Original article

Mosquito larvicidal activity of pyrrolidine-2,4-dione derivatives: An investigation against Culex quinquefasciatus and molecular docking studies

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The pyrrolidine-2,4-dione derivatives were used to conduct a larvicidal test on Culex quinquefasciatus larvae of the second instar. Mannich base condensation method was used to synthesis the pyrrolidine-2,4-dione derivatives by grindstone method. The reaction conditions were mild, resulting in high yields. An analysis of the synthesized compounds was carried out using FTIR, 1H NMR, 13C NMR, mass spectrometry, and elemental analysis. Synthesized compounds (1a-h) were evaluated for larvicidal activities. Compound 1e (LD50: 26.06 µg/mL), and 1f (LD50: 26.89 µg/mL), and were notably more active against Culex quinquefasciatus than permethrin (LD50: 26.14 µg/mL). The docking studies also demonstrated that 1e, and 1f are potent larvicides with higher binding energy (~12.6 kcal/mol) than the control in the mosquito odorant binding protein (PDB ID: 3OGN). The larvicidal properties of lead molecules have made them important for use as insecticides.

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1. Introduction

Mosquitoes play an important role in the transmission of malaria (Georges et al., 2008, Govindarajan, 2010). This type of disease has a global impact both economically and socially. In several regions, Culex quinquefasciatus is particularly associated with vector-spread diseases. Larvicides are insecticides designed to kill larval insects. As larvae grow, methoprene prevents them from developing beyond pupa stage (Lawler, 2017). There are mosquitoes transmitted by Culex quinquefasciatus in both rural and urban environments (Alvarez et al., 2006; Bisset et al., 1998). Botanical insecticide studies have been conducted in recent years to come up with alternatives to synthetic insecticides. Their non-toxic, low-toxicity and biodegradable characteristics allow them to be used for insecticides, larvicides, deterrents, repellents, growth inhibitors, and antifeedants (Isman, 2006). The continued use of synthetic insecticides in water, soil, and atmosphere is ecologically unacceptable, as they cause serious environmental problems and contaminate animals and food. The result is that insects, fungi, and bacteria become resistant to it. Diseases spread by insect vectors, such as leishmaniasis, yellow fever, malaria, dengue, and filariasis, also affect public health. In regions with unsanitary conditions, inadequate potable water supplies, and overcrowded areas, these diseases have a significant economic and social impact. A grant for odorant binding proteins (OBPs) was funded for this research. OBPs are small proteins (15 kDa) with six helices (α1-α6) and three disulfide bridges. A pheromone-binding protein (PBP) and a odorant-binding protein (GOBP) are two major classes of these proteins (GOBPs) (Pelosi and Maida, 1995; Zhou, 2010). OBP can be summarized in three groups such as long-chain, middle-chain, and short-chain amino acids.

OBPs act as carriers of chemical signals (semiochemicals) to the olfactory receptors (ORs) so that they can be processed before reaching the neuron. Aedes aegypti, Culex quinquefasciatus, and Nopheles gambiae are common vectors of malaria, filariasis, and

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cephalitis, respectively (Chandre et al., 1998; Barbosa et al., 2010). Insects OBPs have an outstanding pH-dependent mechanism of odorant binding and release, which able to bind odorants at a basic pH (6.5), transport and release them at an acid pH (4.5) (Di Luccio et al., 2013). Focusing of this study, we examined pH (6.5), transport and release them at an acid pH (4.5) (Di Luccio et al., 2013).}

Organic chemistry uses green techniques including reactions of C–H bond activation, asymmetric synthesis, the use of water as a solvent, or even without a solvent, microwaves, ultrasounds, and ultraviolet radiation (Wei and Berkeley, 2018).

Some bioactive naturally existing pyrrolidine-2,4-dione. (also known as tetramic acid) natural compound such as tenuazonic acid, erythroskyrine, nicotine, toosentanin, pyrethrum, and the essential oil of Caesulia axillaris.

Fig. 1 shows that pyrrolidine-2,4-dione (also known as tetramic acid) natural compound such as tenuazonic acid, erythroskyrine, melophlin A, cryptocin, hazzianic acid (Schobert and Schlenk, 2008; Dixon et al., 1999; Aoki et al., 2000; Li et al., 2000). With regard to herbicides, a series of 3-(z-hydroxy-benzylidene)pyrrolidine-2,4-dione derivatives having high efficiency, and tenuazonic acid derivatives with oxime moieties showed herbicidal and anti-fungal activities (Zhu et al., 2009). The pyrrolidine-2,4-dione moiety is located on nitrogenous heterocyclic compounds, such as natural tetramic acids, which are commonly used as antitumors, antivirals, insecticides, fungicides, and herbicides (Mary et al., 1991; Singh et al., 1998; Chen et al., 2008; Cole and Rolinson, 1972; Li et al., 2000). Some of the pyrrolidine-2,4-dione derivatives, and tetramic acid derivatives have impressive active core molecules in various biological system (Han et al., 2012; Si et al., 2011; Zheng et al., 2011; Zhu et al., 2007; Zhu et al., 2005).

As noted earlier, in comparison with tetramic acid, and tenuazonic acid in the oxime ether family, the chemicals with appropriate groups added to the 3-position displayed superior activity against phytopathogenic fungi (Wang et al., 2010; Zhu et al., 2010a, Zhu et al., 2010b; Zhu et al., 2009). Strabilurin A is a chemical compound made up of reactive groups of methoxyacrylates that is used to make fungicides. Their unique mechanism of action as well as high activity, and outstanding environmental tolerance distinguish them from many other available pesticides (Yan et al., 2006). The most common tool for controlling mosquito populations is chemical insecticide (Bowman, et al., 2016), however, non-target organisms and their environmental toxicity limit their use (Nkya et al., 2013; Jayaraj et al., 2017), a number of larval active targets have been identified in previous studies, but chemical insecticides pose many more problems such as resistance to chemicals and disruption of biocontrol systems (Park et al., 2005; Yang et al., 2013). To solve these problems, new mosquito larvae inhibitors are needed, as well as greener methods that can be achieved using pyrrolidine-2,4-dione derivatives synthesized from Mannich condensation method.

2. Materials and methods

Nicolet iS5 from Thermo scientific was used to analyze all compounds using FTIR (4000–400 cm⁻¹). An Bruker DRX-300 MHz, 75 MHz NMR spectrometer was used to analyze the 1H and 13C NMR spectra. An elemental analyzer (the Vario EL III) was used to find the percentage (%) of assemblies (C, H, N, and S). GCMS model Clarus SQ8 (EI) from Perkin Elmer measured the mass spectra.

2.1. Synthesis of compound 1a-h: General procedure

In a mortar, a mixture of cinnamaldehyde (0.01 mol) was mixed with pyrrolidine-2,4-dione (0.01 mol) and substituted amine (0.01 mol) and ground at room temperature. Solid material was extracted by column chromatography (Ethyl acetate4:hexane6). Compounds 1b-1h were prepared by following the above method.

2.1.1. 3-(1-hydrazinyl-3-phenylallyl)pyrrolidine-2,4-dione (1a)

Yield 87%; mp: 142–140 °C; IR(KBr) v: 3214.41, 3069.38, 3011.50, 1739.18, 1611.23 cm⁻¹; 1H NMR (300 MHz): δ 8.61 (s, 2H, NH₂), 8.35 (s, 1H), 7.42–7.40 (dd, 2H, J = 7.36 Hz, J = 7.31 Hz), 7.33–7.0 (d, 1H, J = 7.31 Hz), 7.26–7.22 (d, 2H, J = 6.23 Hz, 1H), 6.51 (s, 1H), 6.19 (s, 1H), 4.54 (s, 2H), 3.76 (d, 1H, J = 7.42 Hz), 3.52 (d, 1H, J = 7.43 Hz), 2.28 (s, NH); 13CN M R (75 MHz): 207.1, 176.5, 176.1, 1726.10, 1721.10, 1610.29 cm⁻¹.

2.1.2. 3-(1-(2-benzylidenehydrazinyl)-3-phenylallyl)pyrrolidine-2,4-dione (1b)

Yield 86%; mp: 167–164 °C; IR(KBr) v: 3212.38, 3078.31, 3018.32, 2978.83, 2932.29, 2852.62, 1721.10, 1610.29 cm⁻¹; 1H NMR (300 MHz): δ 8.45 (s,
1H), 8.31 (s, 1H), 7.54 (d, 1H, J = 7.33 Hz), 7.87–7.80 (d, 2H, J = 7.12 Hz), 7.52–7.50 (dd, 1H, J = 7.31 Hz, 2H, Ar-ring), 7.53–7.51 (dd, 2CH, J = 7.11 Hz), 7.50 (d, 1CH, J = 7.12 Hz), 7.33–7.30 (d, 1H, J = 7.31 Hz), 7.26–7.22 (d, 1H, J = 6.21 Hz), 6.54 (s, 1H), 6.18 (s, 1H), 4.41 (s, -CH2-), 3.78 (d, 1H, J = 7.42 Hz), 3.53 (d, 1H, J = 7.43 Hz), 2.20 (s, NH); 13C NMR (75 MHz): 207.6, 171.83, 1601.21 cm−1; 1H NMR (75 MHz): δ 7.43 (s, NH), 7.50 (d, 1CH, J = 7.12 Hz), 4.56 (s, -CH2-), 3.93 (d, 1H, J = 6.30 Hz, -CH); 13C NMR (75 MHz): 206.1, 176.9 (1C), 134.6, 128.7, 137.0, 132.2, 128.6 (6C, Ph ring), 65.3, 53.8, 52.3; EIMS(m/z): 334.10 (M+, 31%).

2.1.7. 1-((1-(2,4-dioxopyrrolidin-3-yl)-3-phenylallyl)-3-phenylallylidenediurea (1g)

Yield 85%; mp: 147–142 °C; IR(KBr): ν: 3254.08, 3065.15, 3021.30, 1742.13, 1641.20 cm−1; 1H NMR (300 MHz): δ 8.17 (s, NH), 7.50 (d, 1CH, J = 7.11 Hz), 7.48 (d, 1CH, J = 7.12 Hz), 7.43–7.40 (dd, 2H, J = 7.31 Hz, 2H, J = 7.30 Hz), 7.33 (s, 1H), 7.33–7.30 (d, 1H, J = 7.32 Hz, Phenyl ring), 7.27–7.22 (d, 2H, J = 7.33 Hz), 7.21 (s, 1H), 6.55 (s, 1H), 6.12 (s, 1H), 7.26–7.22 (d, 1H, J = 6.21 Hz), 6.50 (s, 1H), 6.11 (s, 1H, CH), 4.47 (s, CH), 3.76 (d, 1H, J = 7.42 Hz), 3.52 (d, 1H, J = 7.43 Hz); 13C NMR (75 MHz): 207.6, 176.9 (1C), 127.9, 128.6, 124.1, 135.6, 134.9, 123.0, 128.8, 134.9, 136.2, 128.7, 129.6, 125.1, 59.3, 52.1, 51.3; EIMS(m/z): 387.47 (M+, 18%).

2.2. Biological activities

2.2.1. Larvicidal activity

As part of the test, compounds (1a-1h) were tested at 10, 25, 50 and 100 μg/mL based on previously described methods (Satish Kumar et al., 2020). By calculating the ratio (% ) of dead larvae to live larvae, we can determine the level of mortality caused by the compounds. By using probit analysis, LD50 was calculated.

2.3. Molecular docking

2.3.1. Ligand preparation

The ligand (1a-1h) were drawn using the Chemdraw 12.0 and Chem3D Pro software. A Protein Data Bank (PDB) file of the ligand molecules was then created for use in docking studies.

2.3.2. Receptor preparation

Downloaded from the protein data bank, a mosquito odorant binding protein is represented by this structure (PDB ID: 3OGN). Discovery Studio 2019 is used to remove ligands and water molecules from the structure. The binding pocket of the receptor was identified using a molecular docking grid box. The binding pocket of the target protein was identified using a co-crystallized ligand and Discovery Studio 2019 program. In the binding pocket, the residues His121 and Phe123 were present.

2.3.3. Identification of binding pocket

The binding pocket of the target protein was identified using a co-crystallized ligand and Discovery Studio 2019 program. In the binding pocket, the residues His121 and Phe123 were present.

2.3.4. Docking

Molecular docking studies were conducted using Schrodinger Maestro 9.2 version to examine the interactions between compounds 1a-1h, and permethrin, the mosquito odorant binding protein. In selecting the docking grid boxes, we considered the amino acid residues that occupied the binding pocket. It consisted of the following dimensions: x: 22, y: 20, and z: 22 Å. A 1.0 Å spacing between x: 18.681, y: 49.66, and z: 11.409 formed the center of the chart. In the Discovery studio and Pymol programs, the interactions were analyzed visually using a value of 8 for exhaustiveness.
2.3.5. Statistical analysis

A minimum of three independent sites were used in the calculations, and the LD_{50} values were calculated by using Microsoft Excel to calculate the standard deviation (SD).

3. Results

Grindstone method was used to synthesize the compounds (1a-h) through pyrrolidine-2,4-dione ground together with cinnamaldehyde, and substituted amine. Following this, the samples were purified using column chromatography. Scheme 1 shows the outline of the synthetic route. Yields were between 88 and 92% for the compounds. An analysis of the obtained compounds was carried out by FT-IR, \(^1\)H, \(^{13}\)C NMR spectroscopy. The IR spectrum of compounds shows bands at 1601–1618, 1720–1742, 3202–3254, and 3014–3078 cm\(^{-1}\) conforming to the -C=O, -C=O, -NH, and -CH-NH- groups, respectively.

The protons presence in compounds (1a-h) were confirmed from \(^1\)H NMR spectrum, which obtained peaks at \(\delta\) 8.21–8.45, 3.75–3.79, 4.41–4.56, 6.51–6.58, and 6.13–6.18 ppm, matching with protons such as -NH, -4-CH, -CH\(_2\), -CH=CH-, and -CH=CH-, groups. The carbons presence in compounds (1a-h) were confirmed from \(^{13}\)C NMR spectrum, which obtained values at \(\delta\) 53.2–54.9, 52.3–52.6, 135.2–136.6, 176.9–177.3, 206.9–207.6, and 127.9–128.4 ppm, matching with -CH\(_2\), -CH=CH-, -C=O, -C=O, and -CH=CH- groups. The mass spectrum and elemental analyses of all these compounds were used to determine their conformation.

The second instar larvae of Culex quinquefasciatus were tested against eight compounds (1a-1h). Based on the relationship between structure and activity, the final compounds contained pyrrolidine-2,4-dione with substituted amines and thus exerted larvicidal and toxic effects.

4. Discussion

The grindstone method is often more efficient than a traditional organic reaction and can even be more selective in some cases (Abdel Hameed, 2015). It has many other advantages, including low costs, high reproducibility, mild conditions, a short reaction time, less pollution, and simplicity in process and handling (Li et al., 2011). As a result, grindstone chemistry has gained increasing attention in greener organic transformations in the past decade.

We synthesize target compounds by grinding stone method using the reaction mixture of cinnamaldehyde (0.01 mol), substituted amine (0.01 mol), and pyrrolidine-2,4-dione (0.01 mol) at room temperature. The reaction mixture was ground for 30 min. After the reaction was complete, 

\(\text{H}_2\text{O}\) was added and EtOAc was used to extract the solution. The solvents were evaporated and the solution was purified using column chromatography on silica gel, filtered through Celite, and concentrated under vacuum. Solid material was extracted with ethyl acetate:hexane6 column chromatography.

Compound 1e (LD_{50}: 26.06 \(\mu\)g/mL) and 1f (LD_{50}: 26.89 \(\mu\)g/mL) showed a higher larvicidal activity than other compounds and then permethrin (LD_{50} of 26.14 \(\mu\)g/mL). At 100 \(\mu\)g/mL for compounds 1e and 1f, 100% of the mortality rates were achieved, and 1c also reached 100% mortality at 100 \(\mu\)g/mL. However, the compound 1e and 1f shows highly active compared to 1c (27.91 \(\mu\)g/mL) due to the amide group. This suggests that the presence of amide and pyrrolidin-2,4-dione moiety may be the reason for the observed biological effects of compounds 1e and 1f, respectively. In compound 1a, mortality was 86% at 100 \(\mu\)g/mL, since hydrazine hydrazide, phenylalylidene and pyrrolidin-2,4-dione were presented in compound 1a. Low activity for compound 1d, 1g, and 1h are obtained with a mortality rate of 70–78% with LD_{50} values of 53.06–54.22 \(\mu\)g/mL range. This suggests that the presence of the p-tolylamino, pyrrolidine-2,4-dione of compound 1d, 3-phenylallyl, 3-phenylallylidene) urea, and methylamino, 3-phenylallyl, pyrrolidine-2,4-dione groups in compound 1b led to a 61% mortality rate at 100 \(\mu\)g/mL. Therefore, the above analysis indicates that compounds 1e and 1f were significantly active in larvicidal screening. LD_{50} values and mortality percentages are shown in Table 1.

Schrodinger Maestro 9.2 is the software used to determine the docking behaviour of compounds 1e, 1f, and permethrin with 3OGN protein. 2D representation molecule docked with receptor of compound 1a-1h shown in Fig. 2(a-h). The compounds 1e and 1f have much lower binding affinity (\(-12.6\) kcal/mol) than permethrin with (\(-8.5\) kcal/mol) (Sathish Kumar et al., 2020) in 3OGN protein respectively. Permethrin was used as a standard, since it is a commercially available mosquito insecticide. The hydrogen

![Scheme 1. Synthetic route of compound pyrrolidine-2,4-dione derivatives.](image-url)
bond plays a significant role in the stability of protein-ligand binding, and the favourable distance between the H-donor and the H-acceptor atoms is less than 3.5 Å. Hydrogen bond distances of less than 3.5 Å were found in compounds (1a-h) with strong hydrogen bonds with respective 3OGN proteins. Hydrogen bond interactions with receptor 3OGN were formed by compounds 1e and 1f. Phe123

Table 1

| Compounds | % of Mortality | LD₅₀ [µg/mL] |
|-----------|---------------|-------------|
|           | 25 µg/mL      | 50 µg/mL    | 100 µg/mL |
| 1a        | 35.1 ± 0.7    | 70.2 ± 0.2  | 86.2 ± 0.2 | 33.91 |
| 1b        | 21.2 ± 0.1    | 47.1 ± 0.1  | 61.0 ± 0.9 | 64.20 |
| 1c        | 41.3 ± 0.6    | 88.3 ± 0.2  | 100 ± 0.1  | 27.91 |
| 1d        | 21.6 ± 0.1    | 42.5 ± 0.1  | 78.1 ± 0.7 | 53.46 |
| 1e        | 48.2 ± 0.9    | 86.2 ± 0.1  | 100 ± 0.0  | 26.06 |
| 1f        | 47.1 ± 0.2    | 85.5 ± 0.2  | 100 ± 0.0  | 26.89 |
| 1g        | 22.1 ± 0.3    | 46.8 ± 0.3  | 74.8 ± 0.1 | 53.06 |
| 1h        | 28.9 ± 0.1    | 43.0 ± 0.4  | 70.9 ± 0.2 | 54.22 |
| Permethrin| 51.1 ± 0.1    | 76.3 ± 0.5  | 100 ± 0.0  | 26.14 |

* Values are mean ± SD (n = 3).

Fig. 2. 2D representation molecule docked with receptor of compound 1a-1h.
is an amino acid residue that interacts with hydrogen and has a bond length of 1.94 Å. The amino acid residues Tyr10, Leu15, Leu22, Leu56, Phe59, Ala62, Leu73, Leu76, His87, Leu80, Met84, Ala88, Met91, Gly92, Cys95, His111, Thr114, His121, Tyr122 and Phe123 were involved in hydrophobic interactions. The interaction of the compound \(1e\) with the mosquito odorant binding protein (PDB ID: 3OGN) protein is shown in Fig. 3. The 3D representation of inhibitor molecule docked into the receptor was shown in Fig. 3a. The helix representation of inhibitor molecule docked into the receptor was shown in Fig. 3b. The inhibitor molecule docked into the binding pocket of the receptor was shown in Fig. 3c. The 2D representation molecule docked with receptor was shown in Fig. 3d. The permethrin receptor 3OGN does not form a hydrogen bond with the permethrin. The results of molecular docking were summarized in Table 2.

**Table 2**
Docking interactions between compounds (1a-1h).

| Compounds | Dock Score | Interacting residues | Bond length |
|-----------|------------|----------------------|-------------|
| 1a        | −8.8       | His 121, Phe 123(2)  | 2.38, 2.05, 2.18 |
| 1b        | −11.4      | Phe 123              | 2.30         |
| 1c        | −10.9      | His 121, Phe 123     | 2.32, 2.32   |
| 1d        | −11.4      | His 121, Phe 123     | 2.33, 2.14   |
| 1e        | −12.6      | Phe 123              | 1.94         |
| 1f        | −12.6      | Phe 123              | 1.94         |
| 1g        | −11.8      | Phe 123              | 2.29         |
| 1h        | −10.7      | His 121, Phe 123     | 1.96, 2.19   |
| Permethrin| −8.5       | –                    | –            |

5. Conclusions

A novel larvicidal active pyrrolidine-2,4-dione derivatives were synthesized by using a Mannich base and grindstone method in this study. It was investigated whether these compounds could be used as larvicides against *Culex quinquefasciatus*. We tested eight compounds and found compound \(1e\) to be the most active (LD<sub>50</sub> = 26.06 g/mL) in contrast to *Culex quinquefasciatus*. The compounds (1a-1h), and permethrin were docked against the 3OGN protein, and compound \(1e\) and \(1f\) achieved the best docking scores. In conclusion, our study suggests that compound is the most effective insecticide, and the chemicals described here could serve as a basis for developing eco-friendly insecticides and biopharmaceuticals.

**Declaration of Competing Interest**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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