. Zhu, Y. Pan, S. Huang, *Synth. Commun.* **2004**, *34*, 3167–3174.
[31] N. M. Yosif, Z. M. Nofal, K. Z. Gadalla, A. H. Mandour, M. A. Salama, *Orient. J. Chem.* **1989**, *5*, 173.
[32] N. M Yousif, Z. M. Nghofal, K. Z. Gadalla, A. H. Mandour, M. A. Salama, *Egypt. J. Pharm. Sci.* **1990**, *31*, 384.
[33] A. G. Hammam, *Egypt. J. Chem.* **1982**, *25*, 471.
[34] G. Hammam, A. El-Fotooh, M. I. Ali, *J. Chem. Eng. Data* **1981**, *26*, 101–102.
[35] V. F. Sedova, V. M. Mamaev, *Khimiya Geterotsiklicheskikh Soedinenii* **1968**, *5*, 921.
[36] V. P. Mamaev, *Khimiya Geterotsiklicheskikh Soedinenii* **1967**, *3*, 571–572.
[37] M. I. Ali, A. El-Fotooh, G. Hammam, *J. Chem. Eng. Data* **1978**, *23*, 351–352.
[38] M. I. Ali, M. A.-F. El-Kaschef, A. El-Fotooh, G. Hammam, Salah A, Khallaf, *J. Chem. Eng. Data* **1979**, *24*, 377–378.
[39] M. I. Ali, A. El-Fotooh, G. Hammam, N. M. Youssef, *J. Chem. Eng. Data* **1981**, *26*, 214–215.
[40] A crystal of 4-(4-fluorophenyl)-3,4,5,6,7,8,9,10-octahydro-1*H*-cyclooctapyrimidine-2-thione (**4o**) was grown by slow evaporation of a solution in DMF. The X-ray single-crystal data were collected at 296(2) K on a Siemens P4 diffractometer by use of graphite monochromated Mo-*Kα* radiation. Structure was solved by direct methods (SHELXS-97) and refined on F_2 by the full-matrix, least-squares method (SHELXL-97). The non-hydrogen atoms were refined anisotropically; hydrogen atoms were refined isotropically with a riding model. Formula: $C_{16}H_{19}N_2SF$ (M = 290.40), block, a = 6.6450(10), b = 8.3240(10), c = 15.040(2) Å, α = 95.32(2), β = 100.860(10), γ = 110.910(10)°, V = 751.51(18) Å^3, Z = 4, space group P-1, ρ = 1.283 g cm^{-3}. CCDC-259469 (for **4o**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
[41] G. Byk, E. Kabha, *J. Comb. Chem.* **2004**, *6*, 596–603.
[42] G. Zigeuner, V. Eisenreich, H. Weichsel, W. Adam, *Monatsh. Chem.* **1970**, *101*, 1731–1744.
[43] C. O. Kappe, *J. Org. Chem.* **1997**, *62*, 7201–7204.

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