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ROYAL SOCIETY OF CHEMISTRY

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An efficient green protocol for the preparation of acetoacetamides and application of the methodology to a one-pot synthesis of Biginelli dihydropyrimidines. Expansion of dihydropyrimidine topological chemical space.

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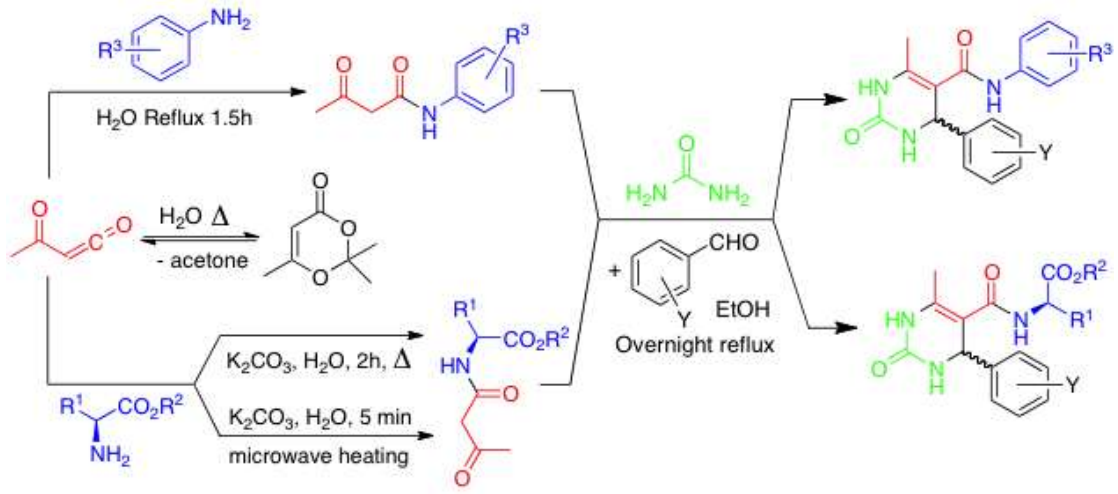
Graphical Abstract

A one pot synthesis of Biginelli dihydropyrimidines. The novel use of the aminoacids allows topological diversification of the chemical space.



Keywords: acetylketene; acetoacetanilides; acetoacetamides; reaction in/on water; Biginelli dihydropyrimidines; chemical space.

Abstract: The present study describes the preparation of *N*-aryl- (**15**) and *N*-alkyl- (**17**) acetoacetamides, in good to excellent yields, using both conventional and microwave heating, by reaction of amine derivatives (**14** and **16**) with 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (TMD, **12**) in aqueous medium. The acetoacetamides were used

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DOI: 10.1039/C5RA14355A

to prepare novel Biginelli dihydropyrimidine derivatives. The introduction of the aminoacid derivatives potentially allows for the exploration of new structural complexity and topologically diversifies the chemical space occupied by this versatile chemical scaffold.

1. Introduction

Derivatives of 1,3-dicarbonyl compounds have a long history in synthetic organic chemistry and are important substrates in multicomponent reactions.[1] One of these multi-component reactions is the Biginelli reaction,[2] the mechanism of which continues to generate debate as it is highly reaction condition dependent.[3] Although this reaction has been known since the late 19th century, the Biginelli reaction continues to attract the interest of many research groups around the world as this class of compounds presents many interesting pharmacological/biological activities including: cardiovascular **4**,[3f, 4] chemical modulators of heat shock protein 70 **5**,[5] anti-tumor **6**,[6] antioxidant **7**,[7] anti-inflammatory,[8] antitubercular **8**,[9] antifungal **9**,[10] antimicrobial **10**,[11] and antiviral **11** properties[12] (Figure 1).

The Biginelli reaction is very versatile and it can be carried out with many variations in all three components providing an extensive number of 3,4-dihydropyrimidin-2(1*H*)-one (or -thione) derivatives, which are also referred to as DHPMs (Figure 1).[2, 3g, 13] Numerous synthetic methodologies have been devised that have principally focused upon reaction efficiency as a function of catalyst and reaction conditions[2i] and more recently it has been recognized that the DHPM scaffold is a highly functionalized substrate that can be readily applied to post-condensation transformations.[2f, 2h]

Additionally, in recent years great advances have been made with respect to the asymmetric synthesis of DHPMs.[14] Recent examples of enantioselective DHPM synthesis include the use of chiral covalently modified nanocomposites,[15] double axially chiral bis-phosphorylimides,[16] chiral amines,[17] chiral phosphoric acids,[18] and a chiral ytterbium complex[19] as asymmetric catalysts. The enantiomers of racemic DHPMs have been resolved by chemical or chiral chromatographic resolution[20] or by enzymatic methods,[21] recent examples include the use of aminoacid derivatives,[22] or chiral sulfoxides[23] as chiral auxiliary and chromatographic separation of the diastereoisomers. (*S*)-Monastrol **6** was obtained by enantioselective enzymatic hydrolysis of the butanoyl phenol esters[24] and racemic acetates were resolved with an immobilized lipase from *Candida Antarctica*.[25]

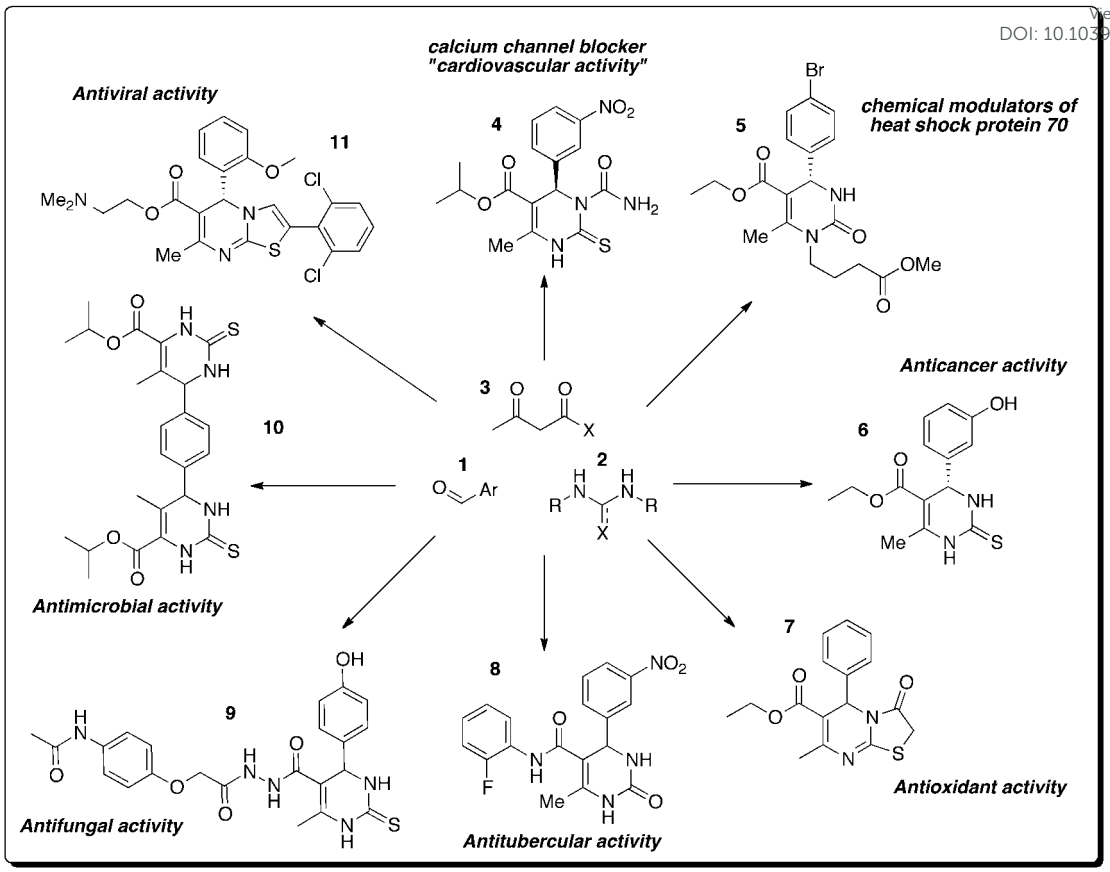

Figure 1: Structurally diverse examples of DHPMs prepared in the last century.

Among the many different examples of DHPMs, the exocyclic amide derivatives are also important (figure 1 for examples) and over the last 10 years, the use of acetoacetamides in Biginelli reactions has increased.[3g, 9a, 26] However, these DHPMs are limited to simple amine derivatives, such as hydrazides and anilides. Subsequent modification of the C5 position (the exocyclic carboxylic acid derivative) is limited.[2f, 2h] This limitation suggests that in order to explore new chemical space[2f, 27] around the DHPM scaffold that it is important to investigate the synthesis and use of novel, or little known, acylacetamide derivatives which may be directly incorporated into the Biginelli reaction. Further, in order to explore new chemical space based upon the DHPM scaffold it is necessary to introduce more complex and topologically diversified building blocks.[28] Additionally, bearing in mind that the DHPMs already occupy a drug-like and biologically active chemical space then the new building blocks, for DHPM synthesis, should also posses similar characteristics and a diverse set of building blocks should be readily available. One interesting possibility, amongst many other options, is the use of acylacetamides derived from aminoacids or peptides.[29]

Thus the present study aimed to develop an environmentally benign methodology for the synthesis of acetoacetamides in water starting from aniline or aminoacid derivatives and a stable precursor of acetylketene. The synthetic methodology was applied to a one-pot, four reagents, synthesis of novel DHPM derivatives. The introduction of the exocyclic aminoacid groups introduces a new spatial and topological complexity to the structures of the DHPMs.

2. Results and Discussion

The 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (TMD – **12**) is a stable equivalent of diketene which can be used to directly generate acetylketene **13** at temperatures above 90^0C, via a pseudo-retro-Diels-Alder reaction, eliminating acetone, or it can be chemically modified so as to permit the synthesis of acylketene derivatives.[30] The synthesis of amides from the reaction of **12** with amines or anilines has typically involved refluxing the substrates in toluene or xylene.[31] A few exceptions include refluxing in THF in the presence of NaOAc for 24 hours,[32] heating in a mixture of biphenyl and diphenyl ether,[33] microwave heating in: THF/DMA,[34] DMF,[35] or in the absence of solvent;[36] or by conventional heating in the presence of the amine,[37] or by the use of dichlorobenzene as solvent.[38]

Initially we had prepared acetoacetanilides **15** by refluxing **12** and **14** in toluene. However, **15** required chromatographic separation from their dehydrated dimers, 4-pyridones.[39] Therefore we sought a more efficient and chemoselective preparation of **5**. Given that the rate of decomposition of **12** becomes appreciable above 90^oC[40] we decided to investigate the use of water as a solvent for the reaction. The use of water could potentially introduce a competing nucleophile (water) for the acetylketene. However, Birney *et al*.[41] have shown that amines are kinetically more reactive than alcohols in trapping acetylketene **13**. Even if water were to compete with the added amine/aniline, the product would be acetoacetic acid. This would decompose under the reaction conditions to give acetone and CO_2 and therefore would not contaminate the desired acetoacetamide products (**15** and **17**). Besides this, any competition between the water and amines for **13** could be offset by the use of an excess of acetylketene precursor. The use of water as a medium for conducting organic reactions has resulted in the discovery of a number of benefits despite the apparent contradiction of the lack of solubility of the hydrophobic organic substrates.[42]

TMD (**12**, 1 equiv.) was added in a single portion to a gently boiling solution/emulsion of **14a** in water that was vigorously stirred in an open flask. With the passage of time it was clear that **12** and **14a** were being consumed and that acetone was evolved from the reaction. After heating the reaction mixture for 1.5 hours, TLC analysis of a sample of the aqueous solution extracted with EtOAc revealed the exclusive formation of **15a**. The aqueous solution was hot filtered through a cotton plug to remove a small quantity of an immiscible, dark, oil. On cooling of the solution large colourless plates of **15a** readily formed. The product **15a** was isolated in 84% yield (table 1). Subsequently, an improved procedure that generally resulted in still higher product yields was developed. This involved the use of an excess of TMD (1.5 equiv.s) and refluxing the reaction for 2.5 hours. Subsequently, the reaction was allowed to cool and a sub-stoichiometric quantity of 2M aqueous HCl (0.8 equiv.s) was added which had the benefit of solubilizing any unreacted aniline/dark oil as well as promoting the crystallization of the product **15a**. The products were isolated by filtration and no further purification was necessary when using this procedure. Additionally, the reaction of **12** and **14a** in water under microwave irradiation at a controlled temperature of 150^0C during 3 minutes gave an equally good yield of **15a**. Nonetheless, the conventional heating methodology in water was successfully applied to a variety of substituted anilines where the substituents span the range of electronic effects (a notable exception was *p*-nitroaniline that formed product but readily hydrolyzed under the reaction conditions) and sterically encumbered 2,6-dimethylaniline **14m** which gave an excellent yield of **15m**. The products were isolated by filtration and found to be of sufficient purity for spectroscopic analysis, thus requiring no further purification (table 1). Additionally secondary alky- and benzyl- anilines (**14o-q**) could also be employed as substrates to give good yields of the tertiary *N*-alkyl- or benzyl- acetoacetanilides (**15o-q**). These products were oils and were separated from the reaction medium by extraction and filtered through a short column of silica to give the final purified product for spectroscopic characterization. The reaction of **14q** was also conducted in refluxing xylenes from which an equivalent yield to the reaction in water was obtained (table 1).

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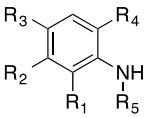
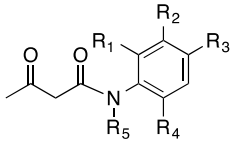
Table 1: Reactions of **12** with **14** conducted in water to give **15**.

 **14** [a]	**Product; yield (%)** [b,c]  **15**	**Lit. yield (%) [ref]**
a All R = H	(**15a**) 84,[b] 94,[c] 90 [d]	70 [e] [31p] ; 67 [e] [31f]
b R_3 = Cl	(**15b**) 77 [b]	52 [e] [31p]
c R_3 = OMe	(**15c**) 77,[b] 97 [c]	73 [e] [31f]
d R_3 = Me	(**15d**) 78 [b]	31 [h] [31e]
e R_3 = COOH	(**15e**) 91 [b]	---
f R_3 = Br	(**15f**) 74 [b]	100 [f] [43]
g R_3 = F	(**15g**) 48,[b] 94 [c]	62 [g] [44]
h R_1 = OMe; R_3 = NO_2	(**15h**) 75,[b] 80 [c]	---
i R_2 = Cl; R_3 = OMe	(**15i**) 65,[b] 95 [c]	63 [h] [45]
j R_2 = OMe	(**15j**) 76 [b]	93 [e] [31p]
k R_1 = OMe	(**15k**) 64 [b]	94 [e] [31g]
l R_2 = CF_3	(**15l**) 46,[b] 60 [c]	90 [i] [46]
m R_1;R_4 = Me	(**15m**) 49,[b] 97 [c]	---
n R_2;R_4 = OMe	(**15n**) 85 [c]	97 [e] [31g, 47]
o R_5 = Me	(**15o**) 74 [c]	85 [e] [48]
p R_5 = Et	(**15p**) 80 [c]	90 [j] [49]
q R_5 = Bn	(**15q**) 60,[c] 64 [e]	35 [j] [49]

[a] all groups R=H unless otherwise indicated; [b] Yield of crystallized product when using one equivalent of TMD in relation to the aniline (reaction time 1.5 hours); [c] Yield of crystallized product when using 1.5 equivalents of TMD in relation to the aniline (reaction time 2.5 hours); [d] Yield of crystallized product after microwave heating for 3 min at 150^{0}C in water; [e] aniline and TMD in refluxing xylenes for 30 mins to 2h; [f] using diketene in refluxing benzene for 10h; [g] anilines and ethyl acetoacetate in refluxing toluene for 10h; [h] anilines and diketene in refluxing toluene for 10h; [i] using diketene at room temperature in HOAc solution with a quantity of $HgSO_4$ as catalyst overnight; [j] diketene added to preheated aniline (90^{o}C) in the absence of solvent for 1h.

In order to validate the efficiency of the aqueous methodology developed in this study, the reaction of **12** with aniline was performed on a 0.10 mol scale. Differently from the previous experiments **12** (0.15 mol) was added from a dropping funnel over a period of 5 minutes to a gently boiling, rapidly stirred,

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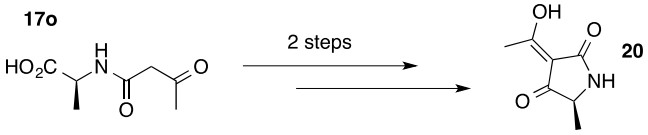
solution/emulsion of aniline in a reduced volume of water (150 mL). The reaction mixture was refluxed for 2.5 hours. The addition of TMD was purposefully regulated so as to avoid the possibility of a very vigorous initial reaction due to the thermal elimination of acetone as a consequence of the scale of the reaction and because of the decreased volume of water in relation to the increased quantity of **14a**. After the heating period, the lightly coloured hot aqueous solution was quickly filtered through a cotton wool plug in a preheated sintered glass funnel with the aid of an applied vacuum. This resulted in the elimination of a small quantity of a dark immiscible oil. The residue was washed with a small quantity of hot water and to the cooling filtrate was added 3N HCl (0.9 equivalents/**14a**). This resulted in the precipitation of the product **15a**. On complete cooling the colourless crystals were isolated by filtration and washed with water. After air drying a 93% yield of **15a** (m.p. 81-3^{o}C) was obtained.

The successful application of the aqueous reaction methodology for the preparation of **15** was extended to the use of aminoacid derivatives **16**. Aminoacid acetoacetamide derivatives **17** have been prepared by the reaction between diketene or cyclobutane-1,3-dione under basic conditions in aqueous medium, and subsequently used as building blocks in organic synthesis.[31c, 50] One example of this strategy is the synthesis of tetramic acids **20** (Scheme 1).[50a, 50e, 50f]

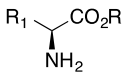
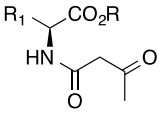
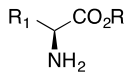
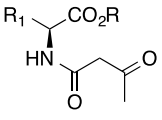
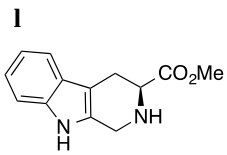
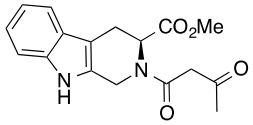
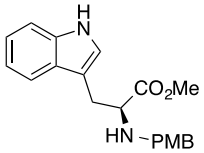
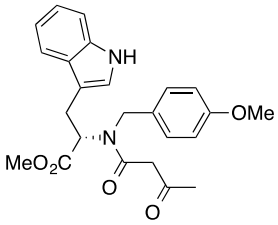
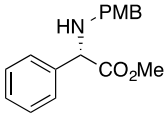
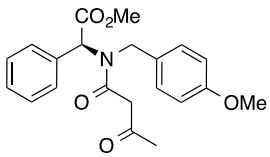


Scheme 1: Synthesis of a tetramic acid from an acetoacetylaminoacid derivative.

Thus, initially a mixture of two equivalents of **12** and L-tryptophan (**16a**) were refluxed in water in the presence of a sub-stoichiometric quantity of K_2CO_3 (80 mol%) in order to neutralize the carboxylic acid group. After refluxing for 2 hours the mixture was acidified (pH ~ 1) and extracted with EtOAc. The crude material was purified by silica gel column chromatography eluting with CH_2Cl_2/EtOAc 50%, and resulted in the desired product in quantitative yield of **17a**. The same reaction performed under microwave irradiation at a controlled temperature of 150^{0}C during 5 minutes resulted in a 90% yield of **17a** after the same isolation methodology. Following these results, we tested the reactivity of other aminoacids and a few aminoesters using the same synthetic method (no K_2CO_3 used in the latter case). In

most cases the respective acetoacetamides were obtained in moderate to excellent yields (**17a-n**) (Table 2). In general, conventional heating gave better yields of products although the microwave heating method was not optimized. However, the latter method provides good to excellent yields after only 5 minutes of heating.

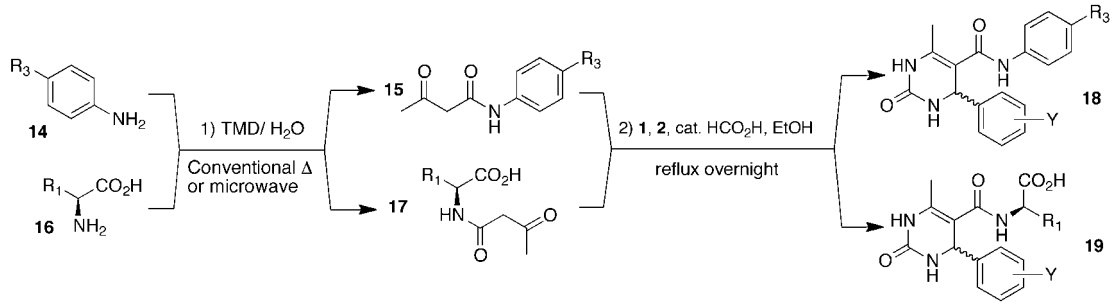
Table 2: Acetoacetamide derivatives from L-amino acids and esters.

Reagent (16) 	**Product; yield (%)** [a,b]  **(17)** **[Lit. Yield %]**	**Reagent (16)** 	**Product; yield (%)** [a,b]  **(17)**
a L-tryptophan	(**17a**) 100,[a] 90[b]	**l** 	 (**17l**) 77,[a] 40[b]
b L-leucine	(**17b**) 100,[a] 93[b]		
c L-valine	(**17c**) 85,[a] 84[b] [50 [50a]]		
d L-methionine	(**17d**) 75,[a] 86[b]		
e L-phenylalanine	(**17e**) 92,[a] 92[b]	**m** 	 (**17m**) 76[a]
f L-phenylglycine	(**17f**) 90,[a] 75[b]		
g L-tyrosine	(**17g**) 72,[a] 45[b]		
h L-cysteine	(**17h**) 42,[a] 50[b]		
i Methyl L-tryptophan	(**17i**) 100,[a] 70[b] [70 [51]]	**n** 	 (**17n**) 84[a]
j Methyl L-phenylalanine	(**17j**) 84,[a] 65[b] [80 [50b]]		
k Methyl L-phenylglycine	(**17k**) 60,[a] 53[b] [60 [31c]]		

[a] Yield for conventional heating in water, 2h reaction time; [b] Yield for Microwave heating, 5 min. reaction time.

With the successful preparation of **15** and **17** by the aqueous medium protocol, it was envisaged that a one-pot process involving four different reagents for the synthesis of Biginelli DHPMs, **12**, **14** or **16**, urea (**2**) and benzaldehyde derivatives (**1**), could be developed. The one-pot methodology would in principle be more efficient as it would eliminate manipulation and purification steps. Thus the one-pot reaction was conducted in the following manner: firstly **15** or **17** were prepared as previously described, the water was removed under reduced pressure, and secondly,

to the residue were added **1**, **2**, and ethanol, along with a catalytic quantity of formic acid. The reactions were refluxed overnight and after cooling the crude Biginelli products **18** or **19** had precipitated. Precipitation was completed by the addition of water and the products were isolated by filtration. Compounds **18** and **19** were purified by recrystallization from EtOH. The Biginelli products **18** and **19** were obtained with good to excellent yields (Tables 3 and 4). As expected all the dihydropyrimidines **18** obtained from the acetoacetanilides **15** were racemic products, whereas the reactions that employed **17** resulted in the formation of a pair of diastereoisomers of **19**. The diastereoselectivity obtained when using **17** was very minor or non-existent (Scheme 2; Table 4).



Scheme 2: *One-pot* synthesis of dihydropyrimidine derivatives **18** and **19**.

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DOI: 10.1039/C5RA14355A

Table 3: Dihydropyrimidine derivatives **18** from a one-pot, four reagents, process using anilines.

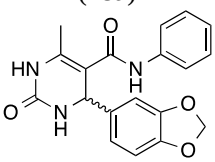
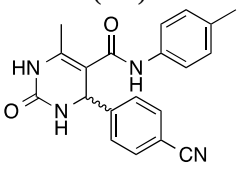
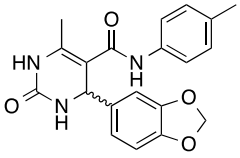
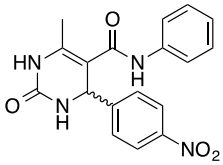
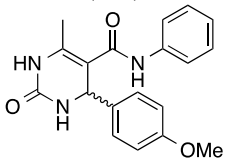
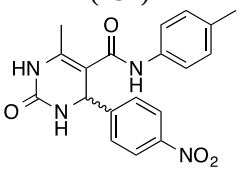
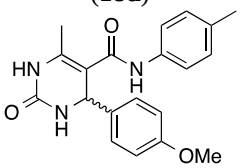
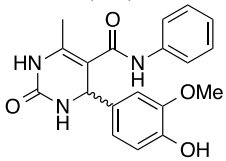
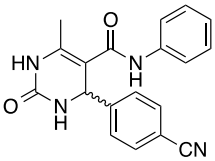
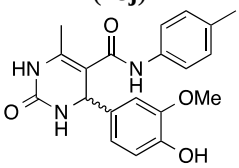
Reagents	Product; yield (%) [a,b] [Lit. Yield (%)]	Reagents	Product; yield (%) [a,b] [Lit. Yield (%)]
12; **14a**; **2**; **1a** [Y= $CH_2(O_2)$]	(**18a**)  86	**12**; **14d**; **2**; **1c** (Y = *p*-CN)	(**18f**)  65
12; **14d**; **2**; **1a** [Y= $CH_2(O_2)$]	(**18b**)  74	**12**; **14a**; **2**; **1d** (Y = *p*-NO_2)	(**18g**)  82 (64 [9a])
12; **14a**; **2**; **1b** (Y = *p*-OMe)	(**18c**)  81 (93 [26b])	**12**; **14d**; **2**; **1d** (Y = *p*-NO_2)	(**18h**)  80
12; **14d**; **2**; **1b** (Y = *p*-OMe)	(**18d**)  67	**12**; **14a**; **2**; **1e** (Y = 3-OMe 4-OH)	(**18i**)  86
12; **14a**; **2**; **1c** (Y = *p*-CN)	(**18e**)  64	**12**; **14d**; **2**; **1e** (Y = 3-OMe 4-OH)	(**18j**)  64

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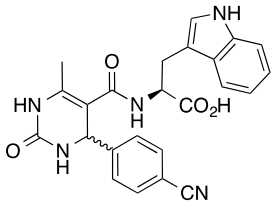
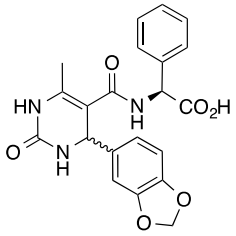
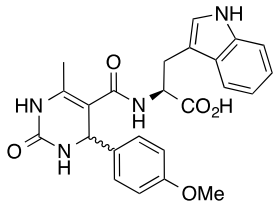
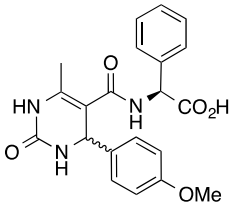
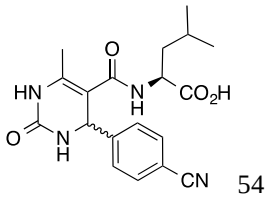
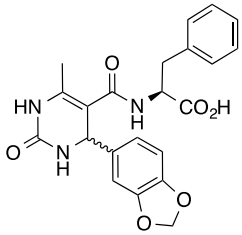
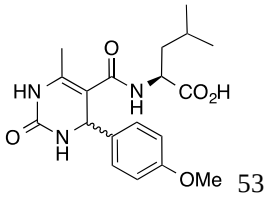
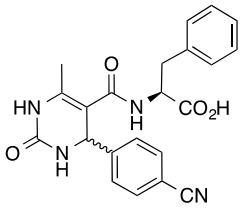
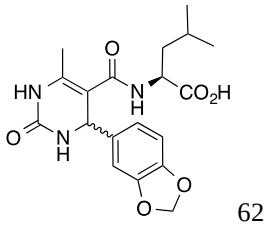
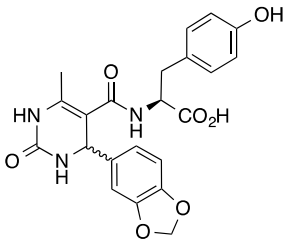
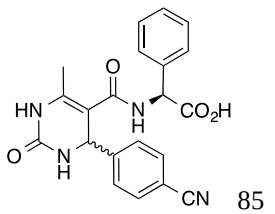
Table 4: Dihydropyrimidine derivatives **19** from a one-pot, four reagents, process using aminoacid derivatives.

Reagents	Product; yield (%) [a,b]	Reagents	Product; yield (%) [a,b]
	(**19a**)		(**19g**)
12; **16a**; **2**; **1c** (Y = *p*-CN) **dr 1.2:1**	 25	**12**; **16f**; **2**; **1a** [Y= $CH_2(O_2)$] **dr 1.5:1**	 74
	(**19b**)		(**19h**)
12; **16a**; **2**; **1b** (Y = *p*-OMe) **dr 1:1**	 50	**12**; **16f**; **2**; **1b** (Y = *p*-OMe) **dr 1.2:1**	 83
	(**19c**)		(**19i**)
12; **16b**; **2**; **1c** (Y = *p*-CN) **dr 1:1**	 54	**12**; **16e**; **2**; **1a** [Y= $CH_2(O_2)$] **dr 1.5:1**	 74
	(**19d**)		(**19j**)
12; **16b**; **2**; **1b** (Y = *p*-OMe) **dr 1:1**	 53	**12**; **16f**; **2**; **1c** (Y = *p*-CN) **dr 2.3:1**	 50
	(**19e**)		(**19k**)
12; **16b**; **2**; **1a** [Y= $CH_2(O_2)$] **dr 1:1**	 62	**12**; **16g**; **2**; **1a** [Y= $CH_2(O_2)$] **dr 1:1**	 70
	(**19f**)		
12; **16f**; **2**; **1c** (Y = *p*-CN) **dr 1.3:1**	 85		

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3. Conclusion

Acetoacetamide derivatives **15** and **17** were successfully prepared with good to excellent yields by the reaction of **12**, a precursor for acetylketene **13** generation, with anilines **14** and aminoacid derivatives **16** by refluxing the reagents in water. The preparation of **17** in aqueous medium was also investigated by comparing conventional heating with microwave heating. The benefit of the latter method being the reduced reaction time, 5 minutes compared with 2 hours. The reaction conditions reported in the present study allow for the "large" scale preparation of acetoacetamides without the need for the use of organic solvents. A one-pot, four reagents, process for the synthesis of Biginelli DHPMs was developed that employed an aqueous methodology for the preparation of **15** and **17** whereby these intermediates were subsequently used without purification in the three component reaction employing **1** and **2** to give good to excellent yields of **18** and **19** after recrystallization. The one-pot methodology for the synthesis of **18** or **19** from **12**, **14** or **16**, **1** and **2** increases the efficiency of the preparation of **18** or **19** by eliminating manipulation and purification of the intermediates **15** and **17**. The introduction of the exocyclic aminoacid groups introduces a new spatial complexity to the structures of the DHPMs and therefore the novel Biginelli products are being screened for pharmacological activity.

4. Experimental

All chemicals and solvents (analytical grade) were received from commercial sources and used without further purification. Analytical thin layer chromatography (TLC) was performed on pre-coated silica gel 60 F_{254} aluminum plates (Merck) with visualization under UV light – 254 and 366 nm. Melting points were determined with a Mel. Temp. II apparatus and are uncorrected. IR spectra were measured on a Nicolet 505 Magma FT-IR spectrometer. High resolution mass spectra (HRMS) were recorded on a Q-TOF instrument (micromass, Manchester, UK). ^{1}H and ^{13}C NMR spectra were recorded at 200 MHz on a Bruker DPX instrument using $CDCl_3$ and or DMSO-d_6 as solvents. The chemical shifts were referenced to the residual non-deuterated solvent signals or relative to TMS as internal standard. Coupling constants *J* are given in Hertz and their multiplicities have the standard designations.

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4.1a Preparation of *N*-aryl acetoacetamides (15) - Aqueous method.

In a round bottom flask, aniline (5 mmol) and distilled water (15 mL) were agitated and heated to reflux. Upon reflux, TMD (8 mmol) was added and the reflux was maintained for 1.5 hours. Upon completion of the reaction as determined by TLC, the reaction mixture was allowed to cool and aqueous 2M HCl (2 mL) was added resulting in the precipitation of a solid. The solid was isolated by filtration and recrystallized from water.

When the product was an oil, it was extracted from the diluted reaction medium with EtOAc and the crude material was purified by silica gel column chromatography eluting with CH_2Cl_2 followed by a CH_2Cl_2/EtOAc gradient up to 50% EtOAc.

4.1b Preparation of *N*-alkyl acetoacetamides (17) – Conventional heating

In a round bottom flask, L-amino acids (5 mmol) were suspended in distilled water (10 mL). Into this suspension K_2CO_3 (80mol% - 4mmol) was added and the mixture heated to reflux. Upon reflux, TMD (10 mmol) was added and reflux was maintained for 2 hours. Upon completion of the reaction as determined by TLC, the reaction mixture was allowed to cool and the mixture was acidified with aqueous 6M HCl (pH ~ 1) and extracted with AcOEt. The organic fractions were united, dried over anhydrous Na_2SO_4, filtered and evaporated under reduce pressure. The crude product was filtered through a short silica gel column eluting with AcOEt.

4.1c Preparation of *N*-alkyl acetoacetamides (17) – MW heating

To a microwave reactor vial were added: L-amino acid (1 mmol), distilled water (4 mL), K_2CO_3 (80mol% - 0.8mmol) and TMD (2 mmol). The microwave heating parameters were: Temp.: As fast as possible, until 150^0C; time duration: 5 min; Pressure: 9.0 Bar (Monowave 300). Upon completion of the reaction as determined by TLC, the reaction mixture was allowed to cool and the mixture was acidified with aqueous 6M HCl (pH ~ 1) and extracted with AcOEt. The organic fractions were united, dried over anhydrous Na_2SO_4, filtered and evaporated under reduce pressure. The crude product was purified by filtration through a short silica gel column using AcOEt as eluent.

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4.2 Physical and Spectroscopic data for the reported compounds.

4.2.1 *N*-(Phenyl)-3-oxobutanamide (15a) Colorless crystals, mp. 82-3^{0}C **IR (cm^{-1}):** 3298, 3255, 3197, 3137, 2953, 2924, 1725, 1713, 1662, 1600, 1553, 1542, 1498, 1446, 1409, 1362, 1341, 1315, 1167, 905, 755, 692, 526, 505.**^{1}H NMR (200 MHz, CDCl$_3$):** δ 2.28 (s, 3H), 3.55 (s, 2H), 7.05-7.12 (t, *J* = 8.0 Hz, 1H), 7.25-7.33 (t, *J* = 8.0 Hz, 2H), 7.49-7.53 (d, *J* = 8.0 Hz, 2H), 9.11 (s, 1H). **^{13}C NMR (50 MHz, CDCl$_3$):** δ 31.2, 49.8, 120.2, 124.5, 128.9, 137.5, 163.5, 205.1.

4.2.2 *N*-(4-Chlorophenyl)-3-oxobutanamide (15b) Colorless crystals, mp. 130-1^{0}C **IR (cm^{-1}):** 3289, 3252, 3189, 3125, 3070, 1712, 1659, 1607, 1554, 1492, 1417, 1399, 1361, 1343, 1314, 1161, 1092, 1015, 834, 816, 764, 671, 508, 436. **^{1}H NMR (200 MHz, DMSO-d$_6$):** δ 2.19 (s, 3H), 3.54 (s, 2H), 7.32-7.36 (d, *J* = 8.0 Hz, 2H), 7.56-7.60 (d, *J* = 8.0 Hz, 2H), 10.20 (s, 1H). **^{13}C NMR (50 MHz, DMSO-d$_6$):** δ 30.2, 52.3, 120.7, 127.0, 128.7, 137.8, 165.2, 202.7.

4.2.3 *N*-(4-Methoxyphenyl)-3-oxobutanamide (15c) Colorless crystals, mp. 114-5^{0}C **IR (cm^{-1}):** 3282, 3252, 3196, 3137, 3077, 3003, 2960, 2836, 1716, 1655, 1608, 1561, 1513, 1421, 1360, 1250, 1161, 1036, 840, 789, 615, 522, 455. **^{1}H NMR (200 MHz, CDCl$_3$):** δ 2.29 (s, 3H), 3.54 (s, 2H), 3.76 (s, 3H), 6.80-6.85 (d, *J* = 10.0 Hz, 2H), 7.39-7.44 (d, *J* = 10.0 Hz, 2H), 8.99 (s, 1H). **^{13}C NMR (50 MHz, CDCl$_3$):** δ 31.1, 49.8, 55.4, 114.1, 121.9, 130.6, 156.6, 163.4, 205.1.

4.2.4 *N*-(4-Methylphenyl)-3-oxobutanamide (15d) Colorless crystals, mp. 87-9^{0}C **IR (cm^{-1}):** 3294, 3255, 3192, 3129, 2958, 2918, 1714, 1658, 1606, 1556, 1513, 1418, 1359, 1343, 1316, 1162, 834, 818, 786, 510, 500. **^{1}H NMR (200 MHz, CDCl$_3$):** δ 2.29 (s, 6H, 2CH$_3$), 3.54 (s, 2H), 7.08-7.12 (d, *J* = 8.0 Hz, 2H), 7.38-7.42 (d, *J* = 8Hz, 2H), 9.03 (s, 1H). **^{13}C NMR (50 MHz, CDCl$_3$):** δ 20.8, 31.1, 49.9, 120.2, 129.4, 134.2, 134.9, 163.4, 205.1.

4.2.5 4-(3-Oxobutanamido)benzoic acid (15e) Pale yellow crystals, mp. 204-6^{0}C. **IR (cm^{-1}):** 3305, 2996, 2887, 2665, 2549, 1678, 1600, 1514, 1406, 1319, 1277, 1160, 852, 769, 540, 503. **^{1}H NMR (200 MHz, DMSO-d$_6$):** δ 2.20 (s, 3H), 3.60 (s, 2H),

6.73-6.88 (d, *J* = 10.0 Hz, 2H), 7.87-7.92 (d, *J* = 10.0 Hz, 2H), 10.39 (s, 1H). **^{13}C NMR (50 MHz, DMSO-d$_6$):** δ 30.2, 52.4, 118.3, 125.3, 130.4, 142.8, 167.2, 202.6. **HRMS (*m/z* + H$^+$):** Obs.: 222.0766; Calc.: 222.0838 ($C_{11}H_{12}NO_4^+$).

4.2.6 *N*-(4-Bromophenyl)-3-oxobutanamide (15f) Brown crystals, mp. 136-7^{0}C **IR (cm^{-1}):** 3288, 3250, 3185, 3120, 3067, 1716, 1658, 1605, 1552, 1489, 1417, 1395, 1360, 1341, 1313, 1239, 1160, 1075, 1011, 832, 816, 760, 654, 536, 505. **^{1}H NMR (200 MHz, CDCl$_3$):** δ 2.31 (s, 3H), 3.57 (s, 2H), 7.42 (s, 4H), 9.24 (s, 1H). **^{13}C NMR (50 MHz, CDCl$_3$):** δ 31.3, 49.4, 117.1, 121.7, 131.9, 136.5, 163.4, 205.3. **HRMS (*m/z* + H$^+$):** Obs.: 255.9973 / 257.9973; Calc.: 256.0092 / 258.0034 ($C_{10}H_{11}NO_2Br^+$).

4.2.7 *N*-(4-Fluorophenyl)-3-oxobutanamide (15g) Colorless crystals, mp. 98-9^{0}C **IR (cm^{-1}):** 3257, 3212, 3153, 3070, 2925, 1721, 1667, 1621, 1569, 1553, 1509, 1414, 1360, 1339, 1314, 1237, 1215, 1167, 839, 799, 518, 501, 465. **^{1}H NMR (200 MHz, CDCl$_3$):** δ 2.30 (s, 3H), 3.56 (s, 2H), 6.94-7.03 (t, *J* = 8.0 Hz, 2H), 7.44-7.51 (dd, *J* = 8.0 Hz, 2H), 9.16 (s, 1H). **^{13}C NMR (50 MHz, CDCl$_3$):** δ 31.2, 49.5, 115.4, 115.8, 121.9, 122.0, 133.5, 133.5, 157.1, 162.0, 163.5, 205.2.

4.2.8 *N*-(2-Methoxy-4-nitrophenyl)-3-oxobutanamide (15h) Yellow crystals, mp. 113-4^{0}C **IR (cm^{-1}):** 3273, 3106, 3080, 1712, 1690, 1616, 1590, 1538, 1509, 1486, 1413, 1343, 1277, 1259, 1222, 1099, 1023, 883, 800, 746, 553. **^{1}H NMR (200 MHz, DMSO-d$_6$):** δ 2.18 (s, 3H), 3.78 (s, 2H), 3.98 (s, 3H), 7.80 (s, 1H), 7.85-7.90 (d, *J* = 10.0 Hz, 1H), 8.39-8.44 (d, *J* = 10.0 Hz, 2H), 9.92 (s, 1H). **^{13}C NMR (50 MHz, DMSO-d$_6$):** δ 30.2, 51.8, 56.5, 105.9, 116.9, 119.2, 134.0, 142.7, 148.4, 166.3, 203.3. **HRMS (*m/z* + H$^+$):** Obs.: 253.0824; Calc.: 253.0884 ($C_{11}H_{13}N_2O_5^+$).

4.2.9 *N*-(3-Chloro-4-methoxyphenyl)-3-oxobutanamide (15i) Purple crystals, mp. 106-7^{0}C. **IR (cm^{-1}):** 3288, 3253, 3124, 2917, 2844, 1720, 1661, 1595, 1539, 1502, 1443, 1399, 1287, 1258, 1215, 1158, 1061, 1025, 871, 820, 731, 689, 537, 498. **^{1}H NMR (200 MHz, CDCl$_3$):** δ 2.30 (s, 3H), 3.56 (s, 2H), 3.85 (s, 3H), 6.82-6.86 (d, *J* = 8.0 Hz, 1H), 7.33-7.37 (d, *J* = 8.0 Hz, 1H), 7.59 (s, 1H), 9.11 (s, 1H). **^{13}C NMR (50 MHz, CDCl$_3$):** δ 31.2, 49.4, 56.3, 112.2, 119.8, 122.4, 122.7, 131.0, 152.0, 163.5,

205.2. **HRMS (*m/z* + H^+):** Obs.: 242.0584 / 244.0584; Calc.: 242.0657 / 244.0599 ($C_{11}H_{13}NO_3Cl^+$).

4.2.10 ***N*-(3-Methoxyphenyl)-3-oxobutanamide (15j)** The product was extracted with EtOAc and the crude material was purified by silica gel column chromatography eluting with CH_2Cl_2 followed by a CH_2Cl_2/EtOAc gradient up to 10 % EtOAc. Pale brown oil. **IR (cm^{-1}):** 3312, 3147, 2960, 2836, 1720, 1667, 1598, 1546, 1454, 1423, 1290, 1256, 1206, 1158, 1044, 856, 774, 689, 522, 457. **^{1}H NMR (200 MHz, $CDCl_3$):** δ 2.30 (s, 3H), 3.56 (s, 2H), 3.78 (s, 3H), 6.66-6.69 (d, *J* = 6.0 Hz, 1H), 7.00-7.08 (t, *J* = 8.0 Hz, 1H), 7.16-7.20 (d, *J* = 8.0 Hz, 2H), 9.13 (s, 1H). **^{13}C NMR (50 MHz, $CDCl_3$):** δ 31.2, 49.8, 55.3, 105.9, 110.4, 112.3, 129.7, 138.6, 160.1, 163.5, 205.2. **HRMS (*m/z* + H^+):** Obs.: 208.0938; Calc.: 208.0974 ($C_{11}H_{14}NO_3^+$).

4.2.11 ***N*-(2-Methoxyphenyl)-3-oxobutanamide (15k)** Beige solid, mp. 85-7^{0}C **IR (cm^{-1}):** 3280, 2971, 2842, 1710, 1676, 1598, 1542, 1488, 1459, 1438, 1365, 1289, 1251, 1221, 1174, 1119, 1045, 1022, 760, 731, 594, 509, 494. **^{1}H NMR (200 MHz, $CDCl_3$):** δ 2.31 (s, 3H), 3.58 (s, 2H), 3.89 (s, 3H), 6.85-7.04 (m, 3H), 8.28-8.32 (d, *J* = 8.0 Hz, 1H), 9.22 (s, 1H). **^{13}C NMR (50 MHz, $CDCl_3$):** δ 31.0, 50.8, 55.8, 110.1, 120.1, 120.9, 124.1, 127.3, 148.3, 163.2, 204.3. **HRMS (*m/z* + H^+):** Obs.: 230.0765; Calc.: 230.0793 ($C_{11}H_{13}NO_3Na$).

4.2.12 ***N*-(3-Trifluoromethylphenyl)-3-oxobutanamide (15l)** Pale yellow solid, mp. 107-9^{0}C **IR (cm^{-1}):** 3306, 3100, 2960, 2929, 1715, 1664, 1616, 1567, 1496, 1424, 1364, 1334, 1316, 1188, 1161, 1116, 1072, 898, 882, 802, 741, 701, 661, 634, 528, 519, 459. **^{1}H NMR (200 MHz, $CDCl_3$):** δ 2.32 (s, 3H), 3.60 (s, 2H), 7.33-7.46 (dd, *J* = 8.0 Hz, 2H), 7.69-7.73 (d, *J* = 8.0 Hz, 2H), 7.85 (s, 1H), 9.43 (s, 1H). **^{13}C NMR (50 MHz, $CDCl_3$):** δ 31.3, 49.3, 116.8, 121.0, 123.1, 126.5, 129.5, 131.7, 138.0, 163.8, 205.3. **HRMS (*m/z* + H^+):** Obs.: 246.0742; Calc.: 246.0807 ($C_{11}H_{11}F_3NO_2^+$).

4.2.13 ***N*-(2,6-Dimethylphenyl)-3-oxobutanamide (15m)** Colourless crystals, mp. 134-5^{0}C. **IR (cm^{-1}):** 3215, 3180, 3035, 2965, 1713, 1669, 1643, 1451, 1475, 1413, 1330, 1179, 1166, 760, 717, 515. **^{1}H NMR (200 MHz, $CDCl_3$):** δ 2.19 (s, 6H, $2CH_3$), 2.31 (s, 3H), 3.59 (s, 2H), 7.05 (s, 3H), 8.46 (s, 1H). **^{13}C NMR (50 MHz, $CDCl_3$):** δ

18.3, 31.0, 49.4, 127.3, 128.1, 133.6, 135.1, 163.9, 204.8. **HRMS (*m/z* + H^+):** Obs.: 206.1179; Calc.: 206.1181 ($C_{12}H_{16}NO_2^+$).

4.2.14 *N*-(2,5-Dimethoxyphenyl)-3-oxobutanamide (15n) Colourless crystals, mp. 71-3^oC **IR (cm^{-1}):** 3062, 3030, 2922, 1721, 1633, 1636, 1600, 1485, 1454, 1358, 1289, 1207, 1083, 1013, 828, 776, 728, 701, 577. **^1H NMR (200 MHz, $CDCl_3$):** δ 2.31 (s, 3H), 3.58 (s, 2H), 3.76 (s, 3H), 3.85 (s, 3H), 6.54 – 6.60 (dd, *J* = 2.0/4.0 Hz, 1H), 6.77 – 6.81 (d, *J* = 8.0 Hz, 1H), 8.04 – 8.05 (d, *J* = 2.0 Hz, 1H), 9.59 (s, 1H). **^{13}C NMR (200 MHz, $CDCl_3$):** δ 30.9, 50.7, 55.7, 56.3, 106.4, 108.7, 110.9, 128.0, 142.5, 153.7, 163.3, 204.1.

4.2.15 *N*-methyl-3-oxo-*N*-phenylbutanamide (15o) The product was extracted with EtOAc and the crude material was purified by silica gel column chromatography eluting with CH_2Cl_2 followed by a CH_2Cl_2/EtOAc gradient up to 50 % EtOAc. Pale brown oil. **IR (cm^{-1}):** 3062, 3040, 2925, 1721, 1656, 1595, 1497, 1379, 1343, 1301, 1124, 924, 776, 702, 561, 540. The product was observed to be a mixture of keto and enol tautomers. **^1H NMR (200 MHz, $CDCl_3$):** δ 1.79 (s, 1H), 2.08 (s, 3H), 3.29 (s, 6H), 4.68 (s, 0.3H), 7.17 – 7.21 (d, *J* = 8.0 Hz, 2H), 7.35 – 7.42 (m, *J* = 8.0 Hz, 3H), 14.25 (s, 0.3H). **^{13}C NMR (200 MHz, $CDCl_3$):** δ 21.6, 30.2, 36.3, 37.2, 49.8, 88.8, 127.2, 127.3, 127.5, 128.2, 129.6, 129.9, 143.3, 143.5, 166.6, 171.8, 202.2.

4.2.16 *N*-ethyl-3-oxo-*N*-phenylbutanamide (15p) The product was extracted with EtOAc and the crude material was purified by silica gel column chromatography eluting with CH_2Cl_2 followed by a CH_2Cl_2/EtOAc gradient up to 50 % EtOAc. Pale brown oil. **IR (cm^{-1}):** 3063, 3041, 2973, 2934, 1720, 1667, 1662, 1595, 1496, 1416, 1261, 1180, 862, 799, 771, 703. The product was observed to be a mixture of keto and enol tautomers. **^1H NMR (200 MHz, $CDCl_3$):** δ 1.09 – 1.16 (t, *J* = 8.0 Hz, 3H), 1.77 (s, 1H), 2.07 (s, 4H), 3.23 (s, 2H), 3.71 – 3.82 (q, *J* = 8.0 Hz, 2.9H), 4.56 (s, 0.2H), 7.13 – 7.17 (d, *J* = 8.0 Hz, 2H), 7.38 – 7.42 (m, *J* = 8.0 Hz, 3H), 14.33 (s, 0.3H). **^{13}C NMR (200 MHz, $CDCl_3$):** δ 12.9, 13.2, 21.6, 30.2, 44.0, 50.2, 89.1, 127.7, 128.3, 128.4, 129.5, 129.8, 141.7, 141.8, 166.1, 171.4, 202.2.

4.2.17 *N*-benzyl-3-oxo-*N*-phenylbutanamide (15q) The product was extracted with EtOAc and the crude material was purified by silica gel column chromatography eluting with CH_2Cl_2 followed by a CH_2Cl_2/EtOAc gradient up to 50 % EtOAc. Pale brown oil. **IR (cm^{-1}):** 3063, 3031, 2925, 1721, 1655, 1637, 1595, 1496, 1359, 1276, 1212, 1157, 1082, 1018, 923, 780, 734, 700, 562, 537. The product was observed to be a mixture of keto and enol tautomers. **^{1}H NMR (200 MHz, $CDCl_3$):** δ 1.83 (s, 1H), 2.11 (s, 3H), 3.33 (s. 2H), 4.67 (s, 0.4H), 4.94 (s, 3H), 6.98 – 7.02 (m, J = 8.0 Hz, 3H), 7.27 – 7.35 (m, 7H), 14.33 (s, 0.3H). **^{13}C NMR (200 MHz, $CDCl_3$):** δ 21.6, 30.3, 50.1, 52.9, 88.9, 127.3, 127.4, 127.7, 128.3, 128.4, 128.7, 129.4, 129.6, 136.9, 137.4, 141.8, 166.6, 202.1.

4.2.18 (3-oxobutanoyl)-*L*-tryptophan (17a) Colourless crystal. m.p. 163-5°C. **IR (cm^{-1}):** 3392, 3345, 2915, 1724, 1710, 1620, 1530, 1358, 1274, 1216, 1198, 739, 620. **^{1}H NMR (200 MHz, DMSO d_6)** δ 10.85 (s, 1H), 8.44 (d, *J* = 7.8 Hz, 1H), 7.53 (d, *J* = 7.4 Hz, 1H), 7.34 (d, *J* = 7.9 Hz, 1H), 7.15 (d, *J* = 2.1 Hz, 1H), 7.03 (dd, *J* = 10.5, 7.8 Hz, 2H), 4.57 – 4.46 (m, 1H), 3.32 (s, 2H), 3.11 (dd, *J* = 18.0, 6.7 Hz, 2H), 2.04 (s, 3H). **^{13}C NMR (50 MHz, DMSO d_6)** δ 203.1, 173.3, 166.3, 136.2, 127.3, 123.8, 121.1, 118.6, 118.3, 111.5, 109.8, 53.2, 51.1, 29.8, 27.2. **$[\alpha]_D$ =** + 17.0 (*c* 0.1 EtOH). **HRMS (*m/z* - H^+)** calc.: 287.1037. Obs.: 287.1040.

4.2.19 (3-oxobutanoyl)-*L*-leucine (17b) Colourless crystal. m.p. 122-3°C. **IR (cm^{-1}):** 3308, 2958, 2875, 2611, 2480, 1724, 1701, 1616, 1560, 1276, 1248, 1154, 1127. **^{1}H NMR (200 MHz, $CDCl_3$)** δ 7.46 (d, *J* = 7.8 Hz, 1H), 4.57 – 4.41 (m, 1H), 3.40 (s, 2H), 2.20 (s, 3H), 1.70 – 1.48 (m, 3H), 0.87 (dd, *J* = 5.7, 2.5 Hz, 6H). **^{13}C NMR (50 MHz, $CDCl_3$)** δ 203.7, 174.5, 165.9, 50.8, 49.8, 40.9, 30.4, 24.6, 22.7, 21.6. **$[\alpha]_D$ =** -22.0 (*c* 0.1 EtOH). **HRMS (*m/z* - H^+)** calc.: 214.1085. Obs: 214.1087.

4.2.20 (3-oxobutanoyl)-*L*-valine (17c) Colourless crystal. m.p. 121-2°C. **IR (cm^{-1}):** 3316, 2926, 2470, 1724, 1698, 1620, 1560, 1250, 1183, 696. **^{1}H NMR (200 MHz, $CDCl_3$)** δ 7.54 (d, *J* = 8.5 Hz, 1H), 4.14 (dd, *J* = 8.5, 4.9 Hz, 1H), 3.18 (s, 2H), 1.99 – 1.82 (m, 4H), 0.66 (dd, *J* = 6.4, 3.4 Hz, 6H). **^{13}C NMR (50 MHz, $CDCl_3$)** δ 202.91, 172.66, 165.70, 56.66, 49.96, 30.01, 29.66, 18.43, 17.10. **$[\alpha]_D$ =** - 5 (*c* 0.1 EtOH). **HRMS (*m/z* - H^+)** calc.: 200.0928. Obs.: 200.0933.

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DOI: 10.1039/C5RA14355A

4.2.21 (3-oxobutanoyl)-*L*-methionine (17d) Brown oil. **IR (cm^{-1}):** 3320, 2923, 2483, 1920, 1721, 1698, 1626, 1557, 1440, 1258, 1183, 711. **^{1}H NMR (200 MHz, $CDCl_3$)** δ 7.83 (d, *J* = 7.5 Hz, 1H), 4.67 (dd, *J* = 12.4, 7.2 Hz, 1H), 3.52 (s, 2H), 2.56 (t, *J* = 7.2 Hz, 2H), 2.27 (s, 3H), 2.23 – 2.15 (m, 1H), 2.09 (s, 3H), 2.06 – 1.96 (m, 1H). **^{13}C NMR (50 MHz, $CDCl_3$)** δ 204.4, 174.2, 167.0, 51.7, 49.4, 31.0, 30.8, 29.9, 15.3. **$[\alpha]_D$** = + 29.0 (*c* 0.1 EtOH). **HRMS (*m/z* - H^+)** calc.: 232.0649. Obs.: 232.0649.

4.2.22 (3-oxobutanoyl)-*L*-phenylalanine (17e) Colourless crystal. m.p. 110-12^{0}C. **IR (cm^{-1}):** 3415, 2944, 1728, 1640, 1531, 1426, 1219, 1162, 1109, 748. **^{1}H NMR (200 MHz, $CDCl_3$ + DMSO d_6)** δ 7.46 (d, *J* = 5.3 Hz, 1H), 7.16 – 7.00 (m, 5H), 4.62 (td, *J* = 7.4, 5.4 Hz, 1H), 3.20 (s, 2H), 2.97 (dt, *J* = 13.9, 7.7 Hz, 2H), 1.99 (s, 3H). **^{13}C NMR (50 MHz, $CDCl_3$ + DMSO)** δ 202.9, 172.6, 165.4 136.1, 129.0, 127.9, 126.3, 53.0, 50.1, 37.1, 29.9. **$[\alpha]_D$** = + 8.0 (*c* 0.1 EtOH). **HRMS (*m/z* - H^+)** calc.: 248.0928. Obs.: 248.0929.

4.2.23 (3-oxobutanoyl)-*L*-phenylglycine (17f) Colourless crystal. m.p. 133-5^{0}C. **IR (cm^{-1}):** 3390, 2963, 1717, 1625, 1544, 1261, 1099, 1026, 800, 721, 658. **^{1}H NMR (200 MHz, $CDCl_3$ + DMSO d_6)** δ 8.33 (d, *J* = 6.6 Hz, 1H), 7.38 – 7.31 (m, 2H), 7.30 – 7.19 (m, 3H), 5.42 (d, *J* = 7.2 Hz, 1H), 3.39 (s, 2H), 2.14 (s, 3H). **^{13}C NMR (50 MHz, $CDCl_3$ + DMSO)** δ 202.8, 171.4, 165.2, 136.4, 128.0, 127.5, 126.8 77.6, 76.4, 56.1, 49.9, 29.8. **$[\alpha]_D$** = - 169.0 (*c* 0.1 EtOH). **HRMS (*m/z* - H^+)** calc.: 234.0772. Obs.: 234.0771.

4.2.24 (3-oxobutanoyl)-*L*-tyrosine (17g) Colourless crystal. m.p. 186-7^{0}C. **IR (cm^{-1}):** 3360, 2964, 2627, 1708, 1627, 1543, 1157, 1252, 1229, 818. **^{1}H NMR (200 MHz, $CDCl_3$ + DMSO d_6)** δ 7.55 (d, *J* = 7.8 Hz, 1H), 6.62 (d, *J* = 8.4 Hz, 2H), 6.31 (d, *J* = 8.4 Hz, 2H), 4.22 (dd, *J* = 7.6, 5.5 Hz, 1H), 2.97 (s, 2H), 2.58 (ddd, *J* = 21.4, 14.0, 6.3 Hz, 2H), 1.74 (s, 3H). **^{13}C NMR (50 MHz, $CDCl_3$ + DMSO d_6)** δ 202.2, 172.1, 165.2, 155.1, 129.3, 126.2, 114.4, 52.9, 49.9, 35.7, 29.1. **$[\alpha]_D$** = + 49.0 (*c* 0.1 EtOH). **HRMS (*m/z* - H^+)** calc.: 264.0877. Obs.: 264.0880.

4.2.25 (3-oxobutanoyl)-*L*-cisteine (17h) Yellow crystal. m.p. 126-8^{0}C. **IR (cm^{-1}):** 3385, 2554, 1716, 1625, 1534, 1359, 1228, 1200, 1165. **^{1}H NMR (200 MHz, $CDCl_3$**

+ DMSO d_6) δ 7.75 (d, *J* = 7.3 Hz, 1H), 4.61 (dt, *J* = 7.4, 4.5 Hz, 1H), 3.33 (s, 2H), 2.84 (ddd, *J* = 8.9, 4.5, 2.8 Hz, 2H), 2.10 (s, 3H), 1.49 (t, *J* = 8.9 Hz, 1H). **^{13}C NMR (50 MHz, $CDCl_3$ + DMSO d_6)** δ 203.1, 171.2, 165.8, 53.7, 50.2, 30.2, 26.2. **$[\alpha]_D$** = + 8.0 (*c* 0.1 EtOH). **HRMS (*m/z* - H^+)** calc.: 204.0336. Obs.: 204.0336.

4.2.26 methyl (3-oxobutanoyl)-*L*-tryptophanate (17i) Pale brown oil. **IR (cm^{-1}):** 3270, 2952, 1752, 1709, 1655, 1548, 1437, 1224, 1209. **^{1}H NMR (200 MHz, $CDCl_3$)** δ 8.48 (s, 1H), 7.53 (d, *J* = 7.5 Hz, 1H), 7.40 – 7.28 (m, 2H), 7.14 (td, *J* = 13.7, 6.7 Hz, 2H), 7.03 (d, *J* = 2.1 Hz, 1H), 4.92 (dd, *J* = 13.2, 5.7 Hz, 1H), 3.69 (s, 3H), 3.32 (d, *J* = 5.7 Hz, 2H), 3.28 (s, 2H), 2.11 (s, 3H). **^{13}C NMR (50 MHz, $CDCl_3$)** δ 203.8, 172.2, 165.6, 136.1, 127.4, 123.1, 122.1, 119.5, 118.4, 111.3, 109.5, 52.9, 52.3, 49.6, 30.6, 27.5. **$[\alpha]_D$** = + 10.0 (*c* 0.1 EtOH). **HRMS (*m/z* - H^+)** calc.: 301.1194. Obs.: 301.1201.

4.2.27 methyl (3-oxobutanoyl)-*L*-phenylalaninate (17j) Pale yellow oil. **IR (cm^{-1}):** 3288, 1755, 1720, 1638, 1354, 1210, 1175. **^{1}H NMR (200 MHz, $CDCl_3$)** δ 7.35 – 7.26 (m, 3H), 7.19 – 7.10 (m, 2H), 4.88 (dt, *J* = 6.8, 5.8 Hz, 1H), 3.73 (s, 3H), 3.39 (s, 2H), 3.13 (qd, *J* = 13.9, 6.2 Hz, 2H), 2.22 (s, 3H). **^{13}C NMR (50 MHz, $CDCl_3$)** δ 203.6, 171.6, 165.3, 135.8, 129.2, 128.5, 127.1, 53.4, 52.3, 49.6, 37.8, 30.7. **$[\alpha]_D$** = + 4.0 (*c* 0.1 EtOH). **HRMS (*m/z* - H^+)** calc.: 286.1050. Obs.: 286.1052.

4.2.28 methyl (3-oxobutanoyl)-*L*-phenylglycine (17k) Pale yellow oil. **IR (cm^{-1}):** 3289, 3038, 2955, 1753, 1726, 1640, 1534, 1354, 1216, 1173, 1156. **^{1}H NMR (200 MHz, $CDCl_3$)** δ 7.95 (d, *J* = 6.1 Hz, 1H), 7.41 – 7.31 (m, 5H), 5.56 (d, *J* = 7.1 Hz, 1H), 3.72 (s, 3H), 3.44 (s, 2H), 2.24 (s, 3H). **^{13}C NMR (50 MHz, $CDCl_3$)** δ 203.8, 170.9, 165.1, 136.0, 128.9, 128.6, 127.2, 56.6, 52.7, 49.4, 30.8. **$[\alpha]_D$** = -21.0 (*c* 0.1 EtOH). **HRMS (*m/z* + Na^+)** calc.: 272.0898. Obs.: 272.0893.

4.2.29 methyl (*S*)-2-(3-oxobutanoyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (17l) Pale brown oil. **IR (cm^{-1}):** 3288, 1755, 1720, 1638, 1354, 1210, 1175. Although the tertiary acetoacetamide derivative is stable on silica gel, it was observed to streak on elution on silica TLC plates. ^{1}H NMR analysis of this compound suggested the presence of multiple conformers due to the rigid amide bond that does not freely rotate on the NMR timescale at room temperature, and tautomers

due to the acidic methylene unit of the 1,3-dicarbonyl system. **HRMS [2M+Na$^+$]** calc.: 651.2425. Obs.: 651.2446.

4.2.30 methyl *N*$^{\alpha}$-(4-methoxybenzyl)-*N*$^{\alpha}$-(3-oxobutanoyl)-*L*-tryptophanate (17m) Pale brown oil. **IR (cm^{-1}):** 3400, 1740, 1633, 1613, 1248, 1177, 748. Although the tertiary acetoacetamide derivative is stable on silica gel, it was observed to streak on elution on silica TLC plates. ^{1}H NMR analysis of this compound suggested the presence of multiple conformers due to the rigid amide bond that does not freely rotate on the NMR timescale at room temperature, and tautomers due to the acidic methylene unit of the 1,3-dicarbonyl system.

4.2.31 methyl (*S*)-2-(*N*-(4-methoxybenzyl)-3-oxobutanamido)-2-phenylacetate (17n) Pale brown oil. **IR (cm^{-1}):** 3400, 1740, 1635, 1612, 1247, 1179, 752. Although the tertiary acetoacetamide derivative is stable on silica gel, it was observed to streak on elution on silica TLC plates. ^{1}H NMR analysis of this compound suggested the presence of multiple conformers due to the rigid amide bond that does not freely rotate on the NMR timescale at room temperature, and tautomers due to the acidic methylene unit of the 1,3-dicarbonyl system.

4.3 Preparation of dihydropyrimidines (18 / 19) from acetoacetanilides (15) or acetoacetamides (17).

In a round bottom flask, the 1,3 dicarbonyl derivatives **15** or **17** (1mmol) were prepared as previously described. After the reflux period the water was removed under reduced pressure to give the crude products that were subsequently dissolved in EtOH (5 mL). Urea **2** (2.5 mmol) and a benzaldehyde derivative **1** (1mmol), followed by formic acid (10 drops), were added and the mixture was heated to reflux overnight. Upon completion of the reaction as determined by TLC, the mixture was diluted with ice cold water and the solid was removed by filtration under reduce pressure. The dihydropyrimidine products were recrystallized from ethanol.

4.3.1 **4-(benzo[*d*][1,3]dioxol-5-yl)-6-methyl-2-oxo-*N*-phenyl-1,2,3,4-tetrahydro pyrimidine-5-carboxamide (18a)** White solid. m.p. 276-7^{0}C **IR (cm^{-1}):** 3377, 3114, 2951, 1710, 1680, 1625, 1597, 779. **^{1}H NMR (200 MHz, DMSO)** δ 9.52 (s, 1H), 8.70 (s, 1H), 7.64 – 7.45 (m, 3H), 7.24 (t, *J* = 7.5 Hz, 2H), 7.00 (t, *J* = 7.2 Hz, 1H),

6.89 – 6.64 (m, 3H), 5.97 (s, 2H), 5.32 (s, 1H), 2.05 (s, 3H). **^{13}C NMR (50 MHz, DMSO)** δ 165.3, 152.4, 147.3, 146.4, 139.2, 138.4, 138.3, 128.5, 123.1, 119.6, 108.0, 106.8, 105.4, 100.9, 54.8, 17.0. **HRMS (*m/z* + H$^+$)** calc.: 352.1292. Obs.: 352.1153.

4.3.2 **4-(benzo[*d*][1,3]dioxol-5-yl)-6-methyl-2-oxo-*N*-(*p*-tolyl)-1,2,3,4-tetrahydro pyrimidine-5-carboxamide (18b)** White solid. m.p. 272-5^{0}C **IR (cm^{-1}):** 3369, 3263, 1716, 1678, 1248, 1038, 789. **^{1}H NMR (200 MHz, DMSO)** δ 9.44 (s, 1H), 8.67 (s, 1H), 7.50 (s, 1H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.05 (d, *J* = 8.3 Hz, 2H), 6.89 – 6.68 (m, 3H), 5.96 (s, 2H), 5.30 (s, 1H), 2.22 (s, 3H), 2.03 (s, 3H). **^{13}C NMR (50 MHz, DMSO)** δ 165.1, 152.5, 147.3, 146.5, 138.3, 138.1, 136.7, 132.1, 128.9, 119.6, 119.6, 108.0, 106.8, 105.5, 100.9, 54.9, 20.4, 17.0. **HRMS (*m/z* + H$^+$)** calc.: 338.1499. Obs.: 338.1505.

4.3.3 **4-(4-methoxyphenyl)-6-methyl-2-oxo-*N*-phenyl-1,2,3,4-tetrahydro pyrimidine-5-carboxamide (18c)** White solid. m.p. 238-40^{0}C **IR (cm^{-1}):** 3403, 3277, 1708, 1673, 1246, 1175, 754. **^{1}H NMR (200 MHz, DMSO)** δ 9.52 (s, 1H), 8.69 (s, 1H), 7.64 – 7.45 (m, 3H), 7.36 – 7.14 (m, 4H), 6.99 (t, *J* = 7.3 Hz, 1H), 6.87 (d, *J* = 8.5 Hz, 2H), 5.37 (s, 1H), 3.70 (s, 3H), 2.04 (s, 3H). **^{13}C NMR (50 MHz, DMSO)** δ 165.4, 158.6, 152.6, 139.2, 138.2, 136.5, 128.5, 127.6, 123.1, 119.6, 113.8, 105.7, 55.1, 54.6, 17.0. **HRMS (*m/z* + H$^+$)** calc.: 366.1448. Obs.: 366.1454.

4.3.4 **4-(4-methoxyphenyl)-6-methyl-2-oxo-*N*-(*p*-tolyl)-1,2,3,4-tetrahydro pyrimidine-5-carboxamide (18d)** White solid. m.p. 233-4^{0}C **IR (cm^{-1}):** 3404, 3279, 1709, 1673, 1627, 1246, 1174, 755. **^{1}H NMR (200 MHz, DMSO)** δ 9.43 (s, 1H), 8.66 (s, 1H), 7.49 (s, 1H), 7.42 (d, *J* = 8.3 Hz, 2H), 7.19 (d, *J* = 8.6 Hz, 2H), 7.04 (d, *J* = 8.3 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 5.34 (s, 1H), 3.70 (s, 3H), 2.21 (s, 3H), 2.03 (s, 3H). **^{13}C NMR (50 MHz, DMSO)** δ 165.2, 158.6, 152.6, 137.9, 136.7, 136.5, 132.0, 128.9, 127.6, 119.7, 113.8, 105.8, 55.1, 54.6, 20.4, 17.0. **HRMS (*m/z* + H$^+$)** calc.: 352.1656. Obs.: 352.1593.

4.3.5 **4-(4-cyanophenyl)-6-methyl-2-oxo-*N*-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (18e)** White solid. m.p. 273-4^{0}C **IR (cm^{-1}):** 3307, 1727, 1664, 1623, 1242, 1190, 746. **^{1}H NMR (200 MHz, DMSO)** δ 9.60 (s, 1H), 8.85 (s, 1H), 7.82 (d, *J* = 7.9 Hz, 2H), 7.70 (s, 1H), 7.59 – 7.40 (m, 4H), 7.25 (t, *J* = 7.6 Hz, 2H), 7.00 (t, *J* =

7.1 Hz, 1H), 5.45 (s, 1H), 2.05 (s, 3H). **^{13}C NMR (50 MHz, DMSO)** δ 165.1, 152.4, 149.5, 139.2, 139.0, 132.6, 128.5, 127.3, 123.2, 119.7, 110.1, 104.5, 54.9, 17.1. **HRMS (*m/z* + H$^+$)** calc.: 336.1346. Obs.: 336.1330.

4.3.6 **4-(4-cyanophenyl)-6-methyl-2-oxo-*N*-(*p*-tolyl)-1,2,3,4-tetrahydro-pyrimidine-5-carboxamide (18f)** White solid. m.p. 285^{0}C **IR (cm^{-1}):** 3303, 1728, 1664, 1623, 1243, 770. **^{1}H NMR (200 MHz, DMSO)** δ 9.53 (s, 1H), 8.83 (s, 1H), 7.82 (d, *J* = 8.2 Hz, 2H), 7.69 (s, 1H), 7.51 – 7.34 (m, 4H), 7.05 (d, *J* = 8.3 Hz, 2H), 5.43 (s, 1H), 2.22 (s, 3H), 2.03 (s, 3H). **^{13}C NMR (50 MHz, DMSO)** δ 164.9, 152.5, 149.5, 139.0, 136.5, 132.6, 132.2, 128.9, 127.3, 119.7, 118.8, 110.1, 104.6, 54.9, 20.4, 17.1. **HRMS (*m/z* + H$^+$)** calc.: 347.1503. Obs.: 347.1564.

4.3.7 **6-methyl-4-(4-nitrophenyl)-2-oxo-*N*-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (18g)** White solid. m.p. 278-9^{0}C **IR (cm^{-1}):** 3375, 3268, 1727, 1667, 1623, 1239, 1150, 747. **^{1}H NMR (200 MHz, DMSO)** δ 9.63 (s, 1H), 8.89 (s, 1H), 8.22 (d, *J* = 8.7 Hz, 2H), 7.75 (s, 1H), 7.60 – 7.45 (m, 4H), 7.24 (t, *J* = 7.8 Hz, 2H), 7.00 (t, *J* = 7.3 Hz, 1H), 5.51 (s, 1H), 2.06 (s, 3H). **^{13}C NMR (50 MHz, DMSO)** δ 165.1, 152.4, 151.5, 146.8, 139.3, 139.0, 128.5, 127.6, 123.8, 123.3, 119.7, 104.5, 54.8, 17.1. **HRMS (*m/z* + H$^+$)** calc.: 353.1244. Obs.: 353.1250.

4.3.8 **6-methyl-4-(4-nitrophenyl)-2-oxo-*N*-(*p*-tolyl)-1,2,3,4-tetrahydropyrimidine-5-carboxamide (18h)** White solid. m.p. 276-7^{0}C **IR (cm^{-1}):** 3375, 3253, 1725, 1667, 1623, 1234, 1107, 771. **^{1}H NMR (200 MHz, DMSO)** δ 9.55 (s, 1H), 8.85 (s, 1H), 8.21 (d, *J* = 8.7 Hz, 2H), 7.73 (s, 1H), 7.52 (d, *J* = 8.7 Hz, 2H), 7.40 (d, *J* = 8.3 Hz, 2H), 7.04 (d, *J* = 8.2 Hz, 2H), 5.48 (s, 1H), 2.21 (s, 3H), 2.04 (s, 3H). **^{13}C NMR (50 MHz, DMSO)** δ 164.9, 152.4, 151.5, 146.8, 139.1, 136.5, 132.3, 129.0, 127.7, 123.9, 119.8, 104.6, 54.8, 20.4, 17.1. **HRMS (*m/z* + H$^+$)** calc.: 367.1401. Obs.: 367.1355.

4.3.9 **4-(4-hydroxy-3-methoxyphenyl)-6-methyl-2-oxo-*N*-phenyl-1,2,3,4-tetra-hydropyrimidine-5-carboxamide (18i)** White solid. m.p. 255-7^{0}C **IR (cm^{-1}):** 3403, 3277, 1708, 1673, 1630, 1246, 1175, 754. **^{1}H NMR (200 MHz, DMSO)** δ 9.50 (s, 1H), 8.90 (s, 1H), 8.64 (s, 1H), 7.54 (d, *J* = 7.7 Hz, 2H), 7.46 (s, 1H), 7.24 (t, *J* = 7.8 Hz, 2H), 6.99 (t, *J* = 7.3 Hz, 1H), 6.82 (s, 1H), 6.70 (s, 2H), 5.33 (s, 1H), 3.67 (s, 3H), 2.03 (s, 3H). **^{13}C NMR (50 MHz, DMSO)** δ 165.5, 152.6, 147.4, 145.9, 139.2, 137.9,

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DOI: 10.1039/C5RA14355A

135.2, 128.5, 123.1, 119.6, 118.6, 115.3, 110.9, 105.7, 55.6, 54.8, 17.0. **HRMS (*m/z* + H^+)** calc.: 354.1448. Obs.: 354.1440.

4.3.10 **4-(4-hydroxy-3-methoxyphenyl)-6-methyl-2-oxo-*N*-(*p*-tolyl)-1,2,3,4-tetra-hydropyrimidine-5-carboxamide (18j)** White solid. m.p. 257-8^{0}C **IR (cm^{-1}):** 3309, 3228, 1694, 1667, 1621, 1254, 1155, 808. **^{1}H NMR (200 MHz, DMSO)** δ 9.42 (s, 1H), 8.91 (s, 1H), 8.60 (s, 1H), 7.50 – 7.34 (m, 3H), 7.04 (d, *J* = 8.3 Hz, 2H), 6.82 (s, 1H), 6.70 (s, 2H), 5.31 (s, 1H), 3.67 (s, 3H), 2.21 (s, 3H), 2.02 (s, 3H). **^{13}C NMR (50 MHz, DMSO)** δ 165.4, 152.6, 147.4, 145.9, 137.6, 136.7, 135.3, 132.1, 128.9, 119.7, 118.6, 115.3, 110.9, 105.8, 55.6, 54.9, 20.4, 17.0. **HRMS (*m/z* + H^+)** calc.: 368.1605. Obs.: 368.1610.

4.3.11 **(4-(4-cyanophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carbonyl)-*L*-tryptophan (19a)** White solid. m.p. > 250^{0}C (dec.) **IR (cm^{-1}):** 3293, 2230, 1698, 1667, 1608, 1515, 1458, 1239, 745. **^{1}H NMR (200 MHz, DMSO – d_6)** δ 10.22 (s, 1H), 8.42 (s, 1H), 7.51 – 7.36 (m, 2H), 7.32 – 7.19 (m, 4H), 7.11 – 6.89 (m, 5H), 5.22 (s, 1H), 4.59 (br, 1H), 3.31 – 3.07 (m, 2H), 1.85;1.89 (s, 3H). **^{13}C NMR (50 MHz, DMSO – d_6)** δ 174.0, 166.3, 166.0, 148.4, 148.2, 139.6, 139.1, 136.1, 132.6, 132.0, 131.9, 127.2, 127.1, 126.7, 123.4, 123.1, 121.0, 118.5, 118.1, 111.2, 110.3, 109.5, 109.2, 103.9, 103.6, 54.9, 53.1, 26.8, 16.8. **HRMS (*m/z* + Na^+)** calc.: 466.1485. Obs.: 466.1474**.**

4.3.12 **(4-(4-methoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carbonyl)-*L*-tryptophan (19b)** White solid. m.p. > 250^{0}C (dec.) **IV (cm^{-1}):** 3289, 3116, 1718, 1667, 1617, 1510, 1245. **^{1}H NMR (200 MHz, DMSO-d_6)** δ 10.14 – 10.10 (d, 2H), 8.34 (s, 2H), 7.46 – 7.23 (m, 4H), 7.05 – 6.77 (m, 12H), 6.73 – 6.60 (m, 4H), 6.52 (d, *J* = 8.6 Hz, 2H), 5.38 (s, 2H), 5.06 (s, 1H), 5.01 (s, 1H), 4.72 – 4.61 (m, 1H), 4.61 – 4.47 (m, 1H), 3.65 (s, 3H), 3.63 (s, 3H), 3.22 – 3.01 (m, 4H), 1.95 (s, 3H), 1.92 (s, 3H). **^{13}C NMR (50 MHz, $CDCl_3$/ DMSO-d_6)** δ 174.0, 173.5, 166.4, 166.2, 160.6, 158.7, 158.5, 153.2, 153.1, 139.5, 138.5, 136.1, 136.0, 135.4, 135.1, 127.5, 127.3, 127.1, 123.3, 123.2, 120.9, 118.4, 118.1, 113.7, 113.6, 111.1, 109.3, 109.0, 104.6, 104.2, 54.9, 52.9, 52.5, 26.8, 16.9. **HRMS (*m/z* + Na^+)** calc.: 471.1638. Obs.: 471.1643.

4.3.13 **(4-(4-cyanophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carbonyl)-*L*-leucine (19c)** White solid. m.p. > 250^{0}C (dec.) **IR (cm^{-1}):** 3411, 3246, 2962, 2234, 1705, 1640, 1497, 1243. **^{1}H NMR (200 MHz, DMSO – d$_6$)** δ 8.57 (s, 1H), 8.49 (s, 1H), 7.64 – 7.32 (m, 12H), 5.43 (s, 1H), 5.33 (s, 1H), 4.28 – 4.20 (m, 1H), 4.17 – 4.09 (m, 1H), 2.03 (s, 3H), 2.01 (s, 3H), 1.49 – 1.31 (m, 4H), 1.23 – 0.95 (m, 2H), 0.79 – 0.70 (m, 6H), 0.70 – 0.60 (m, 6H). **^{13}C NMR (50 MHz, CDCl$_3$/ DMSO-d$_6$)** δ 174.4, 174.3, 166.7, 166.5, 152.9, 152.8, 149.1, 139.3, 136.8, 132.0, 131.9, 127.6, 127.3, 118.5, 110.3, 104.5, 103.6, 55.4, 54.7, 50.7, 50.1, 24.4, 24.1, 22.8, 20.9, 20.8, 17.0, 16.7.

4.3.14 **(4-(4-methoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carbonyl)-*L*-leucine (19d)** White solid. m.p. > 250^{0}C (dec.) **IR (cm^{-1}):** 3414, 3248, 2957, 1705, 1643, 1613, 1514, 1498, 1243. **^{1}H NMR (200 MHz, DMSO-d$_6$)** δ 8.43 (s, 1H), 8.31 (s, 1H), 7.21 – 7.02 (m, 8H), 6.74 (d, *J* = 8.73 Hz, 4H), 5.26 (s, 1H), 5.19 (s, 1H), 4.35 – 4.22 (m, 1H), 4.22 – 4.11 (m, 1H), 3.68 (s, 6H), 2.06 (s, 3H), 2.01 (s, 3H), 1.48 – 1.31 (m, 4H), 1.28 – 1.04 (m, 2H), 0.76 – 0.67 (m, 6H), 0.67 – 0.59 (m, 6H). **^{13}C NMR (50 MHz, DMSO-d$_6$)** δ 174.56, 174.38, 166.78, 166.63, 158.68, 158.65, 153.07, 152.96, 139.38, 135.84, 135.58, 127.67, 113.57, 113.40, 105.74, 104.15, 55.29, 54.93, 54.89, 54.64, 50.53, 50.04, 24.20, 23.97, 22.83, 20.98, 20.93, 17.02, 16.65. **HRMS (*m/z* + Na$^+$)** calc.: 398.1686. Obs.: 398.1686.

4.3.15 **(4-(benzo[*d*][1,3]dioxol-5-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carbonyl)-*L*-leucine (19e)** White solid. m.p. > 250^{0}C (dec.) **IR (cm^{-1}):** 3412, 3247, 2959, 1705, 1644, 1491, 1449, 1248, 1240. **^{1}H NMR (200 MHz, DMSO-d$_6$ + CDCl$_3$)** δ 8.44 (s, 1H), 8.32 (s, 1H), 7.19 (s, 3H), 7.06 (s, 1H), 6.81 – 6.62 (m, 6H), 5.86 (s, 4H), 5.23 (s, 1H), 5.16 (s, 1H), 4.29 (dd, *J* = 14.6, 8.5 Hz, 1H), 4.20 – 4.08 (m, 1H), 2.05 (s, 3H), 2.00 (s, 3H), 1.46 – 1.31 (m, 4H), 1.25 – 0.94 (m, 2H), 0.78 – 0.70 (m, 6H), 0.69 – 0.62 (m, *J* = 6.2 Hz, 6H). **^{13}C NMR (50 MHz, CDCl$_3$ + DMSO-d$_6$)** δ 174.5, 174.4, 166.7, 166.6, 152.9, 152.8, 147.4, 147.3, 146.6, 146.5, 139.4, 137.7, 135.7, 119.8, 119.7, 107.7, 107.5, 107.1, 107.0, 105.6, 104.1, 100.7, 55.6, 54.9, 50.6, 50.0, 24.2, 24.0, 22.9, 20.9, 17.0, 16.6. **HRMS (*m/z* + Na$^+$)** calc.: 412.1479. Obs.: 412.1484.

4.3.16 **2-(4-(4-cyanophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamido)-2-phenylacetic acid (19f)** White solid. m.p. > 250^{0}C (dec.) **IR (cm^{-1}):** 3412, 3247, 2959, 1705, 1644, 1491, 1449, 1248, 1240. **^{1}H NMR (200 MHz, DMSO-d$_6$)** δ 8.79 (s, 1H), 8.73 (s, 1H), 8.38 – 8.29 (m, 1H), 7.76 (d, *J* = 7.6 Hz, 2H), 7.68 (s, 1H), 7.64 (s, 1H), 7.46 – 7.34 (m, 2H), 7.37 – 7.22 (m, 5H), 5.38 (s, 1H), 5.32 (s, 1H), 2.05 (s, 3H). **^{13}C NMR (50 MHz, DMSO-d$_6$)** δ 172.0, 171.9, 166.1, 166.0, 152.6, 149.5, 149.4, 140.0, 138.7, 137.1, 132.4, 128.3, 128.3, 127.8, 127.7, 127.4, 127.4, 118.8, 110.0, 103.6, 103.2, 56.5, 54.9, 54.5, 17.0, 16.9. **HRMS (*m/z* + Na$^+$)** calc.: 413.1220. Obs.: 413.1222.

4.3.17 **2-(4-(benzo[*d*][1,3]dioxol-5-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxamido)-2-phenylacetic acid (19g)** White solid. m.p. > 250^{0}C (dec.) **IR (cm^{-1}):** 3240, 2956, 1715, 1657, 1613, 1524, 1483, 1238, 1041. **^{1}H NMR (200 MHz, DMSO-d$_6$)** δ 8.65 (s, 1H), 8.57 (s, 1H), 8.21 – 8.25 (d, *J* = 6.6 Hz, 1H), 8.08 – 8.11 (d, *J* = 7.4 Hz, 1H), 7.49 (s, 1H), 7.42 (s, 1H), 7.29 (s, 5H), 6.92 – 6.57 (m, 3H), 5.97 (s, 2H), 5.32 (d, *J* = 6.4 Hz, 1H), 5.20 (s, 1H), 2.06 (s, 3H). **^{13}C NMR (50 MHz, DMSO-d$_6$)** δ 172.0, 171.8, 166.2, 166.1, 152.5, 147.2, 146.3, 139.8, 138.3, 138.2, 138.0, 137.2, 137.1, 128.2, 127.6, 119.6, 119.5, 107.8, 107.0, 106.9, 104.4, 103.8, 100.8, 56.4, 54.7, 54.4, 16.9, 16.8. **HRMS (*m/z* + Na$^+$)** calc.: 432.1166. Obs.: 432.1171.

4.3.18 **2-(4-(4-methoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamido)-2-phenylacetic acid (19h)** White solid. m.p. > 250^{0}C (dec.) **IR (cm^{-1}):** 3281, 2929, 2837, 1716, 1659, 1616, 1512, 1279, 1243, 1176. **^{1}H NMR (200 MHz, DMSO-d$_6$ + CDCl$_3$)** δ 8.63 (s, 1H), 8.55 (s, 1H), 7.95 – 7.91 (d, *J* = 6.6 Hz, 1H), 7.80 – 7.76 (d, *J* = 7.1 Hz, 1H), 7.44 (s, 1H), 7.38 (s, 1H), 7.30 – 7.11 (m, 7H), 6.79 (d, *J* = 8.0 Hz, 2H), 5.32 (d, *J* = 6.9 Hz, 1H), 5.25 (s, 1H), 3.72 (s, 3H), 2.07 (s, 3H). **^{13}C NMR (50 MHz, DMSO-d$_6$ + CDCl$_3$)** δ 171.9, 171.7, 166.1, 165.8, 158.5, 158.4, 152.6, 152.5, 140.0, 138.0, 137.2, 137.1, 136.2, 128.0, 127.5, 127.4, 113.5, 113.4, 104.4, 103.6, 56.2, 54.8, 54.5, 54.3, 16.9, 16.8. **HRMS (*m/z* + Na$^+$)** calc.: 418.1373. Obs.: 418.1392.

4.3.19 **(4-(benzo[*d*][1,3]dioxol-5-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carbonyl)-*L*-phenylalanine (19i)** White solid. m.p. > 250^{0}C (dec.) **IR (cm^{-1}):**

3412, 3247, 2959, 1705, 1644, 1491, 1449, 1248, 1240. **^{1}H NMR (200 MHz, DMSO-d$_6$)** δ 8.58 (s, 1H), 8.55 (s, 1H), 7.86 – 7.82 (d, J = 7.99 Hz, 1H), 7.79 – 7.75 (d, J = 7.66 Hz, 1H), 7.49 (s, 1H), 7.44 (s, 1H), 7.26 – 7.04 (m, 5H), 6.85 – 6.40 (m, 3H), 5.97 (s, 2H), 5.13 (s, 1H), 5.03 (s, 1H), 4.47 (s, 1H), 4.30 (s, 1H), 3.12 – 2.80 (m, 2H), 1.87 (s, 3H). **^{13}C NMR (50 MHz, DMSO-d$_6$)** δ 173.4, 173.1, 166.7, 166.4, 152.8, 147.2, 146.3, 139.0, 138.1, 138.0, 137.8, 128.9, 128.1, 128.0, 126.2, 119.4, 119.2, 107.9, 106.8, 106.6, 104.8, 104.4, 100.8, 54.4, 54.1, 53.3, 36.3, 36.0, 16.7, 16.6. **HRMS (*m/z* + Na$^+$)** calc.: 446.1323. Obs.: 446.1329.

4.3.20 **(4-(4-cyanophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carbonyl)-*L*-phenylalanine (19j)** White solid. m.p. > 250^{0}C (dec.) **IR (cm^{-1}):** 3291, 3240, 2232, 1716, 1666, 1618, 1532, 1244, 756. **^{1}H NMR (200 MHz, DMSO-d$_6$)** δ 8.67 (s, 1H), 8.03 – 7.99 (d, *J* = 7.8 Hz, 1H), 7.91 – 7.88 (d, *J* = 7.5 Hz, 1H), 7.77 – 7.55 (m, 3H), 7.34 (d, *J* = 7.9 Hz, 1H), 7.26 – 7.05 (m, 6H), 5.28 (s, 1H), 5.18 (s, 1H), 4.47 (s, 1H), 4.34 (s, 1H), 3.12 – 2.83 (m, 2H), 1.85 (s, 3H). **^{13}C NMR (50 MHz, DMSO-d$_6$)** δ 173.4, 173.2, 166.6, 166.3, 152.7, 149.3, 139.4, 138.4, 138.1, 137.8, 132.3, 128.9, 128.8, 128.2, 128.0, 127.2, 126.9, 126.3, 126.2, 118.8, 109.8, 109.8, 103.9, 103.6, 54.5, 54.3, 53.4, 36.1, 35.9, 16.7. **HRMS (*m/z* + Na$^+$)** calc.: 427.1377. Obs.: 427.1380.

4.3.21 **(4-(benzo[*d*][1,3]dioxol-5-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carbonyl)-*L*-tyrosine (19k)** White solid. m.p. > 250^{0}C (dec.) **IR (cm^{-1}):** 3412, 3247, 2959, 1705, 1644, 1491, 1449, 1248, 1240. **^{1}H NMR (200 MHz, DMSO-d$_6$)** δ 9.19 (s, 1H), 8.57 (s, 1H), 8.55 (s, 1H), 7.78 – 7.74 (d, J = 7.4Hz, 1H), 7.66 – 7.63 (d, J = 7.3Hz, 1H), 7.48 (s, 1H), 7.44 (s,1H), 6.99 – 6.79 (m, 3H), 6.72 – 6.51 (m, 4H), 5.97 (s, 2H), 5.13 (s, 1H), 5.03 (s, 1H), 4.27 (s, 1H), 4.21 (s, 1H), 2.96 – 2.69 (m, 2H), 1.89 (s, 3H). **^{13}C NMR (50 MHz, DMSO-d$_6$)** δ 173.5, 173.2, 166.7, 166.4, 155.8, 152.8, 147.2, 146.3, 139.0, 138.2, 137.8, 129.9, 128.1, 127.8, 119.5, 119.3, 114.9, 114.9, 107.9, 107.8, 106.8, 106.6, 104.8, 104.5, 100.8, 54.8, 54.4, 54.2, 53.8, 35.5, 35.3, 16.8, 16.7. **HRMS (*m/z* + Na$^+$)** calc.: 462.1272. Obs.: 462.1279.

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DOI: 10.1039/C5RA14355A

5. Acknowledgements

The authors thank FAPERJ, CNPq and CAPES for financial assistance. We thank Prof. Marcos Eberlin (Instituto de Química, UNICAMP) and the IPPN-UFRJ facility for HRMS analysis.

6. Supporting information available

Copies of ^{1}H, ^{13}C NMR and HRMS spectra.

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