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Chapter

Introductory Chapter: The Newest Research in Quinazolinone and Quinazoline Derivatives

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1. Introduction

Target searching for new high effective medicinal preparation is considered one of the actual problems of the modern public health. From medicinal preparations are the natural and synthetic origins of quinazolinone-4 derivatives. Quinazolinone derivatives are reported to be physiologically and pharmacologically active [1].

They also exhibit a wide range of activities such as anticonvulsant, anti-inflammatory, antifungal, antimalarial, and sedative. Some of these compounds are identified as drugs used as diuretics, vasodilators, and antihypertensive agents.

Moreover, sulfonamide derivatives have been widely used as bacteriostatic agents. Prompted by the abovementioned facts and in conjunction with our ongoing program on the utility of readily obtainable starting material for the synthesis of heterocyclic systems of biological interest, we have decided to synthesize a series of quinazolinone derivatives having sulfonamide moiety with potentially wide spectrum of biological responses [2, 3]. Information about the biological properties of derivatives of quinazolinone before the end of 60-years ago was more fragmentary.

At the end of 40 years, an alkaloidal compound febrifugin (dichroin) 3-[β-keto-γ(3-oxipiperidine-2) propyl] quinazolone-4 was isolated from Chinese plant Chang-Shan (Dichroa febrifuga Laur.) and has antimalarial activity, 100 times greater than quinine. This compound has not found clinical application, since it is 300 times toxic than quinine alkaloids [4, 9, 10, 21] (**Figure 1**).

However, work with febrifugin encouraged further searching for new biologically active compounds among the derivatives of quinazolinones-4 [4].

Already, on early stages of the studies, chemotherapeutic, anti-inflammatory activity, and hypnotic and hypotensive actions were revealed [5].

Sixty to seventy years ago, more than 300 patents appeared in different countries, denoted synthesis and study of biological activity of this type of compounds. More than 20 medicinal preparations (analgesic, sedative, diuretic, hypotensive,

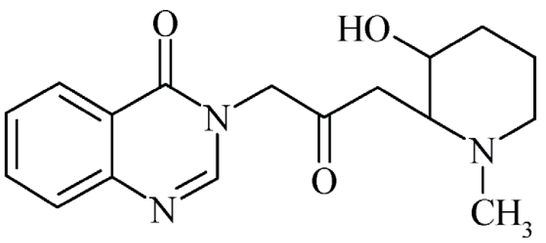

Figure 1.
The structure of the compound febrifugin (dichroin).

cholegogue, bronchodilator, tranquilizer, chemotherapeutic action) of quinazoline derivatives are introduced in medicinal practice [5–7].

Among various quinazolinone derivatives, big attention was attracted to the substituted-(3H) quinazolinones-4, which show the significant hypnotic activity [4].

2-Methyl-3-(o-tolyl) quinazolinone-4, named methaqualone, is broadly used in medicinal practice [5, 8] as sedative and hypnotic. Aside from hypnotic action, methaqualone possesses the anticonvulsant and anti-cough properties and intensifies the action of barbiturates, analgesics, and neuroleptics [7].

The high activity and small toxicity of methaqualone were a motivation for study of the large number of its analogues [9] (**Figure 2**).

Similar analogues of methaqualone such as—a light hypnotic ethaqualone, as well as mecloqualone which is used in medicine as hypnotic and sedative [4, 10].

2-Methyl-3-(o-cyan phenyl) quinazolone-4 is characterized by the highest hypnotic, sedative, and anticonvulsant activity [11]. Strong psychotropic action is showed in triflourmethyl analogue of methaqualone [12].

The series analogues of methaqualone with similar pharmacological properties with ortho-substiuted have an alkyls or other functional groups and in the other positions phenyl residues [4, 13].

Among compounds of this group, the most popular compounds that have been used in practical medicine are 2-methyl-3-(o-methyl-p-chlorphenyl)-5-chlorquinazolone-4 (SL-I64) as tranquilizer and 2-methyl-3-(o-methoxy-p-nitrophenyl) quinazolone-4 (nitromethaqualone) as hypnotic [14]. Quinazolinones-4 render also hypothermic and spasmolytic action [5].

At study of more than 40 derivatives of quinazolines, some qualitative correlations between structure and convulsive activity were revealed [15, 16]. Transition from 3-aryl- to 3-alkylquinazolones-4 saves the sedative, hypnotic, and anticonvulsant properties of compounds [16]. The last type of activity is also characterized for 2-methyl-3-piperazino-alkylquinazolones-4.

Variation of the substituted in position 3 may affect upon biological properties of substances in these compounds. So, 3-cyanalkyl-quinazolones-4, for example, are diuretics, but corresponding to aminoketones and aminohydroxy, derivatives show analgesic, spasmolytic, and anti-inflammatory activities [4].

Derivatives of (1H)-quinazolinones-4 are less studied. For them, the most characterized properties are analgesic, anti-cough, and anti-inflammatory activity [10, 17]. 1,2,3,4-Tetrahydroquinazolones-4 were studied greatly in details.

Some compounds of this line, unsubstituted in position 1, show the antibacterial and cytostatic activities. 1-Alkyl or aryl derivatives are characterized as anti-inflammatory, bronchodilator, and sedative action; 1-dialkylaminoalkyl- and 1-acyl, including substituted aminoacyl-1-tetrahydroquinazolones-4, have manifested themselves as analgesics and tranquilizers, myorelexants, and diuretics.

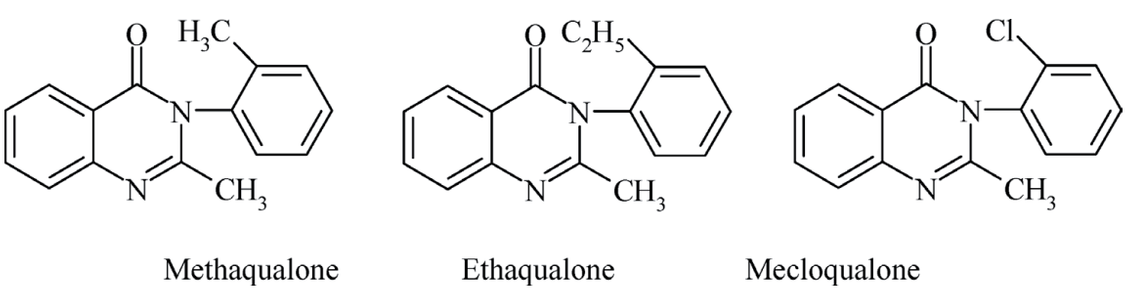

Figure 2.
The structures of methaqualone and its analogues.

Significantly, their parts described antihistamine, cholagogue, and anti-inflammatory properties [10].

N-Heteril derivatives of quinazolinone-4, containing of fragments of antipyrin and thiazole in the position 3, have anti-hypoxic activity [18].

Anagrelide is a quinazoline compound, possessing anti-thrombocyte aggregation activity [19]. Quinazoline-derived doxazosin and terazosin (α_1-adrenoreceptor antagonists) show the highest activity in the cancer of the prostate gland [19, 20].

Mokvizon [21] has been found to be used in practical medicine as cholagogue and hypocholesterolemic remedy (**Figure 3**).

Among 3-alkyliden-1,2.3,4-tetrahydroquinazolones-4, glycozine was used as preparation of hypnotic action.

Introduction of chlorine in position seven and sulfamide group in position six of quinazolines-4 brings the high active diuretics and saluretics of the chlorothiazide type. Diuretic action of the substances increases when they are turning from quinazolones-4 to tetrahydroquinazolones [9].

Compounds, for example, of this type are metolazone, SR 720-22, zaroxoline, quinethazone, hydromox, and others. They are introduced into medicinal practice as diuretics and saluretics [4].

Pharmacological screening has allowed revealing the sedative activity for some derivatives of quinazolinone-4:

4-(2-Phenyl-4-oxoquinazolil) –butyric acid increases the duration of nembutalic sleep in comparison with control on 106% [22, 23] and influences upon parameters of hemodynamic system of awake rats [24–26].

Derivatives of quinazoline-4(3H)-one show antimicrobial, antifungal, antimalarial, antituberculosic, antihypertensive activity, as well as anticonvulsant and sedative actions [27–30].

The pharmacological studies found that the most activity, that these compounds have 2′, 4′-dimethoxyphenyl radical at position 2 of quinazolone cycle.

So, the most anti-inflammatory activity is characterized by 1-acetyl-2-(2′, 4′-dimethoxyphenyl)-3-[(4-methoxyphenyl) or (4-chlorphenyl)]-1,2,3, 4-tetrahydroquinazolinones-4.

High anticonvulsant activity was shown in 1-adamantilacetyl-2-(2′,4′-dimethox yphenyl)-3-benzyl-1,2,3,4-tetrahydroquinazolinone-4 [27].

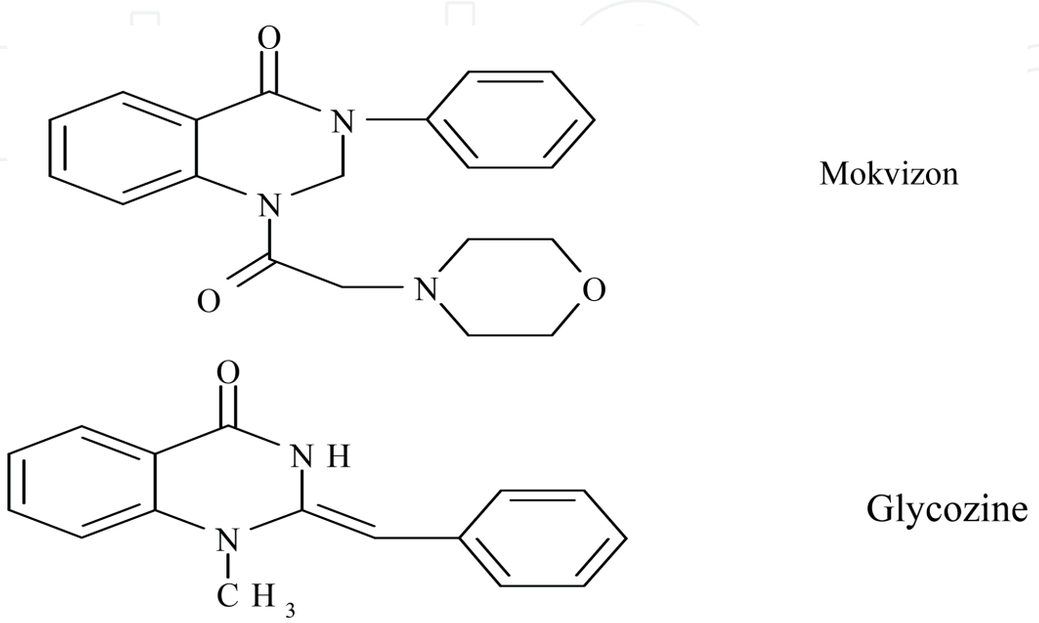

Figure 3.
The structures of mokvizon and glycozine.

2-Styril-4-aminoquinazolinones are characterized by strong activity in respect of gram-positive bacteria, *Mycobacterium tuberculosis*, pathogenic proterozoic infection, pathogenic viruses, and fungi [30].

Pharmacological screening of some derivatives of quinazolinone-4 has allowed revealing for analeptic, anti-inflammatory, and anti-hypoxic activity and slightly toxic:

4-Amino-4′-[2-phenyl-4-oxoquinazoline-3]-diphenylsulfone (QPhD) and 4,4'-bis-[2-phenyl-4-oxoquinazoline-3]-diphenylsulfone (BisQPhD) have analeptic, anti-inflammatory, and anti-hypoxic activities and are slightly toxic [21, 31].

In one study 4-amino-4′-[2-phenyl-4-oxoquinazoline-3]-diphenylsulfone (QPhD) shows strong immunotropic activity surpassing the comparing drug methyluracil [32].

In one study 4-(4-Oxo-2-phenyl-4H-quinazolin-3-yl)-N-pyrimidin-2-yl-benzenesulfonamide (Compound A) and N-(4,6-Dimethyl-pyrimidin-2-yl)-4-(4-oxo-2-phenyl-4H-quinazolin-3-yl)-benzenesulfonamide (Compound B) show strong hepatoprotective and antioxidant activity surpassing the comparing drug Liv-52 [33].

Accessibility of quinazoline derivatives and versatility of their biological activity attract well-earned attention to similar class of substances. The similarity is not only physicochemical properties of pyrimidine and quinazolinone, but also spectrum of biological activity opens the new possibilities for searching for high active compounds in these class substances [10, 34]. The extensive array of information, denoted synthesis, and study of the biological activity of derivatives of quinazolinon-4 is indicative of exclusive possibility of the synthesis of new biologically active compounds. Synthesis of 4-(4-oxo-2-phenyl-4H-quinazolin-3-yl)-N-pyrimidin-2-yl-benzenesulfonamide (Compound A) and N-(4,6-dimethyl-pyrimidin-2-yl)-4-(4-oxo-2-phenyl-4H-quinazolin-3-yl)-benzenesulfonamide (Compound B) showed high antimalarial activity compared with chloroquin [35].

The synthesis of 4-(4-oxo-2-phenyl-4H-quinazolin-3-yl) benzene sulfonamide (Compound A) and N-acetyl-4-(4-oxo-2-phenyl-4H-quinazolin-3-yl)-benzenesulfonamide (Compound C) having analgesic and anti-inflammatory activities but Compound C showed a significant activity than Compound A; also the Compound A has a pharmacological activity more significant than standard drug diclofenac. Further studies are important to ensure their analgesic and anti-inflammatory mechanisms.

The docking study explains the inhibitory effect of the A and C compounds against the in vivo anti-inflammatory and analgesic activity. The compounds A and C have similar effect as diclofenac and indomethacin reference drugs in the in vivo anti-inflammatory and analgesic activity [36].

Synthesis of 4-(4-oxo-2-phenyl-4H-quinazolin-3-yl)-N-pyrimidin-2-yl-benzene sulfonamide (Compound B) and N-(4,6-dimethyl-pyrimidin-2-yl)-4-(4-oxo-2-phenyl-4H-quinazolin-3-yl)-benzene sulfonamide (Compound D) gave a Pa < 0.5 as nootropic by the PASS program, but experiments on animals confirmed the anti-hypoxic activity of the compounds, which means they might occur as new chemical entities. Compound D has shown the strongest anti-hypoxic activity. A docking study of the synthesized derivatives with GluA3 confirmed the result in vitro and revealed that Compound D is an anti-hypoxic agent [37].

Our aim is to focus on all the methods for synthesis and different interesting biological activities of quinazolinone and quinazoline derivatives.

Our major objective of this project is to give the information in a lucid, condensed, and cohesive form and to specially cater the needs of readers in medicine and pharmacy.

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