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Synthesis of 8-methyl-2-phenylquinazolin-4(3*H*)-ones derived Schiff's bases: spectroscopic properties, SAR, docking approaches and their anticancer and antimicrobial activity

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What do these dates mean?

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Highlights

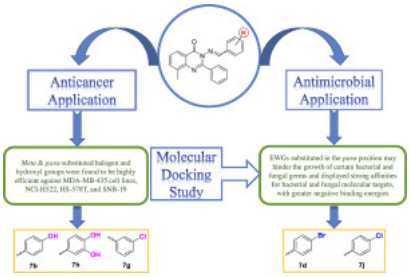
- 8-Methyl-2-phenyl quinazolinone Schiff's base series has been synthesized.
- Efficacy of **7b** and **7h** against MDA-MB-435 and NCI-H522 cell lines, respectively.
- **7g** was effective against breast cancer (HS-578T) and CNS cancer (SNB-19) cell lines.
- **7d** (4-Br) and **7j** (4-Cl) potent against selected bacterial and fungal microorganisms.
- **7d** and **7j** show target affinities with -8 to -12.5 kcal/mol binding energies.

Abstract

A series of new compounds based on 8-methyl-2-phenyl quinazolinone Schiff's base were synthesized from 3-amino quinazolinone intermediates. These compounds were evaluated for their potential as anticancer and antimicrobial agents through docking analysis. Anticancer evaluation was done against sixty different cancer cell lines. Compounds **7b** and **7h** showed strong efficacy against Melanoma (MDA-MB-435 Cell lines) and Non-Small Cell Lung Cancer (NCI-H522), respectively. Compound **7g** was found to be predominantly effective against both breast cancer (HS-578T) and central nervous system cancer (SNB-19). The antimicrobial activity results showed that the newly synthesized compounds **7d** and **7j**, which contain halogen, exhibited potential inhibiting action against selected bacterial and fungal microorganisms. The SAR study revealed that compounds with EDGs like hydroxyl and *meta*-substituted chloro group were found to be more potent in anticancer studies; while compounds with EWGs substituted in the *para* position (**7d** and **7j**) demonstrated higher antimicrobial

activity. Moreover, Antimicrobial docking analysis indicated that compounds **7d** and **7j** have a high affinity towards molecular targets found in both bacteria and fungi, with negative binding energies ranging from -8 to -12.5 kcal/mol. We endorse further evaluation of these compounds in combination with standard antibiotics to potentially increase their synergistic effect.

Graphical Abstract



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Introduction

The investigation of heterocyclic compounds, as well as various aliphatic compounds like sulfonamide, is crucial for the development of novel drugs that are needed by the agrochemical and pharmaceutical industries. These substances play a vital role in advancing science and medicine, as well as creating medicinal drugs. [1], [2], [3], [4]. Quinazolinones and their derivatives was reported for their versatile pharmacological activities especially in antimicrobial properties [5,6]. The fused ring types of quinazolinones heterocycles are considered the most significant group due to their extensive range of therapeutic applications [7], [8], [9], [10], [11], [12]. Microbial infections are responsible for more deaths annually worldwide. Chloramphenicol, Ciprofloxacin and Norfloxacin are well-known antibiotics against a series of bacteria, and Nystatin and Griseofulvin are potent antifungal agents that were reported in various studies [13]. Also, these compounds were FDA-approved for the treatment of patients with microbial infections [14]. Although these compounds have significant therapeutic potential against the microbial infections caused by *E. coli, P. aeruginosa, S. aureus, S. pyogenes, C. albicans, A. niger* and *A. clavatus*, they are becoming resistant among patients and there is an urgent for the development for potent compounds [15], [16], [17]. A variety of FDA-approved medications, including anticancer and antimicrobial drugs, belong to various structural classes of quinazolinone. These drugs, such as Thymitaq as well as Idelalisib for cancer and Albaconazole for fungal infections, have been extensively researched and reviewed. In our ongoing search for more effective anticancer and antimicrobial drugs, we have developed and synthesized a new series of quinazolines based on the aforementioned rational (Fig. 1) [18].

Acylation of anthranilic acid with acyl chloride is a common method to produce 4(3*H*)-quinazolinone. After ring closure with acetic anhydride, the corresponding 1,3-benzoxazin-4-one (benzoxazinone) is derived, which can be treated with various amines to obtain 4(3*H*)-quinazolinone derivatives [19,20]. It's common to have issues with the ring opening of quinazoline during the synthesis of quinazoline from benzoxazinone. To avoid this problem, a modified synthesis technique has been developed for 3-amino-7-chloro-2-phenyl quinazolin-4(3*H*)-one. Instead of using a solvent, it involves a fusion reaction carried out at 250°C [21]. We synthesized a new family of Schiff bases that contain 2,3,6-trisubstituted quinazolinone derivatives beginning with 3-methyl-2-aminobenzoic acid. These results align with prior research and our commitment to enhancing our methods and exploring new approaches to drug development [22], [23], [24], [25], [26], [27], [28], [29], [30], [31], [32].

Section snippets

Chemistry

In the presence of pyridine, we used benzoyl chloride **(2)** to carry out the *N*-acylation of 2-amino-3-methylbenzoic acid **(1)**. This reaction resulted in the formation of 8-methyl-2-phenyl-4*H*-benzo[*d*][1,3]-oxazin-4-one **(3)** through dehydrative cyclization. Next, we attempted to mix it with hydrazine hydrate in ethanol to obtain 3-amino-8-methyl-2-phenylquinazolin-4(3*H*)-one **(4)**, but instead, we ended up with a mixture of *N*-(2-(hydrazinecarbonyl)-6-methylphenyl)benzamide **(5)** due to ring-opening. We…

Spectral characteristics

In order to ensure the accuracy of the proposed structure, each compound was characterized using FTIR, ^{13}C NMR, ^{1}H NMR, and LCMS techniques. The IR spectrum of compound **7a-j** showed an absorption band at 1635-1689 cm^{-1}, which was caused by the C=O group in the quinazoline moiety. Additionally, there was a strong absorption band at 1327-1381 cm^{-1}, which was caused by the C-N linkage present in the rings. The C-Cl stretching vibration appeared at 756-763 cm^{-1}, while the OH broad band appeared at…

SAR study

A study was conducted to investigate the correlation between the structure of a compound and its antimicrobial and anticancer properties. The study found that the only factors that affect the activity of produced compounds are various substitutes (-R) attached to the aromatic ring. The positions of electron-donating groups (EDGs) and electron-withdrawing groups (EWGs) were found to significantly influence the effectiveness of antimicrobials and anticancer agents. It was found that only…

Conclusion

Several new quinazolinone Schiff's base compounds were synthesized from 3-amino quinazolinone intermediates that were obtained by a modified fusion method. These derivatives were then evaluated for their potential as anticancer and antimicrobial agents through docking analysis. When compared to traditional treatments for anticancer activity in a single dose screening, the newly synthesized compounds exhibited weak to low effect against 60 cancer cell lines tested. However, compound **7b** (4-OH)…

CRediT authorship contribution statement

N.R.: Synthesis, characterization, and preparation of the manuscript. G.I.: Molecular docking study, visualization and biological assay of compounds. P.S.R.: Biological assay and molecular docking study with result analysis. R.M.: Analyzed the anticancer and put valuable input in the result discussion. S.S.: Review & editing, supervision, project administration of docking analysis. J.K.: Spectral analyses. S.H.: Valuable inputs for anticancer study. B.Y.P. Design, characterization, supported…

CRediT authorship contribution statement

Naimish Ramani: Writing – original draft, Validation, Methodology, Investigation, Formal analysis, Conceptualization. **Bonny Y Patel:** . **Gopal Italiya:** Writing – original draft, Visualization, Validation, Software, Resources, Methodology, Data curation. **Prasanna Srinivasan Ramalingam:** Writing – original draft, Visualization, Validation, Software, Methodology, Investigation, Data curation. **Rudra Mishra:** Writing – original draft, Validation, Investigation, Formal analysis, Data curation. **Sangeetha**…

Declaration of competing interest

The authors declare that they have no conflicts of interest for this research publication.…

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