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FULL PAPER

Synthesis of chiral 3,4-disubstituted pyrrolidines with antibacterial properties

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Abstract: Chiral aliphatic heterocycles are important structural feature of many pharmaceutical agents. Antibiotic resistance is a serious medical problem, therefore new antibacterial compounds are urgently needed. Herein, we describe synthesis of a series of 3,4-disubstituted pyrrolidine derivatives via organocatalytic Michael addition followed by reductive cyclization. These compounds inhibited growth of standard as well as methicillin-resistant strains of *Escherichia coli* and *Staphylococcus aureus*.

Introduction

Efficient organic synthetic methodologies are indispensable for sustaining development of new drugs.[1] Construction and manipulation of saturated nitrogen heterocycles has been named as one of the challenges of the modern organic synthesis within the framework of drug synthesis.[2] Especially, five-membered nonaromatic nitrogen-containing heterocycles exhibit important pharmacological activities. Pyrrolidine structure occurs in many natural compounds, e.g. nicotine, hygrine, mesembrine, slaframine, or kainic acid. Several marketed drugs, such as almotriptan for treating migraines, asimadoline – k-opioid agonist, mitiglidine – antidiabetic drug, or procyclidine – anticholinergic drug also contain a pyrrolidine moiety.[3] Antiseizure drug ethosuximide, muscle relaxant rocuronium, antibiotic clindamycin, antipsychotic drugs remoxipride and asenapine also belong to the group of pyrrolidine based pharmaceuticals.[4] Sulfonamide derivatives of pyrrolidine are promising therapeutics for the treatment of type 2 diabetes.[5]

A number of pyrrolidine derivatives with antimicrobial activities were described in the literature.[6] Le Goffic proved that pyrrolidine moiety increased antibiotic activity of lincosamide antibiotics.[7] Highly substituted methoxyquinolines with pyrrolidine heterocycle exhibited potent in vitro antibacterial activity against various respiratory pathogens, including multidrug-resistant *Streptococcus pneumoniae* and *Staphylococcus aureus*.[8] Poly-hydroxypyrolidine inhibitor was effective against both *Mycobacterium tuberculosis* as well as *Streptomyces coelicolor*.[9] Zhang *et al*. tested novel benzofuroxan-based pyrrolidine hydroxamates as matrix metalloproteinase inhibitors.[10] They found a derivative demonstrating competitive antitumor activity in vivo. Reddy *et al*. recently synthetized several pyrrolidine chalcone derivatives with anticancer, anti-inflammatory as well as antibacterial activities.[11] Some derivatives were efficient against *Staphylococcus aureus*, *Enterococcus faecalis*, and *Mycobacterium tuberculosis*.[12] Efficiency against *M. tuberculosis* seems promising, as compounds with pyrrolidinone or pyrrolidine cores are able to interact with the enoyl-acyl carrier protein reductase, the essential enzyme for synthesis of the *M. tuberculosis* cell wall.[13]

Antimicrobial activity against *S. aureus* and *E. coli* (Gram-positive and Gram-negative bacteria, respectively) is very interesting as well as representatives of both species often manifest resistance to generally available antimicrobial agents.[14] Moreover, they are frequently associated with biofilm infection in patients with indwelling medical devices.[15] Methicillin resistant *S. aureus* (MRSA) or *E. coli* possessing resistance to a wide-spectrum beta-lactams or aminoglycosides are a serious medical problem.[16] According to World Health Organization antibiotic resistance is one of the biggest threats to global health, food security, and development today. Therefore, searching for new compounds with antimicrobial properties is an essential challenge.

Various synthetic strategies are available for stereoselective construction pyrrolidine core such as dipolar cycloadditions of azomethine ylides,[17] or various reductive amination strategies.[18] In the last two decades, stereoselective organocatalysis developed into one of the pillars of asymmetric catalysis comparable with metal-catalysis and biocatalysis.[19] Organocatalytic methodologies served well also in syntheses of medicinally important and bioactive compounds.[20] Organocatalyzed Michael additions are among the most robust and reliable methodologies, which enable introduction of non-trivial functional groups and can lead to complex molecular architectures with desired functions.[21]

In this context, we decided to prepare a series of new chiral pyrrolidines with potential antibacterial activities. As a vehicle for

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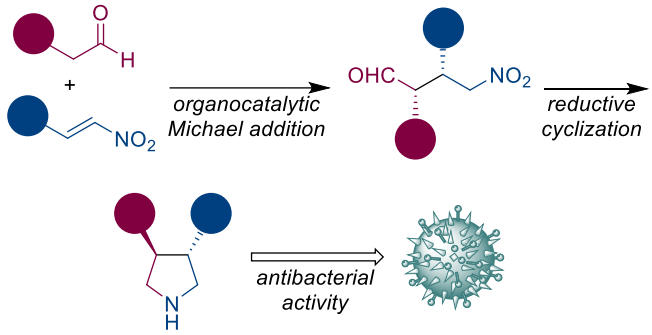
pyrrolidine construction, we have employed organocatalytic Michael addition of aldehydes to nitroalkenes. Stereoselective Michael additions with enolizable carbonyl compounds proceed well via enamine activation.[22] This robust Michael addition provides key chiral intermediates, γ-nitroaldehydes which are subjected to reductive cyclization (Scheme 1).[23] In this paper, we present synthesis of a series of chiral 3,4-disubstituted pyrrolidine derivatives and evaluation of their antibacterial activities.

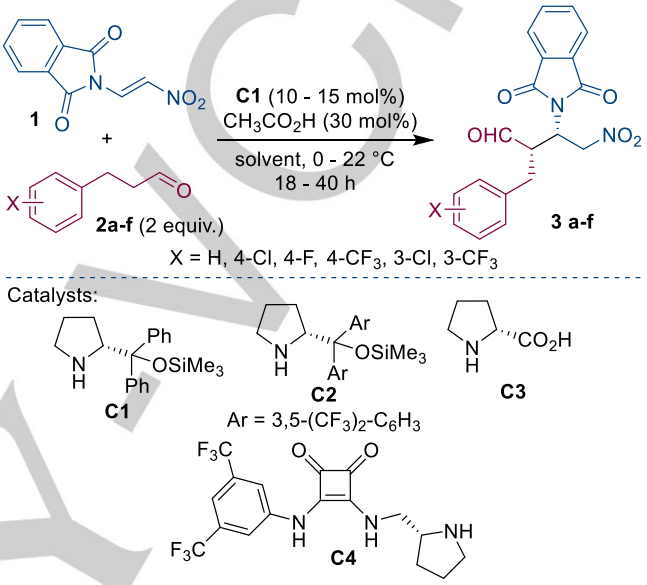


Scheme 1. Concept of this work.

Results and Discussion

Synthesis of pyrrolidines

The first step of the synthesis of chiral pyrrolidines was Michael addition of aldehydes **2a**-**f** to nitroalkene **1** (Scheme 2). We have focused on the 2-phthalimido-1-nitroethene (**1**) as an acceptor because phthalimido group provides convenient synthetic handle for further transformations. Nitroalkene **1** has been used in several organocatalytic transformations.[24] Ma and coworkers employed nitroalkene **1** in the Michael reactions with aldehydes during their investigations of organocatalytic synthesis of oseltamivir.[24a] The combination of diethyl ether as a solvent and Hayashi-Jørgensen catalyst **C1**[22a, 25] gave the adducts in satisfactory yields with high diastereoselectivity and high enantiomeric purity of *syn*-adducts (Table 1). Inspired by the work of Ma, and our previous experiences,[24a, 26] we have performed the reaction in chloroform at first. In order to simplify purification and isolation of the Michael adduct, we tested several other solvents such as dichloromethane, methyl(*tert*-butyl)ether, THF, 1,4-dioxane, 2-methyltetrahydrofurane, and diethylether. The use of Et_2O retained high enantiomeric and diastereomeric purities, and allowed isolation of the major diastereomer of products **3** by trituration. Low diastereoselectivity (3:1) as well as somewhat lower enantioselectivity (85 % ee) were observed in the case of adduct **3d** (Table 1, entry 4). To increase stereoselectivity, we performed Michael addition of aldehyde **2d** under various reaction conditions. We managed to increase the diastereoselectivity to 10:1 using the **C2** catalyst, but the conversion dropped below 10 %. (S)-Proline (**C3**) and pyrrolidine-substituted squaramide **C4** were much less active. As we focused on practicality of this work, we did not continue with larger catalyst screening. We have continued to use catalysts **C1**, which is commercially available, stable and usually provides consistently good results in catalysis. We have observed epimerization of Michael adducts during chromatographic purification. Diastereomeric ratio for adducts **3** changed in favor of *anti*-minor isomer during the column chromatography. Interestingly, trituration of the crude products **3** with Et_2O gave pure *syn*-adducts **3** without necessity of column chromatography.



Scheme 2. Organocatalytic Michael addition of aldehydes **2a**-**f** to nitroalkene **1**.

Absolute configuration of Michael adducts were assigned by comparison of sign of optical rotation and chiral HPLC data for compound **3a** with those reported in the work of Ma.[24a] Stereochemistry of Michael adducts can be rationalized via application of Seebach-Golinski model for enamine additions to nitroalkenes.[27] Here, (*E*)-*anti* enamine generated from an aldehyde and catalyst **C1** attack with its Re face a nitroalkene from its *Si* face. Enamine and nitroalkene are positioned in synperiplanar arrangement due to attractive electrostatic interaction between nitrogens in enamine and nitro group. This arrangement provides *syn*-adducts with (*S*,*S*)-configurations (Scheme 3a).

We have calculated corresponding transition states for the Michael addition of aldehyde **2a** and nitroalkene **1** with catalyst **C1**. Geometries were obtained using long-range corrected hybrid density ωB97X-D functional with 6-31G* basis set.[28] Energies were refined at ωB97X-D/6-311+G** level using C-PCM (Et_2O) solvation model.[29] These calculations show that preferred transition state is 16.7 kJ/mol more favorable than the minor one. This difference is probably due to steric hindrance between approaching nitroalkene and CPh_2(OTMS) moiety (Scheme 3b).

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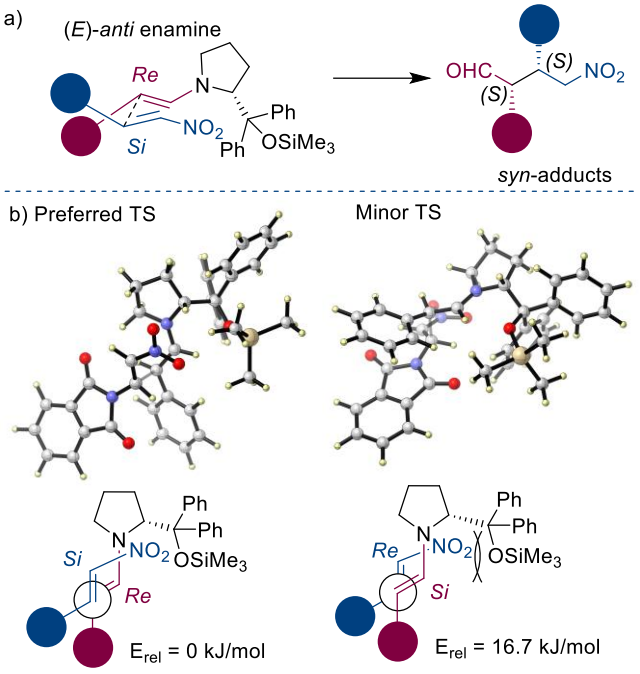


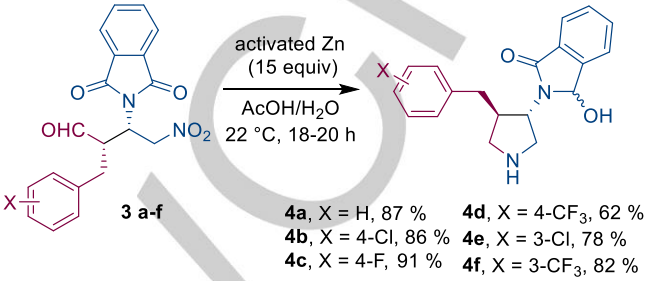
Scheme 3. a) Stereochemical model of the Michael addition of aldehydes **2a**-**f** to nitroalkene **1** catalyzed with **C1**; b) transition states calculated at the ωB97X-D/6-311+G** (Et_2O)//ωB97X-D/6-31G* level of theory.

Table 1. Organocatalytic Michael addition of aldehydes **2a**-**f** to nitroalkene **1** using **C1**.

Entry	X	Solvent	Time (h)	Yield [a]	Syn/anti[b]	ee (*syn*)[c]
1	H	$CHCl_3$	18[d]	41 (**3a**)	10:1	97
2	4-Cl	Et_2O	23[e]	70 (**3b**)	20:1	92
3	4-F	Et_2O	23[e,f]	69 (**3c**)	20:1	99
4	4-CF_3	Et_2O	23[e]	64 (**3d**)	3:1	85
5	3-Cl	Et_2O	40[e]	84 (**3e**)	77:1	99[g]
6	3-CF_3	Et_2O	24[d]	31 (**3f**)	80:1	99

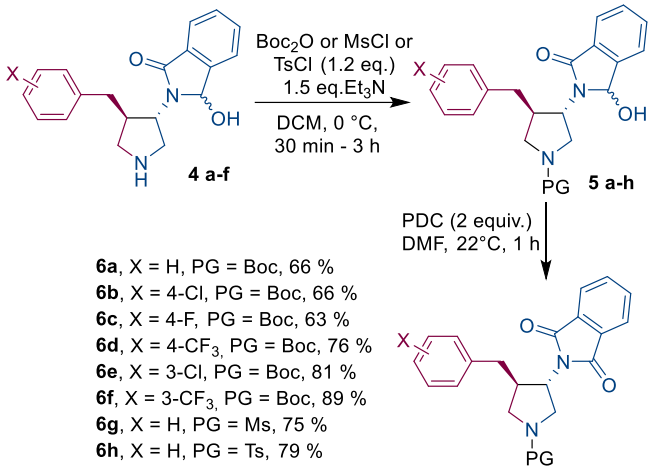
[a] Yield of major isomer gained by trituration with Et_2O; [b] dr was determined by ^1H NMR of crude reaction mixture; [c] ee was determined by HPLC on IC Chiralpak column; [d] 10 mol% of catalyst **C1** were used; [e] 15 mol% of catalyst **C1** were used; [f] 13 mol% of acetic acid were used; [g] determined after derivatization with Wittig reagent Ph_3PCHCO_2Et.

The pyrrolidine scaffold was synthesized by reductive cyclization of Michael adducts **3**. A reduction of nitro group with freshly activated zinc was followed by intramolecular cyclization leading to pyrrolidine **4** (Scheme 4). The yields (62–91 %) of pyrrolidines **4a**-**f** represent average values of several experiments. Pyrrolidine **4e** was prepared under modified conditions ($AcOH/H_2O$/1,4-dioxane; ultrasonic irradiation in a cleaning bath for 1 h, then magnetic stirring at room temperature for 22 h, because of poor solubility of the corresponding Michael adduct **3e**. During the reductive cyclization, one carbonyl group in isoindoline-1,3-dione moiety was also reduced.



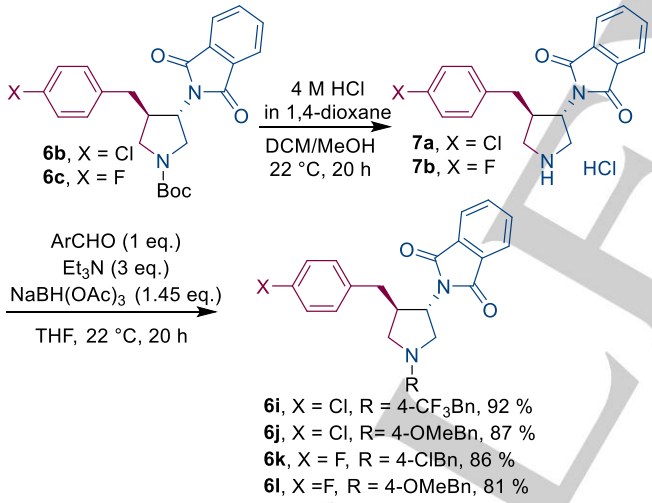
Scheme 4. Reductive cyclization of Michael adducts **3a**-**f**.

Owing to the next reaction steps, it was necessary to protect secondary amino group of pyrrolidines **4a**-**f**. We used *tert*-butoxycarbonyl, mesyl and tosyl protecting groups (Scheme 5). Boc-protected pyrrolidine **5a**-**f** were directly used in the next reaction step without any further purification. Pyrrolidines **5g** and **5h** were obtained after column chromatography with the yields of 82 and 85 %, respectively. The next reaction step was oxidation of 3-hydroxyisoindolin-1-one moiety of compounds **5a**-**h** with pyridinium dichromate (PDC) to isoindoline-1,3-dione moiety (Scheme 4). The corresponding products **6a**-**h** were obtained in 63–89 % yields after column chromatography (average values of several experiments). Nitroalkene **1** has solubility similar with the Michael adducts **3a**-**f** and their mixtures are difficult to separate by trituration with Et_2O. Fortunately, the nitroalkene **1** did not influence the next reaction steps and it was separated later. An important feature of this synthetic method is that only one column chromatography is necessary for these four reaction steps sequence. The overall procedure comprising Michael addition, reductive cyclization, pyrrolidine protection, and oxidation of hemiaminal corresponding products in overall yields up to 60 %.



Scheme 5. Protection and subsequent oxidation of pyrrolidine **4a-f**.

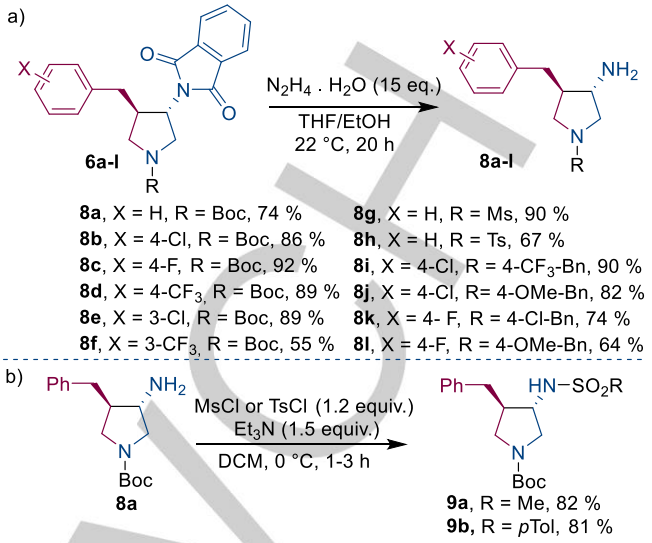
A series of protected pyrrolidines **6a-h** has been extended to derivatives **6i-l** with substituted benzyl group on nitrogen. They were prepared in two steps. After the Boc-group deprotection with 4M HCl, reductive amination afforded corresponding benzyl derivatives **6i-l** in high yields (81–92 %) (Scheme 6).



Scheme 6. Preparation of pyrrolidines **6i-l**.

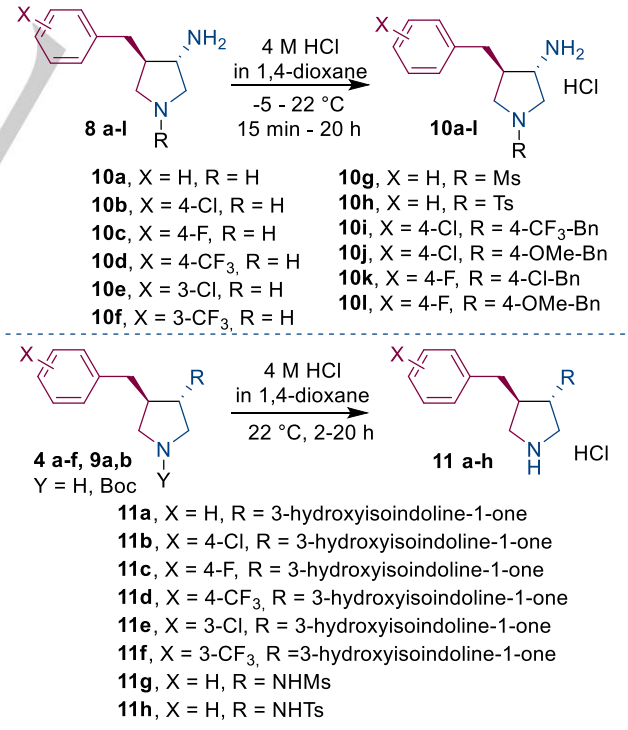
Phthalimido protection group was removed in the next step by hydrazinolysis. The deprotection was performed at room temperature in most cases, except for substrates **6e** and **6g**, which had to be subjected to hydrazinolysis at 50 °C. The products **8a-l** were obtained in yields of 55–92 % after column chromatography (Scheme 7a).

Sulfonamides **9a**,**b** were prepared from amine **8a** by the same procedure as sulfonamides **5g**,**h**. Both products were obtained in high yields after column chromatography (Scheme 7b).



Scheme 7. Hydrazinolysis of phthalimido group (a); preparation of sulfonamides **9a**,**b** (b).

In order to increase their solubility in aqueous media for the needs of biological tests hydrochlorides of pyrrolidines **4a-f**, **8a-l**, and **9a**,**b** were prepared using 4 M HCl in dioxane. The hydrochlorides were isolated after trituration with Et_2O as solids in the yields over 85 % (Scheme 8). For more details see Supplementary Information.



Scheme 8. Preparation of hydrochlorides **10a-l** and **11a-h**.

Biological evaluation

Initially, hydroxyisoindolinone derivative **5g** was screened for antimicrobial activity on both standard strains of *E. coli* and *S. aureus* with MIC_{50} and MIC_{100} 1.25 and 2.5 mg/mL, respectively (3.23 mmol/L, and 6.47 mmol/L).

Then, two representatives of phthalimido substituted pyrrolidines **6g** and **6h** were tested for antimicrobial activity on both bacteria; MIC_{50} were 1.25 mg/mL (3.25, and 2.71 mmol/L) and MIC_{100} 2.5 or > 2.5 mg/mL (6.50, and 5.43 mmol/L).

Hydrochlorides **10b-l** were screened for antimicrobial properties on both standard strains of *E. coli* and *S. aureus*. Results are summarized in Table 2.

Table 2. Antimicrobial activity of hydrochlorides of pyrrolidines **10b-l** on bacteria of *E. coli* and *S. aureus*.

Entry	Compound	Effectiveness in MIC_{50} / MIC_{100} [mmol/L]	
		E. coli	*S. aureus*
1	**10b**	0.180 / 1.440	0.180 / 0.720
2	**10c**	0.387 / 1.511	0.189 / 1.511
3	**10d**	0.164 / 0.328	0.164 / 0.328
4	**10e**	0.360 / 0.720	0.360 / 1.440
5	**10f**	0.656 / 1.313	1.313 / 1.313
6	**10g**	> 1.719	> 1.719
7	**10h**	0.341 / 0.681	0.341 / 1.363
8	**10i**	**0.017 / 0.037**	**0.017 / 0.037**
9	**10j**	**0.084 / 0.170**	**0.084 / 0.170**
10	**10k**	**0.087 / 0.176**	**0.087 / 0.176**
11	**10l**	0.356 / 0.713	0.356 / 0.713

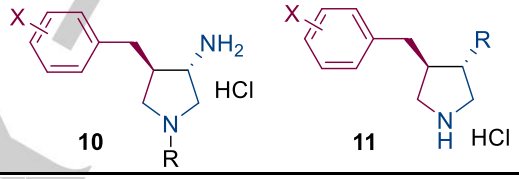
We have evaluated antimicrobial activity also for hydroxyindoline derivative **11a-f** as well as for mesyl and tosyl derivatives **11g** and **11h** (Table 3).

Table 3. Antimicrobial activity of hydrochlorides of pyrrolidines **11b-h** on bacteria of *E. coli* and *S. aureus*.

Entry	Compound	Effectiveness in MIC_{50} / MIC_{100} [mmol/L]	
		E. coli	*S. aureus*
1	**11b**	0.360 / 0.720	0.360 / 0.720
2	**11c**	0.756 / 1.511	0.756 / 1.511
3	**11d**	0.164 / 0.328	0.081 / 0.164
4	**11e**	0.360 / 0.720	0.180 / 0.360
5	**11f**	0.164 / 0.328	0.164 / 0.128
6	**11g**	2.149 / 4.298	2.149 / 4.298
7	**11h**	0.425 / 3.407	0.853 / 3.407

The most efficient derivatives, **10i-k** and **11d-f** were also tested on resistant strains of *E. coli* and *S. aureus* (Table 4). Obtained efficiencies on resistant strains determined in the MIC_{50} or MIC_{100} were the same or very close to those estimated for sensitive standard strains. The derivative **10i** proved to be the most efficient with MIC_{50} and MIC_{100} 17 and 37 µmol/L, respectively, for both resistant bacteria. The same efficient concentrations suggest similar mechanisms of action on both Gram-positive and Gram-negative bacteria.

Table 4. Antimicrobial activity of hydrochlorides of pyrrolidines **10i-k** and **11d-f** on resistant bacteria of *E. coli* and *S. aureus*.



Entry	Compound	Effectiveness in MIC_{50} / MIC_{100} [mmol/L]	
		E. coli R	*S. aureus R*
1	**10i** (X = 4-Cl, R = 4-CF_3Bn)	**0.017 / 0.027**	**0.017 / 0.037**
2	**10j** (X = 4-Cl, R = 4-OMeBn)	0.084 / 0.340	0.170 / 0.340
3	**10k** (X = 4-F, R = 4-ClBn)	0.087 / 0.176	0.086 / 0.176
4	**11d** (X = 4-CF_3, R = 3-hydroxyisoindoline-1-one)	0.164 / 0.328	0.081 / 0.164
5	**11e** (X = 3-Cl, R = 3-hydroxyisoindoline-1-one)	0.360 / > 1.440	0.360 / 1.440
6	**11f** (X = 3-CF_3, R =3-hydroxyisoindoline-1-one)	0.328 / 0.656	0.328 / 0.656

Conclusions

A series of chiral 3,4-disubstituted pyrrolidines was prepared via organocatalytic Michael addition of enolizable aldehydes to nitroalkenes. Michael adducts were formed as *syn*-diastereomers with high enantiomeric purities. These adducts were then reductively cyclized to corresponding trans-3,4-disubstituted pyrrolidines by zinc in acetic acid. Pyrrolidines with phthalimido,

sulphonamide or free amine group were subjected to antibacterial tests.

Some of compounds selected for antimicrobial testing proved to be efficient and inhibited growth of *E. coli* and *S. aureus* bacterial strains regardless of their susceptibility/resistance pattern. Activity against methicillin-resistant strains is of particular interest. The compound **10i** manifested excellent antimicrobial properties and will be assumed for another study.

Experimental Section

General procedure for synthesis of chiral nitroaldehydes 3a-f

(*E*)-2-(2-nitrovinyl)isoindoline-1,3-dione (**1**) (1.09 g, 5.0 mmol) was added to the solution of aldehyde **2a**-**f** (10 mmol) in solvent (14 mL containing 0.08 % water) at 0 °C. Next, the solution of catalyst **C1** (167–254 mg, 0.5–0.75 mmol) in solvent (1 mL) and acetic acid (0.05–0.10 mL, 0.65–1.5 mmol) were added in one portion. The reaction mixture was stirred at 0 °C for 30 min and then 18–40 h at 22 °C. The reaction mixture was concentrated under vacuum to afford crude product as a mixture of diastereomers. The crude product was triturated with diethyl ether to give one diastereomer. Products were obtained as white solids and directly used to the following reaction step without purification, which was not necessary.

Characterization data of nitroaldehydes 3a-f

(2*S*,3*S*)-2-benzyl-3-(1,3-dioxoisoindolin-2-yl)-4-nitrobutanal (3a). White solid (41 %). **M. p.:** 129–130 °C. **$[\alpha]_D^{20}$** -36.2 (c 0.55, $CHCl_3$). **IR (FTIR)**: ν 1771, 1706, 1560, 1380, 1231, 717, 480 cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 9.72 (s, 1H), 7.81–7.67 (m, 4H), 7.16–6.97 (m, 5H), 5.35 (td, *J* = 10.4, 3.4 Hz, 1H), 5.18 (dd, *J* = 13.1, 10.4 Hz, 1H), 4.83 (dd, *J* = 13.1, 3.4 Hz, 1H), 3.76 (dd, *J* = 17.5, 7.6 Hz, 1H), 3.00 (dd, *J* = 14.5, 7.8 Hz, 1H), 2.80 (dd, *J* = 14.5, 7.8 Hz, 1H). **HPLC:** Chiralpak IC column, hexane/*i*-PrOH 60:40, 254 nm, flow rate 0.75 mL/min, *ee* 97%. Spectral data are in agreement with data published in literature.[24a]

(2*S*,3*S*)-2-(4-chlorobenzyl)-3-(1,3-dioxoisoindolin-2-yl)-4-nitrobutanal (3b). White solid (70 %). **M. p.**: 162–164 °C. **$[\alpha]_D^{20}$** = -11.9 (*c* 1, $CHCl_3$). **IR (FTIR)**: ν 1771, 1703, 1552, 1369, 1132, 1092, 858, 719, 528 cm^{-1}. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 9.73 (s, 1H), 7.79–7.70 (m, 4H), 7.04 (d, *J* = 8.3 Hz, 2H), 6.99 (d, *J* = 8.2 Hz, 2H), 5.34 (td, *J* = 10.3, 3.3 Hz, 1H), 5.17 (dd, *J* = 13.2, 10.5 Hz, 1H), 4.82 (dd, *J* = 13.3, 3.4 Hz, 1H), 3.73 (dd, *J* = 17.3, 7.4 Hz, 1H), 3.02 (dd, *J* = 14.6, 7.1 Hz, 1H), 2.74 (dd, *J* = 14.6, 7.6 Hz, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$): δ 199.9, 167.6, 134.6, 134.3, 132.8, 131.0, 129.8, 128.8, 123.6, 73.6, 51.2, 48.0, 32.8. **HPLC:** Chiralpak IC column, hexane/*i*-PrOH 68:32, 221 nm, flow rate 0.65 mL/min, *ee* 92 %. **HRMS-ESI+** (*m/z*): calculated for $[C_{19}H_{15}ClN_2O_5+CH_3OH+Na]^+$: 441.0824; found 441.0826.

(2*S*,3*S*)-3-(1,3-dioxoisoindolin-2-yl)-2-(4-fluorobenzyl)-4-nitrobutanal (3c). White solid (69 %). **M. p.**: 140–141 °C. **$[\alpha]_D^{20}$** = -24.8 (*c* 1, $CHCl_3$). **IR (FTIR)**: ν 1771, 1709, 1550, 1355, 1002, 720 cm^{-1}. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 9.72 (s, 1H), 7.81–7.76 (m, 2H), 7.75–7.71 (m, 2H), 7.03 (dd, *J* = 8.2, 5.3 Hz, 2H), 6.79 (t, *J* = 8.5 Hz, 2H), 5.34 (td, *J* = 10.3, 3.4 Hz, 1H), 5.17 (dd, *J* = 13.2, 10.4 Hz, 1H), 4.82 (dd, *J* = 13.3, 3.4 Hz, 1H), 3.72 (dd, *J* = 17.2, 7.5 Hz, 1H), 2.99 (dd, *J* = 14.6, 7.6 Hz, 1H), 2.78 (dd, *J* = 14.7, 7.1 Hz, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$): δ 200.2, 167.6, 161.7 (d, $J_{C\text{-}F}$ = 246.3 Hz), 134.6, 131.5, 130.0, 123.7, 115.7, 115.5, 73.6, 51.4, 47.9, 32.6. **HPLC**: Chiralpak IC column, hexane/*i*-PrOH 70:30, 221 nm, flow rate 0.60 mL/min, *ee* 99 %. Satisfactory separation of peaks of the racemate was not successfully achieved. **HRMS-ESI+** (*m/z*): calculated for $[C_{19}H_{15}FN_2O_5+CH_3OH+Na]^+$: 425.1119; found 425.1123.

(2*S*,3*S*)-3-(1,3-dioxoisoindolin-2-yl)-4-nitro-2-(4-(trifluoromethyl)benzyl)butanal (3d). White solid (64 %). **M. p.**: 133–137 °C. **$[\alpha]_D^{20}$** = -14.8 (*c* 0.75, $CHCl_3$). **IR** (FTIR): ν 1774, 1711, 1559, 1322, 1065, 1016, 717, 625, 530, 499 cm^{-1}. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 9.76 (s, 1H), 7.70 (s, 2H), 7.29 (d, *J* = 7.8 Hz, 1H), 7.17 (d, *J* = 7.8 Hz, 1H), 5.37 (td, *J* = 10.5, 3.2 Hz, 1H), 5.18 (dd, *J* = 13.0, 10.7 Hz, 1H), 4.85 (dd, J = 13.3, 3.1 Hz, 1H), 3.81 (dd, *J* = 16.2, 7.8 Hz, 1H), 3.16 (dd, *J* = 14.6, 6.3 Hz, 1H), 2.79 (dd, *J* = 14.7, 8.2 Hz, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$): δ 199.4, 167.5, 140.0, 134.6, 130.8, 129.2 (q, $J_{C\text{-}F}$ =32.7 Hz), 128.7, 125.5 (q, $J_{C\text{-}F}$ =3.8 Hz), 123.6 (q, $J_{C\text{-}F}$ = 273.3 Hz), 123.5, 73.5, 51.2, 48.0, 33.1. **HPLC**: Chiralpak IA column, hexane/*i*-PrOH 80:20, 221 nm, flow rate 0.60 mL/min, *ee* 85 %. **HRMS-ESI+** (*m/z*): calculated for $[C_{20}H_{15}F_3N_2O_5+CH_3OH+Na]^+$: 475.1087; found 475.1094.

(2*S*,3*S*)-2-(3-chlorobenzyl)-3-(1,3-dioxoisoindolin-2-yl)-4-nitrobutanal (3e). White solid (84 %). **M. p.**: 183–186 °C. **$[\alpha]_D^{20}$** = -4.9 (*c* 0.55, $CHCl_3$). **IR** (FTIR): ν 1770, 1705, 1556, 1362, 999, 718 cm^{-1}. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 9.74 (s, 1H), 7.74 (dd, *J* = 21.8, 2.6 Hz, 4H), 7.06–7.00 (m, 2H), 6.91 (m, 2H), 5.34 (dd, *J* = 10.3, 7.6 Hz, 1H), 5.24–5.13 (m, 1H), 4.83 (dd, *J* = 13.3, 2.9 Hz, 1H), 3.75 (dd, *J* = 17.0, 7.7 Hz, 1H), 3.03 (dd, *J* = 14.7, 7.0 Hz, 1H), 2.74 (dd, *J* = 14.6, 7.5 Hz, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$): δ 199.8, 167.5, 137.9, 134.6, 134.5, 130.9, 130.0, 128.6, 127.0, 126.6, 123.7, 73.5, 51.2, 47.9, 33.0. **HPLC:** The product **3e** was not determined by HPLC because of poor solubility in the most of organic solvents. **HRMS-ESI+** (*m/z*): calculated for $[C_{19}H_{15}ClN_2O_5+CH_3OH+Na]^+$: 441.0824; found 441.0827.

(2*S*,3*S*)-3-(1,3-dioxoisoindolin-2-yl)-4-nitro-2-(3-(trifluoromethyl)benzyl)butanal (3f). White solid (31 %). **M. p.**: 118–120 °C. **$[\alpha]_D^{20}$** = -21.5 (*c* 1, $CHCl_3$). **IR** (FTIR): ν 1770, 1707, 1559, 1324, 1126, 897, 719 cm^{-1}. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 9.76 (s, 1H), 7.77–7.67 (m, 4H), 7.31-7.20 (m, 4H), 5.36 (td, *J* = 10.3, 3.5 Hz, 1H), 5.18 (dd, *J* = 13.3, 10.3 Hz, 1H), 4.84 (dd, *J* = 13.4, 3.5 Hz, 1H), 3.80 (dd, *J* = 17.0, 6.9 Hz, 1H), 3.13 (dd, *J* = 14.8, 6.9 Hz, 1H), 2.84 (dd, *J* = 14.8, 7.6 Hz, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$): δ 199.6, 167.5, 136.9, 134.5, 131.7, 131.0 (q, $J_{C\text{-}F}$ = 32.4 Hz), 130.8, 129.2, 125.1 (q, $J_{C\text{-}F}$ = 3.7 Hz), 123.7 (q, $J_{C\text{-}F}$ = 3.5 Hz), 123.7, 123.6 (q, $J_{C\text{-}F}$ = 272.4 Hz), 73.5, 51.2, 47.9, 33.1. **HPLC**: Chiralpak IC column, hexane/*i*-PrOH 60:40, 254 nm, flow rate 0.75 mL/min, *ee* 99 %. **HRMS-ESI+** (*m/z*): calculated for $[C_{20}H_{15}F_3N_2O_5+CH_3OH+Na]^+$: 475.1087; found 475.1092.

General procedure for reductive cyclization of nitroaldehydes 3a-f

Freshly activated zinc powder (2.35 g, 36.0 mmol) was added to the suspension of Michael adduct **3a**-**f** (2.4 mmol) in acetic acid/water (1:1, 40 mL) at 0 °C in three portions over the period of 10 min. The reaction mixture was stirred at room temperature for 18–20 h. When the full conversion was observed (TLC), the pH of reaction mixture was adjusted to 12 with 4 M NaOH solution. The white colloid was filtered out and filtrate was extracted with DCM (3×100 mL). The combined organic layers were washed with brine (1×100 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum. The products **4a**-**f** were obtained as yellowish foams and directly used to the next reaction step.

Characterization data for pyrrolidine 4a-f

2-((3*S*,4*R*)-4-benzylpyrrolidin-3-yl)-3-hydroxyisoindolin-1-one (4a). White foam (87 %). **M. p.**: 69–72 °C. **IR** (FTIR): ν 2923, 2851, 1675, 1412, 1372, 1207, 1056, 745, 696, 530, 479 cm^{-1}. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.79–7.74 (m, 1H), 7.57–7.54 (m, 2H), 7.51–7.45 (m, 1.5), 7.26–7.22 (m,

1H), 7.21–7.14 (m, 3.5), 5.97 (s, 0.5H), 5.89 (s, 0.5H), 4.92–4.88 (m, 0.5H), 4.57–4.54 (m, 0.5H), 4.17 (bs, 2H), 3.51 (d, *J* = 11.3 Hz, 0.5H), 3.41 (dd, *J* = 10.3, 8.2 Hz, 0.5H), 3.30–3.20 (m, 1H), 3.17 (dd, *J* = 11.6, 7.1 Hz, 0.5H), 3.11 (dd, *J* = 10.5, 6.1 Hz, 0.5H), 3.02 (dd, *J* = 13.6, 6.0 Hz, 0.5H), 2.89 (dt, *J* = 13.9, 11.2 Hz, 0.5H), 2.83–2.73 (m, 1H), 2.72–2.64 (m, 1H), 2.64–2.58 (m, 1H). Spectral data are in agreement with data published in literature.[24a]

2-((3*S*,4*R*)-4-(4-chlorobenzyl)pyrrolidin-3-yl)-3-hydroxyisoindolin-1-one (4b). White foam (86 %). **M. p.**: 79–81 °C. **$[\alpha]_D^{20}$** +35.0 (*c* 0.8, $CHCl_3$). **IR** (FTIR): ν 2925, 2855, 1674, 1407, 1056, 745, 695 cm^{-1}. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.78 (dd, *J* = 13.0, 7.5 Hz, 1H), 7.58–7.54 (m, 2H), 7.52–7.46 (m, 1H), 7.23 (dd, *J* = 15.8, 8.4 Hz, 2H), 7.15–7.09 (m, 2H), 6.07 (s, 0.5H), 5.97 (s, 0.5H), 4.89 (d, *J* = 11.2 Hz, 0.5H), 4.54 (dd, *J* = 5.7, 2.2 Hz, 0.5H), 3.49 (d, *J* = 11.2 Hz, 0.5H), 3.43–3.35 (m, 1.5H), 3.21–3.16 (m, 0.5H), 3.13 (d, *J* = 10.2 Hz, 0.5H), 3.08 (dd, *J* = 11.3, 6.2 Hz, 0.5H), 3.05–2.99 (m, 1H), 2.77–2.69 (m, 0.5H), 2.68–2.58 (m, 2.5H), 2.53–2.46 (m, 0.5H), 2.31 (bs, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$): δ 167.4&167.0, 143.5&143.4, 138.0&137.5, 132.3&132.2, 132.0&131.9, 133.0&131.3, 130.1&130.0, 129.5&129.4, 128.7&128.5, 123.3&123.1, 123.1&123.0, 81.1&79.9, 56.8&56.3, 51.7&51.6, 51.2&43.3, 49.0&47.5, 39.4&39.2. **HRMS-ESI+** (*m/z*): calculated for $[C_{19}H_{19}ClN_2O_2+H]^+$: 343.1208; found: 343.1210.

2-((3*S*,4*R*)-4-(4-fluorobenzyl)pyrrolidin-3-yl)-3-hydroxyisoindolin-1-one (4c). White foam (91 %). **M. p.**: 64–65 °C. **$[\alpha]_D^{20}$** +28.4 (*c* 1, $CHCl_3$). **IR** (FTIR): ν 3284, 2921, 2855, 1676, 1507, 1217, 745 cm^{-1}. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.77 (dd, *J* = 12.2, 7.5 Hz, 1H), 7.56 (t, *J* = 7.9 Hz, 2H), 7.52–7.44 (m, 1H), 7.16–7.11 (m, 2H), 6.95 (dt, *J* = 15.9, 8.6 Hz, 2H), 6.02 (s, 0.5H), 5.97 (s, 0.5H), 4.88 (d, *J* = 5.2 Hz, 0.5H), 4.53-4.50 (m, 0.5H), 3.46 (d, *J* = 11.2 Hz, 0.5H), 3.42–3.37 (m, 0.5H), 3.34 (dd, *J* = 13.6, 4.9 Hz, 0.5H), 3.21–3.15 (m, 0.5H), 3.12 (d, *J* = 10.1 Hz, 0.5H), 3.07 (dd, *J* = 11.2, 6.3 Hz, 0.5H), 3.04–2.99 (m, 1H), 2.73 (ddd, *J* = 10.6, 5.1, 2.9 Hz, 0.5H), 2.68–2.55 (m, 2H), 2.50 (dd, *J* = 17.4, 7.9 Hz, 0.5H), 2.40–2.35 (bs, 1H), 1.67 (bs, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$): 167.3&166.9, 161.5 (d, *J* = 244.6 Hz)&161.4 (d, *J* = 244.3 Hz), 143.6&143.5, 135.3 (d, *J* =3.1 Hz)&134.8 (d, *J* = 3.2 Hz), 132.15&132.0, 132.0&131.4, 130.2&130.1, 130.1&130.0, 129.5&129.4, 123.3&123.1, 123.0&123.0, 115.4&115.3, 115.2&115.1, 81.2&79.9, 57.0&55.8, 51.9&51.8, 51.4&43.6, 49.4&48.0, 39.4&39.2. **HRMS-ESI+** (*m/z*): calculated for $[C_{19}H_{19}FN_2O_2+H]^+$: 327.1503; found: 327.1503.

3-hydroxy-2-((3*S*,4*R*)-4-(4-(trifluoromethyl)benzyl)pyrrolidin-3-yl)isoindolin-1-one (4d). White foam (62 %). **M. p.**: 68–70 °C. **$[\alpha]_D^{20}$** +23.0 (*c* 1, $CHCl_3$). **IR** (FTIR): ν 3000, 2899, 1731, 1631, 1454, 1347, 1145, 717 cm^{-1}. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.78 (dd, *J* = 14.1, 7.5 Hz, 1H), 7.59–7.55 (m, 1.5), 7.53 (dd, *J* = 11.4, 8.1 Hz, 2.5), 7.48 (dd, *J* = 7.9, 4.0 Hz, 0.5H), 7.30 (t, *J* = 8.6 Hz, 2H), 6.05 (s, 0.5H), 5.97 (s, 0.5H), 4.92 (dd, *J* = 5.2 Hz, 0.5H), 4.57 (dd, *J* = 4.0 Hz, 0.5H), 3.52 (dd, *J* = 11.3 Hz, 0.5H), 3.49-3.39 (m, 1.5H), 3.20 (t, *J* = 9.7 Hz, 1H), 3.16–3.06 (m, 2H), 2.81 (dd, *J* = 3.2 Hz, 1H), 2.78–2.63 (m, 3H), 2.55–2.50 (m, 0.5H). **^{13}C NMR** (151 MHz, $CDCl_3$): 167.4&167.0, 143.5&143.4, 143.6&143.1, 132.3&132.1, 131.9&131.3, 129.6&129.5, 129.1&128.9, 129.2&129.0, 128.8&128.5, 125.5 (q, *J* = 3.6 Hz)&125.3 (q, 3.7 Hz), 124.2 (q, *J* = 271.7 Hz)&124.1 (q, *J* = 271.8 Hz), 123.3&123.0, 123.1&123.0, 81.1&79.9, 56.9&55.7, 51.6&51.6, 51.3&43.1, 49.0&47.4, 39.9&39.6. **HRMS-ESI+** (*m/z*): calculated for $[C_{20}H_{19}F_3N_2O_2+H]^+$: 377.1471; found: 377.1474.

2-((3*S*,4*R*)-4-(3-chlorobenzyl)pyrrolidin-3-yl)-3-hydroxyisoindolin-1-one (4e). White foam (78 %). **M. p.**: 97–100 °C. **$[\alpha]_D^{20}$** +26.3 (*c* 1, $CHCl_3$). **IR** (FTIR): ν 3054, 2853, 1674, 1412, 1373, 1055, 746 cm^{-1}. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.79 (dd, *J* = 14.4, 7.5 Hz, 1H), 7.60–7.54 (m, 2H), 7.53–7.44 (m, 1H), 7.24–7.11 (m, 3H), 7.11–7.02 (m, 1H), 6.08 (s, 0.5H), 5.99 (s, 0.5H), 4.89 (dd, *J* = 5.3 Hz, 0.5H), 4.55 (dd, *J* = 5.9, 2.2 Hz, 0.5H), 3.50 (d, *J* = 11.2 Hz, 0.5H), 3.41 (dd, *J* = 13.6, 4.8 Hz, 1H), 3.22–3.17 (m, 0.5H), 3.15 (d, *J* = 10.2 Hz, 0.5H), 3.09 (dd, *J* = 11.2, 6.3 Hz, 0.5H), 3.04 (dd, *J* = 10.1, 5.7 Hz, 1H), 2.78–2.71 (m, 0.5H), 2.67–2.61 (m, 1.5H), 2.58 (dd, *J* = 13.6, 11.3 Hz, 0.5H), 2.51 (dd, *J* = 9.7, 8.2 Hz, 0.5H), 2.02–1.50 (bs, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$): δ 167.3&166.9, 143.4&143.3, 141.6&141.1, 134.3&134.1, 132.2&132.0, 131.41, 129.9&129.7, 129.5&129.4, 128.9&128.8, 127.0&126.8, 126.7&126.4, 123.3&123.1, 123.1&123.1, 81.0&79.9, 56.9&55.8, 51.9&51.7, 51.4&43.4, 49.2&47.8, 40.0&39.7. **HRMS-ESI+** (*m/z*): calculated for [C19H19ClN2O2+H]+: 343.1208; found: 343.1211.

3-Hydroxy-2-((3*S*,4*R*)-4-(3-(trifluoromethyl)benzyl)pyrrolidin-3-yl)isoindolin-1-one (4f). White foam (82 %). **M. p.**: 78–80 °C. **$[\alpha]_D^{20}$** +27.1 (c 1, $CHCl_3$). **IR** (FTIR): ν 3283, 2924, 1675, 1413, 1325, 1116, 1070, 746, 658 cm^{-1}. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.78 (dd, *J* = 15.2, 7.5 Hz, 1H), 7.59–7.54 (m, 3H), 7.53–7.35 (m, 5H), 6.08 (s, 0.5H), 5.99 (s, 0.5H), 4.90 (dd, *J* = 5.2 Hz, 0.5H), 4.56 (dd, *J* = 6.0, 2.2 Hz, 0.5H), 3.52-3.47 (m, 1H), 3.40 (dd, *J* = 9.5, 7.9 Hz, 0.5H), 3.21–3.13 (m, 1.5H), 3.13–3.08 (m, 0.5H), 3.06 (dd, *J* = 10.2, 5.4 Hz, 0.5H), 2.81–2.76 (m, 1H), 2.76–2.69 (m, 1H), 2.69–2.61 (m, 0.5H), 2.51 (dd, *J* = 9.7, 8.2 Hz, 0.5H), 1.60 (s, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$): δ 167.3&166.9, 143.4&143.4, 140.6&140.1, 132.2&132.1, 132.0&131.9, 131.4&131.4, 130.9&130.7 (q, J = 32.1 Hz), 129.5&129.4, 129.1&128.7, 125.4&125.3 (q, JC-F = 3.8 Hz), 123.6&123.5 (q, $J_{C\text{-}F}$ = 272.4 Hz), 123.4&123.1 (q, $J_{C\text{-}F}$ = 3.7 Hz), 123.3&123.1, 123.1&123.0, 81.0&79.9, 57.0&55.9, 52.0&51.8, 51.4&43.4, 49.3&47.9, 40.1&39.9. **HRMS-ESI+** (*m/z*): calculated for $[C_{20}H_{19}F_3N_2O_2+H]^+$: 377.1471; found: 377.1472.

***N*-Boc protected pyrrolidines 5a-f**

Triethylamine (0.28 mL, 1.95 mmol) and di-*tert*-butyl dicarbonate (340 mg, 1.56 mmol) were at 0 °C added to the solution of pyrrolidine **4a-f** (1.30 mmol) in DCM (19.8 mL). The reaction mixture was stirred at 0 °C for 30 min (the starting material was totally, monitored by TLC). The reaction mixture was then quenched with 10 % aqueous citric acid solution (30 mL) and then was extracted with DCM (3×80 mL). The combined organic layers were washed with brine (1×150 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure. *N*-Boc protected pyrrolidines **5a-f** were obtained as dark yellow foams and directly used to the next reaction step without purification and characterization.

***N*-sulfonamides 5g-h**

Triethylamine (0.21 mL, 1.5 mmol) and methansulfonyl chloride or *p*-toluenesulfonyl chloride (1.2 mmol) were at 0 °C added to the solution of pyrrolidine **4a** (1 mmol) in DCM (15 mL). The reaction mixture was stirred at this temperature for 1–3 h. The reaction mixture was poured into water (20 mL) and then extracted with DCM (3×50 mL). The combined organic layers were dried over Na_2SO_4. Solvent was evaporated under reduced pressure. The crude products were purified by column chromatography using hexanes/EtOAc (2:1) as an eluent. Pyrrolidines **5g,h** were obtained as white foams.

2-((3*S*,4*R*)-4-Benzyl-1-(methylsulfonyl)pyrrolidin-3-yl)-3-hydroxyisoindolin-1-one (5g). White foam (82 %). **M. p.**: 70–73 °C. **$[\alpha]_D^{20}$** -3.1 (*c* 1.05, $CHCl_3$). **IR** (FTIR): ν 3352, 2924, 1670, 1322, 1147, 1039, 74, 697 cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.75 (d, *J* = 8.1 Hz, 1H), 7.76–7.46 (m, 3H), 7.23–6.99 (m, 5H), 5.65 (d, *J* = 11.2 Hz, 0.5H), 5.54 (d, *J* = 11.4 Hz, 0.5H), 4.54 (dd, *J* = 17.3, 8.5 Hz, 0.5H), 4.38 (dd, *J* = 17.5, 8.7 Hz, 0.5H), 4.12 (dd, *J* = 14.3, 7.1 Hz, 0.5H), 3.82–3.57 (m, 2.5H), 3.38 (dt, *J* = 16.2, 8.5 Hz, 0.5H), 3.23-3.06 (m, 1.5), 3.02-2.90 (m, 0.5H), 2.87 (d, *J* = 3.1 Hz, 3H), 2.82–2.51 (m, 2.5H). **^{13}C NMR** (151 MHz, $CDCl_3$): δ 167.6 (2×), 143.4 (2×), 138.7&138.3, 132.71, 131.2&130.9, 130.2&130.1, 128.6

(2×), 128.6&128.5, 126.5 (2×), 123.4&123.3, 123.2&123.1, 82.2&81.6, 56.5&55.8, 51.9&51.7, 49.6&48.9, 42.4&41.9, 37.8&37.6, 35.1&34.9. **HRMS-ESI+** (*m/z*): calculated for $[C_{20}H_{22}N_2O_4S+Na]^+$: 409.1192; found: 409.1194.

2-((3*S*,4*R*)-4-Benzyl-1-tosylpyrrolidin-3-yl)-3-hydroxyisoindolin-1-one (5h). White foam (85 %). **M. p.**: 77–79 °C. **$[\alpha]_D^{20}$** +17.3 (c 0.7, $CHCl_3$). **IR** (FTIR): v 3359, 2922, 1672, 1335, 1153, 1033, 746, 661, 546 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.69 (t, *J* = 8.1 Hz, 3H), 7.62–7.52 (m, 1H), 7.52–7.42 (m, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.21–6.97 (m, 5H), 5.60 (d, *J* = 10.0 Hz, 1H), 4.47–4.26 (m, 1H), 4.17–4.03 (m, 0.5H), 3.72–3.45 (m, 2.5H), 3.29–3.19 (m, 0.5H), 3.00–2.89 (m, 1.5H), 2.87–2.77 (m, 1H), 2.79–2.54 (m, 2H), 2.46 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$): δ 167.7 (2×), 143.9&143.6, 143.6, 138.9&138.3, 133.1&133.0, 132.6 (2×), 131.0&130.8, 129.9 (2×), 129.8, 128.6&128.5, 128.4, 127.6&127.5, 126.4 (2×), 123.2&123.0, 123.2 (2×), 81.8&81.2, 55.9&55.3, 51.7&51.6, 49.9&49.1, 42.1&41.7, 37.8&37.7, 21.6. **HRMS-ESI+** (*m/z*): calculated for $[C_{26}H_{25}N_2O_4S+H]^+$: 485.1505; found: 485.1507.

Oxidation of 3-hydroxyisoindolinones 5a-h

Pyridinium dichromate (PDC) (978 mg, 2.6 mmol) was at RT added to the solution of pyrrolidine **5a**-**h** (1.30 mmol) in DMF (10 mL) and the reaction mixture was stirred at room temperature for 1 h. Reaction mixture was poured into cold water (100 mL) and extracted with EtOAc (3×120 mL). The combined organic layers were washed with brine (1×150 mL) and dried over Na_2SO_4. Solvent was evaporated under reduced pressure. The crude product was purified on silica gel column (hexanes/EtOAc 4:1). Full-protected pyrrolidines **6a**-**h** were obtained as white solids.

Preparation of *N*-Benzyl pyrrolidine derivatives (in two steps):

The 4 M HCl in 1,4-dioxane (3.3 mmol, 0.80 mL) was added to the solution of pyrrolidine **6b,c** (0.33 mmol) in DCM/MeOH (1:1, 4 mL) at room temperature. The reaction mixture was stirred at this temperature for 23 h. When full conversion was achieved (TLC), the solvents were evaporated under reduced pressure to give hydrochloride. The products **7a,b** were obtained by trituration in diethyl ether as light yellow solids (quant. yields) and directly used to the next reaction step.

Triethylamine (0.99 mmol, 0.13 mL), aldehyde (0.33 mmol) and sodium triacetoxyborohydride (0.48 mmol, 101 mg) were added at room temperature to the suspension of hydrochloride **7a,b** in THF (4.4 mL). The reaction mixture was stirred at room temperature for 20 h. Reaction mixture was then diluted in water (40 mL) and extracted with DCM (3×70 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated under vacuum. Crude products were purified by column chromatography (hexanes/EtOAc 4:1–2:1).

Characterization data for protected pyrrolidines 6a-l

***Tert*-butyl (3*R*,4*S*)-3-benzyl-4-(1,3-dioxoisoindolin-2-yl)pyrrolidine-1-carboxylate (6a)**. White solid (66 %). **M. p.**: 107–109 °C. **$[\alpha]_D^{20}$** +5.0 (*c* 0.75, $CHCl_3$). **IR** (FTIR): v 2976, 2924, 1693, 1387, 1152, 880, 702, 650, 530 cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.69 (t, *J* = 6.7 Hz, 4H), 7.06 (d, *J* = 7.2 Hz, 2H), 6.99 (t, *J* = 7.5 Hz, 2H), 6.79 (t, *J* = 7.1 Hz, 1H), 4.54 (dd, *J* = 19.9, 9.8 Hz, 1H), 3.76 (ddd, *J* = 14.7, 10.5, 6.3 Hz, 2H), 3.36–3.57 (m, 1H), 3.56–3.40 (m, 1H), 3.09 (t, *J* = 10.6 Hz, 1H), 2.84 (dd, *J* = 13.7, 6.6 Hz, 1H), 2.60 (dd, *J* = 13.7, 8.2 Hz, 1H), 1.58-1.40 (m, 9H) **^{13}C NMR** (151 MHz, $CDCl_3$): 167.9, 154.2, 138.4, 131.7, 128.4, 128.2, 125.8, 123.0, 79.6, 53.8 (53.2)*, 50.3 (49.8)*, 47.0 (46.6)*, 39.9 (39.2)*, 37.5 (37.4)*, 28.4(2×)*. (*Rotamers) **HRMS-ESI+** (*m/z*): calculated for $[C_{24}H_{26}N_2O_4+Na]^+$: 429.1785; found: 429.1790.

***Tert*-butyl (3*R*,4*S*)-3-(4-chlorobenzyl)-4-(1,3-dioxoisoindolin-2-yl) pyrrolidine-1-carboxylate (6b)**. White solid (66 %). **M. p.**: 139–140 °C. **$[\alpha]_D^{20}$** +4.4 (*c* 1, $CHCl_3$). **IR** (FTIR): v 2974, 1684, 1388, 1127, 712 cm^{-1}. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.72–7.67 (m, 4H), 6.99 (d, *J* = 8.1 Hz, 2H), 6.94 (t, *J* = 6.3 Hz, 2H), 4.52 (dd, *J* = 19.4, 10.1 Hz, 1H), 3.83–3.60 (m, 3H), 3.53–3.40 (m, 1H), 3.07 (dd, *J* = 19.5, 10.1 Hz, 1H), 2.83 (td, *J* = 14.3, 6.1 Hz, 1H), 2.54 (dd, *J* = 13.9, 8.8 Hz, 1H), 1.46 (d, *J* = 19.5 Hz, 9H). **^{13}C NMR** (151 MHz, $CDCl_3$): δ 167.9, 154.2 (154.1)*, 136.8, 164.1 (164.0)*, 132.0, 131.3, 129.7, 128.3, 123.0, 79.7, 53.7 (53.2)*, 50.2 (49.7)*, 47.0 (46.6)*, 39.6 (38.9)*, 36.9 (36.8)*, 28.5 (28.4)*. (*Rotamers) **HRMS-ESI+** (*m/z*): calculated for $[C_{24}H_{25}ClN_2O_4+Na]^+$: 463.1395; found: 463.1400.

***Tert*-butyl (3*S*,4*R*)-3-(1,3-dioxoisoindolin-2-yl)-4-(4-fluorobenzyl) pyrrolidine-1-carboxylate (6c)**. White solid (63 %). **M. p.**: 147–149 °C. **$[\alpha]_D^{20}$** +6.5 (*c* 0.8, $CHCl_3$). **IR** (FTIR): v 2697, 1690, 1686, 1125, 715 cm^{-1}. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.75–7.64 (m, 4H), 7.02 (dd, *J* = 7.6, 5.8 Hz, 2H), 6.68 (t, *J* = 8.3 Hz, 2H), 4.56–4.49 (m, 1H), 3.78 (dt, *J* = 18.4, 9.2 Hz, 1H), 3.76–3.67 (m, 1H), 3.63 (t, *J* = 9.3 Hz, 1H), 3.45 (ddd, *J* = 25.8, 17.5, 8.0 Hz, 1H), 3.07 (dd, *J* = 18.2, 10.3 Hz, 1H), 2.82 (dd, *J* = 13.6, 6.4 Hz, 1H), 2.61–2.52 (m, 1H), 1.46 (d, *J* = 19.1 Hz, 9H). **^{13}C NMR** (151 MHz, $CDCl_3$): δ 167.9, 161.2 (d, $J_{C\text{-}F}$ = 244.6 Hz), 154.2, 134.0 (d, *J* = 4.1 Hz), 134.0 (d, *J* = 2.9 Hz), 131.4 (d, *J* = 4.7 Hz), 129.8 (t, *J* = 7.6 Hz), 123.0, 114.9 (d, *J* = 21.2 Hz), 79.6, 53.8 (53.3)*, 50.2 (49.7)*, 47.0 (46.6)*, 39.7 (39.2)*, 36.7 (36.6)*, 28.5 (28.4)*. (*Rotamers) **HRMS-ESI+** (*m/z*): calculated for $[C_{24}H_{25}FN_2O_4+Na]^+$: 447.1691; found: 447.1694.

***Tert*-butyl (3S,4R)-3-(1,3-dioxoisoindolin-2-yl)-4-(4-(trifluoromethyl) benzyl)pyrrolidine-1-carboxylate (6d).** White solid (76 %). **M. p.** 135–138 °C. **$[\alpha]_D^{20}$** +8.4 (c 1, $CHCl_3$). **IR** (FTIR): v 1690, 1688, 1387, 1317, 1119, 1063, 716 cm^{-1}. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.65 (d, *J* = 5.6 Hz, 4H), 7.21 (d, *J* = 8.3 Hz, 2H), 7.18 (d, *J* = 8.3 Hz, 2H), 4.54 (dd, *J* = 19.1, 10.2 Hz, 1H), 3.84 (dd, *J* = 10.7, 8.1 Hz, 1H), 3.81–3.76 (m, 1H), 3.75–3.66 (m, 1H), 3.66–3.48 (m, 1H), 3.14–3.07 (m, 1H), 3.00–2.93 (m, 1H), 2.64–2.57 (m, 1H), 1.47 (d, *J* = 22.3 Hz, 9H). **^{13}C NMR** (151 MHz, $CDCl_3$): δ 168.0, 154.4 (154.3)*, 142.7, 134.3 (d, J = 9.6 Hz), 131.3 (d, J = 4.3 Hz), 128.9 (d, J = 5.8 Hz), 128.4 (q, JC-F = 32.5 Hz), 125.2 (q, JC-F = 3.5 Hz), 124.87, 123.1, 80.0, 54.0 (53.4)*, 50.4 (49.9)*, 47.2 (46.8)*, 39.7 (39.0)*, 37.6 (37.5)*, 28.7 (28.6)*. (*Rotamers) **HRMS-ESI+** (m/z): calculated for $[C_{25}H_{25}F_3N_2O_4+Na]+$: 497.1659; found: 497.1661.

***Tert*-butyl (3*R*,4*S*)-3-(3-chlorobenzyl)-4-(1,3-dioxoisoindolin-2-yl) pyrrolidine-1-carboxylate (6e)**. White solid (81 %). **M. p.**: 125–126 °C. **$[\alpha]_D^{20}$** +1.2 (*c* 1, $CHCl_3$). **IR** (FTIR): v 2970, 1720, 1694, 1386, 1155, 1116, 882, 715, 531 cm^{-1}. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.74–7.69 (m, 2H), 7.67 (dd, *J* = 5.2, 2.9 Hz, 2H), 7.04 (s, 1H), 6.95 (d, *J* = 7.6 Hz, 1H), 6.91 (d, *J* = 7.7 Hz, 1H), 6.72 (d, *J* = 6.9 Hz, 1H), 4.52 (dt, *J* = 10.1, 8.2 Hz, 1H), 3.80 (dt, *J* = 10.7, 4.6 Hz, 1H), 3.77–3.67 (m, 1H), 3.63 (t, *J* = 9.4 Hz, 1H), 3.56–3.40 (m, 1H), 3.08 (td, *J* = 10.7, 4.6 Hz, 1H), 2.84 (dd, *J* = 13.7, 6.0 Hz, 1H), 2.58-2.52 (m, 1H), 1.46 (d, *J* = 20.2 Hz, 9H). **^{13}C NMR** (151 MHz, $CDCl_3$): δ 167.8, 154.2 (154.1)*, 140.4, 133.9, 133.9, 131.3, 129.5, 128.5, 126.6, 126.0, 123.0, 79.7, 53.8 (53.7)*, 50.1 (49.6)*, 46.9 (46.5)*, 36.64 (39.0)*, 37.2 (37.1)*, 28.5 (28.4)*. (*Rotamers) **HRMS-ESI+** (*m/z*): calculated for $[C_{24}H_{25}ClN_2O_4+Na]^+$: 463.1395; found: 463.1403.

***Tert*-butyl (3S,4*R*)-3-(1,3-dioxoisoindolin-2-yl)-4-(3-(trifluoromethyl) benzyl)pyrrolidine-1-carboxylate (6f)**. White solid (89 %). **M. p.**: 46–48 °C. **$[\alpha]_D^{20}$** +4.4 (*c* 0.75, $CHCl_3$). **IR** (FTIR): v 2974, 1710, 1687, 1383, 1325, 1160, 1117, 881, 716, 529 cm^{-1}. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.69–7.63 (m, 4H), 7.32 (s, 1H), 7.12 (t, *J* = 7.7 Hz, 2H), 7.05-7.02 (m, 1H), 4.60–4.51 (m, 1H), 3.84–3.77 (m, 1H), 3.77–3.72 (m, 1H), 3.72–3.61 (m, 1H), 3.60–3.47 (m, 1H), 3.10 (t, *J* = 10.6 Hz, 1H), 2.93 (dd, *J* = 13.8, 6.1 Hz, 1H), 2.64 (dt, *J* = 13.8, 9.4 Hz, 1H), 1.46 (d, *J* = 20.6 Hz, 9H). **^{13}C NMR** (151 MHz, $CDCl_3$): δ 167.7, 154.2, 139.4, 134.0 (d), 131.8, 131.2, 130.5 (q, $J_{C\text{-}F}$ = 32.3 Hz), 128.7, 125.0 (q, $J_{C\text{-}F}$ = 3.8 Hz), 123.6 (q, $J_{C\text{-}F}$ = 272.4

Hz), 123.1, 127.4 (d), 79.7, 53.7(53.2)*, 50.2(49.7)*, 46.9(46.5)*, 39.7(39.0)*, 37.4(37.3)*, 28.4. (*Rotamers) **HRMS-ESI+** (*m/z*): calculated for $[C_{25}H_{25}F_3N_2O_4+Na]^+$: 497.1659; found: 497.1662.

2-((3*S*,4*R*)-4-benzyl-1-(methylsulfonyl)pyrrolidin-3-yl)isoindoline-1,3-dione (6g). White solid (75 %). **M. p.**: 168–169 °C. **$[\alpha]_D^{20}$** +11.5 (*c* 1, $CHCl_3$). **IR** (FTIR): ν 1705, 1386, 1317, 1145, 1035, 721, 642, 518 cm^{-1}. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.76–7.66 (m, 4H), 7.10–7.03 (m, 4H), 6.89 (dd, *J* = 7.5, 5.3 Hz, 1H), 4.65 (dd, *J* = 18.6, 9.3 Hz, 1H), 3.78–3.67 (m, 3H), 3.48–3.36 (m, 1H), 3.21 (t, *J* = 10.1 Hz, 1H), 2.93 (s, 3H), 2.82 (dd, *J* = 13.9, 7.2 Hz, 1H), 2.67 (dd, *J* = 13.9, 7.8 Hz, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$): δ 167.7, 137.8, 134.1, 131.4, 128.4, 128.4, 126.2, 123.2, 53.8, 51.7, 48.2, 41.0, 37.3, 35.1. **HRMS-ESI+** (*m/z*): calculated for $[C_{20}H_{20}N_2O_4S+Na]^+$: 407.1036; found: 407.1037.

2-((3*S*,4*R*)-4-Benzyl-1-tosylpyrrolidin-3-yl)isoindoline-1,3-dione (6h). White solid (79 %). **M. p.**: 179–182 °C. **$[\alpha]_D^{20}$** +6.9 (*c* 0.85, $CHCl_3$). **IR** (FTIR): ν 1702, 1333, 1323, 1149, 1028, 718, 667, 544 cm^{-1}. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.72 (d, *J* = 8.2 Hz, 2H), 7.69–7.63 (m, 4H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.03–6.96 (m, 4H), 6.85–6.79 (m, 1H), 4.41 (dd, *J* = 18.8, 9.6 Hz, 1H), 3.66–3.57 (m, 3H), 3.39–3.29 (m, 1H), 3.06 (t, *J* = 9.6 Hz, 1H), 2.75 (dd, *J* = 13.9, 7.0 Hz, 1H), 2.54 (dd, *J* = 13.9, 8.1 Hz, 1H), 2.48 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$): δ 167.6, 143.7, 137.9, 134.0, 133.7, 131.3, 129.8, 128.3, 128.3, 127.5, 126.0, 123.1, 53.4, 51.6, 48.4, 40.1, 37.5, 21.6. **HRMS-ESI+** (*m/z*): calculated for $[C_{26}H_{24}N_2O_4S+Na]^+$: 483.1349; found: 483.1352.

2-((3*S*,4*R*)-4-(4-chlorobenzyl)-1-(4-(trifluoromethyl)benzyl)pyrrolidin-3-yl)isoindoline-1,3-dione (6i). White solid (92 %). **M. p.**: 93–95 °C. **$[\alpha]_D^{20}$** +9.4 (*c* 1, $CHCl_3$). **IR** (FTIR): ν 2814, 1702, 1383, 1323, 1120, 1064, 880, 717, 503 cm^{-1}. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.75 (dd, *J* = 5.3, 3.1 Hz, 2H), 7.68 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.57 (d, *J* = 8.0 Hz, 2H), 7.47 (d, *J* = 7.9 Hz, 2H), 7.04 (q, *J* = 8.5 Hz, 4H), 4.55 (q, *J* = 8.1 Hz, 1H), 3.79 (d, *J* = 13.6 Hz, 1H), 3.67 (d, *J* = 13.6 Hz, 1H), 3.17 (dq, *J* = 15.3, 7.7 Hz, 1H), 2.95 (d, *J* = 8.8 Hz, 1H), 2.92 (d, *J* = 8.5 Hz, 2H), 2.81 (dd, *J* = 13.8, 7.7 Hz, 1H), 2.71 (dd, *J* = 13.8, 7.9 Hz, 1H), 2.63 (dd, *J* = 9.2, 5.6 Hz, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$): δ 167.9, 143.1, 134.0, 131.8, 131.6, 130.0, 129.3 (q, *J* = 32.2 Hz), 128.6, 128.3, 126.8, 125.2 (q, *J* = 3.7 Hz), 124.2 (q, *J* = 272.0 Hz), 123.0, 59.6, 58.2, 55.9, 54.3, 41.6, 39.1. **HRMS-ESI+** (*m/z*): calculated for $[C_{27}H_{22}ClF_3N_2O_2+H]^+$: 499.1395; found: 499.1400.

2-((3*S*,4*R*)-4-(4-chlorobenzyl)-1-(4-methoxybenzyl)pyrrolidin-3-yl) isoindoline-1,3-dione (6j). Yellow oil (87 %). **$[\alpha]_D^{05}$** +12.8 (*c* 0.6, $CHCl_3$). **IR** (FTIR): ν 2810, 1706, 1510, 1241, 1170, 881, 716, 529 cm^{-1}. ^{1}H (600 MHz, $CDCl_3$): δ 7.75–7.73 (m, 2H), 7.69–7.67 (m, 2H), 7.26–7.24 (m, 1H), 7.03–7.01 (m, 5H), 6.86–6.84 (m, 2H), 4.53 (q, *J* = 7.8 Hz, 1H), 3.80 (s, 3H), 3.67 (d, *J* = 13.2 Hz, 1H), 3.57 (d, *J* = 12.6 Hz, 1H), 3.15 (dq, *J* = 7.8, 5.4 Hz, 1H), 2.93–2.85 (m, 3H), 2.81 (dd, *J* = 13.8, 7.2 Hz, 1H), 2.69 (dd, *J* = 13.8, 7.8 Hz, 1H), 2.62 (dd, *J* = 9.0, 5.4 Hz, 1H). **^{13}C NMR** (150 MHz, $CDCl_3$): δ 167.9, 158.6, 138.2, 133.9, 131.7, 131.6, 130.9, 130.0, 129.7, 128.2, 123.0, 113.6, 59.5, 58.0, 55.8, 55.2, 54.4, 41.4, 39.2. **HRMS-ESI+** (*m/z*): calculated for $[C_{27}H_{25}ClN_2O_3+H]^+$: 461.1626; found: 461.1631.

2-((3*S*,4*R*)-1-(4-chlorobenzyl)-4-(4-fluorobenzyl)pyrrolidin-3-yl) isoindoline-1,3-dione (6k). White solid (86 %). **M. p.**: 112–114 °C. **$[\alpha]_D^{20}$** +8.7 (*c* 1, $CHCl_3$). **IR** (FTIR): ν 2905, 2841, 2808, 1773, 1698, 1510, 1386, 1039, 802, 704 cm^{-1}. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.76–7.73 (m, 2H), 7.70–7.66 (m, 2H), 7.28 (s, 4H), 7.05 (dd, *J* = 8.2, 5.6 Hz, 2H), 6.78 (t, *J* = 8.6 Hz, 2H), 4.54 (q, *J* = 8.1 Hz, 1H), 3.70 (dd, *J* = 10.7 Hz, 1H), 3.58 (d, *J* = 13.3 Hz, 1H), 3.14 (dq, *J* = 15.2, 7.6 Hz, 1H), 2.94-2.85 (m, 3H), 2.80 (dd, *J* = 13.8, 7.8 Hz, 1H), 2.71 (dd, *J* = 13.8, 7.9 Hz, 1H), 2.62 (dd, *J* = 9.2, 5.4 Hz, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$): δ 167.9, 161.2 (d, *J* = 244.0 Hz), 137.4, 135.2 (d, *J* = 3.1 Hz), 133.9, 132.6, 131.6, 130.03 (d, *J* = 7.8 Hz), 129.8, 128.6, 128.4, 128.2, 59.4, 58.2, 55.9, 54.3, 41.8, 39.1. **HRMS-ESI+** (*m/z*): calculated for $[C_{26}H_{22}ClFN_2O_2+H]^+$: 449.1427; found: 449.1431.

2-((3*S*,4*R*)-4-(4-fluorobenzyl)-1-(4-methoxybenzyl)pyrrolidin-3-yl) isoindoline-1,3-dione (6l). Yellow oil (81 %). **$[\alpha]_D^{20}$** +15.6 (*c* 1, $CHCl_3$). **IR** (FTIR): ν 2903, 2931, 2792, 1700, 1509, 1385, 1217, 1038, 715, 529 cm^{-1}. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.77–7.71 (m, 2H), 7.70–7.65 (m, 2H), 7.25–7.27 (m, 2H), 7.05 (dd, *J* = 8.2, 5.6 Hz, 2H), 6.85 (dd, *J* = 8.5 Hz, 2H), 6.77 (t, *J* = 8.6 Hz, 2H), 4.54 (q, *J* = 8.2 Hz, 1H), 3.80 (s, 3H), 3.67 (dd, *J* = 12.8 Hz, 1H), 3.57 (d, *J* = 12.8 Hz, 1H), 3.14 (dq, *J* = 15.4, 7.7 Hz, 1H), 2.92 (dt, *J* = 15.3, 8.6 Hz, 2H), 2.86 (t, *J* = 8.8 Hz, 1H), 2.81 (dd, *J* = 13.8, 7.8 Hz, 1H), 2.70 (dd, *J* = 13.8, 7.9 Hz, 1H), 2.64 (dd, *J* = 9.2, 5.2 Hz, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$): δ 167.9, 161.2 (d, *J* = 243.9 Hz), 135.4 (d, *J* = 3.2 Hz), 133.9, 131.7, 131.0, 130.0 (d, *J* = 7.7 Hz), 129.7, 128.6, 114.9, 114.8, 113.6, 59.5, 58.1, 55.9, 55.2, 54.4, 41.7, 39.2. **HRMS-ESI+** (*m/z*): calculated for $[C_{27}H_{25}FN_2O_3+H]^+$: 445.1922; found: 445.1925.

Hydrazinolysis of phthalimido protection group

Hydrazine hydrate (0.18 mL, 3.75 mmol) was added at room temperature to the solution of pyrrolidine **6a-l** (0.25 mmol) in THF/EtOH (8:1, 2.7 mL). The reaction mixture was stirred at room temperature (at 50 °C for compounds **6g** and **6e**) for 20 h. The solvent was evaporated under reduced pressure and crude products were purified on silica gel column (DCM/MeOH 95:5). The products were obtained as yellow oils or as yellowish solids.

Characterization data for amines 8a-l

***Tert*-butyl (3*S*,4*R*)-3-amino-4-benzylpyrrolidine-1-carboxylate (8a).** White solid (74 %). **M. p.**: 64–66 °C. **$[\alpha]_D^{20}$** -50.7 (c 1, $CHCl_3$). **IR** (FTIR): ν 3358, 2933, 1679, 1472, 1407, 1366, 1163, 1135, 1076, 878, 743, 699, 543 cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.36–7.23 (m, 3H), 7.19 (t, *J* = 8.9 Hz, 2H), 3.79–3.61 (m, 1H), 3.61–3.43 (m, 1H), 3.25–3.12 (m, 1H), 3.12–2.92 (m, 3H), 2.87 (dd, *J* = 13.7, 5.9 Hz, 1H), 2.63–2.47 (m, 1H), 1.44 (s, 9H), 1.39 (bs, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 154.4, 139.7, 128.7, 128.5, 126.3, 79.3, 59.0 (55.2)*, 53.8 (53.3)*, 50.1 (49.9)*, 48.7 (48.2)*, 37.7 (37.6)*, 28.5. (*Rotamers) **HRMS-ESI+** (*m/z*): calculated for $[C_{16}H_{24}N_2O_2+H]^+$: 277.1911; found: 277.1913.

***Tert*-butyl (3*S*,4*R*)-3-amino-4-(4-chlorobenzyl)pyrrolidine-1-carboxylate (8b).** Yellow oil (86 %). **$[\alpha]_D^{20}$** -53.6 (c 1, $CHCl_3$). **IR** (FTIR): ν 2972, 2930, 2874, 1682, 1364, 1163, 1090, 769 cm^{-1}. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.30–7.22 (m, 2H), 7.13–7.08 (m, 2H), 3.68 (ddd, *J* = 23.8, 18.4, 11.4 Hz, 1H), 3.50 (ddd, *J* = 34.4, 18.6, 10.8 Hz, 1H), 3.16 (t, *J* = 18.2 Hz, 1H), 3.10–2.93 (m, 2H), 2.86 (dd, *J* = 10.8, 5.6 Hz, 1H), 2.59–2.40 (m, 1H), 2.12–2.01 (m, 1H), 1.47 (bs, 2H), 1.44 (s, 9H). **^{13}C NMR** (150 MHz, $CDCl_3$): δ 154.4, 138.1 (138.0)*, 132.1, 130.0, 128.7 (128.6)*, 79.5 (79.4)*, 55.9 (55.1)*, 53.7 (53.1)*, 49.8 (49.7)*, 48.3 (47.9)*, 37.0 (36.9)*, 28.5. (*Rotamers) **HRMS-ESI+** (*m/z*): calculated for $[C_{16}H_{23}ClN_2O_2+Na]^+$: 333.1340; found: 333.1342.

***Tert*-butyl (3*S*,4*R*)-3-amino-4-(4-fluorobenzyl)pyrrolidine-1-carboxylate (8c).** Yellow oil (92 %). **$[\alpha]_D^{20}$** -49.7 (c 0.25, $CHCl_3$). **IR** (FTIR): ν 2932, 1684, 1508, 1402, 1219, 1156, 815, 770 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.14–7.09 (m, 2H), 7.01–6.93 (m, 2H), 3.76–3.63 (m, 1H), 3.58–3.44 (m, 1H), 3.15 (d, *J* = 4.7 Hz, 1H), 3.11–2.93 (m, 2H), 2.86 (dd, *J* = 13.7, 5.1 Hz, 1H), 2.57–2.41 (m, 1H), 2.11–1.98 (m, 1H), 1.70–1.50 (m, 2H), 1.44 (s, 9H). **^{13}C NMR** (151 MHz, $CDCl_3$): δ 161.5 (d, *J* = 244.4 Hz), 154.5, 135.3, 130.03 (d, *J* = 7.8 Hz), 115.3 (d, *J* = 21.2 Hz), 79.4, 56.0 (55.2)*, 53.9 (53.4)*, 49.9 (49.7)*, 48.7 (48.3)*, 36.9 (36.8)*, 28.5. (*Rotamers) **HRMS-ESI+** (*m/z*): calculated for $[C_{16}H_{23}FN_2O_2+Na]^+$: 317.1636; found: 317.1636.

***Tert*-butyl (3*S*,4*R*)-3-amino-4-(4-(trifluoromethyl)benzyl)pyrrolidine-1-carboxylate (8d).** Yellow oil (89 %). **$[\alpha]_D^{20}$** -37.1 (c 0.7, $CHCl_3$). **IR** (FTIR): v 2975, 2933, 1682, 1406, 1321, 1065, 1017, 885, 770 cm^{-1}. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.55 (dd, *J* = 17.5, 7.7 Hz, 2H), 7.29 (dd, *J* = 6.5 Hz, 2H), 3.78-3.64 (m, 1H), 3.55–3.43 (m, 1H), 3.16 (dd, *J* = 7.1 Hz, 1H), 3.09–2.93 (m, 3H), 2.59 (dd, J = 22.5, 9.1 Hz, 1H), 2.17–2.02 (m, 1H), 1.52 (d, *J* = 29.7 Hz, 2H), 1.44 (s, 9H). **^{13}C NMR** (151 MHz, $CDCl_3$): δ 154.4, 143.7, 129.0, 128.8 (q, $J_{C\text{-}F}$ = 32.2 Hz), 125.5, 124.16 (q, $J_{C\text{-}F}$ = 272.0 Hz), 79.6 (79.5)*, 55.9 (55.1)*, 53.6 (53.0)*, 49.8 (49.6)*, 48.0 (47.7)*, 37.4 (37.3)*, 28.4. (*Rotamers) **HRMS-ESI+** (*m/z*): calculated for $[C_{17}H_{23}F_3N_2O_2+H]^+$: 345.1784; found: 345.1783.

***Tert*-butyl (3*S*,4*R*)-3-amino-4-(3-chlorobenzyl)pyrrolidine-1-carboxylate (8e).** Yellow oil (89 %). **$[\alpha]_D^{20}$** -33.4 (c 1, $CHCl_3$). **IR** (FTIR): v 2972, 2930, 1678, 1403, 1364, 1161, 885, 772, 683 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.25–7.15 (m, 3H), 7.08–7.04 (m, 1H), 3.76 (dt, *J* = 17.0, 11.7 Hz, 1H), 3.59–3.47 (m, 1H), 3.34–3.18 (m, 1H), 3.11–3.00 (m, 1H), 2.99–2.88 (m, 1H), 2.73 (bs, 2H), 2.51 (dd, *J* = 22.0, 9.7 Hz, 1H), 2.37–2.30 (m, 1H), 2.22–2.16 (m, 1H), 1.43 (s, 9H). **^{13}C NMR** (151 MHz, $CDCl_3$): δ 154.5 (154.4)*, 141.3 (141.2)*, 134.31, 129.9, 128.8, 126.9, 126.7, 79.9 (79.6)*, 55.5 (54.5)*, 52.5 (51.4)*, 49.5, 46.7 (46.5)*, 37.06, 28.4. (*Rotamers) **HRMS-ESI+** (*m/z*): calculated for $[C_{16}H_{23}ClN_2O_2+Na]^+$: 333.1340; found: 333.1341.

***Tert*-butyl (3*S*,4*R*)-3-amino-4-(3-(trifluoromethyl)benzyl)pyrrolidine-1-carboxylate (8f).** Yellow oil (55 %). **$[\alpha]_D^{20}$** -43.1 (c 1, $CHCl_3$). **IR** (FTIR): v 2923, 1684, 1406, 1326, 1117, 1071, 702, 661 cm^{-1}. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.51–7.45 (m, 1H), 7.45–7.38 (m, 2H), 7.38–7.33 (m, 1H), 3.78–3.65 (m, 1H), 3.56–3.41 (m, 1H), 3.17 (s, 1H), 3.07–2.94 (m, 3H), 2.58 (dd, *J* = 22.2, 8.9 Hz, 1H), 2.09 (ddd, *J* = 22.5, 14.2, 7.5 Hz, 1H), 1.44 (s, 9H), 1.19 (s, 2H). **^{13}C NMR** (150 MHz, $CDCl_3$): δ 154.4, 140.6, 132.1, 130.9 (q, *J* = 32.0 Hz), 129.7, 129.0, 125.3, 124.1 (q, *J* = 272.4 Hz), 123.3 (q, J = 3.8 Hz), 79.4, 56.0 (55.2), 53.7 (53.2), 49.7 (49.7), 48.3 (47.9), 28.4. (*Rotamers) **HRMS-ESI+** (*m/z*): calculated for $[C_{17}H_{23}F_3N_2O_2+Na]^+$: 367.1604; found: 367.1604.

(3*S*,4*R*)-4-Benzyl-1-(methylsulfonyl)pyrrolidin-3-amine (8g). White solid (90 %). **M. p.**: 104–105 °C. **$[\alpha]_D^{20}$** -36.7 (c 1, $CHCl_3$). **IR** (FTIR): v 3377, 861, 1314, 1141, 1016, 750, 702, 513, 460 cm^{-1}. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.30 (t, *J* = 7.5 Hz, 2H), 7.23 (t, *J* = 7.4 Hz, 1H), 7.17 (d, *J* = 7.1 Hz, 2H), 3.68 (dd, *J* = 10.1, 6.4 Hz, 1H), 3.49 (dd, *J* = 9.9, 7.3 Hz, 1H), 3.30 (q, *J* = 6.5 Hz, 1H), 3.12 (dd, *J* = 9.9, 7.2 Hz, 1H), 3.01 (dd, *J* = 10.1, 6.3 Hz, 1H), 2.90 (dd, *J* = 13.8, 6.1 Hz, 1H), 2.82 (s, 3H), 2.59 (dd, *J* = 13.7, 9.0 Hz, 1H), 2.22–2.14 (m, 1H), 1.43 (bs, 2H). **^{13}C NMR** (151 MHz, $CDCl_3$): δ 139.1, 128.7, 128.7, 126.6, 56.0, 55.2, 51.5, 49.1, 37.5, 34.9. **HRMS-ESI+** (*m/z*): calculated for $[C_{12}H_{18}N_2O_2S+H]^+$: 255.1162; found: 255.1162.

(3*S*,4*R*)-4-Benzyl-1-tosylpyrrolidin-3-amine (8h). White solid (67 %). **M. p.:** 54–56 °C. **$[\alpha]_D^{20}$** -36.4 (c 1, $CHCl_3$). **IR** (FTIR): v 3344, 2920, 1583, 1493, 1330, 1155, 1024, 811, 583, 460 cm^{-1}. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.68 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 7.3 Hz, 2H), 7.21 (t, *J* = 7.4 Hz, 1H), 7.07 (d, *J* = 7.2 Hz, 2H), 3.59 (dd, *J* = 10.0, 6.7 Hz, 1H), 3.39 (dd, *J* = 10.1, 7.5 Hz, 1H), 3.07 (q, *J* = 6.8 Hz, 1H), 2.99 (dd, *J* = 10.1, 7.4 Hz, 1H), 2.88 (dd, *J* = 10.0, 6.7 Hz, 1H), 2.75 (dd, *J* = 13.8, 6.0 Hz, 1H), 2.44 (s, *J* = 4.1 Hz, 4H), 2.00 (dq, *J* = 14.5, 7.2 Hz, 1H), 1.31 (bs, 2H). **^{13}C NMR** (151 MHz, $CDCl_3$): δ 143.5, 139.1, 133.6, 129.7, 128.6, 128.6, 127.5, 126.5, 56.0, 55.3, 51.6, 48.8, 37.7, 21.5. **HRMS-ESI+** (*m/z*): calculated for $[C_{18}H_{22}N_2O_2S+H]^+$: 331.1475; found: 331.1474.

(3*S*,4*R*)-4-(4-Chlorobenzyl)-1-(4-(trifluoromethyl)benzyl)pyrrolidin-3-amine (8i). Yellowish oil (90 %). **$[\alpha]_D^{20}$** -29.0 (c 0.5, $CHCl_3$). **IR** (FTIR): v 2900, 1511, 1310, 1120, 970, 520 cm^{-1}. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.53 (d, *J* = 8.0 Hz, 2H), 7.47 (d, *J* = 7.8 Hz, 2H), 7.18 (d, *J* = 8.2 Hz, 2H), 7.10 (d, *J* = 8.2 Hz, 2H), 3.69−3.63 (m, 2H), 3.40−3.36 (m, 1H), 2.98 (dd, *J* = 13.7, 5.9 Hz, 1H), 2.91 (t, *J* = 8.5 Hz, 1H), 2.80−2.75 (m, 1H), 2.75−2.72 (m, 2H), 2.59 (dd, *J* = 13.4, 9.9 Hz, 1H), 2.43−2.36 (m, 1H), 2.20−2.12 (m, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$): δ 142.9, 138.8, 131.9, 130.0, 129.2 (q, $J_{C\text{-}F}$ = 32.2 Hz), 128.7, 128.6, 125.2 (q, $J_{C\text{-}F}$ = 3.7 Hz), 124.2 (q, $J_{C\text{-}F}$ = 271.9 Hz), 62.6, 59.6, 59.1, 56.7, 49.6, 39.1. **HRMS-ESI+** (*m/z*): calculated for $[C_{19}H_{20}ClF_3N_2+H]^+$: 369.1340; found: 369.1342.

(3*S*,4*R*)-4-(4-Chlorobenzyl)-1-(4-methoxybenzyl)pyrrolidin-3-amine (8j). Yellowish oil (82 %). **$[\alpha]_D^{20}$** -18.1 (c 0.2, $CHCl_3$). **IR** (FTIR): v 2920, 1510, 1244, 1032, 813, 516 cm^{-1}. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.28 (d, *J* = 8.4 Hz, 2H), 7.23 (d, *J* = 8.4 Hz, 2H), 7.11 (d, *J* = 8.3 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 3.79 (s, 3H), 3.68 (q, *J* = 12.6 Hz, 2H), 3.27 (q, *J* = 8.3 Hz, 1H), 2.99–2.84 (m, 4H), 2.68–2.59 (m, 2H), 2.38–2.30 (m, 1H), 2.29–2.22 (m, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$): δ 159.1, 138.7, 132.1, 130.3, 129.9, 129.6, 128.8, 63.2, 61.5, 59.4, 58.7, 56.5, 55.4, 48.7, 38.8. **HRMS-ESI+** (*m/z*): calculated for $[C_{19}H_{23}ClN_2O+H]^+$: 331.1572; found: 331.1575.

(3*S*,4*R*)-1-(4-chlorobenzyl)-4-(4-fluorobenzyl)pyrrolidin-3-amine (8k). Yellow oil (74 %). **$[\alpha]_D^{20}$** -14.9 (c 0.7, $CHCl_3$). **IR** (FTIR): v 2920, 2853, 2795, 1219, 1014, 803 cm^{-1}. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.29–7.23 (m, 4H), 7.13 (dd, *J* = 8.1, 5.6 Hz, 2H), 6.92 (t, *J* = 8.6 Hz, 2H), 4.13 (bs, 2H), 3.59 (dd, *J* = 13.2 Hz, 1H), 3.54 (dd, *J* = 13.2 Hz, 1H), 3.29 (dd, *J* = 9.7, 4.0 Hz, 1H), 2.91 (dt, *J* = 14.3, 7.1 Hz, 1H), 2.86 (t, *J* = 8.5 Hz, 1H), 2.78–2.72 (m, 1H), 2.60 (dt, *J* = 12.1, 6.2 Hz, 2H), 2.32–2.24 (m, 1H), 2.20–2.14 (m, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$): δ 161.4 (d, $J_{C\text{-}F}$ = 244.0 Hz), 137.2, 136.0 (d, *J* = 3.2 Hz), 132.6, 130.1, 130.0, 129.9, 115.2 (d, *J* = 21.2 Hz), 62.4, 59.4, 59.1, 56.6, 49.6, 38.9. **HRMS-ESI+** (*m/z*): calculated for $[C_{18}H_{20}ClFN_2+H]^+$: 319.1372; found: 319.1372.

(3*S*,4*R*)-4-(4-Fluorobenzyl)-1-(4-methoxybenzyl)pyrrolidin-3-amine (8l). Yellow oil (64 %). **$[\alpha]_D^{20}$** -22.8 (c 0.2, $CHCl_3$). **IR** (FTIR): v 2910, 2786, 1507, 1242, 1217, 1032, 814 cm^{-1}. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.22 (d, *J* = 8.4 Hz, 2H), 7.13 (dd, *J* = 8.2, 5.6 Hz, 2H), 6.95 (t, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.5 Hz, 2H), 3.79 (s, 3H), 3.57 (d, *J* = 12.8 Hz, 1H), 3.49 (d, *J* = 12.8 Hz, 1H), 3.13 (dd, *J* = 11.0, 5.0 Hz, 1H), 2.84–2.83 (m, 3H), 2.62 (dd, *J* = 13.7, 8.6 Hz, 1H), 2.42 (dd, *J* = 9.5, 4.7 Hz, 1H), 2.19 (dd, *J* = 17.1, 9.1 Hz, 1H), 2.07 (dq, *J* = 14.6, 7.3 Hz, 1H), 1.81 (bs, 2H). **^{13}C NMR** (151 MHz, $CDCl_3$): δ 161.3 (d, $J_{C\text{-}F}$ = 244.0 Hz), 158.7, 136.0 (d, $J_{C\text{-}F}$ = 3.2 Hz), 130.2, 130.0 (d, $J_{C\text{-}F}$ = 7.7 Hz), 130.0, 115.2 (d, $J_{C\text{-}F}$ = 21.1 Hz), 113.6, 62.1, 59.4, 58.8, 56.5, 55.2, 49.5, 38.8. **HRMS-ESI+** (*m/z*): calculated for $[C_{19}H_{23}FN_2O+H]^+$: 315.1867; found: 315.1865.

Sulfonamides **9a**,**b** were prepared from amine **8a** by the same procedure as sulfonamides **5g**,**h**.

Characterization of sulfonamides 9a,b

***Tert*-butyl (3*R*,4*S*)-3-benzyl-4-(methylsulfonamido)pyrrolidine-1-carboxylate (9a).** White solid (82 %). **M. p.**: 100–103 °C. **$[\alpha]_D^{20}$** -41.9 (c 1, $CHCl_3$). **IR** (FTIR): v 3224, 2931, 1697, 1395, 1318, 1132, 984, 764, 742, 536, 515 cm^{-1}. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.31 (t, *J* = 6.9 Hz, 2H), 7.26 –7.21 (m, 1H), 7.17 (d, *J* = 7.2 Hz, 2H), 4.45–4.42 (m, 1H), 3.88–3.84 (m, 1H), 3.72–3.69 (d, *J* = 6.6 Hz, 1H), 3.53–3.48 (2, 1H), 3.24–3.15 (m, 1H), 3.13–3.06 (m, 1H), 2.97–2.89 (m, 4H), 2.64 (s, 1H), 2.37–2.27 (s, 1H), 1.44 (s, 9H). **^{13}C NMR** (151 MHz, $CDCl_3$): δ 154.2, 138.6, 128.7, 126.6, 79.9, 57.1 (56.3*), 51.9 (51.0)*, 49.1 (48.9)*, 46.2 (45.4)*, 41.4 (41.4)*, 37.1 (37.0)*, 28.4. (*Rotamers) **HRMS-ESI+** (*m/z*): calculated for $[C_{17}H_{26}N_2O_4S+Na]^+$: 377.1505; found: 377.1507.

***Tert*-butyl (3*R*,4*S*)-3-benzyl-4-(phenylsulfonamido)pyrrolidine-1-carboxylate (9b).** White solid (81 %). **M. p.:** 56–57 °C. **$[\alpha]_D^{25}$** -27.1 (c 1, $CHCl_3$). IR (FTIR): v 3220, 2973, 1664, 1402, 1326, 1156, 1092, 662, 545

cm^{-1}. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.68 (d, *J* = 7.9 Hz, 1H), 7.29 (d, *J* = 7.9 Hz, 2H), 7.26–7.19 (m, 3H), 7.07–7.01 (m, 1H), 4.58 (d, *J* = 7.5 Hz, 1H), 3.61–3.52 (m, 1H), 3.52–3.46 (m, 1H), 3.46–3.40 (m, 1H), 3.02–2.93 (m, 2H), 2.80–2.70 (m, 1H), 2.51–2.46 (m, 1H), 2.43 (s, 3H), 2.30–2.20 (m, 1H), 1.40 (s, 9H). **^{13}C NMR** (150 MHz, $CDCl_3$): δ 154.2, 143.7, 138.8 (138.5)*, 137.2, 129.9 (129.8)*, 128.7, 128.6, 127.1 (127.0)*, 126.4, 79.7, 56.6 (56.0)*, 51.5 (50.5)*, 49.0 (48.7)*, 46.0 (45.1)*, 36.8 (36.8)*, 28.4, 21.5. (*Rotamers) **HRMS-ESI+** (*m/z*): calculated for $[C_{23}H_{30}N_2O_4S+Na]^+$: 453.1818; found: 453.1823.

Tested bacteria and determination of antimicrobial efficiency

Biological experiments were performed on the reference strains of *E.coli* CCM3954 and *S. aureus* CCM 3953 (Czech Collection of Microorganisms, Brno, Czech Republic), as well as clinical isolates of E. coli originated from urogenital infection (*E. coli* R) and *S. aureus* originated from haemoculture (Collection of Bacterial strain at the Department of Microbiology and Virology, CU Bratislava, *S. aureus* R). *E. coli* R was resistant to beta-lactams (ampicillin, cefoxitin, cefotaxime, cefuroxime, ceftriaxone, ceftazidime, ceftizoxime, cefepime) and quinolone ciprofloxacin. *S aureus* R was resistant to beta-lactams (ampicillin, amoxicillin with clavulanic acid, oxacillin, cefepime, cefotaxime, cefoxitin, ceftazidime, ertapenem), quinolones (ciprofloxacin ofloxacin), aminoglycosides (amikacin, tobramycin), macrolide antibiotic erythromycin, and lincosamide antibiotic clindamycin (all disks were from Oxoid, UK).

The strains were maintained in Skim-Milk Medium (Biolife, Italy) at −20 °C. Before the experiments, the microorganisms were inoculated in Mueller-Hinton Broth (MHB, Biolife, Italy) and cultivated in an incubator with shaking (Multitron S-000115690, Switzerland; 150 RPM) at 37 °C for 18 h. Antimicrobial susceptibility was tested in 96-well plates (Sarstedt, Germany) by microdilution method according to the recommendation of the EUCAST version 9.0 (The European Committee on Antimicrobial Susceptibility Testing, 2019). Briefly; overnight culture of tested bacteria was diluted in MHB to density corresponding to 0.5 McFarland standard (BioMérieux, France) representing approximately 10^8 cells/mL and subsequently diluted to obtain a final concentration of $5x10^5$ cells per well.

The compounds were diluted serially in MHB, the concentration range was from 0.5 to 0.0035 mg/mL and then recalculated to mmol/L. The volume of 100 µL of prepared bacterial culture with 100 µL of solution of tested compounds in appropriate concentration was added into the each well. The microtiter plate was incubated at 37 °C for 24 h in incubator (Thermostatic Cabinet, Germany).

The growth of bacteria was measured spectrophotometrically at OD570 using a reader (Dynex MRX-TC Revelation, USA). Susceptibility was evaluated in terms of MIC_{50} (minimal inhibitory concentration inhibiting the growth of the strain in the presence of the agent by 50% compared to the control sample without antimicrobial agent), and MIC_{100} representing the concentration that inhibits total growth compared to the control sample without agent. Each experiment was repeated at least 3 times with at least 3 parallel samples in each experiment.[30]

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Keywords: asymmetric organocatalysis • Michael addition • reductive cyclization • pyrrolidine • antibacterial activity

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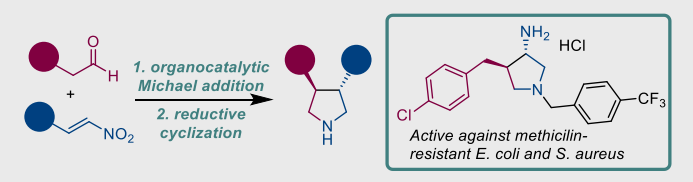

Organocatalytic Michael addition of aldehydes to nitroalkenes followed by reductive cyclization afford chiral 3,4-disubstituted pyrrolidines, which are active against methicillin-resistant strains of *Escherichia coli* and *Staphylococcus aureus*.

Asymmetric organocatalysis

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Synthesis of chiral 3,4-disubstituted pyrrolidines with antibacterial properties