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Green Design, Synthesis, and Molecular Docking Study of Novel Quinoxaline Derivatives with Insecticidal Potential against *Aphis craccivora*

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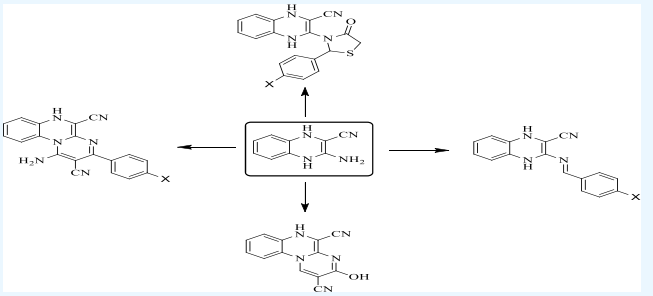
ABSTRACT: An efficient and environmentally friendly method was established for designing novel 3-amino-1,4-dihydroquinoxaline-2-carbonitrile (**1**) *via* the reaction of bromomalononitrile and benzene-1,2-diamine under microwave irradiation in an excellent yield (93%). This targeted amino derivative was utilized for the construction of a series of Schiff bases (**8**−**13**). A new series of thiazolidinone derivatives (**15**−**20**) were synthesized in high yields (89−96%) *via* treatment of thioglycolic acid with Schiff bases (**8**−**13**) under microwave irradiation in high yields (89−96%). Moreover, new pyrimidine derivatives (**26**−**30** and **35**−**38**) were prepared by treatment of compound **1** with arylidenes (**21**−**25**) and/or alkylidenemalononitriles (**31**−**34**) using piperidine as a basic catalyst under microwave conditions. Based on elemental analyses and spectral data, the structures of the new assembled compounds were determined. The newly synthesized quinoxaline derivatives were screened and studied as an insecticidal agent against *Aphis craccivora*. The obtained results indicate that compound **16** is the most toxicological agent against nymphs of cowpea aphids (*Aphis craccivora*) compared to the other synthesized pyrimidine and thiazolidinone derivatives. The molecular docking study of the new quinoxaline derivatives registered that compound **16** had the highest binding score (−10.54 kcal/mol) and the thiazolidinone moiety formed hydrogen bonds with Trp143.



INTRODUCTION

Aphis craccivora, also identified as the cowpea aphid, is among the most threatening crop pests causing direct damage to plants by distorting and delaying plant growth.[1,2] The molasses produced by the vector are applied on the plant and encourage mold growth with soot limiting photosynthesis.[3] It hosts many plants such as Rosaceae, Malvaceae, Asteraceae, Caryophyllaceae, Solanaceae, Chenopodiaceae, and Ranunculaceae families, but it appears to prefer groups of the bean family.[4−6] Aphids are vectors for a number of plant viruses such as mosaic virus, mottle virus, alfalfa mosaic virus, and peanut virus.[7,8]

Nicotinic acetylcholine receptors (nAChRs) are agonist-gated ion channels that belong to the Cys loop superfamily.[9−11] They are widely dispersed throughout the nervous system and take part in the regulation of the main physiological functions and pathophysiological processes.[12−14] Many therapeutic agents, toxicants, and insecticides target these nAChRs that mediate excitatory neurotransmission.[15−17]

There are many strategies for aphid control relying on eco-friendly agrochemicals.[18−20] For example, (*E*)-*β*-farnesene is released from aphid cornicles to alarm others nearby, and it is the major component of warning pheromones for most aphid species.[21] In addition to the alarm feature of (*E*)-*β*-farnesene, it exhibited aphicidal potential at a dose of 100 mg and revealed a synergistic effect when combined with imidacloprid to control aphid breeding.[22] The disadvantage of its use is its instability attributed to its conjugated double bond.[23] Another strategy for aphid control is the use of insect kinins, which are a group of neuropeptides with many biological functions and highly present in arthropods and invertebrates.[24] Insect kinins exhibited aphicidal and antifeedant potential that can control and interfere with biological processes of insects such as muscle contraction, release of digestive enzymes, and water−sodium balance that lead to insect death.[25] Unfortunately, there are many limitations of kinins for application in peptidase inactivation and easy degradation.[26]

Quinoxaline-based compounds are among some molecular structures that have been recorded to be used for many different purposes in agrochemistry and medicine because of their biological potential as anti-inflammatory,[27−29] antimicro-

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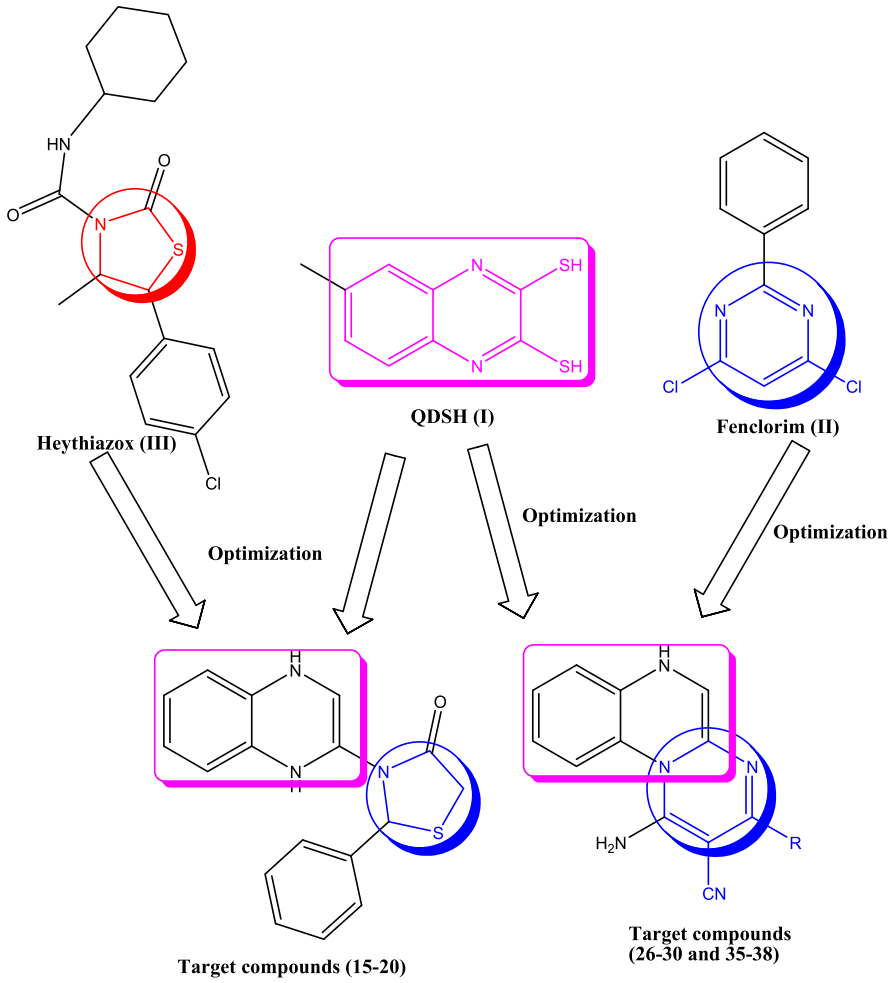


Figure 1. Design strategy of the novel target compounds **15**−**20**, **26**−**30**, and **35**−**38**.

bial,[30−32] antifungal,[33,34] antibiotic,[35,36] and insecticidal agents.[37−39] Moreover, quinoxalines were reported in the literature to be active inhibitors of nicotinic acetylcholine.[40] QDSH (**I**) was reported in the literature to exhibit insecticidal potential utilized for controlling ticks and phytophagous mites[41] (Figure 1).

On the other hand, pyrimidine and thiazolidinone heterocycles attracted chemists' attention due to their biological potential as well as their agrochemical effects. Both heterocycles exhibited potential as anticancer,[42−45] anti-inflammatory,[46−49] hypoglycemic,[50,51] antifungal,[52] antioxidant,[53−55] antibacterial,[31,56,57] and insecticidal agents[58−61] and nicotinic acetylcholine inhibitors.[62−65]

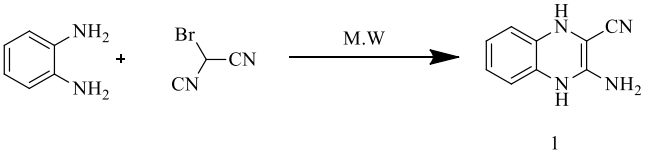
For example, Fenclorim (**II**) is a herbicide used for controlling annual grasses, broadleaf weeds, and some edges[66−68] (Figure 1). On the other hand, Heythiazox (**III**) belongs to a thiazolidinone derivative having nymphicidal and larvicidal potential toward mites and leafhoppers that could be administrated at any plant growth stage from budding till fruiting[69] (Figure 1).

The abovementioned findings and our previous studies related to the discovery of novel bioactive agents[70−78] encouraged us to construct novel quinoxaline derivatives and assess these novel candidates for their insecticidal potential against *Aphis craccivora*. Our design based upon combining the quinoxaline ring with the widely documented insecticidal pyrimidine heterocycle and/or thiazolidinone in one hybrid to obtain pyrimido[1,2-*a*]quinoxaline derivatives (**26**−**30**), **35**−**38**, and thiazolidin-3-yl-1,4-dihydroquinoxaline (**15**−**20**) aims to increase the insecticidal activity and capacity to destroy *Aphis craccivora* as explained in Figure 1. A molecular docking study was carried out to propose the binding mode of the novel target compounds as insecticidal agents.

RESULTS AND DISCUSSION

Chemistry. The parent compound 3-amino-1,4-dihydroquinoxaline-2-carbonitrile (**1**) was simply prepared *via* treating bromomalononitrile and benzene-1,2-diamine under microwave irradiation (Scheme 1). The IR spectrum of compound **1** revealed the appearance of NH_2 and C≡N groups at 3436, 3344, and 2202 cm^{-1}. The ^1H NMR spectrum of compound **1** showed a new singlet signal at δ 10.93 ppm due to one NH group, and also, the aromatic signals corresponding to NH and NH_2 groups appeared in the region δ 7.25−6.66 ppm (NH and

Scheme 1. Synthesis of 3-Amino-1,4-dihydroquinoxaline-2-carbonitrile



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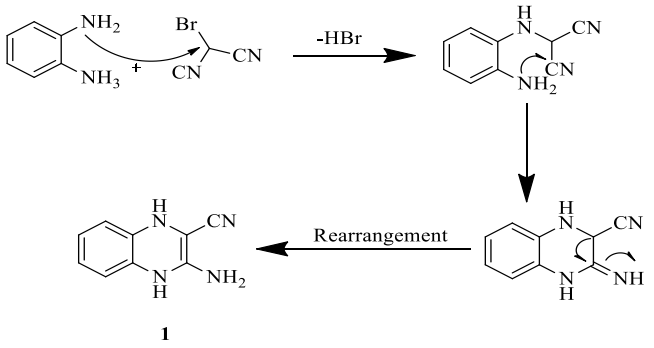
NH_2 disappeared on deuteration). The ^{13}C NMR spectrum of compound **1** indicated the presence of (δ 150.11) C≡N, (130.89, 127.37, 123.43, 120.34, 116.08) CH═CH, and C═C.

A possible mechanism of the formation of compound **1** is described in Scheme 2.

Scheme 2. Possible Mechanisms for the Synthesis of Compound 1



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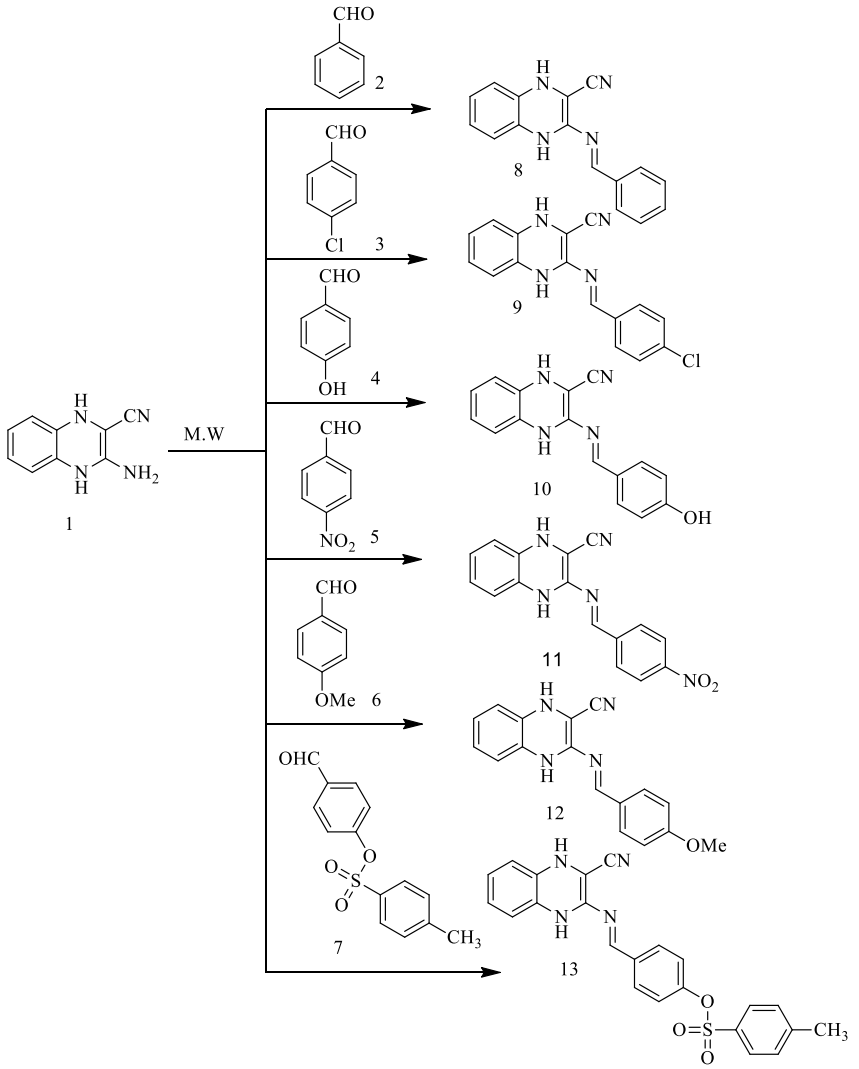
The starting material **1** was smoothly reacted with some aromatic aldehydes **2**−**7**, namely, benzenecarbaldehyde (**2**), 4-chlorobenzenecarbaldehyde (**3**), 4-hydroxybenzenecarbaldehyde (**4**), 4-nitrobenzenecarbaldehyde (**5**), *p*-methoxybenzenecarbaldehyde (**6**), and 4-tosyloxybenzenecarbaldehyde (**7**) *via* microwave irradiation in ethanol for 8−12 min to afford the corresponding Schiff bases (**8**−**13**) (Scheme 3).

The structures of the obtained Schiff bases (**8**−**13**) were established by using IR, ^1H NMR, ^{13}C NMR, and elemental analyses. The IR spectra of these target compounds (**8**−**13**) displayed the absence of NH_2 and CO bands of absorption and the appearance of a new band in the region 1630−1645 cm^{-1} due to CH═N groups. The ^1H NMR (DMSO-d_6) spectra exhibited, in addition to the expected aromatic protons signals, new singlet signals located in δ 8.60−8.25 ppm attributed to N═CH, at δ 10.89 ppm for the proton of the OH group (in compound **10**), at δ 3.89 ppm for the OCH_3 group (compound **12**), and at δ 2.43 ppm for the CH_3 group in compound **13**. Moreover, their ^{13}C NMR spectra indicated new signals that appeared at δ 155.88−152.12 ppm due to the CH═N group. Additionally, elemental analyses and mass spectra of compounds **8**−**13** confirmed the proposed structures. Further, 1,4-dihydroquinoxaline-2-carbonitrile derivatives (**15**−**20**) were synthesized *via* the treatment of thioglycolic acid (**14**) with Schiff bases (**8**−**13**) under microwave irradiation conditions

Scheme 3. Synthesis of Schiff Bases 8−13



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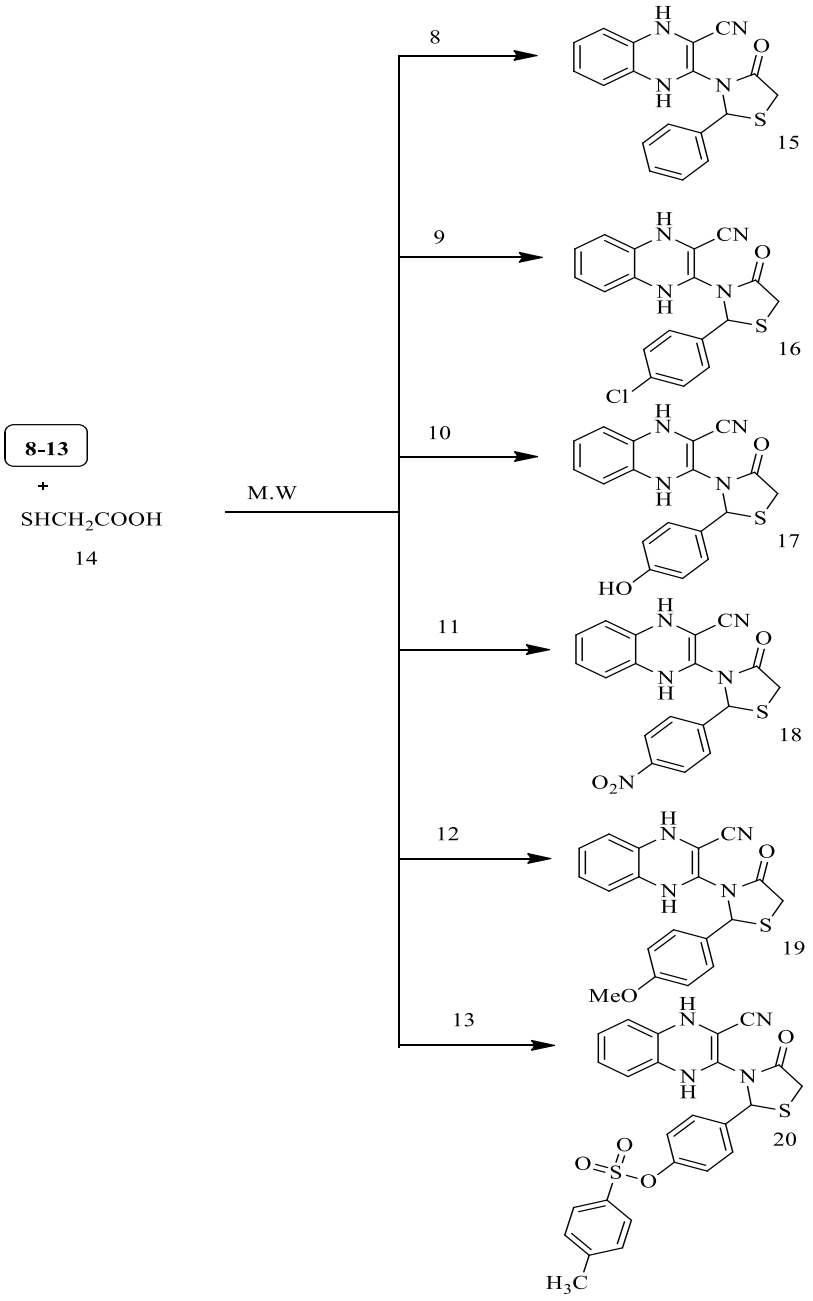
Scheme 4. Synthesis of 3-(4-Oxo-2-phenyl-1,3-thiazolidin-3-yl)-1,4-dihydroquinoxaline-2-carbonitrile Derivatives (15−20)



(Scheme 4). The following are some of the benefits of this process: high yields (89−96%), shorter reaction time (10−15 min), easy workup, lower cost, and safety; pollution issues associated with toxic solvent use were avoided. The optimized results are summarized in Table 1.

The IR spectra of compounds **15−20** showed the appearance of new carbonyl groups within the region 1641−1649 cm^{-1}. Moreover, the ^{1}H NMR (DMSO-d_6) spectra showed, signals other than aromatic protons that are also present, new signals within the region δ 4.03−3.47 ppm consistent with the CH_2 groups and singlet signals related to SCH− groups in the region δ 6.31−5.73 ppm. Furthermore, ^{13}C NMR spectra and elemental analysis results of these compounds (**15−20**) confirmed the proposed structures of the thiazolidinone ring. For example, the spectrum of ^{13}C NMR for compound **20** presented in addition to the expected aromatic signals the appearance of a new signal at δ 21.85 ppm due to the CH_3 group, a new signal at δ 62.15 ppm for the CH_2 group, and at δ 170.84 ppm because of the C−O group. Moreover, its DEPT-135 spectrum revealed no sign of carbonyl groups as well as the appearance of an opposite phase signal at δ 62.83 ppm for the CH_2 group. The possible mechanism for the formation of compounds **15−20** is presented in Scheme 5.

1-Amino-3-phenyl-6*H*-pyrimido[1,2-*a*]quinoxaline-2,5-dicarbonitrile derivatives (**26−30**) were synthesized *via* two methods. The first method was the treatment of compound **1** with some selected aromatic arylidenes (**21−25**) under refluxing in ethanol for 5−7 h. In this traditional method, the reaction took a lot of time with moderate yields (56−65%). The second method was the treatment of the previous mixture under microwave irradiation conditions in ethanol as displayed in Scheme 6 and Table 1. In this simple protocol, the targeted

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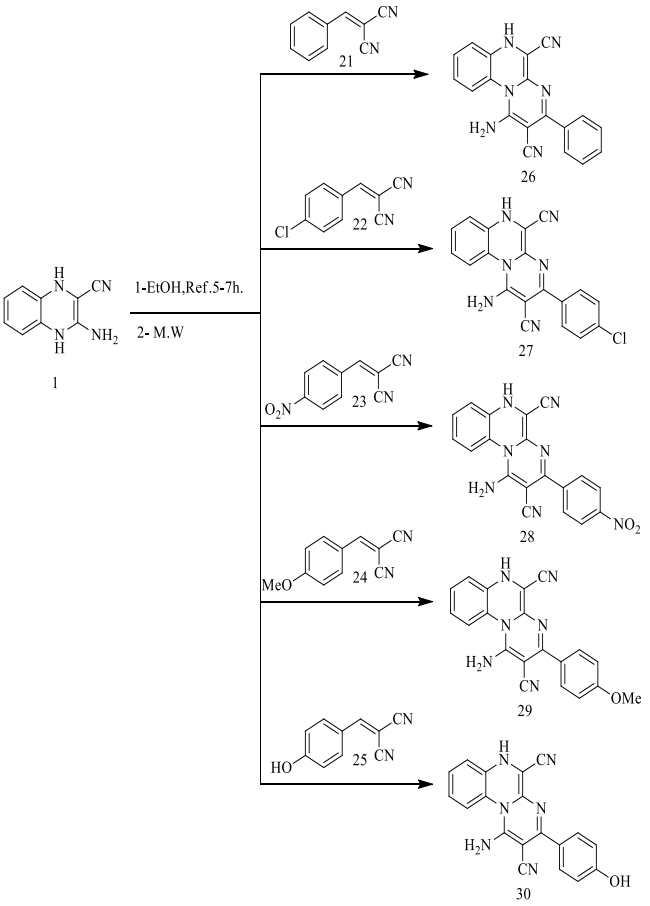
Table 1. The Yields and Required Time for Thiazolidinone and Pyrimidine Formation Using Two Methods

	microwave technique		conventional method	
comp. no.	yield (%)	time (min)	yield (%)	time (h)
15	95	10	52	6
16	89	15	61	7
17	94	11	55	7
18	90	14	62	7
19	96	12	60	6
20	93	12	57	6
26	85	8	56	6
27	88	10	57	5
28	86	9	62	5
29	89	12	60	6
30	87	9	58	7
35	95	11	55	6
36	90	13	59	7
37	94	12	65	6
38	91	10	57	7

products (**26**−**30**) were obtained in high yields (85−89%) within a short reaction time (8−13 min). The optimized results are summarized in Table 1.

The IR spectra of compounds **26**−**30** displayed the appearance of new NH_2 and C≡N groups within the regions 3387−3194 and 2209−2222 cm^{-1}, respectively, which occurred in regions different from those of the starting material. The ^1H NMR spectrum in DMSO-d_6 displayed the aromatic protons signals and singlet signals corresponding to N*H* and NH_2 groups in the region δ 10.24−6.03 ppm. Furthermore, ^{13}C NMR spectra and elemental analyses of compounds **26**−**30** confirmed the expected structures of the pyrimidine ring. The ^{13}C NMR spectrum of compound **27**, for example, displayed the following signals: δ 155.91, 153.53, 136.26, 134.94, 132.31, 131.63, 131.04, 129.88, 129.56, 129.38, 129.30, 128.58, 121.36, 117.69, 113.14 ppm. The formation of the pyrimidines **26**−**30** might be started through the nucleophilic attack of NH_2 groups to activated carbon double bonds and subsequent cyclization *via* another nucleophilic attack of NH groups to C≡N groups.

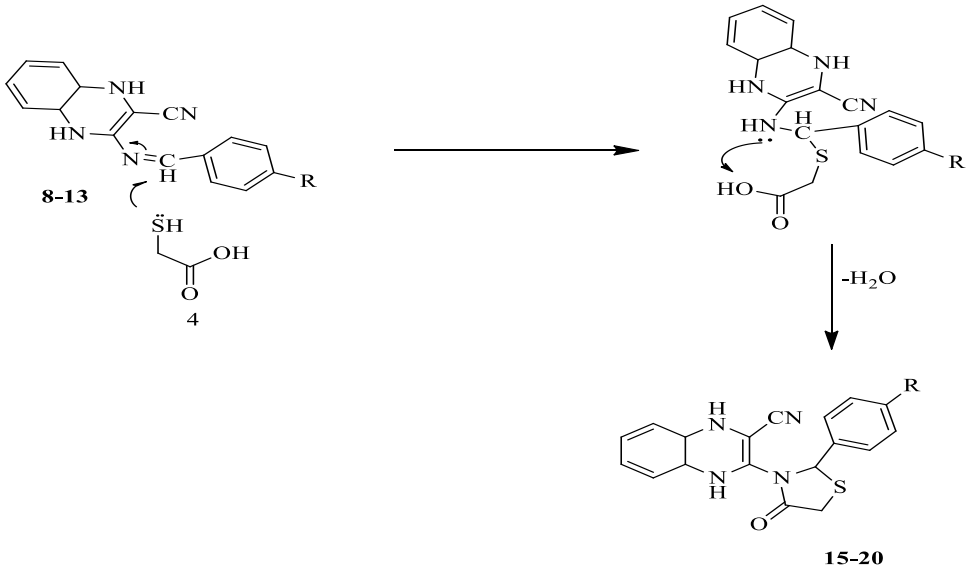
Scheme 6. Synthesis of Pyrimidine Derivatives 26−30



Finally, the obtained intermediate underwent aromatization *via* losing a hydrogen atom to afford the pyrimidine derivatives **26**−**30** (Scheme 7).

The treatment of a compound **1**, with alkylidenemalononitriles (**31**−**34**)[79,80] in ethanol containing few drops of piperidine (2−5 drops), afforded the corresponding pyrimidine derivatives (**35**−**38**) (Scheme 8) in low yields (55−65%). Meanwhile,

Scheme 5. The Possible Mechanism for the Formation of Compounds 15−20



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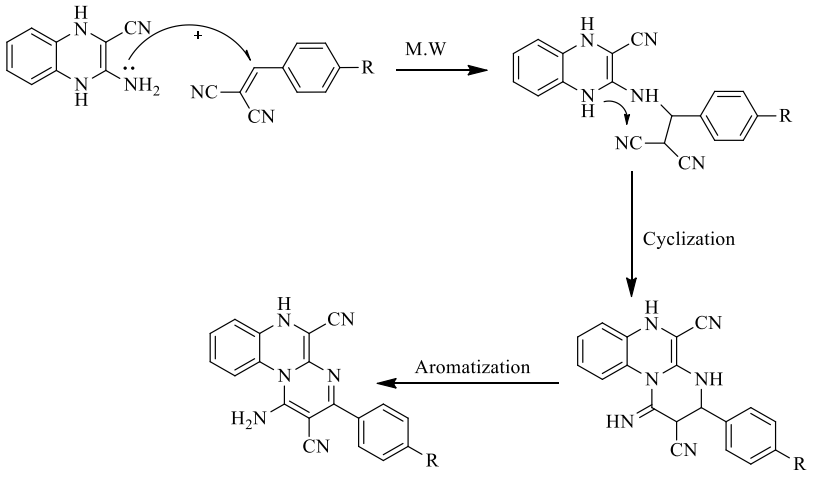
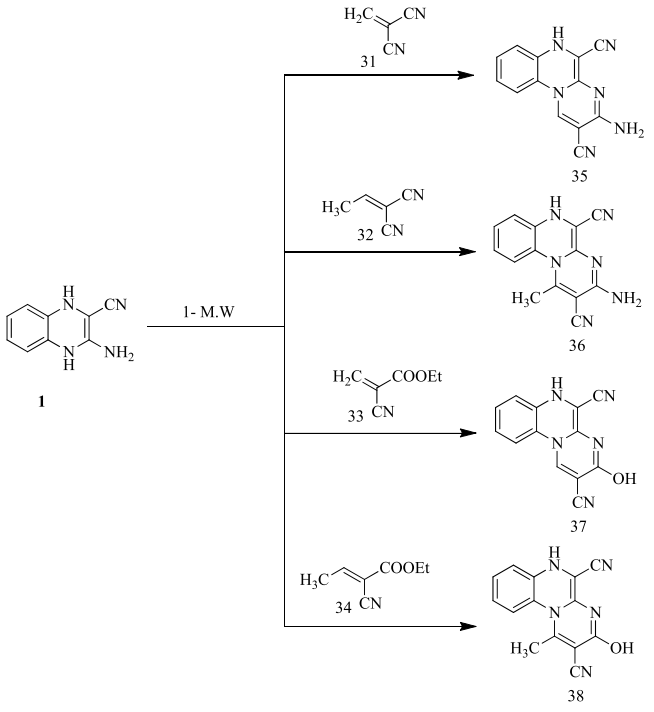
Scheme 7. The Plausible Mechanism for the Formation of Pyrimidine Derivatives 26−30



Scheme 8. Synthesis of Pyrimidine Derivatives 35−38



irradiation of the aforesaid reaction mixture by microwaves for 10−13 min afforded the corresponding pyrimidine derivatives (**35−38**) in excellent yields (90−95%) (Table 1). New structures for these products (**35−38**) were derived from IR, ^{1}H NMR, ^{13}C NMR, and elemental analyses. The IR spectra of compounds **35−38** showed the disappearance of aldehydic C=O groups and the appearance of NH groups at 3222 and at 3204 cm^{-1} (derivatives **35** and **36**, respectively) and OH groups at 3420 and 3446 (in compounds **37** and **38**, respectively), in addition to C≡N groups at 2192−2223 cm^{-1}. ^{1}H NMR spectra of compounds **36−38** showed, in addition to the signals from the aromatic proton, new singlet signals related to N*H* protons at δ 10.21−9.73 ppm (disappeared on deuteration in compounds **35** and **36**). In addition to the appearance of CH_3 protons in compounds **36** and **38** at δ 3.79 and 3.26 ppm, respectively, their ^{13}C NMR spectra showed new signals at δ 28.07 and 21.07 ppm due to CH_3 groups, respectively.

Insecticidal Bioefficacy Screening. *Toxicological Activity Test for Nymphs of Cowpea Aphid (Aphis craccivora) Insects Following Treatment for 24 h.* The insecticidal effectiveness of all synthesized compounds had been evaluated; results of compounds **1**, **9**, **15**, **16**, **18**, **20**, **26**, **27**, **28**, **30**, **37**, and **38** against nymphs of *Aphis craccivora* are illustrated in Table 2. In the 24 h period after the treatment, bioefficacy results of the synthesized pyrimidine and thiazolidinone derivatives exhibited a high to low level of toxicological activity toward nymphs of

Table 2. Insecticidal Activity of Compounds 1, 9, 15, 16, 18, 20, 26, 38, 27, 28, 30, and 37 toward the Nymphs and Adults of Cowpea Aphid (*Aphis craccivora*) Insects after 24 h of Treatment

	nymphs			adults		
comp.	LC_{50} (ppm)	slope	toxic ratio	LC_{50} (ppm)	slope	toxic ratio
1	1.023	0.312 ± 0.031	0.020	2.101	0.362 ± 0.024	0.048
9	0.101	0.382 ± 0.031	0.207	0.570	0.316 ± 0.077	0.178
15	0.227	0.340 ± 0.033	0.092	0.620	0.231 ± 0.023	0.164
16	0.021	0.311 ± 0.032	1	0.102	0.132 ± 0.076	1
18	0.551	0.350 ± 0.035	0.381	1.226	0.233 ± 0.023	0.083
20	0.053	0.303 ± 0.030	0.396	0.267	0.270 ± 0.024	0.382
26	0.444	0.291 ± 0.038	0.047	1.485	0.193 ± 0.023	0.068
38	0.284	0.304 ± 0.032	0.073	1.470	0.247 ± 0.023	0.068
27	0.039	0.301 ± 0.0302	0.538	0.130	0.130 ± 0.077	0.784
28	0.334	0.391 ± 0.0303	0.062	1.660	0.371 ± 0.032	0.061
30	0.787	0.321 ± 0.0301	0.026	2.236	0.362 ± 0.209	0.045

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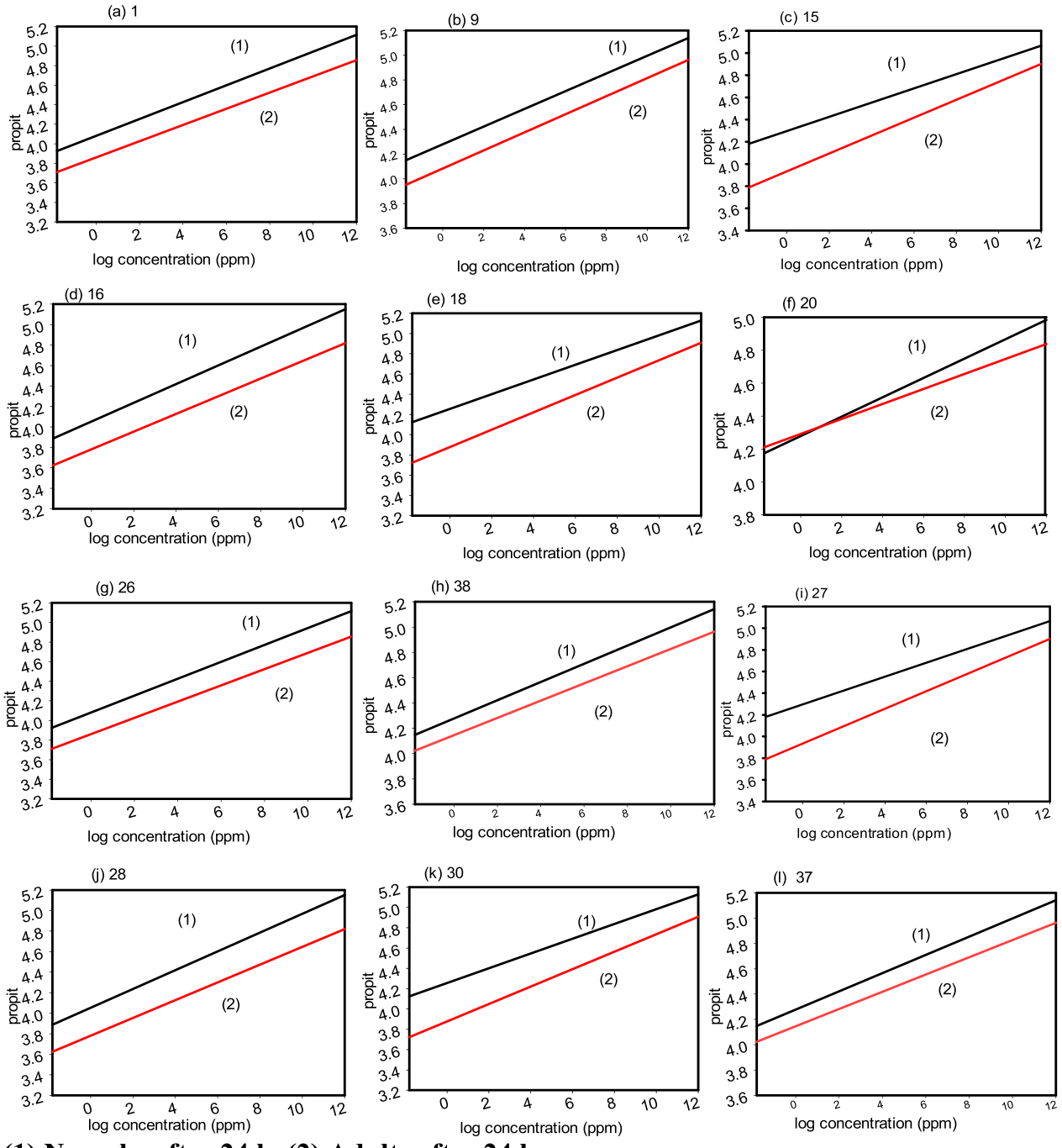

Figure 2. (a–l) Insecticidal activities of compounds **1**, **9**, **15**, **16**, **18**, **20**, **26**, **38**, **27**, **28**, **30**, and **37** for the nymphs and adults of cowpea aphid (*Aphis craccivora*) insects following a 24 h treatment period.

cowpea aphids after 24 h of the testing with LC_{50}. The values range from 0.021 to 1.023, that is, LC_{50} values of compounds **1**, **9**, **15**, **16**, **18**, **20**, **26**, **38**, **27**, **28**, **30**, and **37** were 1.023, 0.101, 0.227, 0.021, 0.551, 0.053, 0.444, 0.284, 0.039, 0.334, 0.787, and 0.944 ppm, respectively. According to this result, compound **16** was the most toxic agent against nymphs of cowpea aphids (*Aphis craccivora*) after the treatment has been completed for 24 h compared to the other synthesized pyrimidine and thiazolidinone derivatives.

Toxicological Activity Test for Adults of Cowpea Aphids (Aphis craccivora) after 24 h of Treatment. Results of compounds **1**, **9**, **15**, **16**, **18**, **20**, **26**, **38**, **27**, **28**, **30**, and **37** were tested against cowpea aphids (*Aphis craccivora*). These can be seen in Table 2. The bioefficacy of synthesized compounds was measured 24 h after treatment, and the compounds exhibited a high to low level of toxicological activity against the adults of cowpea aphids (*Aphis craccivora*) because they were nearly as active as others after 24 h of testing with LC_{50}. The values range from 0.101 to 2.236 for compounds **1**, **9**, **15**, **16**, **18**, **20**, **26**, **38**, **27**, **28**, **30** and **37** with LC_{50} values of 2.101, 0.570, 0.620, 0.102, 1.226, 0.267, 1.485, 1.470, 0.130, 1.660, 2.236, and 1.382 in ppm. This result indicated that compound toxicity was high for compound **16** against adults of *Aphis craccivora* with an LC_{50} value equal to 0.102 ppm.

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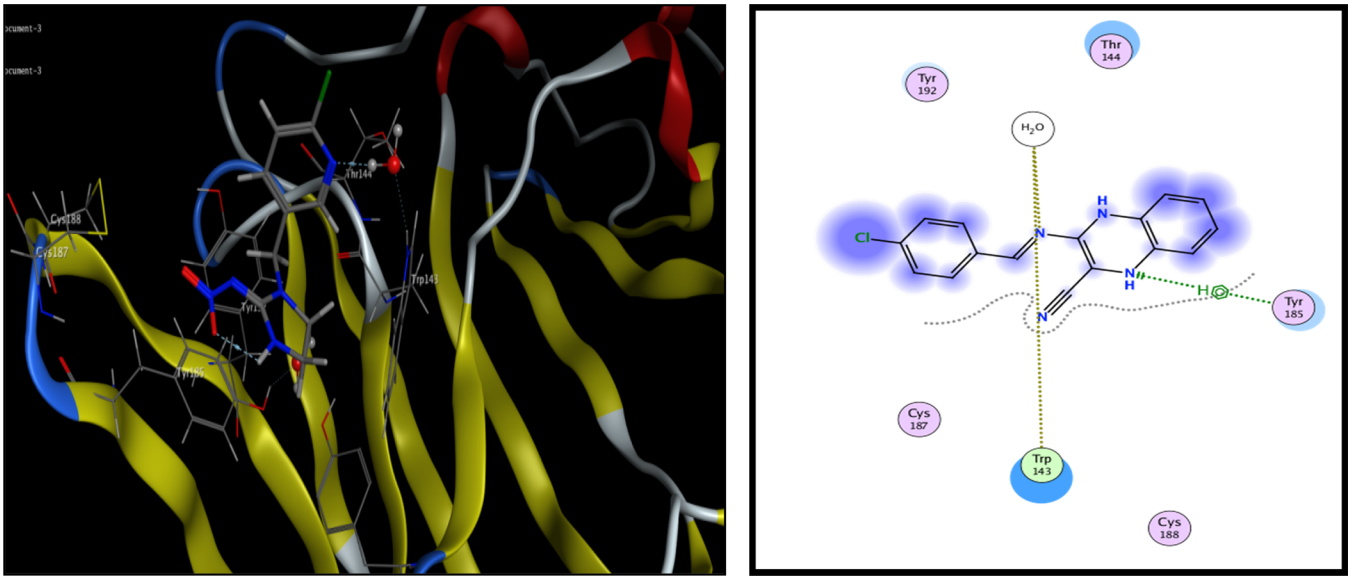
Table 3. The Binding Interactions and Affinity (kcal/mol) of 1, 9, 15, 16, 18, 20, 26, 27, 28, 30, 38, and 37 within AChBP Binding Regions

compound	affinity (kcal/mol)	no. of hydrogen bonds	distance (Å) from the main residue		functional group
1	−5.34	1	Trp143	2.58	NH_2
9	−8.51	1	Trp143	2.69	C═N
15	−8.45	3	Trp143	3.15	C≡N
			Thr144	3.09	NH
			Cys187	2.94	thiazolidinone S
16	−10.54	1	Trp143	3.17	thiazolidinone C═O
18	−7.42	2	Cys147	3.07	NH
			Trp143	2.94	thiazolidinone S
20	−8.42	3	Glu190	2.86	NH
			Tyr192	3.08	C≡N
			Trp143	3.21	S═O
26	−7.39	1	Trp143	2.78	NH_2
27	−9.46	2	Cys188	2.56	NH
			Cys187	3.05	NH
28	−8.27	3	Trp143	2.89	C≡N
			Cys188	3.09	NH
			Trp143	2.62	C≡N
30	−7.07	2	Cys188	3.03	NH
38	−7.11	1	Trp143	2.88	NH_2
37	−7.08	1	Trp143	2.60	NH_2
imidacloprid	−8.17	1	Trp143	2.83	pyridyl N



(A) **(B)**

Figure 3. Possible binding interaction of compound **9** within AChBP. (A) 3D binding with Trp143 and (B) 2D binding of compound **9** inside active sites.

Structure−Activity Relationship. Based on the toxicity value, the structure−activity relationship is shown in Table 2 and Figure 2. From the synthetic pyrimidine and thiazolidinone derivatives, compound **16** was more active in combating nymphs and adults of *Aphis craccivora* than the other pyrimidine and thiazolidinone derivatives. A high level of activity is associated with the compounds **16**, **20**, and **27**, and there is a possibility that it is due to chlorophenyl, CN groups, and benzene sulfanyl moieties in their structure. Based on the toxicity results in Table 2, some structure−activity relationship could be concluded. Adding the thiazolidinone ring to the quinoxaline moiety markedly increased the insecticidal potential of the target compounds against *Aphis craccivora*. This is clear when comparing 3-amino-1,4-dihydroquinoxaline-2-carbonitrile (**1**) (LC_{50} = 2.101 ppm) with thiazolidin-3-ylquinoxaline derivatives **15**−**20**, which exhibited a higher insecticidal potential within the LC_{50} range = 0.102−1.226 ppm. Regarding the substituents on the thiazolidinone moiety, attaching electron-withdrawing groups as *p*-chlorophenyl (compound **16**, LC_{50} = 0.1 ppm) and benzenesulfonate (compound **20**, LC_{50} = 0.26 ppm) to the thiazolidinone ring displayed a higher insecticidal potential than the phenyl ring (compound **15**, LC_{50} = 0.6 ppm). On the other hand, hybridizing the pyrimidine ring with the quinoxaline moiety increased the insecticidal effect of the target compounds

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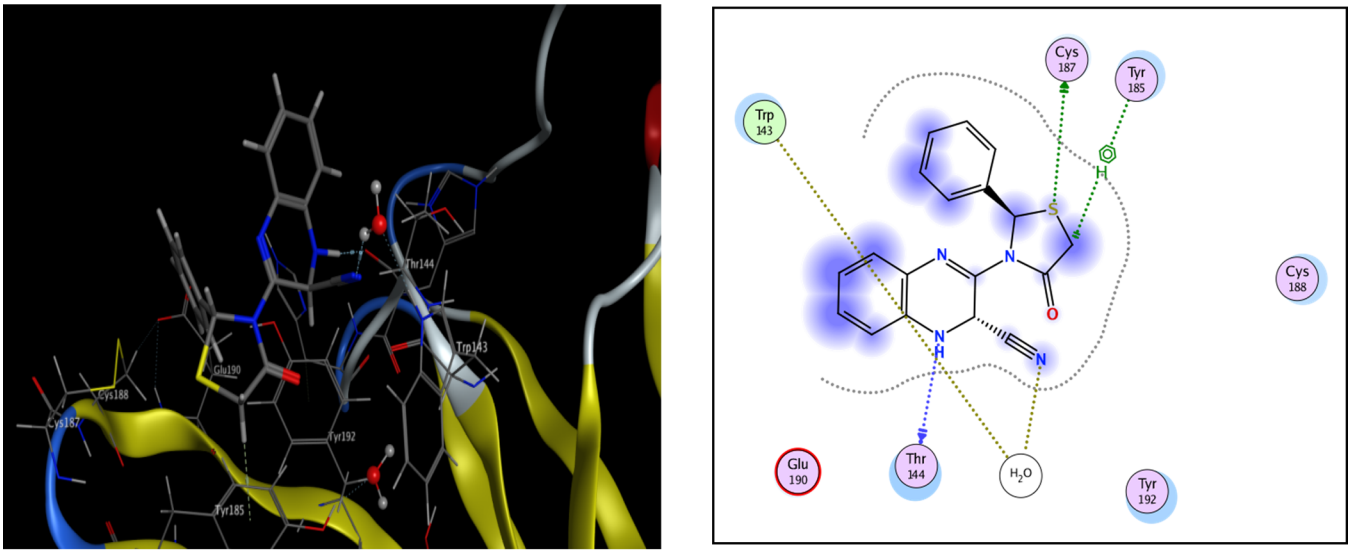

Figure 4. Possible binding interaction of compound **15** throughout AChBP. (A) 3D binding with Trp143, Thr144, and Cys187 and (B) 2D binding of compound **15** inside active sites.

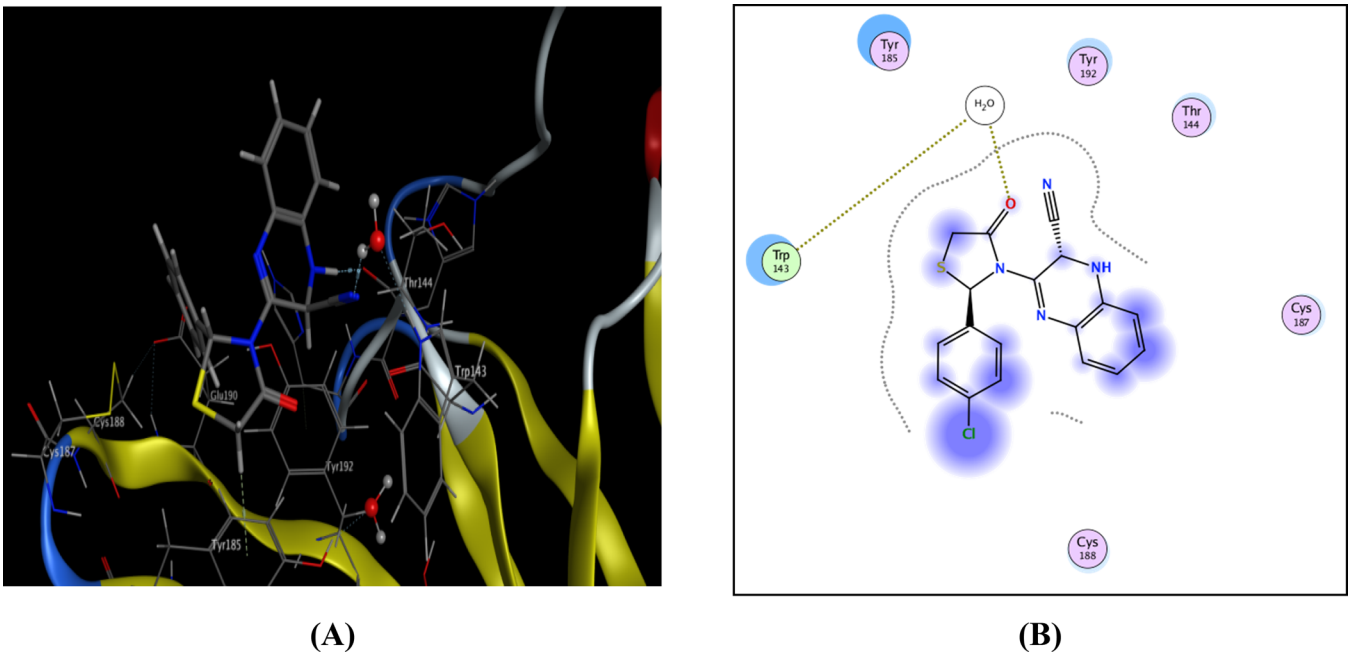

Figure 5. Possible binding interaction of compound **16** throughout AChBP. (A) 3D binding with Trp143 and (B) 2D binding of compound **16** inside active sites.

26 (LC_{50} = 1.485 ppm), **27** (LC_{50} = 0.130 ppm), **28** (LC_{50} = 1.660 ppm), **37** (LC_{50} = 1.382 ppm), and **38** (LC_{50} = 1.470 ppm) except compound **30** (LC_{50} = 2.236 ppm), which recorded a comparable insecticidal effect against *Aphis craccivora* to that registered by the quinoxaline compound **1** (LC_{50} = 2.101 ppm).

From the results recorded in Table 2, we conclude that the most toxic compounds to cowpea aphids are **16**, **20**, and **27**.

Docking Study. Using X-ray crystal structures, a docking study was conducted for acetylcholine (protein AChBP) from *Lymnaea stagnalis* (PDB 2ZJU) due to the unavailability of *Aphis craccivora* crystal structures. The cocrystallized ligand imidaclorid was redocked within the binding region of AChBP with RMSD = 1.3201 and binding energy score = −8.17 kcal/mol. The target compounds **1**, **9**, **15**, **16**, **18**, **20**, **26**, **38**, **27**, **28**, **30**, and **37** were docked within the AChBP and H-bonding amino acid residues, and H-bond lengths and binding energy scores are recorded in Table 3.

Compound **9** displayed similar fitting with the AChBP binding site as imidaclorid with binding score = −8.51 kcal/mol. Furthermore, this compound **9** formed two binding interactions; azomethine N bonded with Trp143 *via* H-bonds, and the quinoxaline moiety interacted with Tyr385 *via* arene-H interactions (Figure 3).

On the other hand, the thiazolidinoquinoxaline derivative **15** produced arene-H interactions with the thiazolidino moiety in

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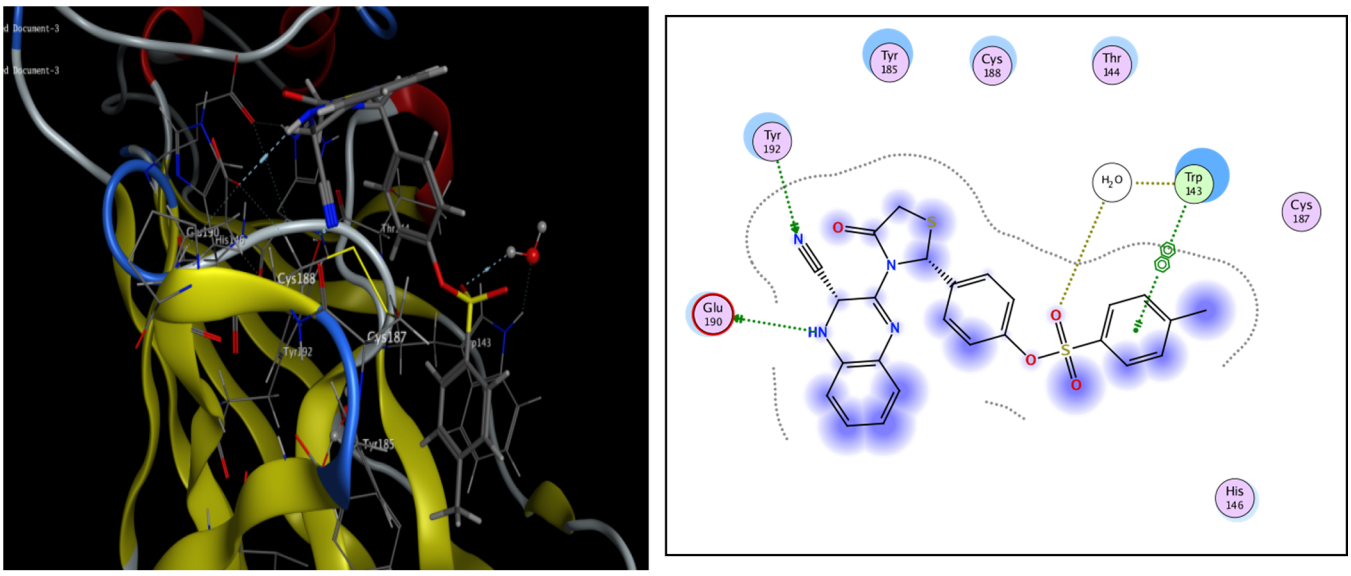
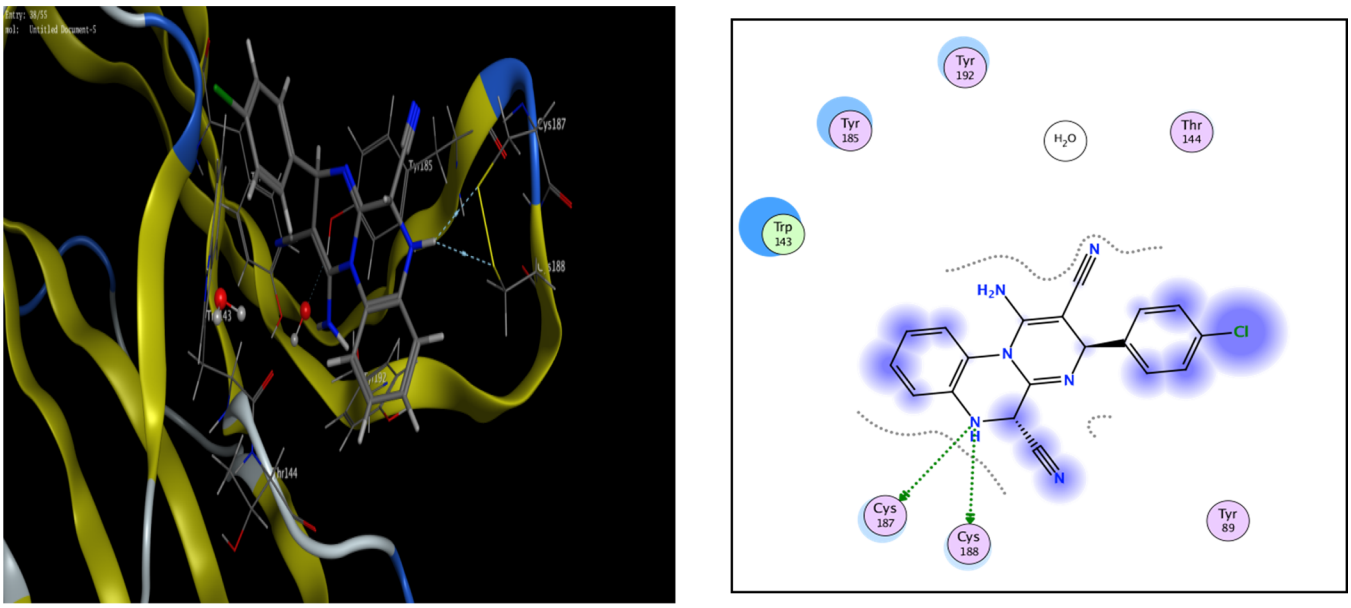


(A) (B)

Figure 6. Possible binding interaction of compound **20** within AChBP. (A) 3D binding with Glu199, Tyr192, and Trp143 and (B) 2D binding of compound **20** inside active sites.



(A) (B)

Figure 7. Possible binding interaction of compound **27** throughout AChBP. (A) 3D binding with Cys187 and Cys188 and (B) 2D binding of compound **27** to active sites.

addition to 3 hydrogen bonds as follows: (i) Trp143 with CN, (ii) Thr144 with quinoxaline NH, and (iii) Cys187 with thiazolidino S (Figure 4).

Regarding the most active compound toward nymph of cowpea aphids (**16**), it registered the highest binding score (−10.54 kcal/mol), and the thiazolidinone C═O formed a hydrogen bond with Trp143 (Figure 5).

In addition, the phenyl ring of compound **20** made hydrophobic interactions with Trp143 with the binding score equal to −8.42 kcal/mol. Additionally, this compound revealed hydrogen bonding with Glu190, Tyr192, and Trp143 as depicted in Figure 6.

Finally, compound **27** formed two hydrogen bonds through interactions of the NH group of quinoxaline with Cys188 and Cys187 amino acid residues (Figure 7).

EXPERIMENTAL SECTION

Chemistry. We purchased all commercially available reagents from Merck, Aldrich, and Fluka and did not purify them further. The reactions were monitored *via* thin-layer chromatography (TLC), using precoated silica gel G/UV-254

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plates (Merck 60F254) and UV light (254/365 nm). Using a Kofler melting point apparatus, melting points were detected and uncorrected. As a result of the attenuated total reflection (ATR) method, FT-IR spectra were recorded with an FT-IR ALPHA Bruker platinum ATR spectrometer and are given in cm^{-1}. ^1H NMR and ^{13}C NMR (DMSO-d_6) spectra were recorded at 400 and 100 MHz, respectively, on a Bruker BioSpin AG spectrometer and DEPT-135 (ppm). Mass spectra were obtained at 70 eV using a GCMS-QP 1000EX spectrometer from Shimadzu. PerkinElmer CHN analyzer models were used to obtain the elemental analyses. Kenstar OM9925E (2450 MHz, 800 W) microwave ovens were used to carry out microwave irradiation.

Synthesis of 3-Amino-1,4-dihydroquinoxaline-2-carbonitrile (1). A mixture of bromomalononitrile (2.0 mmol) and benzene-1,2-diamine (2.0 mmol) was added into 5.0 mL of absolute ethanol; then, the mixture was irradiated in a microwave oven for 5 min. Once the product was cooled to room temperature, the formed precipitate was filtered off, washed with cold ethanol (2 × 10 mL), dried, and crystallized from ethanol.

Yield: 93%; color: brown solid; m.p. 186−188 °C; IR (ATR): 3436, 3344 (NH_2), 3235, 3176 (2NH), 2202 (C≡N) cm^{-1}; ^1H NMR: δ 10.93 (s, 1H, NH), 7.25−6.66 (m, 7H, 4-$CH_{arom.}$ + NH_2, +NH); ^{13}C NMR: δ 150.11, 130.89, 127.37, 123.43, 120.34, 116.08; MS, m/z (%): 172 (M^+, 15); anal. calcd. for $C_9H_8N_4$ (172.19): C, 62.78%; H, 4.68%; N, 32.54%. Found: C, 62.84%; H, 4.62%; N, 32.59%.

Schiff Bases (8−13): General Procedure for Their Synthesis. Mixtures of quinoxaline **1** (2.0 mmol) and (2.0 mmol) aromatic aldehydes, namely, benzenecarbaldehyde (**2**), 4-chlorobenzenecarbaldehyde (**3**), 4-hydroxybenzenecarbaldehyde (4), 4-nitrobenzenecarbaldehyde (**5**), *p*-methoxybenzenecarbaldehyde (**6**), and 4-tosyloxybenzenecarbaldehyde (7) were prepared *via* microwave irradiation in ethanol for 8−12 min to afford the corresponding Schiff bases **8−13**. After cooling to room temperature, the solid product was filtered off and washed in water (3 × 5 mL). After drying, ethanol was used for crystallization.

*3-(Benzylideneamino)-1,4-dihydroquinoxaline-2-carbonitrile (**8**).* Yield: 77%; color: yellow solid; m.p. 148−150 °C; IR (ATR): 3367, 3175 (NH), 2219 (C≡N), 1630 (CH═N) cm^{-1}; ^1H NMR: δ 9.93 (s, 1H, NH), 8.65 (s, 1H, CH═N), 8.60−6.66 (m, 10H, 9-$CH_{arom.}$ and NH); ^{13}C NMR: δ 155.23, 131.68, 128.13, 123.83, 120.53, 116.16, 104.32; MS, m/z (%): 260 (M^+, 30); anal. calcd. for $C_{16}H_{12}N_4$ (260.29): C, 73.83%; H, 4.65%; N, 21.46%. Found: C, 73.76%; H, 4.71%; N, 21.58%.

*3-((4-Chlorobenzylidene)amino)-1,4-dihydroquinoxaline-2-carbonitrile (**9**).* Yield: 70%; color: light yellow solid; m.p. 118−120 °C; IR (ATR): 3368, 3168 (2NH), 2192 (C≡N), 1645 (CH═N) cm^{-1}; ^1H NMR: δ 10.23 (s, 1H, NH), 8.25 (s, 1H, C*H*═N), 8.04−6.66 (m, 9H, 8-$CH_{arom.}$ and NH); ^{13}C NMR: δ 155.88, 150.61, 148.61, 131.40, 130.52, 126.20, 120.14, 108.89, 106.70, 102.17 ppm; MS, m/z (%): 294 (M^+, 25); anal. calcd. for $C_{16}H_{11}ClN_4$ (294.74): C, 65.20%; H, 3.76%; N, 19.01%. Found: C, 65.25%; H, 3.71%; N, 19.12%.

*3-((4-Hydroxybenzylidene)amino)-1,4-dihydroquinoxaline-2-carbonitrile (**10**).* Yield: 75%; color: pale yellow solid; m.p. 126−128 °C; IR (ATR): 3172−3400 (2NH, OH), 2206 (C≡N), 1635 (CH═N) cm^{-1}; ^1H NMR: δ 10.23 (s, 1H, NH), 8.60 (s, 1H, C*H*═N), 8.51−8.31 (m, 9H, 8-$CH_{arom.}$ and N*H*), 10.89 (s, 1H, OH); ^{13}C NMR: δ 153.45, 131.68, 128.13, 123.83, 120.53, 116.16, 103.21; MS, m/z (%): 276 (M^+, 15); anal. calcd. for $C_{16}H_{12}N_4O$ (276.29): C, 69.55%; H, 3.76%; N, 19.01%. Found: C, 65.25%; H, 4.67%; N, 20.14%.

*3-((4-Nitrobenzylidene)amino)-1,4-dihydroquinoxaline-2-carbonitrile (**11**).* Yield: 78%; color: orange solid; m.p. 140−142 °C; IR (ATR): 3375 (NH), 3169 (NH), 2217 (C≡N), 1643 (CH═N) cm^{-1}; ^1H NMR: δ 10.25 (s, 1H, NH), 8.28 (s, 1H, C*H*═N), 8.03−6.66 (m, 9H, 8-$CH_{arom.}$ + N*H*); ^{13}C NMR: δ 152.12, 131.79, 128.23, 123.91, 120.64, 116.31, 103.41; MS, m/z (%): 305 (M^+, 30); anal. calcd. for $C_{16}H_{11}N_5O_2$ (305.29): C, 62.95%; H, 3.63%; N, 22.94%. Found: C, 62.98%; H, 3.67%; N, 22.98%.

*3-((4-Methoxybenzylidene)amino)-1,4-dihydroquinoxaline-2-carbonitrile (**12**).* Yield: 74%; color: brown solid; m.p. 155−157 °C; IR (ATR): 3374, 3168 (2NH), 2219 (C≡N), 1636 (CH═N) cm^{-1}; ^1H NMR: δ 10.25 (s, 1H, N*H*), 8.29 (s, 1H, C*H*═N), 8.01−6.66 (m, 9H, 8-$CH_{arom.}$ + N*H*), 3.89 (s, 3H, OCH_3); ^{13}C NMR: δ 152.10, 131.79, 128.23, 123.91, 120.64, 116.31, 103.41; MS, m/z (%): 290 (M^+, 20); anal. calcd. for $C_{17}H_{14}N_4O$ (290.32): C, 70.33%; H, 4.86%; N, 19.30%. Found: C, 70.35%; H, 4.89%; N, 19.34%.

*4-((3-Cyano-1,4-dihydroquinoxalin-2-yl)imino)-methylphenyl-4-methylbenzenesulfonate (**13**).* Yield: 76%; color: reddish brown solid; m.p. 145−147 °C; IR (ATR): 3374, 168 (2NH), 2298 (CH_3), 2206 (C≡N), 1634 (CH═N) cm^{-1}; ^1H NMR: δ 10.25 (s, 1H, N*H*), 8.24 (s, 1H, C*H*═N), 8.14−6.66 (m, 13H, 12-$CH_{arom.}$ + N*H*), 2.43 (s, 3H, CH_3); ^{13}C NMR: δ 152.12, 131.79, 128.23, 123.91, 120.64, 116.31, 103.41; MS, m/z (%): 430 (M^+, 45); anal. calcd. for $C_{23}H_{18}N_4O_3S$ (430.48): C, 64.17%; H, 4.21%; N, 13.01%; S, 7.45%. Found: C, 64.22%; H, 4.27%; N, 13.04%; S, 7.48%.

Compound Synthesis of 15−20: General Procedures. *Method A (Microwave Method).* A mixture of Schiff bases **15−20** (2.0 mmol) and thioglycolic acid (2.2 mmol) in 5.0 mL of dry toluene was irradiated in an MW oven for an approved time as shown in Table 1. Upon completion of the reaction (TLC was used to check the progress), the reaction mixture was cooled, and to remove the unreacted acid, the reaction mixture was cooled and washed with dilute sodium bicarbonate solution. The organic layer was separated (toluene layer) and removed by a rotary evaporator, yielding the solid product that was purified through crystallization using ethanol.

Method B (Traditional Method). A mixture of appropriate compound Schiff bases **15−20** (2.0 mmol) and thioglycolic acid (2.2 mmol) was refluxed in ethanol (20.0 mL) in dry toluene (5.0 mL) for 14−17 h (TLC monitoring). Cooling was applied to the reaction mixture that was washed with a dilute solution of sodium bicarbonate to remove the unreacted acid. The organic layer was separated (toluene layer) and removed by a rotary evaporator, yielding the solid product that was purified through crystallization using ethanol.

*3-(4-Oxo-2-phenylthiazolidin-3-yl)-1,4-dihydroquinoxaline-2-carbonitrile (**15**).* Yield: 95%; color: brown solid; m.p. 164−166 °C; IR (ATR) cm^{-1}: 3426, 3324 (2NH), 3094 (C−$H_{arom.}$), 2976 (C−$H_{aliph.}$), 2201 (CN), 1649 (C═O); ^1H NMR: δ 7.93−6.75 (m, 11H, $CH_{arom.}$ + 2NH), 6.30 (s, 1H, N−CH−S), 4.30 (s, 2H, CH_2); ^{13}C NMR δ (ppm): 159.58, 130.63, 130.53, 122.92, 121.31, 120.74, 120.68, 120.53, 118.23, 116.08, 111.56, 65.65; MS, m/z (%): 334 (M^+, 25); anal. calcd. for $C_{18}H_{14}N_4OS$ (334.39): C, 64.65%; H, 4.22%; N, 16.75%; S, 9.59%. Found: C, 64.69%; H, 4.24%; N, 16.78%; S, 9.63%.

*3-(2-(4-Chlorophenyl)-4-oxothiazolidin-3-yl)-1,4-dihydroquinoxaline-2-carbonitrile (**16**).* Yield: 89%; color: deep green solid; m.p. 179−181 °C; IR (ATR) cm^{-1}: 3296, 3176 (2NH),

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3056 (C−$H_{arom.}$), 2923 (C−$H_{aliph.}$), 2192 (CN), 1648 (C═O); ^{1}H NMR: δ 12.82 (s, 1H, NH), 8.06−7.03 (m, 10H, $CH_{arom.}$ + NH), 6.31 (s, 1H, CH), 4.25 (s, 2H, CH_2); ^{13}C NMR δ (ppm): 162.22, 155.66, 147.32, 146.36, 136.06, 132.70, 130.84, 130.51, 128.77, 128.48, 128.08, 121.51, 120.42, 96.89, 56.67; MS, *m*/*z* (%): 368 (M^+, 45); anal. calcd. for $C_{18}H_{13}ClN_4OS$ (368.84): C, 58.61%; H, 3.55%; N, 15.19%; S, 8.69%. Found: C, 58.65%; H, 3.48%; N, 15.26%; S, 8.58%.

*3-(2-(4-Hydroxyphenyl)-4-oxothiazolidin-3-yl)-1,4-dihydroquinoxaline-2-carbonitrile (**17**)*. Yield: 94%; color: gray solid; m.p. 192−194 °C; IR (ATR) cm^{-1}: 3314, 3267 (2NH), 3090 (C−$H_{arom.}$), 2981 (C−$H_{aliph.}$), 2193 (CN), 1648 (C═O); ^{1}H NMR: δ 11.43 (br, 1H, OH), 8.017−7.14 (m, 11H, $CH_{arom.}$ + NH), 5.97 (s, 1H, N−CH−S), 4.15 (s, 2H, CH_2); ^{13}C NMR δ (ppm): 173.05, 156.90, 150.87, 146.65, 138.19, 136.46, 133.54, 130.08, 128.35, 128.05, 127.95, 122.76, 120.12, 98.63, 60.96; MS, *m*/*z* (%): 350 (M^+, 16); anal. calcd for $C_{18}H_{14}N_4O_2S$ (350.39): C, 61.70%; H, 4.03%; N, 15.99%; S, 9.15%. Found: C, 61.62%; H, 4.12%; N, 16.07%; S, 9.22%.

*3-(2-(4-Nitrophenyl)-4-oxothiazolidin-3-yl)-1,4-dihydroquinoxaline-2-carbonitrile (**18**)*. Yield: 90%; color: reddish brown solid; m.p. 178−180 °C; IR (ATR) cm^{-1}: 3321, 3298 (2NH), 3097 (C−$H_{arom.}$), 2996 (C−$H_{aliph.}$), 2192 (CN), 1647 (C═O); ^{1}H NMR: δ 9.36 (s, 1H, NH), 8.54−7.32 (m, 9H, $CH_{arom.}$ + NH), 5.73 (s, 1H, N−CH−S), 4.08 (s, 2H, CH_2); ^{13}C NMR δ (ppm): 170.54, 152.54, 148.09, 146.24, 137.87, 135.12, 131.04, 130.0, 127.90, 126.25, 125.61, 121.99, 120.10, 96.11, 59.15; MS, *m*/*z* (%): 379 (M^+, 25); anal. calcd. for $C_{18}H_{13}N_5O_3S$ (379.39): C, 56.98%; H, 3.45%; N, 18.46%; S, 8.45%. Found: C, 57.07%; H, 3.51%; N, 18.37%; S, 8.54%.

*3-(2-(4-Methoxyphenyl)-4-oxothiazolidin-3-yl)-1,4-dihydroquinoxaline-2-carbonitrile (**19**)*. Yield: 96%; color: green solid; m.p. 196−198 °C; IR (ATR) cm^{-1}: 3376, 3265 (2NH), 3091 (C−$H_{arom.}$), 2987 (C−$H_{aliph.}$), 2194 (CN), 1645 (C═O); ^{1}H NMR: δ 12.45 (s, 1H, NH), 8.65−6.81 (m, 9H, $CH_{arom.}$ + NH), 6.21 (s, 1H, CH), 3.82 (s, 3H, OMe), 3.47 (s, 2H, CH_2); ^{13}C NMR δ (ppm): 171.03, 150.83, 150.46, 148.87, 131.12, 129.79, 112.92, 110.47, 109.23, 106.69, 102.85, 62.30, 58.44; MS, *m*/*z* (%): 364 (M^+, 10); anal. calcd for $C_{19}H_{16}N_4O_2S$ (364.10): C, 62.62%; H, 4.43%; N, 15.37%; S, 8.80%. Found: C, 62.71%; H, 4.49%; N, 15.42%; S, 8.73%.

*4-(3-(3-Cyano-1,4-dihydroquinoxalin-2-yl)-4-oxothiazolidin-2-yl)phenyl-4-methylbenzenesulfonate (**20**)*. Yield: 93%; color: deep green solid; m.p. 183−185 °C; IR (ATR) cm^{-1}: 3311, 3204 (2NH), 3081 (C−$H_{arom.}$), 2183 (CN), 1671 (C═O), 1641 (C═O); ^{1}H NMR: δ 10.19 (s, 1H, NH), 7.95−6.90 (m, 13H, $CH_{arom.}$ + NH), 5.59 (s, 1H, N−CH−S), 4.25 (s, 2H, CH_2), 2.44 (s, 3H, CH_3); ^{13}C NMR δ (ppm): 170.84, 148.82, 146.02, 131.50, 130.65, 130.17, 129.29, 127.31, 126.68, 126.01, 124.68, 123.71, 123.44, 122.52, 98.39, 62.15, 21.58; DEPT-135: 130.65, 130.61, 129.29, 128.51, 126.67, 125.76, 125.17, 122.83, 122.78, 97.73, 62.83, 21.86; MS, *m*/*z* (%): 504 (M^+, 35); anal. calcd. for $C_{25}H_{20}N_4O_4S_2$ (504.58): C, 59.51%; H, 4.00%; N, 11.10%; S, 12.71%. Found: C, 59.45%; H, 3.95%; N, 11.17%; S, 12.68%.

Synthesis of Pyrimido[1,2-*a*]quinoxaline-2,5-dicarbonitrile Derivatives 26−38. *Method A (Microwave Method)*. Compound **1** (2 mmol), in a mixture of aliphatic aldehydes (2 mmol), namely, formaldehyde or acetaldehyde, with malononitrile or ethyl cyanoacetate (2 mmol) or arylidine malononitrile (**21**−**25**) (2 mmol) in ethanol (2−5 drops), was irradiated in an MW oven for an approved time as shown in Table 1; upon completion of the reaction (TLC was used to check the progress), using filtration and drying, the solid precipitate was collected from the reaction mixture after it was cooled to room temperature, using dioxane to crystallize.

Method B (Traditional Method). For 5−7 h, the previous mixture was refluxed into a solution of ethanol (2−5 drops) (TLC). After allowing the reaction mixture to cool to room temperature, by pouring the mixture into ice water that has been acidified with hydrochloric acid, filtration was used to collect the solid precipitate, which was dried and crystallized from dioxane.

*1-Amino-3-phenyl-6H-pyrimido[1,2-a]quinoxaline-2,5-dicarbonitrile (**26**)*. Yield: 85%; color: yellow solid; m.p. 214−216 °C; IR (ATR) cm^{-1}: 3314−3278 (NH_2), 3198 (NH), 3082 (C−$H_{arom.}$), 2221 (CN); ^{1}H NMR: δ 10.82 (s, 1H, NH), 8.14−6.94 (m, 11H, $CH_{arom.}$ + NH_2); ^{13}C NMR δ (ppm): 156.03, 154.35, 141.67, 139.09, 136.56, 135.83, 130.87, 129.27, 129.06, 128.24, 127.71, 127.35, 124.50, 116.57, 112.15; MS, *m*/*z* (%): 324 (M^+, 15); anal. calcd. for $C_{19}H_{12}N_6$ (324.34): C, 70.36; H, 3.73; N, 25.91. Found: C, 70.42; H, 3.78; N, 25.96.

*1-Amino-3-(4-chlorophenyl)-6H-pyrimido[1,2-a]quinoxaline-2,5-dicarbonitrile (**27**)*. Yield: 88%; color: red solid; m.p. 227−229 °C; IR (ATR) cm^{-1}: 3387, 3316 (NH_2), 3187 (NH), 3080 (C−$H_{arom.}$), 2222 (CN); ^{1}H NMR: δ 9.80 (s, 1H, NH), 8.48−6.55 (m, 10H, $CH_{arom.}$ + NH_2); ^{13}C NMR δ (ppm): 155.91, 153.53, 136.26, 134.93, 132.31, 131.04, 129.88, 129.56, 129.38, 129.30, 128.58, 121.36, 117.69, 113.14; MS, *m*/*z* (%): 358 (M^+, 10); anal. calcd. for $C_{19}H_{11}ClN_6$ (358.78): C, 63.60; H, 3.09; N, 23.42. Found: C, 63.53; H, 3.16; N, 23.37.

*1-Amino-3-(4-nitrophenyl)-6H-pyrimido[1,2-a]quinoxaline-2,5-dicarbonitrile (**28**)*. Yield: 86%; color: yellow solid; m.p. 204−205 °C; IR (ATR) cm^{-1}: 3365, 3214 (NH_2), 3184 (NH), 3088 (C−$H_{arom.}$), 2216 (CN); ^{1}H NMR: δ 10.03 (s, 1H, NH), 8.64−6.57 (m, 10H, $CH_{arom.}$ + NH_2); ^{13}C NMR δ (ppm): 137.40, 135.38, 134.08, 131.97, 129.97, 129.91, 129.52, 129.22, 128.78, 127.56, 124.06, 116.24; MS, *m*/*z* (%): 369 (M^+, 30); anal. calcd. for $C_{19}H_{11}N_7O_2$ (369.34): C, 61.79; H, 3.00; N, 26.55. Found: C, 61.84; H, 3.13; N, 26.43.

*1-Amino-3-(4-methoxyphenyl)-6H-pyrimido[1,2-a]quinoxaline-2,5-dicarbonitrile (**29**)*. Yield: 89%; color: brown solid; m.p. 208−210 °C; IR (ATR) cm^{-1}: 3328, 3207 (NH_2), 3188 (NH), 3088 (C−$H_{arom.}$), 2981 (C−$H_{aliph.}$), 2188 (CN); ^{1}H NMR: δ 9.19 (s, 1H, NH), 7.41−6.99 (m, 10H, $CH_{arom.}$ + NH_2), 3.92 (s, 3H, OCH_3); MS, *m*/*z* (%): 354 (M^+, 16); anal. calcd. for $C_{20}H_{14}N_6O$ (354.36): C, 67.79; H, 3.98; N, 23.72. Found: C, 67.83; H, 4.01; N, 3.75.

*1-Amino-3-(4-hydroxyphenyl)-6H-pyrimido[1,2-a]quinoxaline-2,5-dicarbonitrile (**30**)*. Yield: 87%; color: red solid; m.p. 208−210 °C; IR (ATR) cm^{-1}: 3452 (OH), 3339, 3194 (NH_2), 3102 (NH), 3079 (C−$H_{arom.}$), 2209 (CN); ^{1}H NMR: δ 12.95 (s, 1H, OH), 8.99 (s, 1H, NH), 8.04−6.70 (m, 10H, $CH_{arom.}$ + NH_2); ^{13}C NMR δ (ppm): 156.56, 154.28, 150.32, 149.81, 146.97, 146.40, 137.19, 132.37, 132.02, 130.81, 130.34, 128.65, 122.49, 121.62, 119.25; MS, *m*/*z* (%): 340 (M^+, 25); anal. calcd. for $C_{19}H_{12}N_6O$ (340.34): C, 67.05; H, 3.55; N, 24.69. Found: C, 67.08; H, 3.59; N, 24.71.

*3-Amino-6H-pyrimido[1,2-a]quinoxaline-2,5-dicarbonitrile (**35**)*. Yield: 95%; color: green solid; m.p. 146−148 °C; IR (ATR) cm^{-1}: 3435, 3348 (NH_2), 3222 (NH), 3070 (C−$H_{arom.}$), 2205 (CN); ^{1}H NMR: δ 10.21 (s, 1H, NH), 8.12 (s, 2H, NH_2), 7.73−7.18 (m, 5H, Ar); ^{13}C NMR δ (ppm): 151.71, 150.74, 146.43, 137.84, 136.17, 131.66, 130.84, 129.29, 128.10, 122.78, 119.58, 116.91; MS, *m*/*z* (%): 248 (M^+, 35); anal. calcd. for

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$C_{13}H_8N_6$ (248.24): C, 62.90%; H, 3.25%; N, 33.85%. Found: C, 62.84%; H, 3.31%; N, 33.93%.

*3-Amino-1-methyl-6H-pyrimido[1,2-a]quinoxaline-2,5-dicarbonitrile (**36**).* Yield: 90%; color: orange solid; m.p. 162−168 °C; IR (ATR) cm^{-1}: 3362, 3310 (NH_2), 3204 (NH), 3082 (C−$H_{arom.}$), 2217 (CN); ^1H NMR: δ 9.73 (s, 1H, NH), 7.37−6.34 (m, 6H, Ar + NH_2), 3.79 (3H, CH_3); ^{13}C NMR δ (ppm): 149.87, 146.65, 137.44, 134.71, 132.41, 131.99, 130.75, 128.65, 122.89, 122.17, 28.07; MS, *m*/*z* (%): 262 (M^+, 11); anal. calcd. for $C_{14}H_{10}N_6$ (262.26): C, 64.11%; H, 3.84%; N, 32.04%. Found: C, 64.18%; H, 3.78%; N, 31.97%.

*3-Hydroxy-6H-pyrimido[1,2-a]quinoxaline-2,5-dicarbonitrile (**37**).* Yield: 94%; color: reddish brown solid; m.p. 145−147 °C; IR (ATR) cm^{-1}: 3420 (OH), 3216 (NH), 3074 (C−$H_{arom.}$), 2223 (CN); ^1H NMR: δ 10.65 (s, 1H, OH), 10.21 (s, 1H, NH), 7.73−7.18 (m, 5H, Ar + CH); ^{13}C NMR δ (ppm): 157.24, 153.51, 148.09, 140.17, 138.97, 132.56, 130.94, 129.20, 128.83, 124.05, 118.34, 116.47; MS, *m*/*z* (%): 249 (M^+, 16); anal. calcd. for $C_{13}H_7N_5O$ (249.22): C, 62.65%; H, 2.83%; N, 28.10%. Found: C, 62.68%; H, 2.76%; N, 28.16%.

*3-Hydroxy-1-methyl-6H-pyrimido[1,2-a]quinoxaline-2,5-dicarbonitrile (**38**).* Yield: 94%; color: reddish brown solid; m.p. 168−170 °C; IR (ATR) cm^{-1}: 3446 (OH), 3204 (NH), 3063 (C−$H_{arom.}$), 2924 (C−$H_{aliph.}$), 2192 (CN); ^1H NMR: δ 9.78 (s, 1H, OH), 7.87−7.38 (m, 5H, Ar + NH), 3.26 (3H, $CH_{3)}$); ^{13}C NMR δ (ppm): 146.89, 146.36, 137.76, 136.53, 132.11, 131.99, 130.80, 130.13, 129.79, 129.00, 128.04, 126.61, 124.97, 123.71, 21.88; MS, *m*/*z* (%): 263 (M^+,25); anal. calcd. for $C_{14}H_9N_5O$ (263.25): C, 63.87%; H, 3.45%; N, 26.60%. Found: C, 63.94%; H, 3.52%; N, 26.56%.

Insecticidal Bioefficacy Screening. The insecticidal activity was evaluated with the leaf dip bioassay on some synthesized pyrimidine and thiazolidinone derivatives.[81−84] We report here the results of lab testing for the target compounds so that we can determine the concentrations required to kill 50% (LC_{50}) of nymphs and adults of cowpea aphid (*Aphis craccivora*) insects. In this study, five concentrations of pyrimidine and thiazolidinone derivatives were prepared, and a surfactant, 0.1% Tween 80, was used. Similar sizes of 50 nymphs and 50 adults of cowpea aphid (*Aphis craccivora*) insects were dipped for 10 s in every concentration of synthesized target compounds; this was repeated three times. The testing of insects was performed by leaving them to dry at room temperature for about half an hour in which the control samples (the samples were soaked in distilled water and Tween 80) of insects were also utilized. After the used insects had dried, they were transferred to disks (9 cm size) and then left for a 24 h period at 22 ± 2 °C and 60 ± 5% relative humidity. Using a new binocular microscope, the aphid mortality was measured 24 h after the test. Aphids that were unable to move were considered dead. The insecticide bioactivity test of every target compound was repeated twice, and Abbott's formula was used to correct the given data.[85] The measured mortality relapse line was dissected by probit analysis.[86] Sun's equations were used to determine the harmfulness index.[87] The batches of cowpea aphid (*Aphis craccivora*) insects were gathered from bean fields of an agricultural research center farm during the 2021/2022 season.

Docking Study. The crystal structure of acetylcholine cocrystallized with imidacloprid was obtained from the Protein Data Bank (code: 2ZJU).[88] MOE2015.06 was utilized to perform this study for the novel constructed quinoxalines inside acetylcholine-active regions. Imidacloprid was redocked within acetylcholine to validate the docking study, and the RMSD was equal to 1.2785. The constructed quinoxalines' 3D structures were built using the MOE molecular builder; then, these quinoxalines were protonated, energy-minimized, and saved as mdb files followed by docking within acetylcholine applying the previously reported procedures.[89−91]

CONCLUSIONS

In this study, novel thiazolidinones **15**−**20** and pyrimidine derivatives **26**−**30** and **35**−**38** possessing quinoxaline moieties were synthesized, and different spectral techniques were used to identify and confirm their chemical structures. The synthesized compounds were evaluated *in vitro* for their insecticidal potential against *Aphis craccivora*. The synthesized compounds **16**, **20**, and **27** displayed the highest toxicity activity against the tested strains. The 4-chlorophenylthiazolidino derivative **16** was the most toxicological agent against nymphs of cowpea aphids (*Aphis craccivora*) with LC_{50} = 0.021 ppm compared to the other synthesized pyrimidine and thiazolidinone derivatives. The molecular docking study of the new quinoxaline derivatives registered that compound **16** had the highest binding score (−10.54 kcal/mol) and the thiazolidinone moiety formed hydrogen bonds with Trp143.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.2c03332.

Data that support the findings of this study including all IR, ^1H NMR, and ^{13}C NMR spectral data for synthesized compounds (PDF)

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Notes

The authors declare no competing financial interest.

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