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AN EFFICIENT METHOD FOR THE PREPARATION OF NEW ANALOGS OF LEUCETTAMINE B UNDER SOLVENT-FREE MICROWAVE IRRADIATION

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Abstract – A simple and efficient microwave-assisted protocol has been developed for the synthesis of new 2-amino-3,4-dihydro-4*H*-imidazol-4-one derivatives of leucettamine B. This solvent-free protocol involves sulphur/nitrogen displacement of 2-ethylthio-5-arylidene-imidazolone **5** with a variety of functionalized polar primary amines **6** and this general method afforded a small library of the desired pure products **7a-n** in yields ranging from 33 to 92% in moderate reaction times (30-100 minutes).

INTRODUCTION

The 2-aminoimidazolone ring is a widely used structural motif in drug discovery. In particular, the 2-aminoimidazolone ring of type **1** (Figure 1) constitutes an interesting pharmacophore that displays a wide variety of pharmacological activities.[1] During these last few years, an increasingly important number of natural products comprising the 2-aminoimidazolone moiety have been isolated from marine sponges.[2] Hymenialdisine is one of the most known alkaloids taking into account its biological activity as potent inhibitor of cyclin-dependent kinases, glycogen synthase kinase-3β and casein kinase 1.[3] Among this class of compounds, the leucettamine B, isolated from the sponge *Leucetta microraphis* Haeckel (alcarea class) of the Argulpelu Reef in Palau,[4] has received little attention although the synthesis of this natural product was reported.[5]

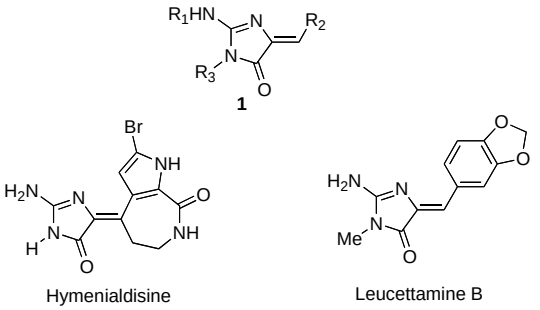


Figure 1. Structure of some marine alkaloids containing a ring of type 1

In the context of our program to prepare libraries of small heterocyclic rings with a potential therapeutic interest,[6] we focused our attention on the 2-aminoimidazolone nucleus of leucettamine B. The few syntheses of analogs, reported in the literature, used the Knoevenagel reaction for the stereoselective exocyclic double bond formation, but suffer some limitations concerning the degree of molecular diversity of the final step. Two methods of activation of C=S bond have been used for the condensation of amines on the arylidene thiohydantoin. The TBHP promoted transamination reaction gives good yields with long reaction time (> 24h) but does not seem adapted for combinatorial and/or parallel synthesis due to the use of a large excess of amines (>16 equiv.) which complicates the purification of the final products (chromatography).[5b] Activation *via* thioether constitutes also a route to 2-aminoimidazolones of type **1,** however displacement with amines in a conventional thermal process requires harsh reaction conditions and gives good results only with non-sterically hindered primary amines.[7,8]

In the light of these observations and due to the potential biological interest of this class of compounds, we wished to develop an efficient methodology for the generation of a collection of compounds containing a ring of type **1** and, more particularly of analogs of leucettamine B with a high degree of molecular diversity. Recently, we have described a practical protocol for the preparation of a parallel solution-phase library of 2-alkylthio-5-arylidene imidazolone by one-pot three-component domino reaction.[6b] This flexible strategy could be useful for the synthesis of analogs of leucettamine B, if we are able to develop an efficient method for the sulfur/nitrogen displacement with a large wide range of amines. The utility of microwave irradiation[9] (μw) to carry out an organic reaction has now become a regular feature. A key advantage of modern scientific microwave apparatus is the ability to control reaction conditions very specifically, monitoring temperature-pressure and the reaction times. The use of this technology for the rapid synthesis of molecules is a useful tool for the medicinal chemistry community, for whom reaction speed is of great importance.[10]

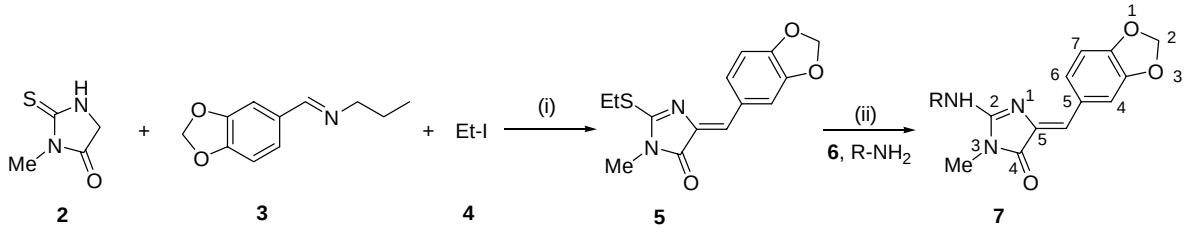
To the best of our knowledge, the benefits of performing the substitution reaction of 2-alkylthio imidazolone with amines under solvent-free microwave irradiation has not been demonstrated to date. So,

we report in this paper our results concerning this new methodology to generate a small library of leucettamine B analogs.

RESULTS AND DISCUSSION

2-Ethylthio 3,5-dihydro-4*H*-imidazol-4-one **5** was prepared in 62% yield by one-pot three-component domino reaction (Scheme 1), using the following partners: aromatic aldimine **3**, iodoethane **4** and 2-thioxo-imidazolidin-4-one **2** which is easily available by reaction between methyl glycinate and commercial methyl isothiocyanate.[6b] With compound **5** in hand, we envisioned the scope and generality of the microwave-assisted sulphur/nitrogen displacement with various selected amines according to the previous biological activities observed on this scaffold.[11]

For microwave irradiation, domestic microwave ovens are frequently used in organic synthesis, due to their low cost and immediate availability. However, mono-mode microwave reactors, specifically designed for chemical synthesis, provide homogeneous heating, temperature control and importantly, improved safety features.[12] The microwave instrument (Synthewave® 402 reactor) comprises a mono-mode cavity that operates at a frequency of 2.45 GHz with a continuous microwave irradiation power from 0 to 300 watts. Inside the cavity, the quartz reactor was exposed to microwave irradiation, and the reaction temperature is measured with the aid of an IR captor[13] (infrared thermometry). The software algorithm regulates the microwave out-put power so that the preselected maximum temperature is maintained for the desired reaction/irradiation time.



Scheme 1. *Reagents and reaction conditions:* (i) **2** 1 equiv., **3** 1 equiv., **4** 1.5 equiv., K_2CO_3 0.5 equiv., MeCN, 60°C, 14 h, 62%. (ii) **6** 1-5 equiv., μω (Synthewave® 402 reactor), 100-155°C, 20-100 min.

For optimization of reaction conditions under microwave dielectric heating, the polar primary amines employed were successively aniline **6a** and different substituted aliphatic amines such as *N*-(3-aminopropyl)imidazole **6h** and 3-aminopropanol **6m**. The other parameters of this reaction were respectively the reaction temperature (from 100 to 155°C), the power for microwave irradiation (from 150 to 300 Watt), the reaction concentration (ratio **5**/**6** from 1 to 4) and the reaction time (from 15 to 60 min.). In order to simplify and generalize the process, the reaction mixtures are precipitated in ethanol (or chloroform) and filtered off to eliminate starting materials and impurities.

The values for optimization of reaction conditions were presented in Table 1. At high temperature, compound **7a** was obtained in moderate yield (58%) using 4 equivalents of **6a** with a microwave power of 240 watts during 40 minutes (entry 3). *When the sulphur/nitrogen displacement was realized in a preheated oil bath at 155°C using exactly the same conditions (40 min., 4 equiv. of **6a**) and in the same open reactor, a yield of 10% of isolated pure product **7a** was obtained*. Comparing the conventional and the solvent-free heating, it seems reasonable to propose that the significantly higher yield may be explained by the rapid heating under microwave irradiation (microwave-flash heating). The desired reaction temperature of 155°C is rapidly reached within 3 minutes by direct microwave heating (in core), in contrast to conventional thermal heating utilizing an oil bath, preheated to 155°C. Taking advantage of the broad range of temperature offered by controlled quartz vessel microwave heating, we found that the irradiation of 2-ethylthio imidazolone **5** (mp = 150-152°C), with 2 equivalents of liquid *N*-(3-aminopropyl)imidazole **6h** at 120°C (240 W) for 60 minutes, allowed full conversion to the product **7h** which was isolated in 72% yield after crystallization in chloroform (entry 6). With 3-aminopropanol **6m**, the product **7m** was conveniently prepared in good yield (81%) by shortening the microwave irradiation time (40 min.) with a lower reaction temperature (100°C, 150 W) but using 3 equivalents of amine (entry 10).

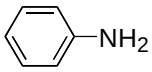
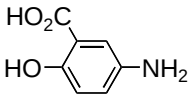
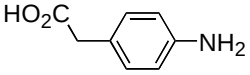
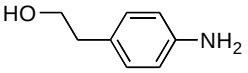
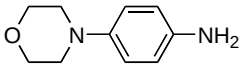
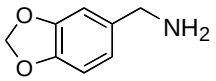
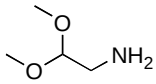
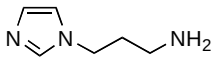
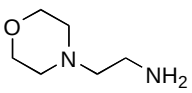
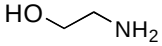
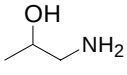
Table 1: Selected optimization of reaction conditions under solvent-less microwave irradiations.

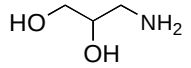
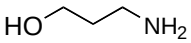
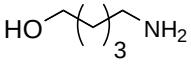
entry	product **7**	reaction conditions					Yield of **7** (%)[a]
		starting reagent **6**	number of equiv.	reaction time (min.)	reaction temperature (°C)	power (Watt)	
1	**7a**	**6a**	2	30	155	300	30
2	**7a**	**6a**	4	30	155	240	54
3	**7a**	**6a**	4	40	155	240	58
4	**7h**	**6h**	2	30	120	240	40
5	**7h**	**6h**	2	50	120	240	67
6	**7h**	**6h**	2	60	120	240	72
7	**7m**	**6m**	1.5	15	100	150	16
8	**7m**	**6m**	3	15	100	150	45
9	**7m**	**6m**	3	30	100	150	77
10	**7m**	**6m**	3	40	100	150	81

[a] Isolated yield after recrystallisation.

Having demonstrated the interest of microwave irradiation for the sulphur/nitrogen displacement using certain primary amines **6**, we sought to increase the structural diversity on the 3,4-dihydro-4*H*-imidazole-4-one core in order to obtain a more-diverse compounds library. For the generality and the scope of this MAOS (microwave-assisted organic synthesis) protocol, we have investigated the use of various aromatic primary amines differently substituted. Diversified aromatic or aliphatic primary amines, containing a carboxylic group (**6b**,**c**) or a hydroxyl function (**6d**, **6k**, **6l**, **6n**), have been selected to widen the spectrum of biological activities of the 2-aminoimidazolone core. Sterically hindered amine comprising a morpholine moiety (**6i**) has been also used in this method.

Table 2: Synthesis of leucettamine B derivatives **7a-n** with various primary amines **6** using solvent-free microwave irradiation reaction conditions.

product	starting reagent		reaction conditions		yield of
7	**6**	structure of reagent **6**	number of equiv.	reaction time (min.)	reaction temperature (°C)	**7** (%)[a]
7a	**6a**		4	40	155	58
7b	**6b**		0.9	90	160	68
7c	**6c**		0.9	90	160	74
7d	**6d**		2	45	160	69
7e	**6e**		1	35	135	75
7f	**6f**		2	60	140	72
7g	**6g**		4.5	100	135	80
7h	**6h**		2	60	120	72
7i	**6i**		3	30	150	92
7j	**6j**		4	50	120	33
7k	**6k**		5	40	100	64

7l	**6l**		3	40	155	42
7m	**6m**		3	40	100	81
7n	**6n**		5	40	100	66

[a] Isolated yield after recrystallization.

Table 2 summarizes the 2-amino imidazolones synthesized as analogs of leucettamine B *via* this solventless sulphur/nitrogen displacement under microwave irradiation by utilizing the Synthewave® 402 reactor. The synthesis results of this small library showed that all 14 reactions were successful, and cleanly generated the 2-amino-3,4-dihydro-4*H*-imidazole-4-ones **7a-n** as confirmed by HRMS. In the majority of cases, very high conversion and good purity of the desired products was observed. Moderate yields were obtained (**7j**: 33%, **7l**: 42%) when 2-amino ethanol **6j** (4 equiv.) and 2,3-dihydroxy propylamine **6l** (3 equiv.) were used indicating that the proportion of final product **7** between the excess of amine **6** and the solvent for crystallization, is an important factor to maintain a good yield. The structural assignment of the 2-aminoimidazolones **7a-n** is based on spectroscopic data (^{1}H, ^{13}C NMR). In all cases, compounds **7** were obtained in a stereospecific way by sulphur/nitrogen displacement under microwave with retention of stereochemistry and the geometry of the exocyclic double bond was attributed as being *Z* by the shielding effect of the carbonyl C-4 on the olefinic proton H-5 (**7a-n:** $\delta_{H\text{-}5}$ = 6.10-6.65 ppm).[14]

In summary, we have demonstrated that sulphur/nitrogen displacement is possible on a 2-ethylthio imidazolone core with polar primary amines using a solvent-free microwave irradiation protocol. To our knowledge, this new approach has never been reported and may be complementary to the methods described in the literature.[5b,7] Our protocol allows a stereocontrolled synthesis of leucettamine B derivatives with a large structural diversity (fourteen new products) and in establishing fast and inexpensive purification methodologies. The target compounds were obtained in good yields coupled to a high purity. The biological activities of this 2-aminoimidazolones library are currently under investigation.

EXPERIMENTAL

General. Melting points were determined on a Kofler melting point apparatus and were uncorrected. Thin-layer chromatography (TLC) was accomplished on 0.2-mm precoated plates of silica gel 60 F-254 (Merck) and visualization was made with ultraviolet light (254 and 312 nm) or with a fluorescence indicator. ^{1}H NMR spectra were recorded on BRUKER AC 300 P (300 MHz) and BRUKER ARX 200 (200 MHz) spectrometers, ^{13}C NMR spectra on BRUKER AC 300 P (75 MHz) spectrometer. Chemical

shifts are expressed in parts per million downfield from tetramethylsilane as an internal standard. Data are given in the following order: δ value, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad), number of protons, coupling constants *J* is given in Hertz. The mass spectra (HRMS) were taken on a VARIAN MAT 311 at an ionizing potential of 70 eV in the Centre Régional de Mesures Physiques de l'Ouest (CRMPO, Rennes). Reactions under microwave irradiations were realized in the Synthewave® 402 apparatus (Merck Eurolab, Div. Prolabo, France). The microwave instrument consists of a continuous focused microwave power output from 0 to 300W. All experiments were performed using stirring option. The target temperature was reached with a ramp of 3 minutes and the chosen microwave power remained constant to keep the mixture at this temperature. The reaction temperature is monitored using calibrated infrared sensor and the reaction time include the ramp period. Acetonitrile was distilled over calcium chloride after standing overnight and stored over molecular sieves (3Å). Solvents were evaporated with a BUCHI rotary evaporator. All reagents were purchased from Acros, Aldrich Chimie, Fluka France and used without further purification. The starting products **2**, **3** and **5** were synthesized according to our previous method.[6b]

General procedure for the synthesis of Leucettamine B derivatives 7a-n from (*5Z*)-5-(1,3-benzodioxol-5-yl)methylene-3-methyl-2-ethylthio-3,4-dihydro-4*H*-imidazole-4-one 5 and primary amines 6 using microwave irradiations under solventless reaction conditions. A mixture of (*5Z*)-5-(1,3-benzodioxol-5-yl)methylene-3-methyl-2-ethylthio-3,4-dihydro-4*H*-imidazole-4-one **5** (0.3 g, 1.03 mmole) and primary amine **6** (from 0.927 to 5.15 mmoles, from 0.9 to 5 equiv.) was placed in a cylindrical quartz reactor (Ø = 1.8 cm). The reactor was then introduced into a Synthewave® 402 Prolabo microwave reactor (P = 300 Watt). The stirred mixture was irradiated at the appropriate reaction temperature (see table 2 with a power level ranging from 50 to 100%) for appropriate reaction time (20-100 minutes, table 2). After microwave dielectric heating, the crude reaction mixture was allowed to cool down at room temperature and ethanol or, diethyl ether or chloroform (10 mol) was added directly in the cylindrical quartz reactor. The resulting precipitated product **7** was filtered off and was purified by recrystallization from ethanol, diethyl ether or chloroform. After drying under under high *vacuum* (10^{-2} Torr) at 30 °C for 1h, the pure (*5Z*)-2-amino-5-(1,3-benzodioxol-5-yl)methylene-3-methyl-3,4-dihydro-4*H*-imidazole-4-one **7** was characterized by ^{1}H, ^{13}C NMR, HRMS.

(*5Z*)-5-[(1,3-Benzodioxol-5-yl)methylene]-3-methyl-2-phenylamino-3,5-dihydro-4*H*-imidazol-4-one (7a): Reaction temperature: 155 °C, reaction time: 40 min. Yield = 58%. Yellow powder, mp 226-228 °C (from Et_2O). ^{1}H NMR (300 MHz, DMSO d_6) δ = 3.22 (s, 3H, C*H*$_3$-N); 6.06 (s, 2H, OC*H*$_2$O); 6.60 (s, 1H, C*H*=); 6.95 (d, 1H, *J* = 8.1 Hz, H-7, Ar); 7.10 (dd, 1H, *J* = 7.2 Hz, *J* = 7.2 Hz, H-4', Ar); 7.37-7.45 (m, 3H,

H-3', H-5', H-6, Ar); 7.91 (d, 2H, *J* = 6.8 Hz, H-2', H6', Ar); 8.00 (s, 1H, H-4, Ar); 9.40 (br s, 1H, N*H*). ^{13}C NMR (75 MHz, DMSO d_6) δ = 26.1, 101.2, 108.4, 109.3, 115.9, 120.3, 123.2, 125.9, 128.6, 129.7, 137,8, 138.7, 147.3, 147.4, 154.9, 168.7. HRMS, *m/z* = 321.1115 found (calculated for $C_{18}H_{15}N_3O_3$, $M^{+\bullet}$ requires 321.1113). Anal. Calcd for $C_{18}H_{15}N_3O_3$: C, 67.28; H, 4.71; N, 13.08. Found: C, 67.32; H, 4.75; N, 13.02.

(5*Z*)-5-[(1,3-Benzodioxol-5-yl)methylene]-3-methyl-2-(3-carboxy-4-hydroxyphenyl)amino-3,5-dihydro-4*H*-imidazol-4-one (7b): Reaction temperature: 160 °C, reaction time: 90 min. Yield = 68%. Yellow powder, mp > 260 °C (from $CHCl_3$). ^{1}H NMR (300 MHz, DMSO d_6) δ = 3.22 (s, 3H, C*H*$_3$-N); 6.06 (s, 2H, OC*H*$_2$O); 6.59 (s, 1H, C*H*=); 6.93-7.00 (m, 2H, H-7, H-5', Ar); 7.70-7.74 (m, 2H, H-4, H-6, Ar); 7.85 (d, 1H, *J* = 7.9 Hz, H-6', Ar); 8.76 (s, 1H, H-2', Ar); 9.40 (br s, 1H, N*H*); 11.50 (br s, 2H, CO_2H, O*H*). ^{13}C NMR (75 MHz, DMSO d_6) δ = 26.0, 101.1, 108.4, 109.9, 112.4, 115.6, 117.1, 121.3, 125.5, 128.0, 129.6, 130.5, 137.6, 147.2, 147.3, 154.7, 157.1, 168.6, 171.9. HRMS, *m/z* = 382.1036 found (calculated for $C_{19}H_{15}N_3O_6$, $M^{+\bullet}$ requires 382.1039). Anal. Calcd for $C_{19}H_{15}N_3O_6$: C, 59.84; H, 3.96; N, 11.02. Found: C, 59.86; H. 3.93; N, 11.07.

(5*Z*)-5-[(1,3-Benzodioxol-5-yl)methylene]-3-methyl-2-(4-carboxymethylphenyl)amino-3,5-dihydro-4*H*-imidazol-4-one (7c): Reaction temperature: 160 °C, reaction time: 90 min. Yield = 74%. Yellowish powder, mp 262-264 °C (from $CHCl_3$). ^{1}H NMR (300 MHz, DMSO d_6) δ = 3.21 (s, 3H, C*H*$_3$-N); 3.57 (s, 2H, C*H*$_2$$CO_2H$); 6.06 (s, 2H, OC*H*$_2$O); 6.58 (s, 1H, C*H*=); 6.96 (m, 1H, H-7, Ar); 7.30 (m, 2H, H-3', H-5', Ar); 7.41 (m, 1H, H-6, Ar); 7.87 (m, 2H, H-2', H-6', Ar); 7.99 (s, 1H, H-4, Ar); 9.38 (br s, 1H, N*H*); 12.20 (br s, 1H, CO_2H). ^{13}C NMR (75 MHz, DMSO d_6) δ = 26.1, 40.2, 101.2, 108.4, 109.3, 115.9, 120.0, 125.8, 129.5, 129.7, 129.8, 137.3, 137.8, 147.3, 147.4, 154.9, 168.7, 172.80. HRMS, *m/z* = 379.1156 found (calculated for $C_{20}H_{17}N_3O_5$, $M^{+\bullet}$ requires 379.1168). Anal. Calcd for $C_{20}H_{17}N_3O_5$: C, 63.32; H, 4.52; N, 11.08. Found: C, 63.37; H, 4.55; N, 11.06.

(5*Z*)-5-[(1,3-Benzodioxol-5-yl)methylene]-3-methyl-2-[4-(2-hydroxyethyl)phenyl]amino-3,5-dihydro-4*H*-imidazol-4-one (7d): Reaction temperature: 160 °C, reaction time: 45 min. Yield = 69%. Yellow powder, mp 210-212 °C (from EtOH). ^{1}H NMR (300 MHz, DMSO d_6) δ = 2.73 (t, 2H, *J* = 6.0 Hz, ArC*H*$_2$$CH_2OH$); 3.21 (s, 3H, C*H*$_3$-N); 3.63 (m, 2H, $ArCH_2$C*H*$_2$OH); 4.66 (br s, 1H, O*H*); 6.06 (s, 2H, OC*H*$_2$O); 6.57 (s, 1H, C*H*=); 6.95 (d, 1H, *J* = 8.0 Hz, H-7, Ar); 7.24 (d, 2H, *J* = 7.6 Hz, H-3', H-5', Ar); 7.43 (d, 1H, *J* = 8.0 Hz, H-6, Ar); 7.82 (d, 2H, *J* = 7.6 Hz, H-2', H-6', Ar); 7.98 (s, 1H, H-4, Ar); 9.32 (br s, 1H, N*H*). ^{13}C NMR (75 MHz, DMSO d_6) δ = 26.6, 38.9, 62.6, 101.7, 108.9, 109.8, 116.2, 120.5, 126.3, 129.5, 130.3, 135.0, 137.1, 138.4, 147.8, 147.9, 155.4, 169.2. HRMS, *m/z* = 365.1364 found (calculated for $C_{20}H_{19}N_3O_4$, $M^{+\bullet}$ requires 365.1376). Anal. Calcd for $C_{20}H_{19}N_3O_4$: C, 65.74; H, 5.24; N, 11.50. Found: C,

65.76; H, 5.22; N, 11.51.

(5*Z*)-5-[(1,3-Benzodioxol-5-yl)methylene]-3-methyl-2-[4-(*N*-morpholinyl)phenyl]amino-3,5-dihydro-4*H*-imidazol-4-one (7e): Reaction temperature: 135 °C, reaction time: 35 min. Yield = 75%. Yellow powder, mp > 260 °C (from EtOH). ^{1}H NMR (300 MHz, DMSO d_6). δ =3.10 (m, 4H, N(C*H*$_2$CH$_2$)$_2$O); 3.20 (s, 3H, C*H*$_3$-N); 3.75 (s, 4H, N(CH$_2$C*H*$_2$)$_2$O); 6.05 (s, 2H, OC*H*$_2$O); 6.52 (s, 1H, C*H*=); 6.94 (d, 1H, *J* = 8.0 Hz, H-7, Ar); 6.97 (d, 2H, *J* = 8.6 Hz, H-3', H-5', Ar); 7.44 (d, 1H, *J* = 8.0 Hz, H-6, Ar); 7.76 (d, 2H, *J* = 8.6 Hz, H-2', H-6', Ar); 7.94 (s, 1H, H-4, Ar); 9.22 (br s, 1H, N*H*). ^{13}C NMR (75 MHz, DMSO d_6) δ = 26.5, 49.2, 66.6, 101.6, 108.9, 109.8, 115.4, 115.7, 121.9, 126.1, 130.4, 131.1, 138.6, 147.6, 147.7, 147.8, 155.4, 169.3. HRMS, *m/z* = 406.1662 found (calculated for $C_{22}H_{22}N_4O_4$, $M^{+\bullet}$ requires 406.1641). Anal. Calcd for $C_{22}H_{22}N_4O_4$: C, 65.01; H, 5.46; N, 13.78. Found: C, 65.03; H, 5.50; N, 13.74.

(5*Z*)-2-[(1,3-Benzodioxol-5-yl)methylamino]-5-[(1,3-benzodioxol-5-yl)methylene]-3-methyl-3,5-dihydro-4*H*-imidazol-4-one (7f): Reaction temperature: 140 °C, reaction time: 60 min. Yield = 72%. Yellow powder, mp 202-204 °C (from EtOH). ^{1}H NMR (300 MHz, DMSO d_6) δ = 3.07 (s, 3H, C*H*$_3$-N); 4.53 (d, 2H, *J* = 5.0 Hz, C*H*$_2$NH); 5.98 (s, 2H, OC*H*$_2$O); 6.02 (s, 2H, OC*H*$_2$O); 6.40 (s, 1H, C*H*=); 6.86-6.92 (m, 3H, H-7, H-6', H-7', Ar); 7.02 (s, 1H, H-4', Ar); 7.42 (d, 1H, *J* = 7.4 Hz, H-6, Ar); 7.97 (s, 1H, H-4, Ar); 8.17 (t, 1H, *J* = 5.0 Hz, N*H*). ^{13}C NMR (75 MHz, DMSO d_6) δ = 25.5, 44.3, 100.8, 101.0, 107.9, 108.2, 108.3, 109.4, 113.1, 121.0, 125.2, 130.3, 132.8, 138.7, 146.3, 146.7, 147.2, 158.0, 169.5. HRMS, *m/z* = 379.1156 found (calculated for $C_{20}H_{17}N_3O_5$, $M^{+\bullet}$ requires 379.1169). Anal. Calcd for $C_{20}H_{17}N_3O_5$: C, 63.32; H, 4.52; N, 11.08. Found: C, 63.35; H, 4.57; N, 11.07.

(5*Z*)-5-[(1,3-Benzodioxol-5-yl)methylene]-3-methyl-2-[(2,2-dimethoxy)ethylamino]-3,5-dihydro-4*H*-imidazol-4-one (7g): Reaction temperature: 135 °C, reaction time: 100 min. Yield = 80%. Yellow powder, mp 184-186 °C (from EtOH). ^{1}H NMR (300 MHz, DMSO d_6) δ = 3.05 (s, 3H, C*H*$_3$-N); 3.40 (s, 6H, 2(OC*H*$_3$)); 3.50 (dd, 2H, *J* = 4.5, 5.1 Hz, C*H*$_2$NH); 4.68 (t, 1H, *J* = 5.1 Hz, C*H*(OMe)$_2$); 6.02 (s, 2H, OC*H*$_2$O); 6.40 (s, 1H, C*H*=); 6.89 (d, 1H, *J* = 8.1 Hz, H-7, Ar); 7.37 (d, 1H, *J* = 8.1 Hz, H-6, Ar); 7.84 (t, 1H, *J* = 4.5 Hz, N*H*); 8.01 (s, 1H, H-4, Ar). ^{13}C NMR (75 MHz, DMSO d_6) δ = 25.2, 43.2, 54.8, 101.1, 102.4, 108.3, 110.3, 117.4, 126.2, 130.1, 137.8, 147.7, 148.3, 157.2, 170.2. HRMS, *m/z* = 333.1339 found (calculated for $C_{16}H_{19}N_3O_5$, $M^{+\bullet}$ requires 333.1325). Anal. Calcd for $C_{16}H_{19}N_3O_5$: C, 57.65; H, 5.75; N, 12.61. Found: C, 57.71; H, 5.79; N, 12.58.

(5*Z*)-5-[(1,3-Benzodioxol-5-yl)methylene]-2-[(imidazol-1-yl)propylamino]-3-methyl-3,5-dihydro-4*H*-imidazol-4-one (7h): Reaction temperature: 120 °C, reaction time: 60 min. Yield = 72%. Yellow

powder, mp 202-204 °C (from $CHCl_3$). ^{1}H NMR (300 MHz, DMSO d_6) δ = 2.10 (m, 2H, $CH_2CH_2CH_2$); 3.04 (s, 3H, CH_3-N); 3.42 (m, 2H, CH_2NH); 4.08 (t, 2H, J = 6.7 Hz, CH_2N); 6.03 (s, 2H, OCH_2O); 6.38 (s, 1H, C*H*=); 6.89-6.93 (m, 2H,, H-7, NC*H*=C, Ar); 7.23 (s, 1H, NC*H*=N, Ar); 7.41 (d, 1H, J = 8.2 Hz, H-6, Ar); 7.67-7.70 (m, 2H, NC*H*=C, N*H*); 7.92 (s, 1H, H-4, Ar). ^{13}C NMR (75 MHz, DMSO d_6) δ = 25.5, 30.2, 38.4, 43.6, 101.0, 108.3, 109.5, 113.0, 119.3, 125.2, 128.4, 130.3, 137.3, 138.7, 146.7, 147.2, 158.1, 169.5. HRMS, *m/z* = 353.1482 found (calculated for $C_{18}H_{19}N_5O_3$, $M^{+\bullet}$ requires 353.1488). Anal. Calcd for $C_{18}H_{19}N_5O_3$: C, 61.18; H, 5.42; N, 19.82. Found: C, 61.25; H, 5.45; N, 19.77.

(*5Z*)-5-[(1,3-Benzodioxol-5-yl)methylene]-3-methyl-2-[(morpholin-1-yl)ethylamino]-3,5-dihydro-4*H*-imidazol-4-one (7i): Reaction temperature: 150 °C, reaction time: 30 min. Yield = 92%. Brown powder, mp 182-184 °C (from Et_2O). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.57 (m, 4H, $N(CH_2CH_2)_2O$); 2.71 (m, 2H, $NHCH_2CH_2N$); 3.13 (s, 3H, CH_3-N); 3.67 (t, 2H, J = 5.1 Hz, $NHCH_2CH_2N$); 3.74 (m, 4H, $N(CH_2CH_2)_2O$); 5.97 (s, 2H, OCH_2O); 6.64 (s, 1H, C*H*=); 6.80 (d, 1H, J = 6.8 Hz, H-7, Ar); 7.32 (d, 1H, J = 6.8 Hz, H-6, Ar); 7.98 (s, 1H, H-4, Ar); N*H* not detected. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 25.2, 37.5, 53.2, 56.6, 66.8, 100.1, 108.3, 110.2, 117.0, 126.1, 130.2, 138.0, 147.6, 147.7, 157.1, 170.2. HRMS, *m/z* = 358.1645 found (calculated for $C_{18}H_{22}N_4O_4$, $M^{+\bullet}$ requires 358.1641). Anal. Calcd for $C_{18}H_{22}N_4O_4$: C, 60.32; H, 6.19; N, 15.63. Found: C, 60.33; H, 6.22; N, 15.62.

(*5Z*)-5-[(1,3-Benzodioxol-5-yl)methylene]-2-[(2-hydroxyethyl)amino]-3-methyl-3,5-dihydro-4*H*-imidazol-4-one (7j): Reaction temperature: 120 °C, reaction time: 50 min. Yield = 33%. Yellow powder, mp 180-182 °C (from EtOH). ^{1}H NMR (300 MHz, DMSO d_6) δ = 3.05 (s, 3H, CH_3-N); 3.49 (s, 2H, CH_2OH); 3.64 (s, 2H, CH_2NH); 4.87 (br s, 1H, O*H*); 6.02 (s, 2H, OCH_2O); 6.36 (s, 1H, C*H*=); 6.90 (d, 1H, J = 7.0 Hz, H-7, Ar); 7.34 (d, 1H, J = 7.0 Hz, H-6, Ar); 7.66 (br s, 1H, N*H*); 7.94 (s, 1H, H-4, Ar). ^{13}C NMR (75 MHz, DMSO d_6) δ = 25.5, 43.9, 59.3, 100.9, 108.2, 109.4, 112.7, 125.1, 130.3, 138.7, 146.6, 147.1, 158.2, 169.51. HRMS, *m/z* = 289.1055 found (calculated for $C_{14}H_{15}N_3O_4$, $M^{+\bullet}$ requires 289.1063). Anal. Calcd for $C_{14}H_{15}N_3O_4$: C, 58.13; H, 5.23; N, 14.53. Found: C, 58.19; H, 5.20; N; 14.55.

(*5Z*)-5-[(1,3-Benzodioxol-5-yl)methylene]-2-[(2-hydroxypropyl)amino]-3-methyl-3,5-dihydro-4*H*-imidazol-4-one (7k): Reaction temperature: 155 °C, reaction time: 40 min. Yield = 64%. Yellow powder, mp 208-210 °C (from EtOH). ^{1}H NMR (300MHz, DMSO d_6) δ = 1.13 (d, 3H, J = 6.2 Hz, CH_3CHOH); 3.07 (s, 3H, CH_3-N); 3.34 (m, 2H, $CHCH_2NH$); 3.97 (m, 1H, CH_3CHOH); 4.93 (br s, 1H, O*H*); 6.03 (s, 2H, OCH_2O); 6.37 (s, 1H, C*H*=); 6.90 (d, 1H, J = 8.1 Hz, H-7, Ar); 7.38 (dd, 1H, J = 1.0, 8.1 Hz, H-6, Ar); 7.65 (br s, 1H, N*H*); 7.96 (d, 1H, J = 1.0 Hz, H-4, Ar). ^{13}C NMR (75 MHz, DMSO d_6) δ = 21.1, 25.5, 48.9, 64.8, 101.0, 108.2, 109.4, 112.7, 125.1, 130.3, 138.7, 146.6, 147.2, 158.3, 169.5. HRMS, *m/z* = 303.1223 found

(calculated for $C_{15}H_{17}N_3O_4$, $M^{+\bullet}$ requires 303.1219). Anal. Calcd for $C_{15}H_{17}N_3O_4$: C, 59.40; H, 5.65; N, 13.85. Found: C, 59.37; H, 5.62; N, 13.82.

(5*Z*)-5-[(1,3-Benzodioxol-5-yl)methylene]-2-[(2,3-hydroxypropyl)amino]-3-methyl-3,5-dihydro-4*H*-imidazol-4-one (7l): Reaction temperature: 155 °C, reaction time: 40 min. Yield = 42%. Yellow powder, mp 128-130°C (from EtOH). ^{1}H NMR (300 MHz, DMSO d_6) δ = 3.06 (s, 3H, C*H*$_3$N); 3.39 (m, 3H, C*H*$_2$OH, C*H*$_2$NH); 3.53 (m, 1H, C*H*OH); 3.76 (m, 1H, C*H*$_2$NH); 4.74 (t, 1H, *J* = 5.7 Hz, O*H*); 5.03 (d, 1H, *J* = 4.7 Hz, O*H*); 6.03 (s, 2H, OC*H*$_2$O); 6.37 (s, 1H, C*H*=); 6.91 (d, 1H, *J* = 8.0 Hz, H-7, Ar); 7.37 (d, 1H, *J* = 8.0 Hz, H-6, Ar); 7.68 (br s, 1H, NH); 7.88 (s, 1H, H-4, Ar). ^{13}C NMR (75 MHz, DMSO d_6) δ = 25.5, 44.7, 63.5, 70.2, 101.0, 108.3, 109.4, 112.8, 125.2, 130.2, 138.4, 146.7, 147.2, 158.5, 169.4. HRMS, *m/z* = 319.1176 found (calculated for $C_{15}H_{17}N_3O_5$, $M^{+\bullet}$ requires 319.1168). Anal. Calcd for $C_{15}H_{17}N_3O_5$: C, 56.42; H, 5.37; N, 13.16. Found: C, 56.40; H, 5.41; N, 13.15.

(5*Z*)-5-[(1,3-Benzodioxol-5-yl)methylene]-2-[(3-hydroxypropyl)amino]-3-methyl-3,5-dihydro-4*H*-imidazol-4-one (7m): Reaction temperature: 100 °C, reaction time: 40 min. Yield = 81%. Yellow powder, mp 198-200 °C (from EtOH). ^{1}H NMR (300 MHz, DMSO d_6) δ = 1.81 (tt, 2H, *J* = 6.5, 6.5 Hz, $CH_2CH_2CH_2$); 3.04 (s, 3H, C*H*$_3$-N); 3.47-3.53 (m, 4H, HOC*H*$_2$CH$_2$C*H*$_2$NH); 4.60 (br s, 1H, O*H*); 6.02 (s, 2H, OC*H*$_2$O); 6.37 (s, 1H, C*H*=); 6.90 (d, 1H, *J* = 8.2 Hz, H-7, Ar); 7.38 (dd, *J* = 1.3, 8.2 Hz, H-6, Ar); 7.60 (br s, 1H, N*H*); 7.95 (d, 1H, *J* = 1.3 Hz, H-4, Ar). ^{13}C NMR (75 MHz, DMSO d_6) δ = 25.4, 32.0, 38.4, 58.3, 101.0, 108.2, 109.4, 112.7, 125.1, 130.3, 138.8, 146.6, 147.2, 158.0, 169.5. HRMS, *m/z* = 303.1196 found (calculated for $C_{15}H_{17}N_3O_4$, $M^{+\bullet}$ requires 303.1219). Anal. Calcd for $C_{15}H_{17}N_3O_4$: C, 59.40; H, 5.65; N, 13.85. Found: C, 59.48; H, 5.63; N, 13.79.

(5*Z*)-5-[(1,3-Benzodioxol-5-yl)methylene]-2-[(5-hydroxypentyl)amino]-3-methyl-3,5-dihydro-4*H*-imidazol-4-one (7n): Reaction temperature: 100 °C, reaction time: 40 min. Yield = 66%. Yellow powder, mp 148-150 °C (from Et_2O). ^{1}H NMR (300 MHz, DMSO d_6) δ = 1.35-1.70 (m, 6H, HOCH$_2$(C*H*$_2$)$_3$CH$_2$NH); 3.04 (s, 3H, C*H*$_3$-N); 3.41 (m, 4H, HOC*H*$_2$(CH$_2$)$_3$C*H*$_2$NH); 4.38 (br s, 1H, O*H*); 6.02 (s, 2H, OC*H*$_2$O); 6.35 (s, 1H, C*H*=); 6.90 (d, 1H, *J* = 8.1 Hz, H-7, Ar); 7.40 (dd, *J* = 1.2, 8.1 Hz, H-6, Ar); 7.62 (br s, 1H, N*H*); 7.96 (d, 1H, *J* = 1.2 Hz, H-4, Ar). ^{13}C NMR (75 MHz, DMSO d_6) δ = 23.0, 25.4, 28.6, 32.1, 41.2, 60.6, 101.0, 108.2, 109.4, 112.5, 125.1, 130.4, 139.0, 146.6, 147.1, 158.0, 169.5. HRMS, *m/z* = 331.1537 found (calculated for $C_{17}H_{21}N_3O_4$, $M^{+\bullet}$ requires 331.1532). Anal. Calcd for $C_{17}H_{21}N_3O_4$: C, 61.12; H, 6.39; N, 12.68. Found: C, 61.16; H, 6.37; N, 12.59.

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