Recent advances on the synthesis and pesticidal activity evaluations of quinazoline derivatives

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Abstract: Quinazoline derivatives, an important structure in drug discovery, have attracted increasing attention from the pharmaceutical researchers because of their various pesticidal activities such as antibacterial, antifungal, insecticidal, herbicidal, antiviral and acaricidal activities. Introducing different pharmacophores into quinazoline framework can afford a series of quinazoline derivatives which possesses better pesticidal activities. This paper reviewed the study on the synthesis and pesticidal activities of the quinazoline derivatives from year 2000 to 2016.

Keywords: quinazoline derivative; synthesis; pesticidal activity; recent advances

Quinazoline (Scheme 1) is a fused heterocycle that is of considerable interest because of their diverse pharmacological profile[1]. The first quinazoline derivative was synthesized in the late 1860s by Griess from anthranilic acid and cyanogen to give the 2-cyanoquinazolinone[2-3].

Many substituted quinazoline derivatives have attracted increasing attention because of their widely and distinct pesticidal activities, including antibacterial activity, antifungal activity, insecticidal activity, herbicidal activity, antiviral activity, and so on.

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on, which encouraged the research activity in this area\textsuperscript{[4-5]}. Quinazoline derivatives were used in the preparation of a variety of functional materials for synthetic medicinal chemistry and also presented in some traditional commercially available pesticides including fenazaquin, fluquinconazole, R-768 and pyrifluquinazon (Scheme 2), which were demonstrated to be of high efficiency, low toxicity and low residue. Over the past decade, the synthesis and bioactivity of quinazoline derivatives had become one of the main areas of interest in medicinal chemistry. The purpose of this review was to collate literatures reported by researchers on quinazoline derivatives for their various pesticidal activities. To the best of our knowledge, this is the first review about the pesticidal activities of quinazoline derivatives from year 2000 to 2016.

1 Antibacterial activity

Wang et al.\textsuperscript{[6-7]} designed and synthesized a series of novel (E)-3-(2-arylideneaminoethyl)-2(4-(trifluoromethoxy)aniline)-4(3\textsubscript{H})-quinazolinone derivatives (I) using aminoethyl moiety to increase the amine bridge of quinazolin-4(3\textsubscript{H})-one amine and various aromatic aldehydes were introduced to the structure (Scheme 3). Bioassay results revealed that some of the target compounds exhibited better antibacterial activities against tobacco bacterial wilt, tomato bacterial wilt, and \textit{Xanthomonas oryzae pv. oryzae} (\textit{Xoo}), with 50\% effective concentration (\textit{EC} \textsubscript{50}) values ranging from 63.73 to 201.52 μg/mL, from 38.64 to 93.31 μg/mL, and from 20.09 to 21.33 μg/mL, respectively, which were superior to those of the commercial antibacterial agents thiodiazole copper and bismethiazol. Moreover, preliminary structure-activity relationship (SAR) analysis indicated that the -CH\textsubscript{3}, -NO\textsubscript{2}, -OH, and \textit{N},\textit{N}-di-CH\textsubscript{3} groups on the benzene ring (substituted for R) could enhance the antibacterial activities of the synthesized compounds. These results indicated that novel arylimine derivatives containing the 4(3\textsubscript{H})-quinazolinone moiety can effectively control tobacco and tomato bacterial wils and \textit{Xoo}.

In 2014, using \textit{o}-aminobenzoic acid as the starting material, as shown in Scheme 4, Yang and \textit{et al}.\textsuperscript{[8-9]} synthesized a new series of arylimine derivatives (I) using aminoethyl moiety to increase the amine bridge of quinazolin-4(3\textsubscript{H})-one amine and various aromatic aldehydes were introduced to the structure (Scheme 3). Bioassay results revealed that some of the target compounds exhibited better antibacterial activities against tobacco bacterial wilt, tomato bacterial wilt, and \textit{Xanthomonas oryzae pv. oryzae} (\textit{Xoo}), with 50\% effective concentration (\textit{EC} \textsubscript{50}) values ranging from 63.73 to 201.52 μg/mL, from 38.64 to 93.31 μg/mL, and from 20.09 to 21.33 μg/mL, respectively, which were superior to those of the commercial antibacterial agents thiodiazole copper and bismethiazol. Moreover, preliminary structure-activity relationship (SAR) analysis indicated that the -CH\textsubscript{3}, -NO\textsubscript{2}, -OH, and \textit{N},\textit{N}-di-CH\textsubscript{3} groups on the benzene ring (substituted for R) could enhance the antibacterial activities of the synthesized compounds. These results indicated that novel arylimine derivatives containing the 4(3\textsubscript{H})-quinazolinone moiety can effectively control tobacco and tomato bacterial wils and \textit{Xoo}.

In 2014, using \textit{o}-aminobenzoic acid as the starting material, as shown in Scheme 4, Yang and

\begin{scheme}
\centering
\includegraphics[width=\textwidth]{Scheme_3.png}
\caption{Synthetic route of compound I}
\end{scheme}

\begin{scheme}
\centering
\includegraphics[width=\textwidth]{Scheme_2.png}
\caption{The structures of the traditional commercial pesticides containing quinazoline moiety}
\end{scheme}
Coworkers\(^8\) had synthesized a series of novel 3-(2-hydroxyethyl)-2-(phenylamino)quinazolin-4(3H)-ones derivatives (2) via Wittig reaction. The antibacterial activities of the target compounds \textit{in vitro} against tobacco bacterial wilt were further tested. The bioassay results showed that the antibacterial activities of all the target compounds were lower than that of the reference drug thiodiazole copper.

Later, Yan \textit{et al.}\(^9\) synthesized a series of novel quinazolinone derivatives bearing 4-phenyl-5-thioxo-1,2,4-triazole Mannich bases unit (3) through a five-step synthetic procedure (Scheme 5) and their antibacterial activities against \textit{Xoo} and \textit{Xanthomonas axonopodis pv. citri} (Xac) were evaluated. The preliminary biological test indicated that most of the title compounds had excellent antibacterial activities against \textit{Xoo} and \textit{Xac} at the concentration of 200 μg/mL.

In 2016, Pan \textit{et al.}\(^{10}\) designed and synthesized a series of novel quinazoline-2,4-dione derivatives containing the 1,2,4-triazole Schiff-base unit (4) based on the connection method of active fragments (Scheme 6). The preliminary antibacterial test indicated that all the target compounds possessed excellent inhibition activities (≥93%) against \textit{Xoo} at the concentration of 200 μg/mL, which was significantly better than those of control agents (thiodiazole copper and bismervathiazol). Moreover, all the target compounds exhibited certain inhibition activities against \textit{Xac} but no inhibition activity against...
Ralstonia solanacearum (R. solanacearum). Meanwhile, the antibacterial tests showed that when R substituent group was -OCH$_3$, the corresponding compounds presented better antibacterial activities.

Yan et al.\textsuperscript{[11]} had reported a series of novel quinazolinone derivatives containing a 1,2,4-triazolylthioether moiety (5) (Scheme 7). The preliminary bioassays indicated that some of the target compounds possessed better antibacterial activities against tobacco bacterial wilt, Xoo, and Xac at the concentrations of 200 and 100 μg/mL, respectively, in comparison with the commercial control agents thiodiazole copper and bismethiazol. Especially, 3-((4-phenyl-5-((4-trifluoromethyl)benzyl)thio)-4H-1,2,4-triazol-3-yl)methyl)quinazolin-4(3H)-one (R = 4-CF$_3$-Ph) exhibited the best inhibitory effect against Xoo and Xac, with the EC$_{50}$ values of 47.6 and 22.1 μg/mL, respectively, which were superior to those of the commercial bactericide bismethiazol.

Scheme 7  Synthetic route of compound 5

2  Antifungal activity

Shalaby et al.\textsuperscript{[12]} have reported the synthesis of novel quinazoline derivatives (compounds 6-9) (Scheme 8) and the antifungal activities against Sclerotium...
**cepivorum** and **Botrytis allii** were evaluated on the PDA media. Bioassay results demonstrated that 6,8-dibromo-4-(ethylthio)-2-isopropylquinazoline (R = -C₂H₅) had the greatest growth reduction effect on **S. cepivorum**, resulted in 68%-88% reduction of fungal growth at the test concentrations, but the number of sclerotia was slightly decreased at 20 μg/mL. Meanwhile, 6,8-dibromo-2-isopropyl-3-((4-methoxybenzylidene)amino)quinazolin-4(3H)-one (R = -N = CH-C₆H₄-4-OCH₃) and 6,8-dibromo-2-(2-hydroxypropan-2-yl)quinazolin-4(3H)-one (9, X = O, Z = -OH) exhibited 57%-65% and 40%-39% reduction in number of sclerotia, respectively, and a moderate reduction on the fungus growth.

Ding *et al.*[^13^] synthesized a series of novel 2-alkoxy-3H-quinazolin-4-ones (10) by a new synthetic method which included aza-Wittig reaction (**Scheme 9**) and subsequent reaction and their antifungal activities against **Pellicularia sasakii**, **Cercospora asparagagas**, **Physalospora piricola**, **Gibberella zeae**, and **Fusarium oxysporum** were investigated at the concentration of 50 μg/mL. The results showed that most of the target compounds exhibited good fungicidal activities. Especially, 2-ethoxy-(p-tolyl)quinazolin-4(3H)-one (Ar = 4-CH₃-Ph, R = Et) demonstrated better antifungal activities against **P. sasakii** with the inhibition rate of 89%.

In 2004, as shown in **Scheme 10**, a rapid one-pot solvent-free procedure had been developed by Dandia *et al.*[^14^] for the synthesis of fluorinated 2,3-disubstituted quinazolin-4(3H)-ones (11) by neat three-component cyclocondensation of anthranilic acid, phenyl acetyl chloride and substituted anilines under microwave irradiation conditions. Their antifungal activities against **Rhizoctonia solani**, **F. oxysporum** and **Colletotrichum capsici** were screened.

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[^13^]: Ding *et al.*.[^13^]

[^14^]: Dandia *et al.*.[^14^]
at the concentrations of 1,000 and 500 μg/mL. Bioassay results showed that 2-phenylmethyl-3-(3-trifluoromethylphenyl)-quinazolin-4(3H)-one (R = 3-CF$_3$) exhibited better antifungal activity against *R. solani*. Meanwhile, 2-phenylmethyl-3-(2-fluorophenyl)-quinazolin-4(3H)-one (R = 2-F) was demonstrated to have the best antifungal activity against *F. oxysporum* and *C. capsici*.

As shown in Scheme 11, Liu and coworkers$^{[15]}$ synthesized a series of novel *N*-aryl-4-aminoquinazoline derivatives (12) by the reaction between 4-chloroquinazoline and arylamines. And their antifungal activities were also determined. The results showed that the new compounds had certain antifungal activities against *Exserohilum turcicum* at the concentration of 500 μg/mL. Among the compounds evaluated, compound 12c showed the best antifungal activity against *E. turcicum* with the inhibition rate of 56.07%.

In 2006, a simple, efficient, and general method had been developed by Ouyang *et al.*$^{[16]}$ for the synthesis of various 3-alkylquinazolin-4-one derivatives (13) from quinazolin-4-one treated with alkyl bromides under phase transfer catalysis condition. The antifungal activities against *F. oxysporum*, *G. zeae*, and *Valsa mali* of the all the synthesized compounds were evaluated at the concentration of 50 μg/mL. Bioassay results showed that the target compounds displayed good *in vitro* antifungal activities. Especially, 6-chloro-3-ethylquinazolin-4-one (X = Cl, R = Et) showed excellent antifungal activity against *G. zeae*, with the inhibition rate of 55.0%, which was better than that of hymexazol (50.4%).

Xu *et al.*$^{[17]}$ synthesized a series of novel *s*-substituted 6-fluoro-4-alkyl(aryl)thioquinazoline derivatives (14) and their antifungal activities were determined. Preliminary bioassay tests showed that some compounds possessed antifungal activities on three phytopathogenic fungi at 500 μg/mL *in vitro*. 
Further bioassays disclosed that 4-ethylthio-6-fluoroquinazoline (R = Et) showed remarkable inhibitory effect on nine kinds of plant pathogenic fungi of *G. zeae*, *F. oxysporum*, *Cytospora mandshurica*, *R. solani*, *Thanatephorus cucumeris*, *Sclerotina sclerotiorum*, *Botrytis cinerea*, and *Colletotrichum gloeosporioides*, with the EC$_{50}$ values of 12.4, 18.2, 19.2, 24.9, 30.8, 26.8, 11.4, 8.3 and 64.2 μg/mL, respectively. Bioassays results showed that 4-ethylthio-6-fluoroquinazoline had broad-spectrum and excellent antifungal activities against most of the tested fungi.

In 2008, Jatav *et al.* [18] synthesized a series of novel 3-(5-substituted phenyl-1,3,4-thiadiazole-2-yl)-2-styryl quinazoline-4(3H)-ones (15) and their antifungal activities against *F. oxysporum* were evaluated via the cup-plate method. Bioassay results showed that some of the target compounds exhibited weaker antifungal activity against *F. oxysporum* comparable to that of clotrimazole.

Scheme 14  Synthetic route of compound 15

Liu *et al.* [19] synthesized a series of 4-thioquinazoline derivatives (16). The results of bioassay showed that some of the target compounds had good antifungal activities against *Fusarium graminearum*, *F. oxysporum*, and *C. mandshurica*.

Especially, 4-(allylthio)quinazoline (R$^1$ = H, R$^2$ = allyl) exhibited good antifungal activity against *F. graminearum*, *F. oxysporum* and *C. mandshurica*, with the EC$_{50}$ values of 25.88, 17.08 and 28.77 μg/mL, respectively, which were superior to those of hymexazol.

Scheme 15  Synthetic route of compound 16

Ma *et al.* [20] synthesized a series of novel 6-bromo-4-alkylthioquinazoline derivatives (17) by the reaction of 6-bromo-4-thiolquinazoline with alkylhalide under the conditions of phase-transfer catalysis. Bioactivities of all the synthesized compounds were tested against *F. graminearum*, *C. mandshurica* and *F. oxysporum*. The preliminary bioassay showed that 6-bromo-4-((2-ethoxyethyl)thio)quinazoline (R = -CH$_2$OC$_2$H$_5$) had certain antifungal activities against *F. graminearum*, *C. mandshurica* and *F. oxysporum* with inhibition rates of 63.8%, 51.9% and 55.1% at the concentration of 50 μg/mL, respectively, which were similar as that of hymexozole.

In 2011, Liu and Huang [21] reported the antifungal activity of 6-bromo-4-ethoxyethylthio quinazoline (18) on plant pathogenic fungi via mycelial growth rate method. The bioassay results showed that the title compound possesses weaker antifungal activity on *G. zeae*, *F. oxysporum*, *C. mandshurica*, *R. solani*, *T. cucumeris*, *S. sclerotiorum*, *B. cinerea*, *P. infestans* and *C. gloeosporioide*, with
EC_{50} values ranging from 17.47 to 70.79 μg/mL, compared with thiophanate methyl.

Using 4-chloroquinazoline, ethyl 3-amino-4-pyrazolecarboxylate and aromatic aldehyde as starting materials, Gao and coworkers \[22\] synthesized a series of novel quinazoline derivatives containing hydrazone moiety (19) and their antifungal activities against \textit{G. zeae} and \textit{C. mandshurica} \textit{in vitro} were evaluated. In particular, (\textit{E})-\textit{N}(2,3-dichlorobenzylidene)-3-(quinazolin-4-ylamino)-1H-pyrazole-4-carbohydrazide (\(R = 2,3\)-di-Cl-Ph) showed the best antifungal activity against \textit{G. zeae}, with the inhibition rate of 62.86%, which was even better than that of hymexazol (53.95%). The SAR results indicated the addition of electron withdrawing groups to benzene ring at R substituent group could increases the antifungal activity.

In 2011, An \textit{et al.} \[23\] synthesized a series of novel dihydrazonylquinazoline derivatives (20) and their fungicidal activities against the \textit{G. zeae}, \textit{F. oxysporum} and \textit{C. mandshurica} were evaluated. The preliminary bioassay showed that some of the target compounds possessed certain fungicidal activities at the concentration of 50 μg/mL.

Bao \textit{et al.} \[24\] synthesized a series of novel quinazolinone derivatives containing 1,2,4-triazolyl-thioether moiety (21) by coupling method of active fragments and their antifungal activities against \textit{G. zeae}, \textit{F. oxysporum}, \textit{P. infestans}, \textit{P. sasaki}, \textit{C. mandshurica} and \textit{R. solani} were evaluated. The results showed that the target compounds had certain antifungal activities against the tested fungus at 50 μg/mL \textit{in vitro} which were lower than those of carbendazim.

Using 3-methyl-4-amino-1,2,4-triazole-5-thione, aromatic aldehydes and 4-chloroquinazoline as starting materials, a series of novel quinazoline derivatives containing 1,2,4-triazole Schiff-base unit
were synthesized by Liu et al.\cite{25}. The antifungal activities of the synthesized compounds were evaluated. The preliminary bioassay showed that some of the target compounds possessed certain fungicidal activities against *G. zeae*, *F. oxysporum*, *P. infestans*, *P. sasakii*, *C. mandshurica* and *R. solani*. Among the title compounds, \((E)-3\text{-methyl-}N-(4\text{-methylbenzylidene})-5\text{-(quinazolin-4-ylthio)}-4H\text{-1,2,4-triazol-4-amine}\ (Ar = 4\text{-CH}_3\text{-Ph})\) exhibited good antifungal activities against *G. zeae*, *F. oxysporum*, *P. infestans* and *C. mandshurica*, with the inhibition rates of 50\%, 71\%, 58\% and 72\%, respectively, which were lower than those of carbendazim.

In 2013, as shown in Scheme 22, a series of novel \(N^3\)-substituted quinazolin-4-one (23) were synthesized by alkyl bromide and quinazolin-4-one, catalyzed by various 3-methylimidazole ionic liquids and TBAB\cite{26}. Their *in vitro* antifungal activity against *F. graminearum*, *F. oxysporum* and *C. mandshurica* were evaluated. Especially, \(N^3\)-allylquinazolin-4-one (\(R = \text{allyl}\)) inhibited *F. graminearum*, *F. oxysporum* and *C. mandshurica* with EC\(_{50}\) values of 28.85, 24.68 and 37.67 μg/mL, respectively. Unfortunately, other tested compounds exhibited low antifungal activities against the tested fungus.

Ou et al.\cite{27} reported a series of novel 2,3-disubstituted quinazolin-4(3H)-ones (24) and their antifungal activities against *F. oxysporum*, *C.
arachidicola, Botryosphaeria berengeriana (B. berengeriana), Alternaria tenuis Nees (A. tenuis), F. graminearum, Phytophthora capsici Leonian (P. capsici), S. sclerotiorum, B. cinerea, R. solani, and P. infestans were investigated. The results showed all the target compounds displayed good antifungal activities against each of the test fungi. Meanwhile, the results of bioactivity assay showed that 2-butyl-3-(3-fluorobenzyl)quinazolin-4(3H)-one (R₁ = H, R₂ = n-Butyl, R₃ = 3-F-Ph) exhibited excellent control efficiency (99.0%) on wheat powdery mildew (Blumeria graminis) in vivo at the concentration of 200 μg/mL, which was similar as that of difenoconazole (99.0%).

Later, El-Hashash et al. [28] synthesized a series of novel 6-iodoquinazolin-4(3H)-one derivatives (25). The fungicidal activities against F. oxysporum and Alternaria alternate of the target compounds were preliminarily evaluated. Bioassay results demonstrated that the target compounds showed excellent activities against the tested fungus at the concentration of 1 and 0.5 mg/mL, which were even better than that of cycloheximide. 

Zeng et al. [29] reported a series of novel 4(3H)-quinazolinone derivatives containing Schiff base moiety (26). The preliminary bioassay data showed that the final compounds exhibited certain fungicidal activities. Phomopsis mangiferae Ahmad was sensitive to most of the compounds. In particular, (E)-7-chloro-3-((2,4-dichlorobenzylidene)amino)ethyl)-2-(phenylamino)quinazolin-4(3H)-one (R = 2,4-di-Cl-Ph) showed potential antifungal activity against Corynespora cassicola and Phomopsis mangiferae with the inhibition rates of 26.21% and 98.18%, respectively, which were similar as that of the fungicide chlorothalonil (25.64% and 100%, respectively) at the concentration of 100 μg/mL. The SAR revealed that electron-withdrawing groups were favorable for improving antifungal activities of the title compounds.

In 2016, Zhang et al. [30] synthesized a series of novel quinazolinone derivatives containing an amide moiety, as shown in Scheme 26, via one-pot method and their in vitro antifungal activities against four plant pathogens including P. capsici, C. gloeosporioides, V. mali and Alternaria alternate were screened. The results showed all the compounds
displayed certain antifungal activities against the tested fungi. Interesting, \((E)-3-((4\text{-methoxybenzyl)}\) amino)-2-styryl-2,3-dihydroquinazolin-4(1\(H\))-one (\(R_1 = \text{o-OCH}_3\text{-Ph-CO-}, R_2 = \text{styryl}\)) exhibited the best bioactivity against \(P.\ capsici\), \(C.\ gloeosporioides\) and \(A.\ alternate\), with the MIC values of 32, 32 and 64, respectively, which were same as those of ketoconazole (32, 32 and 64, respectively).

### 3 Antiviral activity

Gao et al.\(^{[31]}\) developed a simple and general method to synthesize a series of 2-aryl- or 2-methyl-3-\((\text{substituted-benzalamino})\)-4(3\(H\))-quinazolinone compounds (28) and their antiviral activities against tobacco mosaic virus (TMV) were evaluated. Bioassay results showed that the target compounds were found to possess moderate to good anti-TMV activities. Especially, at the concentration of 500 \(\mu\text{g/mL}\), 2-methyl-3-\((2,3\text{-dichlorobenzalamino})\)-4(3\(H\))-quinazolinone (\(R = \text{H}, R_1 = 2,3\text{-di-Cl}, R_2 = \text{Me}\)) have relatively higher curative activity (55.4%) than those of the other target compounds and ningnanmycin (53.5%).

Gao et al.\(^{[32]}\) reported a series of novel quinazolinone derivatives containing Schiff base moiety (29) and their anti-TMV activities at the concentration of 500 \(\mu\text{g/mL}\) were evaluated. Bioassay results showed that the target compounds exhibited...
moderate to good anti-TMV activities. Especially, 3-((2-hydroxy-5-nitrobenzylidene)amino)-2-methylquinazolin-4(3H)-one (R = 5-NO₂) has relatively good curative activity (51.5%) which was same as that of ningnanmycin (53.9%).

Luo et al. [33] reported a simple synthesis of new (quinazolin-4-ylamino) methylphosphonates via microwave irradiation (30) and their antiviral activities against TMV at 500 μg/mL were evaluated. Bioassay results indicated that the title compounds showed moderate to good curative activities against TMV with the values ranging from 30.1% to 52.0%. Among the title compounds, diethyl (2-fluorophenyl) (6-fluoroquinazolin-4-ylamino)methylphosphonate (R¹ = 2-F, R² = 6-F, R³ = Et) exhibited slightly similar curative activity (52.0%) compared to the commercial agent of ningnanmycin (55.9%).

Wang et al. [34] synthesized a series of novel quinazolinone derivatives (31) and their antiviral activities against TMV were determined. Most of the synthesized compounds also exhibited good anti-TMV activities. Especially, N-(4-fluorobenzyl)-2-(4-
fluorophenyl)-5-methoxy-3-methyl-4-oxo-1,2,3,4-tetrahydroquinazoline-6-carboxamide (R = 4-F-Ph) showed similar in vivo inactivation activity against TMV (30.4%) to that of the commercial plant virucide ribavirin (34.2%).

In 2013, two new 4(3H)-quinazolinone compounds (32 and 33) were isolated from a marine fungus *Penicillium oxalicum* 0312F1 by Shen and coworkers.\(^{[34]}\) and their anti-TMV activities were evaluated. Bioactivity assays showed that 2-(4-hydroxybenzyl) quinazolin-4(3H)-one (33) had potent inhibitory activity against TMV, with an EC\(_{50}\) value of 100.80 μg/mL, which was lower than that of ribavirin (65.32 μg/mL).

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Luo et al.\(^{[36]}\) have reported a series of novel (1E,4E)-1-aryl-5-(2-(quinazolin-4-yloxy)phenyl)-1,4-pentadien-3-one derivatives (34). Antiviral bioassays indicated that most of the compounds exhibited promising in vivo antiviral bioactivities against TMV and CMV. Especially, (1E,4E)-1-(4-chloro-3-nitrophenyl)-5-(4-(quinazolin-4-yloxy)phenyl)penta-1,4-dien-3-one (R\(_1\) = H, R\(_2\) = 4-Cl-3-NO\(_2\)-Ph) possessed appreciable curative activity against TMV, with an EC\(_{50}\) value of 352.0 μg/mL, which were even better than that of ningnanmycin (437.6 μg/mL). Meanwhile, (1E,4E)-1-(4-fluorophenyl)-5-(4-(6-methylquinazolin-4-yloxy)phenyl)penta-1,4-dien-3-one (R\(_1\) = 6-CH\(_3\), R\(_2\) = 4-F-Ph) exhibited better protection activity against TMV, with an EC\(_{50}\) value of 243.3 μg/mL, which were even better than that of ningnanmycin (370.8 μg/mL).

Ma et al.\(^{[37]}\) designed and synthesized a series of novel 3-((2-((1E,4E)-3-oxo-5-arylpenta-1,4-dien-1-yl)phenoxy)methyl)-4(3H)-quinazolinone derivatives (35). Antiviral bioassays indicated that some of the target compounds exhibited higher antiviral activities against TMV in vivo than that of the commercial agent ningnanmycin. In particular, 3-((2-((1E,4E)-5-(2-methoxyphenyl)-3-oxopenta-1,4-dien-1-yl)phenoxy)methyl)quinazolin-4(3H)-one (R\(_1\) = H, R\(_2\) = 2-OCH\(_3\), X = 2-O) possessed appreciable curative activity on TMV in vivo, with an EC\(_{50}\) of 132.25 μg/mL, which was superior to that of ningnanmycin (281.22 μg/mL), which suggested that novel 4(3H)-quinazolinone derivatives are promising candidates as potential antiviral agents.

![Scheme 31 The structures of compounds 32 and 33](image1)

![Scheme 32 Synthetic route of compound 34](image2)
quinazolinone derivatives containing 1,4-pentadien-3-one moiety can effectively control TMV.

In 2014, Xiao and coworkers[38] synthesized a series of β-amino acid ester derivatives containing quinazoline and benzothiazoles (36) and their antiviral activities against TMV were evaluated. The results of bioassays showed that some of the target compounds exhibited good curative and protection activity against TMV. Especially, dimethyl 2-(((6-chlorobenzo[d]thiazol-2-yl)amino)(4-((7-chloroquinazolin-4-yl)oxy)phenyl)methyl)malonate (R = 7-Cl, R¹ = -Cl, R² = -CH₃) showed good curative activity against TMV at the concentration of 500 μg/mL, with the inhibition rate of 55.55%, which was close to that of the commercially available antiviral agent ningnanmycin (55.27%). Meanwhile, diethyl 2-(((6-chlorobenzo[d]thiazol-2-yl)amino)(4-((7-chloroquinazolin-4-yl)oxy)phenyl)methyl)malonate (R = 7-Cl, R¹ = -Cl, R² = -C₂H₅) exhibited better protection activity against TMV at 500 μg/mL, with an inhibition rate of 55.96%, which was even better than that of ningnanmycin (52.16%).

Later, Wan et al.[39] reported a series of novel 4-thioquinazoline derivatives containing chalcone moiety (37) and their antiviral activities against TMV were systematically evaluated. Bioassay results showed that most of these compounds exhibited moderate to good anti-TMV activities. In particular, (E)-1-(4-(2-(quinazolin-4-ylthio)ethoxy)phenyl)-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-one (R = 4-CF₃-)

\[ R^1 = -Cl, R^2 = -C₂H₅ \]
Ph) possessed appreciable protection activity against TMV \textit{in vivo}, with the EC$_{50}$ value of 138.1 μg/mL, which was superior to that of ribavirin (436.0 μg/mL).

In 2015, Long \textit{et al.} \cite{40} designed and synthesized a series of novel 1,4-pentadien-3-one derivatives containing 4-thioquinazoline moiety (38). Antiviral bioassay results indicated that most of the title compounds exhibited excellent antiviral activities against TMV and CMV \textit{in vivo}. Among the title compounds, (1\text{E},4\text{E})-1-(4-(trifluoromethoxy)phenyl)-5-(4-(2-((8-methylquinazolin-4-yl)thio)ethoxy)phenyl)-1,4-pentadien-3-one (R$_1$ = 8-CH$_3$, R$_2$ = 4-OCF$_3$-Ph) exhibited the best curative activity against TMV, with the EC$_{50}$ value of 213.5 μg/mL, which was better than that of ningnanmycin (270.9 μg/mL).

\begin{scheme}
\includegraphics[width=\textwidth]{scheme_35.png}
\caption{Synthetic route of compound 37}
\end{scheme}

\begin{scheme}
\includegraphics[width=\textwidth]{scheme_36.png}
\caption{Synthetic route of compound 38}
\end{scheme}
quinazolin-4(3H)-one moiety (39) and their antiviral activities against CMV were evaluated. Results indicated that some of the title compounds exhibited better antiviral activities against CMV. Notably, dimethyl-2-(1-(4-nitrophenyl)-3-oxo-3-(4-((4-oxoquinazolin-3(4H)-yl)methoxy)phenyl)propyl)malonate (Ar = 4-NO2-Ph, R = Me) exhibited excellent curative activity in vivo against CMV, with the EC50 value of 153.78 μg/mL, respectively, which was better than those of ningnanmycin (256.35 μg/mL) and ribavirin (523.34 μg/mL).

4 Insecticidal activity
In 2013, Zhou et al. prepared a series of novel 2,3-dihydroquinazolin-4(1H)-one derivatives (40) and their insecticidal activities against oriental armyworm (Mythimna separata) were evaluated. Bioactivities indicated that most of the compounds showed moderate to high activities at the test concentrations. In particular, 2-(3-bromo-1-(3-chloropyridin-2-yl)-1H-pyrazol-5-yl)-6-chloro-3,8-dimethyl-2,3-dihydroquinazolin-4(1H)-one (R1 = H, R2 = 6-Cl-8-CH3, X = Br, Y = Cl)
showed 80% larvicidal activity against oriental armyworm at the concentration of 5 μg/mL.

Wu et al.\cite{43} reported a series of 6,8-dichloroquinazoline derivatives bearing a sulfide group (41) and their insecticidal activities against *Plutella xylostella* *in vitro* were tested. The bioassay results indicated that the synthesized compounds possessed good insecticidal activities. Among the title compounds, 6,8-dichloro-4-(((6-chloropyridin-3-yl)methyl)thio)quinazoline (R = 6-Cl-Py-CH₂⁻) exhibited better insecticidal activity against *P. xylostella*, with a death rate of 85% at 500 μg/mL, which was lower than that of chlorpyrifos (100%).

Li et al.\cite{44} designed and synthesized a series of novel quinazoline derivatives containing 1,1-dichloropropene moiety (42) and their insecticidal activities against beet armyworm, bollworm, diamondback moths and *Prodenia litura* were evaluated. Bioassays showed that all of the target compounds displayed good insecticidal activities against *P. litura* at the test concentrations.

In 2016, Venugopala and coworkers\cite{45} designed and synthesized methyl 4-(4-chlorophenyl)-8-iodo-2-methyl-6-oxo-1,6-dihydro-4\textsubscript{H}-pyrimido[2,1-b]quinazoline-3-carboxylate (43) and their insecticidal activities against *Anopheles arabiensis* Mosquito were evaluated. Bioassay results showed that higher concentrations of compound 43 (2 and 4 μg/mL) exerted significantly higher mortality (both 100%) than that of the positive control temephos (71.4% and 73.9% at 24 and 48 h, respectively). The positive control K-othrine showed 100% knockdown/mortality from the first 30 min of exposure, while compound 43 killed 70% of the mosquitoes after 24 h of exposure to the highest concentration of 2 μg/mL.

5 Herbicidal activity

Li et al.\cite{46} designed and synthesized 1-methyl-3-(7-fluoro-4-(prop-2-ynyl)-2H-benzo[b]\textsuperscript{1,4}-oxazin-3(4H)-one-6-yl)-2,4(1H,3H)-quinazolinenedione (44) and its herbicidal activity under greenhouse condition was determined. The biological test demonstrated that compound 44, as shown in Scheme 42, exhibited good herbicidal activity to broadleaf weeds at 38 g ai/ha.

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**Scheme 39** Synthetic route of compound 41

**Scheme 40** Synthetic route of compound 42

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Aibibuli and coworker\textsuperscript{[47]} reported a series of novel 2-phenoxy-3\textit{H}-quinazolin-4-ones derivatives (45). The herbicidal evaluation was performed on the model plants barnyard grass (a monocotyledon) and rape (a dicotyledon) and bioassay results showed that the target compounds generally exhibited comparatively lower herbicidal activities. 

Wang\textit{ et al.}\textsuperscript{[48-50]} designed and synthesized a series of novel triketone derivatives containing quinazoline-2,4-dione motif (46) and herbicidal activities against \textit{Echinochloa crus-galli}, \textit{Setaria faberii}, \textit{Digitaria sanguinalis}, \textit{Amaranthus retroflexus}, \textit{Eclipta prostrata}, and \textit{Abutilon juncea in vivo} were evaluated. The greenhouse testing indicated that many of the newly synthesized compounds showed good or excellent herbicidal activities against broadleaf and monocotyledonous weeds at the dosages of 37.5-150 g ai/ha. The SAR in this study indicated that the target compounds had possessed great impact on herbicide activities and may be used for further optimization. Among the compounds evaluated, 3-(2,4-dichlorophenyl)-6-(2-hydroxy-4-methyl-6-oxocyclohex-1-enecarbonyl)-1-methylquinazoline-2,4(1\textit{H},3\textit{H})-dione (R\textsubscript{1} = 5-CH\textsubscript{3}, R\textsubscript{2} = H, R\textsubscript{3} = 2,4-di-Cl, R\textsubscript{4} = H) displayed a broader spectrum of weed control (inhibition > 85\%) at concentrations of 150, 75 and 37.5 g ai/ha.

![Scheme 41 Synthetic route of compound 43](image)

![Scheme 42 The structure of compound 44](image)

![Scheme 43 Synthetic route of compound 45](image)
addition, 3-(2,4-dichlorophenyl)-6-(2-hydroxy-4-methyl-6-oxocyclohex-1-enecarbonyl)-1-methylquinazoline-2,4(1H,3H)-dione (R\(^1\) = 5-CH\(_3\), R\(^2\) = H, R\(^3\) = 2,4-di-Cl, R\(^4\) = H) also demonstrated comparatively superior crop selectivity to mesotrione, thus possessing great potential for weed control in the field. Meanwhile, the results of greenhouse experiments showed that 1-ethyl-6-(2-hydroxy-6-oxocyclohex-1-enecarbonyl)-3-(o-tolyl)quinazoline-2,4(1H,3H)-dione (R\(^1\) = H, R\(^2\) = H, R\(^3\) = 2-CH\(_3\), R\(^4\) = Et) exhibited 100% control against both the selected monocotyledon weeds and the selected dicotyledon weeds at a concentration of 75 g ai/ha. And even at a dosage as low as 37.5 g ai/ha it still displayed very strong herbicidal activity (inhibition > 90%) against five of the six weeds tested. In addition, it was also demonstrated to be selective for maize (injury < 10%) by post-emergence application at a dosage of 150 g ai/ha, suggesting its potential for weed control in maize fields.

6 Acaricidal activity

In 2000, Lamberth \textit{et al.}\[51\] synthesized compound 47 and its acaricidal activity against \textit{European red mite} and \textit{Panonychus ulmi} was determined. Bioassay results showed that, 8-10 days after the treatment, compound 47 showed good contact activity against \textit{European red mite} with the LC\(_{95}\) value of 2 ng/mL.
Meanwhile, field trials also indicated that compound 47 has an appreciable control efficiency of 100% against *European red mite* at 5-10 g ai/ha.

### 7 Conclusions

In this review, the recent development in the synthesis and pesticidal activities, including antibacterial, antifungal, insecticidal, herbicidal, antiviral, and acaricidal activity of quinazoline derivatives from year 2000 to 2016 was included. Investigations over the last few years have revealed that the quinazoline derivatives exhibited a wide variety of pesticidal activities. SAR analysis results showed that at the presence of C=N or triazolyl at 2- or 3-position of quinazoline framework, the corresponding compounds presented good antibacterial activities. Meanwhile, 4-thioquinazoline derivatives displayed better antifungal activities. Moreover, the antiviral activity test demonstrated that the presence of Schiff base group at the 3-position of quinazoline framework, and at the presence of phosphoramidate or chalcone group at 3-position of quinazoline framework, the corresponding compounds were demonstrated to have excellent antiviral activities. In addition, introducing pyrazole group to the quinazoline framework could increase the insecticidal activity. The quinazoline derivatives should provide an excellent starting point for the further investigation. During the last years, a number of research groups have reported a variety of synthetic approaches to biologically active natural/synthetic quinazoline derivatives. In conclusion, quinazoline chemistry has a very rich past to its credit and a very bright present, coupled with a highly promising future from both the theoretical study and application point of view.

### References:


[46] LI B, LIU Z L, XU J D, et al. The synthesis and herbicidal activity of 1-methyl-3-[7-fluoro-4-(prop-2-ynyl)-2H-benzo[b][1,4]oxazin-3(4H)-one]-2-methyl-3-


