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FULL PAPER

One-pot access towards 4,5-disubstituted 2-amino-1*H*-imidazoles starting from Mannich substrates and their transformation utilities

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Abstract: An efficient protocol for the preparation of 4,5-difunctionalised 2-amino-1*H*-imidazoles as fragment-like structures was developed in isolated yields up to 95%. The demonstrated one-pot manner includes an intramolecular oxidative annulation and ring cleavage sequence starting from Mannich precursors. The suggested one pot sequential synthetic methodology is easy to apply in automatic and robotic chemistry laboratory for which a rapidly increasing demand is foreseen because of the ongoing revolution in the field of continuous manufacturing of pharmaceutical drug substances and products. Further transformation utilities such as Groebke–Blackburn–Bienaymé 3CR and formation of marine alkaloid analogues were also represented.

The 2-amino-1*H*-imidazole (2-AI) core is a general motif occurring in various marine alkaloids isolated from sponges (representative examples **A–D**, Figure 1),[1] possessing a broad range of pharmaceutical properties such as cytotoxic behaviour and antibacterial and antiviral activities. For some related structures incorporating 2-AI, adrenergic, serotonine and histamin receptor antagonist and enzyme-inhibition effects were found depending on the substitution pattern.[2] In addition, they may act as organocatalysts, due to their hydrogen bond donor and/or acceptor ability.[3]

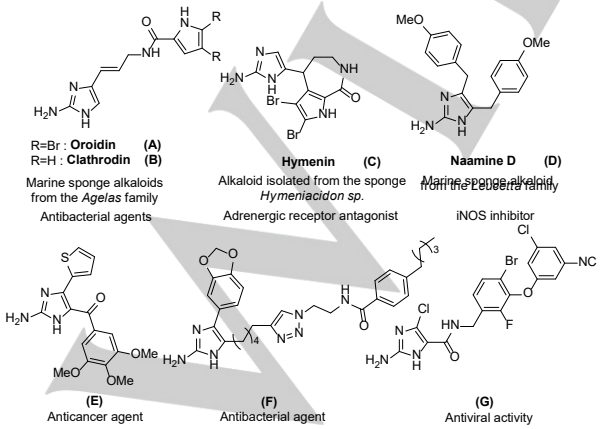
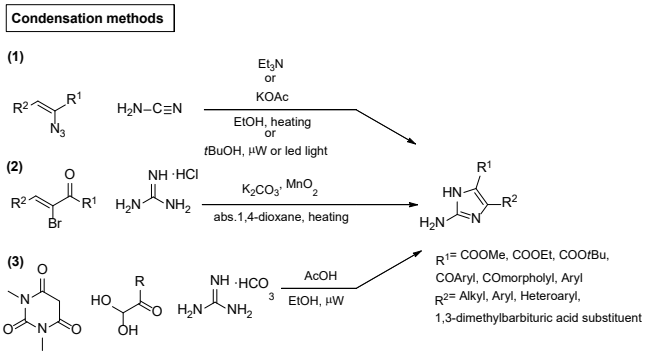


Figure 1. Representative examples of natural and synthetic bioactive 2-AI frameworks.

Among various synthetic approaches, formation of the 4,5-disubstituted 2-AI scaffold has attracted a great deal of attention due to the encoded biological potential and importance for drug design (examples **E–G**, Figure 1)[4] including several condensation reactions[5-7] as well as cleavage of the imidazo[1,2-*a*]pyrimidine ring.[8-11] For condensation procedures, iminophosphorane-mediated or base-catalysed annulation of vinyl azides have been presented exploiting isocyanates,[5a] imidates or thioamidium reagents[5b] as well as cyanamide under conventional heating[5c] or microwave and visible light irradiations[5d] (Entry 1, Scheme 1). The treatment of diaryl or dialkyl diketones with *N*,*N*-dimethylguanidine followed by Pd-catalysed hydrogenation led to 4,5-substituted 2-AI analogues.[6a] Similar condensation procedures including the reaction of α-haloketones,[6b-c] alkenones[6d] (Entry 2, Scheme 1) or diaryl α-hydroxyketones (aroins)[6e] with *N*-acetylguanidine or guanidine salts have also been reported. A three-component condensation was also described by the assembly of 1,3-dimethylbarbituric acid, arylglyoxal hydrates and guanidine salts (Entry 3, Scheme 1).[7]

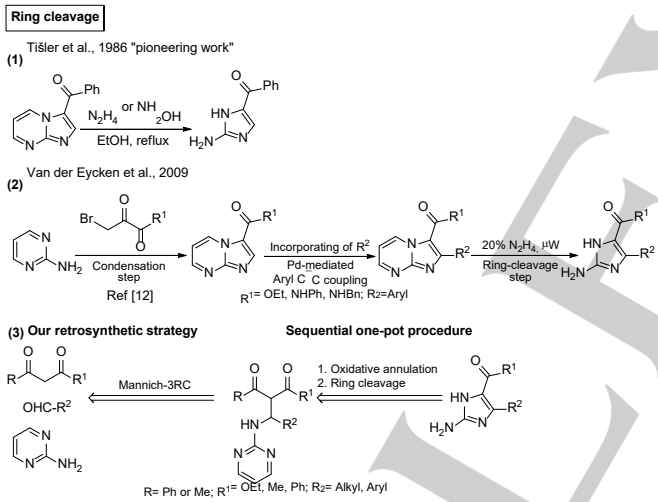


Scheme 1. Condensation procedures for the synthesis of 4,5-disubstituted 2-AI compounds.

The first method to form the 2-AI core via the fused systems based on 2-aminopyrimidines condensation and the deprotection of the resulted bicycles to afford 4-benzoyl-substituted 2-AI derivatives was demonstrated by Tišler and co-workers (Entry 1, Scheme 2).[8] Afterwards, Van der Eycken published a microwave-assisted one-pot, two-step protocol for the synthesis

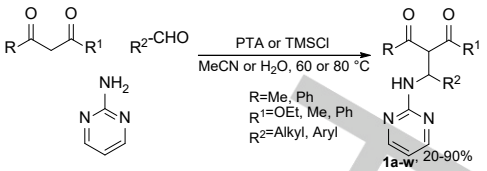
of 1,4-, 1,5- and 1,4,5-substituted 2-AI compounds.[9] First, imidazo[1,2-*a*]-pyrimidine salts were formed by condensation of 2-aminopyrimidines and α-bromocarbonyl reagents. The desired compounds were obtained by opening the heterocycle salts by means of hydrazine. Later, they tested secondary amines for the controlled cleavage of fused imidazopyrimidines.[10] Similar results involving a microwave-assisted procedure were also demonstrated for the preparation of 4,5-disubstituted 2-AI starting from 2-arylimidazo[1,2-*a*]pyrimidines[11] (Entry 2, Scheme 2). Van der Eycken also reported a multi-step process to introduce C4 ester or amide functions (R^1 = OR, NHR) and C5 aryl (R^2) substituents. This latter arylation step was carried out via a Pd-mediated reaction.[12]

In our previous report, we described the synthesis of imidazo[1,2-*a*]pyrimidine frameworks by oxidative annulation of Mannich precursors.[13] As a continuation of our research, herein we demonstrate an efficient, sequential, one-pot synthetic protocol for the preparation of structurally diverse 4,5-disubstituted 2-AI scaffolds via Mannich three-component reaction (3CR) starting from β-ketoesters, 2-aminopyrimidine and aldehydes followed by an oxidative annulation and a ring cleavage sequence (Entry 3, Scheme 2). Our concept is based on achieving valuable, unique and easily transformable 2-AI fragments as precursors for the construction of pharmacologically relevant, highly diverse and more complicated structures.



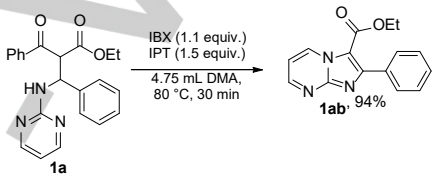
Scheme 2. Ring cleavage procedures towards 4,5-disubstituted 2-AI.

For construction of the desired chemical library, the M-3CR reactions [13],[14] were accomplished by the treatment of 2-aminopyrimidine with some β-keto esters and either aliphatic or aromatic aldehydes affording Mannich substrates **1a–w** as diastereomeric mixtures in yields up to 90% (**Scheme 3**).



Scheme 3. The synthetic protocol for the preparation of Mannich precursors.

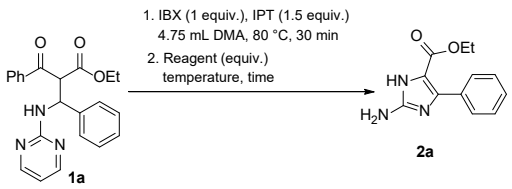
Before the investigation of the sequential one-pot procedure, the formation of key intermediate **1ab** was investigated.[13] For this study, ethyl 2-benzoyl-3-phenyl-3-(pyrimidin-2-yl)amino-propanoate **1a** was selected as model substrate for optimisation. Utilising slightly modified reaction conditions, the reaction of **1a** with iodoxybenzoic acid (IBX) and *N*-iodophtalimide (IPT) in 4.75 mL dimethylacetamide (DMA) at 80°C led to the desired heterocycle in an excellent isolated yield of 94% (Scheme 4).



Scheme 4. Preparation of the crucial intermediate 1ab

Afterwards, exploiting the observed optimal parameters for the generation of **1ab** (*see* Table S1.), both the ring cleavage procedure and the one-pot protocol could be studied. Repeating the ring-closing assembly followed by the addition of 4 equivalents of hydrazine hydrate afforded the desired 2-AI product **2a** isolated in an overall yield of 58% (X-ray structure on Figure 2.). However, full conversion could not be achieved even after 48 hours (Entry 1, Table 1). Increasing the amount of hydrazine hydrate up to 6 or 8 equivalents improved the yields of **2a** (74 and 78%) in shorter reactions (Entry 2 and 3). Because of the unfavourable properties of hydrazine monohydrate, we investigated the applicability of the hydrochloride salt of hydroxylamine. Because of the low boiling point of the hydroxylamine base (liberated by TEA; 58 °C), the reaction temperature was decreased from 80 °C to 50 °C, which improved the yield of **2a** to 80% from 67% (Entries 4 and 5). Of other bases tested (Entries 6–8), Na_2CO_3 gave the best result (82%, Entry 8). Any efforts such as the use of further additives were not successful to increase the yield (Entries 9, 10). Finally, applying a mixture of $NH_2OH{\cdot}HCl$ and the base in an increased amount (10 equivalents each) led to a superior result (92% yield, Entry 11). When the model reaction was carried out either at room temperature or using an about two-fold amount of DMA solvent or 10 equivalents of methyl hydrazine (control experiment), lower yields were experienced (Entries 12-15).

Table 1. Optimisation of one-pot protocol, ring-cleavage reaction conditions.



Entry	Reagent(s) (equiv.)	Temp. [°C]	Time [h]	Yield [%][a]
1[b]	$NH_2NH_2·H_2O$ (4)	80	48	58
2	$NH_2NH_2·H_2O$ (6)	80	16	74
3	$NH_2NH_2·H_2O$ (8)	80	1	78
4	$NH_2OH·HCl$/TEA (8/8)	80	16	67
5	$NH_2OH·HCl$/TEA (8/8)	50	16	80
6	$NH_2OH·HCl$/DIPEA (8/8)	50	16	50
7	$NH_2OH·HCl$/DBU (8/8)	50	16	65
8	$NH_2OH·HCl/Na_2CO_3$ (8/8)	50	16	82
9[c]	$NH_2OH·HCl/Na_2CO_3$ (8/8)	50	16	78
10[d]	$NH_2OH·HCl/Na_2CO_3$ (8/8)	50	16	72
11	$NH_2OH·HCl/Na_2CO_3$ (10/10)	50	16	92
12[e]	$NH_2OH·HCl/Na_2CO_3$ (10/10)	rt	24	40
13[f]	$NH_2OH·HCl/Na_2CO_3$ (10/10)	50	16	60
14[g]	$MeNHNH_2$ (10)[h]	50	1	84

Reaction conditions: 0.25 mmol of **1a**. [a] Isolated overall yields after column chromatography, full conversion (TLC), [b] 75% conversion, [c] Addition of sodium dithionite/TEA (3/3 equiv.), [d] Addition of sodium thiosulfate pentahydrate/TEA (3/3 equiv.), [e] 60% conversion, [f] Reaction carried out in 10 ml DMA. [g] 0.125 mmol of **1a**, 2.4 mL DMA. [h] according to the Ref. [15]

With the optimal conditions in hand, the sequential one-pot strategy was extended for the synthesis of other 4,5-disubstituted 2-AI scaffolds (Table 2). In terms of substitution effect, the presence of EWG groups in *meta*/*ortho*/*para* position afforded higher yields in comparison with those of the ED groups. Target compounds **2b**–**2k** were obtained in good to excellent yields up to 94% for **2f** and **2k** (R^2 = 3-$NO_2C_6H_4$ and 3,5-di$CF_3C_6H_3$). The introduction of ED functions on phenyl and/or changing R^1 = OEt into phenyl resulted in lower yields (**2l–2q**, 32–67%, **2v**, 40% and **2w**, 62%). In addition, the lowest yield was observed in the combination of R^1 = OEt, R^2 = 3,4,5-triOMePh (**2m**, 32%). For R^2 = alkyl, medium yields were observed (**2r**, 62%, **2s**, 51%) similar to other ED-substituted variants. A superior isolated yield was achieved when R^1 = Me and R^2 = 3-NO_2Ph substituents were used (**2u**, 95%).

Seven analogues (**2a**, **2f**, **2i**, **2j**, **2s**, **2u** and **2w**) were furnished in gram-scale synthesis with similar results.

Table 2. Substrate scope.

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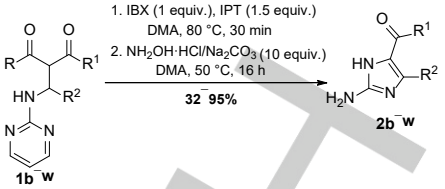


Substrate	Product	R^1	R^2	Yield [%][a]
1b	**2b**	OEt	3-FC_6H_4	88
1c	**2c**	OEt	3-ClC_6H_4	75
1d	**2d**	OEt	3-BrC_6H_4	90
1e	**2e**	OEt	3-IC_6H_4	70
1f	**2f**	OEt	3-$NO_2C_6H_4$	94
1g	**2g**	OEt	2-$CF_3C_6H_4$	60
1h	**2h**	OEt	3-$CF_3C_6H_4$	78
1i	**2i**	OEt	4-$CF_3C_6H_4$	84
1j	**2j**	OEt	2,4-di$CF_3C_6H_3$	90
1k	**2k**	OEt	3,5-di$CF_3C_6H_3$	94
1l	**2l**	OEt	3-$MeOC_6H_4$	62
1m	**2m**	OEt	3,4,5-tri$MeOC_6H_2$	32
1n	**2n**	OEt	2-MeC_6H_4	50
1o	**2o**	OEt	3-MeC_6H_4	67
1p	**2p**	OEt	4-MeC_6H_4	52
1q	**2q**	OEt	3,5-diMeC_6H_3	48
1r	**2r**	OEt	cPro	62
1s	**2s**	OEt	cHex	51
1t	**2t**	Me	4-$CF_3C_6H_4$	77[b]
1u	**2u**	Me	3-$NO_2C_6H_4$	95[b]
1v	**2v**	Ph	4-$CF_3C_6H_4$	62
1w	**2w**	Ph	3-$NO_2C_6H_4$	40

Reaction conditions: 0.25 mmol of **1a**, 4.75 mL DMA. [a] Isolated overall yields after column chromatography, full conversion (TLC), [b] R = Me.

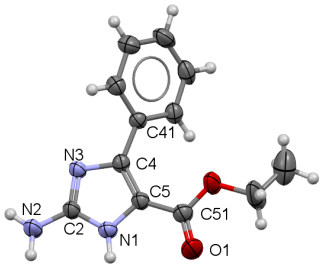


Figure 2. ORTEP view of structure of **2a** at 50% probability level with partial numbering scheme. Selected bond lengths (Å) and angles (o): C(2)–N(3) 1.331(4), C(4)–C(5) 1.380(4), N(1)–C(2) 1.336(4), N(2)–C(2) 1.347(4), C(51)–O(1) 1.203(4), N(3)–C(4) 1.382(4), C(2)–N(1)–C(5) 107.3(3), C(5)–C(51)–O(1) 123.1(3), N(3)–C(2)–N(2) 124.0(3).

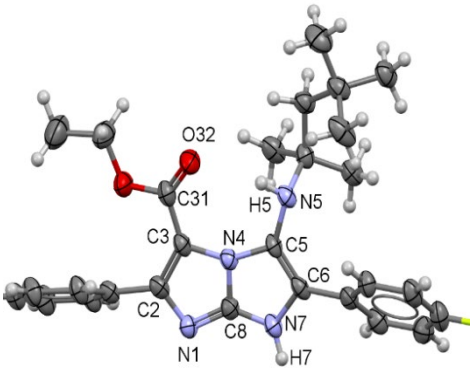
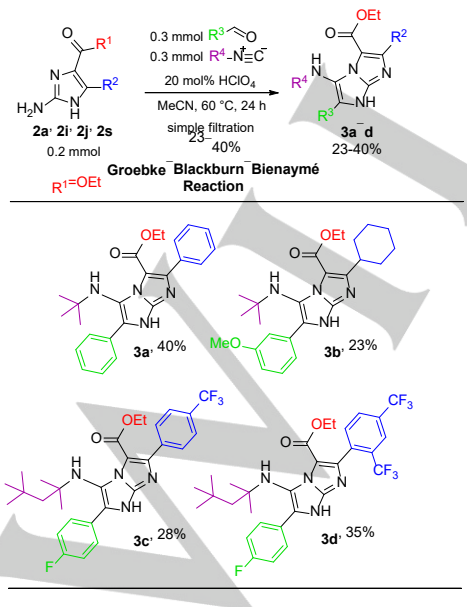


Figure 3. ORTEP view of structure of **3c** at 50% probability level with partial numbering scheme. Selected bond lengths (Å) and angles (o): C(2)–C(3) 1.400(6), N(4)–C(5) 1.417(5), N(1)–C(2) 1.371(6), N(1)–C(8) 1.343(6), C(31)–O(32) 1.224(5), C(5)–C(6) 1.358(7), C(8)–N(7)–C(6) 107.1(4), C(3)–C(31)–O(32) 124.8(4), C(2)–N(1)–C(8) 103.2(4).

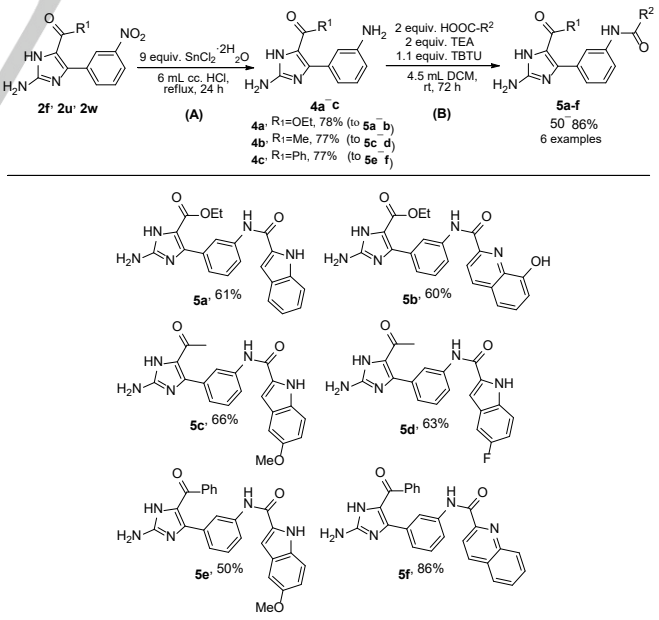
To highlight the importance of the structural entity of 4,5-disubstituted 2-AI, representative synthetic routes were introduced towards bicyclic 5:5 ring systems such as the unique 1*H*-imidazo[1,2-*a*]imidazole scaffold utilising the multicomponent Groebke–Blackburn–Bienaymé (GBB-3CR, **3a–d**) reaction (Scheme 5).

For GBB-3CR, compounds **2a**, **2i**, **2k** and **2s** were reacted with aryl aldehydes and alkyl isocyanides in the presence of $HClO_4$ as catalyst (20 mol%) to afford highly substituted 1*H*-imidazo[1,2-*a*]imidazole analogues **3a–d** in yields of 23–40%. Noteworthy is the successful exploitation of 4,5-disubstituted 2-aminoimidazoles for the construction of 2,3,5,6-tetrasubstituted 1*H*-imidazo[1,2-*a*]imidazoles via GBB-3CR. It is in sharp contrast to previous findings,[16] that a substituent on the C4 atom hinders the ring-closing step affording no conversion. On the other hand, the scope and limitation revealed, that neither alkyl aldehydes (pivalaldehyde or cyclohexyl carbaldehyde) nor aryl/benzyl isocyanides was effective in this GBB methodology. The structure of product **3c** was further confirmed by X-ray analysis (Figure 3).



Scheme 5. Representation of synthetic routes to the preparation of 1*H*-imidazo[1,2-*a*]imidazoles **3**.

Inspired by the results of medicinal chemistry research,[2b,2d] a simple and convenient synthetic route was developed by utilisation of selected 3-nitrophenyl-substituted 2-AI compounds **2f**, **2u** and **2w** as precursors for the preparation of structurally modified marine sponge alkaloid analogues with diverse substitution patterns at the C4 and C5 positions (Scheme 6). First, the reduction step (A) was carried out induced by $SnCl_2$ in concentrated HCl to form the corresponding 3-aminophenyl intermediates (**4a–c**, 77–78%). In the next step, amine coupling (B) mediated by TEA/TBTU gave target amides **5a–f** containing both indole and quinoline units in yields up to 86%.



Scheme 6. Synthesis of marine sponge alkaloid analogues **5a–f**.

A convenient, sequential one-pot access was demonstrated towards the preparation of C4/C5-functionalised 2-AI structures as valuable fragment-like heterocycles. Utilisation of Mannich precursors and exploiting the IBX/IPT-mediated intramolecular oxidative annulation as well as hydroxylamine-induced ring cleavage sequence, a highly diverse 2AI chemical library was generated. Further modifications have also been performed including the Groebke–Blackburn–Bienaymé 3CR process towards unique 1*H*-imidazo[1,2-*a*]imidazoles with four diversity points. Other efforts to synthesize potential pharmacones such as structurally modified marine alkaloid analogues were also carried out.

Mannich precursors (1a-w)[13], [14]

Ethyl 2-benzoyl-3-phenyl-3-(pyrimidin-2-ylamino)propanoate (1a)

White solid, 75% isolated yield; Silica gel TLC R*f* = 0.63 (Toluene/MeCN 3:1) Diastereoisomers ratio: 54:46. ^{1}H NMR (500 MHz, DMSO-d_6) maior diastereoisomer δ 8.27 (d, *J* = 4.8 Hz, 2H; Ar-H), 8.04 (dd, *J* = 8.3, 1.2 Hz, 2H; Ar-H), 7.78 (d, *J* = 9.2 Hz, 1H; Ar-H), 7.71 (t, *J* = 7.4 Hz, 1H, Ar-H), 7.52 – 7.47 (m, 4H; Ar-H), 7.31 (t, *J* = 7.6 Hz, 2H; Ar-H), 7.23 (t, *J* = 7.3 Hz, 1H; Ar-H), 6.56 (t, *J* = 4.8 Hz, 1H), 5.89 (dd, *J* = 10.4, 9.3 Hz, 1H), 5.31 (d, *J* = 10.7 Hz, 1H; CH), 3.77 (q, *J* = 7.1 Hz, 2H; CH_2), 0.79 (t, *J* = 7.1 Hz, 3H; CH_3). ^{1}H NMR (500 MHz, DMSO-d_6) minor diastereoisomer δ 8.27-8.17 (m, 2H; Ar-H), 7.83 (dd, *J* = 8.4, 1.3 Hz, 2H; Ar-H), 7.74 (d, *J* = 9.7 Hz, 1H; Ar-H), 7.66 – 7.59 (m, 1H; Ar-H), 7.59 (t, *J* = 7.1 Hz, 2H), 7.44 (d, *J* = 6.9 Hz, 2H), 7.16 (t, *J* = 7.7 Hz, 2H), 7.07 (t, *J* = 7.4 Hz, 1H; Ar-H), 6.58 (t, *J* = 4.8 Hz, 1H), 5.95 (t, *J* = 10.1 Hz, 1H), 5.45 (d, *J* = 10.6 Hz, 1H; CH), 4.12 – 3.95 (m, 2H; CH_2), 0.98 (t, *J* = 7.1 Hz, 3H; CH_3). ^{13}C NMR (126 MHz, DMSO) mixture of two diastereoisomers δ 193.52 (s; C_{quat}), 192.72 (s; C_{quat}), 167.66 (s; C_{quat}), 167.00 (s; C_{quat}), 161.87 (s; C_{quat}), 161.85 (s; C_{quat}), 141.31 (s; C_{quat}), 141.26 (s; C_{quat}), 136.54 (s; C_{quat}), 136.25 (s; C_{quat}), 134.47 (s; Ar-*C*H), 134.41 (s; Ar-*C*H), 129.42 (s; Ar-*C*H), 129.39 (s; Ar-*C*H), 129.11 (s; Ar-*C*H), 128.72 (s; Ar-*C*H), 128.49 (s; Ar-*C*H), 128.46 (s; Ar-*C*H), 128.23 (s; Ar-*C*H), 128.18 (s; Ar-*C*H), 127.78 (s; Ar-*C*H), 127.57 (s; Ar-*C*H), 111.24 (s; Ar-*C*H), 111.15 (s; Ar-*C*H), 61.51 (s; *C*H_2), 61.41 (s; *C*H_2), 59.58 (s; *C*H), 59.07 (s; *C*H), 54.38 (s; *C*H), 54.25 (s; *C*H), 14.22 (s; *C*H_3), 13.92 (s; *C*H_3). HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{22}H_{22}N_3O_3^+$ 376.1656 (100%); Found 376.1653.

Ethyl 2-benzoyl-3-(3-fluorophenyl)-3-(pyrimidin-2-ylamino) propanoate (1b)

White solid, 66% yield; Silica gel TLC R*f* = 0.61 (Toluene/MeCN 3:1) Diastereoisomers ratio: 58:42. ^{1}H NMR (500 MHz, DMSO-d_6) maior diastereoisomer δ 8.28 (d, *J* = 4.7 Hz, 2H; Ar-H), 8.04 (d, *J* = 7.0 Hz, 2H; Ar-H), 7.80 – 7.69 (m, 3H; Ar-H), 7.60 (t, *J* = 7.8 Hz, 2H, Ar-H), 7.39 – 7.28 (m, 4H; Ar-H), 7.07 (tdd, *J* = 7.9, 2.7, 1.3 Hz, 1H; Ar-H), 6.59 (t, *J* = 5.0 Hz, 1H), 5.89 (dd, *J* = 10.6, 9.2 Hz, 1H), 5.31 (d, *J* = 10.7 Hz, 1H; CH), 3.81 (q, *J* = 7.1 Hz, 2H; CH_2), 0.82 (t, *J* = 7.1 Hz, 3H; CH_3). ^{1}H NMR (500 MHz, DMSO-d_6) minor diastereoisomer δ 8.25 (d, *J* = 9.5 Hz, 2H; Ar-H), 7.85 (d, *J* = 7.3 Hz, 2H; Ar-H), 7.64 (t, *J* = 7.4 Hz, 1H; Ar-H), 7.51 (t, *J* = 7.8 Hz, 2H; Ar-H), 7.28 – 7.19 (m, 2H; Ar-H), 6.91 (tdd, *J* = 8.9, 2.6, 1.1 Hz, 1H; Ar-H), 6.64 – 6.58 (m, 1H), 5.95 (t, *J* = 10.1 Hz, 1H), 5.44 (d, *J* = 10.6 Hz, 1H; CH), 4.12 – 3.95 (m, 2H, CH_2), 0.98 (t, *J* = 7.1 Hz, 3H; CH_3). ^{13}C NMR (126 MHz, DMSO-d_6) mixture of two diastereoisomers δ 193.40 (s; C_{quat}), 192.48 (s; C_{quat}), 167.47 (s; C_{quat}), 166.87 (s; C_{quat}), 162.37 (dd, J_{C-F} = 243.3, 20.0 Hz; C_{quat}), 161.76 (s; C_{quat}), 161.75 (s; C_{quat}), 144.28 (d, *J* = 6.6 Hz; C_{quat}), 144.13 (d, *J* = 6.6 Hz; C_{quat}), 136.42 (s; C_{quat}), 136.11 (s; C_{quat}), 134.57 (s; Ar-*C*H), 130.54 (s; Ar-*C*H), 130.48 (s; Ar-*C*H), 130.41 (s; Ar-*C*H), 129.45 (s; Ar-*C*H), 129.15 (s; Ar-*C*H), 128.75 (s; Ar-*C*H), 124.50 (s; Ar-*C*H), 114.89 (s; Ar-*C*H), 114.72 (s; Ar-*C*H), 114.69 (d, *J* = 21.2 Hz; Ar-*C*H), 114.48 (d, *J* = 20.9 Hz; Ar-*C*H), 111.50 (s; Ar-*C*H), 111.43 (s; Ar-*C*H), 61.63 (s; *C*H_2), 61.56 (s; *C*H_2), 59.32 (s; *C*H), 58.94 (s; *C*H), 54.02 (s; *C*H), 53.91 (s; *C*H), 14.21 (s; *C*H_3), 13.94 (s; *C*H_3). HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{22}H_{21}FN_3O_3^+$ 394.1562 (100%); Found 394.1559.

Ethyl 2-benzoyl-3-(3-chlorophenyl)-3-(pyrimidin-2-ylamino) propanoate (1c)

White solid, 69% yield; Silica gel TLC R*f* = 0.65 (Toluene/MeCN 3:1) Diastereoisomers ratio: 60:40. ^{1}H NMR (500 MHz, DMSO-d_6) maior diastereoisomer δ 8.29 (d, *J* = 4.7 Hz, 2H; Ar-H), 8.05 (d, *J* = 7.3 Hz, 2H; Ar-H), 7.80 (d, *J* = 9.1 Hz, 1H; Ar-H), 7.72 (t, *J* = 7.4 Hz, 1H; Ar-H), 7.62 – 7.57 (m, 3H; Ar-H), 7.45 (d, *J* = 7.6 Hz, 1H; Ar-H), 7.36 (t, *J* = 7.7 Hz, 1H; Ar-H), 7.31 (d, *J* = 8.5 Hz, 1H; Ar-H), 6.59 (t, *J* = 4.9 Hz, 1H; Ar-H), 5.86 (dd, *J* = 10.8, 9.1 Hz, 1H), 5.30 (d, *J* = 10.8 Hz, 1H; CH), 3.81 (q, *J* = 7.1 Hz, 2H; CH_2), 0.82 (t, *J* = 7.1 Hz, 3H; CH_3). ^{1}H NMR (500 MHz, DMSO-d_6) minor diastereoisomer δ 8.27 – 8.21 (m, 2H; Ar-H), 7.85 (d, *J* = 7.3 Hz, 2H; Ar-H), 7.76 (d, *J* = 9.6 Hz, 1H; Ar-H), 7.64 (t, *J* = 7.4 Hz, 1H; Ar-H), 7.55 – 7.48 (m, 3H; Ar-H), 7.39 (d, *J* = 7.7 Hz, 1H; Ar-H), 7.21 (t, *J* = 7.8 Hz, 1H; Ar-H), 7.15 (d, *J* = 8.0 Hz, 1H; Ar-H), 6.64 – 6.58 (m, 1H; Ar-H), 5.92 (t, *J* = 10.1 Hz, 1H), 5.44 (d, *J* = 10.6 Hz, 1H; CH), 4.12 – 3.96 (m, 2H; CH_2), 0.98 (t, *J* = 7.1 Hz, 3H; CH_3). ^{13}C NMR (126 MHz, DMSO-d_6) mixture of two diastereoisomers δ 193.41 (s; C_{quat}), 192.37 (s; C_{quat}), 167.46 (s; C_{quat}), 166.84 (s; C_{quat}), 161.72 (s; C_{quat}), 161.70 (s; C_{quat}), 143.86 (s; C_{quat}), 143.73 (s; C_{quat}), 136.38 (s; C_{quat}), 136.08 (s; C_{quat}), 134.59 (s; Ar-*C*H), 133.27 (s; C_{quat}), 133.16 (s; C_{quat}), 130.48 (s; Ar-*C*H), 130.39 (s; Ar-*C*H), 129.46 (s; Ar-*C*H), 129.16 (s; Ar-*C*H), 128.76 (s; Ar-*C*H), 128.03 (s; Ar-*C*H), 127.98 (s; Ar-*C*H), 127.87 (s; Ar-*C*H), 127.65 (s; Ar-*C*H), 127.16 (s; Ar-*C*H), 127.08 (s; Ar-*C*H), 111.54 (s; Ar-*C*H), 111.47 (s; Ar-*C*H), 61.65 (s; *C*H_2), 61.60 (s; *C*H_2), 59.32 (s; *C*H), 58.90 (s; *C*H), 54.00 (s; *C*H), 53.92 (s; *C*H), 14.21 (s; *C*H_3), 13.93 (s; *C*H_3). HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{22}H_{21}ClN_3O_3^+$ 410.1266 (100%), 412.1237 (32.0%); Found 410.1263, 412.1227.

Ethyl 2-benzoyl-3-(3-bromophenyl)-3-(pyrimidin−2-ylamino) propanoate (1d)

White solid, 74% yield; Silica gel TLC R*f* = 0.65 (Toluene/MeCN 3:1) Diastereoisomers ratio: 60:40. ^{1}H NMR (500 MHz, DMSO-d_6) maior diastereoisomer δ 8.29 (d, *J* = 4.7 Hz, 2H; Ar-H), 8.05 (d, *J* = 7.3 Hz, 2H; Ar-H), 7.80 (d, *J* = 9.1 Hz, 1H; Ar-H), 7.74 – 7.69 (m, 2H; Ar-H), 7.60 (t, *J* = 7.8 Hz, 2H; Ar-H), 7.55 – 7.47 (m, 3H; Ar-H), 6.59 (t, *J* = 4.9 Hz, 1H), 5.85 (dd, *J* = 10.8, 9.1 Hz, 1H), 5.30 (d, *J* = 10.8 Hz, 1H; CH), 3.81 (q, *J* = 7.2 Hz, 2H; CH_2), 0.82 (t, *J* = 7.1 Hz, 3H; CH_3). ^{1}H NMR (500 MHz, DMSO-d_6) minor diastereoisomer δ 8.26 – 8.23 (m, 2H; Ar-H), 7.85 (d, *J* = 7.3 Hz, 2H; Ar-H), 7.76 (d, *J* = 9.6 Hz, 1H; Ar-H), 7.67 – 7.62 (m, 2H; Ar-H), 7.44 (t, *J* = 8.8 Hz, 2H; Ar-H), 7.29 (t, *J* = 7.9 Hz, 2H; Ar-H), 7.14 (t, *J* = 7.8 Hz, 1H; Ar-H), 6.64 – 6.58 (m, 1H), 5.90 (t, *J* = 10.1 Hz, 1H), 5.43 (d, *J* = 10.7 Hz, 1H; CH), 4.12 – 3.96 (m, 2H; CH_2), 0.98 (t, *J* = 7.1 Hz, 3H; CH_3). ^{13}C NMR (126 MHz, DMSO-d_6) mixture of two diastereoisomers δ 193.43 (s; C_{quat}), 192.34 (s;

C_{quat}), 167.45 (s; C_{quat}), 166.84 (s; C_{quat}), 161.70 (s; C_{quat}), 161.68 (s; C_{quat}), 144.11 (s; C_{quat}), 143.97 (s; C_{quat}), 136.37 (s; C_{quat}), 136.08 (s; C_{quat}), 134.59 (s; Ar-*C*H), 130.92 (s; Ar-*C*H), 130.85 (s; Ar-*C*H), 130.77 (s; Ar-*C*H), 130.69 (s; Ar-*C*H), 130.54 (s; Ar-*C*H), 129.47 (s; Ar-*C*H), 129.16 (s; Ar-*C*H), 128.76 (s; Ar-*C*H), 127.56 (s; Ar-*C*H), 127.46 (s; Ar-*C*H), 121.90 (s; C_{quat}), 121.82 (s; C_{quat}), 111.55 (s; Ar-*C*H), 111.48 (s; Ar-*C*H), 61.65 (s; *C*H_2), 61.61 (s; *C*H_2), 59.36 (s; *C*H), 58.90 (s; *C*H), 53.97 (s; *C*H), 53.90 (s; *C*H), 14.21 (s; *C*H_3), 13.94 (s; *C*H_3). HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{22}H_{21}BrN_3O_3^+$ 454.0761 (100.0%), 456.0741 (97.3%); Found 454.0756, 456.0734.

Ethyl 2-benzoyl-3-(3-iodophenyl)-3-(pyrimidin-2-ylamino) propanoate (1e)

White solid, 42% isolated yield; Silica gel TLC R*f* = 0.63 (Toluene/MeCN 3:1) Diastereoisomers ratio: 60:40. ^{1}H NMR (500 MHz, DMSO-d_6) mixture of two diastereoisomers δ 8.29 (d, *J* = 4.8 Hz, 2H; Ar-H), 8.27 – 8.20 (m, 2H; Ar-H), 8.04 (d, *J* = 7.3 Hz, 2H; Ar-H), 7.89 (s, 1H; Ar-H), 7.84 (d, *J* = 7.0 Hz, 2H; Ar-H), 7.78 (d, *J* = 9.1 Hz, 1H; Ar-H), 7.74 (d, *J* = 9.9 Hz, 1H; Ar-H), 7.71 (d, *J* = 7.4 Hz, 1H; Ar-H), 7.65 (t, *J* = 7.4 Hz, 1H; Ar-H), 7.63 – 7.57 (m, 3H; Ar-H), 7.55 – 7.48 (m, 2H; Ar-H), 7.44 (d, *J* = 7.8 Hz, 1H; Ar-H), 7.13 (t, *J* = 7.8 Hz, 1H; Ar-H), 6.98 (t, *J* = 7.8 Hz, 1H; Ar-H), 6.62 – 6.60 (m, 1H), 6.59 (t, *J* = 4.9 Hz, 1H), 5.86 (t, *J* = 10.1 Hz, 1H), 5.85 – 5.77 (m, 1H), 5.41 (d, *J* = 10.6 Hz, 1H; CH), 5.27 (d, *J* = 10.8 Hz, 1H; CH), 4.12 – 3.96 (m, 2H; CH_2), 3.81 (q, *J* = 7.0 Hz, 2H; CH_2), 0.98 (t, *J* = 7.1 Hz, 3H; CH_3), 0.83 (t, *J* = 7.1 Hz, 3H; CH_3). ^{13}C NMR (126 MHz, DMSO-d_6) mixture of two diastereoisomers δ 193.50 (s; C_{quat}), 192.34 (s; C_{quat}), 167.48 (s; C_{quat}), 166.84 (s; C_{quat}), 161.69 (s; C_{quat}), 161.68 (s; C_{quat}), 143.94 (s; C_{quat}), 143.78 (s; C_{quat}), 136.79 (s; Ar-*C*H), 136.69 (s; Ar-*C*H), 136.59 (s; Ar-*C*H), 136.38 (s; C_{quat}), 136.35 (s; Ar-*C*H), 136.12 (s; C_{quat}), 134.57 (s; Ar-*C*H), 130.78 (s; Ar-*C*H), 130.68 (s; Ar-*C*H), 129.46 (s; Ar-*C*H), 129.43 (s; Ar-*C*H), 129.15 (s; Ar-*C*H), 128.75 (s; Ar-*C*H), 127.92 (s; Ar-*C*H), 127.80 (s; Ar-*C*H), 111.51 (s; Ar-*C*H), 111.44 (s; Ar-*C*H), 95.06 (s; C_{quat}), 95.03 (s; C_{quat}), 61.62 (s; CH_2), 61.61 (s; *C*H_2), 59.42 (s; *C*H), 58.86 (s; *C*H), 53.86 (s; *C*H), 53.79 (s; *C*H), 14.22 (s; *C*H_3), 13.97 (s; *C*H_3). HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{22}H_{21}IN_3O_3^+$ 502.0623 (100.0%); Found 502.0620.

Ethyl 2-benzoyl-3-(3-nitrophenyl)-3-(pyrimidin-2-ylamino) propanoate (1f)

White solid, 62% isolated yield; Silica gel TLC R*f* = 0.57, 0.55 (Toluene/MeCN 3:1) Diastereoisomers ratio: 62:38. ^{1}H NMR (500 MHz, DMSO-d_6) maior diastereoisomer δ 8.46 (t, *J* = 1.9 Hz, 1H; Ar-H), 8.30 (d, *J* = 4.8 Hz, 2H; Ar-H), 8.13 (ddd, *J* = 8.2, 2.3, 1.0 Hz, 1H; Ar-H), 8.07 (d,*J* = 7.2 Hz, 2H; Ar-H), 7.98 – 7.91 (m, 3H; Ar-H), 7.73 (t, *J* = 7.4 Hz, 1H; Ar-H), 7.53-7.47 (m, 2H; Ar-H), 7.61 (t, *J* = 7.8 Hz, 2H; Ar-H), 6.60 (t, *J* = 4.8 Hz, 1H), 5.98 (dd, *J* = 10.8, 9.0 Hz, 1H), 5.40 (d, *J* = 10.9 Hz, 1H; CH), 3.85 – 3.75 (m, 2H; CH_2), 0.79 (t, *J* = 7.1 Hz, 3H; CH_3). ^{1}H NMR (500 MHz, DMSO-d_6) minor diastereoisomer δ 8.39 (t, *J* = 1.9 Hz, 1H; Ar-H), 8.29 – 8.20 (m, 2H; Ar-H), 7.98 – 7.91 (m, 3H; Ar-H), 7.89 (d, *J* = 7.8 Hz, 1H; Ar-H), 7.84 (d, *J* = 7.2 Hz, 2H; Ar-H), 7.67 – 7.63 (m, 2H; Ar-H), 6.63 (t, *J* = 4.8 Hz, 1H), 6.02 (dd, *J* = 10.6, 9.8 Hz, 1H), 5.52 (d, *J* = 10.7 Hz, 1H; CH), 4.15 – 3.97 (m, 2H; CH_2), 0.99 (t, *J* = 7.1 Hz, 3H; CH_3). ^{13}C NMR (126 MHz, DMSO-d_6) mixture of two diastereoisomers δ 193.43 (s; C_{quat}), 192.25 (s; C_{quat}), 167.35 (s; C_{quat}), 166.79 (s; C_{quat}), 161.62 (s; C_{quat}), 161.58 (s; C_{quat}), 148.20 (s; C_{quat}), 148.01 (s; C_{quat}), 143.69 (s; C_{quat}), 143.51 (s; C_{quat}), 136.31 (s; Ar-*C*H), 135.97 (s; Ar-*C*H), 135.37 (s; Ar-*C*H), 135.32 (s; Ar-*C*H), 134.68 (s; Ar-*C*H), 134.66 (s; Ar-*C*H), 130.21 (s; Ar-*C*H), 130.07 (s; Ar-*C*H), 129.48 (s; Ar-*C*H), 129.46 (s; Ar-*C*H), 129.23 (s; Ar-*C*H), 128.78 (s; Ar-*C*H), 123.02 (s; Ar-*C*H), 122.88 (s; Ar-*C*H), 122.74 (s; Ar-*C*H), 111.74 (s; Ar-*C*H), 111.68 (s; Ar-*C*H), 61.78 (s; *C*H_2), 61.74 (s; *C*H_2), 59.11 (s; *C*H), 58.86 (s; *C*H), 53.98 (s; *C*H), 53.90 (s; *C*H), 14.21 (s; *C*H_3), 13.90 (s; *C*H_3). HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{22}H_{21}N_4O_5^+$ 421.1507 (100.0%); Found 421.1506.

Ethyl 2-benzoyl-3-(pyrimidin-2-ylamino)-3-(2-(trifluoro-methyl)phenyl)propanoate (1g)

White solid, 41% isolated yield; Silica gel TLC R*f* = 0.67, 0.63 (Toluene/MeCN 3:1) Diastereoisomers ratio: 64:36. ^{1}H NMR (500 MHz, DMSO-d_6) maior diastereoisomer δ 8.27 (d, *J* = 4.7 Hz, 1H; Ar-H), 8.19 (d, *J* = 4.8 Hz, 2H; Ar-H), 8.03 (d, *J* = 7.9 Hz, 1H; Ar-H), 7.96 (d, *J* = 7.2 Hz, 2H; Ar-H), 7.79 (d, *J* = 8.2 Hz, 1H; Ar-H), 7.71 – 7.43 (m, 10H; Ar-H), 6.54 (t, *J* = 4.8 Hz, 1H), 6.46 – 6.39 (m, 1H), 5.32 (d, *J* = 10.0 Hz, 1H; CH), 3.73 (qd, *J* = 7.1, 4.3 Hz, 2H; CH_2), 0.71 (t, *J* = 7.1 Hz, 3H; CH_3). ^{1}H NMR (500 MHz, DMSO-d_6) minor diastereoisomer δ 7.89 (d, *J* = 7.9 Hz, 1H; Ar-H), 7.72 – 7.42 (m, 10H; Ar-H), 7.33 (t, *J* = 7.6 Hz, 1H; Ar-H), 6.60 (t, *J* = 4.8 Hz, 1H), 6.45 – 6.38 (m, 1H), 5.49 (d, *J* = 9.6 Hz, 1H; CH), 4.05 – 3.84 (m, 2H; CH_2), 0.94 (t, *J* = 7.1 Hz, 3H; CH_3). ^{13}C NMR (126 MHz, DMSO-d_6) mixture of two diastereoisomers δ 193.36 (s; C_{quat}), 192.96 (s; C_{quat}), 167.99 (s; C_{quat}), 166.91 (s; C_{quat}), 161.53 (s; C_{quat}), 161.40 (s; C_{quat}), 158.26 (s; C_{quat}), 140.38 (s; C_{quat}), 139.78 (s; C_{quat}), 136.69 (s; C_{quat}), 136.31 (s; C_{quat}), 134.30 (s; Ar-*C*H), 134.21 (s; Ar-*C*H), 132.82 (s; Ar-*C*H), 132.79 (s; Ar-*C*H), 130.35 (s; Ar-*C*H), 129.36 (s; Ar-*C*H), 129.35 (s; Ar-*C*H), 129.21 (s; Ar-*C*H), 128.85 (s; Ar-*C*H), 128.47 (s; Ar-*C*H), 128.34 (s; Ar-*C*H), 128.24 (s; Ar-*C*H), 127.89 – 127.13 (m; C_{quat}), 127.54 (q, *J* = 29.3 Hz; C_{quat}), 126.48 (q, *J* = 5.5 Hz; Ar-*C*H), 126.27 (q, *J* = 5.4 Hz; Ar-*C*H), 125.97 (s; C_{quat}), 125.82 (s; C_{quat}), 111.44 (s; Ar-*C*H), 111.41 (s; Ar-*C*H), 61.67 (s; *C*H_2), 61.32 (s; *C*H_2), 59.10 (s; *C*H), 58.85 (s; *C*H), 49.78 (s; *C*H), 49.76 (s; *C*H), 14.03 (s; *C*H_3), 13.67 (s; *C*H_3). HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{23}H_{21}F_3N_3O_3^+$ 444.1530 (100.0%); Found 444.1529.

Ethyl 2-benzoyl-3-(pyrimidin-2-ylamino)-3-(3-(trifluoro-methyl)phenyl)propanoate (1h)

White solid, 40% yield; Silica gel TLC R*f* = 0.63 (Toluene/MeCN 3:1) Diastereoisomers ratio: 64:36. ^{1}H NMR (500 MHz, DMSO-d_6) mixture of two diastereoisomers δ 8.29 (d, *J* = 4.7 Hz, 2H; Ar-H), 8.25 (d,*J* = 7.6 Hz, 2H; Ar-H), 8.05 (d, *J* = 7.2 Hz, 2H; Ar-H), 7.89 (s, 1H; Ar-H), 7.88 – 7.84 (m, 2H; Ar-H), 7.84 – 7.78 (m, 3H; Ar-H), 7.72 (t, *J* = 7.4 Hz, 2H; Ar-H), 7.65 – 7.54 (m, 5H; Ar-H), 7.49 (t, *J* = 7.8 Hz, 1H; Ar-H), 7.46 – 7.39 (m, 1H; Ar-H), 6.62 (t, *J* = 4.8 Hz, 1H), 6.59 (t, *J* = 4.8 Hz, 1H), 6.02 – 5.97 (m, 1H), 5.96 – 5.91 (m, 1H), 5.49 (d, *J* = 10.6 Hz, 1H; CH), 5.36 (d, *J* = 10.8 Hz, 1H; CH), 4.14 – 3.95 (m, 2H; CH_2), 3.77 (q, *J* = 7.1 Hz, 2H; CH_2), 0.99 (t, *J* = 7.1 Hz, 3H; CH_3), 0.77 (t, *J* = 7.1 Hz, 3H; CH_3). ^{13}C NMR (126 MHz, DMSO-d_6) mixture of two diastereoisomers δ 193.62 (s; C_{quat}), 192.28 (s; C_{quat}), 167.45 (s; C_{quat}), 166.84 (s; C_{quat}), 142.72 (s; C_{quat}), 142.53 (s; C_{quat}), 136.35 (s; C_{quat}), 136.09 (s; C_{quat}), 134.62 (s; Ar-*C*H), 134.57 (s; Ar-*C*H), 132.66 (s; Ar-*C*H), 132.59 (s; Ar-*C*H), 129.70 (s; Ar-*C*H), 129.57 (s; Ar-*C*H), 129.48 (s; Ar-*C*H), 129.40 (s; Ar-*C*H), 129.16 (s; Ar-*C*H), 128.70 (s; Ar-*C*H), 124.70 (dq, *J* = 8.4, 4.4 Hz; Ar-*C*H), 124.44 (q, *J* = 3.7 Hz; Ar-*C*H), 111.61 (s; Ar-*C*H), 111.54 (s; Ar-*C*H), 61.68 (s; *C*H_2), 61.59 (s; *C*H_2), 59.30 (s; *C*H), 58.79 (s; *C*H), 54.17 (s; *C*H), 54.04

(s; *C*H), 14.21 (s; *C*H_3), 13.79 (s; *C*H_3). HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{23}H_{21}F_3N_3O_3^+$ 444.1530 (100.0%); Found 444.1528.

Ethyl 2-benzoyl-3-(pyrimidin-2-ylamino)-3-(4-(trifluoromethyl)phenyl)propanoate (1i)

The substrate has been characterized in the previous work.[13]

Ethyl 2-benzoyl-3-(2,4-bis(trifluoromethyl)phenyl)-3-(pyrimidin-2-ylamino)propanoate (1j)

White solid, 22% isolated yield; Silica gel TLC R*f* = 0.69, 0.65 (Toluene/MeCN 3:1) Diastereoisomers ratio: 69:31. ^{1}H NMR (500 MHz, DMSO-d_6) maior diastereoisomer δ 8.31 (d, *J* = 8.4 Hz, 1H; Ar-H), 8.20 (d, *J* = 4.8 Hz, 2H; Ar-H), 8.15 (d, *J* = 8.3 Hz, 2H; Ar-H), 7.98 (d, *J* = 7.2 Hz, 2H; Ar-H), 7.95 (s, 1H; Ar-H), 7.57 (t, *J* = 7.8 Hz, 2H; Ar-H), 7.48 (t, *J* = 7.8 Hz, 1H; Ar-H), 6.57 (t, *J* = 4.8 Hz, 1H), 6.43 (dd, *J* = 10.1, 8.5 Hz, 1H), 5.36 (d, *J* = 10.2 Hz, 1H; CH), 3.74 (qd, *J* = 7.1, 4.5 Hz, 2H; CH_2), 0.69 (t, *J* = 7.1 Hz, 3H; CH_3). ^{1}H NMR (500 MHz, DMSO-d_6) minor diastereoisomer δ 8.29 (d, *J* = 4.8 Hz, 2H; Ar-H), 7.97 (d, *J* = 8.3 Hz, 2H; Ar-H), 7.91 (d, *J* = 8.4 Hz, 1H; Ar-H), 7.88 (s, 1H; Ar-H), 7.78 (d, *J* = 7.2 Hz, 2H; Ar-H), 7.69 (t, *J* = 7.4 Hz, 2H; Ar-H), 7.62 (t, *J* = 7.4 Hz, 1H; Ar-H), 6.63 (t, *J* = 4.8 Hz, 1H), 6.45 (t, *J* = 9.5 Hz, 1H), 5.55 (d, *J* = 9.6 Hz, 1H; CH), 4.04 – 3.87 (m, 2H; CH_2), 0.94 (t, *J* = 7.1 Hz, 3H; CH_3). ^{13}C NMR (126 MHz, DMSO-d_6) mixture of two diastereoisomers δ 193.46 (s; C_{quat}), 192.52 (s; C_{quat}), 167.81 (s; C_{quat}), 166.80 (s; C_{quat}), 161.43 (s; C_{quat}), 161.26 (s; C_{quat}), 145.62 (s; C_{quat}), 144.63 (s; C_{quat}), 136.56 (s; C_{quat}), 136.14 (s; C_{quat}), 134.38 (s; Ar-*C*H), 134.34 (s; Ar-*C*H), 131.90 (s; Ar-*C*H), 130.75 (s; Ar-*C*H), 129.76 (q, *J* = 4.0 Hz; Ar-*C*H), 129.39 (s; Ar-*C*H), 129.36 (s; Ar-*C*H), 128.99 (q, *J* = 44.9, 39.6 Hz; C_{quat}), 128.90 (s; Ar-*C*H), 128.52 (s; Ar-*C*H), 123.32 – 123.09 (m; Ar-*C*H), 111.74 (s; Ar-*C*H), 61.84 (s; *C*H_2), 61.50 (s; *C*H_2), 58.82 (s; *C*H), 58.68 (s; *C*H), 49.75 (s; *C*H), 14.00 (s; *C*H_3), 13.51 (s; *C*H_3). HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{24}H_{20}F_6N_3O_3^+$ 512.1404 (100.0%); Found 512.1385.

Ethyl 2-benzoyl-3-(3,5-bis(trifluoromethyl) phenyl)-3-(pyrimidin-2-ylamino)propanoate (1k)

The substrate has been characterized in the previous work.[13]

Ethyl 2-benzoyl-3-(3-methoxyphenyl)-3-(pyrimidin-2-yl amino)propanoate (1l)

White solid, 30% isolated yield; Silica gel TLC R*f* = 0.59, 0.53 (Toluene/MeCN 3:1) Diastereoisomers ratio: 68:32. ^{1}H NMR (500 MHz, DMSO-d_6) maior diastereoisomer δ 8.27 (d, *J* = 4.7 Hz, 2H; Ar-H), 8.04 (d, *J* = 7.2 Hz, 1H; Ar-H), 7.85 (d, *J* = 7.2 Hz, 2H; Ar-H), 7.73 – 7.57 (m, 4H; Ar-H), 7.51 (t, *J* = 7.8 Hz, 2H; Ar-H), 7.12 – 7.01 (m, 3H; Ar-H), 6.98 (d, *J* = 7.7 Hz, 1H; Ar-H), 6.64 (ddd, *J* = 8.1, 2.6, 0.9 Hz, 1H; Ar-H), 6.59 (t, *J* = 4.8 Hz, 1H), 5.93 (t, *J* = 10.2 Hz, 1H), 5.44 (d, *J* = 10.7 Hz, 1H; CH), 4.14 – 3.94 (m, 2H; CH_2), 3.63 (s, 3H; CH_3), 0.98 (t, *J* = 7.1 Hz, 3H; CH_3). ^{1}H NMR (500 MHz, DMSO-d_6) minor diastereoisomer δ 8.23 (d, *J* = 4.7 Hz, 2H; Ar-H), 7.74 – 7.57 (m, 4H; Ar-H), 7.22 (t, *J* = 7.9 Hz, 1H; Ar-H), 7.11 – 7.03 (m, 3H; Ar-H), 6.80 (ddd, *J* = 8.2, 2.6, 0.9 Hz, 1H; Ar-H), 6.56 (d, *J* = 4.8 Hz, 1H), 5.90 – 5.84 (m, 1H), 5.30 (d, *J* = 10.6 Hz, 1H; CH), 3.80 (q, *J* = 7.1 Hz, 2H; CH_2), 3.73 (s, 3H; CH_3), 0.82 (t, *J* = 7.1 Hz, 3H; CH_3). ^{13}C NMR (126 MHz, DMSO-d_6) mixture of two diastereoisomers δ 193.44 (s; C_{quat}), 192.80 (s; C_{quat}), 167.63 (s; C_{quat}), 166.97 (s; C_{quat}), 161.87 (s; C_{quat}), 159.50 (s; C_{quat}), 159.37 (s; C_{quat}), 142.89 (s; C_{quat}), 142.76 (s; C_{quat}), 136.56 (s; C_{quat}), 136.27 (s; C_{quat}), 134.47 (s; Ar-*C*H), 134.41 (s; Ar-*C*H), 129.53 (s; Ar-*C*H), 129.50 (s; Ar-*C*H), 129.42 (s; Ar-*C*H), 129.39 (s; Ar-*C*H), 129.12 (s; Ar-*C*H), 128.75 (s; Ar-*C*H), 120.58 (s; Ar-*C*H), 120.54 (s; Ar-*C*H), 114.08 (s; Ar-*C*H), 113.98 (s; Ar-*C*H), 112.91 (s; Ar-*C*H), 112.83 (s; Ar-*C*H), 111.27 (s; Ar-*C*H), 111.20 (s; Ar-*C*H), 61.50 (s; *C*H_2), 61.43 (s; *C*H_2), 59.48 (s; *C*H), 58.97 (s; *C*H), 55.48 (s; *C*H_3), 55.34 (s; *C*H_3), 54.31 (s; *C*H), 54.20 (s; *C*H), 14.22 (s; *C*H_3), 13.96 (s; *C*H_3). HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{23}H_{24}N_3O_4^+$ 406.1762 (100.0%); Found 406.1758.

Ethyl 2-benzoyl-3-(pyrimidin-2-ylamino)-3-(3,4,5-trimethoxyphenyl)propanoate (1m)

Pale yellow solid, 25% isolated yield; Silica gel TLC R*f* = 0.47, 0.42 (Toluene/MeCN 3:1) Diastereoisomers ratio: 55:45. ^{1}H NMR (500 MHz, DMSO-d_6) mixture of two diastereoisomers δ 8.03 (d, *J* = 7.4 Hz, 2H), 7.97 (d, *J* = 7.4 Hz, 2H; Ar-H), 7.88 (d, *J* = 7.2 Hz, 2H; Ar-H), 7.83 (d, *J* = 7.4 Hz, 2H; Ar-H), 7.70 (t, *J* = 7.4 Hz, 1H; Ar-H), 7.60 – 7.47 (m, 5H; Ar-H), 7.45 (t, *J* = 7.5 Hz, 2H; Ar-H), 6.84 (s, 2H; Ar-H), 6.73 (s, 2H; Ar-H), 6.57 (ddt, *J* = 19.3, 6.2, 4.7 Hz, 3H), 5.88 (td, *J* = 10.1, 4.4 Hz, 2H), 5.60 (td, *J* = 9.0, 4.6 Hz, 1H), 5.42 (d, *J* = 10.6 Hz, 1H; CH), 5.30 (d, *J* = 10.4 Hz, 1H; CH), 4.04 (dddd, *J* = 18.0, 10.9, 7.1, 3.8 Hz, 2H; CH_2), 3.91 – 3.82 (m, 2H; CH_2), 3.77 (s, 3H; CH_3), 3.75 (s, 3H; CH_3), 3.65 (s, 3H; CH_3), 3.62 (s, 3H; CH_3), 3.61 (s, 3H; CH_3), 3.48 (s, 3H; CH_3), 1.00 (t, *J* = 7.1 Hz, 3H; CH_3), 0.86 (t, *J* = 7.0 Hz, 3H; CH_3). ^{13}C NMR (126 MHz, DMSO) mixture of two diastereoisomers δ 193.87 (s; C_{quat}), 193.01 (s; C_{quat}), 167.70 (s; C_{quat}), 167.02 (s; C_{quat}), 162.14 (s; C_{quat}), 161.89 (s; C_{quat}), 158.46 (s; Ar-*C*H), 158.33 (s; Ar-*C*H), 153.00 (s; C_{quat}), 152.85 (s; C_{quat}), 137.38 (s; C_{quat}), 137.24 (s; C_{quat}), 136.96 (s; C_{quat}), 136.69 (s; C_{quat}), 136.60 (s; C_{quat}), 136.54 (s; C_{quat}), 134.42 (s; Ar-*C*H), 134.23 (s; Ar-*C*H), 129.40 (s; Ar-*C*H), 129.24 (s; Ar-*C*H), 129.14 (s; Ar-*C*H), 129.07 (s; Ar-*C*H), 128.69 (s; Ar-*C*H), 128.65 (s; Ar-*C*H), 128.52 (s; Ar-*C*H), 127.91 (s; Ar-*C*H), 111.28 (s; Ar-*C*H), 111.25 (s; Ar-*C*H), 105.85 (s; Ar-*C*H), 105.68 (s; Ar-*C*H), 61.43 (s; *C*H_2), 61.41 (s; *C*H_2), 60.36 (s; *C*H_3), 60.25 (s; *C*H_3), 59.63 (s; *C*H), 59.01 (s; *C*H), 56.57 (s; *C*H_3), 56.41 (s; *C*H_3), 56.32 (s; *C*H_3), 56.25 (s; *C*H_3), 54.75 (s; *C*H), 54.54 (s; *C*H), 14.24 (s; *C*H_3), 14.03 (s; *C*H_3). HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{25}H_{28}N_3O_6^+$ 466.1973 (100.0%); Found 466.1978.

Ethyl 2-benzoyl-3-(pyrimidin-2-ylamino)-3-(o-tolyl) propanoate (1n)

White solid, 48% isolated yield; Silica gel TLC R*f* = 0.63, 0.59 (Toluene/MeCN 3:1) Diastereoisomers ratio: 84:16. ^{1}H NMR (500 MHz, DMSO-d_6) maior diastereoisomer δ 8.27 (d, *J* = 4.2 Hz, 1H; Ar-H), 7.80 (d, *J* = 7.2 Hz, 2H; Ar-H), 7.71 (d, *J* = 9.5 Hz, 1H; Ar-H), 7.60 (d, *J* = 7.3 Hz, 2H; Ar-H), 7.48 (t, *J* = 7.8 Hz, 2H; Ar-H), 6.96 (t, *J* = 7.7 Hz, 2H; Ar-H), 6.94 – 6.90 (m, 1H; Ar-H), 6.56 (t, *J* = 4.8 Hz, 1H), 6.20 – 6.12 (m, 1H), 5.51 (d, *J* = 10.8 Hz, 1H; CH), 4.10 – 3.97 (m, 2H; CH_2), 2.59 (s, 3H; CH_3), 0.98 (t, *J* = 7.1 Hz, 3H; CH_3). ^{1}H NMR (500 MHz, DMSO-d_6) minor diastereoisomer δ 8.21 (d, *J* = 4.8 Hz, 2H; Ar-H), 8.05 (d, *J* = 7.2 Hz, 2H; Ar-H), 7.68 (d, *J* = 8.2 Hz, 1H; Ar-H), 7.19 (t, *J* = 8.1 Hz, 1H; Ar-H), 7.12 – 7.06 (m, 2H; Ar-H), 6.53 (t, *J* = 4.8 Hz, 1H), 6.21 – 6.13 (m, 1H), 5.33 (d, *J* = 10.7 Hz, 1H; CH), 3.72 (qq, *J* = 10.9, 7.1 Hz, 2H; CH_2), 2.61 (s, 3H; CH_3), 0.69 (t, *J* = 7.1 Hz, 3H; CH_3). ^{13}C NMR (126 MHz, DMSO-d_6) maior diastereoisomer δ 193.61 (s; C_{quat}), 167.78 (s; C_{quat}), 161.86 (s; C_{quat}), 140.06 (s; C_{quat}), 136.57 (s; C_{quat}), 136.34 (s; C_{quat}), 134.31 (s; Ar-*C*H), 130.26 (s; Ar-*C*H), 129.31 (s; Ar-*C*H), 128.69 (s; Ar-*C*H), 127.37 (s; Ar-*C*H), 127.29 (s; Ar-*C*H), 126.29 (s; Ar-*C*H), 111.04 (s; Ar-*C*H), 61.48 (s; *C*H_2), 58.83 (s; *C*H), 49.97 (s; *C*H), 20.07 (s; *C*H_3), 14.23 (s; *C*H_3). ^{13}C NMR (126

MHz, DMSO-d_6) minor diastereoisomer δ 193.58 (s; C_{quat}), 166.97 (s; C_{quat}), 161.84 (s; C_{quat}), 140.02 (s; C_{quat}), 136.51 (s; C_{quat}), 136.22 (s; C_{quat}), 134.45 (s; Ar-*C*H), 129.41 (s; Ar-*C*H), 129.10 (s; Ar-*C*H), 128.09 (s; Ar-*C*H), 127.51 (s; Ar-*C*H), 126.29 (s; Ar-*C*H), 110.98 (s; Ar-*C*H), 61.32 (s; *C*H_2), 59.63 (s; *C*H), 49.65 (s; *C*H), 19.88 (s; *C*H_3), 13.75 (s; *C*H_3). HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{23}H_{24}N_3O_3^+$ 390.1813 (100.0%); Found 390.1811.

Ethyl 2-benzoyl-3-(pyrimidin-2-ylamino)-3-(m-tolyl) propanoate (1o)

The substrate has been characterized in the previous work.[13]

Ethyl 2-benzoyl-3-(pyrimidin-2-ylamino)-3-(p-tolyl) propanoate (1p)

White solid, 35% isolated yield; Silica gel TLC R*f* = 0.61 (Toluene/MeCN 3:1) Diastereoisomers ratio: 51:49. ^{1}H NMR (500 MHz, DMSO-d_6) mixture of two diastereoisomers δ 8.26 (d, *J* = 4.6 Hz, 2H; Ar-H), 8.22 (d, *J* = 4.7 Hz, 2H; Ar-H), 8.04 (d, *J* = 7.2 Hz, 2H; Ar-H), 7.84 (d, *J* = 7.2 Hz, 3H; Ar-H), 7.74 – 7.65 (m, 3H; Ar-H), 7.63 (t, *J* = 7.4 Hz, 1H; Ar-H), 7.59 (t, *J* = 7.8 Hz, 2H; Ar-H), 7.51 (t, *J* = 7.8 Hz, 2H; Ar-H), 7.38 (d, *J* = 8.1 Hz, 2H; Ar-H), 7.33 (d, *J* = 8.1 Hz, 2H; Ar-H), 7.11 (d, *J* = 7.9 Hz, 2H; Ar-H), 6.97 (d, *J* = 7.9 Hz, 2H; Ar-H), 6.57 (t, *J* = 4.8 Hz, 1H; Ar-H), 6.55 (t, *J* = 4.8 Hz, 1H), 5.92 (t, *J* = 10.2 Hz, 1H), 5.85 (dd, *J* = 10.6, 9.2 Hz, 1H), 5.43 (d, *J* = 10.6 Hz, 1H; CH), 5.29 (d, *J* = 10.7 Hz, 1H; CH), 4.02 (ddq, *J* = 35.5, 10.9, 7.1 Hz, 2H; CH_2), 3.78 (q, *J* = 7.1 Hz, 2H; CH_2), 2.24 (s, 3H; CH_3), 2.13 (s, 3H; CH_3), 0.97 (t, *J* = 7.0 Hz, 3H; CH_3), 0.81 (t, *J* = 7.1 Hz, 3H; CH_3). ^{13}C NMR (126 MHz, DMSO-d_6) mixture of two diastereoisomers δ 193.40 (s; C_{quat}), 192.84 (s; C_{quat}), 167.68 (s; C_{quat}), 167.00 (s; C_{quat}), 161.88 (s; C_{quat}), 161.86 (s; C_{quat}), 138.35 (s; C_{quat}), 138.33 (s; C_{quat}), 136.83 (s; C_{quat}), 136.61 (s; C_{quat}), 136.57 (s; C_{quat}), 136.25 (s; C_{quat}), 134.44 (s; Ar-*C*H), 134.41 (s; Ar-*C*H), 129.40 (s; Ar-*C*H), 129.12 (s; Ar-*C*H), 129.02 (s; Ar-*C*H), 128.75 (s; Ar-*C*H), 128.11 (s; Ar-*C*H), 128.08 (s; Ar-*C*H), 111.17 (s; Ar-*C*H), 111.09 (s; Ar-*C*H), 61.48 (s; *C*H_2), 61.39 (s; *C*H_2), 59.57 (s; *C*H), 59.13 (s; *C*H), 54.06 (s; *C*H), 53.95 (s; *C*H), 21.14 (s; *C*H_3), 21.02 (s; *C*H_3), 14.22 (s; *C*H_3), 13.94 (s; *C*H_3). HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{23}H_{24}N_3O_3^+$ 390.1813 (100.0%); Found 390.1809.

Ethyl 2-benzoyl-3-(3,5-dimethylphenyl)-3-(pyrimidin-2-yl amino)propanoate (1q)

White solid, 21% isolated yield; Silica gel TLC R*f* = 0.65 (Toluene/MeCN 3:1) Diastereoisomers ratio: 56:44. ^{1}H NMR (500 MHz, DMSO-d_6) maior diastereoisomer δ 8.26 (d, *J* = 4.8 Hz, 2H; Ar-H), 8.03 (d, *J* = 7.3 Hz, 2H; Ar-H), 7.70 (t, *J* = 9.4 Hz, 2H; Ar-H), 7.58 (t, *J* = 7.8 Hz, 2H; Ar-H), 7.10 (s, 2H; Ar-H), 6.85 (s, 1H; Ar-H), 6.56 – 6.54 (m, 1H), 5.85 – 5.80 (m, 1H), 5.23 (d, *J* = 10.7 Hz, 1H; CH), 3.79 (q, *J* = 7.1 Hz, 2H; CH_2), 2.24 (s, 6H; 2 CH_3), 0.82 (t, *J* = 7.1 Hz, 3H; CH_3). ^{1}H NMR (500 MHz, DMSO-d_6) minor diastereoisomer δ 8.22 (d, *J* = 4.7 Hz, 2H; Ar-H), 7.83 (d, *J* = 7.3 Hz, 2H; Ar-H), 7.64 – 7.60 (m, 2H; Ar-H), 7.50 (t, *J* = 7.7 Hz, 2H; Ar-H), 7.03 (s, 2H; Ar-H), 6.69 (s, 1H; Ar-H), 6.58 – 6.56 (m, 1H), 5.88 (t, *J* = 10.0 Hz, 1H), 5.38 (d, *J* = 10.4 Hz, 1H; CH), 4.09 – 3.95 (m, 2H; CH_2), 2.11 (s, 6H; 2 CH_3), 0.98 (t, *J* = 7.1 Hz, 3H; CH_3). ^{13}C NMR (126 MHz, DMSO-d_6) mixture of two diastereoisomers δ 193.69 (s; C_{quat}), 192.71 (s; C_{quat}), 172.14 (s; C_{quat}), 167.82 (s; C_{quat}), 167.00 (s; C_{quat}), 161.84 (s; C_{quat}), 141.26 (s; C_{quat}), 141.09 (s; C_{quat}), 137.31 (s; C_{quat}), 137.27 (s; C_{quat}), 136.54 (s; C_{quat}), 136.34 (s; C_{quat}), 134.41 (s; Ar-*C*H), 134.28 (s; Ar-*C*H), 129.39 (s; Ar-*C*H), 129.29 (s; Ar-*C*H), 129.16 (s; Ar-*C*H), 129.10 (s; Ar-*C*H), 128.96 (s; Ar-*C*H), 128.72 (s; Ar-*C*H), 125.92 (s; Ar-*C*H), 125.90 (s; Ar-*C*H), 111.15 (s; Ar-*C*H), 111.05 (s; Ar-*C*H), 61.42 (s; *C*H_2), 61.37 (s; *C*H_2), 59.82 (s; *C*H), 59.12 (s; *C*H), 54.15 (s; *C*H), 54.05 (s; *C*H), 21.44 (s; *C*H_3), 21.35 (s; *C*H_3), 14.21 (s; *C*H_3), 13.92 (s; *C*H_3). HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{24}H_{26}N_3O_3^+$ 404.1969 (100.0%); Found 404.1965.

Ethyl 2-benzoyl-3-cyclopropyl-3-(pyrimidin-2-yl amino)propanoate (1r)

Colourless solid, 15% isolated yield; Silica gel TLC R*f* = 0.63, 0.57 (Toluene/MeCN 3:1) Diastereoisomers ratio: 62:38. ^{1}H NMR (500 MHz, Chloroform-*d*) mixture of diastereoisomers δ 8.29 (d, *J* = 4.9 Hz, 1H; Ar-H), 8.27 (d, *J* = 4.8 Hz, 2H; Ar-H), 8.24 (d, *J* = 4.8 Hz, 1H; Ar-H), 8.15 (d, *J* = 4.8 Hz, 1H; Ar-H), 8.09 (d, *J* = 7.1 Hz, 2H; Ar-H), 8.02 (d, *J* = 7.0 Hz, 1H; Ar-H), 7.94 (d, *J* = 7.0 Hz, 1H; Ar-H), 7.89 (d, *J* = 7.0 Hz, 1H; Ar-H), 7.62 – 7.52 (m, 3H; Ar-H), 7.49 (t, *J* = 7.7 Hz, 2H; Ar-H), 7.46 – 7.42 (m, 1H), 6.61 (t, *J* = 4.8 Hz, 1H), 6.56 – 6.47 (m, 2H), 6.45 (t, *J* = 4.8 Hz, 1H), 4.98 (d, *J* = 4.8 Hz, 1H; CH), 4.91 (d, *J* = 5.6 Hz, 1H; CH), 4.17 – 4.05 (m, 4H; 2 CH_2), 1.55 – 1.45 (m, 2H; CH_2), 1.42 – 1.35 (m, 2H; CH_2), 1.18 (t, *J* = 7.1 Hz, 3H; CH_3), 1.11 (t, *J* = 7.1 Hz, 3H; CH_3), 1.01 – 0.94 (m, 1H; CH), 0.79 – 0.73 (m, 1H; CH), 0.55 – 0.43 (m, 4H; 2 CH_2). ^{13}C NMR (126 MHz, $CDCl_3$) mixture of two diastereoisomers δ 194.89 (s; C_{quat}), 194.10 (s; C_{quat}), 168.84 (s; C_{quat}), 168.69 (s; C_{quat}), 158.03 (s; Ar-*C*H), 158.00 (s; Ar-*C*H), 136.80 (s; C_{quat}), 136.73 (s; C_{quat}), 133.56 (s; Ar-*C*H), 133.47 (s; Ar-*C*H), 133.27 (s; Ar-*C*H), 133.03 (s; Ar-*C*H), 128.82 (s; Ar-*C*H), 128.55 (s; Ar-*C*H), 128.35 (s; Ar-*C*H), 128.25 (s; Ar-*C*H), 110.76 (s; Ar-*C*H), 110.57 (s; Ar-*C*H), 61.41 (s; *C*H_2), 61.30 (s; *C*H_2), 57.78 (s; *C*H), 57.04 (s; *C*H), 55.88 (s; *C*H), 54.98 (s; *C*H), 15.90 (s; *C*H), 14.93 (s; *C*H), 13.90 (s; *C*H_3), 13.88 (s; *C*H_3), 4.86 (s; *C*H_2), 4.68 (s; *C*H_2), 3.63 (s; *C*H_2), 3.58 (s; *C*H_2). HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{19}H_{22}N_3O_3^+$ 340.1656 (100.0%), Found 340.1662.

Ethyl 2-benzoyl-3-cyclohexyl-3-(pyrimidin-2-ylamino) propanoate (1s)

Colourless solid, 23% isolated yield; Silica gel TLC R*f* = 0.69, 0.63 (Toluene/MeCN 3:1) Diastereoisomers ratio: 50:50. ^{1}H NMR (500 MHz, Chloroform-*d*) mixture of two diastereoisomers δ 8.22 (d, *J* = 4.7 Hz, 2H; Ar-H), 7.94 (d, *J* = 8.2 Hz, 2H; Ar-H), 7.83 (d, *J* = 8.1 Hz, 2H; Ar-H), 7.60 – 7.51 (m, 3H; Ar-H), 7.52 – 7.37 (m, 2H; Ar-H), 6.44 (t, *J* = 4.7 Hz, 1H), 6.37 (t, *J* = 4.7 Hz, 1H), 6.26 (d, *J* = 10.5 Hz, 1H), 5.95 (d, *J* = 10.6 Hz, 1H), 4.89 – 4.79 (m, 2H; CH_2), 4.77 (d, *J* = 5.3 Hz, 1H; CH), 4.72 (d, *J* = 4.3 Hz, 1H; CH), 4.22 – 4.10 (m, 2H; CH_2), 3.95 (q, *J* = 7.1 Hz, 2H; CH_2), 1.99 – 1.92 (m, 1H), 1.90 – 1.80 (m, 2H), 1.80 – 1.57 (m, 9H), 1.17 (t, *J* = 7.1 Hz, 3H; CH_3), 1.17 – 1.00 (m, 8H), 0.98 (t, *J* = 7.1 Hz, 3H; CH_3). ^{13}C NMR (126 MHz, $CDCl_3$) mixture of two diastereoisomers δ 195.16 (s; C_{quat}), 194.40 (s; C_{quat}), 169.05 (s; C_{quat}), 168.95 (s; C_{quat}), 162.69 (s; C_{quat}), 162.45 (s; C_{quat}), 158.26 (s; Ar-*C*H), 157.97 (s; Ar-*C*H), 136.97 (s; C_{quat}), 136.28 (s; C_{quat}), 133.55 (s; Ar-*C*H), 133.22 (s; Ar-*C*H), 128.79 (s; Ar-*C*H), 128.69 (s; Ar-*C*H), 128.33 (s; Ar-*C*H), 128.19 (s; Ar-*C*H), 110.39 (s; Ar-*C*H), 110.30 (s; Ar-*C*H), 61.56 (s; *C*H_2), 61.35 (s; *C*H_2), 55.95 (s; *C*H), 54.69 (s; *C*H), 53.70 (s; *C*H), 41.86 (s; *C*H), 41.31 (s; *C*H), 31.68 (s; *C*H_2), 30.61 (s; *C*H_2), 29.81 (s; *C*H_2), 29.12 (s; *C*H_2), 26.19 (s; *C*H_2), 26.15 (s; *C*H_2), 26.04 (s; *C*H_2), 25.97 (s; *C*H_2), 25.95 (s; *C*H_2), 24.97 (s; *C*H_2), 13.97 (s; *C*H_3), 13.70 (s; *C*H_3). HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{22}H_{28}N_3O_3^+$ 382.2126 (100.0%), Found 382.2125.

3-((pyrimidin-2-ylamino)(4-(trifluoromethyl)phenyl) methyl)pentane-2,4-dione (1t)

White solid, 47% isolated yield; Silica gel TLC R*f* = 0.53 (Toluene/MeCN 3:1) Diastereoisomers ratio: <95. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.27 (d, *J* = 4.7 Hz, 2H; Ar-H), 7.85 (d, *J* = 9.5 Hz, 1H; Ar-H), 7.70 – 7.63 (m, 4H; Ar-H), 6.61 (t, *J* = 4.8 Hz, 1H), 5.78 (dd, *J* = 11.0, 9.5 Hz, 1H), 4.71 (d, *J* = 10.9 Hz, 1H), 2.26 (s, 3H; CH_3), 1.98 (s, 3H; CH_3). ^{13}C NMR (126 MHz, DMSO-d_6) δ 202.21 (s; C_{quat}), 201.81 (s; C_{quat}), 161.68 (s; C_{quat}), 146.28 (s; C_{quat}), 128.88 (s; Ar-*C*H), 128.30 (q, *J* = 31.5 Hz; C_{quat}), 125.63 (q, *J* = 3.5 Hz; Ar-*C*H), 127.93 – 120.94 (m; C_{quat}), 111.64 (s; Ar-*C*H), 71.91 (s; *C*H), 53.86 (s; *C*H), 31.13 (s; *C*H_3), 30.98 (s; *C*H_3). HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{17}H_{17}F_3N_3O_2^+$ 352.1268 (100.0%); Found 352.1271.

3-((3-nitrophenyl)(pyrimidin-2-ylamino)methyl)pentane-2,4-dione (1u)

White solid, 30% isolated yield; Silica gel TLC R*f* = 0.44 (Toluene/MeCN 3:1) Diastereoisomers ratio: <95. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.39 (t, *J* = 2.0 Hz, 1H; Ar-H), 8.28 (d, *J* = 4.8 Hz, 2H; Ar-H), 8.08 (ddd, *J* = 8.2, 2.4, 1.0 Hz, 1H; Ar-H), 7.95 (d, *J* = 9.5 Hz, 1H; Ar-H), 7.87 (d, *J* = 7.7 Hz, 1H; Ar-H), 7.59 (t, *J* = 7.9 Hz, 1H; Ar-H), 6.62 (t, *J* = 4.8 Hz, 1H), 5.81 (dd, *J* = 11.0, 9.5 Hz, 1H), 4.75 (d, *J* = 11.0 Hz, 1H), 2.30 (s, 3H; CH_3), 2.00 (s, 3H; CH_3). ^{13}C NMR (126 MHz, DMSO-d_6) δ 202.08 (s; C_{quat}), 201.69 (s; C_{quat}), 161.59 (s; C_{quat}), 148.28 (s; C_{quat}), 143.95 (s; C_{quat}), 135.19 (s; Ar-*C*H), 130.12 (s; Ar-*C*H), 122.81 (s; Ar-*C*H), 122.56 (s; Ar-*C*H), 111.79 (s; Ar-*C*H), 71.88 (s; *C*H), 53.70 (s; *C*H), 31.21 (s; *C*H_3), 31.18 (s; *C*H_3). HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{16}H_{17}N_4O_4^+$ 329.1245 (100.0%); Found 329.1246.

1,3-diphenyl-2-((pyrimidin-2-ylamino)(4-(trifluoromethyl) phenyl)methyl)propane-1,3-dione (1v)

White solid, 20% isolated yield; Silica gel TLC R*f* = 0.65 (Toluene/MeCN 3:1) Diastereoisomers ratio: <95. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.23 (d, *J* = 4.7 Hz, 2H; Ar-H), 8.03 (d, *J* = 7.3 Hz, 2H; Ar-H), 7.81 (d, *J* = 7.3 Hz, 2H; Ar-H), 7.78 (d, *J* = 9.2 Hz, 1H; Ar-H), 7.70 (d, *J* = 8.1 Hz, 2H; Ar-H), 7.63 (t, *J* = 7.4 Hz, 1H; Ar-H), 7.58 – 7.49 (m, 5H; Ar-H), 7.42 (t, *J* = 7.8 Hz, 1H; Ar-H), 6.61 – 6.57 (m, 2H), 6.13 (t, *J* = 9.5 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 194.26 (s; C_{quat}), 193.69 (s; C_{quat}), 161.70 (s; C_{quat}), 146.13 (s; C_{quat}), 136.79 (s; C_{quat}), 136.06 (s; C_{quat}), 134.35 (q, ^3J = 2.3 Hz; Ar-*C*H), 129.44 (s; Ar-*C*H), 129.33 (s; Ar-*C*H), 129.09 (s; Ar-*C*H), 129.04 (s; Ar-*C*H), 128.85 (s; Ar-*C*H), 128.14 (q, *J* = 32.0 Hz; C_{quat}), 125.38 (q, *J* = 3.7 Hz; Ar-*C*H), 127.64 – 121.65 (m; C_{quat}), 111.60 (s; Ar-*C*H), 60.29 (s; *C*H), 55.14 (s; *C*H). HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{27}H_{21}F_3N_3O_2^+$ 476.1581 (100.0%); Found 476.1574.

2-((3-nitrophenyl)(pyrimidin-2-ylamino)methyl)-1,3-diphenylpropane-1,3-dione (1w)

White solid, 90% isolated yield, applying method from [14]; Silica gel TLC R*f* = 0.60 (Toluene/MeCN 3:1) Diastereoisomers ratio: <95. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.48 (t, *J* = 2.0 Hz, 1H; Ar-H), 8.45 (d, *J* = 9.2 Hz, 1H; Ar-H), 8.35 (d, *J* = 4.9 Hz, 2H; Ar-H), 8.03 (d, *J* = 7.3 Hz, 2H; Ar-H), 7.94 – 7.88 (m, 2H; Ar-H), 7.84 (d, *J* = 7.3 Hz, 2H; Ar-H), 7.61 (t, *J* = 7.4 Hz, 1H; Ar-H), 7.53 (t, *J* = 7.5 Hz, 1H; Ar-H), 7.49 (t, *J* = 7.7 Hz, 2H; Ar-H), 7.45 (t, *J* = 8.0 Hz, 1H; Ar-H), 7.39 (t, *J* = 7.7 Hz, 2H; Ar-H), 6.81 (d, *J* = 9.7 Hz, 1H), 6.71 (t, *J* = 4.9 Hz, 1H), 6.19 (t, *J* = 9.3 Hz, 1H). ^{13}C NMR (126 MHz, DMSO) δ 194.36 (s; C_{quat}), 193.63 (s; C_{quat}), 159.52 (s; C_{quat}), 148.00 (s; C_{quat}), 142.85 (s; C_{quat}), 136.70 (s; C_{quat}), 135.96 (s; C_{quat}), 135.41 (s; Ar-*C*H), 134.51 (s; Ar-*C*H), 130.06 (s; Ar-*C*H), 129.46 (s; Ar-*C*H), 129.33 (s; Ar-*C*H), 129.06 (s; Ar-*C*H), 128.95 (s; Ar-*C*H), 123.10 (s; Ar-*C*H), 122.77 (s; Ar-*C*H), 111.65 (s; Ar-*C*H), 60.18 (s; *C*H), 55.04 (s; *C*H). HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{26}H_{21}N_4O_4^+$ 453.1558 (100.0%); Found 453.1552.

General procedure for the preparation of 4,5-disubstituted 2-amino-1H-imidazole compounds (2a-w)

To a solution of the Mannich precursor **1a-w** (0.25 mmol) in DMA (4.75 mL), IBX (0.25 mmol, 1 equiv. (156 mg), 45 wt%) and IPT (0.38 mmol, 1.5 equiv. (102 mg)) were added. The reaction mixture was stirred at 80 ºC for 30 minutes. Afterwards, the mixture was cooled to room temperature and $NH_2OH{\cdot}HCl$ (2.5 mmol, 10 equiv. (174 mg)) was added to the reaction mixture. After addition of Na_2CO_3 (2.5 mmol, 10 equiv. (265 mg)), the mixture was stirred at ambient temperature for 15 min, then at 50 °C for 16 hours. When TCL indicated that the reaction was completed, the solution was poured into water and extracted with ethyl acetate (2x10 mL). The organic layer was washed with saturated sodium bicarbonate solution (10 mL) and brine (10 mL). The combined organic layers were dried over Na_2SO_4 and evaporated to dryness. The crude material was subjected to column chromatographic separation (silica gel, eluent: toluene/methanol from 50:1 to 10:1) and recrystallized in diethyl ether/methanol observing the pure products **2a-w**.

Ethyl 2-amino-4-phenyl-1H-imidazole-5-carboxylate (2a)

White solid, 92% yield (53 mg); Silica gel TLC Rf = 0.52 (toluene/2-propanol 3:1); m.p.: 228.4-228.9 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.82 (s, 1H; NH), 7.92 (d, *J* = 7.1 Hz, 2H; Ar-H), 7.35 (t, *J* = 7.5 Hz, 2H; Ar-H), 7.29 (t, *J* = 7.3 Hz, 1H; Ar-H), 5.77 (s, 2H; NH_2), 4.18 (q, *J* = 7.1 Hz, 2H; CH_2), 1.24 (t, *J* = 7.1 Hz, 3H; CH_3). ^{13}C NMR (126 MHz, DMSO) δ 159.88 (s; C_{quat}), 152.11 (s; C_{quat}), 146.48 (s; C_{quat}), 134.64 (s; C_{quat}), 129.18 (s; Ar-*C*H), 128.05 (s; Ar-*C*H), 127.89 (s; Ar-*C*H), 111.89 (s; C_{quat}), 59.77 (s; *C*H_2), 14.79 (s; *C*H_3). FTIR-ATR: υ˜ = 1149 (s) cm^{-1} (C-N), 1299 (s) cm^{-1} (C-O) 1590 (m) cm^{-1} (N-H), 1636 (s) cm^{-1} (C=C), 3059 (m) cm^{-1} (C-H). HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{12}H_{14}N_3O_2^+$ 232.1081 (100.0%); Found 232.1088. These spectroscopic data correspond to the reported data in reference[5b].

Ethyl 2-amino-4-(3-fluorophenyl)-1H-imidazole-5-carboxylate (2b)

White solid, 88% yield (55 mg); m.p.: 191.3-194.0 °C; Silica gel TLC Rf = 0.60 (toluene/2-propanol 3:1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.93 (s, 1H; NH), 7.84 (s, 1H; Ar-H), 7.85 – 7.79 (m, 1H; Ar-H), 7.40 (td, *J* = 8.1, 6.3 Hz, 1H; Ar-H), 7.13 (td, *J* = 8.2, 2.3 Hz, 1H; Ar-H), 5.82 (s, 2H; NH_2), 4.20 (q, *J* = 7.1 Hz, 2H; CH_2), 1.26 (t, *J* = 7.1 Hz, 3H; CH_3). ^{13}C NMR (126 MHz, DMSO-d_6) δ 162.16 (d, *J* = 240.9 Hz; C_{quat}), 159.80 (s; C_{quat}), 152.10 (s; C_{quat}), 144.75 (d, *J* = 2.4 Hz; C_{quat}), 136.89 (d, *J* = 8.9 Hz; C_{quat}), 129.85 (d, *J* = 8.4 Hz; Ar-*C*H), 125.04 (d, *J* = 2.4 Hz; Ar-*C*H), 115.50 (d, *J* = 23.1 Hz; Ar-*C*H), 114.73 (d, *J* = 21.1 Hz; Ar-*C*H), 112.48 (s; C_{quat}), 60.02 (s; *C*H_2), 14.74 (s; *C*H_3). FTIR-ATR: υ˜ = 1137 (s) cm^{-1} (C-F), 1298 (s) cm^{-1} (C-O) or (C-N), 1590 (m) cm^{-1} (N-H). HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{12}H_{13}FN_3O_2^+$ 250.0987 (100.0%); Found 250.0995.

Ethyl 2-amino-4-(3-chlorophenyl)-1H-imidazole-5-carboxylate (2c)

White solid, 75% yield (50 mg); m.p.: 196.1-197.3 °C; Silica gel TLC Rf = 0.62 (toluene/2-propanol 3:1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.95 (s, 1H; NH), 8.06 (s, 1H; Ar-H), 7.93 (d, *J* = 7.5 Hz, 1H; Ar-H), 7.39 (t, *J* = 7.8 Hz, 1H; Ar-H), 7.36 (d, *J* = 8.1 Hz, 1H; Ar-H), 5.83 (s, 2H; NH_2), 4.20 (q, *J* = 7.1 Hz, 2H; CH_2), 1.27 (t, *J* = 7.0 Hz, 3H; CH_3). ^{13}C NMR (126 MHz, DMSO-d_6) δ 159.80 (s; C_{quat}), 152.18 (s; C_{quat}), 144.46 (s; C_{quat}), 136.61 (s; C_{quat}), 132.75 (s; C_{quat}), 129.90 (s; Ar-*C*H), 128.71 (s; Ar-*C*H), 127.79 (s; Ar-*C*H), 127.55 (s; Ar-*C*H), 112.56 (s; C_{quat}), 60.05 (s; *C*H_2), 14.73 (s; *C*H_3). FTIR-ATR: ν̃ = 1152 (m) cm^{-1} (C-N), 1294 (s) cm^{-1} (C-N), 1588 (m) cm^{-1} (N-H), 3073 (m) cm^{-1} (C-H), 3305 (m) cm^{-1} (N-H). HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{12}H_{13}ClN_3O_2^+$ 266.0691 (100.0%), 268.0662 (32.0%), 267.0725 (13.0%); Found 266.0700, 268.0670, 267.0731.

Ethyl 2-amino-4-(3-bromophenyl)-1H-imidazole-5-carboxylate (2d)

Light yellow solid, 90% yield (70 mg); m.p.: 200.0-201.4 °C; Silica gel TLC Rf = 0.62 (toluene/2-propanol 3:1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.95 (s, 1H; NH), 8.19 (s, 1H; Ar-H), 7.97 (d, *J* = 7.8 Hz, 1H; Ar-H), 7.49 (dd, *J* = 7.9, 2.2 Hz, 1H; Ar-H), 7.33 (t, *J* = 7.9 Hz, 1H; Ar-H), 5.82 (s, 2H, NH_2), 4.20 (q, *J* = 7.1 Hz, 2H; CH_2), 1.27 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 159.80 (s; C_{quat}), 152.18 (s; C_{quat}), 144.33 (s; C_{quat}), 136.88 (s; C_{quat}), 131.59 (s; Ar-*C*H), 130.65 (s; Ar-*C*H), 130.20 (s; Ar-*C*H), 127.92 (s; Ar-*C*H), 121.34 (s; C_{quat}), 112.56 (s; C_{quat}), 60.06 (s; *C*H_2), 14.75 (s; *C*H_3). FTIR-ATR: ν̃ = 676 (s) cm^{-1} (C-Br), 1292 (s) cm^{-1} (C-O) or (C-N), 1585 (m) cm^{-1} (N-H), 3054 (m) cm^{-1} (C-H), 3310 (m) cm^{-1} (N-H). HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{12}H_{13}BrN_3O_2^+$ 310.0186 (100.0%), 312.0166 (97.3%), 311.0220 (13.0%), 313.0199 (12.6%); Found 310.0198, 312.0178, 311.0228, 313.0207.

Ethyl 2-amino-4-(3-iodophenyl)-1H-imidazole-5-carboxylate (2e)

Light yellow solid, 70% yield (63 mg); m.p.: 205.8-206.0 °C; Silica gel TLC Rf = 0.64 (toluene/2-propanol 3:1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.93 (s, 1H; NH), 8.35 (s, 1H; Ar-H), 7.98 (d, *J* = 7.9 Hz, 1H; Ar-H), 7.66 (d, *J* = 7.8 Hz, 1H; Ar-H), 7.17 (t, *J* = 7.8 Hz, 1H; Ar-H), 5.81 (s, 2H; NH_2), 4.19 (q, *J* = 7.1 Hz, 2H; CH_2), 1.27 (t, *J* = 7.1 Hz, 3H; CH_3). ^{13}C NMR (126 MHz, DMSO-d_6) δ 159.82 (s; C_{quat}), 152.18 (s; C_{quat}), 144.30 (s; C_{quat}), 137.51 (s; Ar-*C*H), 136.81 (s; C_{quat}), 136.48 (s; Ar-*C*H), 130.23 (s; Ar-*C*H), 128.34 (s; Ar-*C*H), 112.45 (s; C_{quat}), 94.33 (s; C_{quat}), 60.03 (s; *C*H_2), 14.82 (s; *C*H_3). FTIR-ATR: ν̃ = 1295 (s) cm^{-1} (C-O), 1587 (m) cm^{-1} (N-H), 3301 (m) cm^{-1} (N-H). HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{12}H_{13}IN_3O_2^+$ 358.0047 (100.0%); Found 358.0061.

Ethyl 2-amino-4-(3-nitrophenyl)-1H-imidazole-5-carboxylate (2f)

Orange solid, 94% yield (65 mg); m.p.: 251.2-252.8 °C; Silica gel TLC Rf = 0.58 (toluene/2-propanol 3:1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.08 (s, 1H; NH), 8.91 (t, *J* = 2.1 Hz, 1H; Ar-H), 8.46 (dt, *J* = 7.9, 1.4 Hz, 1H; Ar-H), 8.16 (ddd, *J* = 8.2, 2.4, 1.1 Hz, 1H; Ar-H), 7.67 (t, *J* = 8.0 Hz, 1H; Ar-H), 5.90 (s, 2H; NH_2), 4.23 (q, *J* = 7.1 Hz, 2H; CH_2), 1.27 (t, *J* = 7.1 Hz, 3H; CH_3). ^{13}C NMR (126 MHz, DMSO-d6) δ 159.79 (s; C_{quat}), 152.36 (s; C_{quat}), 147.96 (s; C_{quat}), 143.43 (s; C_{quat}), 136.09 (s; C_{quat}), 135.22 (s; Ar-*C*H), 129.66 (s; Ar-*C*H), 123.45 (s; Ar-*C*H), 122.66 (s; Ar-*C*H), 113.11 (s; C_{quat}), 60.26 (s; *C*H_2), 14.69 (s; *C*H_3). FTIR-ATR: ν̃ = 1302 (s) cm-1 (C-N), 1523 (s) cm-1 (N-O), 1583 (m) cm-1 (N-H). HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{12}H_{13}N_4O_4^+$ 277.0932 (100.0%); Found 277.0941.

Ethyl 2-amino-4-(2-(trifluoromethyl)phenyl)-1H-imidazole-5-carboxylate (2g)

White solid, 60% yield (45 mg); m.p.: 231.8-232.8 °C; Silica gel TLC Rf = 0.54 (toluene/2-propanol 3:1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.06 (s, 1H; NH), 7.74 (d, *J* = 7.8 Hz, 1H; Ar-H), 7.64 (t, *J* = 7.5 Hz, 1H; Ar-H), 7.57 (t, *J* = 7.7 Hz, 1H; Ar-H), 7.39 (d, *J* = 7.6 Hz, 1H; Ar-H), 5.73 (s, 2H; NH_2), 3.93 (q, *J* = 7.1 Hz, 2H; CH_2), 0.92 (t, *J* = 7.1 Hz, 3H; CH_3). ^{13}C NMR (126 MHz, DMSO-d_6) δ 159.65 (s; C_{quat}), 152.07 (s; C_{quat}), 144.57 (s; C_{quat}), 135.13 (s; C_{quat}), 132.75 (s; Ar-*C*H), 131.78 (s; Ar-*C*H), 128.58 (s; Ar-*C*H), 128.78 – 127.85 (m; C_{quat}), 131.53 – 123.31 (m; C_{quat}), 126.01 (q, *J* = 5.0 Hz; Ar-*C*H), 113.87 (s; C_{quat}), 59.31 (s; *C*H_2), 14.29 (s; *C*H_3). FTIR-ATR: ν̃ = 1146 (s) cm^{-1} (C-F), 1313 (s) cm^{-1} (C-N), 1034 (m) cm^{-1} (C-N), 1635 (m) cm^{-1} (C=C), 1676 (m) cm^{-1} (C=N), 3323 (m) cm^{-1} (N-H). HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{13}H_{13}F_3N_3O_2^+$ 300.0955 (100.0%); Found 300.0966.

Ethyl 2-amino-4-(3-(trifluoromethyl)phenyl)-1H-imidazole-5-carboxylate (2h)

White solid, 78% yield (58 mg); m.p.: 218.2-219.8 °C; Silica gel TLC Rf = 0.62 (toluene/2-propanol 3:1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.01 (s, 1H; NH), 8.35 (s, 1H; Ar-H), 8.27 (d, *J* = 7.8 Hz, 1H; Ar-H), 7.66 (d, *J* = 7.9 Hz, 1H; Ar-H), 7.61 (t, *J* = 7.8 Hz, 1H; Ar-H), 5.87 (s, 2H; NH_2), 4.21 (q, *J* = 7.0 Hz, 2H; CH_2), 1.25 (t, *J* = 7.1 Hz, 3H; CH_3). ^{13}C NMR (126 MHz, DMSO-d_6) δ 159.83 (s; C_{quat}), 152.31 (s; C_{quat}), 144.27 (s; C_{quat}), 135.47 (s; C_{quat}), 132.79 (s; Ar-*C*H), 129.18 (s; Ar-*C*H), 128.94 (q, ^{3}*J* = 31.7 Hz; C_{quat}), 125.45 (q, *J* = 3.5 Hz; Ar-*C*H), 128.26 – 121.39 (m; C_{quat}), 124.52 (q, *J* = 3.8 Hz; Ar-*C*H), 112.73 (s; C_{quat}), 60.13 (s; *C*H_2), 14.67 (s; *C*H_3). FTIR-ATR: ν̃ = 1112 (s) cm^{-1} (C-F), 1289 (s) cm^{-1} (C-O), 1584 (m) cm^{-1} (N-H), 1646 (s) cm^{-1} (C=C). HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{13}H_{13}F_3N_3O_2^+$ 300.0955 (100.0%); Found 300.0966.

Ethyl 2-amino-4-(4-(trifluoromethyl)phenyl)-1H-imidazole-5-carboxylate (2i)

Off-white solid, 84% yield (63 mg); m.p.: 253.7-254.9 °C; Silica gel TLC Rf = 0.58 (toluene/2-propanol 3:1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.03 (s, 1H; NH), 8.16 (d, *J* = 8.0 Hz, 2H; Ar-H), 7.71 (d, *J* = 8.1 Hz, 2H; Ar-H), 5.86 (s, 2H; NH_2), 4.20 (q, *J* = 7.1 Hz, 2H; CH_2), 1.26 (t, *J* = 7.1 Hz, 3H; CH_3). ^{13}C NMR (126 MHz, DMSO-d_6) δ 159.75 (s; C_{quat}), 152.32 (s; C_{quat}), 144.46 (s; C_{quat}), 138.59 (s; C_{quat}), 129.65 (s; Ar-*C*H), 128.10 (q, *J* = 31.8 Hz; C_{quat}), 124.88 (q, $J_{C\text{-}F}$= 272.0 Hz; C_{quat}), 124.86 (q, *J* = 3.4 Hz; Ar-*C*H), 113.02 (s; C_{quat}), 60.09 (s; *C*H_2), 14.73 (s; *C*H_3). FTIR-ATR: ν̃ = 1105 (s) cm^{-1} (C-F), 1159 (m) cm^{-1} (C-N), 1303 (s) cm^{-1} (C-O), 1317 (s) cm^{-1} (C-N), 1586 (m) cm^{-1} (N-H), 1636 (m) cm^{-1} (C=C), 1662 (m) cm^{-1} (C=C). HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{13}H_{13}F_3N_3O_2^+$ 300.0954 (100%); Found 300.0965.

Ethyl 2-amino-4-(2,4-bis(trifluoromethyl)phenyl)-1*H*-imidazole-5-carboxylate (2j)

Light orange solid, 90% yield (82 mg); Silica gel TLC Rf = 0.63 (toluene/2-propanol 3:1); m.p.: 182.9-183.9 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.24 (s, 1H; NH), 8.09 – 8.02 (m, 2H; Ar-H), 7.68 (d, *J* = 7.9 Hz, 1H; Ar-H), 5.83 (s, 2H; NH_2), 3.95 (q, *J* = 7.1

Hz, 2H; CH_2), 0.93 (t, *J* = 7.1 Hz, 3H; CH_3). ^{13}C NMR (126 MHz, DMSO-d_6) δ 159.40 (s; C_{quat}), 152.43 (s; C_{quat}), 142.93 (s; C_{quat}), 139.59 (s; C_{quat}), 134.35 (s; Ar-*C*H), 129.30 (q, *J* = 33.0 Hz; C_{quat}), 129.77 – 128.95 (m; C_{quat}), 128.76 (q, *J* = 4.0 Hz; Ar-*C*H), 127.07 – 120.24 (m; C_{quat}), 127.38 – 120.11 (m; C_{quat}), 123.06 (dt, ^6J = 9.4, 4.3 Hz; Ar-*C*H), 114.24 (s; C_{quat}), 59.56 (s; *C*H_2), 14.19 (s; *C*H_3). FTIR-ATR: ν̃ = 1064 (m) cm^{-1} (C-N), 1123 (s), 1264 (s), 1342 (s) cm^{-1} (C-F), 1582 (s) cm^{-1} (N-H), 1632 (m) cm^{-1} (C=C), 1689 (m) cm^{-1} (C=N). HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{14}H_{12}F_6N_3O_2^+$ 368.0829 (100.0%); Found 368.0841.

Ethyl 2-amino-4-(3,5-bis(trifluoromethyl)phenyl)-1*H*-imidazole-5-carboxylate (2k)

White solid, 94% yield (86 mg); Silica gel TLC Rf = 0.67 (toluene/2-propanol 3:1); m.p.: 234.9-235.1 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.20 (s, 1H; NH), 8.73 (s, 2H; Ar-H), 8.03 (s, 1H; Ar-H), 5.97 (s, 2H; NH_2), 4.24 (q, *J* = 7.1 Hz, 2H; CH_2), 1.27 (t, *J* = 7.1 Hz, 3H; CH_3). ^{13}C NMR (126 MHz, DMSO-d_6) δ 159.80 (s; C_{quat}), 152.48 (s; C_{quat}), 142.12 (s; C_{quat}), 136.78 (s; C_{quat}), 130.32 (q, J = 32.6 Hz; C_{quat}), 128.99 (s; Ar-*C*H), 123.95 (q, J_{C-F} = 273.0 Hz; C_{quat}), 121.26 (p, *J* = 3.9 Hz; Ar-*C*H), 113.72 (s; C_{quat}), 60.51 (s; *C*H_2), 14.59 (s; *C*H_3). FTIR-ATR: ν̃ = 1119 (s) cm^{-1} (C-F), 1281 (s) cm^{-1} (C-O), 1649 (s) cm^{-1} (C=C), 1670 (w) cm^{-1} (C=C), 1587 (m) cm^{-1} (N-H). HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{14}H_{12}F_6N_3O_2^+$ 368.0829 (100.0%); Found: 368.0843.

Ethyl 2-amino-4-(3-methoxyphenyl)-1*H*-imidazole-5-carboxylate (2l)

Light yellow solid, 62% yield (41 mg); m.p.: 173.5-174.0 °C; Silica gel TLC Rf = 0.44 (toluene/2-propanol 3:1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.82 (s, 1H; NH), 7.59 (s, 1H; Ar-H), 7.57 (d, *J* = 8.2 Hz, 1H; Ar-H), 7.26 (t, *J* = 7.9 Hz, 1H; Ar-H), 6.87 (dd, *J* = 7.9, 2.3 Hz, 1H; Ar-H), 5.79 (s, 2H; NH_2), 4.19 (q, *J* = 7.1 Hz, 2H; CH_2), 3.77 (s, 3H; CH_3), 1.25 (t, *J* = 7.1 Hz, 3H; CH_3). ^{13}C NMR (126 MHz, DMSO-d_6) δ 159.88 (s; C_{quat}), 159.06 (s; C_{quat}), 151.98 (s; C_{quat}), 146.17 (s; C_{quat}), 135.88 (s; C_{quat}), 128.89 (s; C_{quat}), 121.60 (s; Ar-*C*H), 114.35 (s; Ar-*C*H), 113.95 (s; Ar-*C*H), 112.03 (s; C_{quat}), 59.82 (s; *C*H_2), 55.41 (s; *C*H_3), 14.82 (s; *C*H_3). FTIR-ATR: ν̃ = 1279 (s) cm^{-1} (C-O), 1300 (s) cm^{-1} (C-N), 1586 (m) cm^{-1} (N-H), 1635 (m) cm^{-1} (C=C), 3082 (m) cm^{-1} (C-H). HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{13}H_{16}N_3O_3^+$ 262.1187 (100.0%); Found 262.1194.

Ethyl 2-amino-4-(3,4,5-trimethoxyphenyl)-1*H*-imidazole-5-carboxylate (2m)

White solid, 32% yield (26 mg); m.p.: 219.8-220.2 °C; Silica gel TLC Rf = 0.38 (toluene/2-propanol 3:1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.74 (s, 1H; NH), 7.48 (s, 2H; Ar-H), 5.81 (s, 2H; NH_2), 4.21 (q, *J* = 7.1 Hz, 2H; CH_2), 3.79 (s, 6H; CH_3), 3.69 (s, 3H; CH_3), 1.26 (t, *J* = 7.1 Hz, 3H; CH_3). ^{13}C NMR (126 MHz, DMSO-d_6) δ 159.97 (s; C_{quat}), 152.53 (s; C_{quat}), 151.80 (s; C_{quat}), 146.22 (s; C_{quat}), 137.72 (s; C_{quat}), 129.89 (s; C_{quat}), 106.53 (s; Ar-*C*H), 60.51 (s; *C*H_3), 59.85 (s; *C*H_2), 56.20 (s; *C*H_3), 14.94 (s; CH_3). FTIR-ATR: ν̃ = 1068 (m) cm^{-1} (C-N), 1586 (m) cm^{-1} (N-H), 1649 (m) cm^{-1} (C=C), 3092 (m) cm^{-1} (C-H). HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{15}H_{20}N_3O_5^+$ 322.1398 (100.0%); Found 322.1410.

Ethyl 2-amino-4-(*o*-tolyl)-1*H*-imidazole-5-carboxylate (2n)

Light orange solid, 50% yield (31 mg); m.p.: 223.2-224.1 °C; Silica gel TLC Rf = 0.44 (toluene/2-propanol 3:1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.92 (s, 1H; NH), 7.29 – 7.17 (m, 3H; Ar-H), 7.14 (t, *J* = 6.4 Hz, 1H; Ar-H), 5.67 (s, 2H; NH_2), 4.01 (q, *J* = 7.0 Hz, 2H; CH_2), 2.19 (s, 3H; CH_3), 1.06 (t, *J* = 7.0 Hz, 3H; CH_3). ^{13}C NMR (126 MHz, DMSO) δ 136.93 (s; C_{quat}), 130.83 (s; Ar-*C*H), 129.79 (s; Ar-*C*H), 127.96 (s; Ar-*C*H), 125.12 (s; Ar-*C*H), 59.31 (s; *C*H_2), 20.21 (s; *C*H_3), 14.59 (s; *C*H_3). FTIR-ATR: ν̃ = 1141 (s) cm^{-1} (C-N), 1312 (s) cm^{-1} (C-N), 1635 (m) cm^{-1} (N-H), 1671 (m) cm^{-1} (C=N), 3319 (m) cm^{-1} (N-H). HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{13}H_{16}N_3O_2^+$ 246.1238 (100.0%); Found 246.1244.

Ethyl 2-amino-4-(*m*-tolyl)-1*H*-imidazole-5-carboxylate (2o)

Off-white solid, 67% yield (41 mg); m.p.: 202.8-203.9 °C; Silica gel TLC Rf = 0.48 (toluene/2-propanol 3:1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.80 (s, 1H; NH), 7.75 (s, 1H; Ar-H), 7.73 (d, *J* = 8.0 Hz, 1H; Ar-H), 7.23 (t, *J* = 7.6 Hz, 1H; Ar-H), 7.11 (d, *J* = 8.1 Hz, 1H; Ar-H), 5.75 (s, 2H; NH), 4.17 (q, *J* = 7.0 Hz, 2H; CH_2), 2.32 (s, 3H; CH_3), 1.25 (t, *J* = 7.1 Hz, 3H; CH_3). ^{13}C NMR (126 MHz, DMSO-d_6) δ 159.92 (s; C_{quat}), 152.06 (s; C_{quat}), 146.52 (s; C_{quat}), 136.72 (s; C_{quat}), 134.57 (s; C_{quat}), 129.84 (s; Ar-*C*H), 128.66 (s; Ar-*C*H), 127.79 (s; Ar-*C*H), 126.39 (s; Ar-*C*H), 111.87 (s; C_{quat}), 59.75 (s; *C*H_2), 21.58 (s; *C*H_3), 14.77 (s; *C*H_3). FTIR-ATR: ν̃ = 1186 (m) cm^{-1} (C-N), 1310 (s) cm^{-1} (C-O), 1592 (m) cm^{-1} (N-H), 1692 (m) cm^{-1} (N-H), 3335 (m) cm^{-1} (N-H). HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{13}H_{16}N_3O_2^+$ 246.1238 (100.0%); Found 246.1246.

Ethyl 2-amino-4-(*p*-tolyl)-1*H*-imidazole-5-carboxylate (2p)

Light yellow solid, 52% yield (32 mg); m.p.: 221.5-221.8 °C; Silica gel TLC Rf = 0.55 (toluene/2-propanol 3:1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.73 (s, 1H; NH), 7.83 (d, *J* = 7.8 Hz, 2H; Ar-H), 7.16 (d, *J* = 8.0 Hz, 2H; Ar-H), 5.71 (s, 2H; NH_2), 4.17 (q, *J* = 7.1 Hz, 2H; CH_2), 3.32 (s, 3H; CH_3), 1.25 (t, *J* = 7.1 Hz, 3H; CH_3). ^{13}C NMR (126 MHz, DMSO) δ 151.96 (s; C_{quat}), 137.31 (s; C_{quat}), 129.08 (s; Ar-*C*H), 128.51 (s; Ar-*C*H), 59.67 (s; *C*H_2), 21.34 (s; *C*H_3), 14.81 (s; *C*H_3). FTIR-ATR: ν̃ = 1059 (m) cm^{-1} (C-N), 1297 (s) cm^{-1} (C-O), 1588 (m) cm^{-1} (N-H), 3314 (m) cm^{-1} (N-H). HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{13}H_{16}N_3O_2^+$ 246.1238 (100.0%), 247.1271 (14.1%), 247.1208 (1.1%); Found 246.1247.

Ethyl 2-amino-4-(3,5-dimethylphenyl)-1*H*-imidazole-5-carboxylate (2q)

White solid, 48% yield (31 mg); m.p.: 235.7-237.0 °C; Silica gel TLC Rf = 0.57 (toluene/2-propanol 3:1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.77 (s, 1H; NH), 7.54 (s, 2H; Ar-H), 6.93 (s, 1H; Ar-H), 5.73 (s, 2H; NH_2), 4.17 (q, *J* = 7.1 Hz, 2H; CH_2), 2.28 (s, 6H; 2 CH_3), 1.24 (t, *J* = 7.1 Hz, 3H; CH_3). ^{13}C NMR (126 MHz, DMSO-d_6) δ 159.95 (s; C_{quat}), 152.00 (s; C_{quat}), 146.56 (s; C_{quat}), 136.55 (s; C_{quat}), 134.50 (s; C_{quat}), 129.41 (s; Ar-*C*H), 127.09 (s; Ar-*C*H), 111.84 (s; C_{quat}), 59.72 (s; *C*H_2), 21.48 (s; *C*H_3), 14.74 (s; *C*H_3). FTIR-ATR: ν̃ = 1241 (m) cm^{-1} (C-N), 1599 (m) cm^{-1} (N-H), 1669 (s) cm^{-1} C=C), 3325 (m) cm^{-1} (N-H). HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{14}H_{18}N_3O_2^+$ 260.1394 (100.0%); Found 260.1403.

Ethyl 2-amino-4-cyclopropyl-1*H*-imidazole-5-carboxylate (2r)

White solid, 62% yield (30 mg); Silica gel TLC Rf = 0.45 (toluene/2-propanol 3:1); m.p.: 220.3-221.4 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.39 (s, 1H; NH), 5.61 (s, 2H; NH_2), 4.17 (q, *J* = 7.1 Hz, 2H; CH_2), 1.26 (t, *J* = 7.1 Hz, 3H; CH_3), 0.83 – 0.74 (m, 5H; CH, 2 CH_2). ^{13}C NMR (126 MHz, DMSO-d_6) δ 160.58 (s; C_{quat}), 152.43 (s; C_{quat}), 151.59 (s; C_{quat}), 112.07 (s; C_{quat}), 59.20 (s; *C*H_2), 15.03 (s; *C*H_3), 9.44 (s; *C*H), 8.52 (s; *C*H_2). FTIR-ATR: ν̃ = 1062 (m) cm^{-1} (C-N), 1170 (s) cm^{-1} (C-O), 1625 (s) cm^{-1} (C=C), 1585 (m) cm^{-1} (N-H), 3071 (m, broad) cm^{-1} (C-H). HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_9H_{14}N_3O_2^+$ 196.1081 (100.0%); Found 196.1081.

Ethyl 2-amino-4-cyclohexyl-1*H*-imidazole-5-carboxylate (2s)
White solid, 50% yield (30 mg); Silica gel TLC Rf = 0.47 (toluene/2-propanol 3:1); m.p.: 231.9-233.0 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.45 (s, 1H; NH), 5.60 (s, 2H; NH_2), 4.14 (q, *J* = 7.0 Hz, 2H; CH_2), 1.74 (dt, *J* = 12.9, 3.2 Hz, 2H; CH_2), 1.66 (d, *J* = 8.5 Hz, 3H; CH_2, CH), 1.46 (qd, *J* = 12.5, 3.2 Hz, 2H; CH_2), 1.33 – 1.22 (m, 6H; CH_3, CH_2, CH), 1.18 (tt, *J* = 12.7, 3.1 Hz, 1H; *C*H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 59.13 (s; *C*H_2), 36.86 (s; *C*H), 32.44 (s; *C*H_2), 26.68 (s; *C*H_2), 26.26 (s; *C*H_2), 14.91 (s; *C*H_3). FTIR-ATR: ν˜ = 1091 (s) cm^{-1} (C-N), 1589 (m) cm^{-1} (N-H), 1628 (s) cm^{-1} (C=C), 1657 (w) cm^{-1} (C-H), 2852 (m) cm^{-1} (C-H). HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{12}H_{20}N_3O_2^+$ 238.1551 (100.0%); Found 238.1556.

1-(2-amino-4-(4-(trifluoromethyl)phenyl)-1*H*-imidazol-5-yl) ethanone (2t)
Light orange solid, 77% yield (52 mg); m.p.: 258.3-259.8 °C; Silica gel TLC Rf = 0.48 (toluene/2-propanol 3:1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.15 (s, 1H; NH), 7.98 (d, *J* = 8.0 Hz, 2H; Ar-H), 7.74 (d, *J* = 8.2 Hz, 2H; Ar-H), 5.90 (s, 2H; NH_2), 2.20 (s, 3H; CH_3). ^{13}C NMR (126 MHz, DMSO-d_6) δ 152.44 (s; C_{quat}), 130.12 (Ar-*C*H), 128.50 (q, *J* = 32.1 Hz; C_{quat}), 125.07 (q, *J* = 3.4 Hz; Ar-*C*H), 124.80 (q, J_{C-F} = 272.0 Hz; C_{quat}), 28.28 (s; *C*H_3). FTIR-ATR: υ˜ = 1065 (s) cm-1 (C-F), 1172 (m) cm-1 (C-N), 1319 (s) cm-1 (C-N), 1587 (m) cm-1 (N-H), 1655 (m) cm-1 (C=C). HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{12}H_{11}F_3N_3O^+$ 270.0849 (100.0%); Found 270.0859.

1-(2-amino-4-(3-nitrophenyl)-1*H*-imidazol-5-yl)ethanone (2u)
Yellow solid, 95% yield (58 mg); m.p.: 235.1-237.0 °C; Silica gel TLC Rf = 0.50 (toluene/2-propanol 3:1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.24 (s, 1H; NH), 8.78 (s, 1H; Ar-H), 8.35 (d, *J* = 7.8 Hz, 1H; Ar-H), 8.18 (dd, *J* = 8.3, 2.3 Hz, 1H), 7.68 (t, *J* = 8.0 Hz, 1H; Ar-H), 5.99 (s, 2H; NH_2), 2.28 (s, 3H; CH_3). ^{13}C NMR (126 MHz, DMSO) δ 152.41 (s; C_{quat}), 148.05 (s; C_{quat}), 135.51 (s; Ar-*C*H), 129.72 (s; Ar-*C*H), 123.67 (s; Ar-*C*H), 122.91 (s; Ar-*C*H), 28.50 (s; *C*H_3). FTIR-ATR: υ˜ = 1321 (s) cm^{-1} (C-N), 1526 (s) cm^{-1} (N-O), 1642 (m) cm^{-1} (C=C). HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{11}H_{11}N_4O_3^+$ 247.0826 (100.0%); Found 247.0833.

(2-amino-4-(4-(trifluoromethyl)phenyl)-1*H*-imidazol-5-yl) (phenyl)methanone (2v)
Vivid yellow solid, 62% yield (52 mg); m.p.: 274.2-276.9 °C; Silica gel TLC Rf = 0.58 (toluene/2-propanol 3:1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.17 (s, 1H; NH), 7.51 (d, *J* = 8.1 Hz, 2H; Ar-H), 7.45 – 7.40 (m, 4H; Ar-H), 7.38 (t, *J* = 7.5 Hz, 1H; Ar-H), 7.21 (t, *J* = 7.6 Hz, 2H; Ar-H), 6.10 (s, 2H; NH_2). ^{13}C NMR (126 MHz, DMSO-d_6) δ 183.58 (s; C_{quat}), 153.54 (s; C_{quat}), 147.34 (s; C_{quat}), 139.37 (s; C_{quat}), 139.16 (s; C_{quat}), 131.47 (s; Ar-*C*H), 130.12 (s; Ar-*C*H), 129.08 (s; Ar-*C*H), 128.32 (s; Ar-*C*H), 128.52 – 127.49 (m; C_{quat}), 124.59 (q, *J* = 4.2 Hz; Ar-*C*H), 127.65 – 121.34 (m; C_{quat}), 123.00 (s; C_{quat}). FTIR-ATR: υ˜ = 1105 (s) cm^{-1} (C-F), 1321 (s) cm^{-1} (C-N), 1302 (s) cm^{-1} (C-O), 1584 (m) cm^{-1} (N-H), 1652 (m) cm^{-1} (C=C). HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{17}H_{13}F_3N_3O^+$ 332.1006 (100.0%); Found 332.1016.

(2-amino-4-(3-nitrophenyl)-1*H*-imidazol-5-yl)(phenyl) methanone (2w)
Vivid yellow solid, 29% yield (23 mg); m.p.: 246.7-251.1 °C; Silica gel TLC Rf = 0.60 (toluene/2-propanol 3:1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.20 (s, 1H; NH), 8.14 (s, 1H; Ar-H), 8.01 (d, *J* = 8.4 Hz, 1H; Ar-H), 7.82 (d, *J* = 7.8 Hz, 1H; Ar-H), 7.49 – 7.40 (m, 3H; Ar-H), 7.37 (t, *J* = 7.5 Hz, 1H; Ar-H), 7.23 (t, *J* = 7.6 Hz, 2H; Ar-H), 6.13 (s, 2H; NH_2). ^{13}C NMR (126 MHz, DMSO-d_6) δ 183.56 (s; C_{quat}), 153.59 (s; C_{quat}), 147.44 (s; C_{quat}), 146.39 (s; C_{quat}), 139.36 (s; C_{quat}), 136.54 (s; C_{quat}), 135.64 (s; Ar-*C*H), 131.51 (s; Ar-*C*H), 129.49 (s; Ar-*C*H), 129.04 (s; Ar-*C*H), 128.47 (s; Ar-*C*H), 124.03 (s; Ar-*C*H), 123.00 (s; C_{quat}), 122.51 (s; Ar-*C*H). FTIR-ATR: υ˜ = 1187 (m) cm^{-1} (C-N), 1318 (s) cm^{-1} (C-N), 1522 (s) cm^{-1} (N-O), 1584 (m) cm^{-1} (N-H), 1647 (m) cm^{-1} (C=C). HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{16}H_{13}N_4O_3^+$ 309.0983 (100.0%); Found 309.0987.

General procedure for the synthesis of 3a-d
To a 4 mL vial equipped with a magnetic stir bar containing 4,5-disubstituted 2-Al **2a**, **2i**, **2k**, **2s** (0.2 mmol), concentrated perchloric acid (3.4 µL, 0.04 mmol) and MeCN (0.2 mL), the corresponding aldehyde (0.3 mmol, 1.5 equiv.) and isocyanide (0.3 mmol, 1.5 equiv.) were consecutively added and the reaction mixture was stirred at 60 °C for 24 hours. Upon completion of reaction, white crytals were precipitated. Following a simple filtration and recrystallization in MeCN/aceton mixture (4:1), the pure products **3a-d** were observed.

Ethyl 5-(tert-butylamino)-2,6-diphenyl-1*H*-imidazo[1,2-*a*] imidazole-3-carboxylate (3a)
White solid, 40% yield (32 mg); Silica gel TLC Rf = 0.84 (toluene/2-propanol 3:1); m.p./b.p. 186.0-187.6 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.25 (s, 1H; NH), 7.97 (d, *J* = 6.9 Hz, 2H; Ar-H), 7.73 – 7.66 (m, 2H; Ar-H), 7.44 (t, *J* = 7.8 Hz, 2H; Ar-H), 7.43 – 7.36 (m, 3H; Ar-H), 7.30 (t, *J* = 7.4 Hz, 1H; Ar-H), 4.77 (s, 1H; NH), 4.20 (q, *J* = 7.1 Hz, 2H; CH_2), 1.15 (t, *J* = 7.1 Hz, 3H; CH_3), 0.94 (s, 9H; 3 CH_3). ^{13}C NMR (126 MHz, DMSO-d_6) δ 161.41 (s; C_{quat}), 146.15 (s; C_{quat}), 135.41 (s; C_{quat}), 131.45 (s; C_{quat}), 130.37 (s; Ar-*C*H), 128.81 (s; Ar-*C*H), 128.53 (s; Ar-*C*H), 127.78 (s; Ar-*C*H), 127.14 (s; Ar-*C*H), 122.88 (s; C_{quat}), 110.27 (s; C_{quat}), 60.62 (s; *C*H_2), 57.39 (s; C_{quat}), 29.69 (s; *C*H_3), 14.43 (s; *C*H_3). FTIR-ATR: υ˜ = 1615 (m) cm^{-1} (N-H), 1669 (m) cm^{-1} (C=C), 2971 (m) cm^{-1} (C-H), 3307 (m) cm^{-1} (N-H). HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{24}H_{27}N_4O_2^+$ 403.2129 (100.0%); Found 403.2135.

Ethyl 5-(tert-butylamino)-2-cyclohexyl-6-(3-methoxyphenyl)-1*H*-imidazo[1,2-*a*]imidazole-3-carboxylate (3b)
White solid, 23% yield (20 mg) m.p.: 163.0-164.2 °C; Silica gel TLC Rf = 0.86 (toluene/2-propanol 3:1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.03 (s, 1H; NH), 7.56 – 7.47 (m, 2H; Ar-H), 7.31 (t, *J* = 8.0 Hz, 1H; Ar-H), 6.83 (d, *J* = 5.8 Hz, 1H; Ar-H), 4.83 (s, 1H; NH), 4.30 (q, *J* = 7.1 Hz, 2H; CH_2), 3.79 (s, 3H; CH_3), 1.81 (qd, *J* = 8.9, 7.2, 3.0 Hz, 4H; 2 CH_2), 1.71 (d, *J* = 12.5 Hz, 1H; CH), 1.56 (qd, *J* = 13.3, 12.7, 3.5 Hz, 2H; CH_2), 1.40 – 1.18 (m, 7H; 2 CH_2, CH_3), 0.92 (s, 9H; 3 CH_3). ^{13}C NMR (126 MHz, DMSO-d_6) δ 161.70 (s; C_{quat}), 159.52 (s; C_{quat}), 129.82 (s; Ar-*C*H), 123.09 (s; C_{quat}), 119.22 (s; Ar-*C*H), 113.09 (s; Ar-*C*H), 112.36 (s; Ar-*C*H), 109.50 (s; C_{quat}), 60.30 (s; *C*H_2), 57.44 (s; *C*H_2), 55.49 (s; *C*H), 32.77 (s; *C*H_2), 29.61 (s; *C*H_3), 26.69 (s; *C*H_2), 26.23 (s; *C*H_2), 14.80 (s; *C*H_3). FTIR-ATR: υ˜ = 1233 (m) cm^{-1} (C-N), 1600 (m) cm^{-1} (N-H), 1669 (m) cm^{-1} (C=N), 2852 (m) cm^{-1} (C-H), 2991 (m) cm^{-1} (C-H). HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{25}H_{35}N_4O_3^+$ 439.2704 (100.0%); Found 439.2712.

Ethyl 6-(4-fluorophenyl)-2-(4-(trifluoromethyl)phenyl)-5-((2,4,4-trimethylpentan-2-yl)amino)-1*H*-imidazo[1,2-*a*] imidazole-3-carboxylate (3c)

White solid, 28% yield (31 mg) m.p.: 230.2-233.6 °C; Silica gel TLC Rf = 0.90 (toluene/2-propanol 3:1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.28 (s, 1H; NH), 7.97 – 7.88 (m, 4H; Ar-H), 7.77 (d, *J* = 8.0 Hz, 2H; Ar-H), 7.30 (t, *J* = 8.6 Hz, 2H; Ar-H), 4.64 (s, 1H; NH), 4.22 (q, *J* = 7.1 Hz, 2H; CH_2), 1.47 (s, 2H; CH_2), 1.16 (t, *J* = 7.1 Hz, 3H; CH_3), 0.99 (s, 9H; 3 CH_3), 0.88 (s, 6H; 2 CH_3). ^{13}C NMR (126 MHz, DMSO-d_6) δ 161.85 (d, $J_{C\text{-}F}$ = 245.3 Hz; C_{quat}), 161.16 (s; C_{quat}), 146.20 (s; C_{quat}), 139.54 (s; C_{quat}), 131.03 (s; Ar-*C*H), 129.85 (d, *J* = 8.0 Hz; Ar-*C*H), 128.76 (q, *J* = 31.6 Hz; C_{quat}), 128.01 (s; C_{quat}), 128.45 – 121.10 (m; C_{quat}), 124.69 (q, *J* = 3.6 Hz; Ar-*C*H), 123.08 (s; C_{quat}), 122.46 (s; C_{quat}), 115.81 (d, *J* = 21.6 Hz; Ar-*C*H), 110.92 (s; C_{quat}), 61.50 (s), 60.85 (s; *C*H_2), 55.81 (s), 32.08 (s; *C*H_3), 31.77 (s), 28.75 (s; *C*H_3), 14.38 (s; *C*H_3). FTIR-ATR: υ˜ = 1147 (s) cm^{-1} (C-F), 1321 (s) cm^{-1} (C-N), 2946 (m) cm^{-1} (C-H), 3312 (m) cm^{-1} (N-H). HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{29}H_{33}F_4N_4O_2^+$ 545.2535 (100.0%); Found 545.2531.

Ethyl 2-(2,4-bis(trifluoromethyl)phenyl)-6-(4-fluorophenyl)-5-((2,4,4-trimethylpentan-2-yl)amino)-1*H*-imidazo[1,2-*a*] imidazole-3-carboxylate (3d)

White solid, 35% yield (43 mg) m.p.: 208.5-210.3 °C; Silica gel TLC Rf = 0.92 (toluene/2-propanol 3:1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.33 (s, 1H; NH), 8.24 – 8.07 (m, 2H; Ar-H), 7.98 – 7.87 (m, 2H; Ar-H), 7.78 (d, *J* = 8.3 Hz, 1H; Ar-H), 7.31 (t, *J* = 8.9 Hz, 2H; Ar-H), 4.66 (s, 1H; NH), 3.95 (q, *J* = 7.1 Hz, 2H; CH_2), 1.45 (s, 2H; CH_2), 0.97 (s, 9H; 3 CH_3), 0.89 (s, 6H; 2 CH_3), 0.77 (t, *J* = 7.1 Hz, 3H; CH_3). ^{13}C NMR (126 MHz, DMSO-d_6) δ 161.89 (d, $J_{C\text{-}F}$= 245.4 Hz; C_{quat}), 160.70 (s; C_{quat}), 148.70 (s; C_{quat}), 145.94 (s; C_{quat}), 139.61 (s; C_{quat}), 134.18 (s; Ar-*C*H), 129.91 (d, *J* = 8.0 Hz; s; Ar-*C*H), 129.57 (d, *J* = 33.2 Hz; C_{quat}), 129.49 (d, *J* = 30.7 Hz; C_{quat}), 128.81 (q, *J* = 2.8 Hz; C_{quat}), 129.94 – 129.36 (m; C_{quat}), 129.91 – 122.32 (m; C_{quat}), 129.52 – 122.75 (m; C_{quat}), 122.99 (dt, *J* = 8.0, 4.4 Hz; Ar-*C*H), 122.18 (s; C_{quat}), 115.84 (d, ^1J = 21.6 Hz; Ar-*C*H), 112.14 (s; C_{quat}), 61.62 (s), 60.21 (s; *C*H_2), 55.57 (s), 32.05 (s; *C*H_3), 31.73 (s), 28.62 (s; *C*H_3), 13.72 (s; *C*H_3). FTIR-ATR: υ˜ = 1069 (s) cm^{-1} (C-F), 1136 (s) cm^{-1} (C-F), 1155 (s) cm^{-1} (C-F), 1629 (m) cm^{-1} (C=C), 2962 (m) cm^{-1} (C-H), 3318 (m) cm^{-1} (N-H). HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{30}H_{32}F_7N_4O_2^+$ 613.2408 (100.0%); Found 613.2414.

General procedure for the synthesis of 4a-c

1.5 mmol of **2f**, **2u**, **2w** and tin (II) chloride dihydrate (3091 mg, 13.7 mmol, 9 equiv.) were solved in conc. HCl (10 mL). The reaction mixture was refluxed for 24 hours and then allowed to cool at room temperature. After 6 h, the precipitate was filtered off and subsenquently dissolved in 10% NaOH (5 ml). The solvent was evaporated under reduced pressure and the residue was extracted with EtOAc (4x8 ml). The organic phase was dried over Na_2SO_4, and then the solvent was evaporated to dryness. The resulting residue was used in the next step without any further purification.

Ethyl 2-amino-4-(3-aminophenyl)-1*H*-imidazole-5-carboxylate (4a)

Orange solid, 78% yield (288 mg) m.p.: 209.3-211.6 °C; Silica gel TLC Rf = 0.35 (toluene/2-propanol 3:1).^{1}H NMR (500 MHz, DMSO-d_6) δ 10.69 (s, 1H; NH), 7.17 – 7.07 (m, 2H; Ar-H), 6.97 (t, *J* = 7.7 Hz, 1H; Ar-H), 6.50 (d, *J* = 7.3 Hz, 1H; Ar-H), 5.69 (s, 2H; NH_2), 4.95 (s, 2H; NH_2), 4.16 (q, *J* = 7.1 Hz, 2H; CH_2), 1.24 (t, *J* = 7.1 Hz, 3H; CH_3). ^{13}C NMR (126 MHz, DMSO-d_6) δ 159.91 (s; C_{quat}), 151.81 (s; C_{quat}), 148.21 (s; C_{quat}), 147.42 (s; C_{quat}), 135.17 (s; C_{quat}), 128.18 (s; Ar-*C*H), 117.47 (s; Ar-*C*H), 115.16 (s; Ar-*C*H), 113.90 (s; Ar-*C*H), 111.56 (s; C_{quat}), 59.59 (s; *C*H_2), 14.80 (s; *C*H_3). FTIR-ATR: υ˜ = 1021 (m) cm^{-1} (C-N), 1615 (m) cm^{-1} (N-H), 1636 (m) cm^{-1} (N-H), 1662 (m) cm^{-1} (C=N), 3343 (m) cm^{-1} (N-H). HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{12}H_{15}N_4O_2^+$ 247.1190 (100.0%); Found 247.1199.

1-(2-amino-4-(3-aminophenyl)-1*H*-imidazol-5-yl)ethanone (4b)

Orange solid, 77% yield (250 mg) m.p.: 196.1-198.6 °C; Silica gel TLC Rf = 0.33 (toluene/2-propanol 3:1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.71 (s, 1H; NH), 7.03 (t, *J* = 7.7 Hz, 1H; Ar-H), 6.75 (s, 1H; Ar-H), 6.68 (d, *J* = 7.5 Hz, 1H), 6.57 (d, *J* = 7.3 Hz, 1H), 5.82 (s, 2H; NH_2), 5.10 (s, 2H; NH_2), 2.03 (s, 3H; CH_3). ^{13}C NMR (126 MHz, DMSO-d_6) δ 184.66 (s; C_{quat}), 152.64 (s; C_{quat}), 149.57 (s; C_{quat}), 148.59 (s; C_{quat}), 136.33 (s; C_{quat}), 128.68 (s; Ar-*C*H), 123.79 (s; C_{quat}), 117.72 (s; Ar-*C*H), 115.69 (s; Ar-*C*H), 114.15 (s; Ar-*C*H), 27.40 (s; CH_3). FTIR-ATR: υ˜ = 1248 (m) cm^{-1} (C-N), 1620 (m) cm^{-1} (N-H), 3063 (m) cm^{-1} (C-H), 3326 (m) cm^{-1} (N-H). HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{11}H_{13}N_4O^+$ 217.1084 (100.0%); Found 217.1085.

(2-amino-4-(3-aminophenyl)-1*H*-imidazol-5-yl)(phenyl) methanone (4c)

Yellow solid, 77% yield (322 mg) m.p.: 247.0-248.1 °C; Silica gel TLC Rf = 0.38 (toluene/2-propanol 3:1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.87 (s, 1H; NH), 7.41 (d, *J* = 7.0 Hz, 2H; Ar-H), 7.34 (t, *J* = 7.5 Hz, 1H; Ar-H), 7.19 (t, *J* = 7.6 Hz, 2H; Ar-H), 6.65 (s, 1H; Ar-H), 6.61 (t, *J* = 7.7 Hz, 1H; Ar-H), 6.32 (d, *J* = 5.6 Hz, 1H; Ar-H), 6.26 (d, *J* = 7.5 Hz, 1H; Ar-H), 5.95 (s, 2H; NH_2), 4.83 (s, 2H; NH_2). ^{13}C NMR (126 MHz, DMSO-d_6) δ 183.50 (s; C_{quat}), 153.17 (s; C_{quat}), 150.24 (s; C_{quat}), 148.22 (s; C_{quat}), 139.65 (s; C_{quat}), 135.56 (s; C_{quat}), 131.16 (s; Ar-*C*H), 129.00 (s; Ar-*C*H), 128.05 (s; Ar-*C*H), 127.91 (s; Ar-*C*H), 122.13 (s; C_{quat}), 118.24 (s; Ar-*C*H), 115.28 (s; Ar-*C*H), 113.72 (s; Ar-*C*H). FTIR-ATR: υ˜ = 1582 (m) cm^{-1} (N-H), 1653 (m) cm^{-1} (C=C). HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{16}H_{15}N_4O^+$ 279.1241 (100.0%); Found 279.1245.

General procedure for the synthesis of 5a-f

The corresponding carboxylic acid (0.2 mmol, 2 equiv.), triethylamine (28 µL, 0.2 mmol, 2 equiv.) and TBTU (35.3 mg, 0.11 mmol, 1.1 equiv.) were dissolved in dichloromethane (4.5 mL) and stirred at room temperature for 1 h. Then, 0.1 mmol of **4a**, **4b** or **4c** were added. Afterwards, the reaction mixture was stirred at ambient temperature for 72 hours then the mixture was poured into water (10 mL) and extracted with ethyl-acetate (2x10 mL). The combined organic extracts were then washed with saturated $NaHCO_3$ solution (1x20 mL) and brine (1x20 mL). The organic phase was dried over Na_2SO_4, the solvent was removed at reduced pressure and the residue was subjected to the flash column chromatography (silica gel; gradient of toluene:MeOH, 30:1/ 15:1 /9:1) and crystallization from diethyl ether/MeOH mixture affording the **5a-f** crystals.

Ethyl 4-(3-(1H-indole-2-carboxamido)phenyl)-2-amino-1*H*-imidazole-5-carboxylate (5a)

Yellow solid, 61% yield (24 mg) m.p.: 238.9-240.8 °C; Silica gel TLC Rf = 0.55 (toluene/2-propanol 3:1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.71 (s, 1H; NH), 10.85 (s, 1H; NH), 10.23 (s, 1H; NH), 8.27 (s, 1H), 7.78 (d, *J* = 8.2 Hz, 1H; Ar-H), 7.71 (d, *J* = 7.9 Hz, 1H; Ar-H), 7.68 (d, *J* = 8.0 Hz, 1H; Ar-H), 7.48 (d, *J* = 8.7 Hz,

1H; Ar-H), 7.46 (s, 1H; Ar-H), 7.34 (t, *J* = 7.9 Hz, 1H; Ar-H), 7.23 (t, *J* = 7.6 Hz, 1H; Ar-H), 7.08 (t, *J* = 7.4 Hz, 1H; Ar-H), 5.78 (s, 2H; NH_2), 4.19 (q, *J* = 7.1 Hz, 2H; CH_2), 1.25 (t, *J* = 7.1 Hz, 3H; CH_3). ^{13}C NMR (126 MHz, DMSO-d_6) δ 160.12 (s; C_{quat}), 159.90 (s; C_{quat}), 152.09 (s; C_{quat}), 146.34 (s; C_{quat}), 138.68 (s; C_{quat}), 137.25 (s; C_{quat}), 135.17 (s; C_{quat}), 132.04 (s; C_{quat}), 128.09 (s; Ar-*C*H), 127.55 (s; C_{quat}), 124.83 (s; Ar-*C*H), 124.19 (s; Ar-*C*H), 122.21 (s; Ar-*C*H), 121.40 (s; Ar-*C*H), 120.35 (s; Ar-*C*H), 120.18 (s; Ar-*C*H), 112.85 (s; Ar-*C*H), 112.05 (s; C_{quat}), 104.29 (s; Ar-*C*H), 59.82 (s; *C*H_2), 14.75 (s; *C*H_3). FTIR-ATR: υ˜ = 1103 (m) cm^{-1} (C-N), 1641 (m) cm^{-1} (N-H), 3313 (m) cm^{-1} (N-H), 3385 (m) cm^{-1} (N-H). HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{21}H_{20}N_5O_3^+$ 390.1561 (100.0%); Found 390.1567.

Ethyl 2-amino-4-(3-(8-hydroxyquinoline-2-carboxamido) phenyl)-1*H*-imidazole-5-carboxylate (5b)

White solid, 60% yield (25 mg) m.p.: 266.6-269.0 °C; Silica gel TLC Rf = 0.65 (toluene/2-propanol=3/1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.20 (s, 1H), 10.87 (s, 1H; NH), 10.48 (s, 1H), 8.58 (d, *J* = 8.5 Hz, 1H; Ar-H), 8.37 (s, 1H; Ar-H), 8.29 (d, *J* = 8.5 Hz, 1H; Ar-H), 7.91 (d, *J* = 8.3 Hz, 1H; Ar-H), 7.82 (d, *J* = 7.7 Hz, 1H; Ar-H), 7.62 (t, *J* = 7.9 Hz, 1H; Ar-H), 7.53 (d, *J* = 7.0 Hz, 1H; Ar-H), 7.41 (t, *J* = 7.9 Hz, 1H; Ar-H), 7.23 (d, *J* = 7.5 Hz, 1H; Ar-H), 5.79 (s, 2H; NH_2), 4.20 (q, *J* = 7.1 Hz, 2H; CH_2), 1.25 (t, *J* = 7.1 Hz, 3H; CH_3). ^{13}C NMR (126 MHz, DMSO-d_6) δ 162.56 (s; C_{quat}), 159.91 (s; C_{quat}), 154.27 (s; C_{quat}), 152.10 (s; C_{quat}), 147.86 (s; C_{quat}), 146.13 (s; C_{quat}), 138.60, 138.11 (s; C_{quat}), 136.90 (s; C_{quat}), 135.25 (s; C_{quat}), 130.22 (s; Ar-*C*H), 130.19 (s; C_{quat}), 128.23 (s; Ar-*C*H), 125.37 (s; Ar-*C*H), 121.76 (s; Ar-*C*H), 120.56 (s; Ar-*C*H), 119.48 (s; Ar-*C*H), 118.13 (s; Ar-*C*H), 112.15 (s; C_{quat}), 59.86 (s; *C*H_2), 14.75 (s; *C*H_3). FTIR-ATR: υ˜ = 1119 (m) cm^{-1} (C-N), 1152 (m) cm^{-1} (C-N), 1284 (s) cm^{-1} (C-N), 1570 (m) cm^{-1} (C=C), 1648 (s) cm^{-1} (C=C), 3102 (w, br), cm^{-1} (O-H), 3288 (s) cm^{-1} (O-H). HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{22}H_{20}N_5O_4^+$ 418.1510 (100.0%), 419.1544 (23.8%); Found 418.1515, 419.1551.

***N*-(3-(5-acetyl-2-amino-1*H*-imidazol-4-yl)phenyl)-5-methoxy-1*H*-indole-2-carboxamide (5c)**

Light orange solid, 66% yield (26 mg) m.p.: 213.9-215.0 °C; Silica gel TLC Rf = 0.48 (toluene/2-propanol 3:1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.59 (s, 1H; NH), 10.87 (s, 1H; NH), 10.22 (s, 1H; NH), 8.05 (s, 1H; Ar-H), 7.83 (d, *J* = 7.8 Hz, 1H; Ar-H), 7.40 (t, *J* = 7.7 Hz, 1H; Ar-H), 7.38 – 7.34 (m, 3H; Ar-H), 7.14 (d, *J* = 2.4 Hz, 1H; Ar-H), 6.89 (dd, *J* = 8.9, 2.4 Hz, 1H; Ar-H), 5.90 (s, 2H; NH_2), 3.79 (s, 3H; CH_3), 2.12 (s, 3H; CH_3). ^{13}C NMR (126 MHz, DMSO-d_6) δ 184.78 (s; C_{quat}), 160.21 (s; C_{quat}), 154.34 (s; C_{quat}), 152.77 (s; C_{quat}), 148.02 (s; C_{quat}), 138.98 (s; C_{quat}), 136.12 (s; C_{quat}), 132.63 (s; C_{quat}), 132.18 (s; C_{quat}), 128.62 (s; Ar-*C*H), 127.82 (s; C_{quat}), 125.14 (s; Ar-*C*H), 123.92 (s; C_{quat}), 121.77 (s; Ar-*C*H), 120.26 (s; Ar-*C*H), 115.56 (s; Ar-*C*H), 113.70 (s; Ar-*C*H), 104.12 (s; Ar-*C*H), 102.58 (s; Ar-*C*H), 55.77 (s; *C*H_3), 27.82 (s; *C*H_3). FTIR-ATR: υ˜ = 1214 (m) cm^{-1} (C-N), 1602 (m) cm^{-1} (N-H), 1638 (m) cm^{-1} (C=C). HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{21}H_{20}N_5O_3^+$ 390.1561 (100.0%); Found 390.1564.

***N*-(3-(5-acetyl-2-amino-1*H*-imidazol-4-yl)phenyl)-5-fluoro-1*H*-indole-2-carboxamide (5d)**

Light orange solid, 63% yield (24 mg) m.p.: 257.0-259.2 °C; Silica gel TLC Rf = 0.51 (toluene/2-propanol 3:1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.86 (s, 1H; NH), 10.88 (s, 1H; NH), 10.32 (s, 1H; NH), 8.05 (s, 1H), 7.82 (d, *J* = 7.5 Hz, 1H; Ar-H), 7.52 – 7.35 (m, 5H; Ar-H), 7.10 (td, *J* = 9.2, 2.5 Hz, 1H; Ar-H), 5.90 (s, 2H; NH_2), 2.13 (s, 3H; CH_3). ^{13}C NMR (126 MHz, DMSO-d_6) δ 159.96 (s; C_{quat}), 159.75 (s; C_{quat}), 157.70 (d, J_{C-F} = 233.5 Hz; C_{quat}), 138.84 (s; C_{quat}), 134.04 (s; C_{quat}), 133.60 (s; C_{quat}), 128.66 (s; Ar-*C*H), 127.60 (s; C_{quat}), 127.52 (s; C_{quat}), 126.25 (s; C_{quat}), 121.84 (s; Ar-*C*H), 120.32 (s; Ar-*C*H), 115.65 (s; C_{quat}), 114.12 (s; Ar-*C*H), 114.04 (s; Ar-*C*H), 113.03 (d, *J* = 26.8 Hz; Ar-*C*H), 106.36 (d, *J* = 22.8 Hz; Ar-*C*H), 104.39 (d, *J* = 5.1 Hz; Ar-*C*H). FTIR-ATR: υ˜ = 1233 (s) cm^{-1} (C-F), 1167 (m) cm^{-1} (C-N), 1204 (m) cm^{-1} (C-N), 1380 (m) cm^{-1} (C-H), 1608 (m) cm^{-1} (C-N), 1633 (m) cm^{-1} (C=C), 3396 (m) cm^{-1} (N-H). HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{20}H_{17}FN_5O_2^+$ 378.1361 (100.0%); Found 378.1366.

***N*-(3-(2-amino-5-benzoyl-1*H*-imidazol-4-yl)phenyl)-5-methoxy-1*H*-indole-2-carboxamide (5e)**

Yellow solid, 50% yield (23 mg) m.p.: 270.7-273.8 °C; Silica gel TLC Rf = 0.63 (toluene/2-propanol 3:1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.54 (s, 1H; NH), 11.02 (s, 1H; NH), 10.00 (s, 1H; NH), 7.86 (s, 1H; Ar-H), 7.63 (d, *J* = 8.8 Hz, 1H; Ar-H), 7.43 (d, *J* = 7.2 Hz, 2H; Ar-H), 7.36 (d, *J* = 8.9 Hz, 1H; Ar-H), 7.37 – 7.30 (m, 2H; Ar-H), 7.19 (t, *J* = 7.7 Hz, 2H; Ar-H), 7.14 (d, *J* = 2.4 Hz, 1H; Ar-H), 6.99 (t, *J* = 7.9 Hz, 1H; Ar-H), 6.92 – 6.85 (m, 2H; Ar-H), 6.04 (s, 2H; NH_2), 3.79 (s, 3H; CH_3). ^{13}C NMR (126 MHz, DMSO-d_6) δ 183.62 (s; C_{quat}), 159.92 (s; C_{quat}), 154.32 (s; C_{quat}), 153.39 (s; C_{quat}), 149.20 (s; C_{quat}), 139.57 (s; C_{quat}), 138.83 (s; C_{quat}), 135.47 (s; C_{quat}), 132.57 (s; C_{quat}), 132.25 (s; C_{quat}), 131.25 (s; Ar-*C*H), 129.07 (s; Ar-*C*H), 128.15 (s; Ar-*C*H), 127.86 (s; Ar-*C*H), 127.83 (s; C_{quat}), 125.11 (s; Ar-*C*H), 122.43 (s; C_{quat}), 121.23 (s; Ar-*C*H), 119.47 (s; Ar-*C*H), 115.49 (s; Ar-*C*H), 113.68 (s; Ar-*C*H), 103.95 (s; Ar-*C*H), 102.57 (s; Ar-*C*H), 55.77 (s; *C*H_3). FTIR-ATR: υ˜ = 1164 (m) cm^{-1} (C-N), 1591 (m) cm^{-1} (N-H), 1634 (m) cm^{-1} (C=C) or (N-H), 1657 (w) cm^{-1} (C=C), 3326 (m) cm^{-1} (N-H). HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{26}H_{22}N_5O_3^+$ 452.1718 (100.0%); Found 452.1726.

***N*-(3-(2-amino-5-benzoyl-1*H*-imidazol-4-yl)phenyl)quinoline-2-carboxamide (5f)**

Vivid yellow solid, 86% yield (37 mg) m.p.: 301.6-303.9 °C; Silica gel TLC Rf = 0.70 (toluene/2-propanol 3:1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.05 (s, 1H; NH), 10.50 (s, 1H; NH), 8.65 (d, *J* = 8.5 Hz, 1H; Ar-H), 8.28 (d, *J* = 8.5 Hz, 1H; Ar-H), 8.24 (d, *J* = 8.5 Hz, 1H; Ar-H), 8.14 (d, *J* = 8.0 Hz, 1H; Ar-H), 7.99 – 7.94 (m, 1H; Ar-H), 7.95 – 7.92 (m, 1H; Ar-H), 7.78 (t, *J* = 8.0 Hz, 1H; Ar-H), 7.72 (d, *J* = 7.1 Hz, 1H; Ar-H), 7.44 (d, *J* = 7.0 Hz, 2H; Ar-H), 7.31 (t, *J* = 7.4 Hz, 1H; Ar-H), 7.19 (t, *J* = 7.7 Hz, 2H; Ar-H), 7.05 (t, *J* = 7.9 Hz, 1H; Ar-H), 6.97 (d, *J* = 7.7 Hz, 1H; Ar-H), 6.06 (s, 2H; NH_2). ^{13}C NMR (126 MHz, DMSO-d_6) δ 183.62 (s; C_{quat}), 162.82 (s; C_{quat}), 153.44 (s; C_{quat}), 150.43 (s; C_{quat}), 149.14 (s; C_{quat}), 146.33 (s; C_{quat}), 139.64 (s; C_{quat}), 138.71 (s; Ar-*C*H), 137.97 (s; C_{quat}), 135.61 (s; C_{quat}), 131.19 (s; Ar-*C*H), 129.84 (s; Ar-*C*H), 129.41 (s; C_{quat}), 129.06 (s; Ar-*C*H), 128.86 (s; Ar-*C*H), 128.61 (s; Ar-*C*H), 128.17 (s; Ar-*C*H), 128.03 (s; Ar-*C*H), 125.63 (s; Ar-*C*H), 122.55 (s; C_{quat}), 121.34 (s; Ar-*C*H), 119.57 (s; Ar-*C*H), 119.14 (s; Ar-*C*H). FTIR-ATR: υ˜ = 1583 (m) cm^{-1} (N-H), 1648 (m) cm^{-1} (N-H) or (C=C), 3396 (m) cm^{-1} (N-H). HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{26}H_{20}N_5O_2^+$ 434.1612 (100.0%); Found 434.1617.

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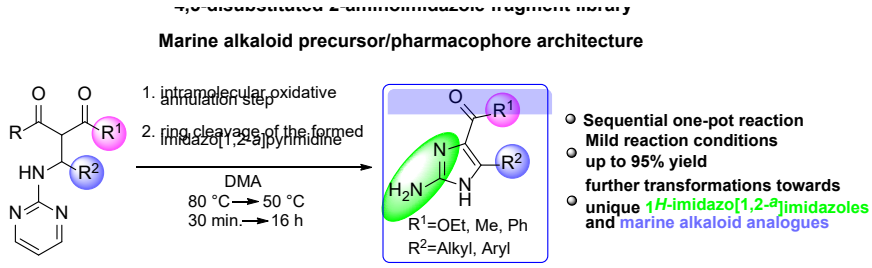
Table of Contents



We disclose an efficient one-pot process towards sophistically decorated, C4/C5-functionalised 2-AI structures as valuable fragment-like frameworks starting from the corresponding Mannich-type substrates. The IBX/IPT-mediated intramolecular oxidative annulation and hydroxylamine-induced ring cleavage sequence were carried out under mild conditions, affording the desired heterocycles in up to 95% yield. In addition, further modifications were also executed including GBB-3CR and preparation of structurally modified marine alkaloid analogues.