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Original Article

Synthesis, Characterization, and Evaluation of *in vitro* Antidiabetic Activity of Novel Pyrrolidine Sulphonamide Derivative

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ABSTRACT

Background: Diabetes is a long-term illness characterized by high blood sugar levels. It is estimated that by 2045, there will be nearly 693 million diabetic patients worldwide, with half of the population remaining undiagnosed. Metformin, insulin, sulfonylureas, and thiazolidinediones were related to several risk factors, including hypoglycemia, bone fracture, weight gain, cardiovascular, renal, and other complications. In the present study, we have explored the DPP-IV inhibitors as a new class of antidiabetic drugs. **Objectives:** The goal of DPP-IV inhibitors is to raise levels of incretins (GLP-1 and GIP), which block glucagon release while boosting insulin secretion, slowing stomach emptying, and reducing blood glucose levels. **Methods:** A series of derivatives substituted on Oxadiazole of sulfonamide pyrrolidine were produced by reacting 1,2,4-oxadiazol and sulfonyl chloride at room temperature in the presence of ethanol and stirring until the reaction was complete. The compounds were characterized using IR, ^{1}H NMR, C^{13} NMR, mass spectroscopy, elemental analysis, and screened for *in vitro* assay of DPP-IV inhibition. **Results and Discussion:** The IC_{50} was calculated for compounds B-I, B-V, B-VI, B-XI, and B-XIII that inhibited enzymes significantly, IC_{50} values ranging from 19.65 ± 2.60 nM to 11.32 ± 1.59 nM, respectively, and Vildagliptin (4.79±1.66 IC_{50} nM) was used as a standard. The most active derivative substituted Oxadiazole of pyrrolidine sulfonamide is B-XI (11.32 ± 1.59 IC_{50} nM) among all synthesized compounds. **Conclusion:** B-XI derivative has shown appreciable DPP-IVinhibitory action. The 1,2,4-oxadiazol-3-yl pyrrolidine-1-sulfonamide derivatives have shown anti-diabetic properties.

Key words: Pyrrolidine sulphonamide derivative, 1,2,4-oxadiazole, *In vitro* study, Antidiabetic, Dipeptidyl peptidase-4.

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INTRODUCTION

Diabetes is a group of chronic metabolic disorders caused by high blood sugar levels over a prolonged period.[1] Diabetes has become a global epidemic problem It was predicted that 451 million diabetics existed in 2017, with this Figure expected to increase to 693 million by 2045.[2] Most patients with type 2 diabetes, even when using anti-diabetic drugs, struggle to maintain sufficient glycemic regulation and develop microvascular and macrovascular diabetic complications.[3,4] Current diabetes therapy has lots of side effects.[5] The most frequent adverse events were hypoglycemia, stomach issues, and weight gain. DPP-IV inhibitors' possible advantages include a complementary mode of action with other anti-diabetic drugs, a desirable adverse-effect history, and a weight-neutral effect.[6,7]

By increasing endogenous GLP-1 levels, a DPP-IV inhibitor activates insulin and suppresses glucagon synthesis causing intestinal hypoglycemia.[8] Incretins and glucagon-like peptide-1 breakdown are suppressed by a DPP-IV inhibitor (GLP-1). DPP-IV inhibitor is an alternative diabetic therapy.[7,9,10] Because of their various pharmaceutical properties, five-member heterocyclic compounds, especially 1,2,4-Oxadiazole, have shown activity against a variety of diseases like Alzheimer's disease, parasitic worms (helminths) and other internal parasites, management and treatment of edematous and another non-edematous disease, infectious diseases, diabetes, pain and cramp, cardiovascular disease, HIV disease, tuberculosis, antioxidant, cancer, seizure disorders, inflammation of a joint.[11] Our efforts to enhance the efficacy, selectivity of the novel 1,2,4- oxadiazole derivative of pyrrolidine sulphonamide as DPP-IV inhibitors.

The sulfonamide moiety ($-SO_2NH_2$) is an active pharmacophore that the clinical and medicinal importance of sulfonamide drugs and compounds in the new drug discovery.[12] They exhibit a wide range of pharmacological activities, such as antimicrobial, antimalarial, anti-HIV, insulin-releasing antidiabetic, high ceiling diuretic, antithyroid, antitumor analgesic, and anti-inflammatory.[13-16] Some laboratories reported entities with sulfonamide portion; compounds 1 (IC_{50}; 6.7 nM) and 2 (IC_{50}; 39 nM) as potent DPP-IV inhibitors.[17] Omarigliptin (MK-3102) is sulfonamide containing moiety, which produces its antihyperglycaemic action by inhibiting the DPP-4 enzyme. Its pharmacokinetic studies have shown that it is suitable for once-a-week dosing, which makes it unique among the other DPP-4 inhibitors.[18,19] In this research we have designed novel 1,2,4- oxadiazole derivatives with sulfonamide and pyrrolidine-2-carbonitrile scaffolds specifically *in vitro* DPP-IV inhibitor assay as antidiabetic activity. In the continuation of our research to develop small molecules as biologically active antihyperglycaemic compounds, new derivatives having a pyrrolidine-2-carbonitrile-sulfonamide backbone hybrid were designed and synthesized in search for new potent DPP-4 inhibitors as antidiabetic agents.[20]

MATERIALS AND METHODS

1, 2, 4-Oxadiazole derivative with sulfonamide and pyrrolidine-2-carbonitrile scaffolds (B-I to B-X) was synthesized by treating 3- amino- 5 -substituted -1,2,4-oxadiazole in the presence of sulfonyl chloride derivative. Sulphonamide was prepared by treating with primary amines with sulfonyl chloride.

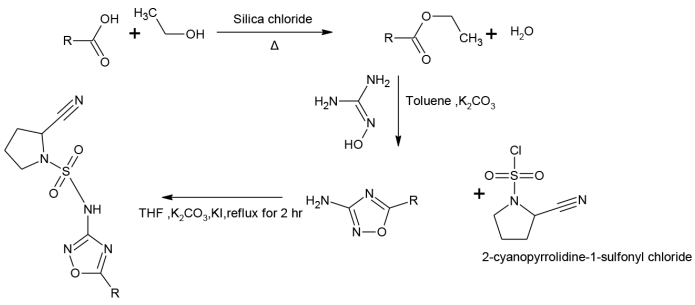
All the reagents and chemicals employed were of analytical grade and were not purified further. Most of the chemicals were purchased from Merck Life Science and Research Lab Fine Chem Industry. Melting points of the compounds were determined on open capillarie on Labronics LT-115 digital. FT-IR spectra were captured by using a Bruker *FTIR*.[21] The NMR spectra of the synthesized compounds were recorded on $CDCl_3$ (unless specified) with TMS as an internal reference (chemical deviation in δ, ppm) using the 100183-SND 400 MHz instruments and the 100186-SND 400 MHz instruments.[22] IR spectra were obtained from the Bruker spectrometer. Elemental analysis of the compounds was carried out by the company Thermo Finnigan. Elemental analysis results were within ± 0.4% of theoretical values.

Step-I: Synthesis of 3- amino- 5 -substituted -1, 2, 4-Oxadiazole

- **Synthesis of carboxylic acid ester:** solution of substituted carboxylic acid (1 mmol) in ethanol (10 ml) was added to a silica chloride (1 mmol). The reaction mixture was refluxed for 5 hr (monitored by TLC) and then cooled. The mixture was purified with column chromatography on silica gel with hexane and ethyl acetoacetate (9:1) as eluent to yield carboxylic acid ester.[23]
- **Synthesis of 3- amino- 5 -substituted -1,2,4- oxadiazole:** To a solution of carboxylic acid ester (0.67 mmol) in toluene (3 ml) was added N"- hydroxyguanidine (1.4 gm) and K_2CO_3 (1.4 mmol). Refluxed and stirred the reaction mixture for 6 hrs. On completion of the reaction, the reation mixture was cooled to room temperature and then diluted with ethyl acetoacetate (25 ml). Product after washed successively with water and brine (1:10). The organic phase was dried on (Na_2SO_4) filtered and concentrated. The residue was chromatographed on SiO_2 in ethyl acetoacetate and hexane (0–20%).[11]

Step-II- Catalyst-free of Synthesis 2-cyano-*N*-(5-substituted -oxadiazol-3-yl)pyrrolidine-1-sulfonamide

Sulfonyl chloride derivative (1 mmol) and 3- amino- 5 -substituted -1, 2, 4- Oxadiazole (2 mmol) (Step II) were added to ethanol (2 ml) at room temperature, and stirring continued until the reaction was complete (monitored by TLC). The mixture was condensed under reduced pressure to remove excess amine only after the reaction had ended and extracted with n-hexane TLC.[24]



2-cyano-*N*-(5-phenyl-1,2,4-oxadiazol-3-yl)pyrrolidine-1-sulfonamide

R=4-Hydroxy Phenyl, 3-Chloro Phenyl, 4-Nitro Phenyl, 2-Chloro Phenyl, 4-Bromo Phenyl, 4-Chloro Phenyl, 2-bromo Phenyl, 4-Methyl Phenyl, 3-Methyl Phenyl, 2-Nitro Phenyl, 4-Trifluoromethyl phenyl, 3,4-Dimethoxy Phenyl, 2-Hydroxy Phenyl, 4-Methoxy Phenyl.

B-I2-cyano-*N*-[5-(4-hydroxyphenyl)-1,2,4-oxadiazol-3-yl] pyrrolidine-1-sulfonamide

IR(KBr):3400,2250,1100,1250,1550,3050,1650,1450,1350;^{1}HNMR(400MHz,$CDCl_3$): 10.5(S,1H),9.67(S,1H),7.85(d,1H),6.91(d,1H),3.8(S,1H),1.2-2.4(m,6H);^{13}CNMR(400MHz,$CDCl_3$): δ (ppm) 164.5-169.3, 144.6, 125-135,50,55,56.1,20-30; *m/z* [M+2H]: 337.06.

B-II *N*-[5-(3-chlorophenyl)-1, 2, 4-oxadiazol-3-yl]-2-cyanopyrrolidine-1-sulfonamide

IR(KBr): 3300,2200,1050,780,1600,3050,1560,1455;^{1}HNMR(400MHz,$CDCl_3$): 10.5(S,1H),8.1(S,1H), 7.60(d,1H), 7.60(t,1H), 3.8(S,1H),1.2-2.4(m,6H); ^{13}CNMR(400MHz,$CDCl_3$): 164.5-169.3 ,134,125-135, 116.2, 45-55, 45.6, 55, ,20.9-29.3; *m/z* [M+H]: 354.78.

B-III 2-cyano-*N*-[5-(4-nitrophenyl)-1,2,4-oxadiazol-3-yl] pyrrolidine-1-sulfonamide

IR(KBr): 3400, 2250, 1100, 1400, 1550, 3050, 1650, 1450; ^{1}HNMR (400MHz,$CDCl_3$): 10.58(S, 1H),3.8(d ,1H),1.2-2.8(m ,6H),8.3(d ,2H), 8.87(d ,2H); ^{13}CNMR(400MHz,$CDCl_3$): 166.5-169.3, 125-135, 147.9, 116.2, 45-55, 20-30; *m/z* [M+2H]: 366.05.

B-IV *N*-[5-(2-chlorophenyl)-1, 2, 4-oxadiazol-3-yl]-2-cyanopyrrolidine-1-sulfonamide

IR(KBr): 3300,2200,1050,780,1600,3050,1560,1455;1H NMR (400 MHz, $CDCl_3$): 10.58(S, 1H),3.8(d ,1H),1.2-2.8(m ,6H),7.91(d ,1H),7.75(d ,1H); 7.38(t,1H),7.38(t,1H); ^{13}CNMR(400MHz,$CDCl_3$):δ(ppm)166.7,169.3, 130-145, 116.2,55,45.6, 20-30; *m/z* [M+H]: 354.04

B-V *N*-[5-(4-bromophenyl)-1, 2, 4-oxadiazol-3-yl]-2-cyanopyrrolidine-1-sulfonamide

IR(KBr):3250,2250,1100,1050,1560,3050,1650,1455; ^{1}H NMR (400 MHz, $CDCl_3$): 10.58(s,1H),3.8(s,1H),1.2-1.8(m,6H),7.62(d,2H),7.66(d,2H); ^{13}CNMR(400MHz,$CDCl_3$): δ 166.7,169.3, 125.1-135.1, 116.2, 45.6,55.6, 20.9-29.3;*m/z* [M+H]+: 397.99.

B-VI 2-cyano-N-[5-(4-chloro phenyl)-1, 2, 4-oxadiazol-3-yl] pyrrolidine-1-sulfonamide

IR(KBr):3300,2200,1200,1400,600,1000,3000,1600,3000,1450

^{1}H NMR (400 MHz, $CDCl_3$):10.5(S, 1H), 3.8(s, 1H), 1.2-2.4(m, 6H), 7.57(d, 2H), 8.12(d, 2H)

^{13}CNMR (400MHz, $CDCl_3$): 169.3, 124.2-134.3, 116.2, 45.6,55, 20.9-29.3

m/z [M+H]: 354.04

B-VII *N*-[5-(2-bromophenyl)-1, 2, 4-oxadiazol-3-yl]-2-cyanopyrrolidine-1-sulfonamide

IR(KBr): 3300,2200,1200,1400,600,1000,3000,1600,3000,1450;1H NMR (400 MHz, $CDCl_3$): 10.5(S,1H),3.8(s,1H),1.2-2.8(m,6H),7.43(d,1H),7.76(d,1H),7.62(t,1H),7.64(t,1H);^{13}CNMR(400MHz,$CDCl_3$): 166.7-169.3, 120.2-139.8, 116.2, 45.6-55, 45.6-55;*m/z* [M+H]+: 397.99.

B-VIII 2-cyano-*N*-[5-(4-methylphenyl)-1, 2, 4-oxadiazol-3-yl] pyrrolidine-1-sulfonamide

IR(KBr): 3300,2200,1200,1400,1400,1000,3000,1600,3000,1450

^{1}H NMR (400 MHz, $CDCl_3$): 10.5 (s,1H),7.60(d,2H),8.70(d,2H), 3.8(s,1H),1.2-2.20(m,6H),2.34(m,3H),3.8(s,1H),1.2-2.20(m,6H);^{13}CN MR(400MHz,$CDCl_3$):166.7,169.3, 124.2-134.3, 116.2,45.6,5520.9-29.3-21.3;*m/z* [M+H]+:334.09

B-IX 2-cyano-*N*-[5-(3-methylphenyl)-1, 2, 4-oxadiazol-3-yl] pyrrolidine-1-sulfonamide

IR(KBr): 3300,2200,1200,1400,1400,1000,3000,1600,3000,1450;^{1}H NMR (400 MHz, $CDCl_3$): 10.5(s,1H),7.49(t,1H),8.18 (d,1H),7.78(s,1H),7.18(d, 1H)2.46(m,3H),3.8(s,1H),1.2-2.4(m,6H);

^{13}CNMR (400MHz, $CDCl_3$): 166.7, 169.3, 124.2-134.3, 116.2, 45.6,55, 20.9-29.3, 21.3; *m/z* [M+H] +:334.09

B-X *N*-[5-(2-nitrophenyl)-1,2,4-oxadiazol-3-yl]-2-cyanopyrrolidine-1-sulfonamide IR(KBr):

3400,2250,1100,1550,1550,3050,1650,1450; ^{1}H NMR (400 MHz, $CDCl_3$): 10.5(s,1H),8(d,1H),8.08(d,1H),7.72(t,1H),7.89(t,1H),3.8(s,1H),1.2-2.4(m,6H); ^{13}CNMR (400MHz,CDCl3): 166.5-169.3, 124.4-150.1, 116.2, 45.6-55, 20.9-29.3; *m/z* [M+2H]: 366.05.

DPP-IV inhibition activity

Synthesized compounds B-I and B-XIV were evaluated for inhibition of DPP-IV *in vitro*. DPP-IV activity was calculated by the rate of hydrolysis of the surrogate substrate with H-Gly-Pro-7-amino-4-methyl coumarin (H-Gly-Pro-AMC) using Vildagliptin as a standard. A derivative evaluation was conducted in amounts of 10 µM in triplicate. Vildagliptin, as a standard was shown to be molecules exhibiting strong inhibiting activity at 100 nM, was further screened for IC_{50} values.[24]

RESULTS

Chemistry

In the above scheme, sulfonyl chloride group substituted on cyanopyrrolidine ring was reacted with primary amine on oxadiazole ring. This reaction was take place by elimination-addition mechanism, going through a sulfene intermediate formation. The reaction was carried out in the presence of ethanol, all the reaction was refluxed with ethanol on the water bath. The yields of synthesized compounds were in the range of 75–87%.

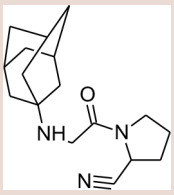
In vitro activity

Synthesized conjugates were tested for their *in vitro* anti-antidiabetic activity against the DPP-IV enzyme. Among the synthesized conjugates, B-II showed the highest percentage inhibition. The B-I showed good percentage inhibition as compared to the standard. (Table 1). B-XI derivative of pyrrolidine sulfonamide (IC_{50} 11.32±1.59µM) and 4 other compounds that display better inhibitory efficacy as the DPP-IV inhibitor and standard Vildagliptin.

DISCUSSION

In this research carboxylic ester was converted to 1,2,4-Oxadiazole derivatives by association with *N*"-hydroxyguanidine. Substituted Aromatic carboxylic acid was converted to the desired 3-(substituted phenyl)-1,2,4-oxadiazol-5-amine in better to good yields. Substituted aromatic carboxylic acids, such as 2-chlorobenzoic acid, 4-methyl benzoic acid, and 4-nitro benzoic acid also gave 16 target products. The structure of 3-(3-chlorophenyl)-1,2,4-oxadiazol-5-amine was further confirmed CHN study, IR, ^{1}H NMR. The structure of 3-(3-chlorophenyl)-1,2,4-oxadiazol-5-amine was confirmed from its IR spectrum which showed a band at primary amine at the band at 3400-3300 and 3330-3250 cm^{-1} two strong bands characteristic of primary amine and carboxylic acid ester at 1750-1735 cm^{-1} strong absorption band C=O vibration are disappeared. ^{1}H NMR spectrum wherein a peak at δ 7.83 for the NH_2 proton of the primary amine appears and wherein an ester peak at δ3.54 of CH_2 and δ1.22 of CH_3 proton of O-CH_2CH_3 disappears. ^{13}C NMR spectrum and also its ESI-MS spectrum with a peak at *m/z* 195.61 for $[M+H]^+$ confirmed the formation of 3-(3-chlorophenyl)-1,2,4-oxadiazol-5-amine.

Table 1: DPP-IV inhibitory activity information of the substances tested.

Sr.no	Code	Substituent	%Inhibition of DPP-IV at 10 *uM*
1	B-I	4-Hydroxy Phenyl	56.32
2	B-II	3-Chloro Phenyl	31.44
3	B-III	4-Nitro Phenyl	38.52
4	B-IV	2-Chloro Phenyl	26.43
5	B-V	4-Bromo Phenyl	44.29
6	B-VI	4 -Chloro Phenyl	49.62
7	B-VII	2-Bromo Phenyl	24.32
8	B-VIII	4-methyl Phenyl	19.62
9	B-IX	3-methyl Phenyl	39.72
10	B-X	2-Nitro Phenyl	24.21
11	B-XI	4-trifluoro Phenyl	66.32
12	B-XII	3,4-Dimethoxy Phenyl	18.18
13	B- XIII	2-Hydroxy Phenyl	38.16
14	B-XIV	4-methoxy Phenyl	17.18
15	Vildagliptin		100

In Scheme–II, sulfonyl chloride reacted with oxadiazole amines continuously stirring it at room temperature until the reaction was completed, and we obtained sulphonamide. Different spectral data, such as IR, ^{1}H NMR, ^{13}C NMR, and mass spectra, were used to identify final compounds structurally N-[3-(3-chlorophenyl)-1,2,4-oxadiazol-5-yl]-2-cyanopyrrolidine-1-sulphonamide (B-II).[15] We studied Physiochemical property in that molecular formula, molecular weight, melting point, elemental analysis. (Table 2).

The structure of B-II was further confirmed CHN study, IR, ^{1}H NMR. The structure of B-II is further confirmed from its IR spectrum which showed a band at 3500-3350 cm^{-1} one band of secondary amine characteristic N-H stretch. ^{1}H NMR spectrum wherein a singlet peak at δ10.58 for secondary amine appears and ^{1}H NMR spectrum wherein a peak at δ 7.83 for the NH_2 proton of the primary amine disappears.

IR spectrum of sulphonamide (S=O sym) is found at 1200-1000 cm^{-1} and (S=O asym) is found at 1420-1300 cm^{-1}. IR spectrum of (–C≡N str.) is found at stretch ~2250. 13C NMR spectrum and also its ESI-MS spectrum with a peak at m/z 353.78 for $[M+H]^+$ confirmed the formation of B-II.

Table 2: Analytical and physical-chemical data of the synthesized compounds.

Comp.	Mol. Formula	Mol. Wt.	M.P. ° C	Yield %	Elemental analyses (found)		
					C	H	N
B-I	$C_{13}H_{13}N_5O_4S$	335.338	156-158	82%	46.56%	3.91%	20.88%
B-II	$C_{13}H_{12}ClN_5O_3S$	353.784	120-122	84%	44.13%	3.42%	19.8%
B- III	$C_{13}H_{12}N_6O_5S$	364.337	168-170	85%	42.86%	3.32%	23.07%
B-IV	$C_{13}H_{12}ClN_5O_3S$	353.784	128-130	79%	44.13%	3.42%	19.8%
B-V	$C_{13}H_{12}BrN_5O_3S$	398.235	131-133	78%	39.21%	3.04%	17.59%
B-VI	$C_{13}H_{12}ClN_5O_3S$	353.784	194-196	79%	44.13%	3.42%	19.8%
B-VII	$C_{13}H_{12}BrN_5O_3S$	398.235	155-157	75%	39.21%	3.04%	17.59%
B-VIII	$C_{14}H_{15}N_5O_3S$	333.366	145-147	85%	50.44%	4.54%	21.01%
B-IX	$C_{14}H_{15}N_5O_3S$	333.366	137-139	74%	50.44%	4.54%	21.01%
B-X	$C_{13}H_{12}N_6O_5S$	364.337	137-139	87%	42.86%	3.32%	23.07%
B-XI	$C_{14}H_{12}F_3N_5O_3S$	387.337	114-116	86%	43.41%	3.12%),	18.08%)
B-XII	$C_{15}H_{17}N_5O_5S$	379.391	126-128	75%	47.49%	4.52%	18.46%
B-XIII	$C_{13}H_{13}N_5O_4S$	335.338	156-158	82%	46.56%	3.91%	20.88%
B-XIV	$C_{14}H_{15}N_5O_4S$	349.365	112-114	79%	48.13%	4.33%	20.05%

Table 3: Inhibition of DPP-4(IC_{50} nM) by selected compounds.

Compound	IC_{50} (nM ± SEM)
B-I	13.9±1.76
B-V	16.05 ±1.64
B-VI	15.98 ±1.98
B-XI	11.32±1.59
B-XIII	19.65 ± 2.60
Vildagliptin	4.79 ± 1.66

All synthesized compound were evaluated for DPP-IV inhibition assay compared to the standard drug Vildagliptin (Table 1). Vildagliptin as a standard, showed 100 percent inhibition. Among all synthesized compounds B-XI derivative showed good inhibition comparable with all synthesized compounds (Table 1). B-I, B-V, B-VI, B-XI, and B-XIII exhibited DPP-IV inhibition of the same magnitude (nM) as Vildagliptin. B-XI derivative of pyrrolidine sulfonamide (IC_{50} 11.32±1.59μM) and 4 other compounds that displayed better inhibitory efficacy as the DPP-IV inhibitor and standard Vildagliptin (4.79±1.66). B-I has the second-highest inhibitor 13.9±1.76 of the derivatives evaluated (Table 2). B-V, B-VI, and XIII were 16.05 ±1.64, 15.98 ±1.98, and 19.65 ± 2.60 with mild inhibitory activity as the DPP-IV inhibitor (Table 3).

CONCLUSION

To find new DPP-IV inhibitors, various scaffolds were developed and their binding affinities for the enzyme were evaluated using *in silico* experiments in comparison to Vildagliptin. Pyrrolidine-1-sulfonamide derivatives nucleus is the significant antidiabetic agent; these compounds can be used for further development to obtain more promising drug candidates. Thus, pyrrolidine-1-sulfonamide derivatives as potent and selective DPP-IV inhibitors for effective type-2 diabetes mellitus treatment. In the future, optimization of pyrrolidine-1-sulfonamide derivatives can lead to the discovery of new potent compounds.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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