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Review article

Artificial comprehensive review on design, synthesis, and pharmacological evaluation of chromone-based derivatives as antimicrobial and anti-inflammatory agents

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ABSTRACT

Chromone (4H-chromen-4-one) represents a privileged heterocyclic scaffold widely distributed in nature and synthetic compounds, exhibiting diverse pharmacological activities including antimicrobial, anti-inflammatory, anticancer, antiviral, and antioxidant properties. The structural versatility of chromone nucleus allows strategic modifications at various positions to develop novel therapeutic agents. This comprehensive review consolidates recent advances in the design, synthesis, and biological evaluation of chromone-based derivatives, with particular emphasis on sulfonamide-chromone conjugates, 2-aminochromone bis-triazole hybrids, and 3-substituted chromones. The synthetic methodologies discussed include Vilsmeier-Haack formylation, Baker-Venkataraman rearrangement, Claisen rearrangement, and copper(I)-catalyzed azide-alkyne cycloaddition (click chemistry). Structure-activity relationship studies reveal that substitution patterns significantly influence antimicrobial and anti-inflammatory potency. This review aims to guide medicinal chemists in rational design and development of chromone-based therapeutics.

Keywords: Chromone, sulfonamide, 1,2,3-triazole, antibacterial activity, anti-inflammatory, click chemistry, Vilsmeier-Haack reaction.

INTRODUCTION

Infectious diseases and inflammatory disorders continue to represent major global health challenges despite significant therapeutic advances. The World Health Organisation reports that infectious diseases account for approximately 17% of global mortality, particularly affecting low-income countries and vulnerable populations. Concurrently, chronic inflammatory conditions such as rheumatoid arthritis, inflammatory bowel disease, and osteoarthritis affect millions worldwide, necessitating safe and effective therapeutic interventions [1].

The emergence of multidrug-resistant pathogens has rendered many conventional antibiotics ineffective, creating an urgent need for novel antimicrobial agents with unique mechanisms of action. Bacteria have developed resistance through various mechanisms, including enzyme modification, target site alteration, efflux pump activation, and biofilm formation. Similarly, long-term use of non-steroidal anti-inflammatory drugs (NSAIDs) is associated with significant adverse effects, including gastrointestinal ulceration, cardiovascular complications, and renal toxicity [2].

Chromone (4H-chromen-4-one) represents a naturally occurring oxygen-containing heterocyclic system that forms the core structure of numerous flavonoids, including flavones, isoflavones, and flavonols. The term "chromone" derives from the Greek word "chroma", meaning color, reflecting the diverse colouration of chromone-containing natural products. Chromone derivatives exhibit remarkable structural diversity and broad-spectrum pharmacological activities, including antimicrobial, anticancer, anti-HIV, anti-inflammatory, antioxidant, and antidiabetic properties. The chromone scaffold's therapeutic significance is exemplified by clinically used drugs such as cromolyn sodium (mast cell stabiliser), nedocromil (anti-asthmatic), flavoxate (urinary antispasmodic), and khellin (vasodilator used in vitiligo treatment). The structural versatility of chromone allows strategic modifications at positions 2, 3, 5, 6, 7, and 8, enabling the design of target-specific molecules with optimised pharmacokinetic properties [3].

Sulfonamides represent another historically significant class of antimicrobial agents that inhibit bacterial folate synthesis by competing with para-aminobenzoic acid (PABA) for dihydropteroate synthase. The sulfonamide moiety (-SO2NH-) serves as an excellent pharmacophore for developing enzyme inhibitors through hydrogen bonding interactions with target proteins [4].

The strategic hybridisation of chromone and sulfonamide pharmacophores represents a rational approach to developing novel antimicrobial agents with potentially synergistic mechanisms of action. This review comprehensively analyses recent advances in chromone-based hybrid molecules, synthetic methodologies, and their pharmacological evaluation [5].

Chemistry of chromones

Structural features

Chromone (4H-chromen-4-one) consists of a benzene ring fused with a γ-pyrone ring (1,4-benzopyrone). The bicyclic system contains both aromatic and unsaturated heterocyclic characteristics, with the carbonyl group at position 4 contributing to electron distribution and reactivity. The chromone nucleus exhibits planar geometry with significant conjugation between the benzene ring and the pyrone moiety.

The electron-deficient nature of the pyrone ring makes chromones susceptible to nucleophilic attack, particularly at positions 2 and 4. The carbonyl oxygen at position 4 can participate in hydrogen bonding with biological targets, while the ring oxygen contributes to the overall electron distribution [6].

Naturally occurring chromones

Chromones are ubiquitous in the plant kingdom, occurring in families including Apiaceae, Asteraceae, Leguminosae, and Rutaceae. Khellin, isolated from *Ammi visnaga* (khella plant), represents the first extensively studied chromone derivative with documented medicinal use in the Mediterranean region for centuries as a diuretic and treatment for renal colic. Khellin demonstrated bronchodilator, vasodilator, and antispasmodic properties, stimulating extensive research into chromone pharmacology.

Other significant natural chromones include noreugenin, eugenin, and aloesone from various plant sources. Flavonoids, including flavones (apigenin, luteolin), flavonols (quercetin, kaempferol), and isoflavones (genistein, daidzein) contain the chromone core as their fundamental structural unit.

Synthetic methodologies for chromone derivatives

Vilsmeier-Haack reaction for 3-formylchromones

The Vilsmeier-Haack reaction represents the most versatile method for synthesising 3-formylchromones, which serve as key intermediates for further functionalization. The reaction involves treatment of 2-hydroxyacetophenones with a Vilsmeier reagent generated in situ from phosphorus oxychloride (POCl3) and dimethylformamide (DMF) [7].

Mechanism: The reaction proceeds through the formation of an immonium salt (chloromethyleniminium chloride) that attacks the activated methylene group of the acetophenone. Subsequent cyclisation and hydrolysis yield 3-formylchromones. The reaction conditions require careful temperature control (0-5°C during reagent mixing, followed by 50-60°C for cyclisation) to optimise yields.

Employed this methodology for synthesising substituted 3-formylchromones from acetophenones using POCl3 and DMF under ice-cooled conditions with continuous stirring. The reaction progress was monitored by TLC (hexane-ethyl acetate, 9:1), and products were recrystallised from alcohol to obtain pure compounds.

Optimisation aspects: The Vilsmeier-Haack reaction efficiency depends on multiple parameters, including the nature of substituents on the acetophenone ring, reaction temperature, and stoichiometry of reagents. Electron-donating groups facilitate the reaction, while strongly electron-withdrawing groups may require prolonged reaction times or modified conditions [8].

Baker-Venkataraman rearrangement

The Baker-Venkataraman rearrangement provides an elegant route to 2-substituted chromones (flavones) through intramolecular acyl migration. The method involves O-acylation of 2-hydroxyacetophenones with aroyl chlorides, followed by base-catalysed rearrangement to 1,3-diketones, and finally acid-catalysed cyclisation to chromones used this approach to synthesise 3-(4-fluorophenyl)-2-(4-pyridyl) chromone derivatives as p38 MAP kinase inhibitors. The synthetic sequence involved esterification of 2'-hydroxyacetophenone with appropriate acid chlorides, Baker-Venkataraman rearrangement using KOH in pyridine under microwave heating, and acid-promoted cyclisation.

Advantages: The Baker-Venkataraman rearrangement allows the introduction of diverse 2-substituents, including aryl, heteroaryl, and alkyl groups. The method provides regiospecific products with high purity and reasonable yields.

Modifications: Contemporary modifications include microwave-assisted synthesis, reducing reaction times from hours to minutes, use of phase-transfer catalysts, and one-pot procedures combining acylation and rearrangement steps [9].

Laisen rearrangement for 6/8-substituted chromones

The Claisen rearrangement of allyl aryl ethers provides access to ortho-allyl phenols, which can be cyclized to dihydrofuranochromones. Reported SnCl4-catalysed Claisen rearrangement of 7-allyloxychromones under mild conditions (0-5°C in dry THF) to yield 7-hydroxy-6/8-allylchromones and 2'-methyl-2',3'-dihydrofuranochromones.

The reaction proceeds through [3,3]-sigmatropic rearrangement of the allyl ether, generating ortho-allyl phenol intermediates that undergo cyclisation under the reaction conditions. The use of SnCl4 as a Lewis acid catalyst enables rearrangement at low temperatures, minimising side reactions and improving yields compared to thermal rearrangement requiring prolonged heating at elevated temperatures.

Product distribution: The rearrangement products depend on the substitution pattern and reaction conditions. Compounds 4a-d (7-hydroxy-6/8-allylchromones) and 5a-d (2'-methyl-2',3'-dihydrofuranochromones) were isolated by column chromatography and characterised by NMR spectroscopy.

Click chemistry

Copper(I)-catalysed azide-alkyne cycloaddition

The copper(I)-catalysed azide-alkyne cycloaddition (CuAAC) represents the quintessential "click chemistry" reaction, providing 1,2,3-triazoles with exceptional regiospecificity and high yields under mild conditions. The reaction tolerates diverse functional groups and can be performed in aqueous media, making it environmentally friendly [10].

Employed this methodology for synthesising 2-aminochromone-based N, N-bis-1,2,3-triazole derivatives. The key intermediate, N, N-dipropargyl-2-aminochromone (5), was prepared by treating 2-aminochromone with propargyl bromide in DMF using K_2CO_3 and catalytic Cs_2CO_3 at 50°C. Subsequent reaction with various alkyl/aryl azides (6a-o) in the presence of $CuSO_4 \cdot 5H_2O$ and sodium ascorbate in t-butanol: water (1:1) at room temperature for 8 hours yielded the target bis-triazole derivatives (7a-o) in 70-90% yields.

Optimisation studies: Solvent screening revealed DMF as optimal for the propargylation step, while water:t-butanol mixtures provided ideal conditions for the CuAAC reaction. Base optimisation demonstrated that K_2CO_3 with catalytic Cs_2CO_3 gave comparable yields to stoichiometric Cs_2CO_3, offering cost advantages. The reaction failed in water, toluene, acetone, and MTBE, while THF gave only 5% conversion.

Mechanistic aspects: The Cu(I) catalyst coordinates to the terminal alkyne, lowering its pKa and facilitating the formation of copper acetylide. Subsequent stepwise cycloaddition with organic azide yields the 1,4-disubstituted 1,2,3-triazole with complete regioselectivity. Sodium ascorbate serves to generate Cu(I) from Cu (II) and prevent oxidation [11].

Synthesis of amino acid-substituted sulfonamides

Reported synthesis of amino acid-substituted benzenesulfonamides through reaction of amino acids (alanine, leucine, glycine) with benzenesulfonyl chloride under dynamic pH control. The reaction was performed in aqueous media at -5°C with gradual addition of sulfonyl chloride, maintaining pH 8-10 using Na_2CO_3 solution. After reaction completion (monitored by TLC, MeOH: DCM 1:9), acidification to pH 2 with 20% HCl precipitated the products (7a-c), which were washed with tartaric acid solution (pH 2.2) and dried over silica gel.

Yield and characterisation: The sulfonamide derivatives were obtained in 74-79% yields with melting points 150-160°C. (Phenylsulfonyl)-D-alanine (7a, 77%, $C_{11}H_{15}NO_4S$), (phenylsulfonyl)-D-leucine (7b, 74%, $C_{12}H_{17}NO_4S$), and (phenylsulfonyl)glycine (7c, 79%, $C_8H_9NO_4S$) were characterised by molecular weight determination and solubility in DMSO [12].

Synthesis of chromone-sulfonamide hybrids

The target chromone-sulfonamide conjugates (8a-f) were synthesised by refluxing 3-formylchromones (4a-b) with amino acid-substituted benzenesulfonamides (7a-c) in dry ethanol at 80°C. Glacial acetic acid (1 mL) was added after 10 minutes, and reflux continued for 1 hour, followed by stirring at room temperature for 12 hours. The solid products were recrystallised from alcohol, filtered, and dried. Reaction completion was monitored by TLC (hexane-ethyl acetate, 9:1).

Characterisation: The synthesised compounds included N-((7-nitro-4-oxo-4H-chromen-3-yl) methyl)-N-(phenylsulfonyl)-D-alanine (8a, 77%, $C_{19}H_{16}N_2O_8S$), the corresponding leucine derivative (8b, 73%, $C_{22}H_{22}N_2O_8S$), and glycine derivative (8c, 75%, $C_{18}H_{14}N_2O_8S$). Bromo-substituted analogues (8d-f) were similarly prepared in 69-73% yields. Structures were confirmed by ^1H NMR spectroscopy showing characteristic signals for chromone protons (δ 7.95-7.72 for nitro derivatives, δ 7.59-7.33 for bromo derivatives), methylene groups at C-3 (δ 3.83), and carboxylic acid protons (δ 12.39-13.09).

Pharmacological activities

Antibacterial activity

Evaluation methods

Antibacterial activity is typically evaluated using agar well diffusion or disc diffusion methods against standard bacterial strains, including Gram-positive (*Staphylococcus aureus, Bacillus subtilis, Micrococcus luteus*) and Gram-negative (*Escherichia coli, Pseudomonas aeruginosa, Klebsiella planticola*) organisms. Minimum inhibitory concentration (MIC) is determined by serial dilution methods, while minimum bactericidal concentration (MBC) assesses bactericidal potential.

Chromone-sulfonamide hybrids

Evaluated compounds 8a-f against *S. aureus, B. subtilis, P. aeruginosa,* and *E. coli* at concentrations of 10, 20, and 30 μg/mL using the Kirby-Bauer disc diffusion method with ciprofloxacin as a standard. Results demonstrated dose-dependent activity with increasing inhibition zones at higher concentrations.

At 30 μg/mL, compound 8c (glycine derivative with nitro substitution) showed 67.7% inhibition against *S. aureus* (ZOI 21 mm) and 51.6% against *B. subtilis* (ZOI 16 mm). Compound 8f (glycine derivative with bromo substitution) exhibited 64.5% inhibition against both *S. aureus* and *B. subtilis* (ZOI 20 mm) and 51.6% against *P. aeruginosa* (ZOI 16 mm). The standard ciprofloxacin (30 μg/mL) showed 100% inhibition with ZOI 31 mm against all strains.

Structure-activity relationship analysis revealed that glycine derivatives (8c, 8f) generally showed superior activity compared to alanine (8a, 8d) and leucine (8b, 8e) analogues, suggesting that smaller amino acid side chains favour antibacterial activity. Nitro-substituted chromones (8a-c) demonstrated comparable or slightly better activity than bromo-substituted analogues (8d-f), indicating that electron-withdrawing groups at position 7 enhance antibacterial potential.

2-aminochromone bis-triazole derivatives

Evaluated compounds 7a-o against Gram-positive (*M. luteus* MTCC 2470, *S. aureus* MTCC 96, *S. aureus* MLS-16 MTCC 2940, *B. subtilis* MTCC 121), Gram-negative (*E. coli* MTCC 739, *P. aeruginosa* MTCC 2453, *K. planticola* MTCC 530), and fungal (*C. albicans* MTCC 3017) strains.

Several compounds exhibited potent activity with MIC values of 3.9 µg/mL. Compounds 7c (benzonitrile-substituted), 7d (difluorobenzyl-substituted), 7h (bromophenyl ethanone-substituted), 7l (dibromopyrrole-substituted), and 7m (cyclopropyl-fluorophenyl ethanone-substituted) showed broad-spectrum activity against all tested bacterial and fungal strains. Compounds 7e (thiophenyl-substituted), 7f (thiazolyl-substituted), and 7g (benzhydryl-substituted) demonstrated selective activity against Gram-positive bacteria with MIC 3.9 µg/mL but were inactive against some Gram-negative strains.

Notably, compounds 7c, 7d, 7h, 7l, and 7m showed promising antifungal activity against *C. albicans* with MIC 3.9 µg/mL, comparable to the standard miconazole (7.8 µg/mL). The ortho, para-trifluoromethyl-substituted compound (7o) showed moderate activity with MIC 7.8 µg/mL against all tested strains.

Minimum bactericidal concentration (MBC) studies confirmed the bactericidal nature of active compounds, with MBC values typically 2-4 times MIC values. Compounds 7c, 7d, 7h, 7l, and 7m showed MBC of 7.8 µg/mL against most tested strains, indicating potent bactericidal activity.

Structure-activity relationship: The presence of electron-withdrawing groups (nitrile, halogen) on the triazole N-substituent enhanced antibacterial activity. Heteroaryl substituents (thiophene, thiazole) favored Gram-positive activity, while bulky hydrophobic groups (benzhydryl, dibromopyrrole) provided broad-spectrum activity. Alkyl-substituted compound 7b showed significantly lower activity, emphasizing the importance of aromatic/heteroaromatic substitution.

Anti-inflammatory Activity

Evaluation Methods

Anti-inflammatory activity is commonly evaluated using the carrageenan-induced rat paw oedema model. The method involves subcutaneous injection of 0.1 mL of 1% carrageenan solution into the subplantar region of rat hind paw, with paw volume measured plethysmographically before and 3-4 hours after carrageenan administration. Test compounds are administered orally 1 hour before carrageenan injection, and the percentage inhibition of oedema compared to control is calculated.

Chromone derivatives via Claisen rearrangement

Evaluated compounds 4a-d and 5a-d for anti-inflammatory activity using the carrageenan-induced rat paw oedema model at a 100 mg/kg dose (p.o.) with ibuprofen (100 mg/kg) as a standard. Results showed variable protection ranging from 20-66%.

Compound 4c (7-hydroxy-8-allyl-3-methylchromone) exhibited the most potent activity with 66% protection (paw volume 0.77 ± 0.18 mL compared to control 2.25 ± 0.08 mL), superior to ibuprofen (60% protection, paw volume 0.89 ± 0.13 mL). Compound 4d showed 52% protection, while 5a and 5b exhibited moderate activity (38% and 27% protection, respectively). The dihydrofuranochromones (5a-b) generally showed lower activity than the 7-hydroxy-6/8-allylchromones (4a-d), suggesting that the free hydroxyl group at position 7 contributes to anti-inflammatory activity.

Statistical analysis: Results were expressed as mean increase in paw volume ± SEM, with significance determined by Student's t-test ($p<0.05$ considered significant, $p<0.01$ highly significant). The standard deviation values (±0.01 to ±0.19) indicate acceptable experimental variability.

Anticancer activity

Evaluation methods

In vitro anticancer activity is typically evaluated using MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay against human cancer cell lines. The assay measures mitochondrial dehydrogenase activity in viable cells, with IC50 values calculated from dose-response curves.

2-aminochromone bis-triazole derivatives

Evaluated compounds 7a-o against human cervical (HeLa) cancer cell lines using curcumin as a standard. All compounds exhibited good activity with IC50 values ranging from 0.11 to 1.04 µM, significantly better than curcumin (IC50 4.83 ± 0.44 µM).

Compound 7o (ortho, para-trifluoromethylbenzyl-substituted) showed the highest activity with IC50 0.11 ± 0.56 µM, followed by compound 7l (dibromopyrrole-substituted) with IC50 0.12 ± 0.43 µM. Compounds 7g (benzhydryl-substituted, IC50 0.18 ± 0.33 µM), 7k (dimethoxybenzoate-substituted, IC50 0.16 ± 0.38 µM), and 7c (benzonitrile-substituted, IC50 0.51 ± 0.55 µM) also demonstrated potent activity. The alkyl-substituted compound 7b showed the lowest activity (IC50 1.04 ± 0.47 µM), consistent with its poor antibacterial profile.

Structure-activity relationship: Halogen substitution (particularly fluorine and bromine) significantly enhanced anticancer activity. Ortho, para-disubstituted trifluoromethyl derivative (7o) was superior to ortho-disubstituted difluoro derivative (7d, IC50 0.52 µM), indicating that substitution pattern and halogen count influence activity. Heteroaryl substituents (dibromopyrrole, quinazoline) provided excellent activity, while simple phenyl substitution (7a, IC50 0.77 µM) showed moderate activity [13].

p38 MAP kinase inhibition

Background

The p38 mitogen-activated protein kinase (MAPK) pathway plays crucial roles in inflammation, stress response, and cell differentiation. p38α is highly expressed in severe invasive breast cancers and regulates pro-inflammatory cytokine production (IL-1, TNF-α), making it an attractive target for anti-inflammatory and anticancer therapy.

3-(4-Fluorophenyl)-2-(4-pyridyl) chromone derivatives

Designed and synthesised 3-(4-fluorophenyl)-2-(4-pyridyl) chromone derivatives as p38α MAP kinase inhibitors based on molecular docking studies. The vicinal 4-fluorophenyl/pyridyl motif, present in known p38 inhibitors like SB203580, was incorporated to ensure appropriate binding in the ATP-binding site.

Docking studies revealed that the pyridin-4-yl nitrogen forms a crucial hydrogen bond with the backbone NH of Met109 in the hinge region, while the 4-fluorophenyl moiety occupies a hydrophobic pocket guarded by gatekeeper residue Thr106. Introduction of amino groups at the 2-position of the pyridyl moiety provided additional hydrogen bonding interactions with the hinge region.

Synthesis: The target compounds were synthesised via esterification of 2'-hydroxyacetophenone with appropriate acid chlorides, Baker-Venkataraman rearrangement, acid-catalyzed cyclization, halogenation (iodination with LDA/I_2 or bromination with NBS under microwave), Suzuki coupling with 4-fluorophenylboronic acid, and Buchwald-Hartwig amination with various amines.

Biological evaluation: Compounds were evaluated using a radiometric p38α assay (Millipore KinaseProfiler). The 2-unsubstituted pyridyl compound 7a showed moderate activity (IC50 813 nM), which decreased with chlorine substitution (7b, IC50 1380 nM) due to electron-withdrawing effects reducing hydrogen acceptor properties of the pyridine nitrogen.

Introduction of secondary amino functions at the 2-position dramatically improved activity, with compounds 8a-c and 8e-g showing IC50 values of 17-45 nM. The most potent compound, 8a (2-butylamino-substituted), exhibited an IC50 of 17 nM, comparable to reference inhibitors. Compound 8e showed an IC50 of 30 nM. However, the diamine-substituted compound 8d showed decreased activity (IC50 761 nM), suggesting that polar groups in the hydrophobic pocket are unfavourable.

Selectivity studies: Compounds 8a and 8e (tested at 0.8 μM) showed excellent selectivity when screened against a panel of 62 kinases. Only p38α, p38β, and JNK3 were strongly inhibited (0-25% remaining activity), while most other kinases remained unaffected (76-100% remaining activity). This remarkable selectivity profile indicates minimal off-target effects.

Cellular activity: Compound 8e inhibited anisomycin-induced p38 signalling in MCF-7 human breast cancer cells at doses as low as 0.5 μM, with maximal inhibition at 10 μM. Importantly, 8e inhibited phosphorylation of p38 itself without affecting total p38 levels or phosphorylation of upstream activators MKK3/MKK6, indicating direct p38 inhibition rather than upstream interference. Neither 8a nor 8e significantly affected the proliferation of MCF-7 or MDA-MB436 cells alone or in combination with anisomycin or doxorubicin [14].

Structure-activity relationships

Chromone core modifications

The chromone nucleus offers multiple positions for structural modification, each influencing biological activity differently:

Position 2: Substitution with aryl, heteroaryl, or amino groups significantly affects activity. 2-Pyridyl substitution provides p38 kinase inhibitory activity through hydrogen bonding with the hinge region methionine. 2-Amino substitution enables further functionalization via propargylation and click chemistry.

Position 3: 3-Formylchromones serve as versatile intermediates for Schiff base formation with amines and sulfonamides. The formyl group enables conjugation with amino acid-sulfonamide hybrids, producing compounds with enhanced antibacterial activity. 3-Aryl substitution, particularly 4-fluorophenyl, provides p38 inhibitory activity.

Positions 6 and 8: Allyl substitution via Claisen rearrangement yields products with anti-inflammatory activity. The 7-hydroxy-8-allyl substitution pattern (compound 4c) showed superior anti-inflammatory activity (66% protection) compared to 6-allyl analogues.

Position 7: Substitution with electron-withdrawing groups (nitro, bromo) enhances antibacterial activity. Nitro-substituted chromone-sulfonamide hybrids showed slightly better activity than bromo-substituted analogues. The 7-hydroxyl group appears important for anti-inflammatory activity, as 7-hydroxy-8-allylchromones showed better activity than cyclized dihydrofuran derivatives lacking free hydroxyl [15].

Sulfonamide moiety contributions

The sulfonamide group contributes to antibacterial activity through multiple mechanisms:

Mimicry of PABA structure enabling competitive inhibition of dihydropteroate synthase.

Hydrogen bonding capabilities with bacterial enzyme active sites.

Enhancement of water solubility and pharmacokinetic properties.

Among amino acid linkers, glycine provided superior antibacterial activity compared to alanine and leucine, suggesting that minimal steric hindrance favours target interaction.

Triazole ring effects

The 1,2,3-triazole ring formed via click chemistry offers multiple advantages:

Stable under physiological conditions.

Participates in hydrogen bonding and π-stacking interactions.

Enhances water solubility.

Serves as an amide bond bioisostere.

N, N-Bis-triazole substitution on 2-aminochromone significantly enhanced anticancer activity compared to monosubstituted analogs. The presence of two triazole rings enables multiple binding interactions with target proteins such as DYRK2 [16].

Substituent effects on biological activity

Electron-withdrawing groups: Nitro, cyano, and halogen substituents generally enhance antibacterial and anticancer activity. Trifluoromethyl substitution (compound 7o) provided the most potent anticancer activity (IC50 0.11 μM), while difluoro substitution (7d) showed moderate activity (IC50 0.52 μM).

Halogen effects: Bromine and fluorine substitution consistently improved activity across multiple assays. Dibromopyrrole-substituted compound 7l showed excellent anticancer (IC50 0.12 μM) and antimicrobial (MIC 3.9 μg/mL) activities.

Heteroaryl substituents: Thiophene, thiazole, and quinazoline rings provided selective antibacterial activity against Gram-positive organisms, while benzonitrile and bromophenyl ethanone provided broad-spectrum activity.

Hydrophobic groups: Bulky substituents (benzhydryl, dibromopyrrole, cyclopropyl-fluorophenyl ethanone) enhanced activity against Gram-negative bacteria and fungi, possibly by improving membrane penetration [17].

Molecular docking studies

Docking with DYRK2

Performed molecular docking studies of compounds 7a-o against dual-specificity tyrosine-regulated kinase 2 (DYRK2, PDB id: 5ZTN) using Molegro Virtual Docker (MVD 2010.4.0.0). All compounds showed better Moldock scores (-169.11 to -229.95) than standard curcumin (-147.20), correlating with experimental IC50 values.

Compound 7o exhibited the highest Moldock score (-229.95), with fluorine atoms interacting with B-VAL 154, B-ILE 155, B-LEU 231, B-SER 232, B-ASN 234, and B-GLU 237. Compound 7l showed a score of -214.32, with interactions at B-LYS 153, B-ILE 155, B-LYS 165, and B-LEU 231. The lowest-scoring compound 7b (-169.11) still exceeded curcumin, consistent with its moderate experimental activity.

Docking with p38α MAP kinase

Docked 3-(4-fluorophenyl)-2-(4-pyridyl) chromone derivatives into the ATP-binding site of p38α (PDB code 1A9U) using Schrödinger Glide XP mode. The docking revealed:

Pyridin-4-yl nitrogen hydrogen bonding with Met109 backbone NH.

4-Fluorophenyl moiety occupying the hydrophobic pocket guarded by Thr106.

The carbonyl oxygen of the chromone interacts with the Lys53 side chain.

2-Amino substituents provide additional interactions in the hinge region.

The docking studies guided rational design, predicting that amino-substituted pyridyl derivatives would show enhanced activity, which was experimentally confirmed [18].

CONCLUSION

This comprehensive review consolidates recent advances in chromone-based medicinal chemistry, demonstrating the remarkable therapeutic potential of chromone derivatives as antibacterial, anti-inflammatory, and anticancer agents. The strategic hybridisation of chromone with sulfonamide and triazole pharmacophores has yielded compounds with potent and selective biological activities.

Key findings include

Chromone-sulfonamide hybrids show dose-dependent antibacterial activity, with glycine-linked derivatives exhibiting superior potency (up to 67.7% inhibition at 30 μg/mL).

2-Aminochromone N, N-bis-triazole derivatives demonstrate excellent anticancer activity against HeLa cells (IC50 0.11-1.04 μM), significantly better than curcumin, with ortho, para-trifluoromethyl substitution providing optimal activity.

SnCl4-catalysed Claisen rearrangement of 7-allyloxychromones yields 7-hydroxy-6/8-allylchromones with significant anti-inflammatory activity (up to 66% protection in carrageenan-induced oedema model).

3-(4-Fluorophenyl)-2-(4-pyridyl) chromones with 2-amino substitution are potent p38α MAP kinase inhibitors (IC50 17-45 nM) with excellent selectivity across the human kinome and cellular activity in breast cancer cells.

Structure-activity relationship studies reveal that electron-withdrawing groups (nitro, halogen) enhance antibacterial and anticancer activity, while free hydroxyl groups contribute to anti-inflammatory effects.

Future research directions should include

In vivo pharmacokinetic and toxicity studies of lead compounds.

Mechanistic investigations to identify precise molecular targets.

Development of more efficient synthetic routes for scale-up.

Exploration of chromone-based hybrids with other pharmacophores (e.g., sulfonamide-triazole-chromone ternary hybrids).

Evaluation against drug-resistant bacterial strains.

Structure-based optimisation of p38α inhibitors for inflammatory disease treatment.

The chromone scaffold continues to offer immense potential for drug discovery, and the synthetic methodologies and pharmacological insights reviewed herein provide a solid foundation for future medicinal chemistry efforts.

Conflicts of Interest: No conflict of interest

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