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.

Introduction

Chalcones are considered as precursor of flavones in the biosynthesis of flavonoids. These are aromatic ketones bearing 1,3-diaryl-2-propen1-one framework and appears to be an open chain flavonoids in which two aromatic rings are joined by three carbons with α-β 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 π 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 α-β unsaturated system of chalcones. Chalcones and its analogues have numerous pharmacological activities such as antimicrobial [4,5], antiinflammatory analgesic, antiviral, antioxidant, anticancer, antimalarial, antiprotozoal, anticonvulsant 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 NO2 reduces the cytotoxic activity, (iii) Replacement of phenyl ring with heterocyclic ring also reduces the cytotoxic potential and napthyl ring on both sides are more beneficial for cytotoxic potential 15. Pyrazolines of methoxy substituted chalconoids of 2-acetyl napthlene 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 IC50 value in the range of 0.037-0.019 μM (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].antimalarial response with an inhibition percentage of 50.8% for Plasmodium falciparum and IC50 of 14.1 μg/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 µg/mL and GI50 in the range of 11.41-43.15 µg/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 ± 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 µM concentration [34]. α-pyranopyrazoline analogues were synthesized and evaluated for antimalarial activity, compound 21 turned to be the most potent analog of the series having IC50 3.1 µg/mL against chloroquine-sensitive strain 3D7 and IC50 of 1.1 µg/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 reveled that it has a good