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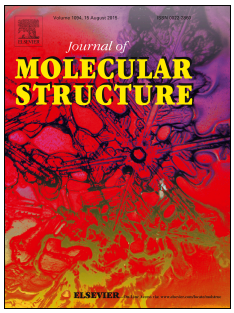

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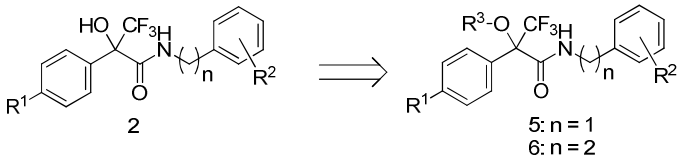

Synthesis, crystal structure, DFT analysis and fungicidal activity of a novel series O-substituted trifluoroatrolactamide derivatives

Hui-Hui Yang, Can Cui, Cong Zhu, Jian-Qiang Li, Rui Wu, Lei Tian, Wei-Guang Zhao*

State Key Laboratory of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, China

*Corresponding author

Tel: + 86 222 350 4279; Fax: + 86 222 350 4279. E-mail: zwg@nankai.edu.cn.

ABSTRACT

A series of O-substituted trifluoroatrolactamide derivatives has been synthesized and fully characterized by ^{1}H NMR, ^{13}C NMR, ^{19}F NMR, HRMS and X-ray diffraction analyses. The fungicidal activity of these compounds was evaluated and the results showed that some of them exhibited potent *in vitro* fungicidal activity against *Erysiphe graminis* and *Pyricularia oryzae*. Their structure-property relationships were investigated using density functional theory calculations. The X-ray crystal structure of one of these compounds adopted a monoclinic space group with the following unit cell parameters: *a* = 24.285(13) Å, *b* = 9.006(5) Å, *c* = 9.794(5) Å, β = 92.110(9)º, V = 2140.6(19) Å3 and Z = 4. A comparison of these experimental results with the theoretical values revealed that there was good agreement between the two sets of data. The subsequent biological evaluation of these compounds showed that some of them exhibited potent *in vitro* fungicidal activity against *Erysiphe graminis* and *Pyricularia oryzae*.

Keywords: Trifluoroatrolactamide; Crystal structure; Density Functional Theory; Fungicidal activity

Introduction

α-Hydroxyacetic acids represent an interesting structural class that has recently received considerable interest from researchers working in a number of different areas. Atrolactic acid is an important α-hydroxyacetic acid with numerous applications in the field of medicine, where it has been used to good effect as a chiral derivatizing agent [1]. Themisone, which is also known as atrolactamide, was discovered to be a potent anticonvulsant in the 1950s [2]. The trifluorinated analogue of themisone, compound **1**, offered increased duration of action with similar activity to phenytoin and no observed toxicity [3]. We recently developed a rapid, eco-friendly and high-yielding procedure for the synthesis of trifluoroatrolactamide using a Passerini reaction under ultrasound irradiation conditions [4]. We also developed an ultrasound-promoted one-pot Passerini/hydrolysis reaction sequence for the rapid generation of a combinatorial library of trifluoroatrolactamides **2**, which possessed excellent broad-spectrum fungicidal activities [5]. In the early 1990s, the α-hydroxy acetamides **3** [6, 7] and **4** [8] were reported to show inhibitory activity against a number of different plant pathogens (in particular, oomycetes diseases). The subsequent alkylation of the hydroxyl group of compound **3** led to the discovery of mandipropamid, which was the first mandelamide-based fungicide to be developed against foliar diseases caused by *Oomycetes* [9]. Herein, we describe our recent efforts towards the development of a novel series of atrolactamide-based compounds **5** with higher fungicidal activities by the alkylation of the corresponding hydroxyl compounds **2**.

Experimental

Materials and methods

^{1}H, ^{13}C and ^{19}F NMR spectra were measured on a Bruker AC-P500 instrument (Bruker, Fallanden, Switzerland) using $CDCl_3$ as a solvent with TMS as an internal reference standard.

Melting points were determined on an X-4 binocular microscope melting point apparatus (Beijing Tech Instruments, Beijing, China) and were uncorrected. HRMS were recorded on an Ionspec 7.0-T Fourier-transform ion-cyclotron resonance mass spectrometer (Bruker, Billerica, MA, USA). The ultrasonic irradiation experiments were conducted on a Nanjing SL2010-N ultrasonic processor (Shunliu, Nanjin, China). All of the reagents used in the current study were purchased as the analytical grade.

Typical Procedure for the Preparation of Trifluoroatrolactamide **2**.

Compound **2** was synthesized by an ultrasound-promoted one-pot Passerini/hydrolysis reaction sequence between 2,2,2-trifluoroacetophenone **7** and isonitrile **8** according to the literature procedure [5]. All of the products were purified by column chromatography.

Typical Procedure for the Preparation of the N-substituted benzyl (or phenethyl)-2-(alkyloxy)-3,3,3-trifluoro-2-(substituted phenyl)propanamides ***5*** *and* ***6****.*

NaH (60% dispersion in mineral oil, 0.09 g, 2.22 mmol) was added to a solution of compound **2** (2.59 mmol) and a catalytic amount of tetrabutylammonium bromide in THF (10 mL) at room temperature, and the resulting mixture was stirred for 15 min. Alkyl bromide (3.88 mmol) was then added to the reaction in a dropwise manner, and the resulting mixture was heated at reflux for 2 h. The mixture was cooled to ambient room temperature and the solvent removed *in vacuo* to give a residue, which was dissolved in EtOAc (30 mL). The organic solution was washed with brine and dried over $MgSO_4$ before being evaporated to dryness *in vacuo* to give a solid, which was recrystallized from EtOH to give compounds **5** and **6**.

The data for compounds **5-1~28 and 6-1~4** can be found in the Supporting Information.

Determination of the crystal structure

Crystals suitable for X-ray crystallography were obtained by the slow evaporation of ethanol solutions of the desired compounds at room temperature. The X-ray intensity data for compound **5-28** were collected with a Rigaku MM-007 rotating anode diffractometer equipped with a Saturn CCD Area Detector System using monochromated Mo-Kα radiation at T = 113(2) K. The structures were solved by direct methods with SHELX-97 [10] and subsequently refined using the same software [11]. All non-hydrogen atoms were refined with anisotropic thermal parameters. All of the hydrogen atoms were placed in their calculated positions. Details of the data collection conditions and the parameters of the refinement process are shown in **Table 1**.

Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 1429628 for this compound.

Theoretical calculations

Compounds **5-21** and **5-28** were selected as suitable representatives of the compound series and their structures were optimized by density functional theory (DFT) calculations using the B3LYP/6-31++G (d, p) basis sets with the Gaussian software package[12, 13]. Vibrational analysis showed that the optimized structures were in accordance with the minimum points on the potential energy surfaces. All of the convergent precision values used in the current study were the system default values, and all of the calculations were carried out on a DELL computer.

Fungicidal Activities

The fungicidal activities of the compounds synthesized in the current study were evaluated against *Pseudoperonospora cubensis, Erysiphe graminis, Puccinia sorghi Schw* (*in vivo*) and *Pyricularia oryzae* (*in vitro*) using previously described methods from the literature [14, 15]. The results of these experiments are summarized in **Tables 2** and **3**.

Results and discussion

Chemistry synthesis

The O-substituted trifluoroatrolactamides reported in the current study were prepared via a facile and efficient three-step procedure, which is described below (see **Scheme 1**).

The trifluoroatrolactamides **2** were prepared according to our previously reported ultrasound-promoted method [4, 5]. Briefly, trifluoroacetophenones were reacted with acetic acid and isonitriles under ultrasonic irradiation and solvent-free conditions at 40 °C for 20 min to give a mixture of O-acetyl trifluoroatrolactamides **9a** and the corresponding cyclized products **9b**. It is noteworthy that the nature of the substituents on the phenyl rings of the isonitrile and phenylethanone substrates had a significant impact on the ratio of the products (i.e., **9a** to **9b**). The reaction mixtures, which were not isolated, were directly hydrolyzed in 15 min by the addition of aqueous sodium hydroxide and methanol at room temperature to give the corresponding trifluoroatrolactamides **2** in good yields. The hydroxyl group of these compounds was subsequently alkylated with various alkyl halides using NaH in THF to furnish the O-substituted trifluoroatrolactamides **5** and **6**. The structures of all of the compounds prepared in the current study were confirmed by ^{1}H NMR, ^{13}C NMR, ^{19}F NMR and high resolution mass spectrometry analyses. The structure of compound **5-28** was further confirmed by single crystal X-ray diffraction analysis.

X-ray crystal structure

Compound **5-28** was recrystallized from ethanol to give colorless needles, which were subjected to X-ray diffraction analysis. The single X-ray crystal structure of compound **5-28** is shown in **Fig. 1**. The results revealed that compound **5-28** crystallized in a monoclinic system with a P2(1)/c space group. The single C(1)-C(8) bond (1.515(4) Å) was shorter in length than

any of the other C-C bonds in the molecule, including the C(9)-C(10) (1.531(4) Å), C(10)-C(13) (1.534(4) Å) and C(10)-C(11) (1.539(5) Å) bonds. The dihedral angle between the planes of the methoxyl-phenyl ring (C(13)-C(18)) and benzene ring (C(19)-C(24)) was 70.7°. The dihedral angle between the planes of the methoxyl-phenyl ring (C(1)-C(6)) and benzene ring (C(19)-C(24)) was 24.8°. The C8-N1-C9-C10-C11 bonds were almost coplanar based on the torsion angles of the C8-N1-C9-C10 (169.5(3)°) and N1-C9-C10-C11 (178.0(3)°) bonds.

The packing of compound **5-28** in the crystalline state is shown in **Fig. 3**. The crystal structure revealed the presence of intermolecular hydrogen bonding interactions between neighboring molecules with N(1)-H(1)...O(2) distances of 2.07(2) Å that stabilized the molecular structure.

Fungicidal activity

The fungicidal activities of all of the compounds prepared in the current study were tested against *Pseudoperonospora cubensis, Erysiphe graminis* and *Puccinia sorghi Schw* (*in vivo*) at a concentration of 400 mg L^{-1}. These compounds were also tested against *Pyricularia oryzae* (*in vitro*) at 25 mg L^{-1}. Some of the compounds exhibited good fungicidal activities. Under equivalent dosage conditions of 25 $\mu g \cdot mL^{-1}$, compounds **5-4**, **5-5**, **5-21**, **6-2** and **6-4** displayed complete control (i.e., 100% inhibition) against *Pyricularia oryzae*. Under equivalent dosage conditions of 400 $\mu g \cdot mL^{-1}$, compounds **5-10**, **6-1** and **6-4** exhibited high levels of control (i.e., 95% inhibition) against *Puccinia sorghi Schw*; compounds **5-5** and **5-13** exhibited 95 and 98% inhibition against *Pseudoperonospora cubensis*; and compounds **5-1**, **5-10**, **5-12**, **5-21** and **5-23** exhibited 100, 100, 98, 100 and 100% inhibition against *Erysiphe graminis*. The nature of the substituents on the phenyl rings of the products had a significant impact on their fungicidal activities. The alkylation of the trifluoroatrolactamides **2** led to an increase in their fungicidal activity, with the Me, Et and allyl units proving to be particularly effective in this regard. The

introduction of substituents at the *ortho*-position of the benzylamine group generally led to a decrease in the fungicidal activity. However, the introduction of a methyl group at the *para*-position of the benzylamine group was an exception to this general trend, with compounds **5-4** and **5-5** exhibiting significant levels of control against *Pyricularia oryzae*. Interestingly, compound **5-21** bearing a 2-Cl group at its R^2 position, exhibited complete control (i.e., 100% percent inhibition) against *Erysiphe graminis* and *Pyricularia oryzae* whilst compound **5-10** bearing an electron-donating methoxy group at the same position only exhibited complete control against *Pyricularia oryzae*. Increasing the alkyl chain length of the compound (i.e., n = 2) compounds **6-2** and **6-4** displayed high levels of fungicidal activity against *Pyricularia oryzae.*

The activities of the most active compounds were measured at a variety of different concentrations using a four-fold serial dilution. As shown in Table 2, compound **5-21** inhibited the growth of *Erysiphe graminis* by 80% at a concentration of 6.25 μg mL^{-1}, as well as inhibiting the growth of *Pyricularia oryzae* by 100% at a concentration of 8.3 μg mL^{-1}. Compounds **5-4**, **5-5** and **6-4** displayed all inhibited the growth of *Pyricularia oryzae* by 50% at a concentration of 8.3 μg mL^{-1}.

Theoretical calculations

The total molecular and frontier molecular orbital energy levels of compounds **5-21** and **5-28** are listed in Table 3. The energy gap between the highest occupied molecular orbital (HOMO) and lowest occupied molecular orbital (LUMO) was calculated at the B3LYP level using DFT. According to the frontier molecular orbital theory, the energy levels of the HOMO and LUMO can have a significant impact on the bioactivity of a compound. The HOMO and LUMO can donate and accept electrons, respectively. Studying the frontier molecular orbital energy levels in this way can therefore provide useful information about the biological mechanism of action of a

compound. Fig. 4 shows that there were noticeable differences in the electron density distributions of the frontier molecular orbitals of compounds **5-21** and **5-28** and that the electron densities of the LUMO and HOMO orbitals were also different from each other. These differences were attributed to differences in the location and quantity of the electron density in these compounds. The results in Fig. 4 clearly show that the HOMO of compound **5-21** was mainly located across the two benzene rings and the amide group, whilst the LUMO was mainly located on only one of the benzene rings and the amide group. This result therefore showed that the electrons were being transferred from the benzene ring to the amide group. In contrast, the HOMO of compound **5-28** was mainly located across the three benzene rings and the amide group, while the LUMO was mainly located on the PhO-benzene ring and amide group. This result indicated that there was an electron transfer from the EtO-benzene ring to the amide group. The main difference between these two molecules was therefore determined to be the direction of the electron transfer process, with the electrons moving in the opposite direction in both cases. This difference in the direct of the electron transfer could explain the difference in the fungicidal activities of these compounds.

Conclusion

We have synthesized a series of O-substituted trifluoroatrolactamides, which were fully characterized by spectroscopic analyses (^{1}H NMR, ^{13}C NMR, ^{19}F NMR, HRMS) and single crystal X-ray diffraction. The structural properties of these compounds were calculated by DFT using the B3LYP/6-31++G(d, p) basis sets. The fungicidal activities of these compounds were tested against four phytopathogenic fungi. The X-ray crystallography data revealed that these compounds were stabilized by hydrogen bonding interactions between the N(1)-H(1)...O(2)

groups of two individual molecules. Notably, some of these compounds exhibited good *in vitro* fungicidal activity against *E. graminis* and *P. oryzae*.

Acknowledgment

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Appendix A. Supplementary material

Further details of the crystal structure investigations may be obtained from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif on quoting the depository number CCDC 1429628. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. Tel: 044-01223-762910; fax: 044-01223-336033; email:deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j. molstruc.

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Table 1.

Crystal data and experimental and refinement parameters of compound **5-28**.

Empirical formula	C_{24} H_{22} F_3 N O_4
Formula weight	445.43
Temperature	113(2) K
Wavelength	0.71073 A
Crystal system, space group	Monoclinic, P2(1)/c
a (Å ^{3})	24.285(13)
b (Å ^{3})	9.006(5)
c (Å ^{3})	9.794(5)
α (º)	90
β (º)	92.110(9)
γ (º)	90
Volume (Å ^{3})	2140.6(19)
Z, Calculated density y (g cm^{-3})	4, 1.382
Absorption coefficient (mm^{-1})	0.111
F(000)	928
Crystal size	0.20 x 0.18 x 0.12 mm
Theta range for data collection	1.68 to 25.02 deg.
Limiting indices	-28<=h<=28, -10<=k<=10, -11<=l<=11
Reflections collected / unique	18899 / 3782 [R(int) = 0.1436]
Completeness to theta = 25.02	100.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9868 and 0.9781
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3782 / 1 / 296
Goodness-of-fit on F^2	1.062
Final R indices [I>2sigma(I)]	R1 = 0.0753, wR2 = 0.1758
R indices (all data)	R1 = 0.1023, wR2 = 0.1957
Extinction coefficient	0.0054(16)
Largest diff. peak and hole (e. Å ^{3})	0.299 and -0.297

Table 2

Fungicidal activities of compounds **5** and **6** (percentage inhibition) against *Pseudoperonospora cubensis*, *Erysiphe graminis*, *Puccinia sorghi Schw* (*in vivo*) and *Pyricularia oryzae* (*in vitro*)

No.	R^1	R^2	R^3	n	*P. cubensis*	*E. graminis*	*P. sorghi Schw*	*P. oryzae*
						400 mg/L		25 mg/L
5-1	H	H	Et	1	0	100	0	0
5-2	H	H	$CH_2C{\equiv}CC_2H_5$	1	0	0	0	0
5-3	H	H	Bn	1	0	0	0	0
5-4	H	4-Me	Me	1	0	0	0	100
5-5	H	4-Me	Et	1	95	60	0	100
5-6	H	4-Me	CH_2=$CHCH_2$	1	0	0	0	50
5-7	H	4-Me	$CH_2C{\equiv}CCH_3$	1	0	0	0	0
5-8	H	4-Me	CH_2-$C{\equiv}CC_2H_5$	1	0	0	0	0
5-9	H	4-Me	Bn	1	0	0	0	0
5-10	H	2-MeO	Me	1	0	100	95	50
5-11	H	2-MeO	Et	1	50	85	0	0
5-12	H	2-MeO	Pr	1	0	98	0	80
5-13	H	2-MeO	CH_2=$CHCH_2$	1	98	60	0	0
5-14	H	2-MeO	Bn	1	0	0	75	0
5-15	H	4-MeO	Me	1	0	70	0	0
5-16	H	4-MeO	$CH_2C{\equiv}CC_2H_5$	1	0	0	0	0
5-17	H	4-MeO	Bn	1	0	0	0	0
5-18	H	4-F	Me	1	0	0	0	80
5-19	H	4-F	CH_2=$CHCH_2$	1	0	85	0	50
5-20	H	4-F	Bn	1	0	0	0	0
5-21	H	2-Cl	Me	1	0	100	0	100
5-22	H	2-Cl	Pr	1	0	0	0	0
5-23	H	2-Cl	CH_2=$CHCH_2$	1	0	100	0	50
5-24	H	2-Cl	Bn	1	0	0	70	0
5-25	Et	4-MeO	Me	1	0	0	0	80
5-26	MeO	4-MeO	Me	1	0	0	0	0
5-27	Ph	4-MeO	Me	1	0	0	0	0
5-28	OPh	4-MeO	Me	1	0	0	0	0
6-1	H	3,4-diMeO	Me	2	0	0	95	0
6-2	H	3,4-diMeO	Et	2	0	0	0	100
6-3	H	3,4-diMeO	Pr	2	0	0	0	0
6-4	H	3,4-diMeO	CH_2=$CHCH_2$	2	0	0	95	100
6-5	H	3,4-diMeO	Bn	2	0	0	0	0

Table 3

Fungicidal activities of compounds **5** and **6** (percentage inhibition) against *Pseudoperonospora cubensis*, *Erysiphe graminis*, *Puccinia sorghi Schw* (*in vivo*) and *Pyricularia oryzae* (*in vitro*)

No.	*P. cubensis*		*E. graminis*				*P. sorghi Schw*		*P. oryzae*			
	400	100	400	100	25	6.25	400	100	25	8.3	2.8	0.9
5-4	0	-	0	-	-	-	0	-	100	80	50	0
5-5	95	20	60	-	-	-	0	-	100	80	50	0
5-10	0	-	100	30	-	-	95	0	50	-	-	-
5-21	0	-	100	95	90	80	0	--	100	100	0	0
5-23	0	-	100	60	40	0	0	-	50	-	-	-
6-1	0	-	0	-	-	-	95	50	0	-	-	-
6-2	0	-	0	-	-	-	0	-	100	50	-	-
6-4	0	-	0	-	-	-	95	70	100	80	50	0
fenaminstrobin	100	100	100	100	100	100	100	100	100	100	100	80

Table 4

Total and frontier molecular orbital energies of compounds **5-21** and **5-28**.

	5-21	**5-28**
E_{total}/Hartree[b]	-1621.42379522	-1582.54682774
E_{HOMO}/Hartree	0.24965	-0.22219
E_{LUMO}/Hartree	-0.02695	-0.01699
ΔE[a]/Hartree	-0.2766	0.2052

[a] $\Delta E = E_{LUMO} - E_{HOMO}$; [b] 1 Hartree = 4.35974417×10^{-18}J = 27.2113845ev

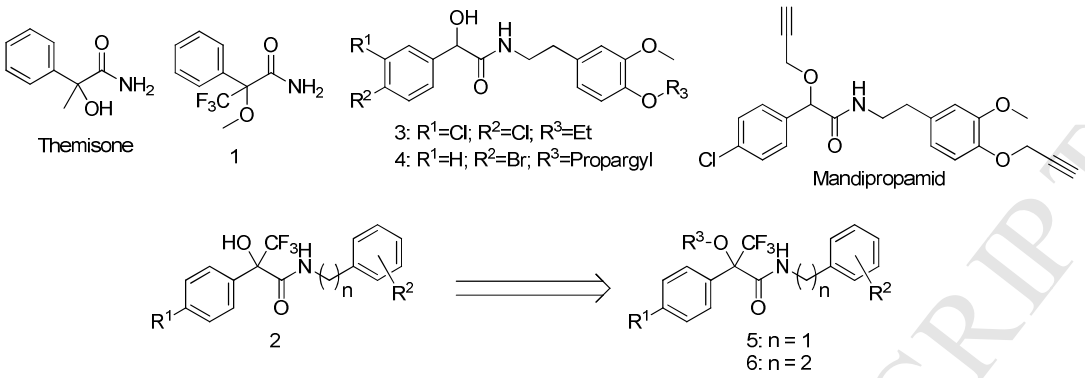


Fig. 1. Structures of some compounds containing an α-hydroxyacetamide moiety and the design of the target compounds based on compound **2**

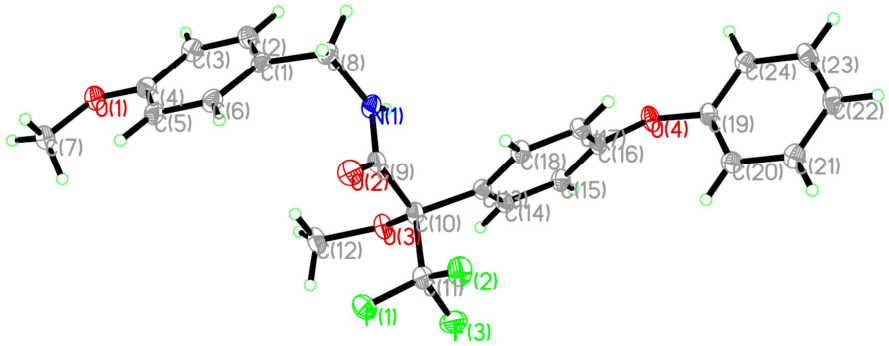


Fig. 2. Crystal structure of compound **5-28** showing the atom numbering scheme.

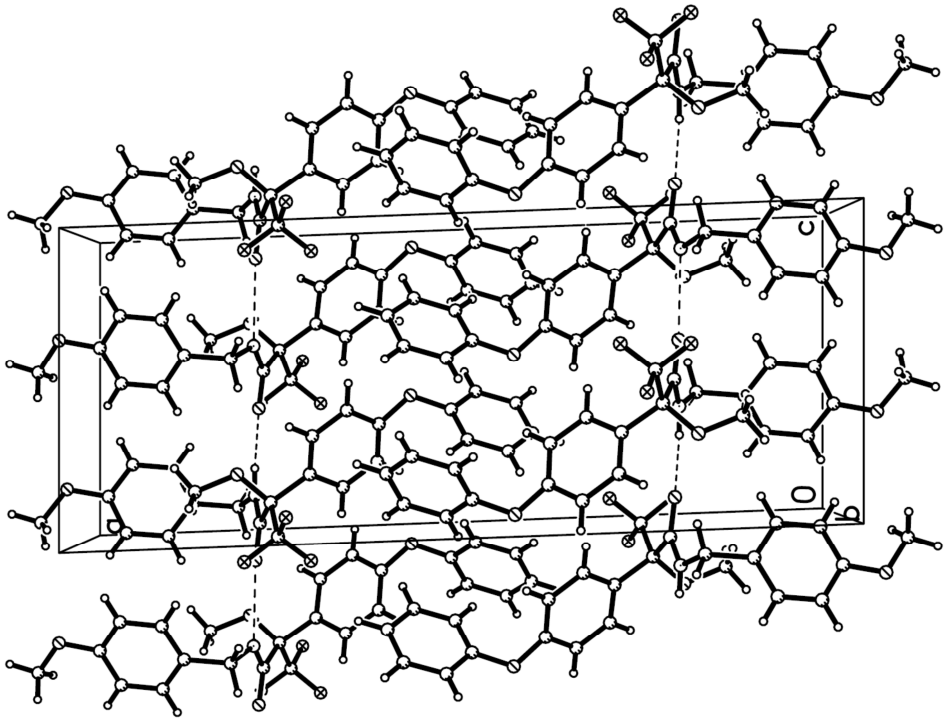


Fig. 3. Crystal Packing diagram of compound **5-28**.

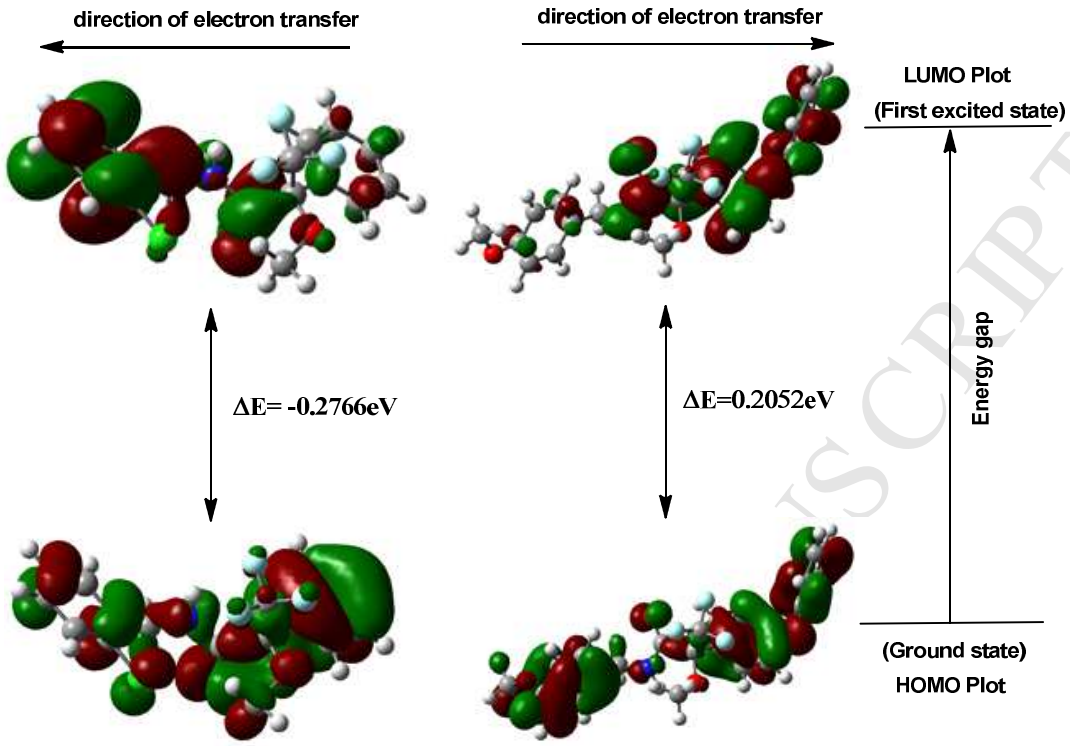
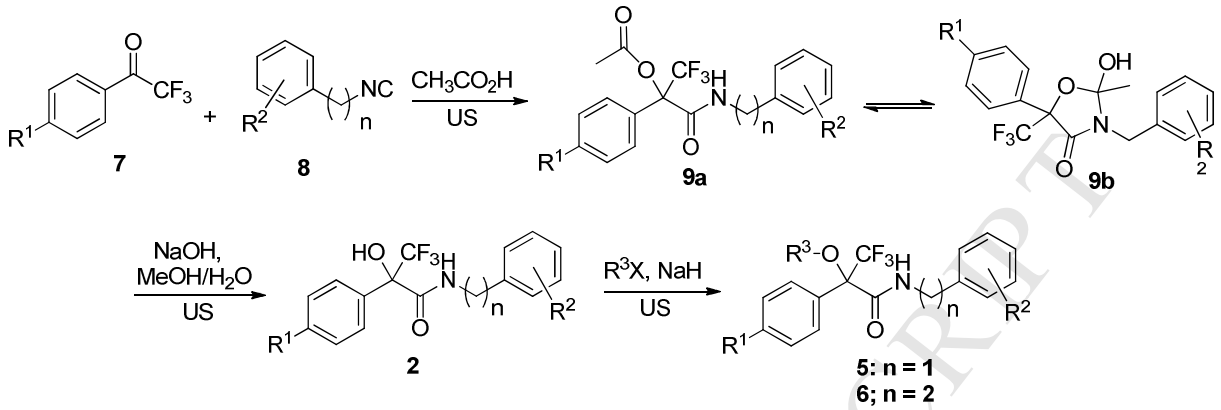


Fig. 4. Frontier molecular orbitals of compounds **5-21** and **5-28**.



Scheme 1. Synthesis of compounds **5** and **6**

Highlights

A series of O-substituted trifluoroatrolactamide derivatives were synthesized.

Their structures were characterized by NMR, MS, IR, X-ray.

Some molecular properties were calculated by density functional theory calculations.

Good fungicidal activities were observed.