Design, Synthesis and Evaluation of Core Scaffold Pyrazolone Fused Thiazolidinone Derivatives as Anticancer Agents

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Authors' contributions

This work was carried out in collaboration among all authors. Author SA designed the study, performed the synthesis, molecular docking, statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors SR and GNL managed the analyses of the study. Author SN managed the literature searches and analysis of results and draft of the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Background: Cancer is the world's second leading cause of death, accounting for an estimate of more than 10 million deaths annually. The most common type of cancers in women are breast, endometrial, cervical, ovarian, colorectal, lung, and skin cancers. Among these, breast cancer is the most common in women of all ages. Human epidermal growth factor receptor 2 breast cancer is widely seen in women which test positive for the protein HER2. This protein is present in one-fifth of every breast cancer cell, which promotes the growth of cancer cells. There are several compounds available for the treatment of HER2 breast cancer in the market with varying promise in their efficacy and safety on HER2 treatment.

Objective: To design synthesis and evaluation of core scaffold pyrazolone fused thiazolidinone derivatives as anticancer agents.
1. INTRODUCTION

There are many pharmaceutical products available in the markets for the treatment of various diseases or medical conditions. However, the pyrazole derivatives possess significant market potential due to their varying biological activities. Pyrazole derivatives are mostly used as anti-bacterial, anti-fungal, anti-inflammatory, anti-tubercular, anti-viral, anticancer, anticonvulsant, neuroprotective, cholecystokinin-1 receptor antagonist, angiotensin-converting enzyme (ACE) inhibitory, fluorescent substances [1–3], dying industry, agrochemicals, etc. Much more research is ongoing on pyrazole chemistry [4–6].

Thiazoles, a class of heterocyclic compounds commonly seen in many potent biologically active drugs such as Sulfathiazole (anti-microbial), Ritonavir (anti-retroviral), Abafungin (anti-fungal drug), and Tiazofurin (anti-cancer) [7]. Compounds containing thiazole nuclei have shown various biological activities which include anti-hypertensive [8], anti-microbial and anti-fungal [9,10], anti-HIV [11], anti-convulsant, and anti-inflammatory activities [12].

Thiazole derivatives produce anticancer activities [13–15] through several mechanisms by targeting inosine monophosphate dehydrogenase (IMPDH) [16], tumor necrosis factor-alpha (TNF-α) [17], and also apoptosis inducers. The new generation of thiazole derivatives with enhanced biological profiles serves as a matrix for the development of advanced anticancer drugs. Many studies on drug design proved that thiazole ring possessing compounds are ideal for the said target activity on cancer. In the current research various aromatic amines synthesized by Schiff base was fused to thiazolidinone nucleus to enhance the activity. Thiazole derivatives have better anticancer properties, it has been demonstrated well through its better binding capacity, less cytotoxic activity on normal cells with improved action on malignant growth cells. The thiazole compound was found to possess better effectiveness in malignant growth by inhibiting the activity of epidermal growth factor receptor kinase. The potential interest in the development of new therapeutic antitumor agents [18,19].

A study by Lv et al., [20] described that thiazolyl-pyrazole analogs shown moderate to the high inhibitory action of epidermal growth factor receptor tyrosine kinase (EGFR TK) with potential antitumor activity. Molecular docking of thiazolyl-pyrazolines indicated that it has a higher binding affinity to epidermal growth factor receptor kinase [21–23]. Many researchers investigated the biological activities of practically substituted heterocyclic compounds [24–26] which are commonly used in biodegradable agrochemicals [27–29] from shoddy research facilities as starting materials [30–32]. Hence, it is important to synthesis a new compound by incorporating the thiazole and pyrazole moieties as one entity with improved biological activity. Moreover, as it has a synergistic impact within the two rings, the addition of a β-Ketoester will be a suitable starting material to achieve this objective.

Methods: In this study, the core scaffold pyrazolone fused thiazolidinone derivatives were designed, synthesized, and analyzed for the anticancer activity using breast carcinoma cell line (MCF-7), against the standard drug Doxorubicin.

Results: Many thiazoles, fused thiazole, and pyrazole derivatives have been found to have anticancer and other properties. In this study, the compound 1-phenyl-3-methyl-5-pyrazolones was allowed to react with diverse benzoyl chloride as well as primary amine derivatives and transformed into ‘A series of Pyrazolone fused Thiazolidinone derivatives 4A1-4A10 and 4B1-4B10. Computational studies by Schrodinger Glide XP using the Protein 3RCD which act on the human epidermal growth factor receptor” was performed on the selected scheme initially and further from the docked score data the synthesis of pyrazolone fused thiazolidinone was performed.

Conclusion: Among the compounds synthesized, five compounds (4A6 − 3.4 kcal/mol, 4B4 − 3.0 kcal/mol, 4A3 − 2.2 kcal/mol, 4B2 − 1.6 kcal/mol, and 4A9 − 1.3 kcal/mol) shown promising binding affinities against epidermal growth factor receptor kinase. The cytotoxic potential of the compounds was examined using a breast carcinoma cell line (MCF-7), which shown cytotoxicity close to Doxorubicin (standard drug). Our findings are an important step forward in the development of novel anticancer agents.

Keywords: Pyrazolones; thiazolidinone; anticancer activity; molecular docking; receptor kinase.
2. MATERIALS AND METHODS

2.1 Synthesis of 5-Methyl-2-Phenyl-2,4-Dihydro-3H-Pyrazol-3-One

A reactant mixture was prepared by adding 0.01mol of phenylhydrazine, 0.01mol of ethyl acetoacetate, and few drops of acetic acid. This orange colour reactant mixture was refluxed until the solution becomes a thick liquid. The mixture was allowed to cool to room temperature and 15 ml of ether was added to it. The formed yellow precipitate was filtered, recrystallized using ethanol, and the purity of the product was estimated by a single spot on the thin layer chromatography (TLC) using iodine vapour as the visualizing agent. Toluene, ethyl acetoacetate and water in the ratio of 8.7:1.2:1.1 (V/V/V) were used as the solvent system for the TLC technique.

2.2 Synthesis of Benzoyl Derivative of 5-Methyl-2-Phenyl-2,4-Dihydro-3H-Pyrazol-3-One

In a round bottom flask, 0.1mol of 5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one was added and dissolved with 80ml of dioxane by application of heat. 0.175mol of calcium hydroxide was added to the reaction mixture by continuous stirring and then 9.9 ml of benzoyl chloride was added dropwise within 1min. The reaction mixture was turned into a thick paste and the temperature has been increased during the first few min. The resultant mixture was then heated using a reflux condenser for about 30 min. Dil. Hydrochloric acid was added to the formed calcium complex, which caused the separation of the cream-coloured crystals. The formed crystals were collected using the Buchner funnel and then recrystallized using n-hexane or methanol which brings bright yellow crystalline solid.

Type of the reaction: Acylation at Carbon Bearing active Hydrogen.

2.3 Synthesis of Schiff Base Derivatives of 5-Methyl-2-Phenyl-2,4-Dihydro-3H -Pyrazol-3-One

A mixture of 0.1mol of an equimolar amine and 0.1mol of corresponding acylpyrazolones was dissolved in 30ml of ethanol in the presence of few drops of acetic acid, under an inert atmosphere. This resultant mixture was then allowed to reflux for about three-four hours, and the completion of the reaction was monitored closely using a TLC with hexane: ethyl acetoacetate (8:2) as a solvent system. The reaction mixture was cooled to room temperature and stirred overnight. A coloured precipitate was formed, which was washed and filtered with ethanol, and then crystallization was carried out from ethanol.

Type of reaction: Addition of Aromatic Amines to Aldehydes, Ketones.

2.4 General Scheme of the Study

The general scheme of the study explains how the compounds are synthesized using the starting materials Phenylhydrazine and Ethyl-3-oxobutanoate.

![Chemical structure diagram]

The FT-IR 1384(Het.CH), 1485 (Aryl CH) 3283(N-H Stretch), 3070(CH+Ar), 1428(C-CH3), 1735,1676 (C=O),1442(C=N stretch). H-NMR ppm 7.290-8.030m:15H;Ar-H):2.46(s;3H;CH3) & 2.3-2.6 (s; 1H; CH). Mass 351.44
The FT-IR 1390 (Het.CH), 1475 (Aryl CH) 3273 (N-H Stretch), 3068 (CH-Ar), 1418 (C-CH3). 1670 (C=O), 1439 (C=N Stretch). H-NMR ppm 7.25-8.43: 15H; Ar-H: 2.46 (s; 3H; CH3) & 2.0-2.4 (s; 1H; CH). Mass 441.43

The FT-IR 1392 (Het.CH), 1481 (Aryl CH) 3280 (N-H Stretch), 3072 (CH-Ar), 1428 (C-CH3). 1676 (C=O), 1602 (C=N Stretch). H-NMR ppm 7.25-8.43: 15H; Ar-H: 2.46 (s; 3H; CH3) & 2.0-2.4 (s; 1H; CH). Mass 96.44

R- Aromatic amines- aniline, p-chloroaniline, m-chloroaniline, p-fluroaniline, m-fluroaniline, p-toludine, m-toludine, p-anisidine, m-anisidine, 4 methoxy 2-nitro aniline
3. COMPUTATIONAL STUDY FOR THE FRAMED SCHEME

3.1 Materials and Methods

Molecular docking studies was performed by Schrodinger Glide XP software.

3.2 Protein Preparation

The human epidermal growth factor receptor kinase enzyme with co crystallized ligand (PDB ID: 3RCD ,2.3.A) was identified from protein data bank. Protein preparation Wizard Module of Schrodinger suite 2016-2 was utilized to set up the protein. Water atoms past 5A and without hydrogen bonds are evacuated. A controlled minimization of energy of the protein structure was done by utilizing OPLS3 force field to correct the orientation side chain, hydroxyl groups and alleviate potential steric dashes.

Thereceptors are framed by extracellular areas transmembrane section and an intracellular district. There are four sections. The section 1 & 3 gives a job in ligand official. Areas 2 & 4 are cysteine build-ups significant for disulfide security. Totally 19-25 amino acid residues are involved in the formation of trans membrane portions. The C-terminal tail containing phosphorylation enacted the intracellular protein kinase movement. Human epiderma growth factor receptors initiations are affected by the structure of the dimer and the character of the ligand.

Table 1. The interactions of the synthesized compounds with active sites of epidermal growth factor receptor kinase

| Compound | Binding energy (Kcal/mol) | No. of H-bonds | Length of H-bonds | Formed amino acids with H-bonds |
|----------|--------------------------|----------------|-------------------|-------------------------------|
| Reference legend: | | | | |
| Erlotinib | − 3.3 | 3 | 3.15A | GLN767 |
| 4B2 | − 1.6 | 1 | 4.43A | GLY772 |
| 4B1 | −0.3 | 1 | 4.26A | VAL702 |
| 4B3 | −1.3 | 1 | 4.46A | LYS721 |
| 4A8 | −1.4 | 4 | 4.16A | MET 742 |
| 4B4 | − 3.0 | 3 | 4.44A | GLY772 |
| 4A6 | − 3.4 | 6 | 4.58A | LYS 721 |
| 4A7 | − 1.1 | 3 | 4.77A | LYS721 |
| 4A3 | − 2.2 | 3 | 4.38A | THR 766 |
| 4B5 | − 0.8 | 1 | 3.93A | Lys721 |
| 4B6 | − 1.1 | 1 | 4.32 A | Lys 721 |
| 4A1 | − | | | |
| 4A2 | − 1.1 | 1 | 3.75A | LYS721 |
| 4A9 | − 1.3 | 2 | 3.60A | GLY772 |
Table 2. IC\textsubscript{50} values of tested compounds standard deviation against MCF-7

| Compound No. | IC\textsubscript{50} (μg/mL) |
|--------------|-------------------------------|
| Doxorubicin  | 3.07 ± 0.27                   |
| 4A2          | 4.39 ± 0.47                   |
| 4B1          | 3.90 ± 0.41                   |
| 4B5          | 2.20 ± 0.13                   |
| 4B3          | 12.5 ± 0.97                   |
| 4A9          | 4.80 ± 0.56                   |

Fig. 1. 3RCD images of the compound 4A9

Fig. 2. 3RCD images of the compound 4B1
3.3 Receptor Grid Generation

Indocking a glide box was produced to characterize the centroid of the dynamic site. Co-crystallized ligand was held in gem structure of the protein planning wizard and it was utilized for the receptor lattice development. Glide grid generation Wizard is utilized to produce Grid Box. The measurements of Glide grid box of the protein were set to 14 Å x 14 Å x 14 Å.

3.4 Ligand Preparation

The ligand structures were produced by 2D sketcher and exposed to ligand preparation module of Schrodinger suite 2016. The chiralities were corrected and by including stereo concoction, ionization the ligands were changed over from 2D to 3D. The ionization and tautomeric state P^6.7-7.1 utilizing Epik module. In last phase of ligand preparation, mixes were limited utilizing optimized potentials for liquid simulations (OPLS-3) until a root mean square deviation of 1.8 Å was accomplished. A solitary low vitality ring affirmation per ligand was produced and ligand were streamlined.

3.5 Glide Ligand Docking

All the ligands are docked into the synergist pocket of human epidermal growth factor kinase receptor kinase protein ((PDB ID: 3RCD). 3RCD is the protein the protein that selected from the protein data bank to target human epidermal growth factor receptor 2. The best docked ligands are selected based on the Glide score. The ideal gathering among the ligands and the receptor were scored utilizing Glide ligand docking Module. Extra precision XP visualizer of Glide module was utilized to analyze the results. The upgrading parameters and the diminishing movement are noted simultaneously to obtain betterment in the result data.

4. RESULTS AND DISCUSSION

The study was aimed to synthesis new compounds by incorporating the thiazole and pyrazole moieties as one entity with improved biological activity targeting breast cancer. There were 20 compounds synthesized in this study, 10 compounds in series A and 10 compounds in series B (4A1-4A10 & 4B1-4B10). The computational study was carried out first using docking software Schrodinger Glide XP, followed by synthesis of designed compounds and then lastly the in-vitro study on the synthesized compounds for anticancer properties. Among all the synthesized compounds, only five compounds shown good activity against breast cancer cells (MCF-7). The compounds that shown anticancer properties are 4A2 (P-chloro aniline derivative), 4B1 (Aniline derivative), 4B5 (m-fluro aniline derivative), 4B3 (m-chloro derivative), and 4A9 (m-anisidine derivative).

When a drug molecule binds to a target, binding energy is released, lowering the overall energy of the complex. The release of binding energy also compensates for any ligand transformation from
its energy minimum to its bound conformation with the protein. Higher negative binding energy means better stability of the complex [32-34].

Epidermal growth factor receptor (EGFR) and vascular endothelial growth factor receptor 2 (VEGFR-2) are promising cancer treatment targets because they play critical roles in tumour development, angiogenesis, and metastasis. The pharmacological potential of the pyrazole fraction has been demonstrated in numerous publications in which pyrazoles have been synthesized and tested against a variety of biological agents. Many biological activities have been reported for pyrazoles, thiazoles, and fused thiazoles; additionally, pyrazole and fused pyrazole systems, such as pyranopyrazole and pyrazolopyrimidines, are promising scaffolds for many anticancer agents [33-35].

The biological profiles of these new generations of thiazole would be a fruitful matrix for the advancement of better anticancer specialists. The drug design component ensures that thiazole is the ideal particle for the stated target activity. Thiazoles have better anticancer activity because they have a better binding domain and less cytotoxicity to normal cells (physiological cells), but they also have site-specific movement to malignant growth cells (pathological cells) [35-38].

The present study was aimed to design, synthesis, and evaluate core scaffold pyrazolone fused thiazolidinone derivatives as anticancer agents. In this study, ethyl acetoacetate was coupled with benzoyl chloride and aromatic amines like para, meta forms of aniline, fluoro anilines, chloro-anilines, 4- methoxy 2 nitro aniline to provide the amino derivatives. Ethyl acetoacetate was used in the above reaction to avoid interference of the active methylene, whereas benzoyl chloride, aromatic amines, and the produced amino derivatives were used as starting materials for the synthesis of the target compounds pyrazolone fused thiazolidinone derivatives. The resultant compound was then allowed to react with thiomalic acid to provide 3-carboxymethyl,4-thiazolidinone. This is an intermediary of the thiomalic acid with primary amines.

The pyrazole derivatives react with benzoyl chlorides and produced intermediates of thiohydrazonate, which then loses water molecule to produce the final isolable thiazolyl-pyrazole derivatives. The analytical data of these synthesized compounds are in accordance with the proposed structures as mentioned in the scheme. These structures were further confirmed when the benzoyl chloride reacts with primary amines (as Schiff base reactant) to produce the typically identical products.

The structures of synthesized compounds are supported by analytical. Docking studies were also carried out on the compounds using the GLIDE XP software. Protein and ligand regularization and optimization were carried out. Each docked compound was scored based on its fit in the ligand-binding pocket (LBP) and binding mode. The newly synthesized compounds were tested for cytotoxicity on human tumour cell lines in this study. Among all the synthesized compounds, only two compounds (A9 and B1) shown highest binding affinity and potential activity on target cells, which was shown in the Fig. 3. 3RCD is the protein selected from the protein bank for the study. The image explains the binding affinity of the protein, and the compound with the target cells.

4. CONCLUSION

We demonstrated a simple and efficient method for synthesizing a wide range of pyrazolone fused thiazolidinone derivatives from inexpensive laboratory-available starting materials. Since then, several pyrazolone fused thiazolidinone derivatives 4A1-4A10 & 4B1-4B10 have been synthesized by reacting Schiff base with primary amine substitutions. Simple synthetic routes were pursued, with no hazardous solvents, catalysts, or heavy metals included. Furthermore, computational studies were performed on all the products, and the results revealed that four new compounds had promising human epidermal growth factor receptor binding affinities. Doxorubicin was used as the standard drug to test the cytotoxicity of the potent products against MCF-7. The benefits of binding affinities were consistent with the data obtained from the practical anticancer screening of the tested compounds.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of
knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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