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Original article

Synthesis, optimization and structure–activity relationships of 3, 5-disubstituted isoxazolines as new anti-tuberculosis agents

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Abstract

In the course of the development of a potent series of nitrofuranylamide anti-tuberculosis agents, we investigated if the exceptional activity resulted in part from the isoxazoline core and if it possessed any intrinsic anti-tuberculosis activity. This led to the discovery of an isoxazoline ester with appreciable anti-tuberculosis activity. In this study we explored the anti-tuberculosis structure–activity relationship of the isoxazoline ester compound through systematic modification of the 3,5-di-substituted isoxazoline core. Two approaches were used: (i) modification of the potentially metabolically labile ester functionality at the 3 position with acids, amines, amides, reverse amides, alcohols, hydrazides, and 1,3,4-oxadiazoles; (ii) substitution of the distal benzyl piperazine ring in the 5 position of the isoxazoline ring with piperazyl-ureas, piperazyl-carbamates, biaryl systems, piperidines and morpholine. Attempts to replace the ester group at C-3 position of isoxazoline with a variety of bioisosteric head groups led to significant loss of the tuberculosis inhibition indicating that an ester is required for anti-tuberculosis activity. Optimization of the isoxazoline C-5 position produced compounds with improved anti-tuberculosis activity, most notably the piperazyl-urea and piperazyl-carbamate analogs.

Keywords: Anti-tuberculosis agents; Antibacterial; Nitrofurans; Isoxazolines; Lead optimization

1. Introduction

Tuberculosis is caused by *Mycobacterium tuberculosis*, a deadly obligate bacterial pathogen. The global effect of tuberculosis is immense [1,2]. According to the World Health Organization, currently one-third of world's population is infected with latent tuberculosis [3]. Based on the trend over the past few years, a total of 225 million new cases and 79 million deaths are expected from tuberculosis between 1998 and 2030. The major concerns for current tuberculosis treatment are its latency, co-infection with HIV, poor patient compliance, and drug resistance issues caused by the emergence of multi-drug resistant tuberculosis (MDR-TB) and the recent advent of extensively drug resistant tuberculosis (XDR-TB) [4]. Most of the drugs in the current tuberculosis regime result from research performed over 50 years ago [5]. At that time with the successful introduction of those agents it was widely believed that tuberculosis could be eliminated and this led to significant underinvestment in the development of new therapeutics to treat tuberculosis for many decades [6]. Today more people die from tuberculosis than ever before, and this has catalyzed a renewed effort to develop improved therapies [7]. Hence, there is an urgent need to develop potent and fast acting anti-tuberculosis drugs with new modes of action to overcome the cross-resistance with current drugs and low toxicity profiles that can be tolerated for long treatment periods required for tuberculosis chemotherapy.

In an ongoing effort to develop novel anti-tuberculosis therapeutics, previously, we reported a series of nitrofuranyl compounds with potent inhibitory activity against *M. tuberculosis* [8–11]. The outstanding *in vitro* activity of *Lee-878* from this series led us to explore if the isoxazoline core was itself

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privileged and if it had any intrinsic anti-tuberculosis activity. A series of non-nitrofuran isoxazolines were subsequently synthesized in which the nitrofuran head group was systematically replaced. This led to the discovery of isoxazoline ester **1**, which showed appreciable anti-tuberculosis activity (MIC: 1.56 μg/mL) (Fig. 1) [12]. Excitingly, this represents a new synthetically tractable anti-tuberculosis chemotype that has not been previously reported. The study described herein concerns our efforts to optimize this hit to increase its metabolic stability and to explore the structural similarity with the oxazolidinone class of antibiotics including linezolid [13–15]. The outline of the approach is displayed in Fig. 1, and features systematic modification and optimization of the isoxazoline ring to replace the 3 position with bioisosteric head groups and the 5 position with modified piperazyl C-rings.

2. Chemistry

2.1. Modifications of the C-5 side chain of the isoxazoline ring

Four series of *C*-5 analogs were synthesized as described in Schemes 1 and 2. Our first target was the synthesis of a set of compounds possessing varying substitutions to the piperazine C-ring of lead compound **1**. *N*-Boc protected phenyl piperazine **4** was synthesized from 4-bromo styrene **2** and Boc-piperazine **3** using standard aromatic amination reaction conditions in 58% yield (Scheme 1) [16]. Olefin **4** was treated with commercially available oxime **5** in the presence of Et_3N in dichloromethane at room temperature to afford isoxazoline **6** following a [3 + 2] regioselective cycloaddition mechanism in 71% yield [17]. The deprotection of Boc protected compound **6** was achieved by treating with trifluoroacetic acid in THF at room temperature to give **7** in quantitative yield. Compound **7** was used as a key intermediate for the synthesis of several derivatives. Disubstituted urea derivatives **8a–e** were synthesized by treating free amine **7** with a variety of alkyl and aryl isocyanates in greater than 80% yields. A set of carbamate derivatives **9a–e** were then synthesized from amine **7** by reaction with the corresponding alkyl chloroformates also in 70–89% yields. *N*-Alkylated derivatives **10a–d** were synthesized from amine **7** by reaction with alkyl halides in moderate yields (48–58%).

For the second series of analogs, the piperazine C-ring was completely replaced with a series aryl rings (Scheme 2, I). The required biaryl systems were synthesized using the Suzuki chemistry. 4-Bromo styrene **2** was treated with a variety of aryl boronic acids in the presence of $Pd(PPh_3)_4$ using 1 M aqueous K_2CO_3 solution in DME at reflux to afford corresponding biaryl compounds **14a–d** in 61–73% yields. These substituted olefins were then reacted to form their corresponding isoxazoline derivatives **15a–d** using identical synthetic conditions described for the synthesis of compound **6**.

For the third series of analogs, the piperazine C-ring was substituted with a piperidine system (Scheme 2, II). These analogs were synthesized using the same aryl amination reaction conditions as described earlier for the synthesis of piperazine analog **4**. Compounds **16a** and **16b** were prepared by nucleophilic aromatic amination of **2** with 4-(4-trifluoromethoxy-phenoxy)-piperidine and piperidine in 78% and 71% yields, respectively. The isoxazoline ring was then constructed on these cores using standard chemistries to afford the target compounds **17a** and **17b** in 74% and 77% yields, respectively.

For the fourth series of analogs, the piperazine C-ring was replaced with heteroaryl oxadiazole rings (Scheme 2, III). The synthetic approach to this series utilized the synthetic utility of phenyl substituted cyano group as a synthon for introduction of heteroaryl rings [18]. Accordingly, 4-cyano styrene was treated with hydroxylamine hydrochloride in ethanol in the presence of Et_3N to produce amidine intermediate **18**. Amidine **18** was treated with triethyl orthoformate and a catalytic amount of boron trifluoride diethyl ether at 80 °C to give 3-phenyl 1,2,4-oxadiazole derivative **19a** in 59% yield. Amidine **18** was treated with benzoyl chloride in pyridine at reflux temperature to afford 3,5-disubstituted 1,2,4-oxadiazole derivative **19b** in 48% yield. The olefin moiety in both **19a** and **19b** was used for the synthesis of isoxazoline derivatives **20a** and **20b**, respectively, using standard procedures in 59% and 60% yields.

2.2. Modifications on C-3 side chain of isoxazoline ring

Synthetic modification to the C-3 side chain ester of the isoxazoline ring in **1** was approached by the synthesis of three

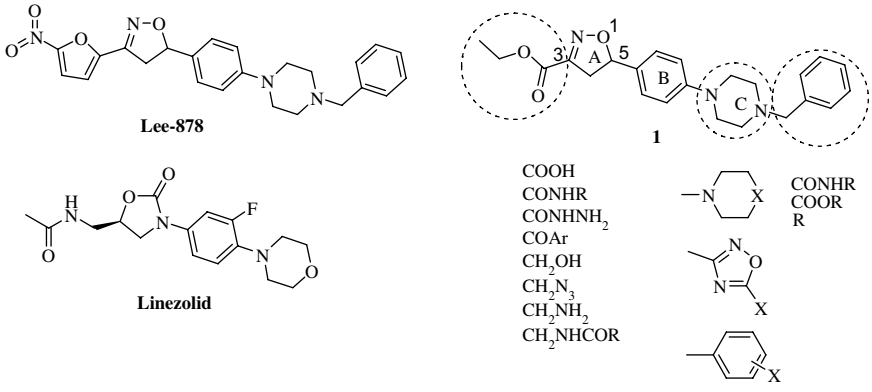
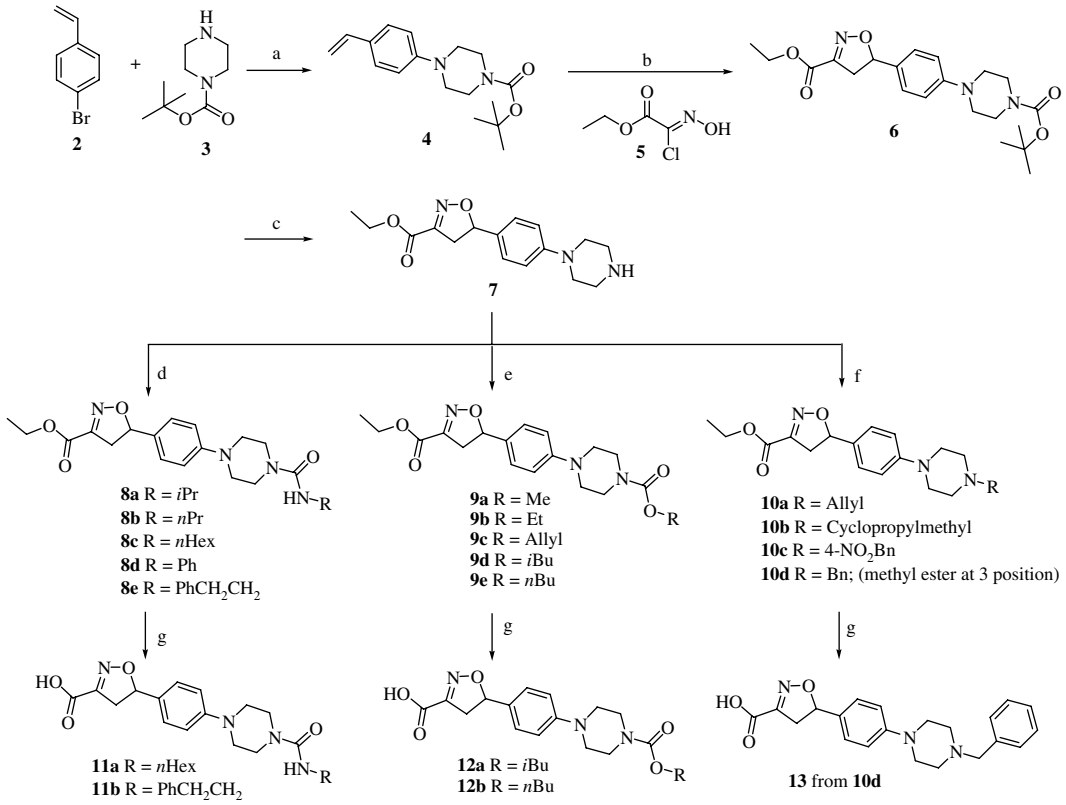
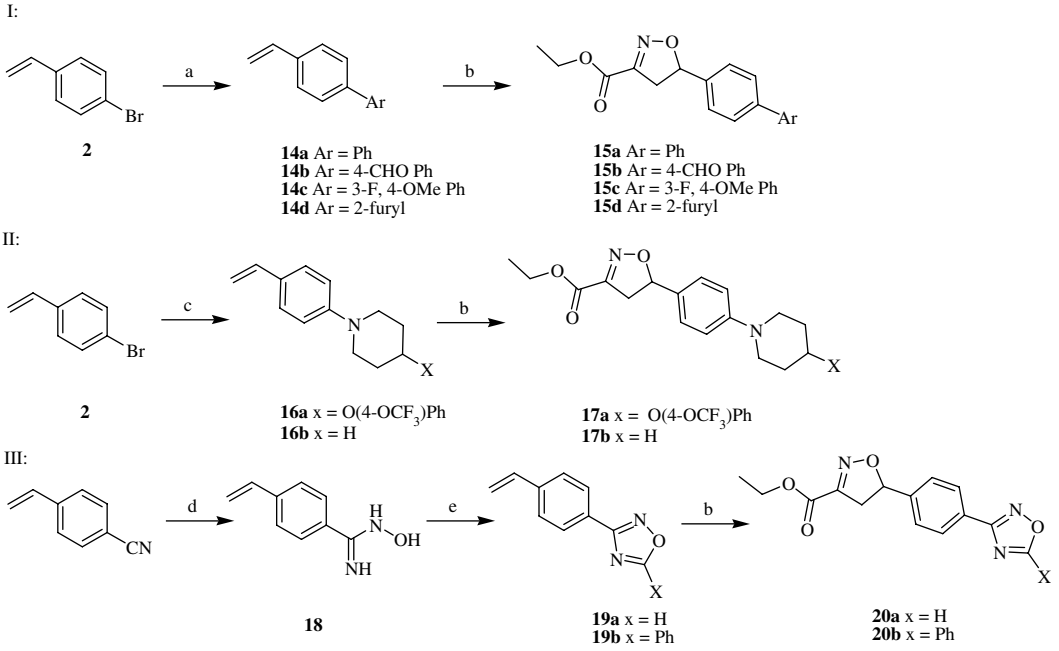


Fig. 1.



Scheme 1. Reagents and conditions: (a) $PdCl_2[P(o\text{-Tol})_3]_2$, NaO*t*Bu, toluene, 100 °C; (b) Et_3N, CH_2Cl_2; (c) TFA, THF, rt; (d) Et_3N, RNCO, CH_2Cl_2, rt; (e) Et_3N, ROCOCl, CH_2Cl_2, rt; (f) K_2CO_3, RBr, DMF; (g) LiOH, THF/H_2O, rt.

series of compounds with acid, amine, amide, reverse amide, alcohol, hydrazide, and 1,3,4-oxadiazole substitutions at the 3 position. The rationale for these substitutions was to use a bioisosteric approach and synthesize derivatives with increased metabolic stability over labile ester functionality of **1** while retaining a similar pattern of heteroatoms. For the first series, free acids with a variety of 5 position substitutions were generated by hydrolysis of the esters **8c**, **8e**, **9d**, **9e** and **10d**, using



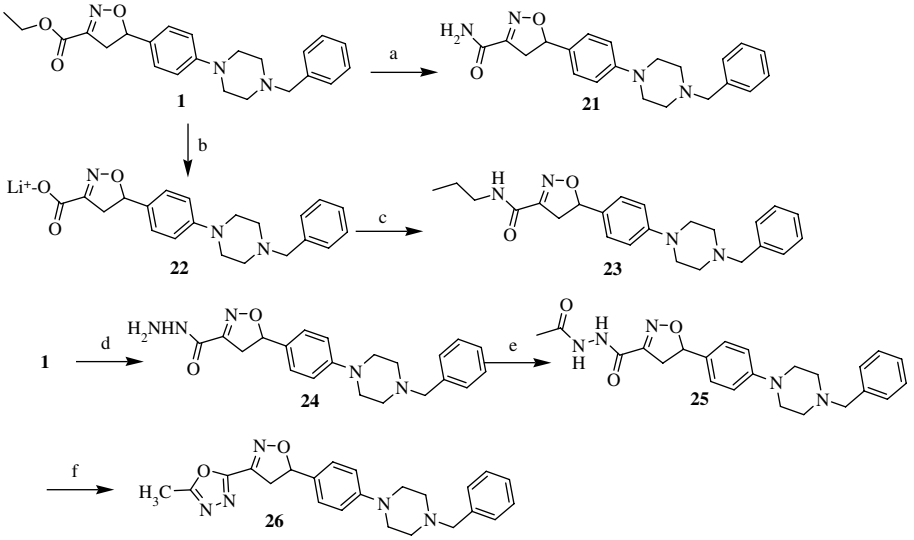
Scheme 2. Reagents and conditions: (a) aryl boronic acid, $Pd(Ph_3P)_4$, 1 M aqueous K_2CO_3, DME, reflux; (b) ethyl chlorooximido acetate, Et_3N, CH_2Cl_2, rt; (c) 4-(4-trifluoromethoxy-phenoxy)-piperidine or piperidine, NaO*t*Bu, $PdCl_2[(o\text{-Tol})_3P]_2$, toluene, reflux; (d) $NH_2OH\cdot HCl$, Et_3N, EtOH, reflux; (e) $CH(OEt)_3$, $BF_3\cdot OEt_2$, reflux or PhCOCl, Py, reflux.

LiOH, in aqueous THF at room temperature to afford the corresponding free acids **11a**, **11b**, **12a**, **12b** and **13** in 62–93% yields (Scheme 1). For the second series, modifications to the C-3 side chain were carried out keeping the isoxazoline 5 position unaltered as found in compound **1**. The ester functionality in **1** was converted into amide **21** in 66% yield by treating with ammonium hydroxide in 1,4-dioxane at room temperature (Scheme 3). Propyl amide **23** was synthesized by hydrolysis of **1**, followed by activation of the resulting free acid *in situ* as acid chloride and coupling to *n*-propyl amine in THF in 59% overall yield. The hydrazide derivative **24** was synthesized by treating the ester with hydrazine hydrate in ethanol at reflux temperature in 52% yield. Then **24** was used to construct a 1,3,4-oxadiazole ring at C-3 position of isoxazoline ring. Accordingly, diacyl hydrazine **25** was synthesized from **24** by treatment with acetyl chloride in dichloromethane using Et_3N as a base in 61% yield. Subsequent treatment of **25** with *p*-TsCl, Et_3N in dichoromethane and 40% aqueous K_2CO_3 sequentially afforded 2,5-disubstituted 1,3,4-oxadiazole analog **26** in 58% yield.

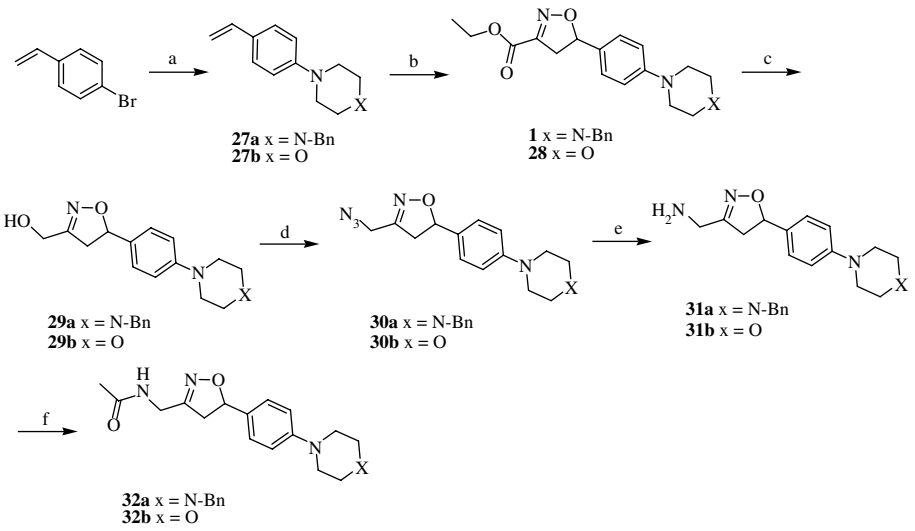
For the third series, free amines and reverse amides were substituted on the C-3 side chain of the isoxazoline ring producing compounds with structural resemblance to the oxazolidinone class of antibiotics. The esters in isoxazoline derivatives **1** and **28**, with C-5 *N*-benzyl piperazine and morpholine moieties, respectively, were reduced into the corresponding primary alcohols **29a** and **29b** by DIBAL-H in THF at 0 °C in 56% and 60% yields. The primary alcohols **29a** and **29b** were then converted into their azides **30a** and **30b** by treating with CBr_4, Ph_3P and NaN_3 in DMF at room temperature in 59% and 61% yields, followed by reduction with Ph_3P in 1,4-dioxane to yield primary amines **31a** and **31b** in 67% and 60% yields. Amines **31a** and **31b** were finally treated with acetyl chloride using Et_3N in CH_2Cl_2 to afford acetamides **32a** and **32b** in 78% and 71% yields (Scheme 4).

3. Anti-tuberculosis activity

All compounds synthesized with the complete isoxazoline moiety were tested against *M. tuberculosis* ($H_{37}Rv$) using microbroth dilution and MIC values were determined by visual inspection [19]. The anti-tuberculosis activities of the new isoxazolines esters bearing varying substitutions to the phenyl B in the C-5 position are shown in Table 1. Compounds with a piperazyl-urea substitution **8a–e** displayed varying anti-tuberculosis activity with MICs ranging from 0.4 to 25 μg/mL. Those with simple substitutions of *i*-propyl **8a** (12.5 μg/mL) and *n*-propyl **8b** (25 μg/mL) were least active with anti-tuberculosis activity inferior to the original hit compound **1** (1.56 μg/mL). Most active in this series were *n*-hexyl **8c** (0.4 μg/mL) and phenethyl **8e** (0.8 μg/mL), which had better MIC values than that of **1**. Compounds in the piperazyl-carbamate series **6** and **9a–e** all demonstrated equal or 1-fold more potent anti-tuberculosis activity than the lead compound **1**. In a comparative analysis it was notable that the pharmacologically more desirable and smaller side chains were much better tolerated in the carbamate series than the urea series (e.g., **9c** and **9d** over **8a** and **8b**). In the alkylated piperazine series **10a–d** and **1**, larger lipophilic substituents were clearly favored by comparing **1**, **10c** and **10d** over **10a** and **10b**. Ethyl ester lead compound **1** and it's methyl ester **10d** had the same MIC value (1.56 μg/mL). For the biphenyl systems **15a–c**, functionalization of the outer phenyl ring was required for appreciable anti-tuberculosis activity and in general activity of this series was lower than that of the previous carbamate series. The biheteroaryl series **15d**, **20a**, and **20b** showed that a furan substitution **15d** was significantly favored over the isosteric oxadiazole ring **20a** and phenyl substitution of the oxadizole ring **20b** restored similar activity to that of furan **15d**. *para*-Substitution of the *C*-5 phenyl with nitrogen-containing alkyl rings produced piperazine compound **7** with



Scheme 3. Reagents and conditions: (a) NH_4OH, 1,4-dioxane, 12 h, rt; (b) LiOH, H_2O/THF; (c) (i) $(COCl)_2$, DCM, cat. DMF; (ii) *n*-$PrNH_2$, THF; (d) $NH_2NH_2 \cdot H_2O$, EtOH, reflux; (e) CH_3COCl, Et_3N, CH_2Cl_2, rt; (f) (i) *p*-$TsCl_2$, Et_3N, CH_2Cl_2, reflux; (ii) 40% K_2CO_3.



Scheme 4. Reagents and conditions: (a) morpholine or 1-benzyl piperazine, NaO*t*Bu, $PdCl_2[(o\text{-Tol})_3P]_2$, toluene, reflux; (b) ethyl chlorooximido acetate, Et_3N, CH_2Cl_2, rt; (c) DIBAL-H, THF, 0 °C; (d) CBr_4, Ph_3P, NaN_3, DMF, rt; (e) Ph_3P, 1,4-dioxane; (f) CH_3COCl, Et_3N,CH_2Cl_2, rt.

limited activity and morpholine compound **28** with no activity. In this series, the simple piperidine derivative **17b** was the most active and it was notably more active than the more complex and lipophilic 4-(4-trifluoromethoxy-phenoxy)-piperidine substitution **17a** that resembles the side chain found in the new anti-tuberculosis agent OPC-68638 [20].

The anti-tuberculosis activity for the optimization of *C*-3 isoxazoline ester position is shown in Table 2. Hydrolysis of the esters to free acids **11a**, **11b**, **12a**, **12b**, **13**, and **22** led to a complete loss in activity when compared to their corresponding esters **8c**, **8e**, **9d**, **9e**, **10d**, and **1** regardless of C-5 substitution. The loss of activity is likely attributed to poor cell membrane penetration. Ester bioisosteric replacements such as primary amide **21**, *n*-propyl amide **23**, hydrazide **24** and 1,3,4-oxadiazole **26** were also largely inactive. Potential metabolite alcohols **29a** and **29b** were inactive when compared to the corresponding esters. Finally, azides **30a**, **30b**, primary amines **31a**, **31b** and reverse amides **32a**, **32b** that mimic linezolid functionalization also had negligible anti-tuberculosis activity. These findings strongly suggest that an ester functionality at the C-3 position of isoxazoline ring is absolutely required for anti-tuberculosis activity in this series.

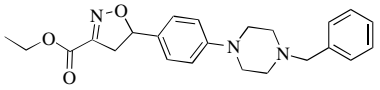
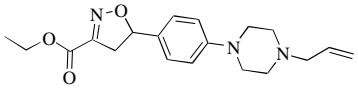
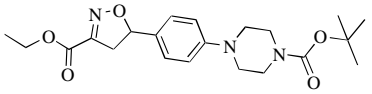
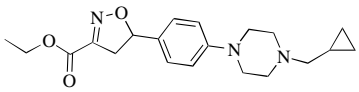
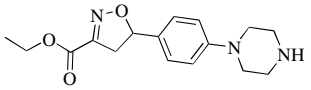
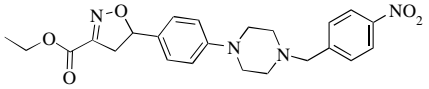
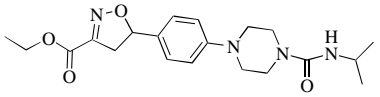
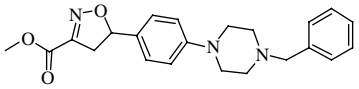
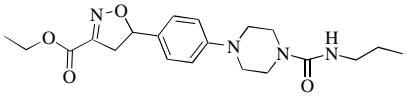
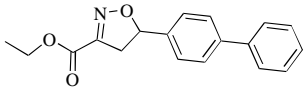
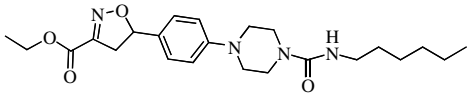
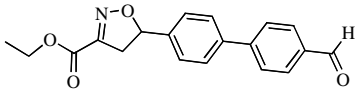
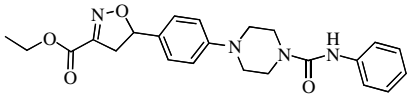
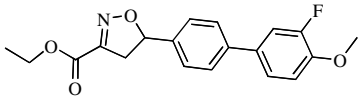
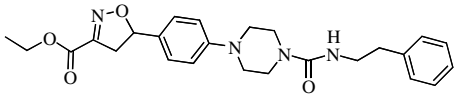
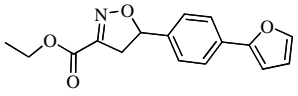
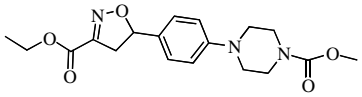
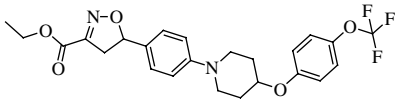
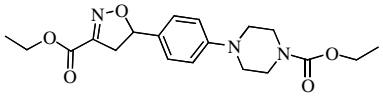
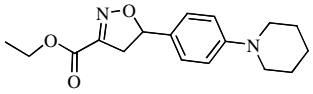
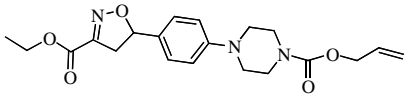
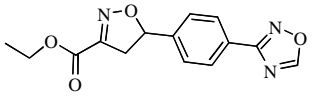
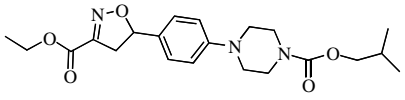
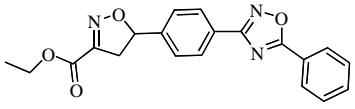
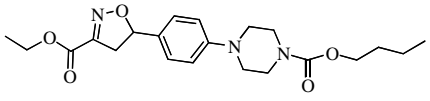
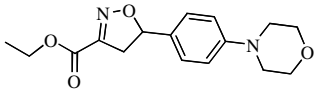
4. Conclusions

There is a clear need to develop novel anti-tuberculosis agents that are chemically tractable and possess drug-like properties. In this study a new interesting chemotype with anti-tuberculosis activity was examined. Optimization of the isoxazoline C-5 position produced compounds with improved anti-tuberculosis activity, including most notably urea analog (**8c**) and carbamates (**9c–e**). Attempts to replace the metabolically labile ester group at the C-3 position of isoxazoline with a variety of bioisosteric head groups led to complete loss of the tuberculosis inhibition. This is unfortunate because the serum stability for these esters is extremely short, precluding the advancement of this class for testing of their efficacy in animal models of tuberculosis. Presumably, the active compounds are taken up as esters by the tubercle bacilli *in vitro* and then hydrolyzed to active free acids once the compounds are internalized in the bacteria. The free acids of the corresponding active esters are presumably inactive *in vitro* as they cannot penetrate the complex *M. tuberculosis* cell wall, perhaps in part due to their residual negative charge. The structural resemblance of this series to the oxazolidinone class of antibiotics was also explored through the synthesis of reverse amides **32b** with high structural similarity to linezolid (Fig. 1). However, **32b** was inactive in contrast to linezolid, which has good anti-tuberculosis activity [21]. This suggests that this series of compounds works through a different mechanism of action, a hypothesis that is further supported by the lack of antimicrobial activity of these compounds against other bacteria including *Staphylococcus aureus, Streptococcus pneumoniae and Escherichia coli*.

5. Experimental

All the anhydrous solvents and starting materials were purchased from Aldrich Chemical Co. (Milwaukee, WI). All reagent grade solvents used for chromatography were purchased from Fisher Scientific (Suwanee, GA) and flash column chromatography silica cartridges were obtained from Biotage Inc. (Lake Forest, VA). The reactions were monitored by thin-layer chromatography (TLC) on precoated Merck 60 F_{254} silica gel plates and visualized using UV light (254 nm). A Biotage FLASH column chromatography system was used to purify mixtures. All ^{1}H NMR spectra were recorded on a Varian INOVA-500 spectrometer. Chemical shifts (δ) are reported in parts per million relative to the residual solvent peak or internal standard (tetramethylsilane), and coupling constants (J) are reported in hertz (Hz). Mass

Table 1
In vitro anti-tuberculosis activity of *C*-5 modified isoxazoline ester analogs

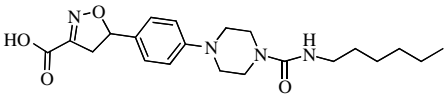
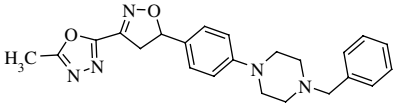
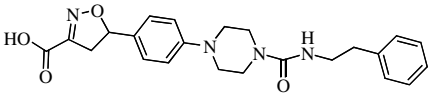
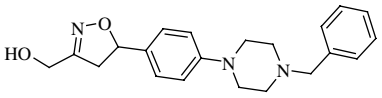
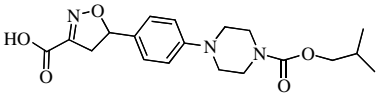
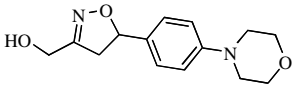
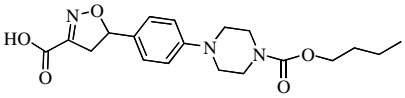
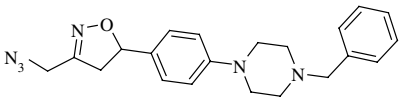
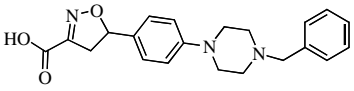
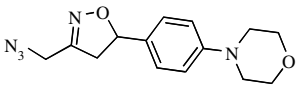
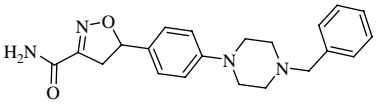
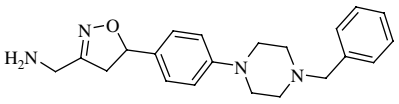
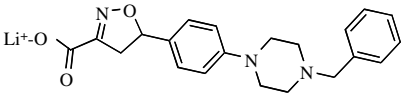
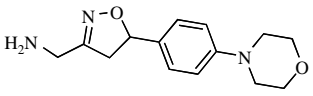
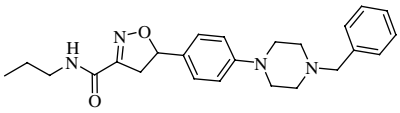
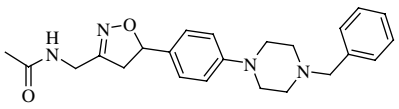
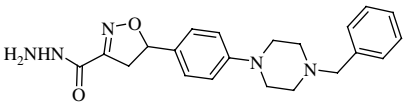
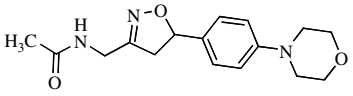
Compd	Structure	MIC (μg/mL)	Compd	Structure	MIC (μg/mL)
1		1.56	**10a**		6.25
6		0.8	**10b**		12.5
7		50	**10c**		0.8
8a		12.5	**10d**		1.56
8b		25	**15a**		100
8c		0.4	**15b**		6.25
8d		6.25	**15c**		3.125
8e		0.8	**15d**		3.25
9a		1.56	**17a**		25
9b		1.56	**17b**		6.25
9c		0.8	**20a**		50
9d		0.8	**20b**		3.125
9e		0.8	**28**		>200

spectra were recorded on a Bruker Esquire LCMS using ESI. Purity of the products was confirmed before testing by analytical RP-HPLC on Shimadzu HPLC system. *Gradient conditions*. solvent A (0.1% TFA in water) and solvent B (acetonitrile): 0–2.00 min 100% A, 2.00–7.00 min 0–100% B (linear gradient), 7.00–8.00 min 100% B, UV detection at 254 nm.

5.1. General procedure for aryl amination reactions

A mixture of 4-bromo styrene (1 mmol), amine (1.3 mmol), NaO*t*Bu (1.5 mmol) and $PdCl_2[P(o\text{-}Tol)_3]_2$ (0.03 mmol) in toluene was heated to reflux for 4 h. The solvent was evaporated under reduced pressure and the crude residue was purified by flash chromatography.

Table 2
In vitro anti-tuberculosis activity of *C*-3 modified isoxazoline analogs

Compd	Structure	MIC (μg/mL)	Compd	Structure	MIC (μg/mL)
11a		>200	**26**		200
11b		>200	**29a**		200
12a		>200	**29b**		>200
12b		>200	**30a**		50
13		>200	**30b**		200
21		200	**31a**		200
22		100	**31b**		>200
23		200	**32a**		>200
24		50	**32b**		>200

5.2. Representative aryl amination

5.2.1. 4-(4-Vinyl-phenyl)-piperazine-1-carboxylic acid tert-butyl ester (*4*)

A mixture of 4-bromo styrene (1.0 g, 5.46 mmol), 1-Boc-piperazine (1.32 g, 7.10 mmol), sodium *tert*-butoxide (0.78 g, 8.19 mmol) and $PdCl_2[P(o\text{-}Tol)_3]_2$ (0.12 g, 0.16 mmol) was heated in anhydrous toluene (20 mL) at 100 °C under argon for 3 h. The reaction mixture was then concentrated under reduced pressure and subjected to flash column chromatography to give **4** (0.91 g) in 58% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.51 (9H, s), 3.18 (4H, s), 3.61 (4H, s), 5.13 (1H, d, $J = 10.7$ Hz), 5.63 (1H, d, $J = 17.5$ Hz), 6.67 (1H, dd, $J = 10.9$, 17.5 Hz), 6.88–6.95 (2H, br d), 7.36 (2H, d, $J = 8.7$ Hz); ESI MS: 311.8 (M + 23).

5.3. General procedure for the synthesis of isoxazoline derivatives

To a cooled (0 °C) solution of olefin (1 mmol) and Et_3N (2 mmol) in CH_2Cl_2, ethyl chlorooximido acetate (1.5 mmol) was added in portions and stirred at room temperature overnight. The reaction mixture was washed with water, brine, dried (anhyd. Na_2SO_4), concentrated under reduced pressure and crude products were purified by flash chromatography.

5.3.1. 4-[4-(3-Ethoxycarbonyl-4,5-dihydro-isoxazol-5-yl)-phenyl]-piperazine-1-carboxylic acid tert-butyl ester (*6*)

To a stirred solution of olefin **4** (0.8 g, 2.77 mmol) in CH_2Cl_2 (10 mL), Et_3N (0.77 mL, 5.55 mmol) and ethyl chlorooximido acetate (0.631 g, 4.16 mmol) were added at 0 °C and stirred at room temperature overnight. The reaction mixture was diluted with excess CH_2Cl_2 (20 mL) and washed with water (20 mL), dried (anhyd. Na_2SO_4), concentrated under reduced pressure and the crude residue was purified by flash chromatography to afford **6** (0.788 g) in 71% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.39 (3H, t, $J = 7.1$ Hz), 1.49–1.51 (9H, s), 3.13–3.27 (5H, m), 3.52–3.65 (5H, m), 4.38 (2H, q, $J = 7.1$ Hz), 5.72 (1H, dd, $J = 9.3$, 11.4 Hz), 6.92 (2H, d, $J = 8.7$ Hz), 7.24 (2H, d, $J = 8.7$ Hz). ESI MS: 426.3 (M + Na); HPLC purity: 97%, $t_R = 6.6$ min.

*5.3.2. 5-(4-Piperazin-1-yl-phenyl)-4,5-dihydro-isoxazole-3-carboxylic acid ethyl ester (**7**)*

A solution of **6** (0.8 g, 1.98 mmol) in THF/TFA (1:1, 10 mL) was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure to give **7** (0.552 g) in 92% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.41 (3H, t, $J = 7.1$ Hz), 3.22 (1H, dd, $J = 9.0$, 17.8 Hz), 3.34–3.42 (4H, br s), 3.43–3.52 (4H, br s), 3.62 (1H, dd, $J = 11.5$, 17.8 Hz), 4.39 (2H, q, $J = 7.1$ Hz), 5.75 (1H, dd, $J = 9.3$, 11.5 Hz), 6.95 (2H, d, $J = 8.8$ Hz), 7.29 (2H, d, $J = 8.5$ Hz), 9.62 (2H, br s); ^{13}C NMR (500 MHz, $CDCl_3$): δ 14.15, 41.08, 43.41, 46.71, 62.24, 84.83, 117.31, 127.45, 132.28, 150.23, 151.26, 160.65; ESI MS: 304.2 (M + 1); HPLC purity: 98%, $t_R = 4.7$ min.

5.4. General procedure for the synthesis of urea and carbamate derivatives

Piperazine TFA salt **7** (1 mmol) was dissolved in anhydrous dichloromethane, and then triethylamine (4 mmol) was added, followed by isocyanate or chloroformate (3 mmol). The reaction mixture was stirred at room temperature overnight and evaporated. The residue was purified by column chromatography.

*5.4.1. 5-[4-(4-Isopropylcarbamoyl-piperazin-1-yl)-phenyl]-4,5-dihydro-isoxazole-3-carboxylic acid ethyl ester (**8a**)*

Yield: 91.1%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.20 (6H, d, $J = 6.6$ Hz), 1.41 (3H, t, $J = 7.1$ Hz), 3.21–3.26 (5H, m), 3.53–3.63 (5H, m), 4.02 (1H, m), 4.29 (1H, d, $J = 6.6$ Hz), 4.39 (2H, q, $J = 7.1$ Hz), 5.74 (1H, dd, $J = 9.0$, 11.2 Hz), 6.95 (2H, d, $J = 8.3$ Hz), 7.27 (2H, d, $J = 8.5$ Hz); ^{13}C NMR (500 MHz, $CDCl_3$): δ 14.17, 23.49, 40.96, 42.71, 43.44, 48.92, 62.17, 85.07, 116.45, 127.36, 151.23, 156.97, 160.73; ESI MS: 411.3 (M + Na); HPLC purity: 99%, $t_R = 5.6$ min.

*5.4.2. 5-[4-(4-Propylcarbamoyl-piperazin-1-yl)-phenyl]-4,5-dihydro-isoxazole-3-carboxylic acid ethyl ester (**8b**)*

Yield: 97.8%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.93 (3H, t, $J = 7.1$ Hz), 1.38 (3H, t, $J = 7.1$ Hz), 1.49–1.60 (2H, m), 3.10–3.28 (7H, m), 3.46–3.64 (5H, m), 4.37 (2H, q, $J = 7.1$ Hz), 4.55 (1H, br s), 5.71 (1H, t, $J = 10.0$ Hz), 6.90 (2H, d, $J = 8.1$ Hz), 7.23 (2H, d, $J = 8.1$ Hz); ^{13}C NMR (500 MHz, $CDCl_3$): δ 11.42, 14.17, 23.46, 40.92, 42.71, 43.60, 48.71, 62.15, 85.16, 116.22, 127.34, 130.31, 151.23, 151.33, 157.71, 160.74; ESI MS: 411.3 (M + Na); HPLC purity: 100%, $t_R = 5.6$ min.

*5.4.3. 5-[4-(4-Hexylcarbamoyl-piperazin-1-yl)-phenyl]-4,5-dihydro-isoxazole-3-carboxylic acid ethyl ester (**8c**)*

Yield: 100%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.91–0.97 (3H, t), 1.22–1.41 (9H, m), 1.40–1.58 (2H, m), 3.16–3.27 (7H, m), 3.48–3.61 (5H, m), 4.36 (2H, q, $J = 7.1$ Hz), 4.58 (1H, t), 5.71 (1H, dd, $J = 9.5$, 11.0 Hz), 6.90 (2H, d, $J = 8.5$ Hz), 7.23 (2H, d, $J = 8.8$ Hz); ^{13}C NMR (300 MHz, $CDCl_3$): δ 13.45, 13.58, 22.01, 26.08, 29.69, 31.01, 40.35, 40.50, 43.07, 48.15, 61.52, 84.57, 115.63, 126.74, 129.74, 150.66, 150.78, 157.17, 160.16; ESI MS: 453.3 (M + Na); HPLC purity: 98%, $t_R = 6.4$ min.

*5.4.4. 5-[4-(4-Phenylcarbamoyl-piperazin-1-yl)-phenyl]-4,5-dihydro-isoxazole-3-carboxylic acid ethyl ester (**8d**)*

Yield: 95.5%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.37 (3H, t, $J = 7.1$ Hz), 3.17–3.26 (5H, m), 3.54–3.66 (5H, m), 4.36 (2H, q, $J = 7.1$ Hz), 5.71 (1H, dd, $J = 9.3$, 11.5 Hz), 6.67 (1H, s), 6.89 (2H, d, $J = 8.5$ Hz), 7.04 (1H, t, $J = 7.3$ Hz), 7.24 (2H, t, $J = 8.8$ Hz), 7.28 (2H, m), 7.37 (2H, d, $J = 7.6$ Hz); ^{13}C NMR (300 MHz, $CDCl_3$): δ 13.59, 40.36, 43.36, 48.16, 61.57, 84.57, 115.68, 119.63, 122.73, 126.78, 128.35, 129.87, 138.41, 150.65, 150.71, 154.54, 160.15; ESI MS: 445.2 (M + Na); HPLC purity: 96%, $t_R = 6.0$ min.

*5.4.5. 5-[4-(4-Phenethylcarbamoyl-piperazin-1-yl)-phenyl]-4,5-dihydro-isoxazole-3-carboxylic acid ethyl ester (**8e**)*

Yield: 82.6%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.38 (3H, t, $J = 7.1$ Hz), 2.85 (2H, t, $J = 6.8$ Hz), 3.17 (4H, t, $J = 5.1$ Hz), 3.21 (1H, dd, $J = 9.3$, 17.8 Hz), 3.47 (2H, t, $J = 4.9$ Hz), 3.52 (2H, q, $J = 6.6$ Hz), 3.57 (1H, dd, $J = 11.5$, 17.8 Hz), 4.37 (2H, q, $J = 7.3$ Hz), 4.48 (1H, t, $J = 5.4$ Hz), 5.71 (1H, dd, $J = 9.3$, 11.2 Hz), 6.89 (2H, d, $J = 8.8$ Hz), 7.19–7.25 (5H, m), 7.32 (2H, t, $J = 7.3$ Hz); ^{13}C NMR (500 MHz, $CDCl_3$): δ 13.59, 35.75, 40.36, 41.47, 43.01, 48.12, 61.53, 84.55, 115.65, 125.91, 126.74, 128.08, 128.30, 129.82, 138.76, 150.64, 150.74, 156.90, 160.18; ESI MS: 473.2 (M + Na); HPLC purity: 98%, $t_R = 6.1$ min.

*5.4.6. 4-[4-(3-Ethoxycarbonyl-4,5-dihydro-isoxazol-5-yl)-phenyl]-piperazine-1-carboxylic acid methyl ester (**9a**)*

Yield: 76.3%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.38 (3H, t, $J = 7.1$ Hz), 3.10–3.25 (5H, m), 3.53–3.67 (5H, m), 3.73 (3H, s), 4.37 (2H, q, $J = 7.1$ Hz), 5.71 (1H, dd, $J = 9.8$, 11.0 Hz), 6.91 (2H, d, $J = 8.5$ Hz), 7.24 (2H, d, $J = 8.3$ Hz); ^{13}C NMR (500 MHz, $CDCl_3$): δ 14.17, 40.93, 43.59, 49.01, 52.76, 62.15, 85.12, 116.54, 127.32, 130.54, 151.22, 151.48, 155.87, 160.74; ESI MS: 384.1 (M + Na); HPLC purity: 98%, $t_R = 5.8$ min.

*5.4.7. 4-[4-(3-Ethoxycarbonyl-4,5-dihydro-isoxazol-5-yl)-phenyl]-piperazine-1-carboxylic acid ethyl ester (**9b**)*

Yield: 89.1%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.27 (3H, t), 1.38 (3H, t), 3.16 (4H, t, $J = 4.9$ Hz), 3.21 (1H, dd, $J = 9.3$, 17.8 Hz), 3.57 (1H, dd, $J = 11.5$, 17.6 Hz), 3.63 (4H, t, $J = 4.9$ Hz), 4.17 (2H, q, $J = 7.1$ Hz), 4.37 (2H, q, $J = 7.1$ Hz), 5.71 (1H, dd, $J = 9.3$, 11.2 Hz), 6.91 (2H, d, $J = 8.8$ Hz), 7.24 (2H, d, $J = 8.8$ Hz); ^{13}C NMR (500 MHz, $CDCl_3$): δ 14.17, 14.70, 40.93, 43.51, 49.03, 61.56, 62.15, 85.14, 116.52, 127.32, 130.49, 151.22, 151.52, 155.49, 160.75; ESI MS: 398.3 (M + Na); HPLC purity: 96%, $t_R = 6.1$ min.

*5.4.8. 4-[4-(3-Ethoxycarbonyl-4,5-dihydro-isoxazol-5-yl)-phenyl]-piperazine-1-carboxylic acid allyl ester (**9c**)*

Yield: 69.6%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.38 (3H, t, $J = 7.1$ Hz), 3.12–3.28 (5H, m), 3.57 (1H, dd, $J = 11.5$, 17.8 Hz), 3.65 (4H, t, $J = 4.9$ Hz), 4.37 (2H, q, $J = 7.1$ Hz), 4.62 (2H, d, $J = 5.4$ Hz), 5.23 (1H, d, $J = 10.5$ Hz), 5.32 (1H, d, $J = 17.1$ Hz), 5.71 (1H, dd, $J = 9.5$, 11.0 Hz), 5.96 (1H, m), 6.92 (2H, d, $J = 8.5$ Hz), 7.24 (2H, d, $J = 8.3$ Hz); ^{13}C NMR (500 MHz, $CDCl_3$): δ 14.15, 40.91, 43.60, 49.01, 62.13, 66.19, 85.10, 116.52, 117.60, 127.30, 130.54, 132.93, 151.20, 151.45, 155.04, 160.72; ESI MS: 410.3 (M + Na); HPLC purity: 98%, $t_R = 6.3$ min.

*5.4.9. 4-[4-(3-Ethoxycarbonyl-4,5-dihydro-isoxazol-5-yl)-phenyl]-piperazine-1-carboxylic acid isobutyl ester (**9d**)*

Yield: 82.0%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.95 (6H, d, $J = 6.6$ Hz), 1.38 (3H, t, $J = 6.8$ Hz), 1.96 (1H, m), 3.12–3.27 (5H, m), 3.53–3.68 (5H, m), 3.90 (2H, d, $J = 6.6$ Hz), 4.37 (2H, q, $J = 6.8$ Hz), 5.71 (1H, dd, $J = 9.8$, 10.7 Hz), 6.92 (2H, d, $J = 8.1$ Hz), 7.24 (2H, d, $J = 8.3$ Hz); ^{13}C NMR (500 MHz, $CDCl_3$): δ 14.17, 19.14, 28.03, 40.93, 43.51, 49.02, 62.14, 71.71, 85.13, 116.51, 127.33, 130.50, 151.22, 151.50, 155.54, 160.74; ESI MS: 426.3 (M + Na); HPLC purity: 89%, $t_R = 6.6$ min.

*5.4.10. 4-[4-(3-Ethoxycarbonyl-4,5-dihydro-isoxazol-5-yl)-phenyl]-piperazine-1-carboxylic acid butyl ester (**9e**)*

Yield: 84.9%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.95 (3H, t, $J = 6.8$ Hz), 1.34–1.45 (5H, m), 1.60–1.68 (2H, m), 3.10–3.26 (5H, m), 3.53–3.68 (5H, m), 4.12 (2H, t, $J = 5.9$ Hz), 4.37 (2H, q, $J = 6.8$ Hz), 5.71 (1H, dd, $J = 10.0$, 10.3 Hz), 6.92 (2H, d, $J = 7.6$ Hz), 7.24 (2H, d, $J = 8.1$ Hz); ^{13}C NMR (500 MHz, $CDCl_3$): δ 13.81, 14.17, 19.22, 31.09, 40.93, 43.52, 49.02, 62.14, 65.50, 85.13, 116.51, 127.32, 130.49, 151.22, 151.51, 155.57, 160.74; ESI MS: 426.3 (M + Na); HPLC purity: 91%, $t_R = 6.7$ min.

5.5. General procedure for the synthesis of alkylated derivatives

Piperazine TFA salt **7** (1 mmol) was dissolved in anhydrous dimethylformamide, and then K_2CO_3 (3 mmol) and alkyl bromide (1.2 mmol) were added. The reaction mixture was stirred at room temperature overnight and evaporated, and the residue was purified by column chromatography on silica gel.

*5.5.1. 5-[4-(4-Allyl-piperazin-1-yl)-phenyl]-4,5-dihydro-isoxazole-3-carboxylic acid ethyl ester (**10a**)*

Yield: 48.3%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.38 (3H, t, $J = 7.3$ Hz), 2.60 (4H, t, $J = 5.1$ Hz), 3.06 (2H, d, $J = 6.6$ Hz), 3.18–3.25 (5H, m), 3.56 (1H, dd, $J = 11.5$, 17.6 Hz), 4.36 (2H, q, $J = 7.3$ Hz), 5.19 (1H, dd, $J = 0.7$, 10.0 Hz), 5.23 (1H, dd, $J = 1.7$, 17.3 Hz), 5.70 (1H, dd, $J = 9.5$, 11.5 Hz), 5.85–5.92 (1H, m), 6.91 (2H, d, $J = 8.8$ Hz), 7.22 (2H, d, $J = 8.8$ Hz); ^{13}C NMR (300 MHz, $CDCl_3$): δ 13.59, 40.28, 48.19, 52.38, 61.18, 61.49, 84.71, 115.26, 117.64, 126.68, 129.05, 134.26, 150.65, 151.10, 160.22; ESI MS: 366.3 (M + Na); HPLC purity: 98%, $t_R = 4.9$ min.

*5.5.2. 5-[4-(4-Cyclopropylmethyl-piperazin-1-yl)-phenyl]-4,5-dihydro-isoxazole-3-carboxylic acid ethyl ester (**10b**)*

Yield: 57.8%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.14 (2H, q, $J = 4.6$ Hz), 0.53–0.57 (2H, m), 0.86–0.94 (1H, m), 1.38 (3H, t, $J = 7.1$ Hz), 2.31 (2H, d, $J = 6.4$ Hz), 2.68 (4H, t, $J = 5.1$ Hz), 3.18–3.28 (5H, m), 3.56 (1H, dd, $J = 11.5$, 17.8 Hz), 4.36 (2H, q, $J = 7.1$ Hz), 5.70 (1H, dd, $J = 9.5$, 11.5 Hz), 6.92 (2H, d, $J = 8.8$ Hz), 7.22 (2H, d, $J = 8.8$ Hz); ^{13}C NMR (500 MHz, $CDCl_3$): δ 4.19, 8.59, 14.41, 41.06, 48.96, 53.38, 62.34, 64.02, 85.55, 116.05, 127.51, 129.79, 151.46, 151.96, 161.03; ESI MS: 380.2 (M + Na); HPLC purity: 96%, $t_R = 5.0$ min.

*5.5.3. 5-{4-[4-(4-Nitro-benzyl)-piperazin-1-yl]-phenyl}-4,5-dihydro-isoxazole-3-carboxylic acid ethyl ester (**10c**)*

Yield: 57.9%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.38 (3H, t, $J = 7.1$ Hz), 2.62 (4H, t, $J = 4.4$ Hz), 3.18–3.28 (5H, m), 3.56 (1H, dd, $J = 11.7$, 17.8 Hz), 3.65 (2H, s), 4.37 (2H, q, $J = 7.1$ Hz), 5.71 (1H, dd, $J = 9.8$, 10.7 Hz), 6.90 (2H, d, $J = 8.5$ Hz), 7.22 (2H, d, $J = 8.5$ Hz), 7.55 (2H, d, $J = 8.3$ Hz), 8.20 (2H, d, $J = 8.5$ Hz); ^{13}C NMR (500 MHz, $CDCl_3$): δ 14.41, 41.09, 49.03, 53.32, 62.37, 85.49, 116.17, 123.86, 127.54, 129.76, 130.07, 146.34, 151.47, 151.78, 161.02; ESI MS: 461.1 (M + Na); HPLC purity: 99%, $t_R = 5.3$ min.

*5.5.4. 5-[4-(4-Benzyl-piperazin-1-yl)-phenyl]-4,5-dihydro-isoxazole-3-carboxylic acid methyl ester (**10d**)*

Complete ester transformation occurred during the post-workup evaporation process in methanol. Yield: 61.2%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.60 (4H, t, $J = 4.2$ Hz), 3.18–3.26 (5H, m), 3.51–3.60 (3H, m), 3.90 (3H, s), 5.70 (1H, dd, $J = 10.0$, 10.7 Hz), 6.89 (2H, d, $J = 8.5$ Hz), 7.20 (2H, d, $J = 8.5$ Hz), 7.24–7.38 (5H, m); ^{13}C NMR (500 MHz, $CDCl_3$): δ 40.71, 48.75, 52.83, 52.97, 63.08, 85.45, 115.81, 127.20, 127.29, 128.32, 129.22, 129.39, 137.96, 150.98, 151.75, 161.21; ESI MS: 402.2 (M + Na); HPLC purity: 98%, $t_R = 5.0$ min.

5.6. General procedures for the synthesis of free acids

Ethyl ester (1 mmol) was dissolved in tetrahydrofuran/water (8 mL) and then lithium hydroxide hydrate (1 mmol) was added. The reaction mixture was stirred at room temperature for 3 h, the solvent was evaporated *in vacuo* at ambient temperature, and then H_2O (10 mL) was added and extracted with ethyl acetate (40 mL). The organic phase was washed with H_2O (3 × 10 mL), dried (anhyd. Na_2SO_4) and evaporated to give free acid. Acid **13** was obtained by the evaporation of the combined aqueous phases, analytical sample was obtained

as white powder after the solid residue was washed with minimum amount of ice-H_2O, filtered, and dried.

*5.6.1. 5-[4-(4-Hexylcarbamoyl-piperazin-1-yl)-phenyl]-4,5-dihydro-isoxazole-3-carboxylic acid (**11a**)*

Yield: 62.7%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.87 (3H, t, $J = 6.0$ Hz), 1.22–1.36 (6H, m), 1.46–1.54 (2H, m), 3.10–3.30 (7H, m), 3.48–3.64 (5H, m), 5.69 (1H, dd, $J = 9.5$, 9.8 Hz), 6.90 (2H, d, $J = 7.6$ Hz), 7.21 (2H, d, $J = 7.3$ Hz); ^{13}C NMR (500 MHz, $CDCl_3$): δ 14.09, 22.60, 26.62, 30.10, 30.34, 31.56, 34.25, 40.92, 41.22, 43.49, 48.96, 84.57, 116.57, 125.54, 127.37, 131.14, 135.79, 150.74, 158.18, 162.18; ESI MS: 425.3 (M + Na); HPLC purity: 98%, $t_R = 5.7$ min.

*5.6.2. 5-[4-(4-Phenethylcarbamoyl-piperazin-1-yl)-phenyl]-4,5-dihydro-isoxazole-3-carboxylic acid (**11b**)*

Yield: 86.0%; ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.74 (2H, t, $J = 7.5$ Hz), 3.08–3.15 (5H, m), 3.23–3.28 (2H, m), 3.43 (2H, t, $J = 5.0$ Hz), 3.57 (1H, dd, $J = 11.5$, 17.8 Hz), 5.68 (1H, dd, $J = 10.0$, 11.0 Hz), 6.73 (1H, t, $J = 5.4$ Hz), 6.78 (2H, d, $J = 8.8$ Hz); 7.18–7.32 (7H, m); ^{13}C NMR (500 MHz, DMSO-d_6): δ 36.49, 40.58, 40.84, 42.40, 43.67, 48.45, 84.87, 116.00, 126.43, 128.04, 128.76, 129.13, 130.14, 140.30, 151.59, 153.02, 157.77, 162.17; ESI MS: 445.1 (M + Na); HPLC purity: 98%, $t_R = 5.4$ min.

*5.6.3. 5-[4-(4-Isobutoxycarbonyl-piperazin-1-yl)-phenyl]-4,5-dihydro-isoxazole-3-carboxylic acid (**12a**)*

Yield: 92.6%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.95 (6H, d, $J = 6.6$ Hz), 1.91–2.00 (1H, m), 3.10–3.26 (5H, m), 3.50–3.72 (5H, m), 3.91 (2H, d, $J = 6.6$ Hz), 5.74 (1H, t, $J = 9.8$ Hz), 6.97 (2H, d, $J = 7.6$ Hz), 7.24 (2H, d, $J = 6.8$ Hz); ^{13}C NMR (500 MHz, $CDCl_3$): δ 19.12, 27.99, 30.35, 43.38, 49.47, 72.05, 85.80, 117.07, 125.54, 127.44, 131.36, 150.88, 155.82, 162.66; ESI MS: 376.3 (M + H); HPLC purity: 98%, $t_R = 5.8$ min.

*5.6.4. 5-[4-(4-Butoxycarbonyl-piperazin-1-yl)-phenyl]-4,5-dihydro-isoxazole-3-carboxylic acid (**12b**)*

Yield: 83.2%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.94 (3H, t, $J = 7.3$ Hz), 1.35–1.45 (2H, m), 1.60–1.68 (2H, m), 3.12–3.26 (5H, m), 3.51–3.72 (5H, m), 4.13 (2H, t, $J = 6.6$ Hz), 5.72 (1H, dd, $J = 9.3$, 9.5 Hz), 6.97 (2H, d, $J = 7.8$ Hz), 7.24 (2H, d, $J = 7.3$ Hz); ^{13}C NMR (500 MHz, $CDCl_3$): δ 13.79, 19.19, 30.35, 31.01, 40.70, 43.34, 49.49, 65.90, 85.55, 117.09, 127.42, 131.44, 150.82, 155.86, 162.64; ESI MS: 376.3 (M + H); HPLC purity: 99%, $t_R = 5.9$ min.

*5.6.5. 5-[4-(4-Benzyl-piperazin-1-yl)-phenyl]-4,5-dihydro-isoxazole-3-carboxylic acid (**13**)*

Yield: 61.9%; ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.83 (4H, br s), 3.30 (4H, overlapped with H_2O peak), 3.13 (1H, dd, $J = 9.8$, 17.8 Hz), 3.59 (1H, dd, $J = 11.2$, 17.8 Hz), 3.90 (2H, s), 5.71 (1H, dd, $J = 10.0$, 10.7 Hz), 6.99 (2H, d, $J = 8.5$ Hz), 7.27 (2H, d, $J = 8.5$ Hz), 7.36–7.52 (5H, m); ^{13}C NMR (300 MHz, DMSO-d_6): δ 40.36, 46.53, 51.29, 60.36, 84.23, 115.38, 127.48, 128.13, 128.42, 129.86, 130.04, 150.31, 152.46, 161.59; ESI MS: 366.3 (M + H); HPLC purity: 100%, $t_R = 4.8$ min.

*5.7. General procedure for the synthesis of biaryl compounds **14a–d** and isoxazoline compounds **15a–d***

A mixture of 4-bromo styrene (1 mmol), aryl boronic acid (1.1 mmol), $Pd(Ph_3P)_4$ (0.03 mmol) and 1 M K_2CO_3 solution in dimethoxy ethane was degassed, and purged with argon twice and heated to reflux overnight. The solvent was evaporated and ethyl acetate was added, the organic phase was washed with water, brine, dried (anhyd. Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by flash chromatography to afford biaryl compounds (**14a–d**) in 50–70% yields. These olefins were converted into the corresponding isoxazolines (**15a–d**) following the general procedure discussed earlier.

*5.7.1. 5-Biphenyl-4-yl-4,5-dihydro-isoxazole-3-carboxylic acid ethyl ester (**15a**)*

Yield: 72.6%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.39 (3H, t, $J = 7.0$ Hz), 3.27 (1H, dd, $J = 8.7$, 17.5 Hz), 3.66 (1H, dd, $J = 8.7$, 17.5 Hz), 4.37 (2H, q, $J = 7.0$ Hz), 5.83 (1H, dd, $J = 8.7$, 11.4 Hz), 7.34–7.46 (5H, m), 7.57–7.62 (4H, m); ESI MS: 296 (M + 1); HPLC purity: 98.6%, $t_R = 6.8$ min.

*5.7.2. 5-(4′-Formyl-biphenyl-4-yl)-4,5-dihydro-isoxazole-3-carboxylic acid ethyl ester (**15b**)*

Yield: 61%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.39 (3H, t, $J = 7.1$ Hz), 3.28 (1H, dd, $J = 8.8$, 17.5 Hz), 3.66 (1H, dd, $J = 8.7$, 17.5 Hz), 4.36 (2H, q, $J = 7.2$ Hz), 5.83 (1H, dd, $J = 8.7$, 11.4 Hz), 7.42–7.45 (2H, m), 7.59–7.67 (4H, m), 7.74 (1H, d, $J = 8.0$ Hz), 7.96 (1H, d, $J = 8.0$ Hz), 10.06 (1H, s); ESI MS: 346 (M + Na); HPLC purity: 99.2%, $t_R = 6.8$ min.

*5.7.3. 5-(3′-Fluoro-4′-methoxy-biphenyl-4-yl)-4,5-dihydro-isoxazole-3-carboxylic acid ethyl ester (**15c**)*

Yield: 70%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.39 (3H, t, $J = 7.3$ Hz), 3.25 (1H, dd, $J = 8.7$, 17.5 Hz), 3.66 (1H, dd, $J = 11.4$, 17.8 Hz), 3.93 (3H, s), 4.37 (2H, q, $J = 7.0$ Hz), 5.81 (1H, dd, $J = 8.7$, 11.4 Hz), 7.02 (1H, t, $J = 8.3$ Hz), 7.29–7.33 (2H, m), 7.38 (2H, d, $J = 8.3$ Hz), 7.54 (2H, d, $J = 8.3$ Hz); ESI MS: 366.1 (M + Na); HPLC purity: 99.0%, $t_R = 6.8$ min.

*5.7.4. 5-(4-Furan-2-yl-phenyl)-4,5-dihydro-isoxazole-3-carboxylic acid ethyl ester (**15d**)*

Yield: 58%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.38 (3H, t, $J = 7.0$ Hz), 3.22 (1H, dd, $J = 9.0$, 17.8 Hz), 3.64 (1H, dd, $J = 11.7$, 17.8 Hz), 4.36 (2H, q, $J = 6.3$ Hz), 5.78 (1H, dd, $J = 9.0$, 11.4 Hz), 6.47–6.48 (1H, m), 6.66 (1H, d, $J = 3.4$ Hz), 7.33 (2H, d, $J = 8.0$ Hz), 7.47 (1H, d, $J = 0.7$ Hz), 7.67 (2H, d, $J = 8.3$ Hz); ESI MS: 286.2 (M + 1); HPLC purity: 99.1%, $t_R = 6.6$ min.

*5.7.5. 5-{4-[4-(4-Trifluoromethoxy-phenoxy)-piperidin-1-yl]-phenyl}-4,5-dihydro-isoxazole-3-carboxylic acid ethyl ester (**17a**)*

Yield: 74.3%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.38 (3H, t, $J = 7.3$ Hz), 1.89–1.95 (2H, m), 2.06–2.11 (2H, m), 3.12–3.16 (2H, m), 3.21 (1H, dd, $J = 9.2$, 17.5 Hz), 3.49–3.59 (3H, m), 4.36 (2H, q, $J = 7.0$ Hz), 4.43–4.46 (1H, m), 5.70 (1H, dd, $J = 9.2$, 11.2 Hz), 6.90–6.94 (4H, m), 7.14 (2H, d, $J = 8.7$ Hz), 7.22 (2H, d, $J = 8.7$ Hz); ESI MS: 501.1 (M + Na); HPLC purity: 98.8%, $t_R = 6.4$ min.

*5.7.6. 5-(4-Piperidin-1-yl-phenyl)-4,5-dihydro-isoxazole-3-carboxylic acid ethyl ester (**17b**)*

Yield: 77%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.38 (3H, t, $J = 7.0$ Hz), 1.55–1.62 (2H, m), 1.66–1.72 (4H, m), 3.17 (4H, t, $J = 5.6$ Hz), 3.21 (1H, dd, $J = 10.7$, 19.0 Hz), 3.55 (1H, dd, $J = 11.4$, 17.5 Hz), 4.36 (2H, q, $J = 7.0$ Hz), 5.68 (1H, dd, $J = 9.2$, 11.2 Hz), 6.90 (2H, d, $J = 8.7$ Hz), 7.19 (2H, d, $J = 8.7$ Hz); ESI MS: 303.2 (M + 1); HPLC purity: 99.0%, $t_R = 4.7$ min.

*5.8. General procedure for the synthesis of **20a** and **20b***

A solution of 4-cyano styrene (1 mmol), $NH_2OH \cdot HCl$ (2 mmol) and Et_3N (1.5 mmol) in EtOH was refluxed for 4 h. The reaction mixture was concentrated under reduced pressure and the crude amidine **18** was used as such for the next reaction without further purification.

To a solution of amidine **18** (1 mmol) in triethyl orthoformate (5 mL), $BF_3 \cdot OEt_2$ (cat)/pyridine (5 mL) or benzoyl chloride (1.2 mmol) was added and the reaction mixtures were heated at 80 °C for 2 h, concentrated under reduced pressure and purified by flash chromatography to afford **19a** and **19b** in 51% and 45% yields, respectively.

Compounds **19a** and **19b** were converted into the corresponding isoxazolines **20a** and **20b** following the synthetic procedure discussed earlier.

*5.8.1. 5-(4-[1,2,4]Oxadiazol-3-yl-phenyl)-4,5-dihydro-isoxazole-3-carboxylic acid ethyl ester (**20a**)*

Yield: 59%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.38 (3H, t, $J = 7.0$ Hz), 3.24 (1H, dd, $J = 8.5$, 17.8 Hz), 3.70 (1H, dd, $J = 11.7$, 17.8 Hz), 4.37 (2H, q, $J = 7.0$ Hz), 5.85 (1H, dd, $J = 8.5$, 11.7 Hz), 7.47 (2H, d, $J = 8.3$ Hz), 8.14 (2H, d, $J = 8.0$ Hz), 8.77 (1H, s); ESI MS: 288.1 (M + 1).

*5.8.2. 5-[4-(5-Phenyl-[1,2,4]oxadiazol-3-yl)-phenyl]-4,5-dihydro-isoxazole-3-carboxylic acid ethyl ester (**20b**)*

Yield: 60%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.39 (3H, t, $J = 7.0$ Hz), 3.25 (1H, dd, $J = 8.5$, 17.5 Hz), 3.70 (1H, dd, $J = 11.7$, 17.8 Hz), 4.37 (2H, q, $J = 7.3$ Hz), 5.86 (1H, dd, $J = 8.7$, 11.7 Hz), 7.48 (2H, d, $J = 8.0$ Hz), 7.54–7.64 (3H, m), 8.21 (4H, t, $J = 8.5$ Hz); ESI MS: 362.3 (M − 1); HPLC purity: 98.4%, $t_R = 7.1$ min.

*5.8.3. 5-[4-(4-Benzyl-piperazin-1-yl)-phenyl]-4,5-dihydro-isoxazole-3-carboxylic acid amide (**21**)*

To a stirred solution of ester **1** in 1,4-dioxane, ammonium hydroxide (2 eq) was added and stirred at room temperature overnight. The reaction mass was concentrated under reduced pressure to give amide **21** in 66% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.61–2.69 (4H, m), 3.2–3.3 (5H, m), 3.53–3.63 (3H, m), 5.49–5.56 (1H, br s), 5.69 (1H, dd, $J = 9.5$, 11.2 Hz), 6.56–6.63 (1H, br s), 6.9 (2H, d, $J = 8.7$ Hz), 7.21 (2H, d, $J = 8.7$ Hz), 7.27–7.3 (1H, m), 7.32–7.38 (4H, m); ESI MS: 387.2 (M + Na); HPLC purity: 99%, $t_R = 4.6$ min.

*5.8.4. Lithium; 5-[4-(4-benzyl-piperazin-1-yl)-phenyl]-4,5-dihydro-isoxazole-3-carboxylate (**22**)*

To a stirred solution of ester **1** in THF/H_2O, LiOH (5 eq) was added and stirred at room temperature for 2 h. The reaction mass was concentrated under reduced pressure to give lithium salt **22** in 90% yield. ^{1}H NMR (500 MHz, D_2O): δ 2.54–2.6 (4H, m), 3.03–3.13 (5H, m), 3.46–3.54 (3H, m), 5.6 (1H, dd, $J = 8.5$, 10.9 Hz), 7.0 (2H, d, $J = 9.0$ Hz), 7.24 (2H, d, $J = 9.0$ Hz), 7.26–7.34 (5H, m); HPLC purity: 100%, $t_R = 4.7$ min.

*5.8.5. 5-[4-(4-Benzyl-piperazin-1-yl)-phenyl]-4,5-dihydro-isoxazole-3-carboxylic acid propyl amide (**23**)*

To a stirred solution of **22** (1 eq) in THF, oxaloyl chloride (2 eq) and DMF (catalytic) were added and stirred at room temperature for 4 h. Then added *n*-propyl amine (6 eq) to the acid chloride and again stirred at room temperature for another 2 h. The reaction mixture was diluted with excess ethyl acetate and washed with 1 N NaOH solution, water, brine, dried (anhyd. Na_2SO_4), concentrated under reduced pressure and purified by flash chromatography to give **23** in 59% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.93 (3H, t, $J = 7.3$ Hz), 1.62 (2H, m), 2.6–2.7 (4H, br s), 3.21–3.32 (5H, m), 3.35 (2H, dq, $J = 1.9$, 7.0 Hz), 3.56–3.66 (3H, m), 5.68 (1H, dd, $J = 9.5$, 11.2 Hz), 6.68–6.74 (1H, m), 6.92 (2H, d, $J = 8.7$ Hz), 7.23 (2H, d, $J = 8.7$ Hz), 7.29–7.33 (1H, m), 7.35–7.42 (4H, m); ESI MS: 429.3 (M + Na); HPLC purity: 100%, $t_R = 5.1$ min.

*5.8.6. 5-[4-(4-Benzyl-piperazin-1-yl)-phenyl]-4,5-dihydro-isoxazole-3-carboxylic acid hydrazide (**24**)*

To a stirred solution of ethyl ester **1** (0.2 g, 0.508 mmol) in ethanol (10 mL), hydrazine hydrate (0.05 mL, 1.017 mmol) was added and the mixture was refluxed overnight. The reaction mixture was concentrated under reduced pressure and the crude residue was purified by flash chromatography to afford **17** (0.1 g) in 52% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.60 (4H, t, $J = 5.1$ Hz), 3.18–3.30 (5H, m), 3.54–3.62 (3H, m), 3.96 (2H, d), 6.89 (2H, d, $J = 8.7$ Hz), 7.19 (2H, d, $J = 8.7$ Hz), 7.24–7.29 (3H, m), 7.31–7.38 (4H, m), 7.78 (1H, br s); ^{13}C NMR (500 MHz, $CDCl_3$): δ 40.60, 48.66, 52.89, 63.05, 84.63, 115.87, 127.26, 128.31, 129.36, 151.62, 152.42; ESI MS: 380.4 (M + 1); HPLC purity: 99.3%, $t_R = 5.4$ min.

*5.8.7. 1-Benzyl-4-{4-[3-(5-methyl-[1,3,4]oxadiazol-2-yl)-4,5-dihydro-isoxazol-5-yl]-phenyl}-piperazine (**26**)*

To a solution of **24** (0.85 g, 2.24 mmol) in CH_2Cl_2 (15 mL), Et_3N (0.93 mL, 6.728 mmol) and acetyl chloride (0.23 mL, 3.36 mmol) were added at 0 °C and stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure and purified by flash chromatography to afford 5-[4-(4-benzyl-piperazin-1-yl)-phenyl]-4,5-dihydro-isoxazole-3-carboxylic acid *N*′-acetyl-hydrazide (**25**) (0.58 g) in 61% yield. Compound **25** (0.47 g, 1.11 mmol) was dissolved in CH_2Cl_2 (20 mL), and Et_3N (0.31 mL, 2.23 mmol) and *p*-TsCl (0.424 g, 2.23 mmol) were added at 0 °C and allowed to reflux gently for 4 h. The reaction mixture was cooled to room temperature and washed vigorously with 40% K_2CO_3 solution, dried (anhyd. Na_2SO_4), concentrated under reduced pressure and purified by flash chromatography to afford **26** (0.26 g) in 58% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.54 (3H, s), 2.60 (4H, t, $J = 5.1$ Hz), 3.18–3.30 (5H, m), 3.54–3.62 (3H, m), 5.52 (1H, dd, $J = 9.5$, 11.2 Hz), 6.84 (2H, d, $J = 8.7$ Hz), 7.04 (2H, d, $J = 8.7$ Hz), 7.26–7.35 (3H, m), 7.93 (2H, d, $J = 8.6$ Hz); ESI MS: 426.4 (M + Na); HPLC purity: 98.5%, $t_R = 5.8$ min.

*5.8.8. 5-(4-Morpholin-4-yl-phenyl)-4,5-dihydro-isoxazole-3-carboxylic acid ethyl ester (**28**)*

Compound **28** was synthesized following the general procedure described earlier in 78% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.38 (3H, t, $J = 7.0$ Hz), 3.17 (4H, t, $J = 4.8$ Hz), 3.21 (1H, dd, $J = 9.7$, 18.3 Hz), 3.56 (1H, dd, $J = 11.4$, 17.8 Hz), 3.85 (4H, t, $J = 4.8$ Hz), 4.36 (2H, q, $J = 7.0$ Hz), 5.71 (1H, dd, $J = 9.2$, 11.4 Hz), 6.90 (2H, d, $J = 8.5$ Hz), 7.23 (2H, d, $J = 8.7$ Hz); ESI MS: 327.1 (M + Na); HPLC purity: 99.7%, $t_R = 5.6$ min.

*5.9. General procedure for the synthesis of **29a** and **29b***

To a stirred solution of ester **1** or **28** (1 mmol) in anhydrous THF, DIBAL-H (2 mmol) was added dropwise at 0 °C and stirred at the same temperature for 4 h. The reaction mass was quenched with saturated solution of potassium sodium tartrate and the product was extracted with EtOAc, washed with water, brine, dried (anhyd. Na_2SO_4) and concentrated. The crude residue was purified by flash chromatography to give pure compounds.

*5.9.1. {5-[4-(4-Benzyl-piperazin-1-yl)-phenyl]-4,5-dihydro-isoxazol-3-yl}-methanol (**29a**)*

Yield: 56%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.60 (4H, t, $J = 5.1$ Hz), 3.01 (1H, q, $J = 8.7$ Hz), 3.19 (4H, t, $J = 5.1$ Hz), 3.37 (1H, q, $J = 8.7$ Hz), 3.56 (2H, s), 4.43 (2H, s), 5.53 (1H, t, $J = 9.2$ Hz), 6.88 (2H, d, $J = 8.7$ Hz), 7.21 (2H, d, $J = 8.7$ Hz), 7.24–7.29 (1H, m), 7.30–7.39 (4H, m); ^{13}C NMR (500 MHz, $CDCl_3$): δ 42.59, 48.89, 52.96, 58.00, 63.06, 82.34, 115.95, 127.10, 127.27, 128.34, 129.32, 130.94, 137.71, 151.34, 158.61; ESI MS: 374.4 (M + 23); HPLC purity: 99%, $t_R = 4.6$ min.

*5.9.2. [5-(4-Morpholin-4-yl-phenyl)-4,5-dihydro-isoxazol-3-yl]-methanol (**29b**)*

Yield: 60%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.02 (1H, dd, $J = 8.7$, 17.0 Hz), 3.16 (4H, t, $J = 4.6$ Hz), 3.41 (1H, dd, $J = 10.7$, 17.0 Hz), 3.86 (4H, t, $J = 4.8$ Hz), 4.46 (2H, d, $J = 5.8$ Hz), 5.57 (1H, dd, $J = 8.7$, 10.5 Hz), 6.90 (2H, d, $J = 8.7$ Hz), 7.25 (2H, d, $J = 6.3$ Hz); ESI MS: 263.1 (M + 1); HPLC purity: 98.7%, $t_R = 4.2$ min.

*5.10. General procedure for the synthesis of **30a** and **30b***

To a stirred solution of alcohol **29a** or **29b** (1 mmol) in anhydrous DMF, CBr_4 (1 mmol), Ph_3P (1 mmol) and NaN_3 (5 mmol) were added sequentially and the resulting mixture was stirred at room temperature for 2 h. The reaction mixtures were quenched with MeOH, filtered and concentrated. The crude residues were purified by flash chromatography.

*5.10.1. 1-[4-(3-Azidomethyl-4,5-dihydro-isoxazol-5-yl)-phenyl]-4-benzyl-piperazine (**30a**)*

Yield: 59%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.60 (4H, t, $J = 4.8$ Hz), 3.01 (1H, q, $J = 7.8$ Hz), 3.20 (4H, t, $J = 5.1$ Hz), 3.37 (1H, q, $J = 7.8$ Hz), 3.56 (2H, s), 4.13 (2H, s), 5.57 (1H, t, $J = 5.1$ Hz), 6.89 (2H, d, $J = 8.7$ Hz), 7.21 (2H, d, $J = 8.5$ Hz), 7.24–7.29 (1H, m), 7.30–7.37 (4H, m); ^{13}C NMR (500 MHz, $CDCl_3$): δ 42.66, 42.71, 47.49, 48.85, 48.89, 52.99, 63.06, 82.91, 115.90, 126.99, 127.06, 128.36, 129.28, 130.45, 151.52, 153.79; ESI MS: 377.4 (M + 1); HPLC purity: 98.5%, $t_R = 5.1$ min.

*5.10.2. 4-[4-(3-Azidomethyl-4,5-dihydro-isoxazol-5-yl)-phenyl]-morpholine (**30b**)*

Yield: 61%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.02 (1H, dd, $J = 8.7$, 17.0 Hz), 3.16 (4H, t, $J = 4.6$ Hz), 3.40 (1H, dd, $J = 10.9$, 17.3 Hz), 3.85 (4H, t, $J = 4.8$ Hz), 4.15 (2H, s), 5.59 (1H, dd, $J = 9.0$, 10.5 Hz), 6.90 (2H, d, $J = 8.5$ Hz), 7.24 (2H, d, $J = 8.5$ Hz); ESI MS: 288.3 (M + 1); HPLC purity: 98.8%, $t_R = 5.3$ min.

*5.11. General procedure for the synthesis of **31a** and **31b***

To a stirred solution of azide **30a** or **30b** (1 mmol) in 1,4-dioxane (5 mL), Ph_3P (1.6 mmol) was added and stirred at room temperature overnight. The reaction mixtures were concentrated under reduced pressure and the crude residues were purified by flash chromatography to afford **31a** or **31b**.

*5.11.1. C-{5-[4-(4-Benzyl-piperazin-1-yl)-phenyl]-4,5-dihydro-isoxazol-3-yl}-methylamine (**31a**)*

Yield: 67%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.67 (2H, br s), 2.59 (4H, t, $J = 4.8$ Hz), 2.95 (1H, q, $J = 8.5$ Hz), 3.19 (4H, t, $J = 5.1$ Hz), 3.32 (1H, q, $J = 8.5$ Hz), 3.56 (2H, s), 3.61 (2H, s), 5.51 (1H, t, $J = 8.7$ Hz), 6.88 (2H, d, $J = 8.5$ Hz), 7.21 (2H, d, $J = 8.5$ Hz), 7.27–7.28 (1H, m), 7.30–7.36 (4H, m); ^{13}C NMR (500 MHz, $CDCl_3$): δ 43.33, 48.90, 53.00, 63.06, 63.15, 82.13, 115.89, 127.02, 128.33, 129.23, 131.08,

137.90, 151.33; ESI MS: 373.1 (M + 23); HPLC purity: 98.8%, $t_R = 4.3$ min.

*5.11.2. C-[5-(4-Morpholin-4-yl-phenyl)-4,5-dihydro-isoxazol-3-yl]-methylamine (**31b**)*

Yield: 60%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.97 (1H, dd, $J = 8.7$, 17.0 Hz), 3.15 (4H, t, $J = 4.8$ Hz), 3.35 (1H, dd, $J = 6.3$, 17.0 Hz), 3.63 (2H, s), 3.85 (4H, t, $J = 4.8$ Hz), 5.53 (1H, dd, $J = 9.0$, 10.5 Hz), 6.89 (2H, d, $J = 8.5$ Hz), 7.24 (2H, d, $J = 8.5$ Hz); ESI MS: 284.2 (M + 23); HPLC purity: 100%, $t_R = 4.0$ min.

*5.12. General procedure for the synthesis of **32a** and **32b***

To a stirred solutions of amines **31a** and **31b** (1 mmol) in CH_2Cl_2 (5 mL), Et_3N (3 mmol) and acetyl chloride (1.5 mmol) were added at 0 °C and allowed to stir at room temperature for 1 h. The reaction mixtures were diluted with excess CH_2Cl_2 (15 mL) and washed with aqueous $NaHCO_3$ (10 mL), dried (anhyd. Na_2SO_4), concentrated under reduced pressure and the crude residues were purified by flash chromatography.

*5.12.1. N-{5-[4-(4-Benzyl-piperazin-1-yl)-phenyl]-4,5-dihydro-isoxazol-3-ylmethyl}-acetamide (**32a**)*

Yield: 78%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.00 (3H, s), 2.59 (4H, t, $J = 4.8$ Hz), 2.96 (1H, q, $J = 8.5$ Hz), 3.19 (4H, t, $J = 5.1$ Hz), 3.30 (1H, q, $J = 8.5$ Hz), 3.55 (2H, s), 4.18 (2H, t, $J = 4.8$ Hz), 5.51 (1H, t, $J = 5.1$ Hz), 6.30 (1H, br s), 6.87 (2H, d, $J = 8.5$ Hz), 7.18 (2H, d, $J = 8.5$ Hz), 7.24–7.28 (1H, m), 7.30–7.36 (4H, m); ^{13}C NMR (500 MHz, $CDCl_3$): δ 22.91, 22.96, 36.95, 37.00, 43.35, 48.85, 48.87, 52.97, 53.03, 62.95, 63.05, 82.41, 82.44, 115.85, 127.03, 127.08, 127.20, 128.31, 128.33, 129.24, 130.52, 137.91, 151.44, 156.15, 170.53; ESI MS: 415 (M + 23); HPLC purity: 98.7%, $t_R = 4.6$ min.

*5.12.2. N-[5-(4-Morpholin-4-yl-phenyl)-4,5-dihydro-isoxazol-3-ylmethyl]-acetamide (**32b**)*

Yield: 71%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.97 (1H, dd, $J = 9.0$, 17.3 Hz), 3.15 (4H, t, $J = 4.8$ Hz), 3.34 (1H, dd, $J = 10.7$, 17.0 Hz), 3.85 (4H, t, $J = 4.8$ Hz), 4.20 (2H, q, $J = 3.4$ Hz), 5.54 (1H, dd, $J = 9.2$, 10.2 Hz), 6.19 (1H, br s), 6.89 (2H, d, $J = 8.5$ Hz), 7.22 (2H, d, $J = 8.5$ Hz); ESI MS: 326.1 (M + Na); HPLC purity: 99.1%, $t_R = 4.2$ min.

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Appendix. Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejmech.2008.04.007.

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