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Synthesis of fused dihydro-pyrimido[4,3-*d*]coumarins using Biginelli multicomponent reaction as key step

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ABSTRACT

A new efficient approach for the synthesis of functionalized dihydro-pyrimido[4,3-*d*]coumarins is described. Use of benzyl- or *tert*-butyl acetoacetate and various salicyl aldehydes in typical Biginelli multicomponent reactions provides esters that can be easily deprotected to yield the corresponding hydroxy acids. Annelation of the latter leads to the target dihydro-pyrimido[4,3-*d*]coumarins. Formation of some unexpected oxo-bridged tetrahydro-pyrimidines is also described. Spectral properties of the synthesized dihydro-pyrimido[4,3-*d*]coumarins indicate the necessity to revisit some compounds previously reported as products of direct one-pot Biginelli condensation involving 4-hydroxycoumarin as dicarbonyl component.

1. Introduction

Functionalized nitrogen-heterocycles play a proeminent role in medicinal chemistry and they have been intensively used as scaffolds for drug development.[1] In this context pyrimidine derivatives are of particular interest because of their pharmacological profile.[2] 4,5,6-Trisubstituted-3,4-dihydropyrimidin-2(1*H*)-ones of type **1**, also known as Biginelli compounds (Fig. 1), are easily accessible via a multicomponent condensation process, first reported more than a century ago.[3] Almost ignored for eight decades,[4] their popularity recently increased. Structurally, they can be considered as 3-aza-analogs of dihydropyridines of Hantzsch type. Based on this similarity, pharmacological studies initially focused on their demonstrated calcium channel modulating properties.[5] More recently, some Biginelli derivatives proved to be promising anti-cancer leads, such as monastrol **2**, which is an inhibitor of a mitotic kinesin.[6] Other compounds, such as **3**, demonstrated inhibitory activity of heat-shock protein Hsp70[7,8] whereas compounds such as **4** exhibited α_{1a}-adrenoceptor antagonist properties.[9]

The easiest way to prepare the 3,4-dihydropyrimidin-2(1*H*)-one core involves a β-ketoester, aldehyde, and urea derivatives in the presence of an acidic catalyst,[10] process known as the Biginelli reaction. In the study of this multicomponent process much emphasis was placed on catalysts screening: a plethora of Bronsted and Lewis acids were reported to mediate the Biginelli reaction, either in solution, solvent-free conditions or in microwave conditions.[11] However, despite the versatility of 1,3-dicarbonyl derivatives as participants into multicomponent reactions,[12] far less attention has been paid to the scoping of the β-ketoesters in the Biginelli condensation[13] as well as to the further functionalization of the Biginelli adducts,[14] in spite of the fact that the structures thus obtained may present significant biological activity.

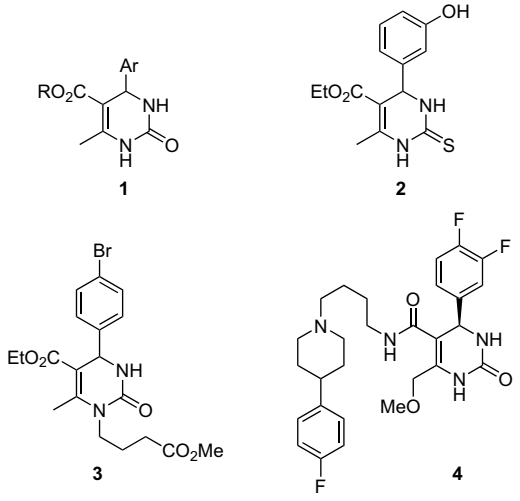

Figure 1. General formula (**1**) and examples of biologically active (**2**–**4**) Biginelli pyrimidinones.

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Since numerous reports demonstrated the potential in medicinal chemistry of fused heterocyclic structures including the pyrimidine core[15] we considered of interest their synthesis. In particular, fused pyrimidocoumarins were shown to exhibit a wide pharmacological profile,[16] underlying the importance of new synthetic methods for facile access into this class of compounds.

Herein, we describe an efficient approach for the preparation of functionalized benzopyrano[4,3-*d*]dihydropyrimidinone derivatives **5** (Scheme 1) via a short synthetic sequence that uses the Biginelli condensation as key step.

2. Results and discussion

2.1. Initial approach and revision

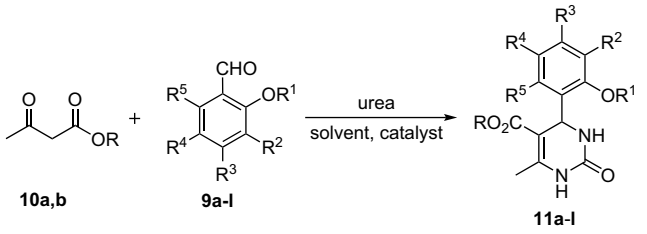
To prepare the benzopyranopyrimidines core, we initially used the most direct approach, a Biginelli-type condensation with 4-hydroxycoumarin **6** as 1,3-dicarbonyl component. This methodology implies the use of preformed benzopyrane derivative and the subsequent formation of the pyrimidinone ring in a multicomponent reaction step (Scheme 1a). Literature survey disclosed the existence of a few precedents dealing with this transformation.[17] However, all attempts to prepare the tricyclic target **7** by multicondensation using various reaction conditions,[18] including those previously reported, failed. We were only able to isolate the adducts **8** resulting from the condensation of the aldehyde with 4-hydroxycoumarin (Scheme 1a), as proved by physical and spectral characteristics.[18] Indeed, treatment of **6** with urea and various aldehydes in presence of acid catalysts led to compounds identical to those obtained in the same reaction conditions in absence of urea (also see discussion in Section 2.4), further substantiating the proposal that the obtained compounds are, in fact adducts of type **8**.

To overcome this apparent failure, we envisaged an alternative synthetic pathway: first the dihydropyrimidine ring is synthesized by multicomponent condensation and followed by the benzopyrane ring closure reaction in the final step (Scheme 1b). This strategy proposes the Biginelli-type condensation using salicyl aldehydes **9** and suitable β-ketoesters **10** to produce the dihydropirimidinone core **11**. Deprotection of the esters **11** to the corresponding free acids **12** followed by lactonization in the last step should yield the target benzopyranopyrimidinones **5**. This approach gives the possibility to conveniently functionalize the coumarin ring, due to the large variety of salicyl aldehydes **9** that are easily available.

2.2. Preparation of Biginelli adducts

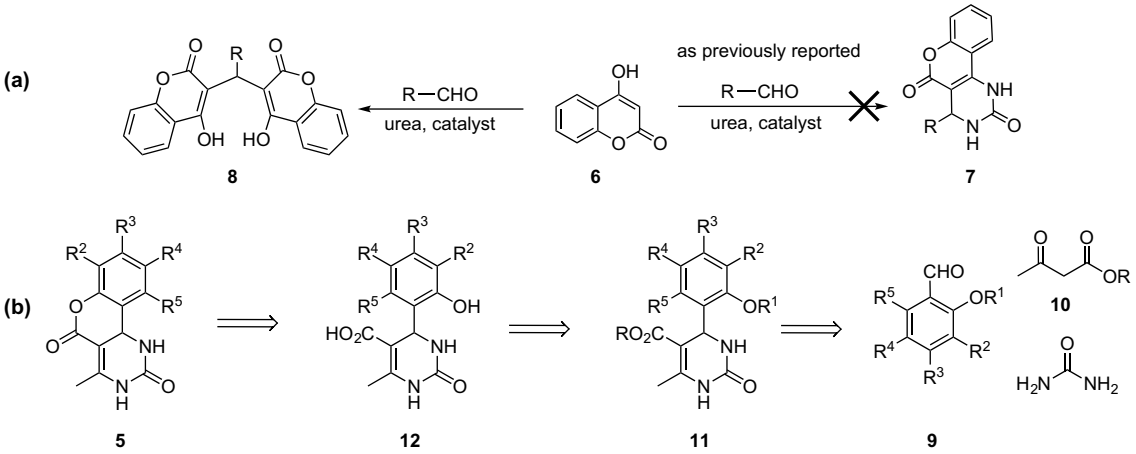
The first step of the synthesis involves the preparation of a series of various (2-salicyl)-3,4-dihydropyrimidin-2-one 5-carboxylates **11**. The choice of the esters was dictated by the effectiveness of their available deprotection methods. Since the alkaline hydrolysis of Biginelli alkyl esters is known to be a low-yielding process,[13,19] we turned our sights to benzyl esters. Indeed, they are known to be easily deprotected by hydrogenolysis, even in the notoriously difficult context of Biginelli-type compounds.[13,19,20] We therefore decided to use the benzyl acetoacetate **10a** as β-ketoester moiety. Additionally, in order to use the same methodology in presence of hydrogenolysis-incompatible functional groups (compounds **11c**–**e**), we also chose *tert*-butyl acetoacetate **10b** as a potential Biginelli-reaction candidate,[21] since *tert*-butyl esters are readily hydrolyzed under acidic conditions. For the mediation of the multicomponent reaction, we used both Bronsted and Lewis acids. Generally, we employed *para*-toluenesulfonic acid (PTSA) as a cheap and accessible catalyst for the Biginelli process.[22] By refluxing the β-ketoester, aldehyde, and urea in ethanol in a molar ratio of 1:1:1.5 in presence of 50 mol % of PTSA, we prepared the desired Biginelli adducts **11a**–**g** in medium to good isolated yields (Table 1, entries 1–7).

Table 1
Preparation of Biginelli adducts **11** from β-ketoesters **10** using salicyl aldehydes **9**



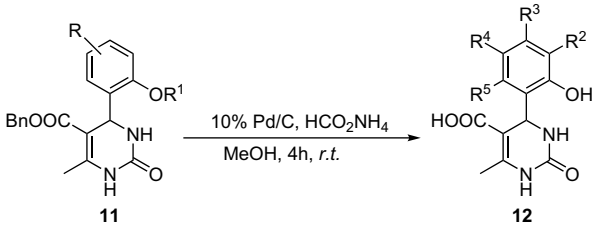
Entry	R	R^1	R^2	R^3	R^4	R^5	Product	Conditions[a]	Yield[b] (%)
1	Bn	H	H	H	H	H	**11a**	A	76
2	Bn	H	OEt	H	H	H	**11b**	A	90
3	Bn	H	H	H	Br	H	**11c**	A	65
4	Bn	H	H	H	Cl	H	**11d**	A	40
5	Bn	H	H	H	NO_2	H	**11e**	A	60
6	Bn	H	H	H	Me	H	**11f**	A	65
7	Bn	H	H	H	–CH=CH–CH=CH–		**11g**	A	40
8	Bn	Bn	H	OMe	H	H	**11h**	B	67
9	Bn	Bn	H	OBn	H	H	**11i**	C	75
10	^{t}Bu	H	H	H	Br	H	**11j**	B	70
11	^{t}Bu	H	H	H	Cl	H	**11k**	C	62
12	^{t}Bu	H	H	H	NO_2	H	**11l**	C	78

[a] A: 50 mol % PTSA, EtOH, reflux, 16 h; B: 10 mol % $Sc(OTf)_3$, MeCN, reflux, 16 h; C: 10 mol % $La(OTf)_3$, MeCN, reflux, 16 h.
[b] Isolated yields of pure products.



Scheme 1. (a) Initial approach to synthesis of benzopyranopyrimidines **7**; (b) revised retrosynthetic analysis.

For some salicyl aldehydes (i.e., R^3=OMe or R^3=OH) isolation of the target Biginelli dihydropyrimidine failed both under Bronsted (PTSA) and Lewis acid [$Sc(OTf)_3$] catalysis. For this reason, in these cases, we decided to prepare the target adducts **11** using the corresponding benzyl-protected salicyl aldehydes **9h** and **9i** and Lewis acids as catalysts[23] (Table 1, entries 8 and 9). Thus, reflux of the reagents in acetonitrile, in the same molar ratio as above, in the presence of 10 mol % of $Sc(OTf)_3$ or $La(OTf)_3$ led to the products **11h** and **11i** in good yields. Moreover, we successfully employed the same Lewis acid catalyzed conditions in order to obtain the *tert*-butyl Biginelli esters **11j–l** (Table 1, entries 10–12).



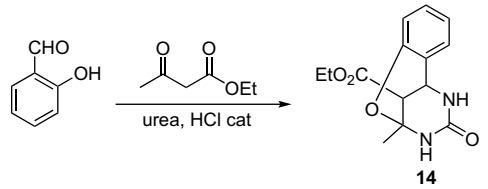
11 **12**

12a: R^2=R^3=R^4=R^5=H (83%)
12b: R^2=OEt, R^3=R^4=R^5=H (90%)
12f: R^2=R^3=H, R^4=Me, R^5=H (92%)
12g: R^2=R^3=H, R^4=R^5=benzo (70%)
12h: R^2=H, R^3=OMe, R^4=R^5=H (60%)

Scheme 2. Deprotection of benzyl esters **11a**, **11b**, and **11f–h**.

2.3. Deprotection of the Biginelli esters

The benzyl-protected Biginelli adducts **11** thus obtained were subjected to the palladium catalyzed hydrogenolysis as described by Kappe.[13a] Hydrogenolysis of compounds **11** yielded the desired products **12** provided that no basic work-up was used (Scheme 2). Basic treatment of the hydrogenolysis reaction led to isolation of the decarboxylated tricyclic oxo-bridged tetrahydro-pyrimidines **13** usually in good yields (Scheme 4). A similar type of compounds (with the carboxy functionality preserved) has previously been reported[24] under different reaction conditions: the one-pot Biginelli condensation between salicyl aldehydes, ethyl acetoacetate, and urea in presence of hydrogen chloride yielded directly **14** (Scheme 3) without isolation of the intermediate Biginelli compound.[24]



14

Scheme 3. Tricyclic oxo-bridged pyrimidines obtained from ethyl acetoacetate and salicyl aldehydes.

The formation of **14** is assumed to take place via an attack of the phenol to the double bond of the dihydropyrimidine ring. This attack is possible only if the dihydropyrimidine ring adopts a boat-like conformation with a diequatorial arrangement of the methoxycarbonyl and hydroxyphenyl group.[24] In our case (Scheme 4), due to steric hindrance caused by the use of the more bulky *tert*-butyl, benzyl β-ketoesters or the 2-hydroxy-1-naphtaldehyde in the multicomponent reaction, the positioning of the phenol hydroxyl for such an attack was unfavorable and thus Biginelli adducts **11** exclusively formed. 4-Aryl-dihydropyrimidine derivatives were described[25] to adopt a boat-like conformation with the aryl substituent in position 4 having an axial, orthogonal orientation. However, deprotection of bulky *tert*-butyl or benzyl esters led to compounds **13** under basic or acidic conditions, except for the compound **11g**, that bears a naphthyl ring. This could be explained by the increased barrier for the inversion of the dihydropyrimidine ring and for the rotation of the *ortho*-substituted aryl groups as described by Kappe.[25] The observed stability of the benzyl **11c** and *tert*-butyl **11j** esters in strong basic medium (0.5 M aq NaOH in 1,4-dioxane) substantiates the steric hindrance hypothesis.

The annelation process is accompanied in our case by decarboxylation. Furthermore, attempted deprotection by hydrogenolysis of the halogen- and nitro-substituted dihydropyrimidines benzyl esters (i.e., **11c–e**) resulted, as expected, in halogen removal or nitro group reduction, respectively. Use of the corresponding *tert*-butyl esters **11j–l** under typical acidic deprotection [trifluoroacetic acid (TFA)] prevented these side-reactions, but unfortunately formation of the oxo-bridged pyrimidines **13** could not be avoided (Scheme 4, compounds **13j–l**).

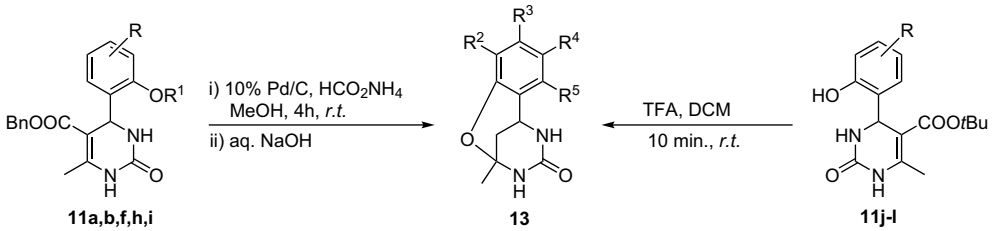
2.4. Preparation of the tricyclic dihydro-benzopyrano [4,3-*d*]pyrimidinones

With the hydroxy acids **12a**,**b** and **12f–h** in hand, we proceeded to the formation of the target benzopyrano[4,3-*d*]pyrimidines **5**. This final step was effectively achieved under the standard conditions employed for amide bond formation: 2 equiv of TBTU (2-(1*H*-benzotriazolyl)-1,1,3,3-tetramethyluronium as activation reagent and 4 equiv of DIPEA (*N*,*N*-diisopropylethylamine) as base, in dichloromethane. Under these conditions, all substrates gave the desired products in high isolated yields (Scheme 5).

The benzopyrano[4,3-*d*]pyrimidines **5** deserve a brief discussion with respect to their spectral properties. Our final target compounds **5** are structurally similar to the previously reported compounds **7** (Scheme 1a), claimed to have been obtained directly by a multicomponent cyclization involving the 4-hydroxycoumarin **6** as enolized dicarbonyl.

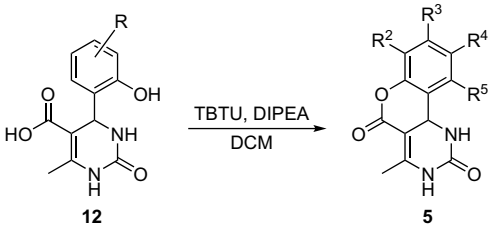
It must be mentioned that all these reports[17] present only incomplete spectral characterization of the products **7** (i.e., incompletely resolved proton NMR spectra and sometimes microanalysis). Although we repeatedly attempted to reproduce these results under various reaction conditions (catalysts, solvents) and different aldehyde components[18] we have never isolated products that presented similar spectral properties to the tricyclic adducts **5**. Moreover, the NMR spectra of the compound resulted from the typical three one-pot multicomponent reaction and the one resulted from condensation between 4-hydroxycoumarin and aldehyde (in absence of urea) were identical.[18]

We comparatively show in Table 2 some selected NMR data for examples of products of series **11**, **12**, **13**, and **5** to those of products **8** and **7** (reported for the latter). Unlike the data reported for the claimed products **7** (identified by us to be in fact condensation adducts **8** between 4-hydroxycoumarin **6** and aldehydes), which exhibit a chemical shift for the benzyl protons (denoted as 4-H in Table 2) well above 6 ppm, the chemical shifts for the benzyl protons in our series of products (denoted 6-H for **11** and **12** and 12-H for **5**, respectively, in Table 2) lay between 5.1 and 5.8 ppm. We consider this to be a diagnostic feature of the spectrum for these families of compounds and this is supported by the different chemical shifts for the benzylic proton peaks shown by the oxo-bridged compounds **13** (denoted as 11-H for products **13** in Table 2), which shift downfield by approximately 1 ppm. Further, each proton belonging to the two NH groups in compounds **5** exhibit different well-defined signals in the 7–10 ppm range. This is in disagreement with the reported spectra of **7** showing the



13a: R^2=R^3=R^4=R^5=H (71%)
13b: R^2=OEt, R^3=R^4=R^5=H (75%)
13f: R^2=R^3=H, R^4=Me, R^5=H (73%)
13h: R^2=H, R^3=OMe, R^4=R^5=H (72%)
13i: R^2=H, R^3=OH, R^4=R^5=H (40%)
13j: R^2=R^3=H, R^4=Br, R^5=H (78%)
13k: R^2=R^3=H, R^4=Cl, R^5=H (64%)
13l: R^2=R^3=H, R^4=NO_2, R^5=H (76%)

Scheme 4. Preparation of oxo-bridged pyrimidines **13** from adducts **11**.



5a: R^2=R^3=R^4=R^5=H (87%)
5b: R^2=OEt, R^3=R^4=R^5=H (90%)
5f: R^2=R^3=H, R^4=Me, R^5=H (87%)
5g: R^2=R^3=H, R^4=R^5=benzo (93%)
5h: R^2=H, R^3=OMe, R^4=R^5=H (92%)

Scheme 5. Lactonization of hydroxy acids **12** to fused tricyclic compounds **5**.

corresponding NH protons being magnetically equivalent and displaying a chemical shift higher than 11 ppm. These signals should be assigned to the enols belonging to the simple 4-hydroxycoumarin-aldehyde condensation adducts **8** shown in Table 2. Moreover, both mass spectra and elemental analysis of compounds **8** confirm the structure we proposed.[18]

3. Conclusions

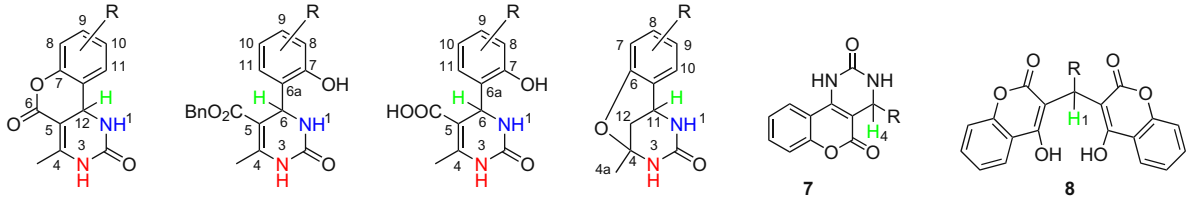
To summarize, we prepared a series of functionalized dihydropyrimido[4,3-*d*]coumarines **5** bearing different substituents on the aromatic ring. The approach is based on a Biginelli multicomponent reaction with benzyl acetoacetate as dicarbonyl precursor. The adducts **11** resulted from this process are easily transformed into the desired fused pyrimido[4,3-*d*]coumarins **5** via an ester hydrogenolysis–lactonization sequence. The hydrogenolysis step requires particular attention with respect to the isolation of products **12**, since formation of the oxo-bridged pyrimidines **13** can easily occur. Although we employed only benzyl acetoacetate as model β-ketoester for this study, other benzyl β-ketoester derivatives may be used as building blocks, in order to generate functional diversity on the pyrimidine core.

4. Experimental

4.1. General

All commercial reagents were purchased from Acros and Aldrich and used without additional purification. Melting points were

Table 2
Selected ^{1}H NMR data (DMSO-d_6) for compounds **5**, **11**, **12**, **13**, **5** reported **7** and compounds **8**



7a: R=Ph
7b: R=4-Cl-C_6H_4
8a: R=Ph
8b: R=4-MeO-C_6H_4

Product	NMR[a] δ (ppm)	Product	NMR[a] δ (ppm)	Product	NMR[a] δ (ppm)	Product	NMR[a] δ (ppm)	Product	NMR[a] δ (ppm)
11a	5.53 (6-H) 7.11 (NH^1) 9.62 (NH^3)	**12a**	5.42 (6-H) 6.94 (NH^1) 9.01 (NH^3)	**5a**	5.50 (12-H) 8.12 (NH^1) 9.60 (NH^3)	**13a**	4.23 (11-H) 7.16 (NH^1) 7.42 (NH^3)	**7a**[17a]	6.1 (4-H) 11.5 (NH)
11b	5.58 (6-H) 7.21 (NH^1) 8.56 (NH^3)	**12b**	5.47 (6-H) 6.94 (NH^1) 9.02 (NH^3)	**5b**	5.46 (12-H) 8.08 (NH^1) 9.58 (NH^3)	**13b**	4.20 (11-H) 7.14 (NH^1) 7.39 (NH^3)	**7b**[17c]	6.1 (4-H) 11.51 (NH)
11f	5.48 (6-H) 7.05 (NH^1) 9.14 (NH^3)	**12f**	5.39 (6-H) 6.73 (NH^1) 8.98 (NH^3)	**5f**	5.45 (12-H) 8.03 (NH^1) 9.58 (NH^3)	**13f**	4.18 (11-H) 6.94 (NH^1) 7.11 (NH^3)	**8a**	6.32 (1-H) 11.8 (OH)
11g	5.13 (6-H) 7.69 (NH^1) 7.65 (NH^3)	**12g**	5.08 (6-H) 7.62 (NH^1) 7.53 (NH^3)	**5g**	5.70 (12-H) 7.83 (NH^1) 10.05 (NH^3)	**13h**	4.17 (11-H) 7.09 (NH^1) 7.42 (NH^3)	**8b**	6.31 (1-H) 11.9 (OH)

[a] Numbering refers to NMR spectra assignment.

determined in open capillary tubes using an electric melting point STUART SMP3 apparatus and are uncorrected. The IR spectra were recorded on a JASCO Fourier Transform Infrared Spectrometer 460 Plus in KBr pellets in the range of 4000–400 cm^{-1}. A JEOL–Delta 400 or Bruker DPX-400 spectrometer (operating at 400 MHz for ^1H and 100 MHz for ^{13}C, respectively) was used for NMR recordings (^1H, ^{13}C, 2D) using DMSO-d_6 or $CDCl_3$ as solvents. Chemical shifts (δ) are reported in parts per million values using residual solvent peak as internal reference. Multiplicities are abbreviated as follows: br—broad; s—singlet; d—doublet; t—triplet; q—quadruplet; and m—multiplet (stands for overlapped peaks and complex signals). Mass spectra were obtained on Finnigan MAT 90 spectrometer using CI technique (150 eV, isobutane) or by ESI technique using a Finnigan LCQ instrument. Elemental analysis was performed on a CHN Elementar Vario EL apparatus. Thin layer chromatography (TLC) was performed on Merck Silica 60 F_{254} plates, visualized by a UV lamp at 254 nm.

4.2. Synthesis of the esters 11a–l

A solution of 1 mmol of aldehyde, 1 mmol of benzyl acetoacetate **10a** or *tert*-butyl acetoacetate **10b**, 1.2 mmol urea and catalyst [PTSA, $Sc(OTf)_3$ or $La(OTf)_3$] in EtOH or MeCN (see Table 1) was heated to reflux overnight, under stirring. The precipitate that formed upon cooling or after addition of water was filtered, washed with ice-water, and 95% EtOH, dried and recrystallized from EtOH or EtOH/AcOEt to yield the pure products **11a–l**.

4.2.1. 6-Methyl-4-(2-hydroxyphenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid benzyl ester ***11a***

Light yellow crystals, mp 228–230 °C (EtOH), R_f=0.24 (silica, DCM/MeOH=95:5); ^1H NMR (400 MHz, DMSO-d_6) δ ppm: 9.62 (s, 1H, 3-N*H*), 9.17 (s, 1H, O*H*), 7.24–7.22 (m, 2H, CH_{arom}), 7.11 (s, 1H, 1-N*H*), 7.10–7.05 (m, 4H, CH_{arom}), 6.96 (d, 1H, *J*=7.2 Hz, 11-*H*), 6.81 (d, 1H, *J*=8.0 Hz, 8-*H*), 6.71 (t, 1H, *J*=7.2 Hz, 10-*H*), 5.53 (d, 1H, *J*=2.8 Hz, 6-*H*), 5.02 [d, 1H, *J*=13.2 Hz, C*H*H(Bn)], 4.96 [d, 1H, *J*=13.2 Hz, CH*H*(Bn)], 2.29 (s, 3H, 4-CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 165.0, 154.6, 152.1, 149.5, 136.6, 129.7, 128.2, 128.0, 127.3, 127.0, 126.9, 118.7, 115.4, 97.1, 64.3, 48.9, 17.7; IR (KBr), cm^{-1}: 3415, 3238, 3128, 2980, 1916, 1698, 1644, 1459, 1218, 1096; MS (CI, 150 eV) *m*/*z*: 339.3 ([M+H]$^+$, 100).

4.2.2. 6-Methyl-4-(3-ethoxy-2-hydroxyphenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid benzyl ester ***11b***

White-yellowish powder, mp 223–224 °C (EtOH/AcOEt), R_f=0.44 (silica, DCM/MeOH=95:5); ^1H NMR (400 MHz, DMSO-d_6) δ ppm: 9.16 (s, 1H, O*H*), 8.56 (s, 1H, 3-N*H*), 7.24–7.22 (m, 2H, CH_{arom}), 7.21 (s, 1H, 1-N*H*), 7.09–7.05 (m, 3H, CH_{arom}), 6.85 (dd, 1H, *J*=8.0, 1.2 Hz, 11-*H*), 6.67 (t, 1H, *J*=8.0 Hz, 10-*H*), 6.61 (dd, 1H, *J*=8.0, 1.2 Hz, 9-*H*), 5.58 (d, 1H, *J*=2.8 Hz, 6-*H*), 5.03 [d, 1H, *J*=13.2 Hz, C*H*H(Bn)], 4.96 [d, 1H, *J*=13.2 Hz, CH*H*(Bn)], 4.03 (q, 2H, *J*=7.2 Hz, CH_2CH_3), 2.29 (s, 3H, 4-CH_3), 1.34 (t, 3H, *J*=7.2 Hz, CH_2CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 165.0, 151.9, 149.3, 146.6, 143.7, 136.6, 130.3, 128.0, 129.2, 126.8, 118.8, 118.5, 111.6, 99.3, 64.2, 64.0, 49.7, 17.6, 14.6; IR (KBr), cm^{-1}: 3413, 3220, 3101, 2976, 2360, 1694, 1646, 1474, 1276, 1095; MS (CI, 150 eV) *m*/*z*: 382.8 ([M]$^+$, 100).

4.2.3. 6-Methyl-4-(5-bromo-2-hydroxyphenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid benzyl ester ***11c***

White powder, mp 245–246 °C (EtOH/AcOEt), R_f=0.22 (silica, DCM/MeOH=95:5); ^1H NMR (400 MHz, DMSO-d_6) δ ppm: 9.23 (s, 1H, O*H*), 7.27–7.22 (m, 5H, 1-N*H*, 3-N*H*, CH_{arom}), 7.11–7.09 (m, 3H, CH_{arom}), 7.01 (d, 1H, *J*=2.8 Hz, 11-*H*), 6.77 (d, 1H, *J*=8.0 Hz, 9-*H*), 5.45 (d, 1H, *J*=2.4 Hz, 6-*H*), 5.04 [d, 1H, *J*=13.2 Hz, C*H*H(Bn)], 4.96 [d, 1H, *J*=13.2 Hz, CH*H*(Bn)], 2.29 (s, 3H, 4-CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 164.9, 154.2, 151.9, 151.9, 149.9, 136.6, 132.3, 130.9, 129.7, 128.2, 127.5, 127.0, 117.7, 108.8, 96.5, 64.5, 49.3, 17.8; IR (KBr), cm^{-1}: 3404, 3215, 3089, 2951, 1890, 1687, 1646, 1493, 1235, 1084; MS (CI, 150 eV) *m*/*z*: 418.7 ([M+H]$^+$, 100).

4.2.4. 6-Methyl-4-(5-chloro-2-hydroxyphenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid benzyl ester ***11d***

White crystals, mp 249–250 °C (EtOH/AcOEt), R_f=0.25 (silica, DCM/MeOH=95:5); ^1H NMR (400 MHz, DMSO-d_6) δ ppm: 9.96 (s, 1H, O*H*), 9.23 (s, 1H, 3-N*H*), 7.27–7.24 (m, 4H, 1-N*H*, CH_{arom}), 7.13–7.09 (m, 3H, CH_{arom}), 6.89 (d, 1H, *J*=2.4 Hz, 11-*H*), 6.81 (d, 1H, *J*=8.0 Hz, 9-H), 5.47 (d, 1H, *J*=2.4 Hz, 6-*H*), 5.04 [d, 1H, *J*=13.2 Hz, C*H*H(Bn)], 4.96 [d, 1H, *J*=13.2 Hz, CH*H*(Bn)], 2.29 (s, 3H, 4-CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 164.8, 153.6, 151.7, 149.8, 136.5, 131.7, 128.1, 127.9, 127.4, 127, 126.9, 122.0, 117.0, 96.4, 64.4, 49.1, 17.7; IR (KBr), cm^{-1}: 3406, 3227, 3101, 2938, 1697, 1647, 1496, 1220, 1085; MS (CI, 150 eV) *m*/*z*: 372.7 ([M]$^+$, 46), 352.8 (100).

4.2.5. 6-Methyl-4-(5-nitro-2-hydroxyphenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid benzyl ester ***11e***

Light yellow crystals, mp 249–251 °C (EtOH), R_f=0.3 (silica, DCM/MeOH=95:5); ^1H NMR (400 MHz, DMSO-d_6) δ ppm: 11.38 (s, 1H, O*H*), 9.32 (s, 1H, 3-N*H*), 8.03 (dd, 1H, *J*=8.8, 2.8 Hz, 9-*H*), 7.80 (d, 1H, *J*=2.8 Hz, 11-*H*), 7.45 (d, 1H, *J*=2.0 Hz, 1-N*H*), 7.23–7.20 (m, 3H, CH_{arom}), 7.08–7.05 (m, 2H, CH_{arom}), 6.96 (d, 1H, *J*=8.8 Hz, 8-*H*), 5.51 (d, 1H, *J*=2.8 Hz, 6-*H*), 5.05 [d, 1H, *J*=13.2 Hz, C*H*H(Bn)], 4.93 [d, 1H, *J*=13.2 Hz, CH*H*(Bn)], 2.31 (s, 3H, 4-CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 164.6, 161.4, 151.4, 150.5, 138.9, 136.2, 130.6, 130.4, 127.8, 127.3, 126.9, 115.6, 99.9, 64.4, 49.4, 17.5; IR (KBr), cm^{-1}: 3415, 3104, 2951, 1698, 1455, 1345, 1242, 1091; MS (CI, 150 eV) *m*/*z*: 383.8 ([M]$^+$, 100).

4.2.6. 6-Methyl-4-(5-methyl-2-hydroxyphenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid benzyl ester ***11f***

White crystals, mp 238–240 °C (EtOH/AcOEt), R_f=0.26 (silica, DCM/MeOH=95:5); ^1H NMR (400 MHz, DMSO-d_6) δ ppm: 9.36 (s, 1H, O*H*), 9.14 (s, 1H, 3-N*H*), 7.25–7.23 (m, 3H, CH_{arom}), 7.10–7.08 (m, 2H, CH_{arom}), 7.05 (br, 1H, 1-N*H*), 6.87 (dd, 1H, *J*=8.0, 1.6 Hz, 8-*H*), 6.72 (d, 1H, *J*=1.6 Hz, 11-*H*), 6.70 (d, 1H, *J*=8.0 Hz, 9-*H*), 5.48 (d, 1H, *J*=2.4 Hz, 6-*H*), 5.03 [d, 1H, *J*=13.2 Hz, C*H*H(Bn)], 4.96 [d, 1H, *J*=13.2 Hz, CH*H*(Bn)], 2.29 (s, 3H, 4-CH_3), 2.11 (s, 3H, 10-CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 165.0, 152.3, 151.9, 149.4, 136.6, 129.3, 128.5, 128.0, 127.4, 127.3, 126.9, 126.9, 115.2, 96.9, 64.2, 49.1, 20.2, 17.7; IR (KBr), cm^{-1}: 3398, 3349, 3213, 3093, 2953, 1697, 1652, 1337; MS (CI, 150 eV) *m*/*z*: 352.9 ([M]$^+$, 100).

4.2.7. 6-Methyl-4-(2-hydroxynaphtyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid benzyl ester ***11g***

White powder, mp 257–259 °C (EtOH), R_f=0.77 (silica, DCM/MeOH=95:5); ^1H NMR (400 MHz, DMSO-d_6) δ ppm: 8.04 (d, 1H, *J*=8.0 Hz, CH_{arom}), 7.86 (d, 1H, *J*=8.0 Hz, CH_{arom}), 7.80 (d, 1H, *J*=8.0 Hz, CH_{arom}), 7.69 (s, 1H, 3-N*H*), 7.65 (br, 1H, 1-N*H*), 7.57–7.53 (m, 1H, CH_{arom}), 7.46–7.35 (m, 6H, CH_{arom}), 7.05 (d, 1H, *J*=8.0 Hz, CH_{arom}), 5.25 [s, 2H, CH_2(Bn)], 5.13 (d, 1H, *J*=1.6 Hz, 6-H), 1.80 (s, 3H, 4-CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 168.5, 154.4, 148.2, 135.8, 130.6, 129.7, 128.5, 128.4, 128.3, 128.0, 127.0, 126.8, 123.6, 121.7, 118.4, 116.7, 99.3, 83.1, 66.1, 43.7, 23.8; IR (KBr), cm^{-1}: 3236, 3101, 2922, 1739, 1689, 1182, 1094; MS (CI, 150 eV) *m*/*z*: 388.8 ([M]$^+$, 100).

4.2.8. 6-Methyl-4-(2-benzyloxy-4-methoxyphenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid benzyl ester ***11h***

White powder, mp 154–155 °C (EtOH), R_f=0.57 (silica, DCM/MeOH=95:5); ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.35–7.33 (m, 5H, CH_{arom}), 7.23–7.21 (m, 2H, CH_{arom}), 7.04–7.02 (m, 2H, CH_{arom}), 6.98 (d, 1H, *J*=8.4 Hz, 11-*H*), 6.72 (d, 1H, *J*=2.0 Hz, 8-*H*), 6.38 (dd, 1H, *J*=8.4, 2.0 Hz, 10-*H*), 5.75 (d, 1H, *J*=2.0 Hz, 6-*H*), 5.10–4.95 (m, 4H,

CH_2Bn), 3.77 (s, 3H, OCH_3), 2.38 (s, 3H, 4-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 165.4, 160.5, 156.9, 136.4, 136.3, 128.6, 128.2, 128.1, 127.7, 127.6, 127.4, 127.4, 104.4, 100.1, 98.1, 70.2, 65.4, 55.3, 49.8, 18.4; IR (KBr), cm^{-1}: 3248, 3131, 2934, 1697, 1643, 1456, 1381, 1219, 1085; MS (ESI, *m*/*z*) 459.1 [M+H]$^+$, 917.0 [2M+H]$^+$, 939.0 [2M+Na]$^+$. Anal. Calcd for $C_{27}H_{26}N_2O_5$ (458.18): C, 70.73; H, 5.72; N, 6.11. Found: C, 70.42; H, 6.04; N, 5.84.

4.2.9. 6-Methyl-4-(2,4-benzyloxyphenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid benzyl ester **11i**

White powder, mp 143–146 °C (EtOH), R_f=0.93 (silica, DCM/MeOH=95:5); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.36–7.29 (m, 10H, CH_{arom}), 7.21–7.18 (m, 3H, CH_{arom}), 7.03–7.00 (m, 2H, CH_{arom}), 6.85 (d, 1H, *J*=9.6 Hz, 11-*H*), 6.82 (dd, 1H, *J*=9.6, 3.2 Hz, 10-*H*), 6.72 (d, 1H, *J*=3.2 Hz, 8-*H*), 5.79 (d, 1H, *J*=2.8 Hz, 6-*H*), 5.66 (br, 1H, 1-N*H*), 5.08–4.95 (m, 4H, 5,7-OCH_2Bn), 4.19 (s, 2H, 9-OCH_2Bn), 2.38 (s, 3H, 4-CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 165.2, 153.1, 150.2, 149.2, 137.0, 136.7, 136.1, 131.6, 128.6, 128.5, 128.2, 128.0, 127.9, 127.6, 127.4, 127.4, 127.3, 114.6, 114.0, 113.1, 97.6, 70.8, 70.5, 65.4, 50.0, 18.5; IR (KBr), cm^{-1}: 3220, 3089, 2947, 1700, 1641, 1494, 1382, 1225, 1091; MS (CI, 150 eV) *m*/*z*: 534.7 ([M]$^+$, 2.5), 317.6 (26), 192.6 (100). Anal. Calcd for $C_{33}H_{30}N_2O_5$ (534.60): C, 74.14; H, 5.66; N, 5.24. Found: C, 73.80; H, 5.74; N, 5.11.

4.2.10. 6-Methyl-4-(5-bromo-2-hydroxyphenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid tert-butyl ester **11j**

White powder, mp 221–223 °C (EtOH), R_f=0.38 (silica, DCM/MeOH=95:5); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 7.63 (s, 1H, O*H*), 7.36 (d, 1H, *J*=2.4 Hz, 11-*H*), 7.33 (dd, 1H, *J*=8.4, 2.8 Hz, 9-*H*), 7.22 (d, 1H, *J*=2.8 Hz, 1-N*H*), 6.75 (d, 1H, *J*=8.4 Hz, 8-*H*), 4.48–4.46 (m, 1H, 6-*H*), 4.35 (br, 1H, 3-N*H*), 1.72 (s, 3H, 4-CH_3), 1.44 (s, 9H, ^{t}Bu); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 167.2, 154.2, 150.0, 131.6, 130.9, 127.8, 118.8, 111.3, 83.6, 81.0, 47.3, 44.1, 27.5, 23.7; IR (KBr), cm^{-1}: 3499, 3232, 3088, 2973, 1743, 1699, 1506, 1475, 1243, 1162, 1085; MS (CI, 150 eV) *m*/*z*: 384.5 ([M]$^+$, 10), 157.7 (100).

4.2.11. 6-Methyl-4-(5-chloro-2-hydroxyphenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid tert-butyl ester **11k**

White powder, mp 209–211 °C (EtOH), R_f=0.84 (silica, DCM/MeOH=95:5); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.13 (dd, 1H, *J*=9.6, 2.8 Hz, 9-*H*), 7.10 (d, 1H, *J*=2.8 Hz, 11-*H*), 6.74 (d, 1H, *J*=9.6 Hz, 8-*H*), 6.33 (d, 1H, *J*=3.2 Hz, 1-N*H*), 6.11 (s, 1H, 3-N*H*), 4.52–4.50 (m, 1H, 6-*H*), 1.85 (s, 3H, 4-CH_3), 1.46 (s, 9H, ^{t}Bu); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 167.0, 151.3, 149.6, 129.8, 127.7, 125.8, 125.4, 118.7, 99.7, 83.1, 48.6, 45.1, 27.9, 24.7; IR (KBr), cm^{-1}: 3400, 3239, 3089, 2975, 1740, 1693, 1510, 1480, 1326, 1244, 1162, 1082; MS (CI, 150 eV) *m*/*z*: 338.6 ([M]$^+$, 100).

4.2.12. 6-Methyl-4-(5-nitro-2-hydroxyphenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid tert-butyl ester **11l**

White powder, mp 221–223 °C (EtOH), R_f=0.4 (silica, DCM/MeOH=95:5); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 11.34 (s, 1H, O*H*), 9.12 (s, 1H, 3-N*H*), 8.05 (d, 1H, *J*=8.0 Hz, 8-*H*), 7.87 (s, 1H, 1-N*H*), 7.34 (d, 1H, *J*=2.4 Hz, 11-*H*), 6.97 (dd, 1H, *J*=8.0, 2.4 Hz, 9-*H*), 5.42 (s, 1H, 6-*H*), 2.25 (s, 3H, 4-CH_3), 1.24 (s, 9H, ^{t}Bu); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 167.1, 161.1, 151.2, 147.9, 136.5, 130.7, 124.4, 123.4, 115.4, 97.4, 78.6, 49.6, 27.3, 17.1; IR (KBr), cm^{-1}: 3457, 3382, 3243, 3092, 2927, 1696, 1676, 1521, 1496, 1335, 1240, 1169, 1093; MS (CI, 150 eV) *m*/*z*: 349.7 ([M+H]$^+$, 12), 249.7 (81), 189.7 (100).

4.3. Preparation of hydroxy acids 12a,b and 12f–h by hydrogenolysis

Dihydropyrimidine benzyl ester **11** (1 mmol), 5% Pd/C (10% w/w), 10 mmol ammonium formate (630 mg), and 10 mL methanol were stirred at rt until the completion of the reaction, monitored by TLC (MeOH/DCM). Methanol was then removed in vacuo and the residue was partitioned between 30 mL ethyl acetate and 10 mL water. The two phases were separated, the organic phase dried over $MgSO_4$, and evaporated. The resulted white solid was recrystallized from ethanol to yield the pure hydroxy acid **12**.

4.3.1. 1,2,3,4-Tetrahydro-6-methyl-2-oxo-4-(2-hydroxyphenyl)-pyrimidine-5-carboxylic acid **12a**

White powder, mp 255–258 °C (EtOH), R_f=0.25 (silica, DCM/MeOH=8:2); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 11.73 (br, 1H, COO*H*), 9.60 (s, 1H, O*H*), 9.01 (s, 1H, 3-N*H*), 7.05 (ddd, 1H, *J*=8.0, 7.6, 1.6 Hz, 9-*H*), 6.96–6.94 (br, 1H, 1-N*H*), 6.96–6.93 (m, 1H, 11-*H*), 6.80 (d, 1H, *J*=8.0 Hz, 8-*H*), 6.72 (t, 1H, *J*=7.6 Hz, 10-*H*), 5.42 (d, 1H, *J*=2.8 Hz, 6-*H*), 2.80 (s, 3H, 4-CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 167.1, 154.5, 152.4, 148.3, 129.6, 128.1, 126.7, 118.7, 115.4, 98.0, 48.9, 17.8; IR (KBr), cm^{-1}: 3495, 3241, 2618, 2499, 1694, 1460, 1280, 110, 1041 MS (CI, 150 eV) *m*/*z*: 205.8 ([M−COOH]$^+$, 100).

4.3.2. 1,2,3,4-Tetrahydro-6-methyl-2-oxo-4-(3-ethoxy-2-hydroxyphenyl)-pyrimidine-5-carboxylic acid **12b**

White powder, mp 275–280 °C (EtOH), R_f=0.41 (silica, DCM/MeOH=8:2); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 11.72 (br, 1H, COO*H*), 9.02 (s, 1H, 3-N*H*), 8.62 (br, 1H, O*H*), 6.94 (d, 1H, *J*=2.8 Hz, 1-N*H*), 6.82 (dd, 1H, *J*=8.0, 1.6 Hz, 11-*H*), 6.68 (t, 1H, *J*=8.0 Hz, 10-*H*), 6.60 (dd, 1H, *J*=8.0, 1.6 Hz, 9-*H*), 5.47 (d, 1H, *J*=2.8 Hz, 6-*H*), 4.02 (q, 2H, *J*=8.0 Hz, CH_2CH$_3$), 2.27 (s, 3H, 4-CH_3), 1.34 (t, 3H, *J*=8.0 Hz, CH$_2$CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 167.2, 152.3, 148.0, 146.6, 143.5, 130.5, 119.0, 112.1, 98.4, 64.0, 49.1, 17.3, 14.3; IR (KBr), cm^{-1}: 3224, 3090, 2980, 2360, 1698, 1585, 1391, 1344, 1289, 1217, 1089; MS (CI, 150 eV) *m*/*z*: 248.9 ([M−COOH]$^+$, 100).

4.3.3. 1,2,3,4-Tetrahydro-6-methyl-2-oxo-4-(5-methyl-2-hydroxyphenyl)-pyrimidine-5-carboxylic acid **12f**

White powder, mp 273–275 °C (EtOH), R_f=0.3 (silica, DCM/MeOH=9:1); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 11.73 (br, 1H, COO*H*), 9.36 (s, 1H, O*H*), 8.98 (s, 1H, 3-N*H*), 6.88–6.84 (m, 2H, 9-*H*, 11-*H*), 6.73 (s, 1H, 1-N*H*), 6.68 (d, 1H, *J*=8.0 Hz, 8-*H*), 5.39 (s, 1H, 6-*H*), 2.28 (s, 3H, 4-CH_3), 2.14 (s, 3H, 10-CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 167.2, 152.3, 152.1, 148.1, 129.5, 128.4, 126.9, 115.3, 99.3, 48.9, 20.3, 17.7; IR (KBr), cm^{-1}: 3398, 3225, 3106, 2925, 1688, 1630, 1467, 1224, 1153, 1046; MS (ESI, *m*/*z*): 263.0 [M+H]$^+$, 809.0 [3M+Na]$^+$, 825.0 [3M+K]$^+$, 525.1 [2M+H]$^+$, 547.1 [2M+K]$^+$.

4.3.4. 1,2,3,4-Tetrahydro-6-methyl-2-oxo-4-(2-hydroxynaphtyl)-pyrimidine-5-carboxylic acid **12g**

White powder, mp 295–296 °C (EtOH), R_f=0.16 (silica, DCM/MeOH=8:2); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.93 (br, 1H, COOH), 8.05 (d, 1H, *J*=8.0 Hz, CH_{arom}), 7.86 (d, 1H, *J*=8.0 Hz, CH_{arom}), 7.79 (d, 1H, *J*=7.2 Hz, CH_{arom}), 7.62 (d, 1H, *J*=2.8 Hz, 1-N*H*), 7.55 (t, 1H, *J*=7.2 Hz, CH_{arom}), 7.53 (s, 1H, 3-N*H*), 7.39 (t, 1H, *J*=7.2 Hz, CH_{arom}), 7.05 (d, 1H, *J*=8.0 Hz, CH_{arom}), 5.09–5.07 (m, 1H, 6-*H*), 3.20 (br, 1H, O*H*), 1.82 (s, 3H, 4-CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 169.9, 154.3, 148.2, 130.6, 129.5, 128.4, 128.2, 126.7, 123.4, 121.6, 118.3, 116.9, 83.2, 44.1, 23.7; IR (KBr), cm^{-1}: 3400, 3257, 3056, 2552, 1680, 1515, 1241, 1092; MS (CI, 150 eV) *m*/*z*: 254.9 ([M−COOH]$^+$, 40), 145 (100), 111 (65).

4.3.5. 1,2,3,4-Tetrahydro-6-methyl-2-oxo-4-(4-methoxy-2-hydroxyphenyl)-pyrimidine-5-carboxylic acid **12h**

White powder, mp 201–203 °C (EtOH), R_f=0.41 (silica, DCM/MeOH=8:2); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 11.70 (br, 1H, COO*H*), 9.63 (s, 1H, O*H*), 8.97 (s, 1H, 3-N*H*), 6.87 (br, 1H, 1-N*H*), 6.64 (d, 1H, *J*=8.8 Hz, 11-*H*), 6.37 (d, 1H, *J*=2.4 Hz, 8-*H*), 6.31 (dd, 1H, *J*=8.8, 2.4 Hz, 10-*H*), 5.34 (d, 1H, *J*=2.8 Hz, 6-*H*), 3.66 (s, 3H, OCH_3), 2.27 (s, 3H, 4-CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm:

167.2, 159.3, 155.5, 152.5, 129.4, 127.5, 122.5, 118.2, 101.4, 48.6, 44.0, 26.4, 17.7; IR (KBr), cm^{-1}: 3495, 3238, 3105, 2933, 1699, 1645, 1445, 1231, 1127, 1034; MS (CI, 150 eV) *m*/*z*: 234.6 ([M−COOH]$^+$, 100).

4.4. Synthesis of the oxo-bridged pyrimidines 13a, 13b, 13f, 13h, 13i, and 13j–l

Dihydropyrimidine benzyl ester **11** (1 mmol), 5% Pd/C (10% w/w), 10 mmol ammonium formate (630 mg), and 10 mL methanol were stirred at room temperature until the completion of the reaction, as monitored by TLC ($MeOH/CH_2Cl_2$=2:8). Methanol was then removed in vacuo and the reaction mixture was treated with 10 mL 0.5 M sodium hydroxide and allowed to stir for 30 min. Filtration under gravity was then performed and the filtrate was acidified with 2 N HCl until pH 3–4. In short time, a precipitate formed, which was filtered and dried. No further purification was necessary.

4.4.1. 9-Methyl-11-oxo-8-oxa-10,12-diazatricyclo[7,3,1,0^{2,7}]-trideca-2,4-6-triene ***13a***

White powder, mp 297–298 °C, R_f=0.74 (silica, DCM/MeOH=4:1); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 7.42 (s, 1H, 3-N*H*), 7.17–7.16 (br, 1H, 1-N*H*), 7.16–7.12 (m, 2H, CH_{arom}), 6.86 (ddd, 1H, *J*=8.0, 7.2, 1.2 Hz, 8-*H*), 6.75 (d, 1H, *J*=8.0 Hz, 7-*H*), 4.23 (dd, 1H, *J*=7.2, 3.2 Hz, 11-*H*), 2.13 (dd, 1H, *J*=12.8, 3.2 Hz, 12-C*H*H), 2.07 (dd, 1H, *J*=12.8, 7.2 Hz, 12-CH*H*), 1.61 (s, 3H, 4-CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 154.7, 151.1, 128.5, 128.4, 125.3, 119.7, 116.4, 81.9, 44.2, 31.9, 26.0; IR (KBr), cm^{-1}: 3242, 3097, 1676, 1503, 1322, 1252, 1134, 1069; MS (CI, 150 eV) *m*/*z*: 205.3 ([M+H]$^+$, 100).

4.4.2. 4-Ethoxy-11-oxo-8-oxa-10,12-diazatricyclo[7,3,1,0^{2,7}]-trideca-2,4-6-triene ***13b***

White powder, mp 259–262 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 7.39 (br, 1H, 3-N*H*), 7.14 (br, 1H, 1-N*H*), 6.82 (dd, 1H, *J*=7.6, 1.2 Hz, CH_{arom}), 6.78 (td, 1H, *J*=7.6, 1.2 Hz, CH_{arom}), 6.72 (dd, 1H, *J*=7.6, 1.2 Hz, CH_{arom}), 4.21–4.19 (m, 1H, 11-*H*), 3.97 (q, 2H, *J*=6.8 Hz, CH_2CH$_3$), 2.11 (dd, 1H, *J*=12.8, 2.0 Hz, 12-CH*H*), 2.07–2.03 (m, 1H, 12-C*H*H), 1.63 (s, 3H, 4-CH_3), 1.31 (t, 3H, *J*=6.8 Hz, CH$_2$CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 155.0, 147.1, 140.9, 126.3, 120.5, 119.7, 112.5, 82.0, 63.5, 44.4, 32.2, 26.5, 14.7; MS (CI, 150 eV) *m*/*z*: 248.3 ([M+H]$^+$, 100).

4.4.3. 4,9-Dimethyl-11-oxo-8-oxa-10,12-diazatricyclo-[7,3,1,0^{2,7}]trideca-2,4-6-triene ***13f***

White powder, mp 295–297 °C, R_f=0.66 (silica, DCM/MeOH=9:1); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 7.37 (s, 1H, 10-*H*), 7.11 (s, 1H, 3-N*H*), 6.95 (d, 1H, *J*=7.6 Hz, 8-*H*), 6.94 (br, 1H, 1-N*H*), 6.64 (d, 1H, *J*=7.6 Hz, 7-*H*), 4.18 (d, 1H, *J*=3.2 Hz, 11-*H*), 2.20 (s, 3H, 9-CH_3), 2.11 (dd, 1H, *J*=12.8, 3.2 Hz, 12-C*H*H), 2.06–2.02 (m, 1H, 12-CH*H*), 1.59 (s, 3H, 4-CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 154.8, 148.8, 128.9, 128.8, 128.3, 125.0, 115.9, 81.7, 44.2, 32.1, 26.1, 19.7; IR (KBr), cm^{-1}: 3223, 3216, 3071, 2931, 1700, 1657, 1513, 1313, 1254, 1176, 1072; MS (ESI, *m*/*z*): 219.1 [M+H]$^+$, 437 [2M+H]$^+$.

4.4.4. 5-Methoxy-9-methyl-11-oxo-8-oxa-10,12-diazatricyclo-[7,3,1,0^{2,7}]trideca-2,4-6-triene ***13h***

White powder, mp 253–255 °C, R_f=0.13 (silica, DCM/MeOH=98:2); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 7.42 (br, 1H, 3-N*H*), 7.09 (br, 1H, 1-N*H*), 7.03 (d, 1H, *J*=8.4 Hz, 10-*H*), 6.44 (d, 1H, *J*=8.4 Hz, 9-*H*), 6.32 (s, 1H, 7-*H*), 4.17 (s, 1H, 11-*H*), 3.68 (s, 3H, OCH_3), 2.09 (d, 1H, *J*=12.8 Hz, 12-C*H*H), 2.03 (d, 1H, *J*=12.8 Hz, 12-CH*H*), 1.59 (s, 3H, 4-CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 159.7, 155.1, 152.4, 129.3, 118.2, 106. 6, 82.2, 55.0, 43.9, 32.5, 26.3; IR (KBr), cm^{-1}: 3236, 3107, 2940, 1688, 1621, 1507, 1287, 1069; MS (ESI, *m*/*z*): 235.1 [M+H]$^+$, 257.1 [M+Na]$^+$, 469.1 [2M+H]$^+$, 491.1 [2M+Na]$^+$.

4.4.5. 5-Hydroxy-9-methyl-11-oxo-8-oxa-10,12-diazatricyclo-[7,3,1,0^{2,7}]trideca-2,4-6-triene ***13i***

Brown powder, mp 286–290 °C, R_f=0.73 (silica, DCM/MeOH=8:2); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.89 (br, 1H, 8-O*H*), 7.29 (br, 1H, 3-N*H*), 7.11 (br, 1H, 1-N*H*), 6.55 (s, 3H, 7-*H*, 9-*H*, 10-*H*), 4.10 (dd, 1H, *J*=7.2, 2.8 Hz, 11-*H*), 2.06 (dd, 1H, *J*=12.8, 2.8 Hz, 12-CH*H*), 2.03–1.99 (m, 1H, 12-CH*H*), 1.56 (s, 3H, 4-CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 155.1, 150.4, 143.6, 125.8, 116.8, 115.6, 114.6, 81.5, 44.5, 32.4, 26.4; IR (KBr), cm^{-1}: 3228, 3123, 1659, 1510, 1383, 1193, 1079; MS (CI, 150 eV) *m*/*z*: 220.0 ([M]$^+$, 100).

4.5. Synthesis of the oxo-bridged pyrimidines 13j–l

Dihydropyrimidine *tert*-butyl esters **11j–l** (1 mmol) and 10 mL of a mixture of 25% trifluoracetic acid in dichloromethane were stirred at rt until the completion of the reaction (10 min), as monitored by TLC ($MeOH/CH_2Cl_2$=2:8). The solvent was then removed in vacuo and the reaction mixture was triturated with ethyl ether. The precipitate formed was filtered and dried. No further purification was necessary.

4.5.1. 4-Bromo-9-methyl-11-oxo-8-oxa-10,12-diazatricyclo-[7,3,1,0^{2,7}]trideca-2,4-6-triene ***13j***

White powder, mp 293–296 °C, R_f=0.57 (silica, DCM/MeOH=9:1); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 7.53 (s, 1H, 3-N*H*), 7.32 (s, 1H, 10-*H*), 7.30 (d, 1H, *J*=8.4 Hz, 7-*H*), 7.14 (s, 1H, 1-N*H*), 6.74 (d, 1H, *J*=8.4 Hz, 8-*H*), 4.28 (s, 1H, 11-*H*), 2.15 (d, 1H, *J*=12.8 Hz, 12-CH*H*), 2.07 (d, 1H, *J*=12.8 Hz, 12-C*H*H), 1.61 (s, 3H, 4-CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 155.6, 151.4, 132.5, 128.7, 120.3, 118.6, 111.6, 83.3, 43.9, 32.6, 26.8; IR (KBr), cm^{-1}: 3232, 3106, 2928, 1696, 1510, 1305, 1166, 1076; MS (ESI, *m*/*z*): 283.1 [M]$^+$.

4.5.2. 4-Chloro-9-methyl-11-oxo-8-oxa-10,12-diazatricyclo-[7,3,1,0^{2,7}]trideca-2,4-6-triene ***13k***

White powder, mp 287–292 °C, R_f=0.57 (silica, DCM/MeOH=9:1); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 7.52 (s, 1H, 3-N*H*), 7.19–7.16 (m, 2H, CH_{arom}), 7.14 (s, 1H, 1-N*H*), 6.79 (d, 1H, *J*=8.0 Hz, 7-*H*), 4.28–4.27 (m, 1H, 11-*H*), 2.15–2.12 (m, 1H, 12-CH*H*), 2.09–2.05 (m, 1H, 12-C*H*H), 1.60 (s, 3H, 4-CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 154.8, 150.3, 128.4, 128.2, 127.5, 123.3, 118.2, 111.6, 82.6, 44.0, 31.7, 26.0; IR (KBr), cm^{-1}: 3225, 3076, 2932, 2602, 1701, 1465, 1226, 1110; MS (CI, 150 eV) *m*/*z*: 205 ([M−Cl]$^+$, 100), 238.9 ([M]$^+$, 48).

4.5.3. 9-Methyl-4-nitro-11-oxo-8-oxa-10,12-diazatricyclo-[7,3,1,0^{2,7}]trideca-2,4-6-triene ***13l***

White powder, mp 261–263 °C, R_f=0.36 (silica, DCM/MeOH=9:1); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.15 (d, 1H, *J*=2.8 Hz, 10-*H*), 8.07 (dd, 1H, *J*=8.8, 2.8 Hz, 8-*H*), 7.75 (s, 1H, 3-NH), 7.27 (s, 1H, 1-N*H*), 6.90 (d, 1H, *J*=8.8 Hz, 7-*H*), 4.48–4.46 (m, 1H, 11-*H*), 2.13 (dd, 1H, *J*=13.2, 2.8 Hz, 12-C*H*H), 2.08–2.05 (m, 1H, 12-CH*H*), 1.67 (s, 3H, 4-CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 154.53, 150.73, 126.25, 123.70, 123.47, 123.28, 117.21, 82.43, 43.80, 31.67, 25.93; IR (KBr), cm^{-1}: 3226, 3081, 2933, 1700, 1587, 1509, 1342, 1172, 1086; MS (ESI, *m*/*z*): 250.0 [M+H]$^+$.

4.6. Preparation of 5 by lactonization of the hydroxy acids 12

The corresponding dihydropyrimidine carboxylic acid **12** (1 mmol) and 2 mmol of TBTU (650 mg) were suspended in 150 mL of DCM. DIPEA (4 equiv, 1 mL) was added and the solution became clear. After 20 min of stirring at rt, a white precipitate formed. The reaction was allowed to stir for 2 h (completed as monitored by TLC), and then the solvent removed was in vacuo. The white precipitate was recrystallized from ethanol to yield the pure adducts **5**.

4.6.1. 4-Methyl-1H-chromeno[4,3-d]pyrimidine-2,5(3H,10bH)-dione **5a**

White powder, mp 245–249 °C (EtOH), R_f=0.4 (silica, AcOEt); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 9.60 (s, 1H, 3-N*H*), 8.12 (br, 1H, 1-N*H*), 7.59 (d, 1H, *J*=8.0 Hz, 11-*H*), 7.32 (t, 1H, *J*=8.0 Hz, 9-*H*), 7.15 (t, 1H, *J*=8.0 Hz, 10-*H*), 7.05 (d, 1H, *J*=8.0 Hz, 8-*H*), 5.50 (d, 1H, *J*=3.2 Hz, 12-*H*), 2.21 (s, 3H, 4-CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 160.8, 151.6, 150.7, 148.2, 128.0, 124.5, 123.8, 123.4, 115.4, 89.3, 47.5, 17.0; IR (KBr), cm^{-1}: 3356, 3233, 3165, 2967, 1699, 1621, 1460, 1396, 1257, 1084; MS (CI, 150 eV) *m*/*z*: 231.2 [(M+H)$^+$, 100). Anal. Calcd for $C_{12}H_{10}N_2O_3$ (230.07): C, 62.60; H, 4.38; N, 12.17. Found: C, 60.64; H, 4.42; N, 12.18.

4.6.2. Ethoxy-4-methyl-1H-chromeno[4,3-d]pyrimidine-2,5(3H,10bH)-dione **5b**

White powder, mp 260–264 °C (EtOH), R_f=0.41 (silica, DCM/MeOH=8:2); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 9.58 (s, 1H, 3-N*H*), 8.08 (s, 1H, 1-N*H*), 7.13 (dd, 1H, *J*=7.6, 2.0 Hz, 10-*H*), 7.10 (d, 1H, *J*=7.6 Hz, 11-H), 7.00 (dd, 1H, *J*=7.6, 2.0 Hz, 9-*H*), 5.46 (s, 1H, 12-*H*), 4.06 (q, 2H, *J*=6.8 Hz, CH_2CH$_3$), 2.20 (s, 3H, 4-CH_3), 1.35 (t, 3H, *J*=6.8 Hz, CH$_2$CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 161.3, 151.7, 151.1, 146.0, 137.9, 126.5, 123.9, 115.3, 112.7, 89.8, 63.9, 48.3, 17.4, 14.5; IR (KBr), cm^{-1}: 3212, 3145, 2979, 1708, 1605, 1487, 1278, 1076; MS (CI, 150 eV) *m*/*z*: 274.8 ([M]$^+$, 100). Anal. Calcd for $C_{14}H_{14}N_2O_4$ (274.10): C, 61.31; H, 5.14; N, 10.21. Found: C, 61.49; H, 5.03; N, 9.89.

4.6.3. 4,9-Dimethyl-1H-chromeno[4,3-d]pyrimidine-2,5-(3H,10bH)-dione **5f**

White powder, mp 288–291 °C (EtOH), R_f=0.65 (silica, AcOEt); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 9.58 (s, 1H, 3-N*H*), 8.03 (s, 1H, 1-N*H*), 7.42 (s, 1H, 11-*H*), 7.11 (d, 1H, *J*=8.0 Hz, 9-*H*), 6.93 (d, 1H, *J*=8.0 Hz, 8-*H*), 5.45 (s, 1H, 12-*H*), 2.29 (s, 3H, 4-CH_3), 2.21 (s, 3H, 10-CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 161.5, 151.9, 151.2, 146.6, 132.9, 124.6, 90.1, 48.1, 20.3, 17.7; IR (KBr), cm^{-1}: 3352, 3241, 3171, 2922, 1719, 1697, 1465, 1260, 1147; MS (ESI, *m*/*z*): 245 [M+H]$^+$. Anal. Calcd for $C_{13}H_{12}N_2O_3$ (244.08): C, 63.93; H, 4.95; N, 11.47. Found: C, 63.86; H, 5.01; N, 11.62.

4.6.4. 4-Methyl-1H-benzo[5]chromeno[4,3-d]pyrimidine-2,5(3H,10bH)-dione **5g**

White powder, mp 249–251 °C (EtOH), R_f=0.5 (silica, AcOEt); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.05 (s, 1H, 3-N*H*), 8.00–7.95 (m, 3H, CH_{arom}), 7.83 (s, 1H, 1-N*H*), 7.66–7.63 (m, 1H, CH_{arom}), 7.52 (td, 1H, *J*=8.0, 1.2 Hz, CH_{arom}), 7.25 (d, 1H, *J*=8.8 Hz, CH_{arom}), 5.70 (s, 1H, 12-*H*), 2.47 (s, 3H, 4-CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 158.6, 153.0, 148.0, 130.9, 130.6, 130.1, 128.3, 127.2, 124.9, 124.0, 117.1, 110.0, 91.8, 46.0, 18.4; IR (KBr), cm^{-1}: 3287, 3117, 3063, 2952, 1705, 1601, 1464, 1281, 1128; MS (CI, 150 eV) *m*/*z*: 206.7 (3), 129.8 (100). Anal. Calcd for $C_{16}H_{12}N_2O_3$ (280.08): C, 68.56; H, 4.32; N, 9.99. Found: C, 68.65; H, 4.20; N, 10.06.

4.6.5. 8-Methoxy-4-Methyl-1H-chromeno[4,3-d]pyrimidine-2,5(3H,10bH)-dione **5h**

White powder, mp 262–264 °C (EtOH), R_f=0.73 (silica, AcOEt); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 9.60 (s, 1H, 3-N*H*), 8.04 (s, 1H, 1-N*H*), 7.51 (d, 1H, *J*=8.0 Hz, 11-*H*), 6.77 (dd, 1H, *J*=8.0, 2.4 Hz, 10-*H*), 6.64 (d, 1H, *J*=2.4 Hz, 8-*H*), 5.42 (s, 1H, 12-*H*), 3.75 (s, 3H, OCH$_3$), 2.23 (s, 3H, 4-CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 159.4, 152.6, 151.5, 149.6, 146.3, 125.4, 116.4, 109.9, 101.5, 90.1, 55.3, 47.5, 17.6; IR (KBr), cm^{-1}: 3358, 3232, 3165, 2965, 1698, 1628, 1444, 1267, 1084; MS (CI, 150 eV) *m*/*z*: 260.5 ([M]$^+$, 100). Anal. Calcd for $C_{13}H_{12}N_2O_4$ (260.08): C, 60.00; H, 4.65; N, 10.76. Found: C, 59.74; H, 4.39; N, 10.48.

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Supplementary data

Experimental details for the preparation of compounds **8**. Selected ^{1}H and ^{13}C NMR spectra of relevant examples of compounds **11**, **12**, **13**, and **5**. Supplementary data associated with this article can be found in the online version at, doi:10.1016/j.tet.2009.05.088.

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