HETEROCYCLES, Vol. 99, No. 1, 2019, pp. 279 - 293.
Received, 18th July, 2018, Accepted, 8th August, 2018, Published online, 3rd September, 2018
DOI: 10.3987/COM-18-S(F)22

PALLADIUM-CATALYZED ARYLATION OF *N*-AMINOIMIDAZOL-2-ONES TOWARDS SYNTHESIS OF CONSTRAINED PHENYLALANINE DIPEPTIDE MIMICS

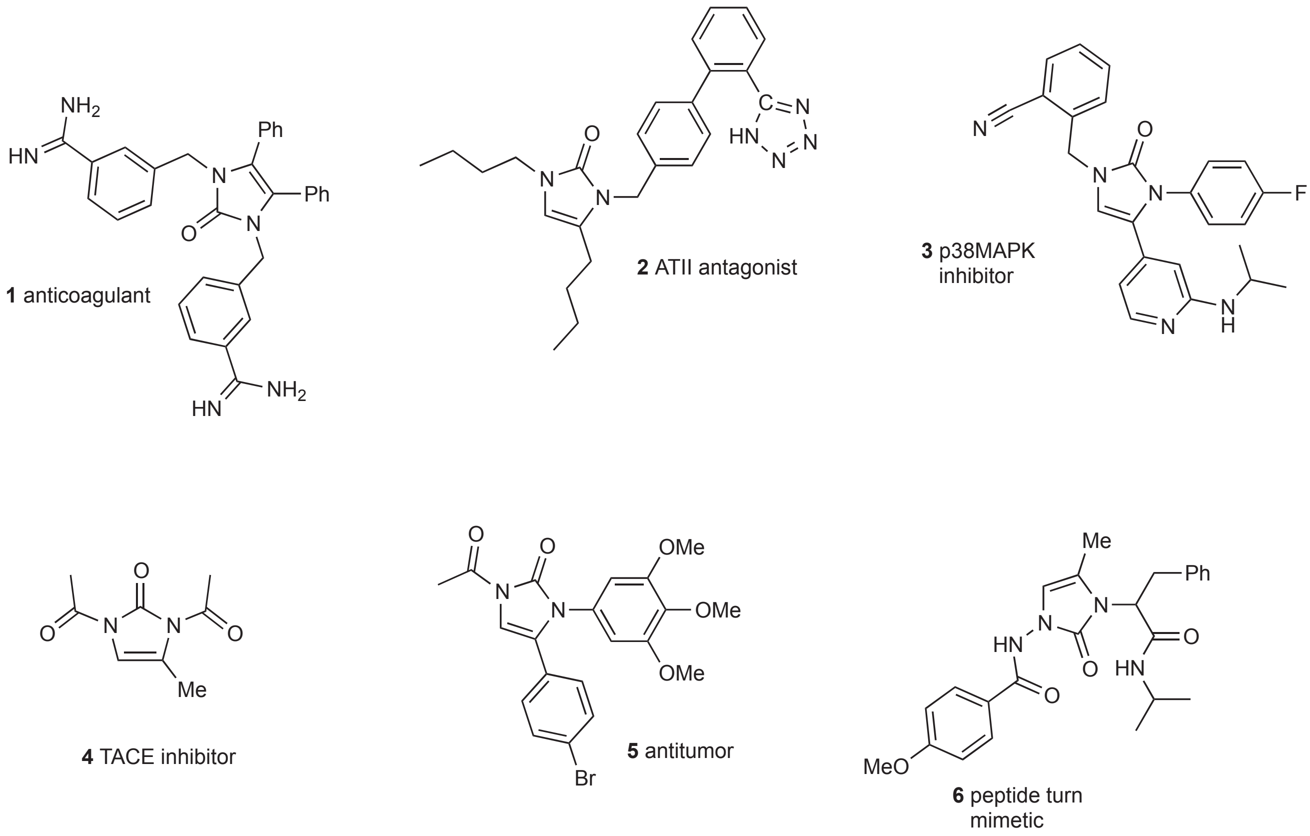
Julien Poupart, Ngoc-Duc Doan, Damien Bérubé, Yousra Hamdane, Caleb Medena, and William D. Lubell*

Département de chimie, Université de Montréal, C.P. 6128, Succursale Centre-Ville, Montréal, Québec H3C3J7, Canada. E-mail: William.Lubell@umontreal.ca

Abstract – *N*-Aminoimidazol-2-ones (e.g., **6**) offer potential to serve as constrained amino amide components that can induce turn conformation in peptide sequences. To add side chain functionality onto this amino amide surrogate, mild conditions have now been developed for palladium-catalyzed arylation of *N*-aminoimidazol-2-ones. A diverse array of aryl iodides reacted at the 5-position of *N*-aminoimidazol-2-one dipeptides **7** and **10** in a general approach for making constrained arylalanine dipeptide turn mimics (e.g., **8** and **11**).

INTRODUCTION

Imidazolones are valuable pharmacophores found in molecules exhibiting notable properties, including antioxidant,[1] anti-inflammatory,[2] anti-oncogenic,[3] anti-Parkinsonian and immunomodulatory activities.[4] For example, 4,5-diphenylimidazolone **1** displayed anticoagulant activity,[5] 4-butylimidazolone **2** exhibited activity as a potent angiotensin II receptor (AT2) antagonist,[6] 4-aminopyridine derivative **3** inhibited p38MAP kinase,[7] *N*,*N*-diacetyl-4-methylimidazol-2-one (**4**) inhibited TNF-α converting enzyme (TACE)[8] and 4-*p*-bromophenylimidazol-2-one **5** demonstrated antitumor activity.[3,9] Related *N*-aminoimidazolone analogs have also exhibited potential as immune-modulator, anti-Parkinsonian and anti-inflammatory agents.[10] Notably, imidazolones with 4- and 5-position aryl substituents (e.g., **1**, **2** and **5**) have displayed enhanced activity;[9] however, such aromatic moieties have typically been introduced during heterocycle synthesis. Arylation of the imidazolone ring may thus offer advantages for combinatorial study of structure-activity relationships (SAR) in medicinal chemistry programs.[9,11]



1 anticoagulant

2 ATII antagonist

3 p38MAPK inhibitor

4 TACE inhibitor

5 antitumor

6 peptide turn mimetic

Figure 1. Biologically relevant imidazolones **1-5** and *N*-aminoimidazolone **6**

In the context of our program in peptide mimicry, *N*-aminoimidazolone (Nai)[12] residues have been explored as constrained amino amide surrogates. In particular, Nai residues have exhibited potential to induce type II' β-turn and inverse γ-turn geometry in model peptides (e.g., **6**).[13] 4-Substituted Nai analogs were prepared by 5-*exo*-dig cyclization of aza-propargylglycine derivatives.[14] Moreover, in model Nai peptides, the 4-position substituent was shown to influence the turn conformation and the χ-dihedral angle geometry of the adjacent *C*-terminal residue.[15]

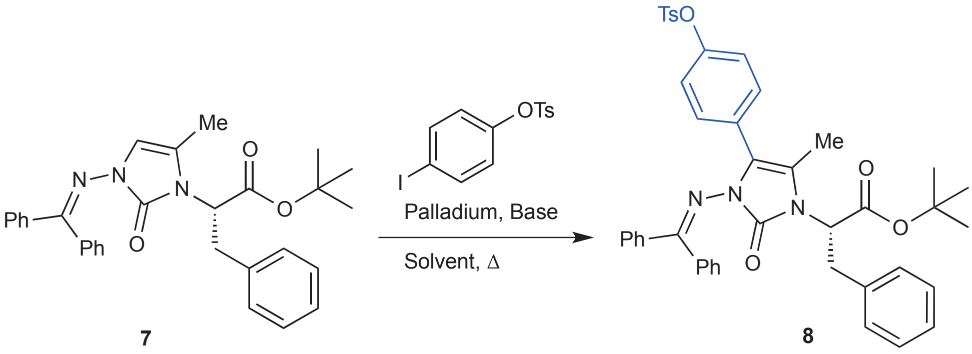
Considering the normal orientations of amino acid side chains, modification of the Nai ring system at the 5-position has been pursued to improve capacity for mimicry of natural peptide geometry and function. Inspired by a recent report on palladium-catalyzed C-H activation and arylation of simple imidazolones,[16] we have pursued the application of similar conditions to add aryl side chains at the 5-position of Nai residues. The success of this approach has now been validated by the preparation of a series of arylalanyl-phenylalanine dipeptides.

RESULTS AND DISCUSSION

Arylation of 1,3-dihydro-2*H*-imidazol-2-one has previously been reported using aryl iodides and bromides with palladium acetate as catalyst.[16] To explore this method using *N*-aminoimidazolones, Nai residue **7** was synthesized by a route featuring aza-glycine alkylation followed by base promoted 5-*exo*-dig cyclisation.[13] Arylation was first examined with *p*-tosyloxyphenyl iodide under different conditions to prepare tyrosine mimic **8a** (Figure 2 and Table 1).[17] Palladium acetate proved more effective than palladium chloride, and $Pd(PPh_3)_2Cl_2$. Moreover, palladium acetate alone reacted more effectively than in the presence of additives such as silver nitrate, triphenylphosphine and BINAP. Highest yields were obtained using 10 mol% palladium acetate in the presence of sodium acetate in DMSO at 80 °C. Acetonitrile and dioxane were ineffective as solvent.

The scope of the Pd-catalyzed arylation was next studied using Nai residue **7** and electron rich and poor aryl iodides. A wide array of *para* and *meta* substituted aryl iodides reacted successfully on *N*-aminoimidazolone **7** (Figure 2). Both electron rich and electron deficient aryl iodides were tolerated in the Pd-catalysed arylation, including methoxy, fluoride, trifluoromethyl, nitro and pyrrolo groups.

Table 1. Optimization of Nai **7** arylation to prepare constrained tyrosine analog **8**[a]

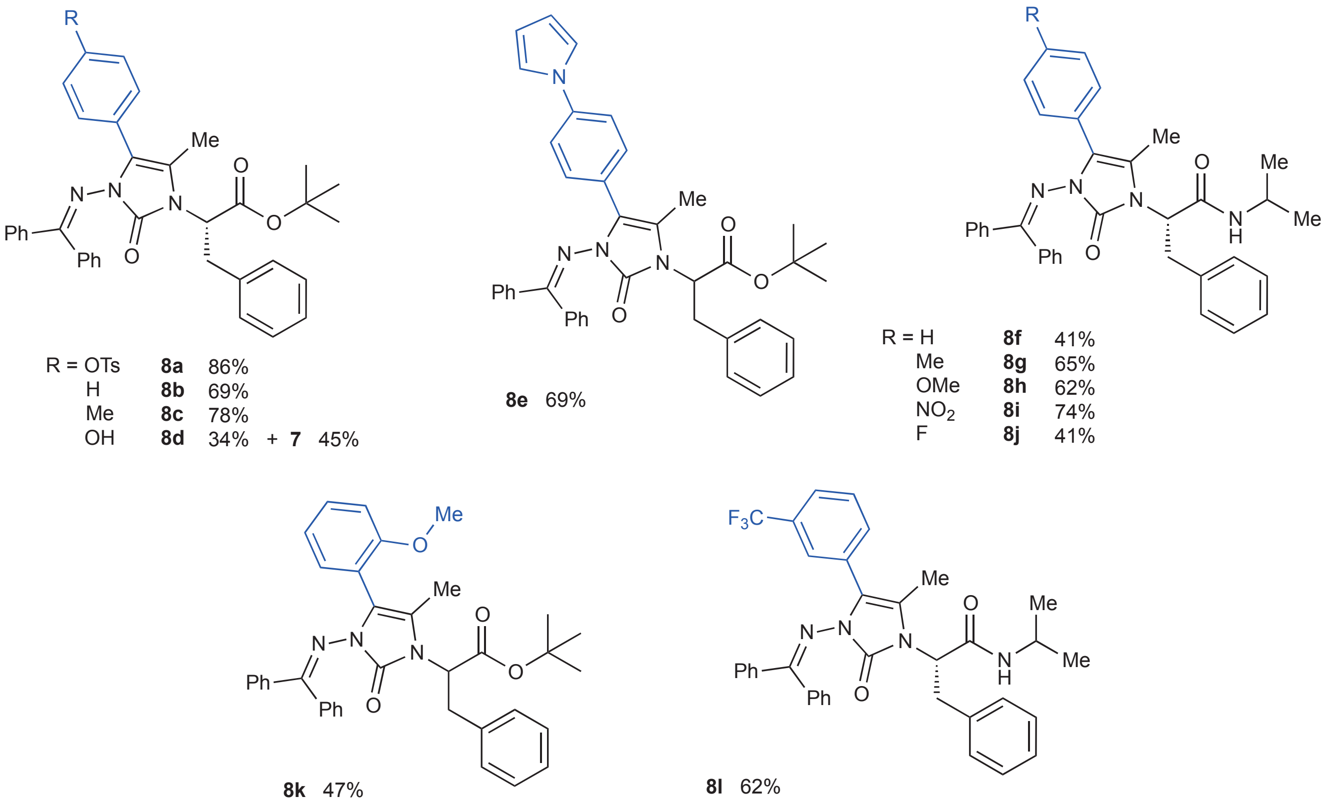


Entry	Catalytic system (mol%)	Solvent	Temperature (°C)	Time (h)	Base	Yield (%)[b]
1	$Pd(OAc)_2$ (10)	MeCN	80	48	NaOAc	Traces[c]
2	$Pd(OAc)_2$ (10)	DMSO	80	18	NaOAc	86
3	$Pd(OAc)_2$ (5)	DMSO	80	18	NaOAc	49
4	$Pd(OAc)_2$ (10)	DMSO	20	96	NaOAc	-[d]
5	$Pd(OAc)_2$ (5) $AgNO_3$ (20)	DMSO	80	48	NaOAc	20
6	$Pd(OAc)_2$ (5) *Rac*-BINAP (10)	DMSO	80	48	NaOAc	39
7	$Pd(OAc)_2$ (5) PPh_3 (10)	DMSO	80	48	NaOAc	traces

8	$Pd(PPh_3)_2Cl_2$ (10)	dioxane	100	72	KOAc	-
9	$PdCl_2$ (10)	DMSO	80	72	NaOAc	-

[a] Reagent and conditions: a mixture of **7**, 4-tosyloxyphenyl iodide (3 equiv), base (3 equiv), catalyst and degassed solvent [1 mM] was heated in a sealed tube under argon for the specified time. [b] Isolated yield. [c] Product detected on TLC but not isolated. [d] No product observed.

Compared to 1,3-dihydro-2*H*-imidazol-2-one,[16] Nai residue **7** required longer reaction times (16 h vs 6 h) and higher catalyst loading (10 mol% vs 5 mol%) to give similarly good yields. On the other hand, 5-aryl-*N*-aminoimidazolones **8** were not produced using aryl bromides. The wide array of 5-aryl substituents that were introduced on Nai residue **7** offer potential for studying structure-activity relationships of a variety of relevant aromatic residues. Notably, phenylalanine Nai analogs **8a-l** were effectively prepared; however, attempts failed to prepare histidine and tryptophan Nai analogs employing respectively 4-iodo-1-tritylimidazole and 3-iodo-*N*-(Boc)-indole as cross-coupling partners under similar conditions with *N*-aminoimidazolone **7**, which was recovered unchanged. Attempts to couple *p*-iodophenol provide unprotected phenol **8d** after a longer reaction time (48 h) without complete conversion. Finally, an attempt to prepare 5-phenyl-Nai **8b** using only 1.2 equivalents of iodobenzene failed to go to completion after 72 h.



R = OTs **8a** 86%
H **8b** 69%
Me **8c** 78%
OH **8d** 34% + **7** 45%

8e 69%

R = H **8f** 41%
Me **8g** 65%
OMe **8h** 62%
NO_2 **8i** 74%
F **8j** 41%

8k 47%

8l 62%

Figure 2. Arylation scope

The arylation conditions were also examined on a more peptide-like scaffold, dipeptide **10**, which was prepared by cleavage of the benzophenone protecting group under aqueous acidic conditions followed by semicarbazide acylation with *p*-methoxybenzoyl chloride. Treatment of Nai-peptide **10** with *p*-iodotoluene and palladium acetate (10 mol%) under the optimized conditions afford 5-arylated Nai-dipeptide **11** in modest yield.

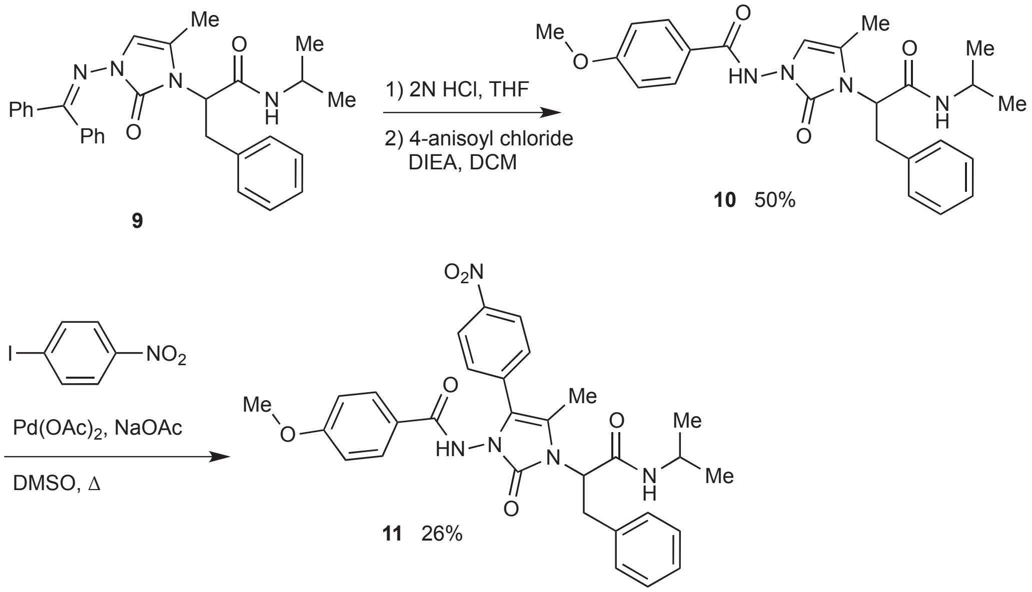
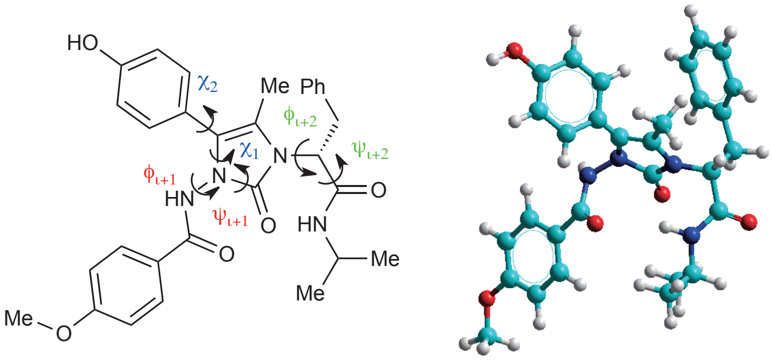


Figure 3. Synthesis of 5-aryl-Nai peptide **11**

To examine the potential of a 5-*p*-hydroxyphenyl Nai residue to serve as a constrained tyrosine residue, a geometry optimization of *p*-methoxybenzoyl-5-(*p*-hydroxyphenyl)-4-(methyl)Nai-Phe-NH*i*Pr **12** was performed using coordinates obtained from the crystal structure of the parent 4-(methyl)Nai peptide **10**.[13] Consistent with the parent structure, the backbone dihedral angles were coherent with a type II' β-turn.[14] Moreover, the side chain dihedral angles, χ_1 and χ_2, of the 5-position aryl substituent were in the *gauche* (–) conformation, due in part to steric interactions with the 4-position methyl group. Notably, the *gauche* (–) conformation is preferred for the aromatic side chain of L-amino acid residues.[18] The 5-(aryl)Nai residue was thus predicted to mimic both the backbone and side chain geometry of aromatic residues situated at the $i + 1$ position of a type II' β-turn.



12

Figure 4. Left: Tetrapeptide mimic **12** and relevant dihedral angles, Right: Minimized structure

CONCLUSION

Mild and versatile palladium-catalyzed arylation of *N*-aminoimidazol-2-one (Nai) residues has been developed in an approach to synthesize mimics of peptide backbone turn conformation and side chain orientation. A wide variety of aryl iodides reacted successfully in the late-stage diversification of the Nai residues. Computational analysis of 5-aryl Nai peptide **12** predicted that the χ values of the side chain corresponded to a *gauche* (–) geometry within a type II' β-turn conformation. Considering the effectiveness of the arylation chemistry and the ability of the 5-aryl-Nai residue to induce turn secondary structure, the described method offers strong potential for mimicry of natural peptide geometry.

EXPERIMENTAL

General chemistry

Unless specified, all reactions were performed under argon atmosphere. All glassware was stored in the oven or flame-dried and let cool under inert atmosphere prior to use. Anhydrous solvents were obtained either by filtration trough drying columns (DCM, THF, MeCN) in a GlassContour system (Irvine, CA) or by distillation over CaH_2 (dioxane). *tert*-Butyl 2-{3-[(diphenylmethylidene)amino]-5-methyl-2-oxo-2,3-dihydro-1*H*-imidazol-1-yl}-3-phenylpropanoate,[13] 2-(3-((diphenylmethylene)amino)-5-methyl-2-oxo-2,3-dihydro-1*H*-imidazol-1-yl)-*N*-isopropyl-3-phenylpropanamide,[13] 4-iodophenyl 4-methylbenzenesulfonate[19] and *p*-methoxybenzoyl chloride[20] were synthesized using published procedures. All other starting materials, reagents and chemicals were purchased from commercial suppliers and used without further purification, except for silver nitrate which was recrystallised from boiling water. The progress of reaction was monitored by thin layer gel chromatography (TLC) plates, visualized under UV light (254 nm) or by staining with $KMnO_4$. Flash chromatography[21] was performed using 230-400 mesh silica gel from SiliCycle Inc. and distilled solvents. Nuclear magnetic resonance spectra (^1H and ^{13}C) were recorded either on a Bruker AMX 300, AV 400, AVII 400 or AMX 500 spectrometer. Specific rotations were determined on a Perkin-Elmer 341 polarimeter at 589, and are reported as follows $[\alpha]_{\lambda}^{temp}$, concentration (*c* in g/100 mL), and solvent. High resolution mass spectrometry (HRMS) was performed by the Centre regional de spectroscopie de masse de l'Université de Montréal. Analytical and preparative supercritical fluid chromatography (SFC) was performed at the Laboratoire d'analyse et de séparation chirale par SFC de l'Université de Montréal and data are reported as follow: temperature, backpressure and retentions times (R*t*).

Computational chemistry

The model of tetrapeptide mimic **12** was created using parameters from the published crystal structure of 4-(methyl)Nai peptide **10**,[13] and minimized using HyperChem 8™ (Molecular mechanics and a Polak-Ribiere conjugate gradient of 0.1 kcal/(Å*mol) in a 16.5 Å^3 periodic box.

Dihedral angles for ideal β-turn, the crystal structure of **10** and computed values for **12**.

Type of turn	ϕ_{i+1}	ψ_{i+1}	ϕ_{i+2}	ψ_{i+2}	$\chi_{1\ i+1}$	$\chi_{2\ i+1}$
Ideal β-II'[14]	60	-120	-80	0	-	-
10[13]	58.9	-153.3	-69.1	-4.6	-	-
12	48.6	-143.7	-62.4	33.6	-41.1	76.0

***tert*-Butyl (*R*)-2-(3-((diphenylmethylene)amino)-4-methyl-2-oxo-5-(4-(tosyloxy)phenyl)-2,3-dihydro-1*H*-imidazol-1-yl)-3-phenylpropanoate (8a)**

tert-Butyl (2*R*)-2-{3-[(diphenylmethylidene)amino]-5-methyl-2-oxo-2,3-dihydro-1*H*-imidazol-1-yl}-3-phenylpropanoate (**7**, 67 mg, 0.14 mmol), 4-iodophenyl 4-methylbenzene-1-sulfonate (156 mg, 0.42 mmol), sodium acetate (34 mg, 0.42 mmol) and palladium acetate (3 mg, 0.014 mmol) were added to 1 mL of degassed DMSO in a pressure vessel. The vessel was purged with argon, sealed, heated to 80 °C and stirred overnight, when complete reaction was ascertained by TLC (disappearance of starting material, R*f* = 0.45 (30% EtOAc/hexanes). The reaction mixture was cooled, and partitioned between DCM (10 mL) and a mixture of brine (8 mL) and 5% citric acid (2 mL). The phases were separated and the aqueous layer was extracted with DCM (10 mL). The combined organic layers were washed with brine (10 mL), dried over magnesium sulfate, filtered and evaporated to a residue that was purified by column chromatography using 15-30% EtOAc/hexanes as eluent. Evaporation of the collected fractions gave 5-aryl Nai **8a** as a yellow oil (87 mg, 86%): R*f* = 0.34 (30% EtOAc/hexanes); $[\alpha]_D^{25}$ –97.1 (*c* 0.22, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8 Hz, 2H), 7.54 (d, *J* = 8 Hz, 2H), 7.45-7.49 (m, 1H), 7.34-7.39 (m, 3H), 7.18-7.22 (m, 5H), 7.13 (d, *J* = 8 Hz, 2H), 7.00-7.02 (m, 2H), 6.81-6.92 (m, 6H), 4.64-4.68 (m, 1H), 3.39-3.43 (m, 2H), 2.40 (s, 3H), 1.49 (s, 9H);

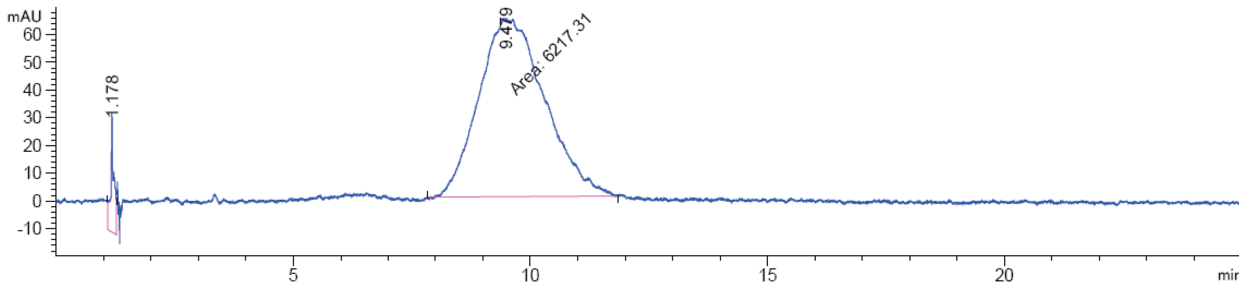
^{13}C NMR (75 MHz, CDCl$_3$) δ 174.6, 168.4, 148.3, 148.1, 145.4, 137.8, 137.1, 135.0, 132.2, 131.2, 130.1, 129.7, 129.6, 129.2, 128.7, 128.4, 128.0, 127.8, 126.6, 122.1, 117.8, 116.1, 82.4, 57.6, 35.4, 29.7, 28.0, 21.7, 9.5. HRMS calcd. for $C_{43}H_{42}N_3O_6S$, [MH$^+$] = 728.2789, found = 728.2802.

tert-Butyl (_S_)-2-(3-((diphenylmethylene)amino)-4-methyl-2-oxo-5-phenyl-2,3-dihydro-1_H_-imidazol-1-yl)-3-phenylpropanoate (8b)

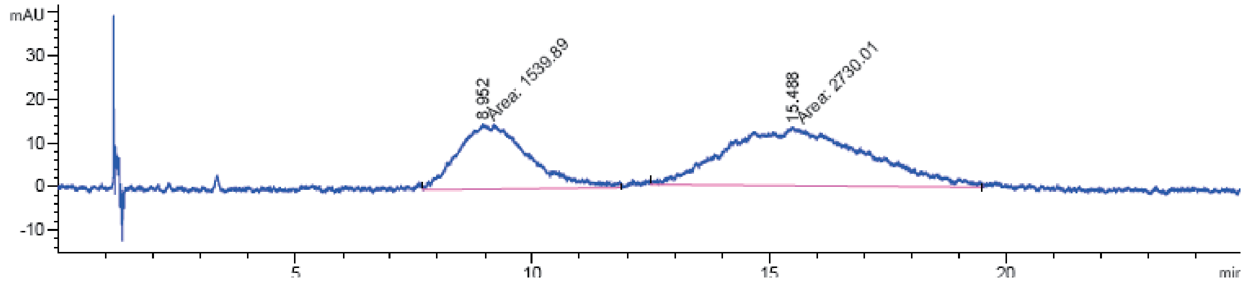
Employing the protocol for the synthesis of 5-aryl-Nai **8a**, Nai **7** (158 mg, 0.33 mmol) was reacted with iodobenzene (112 µL, 1 mmol), and the residue was purified by flash chromatography using 15% EtOAc/hexanes as eluent to provide 5-phenyl-Nai **8b** as yellow foam (128 mg, 69%): R*f* = 0.48 (30% EtOAc in hexanes); $[\alpha]_D^{20}$ –191.7 (*c* 1.06, CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.60-7.58 (m, 2H), 7.48-7.43 (m, 1H), 7.38-7.18 (m, 11H), 7.09-6.99 (m, 6H), 4.68-4.63 (m, 1H), 3.48-3.59 (m, 2H), 1.64 (s, 3H), 1.50 (s, 9H); ^{13}C NMR (101 MHz, CDCl$_3$) δ 174.9, 168.6, 148.1, 138.0, 137.2, 135.3, 131.2, 129.82, 129.4, 129.2, 128.8, 128.5, 128.2, 128.1, 127.9, 127.2, 126.7, 125.9, 119.3, 116.0, 116.0, 82.5, 57.9, 35.6, 28.1, 9.6. HRMS calcd. for $C_{36}H_{36}N_3O_3$, [MH$^+$] = 558.2712, found = 558.2717.

tert-Butyl (_S_)-2-(3-((diphenylmethylene)amino)-4-methyl-2-oxo-5-(_p_-tolyl)-2,3-dihydro-1_H_-imidazol-1-yl)-3-phenylpropanoate (8c)

Employing the protocol for the synthesis of 5-aryl-Nai **8a**, Nai **7** (101 mg, 0.21 mmol) was reacted with iodotoluene (83 µL, 0.64 mmol), and the residue was purified by flash chromatography using 15% EtOAc/hexanes as eluent to provide 5-tolyl-Nai **8c** as yellow foam (92.1 mg, 78%): R*f* = 0.49 (30% EtOAc in hexanes); $[\alpha]_D^{20}$ –185.5 (*c* 1.06, CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.63 (dd, *J* = 1.0, 5.7 Hz, 2H), 7.46 (tt, *J* = 1.2, 6.0 Hz, 1H), 7.39-7.34 (m, 3H), 7.30-7.23 (m, 5H), 7.10-7.01 (m, 4H), 7.01-7.00 (m, 4H), 4.64-4.16 (m, 1H), 3.45-3.35 (m, 2H), 2.33 (s, 3H), 1.64 (s, 3H), 1.50 (s, 9H); ^{13}C NMR (101 MHz, CDCl$_3$) δ 174.6, 168.8, 147.9, 138.1, 137.4, 136.9, 135.5, 131.1, 129.9, 129.4, 129.2, 129.1, 128.9, 128.9, 128.5, 128.1, 127.8, 126.6, 126.3, 119.3, 115.3, 82.3, 57.8, 35.6, 28.1, 21.3, 9.6. HRMS calcd. for $C_{37}H_{38}N_3O_3$, [MH$^+$] = 571.2837, found = 571.2835. An enantiomeric ratio of >99:1 *S*-**8c**:*R*-**8c** was ascertained by SFC analysis on a chiral stationary phase [Chiralcel AD-H 25 cm, 5 µm, 20% i-PrOH, 3 mL/min, 35 °C, 150 bar, R*t* = 9.5 min].



Co-injection of *S*-**8c** and *R*-**8c** gave two peaks that eluted at 9 min and 15.5 min.



tert-Butyl (*S*)-2-(3-((diphenylmethylene)amino)-5-(4-hydroxyphenyl)-4-methyl-2-oxo-2,3-dihydro-1*H*-imidazol-1-yl)-3-phenylpropanoate (8d)

Employing the protocol for the synthesis of 5-aryl-Nai **8a**, Nai **7** (61 mg, 0.13 mmol) was reacted with *p*-iodophenol (84 mg, 0.36 mmol), and the residue was purified by flash chromatography using 20% EtOAc in hexanes as eluent to provide 5-*p*-hydroxyphenyl-Nai **8d** as orange low melting solid (25 mg, 34%): R*f* = 0.62 (50% EtOAc in hexanes); $[\alpha]_D^{25}$ –29.4 (*c* 0.18, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (t, *J* = 6 Hz, 1H), 7.54 (d, *J* = 7.7 Hz, 2H), 7.50-7.19 (m, 9H), 7.00-6.96 (m, 3H), 6.87 (d, *J* = 8.3 Hz, 2H), 6.65 (d, *J* = 8.5 Hz, 1H), 6.31-6.26 (m, 1H), 4.60-4.56 (m, 1H), 3.37-3.32 (m, 2H), 1.55 (s, 3H), 1.44 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.2, 148.0, 138.0, 137.2, 130.8, 130.1, 129.8, 129.4, 129.2, 128.8, 128.5, 128.4, 128.2, 128.1, 127.9, 115.2, 115.0, 82.4, 57.8, 29.8, 28.1, 27.9, 22.8, 14.2, 9.5. HRMS calcd. for $C_{36}H_{35}N_3O_4$, $[M^+]$ = 574.2700, found = 574.2696. Starting Nai **7** was also recovered (27 mg, 45%).

tert-Butyl 2-(5-(4-(1*H*-pyrrol-1-yl)phenyl)-3-((diphenylmethylene)amino)-4-methyl-2-oxo-2,3-dihydro-1*H*-imidazol-1-yl)-3-phenylpropanoate (8e)

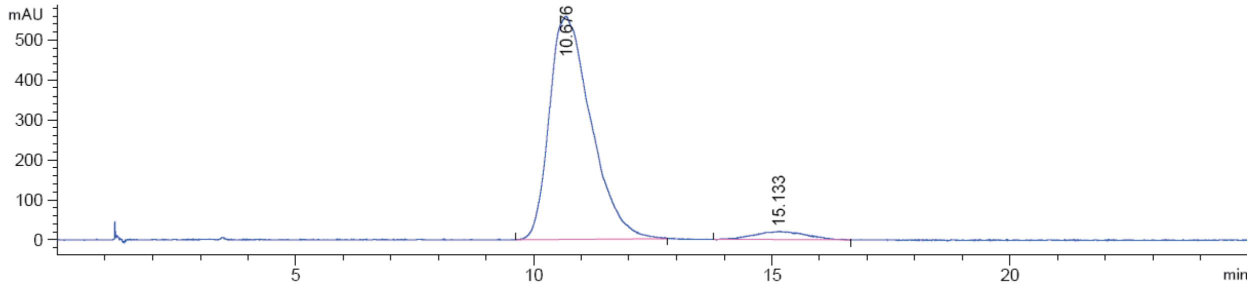
Employing the protocol for the synthesis of 5-aryl-Nai **8a**, Nai **7** (67 mg, 0.14 mmol) was reacted with 1-(4-iodophenyl)-pyrrole (113 mg, 0.42 mmol), and the residue was purified by flash chromatography using 20% EtOAc in hexanes as eluent to provide 5-(4-(1*H*-pyrrol-1-yl)phenyl-Nai **8e** as yellow low melting solid (60 mg, 69%): R*f* = 0.51 (40% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67-7.58 (m, 3H), 7.50-7.28 (m, 8H), 7.25-7.03 (m, 10H), 6.38 (t, *J* = 2.2 Hz, 1H), 6.32 (t, *J* = 2.2 Hz, 1H), 4.69-4.58 (m, 1H), 3.49-3.29 (m, 2H), 1.63 (s, 1H), 1.54 (d, *J* = 1.3 Hz, 2H), 1.46 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 138.5, 137.6, 136.7, 135.1, 131.4, 129.5, 129.3, 129.1, 128.9, 128.4, 128.4, 128.2, 128.1, 128.1, 128.0, 127.0, 126.6, 126.4, 125.7, 119.0, 118.8, 81.2, 53.9, 27.6, 22.0, 9.0. HRMS calcd. for $C_{40}H_{38}N_4O_3$, $[M^+]$ = 623.3017, found = 623.3024.

(*S*)-2-(3-((Diphenylmethylene)amino)-4-methyl-5-phenylimidazolin-2-on-1-yl)-*N*-isopropyl-3-phenylpropanamide (8f)

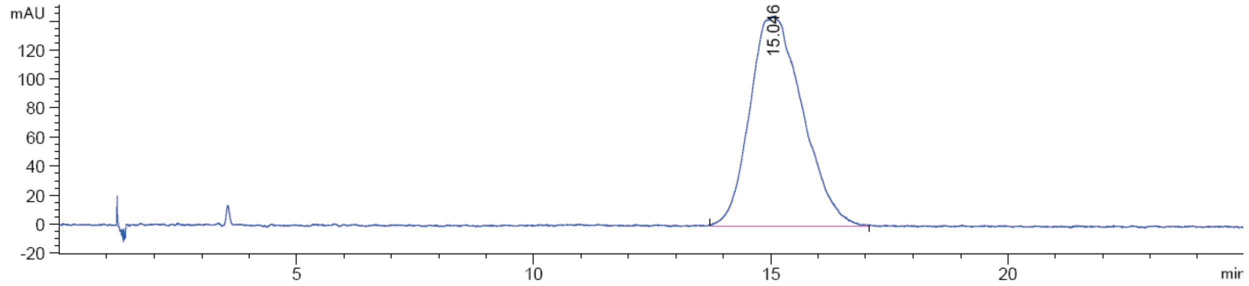
Employing the protocol for the synthesis of 5-aryl-Nai **8a**, (*S*)-2-(3-((diphenylmethylene)amino)-5-methyl-2-oxo-2,3-dihydro-1*H*-imidazol-1-yl)-*N*-isopropyl-3-phenylpropanamide (54 mg, 0.12 mmol) was reacted with iodobenzene (70 mg, 0.35 mmol), and the residue was purified by flash chromatography using 20-30% EtOAc in hexanes as eluent to provide 5-phenyl-Nai amide **8f** as yellow low melting solid (26 mg, 41%): R*f* = 0.51 (50% EtOAc in hexanes); $[\alpha]_D^{20}$ –126.3 (*c* 1.06, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (br. s, 1H), 7.59 (dd, *J* = 1.2, 7.1 Hz, 2H), 7.48-7.44 (m, 1H), 7.38-7.33 (m, 4H), 7.26-7.20 (m, 8H), 7.05-6.97 (m, 6H), 4.48-4.46 (m, 1H), 4.02 (2 overlapping q, *J* = 7.5 Hz, 1H), 3.60-3.55 (m, 1H), 3.29 (dd, *J* = 4.3, 9.4 Hz, 1H) 1.64 (s, 3H), 1.17 (d, *J* = 6.6 Hz, 3H), 1.13 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.9, 169.6, 148.7, 137.7, 137.0, 135.2, 131.5, 129.9, 129.5, 129.4, 129.2, 128.6, 128.6, 128.3, 128.2, 128.0, 127.5, 126.9, 119.9, 116.4, 41.8, 35.8, 22.7, 22.6, 9.6. HRMS calcd. for $C_{35}H_{35}N_4O_2$, $[MH^+]$ = 543.2755, found = 543.2759.

(*S*)-2-(3-((Diphenylmethylene)amino)-4-methyl-5-(*p*-methylphenyl)imidazolin-2-on-1-yl)-*N*-isopropyl-3-phenylpropanamide (8g)

Employing the protocol for the synthesis of 5-aryl-Nai **8a**, (*S*)-2-(3-((diphenylmethylene)amino)-5-methyl-2-oxo-2,3-dihydro-1*H*-imidazol-1-yl)-*N*-isopropyl-3-phenylpropanamide (310 mg, 0.67 mmol) was reacted with *p*-iodotoluene (259 µL, 2.00 mmol), and the residue was purified by flash chromatography using 25% EtOAc in hexanes as eluent to provide 5-tolyl-Nai amide **8g** as yellow low melting solid (251 mg, 65%): R*f* = 0.55 (50% EtOAc in hexanes); $[\alpha]_D^{20}$ –65.9 (*c* 1.06, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (br. s, 1H), 7.59 (dd, *J* = 1.1, 7.1 Hz, 2H), 7.47-7.44 (m, 1H), 7.36-7.27 (m, 4H), 7.24-7.18 (m, 4H), 7.06-6.99 (m, 6H), 6.80 (d, *J* = 8.2 Hz, 2H), 4.44-4.43 (m, 1H), 4.50 (2 overlapping q, *J* = 7.4 Hz, 1H), 3.55 (t, *J* = 11.4 Hz, 1H), 3.27 (dd, *J* = 4.2, 9.5 Hz, 1H), 2.29 (s, 3H), 1.61 (s, 3H), 1.16 (d, *J* = 6.6 Hz, 3H), 1.12 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.8, 169.7, 148.6, 137.8, 137.4, 137.0, 135.3, 131.4, 129.9, 129.5, 129.3, 129.2, 128.2, 128.5, 128.6, 128.2, 128.0, 126.8, 125.7, 119.9, 116.0, 41.7, 35.8, 22.6, 22.6, 21.3, 9.6. HRMS calcd. for $C_{36}H_{37}N_4O_2$, $[MH^+]$ = 557.2911, found = 557.2927. An enantiomeric ratio of >96:4 *S*- **8g**:*R*-**8g** was ascertained by SFC analysis on a chiral stationary phase [Chiralcel AD-H 25 cm, 5 µm, 15% i-PrOH, 3 mL/min, 35 °C, 150 bar, R*t* (major) 10.6 min; R*t* (trace) 15.1 min].



Injection of *R*-**8g** gave a major peak (99%) at 15.1 min.



(*S*)-2-(3-((Diphenylmethylene)amino)-4-methyl-5-(*p*-methoxylphenyl)imidazolin-2-on-1-yl)-*N*-isopropyl-3-phenylpropanamide (8h)

Employing the protocol for the synthesis of 5-aryl-Nai **8a**, (*S*)-2-(3-((diphenylmethylene)amino)-5-methyl-2-oxo-2,3-dihydro-1*H*-imidazol-1-yl)-*N*-isopropyl-3-phenylpropanamide (54 mg, 0.12 mmol) was reacted with *p*-iodoanisole (81 mg, 0.35 mmol), and the residue was purified by flash chromatography using 20-35% EtOAc in hexanes as eluent to provide 5-*p*-methoxylphenyl-Nai amide **8h** as yellow low melting solid (41 mg, 62%): R*f* = 0.49 (50% EtOAc in hexanes); $[\alpha]_D^{20}$ –93.9 (*c* 1.06, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (br. s, 1H), 7.58 (dd, *J* = 1.2, 7.2 Hz, 2H), 7.48-7.44 (m, 1H), 7.36-7.32 (m, 3H), 7.21-7.19 (m, 4H), 7.02-6.99 (m, 4H), 6.95-6.63 (m, 2H), 7.27 (d, *J* = 8.9 Hz, 2H), 4.44-4.43 (m, 1H), 4.00 (2 overlapping q, *J* = 6.7 Hz, 1H), 3.76 (s, 3H), 3.57-3.52 (m, 1H), 3.27 (dd, *J* = 4.3, 9.5 Hz, 1H), 1.59 (s, 3H), 1.16 (d, *J* = 6.6 Hz, 3H), 1.12 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.1, 169.8, 159.1, 148.7, 137.8, 137.0, 135.3, 132.6, 131.5, 130.8, 130.2, 129.9, 129.5, 129.2, 128.7, 128.6, 128.2, 128.0, 126.8, 121.0, 119.6, 115.8, 113.8, 55.4, 41.8, 35.9, 22.6, 9.5. HRMS calcd. for $C_{36}H_{36}N_4O_3$, $[M^+]$ = 573.2860, found = 573.2854.

(*S*)-2-(3-((Diphenylmethylene)amino)-4-methyl-5-(*p*-nitro-phenyl)imidazolin-2-on-1-yl)-*N*-isopropyl-3-phenylpropanamide (8i)

Employing the protocol for the synthesis of 5-aryl-Nai **8a**, (*S*)-2-(3-((diphenylmethylene)amino)-5-methyl-2-oxo-2,3-dihydro-1*H*-imidazol-1-yl)-*N*-isopropyl-3-phenylpropanamide (54 mg, 0.12 mmol) was reacted with *p*-nitroiodobenzene (84 mg, 0.35 mmol), and the residue was purified by flash chromatography using 20-35% EtOAc in hexanes as eluent to provide 5-*p*-nitrophenyl-Nai amide **8i** as orange low melting solid (50 mg, 74%): R*f* = 0.58 (50% EtOAc in hexanes); $[\alpha]_D^{20}$ –124.2 (*c* 1.06, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, *J* = 9.0 Hz, 2H), 7.59 (dd, *J* = 1.2, 7.2 Hz, 2H), 7.49 (dt, *J* = 1.3, 7.4 Hz, 1H), 7.41-7.35 (m, 3H), 7.30-7.27 (m, 2H), 7.24-7.20 (m, 5H), 7.04-7.01 (m, 4H), 4.50-48 (m, 1H), 3.88 (2 overlapping q, *J* = 7.5 Hz, 1H), 3.54 (dd, *J* = 11.4, 2.4, Hz, 1H), 3.28 (dd, *J* = 4.5, 9.3 Hz, 1H), 1.17 (s, 3H), 1.15 (d, *J* = 6.6 Hz, 3H), 1.11 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.5, 169.0, 148.4, 146.4, 137.3, 136.5, 135.2, 134.9, 129.8, 129.2, 129.0, 128.6, 128.5, 128.3, 128.1, 127.0, 123.6, 119.0, 118.4, 41.8, 35.5, 22.5, 22.4, 9.8. HRMS calcd. for $C_{35}H_{34}N_5O_4$, [MH$^+$] = 588.2605, found = 588.2615.

(*S*)-2-(3-((Diphenylmethylene)amino)-4-methyl-5-(*p*-fluoro-phenyl)imidazolin-2-on-1-yl)-*N*-isopropyl-3-phenylpropanamide (8j)

Employing the protocol for the synthesis of 5-aryl-Nai **8a**, (*S*)-2-(3-((diphenylmethylene)amino)-5-methyl-2-oxo-2,3-dihydro-1*H*-imidazol-1-yl)-*N*-isopropyl-3-phenylpropanamide (54 mg, 0.12 mmol) was reacted with *p*-fluoroiodobenzene (77 mg, 0.35 mmol), and the residue was purified by flash chromatography using 20-35% EtOAc in hexanes as eluent to provide 5-*p*-fluorophenyl-Nai amide **8j** as yellow low melting solid (26 mg, 41%): R*f* = 0.43 (50% EtOAc in hexanes); $[\alpha]_D^{20}$ –117.4 (*c* 1.06, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (br. s, 1H), 7.58 (dd *J* = 1.3, 7.2 Hz, 2H), 7.47 (dt, *J* = 1.3, 7.5 Hz, 1H), 7.39-7.30 (m, 3H), 7.29-7.27 (m, 1H), 7.23-7.19 (m, 3H), 7.03-6.92 (m, 9H), 4.60-4.43 (m, 1H), 4.01 (2 overlapping q, *J* = 6.6 Hz, 1H), 3.56 (dd, *J* = 11.3, 2.3 Hz, 1H), 3.28 (dd, *J* = 4.4, 9.4 Hz, 1H), 1.61 (s, 3H), 1.17 (d, *J* = 6.6 Hz, 3H), 1.13 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.0, 169.6, 148.7, 137.7, 136.9, 135.2, 131.7, 131.3, 131.2, 129.9, 129.7, 129.2, 128.7, 128.3, 128.1, 126.9, 124.8, 118.9, 116.5, 115.53, 115.4, 41.8, 35.8, 22.7, 22.6, 9.5. HRMS calcd. for $C_{35}H_{34}FN_4O_2$, [MH$^+$] = 561.2667, found = 561.2660.

tert-Butyl 2-(3-((diphenylmethylene)amino)-5-(2-methoxyphenyl)-4-methyl-2-oxo-2,3-dihydro-1*H*-imidazol-1-yl)-3-phenylpropanoate (8k)

Employing the protocol for the synthesis of 5-aryl-Nai **8a**, Nai **7** (43 mg, 0.09 mmol) was reacted with 2-iodoanisole (36 µL, 0.27 mmol), and the residue was purified by flash chromatography using 15% EtOAc in hexanes as eluent to provide 5-(*p*-methoxyphenyl-Nai **8k** as yellow oil (25 mg, 47%): R*f* = 0.72 (50% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 4 Hz, 2H), 7.42-7.17 (m, 10H), 7.17 (d, *J* = 1.2 Hz, 2H), 7.05 (d, *J* = 5.9 Hz, 2H), 6.92 (d, *J* = 7.5 Hz, 1H), 6.82 (t, *J* = 7.6 Hz, 1H), 6.75 (d, *J* = 7.9 Hz, 1H), 4.65-4.62 (m, 1H), 3.63 (s, 3H), 3.40-3.30 (m, 2H), 1.53 (s, 3H), 1.44 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.8, 157.5, 147.9, 138.1, 135.5, 132.5, 130.4, 129.7, 129.4, 129.3, 129.0, 128.8, 128.4, 127.8, 127.7, 126.4, 120.1, 116.2, 116.0, 110.9, 82.1, 57.5, 55.09, 35.5, 29.7, 28.0, 9.8. HRMS calcd. for $C_{37}H_{37}N_3O_4$, [M$^+$] = 588.2857, found = 588.2864.

(*S*)-2-(3-((Diphenylmethylene)amino)-4-methyl-5-(*m*-trifluoromethyl-phenyl)-imidazolin-2-on-1-yl)-*N*-isopropyl-3-phenylpropanamide (8l)

Employing the protocol for the synthesis of 5-aryl-Nai **8a**, (*S*)-2-(3-((diphenylmethylene)amino)-5-methyl-2-oxo-2,3-dihydro-1*H*-imidazol-1-yl)-*N*-isopropyl-3-phenylpropanamide (54 mg, 0.12 mmol) was reacted with *m*-trifluoromethyl-iodobenzene (94 mg, 0.35 mmol), and the residue was purified by flash chromatography using 20-35% EtOAc in hexanes as eluent to provide 5-*m*-trifluoromethylphenyl-Nai amide **8l** as yellow low melting solid (48 mg, 68%): R*f* = 0.52 (50% EtOAc in hexanes); $[\alpha]_D^{20}$ –121.8 (*c* 1.06, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.96 (br. s, 1H), 7.57 (dd, *J* = 1.2, 7.1 Hz, 2H), 7.48-7.44 (m, 2H), 7.38-7.33 (m, 4H), 7.24-7.17 (m, 7H), 7.08-7.06 (m, 2H), 6.90 (dd, *J* = 1.0, 7.1 Hz, 2H), 4.51-4.48 (m, 1H), 4.03 (2 overlapping q, *J* = 6.6 Hz, 1H), 3.60 (dd, *J* = 11.4, 2.4 Hz, 1H), 3.31 (dd, *J* = 4.4, 9.5 Hz, 1H), 1.65 (s, 3H), 1.18 (d, *J* = 6.6 Hz, 3H), 1.15 (d. *J* = 6.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.3, 169.4, 149.1, 137.6, 136.7, 134.9, 132.3, 131.8, 129.9, 129.8, 129.5, 129.2, 128.8, 128.7, 128.6, 128.3, 128.1, 127.0, 126.1, 122.7, 118.5, 117.4, 62.4, 41.9, 36.0, 22.7, 22.6, 9.6. HRMS calcd. for $C_{36}H_{34}F_3N_4O_2$, $[MH^+]$ = 611.2628, found = 611.2635.

N-(3-(1-(*iso*-Propylamino)-1-oxo-3-phenylpropan-2-yl)-4-methyl-2-oxo-2,3-dihydro-1*H*-imidazol-1-yl)-4-methoxybenzamide (10)

2-(3-((Diphenylmethylene)amino)-5-methyl-2-oxo-2,3-dihydro-1*H*-imidazol-1-yl)-*N*-isopropyl-3-phenylpropanamide (**9**, 349 mg, 0.75 mmol) was dissolved in THF (8 mL) and treated with aqueous HCl (2M, 8 mL, 15 mmol). The mixture was stirred at room temperature for 2 h until complete conversion was ascertained by TLC. The mixture was concentrated under vacuum, diluted with a 4:1 mixture of acetonitrile/water (25 mL). The aqueous layer was separated, washed with hexanes (3 x 15 mL), and freeze-dried. The residue was dissolved in DCM (8 mL), treated with freshly prepared 4-anisoyl chloride (0.20 mL, 1.5 mmol) and DIEA (0.37 mL, 2.25 mmol) and stirred overnight. The reaction mixture was diluted with DCM (10 mL), washed with 5% citric acid (3 x 5 mL) and brine (10 mL), dried over magnesium sulfate and evaporated to a residue that was purified by column chromatography using 20-70% EtOAc in hexanes to give amide **10** as yellow foam (164 mg, 50%): R*f* = 0.41 (80% EtOAc in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 10.87 (s, 1H), 7.79 (d, *J* = 8.9 Hz, 2H), 7.15-7.10 (m, 6H), 6.71 (d, *J* = 9.0 Hz, 2H), 6.03 (s, 1H), 4.53 (dd, *J* = 4.5, 6.8 Hz, 1H), 4.10, (2 overlapping q, *J* = 1.0 Hz, 1H), 3.81 (s, 3H), 3.71 (dd, *J* = 2.4, 11.5 Hz, 1H), 3.51 (dd, *J* = 4.5, 9.3 Hz, 1H), 1.75 (s, 3H), 1.21 (d, *J* = 6.6 Hz, 3H), 1.15 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5, 166.2, 162.8, 154.3, 137.7, 129.8, 129.1, 128.8, 127.0, 122.9, 119.3, 113.6, 110.9, 61.2, 55.5, 42.0, 35.1, 22.6, 22.4, 10.5. HRMS calcd. for $C_{24}H_{29}N_4O_4$, $[MH^+]$ = 436.2183, found = 437.2188.

N-(3-(1-(Isopropylamino)-1-oxo-3-phenylpropan-2-yl)-4-methyl-5-(4-nitrophenyl)-2-oxo-2,3-dihydro-1*H*-imidazol-1-yl)-4-methoxybenzamide (11)

Employing the protocol for the synthesis of 5-aryl-Nai **8a**, *N*-(3-(1-(isopropylamino)-1-oxo-3-phenylpropan-2-yl)-4-methyl-2-oxo-2,3-dihydro-1*H*-imidazol-1-yl)-4-methoxybenzamide (**10**, 84 mg, 0.19 mmol) was reacted with *p*-iodonitrobenzene (144 mg, 0.58 mmol) with stirring for 48 h, and purification by column chromatography using 30-70% EtOAc in hexanes gave

5-*p*-nitrophenyl-Nai peptide **11** as orange low melting solid (28 mg, 26%): R*f* = 0.11 (50% EtOAc in hexanes); ^{1}H-NMR (400 MHz, MeOD-*d*$_4$) δ 8.22 (d, *J* = 8.6 Hz, 2H), 7.79 (d, *J* = 8.2 Hz, 2H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.32-7.22 (m, 5H), 6.98 (d, *J* = 8.7 Hz, 2H), 4.13- 4.07 (m, 1H), 3.84 (s, 3H), 3.54-3.51 (m, 1H), 3.33-3.27 (m, 2H), 1.80 (s, 1H), 1.73 (s, 2H), 1.20-1.19 (m, 6H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 169.8, 162.9, 148.3, 139.1, 138.7, 135.8, 130.8, 130.8, 130.6, 130.4, 129.7, 128.0, 124.7, 115.0, 79.5, 56.0, 53.2, 43.2, 22.4, 22.4, 7.5. HRMS calcd. for $C_{30}H_{31}N_5O_6$, [M$^+$] = 558.2347, found = 558.2355.

ACKNOWLEDGEMENTS

This research was supported by the Natural Sciences and Engineering Research Council of Canada (NSERC) and the Canadian Institute of Health Research (CIHR). The authors thank Dr. Alexandra Fürtös and Karine Gilbert (Université de Montréal) for assistance with mass spectrometry and SFC analysis, as well as Sarah-Ève Papineau for help preparing starting materials.

REFERENCES

1. R. C. Smith and J. C. Reeves, *Biochem. Pharmacol.*, 1987, **36**, 1457.
2. K. Pande, R. Kalsi, T. N. Bhalla, and J. P. Barthwal, *ChemInform*, 1987, **18**.
3. A. Kamal, G. Ramakrishna, P. Raju, A. Viswanath, M. J. Ramaiah, G. Balakishan, and M. Pal-Bhadra, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 4865.
4. K. M. Khan, U. R. Mughal, N. Ambreen, Samreen, S. Perveen, and M. I. Choudhary, *J. Enzyme Inhib. Med. Chem.*, 2010, **25**, 29.
5. R. Mohan and M. M. Morrissey, U.S. Patent No. 5, 612, 363. 1997.
6. J. J. Egan, E. G. McMahon, G. M. Olins, and J. R. Schuh, U.S. Patent No. 6, 984, 633. 2006.
7. A. Kubo, R. Imashiro, H. Sakurai, H. Miyoshi, A. Ogasawara, H. Hiramatsu, T. Nakajima, and T. Nakane, U.S. Patent No. 7, 473, 695. 2009.
8. J. Sheppeck, J. L. Gilmore, X.-T. Chen, and X. He, U.S. Patent No. 7, 211, 671. 2007.
9. N. Xue, X. Yang, R. Wu, J. Chen, Q. He, B. Yang, X. Lu, and Y. Hu, *Bioorg. Med. Chem.*, 2008, **16**, 2550.
10. M. J. Broadhurst, W. H. Johnson, and D. S. Walter, U.S. Patent No. 6, 235, 787. 2001.
11. K. P. Cusack, H. F. Koolman, U. E. Lange, H. M. Peltier, I. Piel, and A. Vasudevan, *Bioorg. Med. Chem. Lett.*, 2013, **23**, 5471.
12. D. J. St-Cyr, Y. García-Ramos, N.-D. Doan, and W. D. Lubell, 'Aminolactam, *N*-Aminoimidazolone, and *N*-Aminoimdazolidinone Peptide Mimics', ed. by W. D. Lubell, Peptidomimetics I. Topics in Heterocyclic Chemistry vol 48, Springer, Cham, 2017.
13. C. Proulx and W. D. Lubell, *Org. Lett.*, 2012, **14**, 4552.

14. C. M. Wilmot and J. M. Thornton, *J. Mol. Biomol.*, 1988, **203**, 221.
15. J. Bezenšek, U. Grošelj, K. Stare, J. Svete, and B. Stanovnik, *Tetrahedron*, 2012, **68**, 516; C. Neochoritis, C. A. Tsoleridis, and J. Stephanidou-Stephanatou, *Tetrahedron*, 2008, **64**, 3527; Y. Zhu and Y. Shi, *Chem. Eur. J.*, 2014, **20**, 13901; G. Crank and H. Khan, *Aust. J. Chem.*, 1985, **38**, 447.
16. J. Lu, X. Tan, and C. Chen, *J. Am. Chem. Soc.*, 2007, **129**, 7768.
17. J. Poupart, D. Doan-Ngoc, and W. D. Lubell, *Proceedings of the 24th Am. Peptide Symp.*, American Peptide Society, 2015, 272.
18. V. J. Hruby, G. Li, C. Haskell-Luevano, and M. Shenderovich, *J. Pept. Sci.*, 1997, **43**, 219; S. Cowell, Y. Lee, J. Cain, and V. Hruby, *Curr. Med. Chem.*, 2004, **11**, 2785.
19. H. Abas, S. M. Linsdall, M. Mamboury, H. S. Rzepa, and A. C. Spivey, *Org. Lett.*, 2017, **19**, 2486.
20. C. A. Snyder, J. P. Selegue, N. C. Tice, C. E. Wallace, M. T. Blankenbuehler, S. Parkin, K. D. Allen, and R. T. Beck, *J. Am. Chem. Soc.*, 2005, **127**, 15010.
21. W. C. Still, M. Kahn, and A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923.