Chemical design and toxicity evaluation of new pyrimidothienotetrahydroisoquinolines as potential insecticidal agents

Adel M. Kamal El-Deana, Aly A. Abd-Ella, Reda Hassanien, Mohamed E.A. El-Sayed, Remon M. Zaki, Shaban A.A. Abdel-Raheem

a Chemistry Department, Faculty of Science, Assiut University, 71516, Assiut, Egypt
b Plant Protection Department, Faculty of Agriculture, Assiut University, 71526, Assiut, Egypt
c Chemistry Department, Faculty of Science, New Valley University, El-Kharj, 72511, Egypt
d Soil, Water, and Environment Research Institute, Agriculture Research Center, Giza, Egypt

ARTICLE INFO

Keywords:
Pyrimidothienotetrahydroisoquinolines
Acetamiprid
Cowpea Aphid
Toxicity
Structure-activity relationships (SAR)

ABSTRACT

Neonicotinoids are the most widely used from all existing pesticides. So, in purpose to discover new pesticides being more effective against the aphid, twelve heterocyclic compounds neonicotinoid analogs have been prepared in a pure state; pyrimidothienotetrahydroisoquinolines 1–12 and their toxicity as potential insecticidal agents against cowpea Aphid, Aphis craccivora Koch was screened. Their characterizations by using spectroscopic analyses were performed. The toxicity data exhibited that the 8-chloropyrimidine compound 4 is more toxic about 2-fold than a reference insecticide, acetamiprid. The other screened compounds showed weak to strong toxicological activities against cowpea aphid.

1. Introduction

Recently, the innovation of neonicotinoids containing pyridine moiety has been deep and competitive efforts [1–3]. Neonicotinoids containing Pyridine moiety have concerned a great attention for a long time since they merge distinctive characteristics and were utilized in all over the world for insects management because of their efficacy, low mammalian toxicity, lack cross-resistance to other insecticides, broad insecticidal spectra, good systemic properties, and a novel mode of action specific for insect nicotinic acetylcholine receptors (nAChRs) [4–9]. However, the need for new derivatives of neonicotinoids has become important [10,11].

Neonicotinoids have various molecular characteristics. The main features for neonicotinoids are: aromatic heterocycle, flexible linkage, hydroheterocycle or guanidine/amidine, and electron withdrawing segment [12].

Although neonicotinoids are the most used compounds in the world in the field of pest control and are considered the least in terms of the negative effects on animal and human therefore they have almost replaced other more toxic organophosphate and carbamate insecticides, but some recent researches concerning the biomonitoring of animal and human exposure to imidacloprid (IMI) as neonicotinoid pesticide reported that a genotoxic effect and DNA damage can be occurred after long-term exposure of rabbits to imidacloprid pesticide [13–15]. Imidacloprid (IMI) also induces a clastogenic effect to the exposed rabbits and oxidative stress [16,17]. This is proving the need for discovering new compounds belong to neonicotinoids pesticides.

Inspired by our promising results described in the first and second parts and as a continuation of our earlier research work aimed to find heterocycles containing pyridine moiety with expected toxicological activities [18,19], we reported here the study of the toxicity of the prepared compounds containing the previous features of neonicotinoid insecticides against cowpea Aphid, Aphis craccivora Koch encouraged to discover heterocyclic compounds with high biological effect and without environmental pollution.

2. Materials and methods

2.1. Instrumentation and chemicals

Measuring the melting points of all synthesized compounds was performed on a Fisher-John apparatus. By using a Vario EL C, H, N, S analyzer, elemental analyses (C, H, N, and S) were conducted. On a Pye-Unicam SP3-100 spectrophotometer IR spectra were obtained by using the KBr disc technique. 1H NMR and 13C NMR spectra were measured on a Joel 400 MHz and Bruker 400 MHz spectrometers using...
2.2. Laboratory bioassay

Toxicity of the title compounds was screened by leaf dip bioassay method [21]. Results of laboratory screening to find out the concentrations of the target compounds which are demanded to kill 50% (LC50) of cowpea aphids were declared here. Six concentrations of solution of each prepared compound plus 0.1% Triton X-100 as a surfactant were utilized. 20 nymphs and 20 adults of insects, nearly have the same size, were immersed for ten seconds in every concentration three times. Insects which treated were permitted to dry at RT for about 0.5 h. Control batches of used insects were also utilized. After the treated batches of insects had dried, they were moved to Petri dishes (9 cm diameter) and remained for 24 h at 22 ± 2 °C, 60 ± 5% relative humidity and photoperiod of 12:12 (light/ dark). With a binocular microscope the aphid mortality was counted after 24 h of test. The aphid that unable of coordinated forward movement was considered dead. The insecticidal activity test of each compound was repeated two times and the obtained data were corrected by Abbott formula [22]. By using a computerized Probit regression analysis program, median lethal concentrations (LC50) and slope values of target compounds were computed and reported as parts per million (ppm) [23].

3. Results and discussion

3.1. Chemistry

The synthesis of tetrahydro [1,3]oxazinothieno[2,3-c]isoquinolines was reported [20]. In continuation of our project in the synthesis and testing the biological activity of the pyridine derivatives; herein twelve compounds were chosen in Fig. 1 to evaluate their toxicity as insecticides. The twelve heterocyclic compounds, namely, 9-phenyl pyrimidinone 1, 9-(p-chlorophenyl)pyrimidinone 2, 9-(p-tolyl) pyrimidinone 3, 8-chloropyrimidine 4, 8-piperidinyl pyrimidine 5, (pyrimidin-8-yl)-p-benzenesulphonamide 6, 2-(pyrimidin-8-yl) amino ethanol 7, 8-hydrazinopyrimidine 8, ethyl pyrimidin-8-yl sulfanyl acetate 9, pyrimidin-8-yl sulfanyl acetylanilide 10 and 2-(pyrimidin-8-yl) hydrozono)propaanoate 12 compounds, were synthesized in pure state according to literature procedure [20] with m.p. 214–216 °C, 208–210 °C, 248–250 °C, 218–220 °C, 150–152 °C, 318–320 °C, 212–214 °C, 294–297 °C, 120–122 °C, 176–178 °C, 192–194 °C, and 250–252 °C respectively.

Elemental analyses and spectral characterization were used to clarify and prove the structures of all synthesized compounds. Elemental analyses results were in accordance with the values that calculated. Spectral characterization data of the synthesized compounds were in a good agreement with their suggested structures [20].

Table 1

Insecticidal activity of acetamiprid and compounds 1–12 against the nymphs and adults of cowpea aphid, A. craccivora, after 24 h of treatments.

| Comp. | Slope ± SE | LC50 (ppm) | Toxicity Ratio | Comp. | Slope ± SE | LC50 (ppm) | Toxicity Ratio |
|-------|------------|------------|----------------|-------|------------|------------|----------------|
|       |            |            |                | Nymphs |            |            |                |
| Aceta- | 0.34 ± 0.02 | 0.045      | 1              | 0.34 ± 0.02 | 0.225 | 1          |
| miprid | 3          | 0.36 ± 0.03 | 0.754          | 0.060 | 0.34 ± 0.02 | 1.628      | 0.138          |
| 4      | 0.31 ± 0.03 | 0.153      | 0.294          | 0.34 ± 0.03 | 0.578 | 0.389      |
| 5      | 0.35 ± 0.02 | 0.802      | 0.056          | 0.36 ± 0.03 | 1.180 | 0.191      |
| 6      | 0.35 ± 0.02 | 0.023      | 1.957          | 0.31 ± 0.03 | 0.221 | 1.018      |
| 7      | 0.32 ± 0.02 | 0.241      | 1              | 0.34 ± 0.02 | 1.295 | 0.174      |
| 8      | 0.35 ± 0.03 | 0.187      | 1              | 0.32 ± 0.02 | 0.792 | 0.264      |
| 9      | 0.33 ± 0.02 | 1.051      | 1              | 0.35 ± 0.02 | 2.975 | 0.076      |
| 10     | 0.36 ± 0.03 | 0.119      | 1              | 0.34 ± 0.03 | 1.207 | 0.186      |
| 11     | 0.36 ± 0.02 | 0.407      | 1              | 0.36 ± 0.03 | 1.092 | 0.206      |
| 12     | 0.36 ± 0.02 | 0.204      | 1              | 0.32 ± 0.02 | 1.066 | 0.211      |

Notes: Toxicity Ratio is calculated as acetamiprid’s LC50 value for baseline toxicity / the compounds’ LC50 value.
4. Structure-action relationship

As a continuation of this work, the structure-activity relationships (SAR) were reported here according to the toxicity values in table below and Fig. 2 as well. It is shown that the chloropyrimidine derivative 4 is more active against cowpea aphid than the other pyrimidothienotetrahydroisoquinoline synthesized derivatives. The high activity associated with compounds 2 and 6 may be due to the presence of the chlorophenyl and benzene sulfonamide moiety respectively in their structure in addition to the general characteristics of the prepared.

Fig. 1. Target compounds that tested for their insecticidal activity.
compounds. Also, toxicity of tetrahydroisoquinoline compounds 10 and 11 is higher than that of 9 analog, this may be due to the presence of sulfanyl acetonophenone and sulfanyl acetonilide moiety respectively in compounds 10 and 11 which may cause the insecticidal activity. The presence of phenyl group may reflect better activity than the tolyl group and this is shown in compounds 1 and 3. Also, compound 7 which contains amino ethanol group possess higher insecticidal activity than compound 8 which contains hydrazino group. Finally, the aphidical activity of compound 12 is higher than that of compound 5 and this may be due to the presence of hydrazono propanoate moiety in compound 12 than piperidinium group in compound 5.

5. Conclusion

A series of pyrimidothienotetrahydroisoquinolines which are analog to neonicotinoid insecticides and contain pyridine moiety were chemically prepared. The toxicity of these compounds was estimated against cowpea aphid, *A. craccivora* and showed that a number of the prepared compounds possess good toxicological activities as insecticides, whereas some of them revealed reasonable aphidical activities. Especially, chloropyrimidine compound 4 had the best insecticidal activity since it exceeded the aphidical activity of a commercial pesticide, acetamiprid. The activity concerning compound 4 may be due to the existence of the chlorine atom attached to the pyrimidine cycle in

Fig. 2. Insecticidal activities of acetamiprid and compounds 1–12 against the nymphs and adults of cowpea aphid, *A. craccivora* after 24 h of treatment.
its molecular structure. Our research demonstrated that the new pyrimidothienotetrahydroisoquinoline derivatives containing pyridine moiety could effectively control cowpea aphids, A. craccivora, and this emphasis our studies done before [18,19]. These results are hopeful and valuable for additional work on the improvement of new and other potent pesticides.

Disclosure of potential conflicts of interest

We have no conflicts of interest to disclose.

References

[1] N. Zhang, M. Tomizawa, J.E. Casida, α-Nitro ketone as an electrophile and nucleophile: synthesis of 3-substituted 2-nitromethylene tetrahydrothiophene and tetrahydrofurans as Drosophila nicotinic receptor probes, J. Org. Chem. 69 (3) (2004) 876–881, https://doi.org/10.1021/jo035457g.

[2] H. Zhang, T. Breeze, A. Bailey, D. Garthwaite, R. Harrington, S.G. Potts, Arthropod pest control for UK oilseed rape-comparing insecticide efficacies, side effects and alternatives, PLoS One 12 (1) (2017), https://doi.org/10.1371/journal.pone.0169475.e0169475.

[3] J.G. Samaritoni, D.A. Demeter, J.M. Giordano, G.B. Watson, M.S. Kempe, T.J. Bruce, Dihydropiperazine neonicotinoid compounds. Synthesis and insecticidal activity, J. Agric. Food Chem. 51 (10) (2003) 3035–3042, https://doi.org/10.1021/jf031185r.

[4] N. Simon-Delso, L. Furlan, D.W. Gibbons, C. Giorio, D. Goulson, P. Fragkiadaki, E. Aebi, A.M. Tsatsakis, Development and application of LC-APCI–MS method for biomonitoring of animal and human exposure to imidacloprid, Chemosphere 93 (10) (2013) 2612–2620, https://doi.org/10.1016/j.chemosphere.2013.09.087.

[5] A.I. Vardavasa, E.A.D. Mitchell, B. Mulhauser, M. Mulot, A. Mutabazi, G. Glauser, A. Aebi, A.K. Tsakalof, A.M. Tsatsakis, Evaluation of oxidative stress in long-term exposed rabbits to subtoxic levels of imidacloprid, Toxicol. Lett. 229B (2014) S226–S248, https://doi.org/10.1016/j.toxlet.2014.06.764.

[6] E.A. Bakhite, A.A. Abd-Ella, M.E.A. El-Sayed, Sh.A.A. Abdel-Raheem, Pyridine derivatives as insecticides. Part 2: synthesis and toxicity of some pyridine derivatives as insecticides. Part 1: synthesis and toxicity of some pyridine derivatives against Cowpea Aphid, Aphis craccivora Koch (Homoptera: Aphididae), J. Agric. Food Chem. 62 (41) (2014) 9982–9986, https://doi.org/10.1021/jf039992y.

[7] E.A. Bakhite, A.A. Abd-Ella, M.E.A. El-Sayed, Sh.A.A. Abdel-Raheem, Pyridine derivatives as insecticides. Part 2: synthesis of some piperidinium and morpholinium cations, J. Agric. Food Chem. 55 (6) (2007) 2620–2625, https://doi.org/10.1021/jf063418a.

[8] R.M. Zaki, Sh.M. Radwan, A.M. Kamal El-Dean, A convenient synthetic method and its pyrimidine derivatives, J. Chin. Chem. Soc. 64 (12) (2017) 1417–1431, https://doi.org/10.1007/s11356-014-3470-y.

[9] E.A.D. Mitchell, B. Mulhauser, M. Mulot, A. Mutabazi, G. Glauser, A. Aebi, A. Kyriakakis, R. Rezaee, D. Kouretas, W. Hayes, A. Tsatsakis, Evaluation of oxidative stress in long-term exposed rabbits to subtoxic levels of imidacloprid, Toxicol. Lett. 229B (2014) S226–S248, https://doi.org/10.1016/j.toxlet.2014.06.764.

[10] E.A. Bakhite, A.A. Abd-Ella, M.E.A. El-Sayed, Sh.A.A. Abdel-Raheem, Pyridine derivatives as insecticides. Part 1: synthesis and toxicity of some pyridine derivatives against Cowpea Aphid, Aphis craccivora Koch (Homoptera: Aphididae), J. Agric. Food Chem. 62 (41) (2014) 9982–9986, https://doi.org/10.1021/jf039992y.

[11] E.A.D. Mitchell, B. Mulhauser, M. Mulot, A. Mutabazi, G. Glauser, A. Aebi, A. Kyriakakis, R. Rezaee, D. Kouretas, W. Hayes, A. Tsatsakis, Evaluation of oxidative stress in long-term exposed rabbits to subtoxic levels of imidacloprid, Toxicol. Lett. 229B (2014) S226–S248, https://doi.org/10.1016/j.toxlet.2014.06.764.