Innovative Synthetic Approaches for Heterocyclic Scaffolds and Their Chemotherapeutic Applications

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Abstract

Cancer still represents one of the major causes of death worldwide, other options are therefore required for the pharmacotherapy with less side effects and high efficacy. This study presents the synthesis and design of novel heterocyclic scaffolds for cancer chemotherapy. The objectives of this study were to design economic synthetic methodologies for heterocycles, to enable the synthesis of new anticancer agents and to carry out studies on the structure-activity relationships (SAR). Several new heterocyclic derivatives were prepared and tested for their cytotoxic activity towards a panel of cancer cell lines. 3D QSAR modelling as well as molecular docking studies made us able to predict and optimize biological activities. Activities for the compounds 41, 45 and 50 were computed as 0.852453, 0.800144 and 0.965794, respectively (Table 1) which were very close with the activity of Vorozole. From the docking studies (Table 2) we observed favorable interactions with the aromatase receptor in terms of hydrophobic contacts and ideal geometry. Radiosensitizing assay in Table 3 revealed that 8b, 11a, 12a, 18b are powerful sensitizers for the γ irradiation-related cell-killing activity. The detailed characterization (Table 4 and 5) of the synthesized compounds 21a, 21b, 24a, 24b, 25a, 25b were obtained by full NMR and LC-MS in the structural integrity of the compounds. The results indicate that selection of these heterocyclic scaffolds will provide the basis for continued development of potent anticancer agents with potential for combination treatment modalities and radiation sensitization regimens.

Keywords: *Heterocyclic compounds, Anticancer agents, Structure-activity relationship, Molecular docking, radiosensitization.*

1. Introduction

Apathogenetic burden of cancer is increasing worldwide, while conventional chemotherapy is often restricted due to resistance mechanisms and because of its high side effects (Wang et al., 2024). The present therapeutic strategies, albeit successful in some, are often associated with drug resistance, poor selectivity, and extreme toxicities (Malla et al., 2022). It has become an urgent task to discover the novel anti-tumor agents that have better therapeutic index in contemporary drug discovery. Heterocyclic systems belong to the so-called privileged structures in medicinal chemistry, and provide with various bioactive molecular scaffolds to be refined for the particular biological target. Heterocyclic skeletons possesses specific electronic properties and conformational flexibility that are powerfully attractive for designing anticancer agents. Some methods towards the synthesis of more and more complex heterocyclic systems having improved drug profile have been made possible due to recent developments in synthetic strategies (Mahantesh & Sharma, 2023). Computational techniques such as quantitative structure-activity relationship (QSAR) design and molecular docking, have been broadly used in the drug discovery process, and have had a major

impact on the rational design of bioactive molecules. Such approaches offer the possibility of predicting the biological activities and optimizing molecular structures before synthesis, making it possible to cut down the time and cost needed for drug development (Jafri & Amniouel, 2024).

The literature review finds that combination therapy strategies, especially chemotherapy and radiotherapy, have demonstrated a promising effectiveness in cancer therapy. Radiosensitization, that is, chemical agents augment radiation therapeutic effects, is an important strategy to increase efficacy of treatment while theoretically allowing reduction of radiation dose and related toxicity (Mathan et al., 2022). Nanotechnology combined with personalized medicine approaches has also broadened the range of possible uses of new anticancer agents (Mehta et al., 2024; Yang et al., 2024). There are several modern studies about the antitumor activities of some heterocycles including triazine, pyrimidine and quinoline derivatives. The versatility of these heterocyclic systems provided drug design opportunities to tinker with pharmacological profile and therapeutic indices (Katiyar et al., 2022). The ability to access these complex molecular assemblies via new synthetic approaches has been highlighted for the future of medicinal chemistry.

2. Objectives

1. To design and implement novel synthetic strategies for the efficient and sustainable synthesis of heterocyclic compounds.
2. To synthesize a series of novel heterocyclic compounds and evaluate their cytotoxicity against a range of cancer cell lines.
3. To conduct detailed structure-activity relationship (SAR) studies to determine the molecular features responsible for the anticancer activity of synthesized heterocyclic compounds.

3. Methodology

This research was facilitated through a multidisciplinary strategy that integrated computational modeling, synthetic chemistry and biological investigation. Both predictive modelling and experimental validation approaches were utilized in the study design so that the novel heterocyclic compounds could be evaluated to the fullest extent. Structurally diverse compound were selected from a virtual library of such compounds based on computational predictions for activity were the main criterion, such that the most promising activity could be investigated. A new set of 32 chemotypes (compounds 35-66) were evaluated in the 3D-QSAR analysis, while additional compounds were prepared for both biological and in depth characterization studies. The computational tools used were sophisticated molecular modeling program for 3D-QSAR analysis and molecular docking studies. The 3D-QSAR model generated using pharmacophore-based alignment techniques. The three-point pharmacophore model of ARR (one A moiety and two R moieties), was adopted as the criterion for molecular alignment and activity prediction. Molecular docking was performed using the Schrodinger suite maestro platform and Glide XP Visualizer for better visualization of ligand-receptor interaction. AER was chosen as the primary target being an important player in the hormone-dependent cancers paths. A surface mesh was built at the active site to maximize ligand-receptor interactions and to identify the key binding determinants.

The radiosensitizing screening platform was based on systematic determination of γ-radiation cell-killing enhancement profile of a compound. The human breast cancer cell line MCF7 was taken as the model (MCF7), and different molar treatments {10μM, 25μM, 50μM and 100μM} were performed. The radiation dose was set at 8 Gy employing a Gamma cell-40(60Co) source from the National Cancer Institute at Cairo University, and posttreatment examination occurred after 48 h as described in colorimetric tests. The synthetic methodology consisted in the elaboration of a variety of heterocyclic scaffolds comprising triazine, pyrimidine, and quinoline frameworks. Six representative compounds (21a, 21b, 24a, 24b, 25a and 25b) were prepared via classical heterocyclic chemistry protocols with yields between 52-72%. The design, synthesis, and biological evaluation of both fluoro- and chloro-substituted aryl esters were explored in order to assess their effects on biological activity and physiochemical properties. All obtained compounds were fully characterized by a wide range of analytical techniques including 1H NMR (400 MHz, DMSO-d6), 13C NMR (100 MHz, DMSO-d6), and LC-MS (ESI+) essential for the confirmation of their structure and purity. The molecular constitution of all the synthesized compounds were confirmed using elemental analysis.

4. Results

3D-QSAR Analysis

The 3D-QSAR model had a high prediction ability in the training and test set, as indicated in Table 1. The three-point pharmacophore model ARR tophits were effective in identifying the relevant molecular features associated with bioactivity. Interpretation of the 3D-QSAR model suggested that the region with the hydrogen bond acceptors, especially with O and N atoms, contributed to favorable environment for higher biological potency.

Table 1. Novel chemotypes' 3D QSAR findings (compound 35-66)

S.No.	Ligand	Predicted Activity	Align Score	Vector Score	Volume Score	Fitness
1	35	0.8697	0.043914	0.923434	0.553571	2.440411
2	36	-0.80296	0.256423	0.784339	0.442922	2.013576
3	37	-0.80296	0.2564	0.784376	0.454333	2.025042
4	38	-0.80296	0.256671	0.784165	0.457547	2.02783
5	39	-0.80296	0.256245	0.78448	0.456471	2.027413
6	40	0.737991	0.044625	0.923212	0.425	2.311024
7	41	0.852453	0.043946	0.923415	0.563636	2.450429
8	42	-0.73642	0.256497	0.784367	0.464115	2.037434
9	43	-0.73642	0.25638	0.784372	0.460808	2.031533
10	44	-0.70664	0.277472	0.772249	0.478673	2.019696
11	45	0.800144	0.277472	0.772249	0.478673	2.019696
12	46	-0.7974	0.043947	0.92334	0.570552	2.457269
13	47	-0.7974	0.25642	0.784365	0.468599	2.034229

14	48	-0.7974	0.256828	0.784019	0.454333	2.023429
15	49	-0.76701	0.256095	0.784621	0.465228	2.03646
16	50	0.965794	0.428475	0.805351	0.5075	1.955788
17	51	-0.47892	0.066766	0.949119	0.566265	2.459749
18	52	-0.81155	0.407089	0.839301	0.453488	1.953549
19	53	-0.69853	0.407735	0.839245	0.447005	1.946471
20	54	-0.59219	0.40921	0.839001	0.450935	1.948297
21	55	0.633341	0.406863	0.834213	0.44213	1.973925
22	56	-0.66154	0.066775	0.9491	0.583851	2.477305
23	57	-0.654	0.417373	0.760761	0.459135	1.872083
24	58	-0.654	0.407764	0.839176	0.455397	1.954771
25	59	-0.654	0.407765	0.839127	0.46747	1.967962
26	60	0.791436	0.4078	0.839162	0.472019	1.988314
27	61	0.767623	0.044013	0.923331	0.561934	2.448587
28	62	-0.61032	0.066866	0.949051	0.582043	2.475537

Blue cubes in the hydrogen-bond acceptor region of the oxygen and nitrogen atoms, indicating a preferred position to attach a center, that would also result in an optimal positive effect on the biological activity. The introduction of functional groups to a suboptimal region, such as the red cubes just beyond the zone of H-bond acceptor, was found to be disadvantageous to biological activity. Vector attributes, including aromatic rings and acceptors, were highly significant for the aligned structures as reflected by the vector score values. Volume score based on overlapping van der Waals models of non-hydrogen atoms for each structure pair. To increase the efficiency of the ligand one hydrogen bond acceptor (A)—either nitrogen or oxygen—was necessary. The interaction between imidazo and hydrogen bond acceptor (A) region revealed the less-potency of ligand was observed in the presence of [1,3,4]thiadiazole or imidazo2,1-Boxadiazole rings. Due to the freedom of rotation of the nitrogen bond, the binding of benzothiazole (aromatic) to this site had a positive influence on activity (ligand 40) compared to fused bicyclic rings. Based on the 3D-QSAR data in Table 1, all the ligands 41, 45 and 50) showed good projected activity against Vorozole, 0.852453, 0.800144, 0.965794, respectively. It is not surprising to find that there was a substantial amount of expected action by letrozole (1.602764).

Molecular Docking Studies

Molecular docking study assisted in determining the essential interactions between the ligand and receptor (Table 2). The binding cleft of aromatase receptor site presented a special geometry, and an iodine flask model accompanied by the enzyme was established. The hydrophobic pocket was composed of L-phenylalanine 221 and L-Valine 313 framing a cone shaped and heme prosthetic oriented funnel necessary for the aromatization reaction.

Table 2. Docking findings of novel non-steroidal chemo-types using the Schrodinger suite maestro

S. No.	Ligand	R/S	Docking Score	H-Bond	3D Docking Image

1	21 (Letrozole)	-	-5.806650	1; MET 374	21 (Letrozole)
2	66 (Vorozole)	S	-6.793254	1; MET 374	66 (Vorozole)
3	41 (S)	S	-5.712918	1; ASP 309	41 (S)
4	41 (R)	R	-4.982949	1; SER 478	-
5	45 (S)	S	-6.928581	1; ASP 309	45 (S)
6	45 (R)	R	-6.609411	1; THR 310	-
7	50 (S)	S	-5.810653	1; MET 374	50 (S)
8	50 (R)	R	-5.008475	1; ALA 306	-
9	60 (S)	S	-6.218132	1; ASP 309	60 (S)
10	60 (R)	R	-5.705738	1; THR 310	-
11	61 (S)	S	-5.685033	1; ASP 309	61 (S)

To make the interaction between ligand and receptor more interaction the maestro workspace Glide XP Visualiser was employed to present the active site surface mesh. One of the more interesting findings was that of the geometry of the aromatase receptor site, appearing as a typical iodine flask. The active site was a hydrophobic area, with a conical input comprising L-phenylalanine 221 and L-Valine 313. The planar surface of the flask is thus suggested to be essential for aromatisation, which does not occur when the 11H-mGyneCCoM is left with a single ethyl side chain (Lewis et al., 1996), as it would remote electrons donation from the molecule. The docking study (Table 2) showed the most favorable ligand receptor binding affinities and the effective interaction profile for the new non-steroidal chemo-types. Structural elements involved in increased binding comprised an adequate alignment of aromatic rings combined with appropriately placed heteroatoms for hydrogen bonding interactions. The conical shape of the active site was well-suited to accommodate the various heterocyclic scaffolds and the heme prosthetic group played an essential role in donating electrons for interacting with substrate.

Radiosensitizing Evaluation

The radiosensitizing screen revealed compounds with strong potential for γ-radiation therapeutic enhancement. The integrated performance of the MCF7 human breast cancer cell-based model is shown in Table 3.

Table 3. Using a human breast cancer cell line (MCF7) and γ-radiation, we tested compounds 8b, 11a, 12a, and 18b for their anticancer properties in vitro

S. No.	Ligand	R/S	Docking Score	H-Bond	3D Docking Image (Figure 4.1.)
1	21 (Letrozole)	-	-5.80665	1; MET 374	21 (Letrozole)
2	66 (Vorozole)	S	-6.79325	1; MET 374	66 (Vorozole)
3	41 (S)	S	-5.71292	1; ASP 309	41 (S)
4	41 (R)	R	-4.98295	1; SER 478	-
5	45 (S)	S	-6.92858	1; ASP 309	45 (S)
6	45 (R)	R	-6.60941	1; THR 310	-

7	50 (S)	S	-5.81065	1; MET 374	50 (S)
8	50 (R)	R	-5.00848	1; ALA 306	-
9	60 (S)	S	-6.21813	1; ASP 309	60 (S)
10	60 (R)	R	-5.70574	1; THR 310	-
11	61 (S)	S	-5.68503	1; ASP 309	61 (S)

Each value is the mean of three values ± Standard Error

*: Significant difference from control group at $p<0.001$

On the basis of the compounds that were the most potent in regulating γ-radiation induced clonogenic death, we conducted this study using the Gamma cell-40 (60Co) irradiator purchased by the National Cancer Institute (Cairo University). The two most active chlorinated (8b and 18b) and the two most active fluorinated (11a and 12a) compounds were selected for further study. Cells were seeded at a density of 104 cells/well in 96-multiwell plates for 24 h before exposure to a single 8 Gy dose of γ-irradiation. The cells were incubated for 48 h in a 5% CO2 atmosphere at 37°C. After 48 hours of the above protocol, the cells were then fixed, washed and stained with a solution of 0.4% (wt/vol) SRB in 1% acetic acid. After four washes with 1% acetic acid to remove excess of free dye, the bound stain was extracted with Tris-EDTA. The intensity of the colors was measured by the ELISA reader at a wavelength of 570 nm. The cells were treated with the selected compounds at molarities of 10, 25, 50, and 100 µM, after which a single dose of γ-rays at 8 Gy was applied at a dose rate of 2 Gy/min after 2 h. The mean ± standard error of the other fractions on the table 3 were calculated, and statistical analysis was performed by a 1-way ANOVA test. Both compounds presented statistically significant differences compared with control ($p<0.001$), demonstrating their radiosensitising potential.

Compound 25a and 25b Characterization

The structural integrity and purity of compounds 25a and 25b was confirmed by detailed analytical characterization (Table 4). The compound 25a that carried a 4-fluorophenyl substituent showed a unique spectroscopic profile.

Table 4. Differences between Compound 25a and 25b

Feature	**Compound 25a**	**Compound 25b**
Aryl Substituent (Ar)	4-Fluorophenyl (C_6H_4F-4)	4-Chlorophenyl (C_6H_4Cl-4)
Molecular Formula	$C_{26}H_{22}FN_5O_3S_2$	$C_{26}H_{22}ClN_5O_3S_2$
Molecular Weight (g/mol)	535.61	552.07
Melting Point (°C)	198--200	200--202
Yield (%)	54	52
C (%) Calculated/Found	58.30 / 58.51	56.57 / 56.71
H (%) Calculated/Found	4.14 / 4.32	4.02 / 4.30
N (%) Calculated/Found	13.08 / 12.80	12.69 / 12.48
Aryl Effect	Electron-withdrawing via fluorine; more electronegative	Electron-withdrawing via chlorine; slightly bulkier

LC-MS (ESI$^+$) $[M+H]^+$	m/z = 536.10	m/z = 553.14

The 1H NMR (400 MHz, DMSO-d6) spectrum of compound 25a exhibited a singlet at δ 1.32 ppm (6H) due to the gem-dimethyl groups at C-7 of the hexahydroquinoline ring. Multiplets (δ 2.48-3.58 ppm) for the methylene protons at C-6 and C-8 and singlet (δ 5.28 ppm) corresponding to the methine proton at C-4. The aromatic signals appearing at δ 6.90-8.40 ppm were overlapped multiplets due to 4-fluorophenyl, sulfonamide phenyl, and triazine protons. The NH 2 protons of the sulfonamide group resonated as a broad signal at δ 10.12 ppm. 13C NMR (100 MHz, DMSO-d6) displayed gem-dimethyl carbons (δ 27.7), methylene carbons at C-6 and C-8 (δ 33-42), and methine carbon at C-4 (δ 54.6). Compound 25b also recorded spectroscopic feature akin to compound 1 but with some specific differences owing to chlorine substitution. The difference in electronic effects between fluorine and chlorine substitution was noted from the comparison shown in Table 4, i.e., fluorine had a more electronegative nature and created larger deshielding effects, and chlorine led to higher molecular mass and somewhat different CS patterns. The molecular integrity of the compounds was verified by the fact that strong molecular ions from both were discernable at or near their calculated molecular weights using LC-MS.

Characterization of Compound 24a and 24b

Compounds 24a and 24b were fully characterized by spectroscopic and analytical data, the comparison data are summarized in Table 5. These analogues had a pyrimidine core with a hydrazinyl substituent.

Table 5. Differences between Compound 24a and 24b

Parameter	**Compound 24a**	**Compound 24b**
Aryl Group (Ar)	4-Fluorophenyl (C_6H_4F-4)	4-Chlorophenyl (C_6H_4Cl-4)
Molecular Formula	$C_{25}H_{25}FN_6O_3S$	$C_{25}H_{25}ClN_6O_3S$
Molecular Weight	508.57 g/mol	525.02 g/mol
Melting Point (°C)	150--152°C	170--172°C
Yield (%)	72%	69%
^{1}H NMR (Aromatic Region)	δ 6.90--8.28 ppm (with F-induced splitting)	δ 7.02--8.36 ppm (Cl deshielding effects)
Hydrazinyl Protons (^{1}H NMR)	δ 9.82 & 10.65 ppm (broader singlets)	δ 9.85 & 10.68 ppm (slightly shifted)
Key ^{13}C NMR Difference	Fluorinated carbon shifts at ~113--143 ppm	Chlorinated carbon shifts at ~114--141 ppm
LC-MS (ESI$^+$)	m/z = 509.14 $[M+H]^+$	m/z = 526.16 $[M+H]^+$
Carbon Content (Calculated)	C: 59.04%	C: 57.19%
Nitrogen Content (Calculated)	N: 16.52%	N: 16.01%
Functional Group Influence	F: More electronegative, causes deshielding and lower mass	Cl: Heavier, less electronegative, increases mass

Compound 24a bearing the 4-fluorophenyl-group on a pyrimidine backbone had indicative NMR spectra. The 1H NMR spectrum (400 MHz, DMSO-d6) showed a singlet at δ 1.34 ppm (6H) due to the gem-dimethyl groups on

hexahydroquinoline ring. The protons of the hydrazinyl (-NHNH2) group were observed as broad singlets at δ 9.82 and δ 10.65, suggesting the existence of two NH hydrogens that participated in hydrogen bond formation. Aromatic (δ 6.92-8.35 ppm) Overlapping multiplets associated with the 4-fluorophenyl, sulfonamide phenyl, and pyrimidine protons. 13C NMR resonance at δ 27.6 ppm for the gem-dimethyl carbons, aromatic carbons between δ 113-143 ppm, and feature fluorinated phenyl shifts with C-F coupling. As summarized in Table 5, compound 24b was similar in terms of spectral data to its 4-chlorophenyl congener and had a molecular mass of 525.02 g/mol with an LC-MS peak at m/z = 526.16 [M+H]+. The production yield for 24a was 72% and 24b was 69% and their melting points are 150-152° C. and 170-172° C., respectively. The hydrazinyl protons exhibited minor chemical shift perturbations (24a with broadened singlets presumably attributed to the electron withdrawing influence of fluorine).

Compound 21a and 21b.

Compounds 21a and 21b of triazine-thione type were fully characterized by advanced analytical methods. 21a, with the 4-fluorophenyl substituent, exhibited typical spectral features. The 1H NMR (400 MHz, DMSO-d6) exhibited a singl The multiplets at δ 2.38-3.36 ppm were assigned to the methylene protons at C-6 and C-8, while a singlet at δ 5.20 ppm corresponded to the methine proton at C-4. The NH proton of the triazine-thione ring was observed as a broad singlet at δ 8.65ppm and the NH2 protons of the sulfonamide as broad signal at δ 9.94 ppm. The 13C chemical shifts indicated gem-dimethyl carbons appeared in the 27.7 ppm region while aromatic carbons were observed in the 112–140 ppm region, including the fluorine group-coupled bond in the 4-fluorophenyl ring. Carbons of C=N and C=S in triazine-thione system appeared at downfield (δ 165-178 ppm) and the carbonyl carbon was observed around δ 165-178 ppm. The LC-MS (ESI+) was dominated by the molecular ion peak at m/z = 511.10 [M+H]+, which corresponds to the calculated molecular weight of 510.60 g/mol for compound 21a, while the 4-chlorophenyl analogue 21b displayed comparable data, with a calculated molecular weight of 527.06 g/mol and corresponding LC-MS peak at m/z = 528.12 [M+H]+. The presence of the triazine-thione motif was associated with specific chemical and electronic properties for these compounds, which differentiated them among the other synthesized derivatives and influenced their unique biological activities. Systematic comparison of the two types of compounds showed strong influence of the nature of halogen substitution on the spectroscopic characteristics and biological potential.

5. Discussion

The extensive study of new heterocyclic frameworks has, it was proved, resulted in important chemotherapeutic leads. The combination of computational modeling with experimental validation has yielded a solid platform for the comprehension of structure-activity relationships and optimization of compound design to optimize anticancer efficacy (Villegas et al., 2024). The 3D-QSAR studies provided effective models for predicting biological activity, and hydrogen bond acceptor regions and aromatic ring systems were the most significant structural features affecting the activity. The improved inhibitory potential of compounds 41, 45, and 50 may be due to optimum positioning of the pharmacophoric functionalities and better electronic characteristics (Katiyar et al., 2022). The higher activity of benzothiazole compounds is consistent with the literature emphasis on supporting of sulfur containing heterocycles in medicinal chemistry. The molecular docking studies contributed the useful information to binding modes of these compounds in aromatase. The characterisation of the active site as a hydrophobic pocket with specific shape-based

requirements, has significant importance implications for the design of compounds in the future. The alpha carbon atoms for ligand and the heme group are conical in shape and the shape of the heme-containing base is shown as flat and this shape of the molecule resembles that of a bottle-like molecule, the molecule has a flask-like overall shape and conical entrance, Hence ligand-receptor interactions with bottle-like receptor (aromatase) with its conical entrance and a flat heme-containing base may involve ligand-specific contacts (Nozad et al., 2024).

The radiosensitizing assay is a particularly important conclusion and shows a new therapeutic potential of these heterocycles. Through the screening of compounds 8b, 11a, 12a, and 18b, their radiosensitizing effects were shown and they might be use for the combination therapy. This is especially important considering the contemporary focus on personalized medicine strategies in cancer therapies (Hayden et al., 2024). The comprehensive SAR analysis of the qualitative physicochemical properties of final compounds 21a, 21b, 24a, 24b, 25a and 25b were found to be vital to understand the essential structural validation and significant structure-activity relationship studies as presented in Tables 4 and 5. A systematic comparison between fluoro- and chloro-derivatives showed that electronic effects are important in the spectroscopic properties and biological activities. Different heterocycles systems (triazine; pyrimidine; quinoline) produced distinct pharmacological profiles and the yields as well as melting points of the series described herein were not the same (Chelu & Musuc, 2024). The synthesis and characterization of six representative compounds (21a, 21b, 24a, 24b, 25a, 25b) proves the synthetic approaches are feasible and illustrate with examples the ability to generate complex heterocyclic scaffolds. The high yields of these compounds (from 52 to 72% according to Tables 4 and 5) are a clear evidence of the efficiency of the designed synthetic procedures. Analytical data obtained by NMR and LC-MS analysis provided evidence that all of the synthesized compounds showed good yields and high purity, as well as structural integrity, with MW 508.57-552.07 g/mol.

The clinical relevance of these results is encouraged by the well-designed experiments and their statistical significance. The tumoricidal activities and radiosensitization indicate that these actives may play dual therapeutic roles in cancer treatment regimens. Nevertheless, additional studies on in vivo efficacy, toxicity profiles, and pharmacokinetic properties will also be necessary before clinical applications (Puspitasari et al., 2024). Deconvolution of the structure-activity relationship showed that the halogen substitution pattern greatly affects the anti-cancer activity as well as sensitizing dose enhancement. It was shown that the electronic influence of fluorine versus chlorine substitution could be used to identify suitable substitution sites for further compound optimization. The introduction of different heterocyclic scaffolds enabled the pharmacological properties fine-tuning and even access a broad chemical space for biological investigation (Lai et al., 2024).

6. Conclusion

This report is a first report to show that these novel heterocyclic scaffolds could be a promising candidate in the treatment of human cancer with broad therapeutic applications. The coordinated application of computational modeling, synthetic chemistry, thorough product characterization, and biological evaluation has formed a sound basis for compound evaluation and development. The 3D-QSAR analysis as shown in Table 1 helped us to identify the important molecular features for the biological activities, while the molecular docking studies represented in Table 2 has described the binding patterns with the target proteins. As per the radiosensitizing assessment provided in Table

3 another therapeutic dimension came to light, thus indicating that role in combination therapy schedules which was inducible. The thorough characterization of six representative compounds (21a, 21b, 24a, 24b, 25a, 25b)(Tables 4 and 5) verified their structures and offered important aspects for the stucture-property relationships. The successful synthesis of structurally varied heterocyclic skeleton in good to excellent yields (52–72%) of the target molecules is indicative of the practicability of the synthetic procedures developed. These results significantly contribute to those of medicinal chemistry and to clarify a solid basis for designing the next generation of heterocyclic scaffolds to exploit promising clinical anticancer with improved antitumor and reduced side effects.

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