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ORIGINAL ARTICLE

One-pot synthesis of novel (2R,4S)-*N*-aryl-4-hydroxy-1-(2,2,2-trifluoroacetyl) pyrrolidine-2-carboxamides via TiO_2-NPs and $Pd(PPh_3)_2Cl_2$ catalysts and investigation of their biological activities

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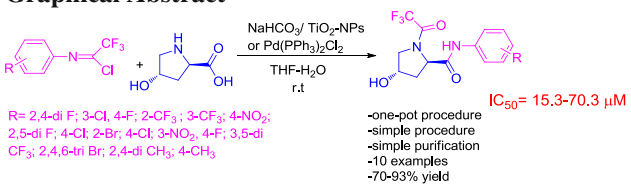
Abstract A new class of (2R,4S)-*N*-aryl-4-hydroxy-1-(2,2,2-trifluoroacetyl)pyrrolidine-2-carboxamide compounds was synthesized by a facile one-pot reaction of trans-4-hydroxy proline and trifluoroacetimidoyl chlorides in the presence of TiO_2-nanoparticles as a catalyst and sodium bicarbonate as a base. Synthesized compounds showed cytotoxicity with IC_{50} values of 15.3–70.3 μM against K562 (Homo sapiens, human) cells. The results of the study provide a valuable method for one-pot synthesis of trans-4-hydroxy proline-based *N*-(2,2,2-trifluoroacetylated) compounds. Also, these compounds show significant pharmaceutical activities as antibacterial and antifungal reagents.

Graphical Abstract



Keywords TiO_2-nanoparticles · Bis(triphenylphosphine)palladium(II)dichloride · K562 (Homo sapiens, human) cells · Pharmaceutical

Introduction

N-heterocyclic compounds play an important role in medicinal chemistry and especially in drug synthesis [1]. N-heterocyclic compounds can be used as additives and modifiers in a wide variety of industries including cosmetics, reprography, information storage, plastics, solvents, antioxidants, and vulcanization accelerators are other important practical applications of these compounds [2].

Proline derivatives have been used in biologically active compounds both in nature and in synthetic chemistry. Pyrrolidine compounds with either an alcohol or amine at the 4-position have been shown as an antiviral drug in the fight against influenza [3]. Trans-4-hydroxyproline is a very stereochemically rich compound that offers multiple sites of functionality. This functionality can be used to attach to different pharmacophores in an attempt to create various libraries of compounds for further medical and biological research.

Among N-containing heterocycles with proline based, Captopril and Enalapril (Fig. 1) attracted attention because of their wide pharmaceutical activity range acting as ACE inhibitors [4].

It was considered that the fluorine atoms or fluorinated compounds play a pivotal role in bioactive compounds, for which they provide an avenue for further structural elaboration [5–8]. Fluorine is an element of great importance in medicinal and organic chemistry, because it gives unique properties to the organic molecules in which it is incorporated, altering their physicochemical and biological properties. Particularly, the trifluoromethyl group (CF_3) is one of the most common fluorinated substituents in medicinal, agricultural, and material sciences [8] because it offers simultaneously high lipophilicity, an elevated electron density and a steric demand similar to that of the isopropyl group [9].

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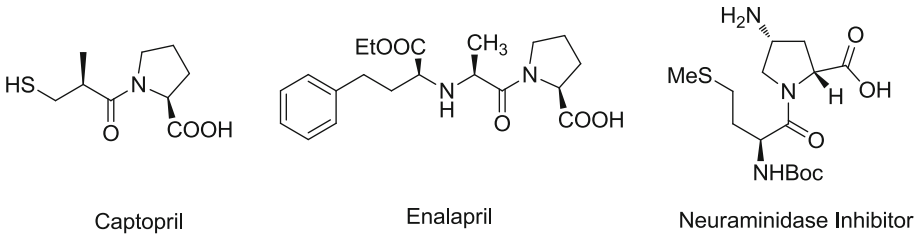
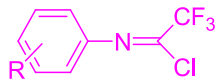


Fig. 1 N-containing heterocycles with a proline core

In recent years, metal oxide nanoparticles have attracted attention due to their potential application in different fields such as catalysis, magnetic recording media, microelectronics, and medicine. Their small size and large specific surface area allow for certain unique and unusual physicochemical properties [10–15]. Among these catalysts, TiO_2 (NPs) was introduced as an alternative support material for heterogeneous catalysts due to the effect of its high surface area stabilizing the catalysts in its mesoporous structure [16,17].

Our interest in fluorine chemistry and trifluoroacetimidoyl chloride reactions, and our attempt to synthesize bioactive organofluorine compounds led us to consider the reaction of trans-4-hydroxy proline with trifluoroacetimidoyl chlorides for the formation of (2R,4S)-*N*-aryl-4-hydroxy-1-(2,2,2-trifluoroacetyl) pyrrolidine-2-carboxamides. As such, in the present paper, an attempt is made to describe a one-pot synthesis of *N*-aryl-4-hydroxy-1-(2,2,2-trifluoroacetyl) pyrrolidine-2-carboxamide compounds to display a range of biological activities.



1a,R= 2,4 di F
1b, R=3 Cl, 4 F
1c, R=2 CF_3
1d, R=3 CF_3
1e, R=4 NO_2
1f, R= 2,5 di F
1g, R= 4 Cl
1h, R=2 Br, 4 Cl
1i, R= 3 NO_2, 4 F
1j, R= 3,5 di CF_3
1k, R=2,4,6 tri Br
1l, R= 2,4 di CH_3
1m, R= 4 CH_3

Scheme 1 Imidoyl chloride derivatives

Results and discussion

Chemistry

One of the most interesting interdisciplinary topics in chemistry is the application of transition metals in organic synthesis. There have been various reactions which would have been impossible to be achieved by conventional synthetic methods. However, these reactions can be catalyzed by transition metals to afford final products easily. More importantly, organopalladium chemistry is said to be playing an important role in organic synthesis [18].

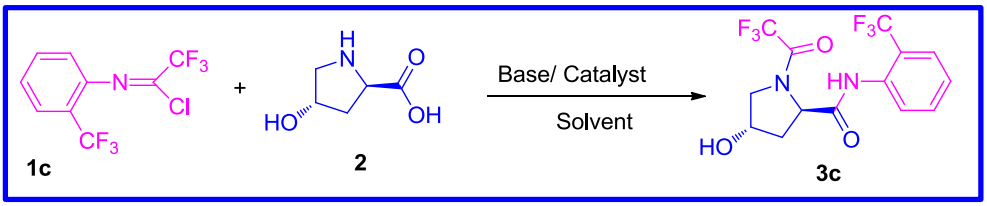
Furthermore, TiO_2 nanoparticles (TNPs) have received special interest due to their multiple potential applications, which are widespread in industry, chemistry and medicine. TiO_2-NPs has been proved to be a good catalyst in organic chemistry. Due to its non-toxicity, high activity, easy availability, reusability, strong oxidizing power, long-term stability and Lewis acidity [19–21].

Imidoyl chloride **1** (Scheme 1) is composed of three active functional groups (halogens, C=N double bond, CF_3, and *N*-aromatic ring) which can be used for the syntheses of new useful fluorinated organic compounds. It should be noted that in the present investigation, the used trifluoroacetimidoyl chlorides were prepared in high yield through refluxing a mixture of trifluoroacetic acid (TFA), amines, PPh_3, and Et_3N in CCl_4 in a one-pot manner [22–25].

As an initial endeavor, a trial reaction was performed with 1 mmol of 2,2,2-trifluoro-*N*-(2-(trifluoromethyl) phenyl) acetimidoyl chloride (**1c**), 1 mmol of trans-4-hydroxy proline (**2**) in acetonitrile or THF as a solvent in the presence of sodium hydride (NaH) as a base at room temperature or under reflux conditions. The reaction was kept 18 h at room temperature and then 12 h under reflux conditions. *No products were obtained finding that only* 2,2,2-trifluoro-*N*-(2-(trifluoromethyl)phenyl)acetimidoyl chloride was hydrolyzed to 2,2,2-trifluoro-*N*-(2-(trifluoromethyl) phenyl)acetamide [24] (Table 1; Scheme 2, entries 1–4). Therefore, this reaction was repeated with 1 mmol of 2,2,2-trifluoro-*N*-(2-(trifluoromethyl)phenyl)acetimidoyl chloride (**1c**), 1 mmol of trans-4-hydroxy proline (**2**) in THF as a solvent in the presence of potassium carbonate (K_2CO_3) as a base and in the presence of 10 mol% of *bis*(*triphenylphosphine*)*palladium*(*II*) *dichloride* ((Pd $(PPh_3)_2Cl_2$)) as a catalyst. After 12 h, a precipitate (**3c**) was separated out and purified, which was characterized by spectroscopic techniques and was found to be (2R,4S)-*N*-aryl-4-hydroxy-1-(2,2,2-trifluoroacetyl)pyrrolidine-2-carboxamide derivative (Table 1, entry 5).

2,2,2-Trifluoro-*N*-(2-(trifluoromethyl)phenyl)acetimidoyl chloride **1c** was chosen as a reprehensive substrate, and optimization studies of catalyst source, solvent, and temperature were taken (Table 1). The reaction of **1c** with trans-4-hydroxy proline (**2**) using different catalysts and solvents with various bases, including K_2CO_3, NaH, and $NaHCO_3$ at room tem-

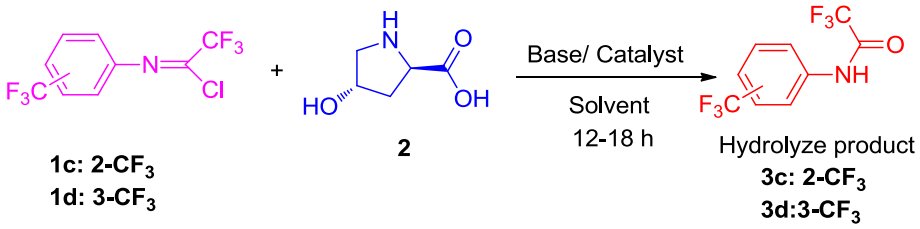
Table 1 Optimization of the reaction conditions for the formation of **3c** from **2** and **1c**



Entry	Base	Catalyst	mol%	Solvent	Condition	Time (h)	Yield[b] (%)
1	NaH	–		CH_3CN	r.t.	18	0
2	NaH	–		THF	r.t.	18	0
3	K_2CO_3	–		CH_3CN	Reflux	12	0
4	K_2CO_3	–		THF	Reflux	12	0
5	K_2CO_3	$Pd(PPh_3)_2Cl_2$	10	THF	r.t.	12	20
6	NaH	$Pd(PPh_3)_2Cl_2$	10	THF	r.t.	12	20
7	$NaHCO_3$	$Pd(PPh_3)_2Cl_2$	10	THF-H_2O	r.t.	12	72
8	$NaHCO_3$	$Pd(PPh_3)_2Cl_2$	5	THF-H_2O	r.t.	12	68
9	$NaHCO_3$	CuI	5	THF	r.t.	18	0
10	$NaHCO_3$	CuI	10	THF	Reflux	12	0

The reaction was carried out with **1a** (1 mmol) and **2a** (1 mmol) in the presence of an catalyst (% mol) in solvent (10 mL). [b] Isolated yield

Scheme 2 Conditions reaction for Hydrolyze **1c** and **1d**



1c: Base: $NaHCO_3$, Catalyst: CuI (10 and 5 mol%) and Solvent: THF-H_2O

Base: K_2CO_3 or NaH and Solvent: CH_3CN

1d: Catalyst: TiO_2 (10 mol %) and Solvent: H_2O

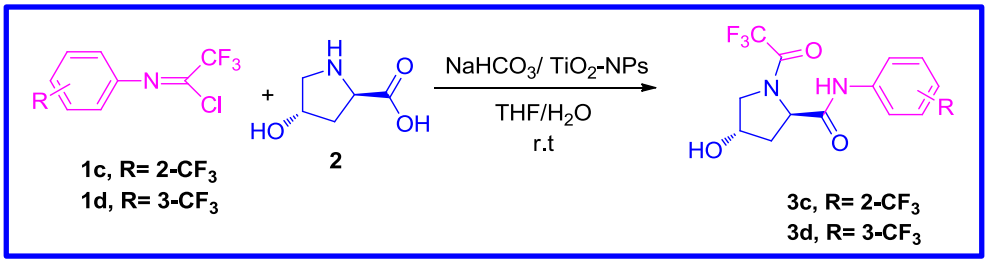
perature or under reflux condition were investigated. Over 70% conversion of **1c** to **3c** (as analyzed by ^{1}H NMR) was observed with $Pd(PPh_3)_2Cl_2$ (5 and 10 mol %), $NaHCO_3$, and THF-H_2O being superior (Table 1, entries 7 and 8). NaHCO3, $Pd(PPh_3)_2Cl_2$ (10 mol%), and THF-H_2O led to higher conversion at room temperature for 12 h (Table 1, entry 7). The use of $Pd(PPh_3)_2Cl_2$ as a catalyst and K_2CO_3 or NaH, as a base in THF led to low conversion (Table 1, entries 5 and 6). The use of K_2CO_3, NaH in CH_3CN as a solvent without a catalyst, and also CuI (10 and 5 mol%) and $NaHCO_3$ in THF-H_2O at room temperature or reflux for 12–18 h resulted in hydrolyzed product [26] (Scheme 2) (Table 1, entries 1–4, 9 and 10).

Although the fact that *bis(triphenylphosphine)palladium (II) dichloride* ($(Pd(PPh_3)_2Cl_2)$) is a good catalyst in this reaction, it does not seem to be ideal due to its price and relatively high catalyst loading.

It has been reported in the literature that copper (I) has been used as a catalyst in C–C and C–N bond formation [27,28]. Accordingly, copper (I) was selected because it is an inexpensive and fairly available catalyst to perform this reaction. Unfortunately, using CuI failed to yield partial conversion to the desired product (Table 1, entries 9, 10). In a pilot experiment, the reaction of 2,2,2-trifluoro-*N*-(2-(trifluoromethyl)phenyl)acetimidoyl chloride **1c** with (2R,4S)-4-hydroxypyrrolidine-2-carboxylic acid **2** in the presence of $Pd(PPh_3)_2Cl_2$ in H_2O-THF was investigated. This reaction afforded (2R, 4S)-4-hydroxy-1-(2,2,2-trifluoroacetyl)-*N*-(2-(trifluoromethyl)phenyl)pyrrolidine-2-carboxamide **3c** in 72% yield after 12 h (Table 1, entry 9).

Reactions of 2,2,2-trifluoro-*N*-(3-(trifluoromethyl)phenyl) acetimidoyl chloride (**1d**) or 2,2,2-trifluoro-*N*-(2-(trifluoromethyl)phenyl)acetimidoyl chloride (**1c**) with (2R,4S)-4-hydroxypyrrolidine-2-carboxylic acid **2** were selected as a model reactions, and they were treated with several different TiO_2 sources to obtain the optimal reaction conditions. The desired products were readily prepared in

Table 2 Optimization of the TiO_2-NPs coupling conditions



Entry	Compounds	TiO_2-NPS (mol%)	Solvent	Time (h)	Yield[b] (%)
1	**1c**	5	H_2O	12	0
2	**1c**	10	H_2O	12	0
3	**1d**	5	THF-H_2O	8	70
4	**1d**	10	THF-H_2O	8	78

The reaction was carried out with **1a** (1 mmol) and 2 (1 mmol) in the presence of an catalyst (mol%) in solvent (10 mL). [b] Isolated yield

excellent yield from the reaction of **1c** and **1d** in the presence of sodium bicarbonate in THF-H_2O at room temperature.

As expected, TiO_2-NPs showed good catalyst properties in organic synthesis. Therefore, it was decided TiO_2-NPs to be used as a catalyst in this reaction. The application of TiO_2-NPs as a catalyst for the reaction of 2,2,2-trifluoro-*N*-(3-(trifluoromethyl)phenyl)acetimidoyl chloride **1d** was, accordingly, investigated. When TiO_2 (10 mol %) was used as a catalyst in H_2O, the resulted yield was very low. In this case, the 2,2,2-trifluoro-*N*-(3-(trifluoromethyl)phenyl)acetimidoyl chloride **1d** was hydrolyzed to 2,2,2-trifluoro-*N*-phenylacetamide [26] (Scheme 2). The use of TiO_2 (10 mol %) led to higher conversion than TiO_2 (5 mol %) in THF-H_2O (Table 2, entries 3, 4).

It should be noted that the reaction was subsequently carried out in the presence of TiO_2-NPs as a catalyst under the same reaction conditions. TiO_2-NPs showed partially more efficient catalytic properties than $Pd(PPh_3)_2Cl_2$, causing to increase reaction yields and decreasing the reaction time (Table 1, entry 8). Therefore, TiO_2-NPs we selected as a catalyst for all reactions. The results of these reactions are shown in Table 3. Eventually, the reusability of this catalyst was also investigated. For the reaction of 2,2,2-trifluoro-*N*-(3-(trifluoromethyl)phenyl)acetimidoyl chloride **1d** with (2R,4S)-4-hydroxypyrrolidine-2-carboxylic acid **2,** the catalyst was recovered by filtration after separating two phases with H_2O and ethyl acetate and dried in the oven (70 °C, 6 h).

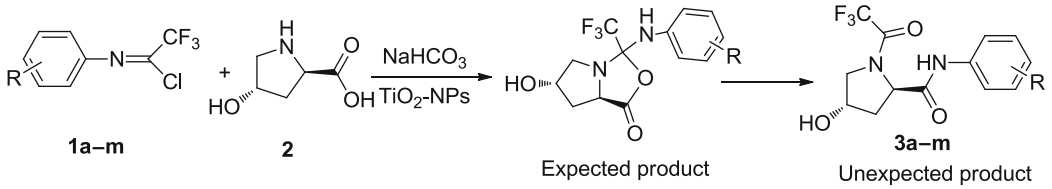
The reaction is assumed to be proceeding via the initial activation of imidoyl by TiO_2-nanoparticles or bis(triphenylphosphine)palladium(II) dichloride to the formation of TiO_2- or pd-imidoyl complex. Then, this activated intermediate is attacked by the nitrogen nucleophilic group of L-proline to replace the chlorine atom by nitrogen. Subsequent attack of the carboxylate anion on the imino group generates the cyclic intermediate 6-hydroxy-3-(arylamino)-3-(trifluoromethyl)tetrahydropyrrolo[1,2-c]oxazol-1(3H)-one (**A**) which undergoes a Mumm-type rearrangement to give the 4-hydroxy-*N*-aryl-1-(2,2,2-trifluoroacetyl)pyrrolidine-2-carboxamide **3a** (Scheme 3).

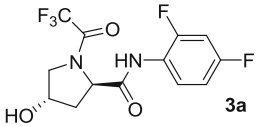
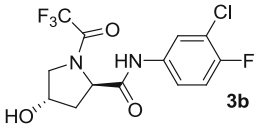
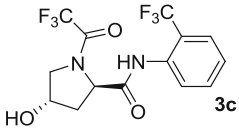
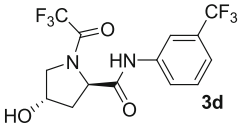
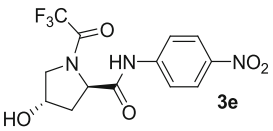
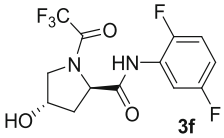
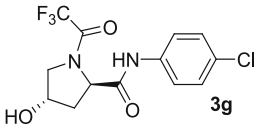
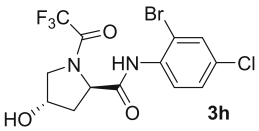
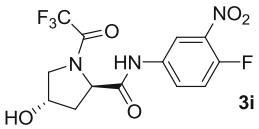
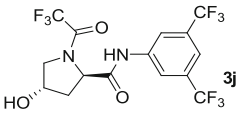
Crystal structure of 3a

Eventually confirmation of the reaction was done through obtaining crystal structure of (2R,4S)-*N*-aryl-4-hydroxy-1-(2,2,2-trifluoroacetyl)pyrrolidine-2-carboxamides **3a** (Fig. 2) as a model. Suitable crystals for X-ray data analysis were obtained by crystallization from ethanol.

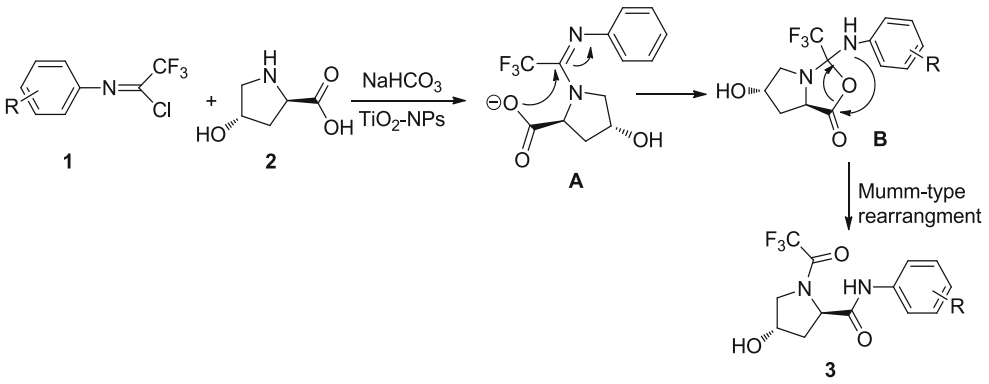
In order to verify the scope and generality of such a reaction, under the optimized conditions various trifluoroacetimidoyl chlorides were reacted with trans-4-hydroxy proline to generate the desired (2R,4S)-*N*-aryl-4-hydroxy-1-(2,2,2-trifluoroacetyl)pyrrolidine-2-carboxamides (Table 3). Trifluoroacetimidoyl chlorides with electron-withdrawing groups as 2,4-di-F (**1a**), 3-Cl-4-F (**1b**), 2-CF_3 (**1c**), 2-CF_3 (**1d**), 4-NO_2 (**1e**), 2,5-di-F (**1f**), 4-Cl (**1g**) 2-Br-4-Cl (**1h**), 3-NO_2-4-F (**1i**) and 3,5-di-CF_3 (**1j**) procured good yields (Table 3). It should be mentioned that no desired product was obtained when a similar reaction was performed with compounds containing electron-donating functionalities *N*-(2,4-dimethylphenyl)-2,2,2-trifluoroacetimidoyl chloride (**1l**), 2,2,2-trifluoro-*N*-(p-tolyl)acetimidoyl chloride (**1m**) and 2,2,2-trifluoro-*N*-(2,4,6-tribromophenyl)acetimidoyl chloride (**1k**) (Table 3, entries 11–13). The first step (attack of –NH– group of proline to imidoyl chloride) is suggested to be very important. Therefore, the electron-withdrawing groups on the imidoyl chloride increase the reaction rate and the electron-donating groups on the imidoyl chloride decrease the reaction rate. In the latter conditions, the speed of hydrolysis is much faster than the attack of L-proline to the imidoyl

Table 3 Scope of the reaction with 2,2,2-trifluoro-*N*-phenylacetimidoyl chloride derivatives (**1a**–**m**)



Entry	Substrate	Products	Yields[a] (%)
1	**1a**	 **3a**	93
2	**1b**	 **3b**	70
3	**1c**	 **3c**	78
4	**1d**	 **3d**	77
5	**1e**	 **3e**	73
6	**1f**	 **3f**	92
7	**1g**	 **3g**	83
8	**1h**	 **3h**	87
9	**1i**	 **3i**	77
10	**1j**	 **3j**	70
11	**1k**	N.R	0
12	**1l**	N.R	0
13	**1m**	N.R	0

The reaction was carried out with 1 (1 mmol) and 2 (1 mmol) in the presence of an catalyst TiO2-NPs (10 mol%) in THF-H2O (10 mL) at r.t. for 8 h. [a] Isolated yield. Determined by NMR, also X-ray crystal data of **3a**



Scheme 3 A plausible reaction pathway

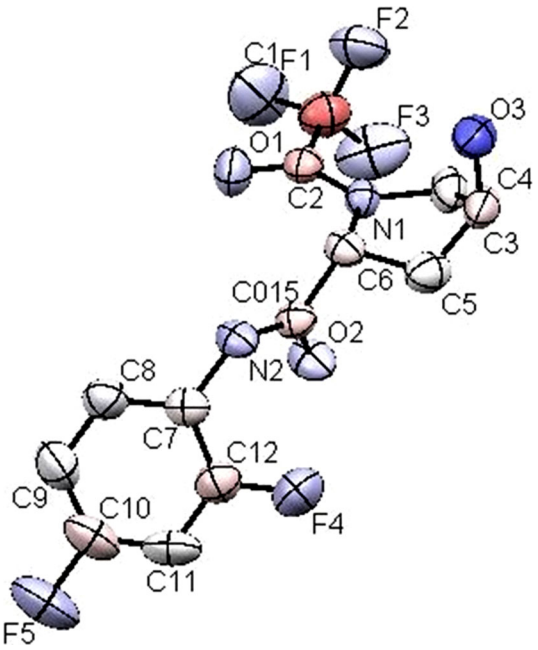


Fig. 2 Crystal structure of **3a** (CCDC 1051505)

because of the steric effect inhibiting the reaction of 2,4,6-dibromo imidoyl with L-proline. Although there are several reports for synthesis of 1-(2,2,2-trifluoroacetyl)pyrrolidine-2-carboxylic acid(*N*-trifluoroacetylationo L-proline) using trifluoroacetic anhydride in the literature, the yields of these methods are not high enough (<50%) [29,30]. Furthermore, to the best of our knowledge, no reports have been published for the synthesis of (2R,4S)-4-hydroxy-*N*-aryl-1-(2,2,2-trifluoroacetyl)pyrrolidine-2-carboxamides in the literature so far. Moreover, since direct transfer of –COOH group of L-proline to amide with the use of amine is not straight forward, this transformation should be carried out in two or more steps [31–33].

Table 4 IC_{50} values (μM) of compounds **3a–3j** against human cancer cell line using the MTT assay

Compounds	K562 cell line		
	24 h	48 h	72 h
3a	8.5	12.2	19.6
3c	6.3	5.3	22.3
3d	10.8	15.2	47.5
3e	11.8	20.1	23.4
3f	–	29.3	45.4
3g	–	50.2	32.4
3h	10	12.6	15.3
3i	25.7	6.1	70.3
3j	22.8	11.6	42.1
MPK-09	–	2.9	7.3

Biology

Assessment of MTT assay and IC_{50}

The *MTT* assay is a colorimetric assay for assessing cell metabolic activity [34]. The *MTT* was performed for all the compounds to show the effects. The synthesized compounds and reference compound MPK-09 mostly showed cytotoxic activity on K562 (*Homo sapiens, human*) cells with following IC_{50} values (listed in Table 4). The cytotoxic and activity observed for all the compounds depends on concentration. While a viability more than of 50% was observed for this compound, the concentration of less than 250 μM was effective on K562 cells. This suggests that compounds as noticeable factors lead the molecules for cytotoxic activity against tumor cells (Table 4).

Compounds **3a**, **3c**, **3d**, **3e**, **3f**, **3g**, **3h**, **3i**, **3j** exhibited cytotoxic activity on LS174Tcells with IC_{50} value, as shown in the diagram (Fig. 3)

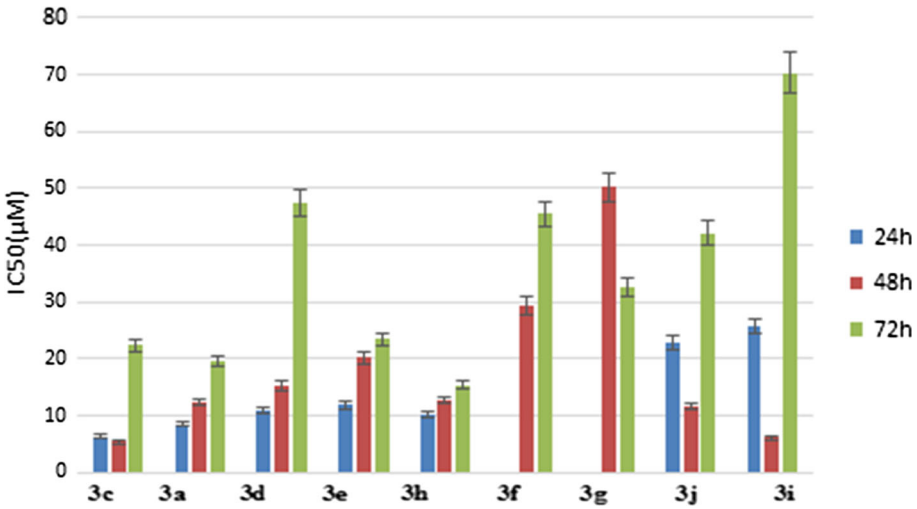


Fig. 3 Summary of IC $_{50}$ data from cytotoxicity assays **3a**–**3j**

Examine of the antibacterial and antifungal activity

The synthesized compounds **3a**–**i** were screened for more antibacterial activities at three various concentrations of 25, 50 and 100 μg/ml. The antibacterial effects of these compounds are presented in Table 5 (see supporting data). All the tested compounds exhibited more activity toward Gram-positive bacteria than Gram-negatives. All the examined compounds inhibited the spore germination against tested fungi. Generally, the compounds mostly displayed slightly higher antifungal activity toward *Penicillium chrysogenum* than *Aspergillus niger*. The most antimicrobial activity is related to **3h** with **3e** and **3d** coming second and third respectively.

The compound **3h** displayed adequate levels of activity in particular against *P. chrysogenum* equivalent to the standard blank 100 μg/well, and **3e** and **3d** are the 2nd and 3rd respectively (Table 5, see supporting data). The minimum inhibitory (MIC), minimum antibacterial (MBC) and minimum antifungal concentration (MFC) of the compounds determined are listed in Table 6 (see supporting data). The MBC value is 2 × MIC in case of *S. aureus* and MFC value is 2 × MIC in case of *P. chrysogenum*. However, other compounds demonstrated bactericidal and fungicidal effects greater than 2 × MIC.

A variety of **3** displayed greatest antimicrobial activity. This compound was a potent antimicrobial agent, particularly against *S. aureus* (27 mm, MIC 12.5 μg/ml) and *P. chrysogenum* (30 mm, MIC 12.6 μg/ml) (Table 7, see supporting data).

Biological assays

Compounds **3a**–**3j** were examined for their antimicrobial activities at three various concentrations of 25, 50 and 100 μg/well. Compounds were dissolved in DMSO at different concentrations of 25, 50 and 100 μg/well. Bacterial strains such as *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, and fungi, including *Aspergillus niger*, *Penicillium chrysogenum* underwent antibacterial and antifungal assessments. In vitro antimicrobial, examinations were carried out through employing agar in well-diffused method against test organisms. Data shown Table 5 are supporting the fact (Table 5, see supporting data).

Conclusion

In summary, the proline scaffold has already been shown to be a bioactive small organic molecule in nature and in pharmacology. In this study, a mild, efficient and one-pot approach was described for the synthesis of (2R,4S)-*N*-aryl-4-hydroxy-1-(2,2,2-trifluoroacetyl)pyrrolidine-2-carboxamides via the TiO_2-nanoparticle-catalyzed reaction of trans-4-hydroxy proline with trifluoroacetimidoyl chlorides. Our TiO_2-nanoparticle-catalyzed reaction is simple with the reaction proceeding smoothly from good to excellent yields. The present investigation includes the modification of the 1- and 2-position of trans-4-hydroxy proline in one-pot. The combination of these two strategies can potentially lead to hundreds of small novel molecules that can be tested for biological activity and further aid drug design. The results of this study provide a valuable method for one-pot synthesis of trans-4-hydroxy proline-based *N*-(2,2,2-trifluoroacetylated) compounds with using of TiO_2-nanoparticles as a cheap cost, non-toxicity and chemical stability catalyst. Also, the antimicrobial and cytotoxic activities of the synthesized compounds. Revealed that compound **3h** displayed the best antimicrobial and antifungal activity among the tested compounds, which then could be applied to further studies for potent novel board-spectrum antimicrobial agents. Further studies on the biological activity of these compounds are in progress in our laboratory.

Experimental section

Material and instruments

All reactions were carried out under a nitrogen atmosphere unless otherwise stated. Reactions were monitored by thin layer chromatography (TLC). All of the NMR spectra were recorded on a Bruker model DRX-300 AVANCE (^{1}H: 300, ^{13}C: 75, F: 282 MHz) and on a Bruker model DRX-400 AVANCE (^{1}H: 400, ^{13}C: 100) NMR spectrometer. Chemical shifts of ^{1}H and ^{13}C-NMR are reported in parts per million (ppm) downfield from tetramethylsilane (TMS) as an internal standard in DMSO-d_6 or $CDCl_3$ as a solvent and ^{19}F-NMR are reported in parts per million (ppm) from $CFCl_3$ as an internal standard in DMSO-d_6 or $CDCl_3$ as a solvent. Data are presented as follows: chemical shift, integration, multiplicity (br = broad signal, s = singlet, d = doublet, q = quartet, m = multiplet), and coupling constant in Hertz (Hz). IR spectra were obtained on a Matson-1000 FT-IR spectrometer. Optical rotation was recorded on an Atago AP-300 polarimeter. Melting points were determined on a Melt-Tem II melting point apparatus and are uncorrected.

Preparation of nanoparticles

Titanium dioxide (TiO_2) nanoparticle was prepared by treatment of titanium dioxide (Merck) by microwave associated method, according to the literature [35]. The TiO_2-nanoparticles then was isolated and characterized by X-ray powder diffraction (XRD) and scanning electron microscope (SEM).

*General procedure for the synthesis of (2R,4S)-N-aryl-4-hydroxy-1-(2,2,2-trifluoroacetyl)pyrrolidine-2-carboxamides (**3a**–**m**)* To a stirred solution of trans-4-hydroxy-L-proline 2 (1.0 mmol) in water (5 mL) was added sodium bicarbonate (1.2 mmol) and TiO_2-nanoparticles (TNPs) (10% mol). Then a solution of acetimidoyl chloride derivatives 1 (1.0 mmol) in THF (5 mL) was added dropwise over a period of 10 min. The mixture was stirred at room temperature for 8 h. After the reaction was completed (monitored by TLC); ethyl acetate (10 mL) was added. Then the organic layer was separated, and aqueous layer was extracted with ethyl acetate (2x10 mL). The aqueous layer is containing TiO_2 -NPs and therefore was separated by filtration. After combination of organic layers, organic phase was dried over $MgSO_4$ and evaporated on a rotary evaporator to give the crude product, which was purified by washing two times with diethyl ether and *n*-hexane (two times) to give pure products.

*(2R,4S)-N-(2,4-difluorophenyl)-4-hydroxy-1-(2,2,2-trifluoroacetyl)pyrrolidine-2-carboxamide (**3a**)* Colorless solid (314 mg, 93% yield): Mp 225–227 °C; IR (KBr, cm^{-1}) 3497, 3281, 3053, 1685, 1615, 1539. ^{1}H NMR (400 MHz, DMSO) δ 10.10 (s, 1H, NH), 7.82 (m,1H, Ar), 7.33 (m, 1H, Ar), 7.07 (m, 1H, Ar), 5.35 (d, J = 2.8 Hz, 1H, 2-H), 4.78–4.82 (m, 1H, 4-H), 4.43 (br, 1H, OH), 3.63–2.76 (m, 2H, 5-H), 1.92–2.29 (m, 2H, 3-H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.17 (NHC=O), 159.84 (dd, J = 244.6, 11.9 Hz, C–F (para)), 154.64 (q, J = 36.4, 0.2 Hz, CF_3–C=O), 153.14 (dd, J = 248.7, 11.9 Hz, C–F (orto)), 125.52 (d, J = 9.6 Hz, C–Ar), 122.16 (dd, J = 11.9, 3.7 Hz, C–Ar), 115.93 (q, J = 288.1 Hz, CF_3–C=O), 111.08 (dd, J = 21.9, 3.5 Hz, C–Ar), 104.15 (dd, J = 26.6, 24.1 Hz, C–Ar), 68.92, 60.07, 55.71, 37.19 ppm. Anal. Calcd for $C_{13}H_{11}F_5N_2O_3$: C, 46.16; H, 3.28; N, 8.28. Found: C, 46.14; H, 3.24; N, 8.24%.

*(2R,4S)-N-(3-chloro-4-fluorophenyl)-4-hydroxy-1-(2,2,2-trifluoroacetyl)pyrrolidine-2-carboxamide (**3b**)*
Bright brown solid (248 mg, 70% yield): Mp 180 dec; IR (KBr, cm^{-1}) 3491, 3273, 3057, 1670, 1603, 1545.^{1}H NMR (400 MHz, DMSO) δ 10.53 (s, 1H, NH), 7.92 (m, 1H, Ar), 7.60 (m, 1H, Ar), 7.40 (m, 1H, Ar), 5.39 (m, 1H, 2-H), 4.60–4.64 (m, 1H, 4-H), 4.44 (br, 1H, OH), 3.64–3.76 (m, 2H, 5-H), 1.95–2.27 (m, 2H, 3-H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.77(NHC=O), 154.61 (q, J = 43.9 Hz, CF_3–C=O), 151.98 (dd, J = 240.1 Hz), C–F (para), 135.84 (d, J = 3.5 Hz, C–Ar), 120.48 (d, J = 8.4 Hz, C–Ar), 119.57 (d, J = 21.0 Hz, C–Cl), 117.03 (d, J = 21.9 Hz, C–Ar), 115.38 (q, J = 288.2 Hz, CF_3–C=O), 68.93, 60.49, 55.76, 37.10 ppm. Anal. Calcd for $C_{13}H_{11}ClF_4N_2O_3$: C, 44.02; H, 3.13; N, 7.90. Found: C, 44.00; H, 3.10; N, 7.87%.

*(2R,4S)-4-hydroxy-1-(2,2,2-trifluoroacetyl)-N-(2-(trifluoromethyl)phenyl)pyrrolidine-2-carboxamide (**3c**)*
Bright brown solid (288 mg, 78% yield): Mp 210–212 °C; IR (KBr, cm^{-1}) 3509, 3272, 3021, 1672, 1589, 1541.^{1}H NMR (300 MHz, DMSO) δ 9.94 (s, 1H, NH), 7.66–7.75 (m, 2H, Ar), 7.40–7.49 (m, 2H, Ar), 5.35 (d, J = 3.2 Hz, 1H, 2-H), 4.74–4.79 (m, 1H, 4-H), 4.42 (br, 1H, OH), 3.60–3.75 (m, 2H, 5-H), 1.93–2.00 (m, 2H, 3-H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.68 (NHC=O), 158.54 (q, J = 31.5 Hz, CF_3–C=O), 137.34 (q, J = 3.8 Hz, C–Ar), 130.19, 126.34, 125.75, 125.00 (q, J = 266.7 Hz), 121.41 (q, J = 30.5 Hz) 119.90, 115.72 (q, J = 268.1 Hz, CF_3–C=O), 68.86, 59.94, 55.61, 36.90 ppm. ^{19}F NMR (282 MHz, DMSO) δ −59.26, −71.41 ppm. Anal. Calcd for $C_{14}H_{12}F_6N_2O_3$: C, 45.42; H, 3.27; N, 7.57. Found: C, 45.40; H, 3.24; N, 7.54%.

*(2R,4S)-4-hydroxy-1-(2,2,2-trifluoroacetyl)-N-(3-(trifluoromethyl)phenyl)pyrrolidine-2-carboxamide (**3d**)*
Colorless solid (285 mg, 77% yield): Mp 194–200 °C; IR (KBr, cm^{-1}) 3503, 3284, 3059, 1676, 1618, 1541. ^{1}H NMR

(400 MHz, DMSO) δ 10.96 (s, 1H, NH), 8.12 (s, 1H, Ar), 7.74 (d, J = 8.0 Hz, 1H, Ar), 7.58 (m, 1H, Ar), 7.74 (d, J = 7.6 Hz, 1H, Ar), 5.42 (d, J = 2.4 Hz, 1H, 2-H), 4.64–4.68 (m, 1H, 4-H), 4.45 (br, 1H, OH), 3.65–3.77 (m, 2H, 5-H), 1.97–2.29 (m, 2H, 3-H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.09 (NHC=O), 159.65 (d, J = 32.3 Hz, CF_3–C=O), 139.38, 130.10, 129.80 (q, J = 32.1 Hz, C–CF_3), 125.36 (q, J = 282.3 Hz, Ar–CF_3), 122.64, 119.90 (q, J = 4.3 Hz, CH–Ar), 115.43 (q, J = 287.6 Hz, CF_3–C=O), 68.94, 60.54, 55.76, 37.10 ppm. Anal. Calcd for $C_{14}H_{12}F_6N_2O_3$: C, 45.42; H, 3.27; N, 7.57. Found: C, 45.40; H, 3.26; N, 7.55%.

*(2R,4S)-4-hydroxy-N-(4-nitrophenyl)-1-(2,2,2-trifluoroacetyl)pyrrolidine-2-carboxamide (**3e**)* Brown solid (253 mg, 73% yield): Mp 250–255 °C; $[\alpha]_D^{25}$ = +0.45 ° (c 0.10, MeOH); IR (KBr, cm^{-1}) 3497, 3283, 1681, 1614, 1597, 1555. ^{1}H NMR (400 MHz, DMSO) δ 10.93 (s, 1H, NH), 8.24 (d, J = 9.2 Hz, 2H, Ar), 7.84 (d, J = 8.8 Hz, 2H, Ar), 5.43 (d, J = 3.2 Hz, 1H, 2-H), 4.58–4.72 (m, 1H, 4-H), 4.46 (br, 1H, OH), 3.66–3.79 (m, 2H, 5-H), 1.98–2.31 (m, 2H, 3-H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.43(NHC=O), 154.68 (q, J = 36.4 Hz, CF_3–C=O), 144.71, 142.41, 125.02, 118.93, 115.94 (q, J = 287.7 Hz, CF_3–C=O), 68.98, 60.63, 55.77, 37.06 ppm. Anal. Calcd for $C_{13}H_{12}F_3N_3O_5$: C, 44.96; H, 3.48; N, 12.10; Found: C, 44.93; H, 3.45; N, 12.12%.

*(2R,4S)-N-(2,5-difluorophenyl)-4-hydroxy-1-(2,2,2-trifluoroacetyl)pyrrolidine-2-carboxamide (**3f**)* White solid (310 mg, 92% yield): Mp 168 °C; $[\alpha]_D^{25}$ = +2.0° (c 0.10, MeOH); IR (KBr, cm^{-1}) 3494, 3280, 3060, 1678, 1631, 1541.^{1}H NMR (400 MHz, DMSO) δ 10.34 (s, 1H, NH), 7.89 (m, 1H, Ar), 7.35 (m, 1H, Ar), 7.00 (m, 1H, Ar), 5.38 (br, 1H, 2-H), 4.89 (m, 1H, 4-H), 4.44 (br, 1H, OH), 3.64–3.73 (m, 2H, 5-H), 1.96–2.30 (m, 2H, 3-H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.57 (NHC=O), 159.09 (d, J = 35.7 Hz, CF_3–C=O), 157.75 (d, J = 238.8 Hz, C–F (meta)), 149.08 (d, J = 242.2 Hz, C–F (orto)), 126.99 (d, J = 25.0 Hz, C–Ar), 116.43 (dd, J = 21.9, 10.0 Hz, C–Ar), 115.98 (q, J = 287.7 Hz, CF_3–C=O), 110.93 (dd, J = 24.5, 8.3 Hz, C–Ar), 109.48 (dd, J = 29.8, 11.6 Hz, C–Ar), 68.95, 60.15, 55.72, 37.13 ppm. Anal. Calcd for $C_{13}H_{11}F_5N_2O_3$: C, 46.16; H, 3.28; N, 8.28; Found: C, 46.11; H, 3.23; N, 8.21%.

*(2R,4S)-N-(4-chlorophenyl)-4-hydroxy-1-(2,2,2-trifluoroacetyl)pyrrolidine-2-carboxamide (**3g**)* Cream solid (279 mg, 83% yield): Mp 86–90 °C; $[\alpha]_D^{25}$ = +3.52° (c 0.20, MeOH); IR (KBr, cm^{-1}) 3492, 3298, 30148, 1680, 1615, 1535. ^{1}H NMR (400 MHz, DMSO) δ 10.44 (s, 1H, NH), 7.37–7.73 (m, 4H, Ar), 5.63 (d, J = 4.8Hz, 1H, 2-H), 4.64 (m, 1H, 4-H), 4.44 (br, 1H, OH), 3.64–3.76 (m, 2H, 5-H), 1.99–2.01 (m, 2H, 3-H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.64 (NHC=O), 158.08 (q, J = 32.8 Hz, CF_3–C=O), 135.25, 128.93 (2C, Ar), 128.67, 122.60 (2C, Ar), 114.58 (q, J = 285.7 Hz, CF_3–C=O), 68.91, 60.52, 55.74, 37.12 ppm. Anal. Calcd for $C_{13}H_{12}ClF_3N_2O_3$: C, 46.37; H, 3.59; N, 8.32; Found: C, 46.30; H, 3.54; N, 8.27%.

*(2R,4S)-N-(2-bromo-4-chlorophenyl)-4-hydroxy-1-(2,2,2-trifluoroacetyl)pyrrolidine-2-carboxamide (**3h**)* White solid (360 mg, 87% yield): Mp 231–236 °C; $[\alpha]_D^{25}$ = +1.0 ° (c 0.20, MeOH);IR (KBr, cm^{-1}) 3491, 3274, 3027, 1682, 1584, 1572, 1526.^{1}H NMR (400 MHz, DMSO) δ 9.95 (s, 1H, NH), 7.83 (m, 1H, Ar), 7.53–7.55 (m, 1H, Ar), 7.46–7.49 (m, 1H, Ar), 5.38 (d, J = 3.2 Hz, 1H, 2-H), 4.79 (m, 1H, 4-H), 4.45 (br, 1H, OH), 3.63–3.77 (m, 2H, 5-H), 2.00–2.31 (m, 2H, 3-H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.02 (NHC=O), 154.63 (q, J = 37.2 Hz, CF_3–C=O), 134.85, 131.88, 130.37, 128.34, 128.07, 118.75, 115.99 (q, J = 287.7 Hz, CF_3–C=O), 68.89, 60.08, 55.65, 37.09 ppm. Anal. Calcd for $C_{13}H_{11}BrClF_3N_2O_3$: C, 37.57; H, 2.67; N, 6.74; Found: C, 37.53; H, 2.62; N, 6.70%.

*(2R,4S)-N-(4-fluoro-3-nitrophenyl)-4-hydroxy-1-(2,2,2-trifluoroacetyl)pyrrolidine-2-carboxamide (**3i**)* Cream solid (281 mg, 77% yield): Mp 201–205 °C; $[\alpha]_D^{25}$ = +1.35° (c 0.10, MeOH); IR (KBr, cm^{-1}) 3484, 3272, 3066, 1676, 1626, 1544, 1499. ^{1}H NMR (400 MHz, DMSO) δ 10.90 (s, 1H, NH), 7.82–8.36 (m, 3H, Ar), 5.43 (m, 1H, H-2), 4.65 (m, 1H, 4-H), 4.46 (br, 1H, OH), 3.65–3.78 (m, 2H, 5-H), 2.04–2.31 (m, 2H, 3-H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.56 (NHC=O), 159.45 (d, J = 32.0 Hz, CF_3–C=O), 150.95 (d, J = 246.8 Hz, CF–Ar), 140.41, 135.66 (d, J = 21.0 Hz, C–NO_2–Ar), 121.15 (d, J = 8.0 Hz, C–Ar), 118.81 (d, J = 21.0 Hz, C–Ar), 116.48 (d, J = 8.5 Hz, C–Ar), 115.27 (q, J = 285.0 Hz, CF_3–C=O), 68.94, 60.61, 55.74, 37.00 ppm. Anal. Calcd for $C_{13}H_{11}F_4N_3O_5$: C, 42.75; H, 3.04; N, 11.50; Found: C, 42.70; H, 3.00; N, 11.43%.

*(2R,4S)-N-(3,5-bis(trifluoromethyl)phenyl)-4-hydroxy-1-(2,2,2-trifluoroacetyl)pyrrolidine-2-carboxamide (**3j**)* Pink solid (306 mg, 70% yield): Mp 250 °C; $[\alpha]_D^{25}$ = +0.81° (c 0.10, MeOH); IR (KBr, cm^{-1}) 3490, 3277, 3089, 1675, 1556, 1474. ^{1}H NMR (400 MHz, DMSO) δ 10.80 (s, 1H, NH), 8.53–8.54 (m, 1H, Ar), 7.84–7.86 (m, 1H, Ar), 7.55–7.60 (m, 1H, Ar), 5.42 (d, J = 3.6 Hz, 1H, H-2), 4.64 (m, 1H, 4-H), 4.46 (br, 1H, OH), 3.65–3.78 (m, 2H, 5-H), 1.98–2.30 (m, 2H, 3-H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.10 (NHC=O), 158.54 (q, J = 31.5 Hz, CF_3–C=O), 137.96 (d, J = 1.9 Hz), 132.65, 123.56, 123.50 (q, J = 268.1 Hz, CF_3), 116.89, 115.37 (q, J = 268.0 Hz, CF_3–C=O), 68.94, 60.52, 55.75, 37.07 ppm. Anal. Calcd for $C_{15}H_{11}F_9N_2O_3$: C, 41.11; H, 2.53; N, 6.39; Found: C, 41.08; H, 2.50; N, 6.35%.

Supporting information

Experimental procedures and compound characterization data for all new compounds.

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