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Structural–activity relationship study of highly-functionalized imidazolines as potent inhibitors of nuclear transcription factor-κB mediated IL-6 production

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ABSTRACT

We herein describe the synthesis and anti-inflammatory properties of a small library of imidazoline-based NF-κB inhibitors. The structure–activity relationship of various substituents on an imidazoline core structure was evaluated for the ability to inhibit NF-κB mediated IL-6 production. Optimization of the scaffolds was pursued by correlating luciferase-based NF-κB reporter assays with inhibition of IL-6 production in IL-1β stimulated human blood. Several derivatives were found to inhibit NF-κB mediated IL-6 production in the nanomolar range in IL-1β stimulated human blood.

1. Introduction

The mammalian transcription factor NF-kappaB (NF-κB) is an ubiquitous transcription factor responsible for the regulation of more than 150 genes[1,2] impacting virtually every aspect of cellular adaptation including responses to stress,[3] inflammatory stimuli,[4] activation of immune cell function,[5] cellular proliferation, programmed cell death (apoptosis),[6] and oncogenesis.[7–11] In normal non-stimulated cells, NF-κB is typically sequestered in the cytoplasm by NF-κB's inhibitory protein, IκB.[12] Upon stimulation by an appropriate extracellular signal, such as pro-inflammatory cytokines TNF-α and IL-1β, the NF-κB pathway becomes activated.[5,13,14,2,15] During this process IκB undergoes a phosphorylated-driven polyubiquination and proteasomal degradation, resulting in the release of NF-κB.[12] Liberation of NF-κB allows for its rapid translocation into the nucleus.[16] Following its nuclear translocation, NF-κB binds to DNA and initiates the transcription of a host of pro-inflammatory signaling genes. Subsequently, deregulation of the NF-κB pathway has been directly implicated in the pathogenesis of inflammatory diseases such as rheumatoid arthritis (RA),[17,18] inflammatory bowel disease,[19–21] helicobacter pylori-associated gastritis,[22] atherosclerosis,[23] multiple sclerosis[24] and asthma.[25] Given the critical role of NF-κB-mediated expression of cytokines, this transcription factor has been actively pursued as a therapeutic target for these types of inflammatory disorders.[4,26]

It is well documented that NF-κB stimulates the expression of multiple genes responsible for many aspects of inflammatory responses and the pathogenesis of inflammatory diseases.[27,28] For instance, NF-κB increases the production of inflammatory enzymes such as inducible cylooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS).[29] Recruitment of immune cells into inflamed tissue is regulated by chemokines (IL-8, MIP-1α, RANTES) produced by NF-κB transcription. NF-κB also expresses cell surface adhesion proteins (ICAM-1, VCAM-1 and E-selectin), which are required for adhesion of immune cells to the blood vessel endothelium and thus, initiation of an inflammatory response.[30] Furthermore, cytokines (IL-1, IL-2, IL-6 and TNF-α) expressed by NF-κB induce the amplification of inflammatory signals. Of these cytokines, IL-6[31–33] and TNF-α[34–38] have been identified as key targets in rheumatoid arthritis (RA) and other inflammatory disorders. Pharmacologic intervention in RA was improved drastically with the advent of biologicals that specifically target IL-6[32] or TNF-α.[39–41] Unfortunately, these and alternative treatment options for RA are limited, suffer from high costs and involve undesirable methods of administration. Furthermore, these therapies lack data pertaining to their long-term safety, tolerability and sustained efficacy.[40] In addition, variability in responses to these anti-inflammatory drugs is found due to the complex network of alternative cytokine-mediated pathways.[42] Inhibition of pro-inflammatory transcription factors, such as NF-κB, may therefore represent a better alternative to modulate the complex cytokine network that induces inflammatory response.[27] In addition, inhibition of NF-κB mediated gene transcription by a small molecule would represent an attractive therapeutic alternative to the current clinical options,

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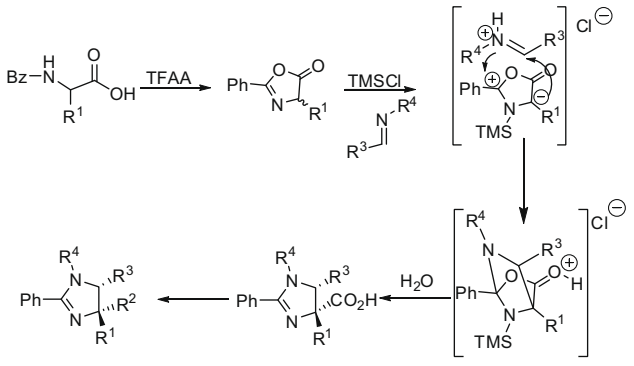
which still primarily include anti TNF-α mAbs and anti IL-6 receptor antibodies.[28,43]

Previously in our lab, we prepared a class of imidazoline scaffolds as potent inhibitors of NF-κB mediated gene transcription. The molecular target of these compounds is still elusive but inhibition of NF-κB mediated gene transcription was shown to proceed via the modulation of IκBα degradation.[44,45] A small series of this class of imidazolines was investigated for its potential anti-inflammatory activity and found to inhibit both TNF-α and IL-6 production in human blood stimulated by IL-1β.[46] In our efforts to improve the potency and develop a better understanding of the structural requirements for biological activity, we herein describe the synthesis and anti-inflammatory properties of several imidazoline derivatives functionalized at the R^1–R^4 positions (Scheme 1). Biological evaluation of this library of imidazolines led to the discovery of several analogues with the ability to substantially inhibit NF-κB mediated transcription in cell culture and cytokine production in stimulated human blood. Optimization of the scaffolds was pursued by correlating luciferase-based NF-κB reporter assays with inhibition of IL-6 production in IL-1β stimulated human blood to ensure the optimization was through NF-κB mediated IL-6 inhibition. The results indicated discrete structure–activity relationships for these highly-substituted imidazolines with respect to NF-κB mediated gene transcription.

2. Results and discussion

2.1. Chemistry

The imidazoline derivatives were prepared via a 1,3-dipolar cycloaddition reaction previously developed in our laboratory (Scheme 1).[47–50] Cyclodehydration of *N*-benzoyl protected amino acid derivatives with TFAA provided azlactones without the need for further purification. The azlactones were subsequently treated with the desired imine in the presence of TMSCl to provide the imidazoline carboxylate, which was isolated by filtration. Diversity at the R^1 position could be easily accessed by varying the starting amino acid. The resulting imidazoline carboxylates were treated with $TMSCHN_2$ to yield the methyl esters **1**–**5** in excellent yield (Table 1). Next, we examined the variability that could be tolerated at the R^2 position by synthesizing esters **6**–**8** via the acid chloride (Table 2). Imidazolines **9** and **10** were synthesized by treating *dl*-(4*R*,5*R*)-1-benzyl-4,5-dihydro-2,4,5-triphenyl-1*H*-imidazole-4-carboxylic acid[48] with EDCI and DMAP in the presence of benzyl alcohol and $(NH_4)_2CO_3$, respectively. To study the effect of the R^3 and R^4 domains, a number of imines (prepared from their corresponding aldehydes and amines) underwent the 1,3-dipolar cycloaddition to afford imidazolines **11**–**25** (Tables 3 and 4). Imidazoline **12** was reduced to imidazoline **13** utilizing $SnCl_2$ in refluxing ethanol.



Scheme 1. Synthesis of imidazoline scaffolds.

Table 1
EC_{50} values of inhibition of luciferase production in pNF-κB-luc HeLa cells following TNF-α activation. IC_{50} values for inhibition of IL-6 production in human whole blood following IL-1β stimulation

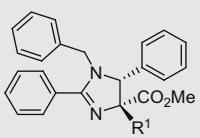
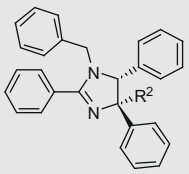
Entry	 R^1	Inhibition of HeLa NF-κB-luc EC_{50} (μM)	Inhibition of IL-6 in human blood IC_{50} (μM)
1	CH_3	>20	3
2	$CH(CH_3)_2$	~20	7.1
3	Ph	7.5	3
4	Bn	5.3	4.1
5	Indoyl-3-methyl	13	16.1

Table 2
EC_{50} values of inhibition of luciferase production in pNF-κB-luc HeLa cells following TNF-α activation. IC_{50} values for inhibition of IL-6 production in human whole blood following IL-1β stimulation

Entry	 R^2	Inhibition of HeLa NF-κB-luc EC_{50} (μM)	Inhibition of IL-6 in human blood IC_{50} (μM)
3	CO_2Me	7.5	3
6	CO_2Et	2.5	0.8
7	$CO_2{}^nPr$	2.3	1.9
8	$CO_2{}^iPr$	3.5	1.9
9	CO_2Bn	3.5	5.9
10	$CONH_2$	>20	>20

Imidazoline **6** underwent hydrogenolysis using 10% Pd/C in cyclohexene to afford debenzylated imidazoline **26**. Imidazoline **26** was treated with acetic anhydride, benzoyl chloride, or tosyl chloride in the presence of DMAP and TEA to generate imidazolines **27**, **28** and **29**, respectively.

Table 3
EC_{50} values of inhibition of luciferase production in pNF-κB-luc HeLa cells following TNF-α activation. IC_{50} values for inhibition of IL-6 production in human whole blood following IL-1β stimulation

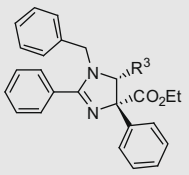
Entry	 R^3	Inhibition of HeLa NF-κB-luc EC_{50} (μM)	Inhibition of IL-6 in human blood IC_{50} (μM)
6	Ph	2.5	0.8
11	4-Pyr	>20	9.4
12	4-Ph–NO_2	3.4	0.5
13	4-Ph–NH_2	10.4	0.5
14	4-Ph–OMe	3.6	1.3
15	4-Ph–F	5	1
16	4-Ph–Cl	1.5	0.3
17	4-Ph–CF_3	1.4	0.8
18	2-Furan	7.6	1.9

Table 4
EC_{50} values of inhibition of luciferase production in pNF-κB-luc HeLa cells following TNF-α activation. IC_{50} values for inhibition of IL-6 production in human whole blood following IL-1β stimulation

Entry	R^4	Inhibition of HeLa NF-κB-luc EC_{50} (μM)	Inhibition of IL-6 in human blood IC_{50} (μM)
6	Bn	2.5	0.8
19	4-Bn–OMe	5	1.4
20	4-Bn–Me	1.7	4.6
21	4-Bn–F	5.2	1.2
22	4-Bn–Cl	4.2	1.6
23	4-Bn–Br	2.7	0.5
24	4-Bn–CF_3	6.7	1.5
25	2-Methylfuran	5.5	1.3
26	H	>20	>20
27	Ac	>20	>20
28	Bz	~20	6.6
29	Tos	>20	6.6

2.2. Biological evaluation and structure–activity relationships

The potential of these highly-functionalized imidazolines to inhibit the NF-κB pathway was assessed using two methods. In the first method, the ability of the imidazolines **1**–**29** to modulate NF-κB mediated gene transcription was evaluated using a luciferase reporter assay in human cervical epithelial (HeLa) cells containing a stably transfected NF-κB-luc gene (Panomics, Fremont, CA). These cells maintain, through hygromycin selection, a chromosomal integration of a luciferase reporter construct regulated by multiple copies of the NF-κB response element. The cells were activated with TNF-α (25 ng/mL) in the presence or absence of imidazolines **1**–**29**. Cells were pretreated for 30 min with the imidazolines followed by TNF-α stimulation. The proteasome inhibitor MG-132 (*N*-Cbz-Leu-Leu-leucinal)[51] and DMSO (vehicle) were used as positive and negative controls, respectively, and luciferase production was evaluated after 8 h (see Supplementary data data). All samples were normalized to the TNF-α activation control. The results are summarized in Tables 1–4. Treatment of HeLa/NF-κB-luc cells with imidazolines without any TNF-α activation did not induce a significant amount of luciferase activity, indicating that the imidazolines did not stimulate the NF-κB pathway. In order to validate the results from this integrated cell line and demonstrate the reliability of this high-throughput screen, HeLa cells were transiently transfected with 6x κB driver reporter gene pNF-κB-Luc and the internal control plasmid pRL-TK, which provides low levels of *Renilla* luciferase production (see Supplementary data).[46] Similar results were observed using both luciferase-based reporter assays, indicating the data obtained from the stable HeLa/NF-κB-luc cell line was representative of NF-κB mediated gene transcription.

In order to determine the key structural requirements for biological activity of these highly-substituted imidazolines, we first examined the R^1 domain of the scaffold. These derivatives were readily accessible by starting with the natural amino acid precursors: alanine, valine, phenylglycine, phenylalanine and tryptophan, to provide compounds **1**–**5**, respectively (Table 1). Pre-treatment of the HeLa NF-κB-luc cells with imidazolines **1**–**5** for 30 min, followed by TNF-α stimulation resulted in a dose-dependent decrease in luciferase production for three of the compounds (Table 1). The imidazoline methyl esters **3** and **4** were the most active compounds with an EC_{50} value of 7.5 and 5.3 μM, respectively, for inhibition of NF-κB mediated luciferase activity in HeLa cells (Table 1). The data in Table 1 indicate increased hydrophobicity at the R^1 position (compounds **1**–**4**) leads to a decrease in NF-κB mediated luciferase production.

The imidazoline library was further evaluated for it's ability to inhibit NF-κB mediated cytokine production in stimulated whole human blood. Since the cytokine IL-6 is one of the key gene products resulting from NF-κB activation, all compounds were investigated for their ability to inhibit the production of IL-6. Human whole blood was pretreated with the imidazolines **1**–**29** for 2 h, followed by IL-1β thus inducing an NF-κB mediated cytokine response.[52,53] Plasma was harvested and IL-1β induced IL-6 production was measured 22 h after stimulation using a human IL-6 ELISA (R&D Systems). The circulating IL-6 levels in IL-1β stimulated samples were significantly higher (>1000-fold) than in unstimulated or the vehicle treated blood (see Supplementary data). Pretreatment of the blood for 2 h with the imidazolines **1**–**29**, followed by IL-1β stimulation resulted in a strong dose-dependent inhibition of IL-6 production, as compared to the no-drug treated control (see Supplementary data).

Exploration of the R^1 domain revealed consistency with the HeLa NF-κB-luc assay, compounds **3** and **4** were the most potent inhibitors with IC_{50} values for inhibition of IL-1β stimulated IL-6 production of 3.0 μM and 4.1 μM, respectively. Interestingly, even though compound **1** proved to be inactive in the cell-based assay it demonstrated good activity in the blood assay. This may be in part due to its relatively increased hydrophilicity helping to provide improved solubility in the blood assay. Nonetheless, to ensure that optimization of the scaffold was for NF-κB mediated inhibition of IL-6 production, only compounds that indicated a good correlation between the two assays were pursued for further derivatization. Since compound **3** proved to be slightly more active than compound **4** while maintaining consistent activity in both assays, a phenyl group was chosen to be the preferred moiety of R^1 position (R^1 = Ph, Scheme 1).

The next series of analogues focused on evaluating the ester functional group at the R^2 domain. Previously, we reported that this moiety is critical for stability of the imidazoline scaffold and the ester functionality was found to be optimal at the R^2 position.[46] We extended this series to include *n*-propyl and isopropyl esters (**7** and **8**). Again, the inhibition of IL-6 production in stimulated human blood corresponded well with the inhibition of luciferase production in the HeLa cells (Table 2). All esters (compounds **3**, **6–9**) maintained activity in the low micromolar range, whereas the amide **10** was devoid of any significant activity in both assays (Table 2). An increase in potency was observed when comparing methyl ester **3** to ethyl ester **6**, although no significant improvement in biological activity was observed upon evaluating more sterically demanding ester moieties (compounds **7**–**9**). Even though most of the esters illustrated similar activity in the luciferase-based cellular assay, the ethyl ester **6** was found to be the most potent compound in the blood assay yielding an IC_{50} value of 0.8 μM. Due to its potency and stability against hydrolysis by esterases,[46] the ethyl ester **6** was considered our lead compound and was further evaluated for functionalization of the R^3 and R^4 moieties (Tables 3 and 4).

The R^3 position was functionalized by a range of aromatic substituents to study the significance of this region on biological activity (Table 3). The 4-pyridino-substituted imidazoline **11** was the only compound in this series to be void of any activity in the luciferase-based reporter assay and consequently showed weak activity in our whole blood studies (Table 3, IC_{50} 9.4 μM). Furthermore, the 2-furan derivative **18** was only moderately active in both assays indicating hetero-aromatic substituents provide decreased potency compared to the phenyl moiety at the R^3 position. The *para*-chloro-substituted imidazoline **16** proved to be the most potent analogue in this series possessing an IC_{50} value of 0.3 μM in the whole

blood assay. As seen previously, the two assays corresponded relatively well in terms of their relative potencies. For example, several analogues demonstrated low micromolar activity in cell culture (compounds **12**, **16** and **17**) and had nanomolar activity in the blood assay. The only exception was the aniline-substituted imidazoline **13**, which provided moderate activity in the HeLa NF-κB-luc assay but potent activity (Table 3, IC_{50} 0.5 μM) in our whole blood assay. Substitutions on the phenyl group of the R^3 position resulted in potency equal to and better than that of the lead compound **6** indicating that optimization of the R^3 position can lead to imidazolines with improved activity.

We found structural changes to the fourth domain (Table 4, R^4 moiety) to be the most sensitive to derivatization. The halogenated-benzyl series (compounds **21**–**23**) demonstrated that biological activity increased with decreasing polarity on the benzyl group with the 4-bromo-benzyl derivative being slightly more potent than the parent compound **6** in the blood assay. Imidazoline **25** revealed that substitution of the benzyl functional group with a heterocycle resulted in moderate biological activity however; potency was decreased slightly when compared to the compound **6**. Deletion of the R^4 domain, as illustrated by compound **26**, rendered the scaffold inactive in both assays. Replacement of the benzyl group with electron-withdrawing substituents, such as acyl, benzoyl or tosyl (compounds **27**–**29**, respectively), resulted in compounds which were unable to restore overall activity to the potency of the parent compound **6**.

2.3. Pharmacological significance of imidazolines

To verify the imidazolines are non-cytotoxic and represent potentially viable anti-inflammatory agents, all compounds were evaluated for cell death by MTS assay. The results indicated that none of the compounds inhibited proliferation as tested at 10 μM for 24 h in 184B5 cells (transformed healthy breast cells) (see Supplementary data). Furthermore, the lead compound, imidazoline **6**, was analyzed by FACS analysis in HeLa-NF-κB-luc cells. It was found that after 8 h no change in cell cycle was observed, indicating that upon treatment with imidazoline **6** the cells remained healthy (see Supplementary data). To confirm the cell viability data in the whole blood experiments, human white blood cell counts also indicated no significant cellular toxicity at 10 μM or less imidazoline **6** (see Supplementary data). Therefore, the inhibition of luciferase production and inhibition of IL-6 production by imidazoline **6** was not due to a decrease in cell number but rather due to an inhibition of NF-κB transcription. To demonstrate that imidazoline **6** was pharmacologically relevant in the treatment of inflammation, human blood samples were treated with imidazoline **6** 2 h *after* initiation of an inflammatory response induced by IL-1β. Imidazoline **6** was still capable of reducing IL-6 levels after its induction resulting in an IC_{50} value of 2.5 μM after 22 h.[46]

3. Conclusion

Herein we describe the structure–activity relationships of an imidazoline scaffold capable of inhibiting NF-κB mediated gene transcription. Evaluation of the biological activity of this library indicates there is a delicate balance between hydrophobicity and hydrophilicity in the imidazoline scaffold to achieve potent activity in cell culture and human blood. Six compounds from this library were found to be capable of reducing IL-6 production in stimulated human blood at nanomolar IC_{50} values. Furthermore, the activity of the imidazolines in cellular NF-κB reporter assays correlated well with the relative activity of the compounds in stimulated whole human blood assays. The further clinical potential and determination of biological mechanism of these non-cytotoxic small molecule NF-κB inhibitors as potential anti-inflammatory agents is currently under investigation in our laboratories.

4. Experimental

4.1. General Information

All commercial reagents were purchased from commercial suppliers and used without further purification. MG-132 (*N*-Cbz-Leu-Leu-leucinal) was obtained from Calbiochem (San Diego, CA) and IL-1β was obtained from Roche Applied Sciences (Indianapolis, IN). All solvents were reagent grade. THF was freshly distilled from sodium/benzophenone under nitrogen. TEA and TMSCl were freshly distilled from calcium hydride under nitrogen. CH_2Cl_2 was dispensed from a delivery system, which passes the solvents through a column packed with dry neutral alumina. Melting points were obtained using an Electrothermal® capillary melting point apparatus and are uncorrected. Column chromatography was carried out on silica gel 60 (230–400 mesh) supplied by EM Science. Yields refer to chromatographically and spectroscopically pure compounds unless otherwise stated. Infrared spectra were recorded on a Nicolet IR/42 spectrometer. Proton and carbon NMR spectra were recorded on a Varian Unity Plus-500 spectrometer. High-resolution 3KV EI mass spectra was obtained at the RTSF Mass Spectrometry Facility of the Michigan State University, using a Q-ToF Ultima API (Waters Corp., Milford, MA).

4.1.1. General procedure for imidazoline derivatives 1–5

A flame-dried flask under nitrogen was charged with the corresponding imidazoline carboxylate[47–49] (0.50 g, 1.07 mmol) in 9:1 benzene:methanol (50 mL) and cooled to 0 °C. After 5 min, (trimethylsilyl)diazomethane (1.1 mL, 2.13 mmol) was added dropwise and then the reaction mixture was allowed to stir at 0 °C for 3 h.

4.1.1.1. *dl*-(4*R*,5*R*)-Methyl 1-benzyl-4-methyl-2,5-diphenyl-4,5-dihydro-1*H*-imidazole-4-carboxylate (1). The reaction mixture was concentrated to minimal residue and purified via flash column chromatography on silica gel (9:1 ethyl acetate:hexane as eluant) to yield a clear oil (43 mg, 83% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.53 (s, 3H), 3.11 (s, 3H), 3.83 (d, 1H, J = 16.0 Hz), 4.28 (s, 1H), 4.72 (d, 1H, J = 16.0 Hz), 6.93–6.94 (m, 2H), 7.22–7.29 (m, 6H), 7.30–7.33 (m, 2H), 7.46–7.47 (m, 3H), 7.74–7.76 (m, 2H); ^{13}C NMR + **DEPT** (125 MHz, $CDCl_3$): δ 27.05 (–CH3), 48.96 (–CH2), 51.54 (–CH3), 73.14 (–CH), 77.97 (quaternary –*C*), 127.51 (aromatic –*C*H), 127.70 (aromatic –*C*H), 127.79 (aromatic –*C*H), 128.14 (aromatic –*C*H), 128.28 (aromatic –*C*H), 128.64 (aromatic –*C*H), 128.80 (aromatic –*C*H), 130.32 (aromatic –*C*H), 130.68 (aromatic quaternary –*C*), 136.53 (aromatic quaternary –*C*), 137.11 (aromatic quaternary –*C*), 165.90, 172.49; IR (neat): 3031 cm^{-1}, 2967 cm^{-1}, 2949 cm^{-1}, 1734 cm^{-1}, 1595 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{25}H_{25}N_2O_2$ [M+H], 385.1916; found, 385.1899.

4.1.1.2. *dl*-(4*R*,5*R*)-Methyl 1-benzyl-4-isopropyl-2,5-diphenyl-4,5-dihydro-1*H*-imidazole-4-carboxylate (2). The reaction mixture was concentrated to minimal residue and purified via flash column chromatography on silica gel (1:1 ethyl acetate:hexane as eluant) to yield a white solid (197 mg, 76% yield). Mp 128–131 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.70 (d, 3H, J = 6.5 Hz), 0.98 (d, 3H, J = 6.5 Hz), 2.17 (septet, 1H, J = 6.75 Hz), 2.92 (s, 3H), 3.74 (d, 1H, J = 15.0 Hz), 4.37 (s, 1H), 4.59 (d, 1H, J = 15.0 Hz), 6.86–6.88 (m, 2H), 7.20–7.22 (m, 4H), 7.26–7.29 (m, 1H), 7.31–7.34 (m, 2H), 7.47–7.49 (m, 3H), 7.72–7.74 (m, 2H); ^{13}C NMR + **DEPT** (125 MHz, $CDCl_3$): δ 16.22 (–CH3), 18.69 (–CH3), (–CH2), 36.64 (–CH), 48.95 (–CH2), 51.07 (–CH3), 69.52 (–CH), 85.19 (quaternary –*C*), 127.72 (aromatic –*C*H), 127.95 (aromatic –*C*H), 128.24

(aromatic –CH), 128.39 (aromatic –CH), 128.59 (aromatic –CH), 128.66 (aromatic –CH), 128.84 (aromatic –CH), 130.08 (aromatic –CH), 135.78 (aromatic quaternary –C), 138.19 (aromatic quaternary –C), 165.37, 172.41; IR (neat): 3031 cm^{-1}, 2967 cm^{-1}, 1732 cm^{-1}, 1597 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{27}H_{29}N_2O_2$ [M+H], 413.2229; found, 413.2229.

4.1.1.3. *dl*-(4*R*,5*R*)-Methyl 1-benzyl-4,5-dihydro-2,4,5-triphenyl-1*H*-imidazole-4-carboxylate (3). The reaction mixture was concentrated to minimal residue and purified by running through a small silica plug to give the product as a white solid (240 mg, 50% yield). Mp 114–116 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.18 (s, 3H), 3.84 (d, 1H, *J* = 16.0 Hz), 4.63 (d, 1H, *J* = 16.0 Hz), 4.91 (s, 1H), 6.73 (d, 2H, *J* = 7.5 Hz), 7.05 (t, 2H, *J* = 7.5 Hz), 7.10 (t, 1H, *J* = 7.5 Hz), 7.25–7.28 (m, 1H), 7.31–7.34 (m, 3H), 7.37 (d, 4H, *J* = 4.5 Hz), 7.47 (d, 1H, *J* = 1.5 Hz), 7.48(d, 1H, *J* = 2.0 Hz), 7.73 (m, 2H), 7.77 (d, 1H, *J* =3.5 Hz), 7.78 (d, 1H, *J* = 1.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 48.7, 51.8, 73.9, 83.1, 126.8, 127.2, 127.4, 127.5, 128.0, 128.1, 128.3, 128.4, 128.5, 128.6, 128.9, 130.4, 130.5, 136.6, 137.9, 144.0, 165.6, 171.4; IR (neat): 3061 cm^{-1}, 3031 cm^{-1}, 2948 cm^{-1}, 1734 cm^{-1}, 1595 cm^{-1}; HRMS (ESI): *m/z* calculated for $[C_{30}H_{26}N_2O_2+H]^+$ 447.2070; found: 447.2070.

4.1.1.4. *dl*-(4*R*,5*R*)-Methyl 1,4-dibenzyl-2,5-diphenyl-4,5-dihydro-1*H*-imidazole-4-carboxylate (4). The reaction mixture was concentrated to minimal residue and purified via flash column chromatography on silica gel (1:1 ethyl acetate:hexane as eluant) to yield a white solid (74 mg, 78% yield). Mp 97–99 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.16 (d, 1H, *J* = 14.0 Hz), 3.17 (s, 3H), 3.40 (d, 1H, *J* = 16.0 Hz), 3.71 (d, 1H, *J* = 16.0 Hz), 4.27 (d, 1H, *J* = 16.0 Hz), 4.54 (s, 1H), 4.47 (d, 2H, *J* = 7.5 Hz), 7.04–7.07 (m, 2H), 7.10–7.13 (m, 1H), 7.20 (d, 2H, *J* = 7.0 Hz), 7.26–7.28 (m, 4H), 7.30–7.36 (m, 4H), 7.43 (d, 1H, *J* = 1.5 Hz), 7.44 (d, 1H, *J* = 2.0 Hz), 7.64–7.66 (m, 2H); ^{13}C NMR + **DEPT** (125 MHz, $CDCl_3$): δ 44.49 (–CH2), 48.88 (–CH2), 51.50 (–CH3), 70.11 (–CH), 81.92 (quaternary –C), 126.66 (aromatic –CH), 127.11 (aromatic –CH), 127.44 (aromatic –CH), 127.73 (aromatic –CH), 128.03 (aromatic –CH), 128.20 (aromatic –CH), 128.37 (aromatic –CH), 128.49 (aromatic –CH), 128.50 (aromatic –CH), 130.10 (aromatic –CH), 130.83 (aromatic quaternary –C), 131.41 (aromatic –CH), 135.86 (aromatic quaternary –C), 136.12 (aromatic quaternary –C), 137.17 (aromatic quaternary –C), 166.20, 172.08; IR (neat): 3063 cm^{-1}, 3029 cm^{-1}, 2948 cm^{-1}, 2926 cm^{-1}, 1732 cm^{-1}, 1595 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{31}H_{29}N_2O_2$ [M+H], 461.2229; found, 461.2245.

4.1.1.5. *dl*-(4*R*,5*R*)-Methyl 4-((1*H*-indol-2-yl)methyl)-1-benzyl-2,5-diphenyl-4,5-dihydro-1*H*-imidazole-4-carboxylate (5). The reaction mixture was concentrated to minimal residue and purified via flash column chromatography on silica gel (9:1 ethyl acetate:hexane as eluant) to yield a yellow solid (11 mg, 14% yield). Mp 175–176 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.79 (d, 1H, *J* = 14.5 Hz), 2.87 (d, 1H, *J* = 15.0 Hz), 3.45 (s, 3H), 3.89 (d, 1H, *J* = 16.0 Hz), 4.70 (d, 1H, *J* = 16.0 Hz), 4.98 (s, 1H), 6.83–6.84 (m 1H), 6.87–6.90 (m, 1H), 6.94–6.98 (m, 3H), 7.07 (d, 1H, *J* = 8.0 Hz), 7.20–7.26 (m, 5H), 7.28–7.35 (m, 4H), 7.44–7.46 (m, 3H), 7.40–7.76 (m, 2H), 8.16 (br s, 1H); ^{13}C NMR + **DEPT** (125 MHz, $CDCl_3$): δ 31.91 (–CH2), 48.76 (–CH2), 52.24 (–CH3), 69.69 (–CH), 79.41 (quaternary –C), 110.51 (aromatic quaternary –C), 110.60 (aromatic –CH), 118.58 (aromatic –CH), 118.84 (aromatic –CH), 121.08 (aromatic –CH), 123.65 (aromatic –CH), 127.46 (aromatic –CH), 128.01 (aromatic quaternary –C), 128.09 (aromatic –CH), 128.44 (aromatic –CH), 128.56 (aromatic –CH), 128.59 (aromatic –CH), 128.72 (aromatic –CH), 130.16 (aromatic –CH), 130.97 (aromatic quaternary –C), 135.56 (aromatic quaternary –C), 136.05 (aromatic quaternary –C), 136.70 (aromatic quaternary –C), 166.01, 175.58; IR (neat): 3059 cm^{-1}, 2924 cm^{-1}, 2855 cm^{-1}, 1728 cm^{-1}, 1593 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{33}H_{30}N_3O_2$ [M+H], 500.2338; found, 500.2345.

4.1.2. General procedure for imidazoline derivatives 6–8

Into a flame-dried flask under nitrogen was placed *dl*-(4*R*,5*S*)-(1-benzyl-4,5-dihydro-2,4,5-triphenyl-1*H*-imidazole-4-carboxylic acid[48] (20.0 g, 46.3 mmol,) and dichloromethane (300 mL). After cooling the reaction mixture to 0 °C, oxalyl chloride (11.7 mL, 138.8 mmol) was added over 5 min followed by DMF (10 μL/1 mL of dichloromethane). The reaction mixture was allowed to stir at 0 °C for 2 h after which the solvent was removed on the rotary evaporator. The residue was placed on a vacuum line for 1 h. The flask was then placed under nitrogen and cooled to 0 °C and ethanol (**6**), *n*-propanol (**7**) or isopropanol (**8**) (equal volume to CH_2Cl_2) was added. After stirring for an addition 2.5 h the alcohol was removed on the rotary evaporator and dichloromethane (300 mL) was added. The organic solution was washed with saturated $NaHCO_3$ solution (1 × 100 mL) and H_2O (1 × 100 mL), dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure.

4.1.2.1. *dl*-(4*R*,5*R*)-Ethyl 1-benzyl-4,5-dihydro-2,4,5-triphenyl-1*H*-imidazole-4-carboxylate (6). The product was purified using flash column chromatography on silica gel (1:1 hexane:ethyl acetate as eluant) to give a white solid (16.1 g, 76% yield). Mp 86–88 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.83 (t, 3H, *J* = 7.2 Hz), 3.63 (qq, 1H, *J* = 7.2 Hz), 3.73 (qq, 1H, *J* = 7.2 Hz), 3.86 (d, 1H, *J* = 16.0 Hz), 4.64 (d, 1H, *J* = 15.5 Hz), 4.96 (s, 1H), 6.78 (d, 2H, *J* = 7.0 Hz), 7.09 (t, 2H, *J* = 7.2 Hz), 7.14 (t, 1H, *J* = 7.2 Hz), 7.28–7.32 (m, 1H), 7.34–7.38 (m, 3H), 7.39–7.45 (m, 4H), 7.49–7.51 (m, 3H), 7.79–7.81(m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.4, 48.6, 60.9, 73.7, 82.8, 126.7, 127.1, 127.2, 127.3, 127.9, 128.1, 128.2, 128.3, 128.4, 128.5, 128.8, 130.2, 130.6, 136.6, 137.9, 144.1, 165.3, 170.7; IR (neat): 3173 cm^{-1}, 3061 cm^{-1}, 3031 cm^{-1}, 2981 cm^{-1}, 1732 cm^{-1}, 1597 cm^{-1}; HRMS (ESI): *m/z* calculated for $[C_{31}H_{28}N_2O_2+H]^+$ 461.2229; found: 461.2225.

4.1.2.2. *dl*-(4*R*,5*R*)-Propyl 1-benzyl-2,4,5-triphenyl-4,5-dihydro-1*H*-imidazole-4-carboxylate (7). The product was purified using flash column chromatography on silica gel (1:1 hexane:ethyl acetate as eluant) to give a white solid (170 mg, 67% yield). Mp 88–90 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.63 (t, 3H, *J* = 7.25 Hz), 1.20 (sextet, 2H, *J* = 7.0 Hz), 3.40 (dt, 1H, *J* = 10.5, 6.5 Hz), 3.89 (dt, 1H, *J* = 10.5, 6.5 Hz), 3.81 (d, 1H, *J* = 16.0 Hz), 4.60 (d, 1H, *J* = 16.0 Hz), 4.91 (s, 1H), 6.74 (d, 2H, *J* = 7.0 Hz), 7.05–7.08 (m, 2H), 7.10–7.13 (m, 1H), 7.24–7.27 (m, 1H), 7.30–7.33 (m, 3H), 7.34–7.39 (m, 4H), 7.46–7.47 (m, 3H), 7.73–7.76 (m, 4H); ^{13}C NMR + **DEPT** (125 MHz, $CDCl_3$): δ 10.23 (–CH3), 21.30 (–CH2), 48.63 (–CH2), 66.54 (–CH2), 73.79 (–CH), 82.92 (quaternary –C), 126.81 (aromatic –CH), 127.17 (aromatic –CH), 127.35 (aromatic –CH), 127.37 (aromatic –CH), 127.82 (aromatic quaternary –C), 127.98 (aromatic –CH), 128.14 (aromatic –CH), 128.31 (aromatic –CH), 128.41 (aromatic –CH), 128.49 (aromatic –CH), 128.58 (aromatic –CH), 128.82 (aromatic –CH), 130.33 (aromatic –CH), 136.58 (aromatic quaternary –C), 137.85 (aromatic quaternary –C), 144.02 (aromatic quaternary –C), 165.47, 170.68; IR (neat): 3064 cm^{-1}, 3030 cm^{-1}, 2967 cm^{-1}, 1732 cm^{-1}, 1595 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{32}H_{31}N_2O_2$ [M+H], 475.2386; found, 475.2383.

4.1.2.3. *dl*-(4*R*,5*R*)-Isopropyl 1-benzyl-2,4,5-triphenyl-4,5-dihydro-1*H*-imidazole-4-carboxylate (8). The product was purified using flash column chromatography on silica gel (1:1 hexane:ethyl acetate as eluant) to give a white solid (118 mg, 47% yield). Mp 109–111 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.63 (d, 3H, *J* = 6.5 Hz), 0.85 (d, 3H, *J* = 6.5 Hz), 3.77 (d, 1H, *J* = 15.5 Hz), 4.48 (septet, 1H, *J* = 6.25 Hz), 4.58 (d, 1H, *J* = 15.5 Hz), 4.90 (s, 1H), 6.73 (d, 2H,

J = 7.5 Hz), 7.06–7.09 (m, 2H), 7.11–7.14 (m, 1H), 7.24–7.28 (m, 1H), 7.30–7.34 (m, 3H), 7.35–7.37 (m, 4H), 7.46–7.47 (m, 3H), 7.72–7.74 (m, 4H); ^{13}C NMR + **DEPT** (125 MHz, $CDCl_3$): δ 20.75 (–CH3), 21.21 (–CH3), 48.52 (–CH2), 68.58 (–CH), 73.58 (–CH), 82.72 (quaternary –*C*), 126.76 (aromatic –*C*H), 127.17 (aromatic –*C*H), 127.28 (aromatic –*C*H), (aromatic –*C*H), 127.29 (aromatic –*C*H), 127.92 (aromatic –*C*H), 128.26 (aromatic –*C*H), 128.34 (aromatic –*C*H), 128.39 (aromatic –*C*H), 128.52 (aromatic –*C*H), 128.77 (aromatic –*C*H), 130.17 (aromatic –*C*H), 130.77 (aromatic quaternary –*C*), 136.80 (aromatic quaternary –*C*), 138.17 (aromatic quaternary –*C*), 144.26 (aromatic quaternary –*C*), 165.20, 170.09; IR (neat): 3063 cm^{-1}, 3030 cm^{-1}, 2980 cm^{-1}, 2936 cm^{-1}, 1728 cm^{-1}, 1595 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{32}H_{31}N_2O_2$ [M+H], 475.2386; found, 475.2388.

4.1.2.4. *dl*-(4*R*,5*R*)-Benzyl 1-benzyl-4,5-dihydro-2,4,5-triphenyl-1*H*-imidazole-4-carboxylate (9). To a stirred solution of *dl*-(4*R*,5*R*)-(1-benzyl-4,5-dihydro-2,4,5-triphenyl-1*H*-imidazole-4-carboxylic acid[48] (200 mg, 0.43 mmol) in dichloromethane was added 1-ethyl-(3-dimethylaminopropyl) carbodiimide (120 mg, 0.64 mmol). After 5 min was added 4-(*N*,*N*-dimethylamino)pyridine (52 mg, 0.43 mmol). After stirring for an addition 10 min. benzyl alcohol (92 mg, 0.85 mmol) was added. The reaction mixture was stirred at room temperature overnight. The reaction mixture was washed with 10% HCl solution (1 × 5 mL), saturated $NaHCO_3$ solution (1 × 5 mL), H_2O (1 × 5 mL) and brine solution (1 × 5 mL). The product was extracted using dichloromethane, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The product was purified using column chromatography on silica gel (9:1 dichloromethane:ethyl acetate as eluant) to give a light yellow oil (120 mg, 54% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.79 (d, 1H, J = 15.5 Hz), 4.50 (d, 1H, J = 12.5 Hz), 4.61 (d, 1H, J = 15.5 Hz), 4.76 (d, 1H, J = 12.5 Hz), 4.92 (s, 1H), 6.74 (d, 2H, J = 7.5 Hz), 6.95 (dd, 2H, J = 7.5, 2.5 Hz), 7.04–7.08 (m, 2H), 7.10–7.13 (m, 1H), 7.17–7.21 (m, 3H), 7.27–7.29 (m, 4H), 7.30–7.34 (m, 4H), 7.47–7.49 (m, 3H), 7.74–7.77 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 48.6, 66.6, 73.7, 82.7, 126.8, 127.1, 127.4, 127.5, 127.7, 127.9.0, 128.0 (2 peaks), 128.4 (2 peaks), 128.5, 128.6, 128.8, 130.4, 135.4, 136.3, 137.3, 143.5, 165.6, 170.3; IR (neat): 3063 cm^{-1}, 3032 cm^{-1}, 2924 cm^{-1}, 1740 cm^{-1}, 1593 cm^{-1}; HRMS (ESI): *m/z* calculated for $[C_{36}H_{30}N_2O_2+H]^+$ 523.2386; found: 523.2390.

4.1.2.5. *dl*-(4*R*,5*R*)-1-Benzyl-4,5-dihydro-2,4,5-triphenyl-1*H*-imidazole-4-carboxamide (10). To a stirred solution of *dl*-(4*R*,5*R*)-(1-benzyl-4,5-dihydro-2,4,5-triphenyl-1*H*-imidazole-4-carboxylic acid[48] (100 mg, 0.21 mmol,), *N*-hydroxybenzotriazole (32 mg, 0.23 mmol), 1-ethyl-(3-dimethylaminopropyl) carbodiimide (45 mg, 0.23 mmol) in anhydrous THF (2 mL) was added *N*,*N*-diisopropylethylamine (30 mg, 0.23 mmol). The reaction mixture was stirred at ambient temperature for 10 min. Then ammonium carbonate (50 mg, 0.64 mmol,) was added in one portion and the resulting suspension was stirred at ambient temperature overnight. The reaction mixture was concentrated to minimal residue. The residue was treated with 1:1 saturated $NaHCO_3$ solution: H_2O (2 mL) and stirring was continued for 2 h. The mixture was placed into a separatory funnel and the product was extracted using ethyl acetate, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The product was purified using column chromatography on silica gel (3:7 hexane:ethyl acetate as eluant) to give a light yellow solid (65 mg, 71% yield). Mp 65–68 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.80 (d, 1H, J = 16.5 Hz), 4.56 (d, 1H, J = 16.5 Hz), 4.86 (s, 1H), 5.15 (br s, 1H), 6.71 (d, 2H, J = 7.5 Hz), 7.05 (t, 2H, J = 7.5 Hz), 7.11 (t, 1H, J = 7.2 Hz), 7.26–7.28 (m, 1H), 7.30–7.36 (m, 7H), 7.50–7.54 (m, 3H), 7.71–7.73 (m, 2H), 7.79 (d, 2H, J = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 48.4, 74.3, 81.6, 126.3, 126.9, 127.3, 127.4, 128.1, 128.3, 128.4, 128.5, 128.8, 130.6, 136.7, 137.8, 144.8, 165.4, 173.4; IR (NaCl): 3442 cm^{-1}, 3063 cm^{-1}, 3031 cm^{-1}, 2926 cm^{-1}, 1688 cm^{-1}, 1591 cm^{-1}; HRMS (FAB): *m/z* calculated for $[C_{29}H_{25}N_3O+H]^+$ 432.2076; found: 432.2073.

4.1.3. General procedure for compounds 11, 12, 14–18

A solution of benzyl amine (0.2 g, 2.11 mmol) and appropriate aldehyde (0.2 g, 2.11 mmol) in 50 mL of anhydrous benzene was refluxed under nitrogen for 3 h and then concentrated in vacuo. The resulting residue was redissolved into 50 mL of anhydrous dichloromethane. Then 2,4-diphenyl-5(4*H*)-oxazolone (0.5 g, 2.11 mmol) and chlorotrimethylsilane (0.3 g, 2.74 mmol) were added and the mixture was refluxed under nitrogen for 22 h. The solution was concentrated in vacuo and the resulting residue was resuspended in ethyl acetate producing a white solid precipitate (0.5 g) which was isolated via filtration. The crude solid was then dissolved into 15 mL of ethanol, treated with 1 mL of concentrated H_2SO_4, and refluxed for 21 h. The solution was concentrated in vacuo and then dissolved into dichloromethane before being washed with saturated $NaHCO_3$ solution (3 × 20 mL) and brine solution (1 × 20 mL). The organic fraction was dried over sodium sulfate and then concentrated in vacuo.

4.1.3.1. *dl*-(4*R*,5*R*)-Ethyl 1-benzyl-2,4-diphenyl-5-(pyridin-4-yl)-4,5-dihydro-1*H*-imidazole-4-carboxylate (11). The resulting crude residue was purified via column chromatography using silica gel (100% ethyl acetate) to afford the product as a clear oil (220 mg, 23% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.83 (t, 3H, J = 7.5 Hz), 3.66 (dq, 1H, J = 11, 7 Hz), 3.75 (dq, 1H, J = 11, 7.5 Hz), 3.83 (d, 1H, J = 15.5 Hz), 4.62 (d, 1H, J = 15.5 Hz), 4.86 (s, 1H), 6.74 (d, 2H, J = 7.5 Hz), 7.05–7.08 (m, 2H), 7.12–7.14 (m, 1H), 7.28–7.37 (m, 5H), 7.49–7.52 (m, 3H), 7.71–7.72 (m, 2H), 7.79–7.81 (m, 2H), 8.63 (d, 2H, J = 6.0 Hz); ^{13}C NMR + **DEPT** (125 MHz, $CDCl_3$): δ 13.39 (–CH3), 49.24 (–CH2), 61.20 (–CH2), 72.62 (–CH), 83.06 (quaternary –*C*), 122.95 (aromatic –*C*H), 126.49 (aromatic –*C*H), 127.14 (aromatic –*C*H), 127.56 (aromatic –*C*H), 127.61 (aromatic –*C*H), 128.11 (aromatic –*C*H), 128.43 (aromatic –*C*H), 128.65 (aromatic –*C*H), 128.77 (aromatic –*C*H), 129.93 (aromatic quaternary –*C*), 130.60 (aromatic –*C*H), 135.86 (aromatic quaternary –*C*), 143.34 (aromatic quaternary –*C*), 147.28 (aromatic quaternary –*C*), 149.93 (aromatic –*C*H), 165.71, 170.23; IR (neat): 3063 cm^{-1}, 2982 cm^{-1}, 1734 cm^{-1}, 1597 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{30}H_{27}N_3O_2$ [M+H], 462.2182; found, 462.2177.

4.1.3.2. *dl*-(4*R*,5*R*)-Ethyl 1-benzyl-5-(4-nitrophenyl)-2,4-diphenyl-4,5-dihydro-1*H*-imidazole-4-carboxylate (12). The resulting crude solid was purified via column chromatography (1:1 ethyl acetate:hexane as eluant) affording the title compounds as a white solid (540 mg, 51% yield). Mp 173–174 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.83 (t, 3H, J = 7.5 Hz), 3.64 (dq, 1H, J = 11, 7 Hz), 3.74 (dq, 1H, J = 11, 7 Hz), 3.81 (d, 1H, J = 16 Hz), 4.60 (d, 1H, J = 16 Hz), 4.93 (s, 1H), 6.71 (d, 2H, J = 7.5 Hz), 7.03–7.10 (m, 2H), 7.10–7.13 (m, 1H), 7.27–7.35 (m, 3H), 7.48–7.51 (m, 3H), 7.54 (d, 2H, J = 8.5 Hz), 7.67–7.69 (m, 2H), 7.77–7.80 (m, 2H), 8.21 (d, 2H, J = 9.5 Hz); ^{13}C NMR + **DEPT** (125 MHz, $CDCl_3$): δ 15.59 (–CH3), 49.46 (–CH2), 61.30 (–CH2), 73.16 (–CH), 83.32 (quaternary –*C*), 123.61 (aromatic –*C*H), 126.49 (aromatic –*C*H), 127.25 (aromatic –*C*H), 127.69 (aromatic –*C*H), 127.75 (aromatic –*C*H), 128.24 (aromatic –*C*H), 128.53 (aromatic –*C*H), 128.76 (aromatic –*C*H), 128.87 (aromatic –*C*H), 128.96 (aromatic –*C*H), 129.98 (aromatic –*C*H), 130.74 (aromatic –*C*H), 135.83 (aromatic quaternary –C), 143.45 (aromatic quaternary –*C*), 146.09 (aromatic quaternary –*C*), 147.76 (aromatic quaternary –*C*), 165.78, 170.42; IR (neat): 3063 cm^{-1}, 2982 cm^{-1}, 1732 cm^{-1}, 1597 cm^{-1}, 1350 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{31}H_{27}N_3O_4$ [M+H], 506.2080; found, 506.2076.

4.1.3.3. *dl*-(4*R*,5*R*)-Ethyl 1-benzyl-5-(4-methoxyphenyl)-2,4-diphenyl-4,5-dihydro-1*H*-imidazole-4-carboxylate (14). The resulting crude solid was purified via column chromatography using silica gel (1:1 ethyl acetate:hexane as eluant) to afford the product as an off-white solid (336 mg, 36% yield). Mp 143–144 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.85 (t, 3H, J = 7 Hz), 3.64 (dq, 1H, J = 10.5, 7.5 Hz), 3.74 (dq, 1H, J = 10.5, 7 Hz), 3.80 (d, 1H, J = 16.0 Hz), 3.81 (s, 3H), 4.57 (d, 1H, J = 15.5 Hz), 4.86 (s, 1H), 6.74 (d, 2H, J = 7.5 Hz), 6.89 (d, 2H, J = 8.5 Hz), 7.04–709 (m, 2H), 7.09–7.20 (m, 1H), 7.25–7.33 (m, 5H), 7.44–7.47 (m, 3H), 7.72–7.74 (m, 4H); ^{13}C NMR + **DEPT** (125 MHz, $CDCl_3$): δ 13.58 (–CH3), 48.45 (–CH2), 55.25 (–CH3), 60.94 (–CH2), 73.33 (–CH), 82.66 (quaternary –*C*), 113.82 (aromatic –*C*H), 126.79 (aromatic –*C*H), 127.12 (aromatic –*C*H), 127.27 (aromatic –*C*H), 127.30 (aromatic –*C*H), 127.94 (aromatic –*C*H), 128.37 (aromatic –*C*H), 128.53 (aromatic –*C*H), 128.77 (aromatic –*C*H), 129.34 (aromatic –*C*H), 129.76 (aromatic –*C*H), 130.20 (aromatic –*C*H), 130.76 (aromatic quaternary –*C*), 136.76 (aromatic quaternary –*C*), 144.17 (aromatic quaternary –*C*), 159.59 (aromatic quaternary –*C*), 165.30, 170.90; IR (neat): 3032 cm^{-1}, 2934 cm^{-1}, 1732 cm^{-1}, 1595 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{32}H_{30}N_2O_3$ [M+H], 491.2335; found, 491.2332.

4.1.3.4. *dl*-(4*R*,5*R*)-Ethyl 1-benzyl-5-(4-fluorophenyl)-2,4-diphenyl-4,5-dihydro-1*H*-imidazole-4-carboxylate (15). The resulting crude solid was purified via column chromatography using silica gel (1:1 ethyl acetate:hexane) to afford the product as a white solid (124 mg, 12% yield). Mp 96–97 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.84 (t, 3H, J = 7.5 Hz), 3.67 (dq, 1H, J = 10.5, 7.5 Hz), 3.76 (dq, 1H, J = 10.5, 7 Hz), 3.84 (d, 1H, J = 16.0 Hz), 4.63 (d, 1H, J = 15.5 Hz), 4.92 (s, 1H), 6.75–6.78 (m, 2H), 7.06–7.12 (m, 4H), 7.12–7.16 (m, 1H), 7.28–7.42 (m, 5H), 7.48–7.54 (m, 3H), 7.72–7.80 (m, 4H); ^{13}C NMR + **DEPT** (125 MHz, $CDCl_3$): δ 13.53 (–CH3), 48.73 (–CH2), 61.04 (–CH2), 73.01 (–CH), 82.78 (quaternary –*C*), 115.35 (d, J = 21.6 Hz, aromatic –CH), 126.68 (aromatic –*C*H), 127.11 (aromatic –*C*H), 127.39 (aromatic –*C*H), 127.43 (aromatic –*C*H), 128.01 (aromatic –*C*H), 128.40 (aromatic –*C*H), 128.59 (aromatic –*C*H), 128.77 (aromatic –*C*H), 129.73 (d, J = 8.0 Hz, aromatic –*C*H), 130.37 (aromatic –*C*H), 130.43 (aromatic –*C*H), 133.77 (d, J = 3.0 Hz, aromatic quaternary –*C*), 136.40 (aromatic quaternary –*C*), 143.90 (aromatic quaternary –*C*), 162.61 (d, J = 245 Hz, aromatic quaternary –*C*), 165.39, 170.70; IR (neat): 3063 cm^{-1}, 2982 cm^{-1}, 1732 cm^{-1}, 1597 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{31}H_{27}N_2O_2F$ [M+H], 479.2135; found, 479.2130.

4.1.3.5. *dl*-(4*R*,5*R*)-Ethyl 1-benzyl-5-(4-chlorophenyl)-2,4-diphenyl-4,5-dihydro-1*H*-imidazole-4-carboxylate (16). The resulting crude solid was recrystallized using ethyl acetate/hexane to afford the product as a white crystalline solid (6.23 g, 50% yield). Mp 165–166 °C; ^{1}H NMR (500 MHz, $CDCl_3$) (TMS): δ 0.86 (t, 3H, J = 7.0 Hz), 3.66 (dq, 1H, J = 11, 7.5 Hz), 3.75 (dq, 1H, J = 11, 7.5 Hz), 3.80 (d, 1H, J = 15.5 Hz), 4.61 (d, 1H, J = 15.5 Hz), 4.87 (s, 1H), 6.74 (d, 2H, J = 7.0 Hz), 7.05–7.08 (m, 2H), 7.11–7.12 (m, 1H), 7.26–7.29 (m, 1H), 7.31–7.36 (m, 6H), 7.47–7.49 (m, 3H), 7.70–7.72 (m, 2H), 7.75–7.77 (m, 2H); ^{13}C NMR + **DEPT** (125 MHz, $CDCl_3$) (TMS): δ 13.55 (–*C*H3), 48.83 (–*C*H2), 61.12 (–*C*H2), 73.10 (–*C*H), 82.87 (quaternary –*C*), 126.68 (aromatic –*C*H), 127.17 (aromatic –*C*H), 127.46 (aromatic –*C*H), 127.49 (aromatic –*C*H), 128.06 (aromatic –*C*H), 128.45 (aromatic –*C*H), 128.63 (aromatic –*C*H), 128.65 (aromatic –*C*H), 128.81 (aromatic –*C*H), 129.49 (aromatic –*C*H), 130.41 (aromatic quaternary –*C*), 130.43 (aromatic –*C*H), 134.08 (aromatic quaternary –*C*), 136.35 (aromatic quaternary –*C*), 136.63 (aromatic quaternary –*C*), 143.84 (aromatic quaternary –*C*), 165.48, 170.65; IR (KBr): 3063 cm^{-1}, 2980 cm^{-1}, 1732 cm^{-1}, 1595 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{31}H_{27}N_2O_2Cl$ [M+H], 495.1833; found, 495.1834.

4.1.3.6. *dl*-(4*R*,5*R*)-Ethyl 1-benzyl-2,4-diphenyl-5-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1*H*-imidazole-4-carboxylate (17). The resulting crude solid was purified via column chromatography using silica gel (4:6 ethyl acetate:hexane as eluant) to afford the product as a white crystalline solid (159 mg, 14% yield). Mp 155–156 °C; ^{1}H NMR (500 MHz, $CDCl_3$) (TMS): δ 0.78 (t, 3H, J = 7.0 Hz), 3.63 (dq, 1H, J = 11, 7 Hz), 3.73 (dq, 1H, J = 10.5, 7 Hz), 3.82 (d, 1H, J = 16.0 Hz), 4.62 (d, 1H, J = 15.5 Hz), 4.94 (s, 1H), 6.73 (d, 2H, J = 7.5 Hz), 7.04–7.10 (m, 2H), 7.11–7.13 (m, 1H), 7.27–7.32 (m, 1H), 7.32–7.36 (m, 2H), 7.48–7.50 (m, 3H), 7.52 (d, 2H, J = 7.5 Hz), 7.64 (d, 2H, J = 8.0 Hz), 7.71–7.73 (m, 2H), 7.78–7.80 (m, 2H); ^{13}C NMR + **DEPT** (125 MHz, $CDCl_3$) (TMS): δ 13.36 (–*C*H3), 49.05 (–*C*H2), 61.13 (–*C*H2), 73.21 (–*C*H), 83.07 (quaternary –*C*), 125.35 (q, J = 3.6 Hz, aromatic –*C*H), 123.97 (q, J = 270 Hz, quaternary –*C*), 126.62 (aromatic –*C*H), 127.16 (aromatic –*C*H), 127.51 (aromatic –*C*H), 127.56 (aromatic –*C*H), 128.10 (aromatic –*C*H), 128.44 (aromatic –*C*H), 128.65 (aromatic –*C*H), 128.83 (aromatic –*C*H), 130.46 (q, J = 32 Hz, quaternary –*C*), 130.53 (aromatic –*C*H), 136.13 (aromatic quaternary –*C*), 142.44 (aromatic quaternary –*C*), 143.68 (aromatic quaternary –*C*), 165.59, 170.49; IR (neat): 3065 cm^{-1}, 2982 cm^{-1}, 1734 cm^{-1}, 1597 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{32}H_{27}N_2O_2F_3$ [M+H], 529.2103; found, 529.2110.

4.1.3.7. *dl*-(4*R*,5*R*)-Ethyl 1-benzyl-5-(furan-2-yl)-2,4-diphenyl-4,5-dihydro-1*H*-imidazole-4-carboxylate (18). The resulting crude residue was purified via column chromatography using silica gel (4:6 ethyl acetate:hexane) to afford the product as a yellow oil (238 mg, 25% yield). ^{1}H NMR (500 MHz) ($CDCl_3$): δ 1.01 (t, 3H, J = 7.0 Hz), 3.86 (dq, 1H, J = 10.5, 7 Hz), 3.94 (dq, 1H, J = 10.5, 7 Hz), 3.88 (d, 1H, J = 15.5 Hz), 4.54 (d, 1H, J = 15.5 Hz), 5.01 (s, 1H), 6.36–6.39 (m, 2H), 6.81–6.83 (m, 2H), 7.08–7.13 (m, 2H), 7.25–7.28 (m, 1H), 7.31–7.34 (m, 2H), 7.43–7.46 (m, 4H), 7.71–7.75 (m, 4H); ^{13}C NMR + **DEPT** (125 MHz) ($CDCl_3$): δ 13.72 (–CH3), 49.01 (–CH2), 61.27 (–CH2), 67.97 (–CH), 81.21 (quaternary –*C*), 109.30, (aromatic –*C*H), 110.50 (aromatic –*C*H), 126.55 (aromatic –*C*H), 127.08 (aromatic –*C*H), 127.30 (aromatic –*C*H), 127.43 (aromatic –*C*H), 128.03 (aromatic –*C*H), 128.39 (aromatic –*C*H), 128.46 (aromatic –*C*H), 128.68 (aromatic –*C*H), 130.17 (aromatic –*C*H), 130.65 (aromatic quaternary –*C*), 136.51 (aromatic quaternary –*C*), 142.51 (aromatic –*C*H), 143.34 (aromatic quaternary –*C*), 151.41 (aromatic quaternary –*C*), 165.47, 170.75; IR (neat): 3063 cm^{-1}, 2980 cm^{-1}, 1734 cm^{-1}, 1597 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{29}H_{26}N_2O_3$ [M+H], 451.2022; found, 451.2005.

4.1.3.8. *dl*-(4*R*,5*R*)-Ethyl 5-(4-aminophenyl)-1-benzyl-2,4-diphenyl-4,5-dihydro-1*H*-imidazole-4-carboxylate (13). A solution of *dl*-(4*R*,5*R*)-ethyl-1-benzyl-5-(4-nitrophenyl)-2,4-diphenyl-4,5-dihydro-1*H*-imidazole-4-carboxylate **(12)** (0.1 g, 0.2 mmol) H_2O (36 mg, 2.0 mmol) in 10 mL of ethanol was treated with $SnCl_2{\cdot}2H_2O$ (0.3 g, 1.2 mmol). The solution was heated to reflux for 2 h and cooled to room temperature before being poured over ice (~50 g). The pH of the resulting aqueous solution was adjusted (pH 8) using $NaHCO_3$ powder. The solution was then washed with EtOAc (3 × 50 mL). The combined EtOAc washes were dried over sodium sulfate and concentrated in vacuo. The resulting residue was purified via column chromatography using silica gel (100% ethyl acetate as eluant) to afford the product as a white solid (57 mg, 60% yield). Mp 60–62 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.91 (t, 3H, J = 7.5 Hz), 3.68–3.82 (m, 4H) 3.86 (d, 1H, J = 16 Hz), 4.60 (d, 1H, J = 15.5 Hz), 4.86 (s, 1H), 6.68 (d, 2H, J = 8.5 Hz), 6.78 (d, 2H, J = 7.5 Hz), 7.08–7.16 (m, 3H), 7.18 (d, 2H, J = 8 Hz), 7.27–7.30 (m, 1H), 7.35–7.36 (m, 2H), 7.47–7.50 (m, 3H), 7.75–7.78 (m, 4H); ^{13}C NMR + **DEPT** (125 MHz, $CDCl_3$): δ13.57 (–CH3), 48.24 (–CH2), 60.86 (–CH2), 73.48 (–CH), 82.51 (quaternary –*C*), 114.84 (aromatic –*C*H), 126.78 (aromatic –*C*H), 127.07 (aromatic –*C*H), 127.16 (aromatic –*C*H), 127.19 (aromatic –*C*H), 127.86

(aromatic –*C*H), 128.29 (aromatic –*C*H), 128.46 (aromatic –*C*H), 128.70 (aromatic –*C*H), 129.18 (aromatic –*C*H), 130.09 (aromatic –*C*H), 130.84 (quaternary aromatic –*C*), 136.88 (quaternary aromatic –*C*), 144.24 (quaternary aromatic –*C*), 146.51 (quaternary aromatic –*C*), 165.19, 170.96; IR (KBr): 3460 cm^{-1}, 3373 cm^{-1}, 3063 cm^{-1}, 1732 cm^{-1}, 1614 cm^{-1}; HRMS (FAB): *m/z* calcd for $C_{31}H_{29}N_3O_2$ [M+H], 476.2338; found, 476.2332.

4.1.4. General procedure for imidazoline derivatives 19–25

A solution of appropriate amine (0.2 g, 2.11 mmol) and appropriate benzylaldehyde (0.2 g, 2.11 mmol) in 50 mL of anhydrous benzene was refluxed under nitrogen for 12 h and then concentrated in vacuo. The resulting residue was redissolved into 50 mL of anhydrous dichloromethane. Then 2,4-diphenyl-5(4H)-oxazolone (0.5 g, 2.11 mmol) and chlorotrimethylsilane (0.3 g, 2.74 mmol) were added and the mixture was refluxed under nitrogen for an additional 12 h. The solution was concentrated in vacuo and the resulting residue was resuspended in ethyl acetate producing a white solid precipitate (0.4 g) which was isolated via filtration. The white solid was then dissolved into 50 mL of dichloromethane, cooled to 0 °C, and treated with oxalyl chloride (0.3 g, 2.68 mmol) and DMF (30 μL). The solution was stirred for 2 h, concentrated in vacuo, and the residue was cooled to 0 °C. The residue was redissolved into 20 mL of ethanol before being left to stir overnight. The solution was concentrated in vacuo and then dissolved into dichloromethane before being washed with saturated $NaHCO_3$ solution (3×50 mL) and brine solution (1×50 mL). The organic fraction was dried over sodium sulfate and then concentrated in vacuo.

4.1.4.1. *dl*-(4*R*,5*R*)-Ethyl 1-(4-methoxybenzyl)-2,4,5-triphenyl-4,5-dihydro-1*H*-imidazole-4-carboxylate (19). The resulting crude residue was purified via column chromatography using silica gel (1:1 ethyl acetate:hexane) to afford the product as clear oil (88 mg, 51% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.77 (t, 3H, *J* = 7.25 Hz), 3.56 (dq, 1H, *J* = 10.9, 7.0 Hz), 3.66 (dq, 1H, *J* = 10.9, 7.0 Hz), 3.67 (s, 3H), 3.74 (d, 1H, *J* = 15.5 Hz), 4.53 (d, 1H, *J* = 15.5 Hz), 4.88 (s, 1H), 6.62 (d, 2H, *J* = 8.5 Hz), 6.75 (d, 2H, *J* = 8.5 Hz), 7.23–7.25 (m, 1H), 7.29–7.32 (m, 3H), 7.34–7.39 (m, 4H), 7.45–7.46 (m, 3H), 7.71–7.72 (m, 2H), 7.74–7.76 (m, 2H); ^{13}C NMR + **DEPT** (125 MHz, $CDCl_3$): δ 13.38 (–CH3), 48.10 (–CH2), 55.05 (–CH3), 60.87 (–CH2), 73.46 (–CH), 82.71 (quaternary –*C*), 113.69 (aromatic –*C*H), 126.73 (aromatic –*C*H), 127.22 (aromatic –*C*H), 127.88 (aromatic –*C*H), 128.10 (aromatic –*C*H), 128.19 (aromatic –*C*H), 128.36 (aromatic –*C*H), 128.37 (aromatic quaternary –*C*), 128.43 (aromatic –*C*H), 128.49 (aromatic –*C*H), 128.80 (aromatic –*C*H), 130.24 (aromatic –*C*H), 130.54 (aromatic quaternary –*C*), 137.88 (aromatic quaternary –*C*), 144.04 (aromatic quaternary –*C*), 158.76 (aromatic quaternary –*C*), 165.38, 170.67; IR (neat): 3063 cm^{-1}, 3031 cm^{-1}, 2980 cm^{-1}, 2936 cm^{-1}, 1732 cm^{-1}, 1597 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{32}H_{31}N_2O_3$ [M+H], 491.2335; found, 491.2328.

4.1.4.2. *dl*-(4*R*,5*R*)-Ethyl 1-(4-methylbenzyl)-2,4,5-triphenyl-4,5-dihydro-1*H*-imidazole-4-carboxylate (20). The resulting crude residue was purified via column chromatography using silica gel (1:1 ethyl acetate:hexane) to afford the product as a clear oil (85 mg, 28% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.80 (t, 3H, *J* = 7.0 Hz), 2.23 (s, 3H), 3.58 (dq, 1H, *J* = 10.5, 7.0 Hz), 3.68 (dq, 1H, *J* = 10.5, 7.0 Hz), 3.77 (d, 1H, *J* = 16.0 Hz), 4.57 (d, 1H, *J* = 15.5 Hz), 4.92 (s, 1H), 6.62 (d, 2H, *J* = 8.0 Hz), 6.86 (d, 2H, *J* = 7.5 Hz), 7.25–7.29 (m, 1H), 7.31–7.35 (m, 4H), 7.36–7.38 (m, 3H), 7.46–7.47 (m, 3H), 7.73–7.77 (m, 4H); ^{13}C NMR + **DEPT** (125 MHz, $CDCl_3$): δ 13.38 (–CH3), 20.86 (–CH3), 48.27 (–CH2), 60.85 (–CH2), 73.56 (–CH), 82.75 (quaternary –*C*), 126.74 (aromatic –*C*H), 127.01 (aromatic –*C*H), 127.21 (aromatic –*C*H), 127.88 (aromatic –*C*H), 128.09 (aromatic –*C*H), 128.18 (aromatic –*C*H), 128.35 (aromatic –*C*H), 128.46 (aromatic –*C*H), 128.74 (aromatic –*C*H), 128.98 (aromatic –*C*H), 130.18 (aromatic –*C*H), 130.57 (aromatic quaternary –*C*), 133.39 (aromatic quaternary –*C*), 136.87 (aromatic quaternary –*C*), 137.88 (aromatic quaternary –*C*), 144.03 (aromatic quaternary –*C*), 165.39, 170.71; IR (neat): 3058 cm^{-1}, 3031 cm^{-1}, 2978 cm^{-1}, 2925 cm^{-1}, 1732 cm^{-1}, 1597 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{32}H_{31}N_2O_2$ [M+H], 475.2386; found, 475.2414.

4.1.4.3. *dl*-(4*R*,5*R*)-Ethyl 1-(4-fluorobenzyl)-2,4,5-triphenyl-4,5-dihydro-1*H*-imidazole-4-carboxylate (21). The resulting crude residue was purified via column chromatography using silica gel (1:1 ethyl acetate:hexane) to afford the product as a white solid (144 mg, 74% yield). Mp 67–69 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.78 (t, 3H, *J* = 7.0 Hz), 3.68 (dq, 1H, *J* = 10.6, 7.0 Hz), 3.80 (d, 1H, *J* = 15.5 Hz), 4.54 (d, 1H, *J* = 16.0 Hz), 4.85 (s, 1H), 6.65–6.69 (m, 2H), 6.70–6.74 (m, 2H), 7.24–7.29 (m, 1H), 7.31–7.35 (m, 4H), 7.36–7.37 (m, 3H), 7.46–7.49 (m,3H), 7.73–7.76 (m, 4H); ^{13}C NMR + **DEPT** (125 MHz, $CDCl_3$): δ 13.44 (–CH3), 48.11 (–CH2), 61.01 (–CH2), 73.89 (–CH), 82.76 (quaternary –*C*), 115.24 (d, *J* = 21.5 Hz, aromatic –*C*H,), 126.74 (aromatic –*C*H), 127.46 (aromatic –*C*H), 128.02 (aromatic –*C*H), 128.08 (aromatic –*C*H), 128.37 (aromatic –*C*H), 128.50 (aromatic –*C*H), 128.63 (aromatic –*C*H), 128.83 (aromatic –*C*H), 128.84 (d, *J* = 8.2 Hz, aromatic –*C*H), 130.45 (aromatic –*C*H), 132.24 (d, *J* = 3.7 Hz, aromatic quaternary –*C*), 137.75 (aromatic quaternary –*C*), 144.02 (aromatic quaternary –*C*), 161.98 (d, *J* = 244 Hz, aromatic quaternary –*C*), 165.35, 170.50; IR (neat): 3063 cm^{-1}, 3033 cm^{-1}, 2982 cm^{-1}, 2928 cm^{-1}, 1732 cm^{-1}, 1597 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{31}H_{28}N_2O_2F$ [M+H], 479.2135; found, 479.2126.

4.1.4.4. *dl*-(4*R*,5*R*)-Ethyl 1-(4-chlorobenzyl)-2,4,5-triphenyl-4,5-dihydro-1*H*-imidazole-4-carboxylate (22). The resulting crude residue was purified via column chromatography using silica gel (1:1 ethyl acetate:hexane) to afford the product as a white solid (110 mg, 52% yield). Mp 112–115 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.78 (t, 3H, *J* = 7.25 Hz), 3.59 (dq, 1H, *J* = 10.6, 7.0 Hz), 3.68 (dq, 1H, *J* = 10.6, 7.0 Hz), 3.79 (d, 1H, *J* = 16.0 Hz), 4.53 (d, 1H, *J* = 16.0 Hz), 4.85 (s, 1H), 6.64 (d, 2H, *J* = 8.5 Hz), 6.99–7.02 (m, 2H), 7.27–7.30 (m, 1H), 7.32–7.35 (m, 4H), 7.36–7.37 (m, 3H), 7.46–7.48 (m, 3H), 7.73–7.76 (m, 4H); ^{13}C NMR + **DEPT** (125 MHz, $CDCl_3$): δ 13.44 (–CH3), 48.11 (–CH2), 61.03 (–CH2), 74.02 (–CH2), 82.77 (quaternary –*C*), 126.73 (aromatic –*C*H), 127.50 (aromatic –*C*H), 128.05 (aromatic –*C*H), 128.41 (aromatic –*C*H), 128.45 (aromatic –*C*H), 128.52 (aromatic –*C*H), 128.54 (aromatic –*C*H), 128.64 (aromatic –*C*H), 128.78 (aromatic –*C*H), 130.46 (aromatic –*C*H), 133.15 (aromatic quaternary –*C*), 135.11 (aromatic quaternary –*C*), 137.67 (aromatic quaternary –*C*), 143.96 (aromatic quaternary –*C*), 165.30, 170.52; IR (neat): 3061 cm^{-1}, 3030 cm^{-1}, 2980 cm^{-1}, 2930 cm^{-1}, 1732 cm^{-1}, 1595 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{31}H_{28}N_2O_2Cl$ [M+H], 495.1839; found, 495.1862.

4.1.4.5. *dl*-(4*R*,5*R*)-Ethyl 1-(4-bromobenzyl)-2,4,5-triphenyl-4,5-dihydro-1*H*-imidazole-4-carboxylate (23). The resulting crude residue was purified via column chromatography using silica gel (1:1 ethyl acetate:hexane) to afford the product as a white solid (490 mg, 48% yield). Mp 111–113 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.78 (t, 3H, *J* = 7.25 Hz), 3.58 (dq, 1H, *J* = 10.6, 7.2 Hz), 3.68 (dq, 1H, *J* = 10.6, 7.2 Hz), 3.77 (d, 1H, *J* = 16.0 Hz), 4.51 (d, 1H, *J* = 15.5 Hz), 4.84 (s, 1H), 6.58 (d, 2H, *J* = 8.5 Hz), 7.15–7.17 (m, 2H), 7.24–7.31 (m, 1H), 7.32–7.35 (m, 3H), 7.35–7.37 (m, 4H), 7.46–7.48 (m, 3H), 7.72–7.76 (m, 4H); ^{13}C NMR + **DEPT** (125 MHz, $CDCl_3$): δ 13.46 (–CH3), 48.17 (–CH2), 61.02 (–CH2), 74.05 (–CH), 82.88 (quaternary –*C*), 121.24 (aromatic quaternary –*C*), 126.76 (aromatic –*C*H), 127.511 (aromatic –*C*H), 128.06 (aromatic –*C*H), 128.40 (aromatic –*C*H), 128.52 (aromatic –*C*H),128.65 (aromatic –

CH), 128.77 (aromatic –CH), 128.79 (aromatic –CH), 130.42 (aromatic –CH), 130.45 (aromatic quaternary –C), 131.49 (aromatic –CH), 135.74 (aromatic quaternary –C), 137.77 (aromatic quaternary –C), 144.05 (aromatic quaternary –C), 165.29, 170.61; IR (neat): 3061 cm^{-1}, 3034 cm^{-1}, 2984 cm^{-1}, 2930 cm^{-1}, 1732 cm^{-1}, 1595 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{31}H_{28}N_2O_2Br$ [M+H], 539.1334; found, 539.1374.

4.1.4.6. *dl*-(4*R*,5*R*)-Ethyl 2,4,5-triphenyl-1-(4-(trifluoromethyl)-benzyl)-4,5-dihydro-1*H*-imidazole-4-carboxylate (24). The resulting crude residue was purified via column chromatography using silica gel (1:1 ethyl acetate:hexane) to afford the product as a white solid (135 mg, 64% yield). Mp 83–85 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.78 (t, 3H, *J* = 7.0 Hz), 3.59 (dq, 1H, *J* = 10.7, 7.1 Hz), 3.69 (dq, 1H, *J* = 10.6, 7.1 Hz), 3.89 (d, 1H, *J* = 16.5 Hz), 4.61 (d, 1H, *J* = 16.0 Hz), 4.85 (s, 1H), 6.82 (d, 2H, *J* = 8.0 Hz), 7.28–7.30 (m, 3H), 7.32–7.35 (m, 3H), 7.36–7.37 (m, 4H), 7.41–7.48 (m, 3H), 7.74–7.77 (m, 4H); ^{13}C NMR + **DEPT** (125 MHz, $CDCl_3$): δ 13.41 (–CH3), 48.35 (–CH2), 61.08 (–CH2), 74.25 (–CH), 82.75 (quaternary –C), 123.86 (q, *J* = 270 Hz, aromatic quaternary –C), 125.32 (q, *J* = 3.8 Hz, aromatic –CH), 126.69 (aromatic –CH), 127.29 (aromatic –CH), 127.63 (aromatic –CH), 128.03 (aromatic –CH), 128.08 (aromatic –CH), 128.51 (aromatic –CH), 128.57 (aromatic –CH), 128.71 (aromatic –CH), 128.76 (aromatic –CH), 129.63 (q, *J* = 32 Hz, aromatic quaternary –C), 130.62 (aromatic –CH), 137.53 (aromatic quaternary –C), 140.82 (aromatic quaternary –C), 143.87 (aromatic quaternary –C), 165.33, 170.38;; IR (neat): 3063 cm^{-1}, 3036 cm^{-1}, 2983 cm^{-1}, 1732 cm^{-1}, 1597 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{32}H_{28}N_2O_2F_3$ [M+H], 529.2103; found, 529.2104.

4.1.4.7. *dl*-(4*R*,5*R*)-Ethyl 1-(furan-2-ylmethyl)-2,4,5-triphenyl-4,5-dihydro-1*H*-imidazole-4-carboxylate (25). The resulting crude residue was purified via column chromatography using silica gel (1:1 ethyl acetate:hexane) to afford the product as a yellow oil (88 mg, 41% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.81 (t, 3H, *J* = 7.25 Hz), 3.57 (dq, 1H, *J* = 10.5, 7.2 Hz), 3.67 (dq, 1H, *J* = 10.5, 7.2 Hz), 3.90 (d, 1H, *J* = 16.5 Hz), 4.41 (d, 1H, *J* = 16.0 Hz), 4.98 (s, 1H), 5.72 (d, 1H, *J* = 3.0 Hz), 6.06 (dd, 1H, J= 4.0, 2.0 Hz), 7.09 (dd, 1H, *J* = 1.5, 1.0 Hz), 7.09 (dd, 1H, *J* = 1.5, 1.0 Hz), 7.24–7.27 (m, 1H), 7.28–7.37 (m, 5H), 7.41–7.42 (m, 2H), 7.46–7.49 (m, 3H), 7.70–7.72 (m, 2H), 7.78–7.80 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.44 (–CH3), 42.63 (–CH2), 61.02 (–CH2), 74.55 (–CH), 82.95 (quaternary –C), 108.15 (aromatic –CH), 109.93 (aromatic –CH), 126.75 (aromatic –CH), 127.26 (aromatic –CH),128.00 (aromatic –CH), 128.08 (aromatic –CH), 128.26 (aromatic –CH), 128.37 (aromatic –CH), 128.50 (aromatic –CH), 128.87 (aromatic –CH), 130.38 (aromatic –CH), 137.86 (aromatic quaternary –C), 142.26 (aromatic –CH), 143.98 (aromatic quaternary –C), 149.92 (aromatic quaternary –C), 165.76, 170.52; IR (neat): 3061 cm^{-1}, 2982 cm^{-1}, 2934 cm^{-1}, 1734 cm^{-1}, 1597 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{29}H_{27}N_2O_3$ [M+H], 451.2022; found, 451.2013.

4.1.4.8. *dl*-(4*R*,5*R*)-Ethyl 2,4,5-triphenyl-4,5-dihydro-1*H*-imidazole-4-carboxylate (26). A solution of *dl*-(4*R*,5*R*)-ethyl-1-benzyl-2,4,5-triphenyl-4,5-dihydro-1*H*-imidazole-4-carboxylate **(6)** (790 mg, 1.72 mmol), 10 mL of cyclohexene and 50 mL of anhydrous THF was treated with 300 mg of 10% Pd/C. The solution was stirred under reflux for 24 h and then filtered through Celite. The resulting solution was concentrated in vacuo resulting in a yellowish crude solid. The solid was recrystallized (ethyl acetate:hexane) to afford the product as a crystalline white solid (553 mg, 87% yield). Mp 140–142 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.75 (t, 3H, *J* = 7.0 Hz), 3.40–3.53 (m, 1H), 3.67 (dq, 1H, *J* = 11, 7.5 Hz), 5.53 (br s, 1H), 6.13 (br s, 1H), 7.25–7.34 (m, 6H), 7.37–7.40 (m, 2H), 7.42–7.45 (m, 2H), 7.48–7.51 (m, 1H), 7.78 (d, 2H, *J* = 8.0 Hz), 8.00 (d, 2H, *J* = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.23, 29.80, 61.61, 83.95, 126.43, 127.69, 127.72, 127.81, 127.93, 128.19, 128.30, 128.47, 129.81, 131.16, 140.04, 143.25, 162.83, 171.33; IR (neat): 3368 cm^{-1}, 3063 cm^{-1}, 2982 cm^{-1}, 1730 cm^{-1}, 1599 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{24}H_{22}N_2O_2$ [M+H], 371.1760; found, 371.1761.

4.1.4.9. *dl*-(4*R*,5*R*)-Ethyl 1-acetyl-2,4,5-triphenyl-4,5-dihydro-1*H*-imidazole-4-carboxylate (27). A solution of *dl*-(4*R*,5*R*)-ethyl-2,4,5-triphenyl-4,5-dihydro-1*H*-imidazole-4-carboxylate **(26)** (100 mg, 0.3 mmol), acetic anhydride (32.7 mg, 0.32 mmol), triethylamine (30.1 mg, 0.3 mmol) and 20 mL of anhydrous dichloromethane was treated with DMAP (~10 mg). The solution was stirred for 48 h and then washed with 2 M HCl solution (2 × 20 mL) and brine solution (1 × 20 mL). The organic fraction was dried over sodium sulfate and concentrated in vacuo. The resulting crude residue was purified via column chromatography using silica gel (3:7 ethyl acetate:hexane) to afford the product as a white solid (93 mg, 84% yield). Mp 59–61 °C ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.75 (t, 3H, *J* = 7.0 Hz), 1.72 (s, 3H), 3.62 (dq, 1H, *J* = 10.5, 7.5 Hz), 3.70 (dq, 1H, *J* = 10.5, 7 Hz), 5.88 (s, 1H), 7.30–7.38 (m, 4H), 7.40–7.49 (m, 4H), 7.50–7.53 (m, 1H), 7.73 (d, 2H, *J* = 7.0 Hz), 7.78–7.80 (m, 2H); ^{13}C NMR + **DEPT** (125 MHz, $CDCl_3$): δ 13.35 (–CH3), 24.84 (–CH3), 61.41 (–CH2), 72.77 (–CH), 82.42 (quaternary –C), 126.47 (aromatic –CH), 127.36 (aromatic –CH), 127.71 (aromatic –CH), 128.24 (aromatic –CH), 128.51 (aromatic –CH), 128.57 (aromatic –CH), 128.64 (aromatic –CH), 131.13 (aromatic –CH), 131.36 (quaternary aromatic –C), 138.07 (quaternary aromatic –C), 141.04 (quaternary aromatic –C), 160.01, 167.43, 169.31; IR (neat): 3065 cm^{-1}, 2982 cm^{-1}, 1736 cm^{-1}, 1684 cm^{-1}, 1624 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{26}H_{24}N_2O_3$ [M+H], 413.1865; found, 413.1906.

4.1.4.10. *dl*-(4*R*,5*R*)-Ethyl 2,4,5-triphenyl-1-benzoyl-4,5-dihydro-1H-imidazole-4-carboxylate (28). A solution of *dl*-(4*R*,5*R*)-ethyl-2,4,5-triphenyl-4,5-dihydro-1*H*-imidazole-4-carboxylate **(26)** (100 mg, 0.27 mmol) and triethylamine (30.4 mg, 0.3 mmol) in 20 mL of anhydrous dichloromethane was treated with benzoyl chloride (45.0 mg, 0.32 mmol) and DMAP (~20 mg). The solution was stirred at room temperature for 24 h and then washed with 2 M HCl solution (2 × 20 mL), saturated $NaHCO_3$ solution (2 × 20 mL), and brine solution (1 × 20 mL). The solution was then dried over sodium sulfate and concentrated in vacuo. The resulting residue was purified via silica gel column chromatography using silica gel (3:7 ethyl acetate:hexane as eluant) to afford the product as a white solid (94 mg, 73% yield). Mp 61–63 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.82 (t, 3H, *J* = 6.5 Hz), 3.71 (dq, 1H, *J* = 11, 7.5 Hz), 3.79 (dq, 1H, *J* = 10.5, 7 Hz), 5.91 (s, 1H), 7.02–7.06 (m, 4H), 7.18–7.24 (m, 3H), 7.28–7.31 (m, 1H), 7.36–7.40 (m, 4H), 7.45–7.49 (m, 4H), 7.65–7.67 (m, 2H), 7.85–7.87 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$ + **DEPT**): δ 131.41 (–CH3), 61.44 (–CH2), 74.49 (–CH), 82.86 (quaternary –C), 126.51 (aromatic –CH), 127.54 (aromatic –CH), 127.77 (aromatic –CH), 128.04 (aromatic –CH), 128.32 (aromatic –CH), 128.35 (aromatic –CH), 128.57 (aromatic –CH), 128.59 (aromatic –CH), 128.61 (aromatic –CH), 128.90 (aromatic –CH), 130.62 (aromatic quaternary –C), 130.80 (aromatic –CH), 131.27 (aromatic –CH), 134.62 (aromatic quaternary –C), 137.95 (aromatic quaternary –C), 140.59 (aromatic quaternary –C), 161.12, 168.76, 169.41; **IR** (neat): 3061 cm^{-1}, 2982 cm^{-1}, 1749 cm^{-1}, 1721 cm^{-1}, 1599 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{31}H_{27}N_2O_3$ [M+H], 475.2022; found, 475.2028.

4.1.4.11. *dl*-(4*R*,5*R*)-Ethyl 2,4,5-triphenyl-1-tosyl-4,5-dihydro-1*H*-imidazole-4-carboxylate (29). A solution of *dl*-(4*R*,5*R*)-ethyl-2,4,5-triphenyl-4,5-dihydro-1*H*-imidazole-4-carboxylate **(26)** (155 mg, 0.42 mmol) and triethylamine (42.5 mg, 0.42 mmol) in 20 mL of anhydrous dichloromethane was treated with tosyl chloride (87.4 mg, 0.46 mmol) and DMAP (~10 mg). The solution was stirred at room temperature for 22 h and then washed with 2 M HCl solution (2 × 20 mL), saturated $NaHCO_3$ solution (2 × 20 mL), and brine solution (1 × 20 mL). The solution was then dried over

sodium sulfate and concentrated in vacuo. The resulting residue was purified via precipitation (dichloromethane:hexane) to afford the product as a white solid (160 mg, 73% yield). Mp 150–151 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.71 (t, 3H, J = 7.0 Hz), 2.24 (s, 3H), 3.49 (dq, 1H, J = 10.5, 7 Hz), 3.57 (dq, 1H, J = 10.5, 7 Hz), 5.78 (s, 1H), 6.79 (d, 2H, J = 7.5 Hz), 6.96 (d, 2H, J = 8.5 Hz), 7.23–7.36 (m, 3H), 7.37–7.44 (m, 3H), 7.49–7.56 (m, 4H), 7.57–7.60 (m, 2H), 7.89–7.91 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.29, 21.43, 61.59, 75.16, 83.26, 126.67, 127.05, 127.34, 127.47, 127.79, 128.11, 128.54, 128.61, 129.20, 129.81, 130.25, 131.58, 134.74, 138.53, 142.20, 144.08, 160.07, 169.04; IR (neat): 3065 cm^{-1}, 3034 cm^{-1}, 1736 cm^{-1}, 1599 cm^{-1}; HRMS (ESI): m/z calcd for $C_{31}H_{28}N_2O_4S$ [M+H], 525.1848; found, 525.1859.

4.2. Biological methods

4.2.1. Cell culture

The human cell line HeLa-NF-κB-luc was purchased from Panomics Inc (Fremont, CA). The cells were maintained in Dulbecco's Modified Eagle's medium (DMEM, Gibco Invitrogen, Fredrick, MD) containing 4.5 g/L glucose, 3.7 g/L bicarbonate, and supplemented with 5% fetal bovine serum, 100 U/mL penicillin, 100 μg/mL streptomycin, 1 mM sodium pyruvate, 0.2 mM L-glutamine and 100 μg/mL of hygromycin B (Roche). The human cell line 184B5 was purchased from ATCC (Rockville, MD). The cells were maintained in DMEM media containing 4.5 g/L glucose, 3.7 g/L bicarbonate, and supplemented with 10% fetal bovine serum, 100 U/mL penicillin, 100 mg/mL streptomycin, 1 mM sodium pyruvate, and 0.2 μM L-glutamine. Cells were cultured at 37 °C, 5% CO_2 atmosphere, 97% relative humidity and were routinely passaged by trypsin–EDTA (Life technologies, Gran Island NY) treatment according to ATCC protocol.

4.2.1.1. Viability assays. Human white blood cells were counted manually using a BD Unopette Reservoir (Becton Dickenson, Franklin Lakes, NJ) and a hemacytometer. The inhibitory effect of imidazolines on healthy cells 184B5 was assessed by MTS ([3-(4,5-dimethyl thiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2*H*-tetrazolium], inner salt) assay (Promega, Madison, WI). 184B5 cells were seeded in 96 well plates at 5000 cells/well 24 h prior to treatment. The cells were treated with vehicle or imidazoline and incubated at 37 °C, 5% CO_2. Twenty-four hours after treatment 20 μL MTS reagent was added to each well and the plate was further incubated for 4 h at 37 °C, 5% CO_2. Absorbance was measured at 490 nm using a spectrophotometer (Molecular Devices, Sunnyvale, CA) (see Supplementary data).

4.2.1.2. FACS analysis. For the analysis of cell cycle parameters the adherent cell cultures were trypsinized and resuspended in 1 mL of 1 × PBS with 50% FBS. Then the cells were fixed with 70% (v/v) ice cold ethanol overnight. After centrifugation of the cells, the pellet was washed two times with 5 mL of ice cold 1× PBS containing 10% FBS. Then the cell pellet was resuspended in staining solution (PBS containing 50 μg propidium iodide, 10 μL 0.1 M EDTA, 14 units RNaseA). The DNA content was analyzed by flow cytometry using a FACS Vantage SE analyzer with ModFit LT software (see Supplementary data).

4.2.1.3. NF-κB-luc reporter assay. HeLa NF-κB-luc cells (5.0×10^5 cells/mL) were seeded into a 96-well white opaque plate using DMEM medium supplemented with 5% fetal bovine serum, 100 U/mL penicillin, 100 μg/mL streptomycin, 1 mM sodium pyruvate, 0.2 mM L-glutamine, and 100 μg/mL hygromycin B (Roche). After 24 h the cell culture medium was replaced with DMEM medium supplemented with 100 U/mL penicillin and 100 μg/mL streptomycin. Cell cultures were pretreated with vehicle (1% DMSO), 50 μM MG-132 (EMD Biosciences, San Diego, CA) or imidazoline (final concentrations were 20, 10, 5, 1, 0.5, 0.1, 0.05 μM) for 30 min at 37 °C in 5% CO_2. TNF-α (Invitrogen Cytokines & Signaling, Camarillo, CA) was added to a final concentration of 25 ng/mL and the samples were further incubated for 8 h at 37 °C in 5% CO_2. The plate and Steady-Glo luciferase assay reagent (Promega Corporation) were equilibrated to room temperature. An equal volume of Steady-Glo assay reagent was added to each well. The contents of the plate were gently mixed for 5 min and the luminescence of each well was measured using a Veritas microplate luminometer (Turner Biosystems, CA). All reported data are the average of two independent experiments unless otherwise indicated. The data were analyzed using GraphPad Prism 4.0. The data was normalized to TNF-α activation and the EC_{50} values were calculated using the equation for the sigmoidal curve for variable slope.

4.2.1.4. Human whole blood IL-1β challenge. After obtaining the appropriate approval for de-identified human cell lines, human whole blood was obtained through the Jasper Research Clinic, Kalamazoo, MI, from a single healthy, fasted human volunteer and was collected in glass citrated tubes by venipuncture. Only samples with a white blood count falling within the normal range (4800–10,800 white blood cells per liter) were used. To support the viability of white blood cells, blood was diluted 1:10 in RPMI-1640 media supplemented with 10% fetal bovine serum, 100 U/mL penicillin, and 100 μg/mL streptomycin. Aliquots of diluted blood (1 mL) were preincubated with vehicle (0.1% DMSO, final concentration) or imidazoline (final concentrations were 10, 3, 1, 0.3 and 0.1 μM) for 2 h at 37 °C, 5% CO_2. IL-1β (Roche) was added to a final concentration of 200 U/mL and the samples were further incubated for 18 h at 37 °C, 5% CO_2. At the end of the incubation period, the blood samples were centrifuged at 3000 rpm for 5 min. The plasma was removed, snap frozen and stored at −80 °C. IL-6 levels were determined by ELISA (R & D Systems).

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Supplementary data

Experimental data for reporter assays, ELISA IL-6, FACS, MTS, cell counting experiments for all compounds are provided. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2009.03.002.

References and notes

1. Perkins, N. D. *Trends Biochem. Sci.* **2000**, *25*, 434.
2. Baldwin, A. S., Jr. *Annu. Rev. Immunol.* **1996**, *14*, 649.
3. Piva, R.; Belardo, G.; Santoro, M. G. *Antioxid. Redox Signal* **2006**, *8*, 478.
4. D'Acquisto, F.; May, M. J.; Ghosh, S. *Mol. Interventions* **2002**, *2*, 22.
5. Baeuerle, P. A.; Henkel, T. *Annu. Rev. Immunol.* **1994**, *12*, 141.
6. Wang, C. Y.; Mayo, M. W.; Baldwin, A. S., Jr. *Science* **1996**, *274*, 784.
7. Mayo, M. W.; Baldwin, A. S. *Biochim. Biophys. Acta* **2000**, *1470*, M55.
8. Greten, F. R.; Karin, M. *Cancer Lett.* **2004**, *206*, 193.
9. Wang, C. Y.; Cusack, J. C., Jr.; Liu, R.; Baldwin, A. S., Jr. *Nat. Med.* **1999**, *5*, 412.
10. Luo, J. L.; Kamata, H.; Karin, M. *J. Clin. Invest.* **2005**, *115*, 2625.
11. de Martin, R.; Schmid, J. A.; Hofer-Warbinek, R. *Mutat. Res.* **1999**, *437*, 231.
12. Karin, M.; Ben-Neriah, Y. *Annu. Rev. Immunol.* **2000**, *18*, 621.
13. Siebenlist, U.; Franzoso, G.; Brown, K. *Ann. Rev. Cell Biol.* **1994**, *10*, 405.
14. Ghosh, S.; May, M. J.; Kopp, E. B. *Annu. Rev. Immunol.* **1998**, *16*, 225.
15. Morello, S.; Ito, K.; Yamamura, S.; Lee, K. Y.; Jazrawi, E.; Desouza, P.; Barnes, P.; Cicala, C.; Adcock, I. M. *J. Immunol.* **2006**, *177*, 7173.

16. Baeuerle, P. A.; Baltimore, D. *Science* **1988**, *242*, 540.
17. Makarov, S. S. *Arthritis Res.* **2001**, *3*, 200.
18. Okazaki, Y.; Sawada, T.; Nagatani, K.; Komagata, Y.; Inoue, T.; Muto, S.; Itai, A.; Yamamoto, K. *J. Rheumatol.* **2005**, *32*, 1440.
19. Ardizzone, S.; Bianchi Porro, G. *Drugs* **2005**, *65*, 2253.
20. Boone, D. L.; Lee, E. G.; Libby, S.; Gibson, P. J.; Chien, M.; Chan, F.; Madonia, M.; Burkett, P. R.; Ma, A. *Inflamm. Bowel Dis.* **2002**, *8*, 201.
21. Schreiber, S.; Nikolaus, S.; Hampe, J. *Gut* **1998**, *42*, 477.
22. van den Brink, G. R.; ten Kate, F. J.; Ponsioen, C. Y.; Rive, M. M.; Tytgat, G. N.; van Deventer, S. J. H.; Peppelenbosch, M. P. *J. Immunol.* **2000**, *164*, 3353.
23. de Winther, M. P. J.; Kanters, E.; Kraal, G.; Hofker, M. H. *Arterioscler Thromb. Vasc. Biol.* **2005**, *25*, 904.
24. Martin, E.; Robert, G.; Ulrike, S.; Silvia, D.; Gunther, N.; Zettl Uwe, K. *J. Neurol. Sci.* **2008**, *264*, 145.
25. Hart, L. A.; Krishnan, V. L.; Adcock, I. M.; Barnes, P. J.; Chung, K. F. *Am. J. Respir. Crit. Care Med.* **1998**, *158*, 1585.
26. Renard, P.; Raes, M. *Cell Biol.Toxicol.* **1999**, *15*, 341.
27. Tak, P. P.; Firestein, G. S. *J. Clin. Invest.* **2001**, *107*, 7.
28. Barnes, P. J.; Karin, M. *N. Eng. J. Med.* **1997**, *336*, 1066.
29. Pahl, H. L. *Oncogene* **1999**, *18*, 6853.
30. Brasier, A. R. *Cardiovasc. Toxicol.* **2006**, *6*, 111.
31. Adachi, Y.; Yoshio-Hoshino, N.; Nishimoto, N. *Curr. Pharm. Des.* **2008**, *14*, 1217.
32. Nishimoto, N.; Kishimoto, T. *Nat. Clin. Pract. Rheumatol.* **2006**, *2*, 619.
33. Choy, E. *Rheum. Dis. Clin. North Am.* **2004**, *30*, 405.
34. Ghezzi, P.; Cerami, A. *Methods Mol. Med.* **2004**, *98*, 1.
35. Reimold, A. M. *Curr. Drug Targets Inflamm. Allergy* **2002**, *1*, 377.
36. Miossec, P. *Cell Mol. Biol.* **2001**, *47*, 675.
37. Moreland, L. W. *J. Rheumatol.* **1999**, *26*, 7.
38. Feldmann, M.; Brennan, F. M.; Maini, R. N. *Annu. Rev. Immunol.* **1996**, *14*, 397.
39. Maini, R. N.; Elliott, M. J.; Brennan, F. M.; Feldmann, M. *Clin. Exp. Immunol.* **1995**, *101*, 207.
40. Kremer, J. M. *Ann. Int. Med.* **2001**, *134*, 695.
41. Feldmann, M.; Maini, R. N. *Annu. Rev. Immunol.* **2001**, *19*, 163.
42. Handel, M. L.; Nguyen, L. Q.; Lehmann, T. P. *Clin. Exp. Pharmacol. Physiol.* **2000**, *27*, 139.
43. Karin, M. *Proc. Am. Thorac. Soc.* **2005**, *2*, 386.
44. Sharma, V.; Lansdell, T. A.; Peddibhotla, S.; Tepe, J. J. *Chem. Biol.* **2004**, *11*, 1689.
45. Sharma, V.; Peddibhotla, S.; Tepe, J. J. *J. Am. Chem. Soc.* **2006**, *128*, 9137.
46. Kahlon, D. K.; Lansdell, T. A.; Fisk, J. S.; Hupp, C. D.; Friebe, T. L.; Hovde, S.; Jones, A. D.; Dyer, R. D.; Henry, R. W.; Tepe, J. J. *J. Med. Chem.* **2009**, *52*, 1302.
47. Sharma, V.; Tepe, J. J. *Org. Lett.* **2005**, *7*, 5091.
47. Sharma, V.; Tepe, J. J. *Org. Lett.* **2005**, *7*, 5091.
48. Peddibhotla, S.; Jayakumar, S.; Tepe, J. J. *Org. Lett.* **2002**, *4*, 3533.
49. Peddibhotla, S.; Tepe, J. J. *Synthesis* **2003**, *9*, 1433.
50. Fisk, J. S.; Mosey, R. A.; Tepe, J. J. *Chem. Soc. Rev.* **2007**, *36*, 1432.
51. Fiedler, M. A.; Wernke-Dollries, K.; Stark, J. M. *Am. J. Respir. Cell Mol. Biol.* **1998**, *19*, 259.
52. Pereira, S. G.; Oakley, F. *Int. J. Biochem. Cell Biol.* **2007**.
53. Luo, G.; Hershko, D. D.; Robb, B. W.; Wray, C. J.; Hasselgren, P. O. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **2003**, *284*, R1249.