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Synthesis and biological activities of novel 5-substituted-1,3,4-oxadiazole Mannich bases and bis-Mannich bases as ketol-acid reductoisomerase inhibitors

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ABSTRACT

A series of novel 5-substituted-1,3,4-oxadiazole Mannich bases and bis-Mannich bases have been conveniently synthesized in good yields. Their structures were characterized by IR, ^{1}H NMR, ^{13}C NMR and elemental analysis. The preliminary bioassay results indicated that some of the compounds showed promising in vitro fungicidal activities towards several test plant fungi; some of them exhibited significant herbicidal activities against *Brassica campestris* and excellent in vitro inhibitory activities against rice ketol-acid reductoisomerase (KARI). Among 14 novel compounds, **8c**, **8d** and **8m** showed potent KARI inhibitory activities with K_i value of (0.96 ± 0.42), (3.86 ± 0.49) and (3.10 ± 0.71) μmol/L, respectively, and were comparable with IpOHA. These compounds could be novel KARI inhibitors for further investigation. The density functional theory (DFT) calculations and molecular docking were carried out to study the structure–activity relationship (SAR) of the active inhibitors in this Letter.

It is well known that the application of agrochemicals has led to numerous benefits and made a significant contribution to the lifestyles we have come to expect for over many years. In view of the emergence of resistance and pollution problems associated with conventional agrochemicals, there is an urgent need to research and develop more agrochemicals with novel structures, super activity, high selectivity and eco-friendly properties.[1–3]

Plants and microorganisms contain numerous enzymes that are potential targets for the bioactive compounds. Enzymes involved in the biosynthesis of branched chain amino acids (BCAA) leucine, valine and isoleucine are one such example. Some organisms—plants, bacteria and fungi possess the BCAA pathway, while all the mammals including human do not possess this pathway. Therefore, the design and development for novel herbicidal and fungicidal compounds based on the BCAA pathway could be in accord with the research orientation of green agrochemicals. Acetohydroxyacid synthase (AHAS) is the first enzyme in the BCAA pathway, it has already been a successful target for development of herbicides and antifungal reagents, such as sulfonylurea and imidazolinone compounds.[4–6] The success of AHAS inhibitors has stimulated research into inhibitors of other enzymes in the BCAA pathway. Ketol-acid reductoisomerase (KARI, EC 1.1.1.86) is another key enzyme that catalyzes the second step of the pathway. There are only a few KARI inhibitors with potent in vitro activities reported in literatures, such as 2-dimethylphosphinoyl-2-hydroxy acetic acid (Hoe 704),[7] *N*-hydroxy-*N*-isopropyloxamate (IpOHA),[8] cyclopropane-1,1-dicarboxylate (CPD),[9] and thiadiazole compounds.[10] Regrettably, the in vivo activities of all these inhibitors as herbicides are weak. Therefore, more inhibitors of KARI with novel structures and high biological activities remain as a potential source of novel herbicidal or fungicidal compounds.

Due to the interesting structural and versatile biological properties, heterocyclic compounds have attracted much attention not only in organic chemistry but also in medicinal, pharmaceutical and agrochemical chemistry. In particular, they are very important part in almost all kinds of agrochemicals. For examples, Pefurazoate is a kind of fungicides with furan moiety;[11] Pyroxsulam, discovered by the DOW chemical company, and Pyribencarb, discovered by KUMIAI chemical industry Co., LTD are heterocyclic herbicide and fungicide containing pyridine ring, respectively.[12,13] Likewise, oxadiazole compounds are also associated with various agrochemical activities.[14–16]

Moreover, heterocyclic Mannich bases that are derived from the corresponding heterocyclic intermediates also possess various useful properties, however most of which were embodied in their

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pharmacological activities, such as anticancer,[17] antimicrobial,[18] antitumor[19] and antituberculous[20] activities. Overall, the researches of heterocyclic Mannich bases in agrochemical area are relatively few, so further exploration for this topic might provide novel agrochemical candidates. In our early work, we reported the synthesis and biological activities of some interesting 1,2,4-triazole Mannich base structures containing piperazine and (substituted)benzylideneamino groups.[3,21] Some of those compounds displayed favorable herbicidal and in vitro KARI inhibitory activities. Especially, those compounds possessed significant fungicidal activities against some plant fungi such as *Pseudoperonospora cubensis* and *Corynespora cassiicola*. Recently, some phenylpyrazole-containing triazole Mannich bases were also found to be effective for inhibiting the growth of *Rhizoctonia cerealis* and *Cercospora arachidicola* in our lab.[22] Those previous results provided an important initiative to undertake further structural modifications.

Considering all that mentioned above and with our pursuit to look for novel heterocyclic compounds with promising KARI inhibitory and pesticidal potential, a series of novel 1,3,4-oxadiazole Mannich bases and bis(1,3,4-oxadiazole) Mannich bases with various substituted piperazine moieties were designed. Herein, regarding to the structure of lead compound 1,2,4-triazole Mannich bases,[3,21] the 4-(substituted)benzylideneamino-1,2,4-triazole group was replaced by a 1,3,4-oxadiazole ring, meanwhile furan/pyridine motif was introduced into the 5-position of 1,3,4-oxadiazole ring. These novel compounds have been synthesized successfully via Mannich reaction in this Letter. Their fungicidal, herbicidal and KARI inhibitory activities were investigated and the structure–activity relationships was discussed.

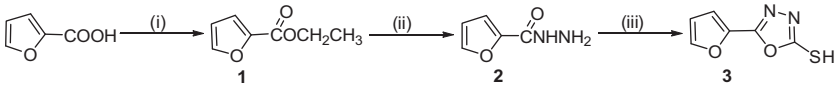
The synthetic routes for the intermediates are shown in Schemes 1 and 2 and for the title compounds—in Scheme 3. According to the reported procedures,[23–26] The intermediates 5-substituted-1,3,4-oxadiazole-2-thiol **3** and **7** were synthesized via multi-step reactions. Just as the thioamide structure (C(=S)—NH—) in 1,2,4-triazole-5-thiol-type compounds,[3,21,22] the intermediate **3** or **7** can exist in either thiol or thione tautomeric forms. Based on the results of our experiment, it was found that the oxadiazole thione isomer undergoes subsequent Mannich reaction via N–H at α-position of thiocarbonyl (C=S). As a result, the condensation of 1,3,4-oxadiazole-2-thiol **3** or **7** with formaldehyde and 4-(substituted benzyl)piperazine, or 4-(substituted pyrimidyl)/phenyl/pyridylpiperazine in ethanol at room temperature resulted in novel Mannich bases—1,3,4-oxadiazole thiones **8a**–**8l** in satisfactory yields (57–94%). Under the similar reaction conditions, bis-Mannich bases, that is, bis(1,3,4-oxadiazole thione) **8m** and **8n** were successfully synthesized in 76% and 65% yield, respectively, using excess formaldehyde and 2:1 molar ratio of intermediate **3** or **7** and piperazine. In general, this approach towards the synthesis of the title compounds possesses noticeable advantages, such as, mild reaction conditions, high yield and short reaction time (2 h).

The title compounds were identified by IR, ^{1}H NMR, and ^{13}C NMR spectra. The measured elemental analyses were also consistent with the corresponding calculated values. In ^{1}H NMR, the chemical shift at δ 14.07–14.65 for intermediates **3** and **7** as a singlet indicates that the compounds existed as the oxadiazole thiol form. For the title compounds, the signal of CH_2 protons neighboring to the oxadiazole ring was observed at δ 5.04–5.17 as a singlet. The piperazine ring proton (CH_2) in **8a**–**8l** appeared at δ 2.82–3.95 and δ 2.37–3.10 as multiplets, respectively. Whereas in the case of bis-Mannich bases **8m** and **8n**, the piperazine ring proton appeared at δ ~2.90 as a singlet due to their symmetric structure. In the ^{13}C NMR spectra of the title compounds, the typical carbon signal at δ 177.4–178.3 was derived from the resonance of thiocarbonyl group (C=S), and such signals in pyridine-3-yl substituted compounds (δ 178.2–178.3) shifted downfield compared with those of furan-2-yl substituted compounds (δ 177.4–177.5).

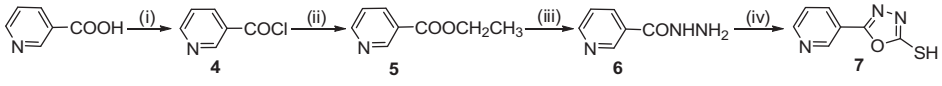
The piperazine carbons of compounds **8m** and **8n** also appeared as one signal at δ ~50.10 as opposed to two signals at δ 50.11–52.90 and δ 43.46–50.27 in compounds **8a**–**8l**. The IR spectra of the compounds showed bands at 1499–1576 cm^{-1} for C=N and 1161–1175 cm^{-1} for C=S stretching.

The in vitro fungicidal results of the oxadiazole Mannich bases **8a**–**8l** and bis-Mannich bases **8m** and **8n** in inhibiting the mycelial growth[27] of six test fungi are listed in Table 1. The commercial fungicides Triadimefon, Carbendazim and Chlorothalonil were used as controls. The known KARI inhibitor CPD was also tested the fungicidal activities at the first time in our lab. As indicated in Table 1, the compounds at the concentration of 50 μg/mL showed obvious in vitro fungicidal activities against several tested fungi, especially for *Physalospora piricola* and *Rhizoctonia cerealis*. For examples, compounds **8d**, **8e**, **8g** and **8m** possessed inhibition rates of 42–50% against *Physalospora piricola*, which were near to that of Triadimefon, and those of the representative triazole Mannich bases TM1 and TM2 we reported before;[21] **8m** also showed 72.8% inhibition towards *Rhizoctonia cerealis*. In addition, **8m** held an inhibition rate of 44.8% against *Cercospora arachidicola* and was more effective than Triadimefon (34.5%). Interestingly, the potent in vitro KARI inhibitor CPD was found to exhibit weak fungicidal activities against almost all the test fungi. In comparison with TM1 and TM2, these oxadiazole Mannich bases overall showed less fungicidal effects against most of test fungi in this study.

The herbicidal activity data based on the rape (*Brassica campestris*) root and barnyardgrass (*Echinochloa crusgalli*) cup tests,[28] and in vitro inhibitory activity data by the continuous assay[9] against rice KARI of the compounds are listed in Table 2. The commercial herbicide Chlorsulfuron, and known potent in vitro KARI inhibitors IpOHA and CPD were used as controls. It was found that at the test concentration of 100 μg/mL, most of the compounds exhibited remarkable herbicidal activities with the inhibition rates of 58.2–81.4% against *Brassica campestris*, while some of these results were comparable with those of the controls,



Scheme 1. The synthesis of the intermediate 5-(furan-2-yl)-1,3,4-oxadiazole-2-thiol (**3**). Reagents and conditions: (i) CH_3CH_2OH, H_2SO_4, reflux,7 h, (ii) $NH_2NH_2{\cdot}H_2O$, CH_3CH_2OH, reflux, 6 h, (iii) CS_2, KOH, CH_3CH_2OH, reflux,7 h.



Scheme 2. The synthesis of the intermediate 5-(pyridin-3-yl)-1,3,4-oxadiazole-2-thiol (**7**). Reagents and conditions: (i) $SOCl_2$, 77 °C, 3 h, (ii) CH_3CH_2OH, Et_3N, CH_2Cl_2, rt, 18 h, (iii) $NH_2NH_2{\cdot}H_2O$, CH_3CH_2OH, reflux, 6 h, (iv) CS_2, KOH, CH_3CH_2OH, reflux, 7 h.

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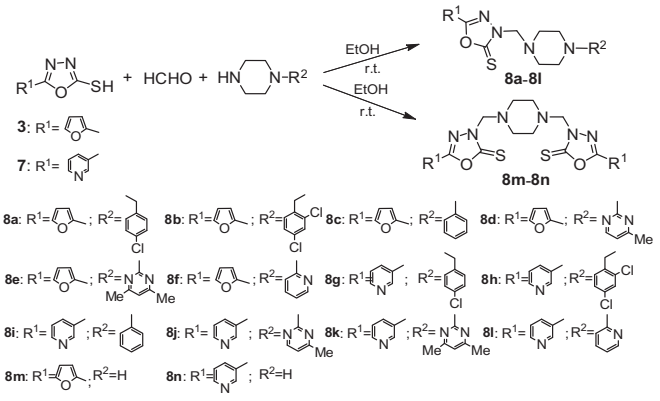

Scheme 3. The synthesis of the title compounds **8a**–**8n**.

such as **8b** (81.4%) and **8m** (77.2%), especially **8b** was even more effective than the best active control Chlorsulfuron (80.4%). Interestingly, furan-2-yl substituted compounds displayed strikingly better herbicidal activities (>62%) against *Brassica campestris* than pyridin-3-yl substituted ones, such as, **8a** versus **8g**, **8b** versus **8h**, **8c** versus **8i**, **8d** versus **8j**, **8e** versus **8k**, **8f** versus **8l** and **8m** versus **8n**. It seemed that 4-chloro or 2,4-dichlorobenzyl-containing compounds exhibited favorable activities than aryl-containing ones in piperazine part. However, when R^1 is furan-2-yl, no big herbicidal activity difference was shown for compounds with different aryl substituents in piperazine ring—phenyl, 4-methylpyrimidin-2-yl, 4,6-dimethylpyrimidin-2-yl, and pyridin-2-yl. It can also be found that all of the compounds showed rather weak herbicidal activities against *Echinochloa crusgalli*, just as those situations in all the controls, which indicates that the title compounds may be more effective against dicotyledonous weeds.

As shown in Table 2, at a 180 μg/mL concentration most of the compounds exhibited excellent in vitro inhibitory activities towards rice KARI, such as **8c**, **8d**, **8e**, **8f**, **8g**, **8i** and **8m**, whose inhibition rates against KARI enzyme were all over 84%, in particular, **8c**, **8d**, **8e** and **8m** held a value of >96%, respectively. Therefore, these compounds were further tested. From Table 3, among the tested compounds, **8c**, **8d** and **8m** held inhibitory activities against KARI with K_i values of (0.96 ± 0.42), (3.86 ± 0.49) and (3.10 ± 0.71) μmol/L, respectively, and were comparable with the control. Pleasingly, **8c** (inhibition regression curve shown in Fig. 1) was more effective than the control IpOHA (2.75 ± 0.72 μmol/L) in the preliminary studies. There are some relativity reflected between in vitro KARI inhibitory and in vivo *Brassica campestris* herbicidal activities to a certain extent—most of the compounds that had excellent KARI inhibitory activities showed favorable *Brassica campestris* herbicidal activities (**8a**, **8c**, **8d**, **8e**, **8f**, **8g**, **8m** and **8n**), and the furan-2-yl compounds exhibited the superiority to pyridine-3-yl compounds for the activities.

In addition, it was found that most of these oxadiazole Mannich bases showed favorable KARI inhibitory activities than those of

Table 2
The herbicidal and in vitro KARI inhibitory activities of the compounds (%, inhibition)

Compd	*Brassica campestris* 100 μg/mL	*Echinochloa crusgalli* 100 μg/mL	KARI (180 μg/mL)
8a	69.0	3.0	79.53
8b	81.4	5.0	28.86
8c	65.1	10.0	99.31
8d	68.4	5.0	98.69
8e	62.3	10.0	99.78
8f	66.9	4.0	84.43
8g	58.2	0	91.32
8h	52.7	0	77.38
8i	49.4	0	86.58
8j	30.7	0	33.64
8k	39.0	0	40.82
8l	45.4	0	51.58
8m	77.2	15.0	96.96
8n	62.7	0	79.78
TM1[21]	50.2	5.1	22.8 (100 μg/mL)
TM2[21]	48.0	20.4	30.0 (100 μg/mL)
TM3[3]	71.1	9.8	
IpOHA[27]	71.6	14.4	100
CPD	76.8	7.0	100
Chlorsulfuron	80.4	29.9	

Table 3
Inhibitory constant K_i of compounds against rice KARI

Compd	K_i (μmol/L)	Compd	K_i (μmol/L)
8c	0.96 ± 0.42	**8g**	11.68 ± 2.26
8d	3.86 ± 0.49	**8i**	45.86 ± 7.10
8e	10.16 ± 2.04	**8m**	3.10 ± 0.71
IpOHA	2.75 ± 0.72[27]		

Table 1
In vitro fungicidal activities of the compounds at the concentration of 50 μg/mL (%, inhibition)

Compd	*Fusarium oxysporum*	*Cercospora arachidicola*	*Physalospora piricola*	*Rhizoctonia cerealis*	*Alternaria solani*	*Gibberella sanbinetti*
8a	10.0	17.2	12.5	38.3	17.6	9.1
8b	5.0	17.2	35.9	49.4	23.5	18.2
8c	7.5	17.2	12.5	39.5	23.5	18.2
8d	10.0	13.8	43.8	35.8	23.5	13.6
8e	7.5	10.3	42.2	30.9	17.6	9.1
8f	2.5	10.3	4.7	27.2	23.5	13.6
8g	7.5	24.1	50.0	25.9	17.6	13.6
8h	0.0	10.3	18.8	29.6	17.6	9.1
8i	5.0	13.8	34.4	30.9	17.6	9.1
8j	5.0	13.8	12.5	30.9	17.6	27.3
8k	5.0	13.8	15.6	25.9	5.9	9.1
8l	2.5	10.3	12.5	23.5	23.5	9.1
8m	17.5	44.8	45.3	72.8	17.6	9.1
8n	7.5	10.3	35.9	35.8	23.5	18.2
TM1[21]	70.8	70.4	30.5		51.8	50.3
TM2[21]	60.8	63.6	41.6		30.2	30.5
CPD	19.4	25.0	30.2	26.8	15.8	14.6
Triadimefon	50.0	34.5	53.1	93.8	52.9	45.5
Carbendazim			100			100
Chlorothalonil	100	75.0			72.2	

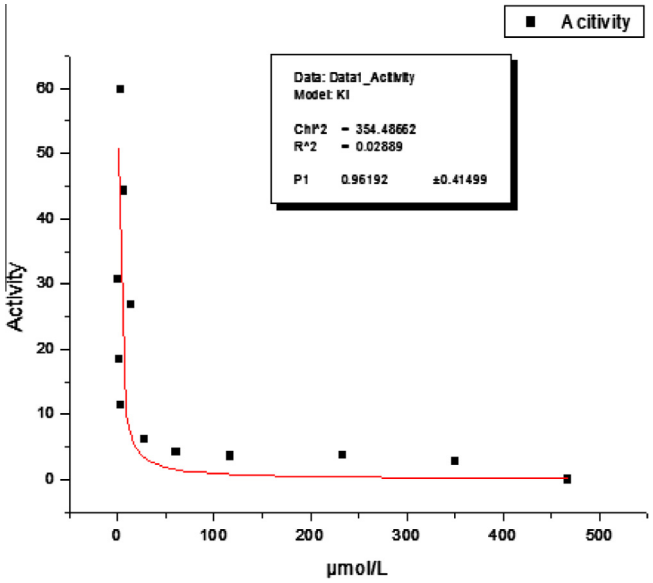

Figure 1. Inhibition regression curve of compound **8c** against rice KARI.

triazole Mannich bases TM1, TM2 and TM3,[21,3] and also herbicidal activity in some cases (Tables 2 and 3).

According to the frontier molecular orbital theory, HOMO has the priority to provide electrons, while LUMO accept electrons in the first place;[29] these two frontier orbitals are the most important factors that affect the bioactivity of compounds.[30] Thus a study of the frontier orbital energy can provide some useful information for the active mechanism. We therefore calculated the frontier molecular orbital of compounds **8c** and **8m** that have different structural characteristics (Mannich base and bis-Mannich base) and good inhibitory activity against KARI by means of DFT/B3LYP.

The DFT-derived graphic results are presented in Figure 2. The red and green parts represent the cloud density of frontier orbitals at HOMO or LOMO states. The total energies of the compounds **8c** and **8m** are −1425.89094662 a.u. and −2121.93230262 a.u., respectively. The energy gap between HOMO and LUMO for both of **8c** and **8m** is rather small (0.119 a.u. and 0.138 a.u., respectively) suggesting that the stability of these two compounds is limited, especially in the case of **8c**. As seen from Figure 2 of **8c** in the HOMO, electrons are mainly delocalized on the piperazine ring and phenyl ring; in the case of **8m**, besides the piperazine ring (major), there are also methylene group (CH_2) and a small part of oxadiazole and furan rings contributing to the HOMO electrons. However, when electron transitions take place, some electrons in HOMO will enter into the LUMO, then, in the LUMOs of **8c** and **8m**, the electrons will mainly be delocalized on the oxadiazole ring and furan ring (both cases are alike), as shown in Figure 2. It is known that the frontier molecular orbitals are located on the main groups which atoms can easily bind with the receptor. Thus, it can be concluded that the oxadiazole ring, furan ring and piperazine ring of **8c** and **8m** probably make major contributions to the activity towards KARI and these are largely through π–π and hydrophobic interactions.

Based on the 1.65 Å high resolution crystal structure of KARI complex (PDB ID: 1YVE), molecular docking calculations were performed on Discovery Studio software. The binding mode of the best active compound **8c** was studied using classical docking procedure. From Figure 3, it was found that there is a strong H bond interaction between the oxadiazole moiety of **8c** and KARI amino acid residue Gln205; piperazine ring, oxadiazole ring and furan ring are surrounded by residues Leu501, Ser518, Leu323, Glu319, Glu496, Glu492, Asp315, Lys252, Pro251 and His226, which indicates there are probably hydrophobic and/or π–π interactions existed between them. These results are in accord with those of DFT calculations.

In summary, a series of novel furan/pyridyl and piperazine-containing 1,3,4-oxadiazole Mannich bases and bis-Mannich bases

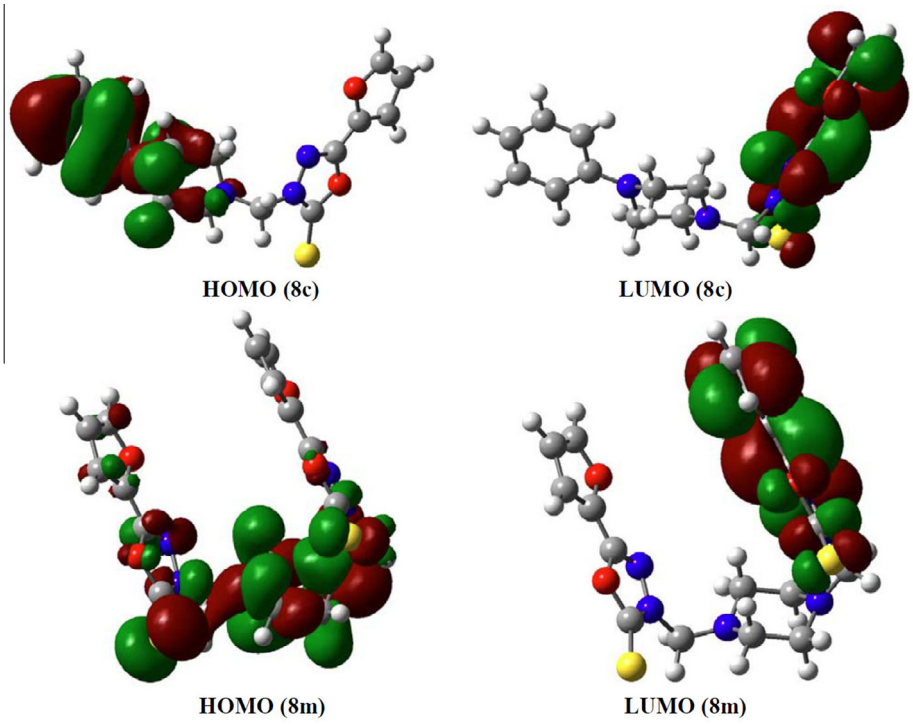

Figure 2. HOMO and LUMO maps for compounds **8c** and **8m** from DFT calculations. The green parts represent positive molecular orbital, and the red parts represent negative molecular orbital.

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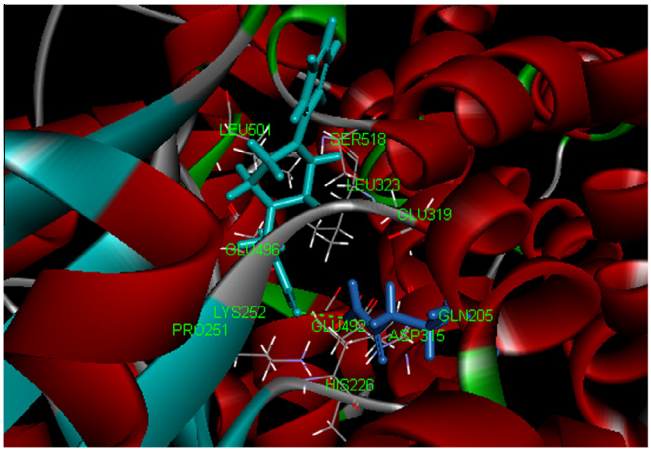

Figure 3. The docking mode of compound **8c** with KARI.

have been conveniently synthesized via Mannich reaction in good yields and structurally confirmed. The preliminary bioassay showed that some of the compounds exhibited promising in vitro fungicidal activity towards several test plant fungi. Pleasingly, among 14 title new compounds, some of them showed significant herbicidal and excellent KARI inhibitory activities; furan-2-yl containing compounds exhibited superiority to pyridine-3-yl ones, such as compounds **8b**, **8c**, **8d**, **8e** and **8m**. Especially, compounds **8c**, **8d** and **8m** showed potent in vitro inhibitory activities against rice KARI and were comparable with IpOHA. These compounds could be novel KARI inhibitors for further investigation. The DFT calculations and molecular docking indicated that the oxadiazole ring, furan ring and piperazine ring of high active inhibitors **8c** and **8m** may make major contributions to their activity towards KARI. The research in this paper will provide useful information for the design and discovery of new agrochemicals targeting at ketol-acid reductoisomerase.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2016.08.059.

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