

# Chalconoid Derived Heterocycles as Potent Bioactive Molecules: A Review

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## Abstract

Although chalcones symbolize an important pharmacophore for variety of biological actions, however their analogues are also reported to be equally important for plethora of biological actions. In the present review, a comprehensive study of chalcones derived molecules (like pyrazoles, isoxazoles, pyridine, pyrimidine) their pharmacological actions, mechanism of action, structure activity relationship studies have been described.

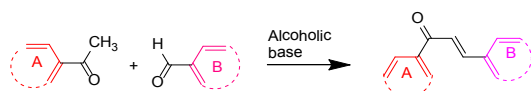
**Keywords:** Chalcones; Pyrazoles; Pyridine; Pyrimidine; Anticancer; Antimicrobial

## Introduction

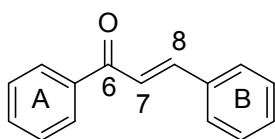
Chalcones are considered as precursor of flavones in the biosynthesis of flavonoids. These are aromatic ketones bearing 1,3-diaryl-2-propen-1-one framework and appears to be an open chain flavonoids in which two aromatic rings are joined by three carbons with  $\alpha$ - $\beta$  unsaturated system. Chalcones are widely spread in nature (fruits, vegetables, spices, tea and soy based food stuff) and their 2'-hydroxy derivatives play an important role in the flavonoid synthesis and biosynthesis as both precursors and products [1]. They contain ketoethylinic group (-CO-CH=CH) and exist in *cis* and *trans* form due to the presence of double bond in which *trans* form is thermodynamically more stable [2]. The conjugated double bond produces the delocalization of  $\pi$  electrons which reduces its electrophilic character and makes it an intermediate for the synthesis of various biologically important heterocycles such as pyrazoline, oxazoline, thiazine, oxazine, pyrimidine etc. Thus synthesis of chalcones has generated vast interest to organic as well as medicinal chemists [3]. Formation of these nuclei involves cyclization of  $\alpha$ - $\beta$  unsaturated system of chalcones. Chalcones and its analogues have numerous pharmacological activities such as antimicrobial [4,5], anti-inflammatory analgesic, antiviral, antioxidant, anticancer, antimalarial, antiprotozoal, anticonvulsant [6-15] (Figure 1).

## Chemistry

In general chalcones are synthesized by Claisen-Schmidt condensation of aldehyde and ketone by base catalyzed or acid catalyzed followed by dehydration to yield chalcones [16].



Chalcones basically consist of three plane moieties, carbon-carbon double bond and two benzene rings. The dihedral angle from the plane of C7/C8/C9 to the phenyl ring A is 13.8(1)° and ring B is 2.6 (1)°. This shows that the C7-C8-C9 fragment lies in the phenyl ring plane [17].



In Figure 2, Xanthohumol (XN), prenylated chalcone from hops (*Humulus lupulus L.*) exhibits a wealth of pharmacological actions

which includes anti-proliferative, anti-inflammatory, antioxidant, proapoptotic, anti-bacterial and anti-adhesive effects [18].

## Analogues of chalcones

### Pyrazoline analogues with various pharmacological activities:

Pyrazole nucleus present in compounds exhibit wide range of biological activity. Introduction of a pyrazole ring in the chalcones between the two aryl rings increase the cytotoxic activity against a series of human cancer cell lines. Dhar et al. [19] synthesized a series of 1-acetyl-3,5-diaryl-4,5-dihydro-(H)- pyrazoles and assayed for *in vitro* cytotoxicity against PC-3, OVCAR, IMR-32, HEP-2 human cancer cell lines, compound 1 showed broad spectrum cytotoxic activity against all the four cell lines. The activity shown by the compounds conclude that (i) Substitution on phenyl ring showed marked effect on cytotoxic activity, (ii) Presence of electron donating groups on phenyl ring led to enhanced activity whereas electron withdrawing group except NO<sub>2</sub> reduces the cytotoxic activity, (iii) Replacement of phenyl ring with heterocyclic ring also reduces the cytotoxic potential and naphthyl ring on both sides are more beneficial for cytotoxic potential<sup>15</sup>. Pyrazolines of methoxy substituted chalconoids of 2-acetyl naphthene were synthesized and its cytotoxic potential was analyzed against HeLa, HCT 15, A549 cancer cell lines. 3,4,5 trimethoxy substituted have shown good activity against these cell lines having IC<sub>50</sub> value in the range of 0.037-0.019  $\mu$ M (2) [20]. Furopyrazole compound 3 induces terminal differentiation of HL-60 cells toward granulocyte lineage and promoted HL-60 cell differentiation by regulation of Bcl-2 and c-Myc proteins [21]. Dhar

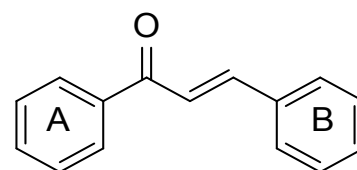


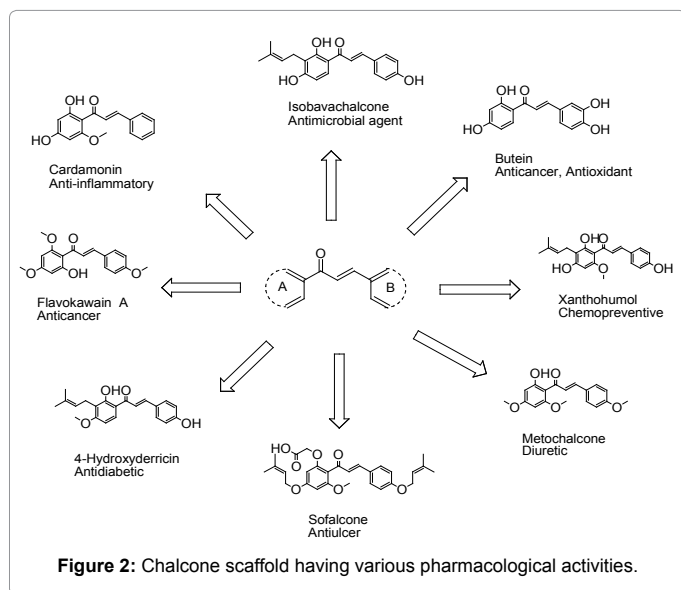
Figure 1: General structure of chalcone.

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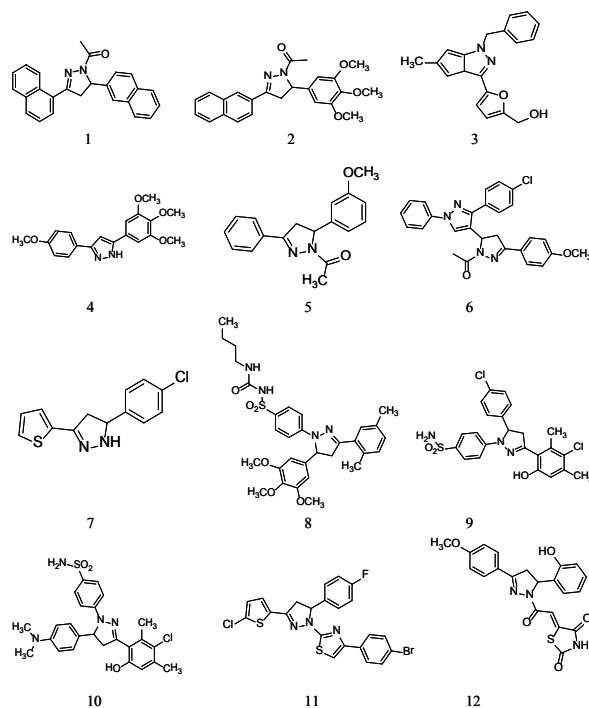
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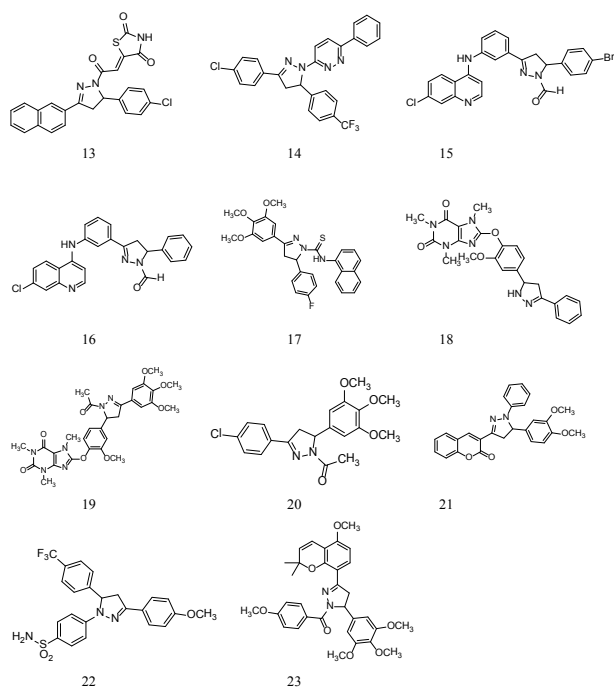
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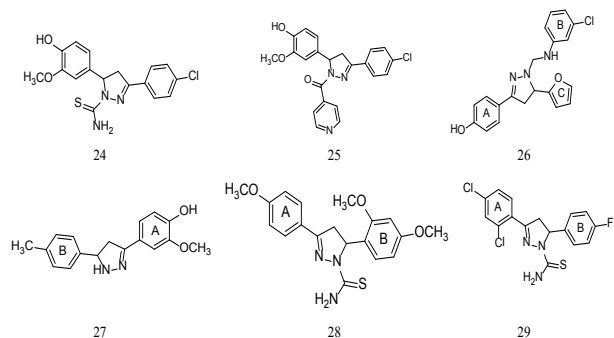
et al. synthesized chalcones and their corresponding analogues and found that introduction of pyrazole moiety increases the rigidity of the molecule and show better cytotoxic activity than their corresponding chalcones 4 [22], compound 5 has shown the ability to inhibit P-glycoprotein-mediated multidrug resistance by direct binding to a purified protein domain containing an ATP-binding site and a modulator interacting region [23] whereas compound 6 was assayed for anticancer activity mainly against leukemia (K-562 and SR), renal cancer (UO-31) and non-small cell lung cancer (HOP-92) cell lines, with the most important  $GI_{50}$  values ranging from 0.04 to 11.4  $\mu M$  [24]. Jainey et al. synthesized thiophene based pyrazolines and evaluated for antitumor, analgesic, anti-inflammatory activity compound 7 showed highest toxicity of 80% at 200  $\mu g/mL$  and it also showed good analgesic, anti-inflammatory activity so compound bearing electron withdrawing groups on phenyl ring are more active as compared to electron donating [25]. Pyrazoline substituted benzenesulfonylurea compound 8 displayed remarkable antiproliferative activity against leukemia, colon, melanoma, ovarian, renal, prostate and breast cancer cell lines with  $GI_{50}$  less than 2  $\mu M$  [26]. 2-pyrazoline bearing benzene sulfonamide moiety (9) have shown good anti-inflammatory activity as compared to the reference drug celecoxib and compound 10 exhibited promising antiproliferative activity with  $GI_{50}$  values less than 2  $\mu M$  against leukemia cancer, in non-small cell lung cancer, in colon cancer [27] and thiazolyl-pyrazolines compound 11 has shown promising activity against A549 cancer cells with an  $IC_{50}$  value of 62.5  $\mu g/mL$  [28]. 5-pyrazoline substituted 4-thiazolidinones were synthesized and evaluated against leukemia cell lines, compound 12 showed  $GI_{50}$  value in the range of 2.12-4.58  $\mu M$  and compound 13 in 1.64-3.20  $\mu M$  these also act as good antitrypanosomal and antiviral agents [29]. Pyrazoline derivative 14 was screened for antiproliferative activity against lung (A549), liver (HepG-2), intestinal (CaCo-2) and Breast (MCF-7) cancer cell lines and it has shown promising activity, its activity was due to apoptosis which proceeds via caspase-3 activation [30]. 2-pyrazoline obtained from [(7-chloroquinoline-4-yl)amino] chalcones were synthesized and evaluated for antitumor and antimalarial activity compound 15 showed remarkable antitumor activity with  $GI_{50}$  value ranging from 0.13 to 0.99  $\mu M$  whereas compound 16 has shown best

antimalarial response with an inhibition percentage of 50.8% for *Plasmodium falciparum* and  $IC_{50}$  of 14.1  $\mu g/mL$  [31]. Novel series of pyrazoline analogues were synthesized and evaluated for anticancer activity against lung cancer cell line (A549) and compound 17 have shown promising anticancer activity with percent cytotoxicity in the range 36.21-71.24  $\mu g/mL$  and  $GI_{50}$  in the range of 11.41-43.15  $\mu g/mL$  [32]. Caffeine based pyrazoline were synthesized and evaluated for antimalarial activity against *Plasmodium falciparum* the compound 18 showed outstanding growth inhibition percentage 85.2  $\pm$  5.4 percent while compound 19 has shown remarkable activity against *Leshmania panamensis* [33]. Series of pyrazolines were synthesized and evaluated for *in vitro* anti-tubercular activity against *Mycobacterium tuberculosis* H37Rv strain. Compound 20 exhibited significant anti-tubercular activity at MIC values 12.5  $\mu M$  concentration [34].  $\alpha$ -pyranopyrazoline analogues were synthesized and evaluated for antimalarial activity, compound 21 turned to be the most potent analog of the series having  $IC_{50}$  3.1  $\mu g/mL$  against chloroquine-sensitive strain 3D7 and  $IC_{50}$  of 1.1  $\mu g/mL$  against chloroquine-resistant strain RKL9. To support the data further docking was done into the active site of falciparum enzyme which showed good interaction with the active site residue [35]. 2-pyrazoline and pyrazoles synthesized as celecoxib analogues and evaluated for *in vitro* COX-1/COX-2 inhibitory activity compound 22 was most selective COX-2 inhibitor [36]. Pyrazoline derivatives originated from pyrano-chalcones have been synthesized and evaluated for their inhibitory potency on the production of inflammatory mediator nitric oxide (NO) in LPS-stimulated RAW 264.7 cells. Compound 23 has shown iNOS activity superior to positive control indomethacin. It also suppress the progress of carrageenan-induced hind paw edema at a dosage of 50 mg/kg/day and docking studies revealed that it has a good binding into the active site of murine iNOS [37] (Figure 3).





Hamada et al. has synthesized acetoxysulfonamide pyrazole derivatives starting from substituted vanillin chalcones and were tested for antimicrobial activity against *Staphylococcus aureus*, *Candida albicans*, and for antioxidant activity, compound 24, 25 which are bearing lipophilic properties and having electron withdrawing groups exhibit great antimicrobial and antioxidant activity [38]. Furan containing pyrazoline compounds (26) having para hydroxyl group in ring A have shown better antioxidant activity than ascorbic acid and reutin [39]. Whereas 2-pyrazoline compounds (27) bearing hydroxyl and methoxy groups in ring A have shown good free radical scavenging activity [40]. Docking study of series of pyrazole derivatives were done using Epidermal Growth Factor Receptor kinase domain (PDB: 1M17) as a target and based on the interaction with the receptor the novel compounds were synthesized and screened for antioxidant and anticancer activity against breast cancer (MCF-7) and lung cancer (A549) cell lines and compounds (28) having electron releasing group on ring B, such as methoxy has shown good antioxidant activity with  $IC_{50}$  21  $\mu\text{g}/\text{mL}$  whereas compound 29 has shown good interaction with the target as it forms hydrogen bonding with the receptor due to the presence of fluorine at para position on ring B and it also showed  $IC_{50}$  3.5  $\mu\text{M}$  against MCF-7 and 17.6  $\mu\text{M}$  against A549 [41] (Figure 4).



Bano et al. synthesized series of substituted pyrazoline derivatives and were docked on the fluconazole-bound CYP51 from *Mycobacterium*

*tuberculosis* (MTCYP51) (PDB No: 1EA1) and then these were subjected to antimicrobial activity against *Staphylococcus aureus*, *Escherichia coli*, *Aspergillus flavus*, *Avicularia versicolor*, *Aspergillus fumigatus* and *Candida albicans* compound 30 having a hydroxyl group at meta position on ring B has shown good antifungal activity against all the strains having MIC within the range of 12.5-3.125  $\mu\text{g}/\text{mL}$  and moderate antibacterial activity. These results were supported by docking studies as the pharmacophore having hydroxyl group has maximum free binding energy i.e., -8.37 kcal/mol [42]. 2-pyrazoline derivatives bearing benzenesulfonamide moieties were synthesized in order to find the novel antimicrobial agents and tested against *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Candida albicans* compound 31 has shown significant antimicrobial activity against all the strains this shows that molecules having benzene-sulphonamide moiety can act as lead in the discovery of novel antimicrobial agents [43]. A series of chalconolides and its pyrazoline derivatives were synthesized by condensing 1-acetylnaphthalenes with 1-naphthaldehyde. Then these heterocycles were characterized and then tested for antimicrobial activity against variety of test organisms such as *Escherichia coli*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Shigella dysentery* and *Salmonella typhi*. The results showed that the compound 32 having chlorine, hydroxyl and dimethylamino groups as substituents on the naphthalene rings are very effective antimicrobial agents [44]. Pyrrazole of 2-acetyl benzofuran were synthesized and subjected to antimicrobial activity against gram-positive and gram-negative bacteria compound 33 have shown remarkable activity against gram negative bacteria with 25 mm zone of inhibition and good activity against gram-positive bacteria with 20 mm zone of inhibition. This

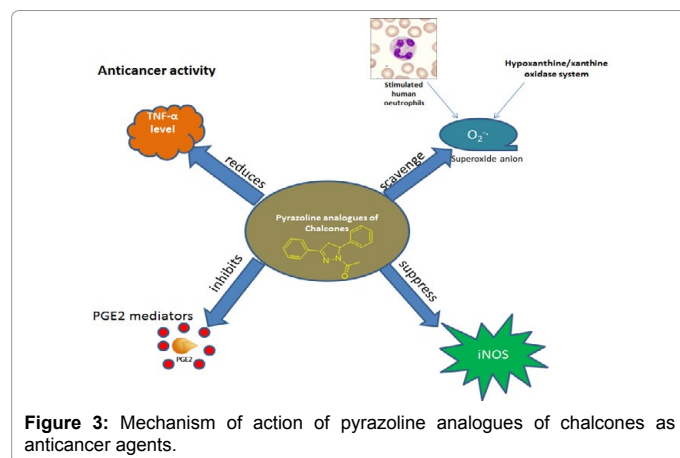


Figure 3: Mechanism of action of pyrazoline analogues of chalcones as anticancer agents.

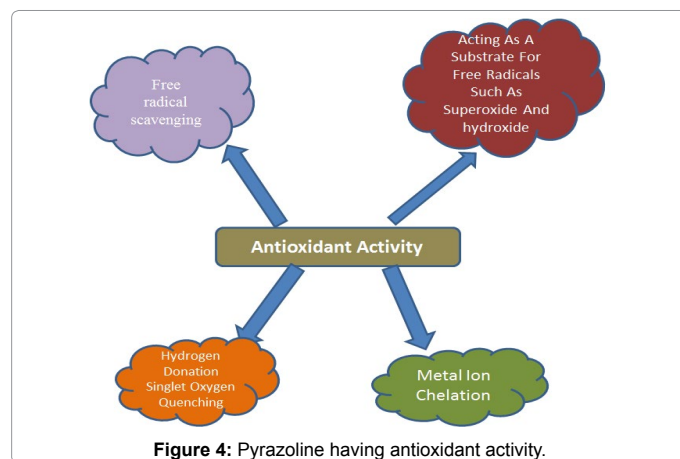
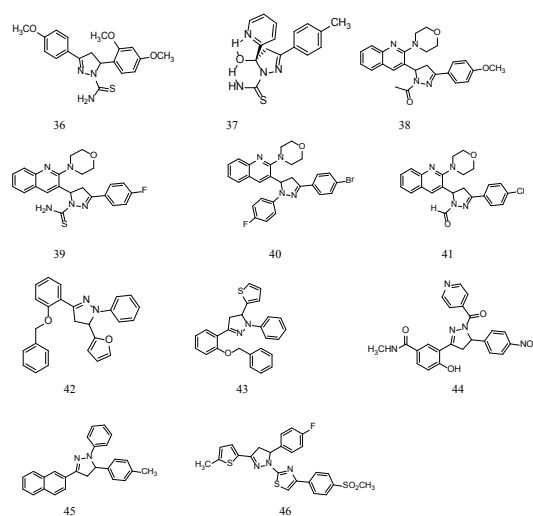
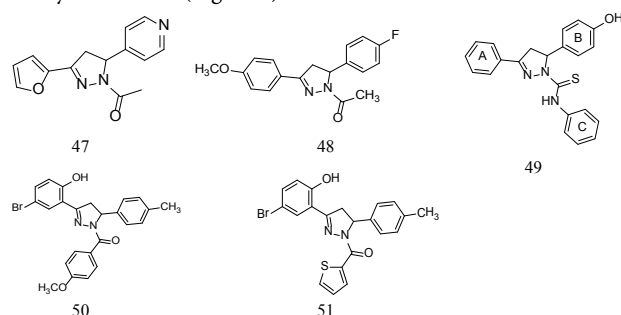


Figure 4: Pyrazoline having antioxidant activity.

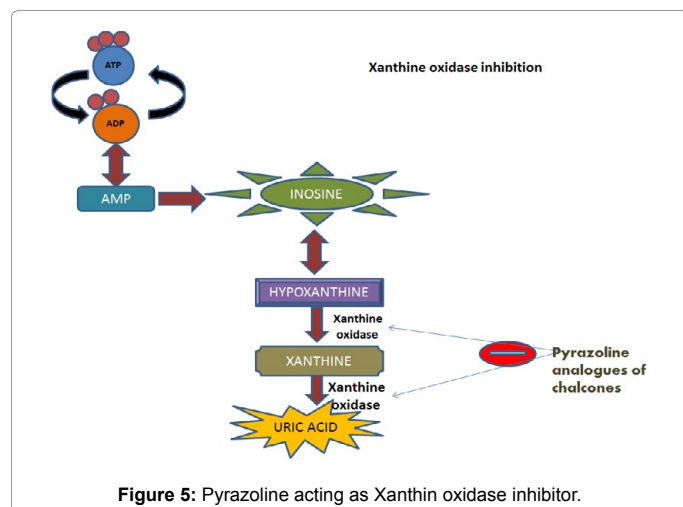
concludes that benzofuran, pyrazoline, and thiazole moieties are vital for the antimicrobial activity [45]. Indole phenyl pyrazoles were synthesized by grind stone method in this aldehyde and ketone were grinded in mortar and pestle in the presence of catalyst which leads to phase change and produces product and these products were tested for antimicrobial activity. Compound 34 has shown promising activity against *Staphylococcus aureus*, *Escherichia coli*, *Aspergillus niger* and *Candida albicans* with 5-13 mm zone of inhibition [46]. 2-pyrazoline derivatives were designed, synthesized and their antimicrobial activity was performed and compound 35 having chloro and nitro group have shown good antimicrobial activity within the range of 20-70  $\mu\text{g}/\text{mL}$  [47] where as Pyrazoline derivatives having N-acyl arms and homologous alkoxy side chain were screened for *in-vitro* anti-inflammatory activity, compound 36 showed most promising activity having  $\text{IC}_{50}$   $173.06 \pm 2.312$  mM which is better than Indomethacin ( $\text{IC}_{50}$   $273.12 \pm 2.33$  mM). This revealed that compounds with odd number of carbons in alkoxy side chain are more active than even one [48]. A series of 1-thiocarbamoyl-3-phenyl-5-hydroxy-5-(2-pyridyl)-4-pyrazolines were synthesized and evaluated for antimicrobial activity compound 37 exhibit potent antibacterial and antifungal activity against *Salmonella typhi*, *Pseudomonas aeruginosa*, *Aspergillus niger* and *Aspergillus fumigatus* having zone of inhibition in the range of 2.5-2 mm [49]. Novel morpholinoquinoline based pyrazoline was designed and synthesized under microwave irradiation and screened for *in vitro* antibacterial, antifungal, antimalarial and antitubercular activity. Compound 38 having methoxy group act as antimalarial agent as it act against *Plasmodium falciparum* and *Streptococcus pneumoniae* at 15  $\mu\text{M}$  (39) have enhanced antifungal activity against *Candida albicans* with  $\text{IC}_{50}$  at 229  $\mu\text{M}$  and compound 40 showed 95% inhibition against *Mycobacterium tuberculosis* (H37Rv) at 47  $\mu\text{M}$  whereas compound 41 is active against *Vibrio cholera* having MIC at 132  $\mu\text{M}$  [50]. Pyrazolines having N-substituted 5-(furan-2-yl)-phenyl and 5-(thiophene-2-yl)-phenyl moiety were synthesized and evaluated for antibacterial activity against gram-positive and gram-negative bacteria, compound 42 has shown MIC in the range of 10-30  $\mu\text{g}$  against all the bacteria [51] whereas compound 43 has shown promising antibacterial activity with MIC in the range of 10-40  $\mu\text{g}$  [52]. This concludes that pyrazoline having furan moiety is more active than thiophene moiety containing pyrazolines. Series of Isoniazide-pyrazolines and phenyl pyrazoline were synthesized and tested for antibacterial, antifungal and antitubercular activity compound 44 having isoniazide moiety exhibits significant antibacterial activity against *Pseudomonas aeruginosa* and *Staphylococcus aureus* with MIC - 3.12  $\mu\text{g}/\text{mL}$  and shows good antifungal activity against *Candida albicans* with same MIC and it also found to have promising antitubercular activity against *Mycobacterium tuberculosis* [53]. 2-naphthylpyrazoline and Thiazolyl-pyrazolines were evaluated for antibacterial and anticandidal activity compound 45 was active against gram negative bacteria [54] and compound 46 was identified to have good inhibitory effect against *Candida zeylanoides* with MIC value of 250  $\mu\text{g}/\text{mL}$  when compared with ketoconazole [55].



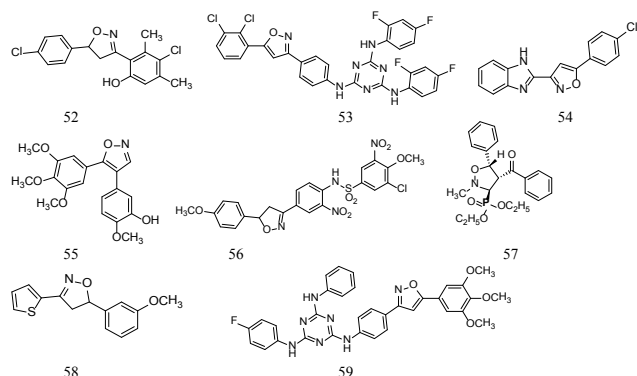
Nepali et al. designed and synthesized series of new pyrazoles and evaluated for *in vitro* xanthine oxidase inhibitory activity compound 47 was found to be most active with  $\text{IC}_{50}$  5.3  $\mu\text{M}$ . The result concludes that the nature and substituents present on the two phenyl rings greatly affect the xanthine oxidase inhibitory activity presence of heteroaryls such as furan, pyridyl and N-acetyl group increases the xanthine oxidase inhibitory activity [55]. Siddiqui et al. synthesized substituted 3,5-diphenyl 2-pyrazoline 1-carboxamide derivatives and tested for anticonvulsant activity compound 48 was protective against maximal electroshock seizure at 100-300 mg/kg dose levels this shows that these can act as a good lead for anticonvulsant agents [56]. Pyrazoline derivative were designed and tested for MAO inhibitory activity and found that compound 49 having ring C increases the potency against MAO inhibitory activity [57] whereas compound 50 act as selective MAO-B inhibitor and compound 51 having bromine atom appeared to be the most selective MAO-A inhibitor [58]. The results revealed that ring C is essential for the activity, six-membered ring appears to be selective for MAO-B inhibitory action and five-membered ring showed selectivity to MAO-A (Figure 5).



**Isoxazole analogues:** Heterocyclic compounds are known to have various pharmacological activities among them five membered heterocycles mainly isoxazoles have gained the interest of organic and medicinal chemist. Various pharmacological activities of isoxazoles are antiviral [59], anti-inflammatory [60], antimicrobial [61], antihyperglycemic [62] and anticancer [63]. Bano et al. synthesized series of substituted isoxazoline derivatives these were docked on the fluconazole-bound CYP51 from *Mycobacterium tuberculosis* (MTCYP51) (PDB No:1EA1) and then these were subjected to antimicrobial activity against *Staphylococcus aureus*, *Escherichia coli*, *Aspergillus flavus*, *Aspergillus fumigatus* and *Candida albicans*, compound 52 has shown moderate antibacterial activity with 16-22 mm zone of inhibition and good antifungal activity with MIC

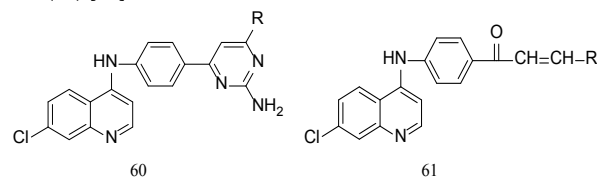


ranging from 6.25-12.5  $\mu\text{M}$  [42]. Solankee et al. reported the synthesis of series of substituted isoxazolines and these were screened for antimicrobial activity against gram-positive, gram-negative bacteria and fungal strains, compound 53 has shown good activity against all the strains which states that compound having methoxy, chloro and nitro groups are more potent as compared to others [64]. Benzimidazole isoxazole were synthesized and screened for antimicrobial and anticancer activity and compound 54 has shown 18-25 mm zone of inhibition against antimicrobial strains and isoxazole moiety bearing molecule showed better anticancer activity [65]. Combrestatin analogues having five membered heterocycles (isoxazole, isoxazoline, oxadiazole) were synthesized and evaluated for cytotoxicity and their ability to inhibit the tubulin assembly. The compound 55 showed good antitubulin activity at 1.2  $\mu\text{M}$  [66]. Isoxazoline was synthesized and tested for antimicrobial activity against *Staphylococcus aureus*, *Bacillus megaterium*, *Aspergillus niger* and *Asterophora parasitica* and compound 56 has shown good activity against all strains with 18-22 mm zone of inhibition [67]. New series of isoxazolidin-3yl-3-phosphonic acids were synthesized and screened for their cytotoxic activity to HeLa and K562 cells compound 57 with  $\text{IC}_{50}$  in 0.1-0.3 mM range were found to be most active [68]. Isoxazole derivative of thiophene have shown moderate antimicrobial activity 58 [69]. New series of isoxazolines has been synthesized and has shown moderate antimicrobial activity 59 [70].

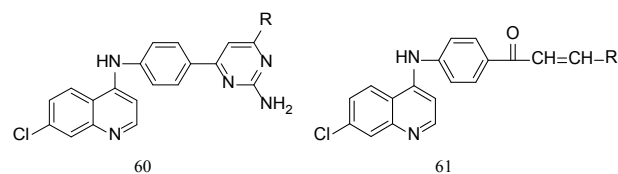


**Pyrimidine analogues:** N-fused analogues of chalcones particularly pyrimidines have received augmented interest due to their plethora of biological actions such as antifungal [71], antibacterial [72], antitumor [73], analgesics [74], anti-inflammatory [75], anti-trichomonal [76], KDR kinase inhibition [77], CRF-1 receptor antagonists [78,79] estrogen receptor ligands, and COX-2 selective inhibition [80].

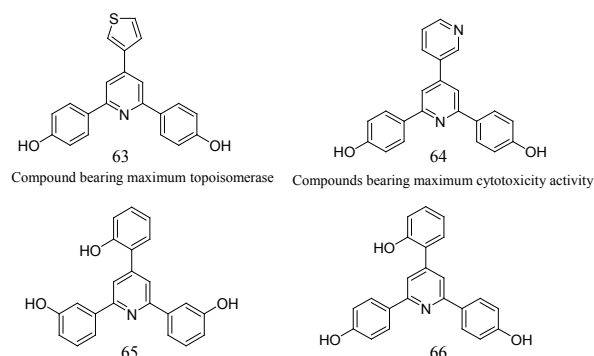
Sharma et al. synthesized a series of quinoliny chalcones and quinoliny pyrimidines and screened them against M. tuberculosis and NF-54 strains of *P. falciparum* among all compounds with 4-amino linkage showed promising activity against NF-54 strains of *P. falciparum*. Six compounds have shown antitubercular activity with MIC in the range of 3.12-12.5 mg/mL and are nontoxic against VERO and MBMDM cell lines. Four compounds showed antimalarial activity with MIC ranging from 1 to 2 mg/mL. The study reported that quinoliny chalcones (61) are antitubercular agents while pyrimidine analogues are active against malaria (60) [81].



In another study a series of pyrimidinyl containing chalcones were synthesized and evaluated for cytotoxicity against several human cancer cell lines. The compounds were screened against KB cells (drug sensitive human oral carcinoma cells) CNE2 cells (drug sensitive human nasopharyngeal carcinoma cells) MGC-803 cells (drug sensitive human gastric carcinoma cells) MCF-7 cells (drug sensitive human breast adenocarcinoma cells) K562 cells (drug sensitive human leukemia cells). The result concluded that compounds containing electron releasing substituents such as methoxyl displayed higher cytotoxicities compared to those with electron withdrawing substituents or no substituents. The compound containing methoxyl group (62) showed more potent cytotoxicity in comparison to curcumin [82].



Chalcones bearing pyridine motifs are also a good source of anticancer agents, compounds possessing dihydroxylated 2,6-diphenyl-4-aryl pyridine derivatives were synthesized via chalcone intermediates and screened for topoisomerase I and II inhibitory activity and cytotoxicity against several cell lines, the position of hydroxyl groups in phenyl rings and types of aryl moieties attached to the central pyridine greatly influenced the pharmacological action [83]. Compounds (63, 64) bearing hydroxyl group at meta or para position of 2- and 6-phenyl rings in combination with 2-furyl, 2-thienyl, or 3-thienyl moiety at 4-position of central pyridine showed significant topo II inhibitory activity and cytotoxicity [84].



In addition, trihydroxylated derivatives are more potent topoisomerase II inhibitors and cytotoxic agents in comparison to dihydroxylated derivatives and similar author also reported topoisomerase II inhibition and cytotoxic potential of monohydroxylated pyridine derivatives (64, 65). Amongst all trihydroxy derivatives of pyridine proved to be the most potent agents against topoisomerase II and cytotoxicity [85,86].

## Conclusion

Chalcones not only itself acting as a molecule with diverse pharmacological actions; instead their analogues are too carrying importance for array of medicinal properties. Ring closure of chalcones results in to heterocyclic scaffolds with varied pharmacological properties. The Pyrazoline analogues are reported to possess cytotoxic, antimicrobial, antioxidant and xanthine-oxidase inhibitory action, whereas isoxazoles derived from chalcones are also acting as a key molecule for bundles of biological actions. Moreover six membered heterocycles especially pyridine and pyrimidine analogues are also proved to be the mines of biological actions. Pyridine analogues with certain substitutions such as hydroxyl at different positions proved to be effective against topoisomerase and cytotoxic action.

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