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Potential Biological Activities of Thioquinazolinones: Recent Updates

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Review Article

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Abstract: Thioquinazolinones are utilized in chemical synthesis of physiological significance and pharmacological utility. Thioquinazolinones are a large class of active chemical compounds exhibiting a broad spectrum of biological activities in animals as well as in humans. Research studies on thioquinazolinones reveals that the derivatives can be used in series of biological activities such as anti HIV, anticancer, antifungal, antibacterial, antimutagenic, anticoccidial, anticonvulsant, anti-inflammatory, CNS depressant, antimalarial, antioxidant, antileukemic activity, antileishmanial activity. This review focused on the various biological activities of thioquinazolinones. The heterocyclic fused rings thioquinazoline have drawn a huge consideration owing to their expanded applications in the field of pharmaceutical chemistry. Thioquinazolinone are reported for their diversified biological activities and compounds with different substitutions bring together to knowledge of a target with understanding of the molecule types that might interact with the target receptors. Thioquinazolinones are an important chemical for the synthesis of various physiological significance and pharmacological utilized molecules. Thioquinazolinone are a large class of biologically active compounds that exhibited broad spectrum of biological activities such as anti-HIV, anticancer, antifungal, antibacterial, antimutagenic, anticoccidial, anticonvulsant, anti-inflammatory, antidepressant, antimalarial, antioxidant, antileukemic, and antileishmanial activities and other activities. Thioquinazolinone used as advantaged scaffold, the alteration is made with different substituent.

Keywords: Thioquinazolinones, broad spectrum, biological activities.

INTRODUCTION

Although several chemotherapeutic agents are currently being used to treat human cancers, either alone or in combination, they have limited effectiveness and the response rates remain largely unimproved in clinical trials[1, 2]. Quinazolines are type of fused heterocycles that has unique interest because of the diverse range of their biological properties, for example, anticancer, diuretic, anti-inflammatory, anticonvulsant and antihypertensive activities[3] .

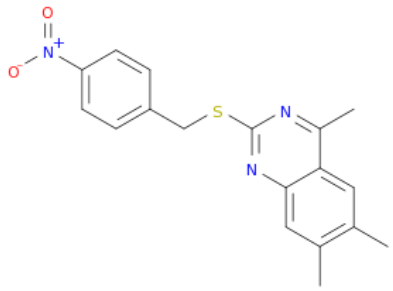
Quinazoline is a fused six-member aromatic ring (a benzene ring and a pyrimidine ring are fused). Quinazoline is a fused bicyclic compound earlier known as benzo-1, 3-diazine. It was first prepared in the laboratory in 1903 by Gabrie[4]. Although its derivative were known much earlier. The name quinazoline (German: Chinazolin) was first proposed for this compound by weddige on observing that this was isomeric with the compounds cinnoline and quinoxaline. Paal and Bush suggested the numbering of quinazoline ring system, which is currently used[5,7].

Given the fact that the class of these substances is quite small in numbers, and the medicines available have low activity, and significant side effects, one of the challenging tasks of experimental pharmacology is finding out new highly efficient substances that able to improve physical endurance. The promising ones in this respect are derivatives of quinazoline[7,10]. According to the results of previous studies, among 15 new 5-R-thio-tetrazolo[1,5-c] quinazoline derivatives four compounds that most increased duration of swimming test under conditions of normo-, hyper- and hypo-thermia[9-11]. The above substances were synthesized at the department of organic chemistry of Zaporizkyi State Medical University under the leadership of professor Antypenko[7]. To find a leading compound, it was reasonably to investigate the effect of the most active compounds on the physical endurance of rats.

Chemical Structure Description

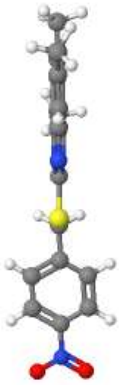
A chemical structure of a molecule includes the arrangement of atoms and the chemical bonds that hold the atoms together. The 4,6,7-trimethyl-2-[(4-nitrobenzyl)thio]quinazoline molecule contains a total of 43 bond(s). There are 26 non-H bond(s), 19 multiple bond(s), 4 rotatable bond(s), 2 double bond(s), 17 aromatic bond(s), 3 six-membered ring(s), 1 ten-membered ring(s), 1 nitro group(s) (aromatic), 1 sulfide(s) and 1 Pyrimidine(s).

Images of the chemical structure of 4,6,7-trimethyl-2-[(4-nitrobenzyl)thio]quinazoline are given below:



2-dimensional (2D) chemical structure image of 4,6,7-trimethyl-2-[(4-nitrobenzyl)thio]quinazoline

The 2D chemical structure image of4,6,7-trimethyl-2-[(4-nitrobenzyl)thio]quinazoline is also called skeletal formula, which is the standard notation for organic molecules. The carbon atoms in the chemical structure of 4,6,7-trimethyl-2-[(4-nitrobenzyl)thio]quinazoline are implied to be located at the corner(s) and hydrogen atoms attached to carbon atoms are not indicated – each carbon atom is considered to be associated with enough hydrogen atoms to provide the carbon atom with four bonds.



3-dimensional (3D) chemical structure image of 4,6,7-trimethyl-2-[(4-nitrobenzyl)thio]quinazoline

The 3D chemical structure image of4,6,7-trimethyl-2-[(4-nitrobenzyl)thio]quinazoline is based on the ball-and-stick model which displays both the three-dimensional position of the atoms and the bonds between them. The radius of the spheres is therefore smaller than the rod lengths in order to provide a clearer view of the atoms and bonds throughout the chemical structure model of 4,6,7-trimethyl-2-[(4-nitrobenzyl)thio]quinazoline.

Thio quinazoline

Synthesis and antimicrobial activity of novel Quinazoline as a core unit containing different Substituted Phenyl/Heterocyclic derivatives. The antimicrobial activity study revealed that all the tested compounds showed good antibacterial and antifungal activities against pathogenic strains. The structure and biological activity relationship of title compounds indicate that the presence of electron withdrawing groups like–CF_3 and Thiophene ring attached to the Quinazoline ring were responsible for good antimicrobial activity and hence compounds 8i, 8d, 8h and 8g exhibited more potent anti-microbial activity of all tested pathogenic strains[11].

Characteristics of a modified electrode prepared by electrodeposition of anthio-quinazoline derivative on the multi-wall carbon nanotubes modified glassy carbon electrode (QMWCNT-GCE). In this work, a QMWCNT–GCE was fabricated, and several methods were used to characterize this modified electrode. It was observed that hydroxylamine oxidation was catalyzed at the QMWCNT–GCE surface, and its peak potential shifted to a less positive potential toward the MWCNT–GCE and AGCE. The standard heterogeneous rate constant, k', and the transfer coefficient, α, were calculated using cyclic voltammetry. The overall number of electrons involved in the catalytic oxidation of hydroxylamine was also calculated. In amperometric measurements, there appeared two linear calibration ranges for hydroxylamine and NO^{2-}. Also, QMWCNT–GCE was used to determine hydroxylamine in the presence of NO^{2-}. Finally, the modified electrode was applied for the determination of hydroxylamine and NO2 – in water samples[12].

Synthesis of four new 4-thio-5,8-dideazafolic acid analogues and a 4-(methylthio) analogue structurally related to the thymidylate synthase (TS) inhibitor N10-propargyl-5,8-dideazafolic acid. Three N10-propargyl-4-thio-5,8-dideazafolic acid analogues had C2 amino, hydrogen, and methyl substituents. A 4-thio and a 4-(methylthio) compound each with hydrogen at C2 and ethyl at N10 were also synthesized. In general, the synthetic route involved thionation of the appropriate 4-oxoquinazoline; the sulfur thus introduced was then protected by methylation. Further protection with a pivaloyl group was required for the quinazoline bearing a 2-amino substituent. The protected quinazolines were treated with N-bromosuccinimide and the resulting 6-(bromomethyl) compounds were then coupled to the appropriateN-monoalkylated diethyl N-(4-aminobenzoyl)-L-glutamate in N,N-dimethylacetamide with calcium carbonate as base. The 4-thio-5,8-dideazafolic acids were obtained by removal of the methylthio group with sodium hydrosulfide, followed by deprotection of the carboxyl groups with cold dilute alkali. For the compound containing a pivaloyl protecting group, hot

dilute alkali was used. To obtain the 5,8-dideazafolic acid containing a 4-(methylthio) substituent, the corresponding diester was treated with lithium hydroxide which selectively deprotected the carboxyl groups. The five compounds were tested as inhibitors of L1210 TS. It was found that replacement of the 4-oxygen of the quinazoline moiety by sulfur did not alter the TS inhibition. However, the introduction of a methylthio substituent at position 4 severely impaired TS inhibition. All 4-thio compounds were less cytotoxic to L1210 cells in culture than their 4-oxo counterparts[13].

A new series of quinazoline derivatives (**3**–**26)** was synthesized and characterized via physicochemical and spectral means. Treatment of 2-amino-5-methylbenzoic acid with butyl isothiocyanate resulted in the new 2-thioxoquinazolin-4-one (**3)**. Alkylation and hydrazinolysis of the inherent thioxo group in (**1**–**3**) afforded the corresponding thioethers (**4**–**23**) and hydrazine derivatives (**24** and **25**), then **24** was further transformed into tricyclic derivative **26** via cyclocondensation reaction. Compounds **1** and **2,**which were previously synthesized, were found to exhibit anticancer activity. The cytotoxicity of all compounds was evaluated *in vitro* against the HeLa and MDA-MB231 cancer cell lines, including **1** and **2** for comparison, using MTT assay. The treatment of the cells was performed with the synthesized compounds and gefitinib at 0, 1, 5, 10, 25, and 50 μM and incubated for 24 h in 50% DMSO. The IC_{50} values of the target compounds were reported in μM, using gefitinib as a standard. Our results indicated that all compounds exhibited significant *in vitro* cytotoxicity against both cell lines. While compounds **1**–**3** showed good activity, compounds **21**–**23** were found to be more potent than gefitinib. Thus, compounds **21**–**23** may be potential anticancer agents, with IC_{50} values ranging from 1.85 to 2.81 μM in relation to gefitinib (IC_{50} = 4.3 and 28.3 μM against HeLa and MDA-MB231 cells[14].

Quinazoline, a heterocyclic compound, has been extensively studied and used in certain specific biological activities. The quinazoline-4(3H)-one and its derivatives constitute an important class of fused heterocycles that are found in more than 200 naturally occurring alkaloids. With passage of time, newer and more complex variants of the quinazolinone structures are being discovered. The stability of the quinazolinone nucleus has inspired researchers to introduce many bioactive moieties to this nucleus to create new potential medicinal agents. With a view to explore the versatile lead molecule 4(3H)-quinazolinones, a series of novel 2-methyl-3-(1’3’4-thiadiazole-2- yl)-4-(3H) quinazolinones have been synthesized by reacting 2-amino-5-aryl/alkyl-1’3’4’-thiadiazoyl with 2-substituted benzoxazin-2-one. The designed compounds have shown antibacterial activity on Staphylococcus aureus, Bacillus subtilis and Escherichia coli. In the journey of a compound to be established as a lead and finally to a drug, the problem of solubility is a major challenge for medicinal chemists and formulation scientists. The present review has touched all these issues with a hope that some of t the quinazoline derivative with sufficient bioavailability could help us to counter the menace of antibiotic resistance[15].

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