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QUINAZOLINE-CHALCONE HYBRID: DIFFERENT SYNTHETIC SCHEMES AND BIOLOGICAL ACTIVITIES –A REVIEW

Priyanka Bobde*, L. A. Kawale and Darshana Patil

Department of Pharmaceutical Chemistry, M.V.P Samaj's College of Pharmacy, Nashik, India.

***Corresponding Author: Priyanka Bobde**
Department of Pharmaceutical Chemistry, M.V.P Samaj's College of Pharmacy, Nashik, India.

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ABSTRACT
Quinazolines are important class of six membered heterocyclic compounds: are widely found as the core scaffold in a large variety of compounds that possess important biological activities like anti-inflammatory, antihypertensive, anticancer, anticonvulsant, antibacterial, antitubercular, antifungal, antiviral, antidepressant, antidiabetic and analgesic. On other hand chalcone is part of flavonoids and isoflavonoids. Chemically it is 1,3 diaryl-2-propan-1-one. It is made up of two aromatic ring joined together by three carbon bridge having carbonyl moiety and α, β unsaturation. Chalcone are synthesized by Claisen Schmidt condensation of aldehyde and ketone in equimolar concentration. It has various biological activities like antibacterial, antifungal, anti-inflammatory, antihyperglycemic, anti-HIV and anticancer. Quinazoline-chalcone hybrids show potent biological activities and solve drug resistance problem. Also avoid combinational therapy. The present review focus on the different schemes of synthesis and biological activities of quinazoline-chalcone hybrid.

KEYWORDS: Quinazoline-chalcone hybrid, Claisen-Schmidt condensation, heterocyclic compound, anticancer, CNS-activity, antimicrobial activity.

INTRODUCTION

Heterocyclic chemistry is very important of synthetic organic chemistry, covering wide variety of bioactive molecules. Among six membered heterocycles, quinazoline have important position and is generally found in a wide variety of natural product, synthetic pharmaceutical molecule and natural product. [1]

Quinazoline is benzopyrimidine derivative made up of two six membered ring benzene and pyrimidine fused together known as 1, 3 diazine. It was first prepared in 1903 by Gabriel. Most commonly used heterocyclic compound is quinazoline, because wide range of biological and pharmacological activities.[2] They have following biological activities-

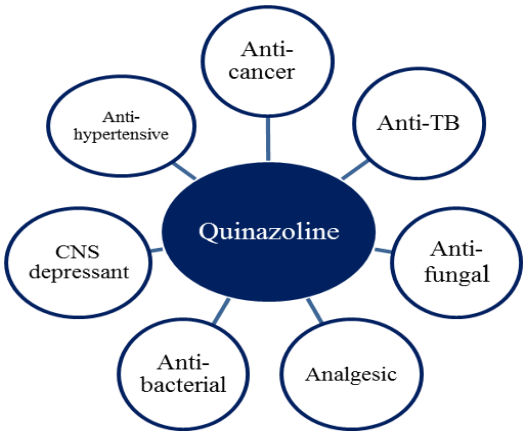
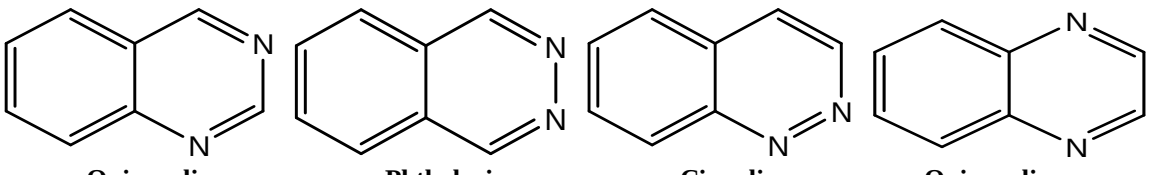


Fig 1: Biological Activities of Quinaziline.

Quinazoline is a class of bicyclic ring system benzene ring fused with two nitrogen containing aromatic ring such as pyrimidine, pyrazine, pyridazine. These are the isomer of quinazoline.



Quinazoline **Phthalazine** **Cinnoline** **Quinaxaline**

Fig 2. Quinazoline Isomer.

Chalcone are major class of flavonoids because of their wide spectrum biological activities such antimicrobial, anticonvulsant, anticancer, antioxidant, anti-inflammatory, antiviral and antimalarial activity.[3] Chalcone synthesized by Claisen-Schmidt condensation of substituted aldehyde and substituted ketone.[4] The general structure of chalcone are-

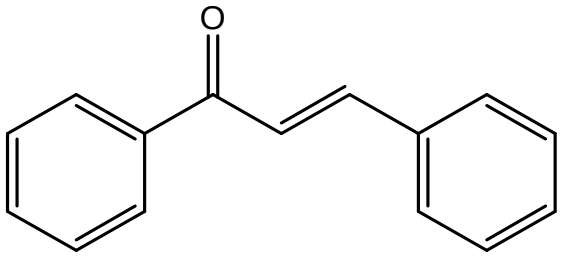


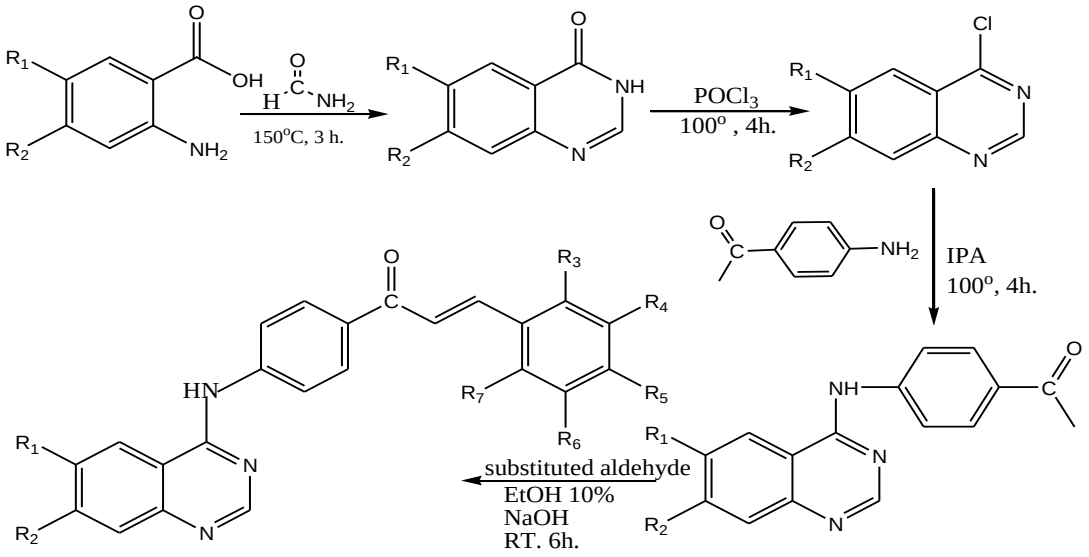
Fig 3. Structure of Chalcone.

Hybrid drug concept arises from combination therapy. Combination of quinazoline and chalcone improve the biological activities of the drugs.[4] The hybrid of quinazoline and chalcone solve drug resistance, lack of selectivity and side effects of other drugs like problem. Also avoid combination therapy.[5]

DIFFERENT SCHEMES OF SYNTHESIS

The wide range of biological activities associated with quinazoline-chalcone hybrid. Various methods developed for the preparation of substituted quinazoline bearing a chalcone moiety. In this review discuss about different scheme for synthesis of quinazoline-chalcone hybrid.

Thiriveedhi A*et al* reported the synthesis of quinazoline chalcone derivatives. The chalcone prepared by the Claisen-schmidt condensation of substituted benzaldehyde with substituted 1-(4-(3, 4-dihydroquinazoline-4-ylamino phenyl) ethanone. Firstly prepared 4-chloro quinazoline from anthranillic acid and formamide then replace chloro group with 4-amino acetophenone. This reaction is called as nucleophillic displacement reaction.[5]

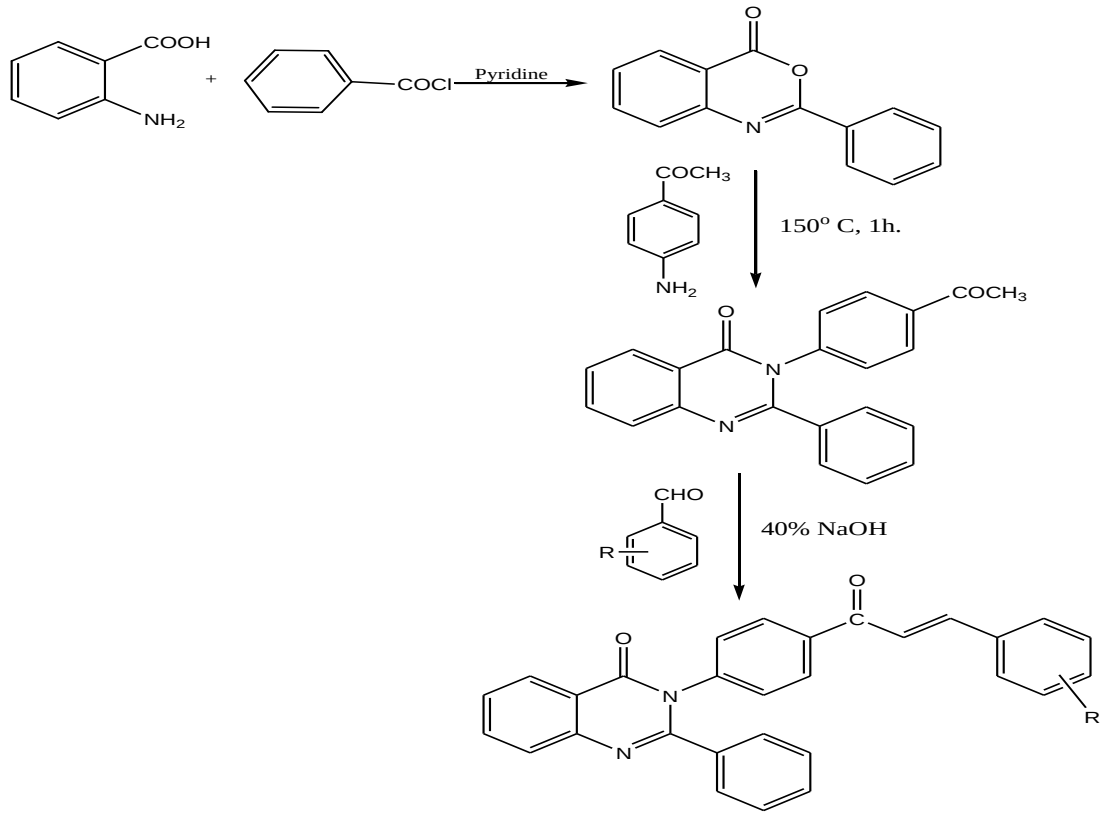


a-r

SCHEME 1

a = R_1=R_2=H, R_5=F, R_3=R_4=R_6 =R_7=H
b = R_1=R_2=H, R_5=CF_3, R_3=F, R_4=R_6 =R_7=H
c = R_1=R_2=H, R_5=F, R_4= Cl, R_3=R_6 =R_7=H
d = R_1=R_2=H, R_5=OCH_3, R_4=F,R_3=R_6 =R_7=H
e = R_1=R_2=H, R_3=R_5=OCH_3, R_4=R_6 =R_7=H
k = R_1=R_2=H, R_4=R_5=OCH_3, R_3=R_6 =R_7=H
l=R_1=R_2=OCH_3,R5=OCH_3,R_4=F,R_3=R_6=R_7=H
m= R_1=R_2=OCH_3, R_3=R_5=OCH_3,R_4=R_6 =R_7=H
n=R_1=R_2=OCH_3, R_4=R_5=OCH_3,R_3=R_6=R_7=H
f= R_1=R_2=H, R_4=R_6=OCH_3, R_3=R_5 =R_7=H
g=R_1=R_2=H, R_3=R_5=R_7=OCH_3, R_4=R_6=H
h= R_1=R_2=H, R_4=R_5=R_6=OCH_3, R_3=R_7=H
i=R_1=R_2=OCH3, R_5=F,R_3=R_4=R_6 =R_7=H
j= R_1=R_2=OCH_3, R_5=CF_3,R_3=F,R_4=R_6 =R_7=H
o= R_1=R_2=OCH_3, R_5=F,R_4=Cl, R_3=R_6 =R_7=H
p=R_1=R_2=OCH_3, R_4=R_6=OCH_3,R_3=R_5=R_7=H
q=R_1=R_2=OCH_3, R_3=R_5=OCH_3,R_4=R_6=H
r=R_1=R_2=OCH3, R_4=R_5=R_6=OCH_3,R_3=R_7=H

Rao GS *et al*prepared a series of 3-phenyl substituted quinazolinone derivative via chalcone by using anthranillic acid and benzoyl chloride.[6]

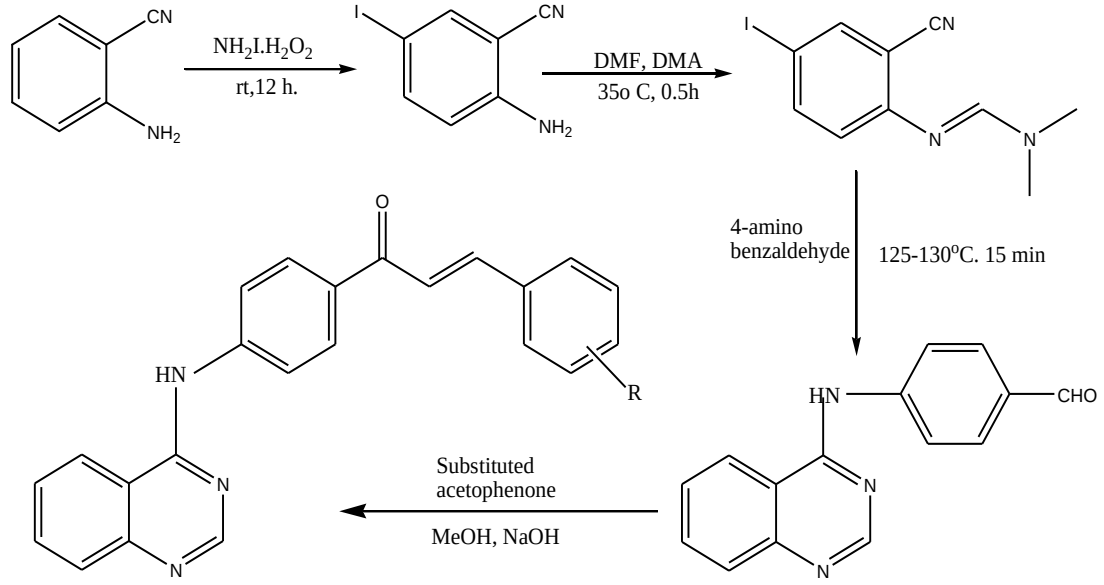


Q_1-Q_4

SCHEME 2.

Q_1 - R= p-chloro Q_3 – R= p-Methyl
Q_2 – R= p-Nitro Q_4 – R= p-Methoxy

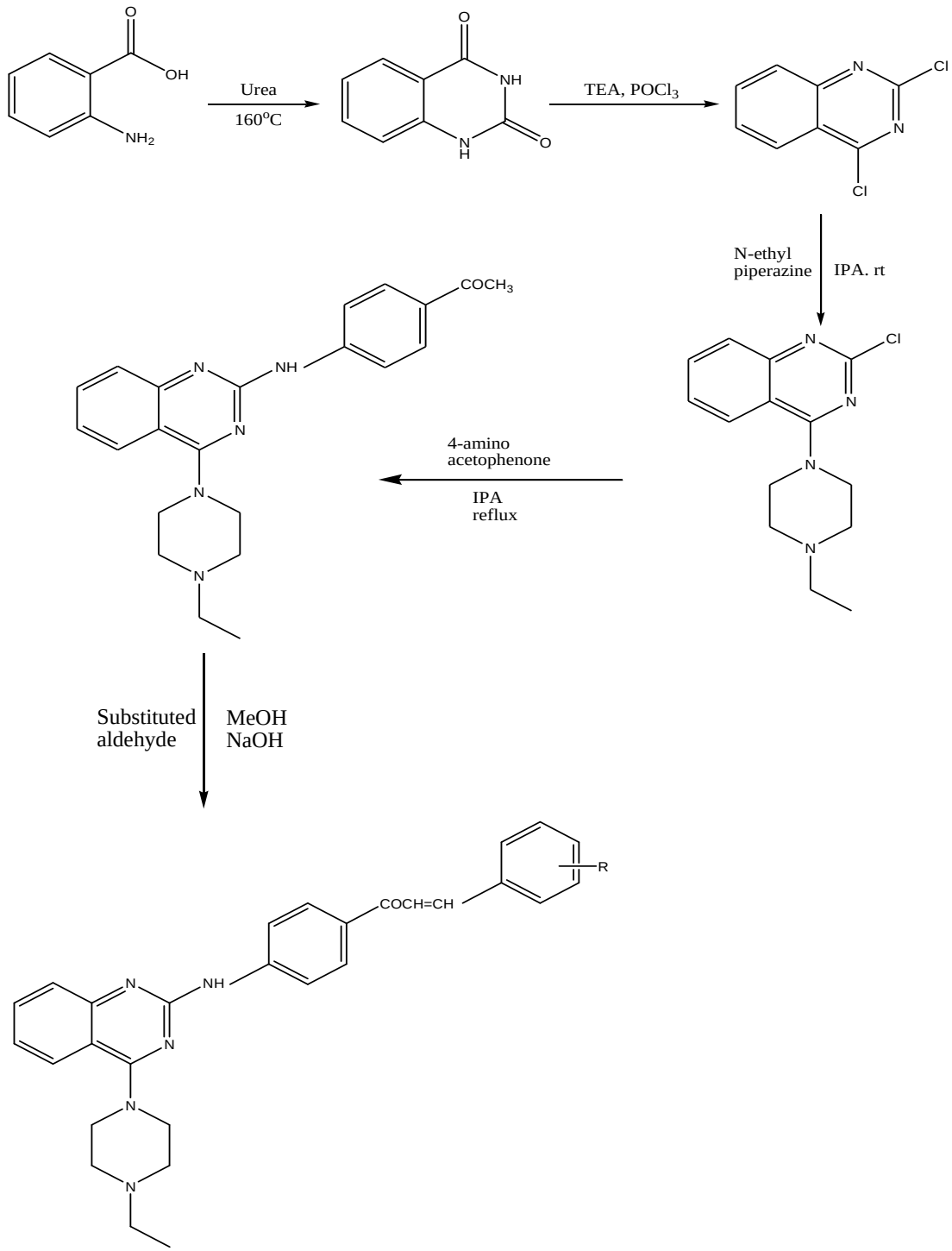
Zhang Y *et al* synthesized quinazoline from 2-aminobenzonitrile.[7] The 4-aminobenzaldehyde linked with quinazoline then reacts with substituted acetophenone obtained quinazoline-chalcone hybrid.[9]



SCHEME 3.

R=H R=2-fluoro 4-trifluoromethyl
R=3-Chloro R=4-Trifluoromethyl
R=4-Chloro R=3-fluoro
R=4-Bromo R=3,4-dimethoxy
R=3-Bromo R= 4-methoxy

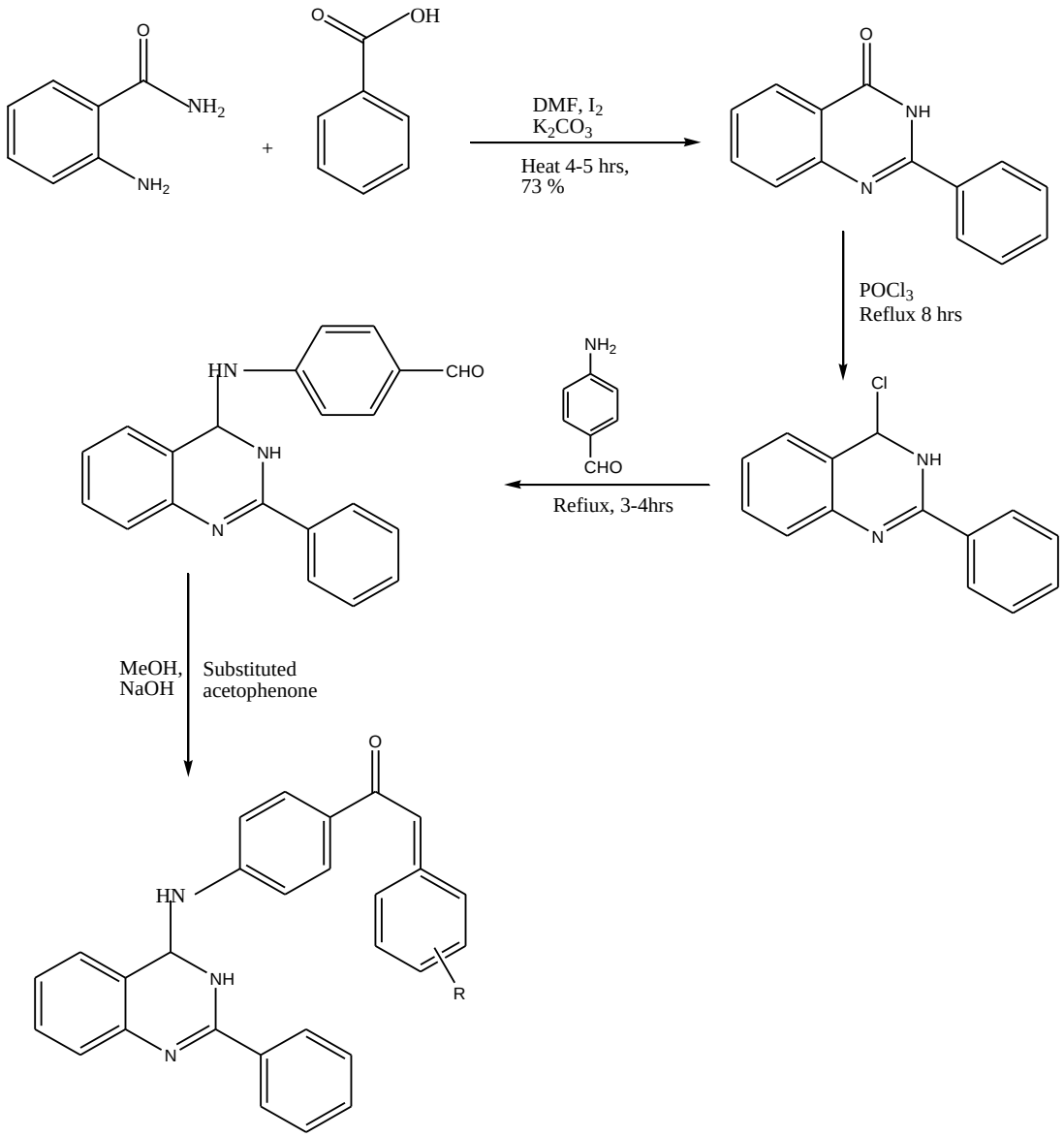
ShahDR *et al*synthesized quinazoline by using anthranillic acid and urea. Then substitution of chalcone by Claisen Schmidt condensation.[8,9]



SCHEME 4.

R=H	R=2-fluro-4-trimethyl
R=3-Chloro	R=4-trifluoromethyl
R=4-Chloro	R=3=fluoro
R=4-Bromo	R=3,4 dimethoxy
R=3-Bromo	R=4=methoxy

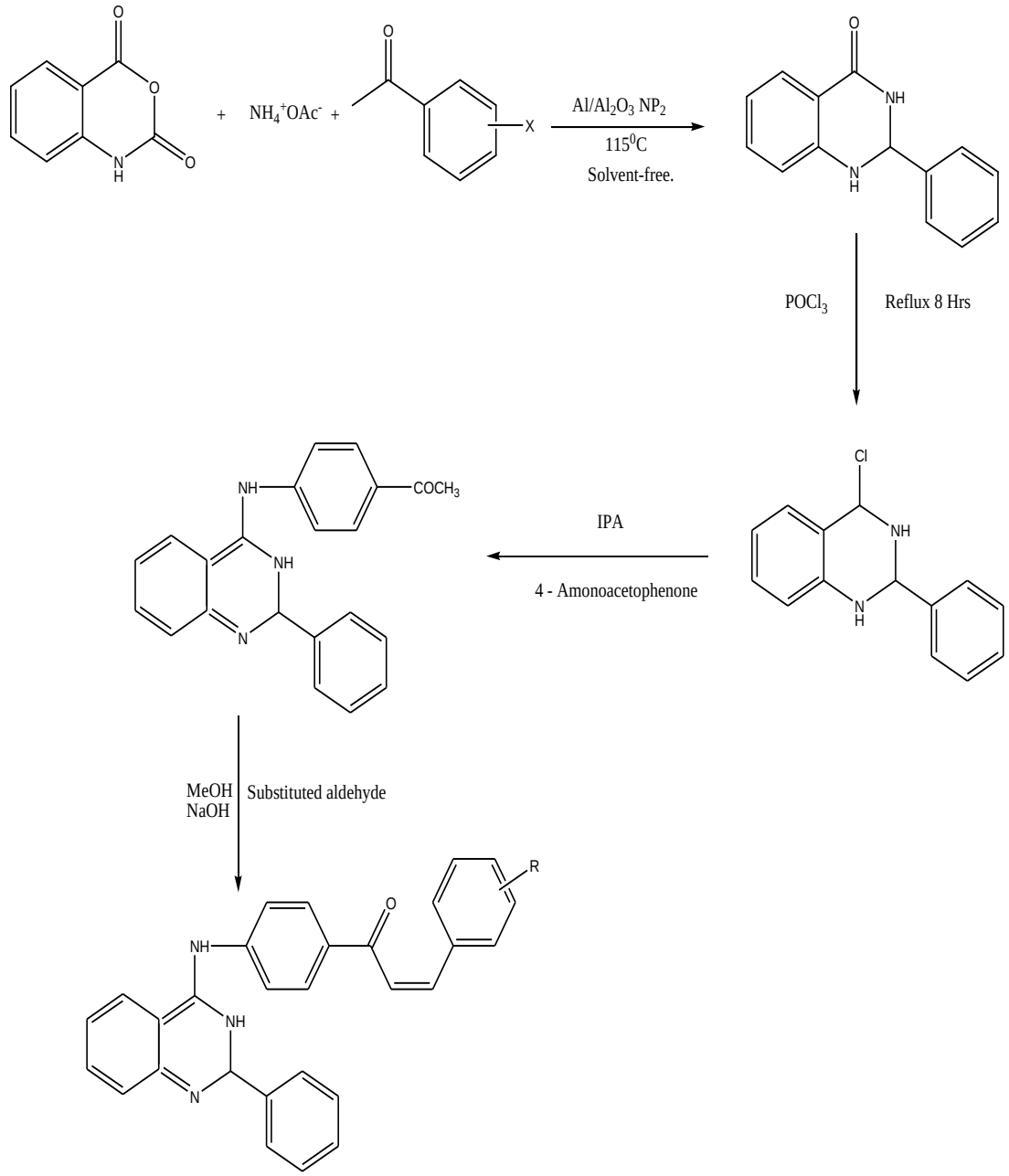
Madhavi S *et al* synthesized chalcone incorporated quinazoline derivatives.In this reaction2-phenylquinazolinefirstlypreparedfromanthranillicacidandbenzaldehydeinpresence of $k_2Cr_2O_7$ then chalcone prepared by claisen - schemide condensation by addition of 4 - aminobenzalidehyde at position 4 of 2 -phenyl quinozaline .[10]



SCHEME 5.

R=H R=3-Chloro
R= 4-Chloro R= 3-Fluoro
R= 4-Bromo R= 3,4-dimethoxy
R= 3-Bromo R= 4-methoxy
R = 2-fluro-4-trifluoromethyl

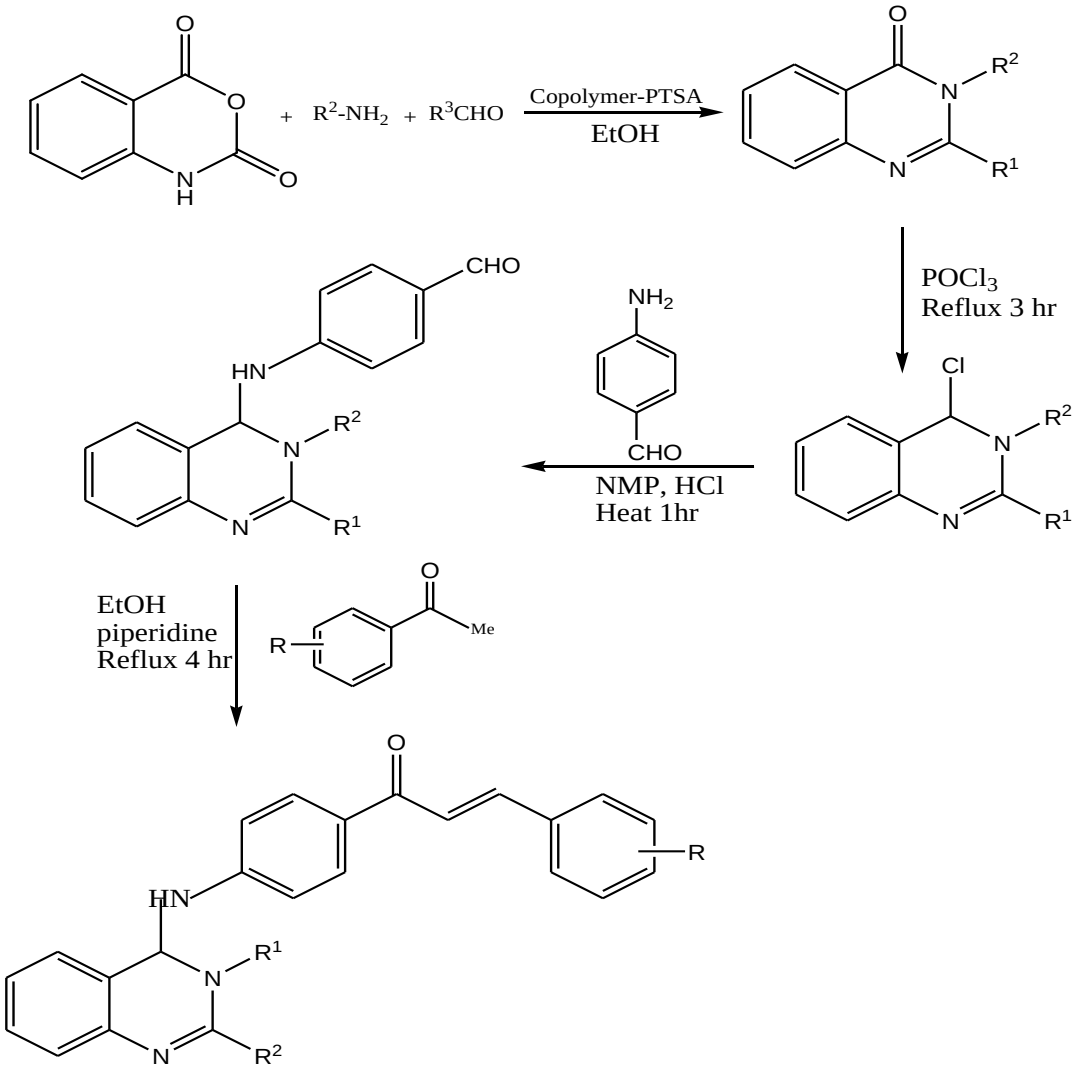
Kassaee MJ *et al*synthesized 2-phenyl-2,3-dihydro quinazoline-4(1H)-onevia Al/Al_2O_3 then incorporation of Chalcone by Claisen-Schmidt condensation.[7,10,11]



SCHEME 6.

R=3- Chloro	R=3-Bromo
R=4-Chloro	R=4-Bromo
R=3,4-Dimethoxy	R=3-Methoxy
R=2-fluoro-4-trifluoromethyl	R=3-fluoro

Teluri A *et al* Synthesized 2,3 substituted quinazoline from isatoicunhydride then substitution of 4-aminobenzaldehyde at 4-position of quinazoline. The substituted quinazoline reacts with acetophenone form a chalcone.[10,12]



SCHEME 7.

R	R_1	R_2
3-Chloro	Me	Ph
4-Chloro	Me	4-Cl C_6H_4
4-Bromo	Et	Ph
3-Bromo	Et	4-Cl C_6H_4
2-fluoro-4-trifluoromethyl	Ph	Ph
3-Fluoro	Ph	4-Cl C_6H_4
3,4-dimethoxy	Ph	4-Cl C_6H_4
3-methoxy	Ph	4-Cl C_6H_4

Biological Activities of Quinazoline-Chalcone

Quinazoline, chalcone and their derivatives were evaluated for various biological activities by several researchers. The hybrid of both compounds helpful in increasing biological activities and decreases the resistance of drug. Here we are presenting several biological activities of quinazoline-chalcone hybrid and their derivatives.

1. Antibacterial activity

Development of new antibacterial agent with novel chemical scaffolds and new mechanism of action is vital due to increasing bacterial resistance to traditional antibiotics such as Penicillin and Tetracyclin. Quinolone antibacterials have broad spectrum of in vitro activity and in vivo chemotherapeutics efficacy.[2] But current quinolones suffer from various drawbacks such as limited activities against clinically important gram positive such as *Streptococcus pneumonia, Streptococcus pyrogens, Staphylococcus aureus* and *enterococcus*, low activity against anaerobes and increasing quinolones resistance. To avoid these problems quinazoline-chalcone play important role. Quinazoline ring shows antibacterial activity is reported. The substitution at 3-position of quinazoline increases the antimicrobial activity.[6] Chalcone is also reported for antibacterial activity. The substitution of chalcone at third position of quinazoline increases antibacterial activity of drug and reduces the side effect.[13]

2. Anticancer activity

Cancer is one of the most serious problem in world and its rises in developing countries. Surgical operation, irradiation and chemotherapt still remain option for cancer management. So, development of new anticancer agent required.[5] Quinazoline and chalcone derivatives

reported as anticancer activity. Quinazoline linked chalcone evaluated for different type of human cancer such as lung, leukemia, melanoma, ovarian, renal, prostate and breast cancer.[10] The quinazoline linked chalcone exhibit wide spectrum activity against different cell line.[14]

3. Anticonvulsant activity

Epilepsy is common neurological disorder affect people of all ages. Approximately 50 million people worldwide have epilepsy. Current available anticonvulsants have undesirable side effects. Therefore, continued search of new and safer anticonvulsants is necessary.[9] Most frequently encountered heterocyclic is quinazoline which have diverse pharmacological activities. Substitution of methyl group at 2 position and substituted aromatic ring at 3 position shows antidepressant and anticonvulsant activity.[15] Also, Chalcone possess anticonvulsant activity is reported. The hybrid of quinazoline- chalcone increases anticonvulsant activity and avoid combinational therapy.[16]

4. Antifungal activity

IFIs (Invasive fungal infection) are often life threatening and associated with high mortality in immunocompromised hosts such as patients in AIDS and patient undergoing organ transplants or anticancer therapy.[17] Available antifungal agents are polyene and azoles. These antifungal agents suffered from narrow spectrum, low bioavailability, limited efficacy, high toxicity and severe drug resistance.[18] To overcome these disadvantages, need to discover new antifungal agent. Among the all heterocyclic molecule quinazoline is important because of their broad-spectrum activity. Quinazoline active against Candia, *Aspergillus*, and *Cryptococcus* species.[19] Chalcone has various biological activities such as antifungal, anticonvulsant, anticancer etc. The quinazoline-chalcone hybrid reduces IFIs and side effects of current antifungal drugs.[20]

CONCLUSION

Quinazoline moiety and its derivative studied commonly in past time and found potent in various biological activities. Also, chalcone and its derivative studied and found potent for various biological activities. The hybrid of both drug exhibit synergistic effect compares to the individual pharmacophores and avoid multidrug therapy. This article mainly focused on quinazoline-chalcone hybrid and its derivatives and briefly discussed about synthetic strategies and their biological activities. This review useful to the researchers for new synthetics approach and biological activities of new molecule.

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