REVIEW ARTICLE

Curcumin-based bioactive heterocycles derived via multicomponent reactions

Amol A. Nagargoje[1,2] | Mubarak H. Shaikh[1,3] | Bapurao B. Shingate[1]

[1]Department of Chemistry, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad, Maharashtra, India

[2]Department of Chemistry, Khopoli Municipal Council College, Khopoli, Maharashtra, India

[3]Department of Chemistry, Radhabai Kale Mahila Mahavidyalaya, Ahmednagar, Maharashtra, India

Correspondence
Bapurao B. Shingate, Department of Chemistry, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad, Maharashtra 431004, India.
Email: bapushingate@gmail.com

Abstract

Curcumin is an important phytochemical, found in the Asian countries, especially in the Indian subcontinent. The use of this "privileged natural product" in the diversity-oriented synthesis of curcumin-based heterocycles via multicomponent reactions (MCRs) is the subject of interest for many medicinal chemists across the globe. This review particularly focuses on the reactions involving curcuminoids as one of the reactants in the MCRs of curcuminoid to synthesize curcumin-based heterocycles. Also, the various pharmacological activities of curcumin-based heterocycles generated via the MCR approach are discussed. The research work published in the last 10 years is in the focus of this review article.

KEYWORDS
Biginelli reaction, curcumin-based heterocycles, Hantzsch reaction, multicomponent reactions, pharmacological activities

1 | INTRODUCTION

Natural products (NPs) played an important role in the drug discovery process by offering scaffold diversity and structural complexity.[1] They are structurally optimized for enhancing biological potential. Their use in traditional Ayurveda practices in the Asian subcontinent revealed their efficacy and safety. NPs are enriched with bioactive molecules acquiring broader chemical space as compared to synthetic organic molecules. The use of NPs for treating illness or to prevent illness has been known since ancient times to humans. Enhancing the therapeutic potential of original NP by structural modifications is one of the approach in the drug discovery process.[2] Among these modified NPs, curcumin is found as a lead molecule exhibiting a broad spectrum of biological activities.[3–7] Curcumin is a yellow solid extracted from the dried rootstalk of the turmeric plant known as *Curcuma longa* of the ginger family. Chemically, curcumin is 1,7-*bis*(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione (Figure 1). It has two backbones, a ketone and active methylene group separating the backbones and a terminal *meta*-methoxy-*para* hydroxyl phenyl ring on each side. Originally, it was used as flavoring and coloring agent in Asian cooking recipes. It is commonly known as Indian saffron. It has been used extensively, particularly in Asia as a spices, food preservatives, cosmetics, botanical supplements, medicines, flavoring agents, and coloring agents since ancient times.[8] These curcuminoids are usually aromatic, carminative and are used to treat various ailments in India, China, and other Asian countries. Curcumin **1** is one of the major forms of curcuminoids present in turmeric, the other two being demethoxycurcumin **2** and *bis*-demethoxycurcumin **3**[9] (Figure 1).
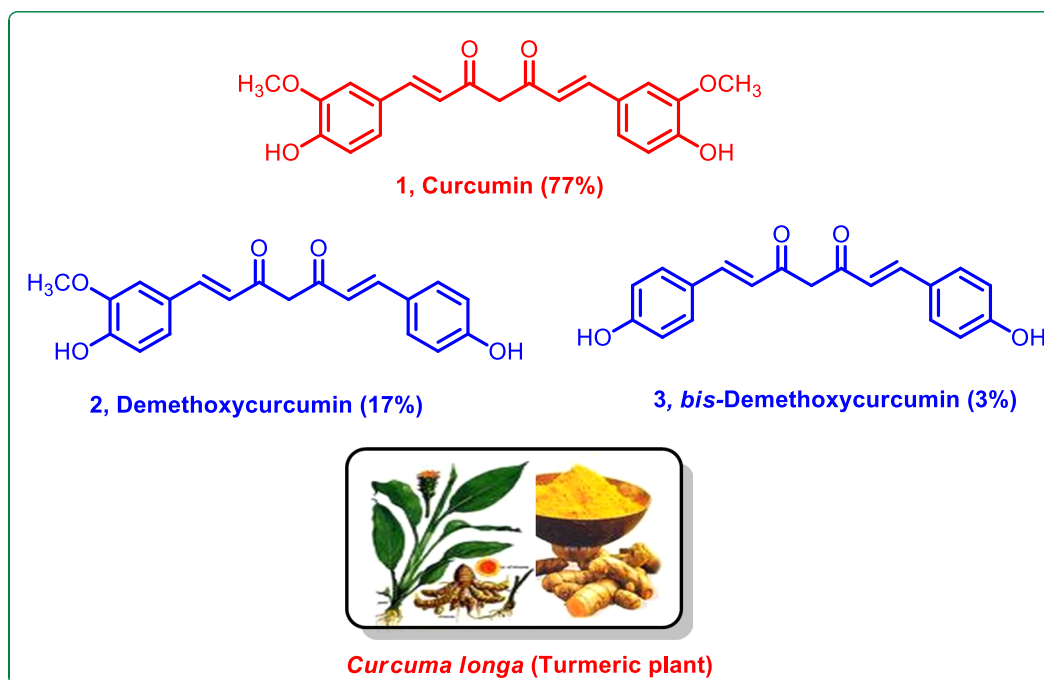
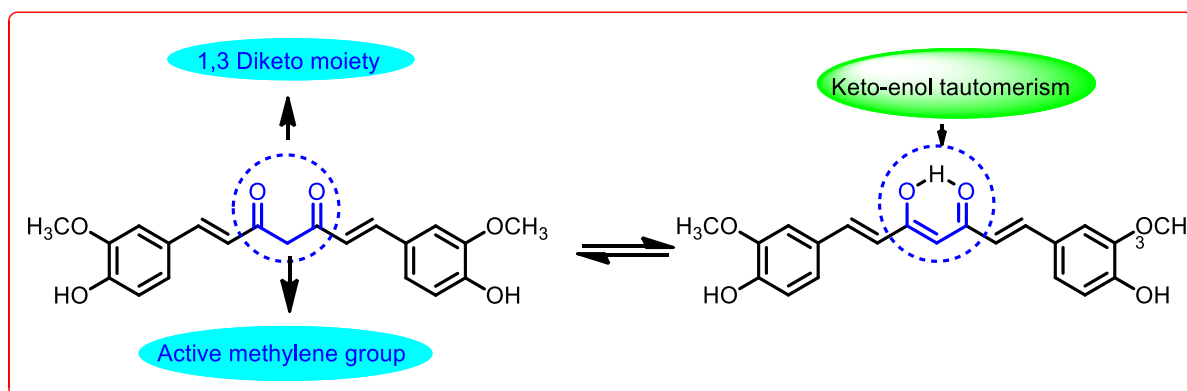**FIGURE 1** Major forms of curcuminoids present in turmeric.[9]

FIGURE 2 Groups responsible for the instability of curcumin under physiological conditions.

During the last two decades, literature reveals that, curcuminoids exhibits a broad spectrum of pharmacological activities like antimalarial,[10,11] antioxidant,[12] anti-human immunodeficiency virus (HIV),[13] anti-inflammatory,[14–16] anticancer,[17] anti-infective,[18] anticardiac,[19] biomedical applications,[20] anti-Parkinson,[21] anti-Alzheimer's,[22] antiangiogenesis,[23] antibacterial,[24,25] antiparasitic,[26] enhancement of wound healing,[5] antipsoriasis disease,[27] and so forth. These broad spectrum biological activities attracted researchers worldwide to explore the therapeutic potential of curcumin against various diseases and to carry out clinical trials.[28] The most important feature of

this molecule is an absence of toxicity, hence a large amount of curcumin can be consumed without any harmful side effects, which makes it as an important scaffold for therapeutic development. In spite of the diverse biological activities and safety profile exhibited by curcumin, the clinical usefulness is restricted due to its poor oral bioavailability,[29] and poor pharmacokinetic profile.[13] Another limitation associated with curcumin is poor water solubility and poor plasma solubility. The study revealed that the presence of β-diketone moiety and the active methylene group is responsible for poor oral absorption, weak pharmacokinetics, and instability of curcumin under
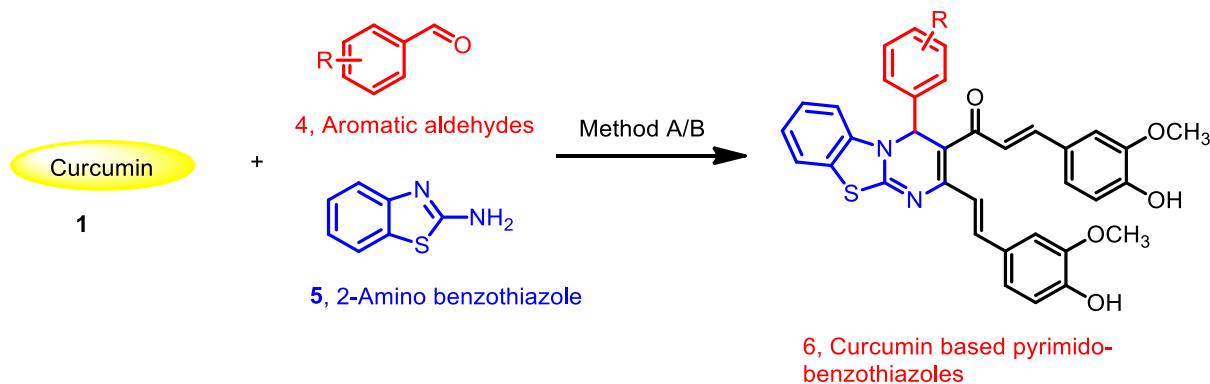
SCHEME 1 Synthesis of curcumin-based pyrimido-benzothiazole derivatives. Reagents and conditions: (A)[42] Pyridine, MeOH, 60–65°C, reflux, 15–20 h, 67%–86%; (B)[53] calcined hydrotalcite (Mg–Al–CO$_3$ & Ca–Al–CO$_3$), 70°C, 5–7 h, 72%–85%.
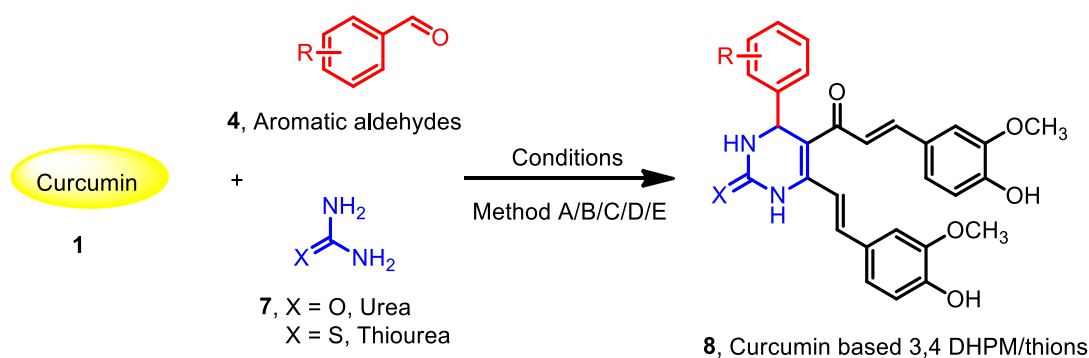
SCHEME 2 Synthesis of curcumin based 3,4-DHPM/thiones. Reagents and conditions: (A)[70] Conc. H$_2$SO$_4$, EtOH, reflux, 8–12 h, 71%–82%. (B)[71] Chitosan (0.08 g), water, 60°C, 80–90 min, 94%–97%. (C)[72] SnCl$_2$·2H$_2$O (0.015 mmol), 80°C, 80–90 min, 92%–97%. (D)[73] Piperidine (0.001 mol%), MeOH, reflux, 60–65°C, 62%–87%. (E)[38] H$_3$PMo$_{12}$O$_{40}$, (5 mol%), conventional/microwave heating, 80%–98%. DHPM, dihydropyrimidones.

physiological conditions[30] (Figure 2). Thus, there is always a need to synthesize new curcumin derivatives with a similar safety profile, but increased activity and improved oral bioavailability.

Curcumin derivatives/analogs/hybrids are important lead molecules in medicinal chemistry research.[31–41] Use of curcumin as one of the reactant/substrate in various two components and multicomponent reactions (MCRs) generates new curcumin-based heterocycles of enhanced therapeutic potential. Curcumin-pyrazole/isoxazole,[40] curcumin-3,4-dihydropyrimidones (DHPM)/thions,[38] curcumin-benzothiazole,[42] curcumin-based pyrano[3,2-d]pyrimidine,[43] and so forth are some of the curcumin-derived heterocycles of biological interest.

This review particularly focused on recent advances in the synthetic methodologies and pharmacological activities of curcuminoid-based heterocycles published during the last 10 years. Moreover, emphasis has been given on synthetic methodologies in which curcuminoids are used as one of the reactant/substrate in MCR to synthesize curcuminoid-based heterocycles. Also, the

pharmacological properties of curcuminoid-based heterocycles were also discussed.

2 | CURCUMINOIDS IN MCRs

In the context of contemporary drug development, MCRs-those combining three or more reactants in a single pot and producing a structure with functional diversity-are effective strategies for promoting green chemistry. Compared to traditional stepwise protocols, they have a number of benefits, including simplicity, efficiency, and selectivity, convergence, and atom economy. MCRs are a powerful tool in the synthesis of diversely oriented complex molecules from simple starting materials.[44–46] A synthesis of pharmaceutically active heterocycles using MCRs is an important domain in synthetic organic chemistry.[47] The use of NPs as starting material in MCRs is one of the most efficient way in diversity-oriented synthesis of NP-derived synthetic libraries of therapeutically active compounds.[38,46] This approach allows the synthesis of large numbers of biologically active conjugates using simple starting
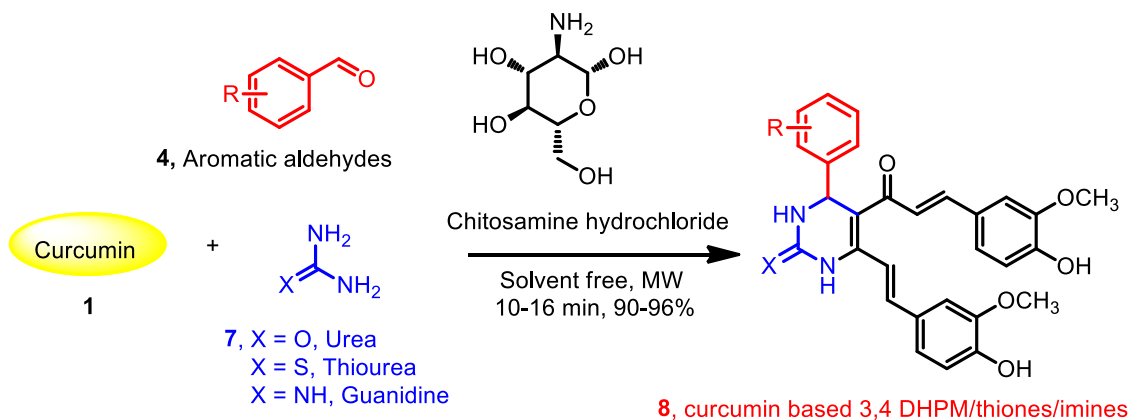
SCHEME 3 Synthesis of curcumin based 3,4-DHPM/thiones/imines. DHPM, dihydropyrimidones.

materials. Structural modifications on the curcuminoid have been widely reported by organic and medicinal chemists all over the world.[42,48] Recent literature suggests that broad-spectrum phytochemical properties of curcumin lead the researchers to use curcuminoids as one of the important scaffold in MCR like the Biginelli reaction, Hantzsch reaction, Tandem reaction, and so forth.[38,49]

2.1 | Curcumin based pyrimido-benzothiazole derivatives

The Biginilli reaction is the important MCR and used for the synthesis of biologically active 4H-pyrimido[2,1-b]benzothiazoles and their derivatives.[50] Benzothiazole serves as a key template in the development of bioactive agents with a wide spectrum of activities.[51] Sahu et al.[52] have developed[42] a one-pot, simple, efficient procedure for the synthesis of curcumin-based 4H-pyrimido[2,1-b]benzothiazole derivatives (Scheme 1). This reaction utilizes curcumin 1, aromatic aldehydes 4 and 2-aminobenzothiazole 5 in the presence of pyridine as a catalyst under reflux conditions to produces curcumin-based 4H-pyrimido [2,1-b][1,3]benzothiazole derivatives 6 in 67%–86% yield (Scheme 1). The reaction takes place in the presence of pyridine catalyst using methanol as a solvent. In the first step of the mechanism aromatic aldehydes reacts with curcumin via Knoevenagel condensation followed by Michael's addition of Knoevenagel adduct with substituted benzothiazole to the product (Scheme 1). Furthermore, the same research group have been reported[52] eco-friendly protocol for the synthesis of curcumin-based benzothiazole conjugates 6 in 72%–85% yield using environmentally benign calcined hydrotalcite (Mg–Al–CO$_3$ and Ca–Al–CO$_3$) as a catalyst under solvent-free conditions. The O^{2-} ion as basic sites in the calcined hydrotalcite was responsible for their catalytic activity. Also, the catalytic activity of calcined hydrotalcite was depend on the molar ratio of metal ions, calcination temperature, and crystallinity. The main advantages of using hydrotalcite was the reusability of catalyst, good yield, solvent-free conditions, environmentally benign catalyst, and

easy to work up procedure (Scheme 1). Agarwal et al.[53] synthesized curcumin-based 4H-pyrimido [2,1-b]benzothiazole derivatives 6 in good yield (69%–83%) by MCR of curcumin 1, aromatic aldehydes 4 and 2-aminobenzothiazole 5 using the same protocol reported[42] by Sahu et al.[52]

2.2 | Curcumin-based dihydropyrimidinone (DHPM)/thiones derivatives

3,4-DHPMs and their derivatives are considered as "privileged structures" of immense biological potential. DHPMs exhibit wide range of biological properties like anti-inflammatory,[54] anti-HIV,[55] antifungal,[56] antioxidant,[57] anticancer,[58] antibacterial,[59] antihypertensive,[60] analgesic,[61] anticonvulsant,[62] antisevere acute respiratory syndrome,[63] and antifilarial activity.[64–69] Therefore, there is a need of the development of new synthetic protocols to access these existing and novel structural motifs. Classical Biginelli reaction can be modified at keto–ester counterpart with curcumin, which can produce curcumin clubbed DHPMs easily.

Sharma et al.[70] synthesized curcumin clubbed 3,4-dihydropyrimidin-2(1H)-one/thione derivatives 8 using simple, efficient, and improved Biginelli reaction by a one-pot multicomponent cyclocondensation of curcumin 1, aromatic aldehydes 4, and urea/thiourea 7 in EtOH–conc. H$_2$SO$_4$ with good yield (71%–82%) (Scheme 2). Lal et al.[71] developed chitosan (0.08 g in 2% AcOH) mediated, an efficient biodegradable and recyclable green catalyst for the one-pot multicomponent synthesis of curcumin-based 3,4-DHPM/thiones 8 in aqueous media from curcumin 1, aromatic aldehydes 4 and urea/thiourea 7 in an excellent yield (94%–97%) (Scheme 2). The primary amino (–NH$_2$) group present in chitosan can be considered as responsible for catalyzing the activity of the chitosan. Further, the same group have reported[72] another protocol for curcumin-based 3,4-DHPM/thiones 8 in large yield (92%–97%) using SnCl$_2$·2H$_2$O as a catalyst at 80°C under solvent-free condition. Sahu et al.[73] reported piperidine catalyzed synthesis of curcumin-based 3,4-DHPM/thiones 8 via Biginelli reaction in methanol under reflux conditions in good yield (62%–87%) (Scheme 2). Khellafi et al.[38] developed an efficient protocol for the synthesis of curcumin-based
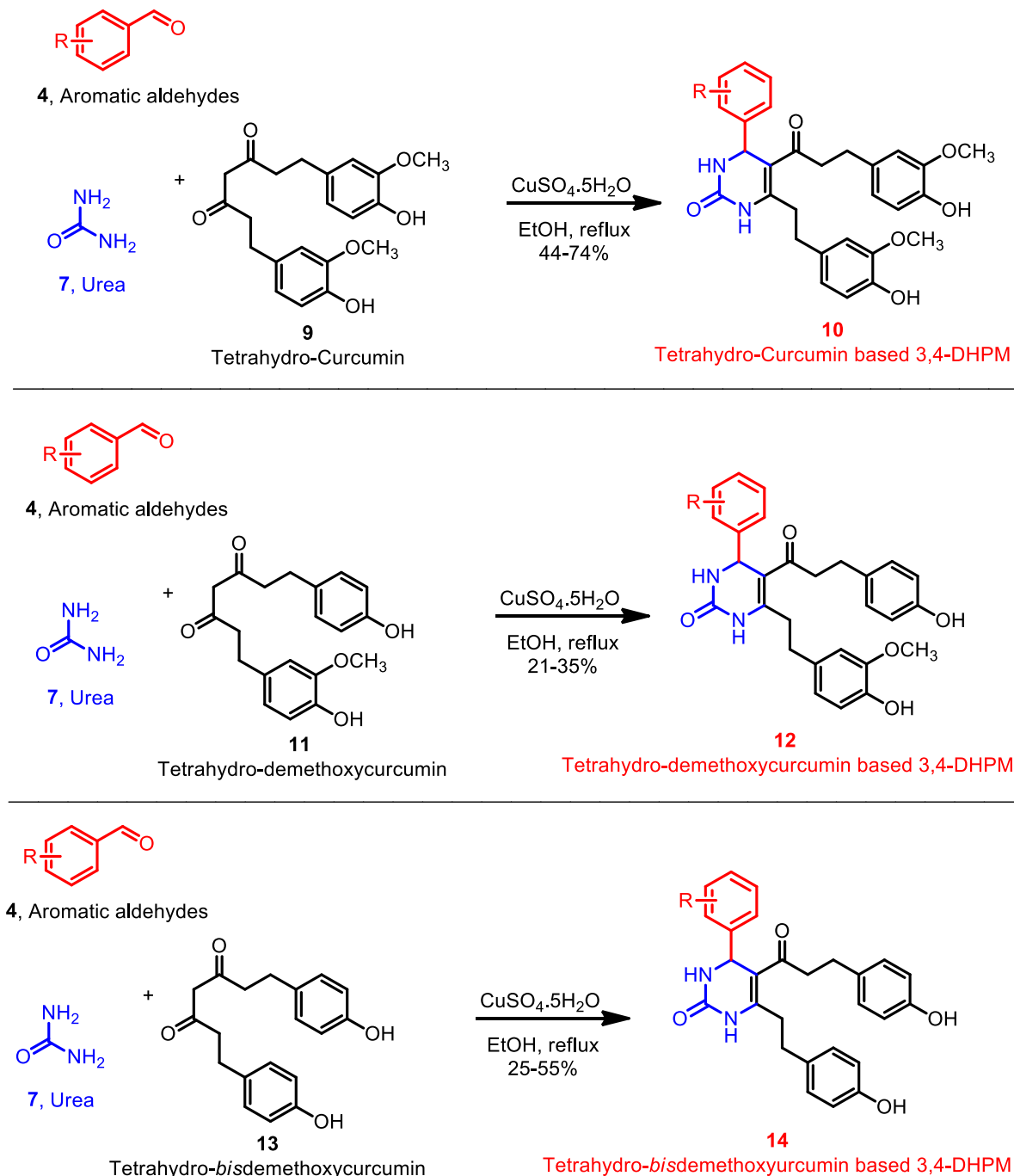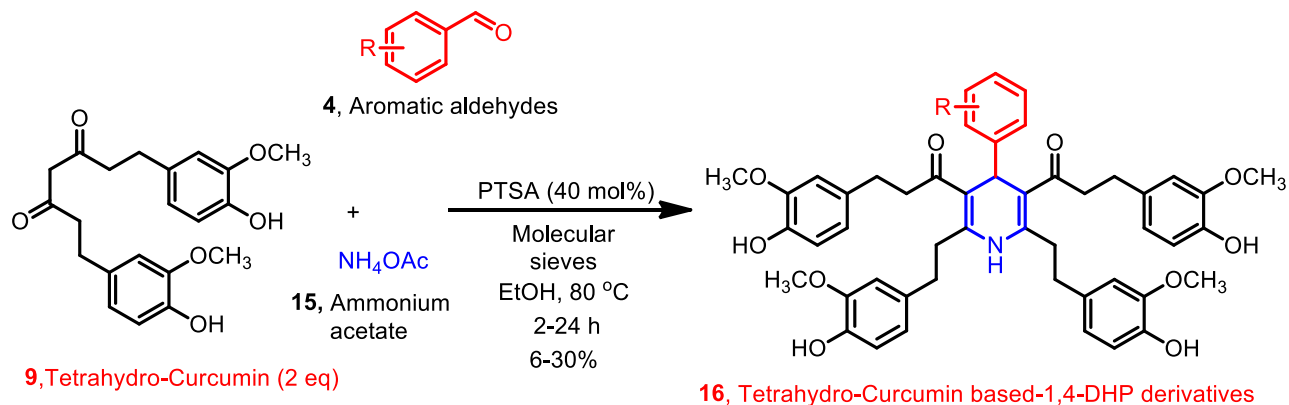
SCHEME 4 Synthesis of racemic THC-based-DHPM derivatives. DHPM, dihydropyrimidones; THC, tetrahydrocurcumin.

3,4-DHPM/thiones **8** using 5 mol% hetero-poly-acid catalyst ($H_3PMo_{12}O_{40}$) at 80°C for 6–9 h and microwave irradiation (2–3 min) in excellent yields (Scheme 2).

Lal et al.[74] reported curcumin-based 3,4-DHPM/thiones/imines **8** by using one-pot cyclocondensation of curcumin **1**, aromatic aldehydes **4**, and urea/thiourea/guanidine **7** in the presence of chitosamine hydrochloride as a biodegradable and a nontoxic catalyst under solvent-free microwave irradiation (10–16 min) in good to excellent yield (90%–96%) (Scheme 3).

2.3 | Tetrahydrocurcumin (THC) derived DHPM derivatives

THC research is increasing because it is more superior to curcumin in terms of solubility in water, chemical stability, bioavailability, and antioxidant activity.[75,76] THC is the major metabolite derived from curcumin with multiple medicinal properties.[77,78] THC can be a suitable substrate for the construction of DHPM derivatives using the MCR approach by Biginelli condensation reaction.

SCHEME 5 Synthesis of THC-based-1,4-DHP derivatives via the Hantzsch reaction. DHP, dihydropyridine; PTSA, *para*-toluene sulfonic acid; THC, tetrahydrocurcumin.

Arunkhamkaew et al.[79] reported the synthesis of racemic THC **9**, tetrahydrodemethoxycurcumin **11** (THDC), and tetrahydro-bisdemethoxycurcumin **13** (THBDC) derived DHPM analogs **10**, **12**, and **14** by Biginelli reaction with aromatic aldehydes **4** and urea **7** in the presence of copper sulfate as a catalyst in moderate to good yields (21%–74%) (Scheme 4).

2.4 | Curcumin/THC based 1,4-dihydropyridine (DHP) derivatives

Hantzsch MCR is the important pathway to construct bioactive-1,4-DHP derivatives from active methylene compound, aromatic aldehyde, and ammonium acetate.[80–82] 1,4-DHPs are important motif present in many natural and synthetic bioactive compounds with a broad spectrum of biological activities.[83,84] For the creation of 1,4-DHP derivatives from the THC precursor, the Hantzsch reaction was employed. Ajavakom et al.[85] reported tetrehydrocurcumin based-1,4-DHP derivatives **16** via multicomponent Hantzsch reaction of THC **9**, aromatic aldehydes **4**, and ammonium acetate **15** in the presence of *para*-toluene sulfonic acid (PTSA) (40 mol%) as a catalyst, and molecular sieves as a dehydrating agent with 6%–30% yield (Scheme 5).

Khajeh Dangolani et al.[86] reported curcumin-based DHP-3-carbonitrile derivatives **19**, **20**, and curcumin-based DHP-3-carboxylate derivatives **22** via one pot MCR of curcumin **1**, aromatic aldehydes **4**, aromatic amines **18**, malononitrile **17**, or ethyl-2-cyanoacetate **21** in the presence of PTSA as catalyst under reflux conditions in ethanol in good to excellent yields (Scheme 6).
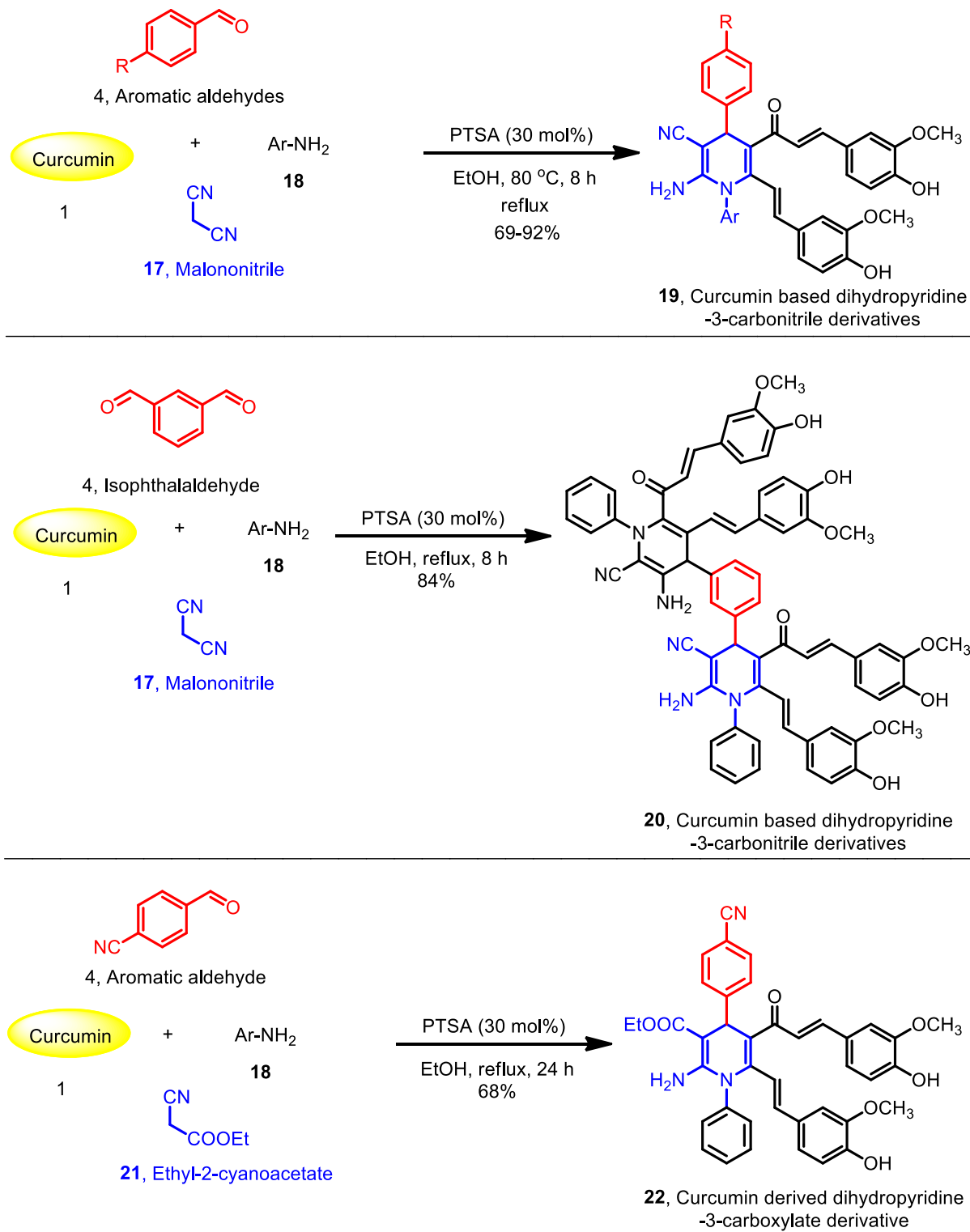
2.5 | Curcumin-based pyrano-pyrimidine derivatives

Pyrano-pyrimidine scaffolds have received the attention of chemists in recent decades due to their wide scope in the synthesis of molecules of biological interest.[87–90] Yousefi

et al.,[35] described the MCR of curcumin with barbituric acid **23** and aromatic aldehydes **4** in the presence of PTSA as the catalyst to provide the curcumin-based pyrano[2,3-d]pyrimidine derivatives **24** in excellent yields (82%–87%) (Scheme 7). Ganesan et al.[91] developed the synthesis of curcumin-based pyrano[2,3-d]pyrimidine derivatives **24** using oleic acid as the environment-friendly catalyst in excellent yield (87%–88%) (Scheme 7). Panahi et al.[43] reported magnetic nanoparticle-supported sulphanilic acid (MNP-SAA) catalyzed synthesis of curcumin-based pyrano[2,3-d]pyrimidine derivatives **24** in good to excellent yields (81%–90%) (Scheme 7). The MNP-SAA catalyzes the reaction by providing acidic protons of sulphanilic acid. The advantage of this protocol is operational simplicity for the isolation of the product from the catalyst by the external magnetic field. Further, Yousefi et al.[92] reported the pyrano[2,3-d]pyrimidine derivatives **24** via the same methodology with MNP-SAA catalyst at 80°C and screened for their antidiabetic properties.

Ghaffarian et al.[93] reported synthesis of curcumin-based pyrano[2,3-d]pyrimidine-2,4(3H)-dione derivatives **24** using nanocomposite based on metal-organic framework concept. The one pot multi-component cyclocondensation of curcumin **1**, aromatic aldehydes **4**, and barbituric acid **23** in the presence of $CoFe_2O_4$@OCMC@Cu(BDC) as a catalyst to **24** in shorter reaction time with excellent yield (81%–93%) (Scheme 7). Mehrabi et al.[94] reported curcumin-based pyrano[2,3-d]pyrimidine derivatives **24** via one-pot MCR of curcumin **1**, aromatic aldehydes **4**, and barbituric acid **23** using borax ($Na_2H_{20}B_4O_{17}$) (10 mol%) as a catalyst in ethanol under reflux condition in good yield (70%–88%) (Scheme 7).

Najafi et al.[95] reported the synthesis of curcumin-based pyrano[2,3-d] pyrimidine-2,4(3H)-dione derivatives **26** via a three-component reaction of curcumin **1**, aromatic aldehydes **4**, and 1,3-dimethylbarbituric acid **25** in the presence of $NiCo_2O_4$@OCMC@Zn(BDC) nanocomposite as a catalyst in high yields (79%–95%) with short time (4–6 h) (Scheme 8). The nanocomposite acts as a Lewis acid and enhances the electrophilicity of the carbonyl group of the aldehydes **4** and curcumin **1** by forming a coordinate bond.

SCHEME 6 Curcumin-based 1,4-dihydropyridine (1,4-DHP) derivatives. PTSA, *para*-toluene sulfonic acid.

2.6 | Curcumin based dihydropyrano[3,2-*b*] chromenedione derivatives

One of the most popular 3-hydroxypyran-4-one derivatives, Kojic acid, exhibits a variety of pharmacological activities and is used in the MCR to offer product diversity with enhanced medicinal properties.[96–98] Organic and medicinal chemistry researchers have expressed a significant deal of interest in the synthesis of kojic acid derivatives as a readily available and biologically active precursor.[99,100] Reddy et al.,[101] reported InCl₃-catalyzed three-component reaction of kojic acid **27**, aromatic aldehydes
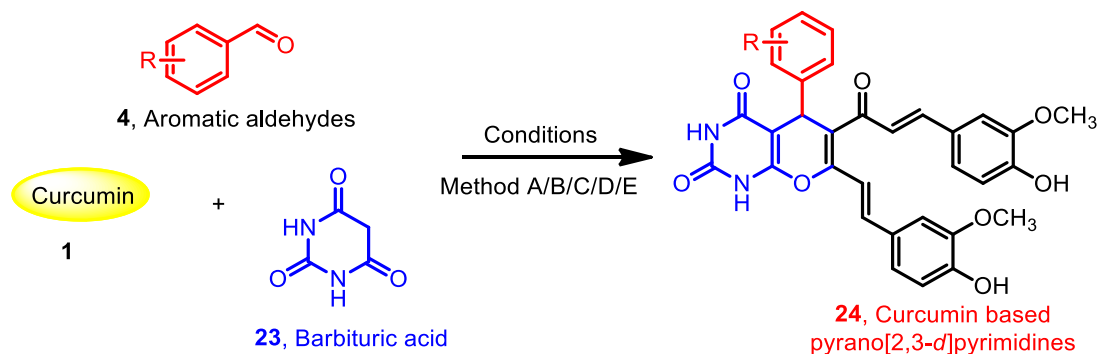
SCHEME 7 Synthesis of curcumin based pyrano[2,3-d]pyrimidine derivatives. Reagents and conditions: (A)[35] PTSA (50 mol%), EtOH, reflux, 8 h, 82%–87%; (B)[91] oleic acid, EtOH, reflux, 6 h, 87%–88%; (C)[92] MNP-SAA (10 mol%), EtOH, 80°C, 12 h, 81%–90%; (D)[93] CoFe$_2$O$_4$@OCMC@Cu(BDC) (0.003 g), EtOH, 80°C, reflux 2 h, 81%–93%; (E)[94] borax (10 mol%), EtOH, reflux, 24–36 h, 70%–88%. MNP-SAA, magnetic nanoparticle-supported sulphanilic acid; PTSA, para-toluene sulfonic acid.
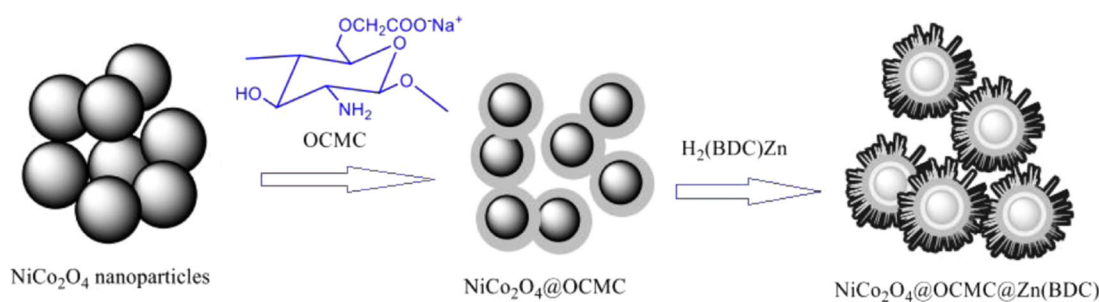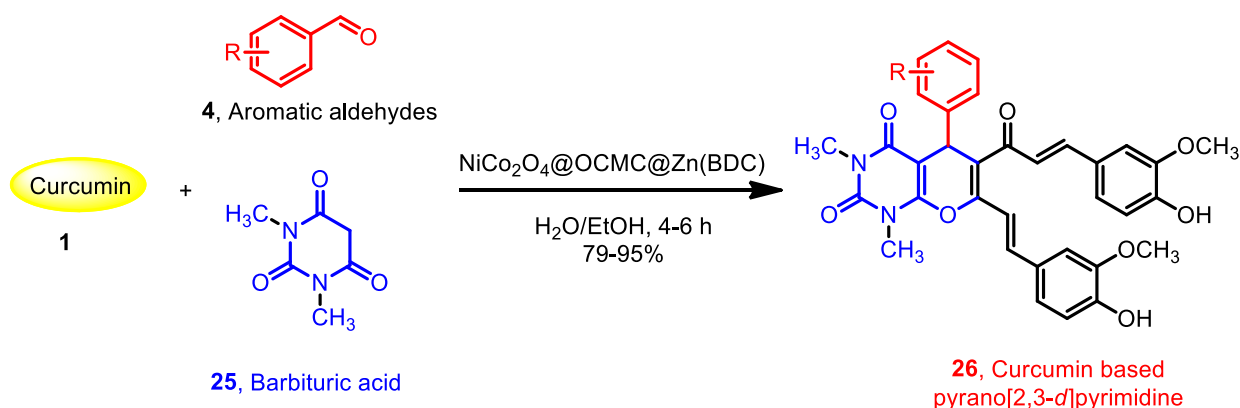
SCHEME 8 Synthesis of curcumin based pyrano[2,3-d]pyrimidine-2,4(3H)-diones using NiCo$_2$O$_4$@OCMC@Zn(BDC) nanocomposite.

4, and a curcumin 1 to the corresponding curcumin-based dihydropyrano[3,2-b]chromenedione derivatives 28 under solvent-free conditions in good yield (65%–95%) (Scheme 9).

2.7 | Curcumin-based 4H-pyran derivatives

Functionalized 4H-pyrans is a key scaffold in many natural and NP-based synthetic compounds.[102–104] Due to their structure, functionality, and biological activity, 4H-pyran derivatives are desirable molecules to study. Brahmachari and Mandal[105] reported synthesis of curcumin-based 4H-

pyrans 29 via one-pot multicomponent tandem reaction between curcumin 1, aromatic aldehydes 4, and malononitrile 17 in the presence of sodium formate in ethanol at ambient condition in 70%–81% yield (Scheme 10). The Knoevenagel adduct is formed via the reaction between malononitrile 17 and aromatic aldehyde 4 under basic sodium formate in ethanol. The enol-form of curcumin 1 reacts in situ formed Knoevenagel adduct via Michael addition followed by intramolecular ring closure to the desired product 29. Tavaf et al.[106] reported curcumin-based 4H-pyran derivatives 29 via a MCR of curcumin 1, aromatic aldehydes 4, and malononitrile 17 using PTSA (30 mol%) as a catalyst in ethanol in good yield (81%–89%) (Scheme 10).
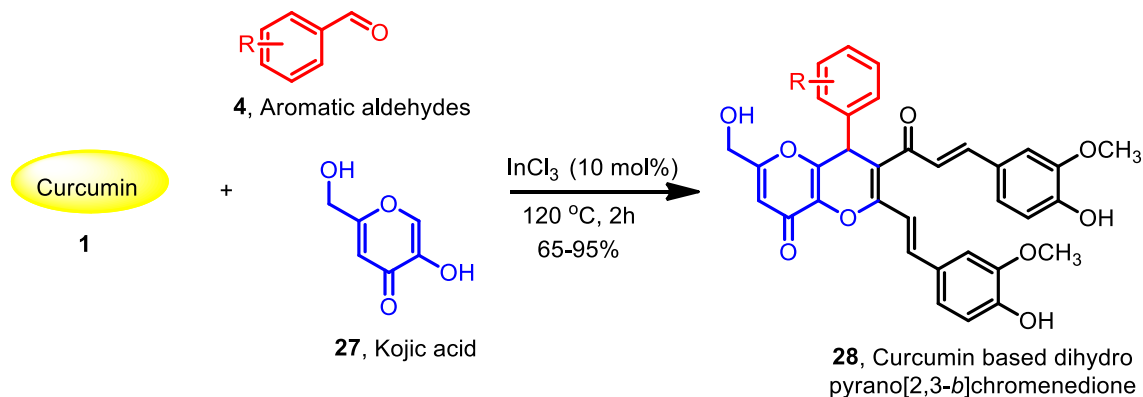
SCHEME 9 Curcumin based dihydropyrano[2,3-*b*]chromenedione derivatives.
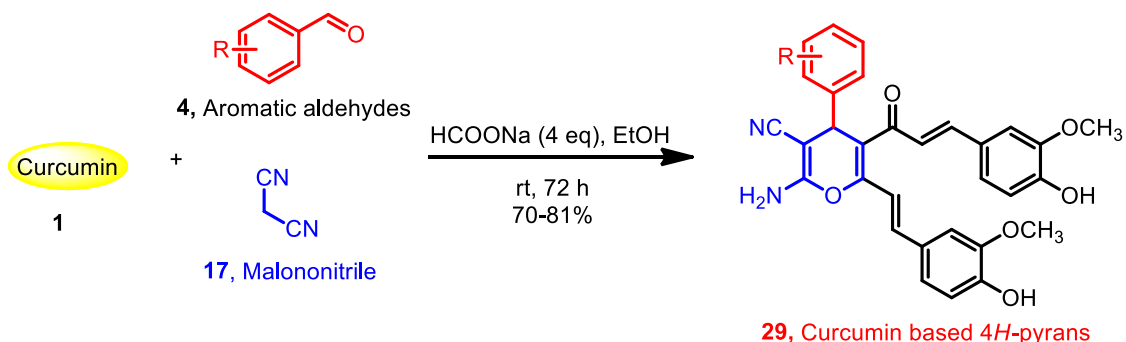
SCHEME 10 Synthesis of curcumin-clubbed 4*H*-pyran derivatives.

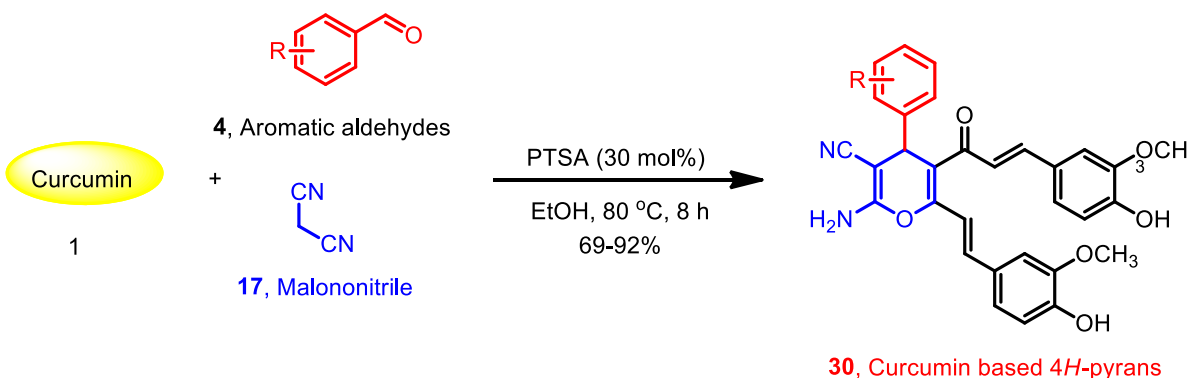**SCHEME 11** Synthesis of curcumin based 4*H* pyrans derivatives.

Dangolani et al.[86] reported curcumin-based aminocarbonitrile derivatives incorporating 4*H*-pyrans **30** via one-pot MCR of curcumin **1**, aromatic aldehydes **4**, and malononitrile **17** in the presence of PTSA with good to excellent yields (69%–92%) (Scheme 11).

2.8 | Curcuminoids-tethered coumarin derivatives

Coumarin is an important scaffold for medicinal chemistry researchers due to its unique physicochemical characteristics and the facile and adaptable way that it may be synthesized into a wide range of functionalized coumarins.[107,108] Wide range of coumarin derivatives have been synthesized and evaluated to target a variety of pharmacological targets.[109–111] Moura et al.[112] reported curcuminoid-tethered coumarin derivatives **33** via mechanochemical (ball milling method) MCR of curcumin **1**/demethoxycurcumin **2**/bisdemethoxycurcumin **3** with 4-carboxybenzaldehyde **31** and 4-hydroxycoumarin **32** in good yield (90%–92%). The reaction proceeds in two steps namely, Knoevenagel condensation followed by Michael addition reaction (Scheme 12).

Curcumin, **1**, R^1 & R^2 = OCH_3
Demethoxycurcumin, **2**, R^1 = H, R^2 = OCH_3
*Bis*demethoxycurcumin, **3**, R^1 & R^2 = H
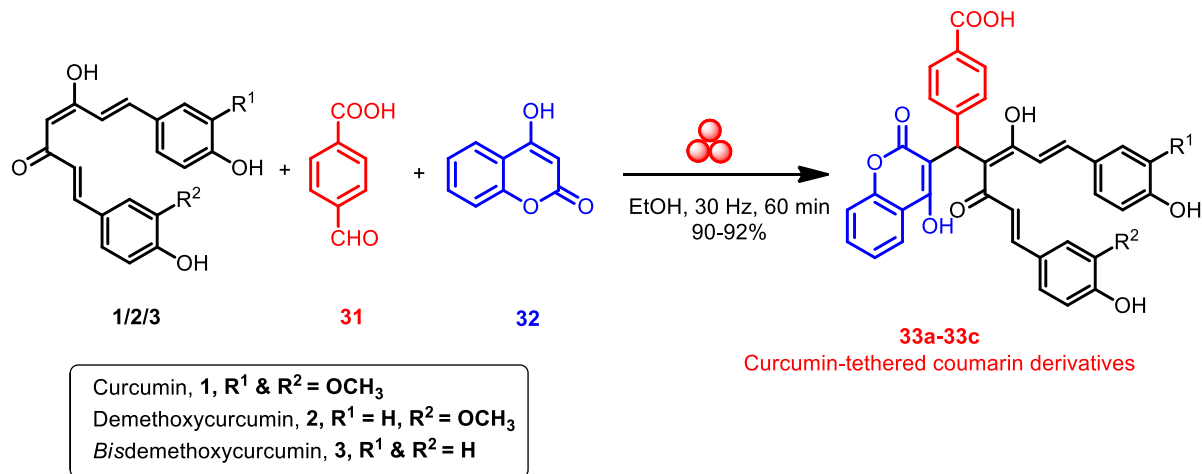
SCHEME 12   Synthesis of curcuminoid-tethered coumarin derivatives.

2.9 | Curcumin–furochromone conjugates tethered with heterocycles

Borik et al.[113] reported diversity-oriented synthesis of new curcumin–furochromone conjugates **39–42** tethered with heterocycles via MCR approach. Curcumin **1** and furochromone carbaldehyde **34** were treated with 3-amino-5-methylisoxazole **35** in ethanol to **39** with 55% yield. Furthermore, curcumin **1** and **34** were reacted with thiazol-2-amine **36** to the **40** with a 35% yield. Similarly, curcumin **1** and **34** with *p*-toluidine **37** and 1-naphthylamine **38** separately in a one-pot MCR approach under reflux conditions to the derivatives **41** and **42** in yield 36% and 47%, respectively (Scheme 13).

The functionalization on curcumin **1**, furochromone carbaldehyde **34** with hydrazines **43** gave **45** with good yield (45%–90%) (Scheme 14). Curcumin **1** and **34** on reaction with hydroxylamine hydrochloride **44** resulted to **46** in 76% yield. The one-pot three component condensation of curcumin **1**, furochromone carbaldehyde **34** with urea/thiourea **7** give **47** in 78%–88% yields. Furthermore, reactions of **1** and **34** with malononitrile **17** in one pot MCR under different conditions produce curcumin–furochromone conjugates **48** in 76% yield. Curcumin **1**, furochrome carbaldehyde **34** with hydrazine hydrate **43** and malononitrile **17** produces **49** in 87% yield (Scheme 14).

2.10 | Curcumin-based highly functionalized cyclohexene derivatives

Many NPs were use functionalized cyclohexene derivatives as their fundamental building blocks, and these molecules are the basis for useful substances with biological functions.[114,115] Bhuvaneswari et al.[116] reported an efficient one-pot multicomponent double Michael addition strategy in the presence of 1,4-diazabicyclo [2.2.2] octane **50** (10 mol%) in ethanol for the synthesis of functionalized cyclohexene derivatives **51** and **52** from curcumin **1**, aromatic

aldehydes **4** and malononitrile **17** or ethyl cyanoacetate **21** in good yield (80%–90%) (Scheme 15).

3 | PHARMACOLOGICAL ACTIVITIES OF CURCUMIN-BASED HETEROCYCLES VIA MCR APPROACH

3.1 | Antimicrobial properties

Curcumin and its heterocyclic derivatives are promising and the key template in the development of potential antimicrobial,[117] antioxidant,[118] anti-inflammatory,[119] anticancer,[120] antidiabetic,[121] anti-Alzheimer,[122] and antitubercular agents.[123–126] Synthetic manipulations on curcumin to obtain curcumin based heterocyclic compounds via MCR approach generates the molecules of enhanced therapeutic potential.[127]

Sahu et al.[42] reported curcumin-based 4*H*-pyrimido[2,1-*b*] benzothiazole derivatives displayed excellent antimicrobial activity. Compounds **53–55** (Figure 3) were the most active antimicrobial agents. Compound **53** displayed promising antifungal potential against *Aspergillus niger* and *Aspergillus fumigates* with minimum inhibitory concentration (MIC_{95}) of 10 and 15 μM/mL, respectively as compared to standard drug fluconazole (18 μM/mL). Compound **54** also active against the fungal strain *Aspergillus flavus* (MIC_{95}, 11 μM/mL). Compound **55** exhibited excellent antibacterial activity against the bacterial strain *Staphylococcus aureus* with MIC_{95} of 1.25 μM/mL as compared to standard drug ciprofloxacin (MIC_{95}, 1.25 μM/mL) (Figure 3).

The in vitro antimicrobial activity of curcumin-based-4*H*-pyrimido [2,1-*b*]benzothiazole derivatives **56–63** (Figure 4) displays potent activity against fungal and bacterial strains.[53] The antibacterial activity of compounds **56** (MIC: 30.8 μM/mL), **58** (MIC: 28.6 μM/mL), **59** (MIC: 25.7 μM/mL), and **62** (MIC: 28.5 μM/mL) were most active against bacterial strain *Bacillus cereus* as compared to standard drug ampicillin (MIC: 38 μM/mL).
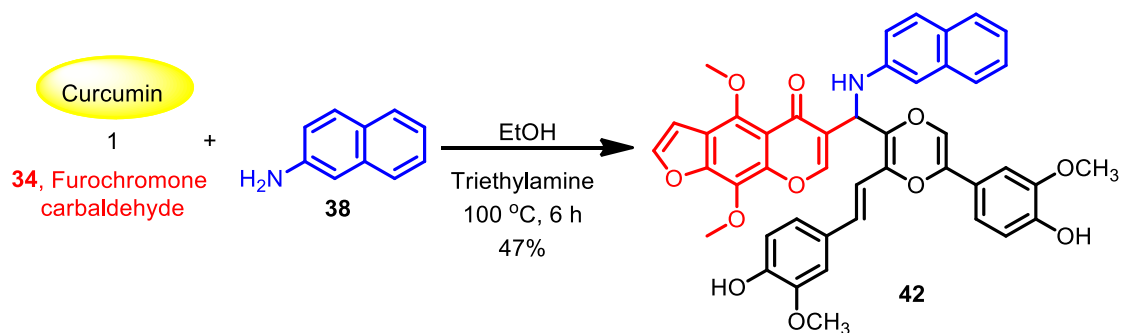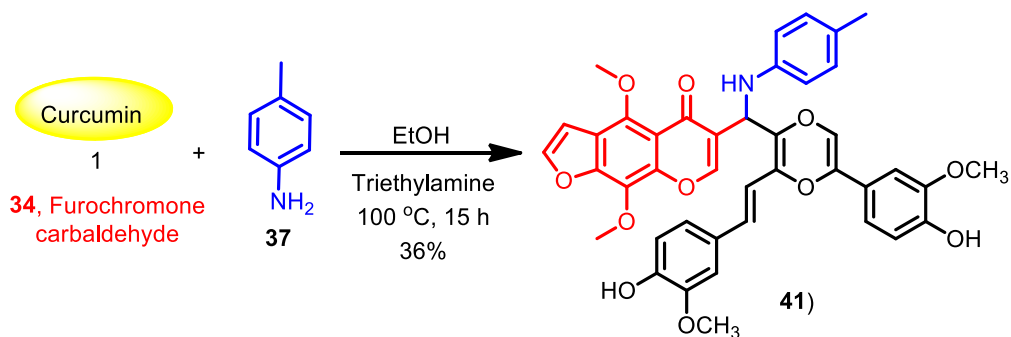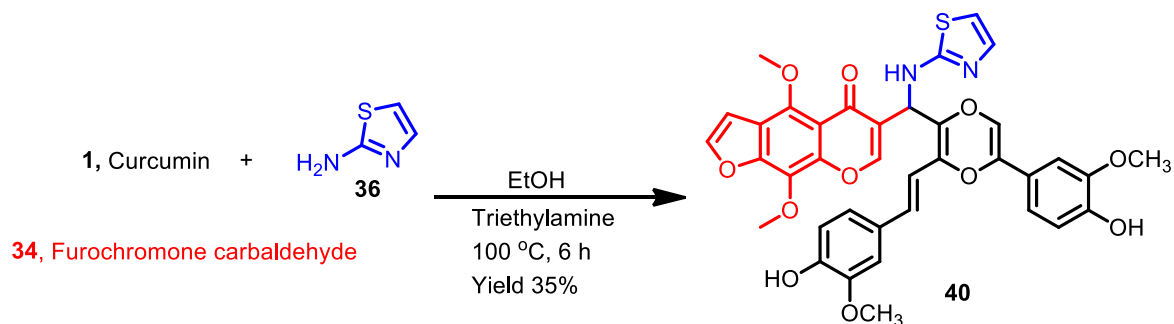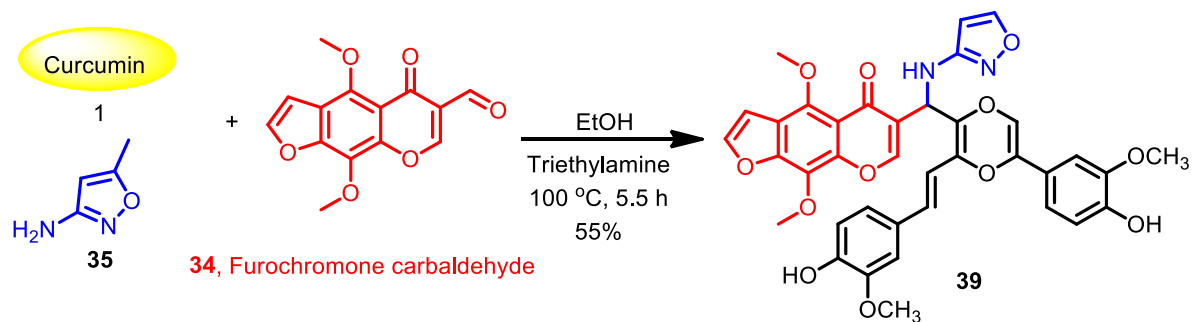
SCHEME 13 Multicomponent reaction synthesis of functionalized curcumin–furochromone conjugates.
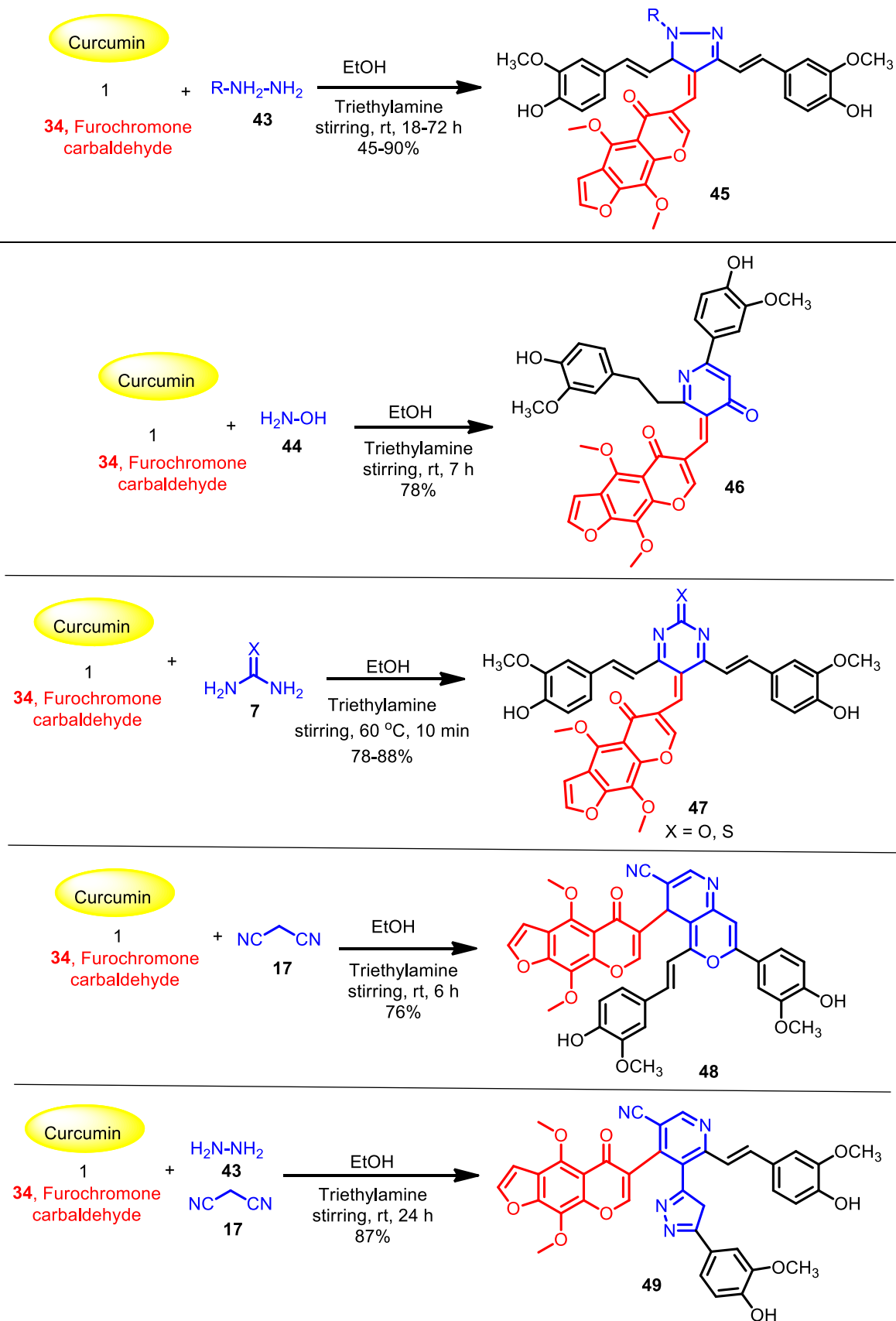
SCHEME 14 Multicomponent reaction synthesis of functionalized curcumin–furochromone conjugates.
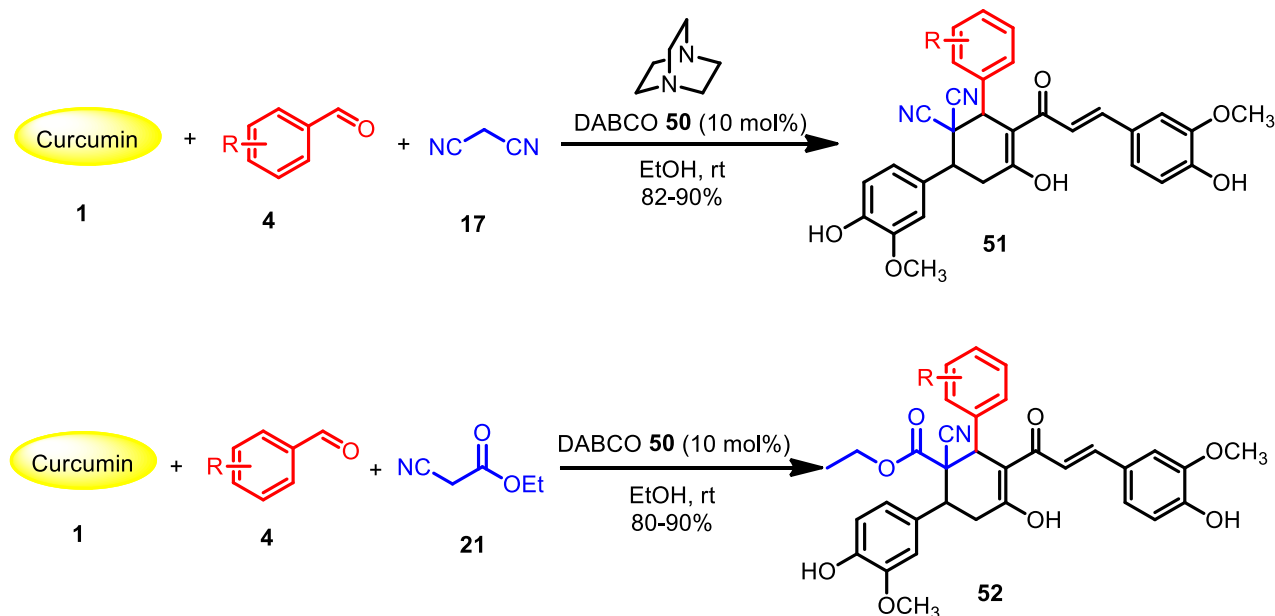
SCHEME 15 Curcumin-based functionalized cyclohexene derivatives.
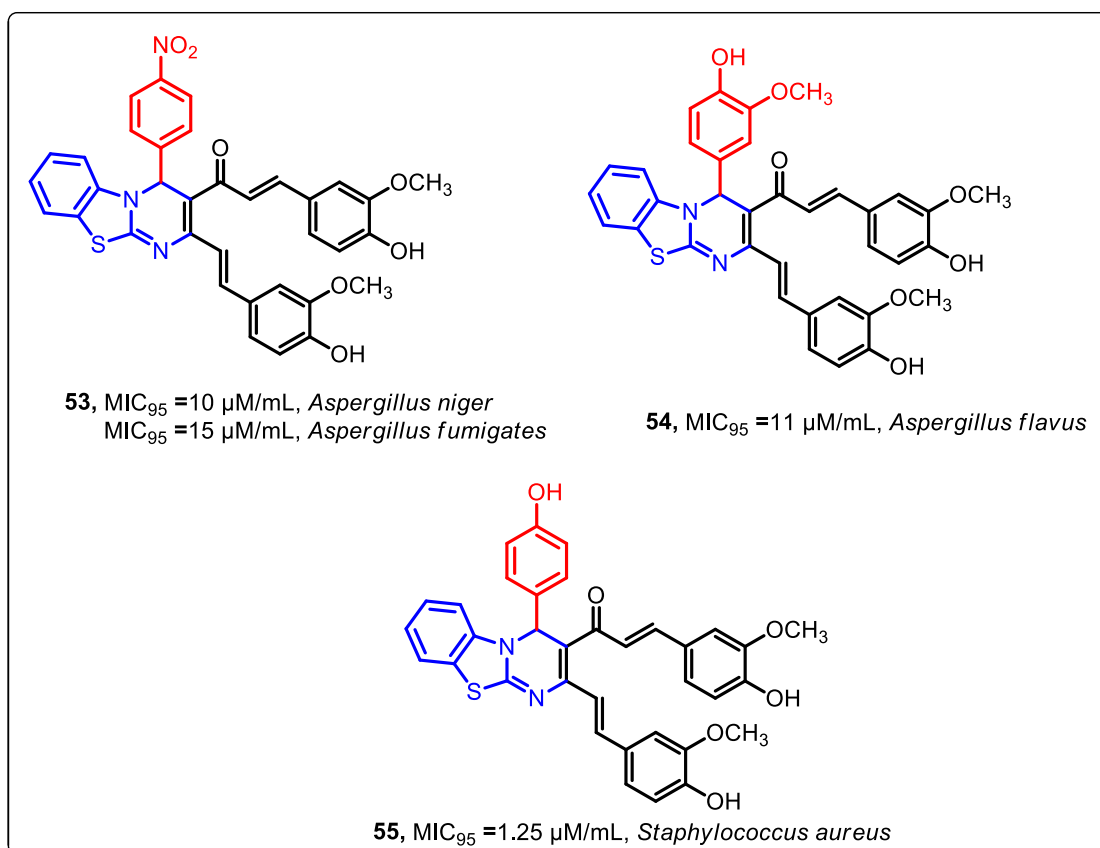
FIGURE 3 Curcumin-based 4H-pyrimido[2,1-b]benzothiazole derivatives as antimicrobial agents. MIC, minimum inhibitory concentration.

Furthermore, the compounds **56** (MIC: 56.2 µM/mL), **57** (MIC: 53.6 µM/mL), **58** (MIC: 43.2 µM/mL), **59** (MIC: 50.8 µM/mL), **60** (MIC: 62.7 µM/mL), **62** (MIC: 40.8 µM/mL), and **63** (MIC: 30.0 µM/mL), were active against bacterial strain *S. aureus* as

compared to ampicillin (MIC: 64 µM/mL). Moreover, the compounds **56** (MIC: 50.6 µM/mL), **57** (MIC: 48.6 µM/mL), **58** (MIC: 37.1 µM/mL), **59** (MIC: 44.3 µM/mL), **60** (MIC: 56.1 µM/mL), **62** (MIC: 47.8 µM/mL), and **63** (MIC: 32.5 µM/mL) were active
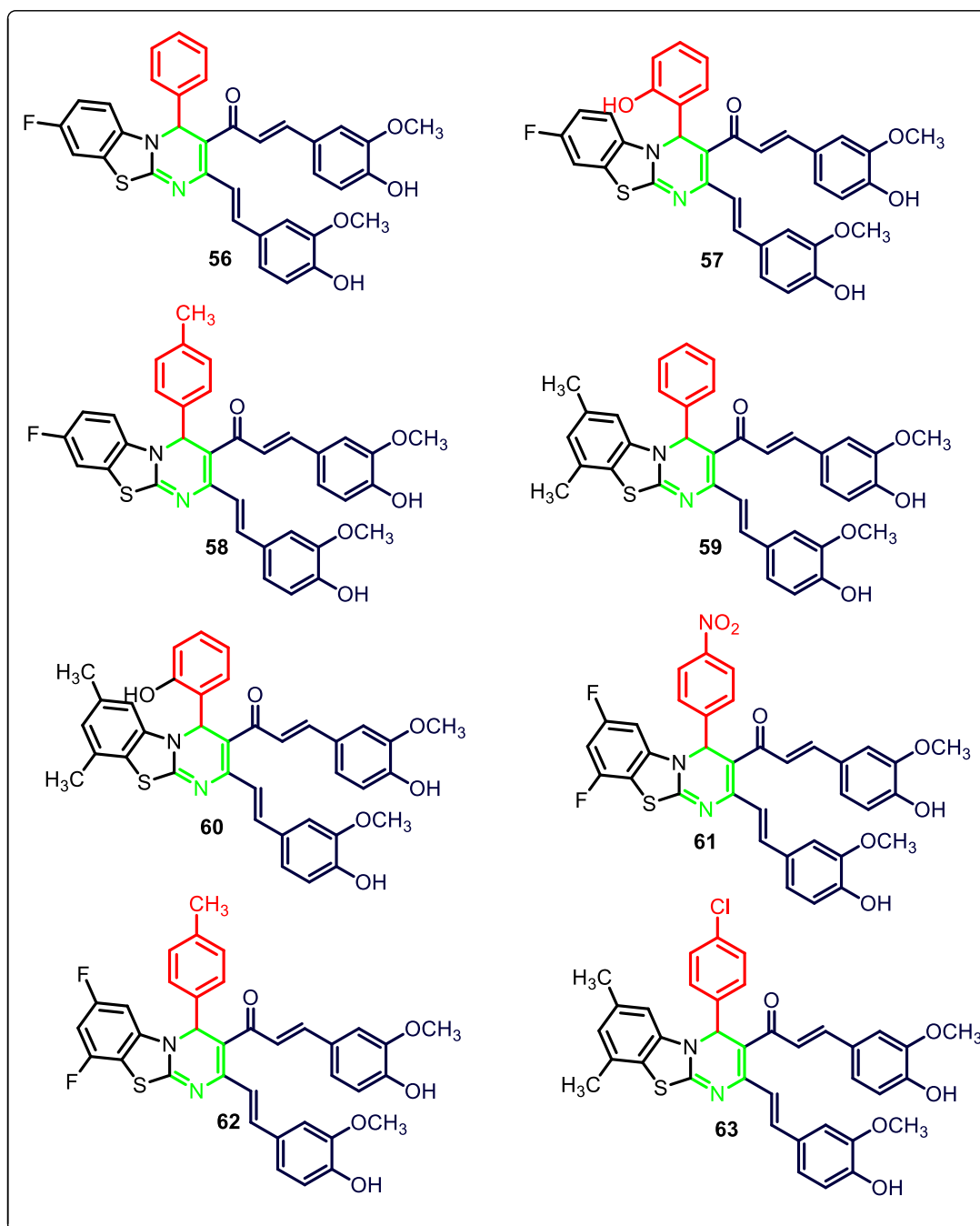
FIGURE 4 Most active antimicrobial curcumin based *4H*-pyrimido [2,1-*b*]benzothiazole derivatives.

against bacterial strain *Pseudomonas aeruginosa* as compared to ampicillin (MIC: 60 µM/mL). The antifungal activity of compounds **56** (MIC: 31.6 µM/mL), **57** (MIC: 26.5 µM/mL), **58** (MIC: 30.4 µM/mL), **59** (MIC: 24.3 µM/mL), **60** (MIC: 36.1 µM/mL), and **63** (MIC: 32.8 µM/mL) were most active against a fungal strain *A. niger* as compared to the standard drug fluconazole (MIC: 36.3 µM/mL). The compounds **56** (MIC: 36.2 µM/mL), **57** (MIC: 34.8 µM/mL), **58** (MIC: 26.2 µM/mL), **59** (MIC: 37.6 µM/mL), **60** (MIC: 39.5 µM/mL), **62** (MIC: 30.5 µM/mL), and **63** (MIC: 35.5 µM/mL) were most active against a fungal strain *Alternaria solani* as compared to fluconazole (MIC: 40.3 µM/mL).

Furthermore, the compounds **56** (MIC: 33.4 µM/mL), **57** (MIC: 30.3 µM/mL), **58** (MIC: 21.1 µM/mL), **59** (MIC: 34.8 µM/mL), **60** (MIC: 36.2 µM/mL), **62** (MIC: 32.4 µM/mL), and **63** (MIC: 30.5 µM/mL) were most active against a fungal strain *Fusarium culmorum* as compared to fluconazole (MIC: 36.3 µM/mL). In addition, the compounds **56** (MIC: 31.2 µM/mL), **57** (MIC: 29.4 µM/mL), **58** (MIC: 30.3 µM/mL), **59** (MIC: 25.9 µM/mL), **60** (MIC: 47.6 µM/mL), **61** (MIC: 38.7 µM/mL), **62** (MIC: 25.4 µM/mL), and **63** (MIC: 35.5 µM/mL) were most active against a fungal strain *Rhizopus stolonifer* as compared to fluconazole (MIC: 40.3 µM/mL).
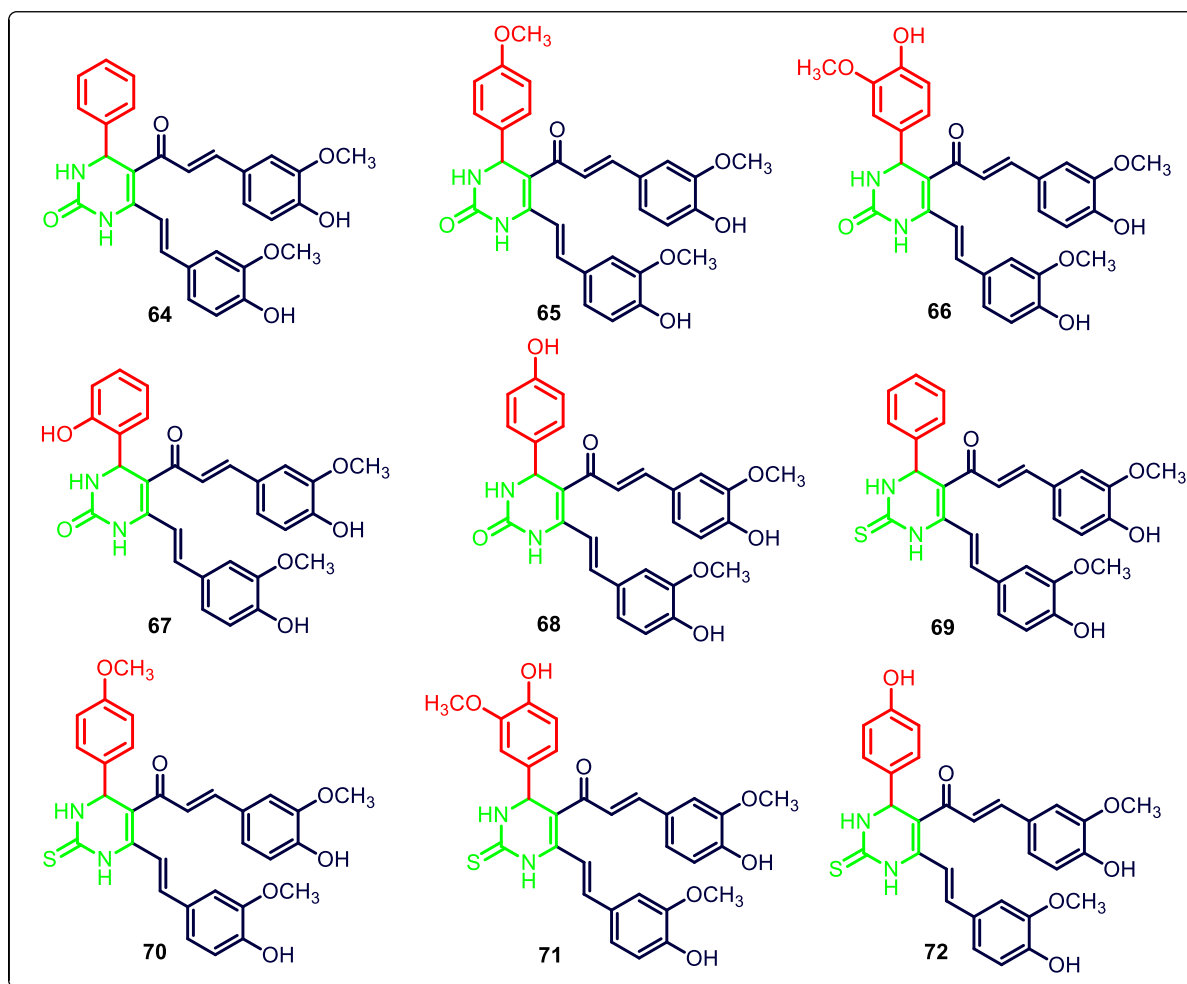
FIGURE 5 Structures of curcumin-based 3,4-DHPM derivatives with antimicrobial activity.
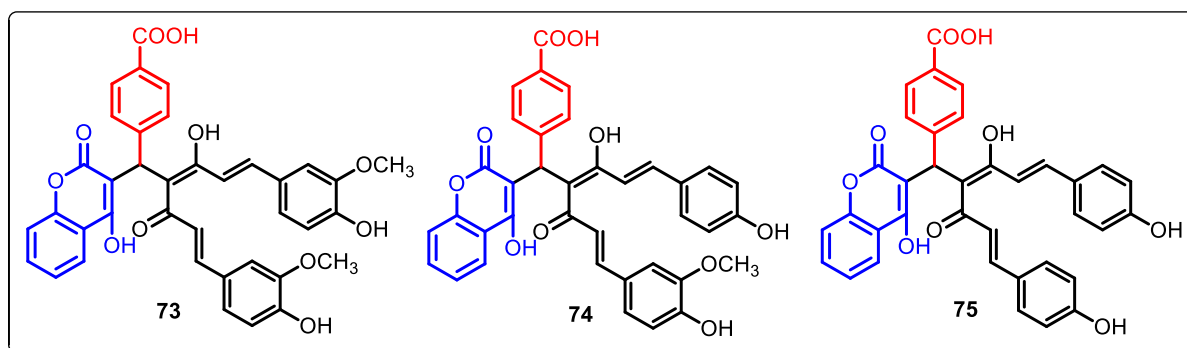
FIGURE 6 Curcuminoid-tethered-coumarin derivatives with antibacterial activity.

The antifungal and antibacterial activity of curcumin-based 3,4-DHPMs derivatives were reported by Lal et al.[72] The compounds **64**, **67**, and **68** (Figure 5) were most active and equipotent against the bacterial strain *Escherichia coli* with MIC of 20 µM/mL as compared to ampicillin (MIC: 20 µM/mL).

Compound **70** (Figure 5) exhibited fourfold promising activity with MIC of 20 µM/mL against *Burkholderia pseudomallei* (ampicillin, MIC: 80 µM/mL). Against the bacterial strain *Pseudomonas aeruginosa*, the

compound **64** displayed MIC: 80 µM/mL. Compound **68** displayed potential against *Salmonella typhi* (MIC: 20 µM/mL, ampicillin MIC: 20 µM/mL). The compounds **64** (MIC: 40 µM/mL), **66** (MIC: 40 µM/mL), **68** (MIC: 20 µM/mL), **69** (MIC: 40 µM/mL), and **71** (MIC: 40 µM/mL) were the most active against *S. aureus* as compared to ampicillin (MIC: 40 µM/mL). Further, antifungal activity for the compounds **65**, **68**, **70**, **71**, and **72** with MIC: 40 µM/mL, better than fluconazole (MIC: 80 µM/mL) and most active against *A. flavus* (Figure 5).

65, R = -4-OCH_3

66, R = -3-OCH_3, -4-OH

76, R = -4-Cl
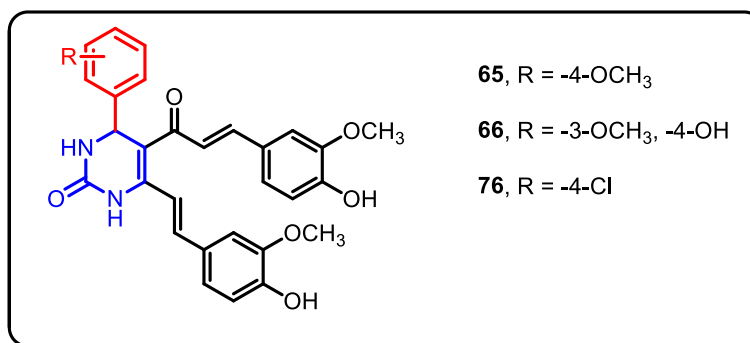
FIGURE 7 Anticancer curcumin based 3,4-DHPM derivatives. DHPM, dihydropyrimidones

77, IC_{50} = 12.5 μM (HCT-116)

78, IC_{50} = 12.5 μM (HCT-116 & QG-56)

79, IC_{50} = 12.5 μM (QG-56)

80, IC_{50} = 12.5 μM (HeLa)
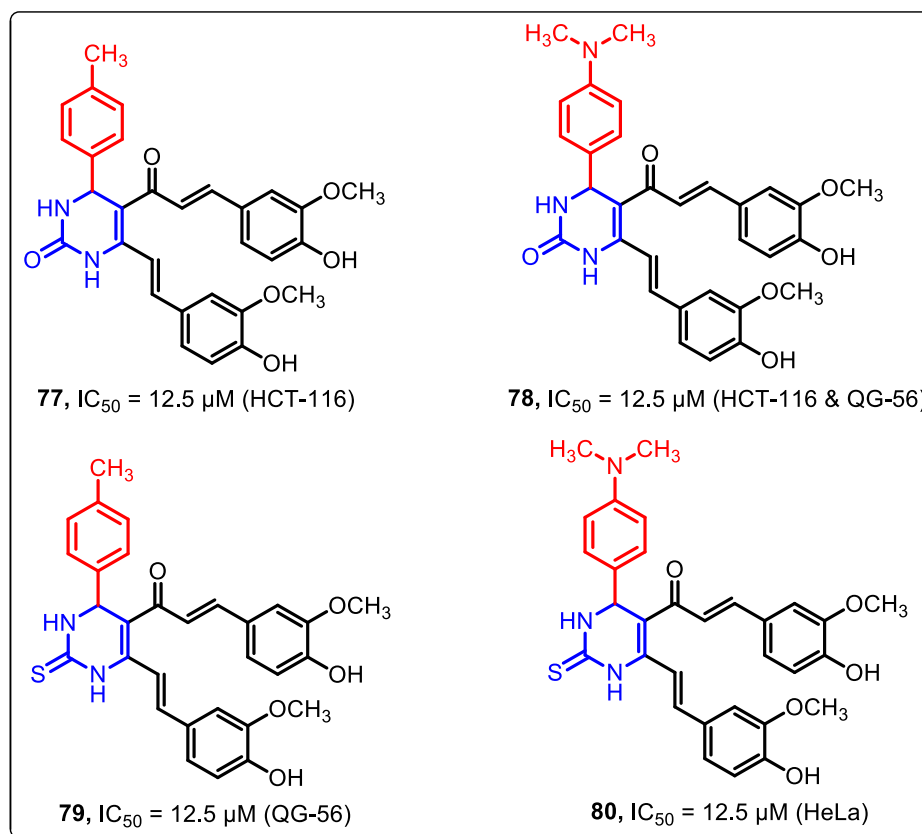
FIGURE 8 Curcumin-based 3,4-DHPM/thiones/imines as anticancer agents. DHPM, dihydropyrimidones; IC_{50}, half maximal inhibitory concentration.

The curcuminoid-tethered coumarin derivatives **73–75** (Figure 6) were displayed[112] antibacterial activity against *S. aureus* with MIC of 2.94 μM/mL and fourfold active as compared to curcumin. However, these compounds **73–75** are inactive against *E. coli*.

3.2 | Anticancer properties

Curcumin has received great attention over the last two decades as an anticancer agent.[17,128–130] Recent literature revealed that DHPMs exhibited a broad spectrum of anticancer activity.[131,132]

The curcumin-based 3,4-DHPMs displayed[72] potential cytotoxicity against Hep-G2 (human hepatocarcinoma), human colorectal carcinoma cell line (HCT-116, human colon carcinoma), and human lung carcinoma cell lines (QG-56). The compounds **64**, **66**, and **68** (Figure 5) displayed moderate cytotoxicity as compared to adriamycin and better cytotoxicity as compared to curcumin. Compound **64** was active against Hep-G2 and HCT-116 cells with a half maximal inhibitory concentration (IC_{50}) value of 25 μM/mL (adriamycin IC_{50}: 2.5–5.0 μM/mL). Compound **66** displayed an IC_{50} value of 25 μM/mL against Hep-G2 and compound **68** exhibited an IC_{50} value of 25 μM/mL against Hep-G2 and IC_{50} value of 12.5 μM/mL against HCT-116 cells.

40, IC_{50} = 20 µg/mL (MCF-7)

41, IC_{50} = 23 µg/mL (MCF-7)

47a, IC_{50} = 18 µg/mL (HEPG2)

47b, IC_{50} = 22 µg/mL (HEPG2)
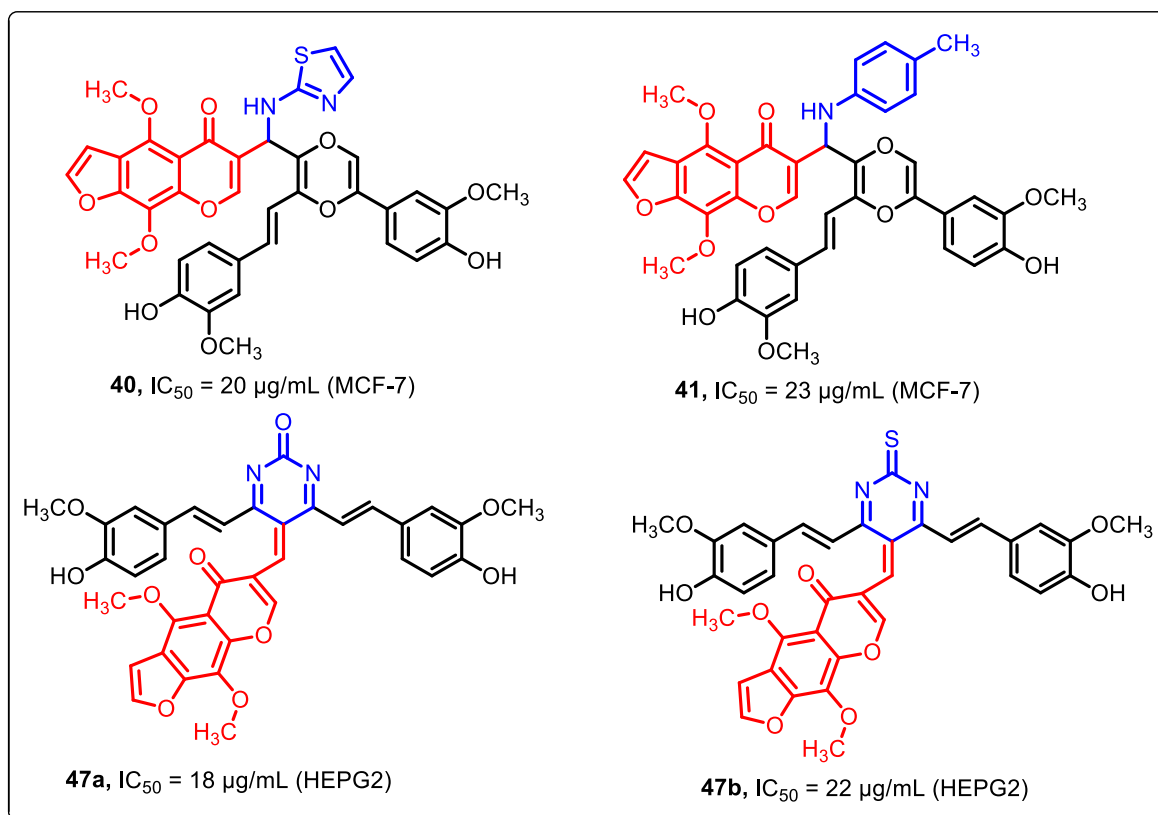
FIGURE 9 Most active anticancer heterocyclic curcumin derivatives. IC_{50}, half maximal inhibitory concentration.

81, 15 µM/mL (MCF-7)

82, 10 µM/mL (MCF-7)
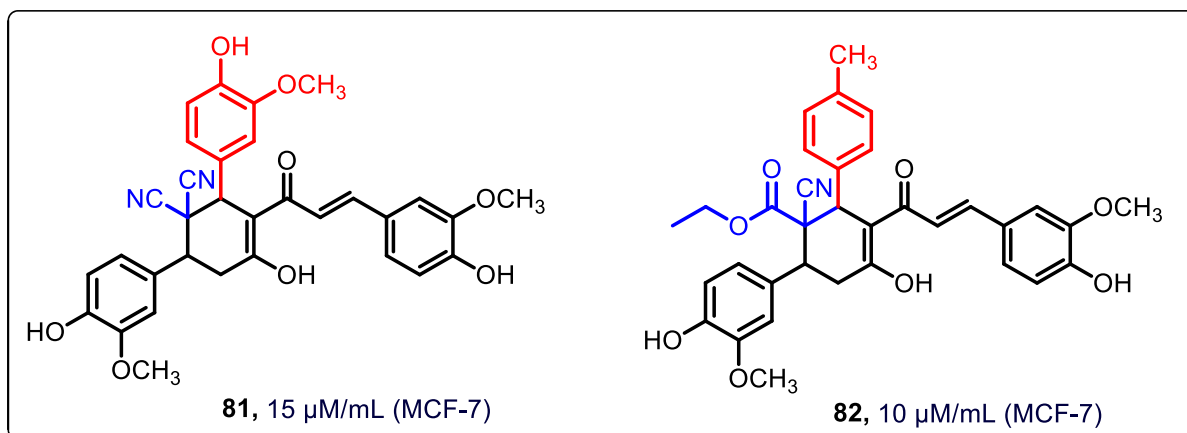
FIGURE 10 Most active anticancer curcumin-derived highly functionalized cyclohexene derivatives.

Sharma et al.[70] synthesized the curcumin-based 3,4-DHPM derivatives **65**, **66**, and **76** (Figure 7) and displayed anticancer activity. Compound **65** showed maximum activity with a mean growth percent (GP) of 88.90, compound **66** with a mean GP of 91.80 and 76 with a mean GP of 95.29. The compound **65** was highly active on the human breast cancer cell line (MDA-MB231, GP = 55.45), human prostate cancer cell line (PC-3, GP = 58.50), human glioblastoma cell line (SNB-75, central nervous system [CNS] cancer, GP = 59.60), human myeloma cell lines (RPMI-8226, leukemia, GP = 60.07), human acute T lymphoblastic

leukaemia (MOLT-4, GP = 64.11), human Caucasian acute lymphoblastic leukemia cell line (CCRF-CEM; leukemia, GP = 72.84) and triple-negative breast cancer epithelial cell line (HS-578T, breast cancer, GP = 73.39). The compound **66** showed maximum activity on HT-29 (colon cancer, GP = 54.06), SNB-75 (CNS cancer, GP = 65.81), MDA-MB231 (breast cancer, GP = 67.70), and CCRF-CEM (leukemia, GP = 69.79), while compound **76** showed maximum activity on RPMI-8226 (leukemia, GP = 72.79), MOLT-4 (leukemia, GP = 73.57), MDA-MB231/ATCC (breast cancer, GP = 73.63), and SNB-75 (CNS cancer, GP = 75.49).

64, (IC$_{50}$, 1.72 µg/mL)   **67,** (IC$_{50}$, 2.14 µg/mL)   **87,** (IC$_{50}$, 2.36 µg/mL)

68, (IC$_{50}$, 2.72 µg/mL)   **88,** (IC$_{50}$, 3.86 µg/mL)   **89,** (IC$_{50}$, 2.91 µg/mL)

69, (IC$_{50}$, 1.58 µg/mL)   **90,** (IC$_{50}$, 1.96 µg/mL)   **91,** (IC$_{50}$, 2.12 µg/mL)

72, (IC$_{50}$, 2.59 µg/mL)   **92,** (IC$_{50}$, 3.42 µg/mL)   **93,** (IC$_{50}$, 2.76 µg/mL)

94, (IC$_{50}$, 1.86 µg/mL)   **95,** (IC$_{50}$, 2.71 µg/mL)   **96,** (IC$_{50}$, 2.84 µg/mL)
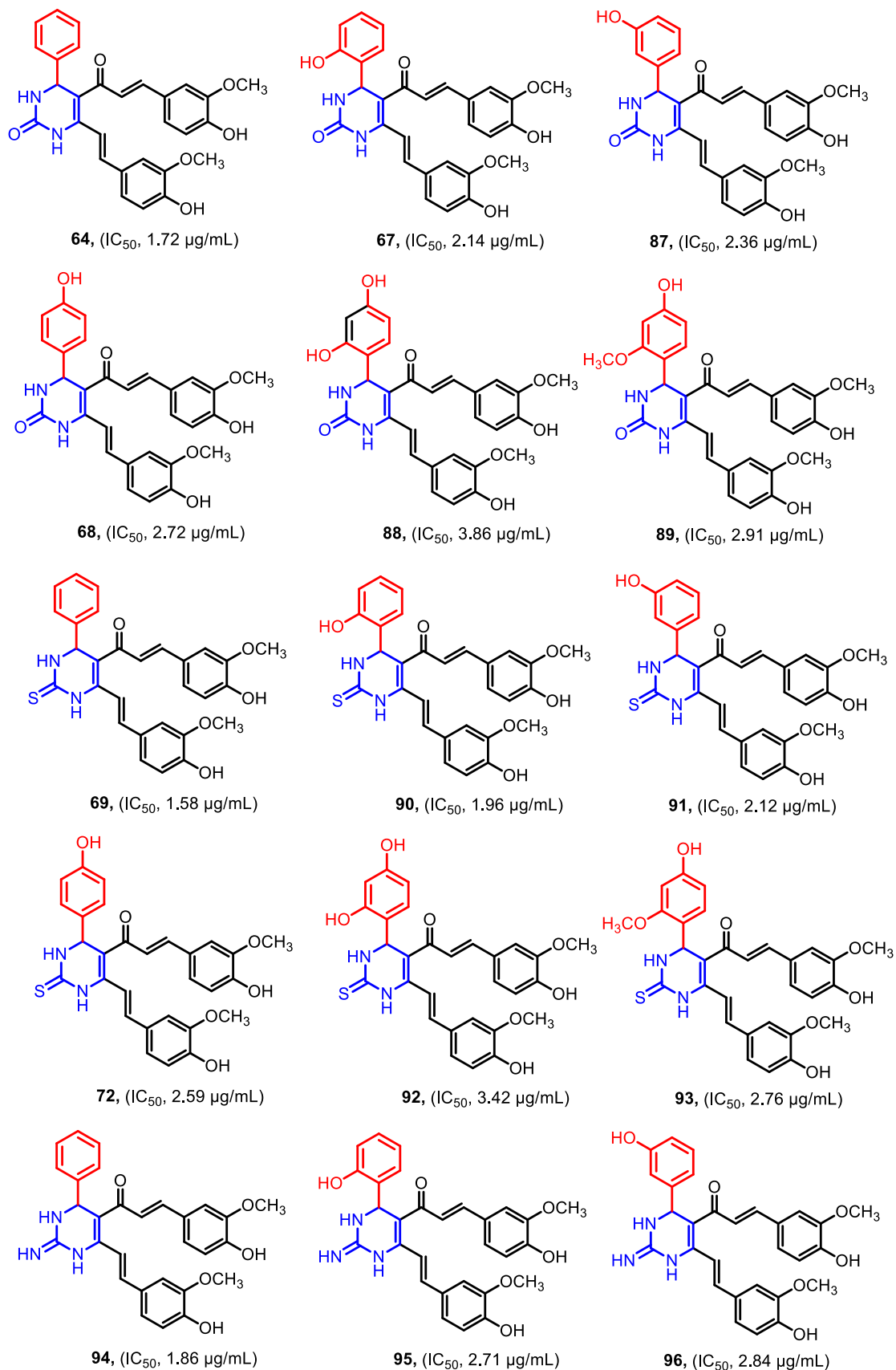
FIGURE 11   Antioxidant activity of curcumin-based 3,4-DHPM derivatives. DHPM, dihydropyrimidones; IC$_{50}$, half maximal inhibitory concentration.

93, (IC$_{50}$, 13.9 ± 0.10 & 16.9 ± 0.11 µg/mL)   **94,** (IC$_{50}$, 17.4 ± 0.65 µg/mL)   **95,** (IC$_{50}$, 17.0 ± 0.11 µg/mL)
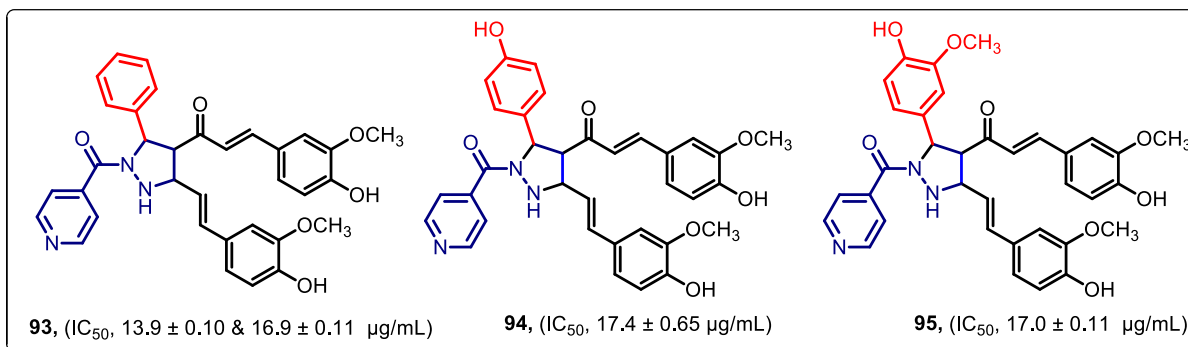
FIGURE 12   Antioxidant activity of curcumin-derived derivatives. IC$_{50}$, half maximal inhibitory concentration.

96
4.563 ± 0.122 µM, Antioxidant   **97**
5.082 ± 0.031 µM, Antioxidant   **98**
3.686 ± 0.076 µM, Antioxidant
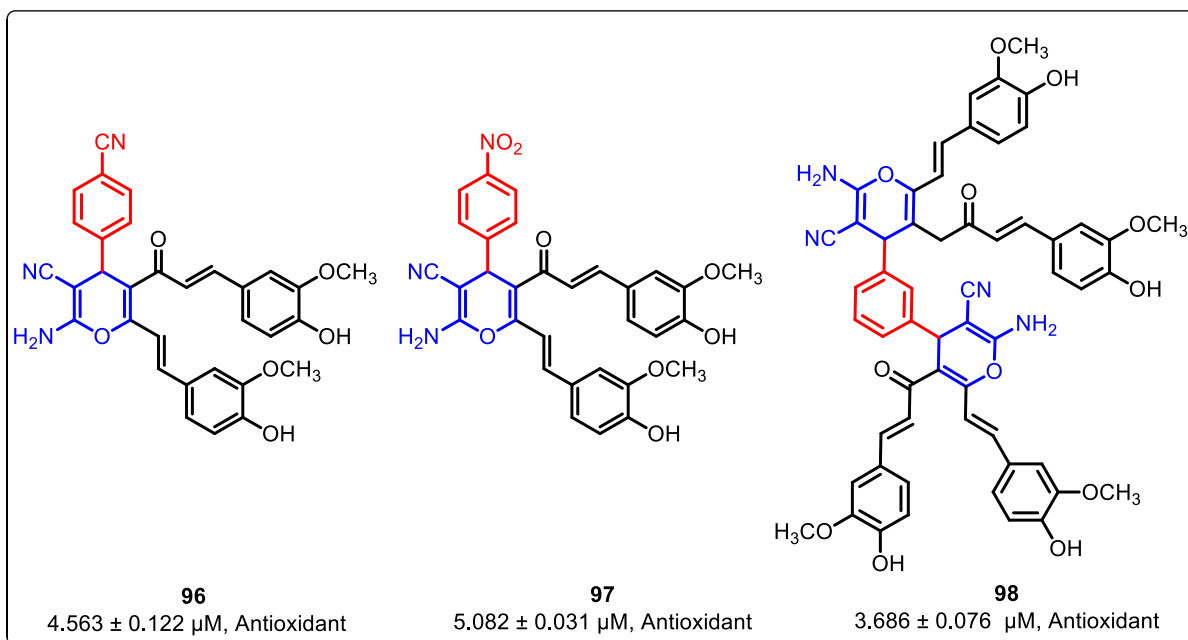
FIGURE 13   Antioxidant curcumin based 4*H*-pyran derivatives.

The cytotoxicity of curcumin based-3,4-DHPM/thiones were reported[73] using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay (MTT) assay against HeLa, HCT-116, and QG-56 cells. The compound **80** (Figure 8) was active against HeLa cells with an IC$_{50}$ value of 12.5 µM as compared to standard curcumin and adriamycin (IC$_{50}$: 12.5 µM & 50 µM, respectively).

The compound **77**, **78**, and **80** were active against HCT-116 cells with IC$_{50}$ 12.5 µM (curcumin, 50 µM and adriamycin, 5 µM). The compounds **78** and **79** were most active against cancer cell line QG-56 (IC$_{50}$: 12.5 µM) (Figure 8).

Borik et al.[113] reported heterocyclic derivatives of curcumin and screened for in vitro anticancer activity against human hepatocellular carcinoma (Hep-G2) and breast carcinoma (MCF-7) cell lines using the MTT calorimetric assay.[133] Doxorubicin (DOX) and 5-fluorouracil (5-FU), were used as reference drugs. The compound **40** and **41** displayed potential cytotoxicity against MCF-7 with IC$_{50}$ values of 20 and 23 µg/mL, respectively (standard: 5-FU, IC$_{50}$:

13.35 µg/mL). The compound **47a** and **47b** displayed potential cytotoxicity against Hep-G2 with IC$_{50}$ values of 18 and 22 µg/mL, respectively (DOX, IC$_{50}$: 14.70 µg/mL) (Figure 9).

Bhuvaneshwari et al.[116] reported curcumin-derived highly functionalized cyclohexene derivatives **81** and **82** cytotoxicity activity against human breast cancer cells (MCF-7) and normal human breast cells (HBL-100) via MTT assay. The compound **81** and **82** exhibited a dose-dependent decline in the viability of MCF-7 cells with IC$_{50}$ values 15 and 10 µM/mL, respectively. However, these compounds were not cytotoxic to HBL-100 at exposure up to µM/ mL suggesting their selectivity at lower concentrations (Figure 10).

3.3 | Antioxidant activity

Curcumin has been proven to be an antioxidant agent.[134,135] The antioxidant potential[75] of curcumin-based 3,4-DHPM/thione/
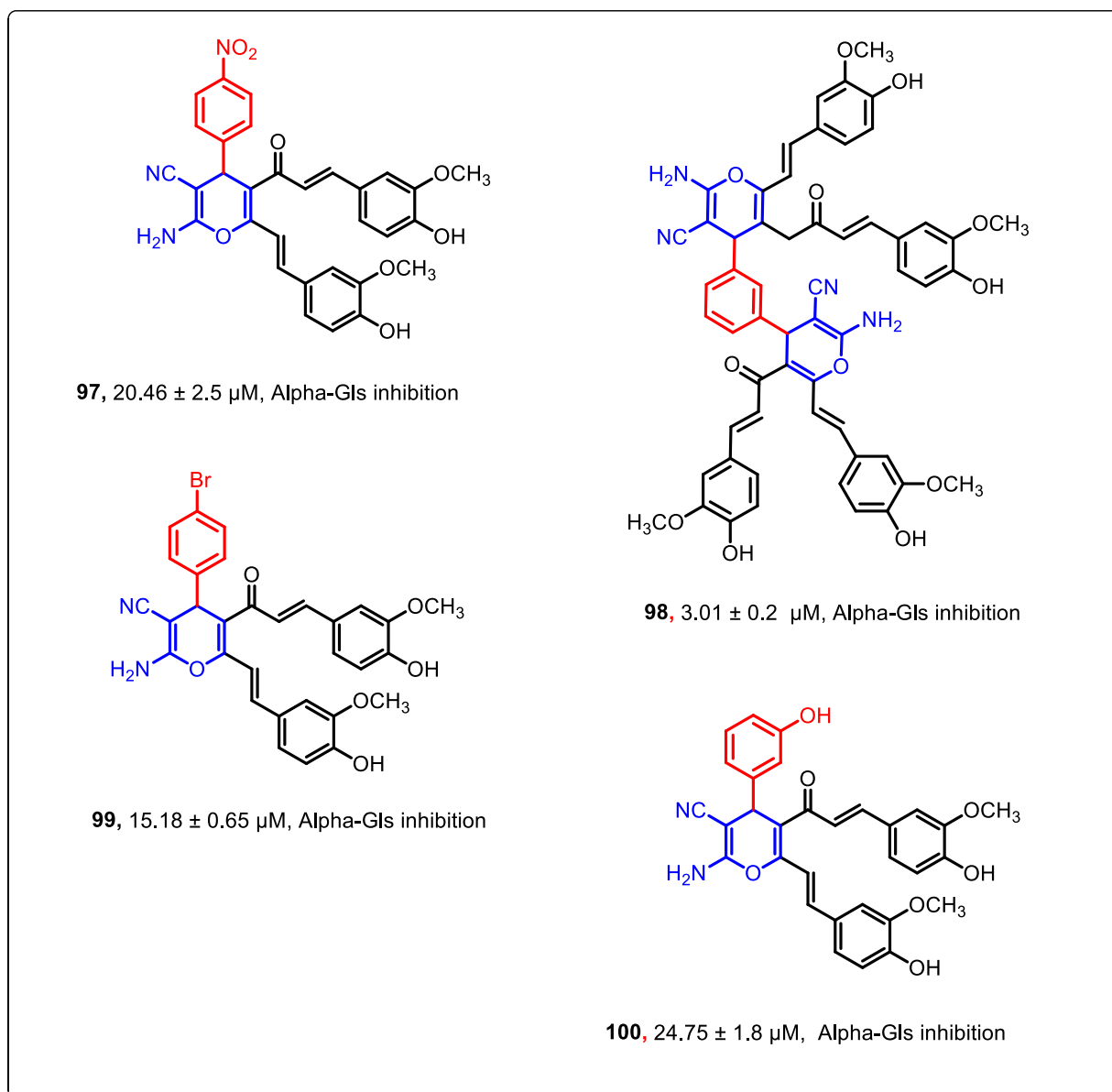
FIGURE 14 Antidiabetic activity of curcumin-4*H*-pyran derivatives.

imines by the ferric reducing ability of plasma assay showed that the compounds **68**, **72**, **83–85**, and **87–92** (Figure 11) were more potent than curcumin (standard). The compounds **64**, **67–69**, **72**, and **84–92** showed more antioxidant activity than ascorbic acid, and the compounds **68**, **72**, **84**, and **88** were more antioxidant than quercetin. The antioxidant activity by the cupric reducing antioxidant capacity method showed that the compounds **64**, **67–69**, **72**, and **84–92** were of greater antioxidant capacity than ascorbic acid. The compounds **67**, **68**, **72**, **84–88**, and **90–92** showed greater antioxidant capacity than curcumin. The compounds **68**, **84**, and **88** displayed greater antioxidant activity than quercetin. In the deoxyribose radical scavenging activity assay, the antioxidant potential of the compounds **64**, **67–69**, **72**, and **84–92** were greater than curcumin (IC$_{50}$: 1.01 µg/mL). The compounds **67**, **68**, **72**, **83–85**, and **87–92** exhibited greater antioxidant activity than quercetin (IC$_{50}$: 1.72 µg/mL). The compound

84 showed greater antioxidant activity than ascorbic acid (IC$_{50}$: 3.76 µg/mL) (Figure 11). The curcumin-based 4-aryl-3,4-DHPM/thiones derivatives[38] **84** and **88** showed antioxidant activity using 2,2-diphenyl-1-picrylhydrazyl assay (DPPH) radical scavenging assay and were most active (IC$_{50}$: 2.91 & 3.42 µg/mL) as compared to ascorbic acid (IC$_{50}$: 0.1 µg/mL) (Figure 11).

Goyal et al.[136] reported the antioxidant activity of curcumin-derived derivatives using DPPH and hydroxyl radical scavenging assay. The compound **93** (IC$_{50}$: 13.9 ± 0.10 and 16.9 ± 0.11 µg/mL), **94** (IC$_{50}$: 17.4 ± 0.65 µg/mL), and **95** (IC$_{50}$: 17.0 ± 0.11 µg/mL) displayed significant radical scavenging activity as compared to standard drug ascorbic acid (IC$_{50}$: 11.6 ± 0.14 µg/mL) and butylated hydroxytoluene (IC$_{50}$: 14.3 ± 0.11 µg/mL) (Figure 12).

Tavaf et al.[106] reported curcumin-derived 4*H*-pyran derivatives for in vitro antioxidant activity using Trolox (vitamin E analog) as a
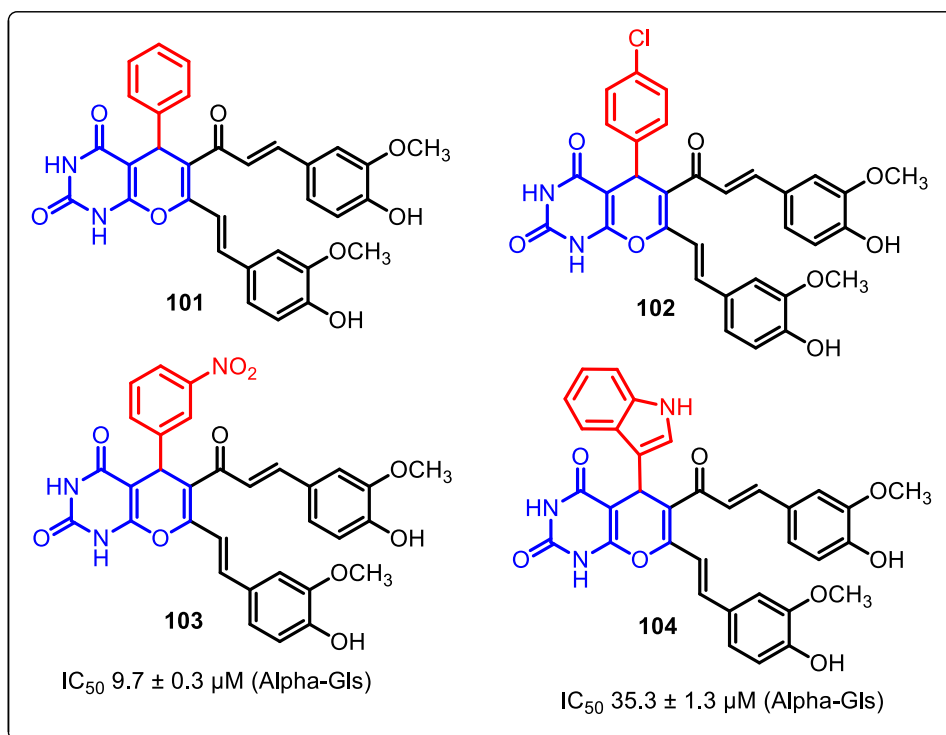
FIGURE 15 Antidiabetic activity of curcumin based-pyrano[2,3-*d*] pyrimidine-2,4(3*H*)-diones. IC$_{50}$, half maximal inhibitory concentration.
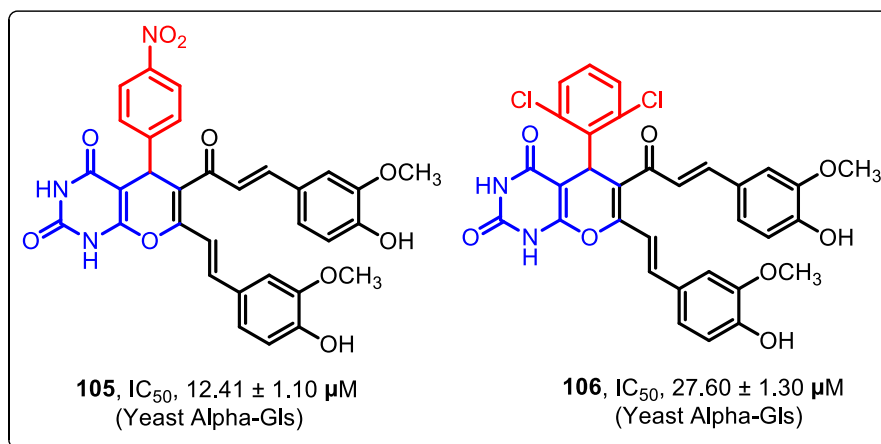
FIGURE 16 Antidiabetic activity of curcumin based pyrano[2,3-*d*]pyrimidine derivatives. IC$_{50}$, half maximal inhibitory concentration.

standard.[137] The compounds **96**, **97**, and **98** exhibited higher antioxidant activity with standard deviations of 4.563 ± 0.122, 5.082 ± 0.031, and 3.686 ± 0.076 µM, respectively. The higher antioxidant activity of these compounds may be due to the presence of strong electron-withdrawing groups (NO$_2$ and CN) present on the aromatic ring and aldehyde (Figure 13).

3.4 | Antidiabetic properties

Curcumin is used to create new inhibitors to limit the activity of α-glucosidase (α-Gls) and α-amylase (α-Amy). It is an important

therapeutic approach not only to block dietary carbohydrate absorption but also to take advantage of their additional health-promoting properties. Curcumin displays a number of positive effects on diabetes. The recent findings suggest that curcumin can be used as a key component in the creation of new antidiabetic medications.[138,139]

The curcumin-based 4*H*-pyran derivatives[106] **97–100** (Figure 14) were evaluated for in vitro antidiabetic activity by measuring inhibition of α-Amy and α-Gls enzymes. The compounds **97–100** displayed improved inhibition against α-Gls with IC$_{50}$ values of 20.46 ± 2.5, 15.18 ± 0.65, 24.75 ± 1.8, and 3.01 ± 0.2 µM, respectively. The compounds **96–100** exhibited lower than 20% inhibitory
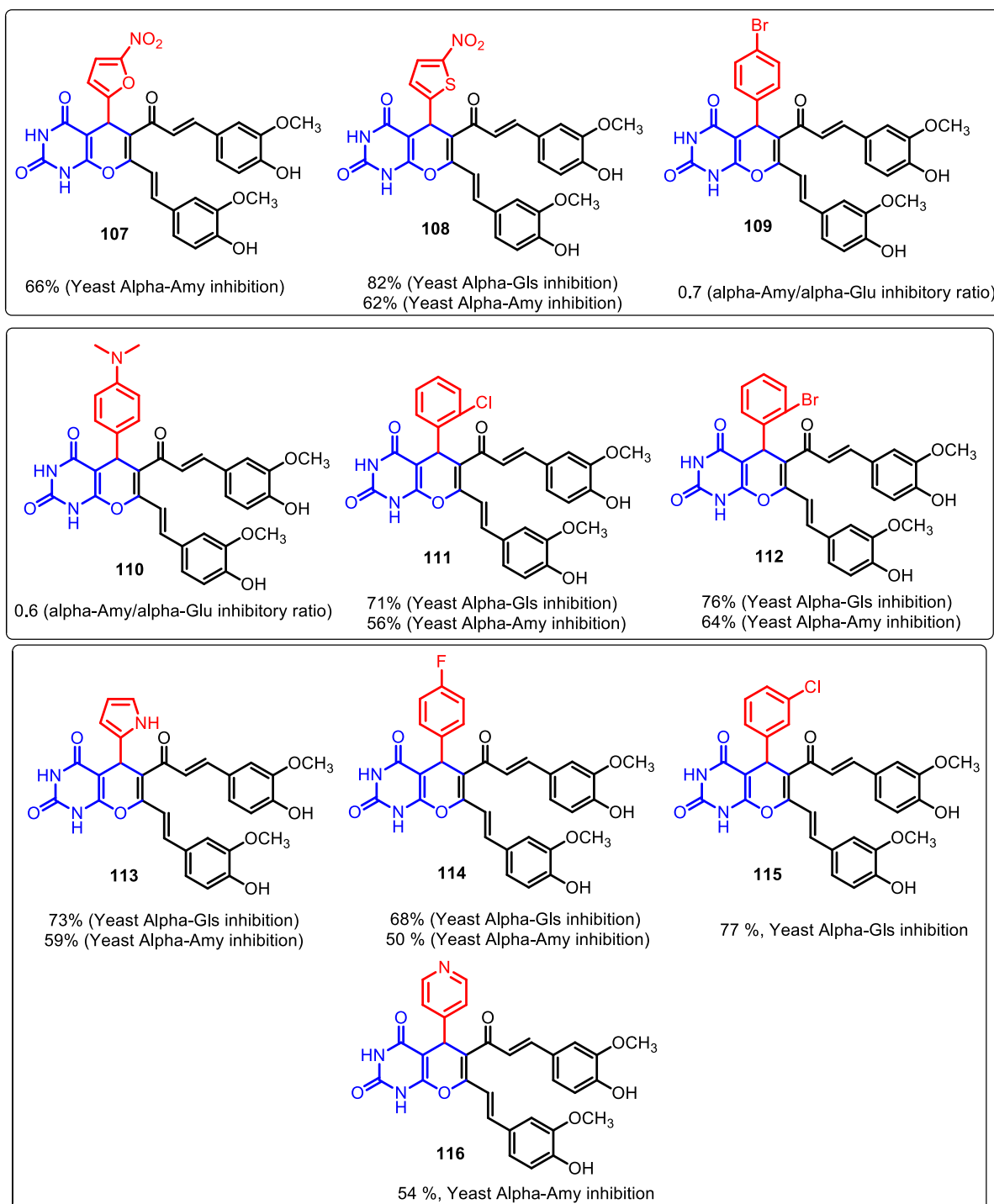
FIGURE 17 Antidiabetic curcumin based pyrano[2,3-*d*]pyrimidine derivatives.

activity against enzyme α-Amy and in turn is much less than standard drug acarbose.

The antidiabetic properties of curcumin-based pyrano[2,3-*d*] pyrimidine derivatives **101–104** (Figure 15) by using α-Amy and α-Gls inhibition was reported.[35] The compounds **103** and **104** displayed inhibition against yeast α-Gls with IC_{50} values 9.7 ± 0.3 and 35.3 ± 1.3 μM, respectively. The inhibitions of α-Amy show that compound **101** and **102** have similar inhibitory action against α-Amy

as compared to the marketed drug acarbose. The compound **103** and **104** displayed moderate inhibition against mouse α-Amy indicates the usefulness of these derivatives in minimizing side effects of existing antidiabetic drugs.

The curcumin-based pyrano[2,3-*d*]pyrimidine derivatives were re-ported for their inhibitory activity against α-Amy and α-Gls enzymes.[92] The compounds **105** (IC_{50}: 12.41 ± 1.10 μM) and **106** (IC_{50}: 27.60 ± 1.30 μM) efficient inhibits both yeast α-Gls as compared to the
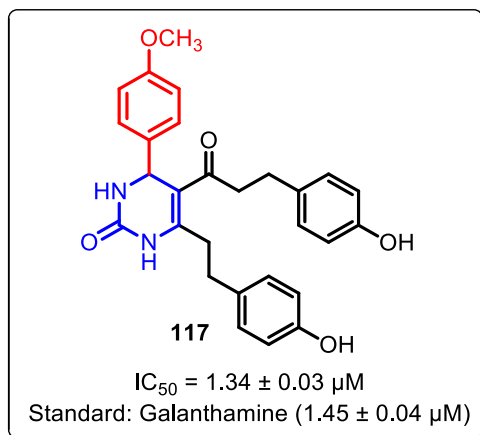
FIGURE 18 Most active THBDC-based DHPM analog. DHPM, dihydropyrimidones; THBDC, tetrahydrobis demethoxycurcumin.

drug acarbose (IC$_{50}$: 206.57 µM). Acarbose inhibits mouse α-Gls with IC$_{50}$ value of 26.54, while the compound **105** and **106** inhibits mouse α-Gls with the IC$_{50}$ values of 106.80 and 46.04 µM, respectively. Also, the compound **105** and **106** displayed minimum (15%) inhibition against pancreatic α-Amy and important in terms of minimizing the possible gastrointestinal side effects (Figure 16).

Mehrabi et al.[94] reported the curcumin-based pyrano[2,3-*d*]pyrimidine derivatives for their inhibition against α-Amy and α-Gls enzymes. The compounds **108**, **111**–**115** displayed potential inhibition of α-Glu enzyme than curcumin, and the compounds **107**, **108**, **111**–**114**, and **116** were the strongest inhibitors of α-Amy enzyme (Figure 17).

The compound **109** had the lowest IC$_{50}$ value for both enzymes. The compounds **109** and **110** displayed lower values of α-Amy/α-Glu inhibitory ratio. The compound **110** exhibited the strongest antioxidant properties and minimum inhibition of α-Amy can be used for further studies for the treatment of diabetes mellitus.

3.5 | Acetylcholinesterase inhibitory (AChE) properties

Curcuminoids are considered as useful in Alzheimer's disease (AD) and possess AChE and memory-enhancing activities.[22,140] Arunkhamkaew et al.[79] reported THC, THDC, and THBDC-DHPM analogs. These derivatives were studied as AChE for AD. The inhibitory activity of the analog **117** against the AChE, revealed that THBDC-clubbed-DHPM bearing a 4-OCH$_3$ phenyl group has a highly effective inhibitory activity of AChE with an excellent IC$_{50}$ value of 1.34 ± 0.03 µM, and marginally potent than standard galanthamine (Figure 18).

4 | CONCLUSION AND FUTURE PERSPECTIVES

This review highlights the synthetic methodologies for curcumin-based heterocycles via MCRs, where curcumin was used as one of the reactant. Therefore, many efficient approaches for the synthesis of curcumin-based pyrimido-benzothiazoles, DHPMs, DHPs, pyrano-pyrimidines, 4*H*-pyrans, coumarins, and chromone derivatives were documented. The second section discusses medicinal attributes of curcumin-based heterocycles via MCR approach such as antimicrobial, anticancer, antioxidant, antidiabetic, and AChE inhibitory activities. In view of the numerous advantages and methodologies for curcumin-based heterocycles such as use of homogeneous, heterogeneous, mixed metal oxides and microwave irradiation requires harsh reaction conditions and longer reaction time with lower yields. Hence, there is a need of more efficient and green catalyst for the synthesis of curcumin-based heterocycles in minimum time with higher yield. Though the molecules via MCR approach have some pharmacological properties, there is a need of more pharmacological screening for their therapeutic properties.

CONFLICTS OF INTEREST STATEMENT

The authors declare no conflicts of interest.

ORCID

Bapurao B. Shingate http://orcid.org/0000-0001-7207-0794

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