

A REVIEW ON THIOPHENE-BASED HYBRIDS: ADVANCES IN SYNTHESIS AND MULTITARGET PHARMACOLOGICAL APPLICATIONS

Priya A.^{1*}, Mahesh Kumar N.² and Dr. Shachindra L. Nargund³

^{1,2}PG Scholar, Department of Pharmaceutical Chemistry, Nargund College of Pharmacy, Bengaluru-560085, India.

³Professor, Department of Pharmaceutical Chemistry, Nargund College of Pharmacy, Bengaluru-560085, India.



*Corresponding Author: Priya A.

PG Scholar, Department of Pharmaceutical Chemistry, Nargund College of Pharmacy, Bengaluru-560085, India.

<https://doi.org/10.5281/zenodo.17119203>

Citation

Priya A.1*, Mahesh Kumar N.2 and Dr. Shachindra L. Nargund3. (2025). A REVIEW ON THIOPHENE-BASED HYBRIDS: ADVANCES IN SYNTHESIS AND MULTITARGET PHARMACOLOGICAL APPLICATIONS. World Journal of Pharmaceutical and Life Science, 11(9), 20–36.

Article Received on 24/06/2025

Article Revised on 14/07/2025

Article Accepted on 03/08/2025

ABSTRACT

Recent advancements in medicinal chemistry have underscored the versatility of heterocyclic frameworks, particularly thiophene, in the pursuit of novel therapeutic agents. Thiophene-based hybrids are increasingly recognised as dynamic platforms for innovation, as scientists strategically merge the thiophene core with other bioactive motifs to construct multifunctional drug candidates. This hybridisation approach responds directly to modern demands: improved selectivity, reduced toxicity, and the ability to address complex diseases through multi-target mechanisms. Groundbreaking synthetic methods such as click chemistry, green synthesis, and AI-driven molecular design now play pivotal roles in tailoring thiophene hybrids for enhanced pharmacological properties. Current research extends far beyond traditional applications, with thiophene hybrids showing promise in fields such as oncology, antimicrobial therapy, neurodegeneration, and metabolic disorders. Furthermore, drug repurposing and fragment-based drug design have accelerated the identification of new thiophene-based hybrids with clinically relevant functionality. This review consolidates contemporary strategies and therapeutic outcomes, highlighting how innovative approaches to thiophene-based hybrids are redefining the frontiers of drug discovery. As the integration of computational and experimental methods deepens, thiophene hybrids stand at the forefront of next-generation medicinal chemistry, offering new hope for challenging medical conditions.

KEYWORDS: Antimicrobial therapy; Bioactive motifs; Medicinal Chemistry; Synthetic methods; Therapeutic outcomes; Thiophene hybrids.

INTRODUCTION

Thiophene, a five-membered heteroaromatic compound containing four carbon atoms and one sulfur atom, is a foundational building block in medicinal chemistry, due to its unique physicochemical properties, including aromatic stability, electron-rich nature, and synthetic flexibility. These attributes allow for easy derivatisation

and incorporation into diverse molecular frameworks, making thiophene a valuable core in drug design. Over the past two decades, thiophene derivatives have been associated with a wide spectrum of biological activities such as anti-inflammatory, antimicrobial, antiviral, and notably, anticancer effects.

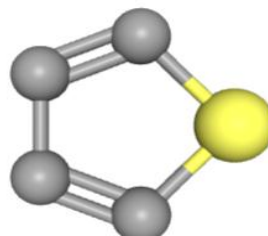
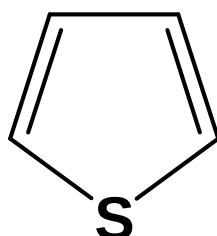


Fig. 1- 2D and 3D structure of basic thiophene scaffold.

One of the most promising strategies in modern drug discovery involves the development of **hybrid molecules**-compounds that merge two or more pharmacophores into a single entity. This hybridisation

approach often leads to enhanced potency, improved selectivity, and multi-target engagement, which are crucial for treating complex diseases like cancer. Thiophene-based hybrids have particularly shown great

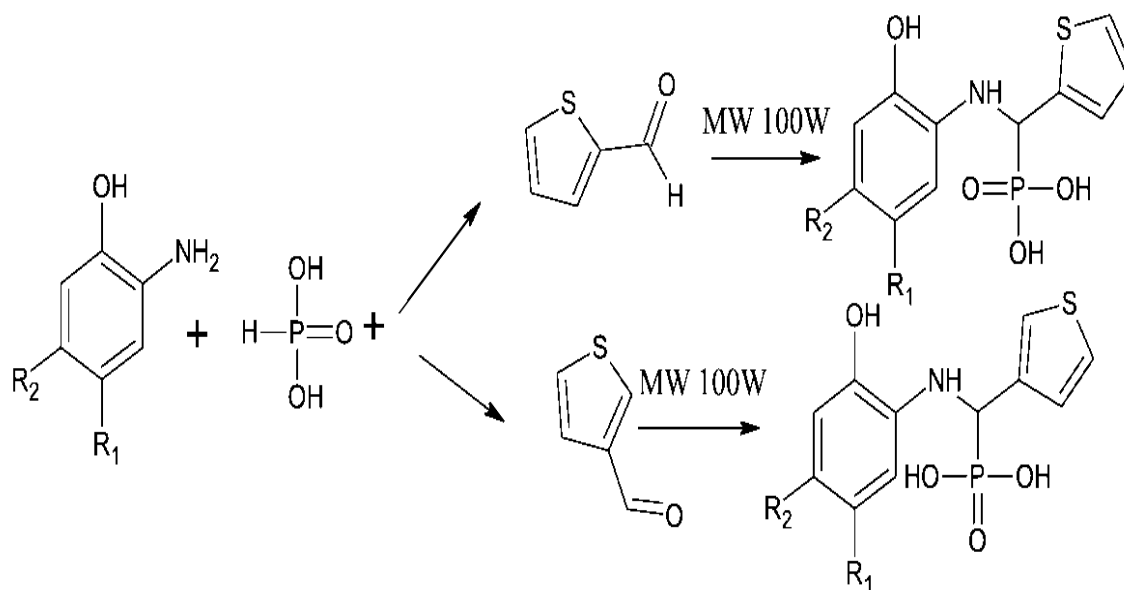
potential in overcoming limitations of traditional monotherapy by interacting with multiple cellular targets involved in tumour progression, angiogenesis, and drug resistance. Advancements in synthetic organic chemistry have facilitated the efficient construction of thiophene hybrids through reactions such as Suzuki coupling, click chemistry, and multicomponent reactions. Furthermore, computational tools like molecular docking, pharmacophore modelling, and ADME prediction have accelerated the identification of promising candidates with favourable pharmacological profiles. This review aims to provide a comprehensive overview of the latest developments in the synthesis, biological evaluation, and pharmacological relevance of thiophene-based hybrids. Special attention is given to their role in anticancer research, highlighting key molecular targets and the innovative design strategies shaping the next generation of therapeutics.

DIFFERENT SYNTHETIC STRATEGIES

The synthesis of thiophene-based hybrid molecules has become a key area of interest in medicinal chemistry due to the thiophene ring's unique ability to integrate with various pharmacophores. Traditional synthetic strategies often involve multi-component reactions (MCRs), cross-coupling reactions (such as Suzuki–Miyaura or Heck reactions), and nucleophilic substitutions, enabling the

rapid assembly of structurally diverse molecules. Among these, microwave-assisted synthesis has emerged as an efficient and eco-friendly approach, offering shorter reaction times, higher yields, and cleaner reaction profiles. This method is particularly useful in synthesizing α -amino phosphonates and other bioactive hybrids under catalyst-free conditions. To fully realize the therapeutic potential of thiophene-based hybrids, a variety of innovative and efficient synthetic strategies have been explored.

Tlidjane et al. reported the green synthesis of novel α -amino phosphonic acids incorporating thiophene rings via a microwave-assisted three-component reaction involving amino phenols, thiophene carboxaldehydes, and phosphorus acid in ethanol without catalysts. These compounds demonstrated remarkable antioxidant and antifungal properties, outperforming standard agents like BHT and BHA. Density Functional Theory (DFT) studies revealed favourable electronic properties, while molecular docking indicated strong inhibitory interactions with SARS-CoV-2 main protease. The thiophene moiety contributed to enhanced binding and stability of the hybrids. This study highlights the promise of microwave-assisted synthesis in rapidly generating bioactive thiophene-based scaffolds for future therapeutic development (**Scheme 1**).^[1]

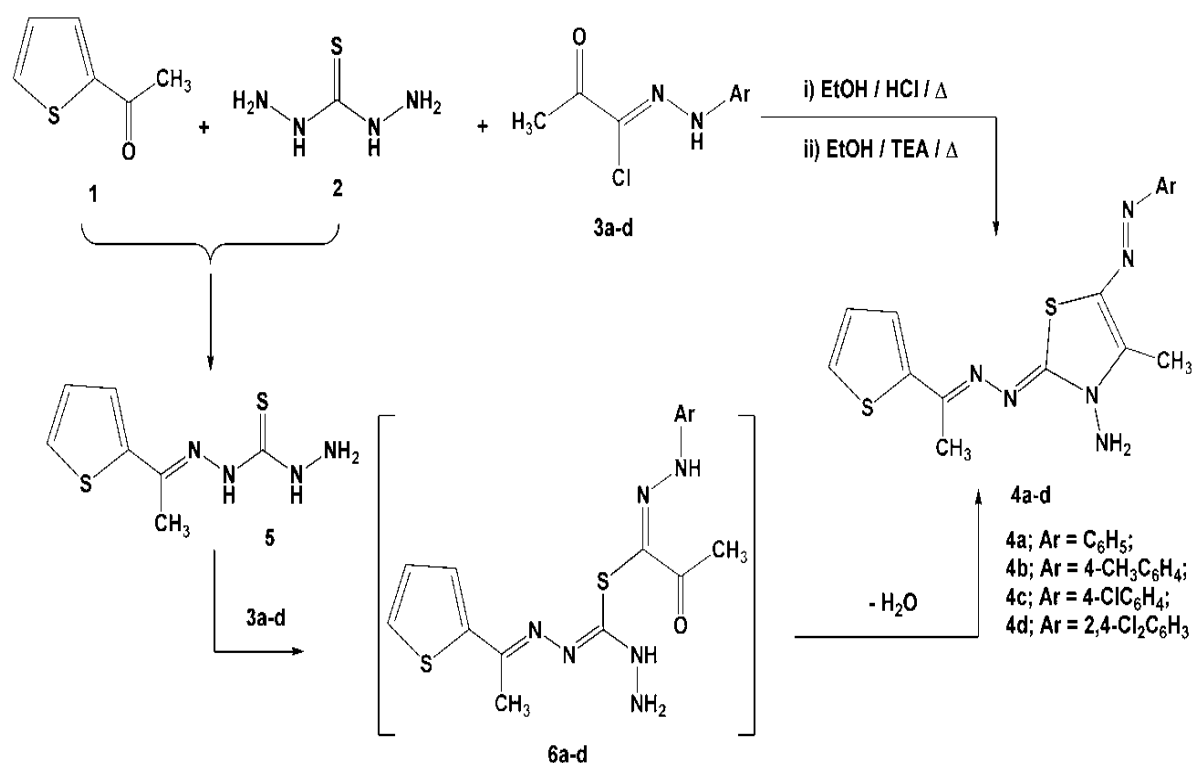


Scheme 1

Scheme 1. Synthesis sequences of α -amino phosphonic acids with (5N2TPA, 5N3TPA: $R_1 = H$, $R_2 = N_2$, 4M3TPA: $R_1 = CH_3$, $R_2 = H$, 5M3TPA: $R_1 = H$, $R_2 = CH_3$)

Gomha et al. synthesised novel thiazole–thiophene hybrids by a multicomponent reaction involving 2-acetylthiophene, thio-carbohydrazide, and hydrazonoyl chlorides or halo carbonyl compounds under reflux with triethylamine in ethanol, yielding compounds 4a–d. Among the series, 4b and 13a exhibited potent cytotoxic

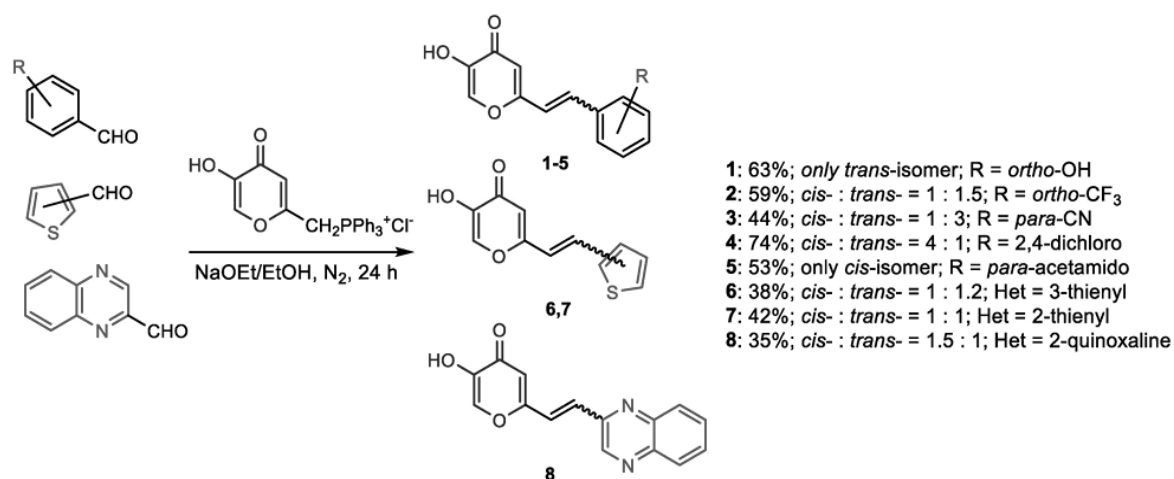
activity against MCF-7 breast cancer cells with IC_{50} values of 10.2 and 11.5 μM , outperforming cisplatin. (**Scheme 2**).^[2]



Scheme 2. Synthesis of aminothiazole derivatives 4a–d.

Mlakić et al. synthesised novel resveratrol–thiophene and resveratrol–maltol hybrids as cholinesterase inhibitors and antioxidants. Thiophene derivatives (II, III) exhibited potent AChE/BChE inhibition and antioxidant activity comparable to galantamine, while maltol hybrids showed weaker effects. The resveratrol–maltol compounds (1–8) were synthesised via a Wittig reaction between a 4-pyranone phosphonium salt and

various aryl/heteroaryl aldehydes. The phosphonium salt was prepared by chlorination of kojic acid, followed by reaction with triphenylphosphine. Synthesised compounds were purified by column and TLC methods. These results highlight thiophene–resveratrol hybrids as promising multifunctional candidates for neurodegenerative diseases (Scheme 3).^[3]

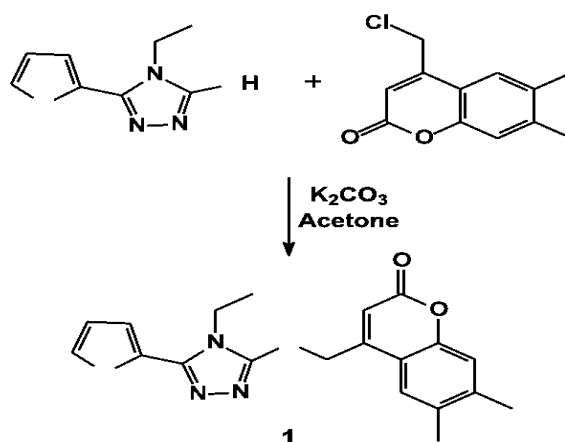
Scheme 3. Synthesis of new 5-hydroxy-2-styryl-4H-pyran-4-ones 1–8 as chromatographically separated *cis*- and *trans*- isomers.

Omar et al. synthesized a novel coumarin–triazole–thiophene hybrid as a potential SARS-CoV-2 inhibitor. The synthetic route involved a multi-step procedure starting from 4-hydroxycoumarin and propargyl bromide to form propargylated coumarin, which was subjected to

a Cu(I)-catalyzed azide-alkyne cycloaddition (“click reaction”) with a thiophene-containing azide to form the final hybrid. Structural confirmation was carried out using FT-IR, NMR (¹H & ¹³C), and mass spectrometry. ADMET prediction showed drug-likeness and favorable

bioavailability. Molecular docking with key SARS-CoV-2 targets (Mpro, RdRp, Spike) showed strong binding affinities. Molecular dynamics simulations confirmed the

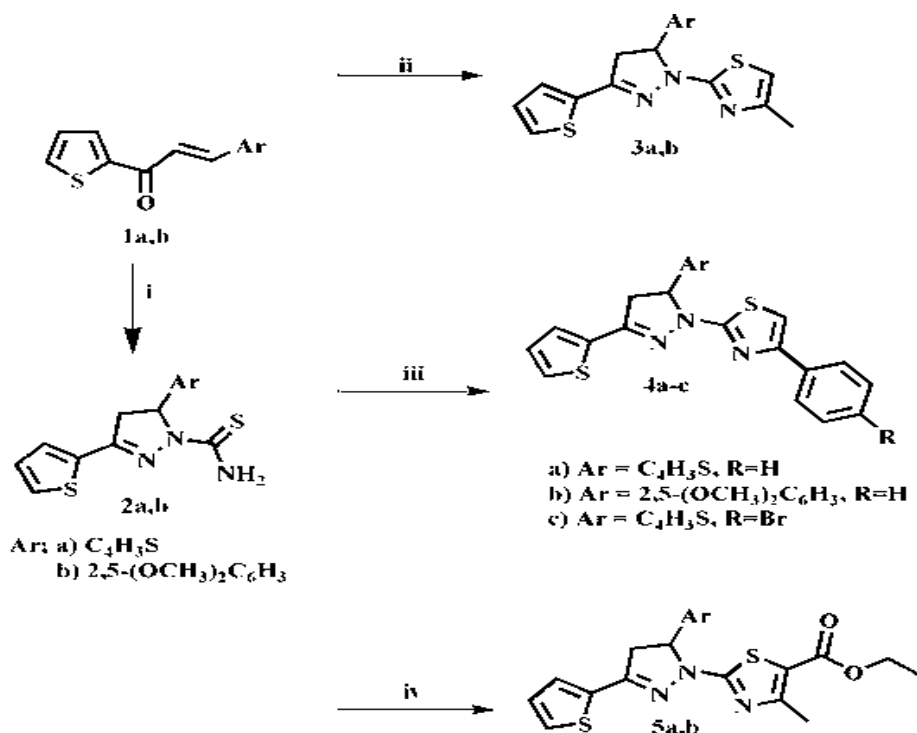
stability of the ligand–protein complexes. The hybrid holds promise as an antiviral scaffold against COVID-19 (Scheme 4).^[4]



Scheme 4. Synthesis of coumarin-triazole-thiophene hybrid (1).

Dawood et al. designed and synthesized a new series of thiophenyl-pyrazolyl-thiazole hybrids as potent dihydrofolate reductase (DHFR) inhibitors with antimicrobial potential. The synthetic strategy involved the formation of hydrazonoyl chloride intermediates, which underwent cyclization with potassium thiocyanate to yield thiazole cores, further condensed with thiophene

aldehydes and pyrazolyl moieties. Reaction conditions included reflux in ethanol with acetic acid or triethylamine as catalysts. The compounds were tested against various Gram-positive and Gram-negative bacteria and showed potent activity, especially against *S. aureus* (Scheme 5).^[5]

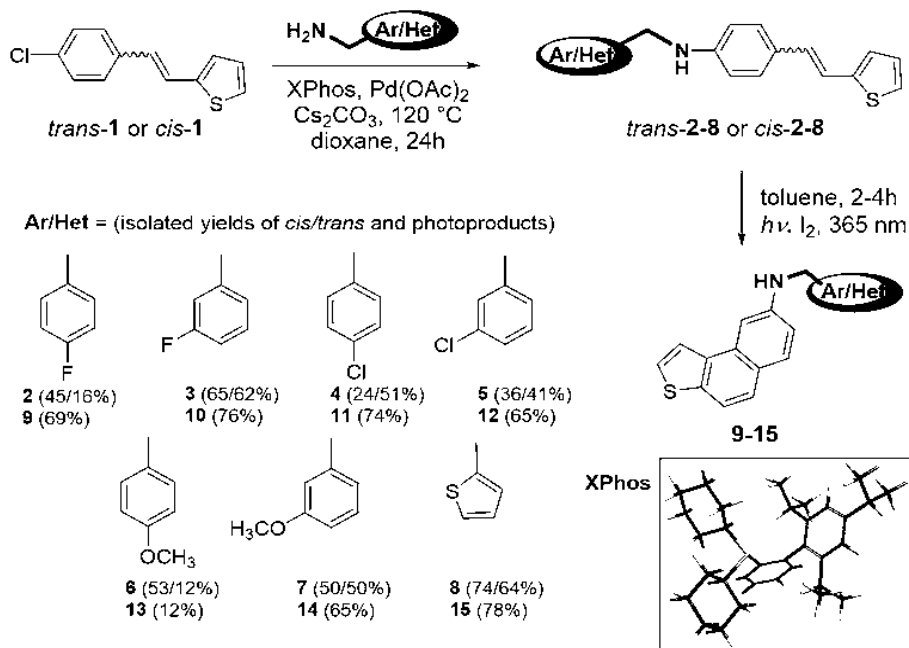


“Reagents and conditions: (i) $NH_2CSNHNH_2$, EtOH, KOH, reflux for 8 h; (ii) H_3CCOCH_2Cl , CH_3COONa , EtOH, reflux for 6–8 h; (iii) $PhCOCH_2Br$ /4- $BrPhCOCH_2Br$, CH_3COONa , EtOH, reflux for 6–8 h; (iv) $CH_3COCH(Cl)COOC_2H_5$, CH_3COONa , EtOH, reflux for 6–8 h.

Scheme 5. Synthesis of New Thiophenyl-pyrazolyl-thiazole Hybrids 3–5^a.

Mrakić et al. synthesized novel *cis*- and *trans*-amino stilbene derivatives (2–8) and evaluated their synthesis efficiency, acid resistance, photophysical, and photochemical behaviour. Photocyclization products (9–15) were also assessed, with *cis*-8 and its product 15 showing promising cholinesterase (ChE) inhibitory activity. The study confirms the critical role of the thiophene moiety, particularly in the *cis*-configuration or

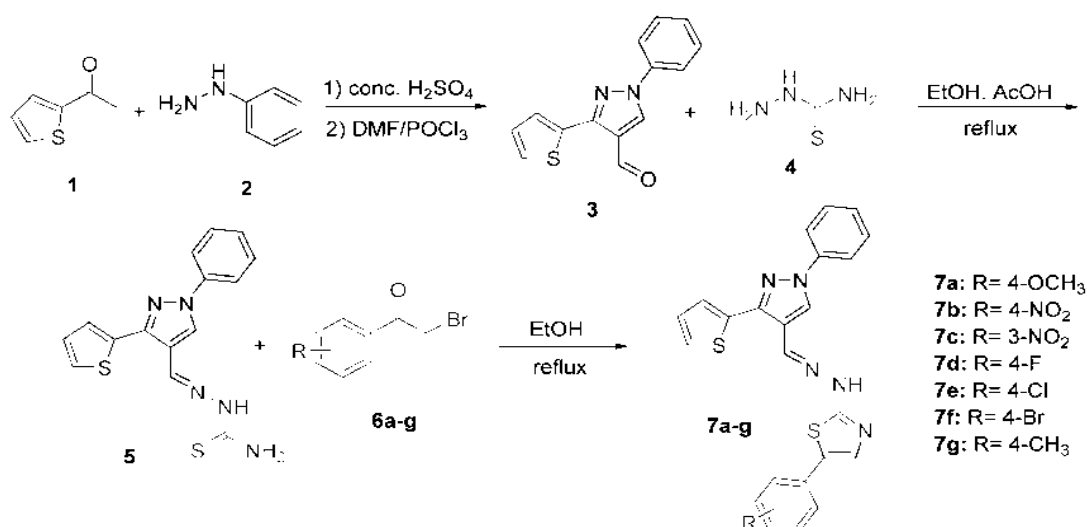
planar thieno-naphthalene structures, for effective butyrylcholinesterase (BChE) inhibition. The *trans*-isomers (*trans*-2–8) exhibited consistent absorbance wavelengths and stability across pH changes, resembling known amino-stilbene dyes. These findings suggest potential for developing thiophene-based ChE inhibitors and functional styryl dyes. Further modifications are encouraged to enhance biological activity (**Scheme 6**).^[6]



Scheme 6. Synthesis and photocyclization reactions of styryl-thiophene benzylamines 2–8.

Bhagwat et al. synthesized seven novel pyrazolyl-thiazole derivatives of thiophene via a multi-step reaction sequence. The procedure began with the preparation of thiophene-based hydrazones, which were condensed with appropriate isothiocyanates to form thiosemicarbazides. These intermediates underwent cyclization under acidic conditions to yield thiazole rings, followed by pyrazole ring formation through condensation with β -diketones.

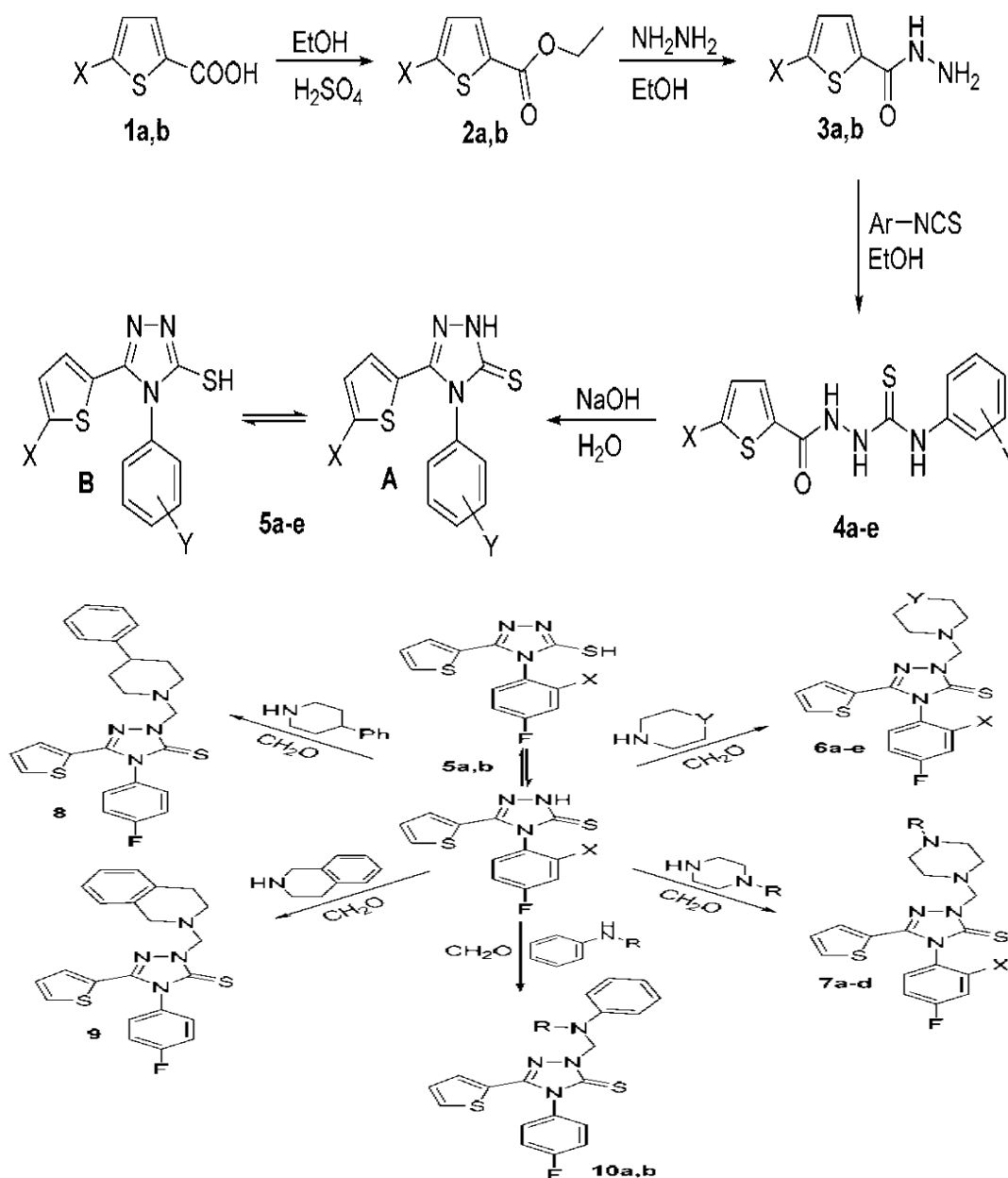
The synthesized compounds were purified and confirmed using NMR and mass spectrometry. Antimicrobial screening revealed strong activity against several bacterial and fungal strains. Antioxidant assays showed effective radical scavenging. DFT and molecular docking supported the biological results, indicating therapeutic potential (**Scheme 7**).^[7]



Scheme 7. Synthetic route for the pyrazolyl-thiazole derivatives.

El-Emam et al. synthesized a series of thiophene-linked 1,2,4-triazole-3-thiones by reacting thiophene-2-carbohydrazide or 5-bromothiophene-2-carbohydrazide with various haloaryl isothiocyanates, followed by cyclization in aqueous NaOH. The resulting intermediates (5a–e) were further modified using secondary amines and formaldehyde to yield aminomethyl derivatives (6a–e, 7a–e, 8, 9, 10a, 10b).

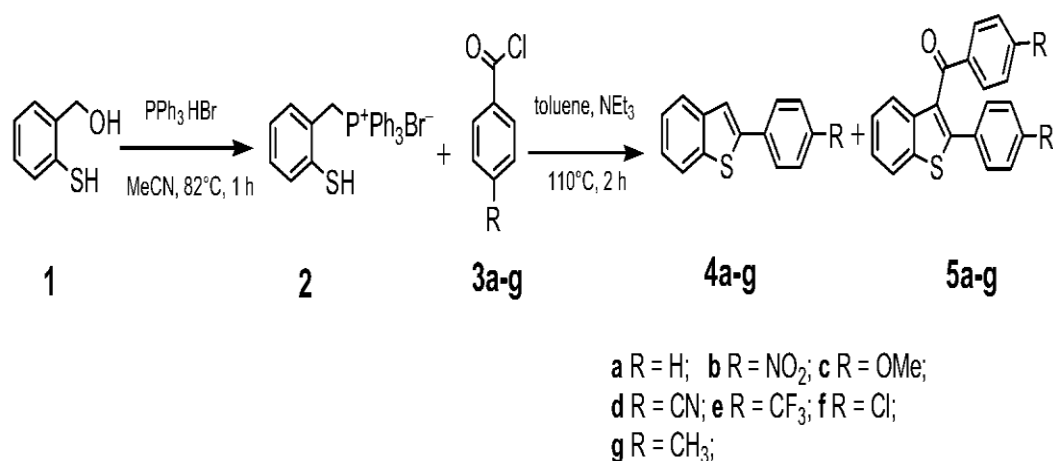
These compounds showed significant antibacterial activity, especially against *E. coli* and Gram-positive strains, though they were mostly inactive against fungi. Several derivatives (5e, 6a–e, 7a–d, 10a) demonstrated potent antiproliferative activity against HepG-2 and MCF-7 cell lines ($IC_{50} < 25 \mu M$) (**Scheme 8**).^[8]



Scheme 8. Synthesis of compounds 5a-e, 6a-e, 7a-d, 8, 9, 10a, and 10b.

Delogu et al. synthesized a novel series of benzothiophene-based heterocycles, including benzothiophenes (4a–4i) and benzothiophene–chalcone hybrids (5a–5i), and evaluated their inhibitory activity against acetylcholinesterase (AChE) and butyrylcholinesterase (BChE). The chalcone hybrids from series 5 showed superior inhibitory potency, with compound 5f emerging as the most effective AChE

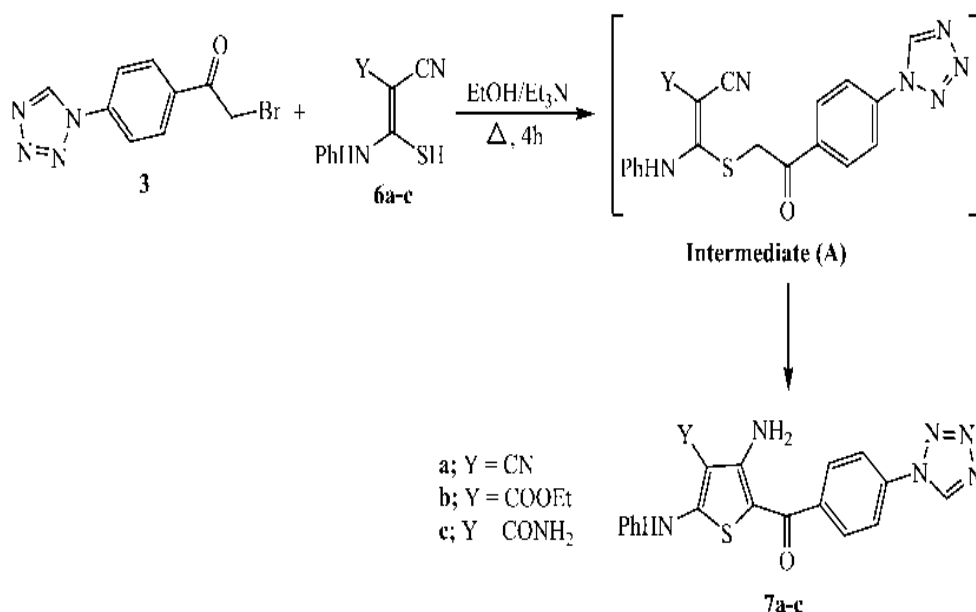
inhibitor ($IC_{50} = 62.10 \mu M$) and 5h showing potent BChE inhibition ($IC_{50} = 24.35 \mu M$), comparable to the reference drug galantamine ($IC_{50} = 28.08 \mu M$). Cytotoxicity against SH-SY5Y cells was assessed to ensure safety, and *in-silico* ADME predictions confirmed favorable drug-like properties (**Scheme 9**).^[9]



Scheme 9: Synthetic route for obtaining 2-phenyl benzothiophenes 4a–4g and 3-benzoyl-2-phenylbenzothiophenes 5a–5g.

Abualnaja et al. reported the synthesis of tetrazole-based hybrids incorporating thiazole, thiophene, and thiadiazole moieties through multi-step chemical reactions. The structures of the synthesized compounds were confirmed using IR, NMR, and mass spectrometry. Density Functional Theory (DFT/B3LYP) calculations revealed that thiadiazole derivatives (9a–c) had lower energy gaps (ΔE) than their thiophene (7a–c) and thiazole (5a–c) counterparts, indicating higher electronic reactivity. Antimicrobial evaluation showed that compounds 5b, 5c, and 7b exhibited significant

antibacterial activity against *S. aureus* and *S. pneumoniae*, while 9a was effective against Gram-negative bacteria such as *S. typhimurium* and *E. coli*. Additionally, 5a–b, 7a, 7c, and 9c demonstrated promising antifungal activity against *C. albicans*. Molecular docking studies against the ATP-binding domain of *S. aureus* DNA gyrase (PDB ID: 4URO) supported the observed biological activities. The study highlights these tetrazole-linked hybrids as promising antimicrobial candidates for further drug development (Scheme 10).^[10]



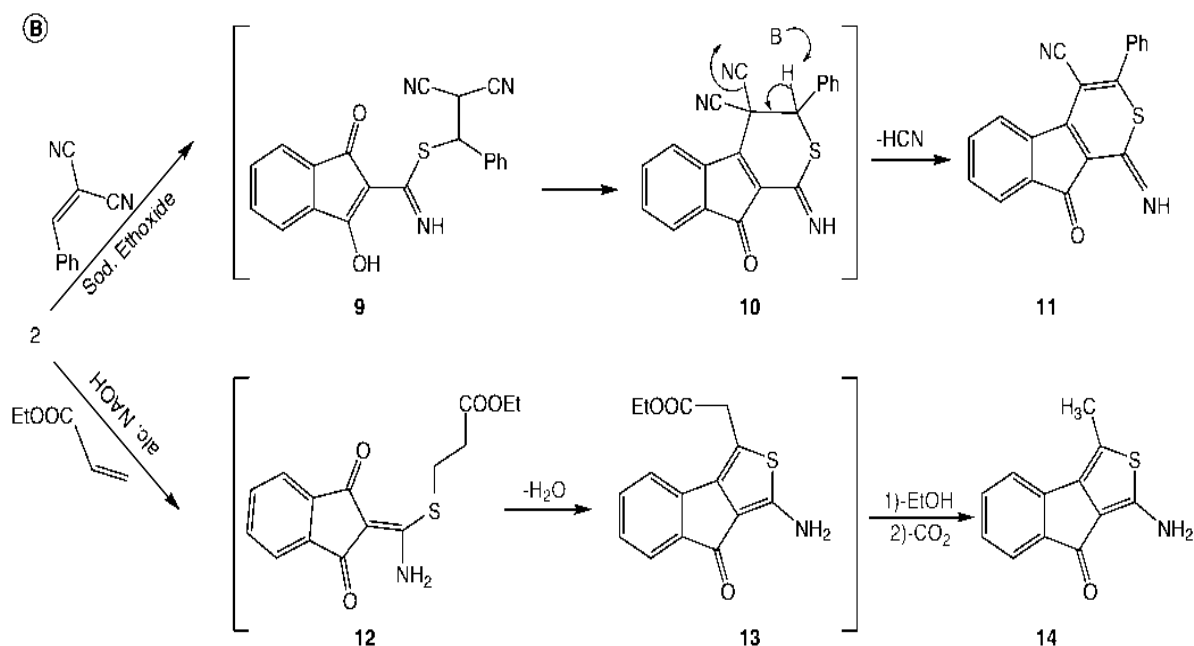
Scheme 10: Synthesis of tetrazole-thiophene hybrids 7a–c.

Abdellattif et al. designed and synthesized novel indandione-based derivatives through reactions with various electrophilic and nucleophilic reagents, yielding a series of compounds (3, 4, 8, 11, 14, 16, 19–23). Among these, compounds 8, 11, 16, 20, and 23 were evaluated for their anticancer activity against OVCAR-3 (ovarian) and HeLa (cervical) cancer cell lines, using

cisplatin and LLC-MK2 cells as references. Spectral analysis and *in-silico* modelling were employed to support the structural and biological evaluation. Notably, compound 23 showed the highest cytotoxic activity against HeLa cells, while compound 20 was most effective against OVCAR-3 cells. Molecular dynamics simulations confirmed their stable binding at 100 ns,

highlighting these indenothiophene and indenopyrazole derivatives as promising anticancer leads (Scheme

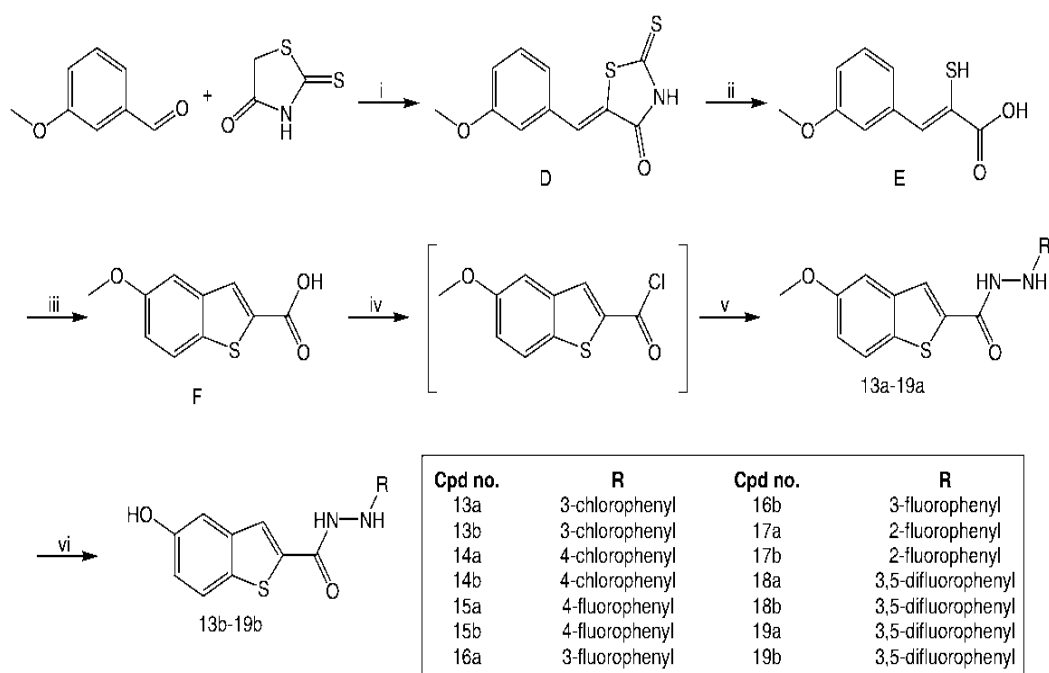
11).^[11]



Scheme 11. Synthesis of a new series of indane derivatives 11 and 14.

Abd El-Rahman et al. developed a series of 5-hydroxybenzothiophene derivatives as potential multi-kinase inhibitors to address cancer chemoresistance. These compounds were designed to target multiple cancer-related pathways simultaneously. Among them, compound 16b, featuring a 5-hydroxybenzothiophene hydrazide scaffold, demonstrated potent anticancer activity with low IC₅₀ values across various cancer cell

lines, particularly showing strong efficacy against U87MG glioblastoma cells. It induced G2/M phase cell cycle arrest, triggered apoptosis, and inhibited cell migration by modulating apoptotic markers. These findings suggest that 16b is a promising lead compound for the development of novel multi-targeted anticancer agents based on the benzothiophene core (Scheme 12).^[12]

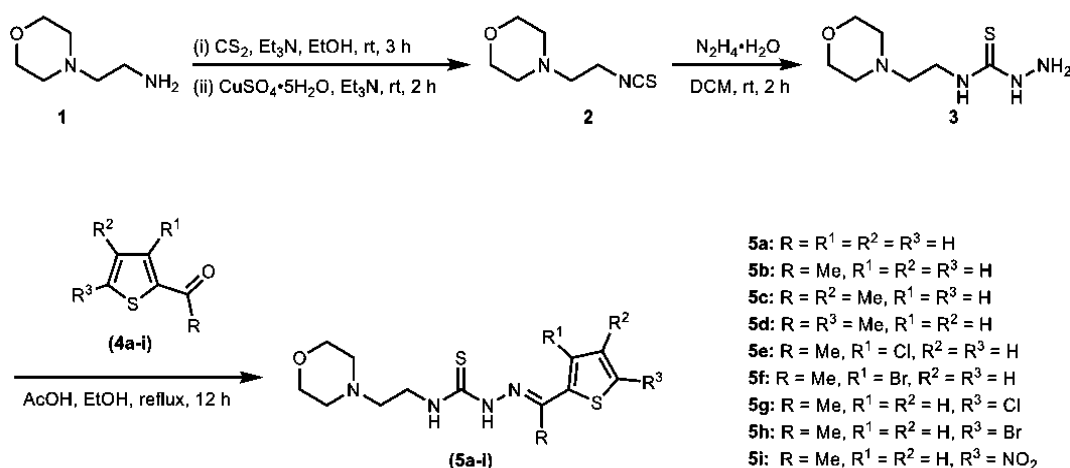


Scheme 12: Synthesis of compounds 13b-19b. Reagents and conditions: (i) 0.17 equiv. of anhydrous sodium acetate, 1 mL glacial acetic acid in toluene, reflux, 4 h; (ii) 15% aqueous NaOH, 60-70 °C, 1 h; (iii) 1.5 equiv. of

iodine in dry THF, reflux, 42 h; (iv) 4 equiv. of oxalyl chloride, catalytic DMF in dry DCM, reflux, 3 h; (v) 1 mL DIPEA, 2 equiv. of the appropriate phenyl hydrazine hydrochloride in dry THF, RT, 18 h; (vi) 5 mL BBr₃ in DCM, RT, overnight. Cpd: Compound; RT: Room temperature.

Munir et al. designed and synthesized a novel series of morpholine–thiophene hybrid thiosemicarbazone derivatives (5a–i) targeting the urease enzyme, a key virulence factor in ureolytic bacterial infections. The compounds were structurally confirmed by FTIR, ¹H NMR, ¹³C NMR, and mass spectrometry, with a diverse range of substituents tolerated on the thiophene ring. In vitro urease inhibition assays revealed that most compounds surpassed the activity of the standard inhibitor, thiourea. Notably, compound 5g, bearing a 5-

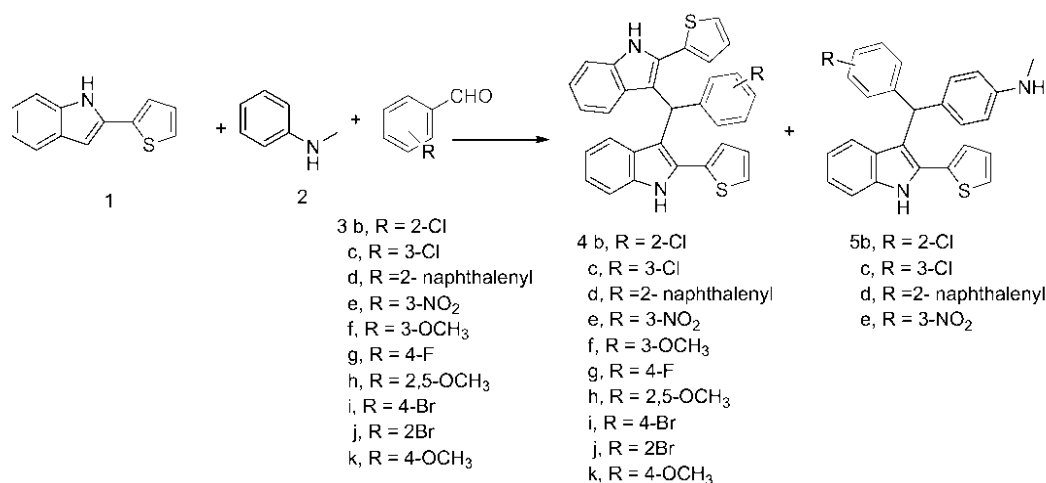
chlorothiophene moiety, exhibited potent uncompetitive inhibition with an IC₅₀ of 3.80 ± 1.9 μM. Molecular docking showed a strong binding affinity of 5g to the urease active site, supported by favorable docking scores and binding free energies. ADME analysis indicated good drug-likeness with no Lipinski violations, highlighting 5g as a promising lead for anti-ureolytic drug development (**Scheme 13**).^[13]



Scheme 13. Synthetic layout for morpholine–thiophene hybrid thiosemicarbazones.

Abdelazeem et al. synthesised and evaluated sixteen novel 2-(thiophen-2-yl)-1H-indole derivatives for their anticancer potential, particularly against the HCT-116 colon cancer cell line. Two synthetic series were developed: methylene bis(indole-thiophene) derivatives and (indol-3-yl) methyl aniline hybrids, using aldehyde-based condensation and multicomponent reactions. Cytotoxic screening across several cancer cell lines revealed selective activity toward HCT-116 cells, with

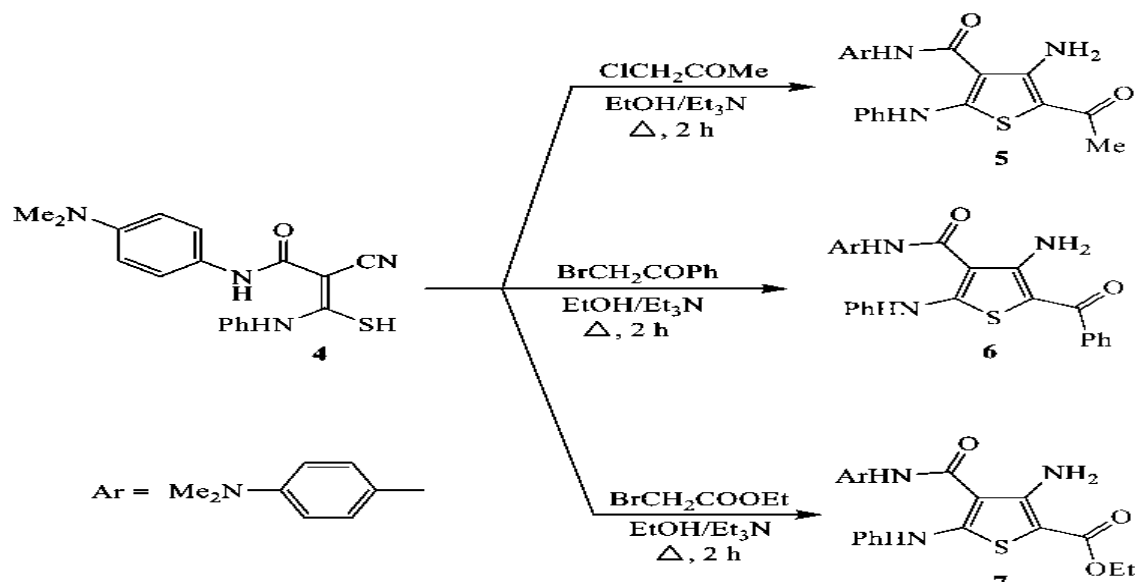
compounds 4g, 4a, and 4c displaying potent IC₅₀ values of 7.1, 10.5, and 11.9 μM, respectively. Mechanistic studies showed that these compounds induced S and G2/M phase cell cycle arrest, upregulated tumour suppressor miRNAs (miR-30C, miR-107), and downregulated oncogenic markers (miR-25, IL-6, and C-Myc) (**Scheme 14**).^[14]



Scheme 14: Synthesis of (methylene)bis(2-(thiophen-2-yl)-1H-indole) derivatives 4b–k, and (2-(thiophen-2-yl)-1H-indol-3-yl) methyl aniline derivatives 5b–e.

Metwally et al. synthesized diverse thiazole, thiophene, and 2-pyridone derivatives incorporating a dimethylaniline moiety for anticancer evaluation. Thiazoles (2–3) and thiophenes (5–7) were obtained by reacting thiocarbamoyl intermediate **4** with α -halogenated agents under basic conditions. The 2-pyridone series (9a–f) was synthesized via Michael addition of malononitrile to α , β -unsaturated nitriles (8a–f). Compounds **2**, **6**, **7**, and **9c** displayed potent

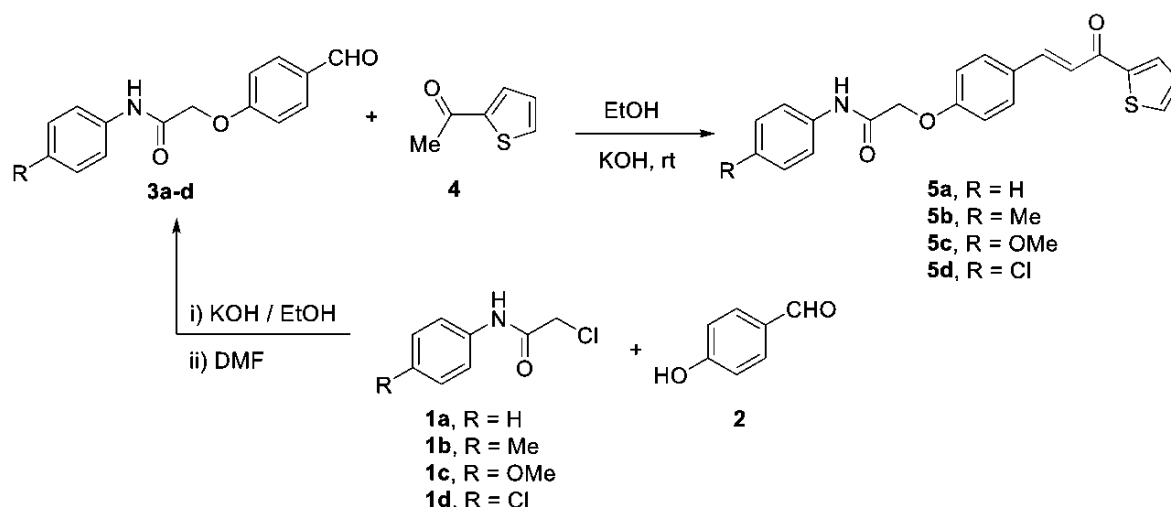
cytotoxicity in HepG-2 and MDA-MB-231 cells. Compound **2** was most effective ($IC_{50} = 1.2 \mu M$), comparable to doxorubicin. ADME and PASS predictions confirmed good drug-likeness and antimitotic potential. Molecular docking revealed strong binding of compound **9d** with CDK1 (-8.12 kcal/mol) and compound **6** with BPTI (-7.51 kcal/mol) (**Scheme 15**).^[15]

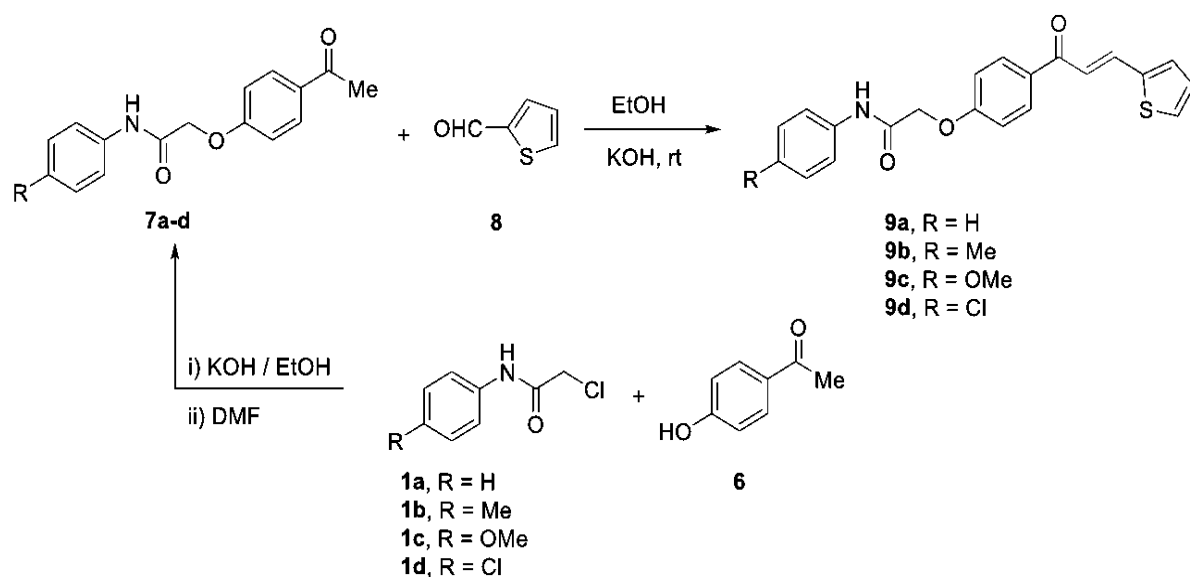


Scheme 15. Synthesis of 4-amino-5-substituted thiophene derivatives **5**, **6**, and **7**.

Ibrahim et al. synthesized eight novel chalcones incorporating thiophene and phenoxy acetamide moieties, confirmed via spectral techniques including IR, NMR, and MS. The compounds were screened for cytotoxicity using the SRB assay; compound **5c** exhibited the most potent effect against MCF7 and HEP2 cells with IC_{50} values of 9.5 and 12 $\mu g/mL$, respectively. RT-PCR revealed significant downregulation of KI-67,

Survivin, IL-1 β , IL-6, COX-2, and AKT1 genes. Flow cytometry showed cell cycle arrest at G0/G1 and G2/M phases. ELISA analysis indicated apoptosis induction via upregulation of Caspase 8/9, P53, and BAX, and suppression of MMP2/9, BCL2, and MDA. Wound healing assay confirmed reduced cell migration. Docking studies validated strong binding of **5c** to mutant P53 (Y220C) and BCL2 proteins (**Scheme 16**).^[16]

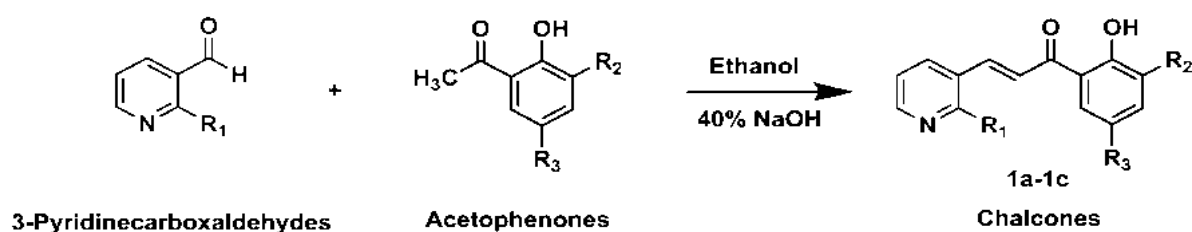




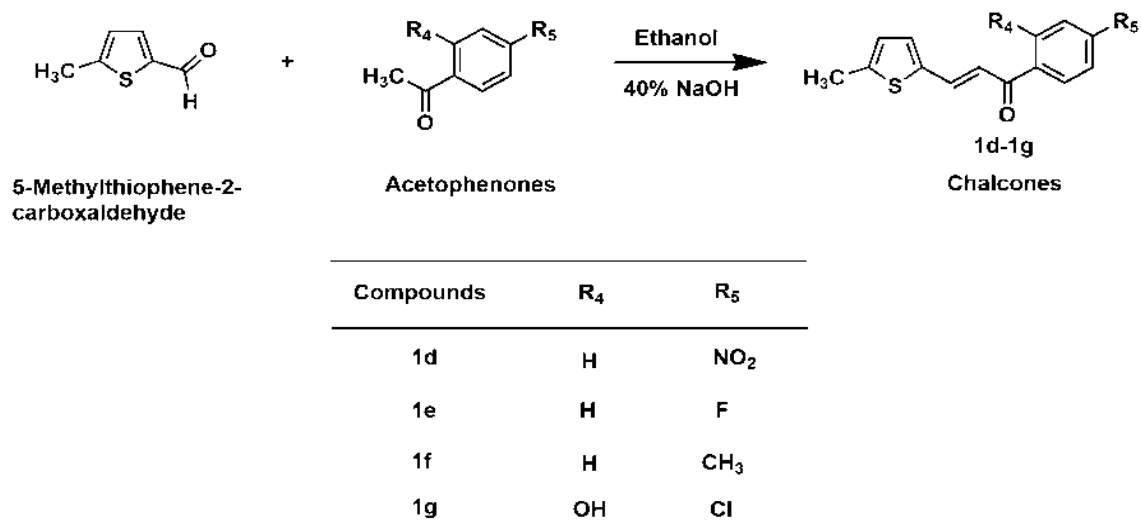
Scheme 16: Synthesis of 5a–d and 9a–d.

Akhter et al. synthesised seven chalcone derivatives—three containing pyridine and four containing thiophene moieties—via Claisen–Schmidt condensation, of which five were novel compounds. Structural elucidation was confirmed using IR, ^1H -NMR, and HRMS spectroscopy. Antimicrobial screening using agar disc diffusion revealed that compound 1c showed superior activity, outperforming ceftriaxone and amphotericin B against several bacterial and fungal strains. Notably, 1c exhibited strong inhibition zones against *Bacillus cereus*, *Shigella*

sonnei, and *Shigella boydii*. ADME predictions confirmed drug-likeness with no toxicological risks. Molecular docking revealed binding affinities ranging from -6.3 to -9.6 kcal/mol against selected protein targets. Molecular dynamics simulation of 1c showed minimal RMSD/RMSF values (<2 Å), suggesting excellent binding stability. The study highlights chalcone 1c as a potent, stable antimicrobial candidate. (Scheme 17).^[17]



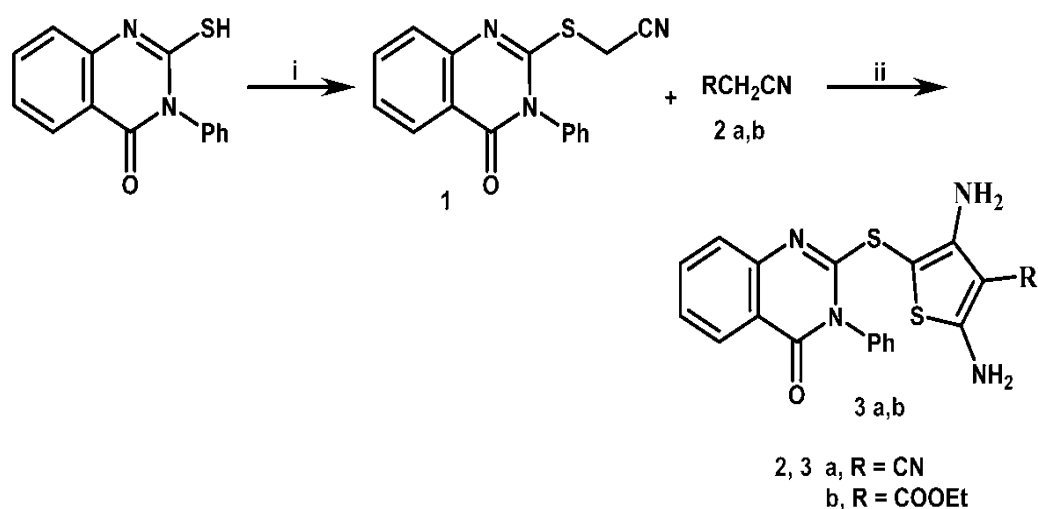
Compounds	R ₁	R ₂	R ₃
1a	H	H	Br
1b	Cl	H	Br
1c	H	NO ₂	Cl



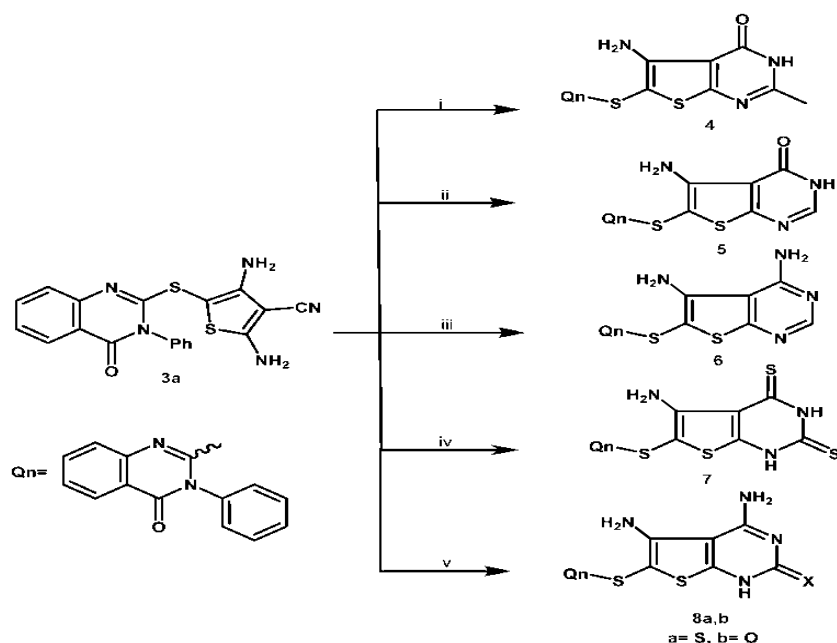
Scheme 17: Synthesis of chalcone derivatives containing a thiophene moiety.

Als fouk et al. synthesized a novel series of quinazolinone derivatives incorporating thiophene, thienopyrimidine, and thienopyridine scaffolds (compounds 3a, b–11) via multistep reactions. In vitro antiproliferative activity was screened using the MTT assay against various cancer cell lines, where compounds 6, 8a, and 8b exhibited the strongest effects with low toxicity toward normal WI-38 cells. Enzyme inhibition

assays revealed potent p38 α MAPK kinase inhibition, surpassing the standard SB 202190. Apoptotic assays confirmed upregulation of Bax and caspase-3 and downregulation of Bcl-2. Compound 8a induced G2/M phase arrest in MCF-7 cells and exhibited strong necrotic/apoptotic effects. Molecular docking showed strong binding affinity (–11.28 kcal/mol for 8a) (Schemes 18 and 19).^[18]



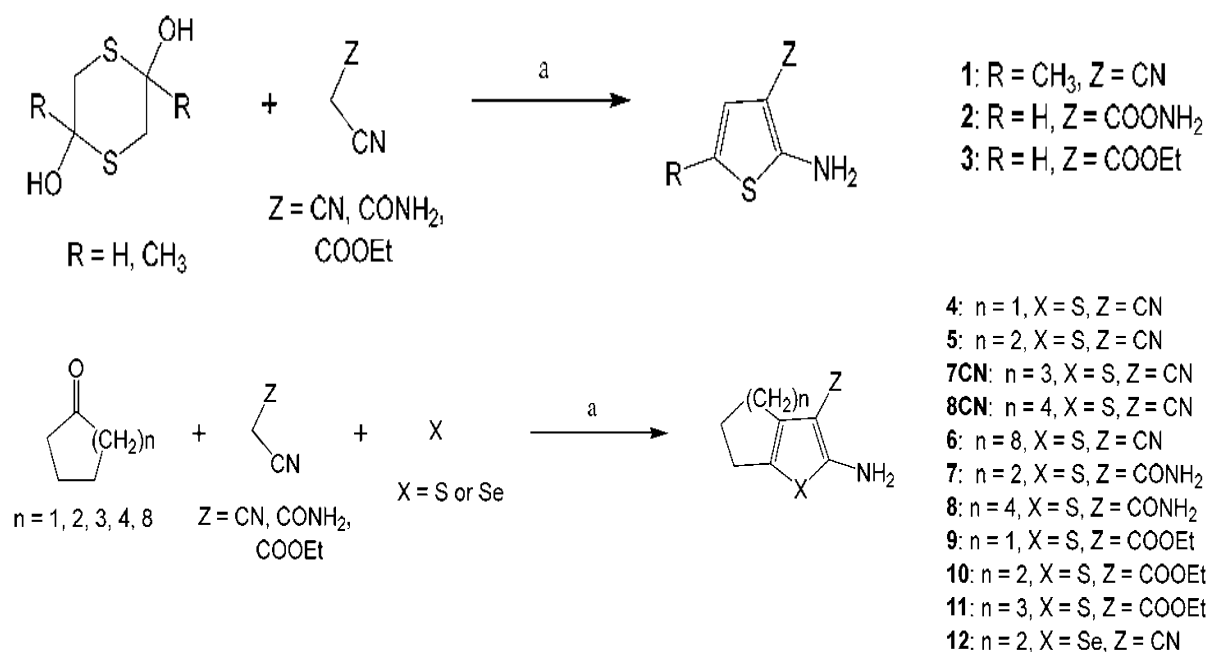
Scheme 18. Synthetic path way for synthesis of 2,4-diamino-thiophene-3-carbonitriles 3a,b. Reagents and conditions: (i) chloro-acetonitrile, sodium acetate, dry DMF, stirring for 30 minutes, refluxing for 5 h; (ii) S, malononitrile and/or ethyl cyanoacetate, absolute ethanol, few drops of triethylamine, reflux for 7 h.



Scheme 19. Synthetic pathway for synthesis of different substituted thienopyrimidines 4–8a, b. Reagents and conditions: (i and ii) acetic anhydride and/or formic acid, reflux for 24 h; (iii) formamide, reflux for 12 h; (iv) carbon disulphide, pyridine, reflux on water bath for 10 h; (v) thiourea and/or urea, ethanolic sodium ethoxide, reflux for 9 h.

de Araújo et al. synthesized several 2-aminothiophene (2-AT) and 2-aminoselenophene (2-AS) derivatives using the Gewald multicomponent reaction to explore their antileishmanial potential. Structural modifications were introduced at the C-3, C-4, and C-5 positions, along with sulfur-to-selenium bio-isosterism. Spectroscopic characterization (IR, NMR, MS) confirmed the structures. In vitro assays against *Leishmania amazonensis* and macrophage cytotoxicity testing were

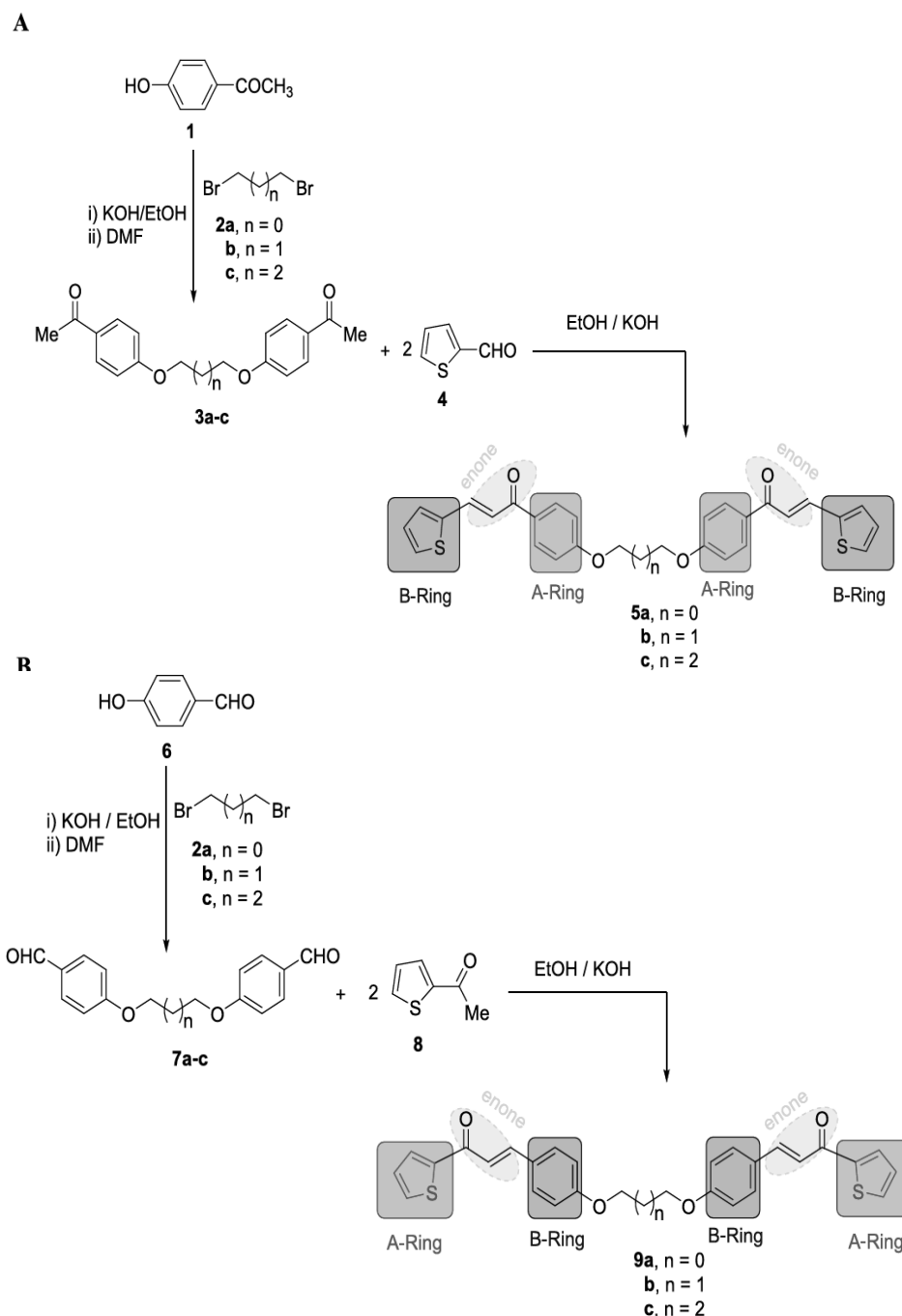
performed. Several compounds exhibited potent activity ($IC_{50} < 10 \mu M$), with modifications at C-4 and C-5 (e.g., cycloalkyl or piperidinyl groups) enhancing efficacy. The carbonitrile group at C-3 was found non-essential. S/Se bioisosterism improved potency without compromising safety. These findings highlight 2-aminothiophenes as promising leads for novel antileishmanial drugs (**Scheme 20**).^[19]



Scheme 20. Synthesis of 2-AT using 1,4-dithiane-2,5-diol derivatives: (a) morpholine, ethanol, reflux, 2-3 h.

Fathi et al. synthesized two new series of bis-chalcone derivatives (5a–c and 9a–c) bearing thiophene moieties using the Claisen–Schmidt condensation reaction. The synthesized compounds were evaluated for anticancer activity against breast (MCF-7), colon (HT-29), and lung (A549) cancer cells using MTT and mechanistic assays. Compounds 5a, 5b, 9a, and 9b exhibited significant

cytotoxicity, with 5b showing the lowest IC_{50} ($4.05 \pm 0.96 \mu\text{M}$) against breast cancer. These compounds induced sub-G1 cell cycle arrest, apoptosis, and necrosis, while modulating pro/anti-apoptotic genes and inhibiting MMP-2/9 activity (**Scheme 21**).^[20]



Scheme 21. Synthesis of Bis(chalcones) 5a–c (A) and 9a–c (B).

BIOLOGICAL PROFILING OF THIOPHENE-CONJUGATED MOLECULES IN DRUG DISCOVERY

Thiophene-containing hybrids exhibit a broad spectrum of biological activities due to their electron-rich heterocyclic structure and ability to engage in diverse

molecular interactions. Their incorporation into drug-like scaffolds enhances pharmacodynamic and pharmacokinetic profiles, making them valuable candidates in drug discovery. Recent literature highlights their utility across various therapeutic areas.

➤ Anticancer Activity

Thiophene hybrids have demonstrated potent antiproliferative properties against multiple human cancer cell lines. For instance, **Als fouk et al.** synthesized thiophene-linked quinazolinone derivatives that inhibited p38 α MAPK kinase and induced apoptosis in MCF-7 cells by upregulating Bax and caspase-3 while downregulating Bcl-2. Compounds 6, 8a, and 8b showed

IC₅₀ values below 0.31 μ M and arrested the cell cycle at the G2/M phase.^[17] Similarly, **Fathi et al.** designed bis-chalcone derivatives with thiophene moieties, which showed cytotoxicity in breast, colon, and lung cancer cells. Compounds 5a, 5b, 9a, and 9b induced sub-G1 arrest, caspase activation, and matrix metalloproteinase inhibition, indicating their role in anti-metastatic and pro-apoptotic signalling.^[20]

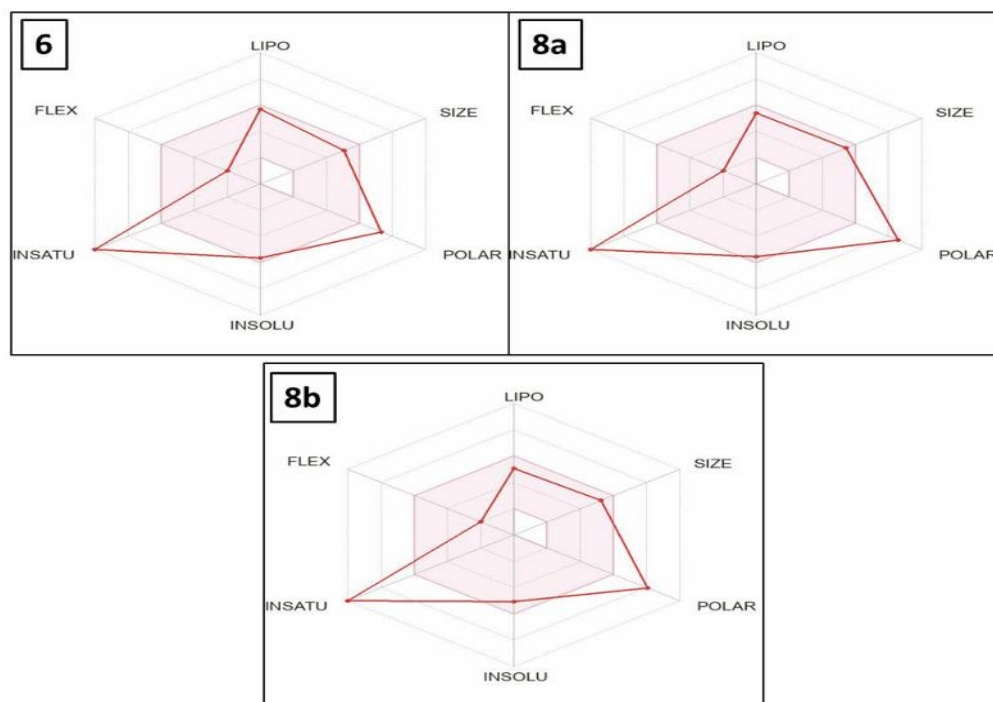


Fig. 2- The effective thieno [2,3-d] pyrimidine derivatives 6, 8a, and 8b's bioavailability radar map.^[17]

➤ Antimicrobial Activity

In a comprehensive study by **Akhter et al.**, thiophene-chalcone hybrids were assessed for antimicrobial potential. Several derivatives exhibited significant antibacterial and antifungal activity. Molecular docking

confirmed their binding affinity toward microbial enzymes, while ADMET predictions validated their drug-like properties, supporting their use as antimicrobial agents.^[18]

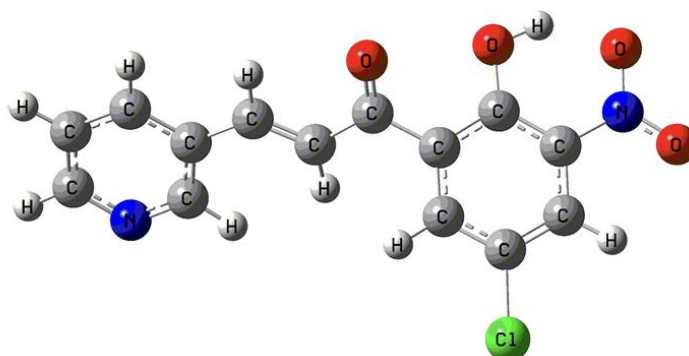


Fig. 3- Optimized molecular structure of synthesized compound 1c with a basis setup B3LYP/6-31G.

➤ Anti-Inflammatory and Antioxidant Activity

Ibrahim et al. reported the synthesis of chalcones containing phenoxy acetamide and thiophene frameworks. These compounds demonstrated anti-inflammatory effects through downregulation of COX-2, IL-6, and TNF- α , alongside antioxidant activity. Elevated

caspase expression and DNA fragmentation assays further confirmed the induction of apoptosis in MCF-7 and HEP2 cells.^[16]

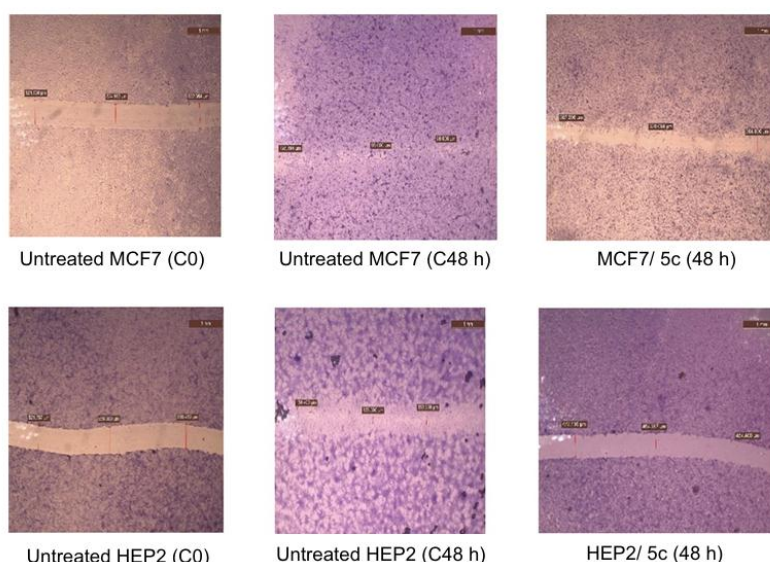


Fig. 4- Evaluation of migration.

➤ Antileishmanial Activity

The study by **de Araújo et al.** explored the antileishmanial properties of 2-aminothiophene and 2-aminoselenophene derivatives. Chemical modifications at positions C-3 to C-5 enhanced activity against *Leishmania amazonensis*, with IC_{50} values $<10 \mu M$. Importantly, these compounds were non-toxic to macrophages, supporting their potential role in the therapy of neglected tropical diseases.^[19]

➤ Enzyme Inhibition

Multiple thiophene hybrids have shown promising enzyme inhibition profiles. In the study by **Alsfouk et al.**, the p38 α MAPK inhibition was significant^[17], while **Fathi et al.** reported inhibition of matrix metalloproteinases (MMP-2 and MMP-9), enzymes associated with cancer invasion and metastasis. These interactions were validated through molecular docking and western blot analysis.^[20]

CONCLUSION

Thiophene-based hybrids have gained prominence as promising scaffolds in modern drug discovery due to their structural diversity, synthetic ease, and broad pharmacological potential. These compounds exhibit a wide range of biological activities, including anticancer, antimicrobial, antioxidant, anti-inflammatory, and antileishmanial effects. Their ability to modulate multiple biological targets—such as kinases, enzymes, and signalling pathways—supports their application as multitarget therapeutic agents. In oncology, thiophene derivatives act through mechanisms like apoptosis induction, cell cycle arrest, and kinase inhibition, offering potential against resistant cancer types. Additionally, 2-aminothiophene analogues have shown notable antileishmanial activity, highlighting their relevance in treating neglected tropical diseases. The favourable ADMET profiles of these hybrids contribute to their drug-likeness and clinical viability. As the focus of medicinal chemistry shifts toward multitarget and

mechanism-based drug development, thiophene-based hybrids offer a valuable framework for future therapeutics.

ACKNOWLEDGMENT

The authors gratefully acknowledge the Management of Nargund College of Pharmacy and the Department of Pharmaceutical Chemistry for their valuable support.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. Tlidjane H, Chafai N, Chafaa S, Bensouici C, Benbouguerra K. New thiophene-derived α -aminophosphonic acids: Synthesis under microwave irradiations, antioxidant and antifungal activities, DFT investigations and SARS-CoV-2 main protease inhibition. *J Mol Struct*, 2022; 1250: 131853.
2. Gomha S, Riyadh S, Huwaimel B, Zayed M, Abdellattif M. Synthesis, molecular docking study, and cytotoxic activity against MCF cells of new thiazole–thiophene scaffolds. *Molecules*, 2022; 27(14): 4639.
3. Mlakić M, Fodor L, Odak I, Horváth O, Lovrić MJ, Barić D, et al. Resveratrol–maltol and resveratrol–thiophene hybrids as cholinesterase inhibitors and antioxidants: Synthesis, Biometal chelating capability and crystal structure. *Molecules*, 2022; 27(19): 6379.
4. Omar RA, Koparir P, Sarac K, Koparir M, Safin DA. A novel coumarin-triazole-thiophene hybrid: Synthesis, characterization, ADMET prediction, Molecular Docking and molecular dynamics studies with a series of SARS-COV-2 proteins. *J Chem Sci*, 2023; 135(1): 14.
5. Dawood DH, Sayed MM, Tohamy ST, Nossier ES. New thiophenyl-pyrazolyl-thiazole hybrids as DHFR inhibitors: Design, synthesis, antimicrobial

- evaluation, molecular modeling, and biodistribution studies. *ACS Omega*, 2023; 8(42): 39250–39268.
6. Mlakić M, Odak I, Faraho I, Bosnar M, Banjanac M, Lasić Z, et al. Synthesis, photochemistry, computational study and potential application of new styryl-thiophene and naphtho-thiophene benzylamines. *Int J Mol Sci*, 2022; 24(1): 610.
 7. Bhagwat SK, Pawar TJ, Kulkarni SA, Patil AA, More RA, Jimenez-Halla JO, et al. Synthesis, characterization, biological activities, and computational studies of pyrazolyl-thiazole derivatives of thiophene. *RSC Adv*, 2024; 14(52): 39004–39016.
 8. El-Emam NA, El-Ashmawy MB, Mohamed AA, Habib E-SE, Thamotharan S, Abdelbaky MS, et al. Thiophene-linked 1,2,4-triazoles: Synthesis, structural insights and antimicrobial and chemotherapeutic profiles. *Pharmaceuticals*, 2024; 17(9): 1123.
 9. Delogu G, Begala M, Matos M, Crucitti D, Sogos V, Era B, et al. A new class of benzo[b]thiophene-chalcones as cholinesterase inhibitors: Synthesis, biological evaluation, molecular docking and ADME studies. *Molecules*, 2024; 29(16): 3748.
 10. Abualnaja MM, Alalawy AI, Alatawi OM, Alessa AH, Fawzi Qarah A, Alqahtani AM, et al. Synthesis of tetrazole hybridized with thiazole, thiophene or thiadiazole derivatives, molecular modelling and antimicrobial activity. *Saudi Pharm J.*, 2024; 32(3): 101962.
 11. Abdellattif MH, Assy MG, Elfarargy A, Ramadan F, Elgendy MS, Emwas A-HM, et al. Novel candidates synthesis of indenopyrazole, indenoazine and indenothiophene, with anticancer and *in silico* studies. *Future Med Chem*, 2024; 16(14): 1429–1447.
 12. Abd El-Rahman YA, Chen P-J, ElHady AK, Chen S-H, Lin H-C, El-Gamil DS, et al. Development of 5-hydroxybenzothiophene derivatives as multi-kinase inhibitors with potential anti-cancer activity. *Future Med Chem*, 2024; 16(12): 1239–1254.
 13. Munir R, Zaib S, Zia-ur-Rehman M, Javed H, Roohi A, Zaheer M, et al. Exploration of morpholine-thiophene hybrid thiosemicarbazones for the treatment of ureolytic bacterial infections via targeting urease enzyme: Synthesis, biochemical screening and computational analysis. *Front Chem*, 2024; 12: 1403127.
 14. Abdelazeem NM, Gouhar SA, Fahmy CA, Elshahid ZA, El-Hussieny M. Evaluation of newly synthesized 2-(thiophen-2-yl)-1H-indole derivatives as anticancer agents against HCT-116 cell proliferation via cell cycle arrest and down regulation of miR-25. *Sci Rep*, 2024; 14(1): 20045.
 15. Metwally HM, Younis NM, Abdel-Latif E, El-Rayyes A. New thiazole, thiophene and 2-pyridone compounds incorporating dimethylaniline moiety: Synthesis, cytotoxicity, ADME and molecular docking studies. *BMC Chem*, 2024; 18(1): 52.
 16. Ibrahim NS, Sayed HA, Sharaky M, Diab HM, Elwahy AH, Abdelhamid IA. Synthesis, cytotoxicity, anti-inflammatory, anti-metastatic and anti-oxidant activities of novel chalcones incorporating 2-phenoxy-n-arylacetamide and thiophene moieties: Induction of apoptosis in MCF7 and HEP2 cells. *Naunyn Schmiedebergs Arch Pharmacol*, 2024; 397(12): 10091–10107.
 17. Alsouk AA, Othman IM, Anwar MM, Saleh A, Nossier ES. Design, synthesis, and *in silico* studies of new quinazolinones tagged thiophene, thienopyrimidine, and thienopyridine scaffolds as antiproliferative agents with potential p38 α MAPK kinase inhibitory effects. *RSC Adv*, 2025; 15(2): 1407–1424.
 18. Akhter F, Marufa SS, Shohag SM, Nishino H, Alam MS, Haque MdA, et al. Synthesis, antimicrobial evaluation, ADMET prediction, molecular docking and dynamics studies of pyridine and thiophene moiety-containing chalcones. *R Soc Open Sci*, 2025; 12(1).
 19. de Araújo RS, Bernardo VG, Tibúrcio R da, Bedor DC, Campos ML, Pontarolo R, et al. 2-aminothiophene derivatives—new drug candidates against leishmaniasis: Drug design, synthesis, pharmacomodulation, and antileishmanial activity. *Pharmaceuticals*, 2025; 18(1): 125.
 20. Fathi EM, Salem ME, Sroor FM, Mohamed FG, Elwahy AH, Abdel-Megid M, et al. Synthesis and evaluation of novel bis-chalcone derivatives containing a thiophene moiety as potential anticancer agents: *In vitro*, *in silico*, and mechanistic studies. *ACS Omega*, 2025; 10(24): 25921–25937.