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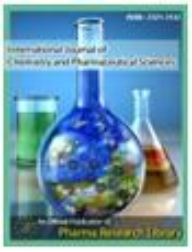

R E V I E W A R T I C L E

Synthesis of Some Substituted Quinazoline Moieties: A Review

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A B S T R A C T

Quinazoline is an aza derivative of the quinoline, it is also known as 1,3-diazanaphthalene. It has broad spectrum of activity which are anti-inflammatory, anti-bacterial, anti-microbial, anti-HIV, anti-cancer, and many more due to these biological effects it has drawn more interest in synthesis and derivatization of this moiety as much as possible. As the quinazoline is a promising molecule we have focused on the synthesis of this moiety by various ways.

Keywords: Quinazoline, quinazolinone, quinazolone.

A R T I C L E I N F O

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C O N T E N T S

1. Introduction

Quinazoline 4-one ring system has been consistently rewarded as a promising molecule because of its broad spectrum pharmaceutical activity. The quinazoline skeleton appears in many alkaloids, most commonly in the form of 4-(3H)-quinazolinone [1]. The quinazolinone moiety is an important pharmacophore showing many types of pharmacological activities. Like benzodiazepines, the quinazolines are considered to be a privileged structure for drug development [2-4]. Aromatic quinazolines have been shown to possess tyrosine kinase inhibiting effects, useful to inhibit tumor growth [5]. Quinazoline is a bicyclic compound consisting of a pyrimidine system fused at 5, 6 with benzene ring having broad spectrum of medicinal values such as anti bacteria[13] anti fungal[14,15

] anti cancer[16,17],anti-inflammatory [18-22], antiviral [23], anti tuberculosis [24], CNS depressant activity[25], Anti-parkinsonism[26-28], bronchodilator activity[29] etc.

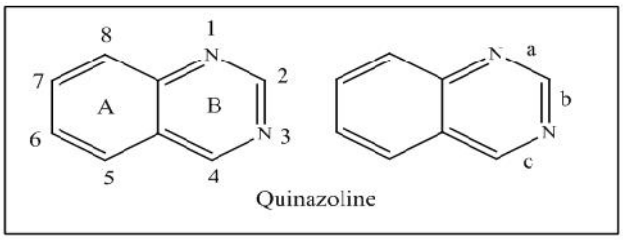

Figure1: Chemical structure of quinazoline

2. Synthesis

A number of methods for the synthesis of quinazolines are known [30-34]. We found basic types of synthetic strategies for the synthesis of substituted quinazolines:

I. Condensation of Anthranilic acid and amides

Quinazolin-4-(3H)-one analogues were prepared by the reaction between anthranilic acid, acid chloride and primary amine.

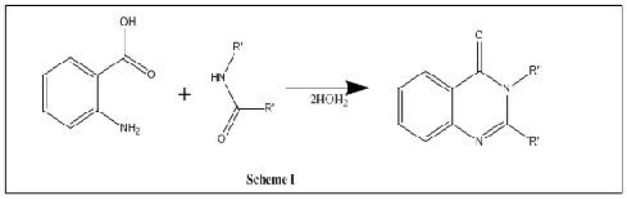

Figure 2: Scheme I

The 4-(3H)-quinazolinones are the formal condensation products of Anthranilic acid and amides, and they can also be prepared in this fashion through the Niementowski quinazolinone synthesis [45].

II. Condensation of Anthranilic acid acetyl chloride and aniline/3-aminophenol/ ethylamine / methylamine to give 2, 3-di-substituted quinazolinone: Equimolar amount of Anthranilic acid, acetyl chloride and aniline/3-aminophenol/ ethylamine / methylamine were placed in 150 ml two necked flask. The mixture was refluxed by microwave irradiation in scientific microwave oven at reflux temperature (power input: 560 W, 9P) for 07 min/ for 10 min/ for 10 min/for 10 min, gives the product quinazolinone. [46]

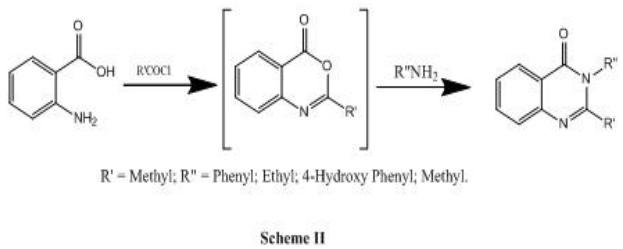

Figure 3: Scheme II

III.Synthesis of 2- [6- bromo- 2- phenyl- 4- oxoquinazolin- 3(4H)- yl]- N- substituted acetamide

5-Bromoanthranilic acid [I] (0.1mol) was dissolved in excess of freshly distilled benzoyl chloride and heated under reflux for 4 hrs. The excess of benzoyl chloride was distilled-off under reduced pressure. The compound obtained on cooling was repeatedly washed with small portions of pet. Ether (60º-80ºC) to get a color less crystalline solid [II]. 6-Bromo 2-phenyl 1, 3, 4-benzoxazinone [II] (0.01mol) and glycine ethyl ester (0.01mol) are taken in a round bottom flask then pyridine (freshly distilled and dried) was added slowly while shaking. The mixture was heated under refluxed for 8 hrs. Excess of pyridine was distilled off under reduced pressure, then the solution was poured into a beaker contained crushed ice, to get the product. It was filtered under suction, washed with portions of ice cold water and dried at 100ºC. The product was purified by recrystallisation with ethanol to get a colorless crystalline solid[III].Ethyl [6-bromo-2-phenyl-4-oxoquinazolin-3(4H)-yl] acetate [III] (0.01 mol) and corresponding primary amines (0.01 mole) are taken in a round bottom flask then glacial acetic acid was added slowly while shaking. The mixture was heated under refluxed for 4-6 hrs. After cooling, the contents were poured into crushed ice. The resulting solid was washed with distilled water, filtered, dried in vaccum and recrytallized from warm ethanol [IV].[47]

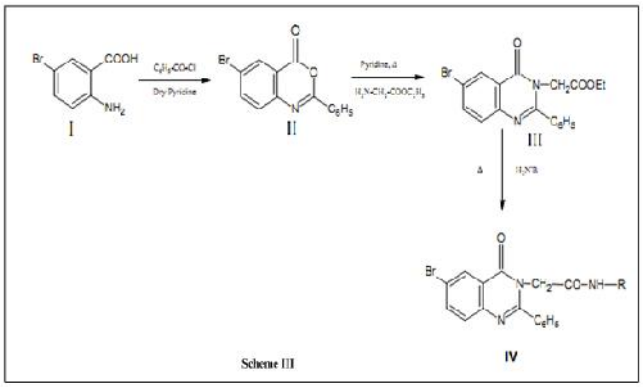

Figure 3: Scheme IV

IV. Condensation of substituted benzothiazole with 2-[(chloroacetyl) amino] benzoic acid: The reaction of substituted benzothiazole with 2-[(chloroacetyl) amino] benzoic acid to get 2-(chloromethyl)-3-(6-substituted-1, 3-benzothiazole-2-yl) quinazoline-4(3H)-one (IIa-d). By treating IIa-d with different substituted amines to get (IIIa1-a4 – IIId1-d4)O-Amino benzoic acid is reacted with chloroacetyl chloride in the presence of benzene to form 2[(chloroacetyl) amino] benzoic acid (I) which on reaction with different substituted benzothiazole in the presence of toluene and PCl5 gives 2-(chloromethyl) 3[6(substituted) 1,3-benzothiazole–2-yl] quinazoline-4(3H)-ones (2a-d)which were later treated with different substituted amine to yield 2-(amilomethyl)-3-(6-substituted-1, 3-benzothiazole-2-yl) quinazolin-4 (3H)-ones (Scheme 1).

(IIIa1) 2-(Anilinomethyl)-3-(6-methyl-1, 3-benzothiazol-2-yl) quinazolin-4(3H)-one

(IIIa2) 3-(6-Methyl-1,3-benzothiazol-2-yl)-2-{[(4-methyl phenyl)amino]methyl} quinazolin-4(3H)-one

(IIIa3) 2-{[(4-Methoxyphenyl) amino] methyl}-3-(6-methyl-1, 3-benzothiazol-2-yl) quinazolin-4(3H)-one
(IIIa4) 2-{[(4-Chlorophenyl) amino] methyl}-3-(6-methyl-1, 3-benzothiazol-2-yl) quinazolin -4(3H)-one
(IIIb1) 2-(Anilinomethyl)-3-(6-methoxy-1, 3-benzothiazol-2-yl) quinazolin-4 (3H)-one
(IIIb2) 2-(-(4-Methyl) anilinomethyl)-3-(6-methoxy-1,3-benzothiazol-2-yl)quinazolin -4 (3H)-one
(IIIb3 2-(-(4-Methoxy) anilinomethyl)-3-(6-methoxy-1, 3-benzothiazol-2-yl) quinazolin-4 (3H)-one
(IIIb4)2-{[(4-Chlorophenyl)amino] methyl}-3-(6-methoxy-1, 3-benzothiazol-2-yl) quinazolin-4(3H)-one
(IIIc1)2-(Anilinomethyl)-3-(6-chloro-1,3-benzothiazol-2-yl)quinazolin-4(3H)-one
(IIIc2)3-(6-Chloro-1,3-benzothiazol-2-yl)-2-{[(4-methyl phenyl) amino] methyl} quinazolin-4(3H)-one
(IIIc3)3-(6-Chloro-1,3-benzothiazol-2-yl)-2-{[(4-methoxy phenyl) amino] methyl} quinazolin-4(3H)-one
(IIIc4)3-(6-Chloro-1, 3-benzothiazol-2-yl)-2-{[(4-chlorophenyl) amino] methyl} quinazolin-4(3H)-one
(IIId1)2-(Anilinomethyl)-3-(6-fluoro-1,3-benzothiazol-2-yl) quinazolin-4(3H)-one
(IIId2)3-(6-Fluoro-1, 3-benzothiazol-2-yl)-2-{[(4-methyl phenyl) amino] methyl} quinazolin-4(3H)-one
(IIId3) 3-(6-Fluoro-1, 3-benzothiazol-2-yl)-2-{[(4-methoxyphenyl) amino] methyl} quinazolin-4(3H)-one
(IIId4) 2-{[(4-Chlorophenyl) amino] methyl}-3-(6-fluoro-1, 3-benzothiazol-2-yl) quinazolin-4(3H)-one

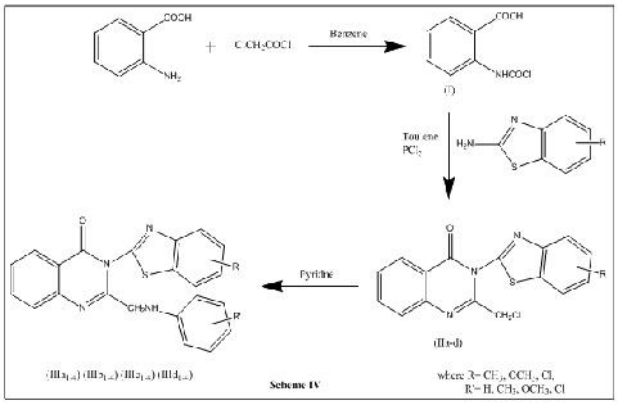

Figure 3: Scheme V

VI. Condensation of the corresponding 2-amino-N-phenylthiobenzamides with acetone: 2,2-Dimethyl-3-phenyl-1,2-dihydroquinazoline-4(3H)-thiones (1a-k) were synthesized by condensation of the corresponding 2-amino-N-phenylthiobenzamides with acetone under the catalysis by silica gel. The reaction mixtures were allowed to stand at room temperature for 24 h, then concentrated in vacuo, and the products 1 were isolated by column chromatography on silica gel using petroleum ether with acetone as the mobile phase. The starting 2-amino-N-phenylthiobenzamides were prepared by a two-step process from 2-amino-N-henylbenzamides. Treatment of 2-amino-N-phenylbenzamide with phosphorus decasulfide in pyridine afforded the corresponding pyridinium salt. Hydrolysis of the pyridinium salt in a toluene-water system gave 2-amino-N-phenyl thiobenzamide [49]. 2-Methyl-3-phenyl quinazoline-4(3H)-thiones (2a-g) were prepared by thionation of the corresponding 2-methyl-3-phenylquinazolin-4(3H)-ones with phosphorus decasulfide in pyridine. The syntheses are outlined in Scheme 1. The characteristic data of compounds 1a-k and 2a-g are given in Tables 1 and 2. Characteristic data of the intermediates were [50] or will be published elsewhere.

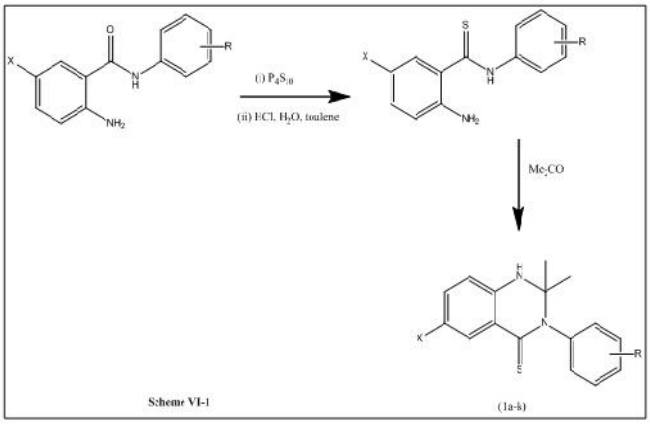

Figure 7: Scheme VI- 1

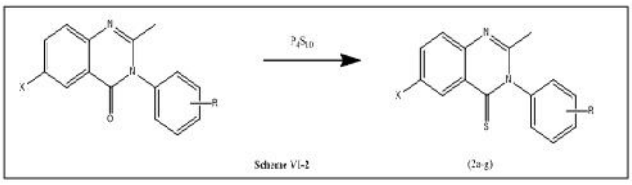

Figure 8: Scheme VI- 2

Efficient methods for synthesis of quinazolin-4-ones are e.g. acylation of 2-aminobenzamides with an appropriate acyl chloride followed by cyclization in basic medium [51], or one-pot synthesis under solvent-free conditions [52].

VII. Synthetic o-chlorobenzoic acid with amines:
Synthetic efforts started from o-chlorobenzoic acid (I). Amination (II), esterification, followed by reaction with isocyanates resulted in 1, 3-disubstituted quinazol-2, 4-diones (III).

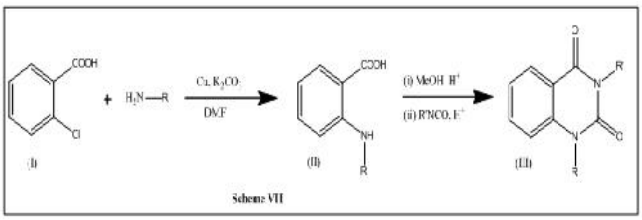

Figure 9: Scheme VII

VIII. Synthesis from 1-methyl-benzoxazin-2, 4-Dione:
Alternately synthesis starts from 1-methyl-benzoxazin-2, 4-dione (I) in two steps. Primarily, reaction of 4-aminobutyric acid resulted in 4-(2-(methylamino) benzamido) butanoic acid (II) followed by cyclisation resulted in a product (III) (4-(1-methyl-2, 4-dioxo-1, 2-dihydroquinazolin-3(4H)-yl)butanoic acid). Reactions are given in Scheme-2.

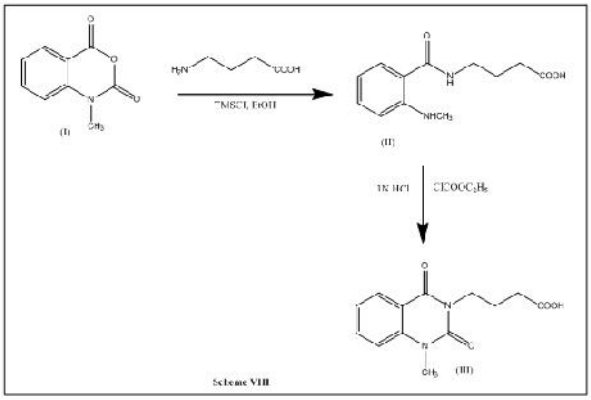

Figure 10: Scheme VIII

IX. Condensation of o-aminobenzonitrile:
O-aminobenzonitrile undergoes reduction in presence of alcohol/ raney nickel further reacts with furanaldehyde to give 2-(furan-2-yl)-1, 2-dihydroquinazolin-4-amine (I) Typical example has been outlined in Scheme 5.

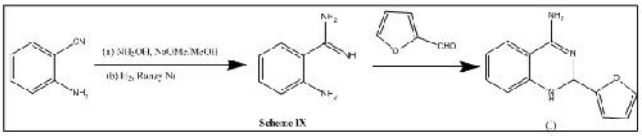

Figure 11: Scheme IX

X. Reaction of 2-azido-4-chlorobenzoic acid 19 with benzyl nitrile: The reaction of 2-azido-4-chlorobenzoic acid (I) with benzyl nitrile resulted into 7-chloro-3-phenyl-[1, 2, 3] triazolo [1, 5-a] quinazolin-5(4H)-one (II) in a single step. The reaction is outlined in Scheme 6.

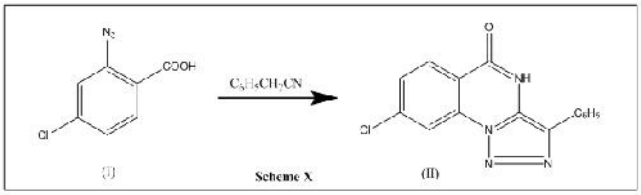

Figure 12: Scheme X

XI. Condensation of 2-amino benzylamine with γ-butyro lactone:

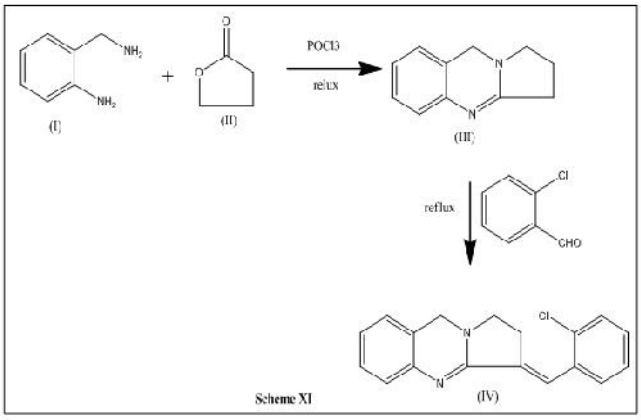

Figure 13: Scheme XI

2, 3-fused pyrrolidinohydro quinazolines are also found to have great potential as drug in asthmatic diseases. Synthesis starting from condensation of 2-amino benzylamine (I) with γ-butyro lactone (II) gave the intermediate, 1, 2, 3, 9-tetrahydro pyrrolo[2, 1-b] quinazoline (III), which was further condensed with benzaldehyde to yield the product (Z)-3-(2-chlorobenzylidene)-1, 2, 3, 9-tetrahydropyrrolo [2, 1-b] quinazoline (IV).

XII. o-isocyanides benzonitrile 25 on reaction with hydrazine: o-isocyanides benzonitrile (I) on reaction with hydrazine produced 9-chloro-2-(furan-2-yl)-[1,2,4] triazolo [1, 5-c] -quinazolin-5(6H)-one (II) in step-1, which is further Chlorinated to 5, 9-dichloro-2-(furan-2-yl)-[1, 2, 4] triazolo [1, 5-c] quinazoline (III) followed by amination the target compound 9-chloro-2-(furan-2-yl)-[1, 2, 4] triazolo[1, 5-c] Quinazolin-5-amine (IV) was obtained as shown in Scheme 8.[53]

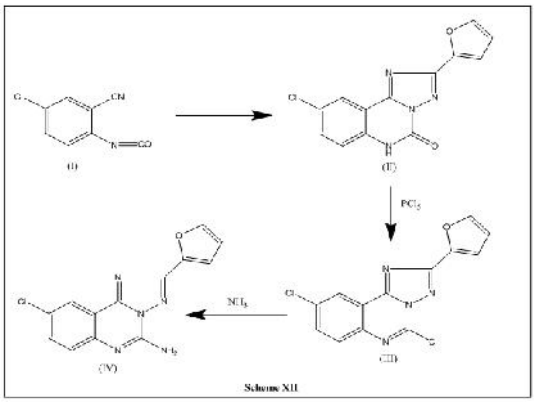

Figure 14: Scheme XII

4. Conclusion

Quinazoline is considered to be an important pharmacophore in medicinal chemistry which is capable of binding at multiple sites. The quinazoline was synthesized by the traditional methods and it is cost effective and can also be synthesized in lab scale. Different structural modifications results in their efficacy and usefulness in treatment, they exert various different physicochemical owing to their diverse therapeutic effect thus we can say that this review for the synthesis of the quinazoline would be very useful.

5. Conflict of Interests

The author declares that there is no conflict of interests regarding the publication of this paper.

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