World Journal of Pharmaceutical and Life Sciences
WJPLS
www.wjpls.org
SJIF Impact Factor: 7.409

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

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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.

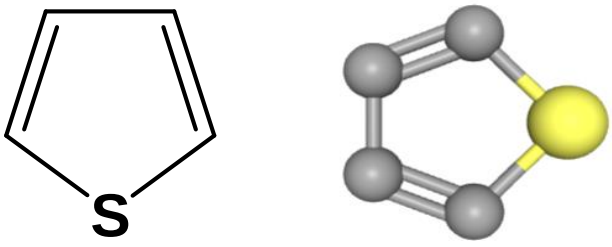


Fig. 1- 2D and 3D structure of basic thiophene scaffold.

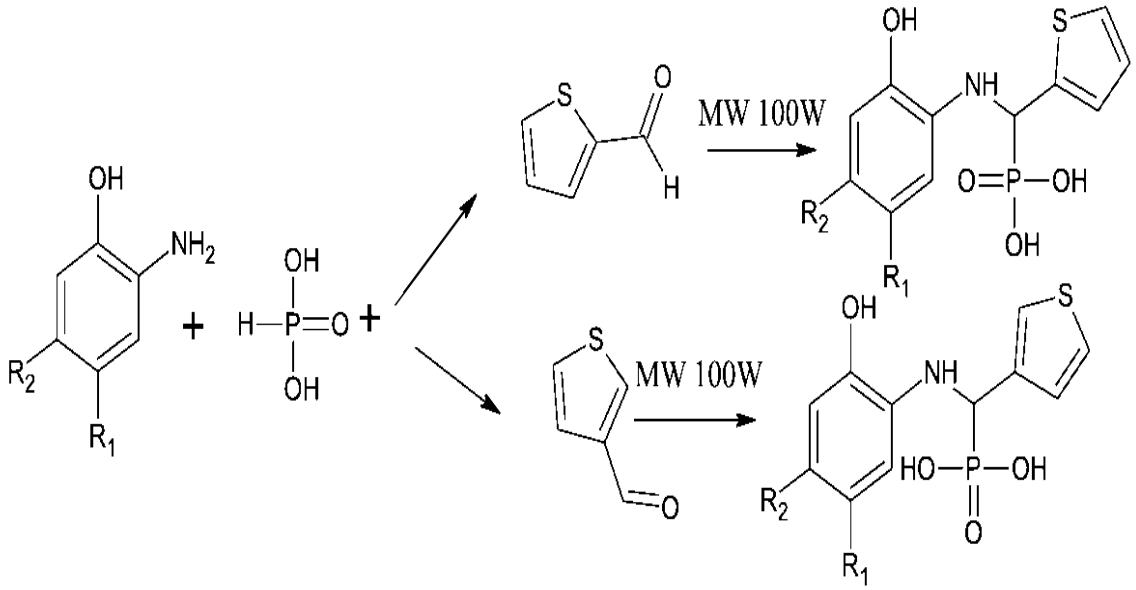
One of the most promising strategies in modern drug discovery involves the development of **hybrid molecules**-compounds that merge two or more pharmacophores into a single entity. This hybridisation approach often leads to enhanced potency, improved selectivity, and multi-target engagement, which are 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.

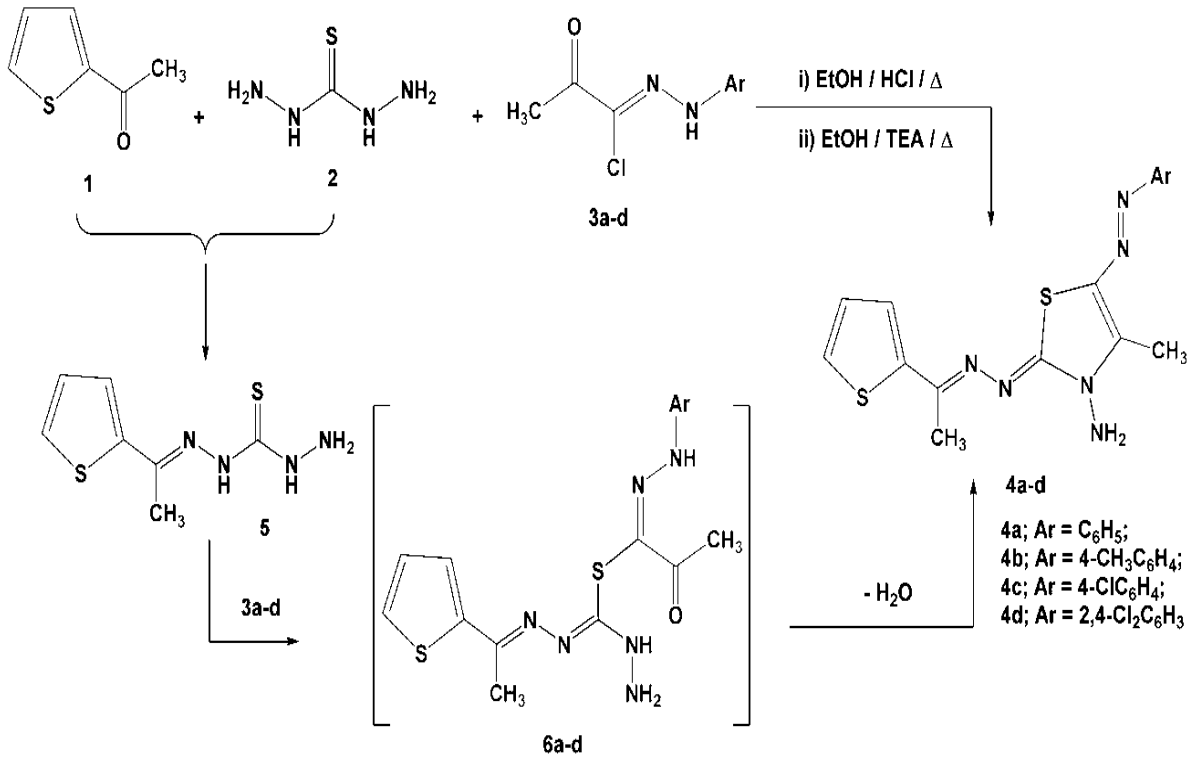
Tlidjane et al. reported the green synthesis of novel α-amino phosphonic acids incorporating thiophene rings via a microwave-assisted three-component reaction involving amino phenols, thiophene carboxaldehydes, and phosphorus acid in ethanol without catalysts. These compounds demonstrated remarkable 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

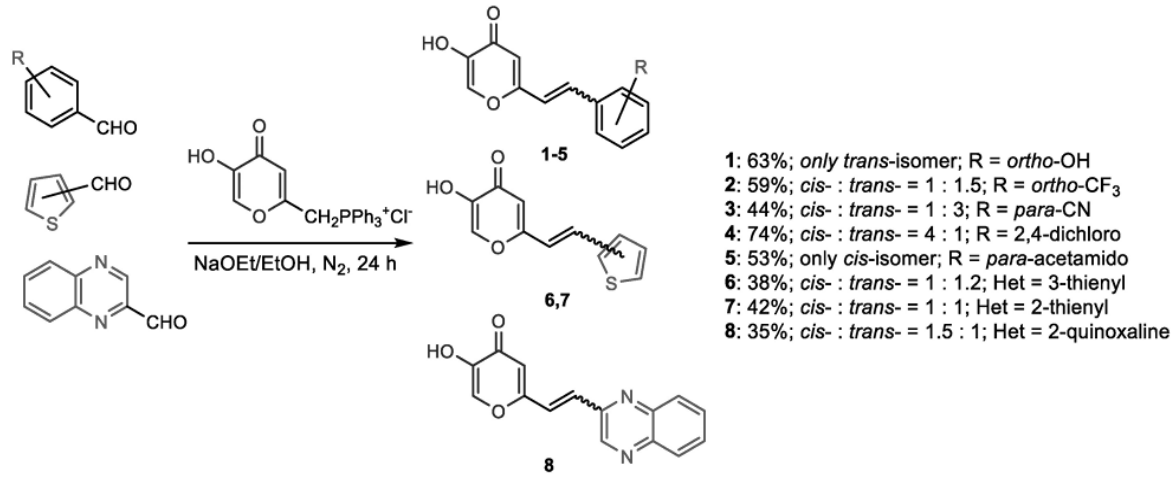
Scheme 1. Synthesis sequences of α-amino phosphonic acids with (5N2TPA, 5N3TPA: R_1 = H, R_2 = N_2, 4M3TPA: R_1 = CH_3, R_2 = H, 5M3TPA: R_1 = H, R_2 = CH_3)

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.

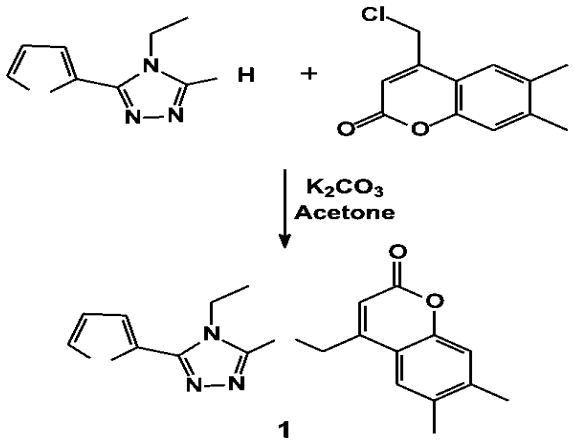
Mlakić et al. synthesised novel resveratrol–thiophene and resveratrol–maltol hybrids as cholinesterase inhibitors and antioxidants. Thiophene derivatives (II, III) exhibited potent AChE/BChE inhibition and antioxidant activity comparable to galantamine, while maltol hybrids showed weaker effects. The 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.

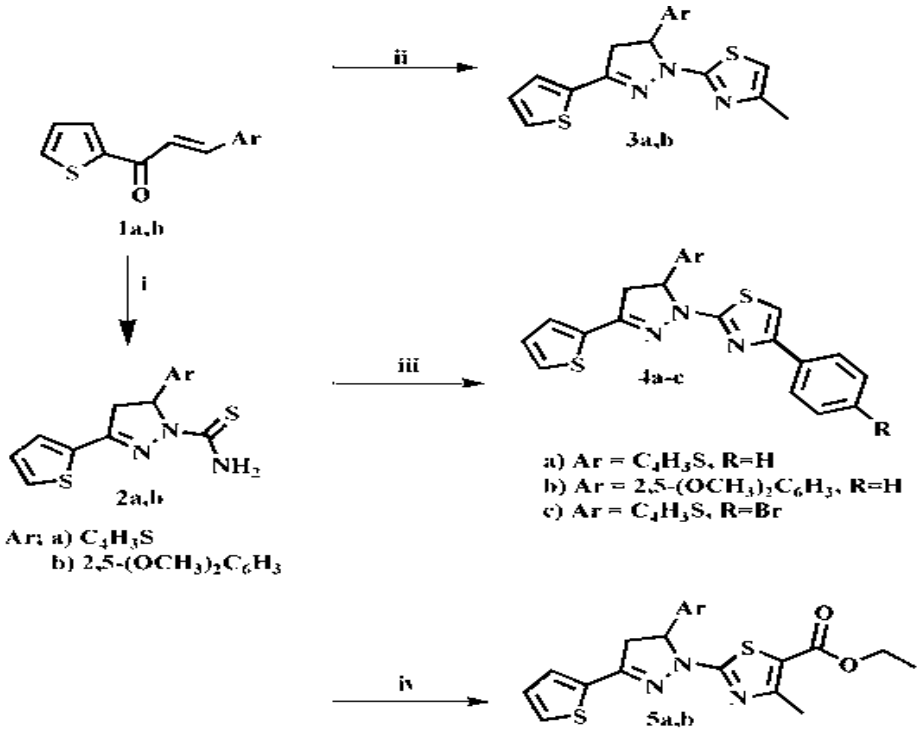
Omar et al. synthesized a novel coumarin–triazole–thiophene hybrid as a potential SARS-CoV-2 inhibitor. The synthetic route involved a multi-step procedure starting from 4-hydroxycoumarin and propargyl bromide to form propargylated coumarin, which was subjected to a Cu(I)-catalyzed azide-alkyne cycloaddition ("click reaction") with a thiophene-containing azide to form the final hybrid. Structural confirmation was carried out using FT-IR, NMR (^{1}H & ^{13}C), 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).

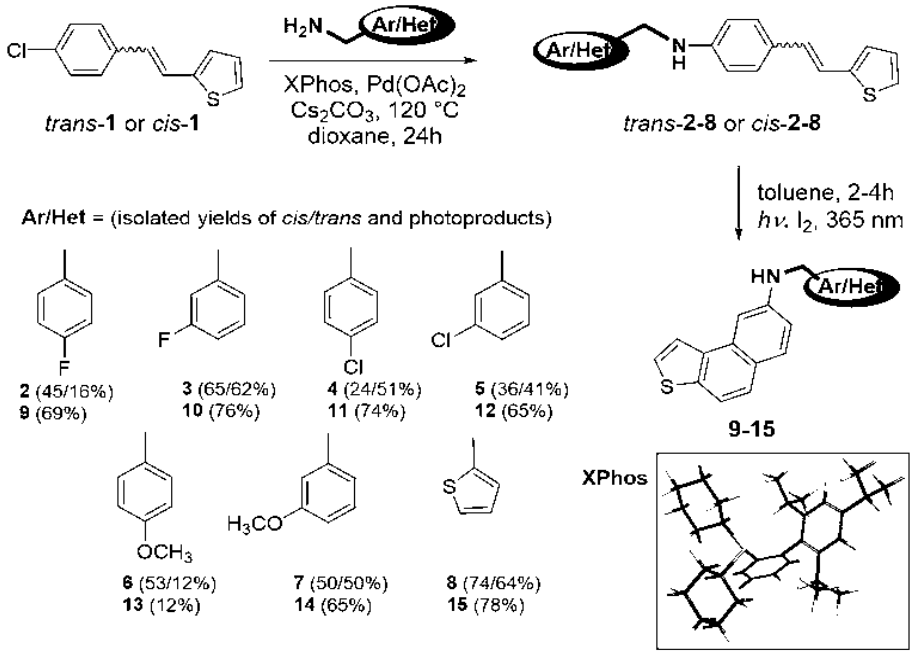
Dawood et al. designed and synthesized a new series of thiophenyl–pyrazolyl–thiazole hybrids as potent dihydrofolate reductase (DHFR) inhibitors with antimicrobial potential. The synthetic strategy involved the formation of hydrazonoyl chloride intermediates, which underwent cyclization with potassium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

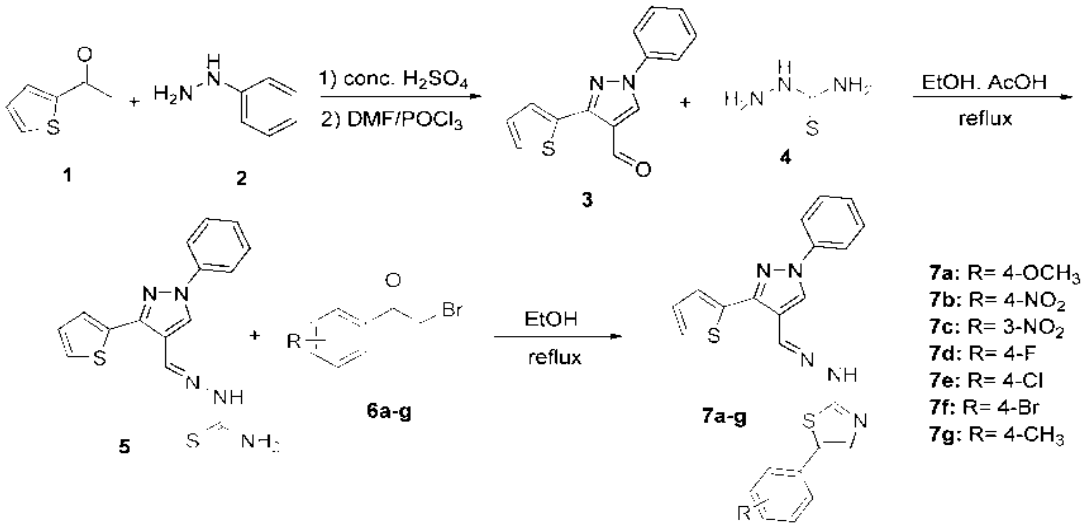
Scheme 5. Synthesis of New Thiophenyl-pyrazolyl-thiazole Hybrids 3–5[a].

Mlakić 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]



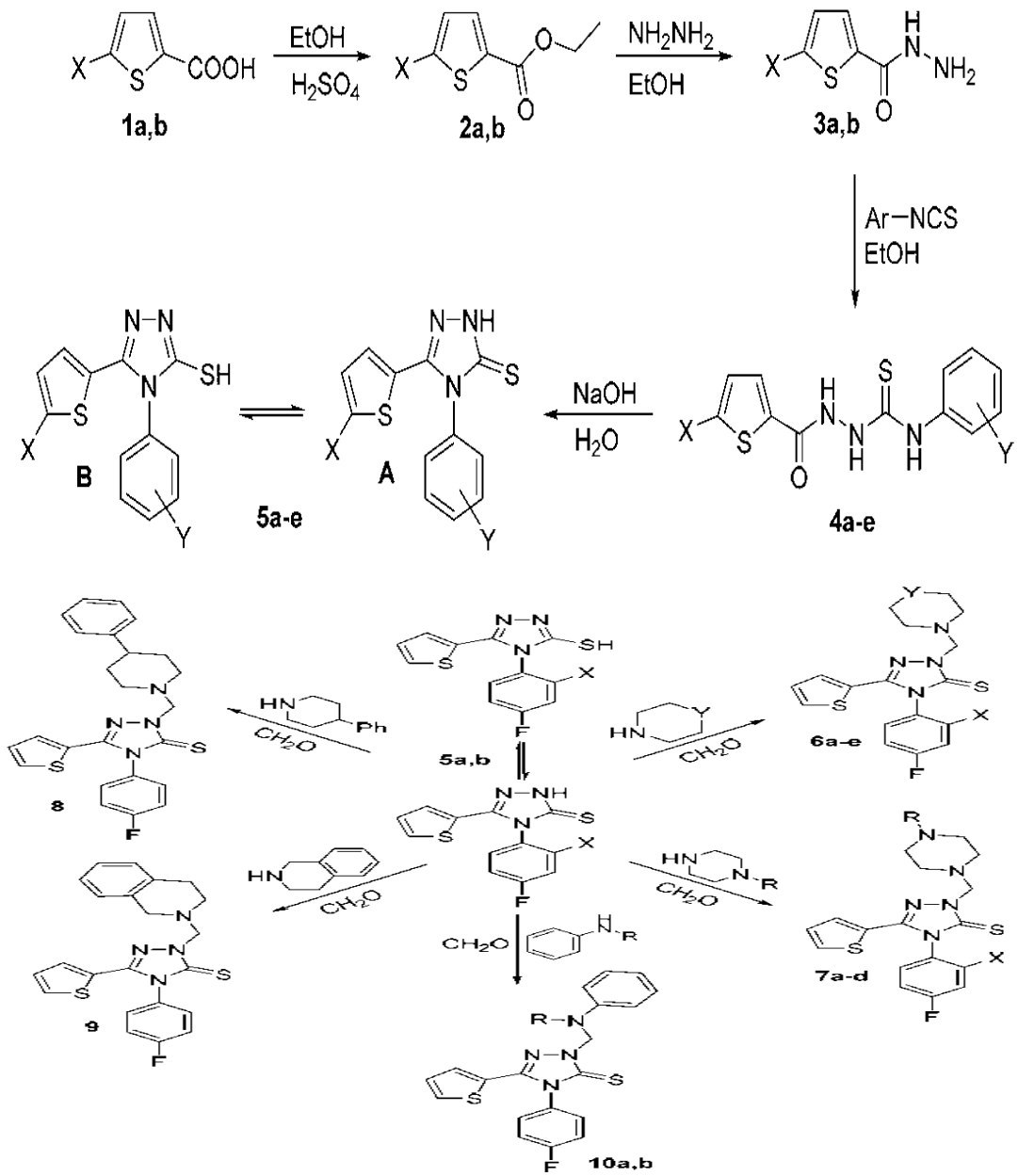
Scheme 6. Synthesis and photocyclization reactions of styryl-thiophene benzylamines 2–8.

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]



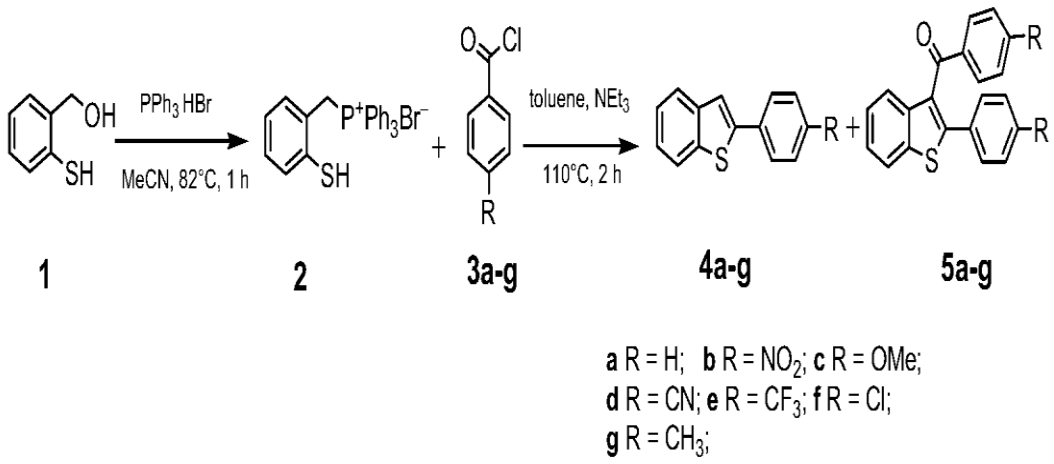
Scheme 7. Synthetic route for the pyrazolyl–thiazole derivatives.

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 µM) (**Scheme 8**).[8]



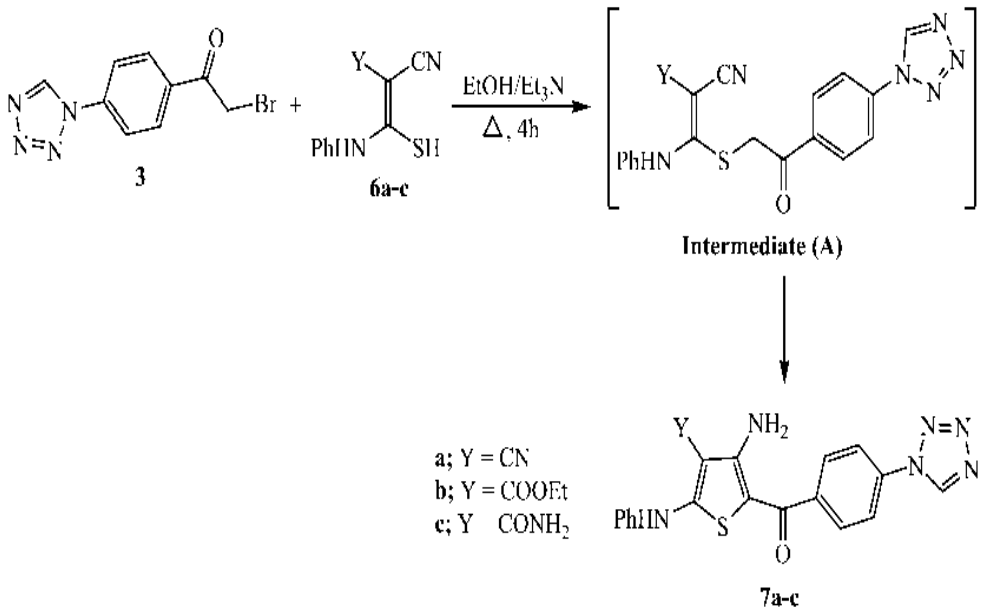
Scheme 8. Synthesis of compounds 5a-e, 6a-e, 7a-d, 8, 9, 10a, and 10b.

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 µM) and 5h showing potent BChE inhibition (IC_{50} = 24.35 µM), comparable to the reference drug galantamine (IC_{50} = 28.08 µM). 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.

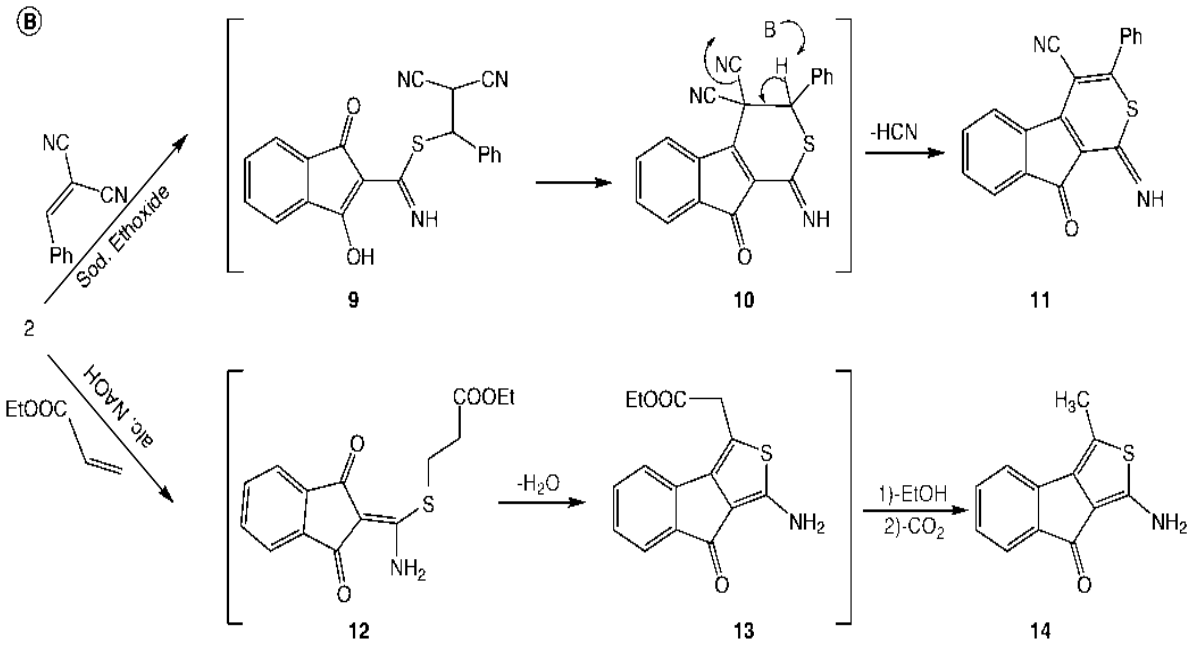
Abualnaja et al. reported the synthesis of tetrazole-based hybrids incorporating thiazole, thiophene, and thiadiazole moieties through multi-step chemical reactions. The structures of the synthesized compounds were confirmed using IR, NMR, and mass spectrometry. Density Functional Theory (DFT/B3LYP) 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.

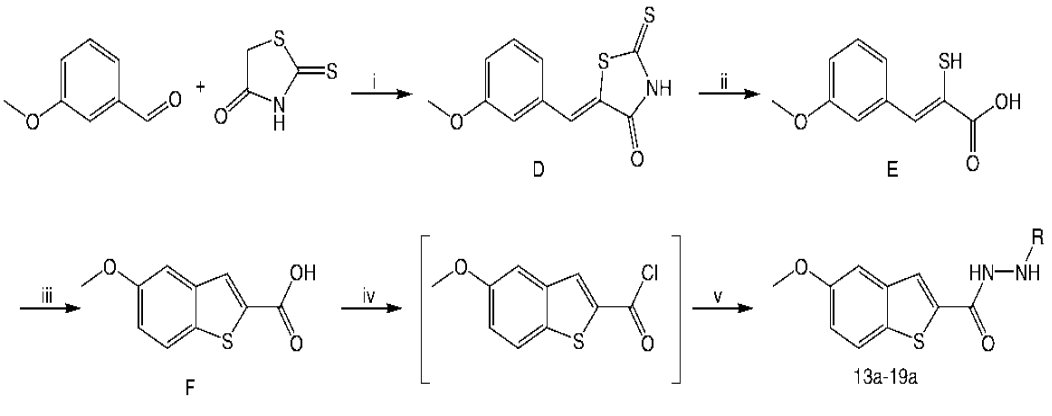
Abdellattif et al. designed and synthesized novel indandione-based derivatives through reactions with various electrophilic and nucleophilic reagents, yielding a series of compounds (3, 4, 8, 11, 14, 16, 19–23). Among these, compounds 8, 11, 16, 20, and 23 were evaluated for their anticancer activity 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 IC_{50} 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]

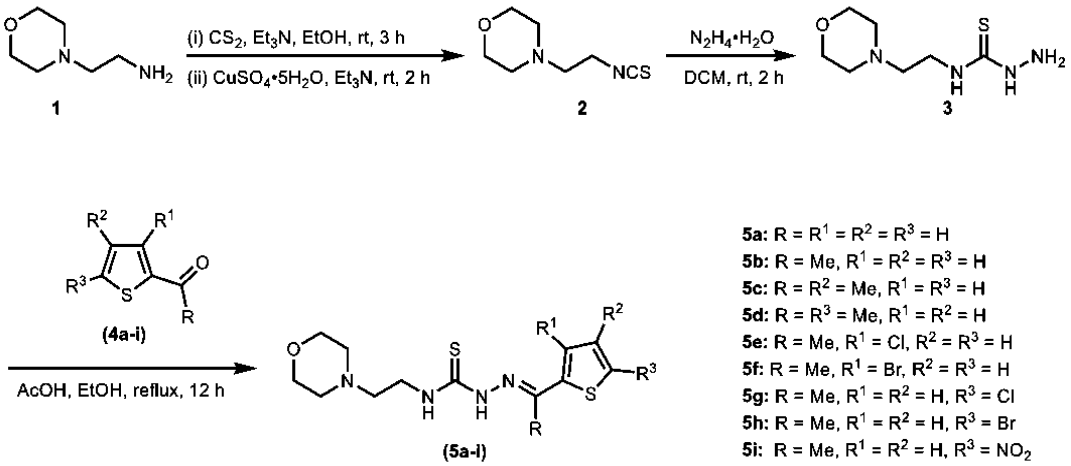


Cpd no.	R	Cpd no.	R
13a	3-chlorophenyl	16b	3-fluorophenyl
13b	3-chlorophenyl	17a	2-fluorophenyl
14a	4-chlorophenyl	17b	2-fluorophenyl
14b	4-chlorophenyl	18a	3,5-difluorophenyl
15a	4-fluorophenyl	18b	3,5-difluorophenyl
15b	4-fluorophenyl	19a	3,5-difluorophenyl
16a	3-fluorophenyl	19b	3,5-difluorophenyl

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

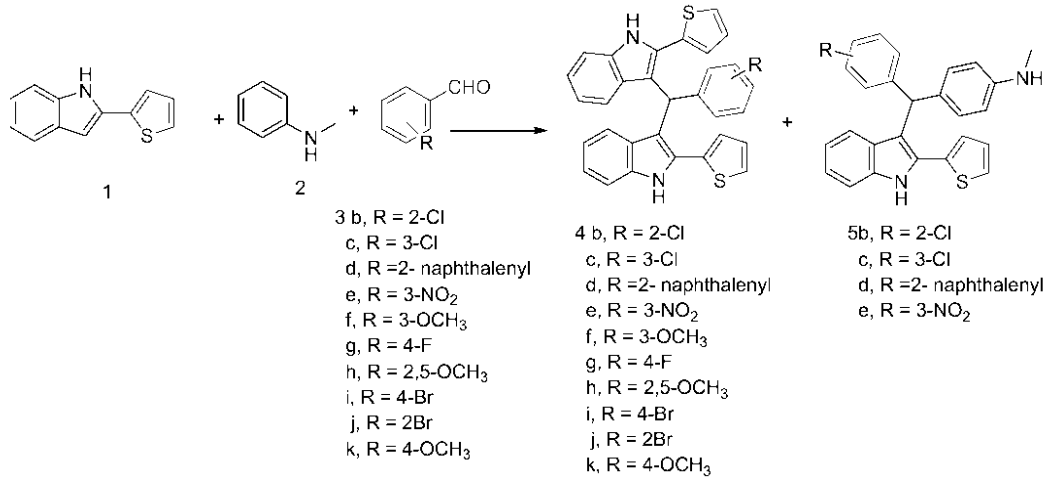
iodine in dry THF, reflux, 42 h; (iv) 4 equiv. of oxalyl chloride, catalytic DMF in dry DCM, reflux, 3 h; (v) 1 mL DIPEA, 2 equiv. of the appropriate phenyl hydrazine hy dr ochloride in dry THF, RT, 18 h; (vi) 5 mL BBr 3 in DCM, RT, overnight. Cpd: Compound; RT: Room temperature.

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, ^{1}H NMR, ^{13}C 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 IC_{50} 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]



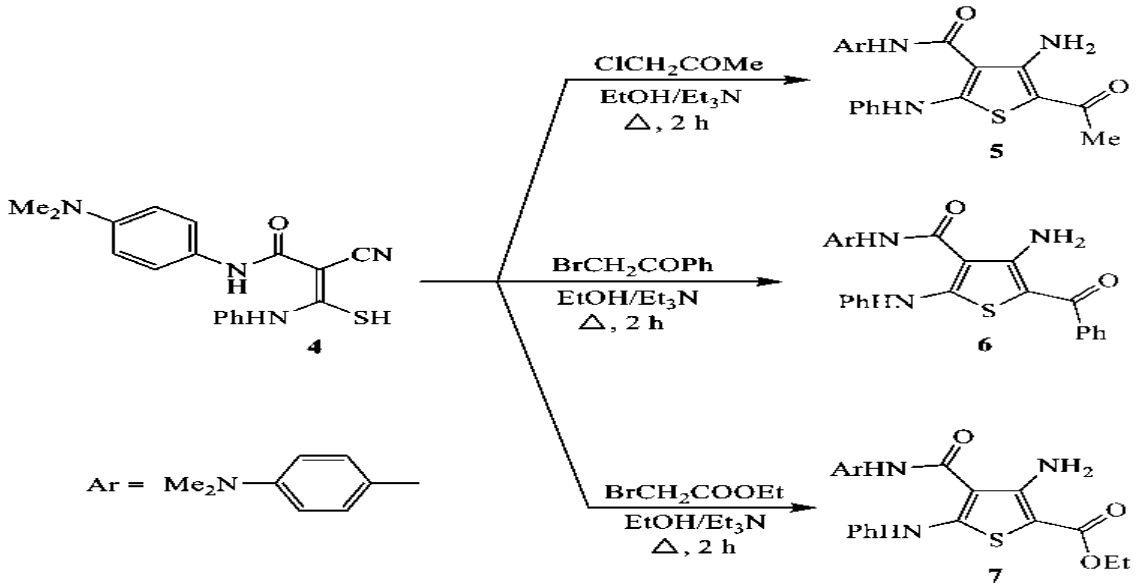
Scheme 13. Synthetic layout for morpholine-thiophene hybrid thiosemicarbazones.

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 IC_{50} 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]



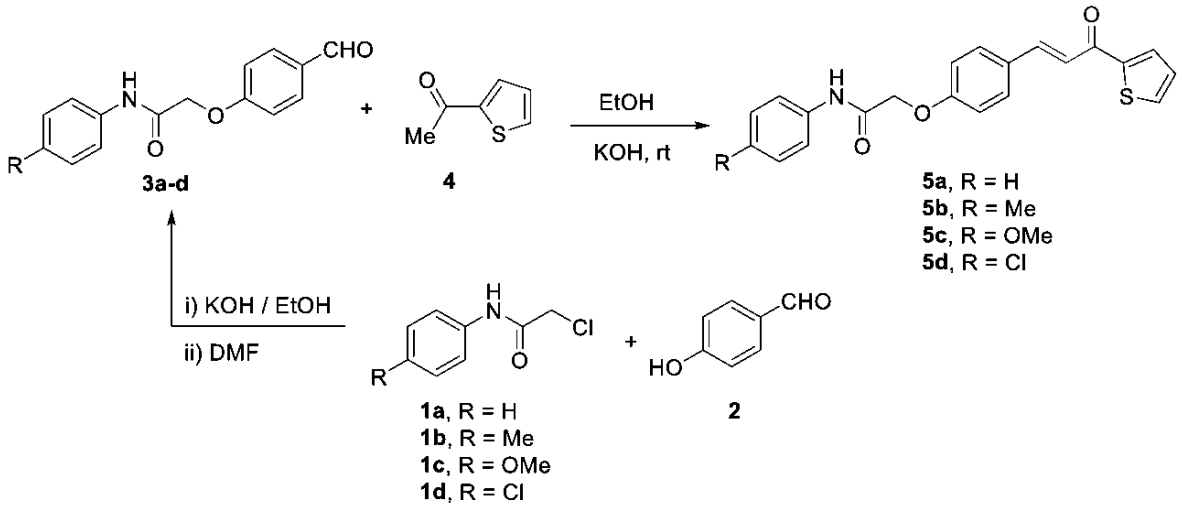
Scheme 14: Synthesis of (methylene)bis(2-(thiophen-2-yl)-1H-indole) derivatives 4b–k, and (2-(thiophen-2-yl) 1H-indol-3-yl) methyl) aniline derivatives 5b–e.

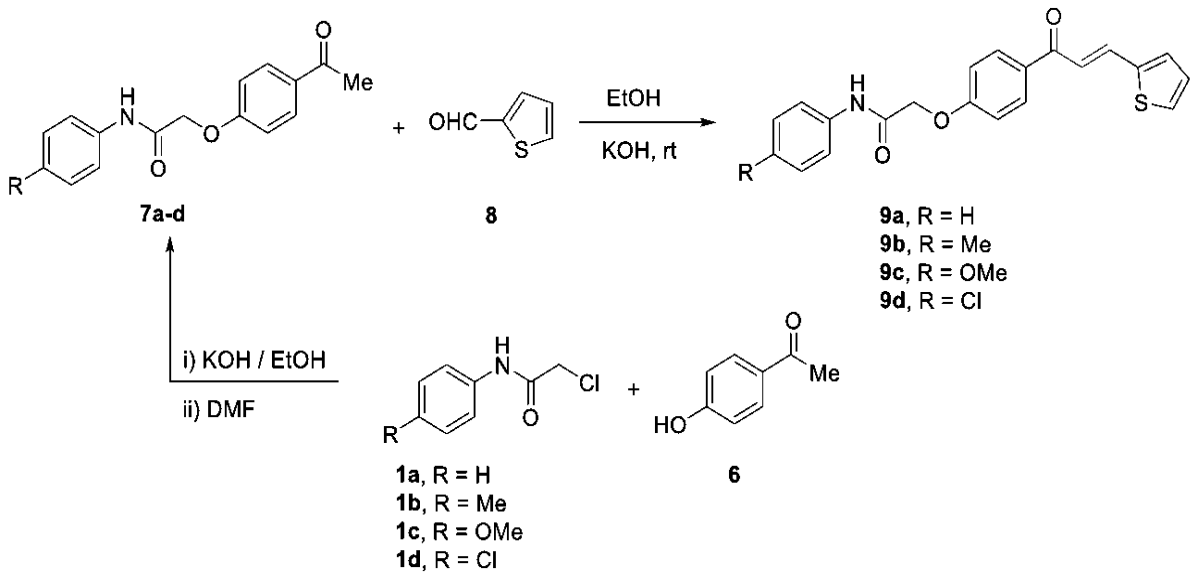
Metwally et al. synthesized diverse thiazole, thiophene, and 2-pyridone derivatives incorporating a dimethylaniline moiety for anticancer evaluation. Thiazoles (2–3) and thiophenes (5–7) were obtained by reacting thiocarbamoyl intermediate 4 with α-halogenated agents under basic conditions. The 2-pyridone 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 µM), 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-substitited thiophene derivatives 5, 6, and 7.

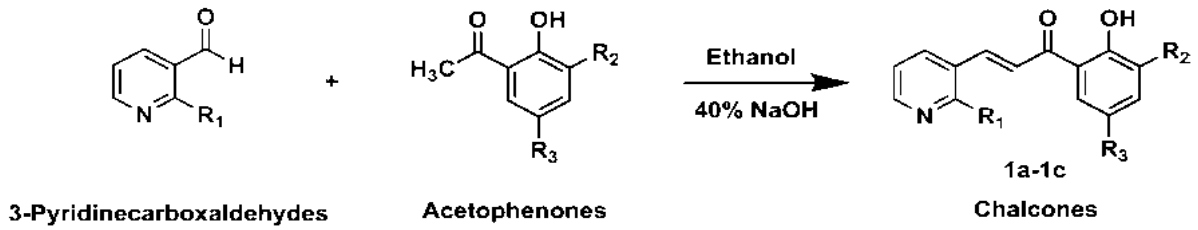
Ibrahim et al. synthesized eight novel chalcones incorporating thiophene and phenoxy acetamide moieties, confirmed via spectral techniques including IR, NMR, and MS. The compounds were screened for cytotoxicity using the SRB assay; compound 5c exhibited the most potent effect against MCF7 and HEP2 cells with IC_{50} values of 9.5 and 12 µg/mL, respectively. RT-PCR revealed significant downregulation of KI-67, Survivin, IL-1β, 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]



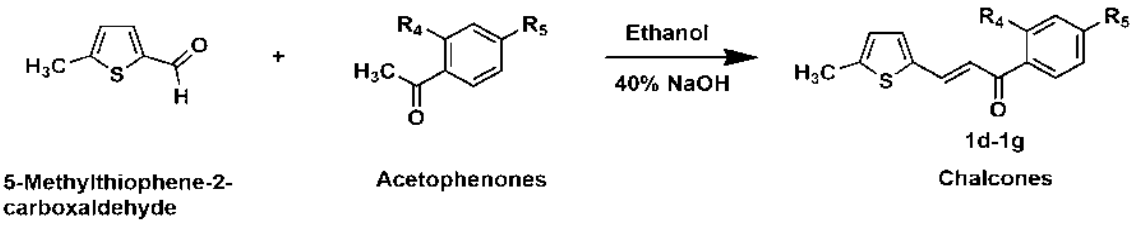


Scheme 16: Synthesis of 5a–d and 9a–d.

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, ^{1}H-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]



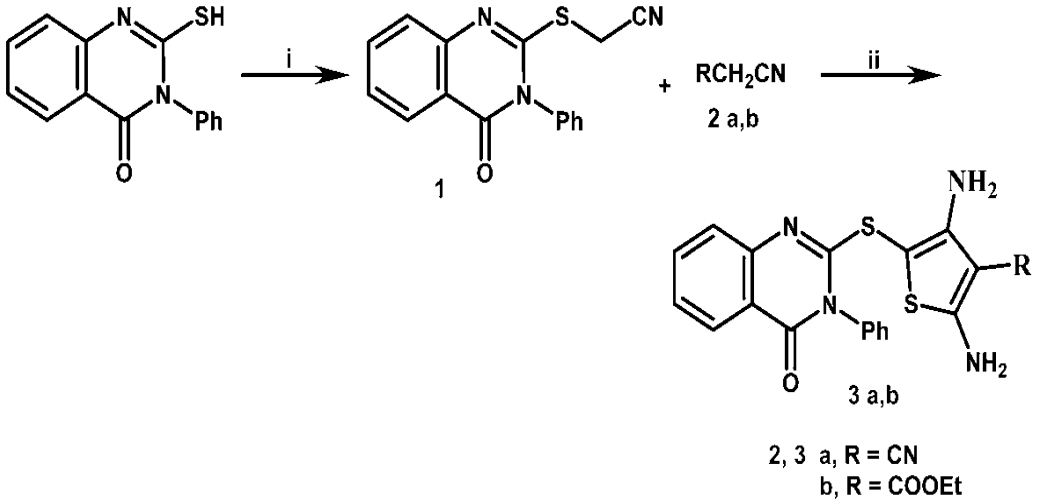
Compounds	R_1	R_2	R_3
1a	H	H	Br
1b	Cl	H	Br
1c	H	NO_2	Cl



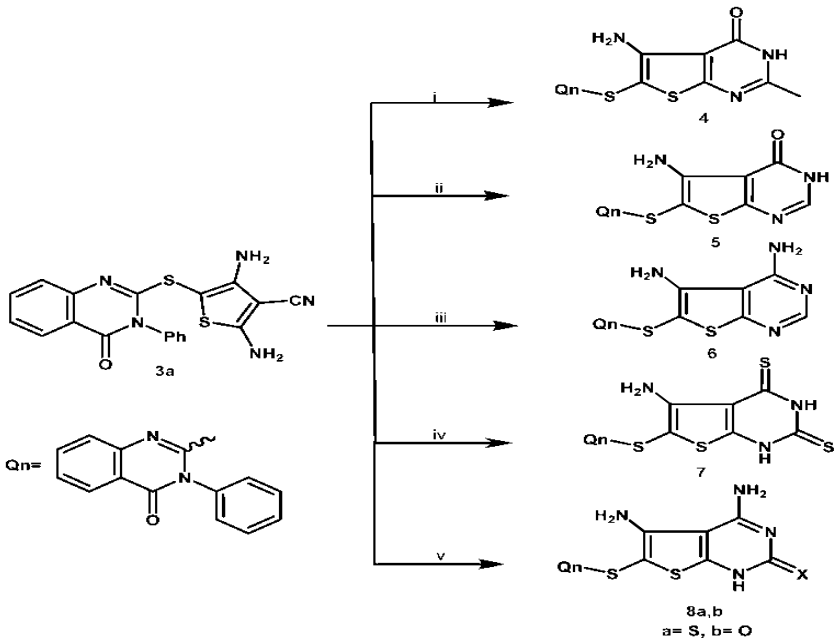
Compounds	R_4	R_5
1d	H	NO_2
1e	H	F
1f	H	CH_3
1g	OH	Cl

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

Alsfouk 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 p38α 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]

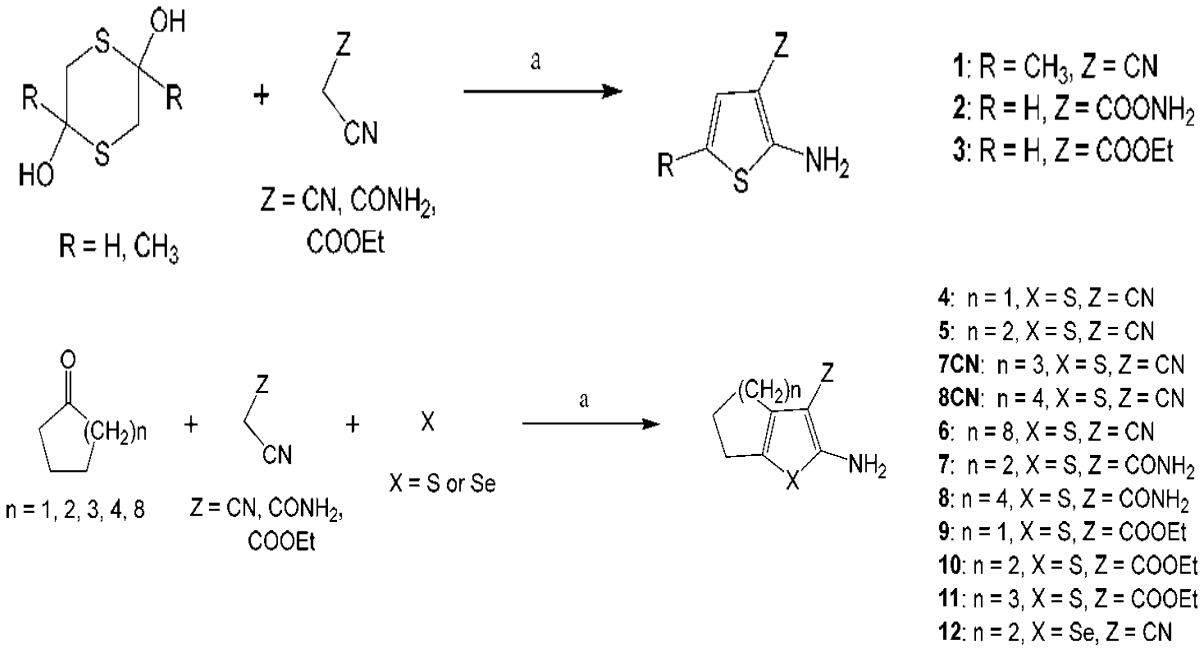


Scheme 18. Synthetic path way for synthesis of 2,4-diamino-thiophene-3-carbonitriles 3a,b. Reagents and conditions: (i) chloro-acetonitrile, sodium acetate, dry DMF, stirring for 30 minutes, refluxing for 5 h; (ii) S, malononitrile and/or ethyl cyanoacetate, absolute ethanol, few drops of triethylamine,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



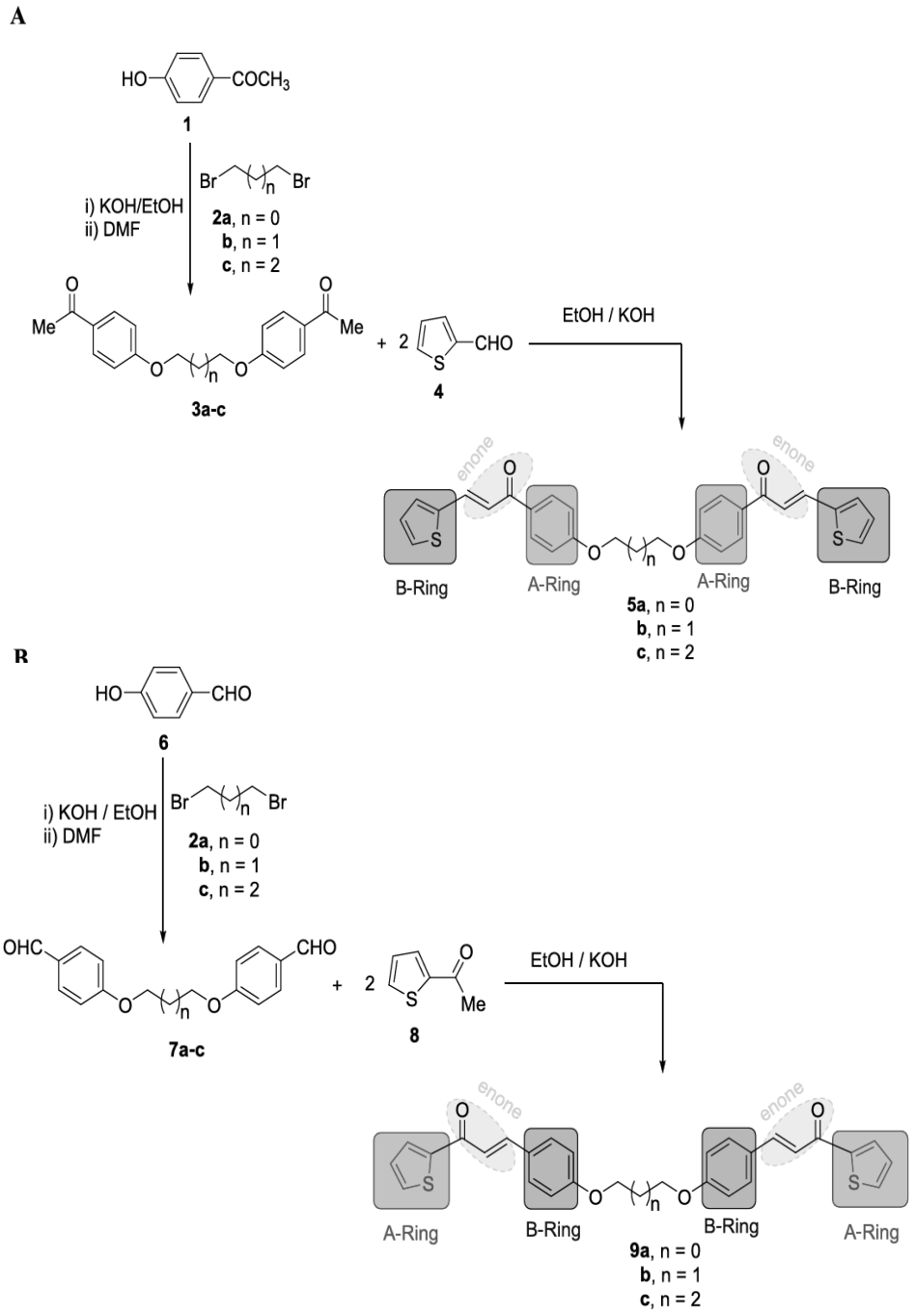
Scheme 19. Synthetic pathway for synthesis of different substituted thienopyrimidines 4–8a, b. Reagents and conditions: (i and ii) acetic anhydride and/or formic acid, reflux for 24 h;(iii) formamide, reflux for 12 h; (iv) carbon disulphide, pyridine, reflux on water bath for 10 h; (v) thiourea and/or 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 µM), 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 ± 0.96 μM) 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, **Alsfouk et al.** synthesized thiophene-linked quinazolinone derivatives that inhibited p38α 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 IC_{50} values below 0.31 µM 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]

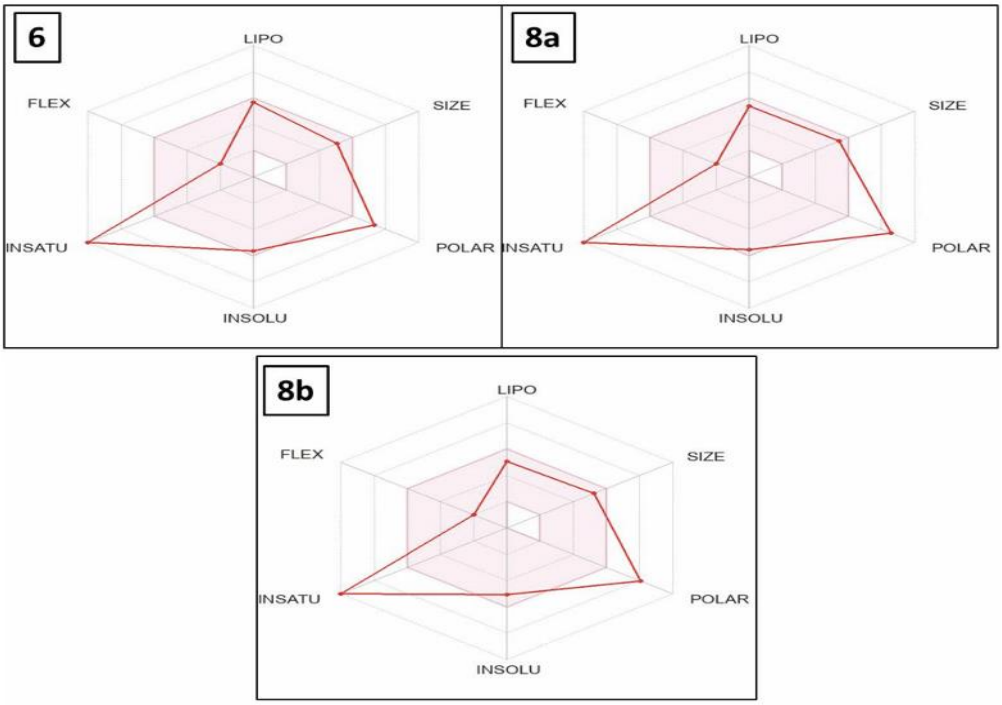


Fig. 2- The effective thieno [2,3-d] pyrimidine derivatives 6, 8a, and 8b's bioavailability radar map.[17]

➢ **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]

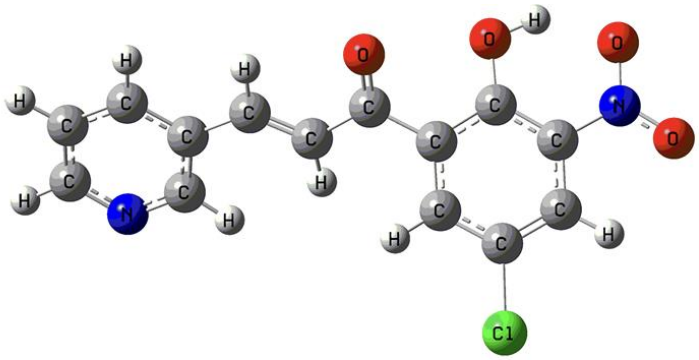


Fig. 3- Optimized molecular structure of synthesized compound 1c with a basis setup B3LYP/6-31G.

➢ **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]

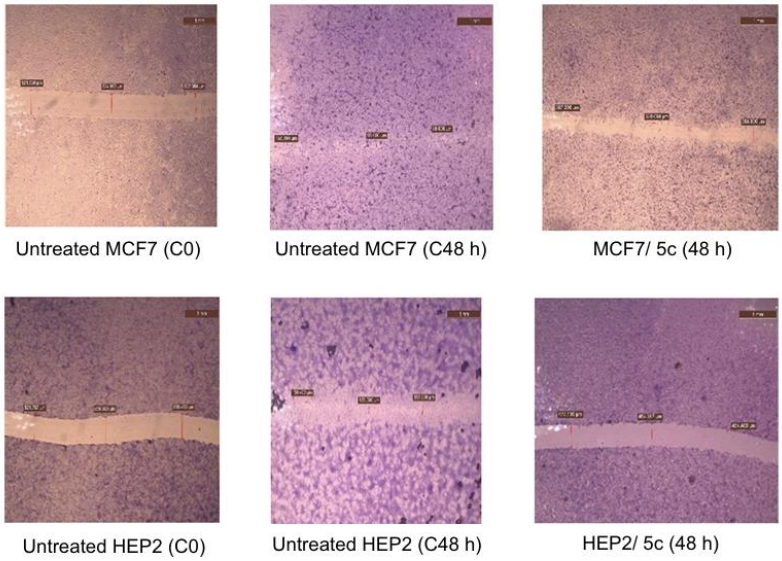


Fig. 4- Evaluation of migration.

➢ **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 µM. 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 p38α 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.

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