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RESEARCH ARTICLE

THIENYL CHALCONES: SMALL MOLECULES THAT PLAY PIVOTAL ROLES

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ABSTRACT

The small molecules, in particular chalcones are regarded as buildingblocks for the construction of varied classes of biologically potent heterocycles such as pyrazoles, isoxazoles, triazoles, benzothiazepines, etc. The chalcones are basically derived from aromatic aldehydes and aromatic ketones; in which aromatic group may be a phenyl or heterocylic ring. In recent years, the heteroaryl, in particular thiophene ring containing chalcones have attracted the larger interest among the researchers all over the world, due to their diverse applications, viz., useful scaffolds in organic synthesis, bioactive nature in medicinal chemistry, and varied physicochemical properties. There has been a significant interest in recent years in developing simple, clean, non-toxic, cost-effective and eco-friendly procedures for the synthesis, and the exploration of these molecules to wide range of biological potencies. In this context, this review article presents the developments in the synthetic strategies for thienyl chalcones, their utility as synthons for preparation of bioactive molecules, pharmaceutical applications, and physico-chemical properties in the last ten years.

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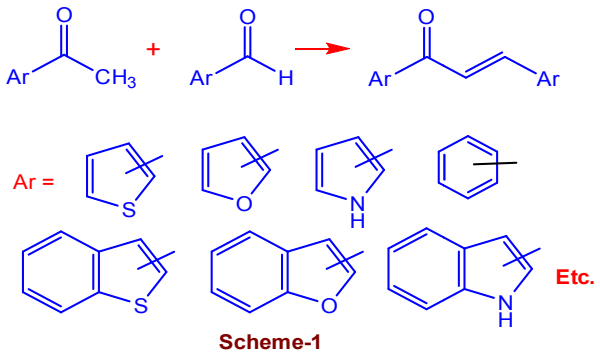
INTRODUCTION

Chalcones constitute an important class of naturally occurring flavonoids or synthetic analogues, and were known for biological activities such as anti-inflammatory, antioxidant, antileishmanial, antitubercular, anticancer, anti-HIV, antibacterial, antimalarial, anti-tuberculosis, and antiulcer etc.Chalcones are generally 1,3-diarylprop-2-en-1-ones results from the condensation reaction between aromatic, heteroaromatic ketones and aromatic, heteroaromatic aldehydes (Scheme-1).



Scheme-1

In particular, thiophene conjugated chalcones and their derivatives possess diverse applications. They were extensively used as useful scaffolds for the construction of biologically potent molecules, and studied for their varied biological applications and physico-chemical properties. The present review summarizes developments in the synthetic protocols, utility as synthons in the construction of biologically active heterocycles, pharmacological applications and physicochemical properties of thiophene containing chalcones over the last few years.

Synthesis and synthetic applications: Literature reveals that various methodologies have been developed and reported for the synthesis of thiophene conjugated chalcones. Amongst the methods developed, the more commonly employed method by the researchers all over the world being; the base catalyzed Claisen–Schmidt condensation reaction of aromatic aldehydes and aromatic ketones.A library of chalcones, (*E*)-1-(2,5-dimethyl-3-thienyl)-3-(substituted phenyl)-2-propen-1-ones were synthesized by Claisen–Schmidt reaction of 3-acetyl-2,5-dimethyl thiophene and substituted benzaldehydes in good yields (Scheme-2) (1). The effects of substituents of these chalcones were studied by their spectral data, and were correlated with Hammett substituent constants. The synthesized compounds have shown antibacterial, antifungal, antioxidant and insect antifeedant activities.

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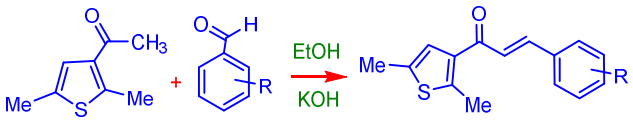
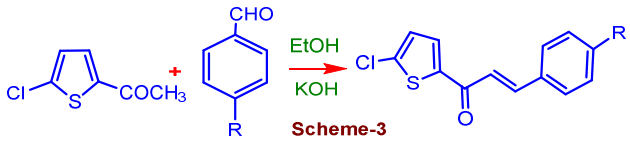


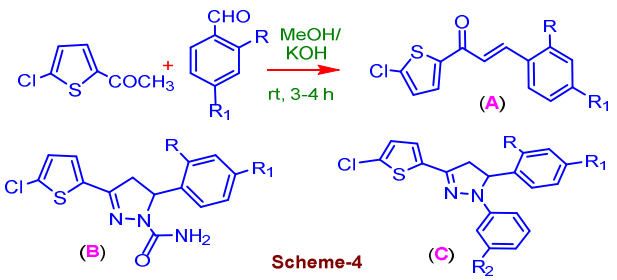
Scheme-2

Naveen and co-workers (2) reported the synthesis and crystallographic characterisation of thienyl chalcones derived from 5-chlro-2-acetyl thiophene via base catalyzed condensation reaction with aromatic aldehydes. Later, they transformed (*E*)-1-(5-chlorothiophen-2-yl)-3-(p-tolyl)prop-2-en-1-one to pyrazole carbothioamide through (3+2) annulation reaction with thiosemicarbazide (3). Chalconeswere considered to be a valid scaffold for the design of monoamine oxidase (MAO) inhibitors. This amplified the momentum for the discovery of heteroaryl based chalcone MAO inhibitors. Mathew *et al*(4) synthesized a series of chlorinated thienyl chalcone derivatives via Claisen=Schmidt reaction of 5-chloro thiophene-1-al with substituted acetophenones having a different functional groups at the para- position (Scheme-3). They have investigated for their ability to inhibit human MAO-A and MAO-B. Results reveals that all designedchalcone derivatives inhibited hMAO-B potently and selectively with competitive mode of inhibition, and are observed to be completely non-toxic with 74.88% viable cells to hepatic cells at 100 µM concentration.



Scheme-3

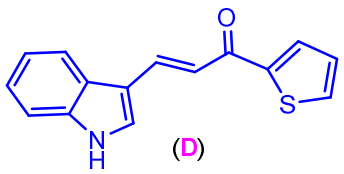
Ghinet and co-workers (6) employed ultrasound technique to synthesize a broad range of chalcone derivatives following Claisen-Schmidt condensation of (hetero)aryl ketones and (hetero)aryl aldehydes, the method found easier and faster in comparison with classical magnetic stirring method, and lithium hydroxide is the best basic catalyst of the studied condensations. The synthesized compounds showed inhibitory activity on the target protein and cytostatic effect on different cell lines with particular activity against MCF7, a breast cancer cells. Shashikanth *et al* (7, 8) developed the new protocol for the construction of medicinally important lignans and their conjugates starting from thienyl chalcones, their protocol proceeds via cyclopropanation of chalcones leads to the target lignans. Prabhudeva and co-workers reported the synthesis of series of (*E*)-1-(5-chlorothiophen-2-yl)-3-(aryl)prop-2-en-1-ones (A) by the reaction of 5-chloro-2-acetylthiophene with substituted aromatic aldehydes in the presence of KOH in ethyl alcohol under reflux conditions. They were successful in transforming these chalcones in to pyrazole carboxamides (B) by their reaction with semicarbazide which displayed antimicrobial activities (9), and 2-pyrazoline derivatives (C) by their reaction with phenylhydrazines, which displayed antimicrobial, antioxidant and anti-inflammatory activities (Scheme-4) (10).



Scheme-4

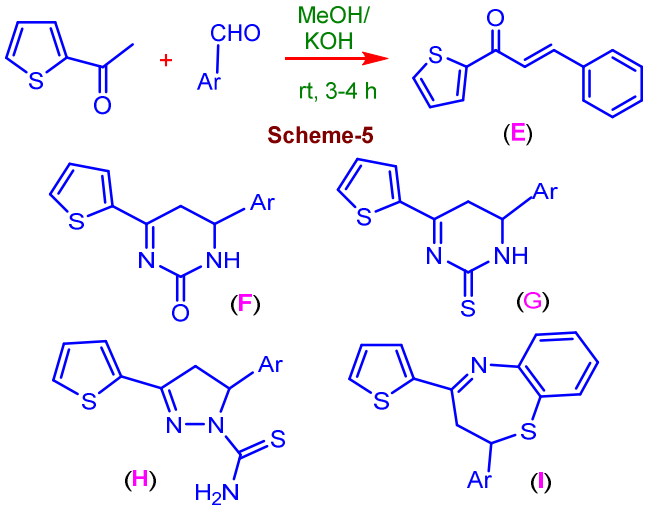
Raghavendra and coworkers extensively carried out their work on thiophene conjugated chalcones, and their post transformation in to various classes of bioactive heterocycles. Initially, they were synthesized thienyl chalcones via Claisen-Schmidt reaction of 2-acetyl thiophene with aromatic aldehydes. Then they were successfully carried out the reactions of thienyl chalcones with phenylhydrazines to get pyrazole derivatives (11, 12), with 2-aminothiophenol to get benzothiazepines (13, 14) in good yields.

Pharmacological applications: Thienyl chalcones and their derivatives are of great interest in medicinal chemistry due to their numerous biochemical and pharmacological applications. 2-Thiophenyl substituted chalcones were non cytotoxic against Mo7e and BA/F3 cells. In this context, Kannan and co-workers (15) designed and synthesized (*E*)-3-(1H-indol-3-yl)-1-(thiophen-2-yl)prop-2-en-1-ones (D), and assessed for its activity againstH_{37}Rv strain of Mycobacterium tuberculosis. It was found that, the compound displayed high anti-tubercular activity at 50 µg/ml with MIC value of 197 µM, and cytotoxicity assay showed that it was non-cytotoxic to human megakaryocytes and murine B cells.



(D)

The chalcones (*E*)-3-phenyl-1-(thiophen-2-yl)prop-2-en-1-ones (E) were reported by the reaction of 2-acetyl thiophene and substituted aromatic aldehydes through Claisen-Schmidt approach in good yields (Scheme-5). The reaction of the chalcones (E) with urea, thiourea, thiosemicarbazide and 2-amino thiophenol yieldedpyrimidin-2-ones(F) (16), pyrimidin-2-thione(G) (17), pyrazole carbothioamides(H) (18), and benzothiazepines (I) (19), respectively. These synthesized compounds exhibited antimicrobial and antioxidant properties.

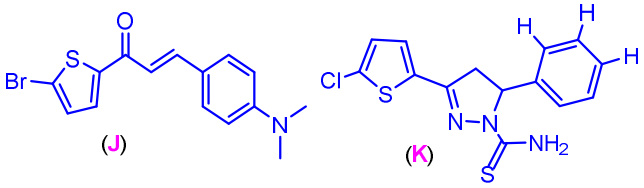


Scheme-5 (E)

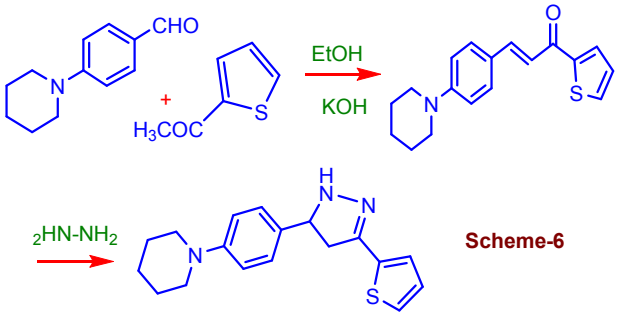
(F) (G) (H) (I)

Soliman and co-workers (20) synthesized (*E*)-1-(5-bromothiophen-2-yl)-3-[4-(dimethylamino) phenyl] prop-2-en-1-one (**J**) to investigate the electrostatic potential surface and analyze the natural bond orbital toward the binding characteristics. Their studies on molecular dynamics simulations showed that, the molecular level interactions and relative energies of the hMAO isoforms: hMAO-A and hMAO-B with three potent and selective hMAO-B inhibitors.

The results of both continuous and accelerated molecular dynamics simulations demonstrated a distinct preference of the three ligands to bind to hMAO-B rather than hMAO-A. Synthesized 3-(5-chlorothiophen-2-yl)-5-phenyl-4,5-dihydro-1H-pyrazole-1-carbothioamide (**K**) have shown antimicrobial and free radical scavenging potencies (21).



Schinazi *et al.* (22) reported the synthesis of series of thiophene conjugated pyrazoline derivatives by the reaction of thiophene-piperidyl chalcones (Scheme-6). The target compounds characterized by spectroscopic methods were screened for cytotoxic and anti-HIV-1 activities. Results of the investigations revealed that thienyl chalcones and pyrazoline derivatives demonstrated potential anti-HIV activity. However, only two compounds of the series displayed no cytotoxicity in primary human cells. Bioassay results show that the type and positions of the substituents seem to be critical for their cytotoxic and anti-HIV-1 activities.

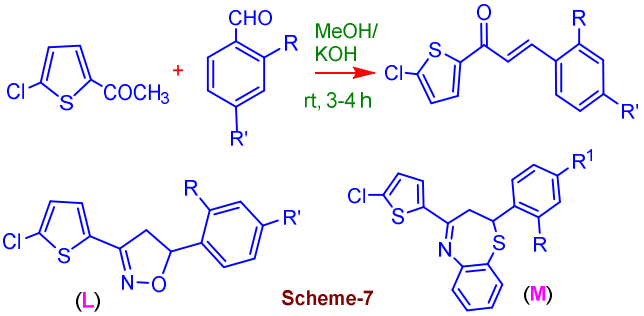


Scheme-6

The chalcone derivative 1-(3-bromo-2-thienyl)-3-[4-(dimethylamino)-phenyl] prop-2-en-1-one was investigated for physico-chemical properties, and which showed MAO-A and MAO-B inhibition potential (23). Mitochondrial enzymes monoamine oxidases were thought to be an emerging and useful therapeutic target for neurodegenerative disorders. Monoamine oxidases A (MAO-A) is related with metabolism of amine neurotransmitters in the brain, whereas MAO-B is concerned with aging related neurodegenerative disorders. Therefore, the discovery of potent MAO-A and B inhibitors is very crucial. Iqbal and wo-workers (24) designed and synthesized a series of quinolyl-thienyl chalcones and tested against MAO-A and B. Results indicated that, some of the compounds shown potent inhibition properties with an IC_{50} values of 0.047 µM 0.063 µM against MAO-A and MAO-B, respectively.

The chalcones3-aryl-1-(5-chlorothiophen-2-yl)prop-2-en-1-ones, prepared via Claisen-Schmidt reaction of 5-chloro-2-acetylthiophene with aromatic aldehydes in methyl alcohol were found suitable for (3+2) annulations. The reaction of these chalcones with hydroxylamine hydrochloride in methyl alcohol in the presence of Amberlyst-15 catalyst under reflux conditions yielded thiophene-isoxazoles (**L**) (25); and with 2-aminothiophenol in citrus juice medium in the presence of tetrabutylammonium bromide (TBAB) under reflux conditions yielded benzothizepine analogues (**M**) (26) (Scheme-7).

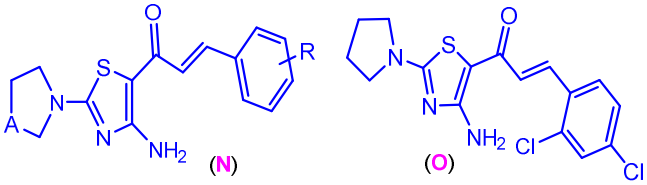
The synthesized isoxazoles and benzothiazepines shown potent antimicrobial activities against the tested organisms.



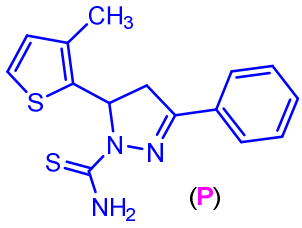
Scheme-7

Jayaprakash and co-workers (27) synthesized the series of (2*E*)-1-(5-bromothiophen-2-yl)-3-(para-substituted phenyl) prop-2-en-1-ones and tested for inhibitory activity toward human monoamine oxidase (hMAO). The results reveals that all compounds found to be competitive, selective, and reversible toward hMAO-B except (2*E*)-1-(5-bromothiophen-2-yl)-3-(4-nitrophenyl)prop-2-en-1-one and (2*E*)-1-(5-bromothiophen-2-yl)-3-(4-chlorophenyl)prop-2-en-1-one, which were selective inhibitors of hMAO-A. The compound, (2E)-1-(5-bromothiophen-2-yl)-3-[4-(dimethylamino)phenyl] prop-2-en-1-one, showed the best inhibitory activity and higher selectivity toward hMAO-B, with Ki and SI values of 0.11±0.01 µm and 13.18, respectively. Chalcones are used as precursors in the synthesis of pyrazoles (28), isoxazoles (29), pyrrolines (30), thiadiazoles (31) and dyestuffs (32).

Foroumadi *et al.* (33) reported the synthesis of a series of 4-amino-5-cinnamoylthiazoles (N), and tested for their *in vitro* antiproliferative activities against three different human cancer cell lines including MCF-7, HepG2 and SW480. The results reveals that, most of compounds significantly prevent proliferation of tested cell lines, in particular the compound (*E*)-1-(4-amino-2-(pyrrolidin-1-yl)thiazol-5-yl)-3-(2,4-dichlorophenyl)prop-2-en-1-one (O), a pyrrolidine derivative with IC_{50}s = 10.6–18.4 µg/ml excellent activity, and induced apoptosis and cause cell cycle arrest at the G2 phase.

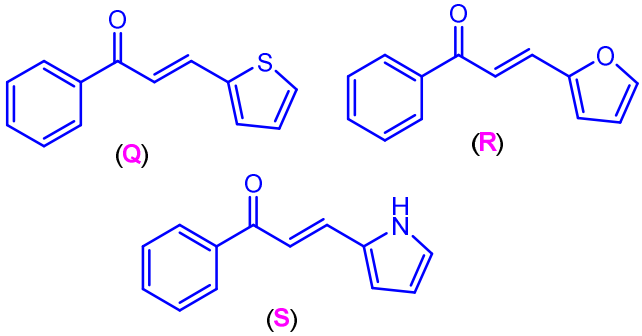


Vascular endothelial growth factor Receptor-2 (VEGFR-2) kinase inhibition is one of the well stablished strategies to promptly tackle tumor growth by suppression of angiogenesis. In this view, Khan and co-workers (34) studied the structure-based virtual screening methodology of for series of quinolyl-thienyl chalcones, which show strong potential as VEGFR-2 kinase inhibitors. The results of an *in vitro* VEGFR-2 kinase inhibitory activity of the compounds indicated the significant inhibition of human umbilical vein endothelial cells (HUVEC) and proliferation. *In silico* lead repurposing of some known thiophenyl analogs of chalcones as potential antibacterials. A series of compounds 5-(3-methylthiophen-2-yl)-3-phenyl-4,5-dihydro-1H-pyrazole-1-carbothioamides (**P**) prepared by the reaction of methyl thienyl-chalcones and thiosemicarbazide displayed potent antimicrobial and anti-inflammatory activities (35).



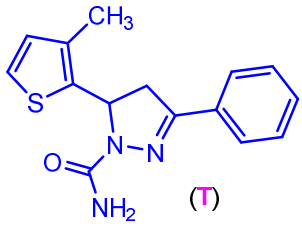
(P)

Chalcones and chalcone-based compounds were reported to act as selective inhibitors of hMAO-B. Therefore, the continuous efforts in the development of novel and effective inhibitors of human monoamine oxidases (hMAOs) promoted the discovery of new agents able to effectively and selectively bound one of the two isoforms (hMAO-A and hMAO-B). Carradori and co-workers (36) focused their studies on the correlation of the chalcones (**Q**,**R**,**S**) with different groups on their structural characteristics or common molecular properties. They were elaborately analyzed and discussed the structure-activity relationship (SAR) with multi-target approach of the chalcone derivatives.



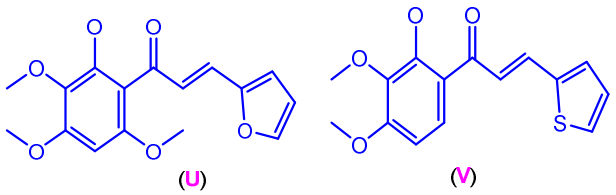
(Q) (R) (S)

In the recent times, the common diseases like food poisoning, pneumonia, diarrhea etc. have been observed to be drug resistant. In this regard, Rao and co-workers (37) studied in silico modelling and in vitro evaluation against *V. cholerae,S. typhimurium* and *K. Pneumoniae* for some known thienyl chalcones**.** These derivatives were first simulated for their anti-bacterial efficacy *in silico* and consequently confirmed *in vitro* to confirm the findings. The results were correlated and SAR was devices based on the results. A series of compounds 5-(3-methylthiophen-2-yl)-3-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamides (T) prepared by the reaction of methyl thienyl-chalcones and semicarbazide shown anti-inflammatory potencies (38).



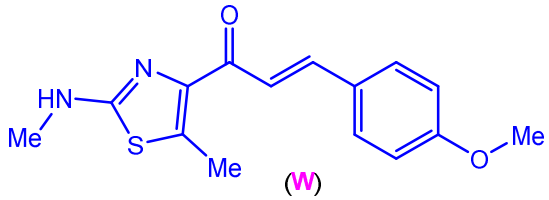
(T)

Teixeira and co-workers (39) demonstrated that, the chalcones (*E*)-3-(furan-2-yl)-1-(2-hydroxy-3,4,6- trimethoxyphenyl) prop-2-en-1-one (U) and (*E*)-1-(2-hydroxy-3,4-dimethoxyphenyl)-3-(thiophen-2-yl) prop-2-en-1-one (V) prepared by Claisen-Schmidt condensation reaction, did not present intrinsic activity against the tested bacterial strains; however, they were able to potentiate the activity of norfloxacin against the SA1199B (NorA) strain, as well as the activity of ciprofloxacin against the K2068 (MepA) strain. They act as promising compounds as adjuvants to the norfloxacin and ciprofloxacin antibiotics in the treatment of infections caused by *S. aureus*.



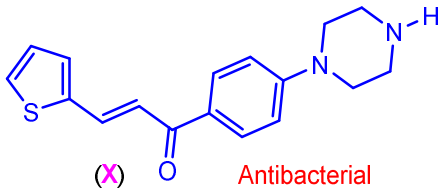
(U) (V)

The crucial need for novel antitumor agents with high selectivity toward cancer cells has promoted Farghaly and co-workers (40) design and synthesize series thiazole-based chalcones. Their results on the anti-proliferative activity of the synthesized compounds against human cancer cell lines; HepG-2, A549 and MCF-7 indicated that, amongst the series, the compound 3-(4-methoxyphenyl)-1-(5-methyl-2-(methylamino)thiazol-4-yl)prop-2-en-1-one (**W**) showed significant and broad antitumor activity that was more potent than Doxorubicin**.** Further, its effect on the normal cell cycle profile in A549 cells demonstrated cell cycle arrest at the G2/M phase together with rise in the percentage of the apoptotic pre-G1 cells. Furthermore, all compounds increased both active caspase-3 and p53 levels by 8.76–10.56 and 6.85–10.36 folds, respectively higher than the control which indicates their potential to induce apoptosis.



(W)

A series of new thienyl chalcone derivatives bearing piperazine moiety (X) have been designed and prepared based on the principle of bioisosteres and molecular hybridization. Their antibacterial activities against *S. aureus Rosenbach*, *E. coli* and *B. subtilis* were evaluated. The results showed that thienyl chalcone derivatives exhibited good selective inhibitory activities against the three tested strains, respectively. Amongst the series, the compounds (*E*)-1-[4-(4-methylcinnamatemethylpiperazinyl)-phenyl]-3-(thien-2-yl)propyl-2-ketene and (*E*)-1-{4-[4-(2-oxophenethyl)piperazinyl]phenyl}-3-(thien-2-yl)propyl-2-kete-ne were found to be very sensitive to *Bacillus subtilis*, and the minimum inhibitory concentration (MIC) is 4.0 µg/mL against *Bacillus subtilis* (41).

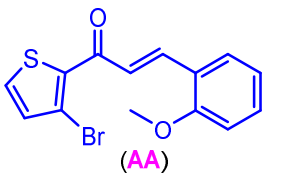


(X)

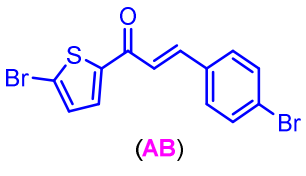
Super-activation of cholinesterases like acetylcholinesterase and butyrylcholinesterase are linked to various neurological problems most precisely Alzheimer's disease (AD), which leads to senile dementia. Therefore, cholinesterases inhibition are a promising strategy for the treatment of Alzheimer's disease. In this context, Iqbal and co-workers (42) designed series of piperidyl-thienyl and 2-pyrazoline derivatives of chalcones and tested for their cholinesterases (AChE & BChE)

inhibitory activity. The results of their study indicated that, all compounds shown selective inhibitor of AChE. However, one of the the piperidyl chalcones derivatives having IC_{50} of 0.16 ± 0.008 µM found to be the most potent inhibitors of AChE, exhibiting ≈142 and ≈ 173-fold greater inhibitory potential compared to the reference inhibitor. The interaction between halogenated thienyl chalcones and human serum albumin (HAS) was evaluated *in vitro* under simulated physiological condition by spectroscopic techniques, zeta potential and molecular docking by Netto-Ferreia and co-workers (43). The study records that the interaction is spontaneous, moderate and does not perturb significantly the HSA structure. Molecular docking results suggested hydrogen bonding and hydrophobic interactions as the main binding forces in the association between HSA and all thiophene chalcones.

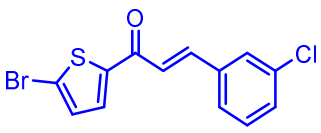
Physico-Chemical properties: Thienyl chalcones are extensively studied for their physico-chemical properties like, NLO, conducting properties, SAR all over the world more in recent years. For instance, Naik *et al*. have extensively studied the physico-chemical properties of thienyl-chalcones. They were synthesized and characterized a library of thiophene containing chalcones, and their computational analysis demonstrated that, these chalcones possess promising physico-chemical properties and established the structure property relationship. For instance, the compound (2*E*)-1-(3-bromothiophen-2-yl)-3-(2-methoxyphenyl)prop-2-en-1-one (AA) (44) exhibit non-linear optical (NLO) properties with agreeable optical limiting threshold values, and its static first and second hyper-polarizabilty values are 17 and 67 times than the reference compound urea. The compounds, (***E***)-1-(5-bromo-2-thienyl)-3-(4-bromophenyl)prop-2-en-1-one (AB), (***E***)-1-(5-bromo-2-thienyl)-3-(3-chlorophenyl)prop-2-en-1-one (AC), and (*E*)-1-(5-bromo-2-thienyl)-3-(2-methoxyphenyl)prop-2-en-1-one (AD), synthesized were characterized by spectroscopic and crystallographic analysis (45). The XRD studies shown that, all these molecules adopt ***trans*** configuration with respect to C_6=C_7 double bond. The chalcones have high thermal stability, a wide transparency in the visible region and small optical band gaps. The continuous wave (CW) laser (532 nm) Z-scan analysis data showed that, these chalcones exhibit optical limiting and all optical switching behavior. The study proved that these thiophene chalcones are potential materials for optical device applications.



(AA)



(AB)



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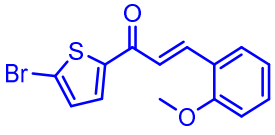
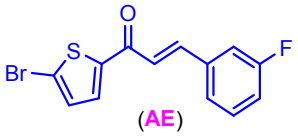
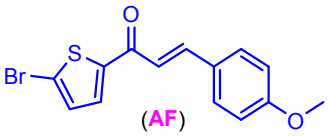


(AD)

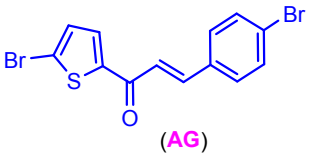
The two sets of synthesized, and characterized compounds, (*E*)-1-(5-bromothiophen-2-yl)-3-(3-fluorophenyl) prop-2-en-1-one (AE), (*E*)-1-(5-bromothiophen-2-yl)-3-(4-methoxyphenyl) prop-2-en-1-one (AF) (46), and (*E*)-3-(4-bromophenyl)-1-(5-bromothiophen-2-yl)prop-2-en-1-one (AG), (*E*)-1-(5-bromothiophen-2-yl)-3-(4-fluorophenyl)prop-2-en-1-one (AH) (47) were studied for their structural, linear optical, thermal and nonlinear optical properties. The thermal analysis (DSC, TGA, DTA and DTG) shown that thesemolecules are thermally stable up to their melting points. The linear optical properties were studied in the UV–Vis-NIR region, and the MEP and NBO of the molecules are studied by DFT method. Third-order NLO parameters were determined unambiguously from Z-scan data analysis. Computationally, the dipole moment, static and dynamic polarizability and hyper-polarizability of the chalcones were determined by TD-DFT and TD-HF method. The obtained results suggest that the studied thiophene- chalcones may be used in optical device as frequency generator, optical limiter and optical switch.



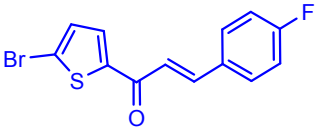
(AE)



(AF)

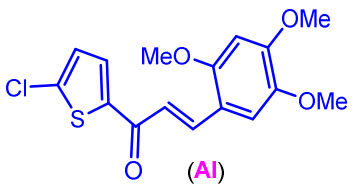


(AG)

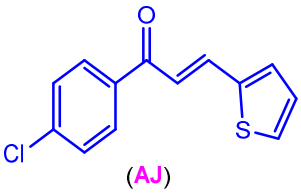


(AH)

Grown single crystals of 1-(5-chlorothiophen-2-yl)-3-(2,4,5-trimethoxyphenyl)prop-2-en-1-one, (AI) (48) showed nonlinear optical, mechanical, load dependence hardness properties, and was dimensionally stable up to 112 °C. The synthesized and crystallized compound 1-(4-chlorophenyl)-3-(thiophen-2-yl)prop-2-en-1-one (AJ) showed temperature dependence on Raman spectra, and was supported by correlation of DFT calculations with experimental results. A reasonable agreement was observed between theoretical and experimental Raman spectrum taken at 10 K since anharmonic effects of the molecular motion is reduced at low temperatures, leading to a more comprehensive assignment of the vibrational modes. While with increase in the temperature up to 393 K, showed the typical phonon anharmonicity behavior associated to changes in the Raman line intensities, line-widths and red-shift, in special in the external mode region (49).

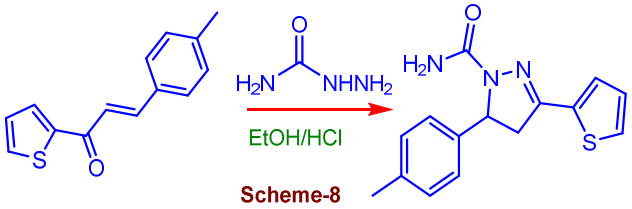


(AI)



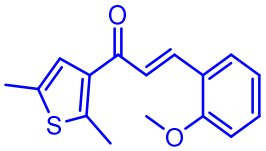
(AJ)

Barakat and co-workers (50) studied physical properties of the 3-(thiophene-2-yl)-5-p-tolyl-4,5-dihydro-1H-pyrazole-1-carboxamide, which they obtained by the (3+2) annulation reaction of (*E*)-1-(thiophen-2-yl)-3-(p-tolyl)prop-2-en-1-one with semicarbazide (Scheme-8).

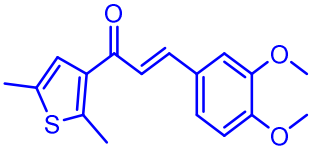


Scheme-8

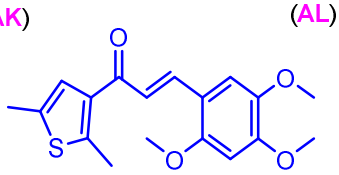
Chalcone derivatives gained significant consideration from scientific community due to their potential applications ranging from better biological activity to the efficient semiconducting properties. In this context, Irfan and co-workers (51) extensively investigated the chalcones (2*E*)-1-(2,5-dimethyl-3-thienyl)-3-(2-methoxyphenyl)prop-2-en-1-one (AK), (2*E*)-3-(3,4-dimethoxyphenyl)-1-(2,5-dimethylthiophen-3-yl)prop-2-en-1-one (AL), and (*E*)-1-(2,5-dimethyl-3-thienyl)-3-(2,4,5-trimethoxyphenyl)prop-2-en-1-one (AM) for their optoelectronic, charge transport (CT) and nonlinear optical (NLO) response. The results of their study showed that, the nature of the p-type and ambipolar charge transport behaviour of the compounds 1–3 is limelighted on the basis of their ionization potentials, electron affinities, reorganization energies, transfer integrals and intrinsic mobility. The mono- and disubstituted methoxy chalcone derivatives show the ambipolar performance owing to the better transfer integral and intrinsic mobility values for hole and electron. Whilst tri-methoxy at peripheral would lead the p-channel characteristics due to the balanced reorganization energy (hole and electron) and superior hole transfer integrals leads to higher hole intrinsic mobility. How methoxy groups change nature of the thiophene based heterocyclic chalcones from p-channel to ambipolar transport semiconducting materials.



(AK)

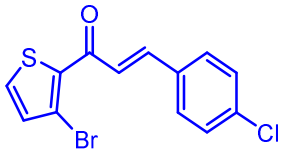


(AL)

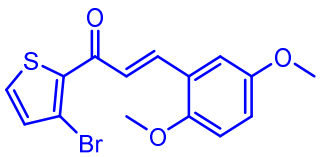


(AM)

Aayisha and co-workers (52) have demonstrated that, their synthesized compound (2*E*)-1-(3-bromo-2-thienyl)-3-(4-chlorophenyl)-prop-2-en-1-one (AN) has solvational electronic, MEP and NLO properties. Ben Geoffrey and co-workers (53) reported from their extensive study that, the chalcone (2*E*)-1-(3-bromo-2-thienyl)-3-(2,5-dimethoxyphenyl) prop-2-en-1-one (AO) has shown molecular structure stability, MEP and Global chemical reactivity. The quantitative SAR studies established the relationship between chemical descriptors and eNOS inhibition.

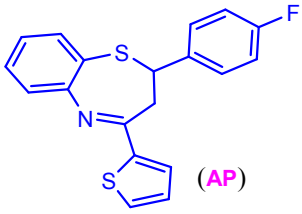


(AN)

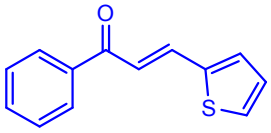


(A0)

The synthesized chalcones (2*E*)-3-[4-(benzyloxy)phenyl]-1-(thiophen-2-yl)prop-2-en-1-one and (2*E*)-3-(anthracen-9-yl)-1-(thiophen-2-yl)prop-2-en-1-one, have proven to have NLO and thermal stability properties (54). The compound 2-(4-fluorophenyl)-4-(thiophen-2-yl)-2, 3-dihydrobenzo[*b*][1, 4]thiazepine(**AP**) obtained from substituted thienyl-chalcone showed good physicochemical properties (55). The thienyl chalcone 3-(5-bromo-2-thienyl)-1-(4-nitrophenyl)-prop-2-en-1-one (**AQ**) exhibited optical, and electronic transitions properties. TD-DFT calculations of the compound reveal that the electron donor and acceptor group substitution on the 1-phenyl-3-(thiophen-2-yl)prop-2-en-1-one affects its absorption and nonlinear activity (56).



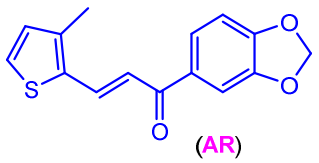
(AP)



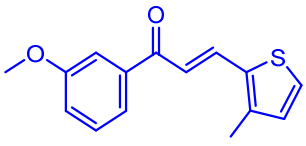
(AQ)

Echevarria *et al*. (57) showed that two sets of dialkylamino-substituted halogenated thienyl chalcones have the complementary intramolecular charge transfer (ICT) transitions. They demonstrated that the first (and stronger) ICT takes place from the 4-(dialkylamino)phenyl moiety to the enone, the second ICT involves the thienyl substituent as the donor. The former is evidenced by a robust solvatochromic shift in both absorption and emission spectra, implying a large increase in the dipole moment upon excitation to the lowest excited state. The latter, a short-range ICT process, is confirmed upon photoexcitation of the higher energy bands, and its enhancement by the larger polarizability of the iodine substituent.

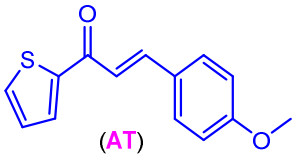
Kumara and co-workers extensively studied the physico-chemical properties of three pyrazoles 3-(benzo[d][1,3]dioxol-5-yl)-5-(3-methylthiophen-2-yl)-4,5-dihydro-1H-pyrazole-1-carboxamide (58), 3-(3-methoxyphenyl)-5-(3-methylthiophen-2-yl)-4,5-dihydro-1H-pyrazole-1-carboxamide (59), 5-(4-methoxyphenyl)-3-(thiophen-2-yl)-4,5-dihydro-1*H*-pyrazole-1-carbothioamide (60), 1-(3-chlorophenyl)-3-(5-chlorothiophen-2-yl)-5-phenyl-4,5-dihydro-1*H*-pyrazole(61), and 5-(3,4-Dimethoxyphenyl)-3-(thiophen-2-yl)-4,5-dihydro-1*H*-pyrazole-1-carboxamide (62). They obtained all these pyrazole derivatives were synthesized from their prepared thienyl-chalcones (AR), (AS),(AT),(AU), and (AV), respectively.



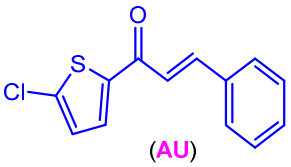
(AR)



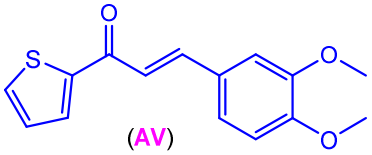
(AS)



(AT)



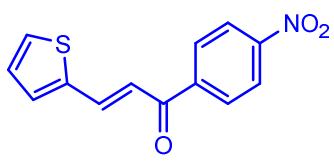
(AU)



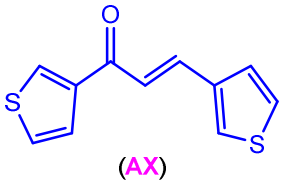
(AV)

Physical characterization of 1-(4-nitrophenyl)-3-(2-thienyl)prop-2-en-1-one (AW), a heterocyclic thienyl chalcone for structural, optical, thermal and vibrational properties was reported by Pizani and co-workers (63). The report revealed that the electrical charge mobility in the molecule occurs

from thiophene to benzene ring. The potential energy distribution (PED) analysis leads to a more comprehensive interpretation of the vibrational spectra and origin of instability the investigated material. Soto-Delgado and co-workers (64) reported the synthesis of chalcone, 1,3-di(thiophene-3-yl)prop-2-en-1-one (AX) by the base catalyzed reaction of thiophene-2-aldehyde and 2-acetyl thiophene. The studies on the physico-chemical properties of the compounds showed that, the compound is an essentially planar molecular with its terminal thiophene rings. Electrochemical records reveal an anodic profile with an unsymmetrical irreversible peak at 1.77 V and a shoulder at 1.62 V **vs** SCE, a behavior interpretable as due to the oxidation of reactive sites present in the molecule.



(AW)



(AX)

Conclusion

Thiophene conjugated chalcones havewide range of importance in synthetic and medicinal chemistry, also exhibits broad spectrum of physico-chemical properties. In this review paper, we have attempted to summarize the developments in the synthetic protocols of thienyl chalcones and their explorations as bioactive molecules in the recent years together. The background survey behind the synthesis of thienyl chalcones, and their utility as scaffolds in the synthesis of bioactive heterocycles, and biological activity properties were critically discussed in depth.The discussion we made on the physico-chemical properties of thienyl chalcone derivatives, and would be useful for researchers working in this area.To sum up, the article presents the overall developments in the synthetic routes, utility as synthons for bioactive molecules, medicinalapplications. The chalcones can be used in NLO devices for optical limiting and optical switching applications. The molecules can be used in NLO devices for frequency generation, optical limiting and optical switching applications.

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