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Solution-phase parallel synthesis of 4,6-diaryl-pyrimidine-2-ylamines and 2-amino-5,5-disubstituted-3,5-dihydro-imidazol-4-ones via a rearrangement

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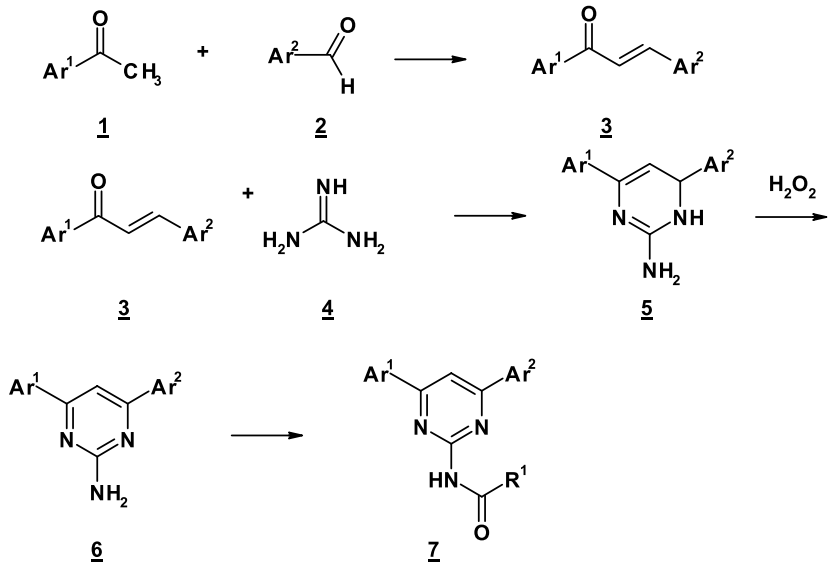
Abstract—The reaction of chalcones and guanidine was investigated in the presence of an oxidizing agent. Depending on the order of the addition either a 4,6-diaryl-pyrimidine-2-ylamine or 2-amino-5,5-disubstituted-3,5-dihydro-imidazol-4-one was obtained. The structures of the imidazolinones were elucidated by NMR spectroscopy and X-ray crystallography and for its formation a mechanism was proposed. © 2003 Published by Elsevier Science Ltd.

Chalcones have been very attractive starting materials in combinatorial chemistry from the initial years: they are easy to prepare with large variability at the two aromatic rings and the enone provides a bifunctional site for 1,3-dinucleophiles affording several heterocyclic ring-systems while incorporating other diversity elements.[1] In continuing our efforts towards creating new combinatorial libraries and compounds, we decided to start with a route (Scheme 1) for the synthesis of new 4,6-diaryl-2-amino-pyrimidine derivatives (**6**).[2]

According to the literature, the desired target compounds (**6**) were prepared from the 1,3-diaryl-propenones (**3**) and guanidine (**4**) by refluxing them together in a basic alcoholic



Scheme 1.

Keywords: chalcon; 2-amino-pyrimidine; 2-amino-5-benzyl-5-phenyl-3,5-dihydro-imidazol-4-one.

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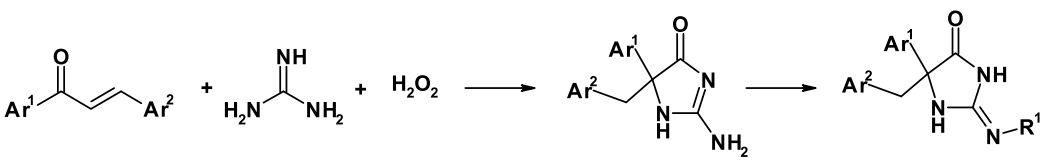
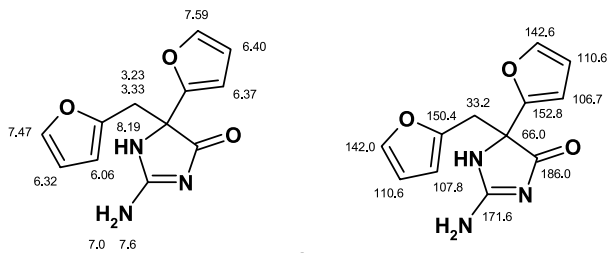


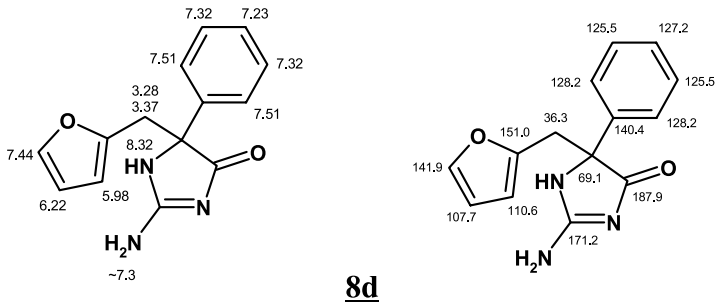
3 **4** **8** **9**

Scheme 2.



8b

Figure 1.



8d

Figure 2.

product isolation of the required pyrimidine-products yielding 40–70%, with no difficulties in purification.

In order to further simplify the performance of the parallel synthesis technology, we attempted to add the reagents and oxidizing agent together in one portion. Surprisingly, due to this modification instead of the 2-amino-pyrimidine, an entirely different product was obtained in each case, in a reasonably good yield (Scheme 2).

The compounds had a molecular ion $[(M+H)^{+}+18]$ compared to the 2-amino-pyrimidine in MS experiments and the IR spectra showed bands ($\sim$1700 cm^{-1}) corresponding to carbonyl functionality. The core structure was identified by using different NMR spectroscopic techniques

media.[2–7] Some authors gave different mechanistic suggestions for their experimental findings, where e.g. either hydrogen evolution[3] or hydride ion migration[4] was considered. In contrary to the literature—performed on a much larger scale (up to about several hundred mmoles)—we isolated the dihydro-pyrimidine type compounds (**5**) as major products instead of the expected aromatized species (**6**). Their ^{13}C NMR spectra unambiguously revealed the presence of the dihydro-pyrimidine moiety (see Section 1). Presumably, in their small-scale performance simply exposure to air oxygen could cause the oxidation of the dihydro-intermediate, leading to the isolated, fully aromatized pyrimidine ring.[7] Continuing our efforts on a larger scale production, it was essential to find an efficient oxidizing agent to replace air oxygen. Although we have tested several reagents, hydrogen peroxide proved to be the most efficient one and in addition it is clean, cheap and easily accessible. In our initial approach (Scheme 1), we dissolved the corresponding 'chalcone' (**3**) and guanidine (**4**) in a mixture of ethanol-50% aqueous KOH, and refluxed for 3 hours, by which time the dihydro-pyrimidine (**5**) had formed. At this point, hydrogen peroxide (30% aqueous solution) was added to the hot solution. By a portionwise addition of the oxidizing agent in large excess, not only was the aromatization completed, but all the undesired tarry side-products were oxidatively degraded resulting in a clean solution in each case. This procedure allowed an easy

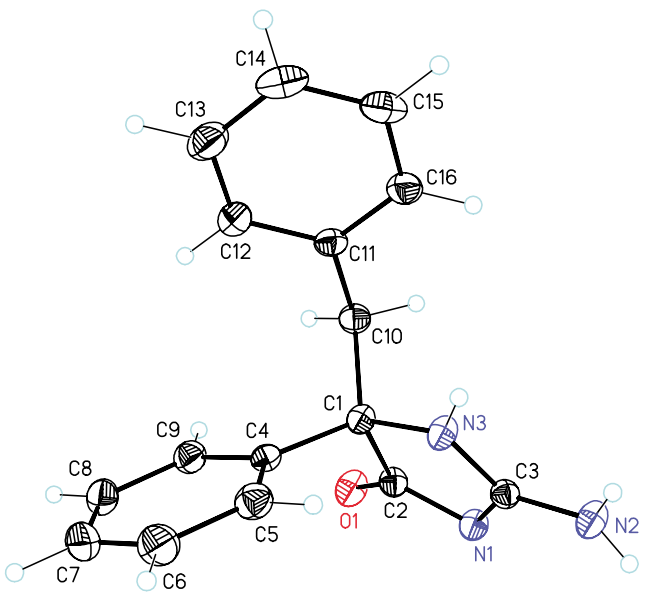


Figure 3. The Ortep diagram of **8a**.

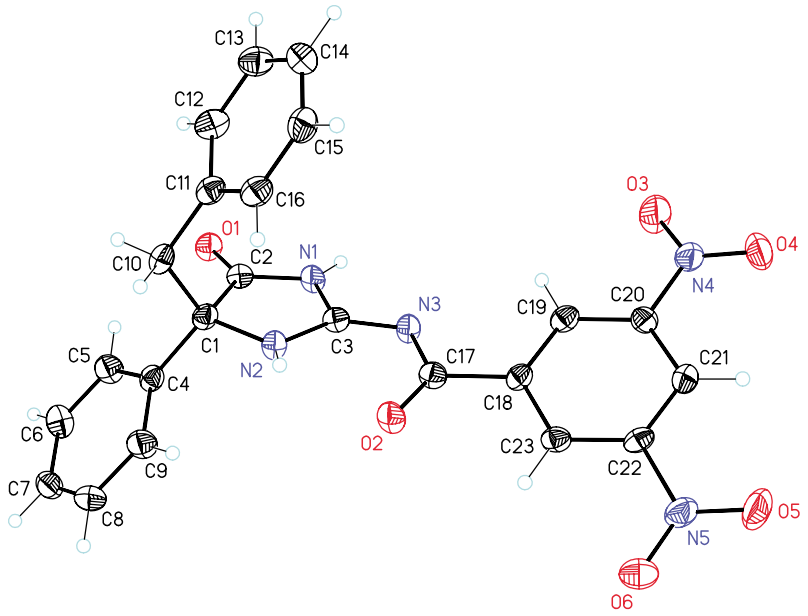
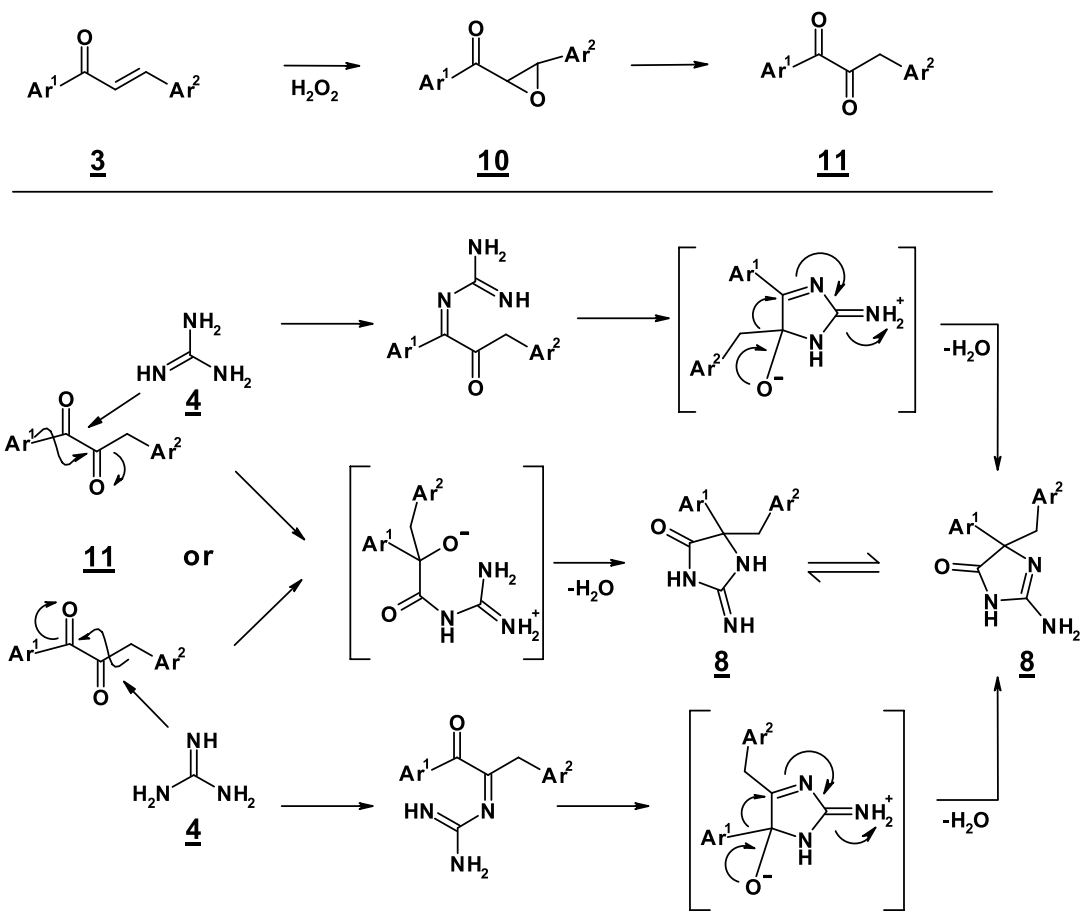


Figure 4. The Ortep diagram of **9a**.

[^{1}H 1D, ^{13}C 1D, DEPT, DPFGNOE (^{1}H 1D), ^{1}H–^{13}C HSQC 2D, ^{1}H–^{13}C HMBC 2D]. First, **8b**, which derived from an identically substituted 1,3-diaryl-propenone, provided evidence for the presence of the 2-amino-5,5-disubstituted-imidazolin-4-one ring-system. Figure 1 shows the ^{1}H and ^{13}C NMR spectroscopy shift assignments for **8b**.

Secondly, the NMR spectrum of **8d**, coming from a 'non-symmetrically' substituted chalcone-analogue (**3**, Ar^1=C_6H_5, Ar^2=furan-2-yl) was examined (Fig. 2).

In the ^{1}H 1D spectra of compounds **8b** and **8d** the CH_2 protons formed an AB multiplet, which is characteristic for



Scheme 3.

having a neighboring chiral center. In the DPFGNOE measurement of **8d** the excitation of the NH signal at 8.3 ppm confirmed the close proximity of the 2- or 6-(*ortho*) protons but did not show the same effect with the CH_2 groups. On the other hand, the excitation of the CH_2 protons showed a close proximity to an *ortho* proton from the phenyl-group and with H-3 of the furyl-ring. The analogue NOE experiment with compound **8b** confirmed the assignations of the furan ring protons. The DEPT and HSQC experiments provided evidence for the presence of the quaternary sp^3 carbon (66.0 ppm) in the 3,5-dihydro-imidazol-4-one rings. The C=O carbon signal was inside the expected lactam-like region and in the 7 Hz HMBC experiments the multi-bonded correlation (coupling) of the CH_2 protons gave more intensive signals on the quaternary carbon than with the carbonyl group. This supports that the carbonyl group belongs to the 5-membered ring system. For **8d** the HMBC 2D correlation spectra revealed that the aromatic protons in *meta* position correlated with the quaternary carbon but not with the carbonyl carbon. This indicates that the phenyl ring was linked directly to the quaternary carbon centre. All the other single and multiple bonded $^1H-^{13}C$ correlation were in full accordance with the proposed structures. These spectral data strongly supported the existence of a 5-membered ring (general formula of **8**, Scheme 2) instead of a 6-membered core and also proved the expected regiochemistry: in **8d** the furan ring is connected through a methylene (a benzyl-like substitution), while the phenyl group is adjacent to the carbonyl functionality.

The structure of the substituted heterocyclic ring was unequivocally proved by X-ray analysis of **8a** and **9a** (Figs. 3 and 4).[8] In both cases, the atoms N1, N2, N3 and C3 have sp^2-characters, which means the double bond is delocalized in the 5-membered ring. A hydrogen was clearly localized

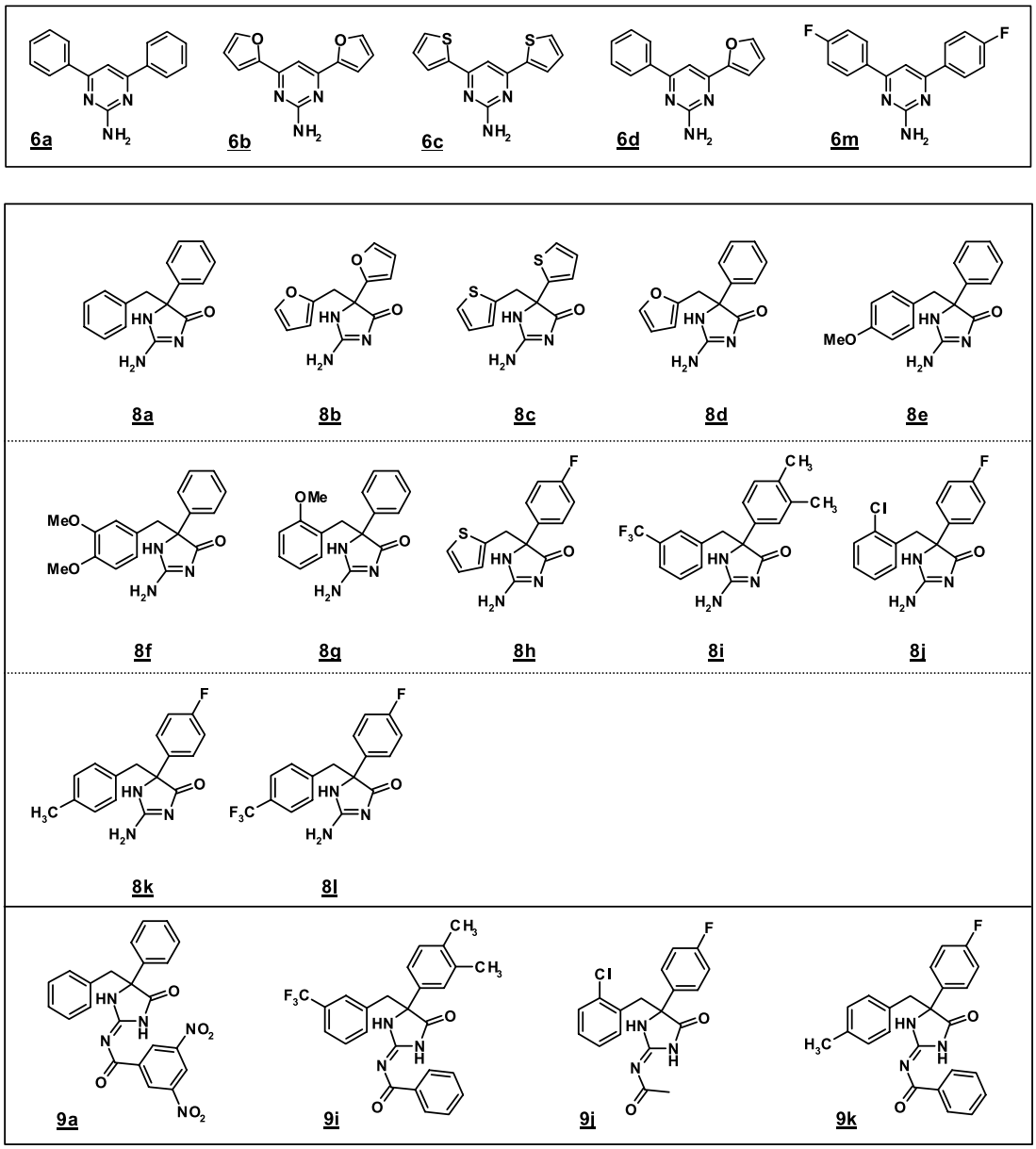


Figure 5.

on N3 in **8a** and attached to N1 and N2 in **9a**. This substitution dependent phenomenon requires further investigation, which will be a subject of a separate paper.

To the best of our knowledge, the presented core structure with this substitution pattern is unprecedented in the literature. According to our considerations, the found structure is apparently a result of a rearrangement with a migration of an aromatic- or hetaryl-ring in the proximity of the carbonyl functionality (Ar^1-group in **3**).

Here, we suggest the following mechanism for this rearrangement, leading to the produced 5-membered ring structures (Scheme 3).

The initial step of the sequence of events is a rapid epoxide formation of chalcones. This is a well established reaction just like the isomerization of the chalcone–epoxide to the corresponding 1,2-dione (**11**).[9–11] As a partial evidence for the above suggestion, we have reacted the chalcone–epoxide **10** [Ar^1=Ar^2=C_6H_5] with guanidine (**4**) under the same conditions but in the absence of H_2O_2. As a result, we obtained the expected product **8** in good isolated yield and within shorter reaction time. Furthermore, the presence of the 1,2-diketone intermediate was confirmed by trapping it with *o*-phenylene-diamine. From the **11** intermediate two major pathways can be envisaged.

First, similarly to a 'benzil–benzilic acid rearrangement'—the electron-rich guanidine (**4**) N-atom could attack one of the carbonyl carbons initiating the aryl (or aryl–methyl) migration leading to the rearranged product **8** via an open chain intermediate. Second, the intermediate **11** could form 5-membered ring-closed intermediates—via initial condensation products—in which the aryl (or aryl–methyl) migration take place resulting in an identical rearranged product (**8**). Both feasible pathways lead to the same product regardless of which groups are migrating, thus, two isomeric intermediates can be taken into account. Further investigations on the mechanism will be conducted in our lab and subjected to a separate paper.

As a conclusion, we developed:

(a) a practical method for large scale preparation of 2-aminopyrimidines with a simple and easily applicable work-up process,
(b) preparative process for new types of 5,5-disubstituted-2-amino-4,5-dihydro-imidazol-4-ones, of which structures are closely resembling to the natural product creatinine.

The major reaction path to either of the above product types can be directed and controlled simply by changing the order of the reagent addition.

Based on our results, we were able to build up chemical libraries of type either **6** or **8** together with some *N*-acylated analogues (**9**) in solution phase parallel synthesis utilizing a cascading matrix technology,[14] called CMT, where manual and robotized parallel synthesis stations of different size reflects the sequential diversity building approach.[15]

Some of the library representatives synthesised are shown in Figure 5. In our synthesis, the conditions were not fully optimized, thus, the yield generally varied in the range of 30–70%.

1. Experimental

All the 1,3-diaryl-propenones (**3**) used were prepared according to the known literature procedure.[12] The ^1H and ^{13}C NMR spectra were recorded at 298 K on a Varian INOVA (400 MHz) spectrometer with TMS as an internal reference. Throughout the spectral assignations, the Ar^1 and Ar^2 ring-marks refer to the aryl groups that link directly or through a methylene bridge to the quaternary carbon centre, respectively in full accordance with the substituent pattern of the general structure **8**.

For the HPLC runs a LaChrom system (Merck–Hitachi) was used connected to an autosampler and a fraction collector based on a Cavro RSP 9000 (Cavro Scientific Instruments, Inc.) robotic workstation. The column was filled in a reversed phase packing material purchased from Merck (Purospher STAR RP-18 endcapped, 3 μm, 30×4 mm). The detection wavelengths were 220 or 254 nm.[16]

Melting points are uncorrected and were measured on a standard Boetius apparatus.

MS data were collected on a Mariner (Perseptive Biosystems) mass spectrometer using an APCI interface.[17] HRMS experiments were performed on a MICROMASS LCT spectrometer using electrospray interface with a lock-mass sign of tetrabutylammonium ion.

IR spectra were measured on a Nicolet FTIR MAGNA 750 spectrophotometer. Crystal analysis were performed on a Bruker-Smart-CCD surface detection system, using Mo Kα radiation, a graphite monochromator and a rotating anode M18X-HF from MACScience Co., Ltd.

For parallel synthesis the RoboSynthon™ cascading reactor family (ComGenex International, So. San Francisco) was employed.

1.1. Typical experimental procedure for preparation of 4,6-diaryl-pyrimidine-2-ylamines

1.1.1. 4,6-Di-thiophen-2-yl-pyrimidin-2-ylamine (6c).[4] 1,3-Di-thiophen-2-yl-propenone (**3** [Ar^1=Ar^2=thiophen-2-yl]; 20.0 g, 90.8 mmol), guanidine hydrochloride (**4** HCl; 13.0 g, 136.1 mmol), ethanol (200 mL) and 50% aqueous KOH solution (40 mL) were mixed together then heated up and stirred at reflux temperature for 1 h. Under the same conditions, 30% aqueous H_2O_2 (31.0 mL, ca. 303 mmol) was added to the above mixture in small portions over a period of 1 h. The ethanol was removed under reduced pressure in a rotary evaporator and water (~200 mL) was added to the residue. The precipitated title compound was filtered off, washed thoroughly on the funnel with pure water in more cycles and carefully drawn off. The slightly still wet crude solid was re-crystallised from ethanol and the

so-obtained pure, crystalline product was dried finally in a vacuum desiccator over P_2O_5/KOH. Yield: 14.04 g (60%) pale yellow crystals. Mp 161–164°C; ν_{max} (KBr):3330 (H-bridged, $\nu_{as}NH_2$), 3219 (H-bridged, ν_sNH_2), 1641 (H-bridged, β_sNH_2), 1568 (pyrimidin-skeletal), 758 and 718 ($\gamma C_{Ar}H$) cm^{-1}; δ_H (DMSO-d6) 6.7 s (2H, s, NH_2), 7.23 (2H, dd, J=5+4 Hz, 2×^{Ar}H-4), 7.64 (1H, s, H-5), 7.73 (2H, dd, J=5+1 Hz, 2×ArH-5), 8.05 (2H, dd, J=4+1 Hz, 2×ArH-3); HPLC purity (254 nm): 100%; MS (APCI) m/z 260 [(M+H)$^+$]; HRMS (ES): calculated for $C_{12}H_{10}N_3S_2$ [(M+H)$^+$] 260.0316, found 260.0313.

1.1.2. 4,6-Diphenyl-pyrimidin-2-ylamine (6a)[6,13,18] [CAS No. 40230-24-8]. The experimental procedure was similar to that described for compound **6c** starting from 1,3-diphenyl-propenone (**3**, Ar^1=Ar^2=C_6H_5).

Compound **6a** (45%, bright yellow crystals), mp 126–129°C (135–137°C)[18]; ν_{max} (KBr): 3469 ($\nu_{as}NH_2$), 3316 (ν_sNH_2), 1630 (shoulder, β_sNH_2), 1602 and 1587 ($\nu C_{Ar}C_{Ar}$), 1567 and 1544 (pyrimidin-skeletal), 765 ($\gamma C_{Ar}H$) cm^{-1}; δ_H (DMSO-d6) 6.62 (2H, brs, NH_2), 7.50 (6H, m, Ar*H*), 7.64 (1H, s, H-5), 8.22 (4H, m, Ar*H*); HPLC purity (254 nm): 99%; MS (APCI) m/z 248 [(M+H)$^+$]; HRMS (ES): calculated for $C_{16}H_{14}N_3$ [(M+H)$^+$] 248.1188, found 248.1184.

Data are consistent with that reported in the literature,[6,13,18] although herewith we provide a more accurate assignation.

1.1.3. 4,6-Di-furan-2-yl-pyrimidin-2-ylamine (6b). The experimental procedure was similar to that described for compound **6c** starting from 1,3-di-furan-2-yl-propenone (**3**, Ar^1=Ar^2=furan-2-yl).

Compound **6b** (37%, brownish solid), mp 214–229°C; ν_{max} (KBr): 3308 (H-bridged, $\nu_{as}NH_2$), 3191 (H-bridged, ν_sNH_2), 1631 (β_sNH_2), 1603 ($\nu C_{Ar}C_{Ar}$), 1560 (pyrimidin-skeletal), 765 and 745 ($\gamma C_{Ar}H$), 591 (furan ring def.) cm^{-1}; δ_H (DMSO-d6) 5.38 (2H, brs, NH_2), 6.58 (2H, dd, J=3.5+2 Hz, 2×^{Ar}H-4), 7.20 (2H, dd, J=3.5+1 Hz, 2×ArH-3), 7.35 (1H, s, H-5), 7.64 (2H, dd, J=2+1 Hz, 2×ArH-5); HPLC purity (254 nm): 91%; MS (APCI) m/z 228 [(M+H)$^+$]; HRMS (ES): calculated for $C_{12}H_{10}N_3O_2$ [(M+H)$^+$] 228.0773, found 228.0775.

1.1.4. 4-Furan-2-yl-6-phenyl-pyrimidin-2-ylamine (6d).[4] The experimental procedure was similar to that described for compound **6c** starting from 3-furan-2-yl-1-phenyl-propenone (**3**, Ar^1=C_6H_5, Ar^2=furan-2-yl).

Compound **6d** (40%, pale yellow solid), mp 149.5–151°C; ν_{max} (KBr): 3325 (H-bridged, $\nu_{as}NH_2$), 3202 (ν_sNH_2), 1645 (β_sNH_2), 1590 ($\nu C_{Ar}C_{Ar}$), 1559 (pyrimidin-skeletal), 771 ($\gamma C_{Ar}H$), 591 (furan ring def.) cm^{-1}; δ_H (DMSO-d6) 5.95 (2H, s, NH_2), 6.59 (1H, dd, J=3.5+2 Hz, ^{Ar2}H-4), 7.20 (1H, dd, J=3.5+1 Hz, ^{Ar2}H-3), 7.40 (1H, s, H-5), 7.48 (3H, m, ^{Ar1}H-3+^{Ar1}H-4+^{Ar1}H-5), 7.65 (2H, dd, J=2+1 Hz, ^{Ar2}H-5), 8.07 (2H, m, ^{Ar1}H-2+^{Ar1}H-6); HPLC purity (254 nm): 93%; MS (APCI) m/z 238 [(M+H)$^+$]; HRMS (ES): calculated for $C_{14}H_{12}N_3O$ [(M+H)$^+$] 238.0980, found 238.0981.

Data are consistent with that reported in the literature,[4] although herewith we provide a more accurate assignation.

1.1.5. 4,6-Bis-(4-fluoro-phenyl)-pyrimidin-2-ylamine (6m). The experimental procedure was similar to that described for compound **6c** starting from 1,3-bis-(4-fluoro-phenyl)-propenone (**3**, Ar^1=Ar^2=4-F–C_6H_4).

Compound **6m** (49%, whitish solid), mp 207.5–210.5°C; δ_H (DMSO-d6) 5.80 (2H, s, NH_2), 7.17 (4H, m, 2×^{Ar}H-3+^{Ar}H-5), 7.40 (1H, s, H-5), 8.13 (4H, m, 2×^{Ar}H2+^{Ar}H-6); HPLC purity (254 nm): 95%; MS (APCI) m/z 284 [(M+H)$^+$]; HRMS (ES): calculated for $C_{16}H_{12}F_2N_3$ [(M+H)$^+$] 284.0999, found 284.0998.

1.1.6. 6(or4)-(4-Fluoro-phenyl)-4(or6)-(3-methyl-thiophen-2-yl)-1,6-dihydro-pyrimidin-2-ylamine (5, Ar^1=4-FC_6H_4, Ar^2=3-Me-thiophen-2-yl). The experimental procedure was similar to that described for compound **6c** starting from 1-(4-fluoro-phenyl)-3-(3-methyl-thiophen-2-yl)-propenone (**3**, Ar^1=4-F–C_6H_4, Ar^2=3-CH_3-thiophen-2-yl) with the only exception, that the addition of H_2O_2 was omitted. δ_H (DMSO-d6) 2.22 (3H, s, C*H*$_3$), 5.46 (1H, d, J=4.5 Hz, H-6), 5.51 (1H, d, J=4.5 Hz, H-5), 6.86 (1H, d, J=5 Hz, ^{Ar2}H-4), 7.18 (2H, m, ^{Ar1}H-3+^{Ar1}H-5), 7.36 (1H, d, J=5 Hz, ^{Ar2}H-5), 7.71 (2H, m, ^{Ar1}H-2+^{Ar1}H-6), 8.2 (2H, brs, NH_2), 9.6 (1H, brs, N1–H); δ_C (DMSO-d6) 13.9 (*C*H$_3$), 47.0 (C-6), 101.1 (C-5), 116.1 (^{Ar1}C-3+^{Ar1}C-5), 125.3 (^{Ar2}C-5), 128.7 (^{Ar1}C2+^{Ar1}C-6), 129.8 (^{Ar1}C-1), 131.3 (^{Ar2}C-4), 133.4 (^{Ar2}C-2), 134.5 (^{Ar2}C-3), 140.9 (C4), 152.5 (C-2), 163.2 (^{Ar1}C-4).

1.2. Typical experimental procedure for preparation of 2-amino-5-(Ar^1-yl)-5-(Ar^2-yl)-methyl-3,5-dihydro-imidazol-4-ones

1.2.1. 2-Amino-5-benzyl-5-phenyl-3,5-dihydro-imidazol-4-one (8a). 1,3-Diphenyl-propenone (**3** [Ar^1=Ar^2=C_6H_5], 20.0 g, 96.0 mmol), guanidine hydrochloride (**4** HCl, 13.75 g, 143.9 mmol, 1.5 M equiv.), ethanol (300 mL), 50% aqueous KOH solution (20.0 mL) and 30% aqueous H_2O_2 (7.35 mL, ~72 mmol, 0.75 M equiv.) were mixed together at rt, then stirred at 80°C for 2 h. The ethanol was removed under reduced pressure in a rotary evaporator and water (~200 mL) was added to the residue. The precipitated product was filtered off, washed thoroughly on the funnel with pure water in more cycles (Σ~500 mL) and carefully drawn off. The slightly still wet filter cake was admixed with 150 mL of ethanol and the so-obtained suspension refluxed for 15 min. After cooling to rt, the crystals were filtered off, washed twice with small amounts of ethanol and finally dried in a vacuum desiccator over P_2O_5/KOH. Yield: 15.0 g (59%) white crystals. Mp 336.5–338.5°C (deg.); ν_{max} (KBr): 3373, 3286 (νNH), 3033 ($\nu C_{Ar}H$), 1703 (νC=O$_{lactam}$), 1659 (νC=N), 1492 ($\nu C_{Ar}C_{Ar}$), 698 (aromatic ring def.) cm^{-1}; δ_H (DMSO-d6) 3.10 (1H, d, J=13.5 Hz, CH_2-A), 3.31 (1H, d, J=13.5 Hz, CH_2-B), 6.8–7.8 (2H, brs, NH_2), 7.2 (5H, m, ^{Ar2}H-2+^{Ar2}H-3+^{Ar2}H-4+^{Ar2}H-5+^{Ar2}H-6), 7.27 (1H, m, ^{Ar1}H-4), 7.34 (2H, m, ^{Ar1}H-3+^{Ar1}H-5), 7.54 (2H, m, ^{Ar1}H-2+^{Ar1}H-6), 8.24 (1H, brs, N3-H); δ_C ($CDCl_3$+TFA) 44.8 (–*C*H$_2$–); 71.7 (C-5); 125.0 129.1, 129.5 and 130.0 (^{Ar1}C-2+^{Ar1}C-3+^{Ar1}C-5+^{Ar1}C-6+^{Ar2}C-2+^{Ar2}C-3+^{Ar2}C-5+^{Ar2}C-6); 128.6 and 129.9 (^{Ar1}C-4+^{Ar2}C-4); 132.0 and 134.3 (^{Ar1}C1+^{Ar2}C-1); 156.5 (C-2); 174.7 (C-4); HPLC purity (220 nm): 96%; HRMS (ES): calculated for $C_{16}H_{16}N_3O$ [(M+H)$^+$] 266.12932, found 266.1298.

1.2.2. 2-Amino-5-furan-2-yl-5-furan-2-ylmethyl-3,5-dihydro-imidazol-4-one (8b). The experimental procedure was similar to that described for compound **8a** starting from 1,3-di-furan-2-yl-propenone (**3**, Ar^1=Ar^2= furan-2-yl).

Compound **8b** (29%, whitish solid), mp 232–234°C (deg.); ν_{max} (KBr): 3354 (νNH), 1708 (νC=O_{lactam}), 1653 (νC=N), 1564, 1488 ($\nu C_{Ar}C_{Ar}$) cm^{-1}; δ_H (DMSO-d6) 3.23 (1H, d, CH_2Fig. 2A), 3.33 (1H, d, CH_2-B), 6.06 (1H, ^{Ar2}H-3), 6.32 (1H, ^{Ar2}H-4), 6.37 (1H, ^{Ar1}H-3), 6.40 (1H, ^{Ar1}H-4), 7.0 (1H, brs, NH_2), 7.47 (1H, ^{Ar2}H-5), 7.59 (1H, ^{Ar1}H-5), 7.6 (1H, brs, NH_2), 8.19 (1H, s, N3-H); δ_C (DMSO-d6) 33.2 (–*C*H_2–), 66.0 (C-5), 106.7 (^{Ar1}C-3), 107.8 (^{Ar2}C-3), 110.6 (^{Ar1}C-4+^{Ar2}C-4), 142.0 (^{Ar2}C-5), 142.6 (^{Ar1}C-5), 150.4 (^{Ar2}C-2), 152.8 (^{Ar1}C-2), 171.6 (C-2), 186.0 (C-4); HPLC purity (220 nm): 98%; HRMS (ES): calculated for $C_{12}H_{12}N_3O_3$ [(M+H)$^+$] 246.08784, found 246.0876.

1.2.3. 2-Amino-5-thiophen-2-yl-5-thiophen-2-ylmethyl-3,5-dihydro-imidazol-4-one (8c). The experimental procedure was similar to that described for compound **8a** starting from 1,3-di-thiophen-2-yl-propenone (**3**, Ar^1= Ar^2=thiophen-2-yl).

Compound **8c** (29%, whitish solid), mp 307–310°C (deg.); ν_{max} (KBr): 3357 (νNH), 3069 ($\nu C_{Ar}H$), 1706 (νC=O_{lactam}), 1655 (νC=N), 1561, 1489 ($\nu C_{Ar}C_{Ar}$), 699 (aromatic ring def.) cm^{-1}; δ_H (DMSO-d6) 3.37 (1H, d, J=14 Hz, CH_2-A), 3.49 (1H, d, J=14 Hz, CH_2-B), 6.86 (1H, dd, J=3.5+1 Hz, ^{Ar2}H-3), 6.90 (1H, dd, J=5+3.5 Hz, ^{Ar2}H-4), 7.07.8 (2H, brs, NH_2), 7.00 (1H, dd, J=5+4 Hz, ^{Ar1}H-4), 7.08 (1H, dd, J=4+1.5 Hz, ^{Ar1}H-3), 7.30 (1H, dd, J=5+1 Hz, ^{Ar2}H-5), 7.41 (1H, dd, J=5+1.5 Hz, ^{Ar1}H5), 8.45 (1H, s, N3-H); δ_C (DMSO-d6) 39.0 (–*C*H_2–), 69.4 (C-5), 124.4 (^{Ar2}C-5), 125.5 (^{Ar2}C-3), 125.7 (^{Ar1}C-5), 127.1 (^{Ar1}C-3), 127.6 (^{Ar1}C-4), 128.0 (^{Ar2}C-4), 137.6 (^{Ar2}C-2), 145.3 (^{Ar1}C-2), 171.7 (C-2), 187.3 (C-4); HPLC purity (220 nm): 100%; HRMS (ES): calculated for $C_{12}H_{12}N_3OS_2$ [(M+H)$^+$] 278.04216, found 278.0425.

1.2.4. 2-Amino-5-furan-2-ylmethyl-5-phenyl-3,5-dihydro-imidazol-4-one (8d). The experimental procedure was similar to that described for compound **8a** starting from 3-furan-2-yl-1-phenyl-propenone (**3**, Ar^1=C_6H_5, Ar^2= furan-2-yl).

Compound **8d** (56%, whitish solid), mp <228°C (deg.); ν_{max} (KBr): 3362 (νNH), 1703 (νC=O_{lactam}), 1651 (νC=N), 1494 ($\nu C_{Ar}C_{Ar}$), 697 (aromatic ring def.) cm^{-1}; δ_H (DMSO-d6) 3.28 (1H, d, CH_2-A), 3.37 (1H, d, CH_2-B), 5.98 (1H, ^{Ar2}H-3), 6.22 (1H, ^{Ar2}H-4), 7.23 (1H, ^{Ar1}H-4), 7.32 (2H, ^{Ar1}H-3+^{Ar1}H-5), 7.44 (1H, ^{Ar2}H-5), 7.51 (2H, ^{Ar1}H-2+^{Ar1}H-6), ~7.3 (2H, br, NH_2), 8.32 (1H, s, N3-H); δ_C (DMSO-d6) 36.3 (–*C*H_2–), 69.1 (C-5), 107.7 (^{Ar2}C-4), 110.6 (^{Ar2}C-3), 125.5 (^{Ar1}C-3+^{Ar1}C-5), 127.2 (^{Ar1}C-4), 128.2 (^{Ar1}C-2+^{Ar1}C6), 140.4 (^{Ar1}C-1), 141.9 (^{Ar2}C-5), 151.0 (^{Ar2}C-2), 171.2 (C2), 187.9 (C-4); HPLC purity (220 nm): 96%; HRMS (ES): calculated for $C_{14}H_{14}N_3O_2$ [(M+H)$^+$] 256.10858, found 256.1084.

1.2.5. 2-Amino-5-(4-methoxy-benzyl)-5-phenyl-3,5-dihydro-imidazol-4-one (8e). The experimental procedure was similar to that described for compound **8a** starting from 3-(4-methoxy-phenyl)-1-phenyl-propenone (**3**, Ar^1=C_6H_5, Ar^2=4-CH_3O–C_6H_4).

Compound **8e** (64%, whitish solid), mp 304–311°C (deg.); ν_{max} (KBr): 3353 (νNH), 1700 (νC=O_{lactam}), 1652 (νC=N), 1611, 1511 ($\nu C_{Ar}C_{Ar}$), 696, 648 (aromatic ring def.) cm^{-1}; δ_H (DMSO-d6) 3.02 (1H, d, J=14 Hz, CH_2-A), 3.23 (1H, d, J=14 Hz, CH_2-B), 3.70 (3H, s, OCH_3), 6.75 (2H, m, ^{Ar2}H-3+^{Ar2}H-5), 6.8-7.4 (2H, brs, NH_2), 7.08 (2H, m, ^{Ar2}H-2+^{Ar2}H-6), 7.28 (1H, m, ^{Ar1}H-4), 7.38 (2H, m, ^{Ar1}H-3+^{Ar1}H-5), 7.55 (2H, m, ^{Ar1}H-2+^{Ar1}H-6), 8.2 (1H, brs, N3-H); δ_C (DMSO-d6) 42.6 (–*C*H_2–), 54.8 (O*C*H_3), 70.5 (C-5), 113.0 (^{Ar2}C-3+^{Ar2}C-5), 125.4 (^{Ar1}C-2+^{Ar1}C-6), 126.9 (^{Ar1}C-4), 127.9 (^{Ar2}C-1), 128.0 (^{Ar1}C-3+^{Ar1}C-5), 131.1 (^{Ar2}C-2+^{Ar2}C-6), 141.1 (^{Ar1}C1), 157.9 (^{Ar2}C-4), 170.4 (C-2), 188.0 (C-4); HPLC purity (220 nm): 99%; HRMS (ES): calculated for $C_{17}H_{18}N_3O_2$ [(M+H)$^+$] 296.13988, found 296.1399.

1.2.6. 2-Amino-5-(3,4-dimethoxy-benzyl)-5-phenyl-3,5-dihydro-imidazol-4-one (8f). The experimental procedure was similar to that described for compound **8a** starting from 3-(3,4-dimethoxy-phenyl)-1-phenyl-propenone [**3**, Ar^1=C_6H_5, Ar^2=3,4-$(CH_3O)_2$–C_6H_4].

Compound **8f** (60%, whitish solid), mp 306–309°C (deg.); ν_{max} (KBr): 3347 (νNH), 3064 ($\nu C_{Ar}H$), 1701 (νC=O_{lactam}), 1664 (νC=N), 1616, 1516 ($\nu C_{Ar}C_{Ar}$) cm^{-1}; δ_H (DMSO-d6) 3.02 (1H, d, J=13.5 Hz, CH_2-A), 3.19 (1H, d, J=13.5 Hz, CH_2-B), 3.64+3.70 (2×3H, 2×s, 2×OCH_3), 6.66 (1H, dd, J=8+2 Hz, ^{Ar2}H-6), 6.74 (1H, d, J=2 Hz, ^{Ar2}H-2), 6.76 (1H, d, J=8 Hz, ^{Ar2}H-5), 6.8–7.4 (2H, brs, NH_2), 7.26 (1H, m, ^{Ar1}H-4), 7.35 (2H, m, ^{Ar1}H-3+^{Ar1}H5), 7.53 (2H, m, ^{Ar1}H-2+^{Ar1}H-6), 8.2 (1H, brs, N3-H); δ_C (DMSO-d6) 43.2 (–*C*H_2–), 55.3 (2×O*C*H_3), 70.5 (C-5), 111.1 (^{Ar2}C-5), 114.2 (^{Ar2}C-6), 122.2 (^{Ar2}C-2), 125.5 (^{Ar1}C-2+^{Ar1}C-6), 126.9 (^{Ar1}C-4), 127.9 (^{Ar1}C-3+^{Ar1}C-5), 128.4 (^{Ar2}C-1), 141.1 (^{Ar1}C1), 147.5 (^{Ar2}C-3), 147.8 (^{Ar2}C-4), 170.5 (C-2), 188.0 (C-4); HPLC purity (220 nm): 97%; HRMS (ES): calculated for $C_{18}H_{20}N_3O_3$ [(M+H)$^+$] 326.15044, found 326.1515.

1.2.7. 2-Amino-5-(2-methoxy-benzyl)-5-phenyl-3,5-dihydro-imidazol-4-one (8g). The experimental procedure was similar to that described for compound **8a** starting from 3-(2-methoxy-phenyl)-1-phenyl-propenone [**3**, Ar^1=C_6H_5, Ar^2=2-(CH_3O)-C_6H_4].

Compound **8g** (43%, whitish solid), mp 306–309°C (deg.); ν_{max} (KBr): 3369 (νNH), 1701 (νC=O_{lactam}), 1658 (νC=N), 1587, 1493 ($\nu C_{Ar}C_{Ar}$), 753 ($\gamma C_{Ar}H$), 697 (aromatic ring def.) cm^{-1}; δ_H (DMSO-d6) 3.18 (1H, d, J=14 Hz, CH_2-A), 3.31 (1H, d, J=14 Hz, CH_2-B), 3.75 (3H, s, OCH_3), 6.6–7.6 (2H, brs, NH_2), 6.77 (1H, dd, J=8+7.5 Hz, ^{Ar2}H-5), 6.9 (1H, d, J=7 Hz, ^{Ar2}H-3), 6.99 (1H, d, J=8 Hz, ^{Ar2}H-6), 7.18 (1H, dd, J=7.5+7 Hz, ^{Ar2}H-4), 7.28 (1H, m, ^{Ar1}H-4), 7.34 (2H, m, ^{Ar1}H-3+^{Ar1}H-5), 7.50 (2H, m, ^{Ar1}H-2+^{Ar1}H-6), 7.7 (1H, s, N3-H); δ_C (DMSO-d6) 37.1 (–*C*H_2–), 55.4 (O*C*H_3), 70.1 (C-5), 110.6 (^{Ar2}C-3), 119.9 (^{Ar2}C-5), 124.2 (^{Ar2}C-1), 125.3 (^{Ar1}C-2+^{Ar1}C-6), 126.9 (^{Ar1}C-4), 127.9 (^{Ar1}C-3+^{Ar1}C-5+^{Ar2}C-6), 130.8 (^{Ar2}C-4), 141.1 (^{Ar1}C1), 157.6 (^{Ar2}C-2), 170.9 (C-2), 188.1

(C-4); HPLC purity (220 nm): 94%; HRMS (ES): calculated for $C_{17}H_{18}N_3O_2$ [$(M+H)^+$] 296.13988, found 296.1396.

1.2.8. 2-Amino-5-(4-fluoro-phenyl)-5-thiophen-2-ylmethyl-3,5-dihydro-imidazol-4-one (8h). The experimental procedure was similar to that described for compound **8a** starting from 3-(4-fluoro-phenyl)-1-thiophen-2-yl-propenone (**3**, Ar^1=4-F–C_6H_4, Ar^2=thiophen-2-yl).

Compound **8h** (50%, whitish solid), mp 326–329°C (deg.); δ_H (DMSO-d6) 3.14 (1H, d, J=14 Hz, CH_2-A), 3.25 (1H, d, J=14 Hz, CH_2-B), 6.8–7.8 (2H, brs, NH_2), 6.84 (1H, dd, J=5+1 Hz, ^{Ar2}H-5), 7.10 (1H, dd, J=3+1 Hz, ^{Ar2}H-3), 7.17 (2H, m, ^{Ar1}H-3+^{Ar1}H5), 7.34 (1H, dd, J=5+3 Hz, ^{Ar2}H-4), 7.56 (2H, m, ^{Ar1}H-2+^{Ar1}H-6), 8.3 (1H, brs, N3-H); δ_C (DMSO-d6) 38.7 (–CH_2–), 70.3 (C-5), 115.3 (^{Ar1}C-3+^{Ar1}C-5), 124.0 (^{Ar2}C-5), 125.4 (^{Ar2}C-3), 128.0 (^{Ar1}C-2+^{Ar1}C-6), 129.8 (^{Ar2}C-4), 136.5 (^{Ar2}C-2), 137.3 (^{Ar1}C-1), 161.9 (^{Ar1}C-4), 170.9 (C2), 188.7 (C-4); MS (APCI) m/z 290 [$(M+H)^+$]; HRMS (ES): calculated for $C_{14}H_{13}FN_3OS$ [$(M+H)^+$] 290.0763, found 290.0761.

1.2.9. *N*-(4-Benzyl-5-oxo-4-phenyl-4,5-dihydro-1*H*-imidazol-2-yl)-3,5-dinitro-benzamide (9a). 2-Amino-5-benzyl-5-phenyl-3,5-dihydro-imidazol-4-one (**8**, 2.00 g, 7.5 mmol) was dissolved in a mixture of 1,4-dioxane (20 mL) and triethylamine (1.50 mL, 1.09 g, 10.8 mmol). 3,5-Dinitro-benzoyl chloride (1.73 g, 7.5 mmol) was added slowly to the above solution, and the mixture was stirred at rt for 2 days. The solvent was evaporated under reduced pressure. The residual brown solid was thoroughly triturated with distilled water, then filtered off. The solvent was drawn off and the solid phase was washed on the funnel with 3% aq. HCl, 3% aq. Na_2CO_3 solution, water and ethanol, respectively. The still impure sample was dissolved in a mixture of 1,4-dioxane and 25% aq. NH_3 solution and the mixture was allowed to stand under ambient temperature overnight. The mixture was concentrated to about 2/3 volume, from which—after cooling and scratching—the title product was crystallised. The product crystals were filtered off, washed with some 1,4-dioxane and dried in a vacuum desiccator over P_2O_5/KOH. Yield: 1.03 g (30%) white solid, mp 310–313°C (deg.); ν_{max} (KBr): 3337 and 3201 (νNH), 3090 ($\nu C_{Ar}H$), 1744 (amide, imidazole-ring), 1641 (amide I, *sec*amide), 1596 ($\nu C_{Ar}C_{Ar}$), 1544 (amide II, *sec*amide +$\nu_{as}NO_2$), 1343 ($\nu_s NO_2$), 724 ($\gamma C_{Ar}H$) cm^{-1}; δ_H (DMSO-d6) 3.52 (1H, d, J=13.5 Hz CH_2-A), 3.70 (1H, d, J=13.5 Hz, CH_2-B), 7.2–7.4 (5H, m, ^{Ar2}H-2+^{Ar2}H-3+^{Ar2}H-4+^{Ar2}H5+^{Ar2}H-6), 7.50 (1H, m, ^{Ar1}H-4), 7.58 (2H, m, ^{Ar1}H-3+^{Ar1}H-5), 7.78 (2H, m, ^{Ar1}H-2+^{Ar1}H-6), 9.02 (1H, dd, J=1.5+1.5 Hz, H-4 in 3,5-$(NO_2)_2C_6H_3$), 9.16 (2H, dd, J=2+1.5 Hz, H-2 and H-6 in 3,5-$(NO_2)_2C_6H_3$), 10.78 and 11.6 (2×1H, 2×brs, C(O)N*H*); δ_C (DMSO-d6) 42.2 (–CH_2–), 70.5 (C-5), 121.3 (C-4 in 3,5-$(NO_2)_2C_6H_3$), 125.9 (^{Ar1}C-3+^{Ar1}C-5), 127.4 (^{Ar1}C-4), 128.2 (^{Ar2}C-3+^{Ar2}C-5), 128.6 (^{Ar1}C-2+^{Ar1}C-6), 128.8 (^{Ar2}C-4), 128.9 (C-2 and C6 in 3,5-$(NO_2)_2C_6H_3$), 130.5 (^{Ar2}C-2+^{Ar2}C-6), 134.6 (^{Ar2}C-1), 137.9 (C-1 in 3,5-$(NO_2)_2C_6H_3$), 140.0 (^{Ar1}C-1), 148.4 (C-3 and C-5 in 3,5-$(NO_2)_2C_6H_3$), 160.7 (C-2), 171.9 and 175.2 (2×C=O); HPLC purity (254 nm): 93%; MS (APCI) m/z 460 [$(M+H)^+$]; HRMS (ES): calculated for $C_{23}H_{18}N_5O_6$ [$(M+H)^+$] 460.1257, found 460.1263.

1.2.10. 2-Amino-5-benzyl-5-phenyl-3,5-dihydro-imidazol-4-one (8a) (analogous procedure from chalcon–epoxide). Phenyl-(3-phenyl-oxiranyl)-methanone (2-benzoyl-3-phenyl-oxirane, chalcon–epoxide (**10** [Ar^1=Ar^2=C_6H_5], 1.00 g, 4.46 mmol), guanidine hydrochloride (**4**×HCl, 639 mg, 6.68 mmol, 1.5 M equiv.), ethanol (15 mL), and 50% aqueous KOH solution (1.0 mL) were mixed together at rt, then stirred at 80°C for 20 min. The precipitated product was filtered off, washed thoroughly on the funnel with pure water and finally dried in a vacuum desiccator over P_2O_5/KOH. Yield: 1.03 g (87%) white crystals.

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