

Synthesis of Some Novel 11b-Substituted Pyrimido[6,1-a]-isoquinoline Derivatives

Plamen A. Angelov *, Iliyan I. Ivanov and Atanas P. Venkov †

Department of Organic Chemistry, University of Plovdiv, 24 "Tsar Asen" str., 4000 Plovdiv, Bulgaria, Tel. (+359) 032-261535.

† Dr. Venkov passed away on 21.07.2003, while this project was already in progress. We would like to dedicate this paper to his memory.

* Author to whom correspondence should be addressed; E-mail: angelov@argon.acad.bg

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Abstract: A series of novel 11b-substituted 1,6,7,11b-tetrahydropyrimido[6,1-a]-isoquinoline-2,4-diones and 4-thioxo-1,3,4,6,7,11b-hexahydropyrimido[6,1-a]isoquinolin-2-ones were synthesized, utilizing two alternative strategies for ring closure of tetrahydroisoquinoline intermediates obtained from N-phenethyl enaminones.

Keywords: Tetrahydroisoquinolines, pyrimido[6,1-a]isoquinolines, enaminones.

Introduction

A broad range of biological activities has been reported for compounds containing the pyrimido[6,1-a]isoquinoline ring system and a number of these compounds are patented as potential therapeutic agents [1,2]. Amongst the reported ones are antihypertensive, bronchodilator and anti-allergic activities. The antihypertensive agent Trequinsin [3], for instance, is one of the most potent *in vitro* inhibitors of platelet phosphodiesterase and platelet aggregation known to date [4]. This makes the pyrimido[6,1-a]-isoquinoline skeleton an important synthetic target and a lot of research has been directed towards it. Compounds of this type are usually synthesized by ring closure of suitable tetrahydroisoquinolines

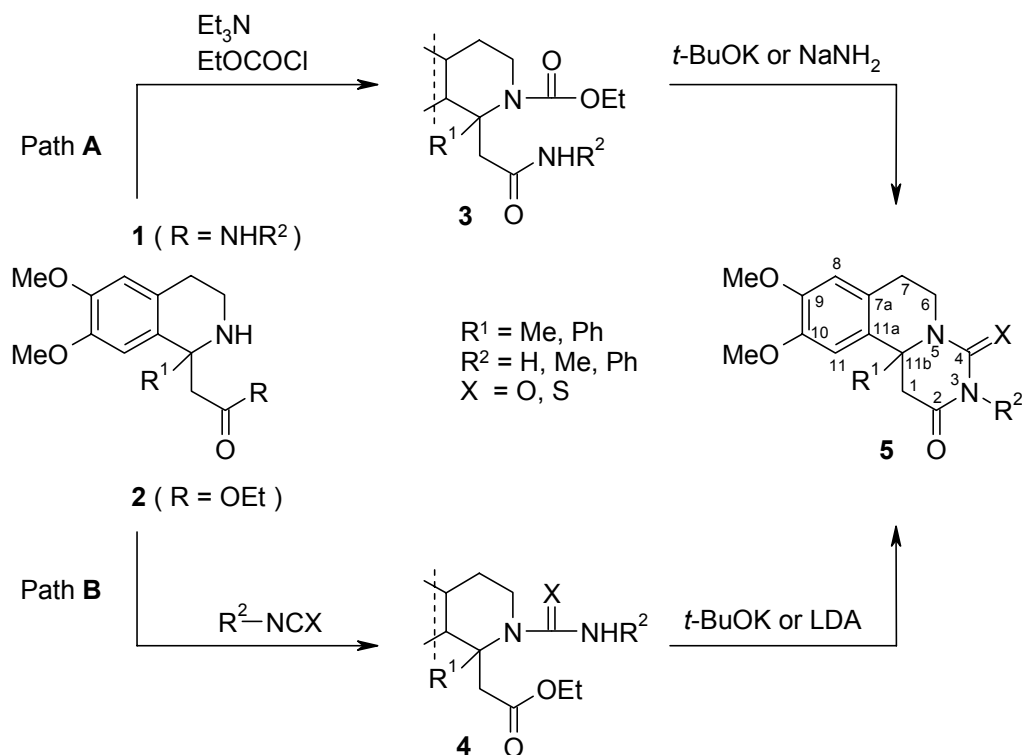
[1,3,5-11], Bischler-Napieralsky cyclization of 1-(3,4-dimethoxyphenylethyl)barbituric acid [2] or other appropriate N-phenethyl amides [12,13]. Cyclizations of pyrimidine intermediates via N-acyliminium ions are also known [14,15]. Despite these numerous publications, however, there are very few examples of 11b-substituted pyrimido[6,1-a]isoquinolines [11,15], a fact attributable to the lack of suitable starting materials.

In a previous communication we reported on the synthesis of 1,1-disubstituted tetrahydroisoquinolines via Pictet-Spengler reaction of N-phenethyl enaminones [16]. Some of these compounds are an excellent starting point for construction of the pyrimido[6,1-a]isoquinoline skeleton. To demonstrate this, now we have synthesized a series of novel 1,6,7,11b-tetrahydropyrimido[6,1-a]-isoquinoline-2,4-diones and 4-thioxo-1,3,4,6,7,11b-hexahydropyrimido[6,1-a]isoquinolin-2-ones (**5**) bearing methyl or phenyl substituents at the 11b position.

Results and Discussion

The synthesis of the targets **5** was accomplished by two different strategies (Scheme 1), starting from tetrahydroisoquinolin-1-yl acetamides (**1**, Path A) or ethyl esters of tetrahydroisoquinolin-1-yl acetic acids (**2**, Path B).

Scheme 1.



Since compounds of type **1** are generally available in higher yields than those of type **2** [16], our initial studies focused on Path A. The reactions of **1a-e** with ethyl chlorocarbonate were carried out in the presence of Et₃N as HCl scavenger and afforded the corresponding urethanes **3a-e** in good yields (80 – 90%). The intermediates **3** obtained in this way were cyclized to **5** with the aid of strong bases like NaNH₂ or *t*-BuOK. The yields of **5** are nearly quantitative after refluxing **3** and 1.2 equiv. of base in THF as the solvent for 1h. The rate of cyclization in general increases with the acidity of the amide group NH in **3**. As an alternative, compounds **5** could be synthesized by cyclocondensation of **2** and isocyanates – Path B. To prove this, compounds **2d,e** were reacted with phenyl isocyanate and the resulting ureas **4d,e** were cyclized at r.t. in THF solution in the presence of *t*-BuOK or LDA. The products **5d** and **5e** obtained in this way were identical with the ones obtained via path A.

Path B also allows for the synthesis of the 4-thioxo derivatives **5f** and **5g**, when isothiocyanates are used instead of isocyanates. The limiting step in this case was the formation of the thioureas **4f,g**. In contrast to the isocyanates, the isothiocyanates did not react with **2** at r.t., although the reaction proceeded smoothly at elevated temperatures (100 - 120 °C), leading directly to the final products **5f,g**. The intermediate thioureas **4f,g** are much more reactive than the corresponding oxo-analogues and cyclize immediately upon formation. For this reason they were not isolated and characterized. The reactions of **2** with isothiocyanates in refluxing solvents, like toluene or xylene, required prolonged heating and the yields of **5** did not exceed 65%. Better results were obtained under solvent-free conditions – thus heating of **2** with two equiv. of methyl or phenyl isothiocyanate for 10 min. at 120 °C afforded the expected products **5f, g** in 87 and 81 % yields respectively.

Table 1. Yields of intermediates (**3**, **4**) and end products **5** obtained according to Scheme 1.

Entry	R ¹	R ²	X	Path	Yield (%) ^a		
					3	4	5
a	C ₆ H ₅	CH ₃	O	A	87	–	93
b	CH ₃	H	O	A	85	–	91
c	CH ₃	CH ₃	O	A	89	–	95
d	CH ₃	C ₆ H ₅	O	A	90	–	93
				B	–	95	94
e	C ₆ H ₅	C ₆ H ₅	O	A	84	–	86
				B	–	93	88
f	CH ₃	CH ₃	S	B	–	–	87
g	CH ₃	C ₆ H ₅	S	B	–	–	81

^aExcept for entries **f** and **g**, yields of **5** are based on the corresponding intermediate **3** or **4**.

Apart from the standard NMR measurements, DEPT and HMQC experiments were used to confirm the structures of **5**. A peculiarity common to all of the final products **5** is the very strongly pronounced

nonequivalency of the diastereotopic protons in the C-6 methylene group – the signals for these protons appear as multiplets separated by average 1.5 ppm apart from each other (Figure 1, **5b**). This could be explained as a combined effect of the conformational constraint of the ring system and the magnetic anisotropy of the nearby C-4 carbonyl group. Thus, the equatorial hydrogen at C-6 is fixed in closer proximity to the carbonyl group and falls within its deshielding zone. The AM1-optimized geometry [17] of **5b** clearly illustrates the different orientations of the hydrogens at C-6 (Figure 2). Because of the larger deshielding zone of the thiocarbonyl group the downfield shift of the equatorial hydrogen is greater in the thioxo compounds **5f,g**. In these two compounds the distance between the two signals for CH_2N reaches 2.5 ppm (Figure 1, **5f**).

Figure 1. Representative ^1H -NMR cuts (2.5 – 6.0 ppm region) showing the methylene signals and the downfield shift of the equatorial hydrogen at C-6.

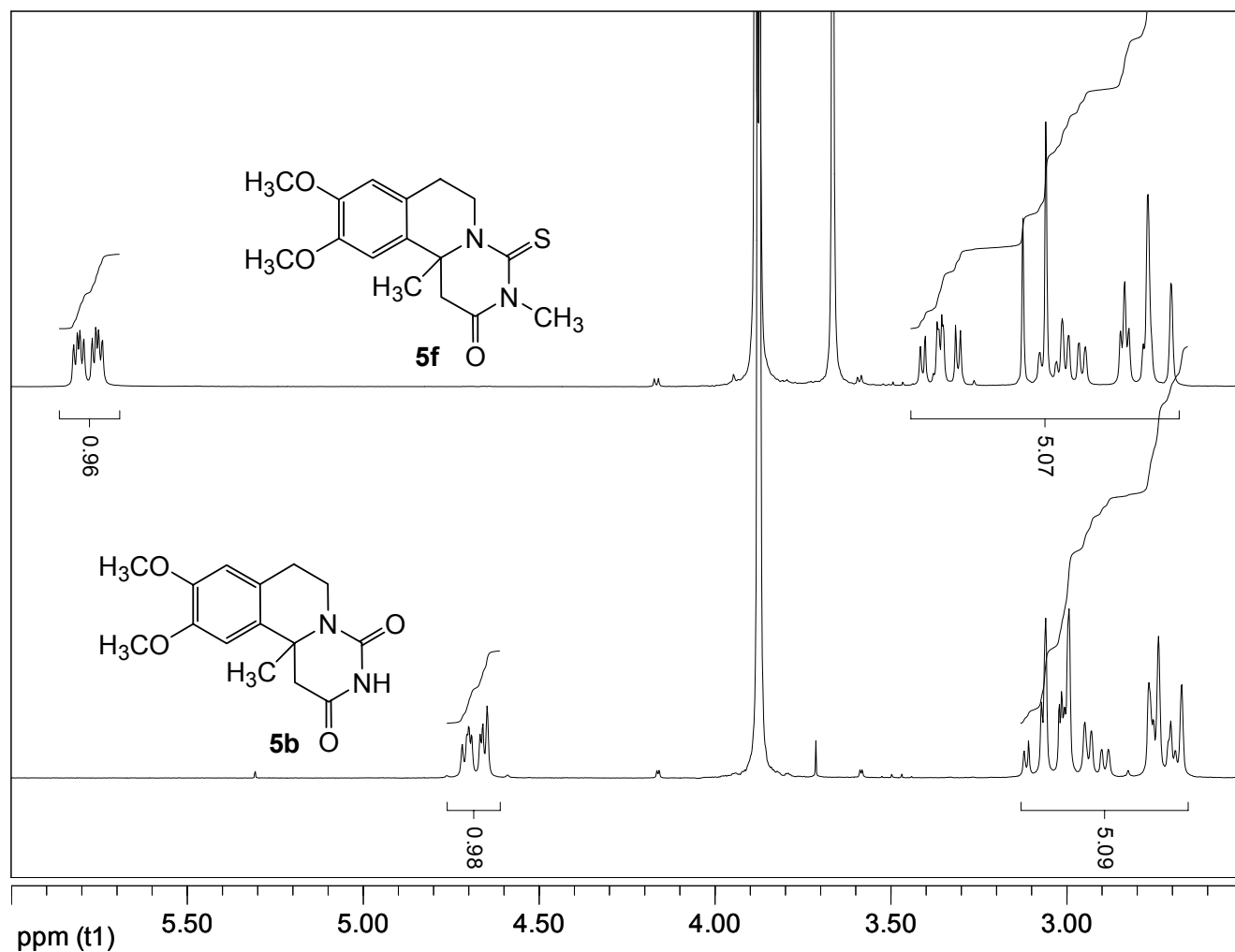
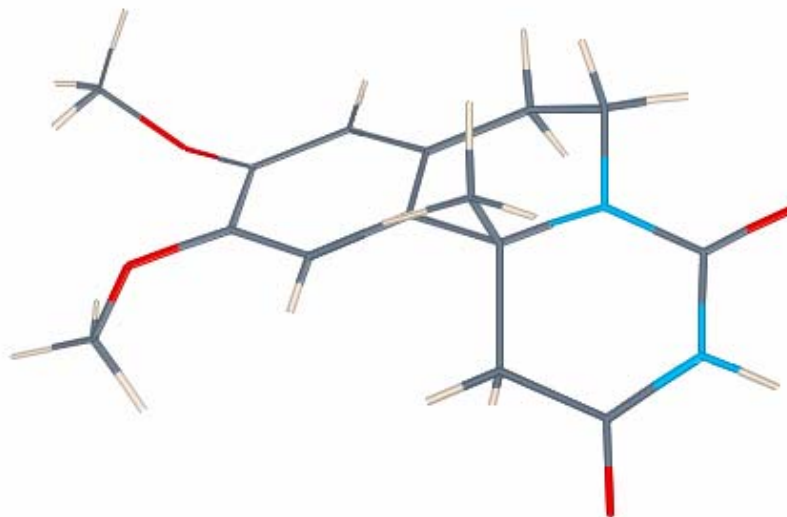


Figure 2. 3D Model of **5b**, showing the different orientations of the hydrogens at C-6. Calculations were performed using the PC GAMESS version [18] of the GAMESS (US) QC package [19].



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Experimental

General

Melting points were determined on a Boëtius hotstage apparatus and are uncorrected. NMR spectra were recorded on a Bruker DRX-250 device using CDCl_3 as solvent. Chemical shifts (δ , ppm) are downfield from TMS as internal standard and coupling constants are in Hz. IR spectra were recorded on a Perkin-Elmer 1750 FTIR device in KBr pellets and absorption is given in cm^{-1} . All new compounds had elemental analyses within 0.4% of the theoretical values as well as correct molecular ion peaks by mass spectrometry.

Synthesis of tetrahydroisoquinolines **1** and **2**

Compounds **1b,d** and **2d-g** are described in reference [16]. Compounds **1a,c,e** are novel and were synthesized as follows: the corresponding β -ketoamide [20] (2 mmol) and Na_2SO_4 (0.6 g) were added to a solution of homoveratrylamine (2 mmol) in CH_2Cl_2 (10 mL). The mixtures were stirred at r.t. for 14 days (entries **a,e**) or 2 days (entry **c**). Then, the sulfate was filtered off and the solvent distilled. To the

enaminones obtained in this way methanesulfonic acid (7 – 8 mL) was added and the mixtures were stirred at r.t. for 4 days (entries **a,e**) or 2 days (entry **c**). After that, water (200 mL) was added, the pH brought to 9-10 with 25% aq. NH_3 and the tetrahydroisoquinolines **1** were extracted with CH_2Cl_2 (3×50 mL). After distillation of the solvent the products crystallize upon trituration with ether (or petroleum ether for **1c**). The mother liquors could be further purified by column chromatography on neutral alumina, using ether as eluent.

2-(6,7-Dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-N-methyl-acetamide (1a): Yield 83 %; mp 107 – 108 °C; IR: ν_{NH} 3481, 3269; $\nu_{\text{C=O}}$ 1651; $^1\text{H-NMR}$: 2.56 (d, $^3J = 4.8$, 3H, CONHCH_3), 2.68 – 3.10 (m, 5H, $\text{CH}_2\text{CH}_2\text{NH}$), 3.15 – 3.34 (AB quartet, $^2J = 15.9$, 2H, CH_2CO), 3.74 (s, 3H, CH_3O), 3.87 (s, 3H, CH_3O), 6.50 (s, 1H, Ar-H), 6.60 (s, 1H, Ar-H), 7.14 – 7.32 (m, 5H, C_6H_5), 8.63 (br, 1H, CONHCH_3); $^{13}\text{C-NMR}$: 25.17, 30.10, 39.87, 48.73, 55.54, 55.77, 60.23, 110.15, 111.22, 120.89, 125.53, 128.34, 129.91, 135.65, 138.30, 146.36, 147.73, 171.35.

2-(6,7-Dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-N-methyl-acetamide (1c): Yield 90 %; mp 68 – 70 °C; IR: ν_{NH} 3416, 3268; $\nu_{\text{C=O}}$ 1657; $^1\text{H-NMR}$: 1.47 (s, 3H, CH_3), 1.78 (br s, 1H, NH), 2.45 (d, $^2J = 15.6$, 1H, $0.5 \times \text{CH}_2\text{CO}$), 2.69 – 3.20 (m, 4H, $\text{CH}_2\text{CH}_2\text{NH}$), 2.72 (d, $^3J = 4.8$, 3H, CONHCH_3), 2.79 (d, $^2J = 15.6$, 1H, $0.5 \times \text{CH}_2\text{CO}$), 3.85 (s, 6H, $2 \times \text{CH}_3\text{O}$), 6.52 (s, 1H, Ar-H), 6.64 (s, 1H, Ar-H), 8.45 (br, 1H, CONHCH_3); $^{13}\text{C-NMR}$: 25.11, 28.54, 30.24, 39.66, 46.47, 55.78, 55.79, 60.19, 109.05, 111.13, 129.07, 134.51, 146.06, 148.12, 172.67.

2-(6,7-Dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-N-phenyl-acetamide (1e): Yield 76 %; mp 202 – 204 °C; IR: ν_{NH} 3317, 3240; $\nu_{\text{C=O}}$ 1684; $^1\text{H-NMR}$: 2.69 – 3.05 (m, 5H, $\text{CH}_2\text{CH}_2\text{NH}$), 3.13 (d, $^2J = 15.8$, 1H, $0.5 \times \text{CH}_2\text{CO}$), 3.36 (d, $^2J = 15.8$, 1H, $0.5 \times \text{CH}_2\text{CO}$), 3.73 (s, 3H, CH_3O), 3.82 (s, 3H, CH_3O), 6.54 (s, 1H, Ar-H), 6.57 (s, 1H, Ar-H), 6.96 – 7.37 (m, 10H, $2 \times \text{C}_6\text{H}_5$), 11.12 (s, 1H, CONHC_6H_5); $^{13}\text{C-NMR}$: 29.12, 38.40, 47.94, 55.58, 55.90, 61.02, 110.11, 111.16, 119.78, 123.34, 126.47, 127.18, 127.31, 128.28, 128.59, 128.69, 138.30, 146.66, 147.39, 147.80, 168.84.

Synthesis of urethanes **3** – general procedure:

The solvents used in these preparations were 1,2-dichloroethane (**3c,d**), toluene (**3a,e**) and acetonitrile (**3b**). Ethyl chlorocarbonate (2 mmol) was added to a stirred solution of the corresponding tetrahydroisoquinoline **1** (1 mmol) and Et_3N (1 mmol) in the specified solvent (15 mL) and the mixture was heated at reflux temperature for 1 h. The solvent was then evaporated *in vacuo*, the solid residue taken with CH_2Cl_2 (100 mL) and washed with 5% aq. hydrochloric acid (150 mL). The organic phase was dried, the solvent distilled off and the residue trituated with Et_2O or petroleum ether to crystallize.

6,7-Dimethoxy-1-methylcarbamoylmethyl-1-phenyl-3,4-dihydro-1H-isoquinoline-2-carboxylic acid ethyl ester (3a): mp 127 – 128 °C; IR: ν_{NH} 3349; $\nu_{\text{C=O}}$ 1701, 1650; $^1\text{H-NMR}$: 1.21 (t, $^3J = 7$, 3H,

CO₂CH₂CH₃), 2.64 (d, ³J = 4.8, 3H, CONHCH₃), 2.84 – 2.89 (m, 2H, CH₂CH₂N), 3.10 (d, ²J = 14.1, 1H, 0.5 × CH₂CO), 3.47 (q, ³J = 7, 2H, CO₂CH₂CH₃), 3.60 (s, 3H, CH₃O), 3.85 (s, 3H, CH₃O), 3.90 – 4.20 (m, 3H, CH₂CH₂N + 0.5 × CH₂CO), 5.18 (br s, 1H, CONHCH₃), 6.26 (s, 1H, Ar-H), 6.58 (s, 1H, Ar-H), 7.12 – 7.31 (m, 5H, C₆H₅).

1-Carbamoylmethyl-6,7-dimethoxy-1-methyl-3,4-dihydro-1H-isoquinoline-2-carboxylic acid ethyl ester (3b): mp 154 – 155 °C; IR: ν_{NH} 3416, 3347, 3227; ν_{C=O} 1685, 1658; ¹H-NMR: 1.31 (t, ³J = 7, 3H, CO₂CH₂CH₃), 1.75 (s, 3H, CH₃), 2.65 – 2.91 (m, 2H, CH₂CH₂N), 2.75 (d, ²J = 13.7, 1H, 0.5 × CH₂CO), 3.44 – 3.51 (m, 1H, 0.5 × CH₂CH₂N), 3.86 (s, 3H, CH₃O), 3.88 (s, 3H, CH₃O), 3.92 (d, ²J = 13.7, 1H, 0.5 × CH₂CO), 3.94 – 4.04 (m, 1H, 0.5 × CH₂CH₂N), 4.18 (q, ³J = 7, 2H, CO₂CH₂CH₃), 5.42 (br s, 1H, 0.5 × CONH₂), 5.69 (br s, 1H, 0.5 × CONH₂), 6.55 (s, 1H, Ar-H), 6.83 (s, 1H, Ar-H).

6,7-Dimethoxy-1-methyl-1-methylcarbamoylmethyl-3,4-dihydro-1H-isoquinoline-2-carboxylic acid ethyl ester (3c): mp 144 – 145 °C; IR: ν_{NH} 3360; ν_{C=O} 1692, 1640; ¹H-NMR: 1.33 (t, ³J = 7, 3H, CO₂CH₂CH₃), 1.71 (s, 3H, CH₃), 2.61 – 2.90 (m, 2H, CH₂CH₂N), 2.68 (d, ³J = 4.8, 3H, CONHCH₃), 2.70 (d, ²J = 13.5, 1H, 0.5 × CH₂CO), 3.41 – 3.50 (m, 1H, 0.5 × CH₂CH₂N), 3.86 (s, 3H, CH₃O), 3.87 (s, 3H, CH₃O), 3.93 (d, ²J = 13.5, 1H, 0.5 × CH₂CO), 3.93 – 4.05 (m, 1H, 0.5 × CH₂CH₂N), 4.16 (q, ³J = 7, 2H, CO₂CH₂CH₃), 5.23 (br s, 1H, CONHCH₃), 6.57 (s, 1H, Ar-H), 6.81 (s, 1H, Ar-H).

6,7-Dimethoxy-1-methyl-1-phenylcarbamoylmethyl-3,4-dihydro-1H-isoquinoline-2-carboxylic acid ethyl ester (3d): mp 169 – 170 °C; IR: ν_{NH} 3300; ν_{C=O} 1689, 1668; ¹H-NMR: 1.35 (t, ³J = 7, 3H, CO₂CH₂CH₃), 1.69 (s, 3H, CH₃), 2.58 – 2.88 (m, 2H, CH₂CH₂N), 2.83 (d, ²J = 14.0, 1H, 0.5 × CH₂CO), 3.38 – 3.49 (m, 1H, 0.5 × CH₂CH₂N), 3.87 (s, 3H, CH₃O), 3.89 (s, 3H, CH₃O), 3.90 – 4.04 (m, 1H, 0.5 × CH₂CH₂N), 4.01 (d, ²J = 14.0, 1H, 0.5 × CH₂CO), 4.20 (q, ³J = 7, 2H, CO₂CH₂CH₃), 6.56 (s, 1H, Ar-H), 6.79 (s, 1H, Ar-H), 7.02 – 7.61 (m, 6H, CONHC₆H₅).

6,7-Dimethoxy-1-phenyl-1-phenylcarbamoylmethyl-3,4-dihydro-1H-isoquinoline-2-carboxylic acid ethyl ester (3e): mp 172 – 173 °C; IR: ν_{NH} 3355; ν_{C=O} 1699, 1658; ¹H-NMR: 1.25 (t, ³J = 7, 3H, CO₂CH₂CH₃), 2.80 – 2.86 (m, 2H, CH₂CH₂N), 3.12 (d, ²J = 14.1, 1H, 0.5 × CH₂CO), 3.53 (q, ³J = 7, 2H, CO₂CH₂CH₃), 3.68 (s, 3H, CH₃O), 3.84 (s, 3H, CH₃O), 3.87 – 4.19 (m, 2H, CH₂CH₂N), 4.03 (d, ²J = 14.1, 1H, 0.5 × CH₂CO), 6.30 (s, 1H, Ar-H), 6.57 (s, 1H, Ar-H), 6.72 (s, 1H, CONHC₆H₅), 6.95 – 7.33 (m, 10H, 2 × C₆H₅).

Synthesis of ureas 4 – general procedure:

Phenyl isocyanate (1.1 mmol) was added to a solution of **2** (1 mmol) in ether (10 - 20 mL) and the mixture was stirred overnight at r.t. The precipitated crystals were filtered off, washed with petroleum ether and dried.

(6,7-Dimethoxy-1-methyl-2-phenylcarbamoyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-acetic acid ethyl ester (**4d**): mp 154 – 155 °C; IR: ν_{NH} 3375; $\nu_{\text{C=O}}$ 1709, 1656; $^1\text{H-NMR}$: 1.05 (t, $^3J = 7.1$, 3H, $\text{CO}_2\text{CH}_2\text{CH}_3$), 1.84 (s, 3H, CH_3), 2.84 – 2.89 (m, 2H, $\text{CH}_2\text{CH}_2\text{N}$), 2.97 (d, $^2J = 16.0$, 1H, $0.5 \times \text{CH}_2\text{CO}$), 3.67 – 3.85 (m, 2H, $\text{CH}_2\text{CH}_2\text{N}$), 3.85 (s, 3H, CH_3O), 3.87 (s, 3H, CH_3O), 3.91 (q, $^3J = 7.1$, 2H, $\text{CO}_2\text{CH}_2\text{CH}_3$), 4.23 (d, $^2J = 16.0$, 1H, $0.5 \times \text{CH}_2\text{CO}$), 6.58 (s, 1H, Ar-H), 6.72 (s, 1H, CONHC_6H_5), 6.77 (s, 1H, Ar-H), 6.98 – 7.31 (m, 5H, C_6H_5).

(6,7-Dimethoxy-1-phenyl-2-phenylcarbamoyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-acetic acid ethyl ester (**4e**): mp 159 – 160 °C; IR: ν_{NH} 3281; $\nu_{\text{C=O}}$ 1732, 1636; $^1\text{H-NMR}$: 1.14 (t, $^3J = 7.1$, 3H, $\text{CO}_2\text{CH}_2\text{CH}_3$), 2.85 – 3.17 (m, 2H, $\text{CH}_2\text{CH}_2\text{N}$), 3.54 (d, $^2J = 13.8$, 1H, $0.5 \times \text{CH}_2\text{CO}$), 3.55 – 3.66 (m, 1H, $0.5 \times \text{CH}_2\text{CH}_2\text{N}$), 3.65 (s, 3H, CH_3O), 3.84 (s, 3H, CH_3O), 3.96 (d, $^2J = 13.8$, 1H, $0.5 \times \text{CH}_2\text{CO}$), 3.99 (q, $^3J = 7.1$, 2H, $\text{CO}_2\text{CH}_2\text{CH}_3$), 4.39 – 4.51 (m, 1H, $0.5 \times \text{CH}_2\text{CH}_2\text{N}$), 6.33 (s, 1H, Ar-H), 6.40 (s, 1H, CONHC_6H_5), 6.59 (s, 1H, Ar-H), 6.92 – 7.54 (m, 10H, $2 \times \text{C}_6\text{H}_5$).

Tetrahydropyrimido[6,1-a]isoquinoline-2,4-diones 5a-e – General Procedure Path A:

A stirred suspension of the corresponding urethane **3** (1 mmol) and powdered sodium amide (1.2 equiv) in THF (10 – 15 mL) was heated at reflux temperature for 1h. The solvent was then evaporated, the solid residue was taken up with small amount of water and extracted with CH_2Cl_2 (75 – 100 mL). The organic phase was washed with water, dried and the solvent distilled off. All products crystallize upon trituration with Et_2O .

Tetrahydropyrimido[6,1-a]isoquinoline-2,4-diones 5d, e – General Procedure Path B:

To a solution of the corresponding urea **4** (1 mmol) in THF (10 – 15 mL) was added LDA (1.2 equiv) and the mixture was stirred for 30 min. at r.t. After that, the solvent was evaporated *in vacuo*, and the solid residue was worked up as described above.

9,10-Dimethoxy-3-methyl-11b-phenyl-1,6,7,11b-tetrahydropyrimido[6,1-a]isoquinoline-2,4-dione (**5a**): mp 205 – 206 °C; IR: $\nu_{\text{C=O}}$ 1707, 1663; $^1\text{H-NMR}$: 2.70 – 3.02 (m, 2H, $\text{CH}_2\text{CH}_2\text{N}$), 3.08 (d, $^2J = 16.4$, 1H, $0.5 \times \text{CH}_2\text{CO}$), 3.17 (s, 3H, NCH_3), 3.59 (d, $^2J = 16.4$, 1H, $0.5 \times \text{CH}_2\text{CO}$), 3.60 – 3.69 (m, 1H, $0.5 \times \text{CH}_2\text{CH}_2\text{N}$), 3.77 (s, 3H, CH_3O), 3.88 (s, 3H, CH_3O), 4.34 – 4.43 (m, 1H, $0.5 \times \text{CH}_2\text{CH}_2\text{N}$), 6.53 (s, 1H, Ar-H), 6.66 (s, 1H, Ar-H), 7.19 – 7.30 (m, 5H, C_6H_5); $^{13}\text{C-NMR}$: 27.67, 28.16, 40.21, 45.49, 55.82, 56.04, 59.62, 108.99, 111.12, 126.04, 126.51, 127.90, 128.69, 130.44, 142.84, 147.94, 148.34, 153.22, 168.15.

9,10-Dimethoxy-11b-methyl-1,6,7,11b-tetrahydropyrimido[6,1-a]isoquinoline-2,4-dione (**5b**): mp 257 – 258 °C; IR: ν_{NH} 3180; $\nu_{\text{C=O}}$ 1722, 1668; $^1\text{H-NMR}$: 1.63 (s, 3H, CH_3), 2.70 (d, $^2J = 16.4$, 1H, $0.5 \times \text{CH}_2\text{CO}$), 2.70 – 3.12 (m, 3H, $\text{CH}_2\text{CH}_2\text{N} + 0.5 \times \text{CH}_2\text{CH}_2\text{N}$), 3.05 (d, $^2J = 16.4$, 1H, $0.5 \times \text{CH}_2\text{CO}$), 3.87

(s, 3H, CH₃O), 3.88 (s, 3H, CH₃O), 4.65 – 4.70 (m, 1H, 0.5 × CH₂CH₂N), 6.58 (s, 1H, Ar-H), 6.62 (s, 1H, Ar-H), 8.84 (s, 1H, NH); ¹³C-NMR: 25.15, 28.80, 36.67, 45.76, 55.82, 55.87, 56.02, 107.75, 111.29, 125.29, 130.81, 148.08, 151.94, 168.58.

9,10-Dimethoxy-3,11b-dimethyl-1,6,7,11b-tetrahydropyrimido[6,1-a]isoquinoline-2,4-dione (5c): mp 185 – 186 °C; IR: ν_{C=O} 1707, 1657; ¹H-NMR: 1.57 (s, 3H, CH₃), 2.71 (d, ²J = 16.2, 1H, 0.5 × CH₂CO), 2.71 – 3.13 (m, 3H, CH₂CH₂N + 0.5 × CH₂CH₂N), 3.07 (d, ²J = 16.2, 1H, 0.5 × CH₂CO), 3.27 (s, 3H, NCH₃), 3.87 (s, 3H, CH₃O), 3.88 (s, 3H, CH₃O), 4.65 – 4.72 (m, 1H, 0.5 × CH₂CH₂N), 6.58 (s, 1H, Ar-H), 6.63 (s, 1H, Ar-H); ¹³C-NMR: 24.88, 27.68, 28.85, 37.44, 46.13, 54.38, 55.77, 55.96, 107.60, 111.21, 125.33, 130.99, 148.00, 152.76, 168.24.

9,10-Dimethoxy-11b-methyl-3-phenyl-1,6,7,11b-tetrahydropyrimido[6,1-a]isoquinoline-2,4-dione (5d): mp 263 – 264 °C; IR: ν_{C=O} 1718, 1666; ¹H-NMR: 1.75 (s, 3H, CH₃), 2.73 – 3.19 (m, 3H, CH₂CH₂N + 0.5 × CH₂CH₂N), 2.92 (d, ²J = 16.2, 1H, 0.5 × CH₂CO), 3.23 (d, ²J = 16.2, 1H, 0.5 × CH₂CO), 3.87 (s, 3H, CH₃O), 3.89 (s, 3H, CH₃O), 4.65 – 4.72 (m, 1H, 0.5 × CH₂CH₂N), 6.62 (s, 1H, Ar-H), 6.65 (s, 1H, Ar-H), 7.19 – 7.48 (m, 5H, C₆H₅); ¹³C-NMR: 25.53, 27.82, 36.38, 45.89, 55.41, 55.68, 56.73, 107.98, 111.09, 125.94, 127.13, 128.52, 131.07, 140.34, 145.34, 148.11, 153.05, 168.12.

9,10-Dimethoxy-3,11b-diphenyl-1,6,7,11b-tetrahydropyrimido[6,1-a]isoquinoline-2,4-dione (5e): mp 277 – 278 °C; IR: ν_{C=O} 1713, 1673; ¹H-NMR: 2.78 – 3.10 (m, 2H, CH₂CH₂N), 3.27 (d, ²J = 16.4, 1H, 0.5 × CH₂CO), 3.69 – 3.78 (m, 1H, 0.5 × CH₂CH₂N), 3.75 (d, ²J = 16.4, 1H, 0.5 × CH₂CO), 3.78 (s, 3H, CH₃O), 3.89 (s, 3H, CH₃O), 4.38 – 4.50 (m, 1H, 0.5 × CH₂CH₂N), 6.58 (s, 1H, Ar-H), 6.69 (s, 1H, Ar-H), 6.96 – 7.39 (m, 10H, 2 × C₆H₅); ¹³C-NMR: 27.70, 41.02, 45.78, 56.12, 57.05, 58.97, 110.06, 111.31, 120.54, 123.13, 125.07, 127.30, 127.76, 128.45, 128.62, 128.69, 138.39, 147.06, 147.41, 148.09, 154.03, 168.36.

4-Thioxo-1,3,4,6,7,11b-hexahydropyrimido[6,1-a]isoquinolin-2-ones 5f,g – General Procedure:

A mixture of the corresponding tetrahydroisoquinoline **2** (1 mmol) and methyl or phenyl isothiocyanate (2 mmol) was heated in an open reaction vessel at 120 °C for 10 min. The mixture was then allowed to cool to r.t. and the obtained crystalline product was washed with ether.

9,10-Dimethoxy-3,11b-dimethyl-4-thioxo-1,3,4,6,7,11b-hexahydropyrimido[6,1-a]isoquinolin-2-one (5f): mp 188 – 190 °C; IR: ν_{C=O} 1702; ¹H-NMR: 1.61 (s, 3H, CH₃), 2.73 (d, ²J = 16.5, 1H, 0.5 × CH₂CO), 2.78 – 3.42 (m, 3H, CH₂CH₂N + 0.5 × CH₂CH₂N), 3.09 (d, ²J = 16.5, 1H, 0.5 × CH₂CO), 3.67 (s, 3H, NCH₃), 3.87 (s, 3H, CH₃O), 3.89 (s, 3H, CH₃O), 5.74 – 5.82 (m, 1H, 0.5 × CH₂CH₂N), 6.57 (s, 1H, Ar-H), 6.66 (s, 1H, Ar-H); ¹³C-NMR: 23.89, 28.75, 34.69, 45.90, 46.08, 55.87, 56.07, 58.20, 107.54, 111.06, 125.62, 130.68, 148.21, 165.71, 180.43.

9,10-Dimethoxy-11b-methyl-3-phenyl-4-thioxo-1,3,4,6,7,11b-hexahydropyrimido[6,1-a]isoquinolin-2-one (**5g**): mp 280 °C (dec.); IR: $\nu_{C=O}$ 1703; $^1\text{H-NMR}$: 1.81 (s, 3H, CH_3), 2.79 – 3.50 (m, 3H, $\text{CH}_2\text{CH}_2\text{N} + 0.5 \times \text{CH}_2\text{CH}_2\text{N}$), 2.97 (d, $^2J = 16.3$, 1H, $0.5 \times \text{CH}_2\text{CO}$), 3.23 (d, $^2J = 16.3$, 1H, $0.5 \times \text{CH}_2\text{CO}$), 3.87 (s, 3H, CH_3O), 3.89 (s, 3H, CH_3O), 5.73 – 5.81 (m, 1H, $0.5 \times \text{CH}_2\text{CH}_2\text{N}$), 6.61 (s, 1H, Ar-H), 6.68 (s, 1H, Ar-H), 7.19 – 7.51 (m, 5H, C_6H_5); $^{13}\text{C-NMR}$: 26.17, 27.62, 46.03, 46.29, 55.57, 55.73, 57.95, 108.07, 111.18, 126.13, 127.87, 128.02, 131.35, 140.97, 145.52, 148.01, 166.02, 180.32.

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