REVIEW

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Recent advancements in the multicomponent synthesis of heterocycles integrated with a pyrano [2,3-*d*]pyrimidine core

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Heterocyclic compounds incorporated with a pyranopyrimidine skeleton have received substantial consideration owing to their privileged, and intelligible biodiversity. Accordingly, this review highlights the multicomponent synthetic routes adopted to prepare heterocyclic compounds incorporated with the pyrano[2,3-*d*]pyrimidine skeleton in the preceding two years. The different sections comprise the synthesis of bicyclic, tricyclic, polycyclic, and spirocyclic systems along with the estimation of the probable mechanistic routes for the reaction pathways. Commonly, the pyran ring closure was the major

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idea of most studies, and the mechanistic pathways of these reactions involved Knoevenagel condensation, Michael addition, and intramolecular cyclocondensation. Besides, the significant biological potency of the compounds recently synthesized from multicomponent reactions is deliberated.

1. Introduction

Pyranopyrimidines are a class of heterocyclic compounds comprising a pyrimidine ring with two nitrogen atoms at "1,3-positions" fused to a pyran ring with one oxygen atom. Numerous isomers are found that include this class of compounds, including 5H-pyrano[2,3-d]pyrimidines, 8H-pyrano[3,2-d]pyrimidines, 8H-pyrano[3,4-d]pyrimidines, and 5H-pyrano[4,3-d]pyrimidines without a conceivable location of a nitrogen atom at the ring junction (Fig. 1). Alternatively, pyranopyrimidine heterocycles have significant and confidential biological and physiological potency since this class of compounds demonstrated antibacterial, antitumor,[1–3] antimicrobial,[4–7] anti-inflammatory,[8,9] antioxidant, antidiabetic,[10,11] tyrosine phosphatase inhibitors,[12] antitubercular,[13] Hh signaling inhibitors in NIH3T3 cells,[14] antihypertensive,[15] antimalarial,[16] antiviral,[17] anticancer,[18,19] and cardiotonic agents.[20,21]

In another route, pyranopyrimidines act as sirtuin inhibitors, for instance, the inhibition activity of SIRT1 was formerly reported by Rotili et al.[22] as shown in Fig. 2 (compounds V–VII). Therefore, due to the distinct biological importance of this class of compounds, its preparation has been targeted in different ways in many types of studies by incorporating other heterocyclic rings or by incorporating the nucleus of derivatives that have multiple biological properties such as the introduction of the curcumin nucleus in the design of the bicyclic pyranopyrimidine nucleus (Fig. 2, compounds VIII–X).[23–28] In addition,

compounds XI displayed potent antimicrobial activities against the diverse bacterial, and fungal species, along with cytotoxic activity against Caco-2 cancerous cell lines complemented with lower cell viability.[29] Furthermore, compound XII showed inhibition toward human immunodeficiency virus type 1 (HIV-I) integrase.[30,31]

The common approach for the synthesis of heterocycles with pyrano[2,3-d]pyrimidine nucleus generally involves multicomponent reactions of barbituric acid, malononitrile, and aryl aldehydes in the presence of a base.[32–34] Consequently, there is a demanding necessity for the synthesis of novel heterocyclic analogs with a pyranopyrimidine core through the reaction of varied cyclic 1,3-dicarbonyl compounds, owing to the noteworthy significance of pyranopyrimidine analogs in pharmaceutical, and biological areas. The prospects of the research were focused on finding novel strategies of suitable conditions, short reaction time, ease of catalyst preparation, efficient catalyst, ease of product purification, accessible reagent, and green protocols. Consequently, based on the above-mentioned findings and in the permanence of our attention on the chemistry of bicyclic systems,[35,36] we focus on highlights in this review, the recent progress in the multicomponent, and multistep synthesis of pyrano[2,3-d]pyrimidines including the discussion of the diverse approaches, reaction conditions, products yields, the proposed mechanisms for the pyranopyrimidine ring construction, and biological profiles.

2. Synthesis of bicyclic systems

In this section, bicyclic pyranopyrimidines positioned the researcher's interest for finding the most reliable conditions for the synthesis of these compounds with improved yields of the products, with the hope also to find a safe catalyst with simple preparation or non-catalytic or solvent-free green conditions. Also, the ease of the separation and purification of the products is preferred over applying the recommended method. In this section, besides, we highlighted the literature on multicomponent synthesis of bicyclic pyranopyrimidines with enaminoester, and enaminonitrile moieties. Accordingly, Oftadeh et al.[37] reported the multicomponent synthesis of pyranopyrimidines with an enaminoester motif under catalytic conditions of the SbCl5/nano-sawdust nanocatalyst. Thus, one-pot three-component reactions of aryl aldehydes with ethyl cyanoacetate and barbituric acid in a mixture of water, and ethanol yielded the respective pyranopyrimidines 1a–j (Scheme 1).

These compounds (Scheme 1) were formerly synthesized under other conditions.[38,39] On the other hand, Shirini, and Kamali,[40] reported the synthesis of pyranopyrimidinone analogs under catalytic conditions using $Fe_3O_4/g-C_3N_4$ nanocomposites in aqueous media. The nanocatalyst is simply prepared, recyclable, and provides reduced reaction time and high product yields.

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I: 5H-pyrano[2,3-d]pyrimidine
II: 8H-pyrano[3,2-d]pyrimidine
III: 8H-pyrano[3,4-d]pyrimidine
IV: 5H-pyrano[4,3-d]pyrimidine
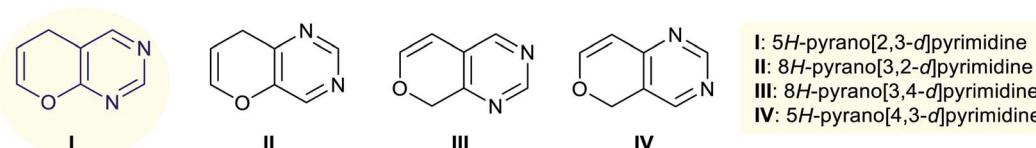
Fig. 1 Possible isomeric structures of pyranopyrimidines.

In another route, the researchers' interests were focused on the synthesis of enaminonitriles of this type of bicyclic pyranopyrimidines owing to the high stability of the nitrile group relative to the ester group. Consequently, Behzadi et al.[41] reported the synthesis of pyranopyrimidine **2a–j** (Scheme 1) bicyclic systems with an enaminonitrile moiety at the pyran ring by a green protocol involving the utility of mefenamic acid as a catalyst. Therefore, reactions of aryl aldehydes with malononitrile, and barbituric acid in ethanol at reflux temperature gave the desired pyranopyrimidines with improved yields (90–98%). The method in this research tended to improve the yields of the products more than that reported in other methods of these compounds.[27,42,43] Also, this method benefits more than the previous method by Oftadeh et al.,[37] in which pyranopyrimidines were prepared with improved yields (R = H, 4-Cl, 3-NO₂, 4-NO₂, 4-Me). The reason for amended yields maybe not be associated with the catalyst efficiency but can be attributed to the nature of enaminoesters relative to the enaminonitrile products.

Successively, Abd-Elaziz et al.[29] have conveyed a simple route for the synthesis of hexahydro-2H-pyrano[2,3-d]pyrimidines **3**. Therefore, three-component one-pot reactions of N,N-diarylthiobarbituric acids with benzaldehyde, and malononitrile or

ethyl cyanoacetate in ethanol/TEA provided the anticipated pyranopyrimidines **3** in reasonable yields. The base enabled the condensation step between benzaldehyde and active methylene and subsequently increased the reactivity of thiobarbituric acids for Michael addition by active methylene proton abstraction (Scheme 2).

The compounds **3a,b** (Scheme 2) displayed potent antibacterial activities against *Bacillus pumilis* (**3a**: 11.3 ± 0.6; **3b**: 16.3 ± 0.6 mm (MIC: 15.6 µg mL⁻¹)), *Streptococcus faecalis* (**3a**: 12.3 ± 0.6; **3b**: 21.7 ± 0.6 mm), *Escherichia coli* (**3a**: 18.3 ± 0.6; **3b**: 20.3 ± 0.6 mm (MIC: 3.91 µg mL⁻¹)), and *Enterobacter cloacae* (**3a**: 21.7 ± 0.6; **3b**: 20.7 ± 0.6 mm), and antifungal potent activities against *Candida albicans* (**3a**: 21.7 ± 0.6; **3b**: 19.3 ± 0.6 mm "MBC = 4 × MIC"), and *Aspergillus niger* (**3a**: 12.3 ± 0.6 (MIC: 15.6 µg mL⁻¹)); (**3b**: 11.3 ± 0.6 mm "MBC = 4 × MIC"). In addition, compound **3b** (IC₅₀ = 138.07 ± 8.21 µg mL⁻¹) exhibited potent cytotoxic activity on Caco-2 cancerous cell lines along with the lowest cell viability percentage at the higher sample concentration applying MTT assay.[29]

A series of formerly reported,[44,45] tetrahydro-2H-pyranopyrimidines **4** were proficiently synthesized in good yields (82–97%) by one-pot multicomponent reactions of N,N-dimethyl barbituric acid with aryl aldehydes and malononitrile in MDW


V: X= O, R= Ph
VI: X= O, R= H
VII: X= S, R= Ph

VIII
Antituberculosis agent

IX
Antidiabetic agent

X
Antioxidant agent

XI
Ar= 4-Me-C₆H₄, 4-OMe-C₆H₄;
X= CO₂Et, CN
Antibacterial, and cytotoxic agents

XII
(HIV-I) integrase inhibitor
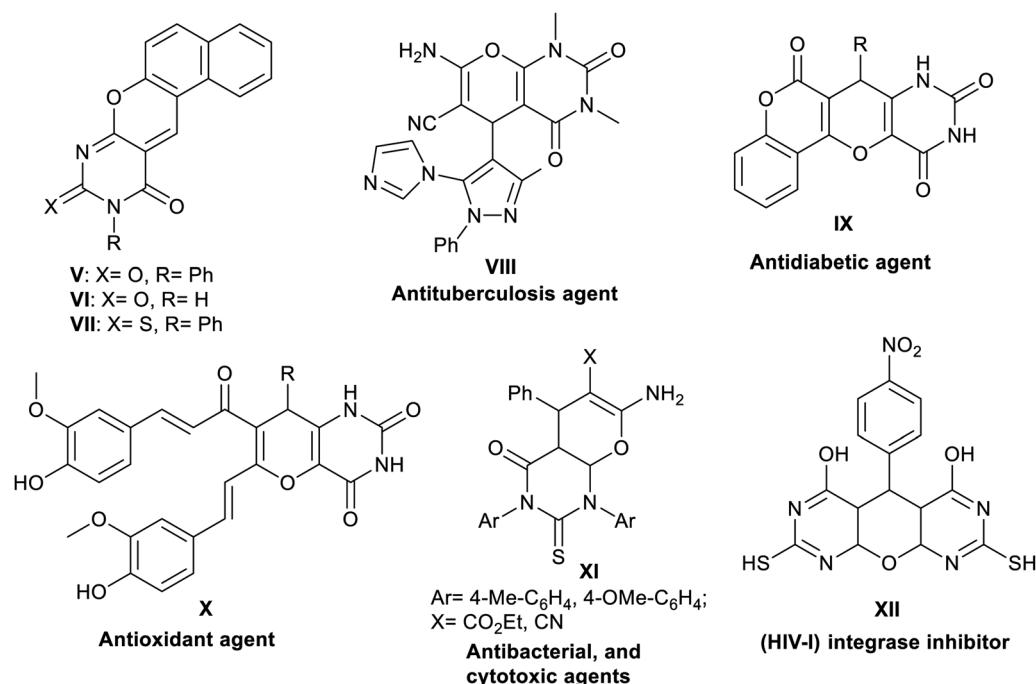
Fig. 2 Structures of biologically active pyranopyrimidine heterocycles.
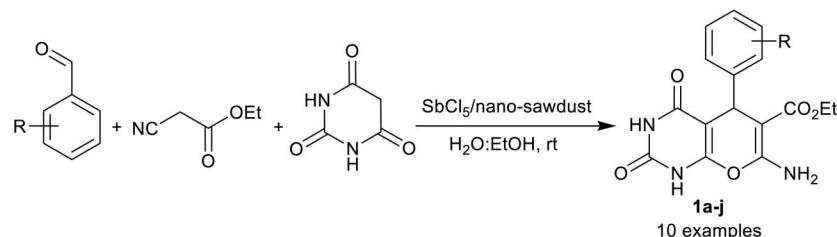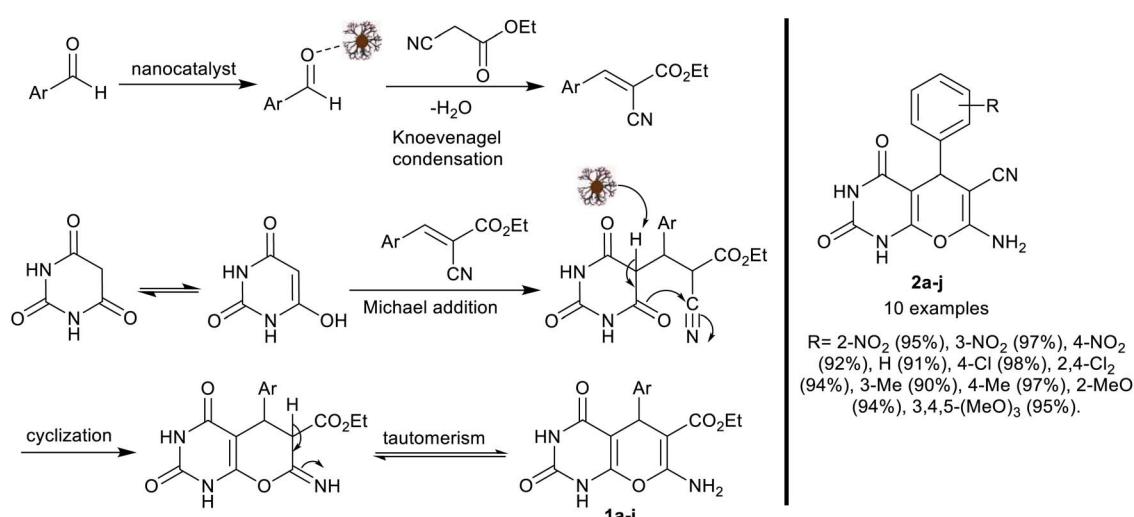
**Scheme 1** Synthesis of tetrahydro-2*H*-pyranopyrimidines.
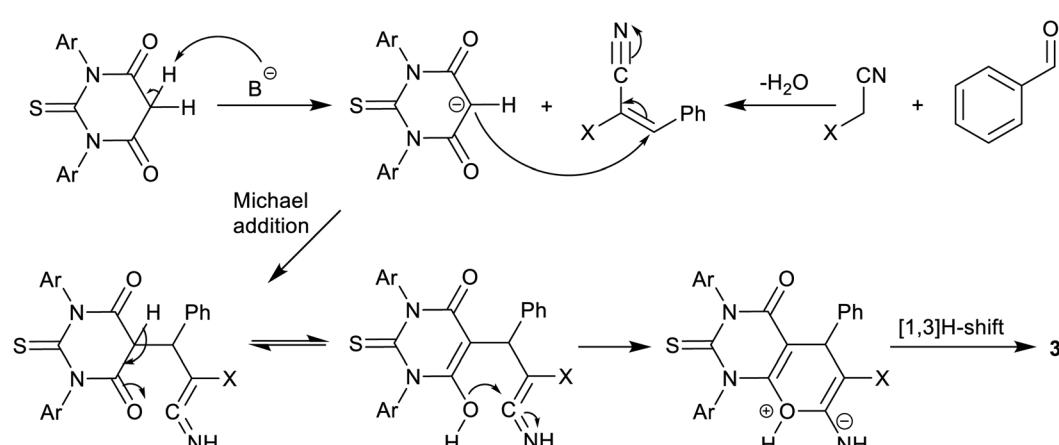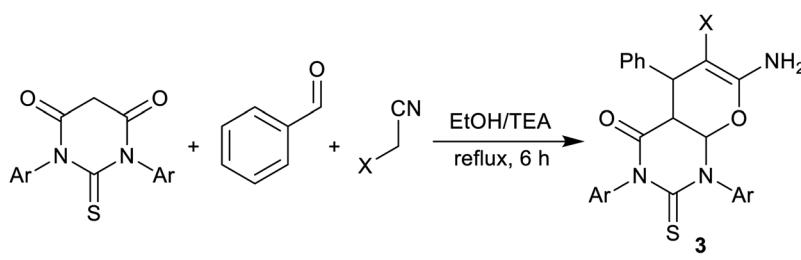
Scheme 2 Synthesis of hexahydro-pyranopyrimidines.

through a green protocol involved the carrying out the reactions under free-catalyst, and heating conditions (Scheme 3). The role of magnetized water involved the activation of the carbonyl group of dimethyl barbituric acid, which enabled the enolization and activate the aldehydic group of aryl aldehydes for condensation with malononitrile, and activation of nitrile groups of the generated intermediates by interaction with nitrogen atoms.[46] Otherwise, Tabassum et al.[47] have developed identical reaction sequences for the synthesis of bicyclic pyranopyrimidines with remarkable yields (90–96%) under catalytic conditions using nano ZnO@PEG. Thus, treatment of aryl aldehydes with malononitrile or methyl cyanoacetate, and barbituric acid through multicomponent one-pot reactions in ethanol at 25 °C gave the desired products 5 (Scheme 3). The catalyst activated aldehydic groups for condensation with active methylene derivatives and subsequently activated the nitrogen atom of the nitrile group in the intramolecular cyclization step of the pyran ring.

Furthermore, Sabbaghnasab et al.[48] have utilized nickel oxide nanoparticles for the green synthesis of tetrahydropyranopyrimidines 6 (Scheme 3) to improve the yield percentages. Thus, one-pot multicomponent reactions of aryl aldehydes with malononitrile, and (thio)barbituric acids in water under catalytic, and heating conditions of NiO nanoparticles presented the

estimated products in 17–95% yields. The technique is predominantly not appropriate for the synthesis of the pyranopyrimidines with progressive yields. Atarod et al.[49] have developed the synthesis of bicyclic systems with cyclic enaminonitrile moiety 7 by multicomponent one-pot reactions of (thio)barbituric acids with malononitrile, and aryl aldehydes. The reactions were advanced using $MgCoFe_2O_4$ nanomaterials as a catalyst to synthesize product 7 with excellent yields (89–98%). The green protocol was attained using a recyclable catalyst in a water/ethanol (1 : 1) mixture under heating conditions. Besides, isophthalaldehyde, and terephthalaldehyde were applied as aryl aldehydes to prepare symmetric aryl bis-pyranopyrimidines 8 (82–87%) (Scheme 3). The role of the nano-catalyst is to activate the aldehydic carbonyl group for Knoevenagel condensation with malononitrile, and activation of the nitrogen atom of the nitrile group for Michael addition, and pyran cyclization steps. Also, a green method has been developed for the synthesis of bicyclic pyranopyrimidinones through three-component one-pot reactions of malononitrile with aryl aldehydes, and barbituric acid under catalytic conditions using poly(4-vinylpyridine) in water at reflux conditions.[50]

Zaharani et al.[51] have developed the synthesis of bicyclic systems with enaminonitrile moiety by the utility of TMDP as an efficient N-heterocycle organocatalyst. The approach in this type


Ar= Ph (97%), 2-MeO-C$_6$H$_4$ (90%), 4-MeO-C$_6$H$_4$ (92%), 2-Br-C$_6$H$_4$ (87%), 3-Br-C$_6$H$_4$ (91%), 3-Cl-C$_6$H$_4$ (82%), 4-Cl-C$_6$H$_4$ (89%), 3-F-C$_6$H$_4$ (92%), 4-F-C$_6$H$_4$ (97%), 2,4-Cl$_2$-C$_6$H$_3$ (85%), 4-CN-C$_6$H$_4$ (95%), 2-NO$_2$-C$_6$H$_4$ (95%), 3-NO$_2$-C$_6$H$_4$ (90%), 4-NO$_2$-C$_6$H$_4$ (97%).

5
12 examples

Ar= 2-OH,5-Cl-C$_6$H$_3$; 2,3-Cl$_2$-C$_6$H$_3$; 2,4-Cl$_2$-C$_6$H$_3$; 2,6-Cl$_2$-C$_6$H$_3$; 3-OH,4-MeO-C$_6$H$_3$; 2-OH,4-NO$_2$-C$_6$H$_3$
R= CN; CO-Me

6
12 examples

a: X= 3-NO$_2$, Y= O (78%);
b: X= H, Y= O (71%);
c: X= 4-NMe$_2$, Y= O (77%);
d: X= 4-MeO, Y= O (64%);
e: X= 2,4-(MeO)$_2$, Y= O (76%);
f: X= 3,4,5-(MeO)$_3$, Y= O (75%);
g: X= 3-OH, Y= O (37%);
h: X= 4-NMe$_2$, Y= S (74%);
i: X= 3-NO$_2$, Y= S (41%);
j: X= 2,4-(MeO)$_2$, Y= S (74%);
k: X= 3,4,5-(MeO)$_3$, Y= S (95%);
l: X= H, Y= S (17%)

7
16 examples

a: X= H, Y= O, Z= Me (93%);
b: X= 3-Br, Y= O, Z= H (89%);
c: X= 2-Cl, Y= O, Z= Me (90%);
d: X= 2,6-Cl$_2$, Y= O, Z= Me (87%);
e: X= 3-Cl, Y= O, Z= H (93%);
f: X= 4-Cl, Y= O, Z= Me (98%);
g: X= 2-F, Y= O, Z= Me (96%);
h: X= 2-MeO, Y= O, Z= H (90%);
i: X= 2-MeO, Y= O, Z= Me (90%);
j: X= 4-OMe, Y= O, Z= Me (96%);
k: X= 2-Me, Y= O, Z= Me (90%);
l: X= 3-Me, Y= O, Z= H (90%);
m: X= 4-Me, Y= O, Z= Me (94%);
n: X= 2-NO$_2$, Y= O, Z= Me (94%);
o: X= 3-NO$_2$, Y= S, Z= H (90%);
p: X= 4-NO$_2$, Y= O, Z= Me (98%)

8
4 examples

a: 3-aryl, Z= H (82%);
b: 4-aryl, Z= H (85%);
c: 3-aryl, Z= Me (85%);
d: 4-aryl, Z= Me (87%)

Scheme 3 Synthesis of tetrahydro-2H-pyranopyrimidines.

of synthesis involved two methods that proceeded under heating conditions either applying TMDP as a dual solvent-catalyst or using a water/ethanol (1 : 1 v/v) mixture as a solvent in the presence of catalytic TMDP. In both methods, (thio)barbituric acids reacted with aryl aldehydes, and malononitrile in one-pot three-component reactions to afford the respective 5-aryl-2-(oxo/thioxo)-tetrahydro-2H-pyranopyrimidines **9a–t** (Scheme 4). Solvent-free conditions "method A" led to better product yields (78–92%) than the use of EtOH/H$_2$O as the solvent (72–88%). The mechanism of these reactions involved tandem Knoevenagel condensation, and subsequently Michael addition (Scheme 4). Formerly, Moosavi-Zare et al.[52] have reported the synthesis of compound **2a** (Ar = 4-Cl-C$_6$H$_4$) using isonicotinic acid (5 mol%) as a catalyst in ethanol at reflux temperatures to be applied in the condensation with 2-hydroxybenzaldehyde and reaction with cobalt(II) chloride hexahydrate for the synthesis of the nano-[Co-4CSP]Cl$_2$ complex. In addition, Khalili et al.[53] have reported the synthesis of bicyclic pyranopyrimidines (a series of 20 examples) by one-pot three-component reactions with the same reactants investigated in this example using various aryl aldehydes. The procedure progresses under catalytic conditions of bis(4-(dimethylamino)-anilino)triazine-grafted on silica-coated nano-Fe$_3$O$_4$ particles (MNPs-TBAN) "prepared from (Fe$_3$O$_4$@SiO$_2$) core–shell magnetic nanoparticles by the treatment with organic-based tags" under solvent-free, and heating conditions. The pyranopyrimidines were synthesized in 87–95% yields, in which the yields of the products were developed than the previously reported methods for the synthesis of these compounds.[24,26,54–57]

Amirnejat et al.[58] reported the synthesis of these bicyclic systems **10a–c** under the catalytic conditions of BaFe$_{12}$O$_{19}$@IM nanocomposite. The nanocatalyst was prepared by the reaction of barium nitrate with iron(III) nitrate nonahydrate, and citric acid in distilled water in an ultrasonic bath for 15 min, subsequently it was treated with ammonia solution (pH = 8) to generate barium hexaferrite nanoparticles. The obtained nanoparticles were treated with IM powder in an ethanol/water mixture under sonication in a water bath to give the desired BaFe$_{12}$O$_{19}$@IM nanocomposite. Compounds **10a–c** (Scheme 5) were previously reported under other different conditions,[59–61] in which the research by Amirnejat et al.[58] aimed to improve the product yields through the utility of the magnetic nanocatalyst. Although the obtained yields of bicyclic pyranopyrimidines are exceptional but rising temperatures by up to 1000 °C during the calcination step may decline the benefits of this method.

Nesaragi et al.[62] have developed the multicomponent synthesis of tetrahydro-2H-pyranopyrimidines through a green protocol under catalytic conditions. Therefore, reactions of aryl aldehydes with malononitrile, and barbituric acid, applying WELPSA "obtained from lemon (Citrus limon)" as an efficient catalyst, yielded the anticipated products **11a–j** in remarkable yields (Scheme 6). The reactions were run under either conventional or microwave irradiation conditions, in which the microwave conditions provided reduced reaction time and higher yields. The WELPSA catalyst activated malononitrile in the Knoevenagel condensation step with aryl aldehydes, supported the enolization of the barbituric acid for the Michael addition at the generated arylidene, proton abstraction and hence enabled the pyran ring cyclization. The compounds also were estimated as SARS-CoV-2 inhibitors by docking studies, in which the results indicated possible interaction forces between the ligands and protein.
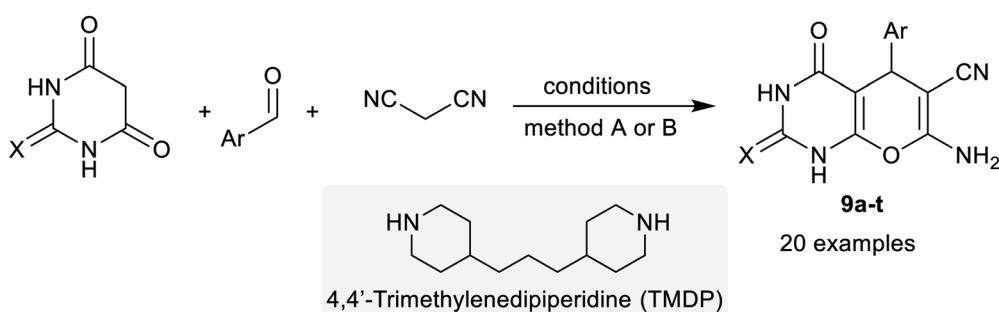

Reagents, and conditions:

Method A: TMDP (0.125 g), 65 °C, 30-65 min (78-92%)

Method B: TMDP (20 mg, 0.1 mmol, 20 mol%), EtOH/H$_2$O (1:1 v/v), 85 °C, 60-110 min (72-88%)

a: Ar= 4-Cl-C$_6$H$_4$, X= O (A: 92%; B: 88%); b: Ar= 4-Cl-C$_6$H$_4$, X= S (A: 90%; B: 85%);
c: Ar= C$_6$H$_5$, X= O (A: 82%; B: 80%); d: Ar= C$_6$H$_5$, X= S (A: 85%; B: 82%);
e: Ar= 3-Cl-C$_6$H$_4$, X= O (A: 78%; B: 75%); f: Ar= 3-Cl-C$_6$H$_4$, X= S (A: 80%; B: 78%);
g: Ar= 2,3-Cl$_2$-C$_6$H$_3$, X= O (A: 82%; B: 78%); h: Ar= 2,3-Cl$_2$-C$_6$H$_3$, X= S (A: 86%; B: 81%);
i: Ar= 2,4-Cl$_2$-C$_6$H$_3$, X= O (A: 85%; B: 83%); j: Ar= 2,4-Cl$_2$-C$_6$H$_3$, X= S (A: 82%; B: 80%);
k: Ar= 4-Br-C$_6$H$_4$, X= O (A: 85%; B: 85%); l: Ar= 4-Br-C$_6$H$_4$, X= S (A: 87%; B: 87%);
m: Ar= 4-NO$_2$-C$_6$H$_4$, X= O (A: 83%; B: 83%); n: Ar= 4-NO$_2$-C$_6$H$_4$, X= S (A: 85%; B: 85%);
o: Ar= 3-NO$_2$-C$_6$H$_4$, X= O (A: 82%; B: 82%); p: Ar= 3-NO$_2$-C$_6$H$_4$, X= S (A: 81%; B: 81%);
q: Ar= 4-CF$_3$-C$_6$H$_4$, X= O (A: 78%; B: 72%); r: Ar= 4-CF$_3$-C$_6$H$_4$, X= S (A: 82%; B: 79%);
s: Ar= 2-furyl, X= O (A: 83%; B: 82%); t: Ar= 2-furyl, X= S (A: 84%; B: 83%).

Scheme 4 Synthesis of 5-aryl-2-(oxo/thioxo)-tetrahydro-2H-pyranopyrimidines.
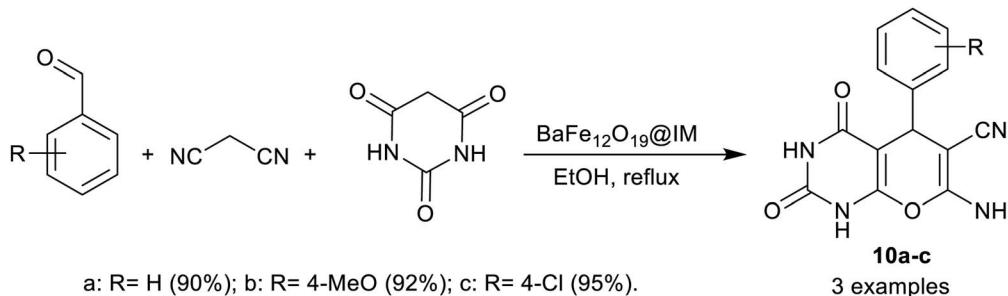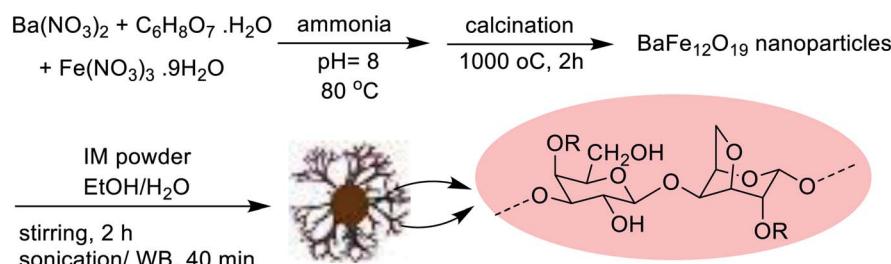
Scheme 5 Synthesis of pyranopyrimidines.

Yelwande *et al.*[63] have reported the synthesis of bicyclic pyranopyrimidines with enaminonitrile moieties (8 examples, 90–95% yields) under catalytic conditions of SnO$_2$/SiO$_2$ (15 wt%) nanocomposite, succeeding in a green protocol in ethanol at room temperature. Furthermore, Moghaddampour *et al.*[64] have reported the preparation and utility of agar-trapped acidic ionic liquid (0.05 g) as a recyclable catalyst for the synthesis of bicyclic pyranopyrimidines **12a–h** with improved yields compared to the previous methods for the preparation of this series of compounds.[65,66] Consequently, aryl aldehydes reacted with

(thio)barbituric acids and malononitrile in water at reflux temperature provided the bicyclic pyranopyrimidines **12a–h** in a green technique, and remarkable yields (Scheme 7). The agar-entrapped IL catalyst was prepared as rough brown crystals by heating agar in water until boiling and completely dissolved agar followed by the addition of [DABCO](SO$_3$H)$_2$(Cl)$_2$ under stirring conditions. This method involves the tolerable facile synthesis of the catalyst and is suitable for enhanced yields.[64]

In another route, a choline chloride-based DES "ChCl/urea/thiourea" supported the multicomponent synthesis of 1,3,4,5-
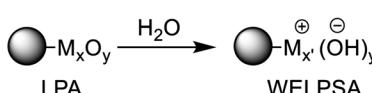
**Scheme 6** Synthesis of tetrahydro-pyranopyrimidines.
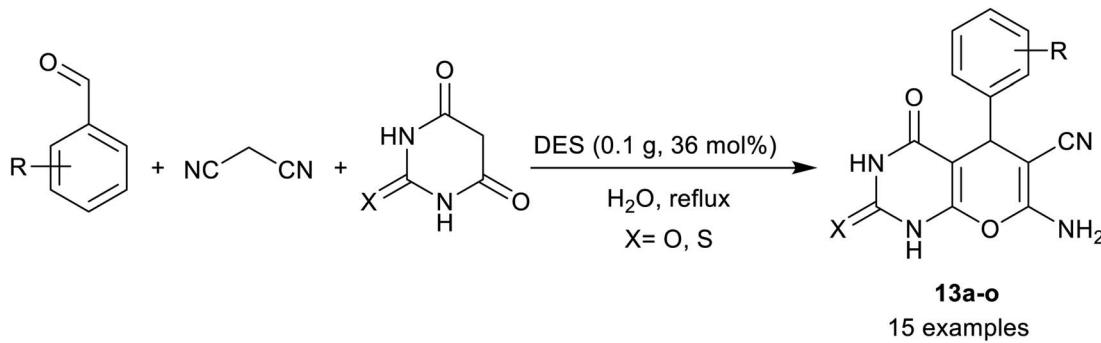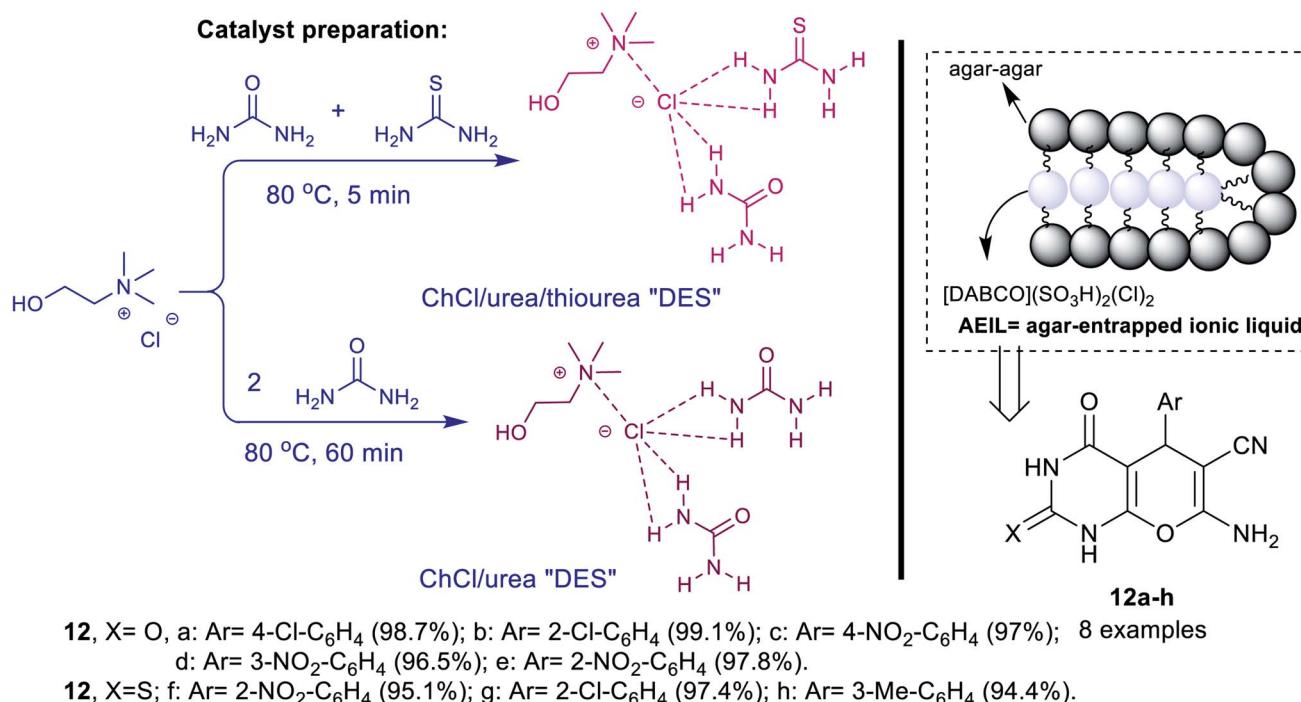
Scheme 7 Synthesis of tetrahydropyranopyrimidines.

tetrahydro-2*H*-pyranopyrimidines **13** that were previously prepared using other catalytic conditions *e.g.* Fe$_3$O$_4$@MCM-41@Zr-piperazine, Fe$_3$O$_4$@Ph-PMO-NaHSO$_4$ nanocatalysts, and DABCO-based ionic liquid {[H$_2$-DABCO] [H$_2$PO$_4$]$_2$}.[67–69] In this investigation, only compound **13k** (X = O, R = 3-OMe, 4-OH, 5-NO$_2$, 93%) is the novel reported one. The method reported a one-pot three-component synthesis of pyranopyrimidines **13** utilizing ChCl/urea/thiourea that tended to improve the yields of the products with a facile route for the catalyst preparation and reduced reaction time. The catalyst is recyclable four times without substantial loss in its activity and efficiently prepared by heating choline chloride with urea and/or thiourea (Scheme 7).[70]

Farahmand *et al.*[71] have reported the utility of Mn-ZIF-8@ZnTiO$_3$ nanocatalyst prepared by sol–gel performance for

improved yields of the precedingly reported tetrahydro-2*H*-pyranopyrimidines **14a–f** through a green protocol (Scheme 8). Thus, a one-pot multi-component approach for the reactions of malononitrile, aryl aldehydes, and barbituric acid in ethanol/water mixture under catalytic conditions accomplished the target compounds **14a–f**. These compounds were synthesized in earlier research using nanocatalysts either of ionic liquid stabilized silica-coated Fe$_3$O$_4$ or SBA-Pr-SO$_3$H "sulfonic acid nanoporous silica".[72,73] This method provided the ease of product work-up, catalyst recyclability, reduced reaction time, and amended yields, but the difficulty of nanocatalyst preparation probably hinders the synthesis of pyranopyrimidines using this technique.

Bhat *et al.*[1] have reported the synthesis of other derivatives of this series "compounds **15a–g**" applying DABCO as an efficient
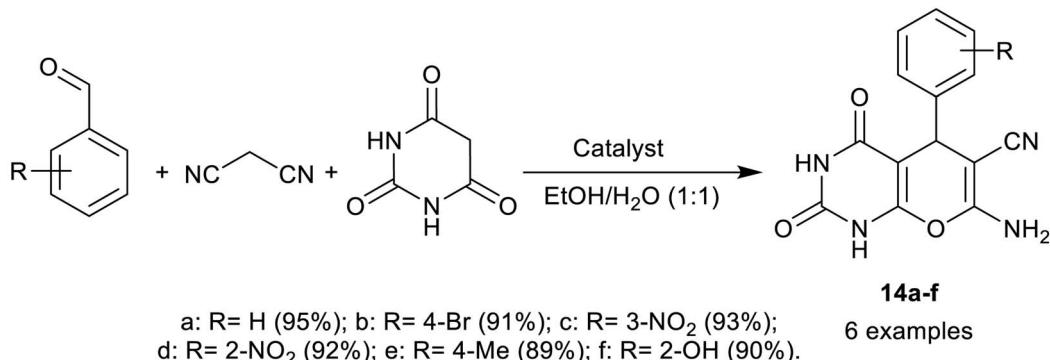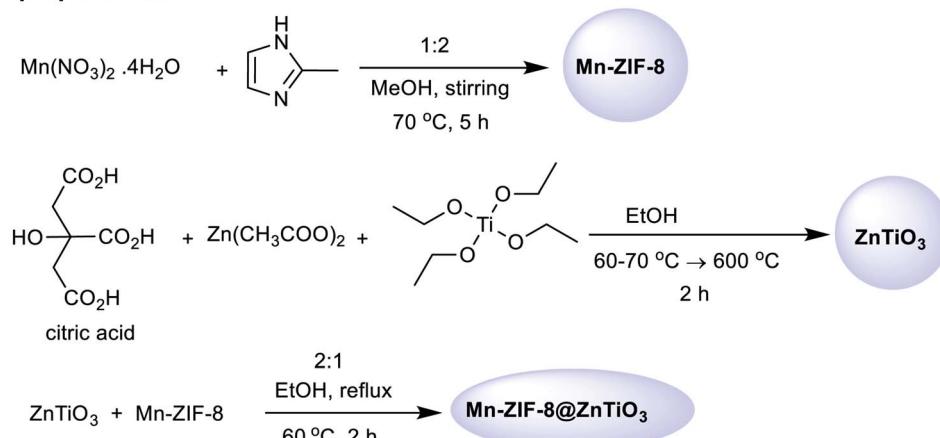
Scheme 8 Synthesis of enaminonitriles of tetrahydro-2*H*-pyranopyrimidines.

catalyst. The reactions proceeded in an ethanol/water mixture to produce the target products **15a–g** in 83–97% yields. The antibacterial activity of this series of pyranopyrimidines was estimated against diverse bacterial species using streptomycin as an antibiotic standard. The results indicated the broadest spectrum was recorded for compound **15e** "R = 4-OH" with a 14 mm inhibition zone diameter against *B. cereus* species, however, compounds **15d** "R = 3-OH", and **15e** "R = 4-OH" displayed the most potent activities against *S. aureus* species with the inhibition zones diameter at 15 mm. Compounds **15b** and **15c** with methoxy substituents revealed the most potent activity against *K. pneumonia* species with an inhibition zone at 14 mm. Also, compounds **15d**, and **15e** were the most potent against *P. aureus* species (IZD = 15 mm), and compound **15e** was the most potent against *E. coli* bacterial species (IZD = 15 mm). A perfect correlation between the experimental results and the perceived POM/DFT/docking calculations was obtained. The nature of the substituents on the phenyl ring employed positive effects on the antimicrobial results. The basic skeleton of pyranopyrimidine along with the enaminonitrile moiety, and substituents at the phenyl ring are needed for potent results of antibacterial activity as the more active compounds were recorded with increased penetration influence on the cell wall of bacterial species. The hydrolysis of the nitrile group into an amide enables intramolecular interaction, resulting in a critical

pattern for antibacterial –NH, HO-pharmacophore sites (Scheme 9). In addition, (–O=C–NH–C=O) as an anti-kinase pharmacophore site was theoretically estimated by POM combinatorial analysis. The hydrolysis of a nitrile group to carboxylic acid led to achieving an *N*,*O*-bidentate site benefit for the future design for therapeutic materials.[1]

Biglari *et al.*[74] have progressed the multicomponent synthesis of enaminonitriles of tetrahydro-2*H*-pyrano[2,3-*d*] pyrimidines **16a–i** utilizing taurine/choline chloride as a green, eutectic solvent and an efficient recyclable catalyst (Scheme 10). The catalyst performed like an amphoteric structure with the ease of interaction with acidic hydrogens and carbonyl groups by both charged sides and the simplicity of catalyst preparation. Thus, the taurine/choline chloride as a green solvent/catalyst was prepared by grinding 2-aminoethane-1-sulfonate "taurine" (1 mol) with 2-hydroxy-*N*,*N*,*N*-trimethyl-ethan-1-aminium chloride "choline chloride" (2 moles) using a mortar at 25 °C for 20 min. The catalysis provided improved product yields, more than that reported in previous methods;[67–69,75] only compound **16h** was merely the new in that report.

Sorkhabi *et al.*[76] developed the synthesis of the formerly reported pyranopyrimidines **17**,[23,24,43,44,77] under catalytic, and heating conditions. The reactions were performed using immobilized magnetic nanoparticles of cobalt ferrite with erbium (Er) coated with folic acid (CoFe₂O₄@FA-Er). The
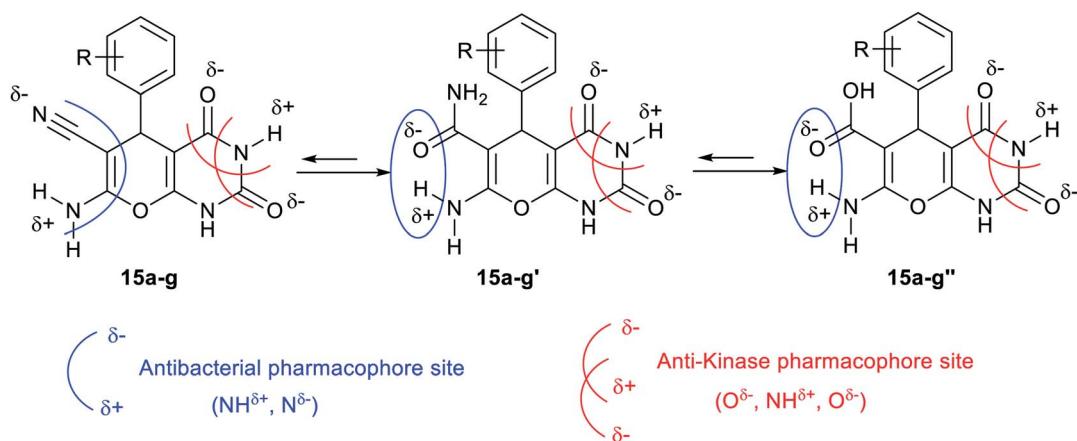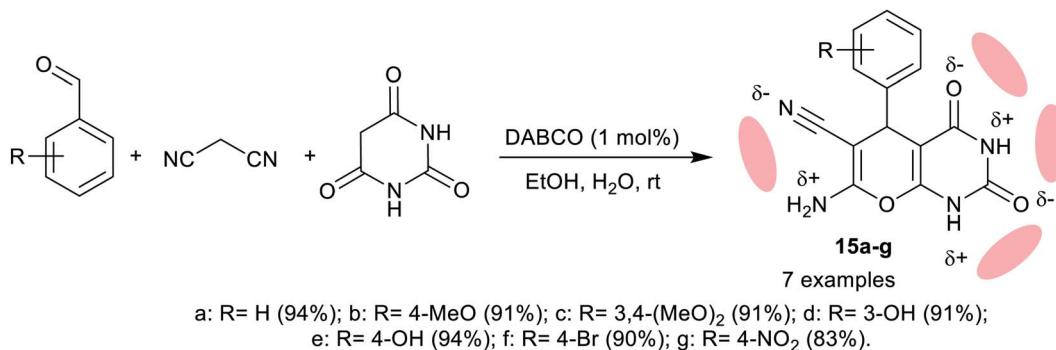
**Scheme 9** Synthesis of tetrahydropyranopyrimidines.

procedure offered efficient yields of the products along with catalyst recyclability. In this sequence, aryl aldehydes reacted with malononitrile and barbituric acid in a one-pot procedure to give the respective pyranopyrimidines **17** (Scheme 11). The products were obtained in 87–96% yields relying on the substituents' nature, and reaction conditions. The products were prepared by heating the reactants under solvent-free conditions (100 °C) or in water under sonication conditions (80 °C). It was noticed that the reactions under solvent-free and conventional conditions gave considerably improved yields of the target products than running the reactions under sonication conditions.

Mohamadpour,[78] has developed the utility of polyethylene glycol 400 (PEG-400) as a green supporting medium for the synthesis of pyranopyrimidines **18a–u** under heating conditions. Thus, this method is a green protocol applied to improving the product yields of pyranopyrimidines **18a–u** under free-catalytic conditions. These series of compounds **18a–u** were earlier synthesized under miscellaneous conditions such as DABCO-based ionic liquids, L-proline, iron ore pellet, nano-sawdust-OSO$_3$H, boric acid, Mn-doped ZrO$_2$, tetrabutylammonium bromide, ZnFe$_2$O$_4$ nanoparticles, and Zn[(L)proline]$_2$.[23,24,32,42,43,65,79–81] In this course, one-pot multicomponent reactions of aryl aldehydes with malononitrile, and N,N-disubstituted barbituric acids furnished the expected pyranopyrimidines **18a–u** (Scheme 12). It was noticed that the

yields of this sequence are dependent on the nature and substituents' position at the phenyl ring, as the electron-withdrawing groups produced improved yields than the electron-donating groups in some cases, and the mono-substitution is preferred over the di-substitution in the phenyl ring. Also, the unsubstituted nitrogen atoms of pyrimidine ring (R′ = H) are preferred over the N,N-dimethyl substitution (R′ = Me) for enhanced yields of the products. Also, various compounds in the pyranopyrimidine series (18 examples, X = O; R′ = H, Me; R = 2-NO$_2$, 3-NO$_2$, 4-NO$_2$, 4-Me, 4-OMe, 4-F, 4-Br, 2-Cl, 4-Cl, 2,4-Cl$_2$, H, 2-OH, 3-OH) were synthesized through a green protocol using ethylene glycol as a solvent under free-catalytic conditions. The method permitted the simplicity of product separation as these compounds are insoluble in hot water, while ethylene glycol was dissolved and recycled.[82]

Mohamadpour,[83] has developed the multicomponent synthesis of bicyclic pyranopyrimidines through the use of supramolecular β-cyclodextrin (10 mol%) as a biodegradable and recyclable catalyst. These series of pyranopyrimidines **19a–s** were previously reported using other catalysts e.g. DABCO-based ionic liquids, L-proline, iron ore pellet, nano-sawdust-OSO$_3$H, boric acid, Mn-doped ZrO$_2$, and Zn[(L)proline]$_2$.[23,24,32,42,65,79,80] This method is a green protocol proceeding in water under heated conditions and enables the catalyst biodegradability, nevertheless, the yields of the products are still not perfect in this approach (76–95%). In this investigation, one-pot three-

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X= O: a: Ar= C_6H_5 (91%); b: Ar= 4-Cl-C_6H_4 (93%); c: Ar= 2-Cl-C_6H_4 (92%); d: Ar= 4-Br-C_6H_4 (94%);
e: Ar= 4-NO_2-C_6H_4 (90%); f: Ar= 3-NO_2-C_6H_4 (88%); g: Ar= 4-MeO-C_6H_4 (91%); X= S:
h: Ar= 3-MeO,4-OH,5-NO_2-C_6H_2 (93%); i: Ar= 4-NO_2-C_6H_4 (90%).
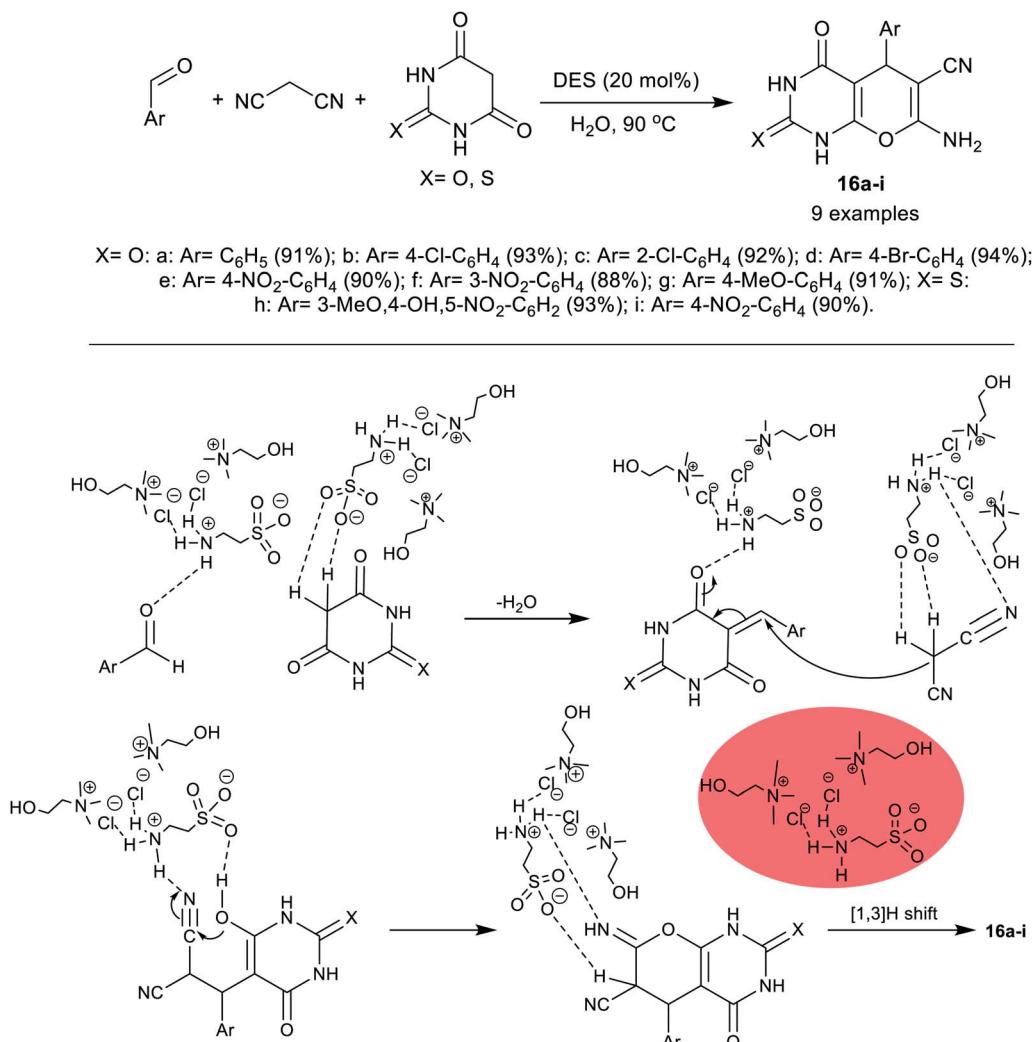
**Scheme 10** Synthesis of enaminonitriles of tetrahydropyranopyrimidines.

component reactions of aryl aldehydes, malononitrile, and *N,N*-disubstituted barbituric acids supported by supramolecular β-cyclodextrin yielded the desired products **19a–s** (Scheme 12).[83] In addition, another performance was described by Mohamadpour,[84] for the synthesis of bicyclic pyranopyrimidines with an enaminonitrile moiety using visible light irradiation in a green protocol. Patila *et al.*[85] synthesized a series of pyranopyrimidine-diones **20a–k** using L-proline-based ionic liquid as an efficacious catalyst. Thus, L-proline-NO_3 catalyzed one-pot multicomponent reactions of aryl aldehydes with malononitrile and *N,N*-dimethyl-barbituric acid under either conventional (80 °C) or ultra-sonication conditions to furnish the anticipated pyranopyrimidines **20a–k** (Scheme 12). The use of ultra-sonication conditions (82–92%) provided much higher yields than those used in a conventional method (86–95%).

Zhang *et al.*[86] advanced the synthesis of two series of pyranopyrimidines using recyclable SCMNPs@urea/Py-CuCl₂ heterogeneous nanoparticles. Thus, three-component reactions involved reactions of (thio)barbituric acids with aryl aldehydes, and malononitrile in a water/ethanol mixture to prepare

compounds **21a–w**, and reactions of barbituric acids with aryl aldehydes, and Meldrum's acid in water to prepare compounds **22a–r** (Scheme 13). Both routes of reactions were attained in a one-pot procedure under catalytic conditions to improve the yields of the products in these series of compounds, which were earlier reported under diverse conditions.[19,26,32,33,65,66,87–92] The method succeeded in synthesizing these compounds following a green protocol with improved product yields. Correspondingly, Badiger *et al.*[93] have applied the utility of agro-waste catalyst WELFSA (water extract lemon fruit shell ash) in ethanol for the synthesis of pyranopyrimidine-triones under ultrasound irradiation at room temperature in a green protocol.

Conversely, AbdEl-Azim *et al.*[8] have established the synthesis of one model of tetrahydro-2*H*-pyranopyrimidine series **21v** (X = S; Ar = 4-Cl-C_6H_4, 88%) (Scheme 13) in ethanol under heating, and catalytic conditions of trimanganese tetraoxide "Mn_3O_4" nanoparticles. Therefore, the reactivity of this compound was investigated through reactions with galactopyranosyl bromide, glucose, ammonium thiocyanate in acetic acid, formic acid, hydroxylamine hydrochloride, malononitrile in sodium

a: R= H (A: Conventional 96%; B: Sonication 92%); b: R= 4-Me (A: 91%; B: 90%);
c: R= 2-OMe (A: 90%; B: 89%); d: R= 3-NO$_2$ (A: 95%; B: 93%); e: R= 4-NO$_2$ (A: 96%; B: 94%);
f: R= 4-OMe (A: 93%; B: 90%); g: R= 4-Br (A: 94%; B: 90%); h: R= 4-Cl (A: 93%; B: 89%);
i: R= 4-OH (A: 90%; B: 88%); j: R= 2,3-Cl$_2$ (A: 89%; B: 87%); k: R= 3-NO$_2$, 4-Cl (A: 87%; B: 87%);
l: R= 2-F (A: 88%; B: 88%).
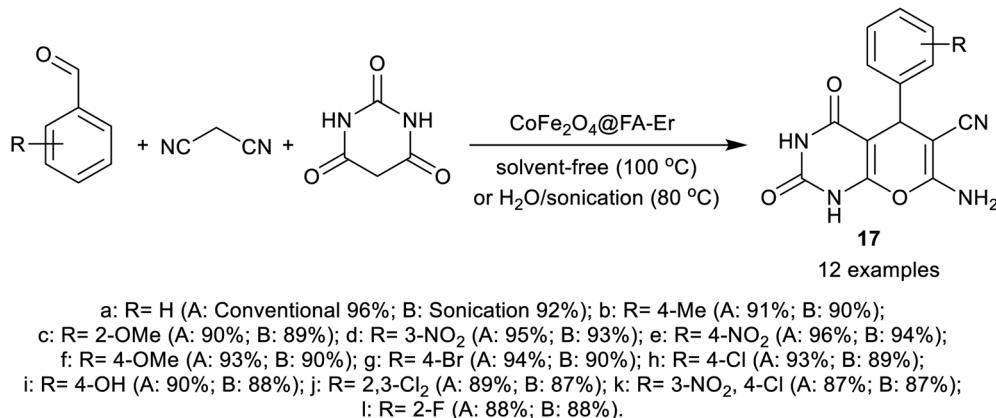
Nano-catalyst Preparation:
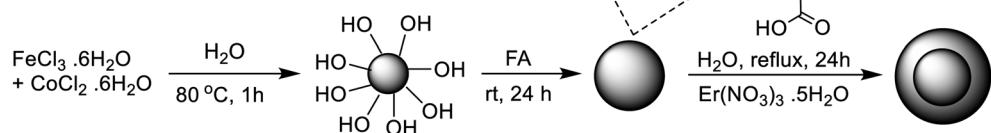
**Scheme 11** Synthesis of bicyclic pyranopyrimidines.

ethoxide, acetyl acetone in acetic acid, acetic anhydride, thio-urea, carbon disulfide, and triethyl orthoformate. Moderate anti-inflammatory activity was recorded for this analog by *in vitro* assessment as compound **21v** inhibited Cox-2 with IC$_{50}$ at 0.34 ± 0.02 μM relative to the standard celecoxib (IC$_{50} = 0.04 \pm 0.01$ μM). The results also indicated its potent activity against Cox-1 (IC$_{50} = 5.3 \pm 0.17$ μM), Lox (IC$_{50} = 4.37 \pm 0.03$ μM) relative to quercetin (IC$_{50} = 3.34 \pm 0.12$ μM), and TNF-α (IC$_{50} = 8.53 \pm 0.15$ μM) in compared to certolizumab (IC$_{50} = 6.90 \pm 0.26$ μM).

More recently, Bahrami *et al.*[94] have designed a series of bicyclic 2,4-dichloro-5,7-diaryl-5*H*-pyrano[2,3-*d*]pyrimidines by the action of CAN (10 mol%) in phosphorus ionic liquid (HTPB) following a green technique. In this procedure, a one-pot four-component reaction of malononitrile with aryl aldehydes, carbon tetrachloride, and acetophenones at room temperature yielded the target bicyclic systems **23a–h** (91–98% yields). The mechanism in this type of reaction was projected by the initial activation of the active methylene of acetophenones, and aryl aldehydes by the catalyst for the Knoeveangel condensation step to generate the arylidene intermediates. Subsequently, the formed intermediate interacted with malononitrile, intra-molecular pyran ring cyclization and reaction with carbon tetrachloride generated the dichloro bicyclic intermediate, which gave the target bicyclic products through HCl elimination (Scheme 14). The method involved the utility of four compo-nents in the route to prepare the bicyclic systems without the use of either barbituric or thiobarbituric acids or their deriva-tives as mentioned in the previous examples in this section.

Therefore, this method is a great approach for researchers to find diverse methods as well as to prepare other derivatives containing the pyranopyrimidine nucleus using other catalysts and reactants as well. Researchers in the fields of pharmaceu-tical, and medicinal chemistry can also develop this class of compounds to assess multiple biological properties that have not yet received researchers' interest.

Formerly, Hasaninezhad *et al.*[95] and Yousefi *et al.*[10] have re-ported the synthesis of pyrano[2,3-*d*]pyrimidine derivatives **25** (Scheme 15) from multicomponent one-pot reactions of curcu-min, aryl aldehydes, and (thio)barbituric acids in ethanol under catalytic, and reflux conditions using the prepared metal nanoparticles such as SAA-MNPs (8 mol%). The antidiabetic properties of these series of bicyclic systems-based curcumin were investigated and the compounds were evaluated as potent inhibitors for α-amylase and α-glucosidase. The results speci-fied that compounds **25** "Ar = 4-NO$_2$-C$_6$H$_4$", and **25**: "Ar = 2,6-Cl$_2$-C$_6$H$_3$" displayed reasonable inhibitory activity against α-glucosidase accompanied by poor inhibitory activity against α-amylase. The compounds showed significant antioxidant char-acteristics as potent, and vital anti-diabetic agents.[95] Hasani-nezhad *et al.*[95] have also evaluated the antibacterial activity of these types of compounds using well diffusion assay against *Lactobacillus plantarum* and *Escherichia coli* species. The results indicated that compound **25** "Ar = 4-NO$_2$-C$_6$H$_4$" has a broad spectrum activity against *E. coli* species (inhibition zone diam-eter = 11 ± 0.1 mm) relative to ampicillin (inhibition zone diameter = 12 ± 0.5 mm).

Scheme 12 Structures of aryl-bicyclic pyranopyrimidines.
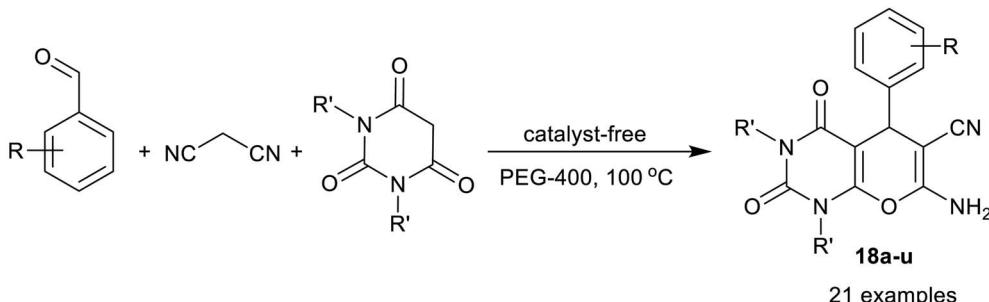
21a: R= 2-OMe, R'= H (91%); b: R= 3-NO$_2$, R'= H (92%); c: R= 2-Cl, R'= H (89%); d: R= 2-Cl, R'= Me (86%); e: R= H, R'= H (94%); f: R= H, R'= Me (93%); g: R= 2,3-Cl$_2$, R'= H (83%); h: R= 4-OMe, R'= H (89%); i: R= 2-OH, R'= H (87%); j: R= 3-OH, R'= H (84%); k: R= 4-NO$_2$, R'= H (92%); l: R= 4-NO$_2$, R'= Me (87%); m: R= 4-Cl, R'= H (81%); n: R= 4-Me, R'= H (92%); o: R= 4-Me, R'= Me (94%); p: R= 2,4-Cl$_2$, R'= H (78%); q: R= 4-Br, R'= H (76%); r: R= 4-Br, R'= Me (79%); s: R= 2,4-(OMe)$_2$, R'= H (86%); t: R= 4-F, R'= H (95%); u: R= 2-NO$_2$, R'= H (93%).

18a-u 21 examples

19a-s 19 examples
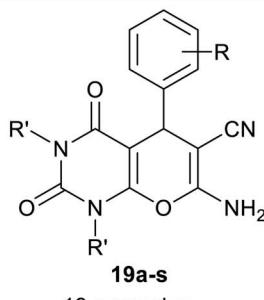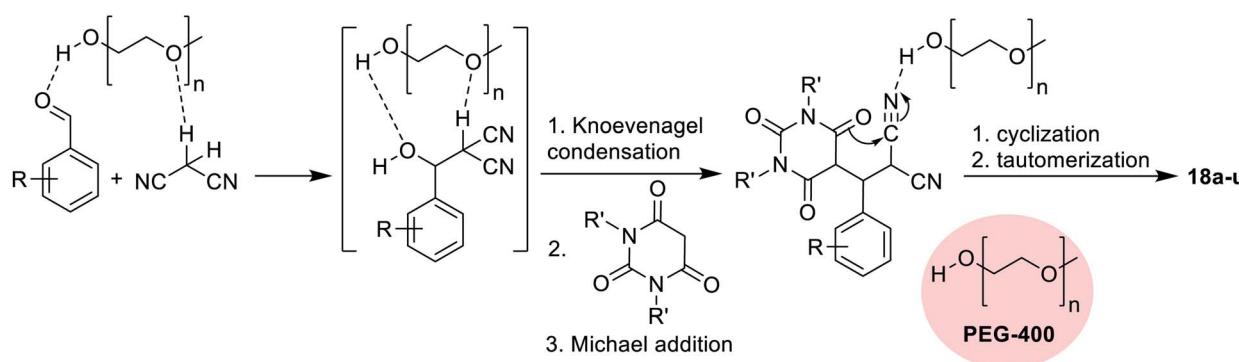
a: R= H, R'= H (93%); b: R= H, R'= Me (91%); c: R= 2,4-(MeO)$_2$, R'= H (83%); d: R= 4-Me, R'= H (89%); e: R= 4-Me, R'= Me (90%); f: R= 2-OH, R'= H (84%); g: R= 3-NO$_2$, R'= H (92%); h: R= 2,4-Cl$_2$, R'= H (81%); i: R= 4-MeO, R'= H (87%); j: R= 4-Cl, R'= H (95%); k: R= 2-NO$_2$, R'= H (95%); l: R= 3-OH, R'= H (80%); m: R= 2-MeO, R'= H (89%); n: R= 4-Br, R'= H (79%); o: R= 4-Br, R'= Me (76%); p: R= 4-F, R'= H (94%); q: R= 4-NO$_2$, R'= H (88%); r: R= 4-NO$_2$, R'= Me (89%); s: R= 2-Cl, R'= H (87%).

20a-k 11 examples
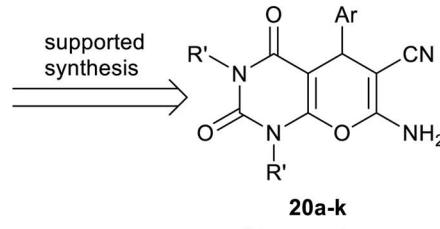
a: Ar= C$_6$H$_5$ (A: 88%; B: 90%); b: Ar= 2-Cl-C$_6$H$_4$ (A: 84%; B: 92%); c: Ar= 4-Cl-C$_6$H$_4$ (A: 92%; B: 94%); d: Ar= 4-Br-C$_6$H$_4$ (A: 90%; B: 92%); e: Ar= 2-NO$_2$-C$_6$H$_4$ (A: 88%; B: 94%); f: Ar= 3-NO$_2$-C$_6$H$_4$ (A: 90%; B: 95%); g: Ar= 4-Me-C$_6$H$_4$ (A: 90%; B: 86%); h: Ar= 4-MeO-C$_6$H$_4$ (A: 92%; B: 88%); i: Ar= 3-OH-C$_6$H$_4$ (A: 82%; B: 88%); j: Ar= 4-OH-C$_6$H$_4$ (A: 86%; B: 90%); k: Ar= 1-naphthyl (A: 88%; B: 86%).

Recently, Mehrabi et al.[96] have reported the multicomponent synthesis of bicyclic dihydropyrano-pyrimidine-dione derivatives through reactions of curcumin with aryl aldehydes, and barbituric acid in a one-pot procedure (Scheme 15). The reactions were developed using catalytic borax with 10% in ethanol at reflux temperature. The antidiabetic activity of dihydropyrano[2,3-d]pyrimidine-dione series was estimated by the

evaluation of their α-Glu/α-Amy inhibitory actions and antioxidant characteristics. Thus, the compounds displayed potent α-Glu and α-Amy enzyme activities along with applicable antioxidant potency. Thus, the in vitro assessments indicated that compounds **26d:** Ar = 5-NO$_2$-fur-2-yl, **26e:** Ar = 5-NO$_2$-thien-2-yl, **26h:** Ar = 2-Cl-C$_6$H$_4$, **26i:** Ar = 2-Br-C$_6$H$_4$, **26j:** Ar = pyrrol-2-yl, **26k:** Ar = 4-F-C$_6$H$_4$, **26l:** Ar = 2-Cl-C$_6$H$_4$, and **26m:** "Ar = 4-

21: X= O, Ar= 4-Me-C$_6$H$_4$ (91%), 4-OMe-C$_6$H$_4$ (92%), 3-OMe-C$_6$H$_4$ (88%), 2-OMe-C$_6$H$_4$ (90%), 4-CN-C$_6$H$_4$ (96%), 4-OH-C$_6$H$_4$ (91%), 4-F-C$_6$H$_4$ (92%), 2,4-Cl$_2$-C$_6$H$_3$ (94%), 4-Cl-C$_6$H$_4$ (96%), 3-Cl-C$_6$H$_4$ (93%), 2-Cl-C$_6$H$_4$ (95%), 4-NO$_2$-C$_6$H$_4$ (95%), 3-NO$_2$-C$_6$H$_4$ (91%), 2-NO$_2$-C$_6$H$_4$ (93%), 4-Br-C$_6$H$_4$ (96%), 3-Br-C$_6$H$_4$ (92%), C$_6$H$_5$ (91%). X= S, Ar= C$_6$H$_5$ (87%), 2-NO$_2$-C$_6$H$_4$ (90%), 3-NO$_2$-C$_6$H$_4$ (89%), 4-NO$_2$-C$_6$H$_4$ (92%), 4-Cl-C$_6$H$_4$ (90%), 4-Br-C$_6$H$_4$ (94%).

22: Ar= 4-NMe$_2$-C$_6$H$_4$ (90%), 4-Me-C$_6$H$_4$ (93%), 3,4,5-(OMe)$_3$-C$_6$H$_2$ (92%), 3-OMe,4-OH-C$_6$H$_3$ (94%), 3-OH,4-OMe-C$_6$H$_3$ (95%), 3,4-(OMe)$_2$-C$_6$H$_3$ (93%), 2,4-(OMe)$_2$-C$_6$H$_3$ (92%), 4-OMe-C$_6$H$_4$ (93%), 4-OH-C$_6$H$_4$ (92%), 2-OH-C$_6$H$_4$ (90%), 4-Cl-C$_6$H$_4$ (95%), 3-Cl-C$_6$H$_4$ (91%), 2-Cl-C$_6$H$_4$ (94%), 4-NO$_2$-C$_6$H$_4$ (94%), 3-NO$_2$-C$_6$H$_4$ (92%), 2-NO$_2$-C$_6$H$_4$ (95%), 4-F-C$_6$H$_4$ (95%), 4-Br-C$_6$H$_4$ (93%), C$_6$H$_5$ (94%).

Scheme 13 Synthesis of tetrahydropyranopyrimidines, and dihydropyranopyrimidine-triones.

pyridyl" showed the most potent inhibition for α-Glu enzyme than the starting curcumin, while compounds **26h**: Ar = 2-Cl-C$_6$H$_4$, **26i**: Ar = 2-Br-C$_6$H$_4$, **26j**: Ar = pyrrol-2-yl, **26k**: Ar = 4-F-C$_6$H$_4$, **26l**: Ar = 2-Cl-C$_6$H$_4$, and **26m**: Ar = 4-pyridyl displayed the stronger inhibition for α-Amy enzyme. The lowest IC$_{50}$ value was recorded for compound **26l** "Ar = 2-Cl-C$_6$H$_4$" as the most potent inhibitor for both enzymes.

Khodarahmi group,[97] have also extended the same preceding reactions with the synthesis of another series of these compounds bearing curcumin skeleton under the same catalytic and heating conditions. The research also has assessed the compounds as antioxidant and glycohydrolase inhibitors. The results indicated that compounds **26h′** (Ar= 2,3,4-(OH)$_3$-C$_6$H$_2$), **26k′** (Ar = 3,5-(OMe)$_2$,4-OH-C$_6$H$_2$), and **26g′** (Ar = 3,5-(OH)$_2$-C$_6$H$_3$) displayed potent activities of the α-Glu enzyme, and

compounds **26h′** (Ar = 2,3,4-(OH)$_3$-C$_6$H$_2$), **26g′** (Ar = 3,5-(OH)$_2$-C$_6$H$_3$), **26k′** (Ar = 3,5-(OMe)$_2$,4-OH-C$_6$H$_2$), **26f′** (Ar = 3,4-(OH)$_2$-C$_6$H$_3$), and **26e′** (Ar = 2,5-(OH)$_2$-C$_6$H$_3$) exhibited the most significant activities against the α-Amy enzyme. On the other hand, compounds **26g′** (Ar = 3,5-(OH)$_2$-C$_6$H$_3$), **26h′** (Ar = 2,3,4-(OH)$_3$-C$_6$H$_2$) and **26k′** (Ar = 3,5-(OMe)$_2$,4-OH-C$_6$H$_2$) (Scheme 15) remarkably inhibited α-Glu than α-Amy along with appropriate results of distinctive antioxidant (using DPPH⋅ assay) and stability properties.

Naik *et al.*[9] have cited an efficacious methodology for bicyclic pyranopyrimidines **27a–j** synthesis through four-component one-pot reactions with relatively good to excellent yields (78–88%). Thus, reactions of 4-hydroxycoumarin with aryl aldehydes, thiobarbituric acid, and piperidine in methanol at room temperature gave the anticipated 2-thioxo-tetrahydro-4*H*-
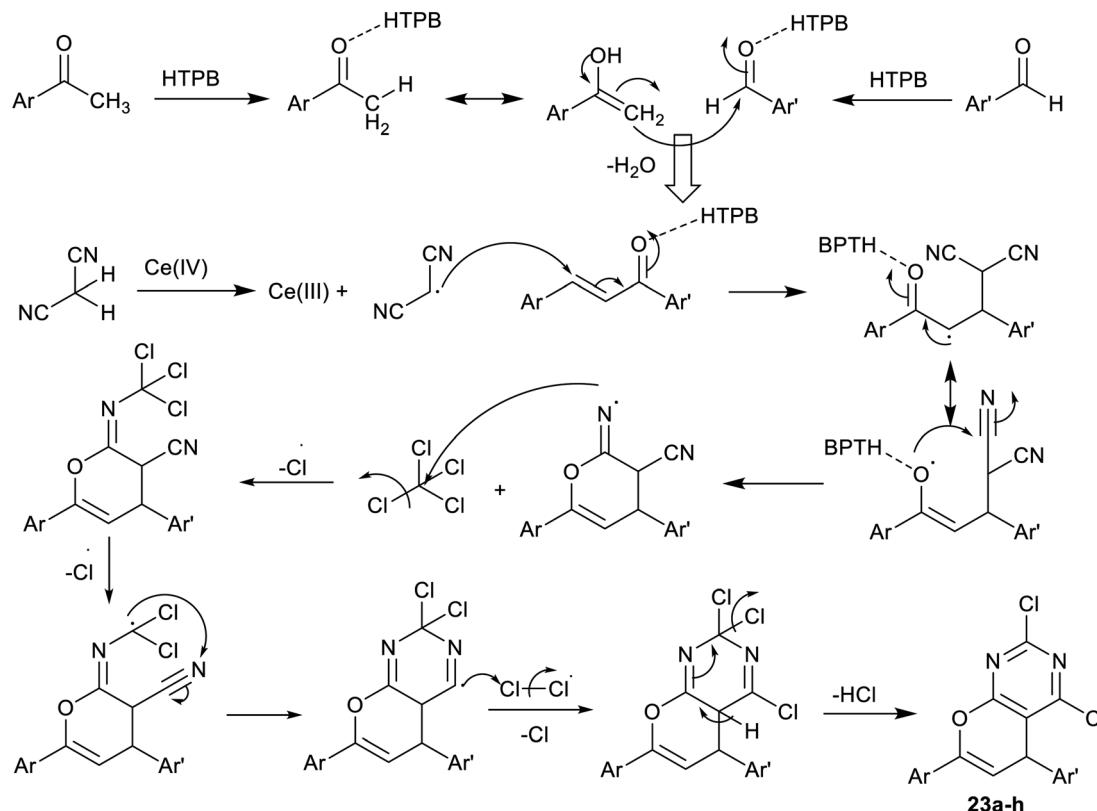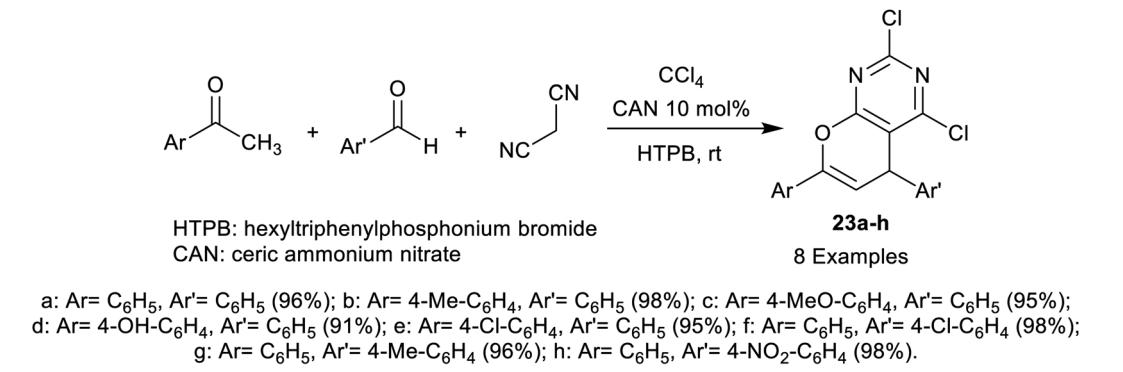
Scheme 14 Synthesis of bicyclic systems under CAN catalytic conditions.

pyranopyrimidin-4-ones **27a–j**. The plausible mechanism of this type of reaction involved arylidene intermediates formation by Knoevenagel condensation, Michael addition, pyran ring cyclization, and pyran-one ring cleavage by the nucleophilic attack of NH of the piperidine (Scheme 16). The compounds cleaved the DNA at the least concentration (100 μg mL^{-1}); this might be due to the effect of the pyrimidine skeleton that interacted with DNA and exhibited advanced sensitivity towards DNA. Moreover, the compounds revealed a broad spectrum of antibacterial activity, *e.g.* compound **27b** (R = 4-Cl-C$_6$H$_4$) displayed the most potent activity against *E. coli* (14.1 ± 0.36 mm), and *P. aeruginosa* (13.1 ± 0.28). In addition, compound **27a** (R = C$_6$H$_5$) revealed good activity only against *E. coli*, while compound **27g** (R = 2-OH-C$_6$H$_4$) revealed moderate to weak activities against Gram-

negative bacterial species, and *S. aureus*. Besides, a protein (bovine serum albumin) denaturation assay was applied to estimate the anti-inflammatory activity of this class of compounds at various concentrations (3.12–50 μg mL^{-1}). Thus, compound **27f** (R = 4-F-C$_6$H$_4$) exhibited the most potent activity (IC$_{50}$ = 5.92 μg mL^{-1}), this is probably assigned to the possible hydrogen bond affinity, non-covalent intermolecular interactions of C–F, and the high electron-withdrawing character of the fluorine atom. Also, compounds **27a** (R = C$_6$H$_5$), **26c** (4-Me-C$_6$H$_4$), and **27d** (R = 4-MeO-C$_6$H$_4$) revealed remarkable activity. Besides, the same series of these compounds "pyranopyrimidine-diones" (Scheme 16) were *in vitro* assessed as potential enzymes for α-amylase and α-glucosidase inhibitors. Accordingly, the potency of the compounds is increased with

25: 13 examples
26: 13 examples
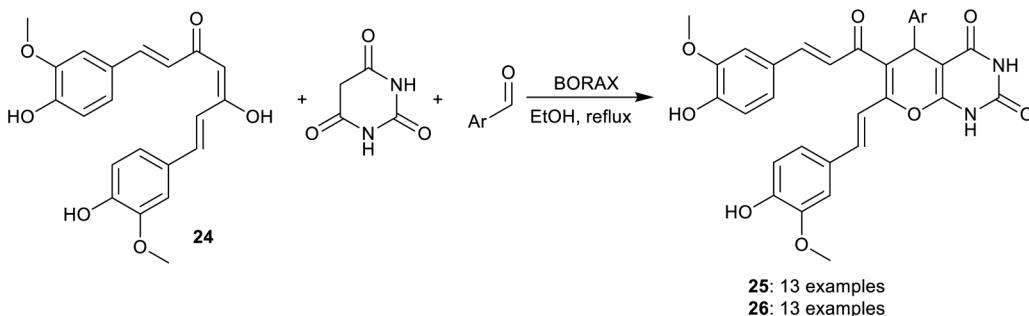
25a: Ar= 4-Cl-C$_6$H$_4$ (88%); b: Ar= indol-3-yl (85%); c: Ar= 3-Br-C$_6$H$_4$ (75%); d: Ar= 5-NO$_2$-fur-2-yl (70%);
e: Ar= 5-NO$_2$-thien-2-yl (87%); f: Ar= 4-Br-C$_6$H$_4$ (78%); g: Ar= 4-NMe$_2$-C$_6$H$_4$ (83%); h: Ar= 2-Cl-C$_6$H$_4$ (75%);
i: Ar= 2-Br-C$_6$H$_4$ (86%); j: Ar= pyrrol-2-yl (78%); k: Ar= 4-F-C$_6$H$_4$ (84%); l: Ar= 2-Cl-C$_6$H$_4$ (85%);
m: Ar= 4-pyridyl (83%). **26a'**: Ar= 2-OH-C$_6$H$_4$; b': Ar= 4-OH-C$_6$H$_4$; c': Ar= 2,3-(OH)$_2$-C$_6$H$_3$;
d': Ar= 2,4-(OH)$_2$-C$_6$H$_3$; e': Ar= 2,5-(OH)$_2$-C$_6$H$_3$; f': Ar= 3,4-(OH)$_2$-C$_6$H$_3$; g': Ar= 3,5-(OH)$_2$-C$_6$H$_3$;
h': Ar= 2,3,4-(OH)$_3$-C$_6$H$_2$; i': Ar= 2-(OH),3-MeO-C$_6$H$_3$; j': Ar= 2-(OH),4-MeO-C$_6$H$_3$;
k': Ar= 4-(OH),3,5-(MeO)$_2$-C$_6$H$_2$; l': Ar= 2-NO$_2$-C$_6$H$_4$; m': Ar= 3-NO$_2$-C$_6$H$_4$.

Scheme 15 Synthesis of dihydropyrano[2,3-d]pyrimidine-diones.

noticeable enzymatic activities for α-glucosidases than for α-amylases owing to the lower concentrations crucial to inhibit enzymatic activity in the case of α-glucosidases than for α-amylases. The results specified that analogs with substituents *e.g.* "R = 4-Cl-C$_6$H$_4$" (IC$_{50}$ = 4.021 Mm), "R = 4-MeO-C$_6$H$_4$" (IC$_{50}$ = 4.101 Mm), "R = 3-MeO, 4-OH-C$_6$H$_3$" (IC$_{50}$ = 4.862 Mm), and "R = 4-OH-C$_6$H$_4$" (IC$_{50}$ = 3.553 Mm) displayed the most potent activities for α-glucosidase but still lower than that of the standard, acarbose (IC$_{50}$ = 0.3268 Mm). Otherwise, compounds

with "R = 2-OH-naphth-3-yl" displayed the most potent activity for α-amylase with IC$_{50}$ = 6.490 Mm.[98]

3. Synthesis of tricyclic systems

Govindan *et al.*[99] have developed the synthesis of tricyclic dihydropyrazolo-pyrano-pyrimidine-diones using a sono-catalyst *e.g.* porphyrin-initiated amine-functionalized PBCMO-amine dendritic polymer. Thus, three-component one-pot reactions of aryl aldehydes with hydrazine, ethyl acetoacetate,

a: R= C$_6$H$_5$ (80%); b: R= 4-Cl-C$_6$H$_4$ (88%); c: R= 4-Me-C$_6$H$_4$ (82%);
d: R= 4-MeO-C$_6$H$_4$ (85%); e: R= 4-Br-C$_6$H$_4$ (85%); f: R= 4-F-C$_6$H$_4$ (78%);
g: R= 2-OH-C$_6$H$_4$ (81%); h: R= 2-OH-naphth-3-yl (78%);
i: R= 3-MeO,4-OH-C$_6$H$_3$ (80%); j: R= 4-OH-C$_6$H$_4$ (80%).

27a-j
10 examples
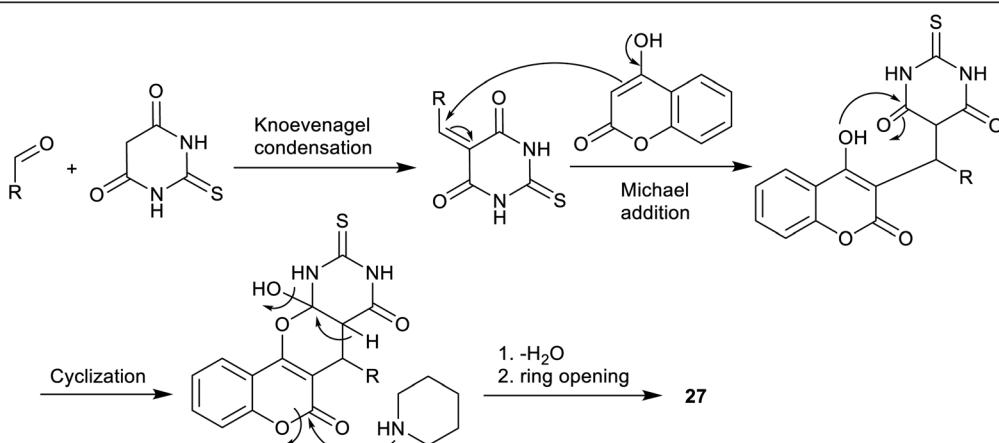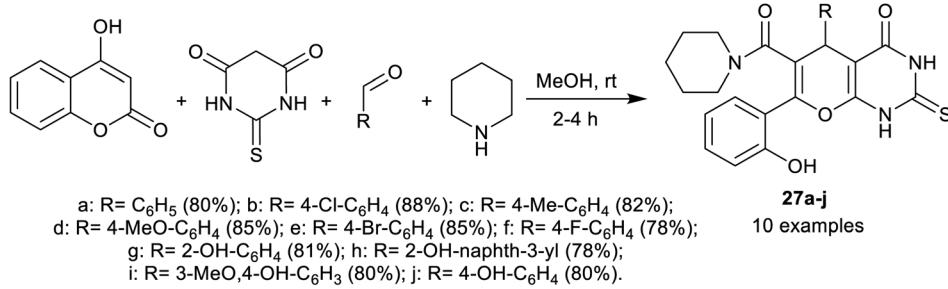
**Scheme 16** Synthesis of tetrahydropyranopyrimidinones.

and barbituric acid under catalytic, solvent-free, and sonication conditions gave the desired pyrazolopyrano-pyrimidine-diones **28** in good yields (85–99%) (Scheme 17). The green procedure is efficient to prepare this class of tricyclic systems with exceptional yields, shortened reaction time, and ease of product separation. The proposed mechanism for this type of reaction involved the pyrazolone ring cyclization from the reaction of EAA with hydrazine. The catalyst activated the active methylene group of barbituric acid for Knoevenagel condensation with aryl aldehydes and activated the active methylene group of the pyrazolone intermediate for addition to the arylidene intermediate. The final step is a cyclization of the pyran ring with the catalyst release and tautomerization to give the tricyclic pyrazolopyrano-pyrimidine-diones **28**.

Wei *et al.*[100] have developed the synthesis of a series of pyrazolo-pyranopyrimidine-diones by four-component one-pot reactions of hydrazine with aryl aldehydes, ethyl acetoacetate, and barbituric acid under catalytic, free-solvent, and heating conditions. The method tended to use SCMNPs@uridine/Zn as an efficient recyclable heterogeneous nanocatalyst in a green protocol with improved product yields (89–97%). In addition,

dihydro-pyrazolo-pyranopyrimidine-diones **29a–u** were synthesized by Akolkar *et al.*[101] using β-cyclodextrin as an efficient biomimetic catalyst under ultrasound-assisted conditions. Accordingly, one-pot four-component reactions of hydrazine hydrate with aryl aldehydes, barbituric acid, and ethyl acetoacetate in water catalyzed by β-cyclodextrin gave the estimated tricyclic systems **29a–u** in 84–93% yields (Scheme 18). The β-cyclodextrin catalyst is recyclable for four cycles. Most of this series of heterocycles were previously reported under various conditions, for example, meglumine and choline chloride/urea deep eutectic solvent.[102–104]

Honari *et al.*[105] have reported a green protocol for the synthesis of pyrazolo-pyranopyrimidine-diones **30** using four-component reactions of hydrazine with aryl aldehydes, barbituric acid, and EAA under catalytic, heating, and solvent-free conditions. Accordingly, the methodology tended to use DBU immobilized on $Fe_3O_4@nSiO_2@mSiO_2$ as a recyclable catalyst that delivered a short reaction time and excellent yields of the products (Scheme 19). The pyrazolone ring was firstly formed by cyclocondensation of ethyl acetoacetate with hydrazine, and subsequent Knoevenagel condensation of aryl aldehydes with


a: Ar= C_6H_5 (99%); b: Ar= 4-Br-C_6H_4 (98%); c: Ar= 1-naphthyl (97%); d: Ar= 4-Cl-C_6H_4 (99%);
e: Ar= 4-NO$_2$-C_6H_4 (99%); f: Ar= 3,4-(MeO)$_2$-C_6H_3 (90%); g: Ar= 4-NMe$_2$-C_6H_4 (96%); h: Ar= 2-furyl (92%);
i: Ar= 4-MeO-C_6H_4 (96%); j: Ar= 2-thienyl (97%); k: Ar= -CH=CH-C_6H_4 (88%); l: Ar= anthracen-9-yl (96%).
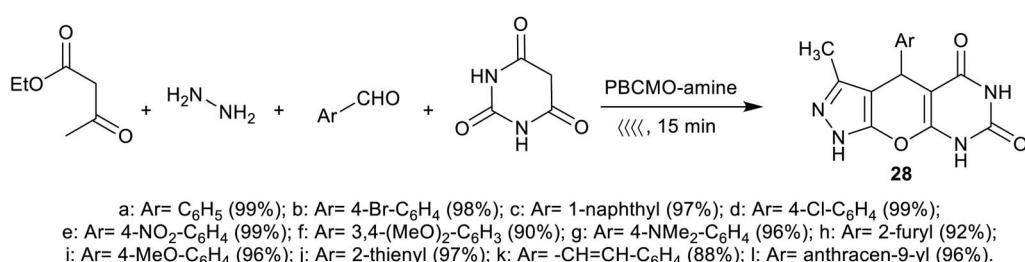
PBCMO-amine dendritic polymer
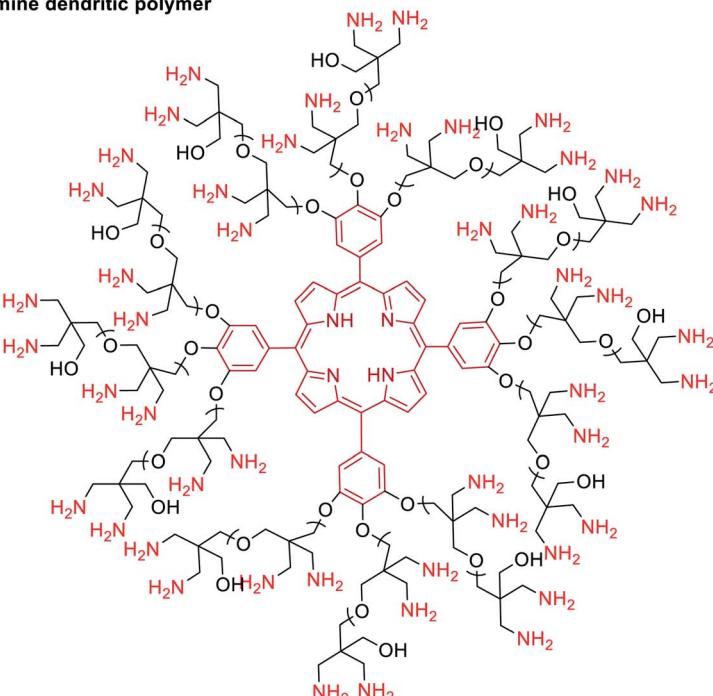
Scheme 17 Synthesis of pyrazolopyrano-pyrimidine-diones.
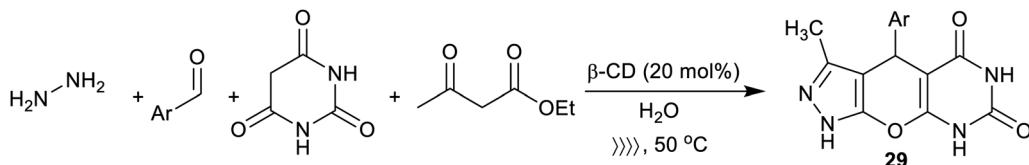
a: Ar= C$_6$H$_5$ (91%); b: Ar= 2-Cl-C$_6$H$_4$ (90%); c: Ar= 3-Cl-C$_6$H$_4$ (88%); d: Ar= 4-Cl-C$_6$H$_4$ (90%);
e: Ar= 2-NO$_2$-C$_6$H$_4$ (87%); f: Ar= 3-NO$_2$-C$_6$H$_4$ (90%); g: Ar= 4-NO$_2$-C$_6$H$_4$ (91%); h: Ar= 4-Br-C$_6$H$_4$ (92%);
i: Ar= 4-F-C$_6$H$_4$ (93%); j: Ar= 2-Me-C$_6$H$_4$ (86%); k: Ar= 4-Me-C$_6$H$_4$ (87%); l: Ar= 2-MeO-C$_6$H$_4$ (86%);
m: Ar= 4-MeO-C$_6$H$_4$ (87%); n: Ar= 3,4,5-(MeO)$_3$-C$_6$H$_2$ (84%); o: Ar= 3-OH,4-MeO-C$_6$H$_3$ (85%);
p: Ar= 2-OH-C$_6$H$_4$ (84%); q: Ar= 3-OH-C$_6$H$_4$ (85%); r: Ar= 4-OH-C$_6$H$_4$ (85%); s: Ar= 4-C$_6$H$_4$-C$_6$H$_5$ (90%);
t: Ar= 2-thienyl (86%); u: Ar= 2-furyl (88%).

Scheme 18 Synthesis of dihydropyrazolo-pyranopyrimidine-diones.

barbituric acid generated the arylidene intermediates. Michael's addition step was supported by the action of the catalyst through activation of the active C$_4$–H of pyrazol-3-one intermediate. Afterward, intramolecular cyclocondensation gave pyrazolo-pyrano-pyrimidine-diones **30**. An earlier approach by Li and coworkers,[104] reported the synthesis of the same products using meglumine as a biodegradable catalyst in water. Although the approach reported by Honari et al.[105] provided improved product yields, the previous green protocol reported by Li et al.[104] is preferred because of the ease of obtaining the catalyst since the Honari method required multi-step synthesis of the applied catalyst "Fe$_3$O$_4$@nSiO$_2$@mSiO$_2$@DBU".

A series of tricyclic pyrazolopyranopyrimidines **31** (Scheme 20) were proficiently synthesized through multicomponent reactions of dimethyl but-2-ynedioate with phenylhydrazine, aryl aldehydes, and barbituric acid under catalytic conditions of L-proline. The performance generally delivered the product with excellent yields. Consistently, the product yield in this sequence is affected by the effect of phenyl ring substituents, e.g., the same substituents at the p-position provided noticeably better yields than the substituents in the m- or o-positions, this behavior was not recorded for nitro or methyl substituents, while the use of heterocyclic aldehydes "Ar = 2-furyl, and 2-thienyl" did not yield the anticipated products. The amphoteric properties of L-proline enable the activation of the oxygen atom of carbonyl group, and hydrogen atom of the NH group by hydrogen bond formation with hydrogen atoms of acidic and basic groups, respectively.[106]

Aher et al.[107] have modified the synthesis of the previously reported, 3-methyl-4-aryl-4,8-dihydropyrazolo[4′,3′:5,6]pyrano[2,3-d]pyrimidine-5,7(1H,6H)-diones,[108,109] with excellent yields (85–96%) through solvent-free four-component one-pot reactions of barbituric acid, hydrazine, aryl aldehydes, and ethyl acetoacetate using tungsten-substituted molybdo-phosphoric acids, H$_3$[PMo$_7$W$_5$O$_{40}$]·24H$_2$O as a catalyst. The Keggin-type catalyst activated oxygen atoms of carbonyl groups for condensation steps to construct pyrazole ring, Knoevenagel condensation of the aldehyde with barbituric acid, and pyran ring cyclization.[107]
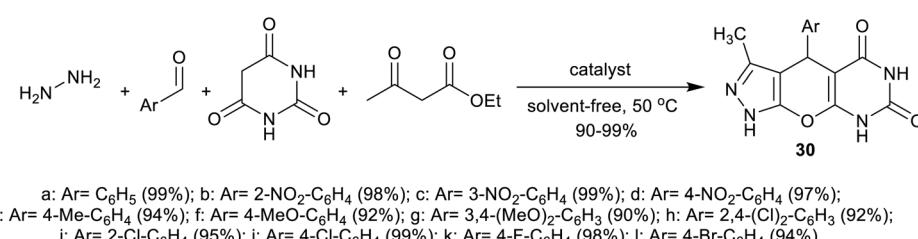

a: Ar= C$_6$H$_5$ (99%); b: Ar= 2-NO$_2$-C$_6$H$_4$ (98%); c: Ar= 3-NO$_2$-C$_6$H$_4$ (99%); d: Ar= 4-NO$_2$-C$_6$H$_4$ (97%);
e: Ar= 4-Me-C$_6$H$_4$ (94%); f: Ar= 4-MeO-C$_6$H$_4$ (92%); g: Ar= 3,4-(MeO)$_2$-C$_6$H$_3$ (90%); h: Ar= 2,4-(Cl)$_2$-C$_6$H$_3$ (92%);
i: Ar= 2-Cl-C$_6$H$_4$ (95%); j: Ar= 4-Cl-C$_6$H$_4$ (99%); k: Ar= 4-F-C$_6$H$_4$ (98%); l: Ar= 4-Br-C$_6$H$_4$ (94%).
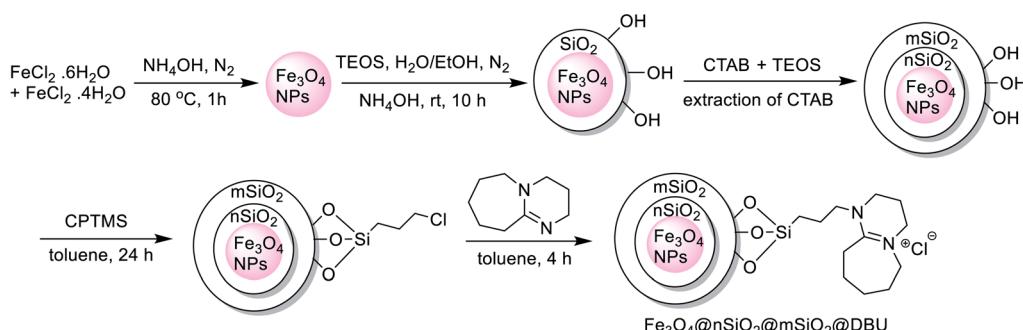
**Scheme 19** Synthesis of dihydropyrazolopyranopyrimidine-diones.
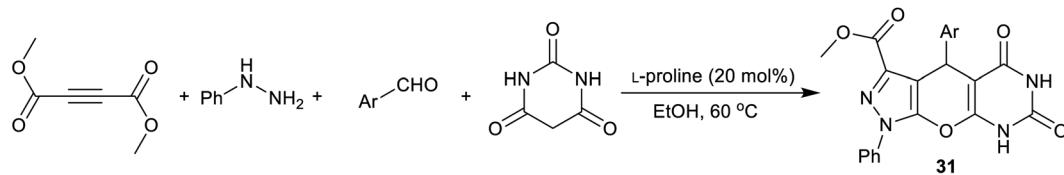
a: Ar= 4-Cl-C₆H₄ (90%); a: Ar= 3-Cl-C₆H₄ (92%); c: Ar= 2-Cl-C₆H₄ (83%); d: Ar= 4-Br-C₆H₄ (92%);
e: Ar= 3-Br-C₆H₄ (87%); f: Ar= 2-Br-C₆H₄ (85%); g: Ar= 3-F-C₆H₄ (87%); h: Ar= 3-OH-C₆H₄ (90%);
i: Ar= 4-OMe-C₆H₄ (91%); j: Ar= 3-OMe-C₆H₄ (90%); k: Ar= 4-OEt-C₆H₄ (87%); l: Ar= C₆H₅ (93%);
m: Ar= 4-Me-C₆H₄ (89%); n: Ar= 3-Me-C₆H₄ (90%); o: Ar= 4-CH(Me)₂-C₆H₄ (83%);
p: Ar= 4-NO₂-C₆H₄ (80%); q: Ar= 3-NO₂-C₆H₄ (84%).
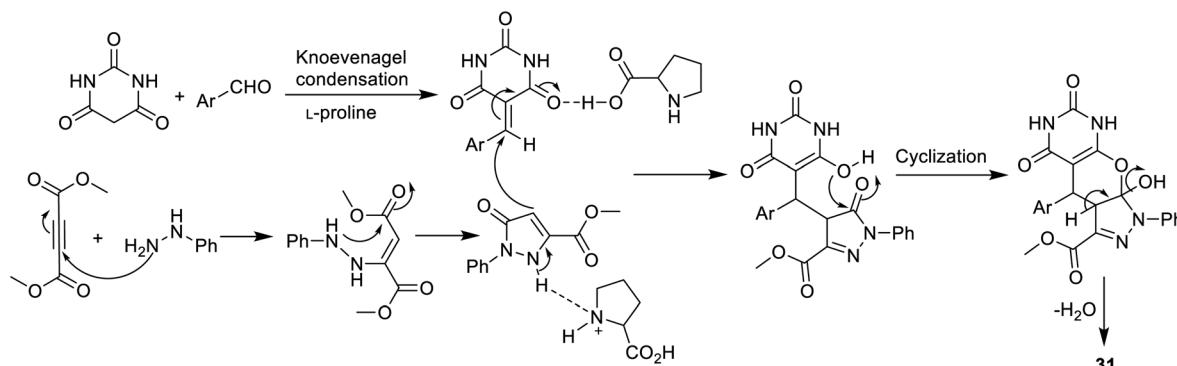
Scheme 20 Synthesis of methyl carboxylates.

Keshavarz *et al.*[110] have progressed a green protocol for the synthesis of the previously reported tricyclic systems 32,[104,108,111–113] using a recyclable heterogeneous organic-inorganic hybrid durable nano-catalyst "γ-Al₂O₃@silane-TMG" (Scheme 21). Thus, four-component one-pot reactions of hydrazine, ethyl acetoacetate, (thio)barbituric acid, and aryl aldehydes in water under gently heating (40 °C), and catalytic conditions gave the anticipated products 32 in 85–98% yields. The procedure efficiently provided the ease of separation of the products without extra purification with column chromatography. The basic character of the nanocatalyst enables the carbonyl group activation in condensation with hydrazine for the cyclization of pyrazolone ring, enolization of pyrazolone intermediate, proton abstraction of the active methylene group of (thio)barbituric acids in condensation with aryl aldehydes, and cyclocondensation of pyran ring after the Michael addition step-mechanism.

a: Ar= C₆H₅, X= O (98%); b: Ar= 2-MeO-C₆H₄, X= O (91%);
c: Ar= 3,4-(MeO)₂-C₆H₃, X= O (90%); d: Ar= 4-Me-C₆H₄, X= O (89%);
e: Ar= 4-Cl-C₆H₄, X= O (97%); f: Ar= 3-NO₂-C₆H₄, X= O (93%);
g: Ar= 4-NO₂-C₆H₄, X= O (96%); h: Ar= 4-OH-C₆H₄, X= O (95%);
i: Ar= 4-Br-C₆H₄, X= O (98%); j: Ar= 2-Cl-C₆H₄, X= O (98%);
k: Ar= C₆H₅, X= S (98%); l: Ar= 3-Cl-C₆H₄, X= S (85%);
m: Ar= 2-Cl-C₆H₄, X= S (87%); n: Ar= 4-Cl-C₆H₄, X= S (89%);
o: Ar= 3-NO₂-C₆H₄, X= S (92%); p: Ar= 4-NO₂-C₆H₄, X= S (95%);
q: Ar= 3-OH-C₆H₄, X= S (93%).
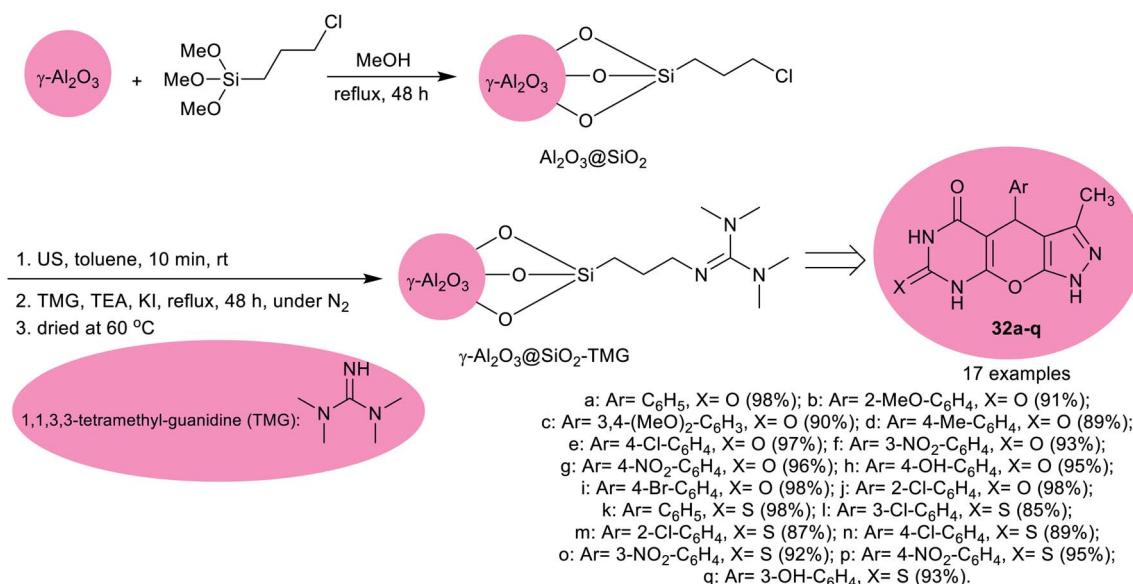
Scheme 21 Synthesis of γ-Al₂O₃@silane-TMG nano-catalyst for the synthesis of pyrazolo-pyranopyrimidinones.

The previous multicomponent synthesis was developed by Patil et al.[114] through the utility of catalytic sulfonic acid functionalized 1,4-diazabicyclo[2.2.2]octane supported on Merrifield resin "[MerDABCO-SO$_3$H]Cl". Thus, one-pot four-component EAA, hydrazine, aryl aldehydes, and barbituric acid in water under catalytic and heating conditions afforded the desired dihydropyrazolo-pyranopyrimidine-diones 33 (Scheme 22). In this research study,[114] the antioxidant, and antimicrobial activities of these compounds by DPPH˙, and agar well diffusion methods, respectively, were assessed. Accordingly, compounds 33b (Ar = 4-NO$_2$-C$_6$H$_4$, 98.38%), 33g (Ar = 3-NO$_2$-C$_6$H$_4$, 90.32%), 33i (Ar = –CH=CH–C$_6$H$_4$, 90.32%), and 33j (Ar = 2-OH, 5-NO$_2$-C$_6$H$_3$, 89.08%) displayed the most potent antioxidant scavenging relative to ascorbic acid. The antioxidant characteristics increases as the molecule can form a stable free radical that traps, and terminate efficiently the free radical reaction. The nitro groups on the phenyl ring increase the stability of the formed free radicals by the resonance effect. The antimicrobial results indicated broad spectrum of compounds 33a (Ar = C$_6$H$_5$, inhibition zone diameter = 18 mm), 33b (Ar = 4-NO$_2$-C$_6$H$_4$, IZD = 20 mm), c (Ar = 4-MeO-C$_6$H$_4$, IZD = 27 mm), 33d (Ar = 4-Me-C$_6$H$_4$, IZD = 25 mm) and 33f (Ar = 4-Cl-C$_6$H$_4$, IZD = 27 mm) exhibited good activity against *S. aureus*. The compounds c (Ar = 4-MeO-C$_6$H$_4$, IZD = 19 mm) and 33d (Ar = 4-Me-C$_6$H$_4$, IZD = 23 mm) revealed a worthy activity against *E. coli*. In addition, compounds 33a (Ar = C$_6$H$_5$, IZD = 23 mm), 33c (Ar = 4-MeO-C$_6$H$_4$, IZD = 27 mm), and 33d (Ar = 4-Me-C$_6$H$_4$, IZD = 27 mm) displayed the most potent antifungal activities against *C. albicans* species.

Ali et al.[115] have cited a multi-step synthesis of tricyclic systems with comparatively good yields. In this route, enaminonitrile 34 reacted with triethyl orthoformate in acetic anhydride to yield the desired ethyl formimidate 35. The reaction of compound 35 with hydrazine hydrate yielded the respective formimidohydrazide 36, which was refluxed in DMF/piperidine to give the target tricyclic system, tetrahydro-pyrazolo-pyrano[2,3-d]pyrimidinyl-4H-chromenone 37 (Scheme 23). Compounds 35 (42.29 ± 0.33%), 36 (53.27 ± 0.30%), and 37 (84.45 ± 0.32%) displayed promising antioxidant activities for scavenging the DPPH-free radicals at a concentration of 100 μg mL^{-1} relative to the result of ascorbic acid (97.56 ± 0.29%). Bakhotmah et al.[116] have reported the synthesis of tricyclic pyrazolopyranopyrimidines with efficient yields by the reactions of compound 34 with each urea or thiourea in sodium ethoxide solution.

Recently, Esmaeili et al.[117] have applied the use of organobase catalyst e.g. DIPEA for developed yields (90–94%) of 2,3-dihydro-pyranothiazolopyrimidines analogs 38. Therefore, three-component one-pot reactions of 7-hydroxy-2,3-dihydro-5H-thiazolo[3,2-a]pyrimidin-5-one with aryl aldehydes and malononitrile in refluxing ethanol yielded the tricyclic heterocycles after a short time. The mechanism for the synthesis of these products as presented in Scheme 24 proposed the action of the catalyst in the proton abstraction for stimulated condensation of aldehydes with malononitrile, and the interaction of active methylene of thiazolo[3,2-a]pyrimidin-5-one with the earlier formed arylidenes.

Malathi et al.[118] successfully synthesized tricyclic pyranopyridopyrimidinones 42 in a simple procedure under microwave irradiation conditions. Thus, multicomponent one-pot reactions of 2-hydroxy-4H-pyrido[1,2-a]pyrimidin-4-one (39) with aryl aldehydes 40, and N-methyl-1-(methylthio)-2-nitroethen-1-amine (41) under solvent-free conditions yielded the predicted products 42 in exceptional yields (79–94%) (Scheme 25). The mechanism proposed for the formation of the products 42 involved Knoevenagel condensation of aldehydes with pyridopyrimidinone 39 to generate the arylidene intermediate, which interacted with compound 41 through Michael

a: Ar= C$_6$H$_5$ (86%); b: Ar= 4-NO$_2$-C$_6$H$_4$ (79%); c: Ar= 4-MeO-C$_6$H$_4$ (81%); d: Ar= 4-Me-C$_6$H$_4$ (83%); e: Ar= 4-pyridyl (90%); f: Ar= 4-Cl-C$_6$H$_4$ (94%); g: Ar= 3-NO$_2$-C$_6$H$_4$ (92%); h: Ar= 2-OH-C$_6$H$_4$ (92%); i: Ar= -CH=CH-C$_6$H$_4$ (73%); j: Ar= 2-OH,5-NO$_2$-C$_6$H$_3$ (88%).
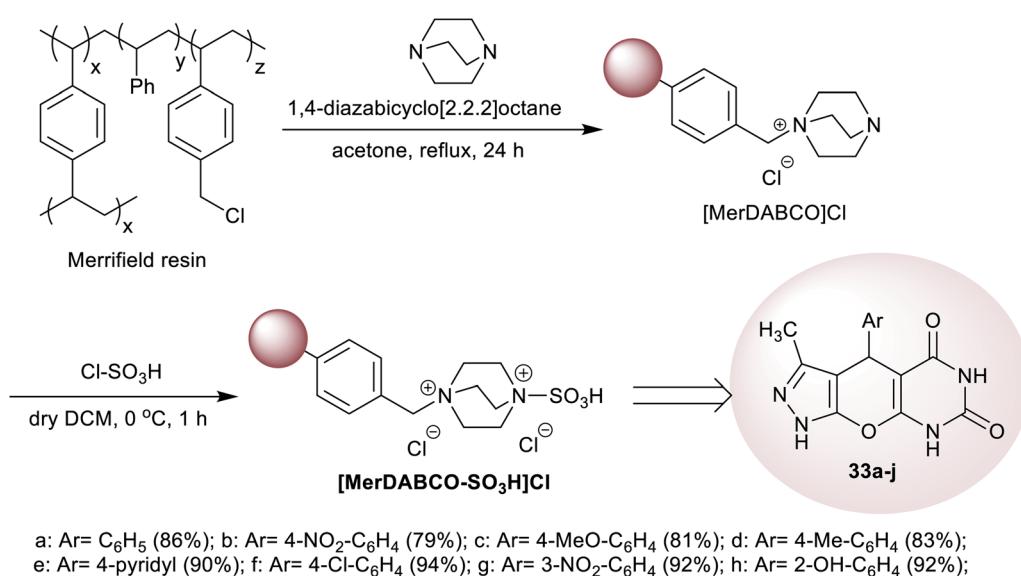
Scheme 22 Catalytic [MerDABCO-SO$_3$H]Cl, for the synthesis of dihydro-pyrazolo-pyranopyrimidine-dione series.
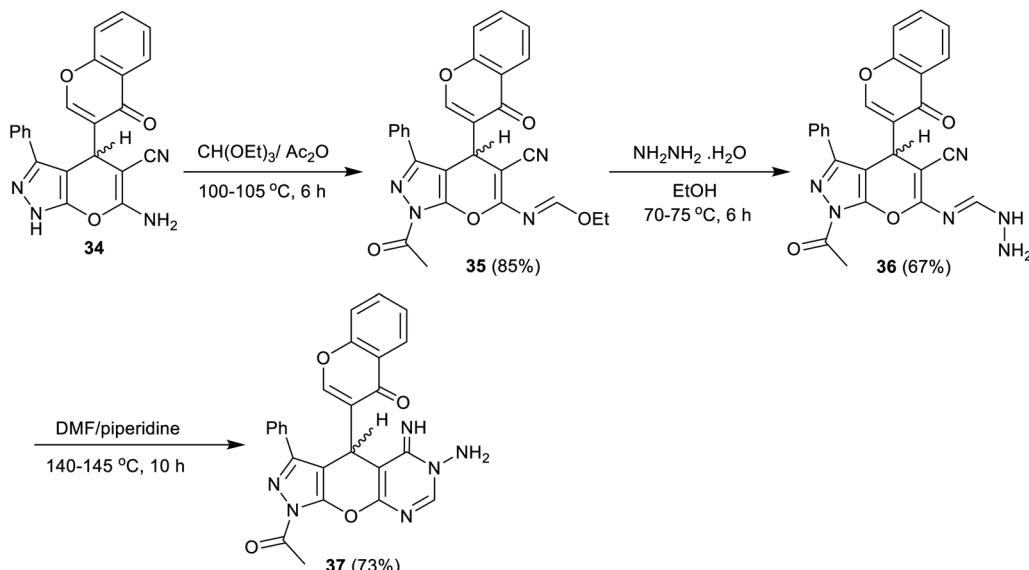
**Scheme 23** Multi-step synthesis of pyrazolopyranopyrimidinyl-4*H*-chromenone.

addition, subsequent imine-enamine tautomerization, and pyran ring closure.

The reactions of 4*H*-pyran **43** with DMF-DMA under heating conditions in THF followed by treatment with hydrazine hydrate in the second step yielded the respective bicyclic 4*H*-pyranopyrimidines **44**. The presence of two activated nucleophilic centers as NH, and NH₂ groups offered further opportunities for reactions with electrophilic carbons and phosphorus compounds. Thus, heating of compound **44** with aryl aldehydes and dichloro(phenyl)-phosphine in THF yielded the desired

a: Ar= 4-Cl-C₆H₄ (91%); b: Ar= 2,6-Cl₂-C₆H₃ (93%); c: Ar= 4-Me-C₆H₄ (90%); d: Ar= 4-CN-C₆H₄ (90%); e: Ar= 3-NO₂-C₆H₄ (93%); f: Ar= 2-Me-C₆H₄ (90%); g: Ar= 3-OMe-C₆H₄ (92%); h: Ar= 3-Me-C₆H₄ (90%); i: Ar= 4-OMe-C₆H₄ (93%); j: Ar= 4-NO₂-C₆H₄ (91%); k: Ar= 2-furyl (90%); l: Ar= 2-thienyl (91%); m: Ar= 1-naphthyl (94%); n: Ar= 2-naphthyl (91%); o: Ar= C₆H₅ (90%).
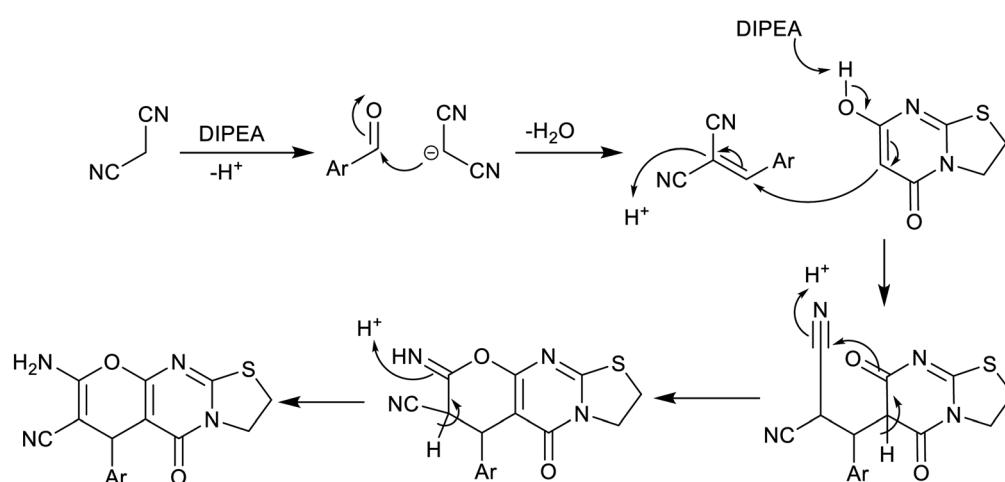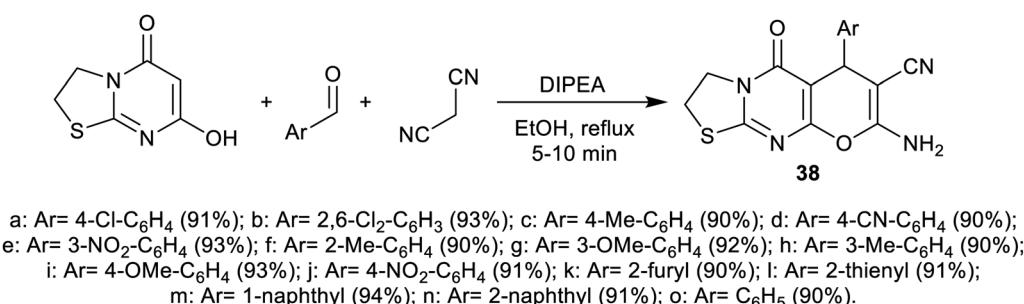
Scheme 24 Synthesis of 2,3-dihydro-pyranothiazolopyrimidines.
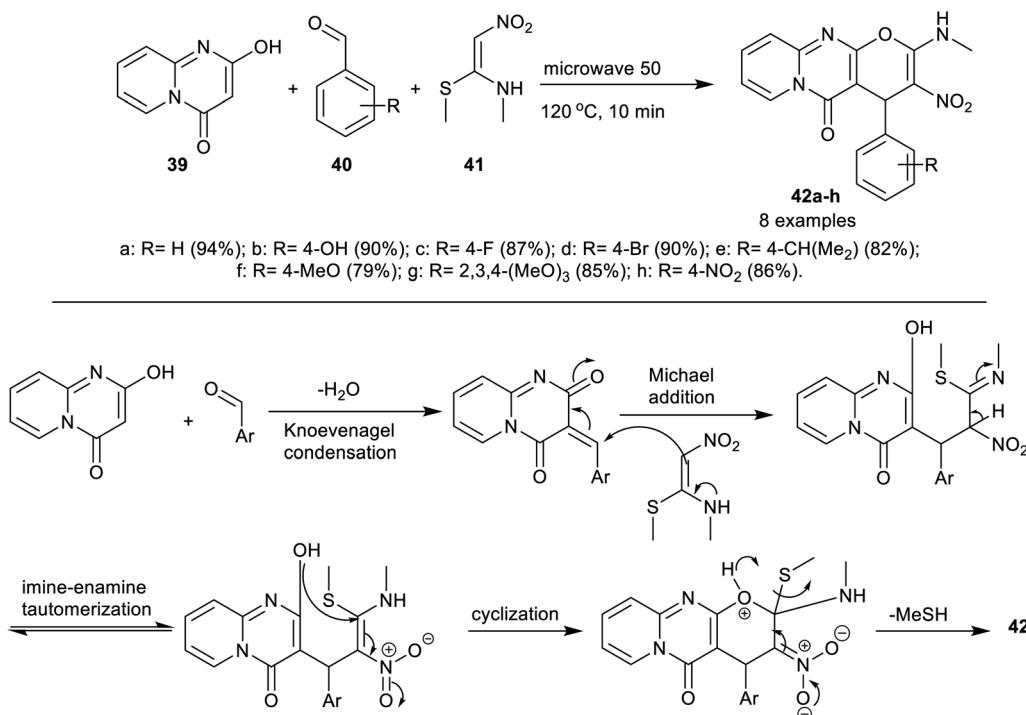
Scheme 25 Synthesis of pyranopyridopyrimidinones.

pyranopyrimido-triazaphininones **45** in noteworthy yields (78–86%) (Scheme 26). The mechanism of this reaction was projected by the formation of *N,N*-dimethyl-formamidine intermediate from the reaction of 4*H*-pyran **43** with DMF-DMA, pyrimidine ring cyclization by reaction with hydrazine hydrate, condensation of the amino group of **44** with aryl aldehydes, and imino group with dichloro(phenyl)-phosphine, hydrolysis, tautomerization, and triazaphosphinine ring cyclization through the Pudovik reaction.[119]

Rimaz *et al.*[120] reported multicomponent one-pot reactions of aryl glyoxal monohydrates **46** (1 equiv.) with (thio)barbituric acids **47** (2 equiv.) in the water containing ammonium acetate to

give the respective hexahydro-4*H*-pyrano-dipyrimidines **48** in moderate to good yields (55–88%). The reactions adopted to synthesize tricyclic analogues with X = 4-Cl, and X = 4-F also produced by-product structures such as "5-(hydroxy(aryl)meth-ylene)-5,9-dihydro-2*H*-pyrano[2,3-*d*:6,5-*d'*]-di-pyrimidine-2,4,6,8-(1*H*,3*H*,7*H*)-tetraones" with 42, and 44% yields, respectively. Reduced yields of these reactions were noticed from the reactions of thiobarbituric acid with aryl glyoxal monohydrates. The projected mechanism for the formation of the product **48** is depicted in Scheme 27. Ammonium acetate enabled the condensation steps in this technique.
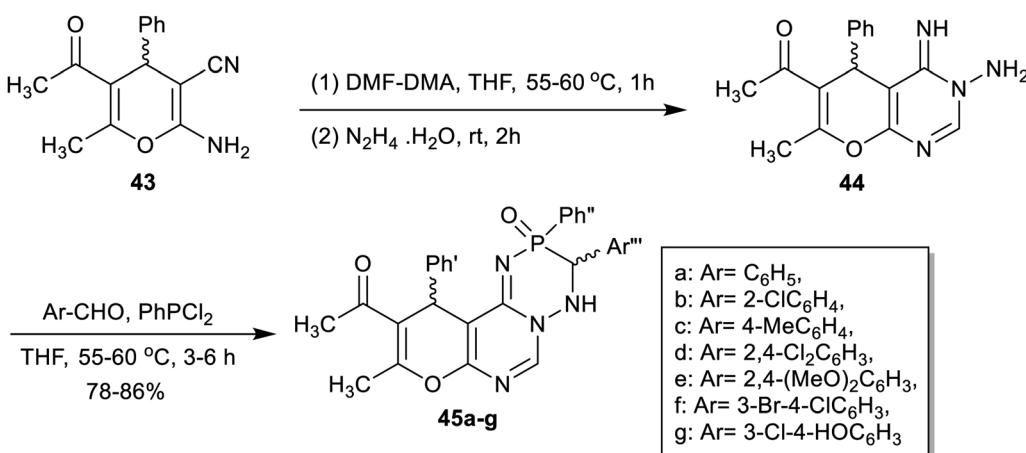
**Scheme 26** Synthesis of dihydro-4*H*-pyranopyrimido[1,2,4,5]triazaphosphinin-2-one analogues.

X= 4-H, 4-Br, 4-Cl, 4-F, 4-OMe, 3,4-(OCH$_2$O), 3-Br
Y= O, S
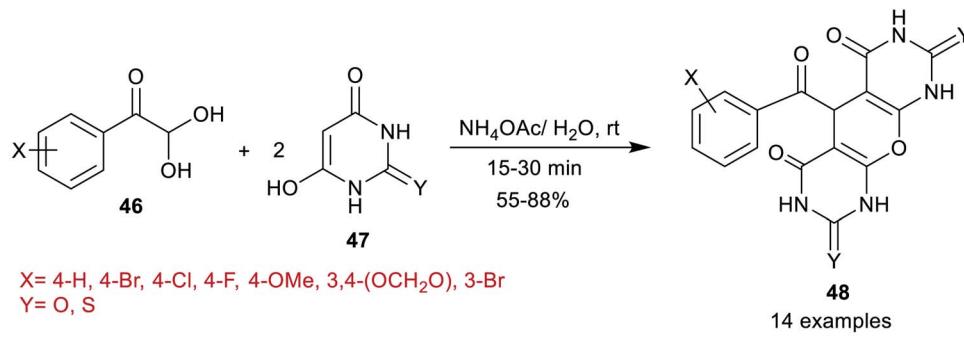
a: X= H, Y= O (70%); b: X= 4-Br, Y= O (62%); c: X= 4-Cl, Y= O (74%); d: X= 4-F, Y= O (69%);
e: X= 4-OMe, Y= O (88%); f: X= 3,4-(OCH$_2$O), Y= O (81%); g: X= 3-Br, Y= S (68%);
h: X= H, Y= S (68%); i: X= 4-Br, Y= S (55%); j: X= 4-Cl, Y= S (59%); k: X= 4-F, Y= S (70%);
l: X= 4-OMe, m: Y= S (72%); n: X= 3-Br, Y= S (75%).
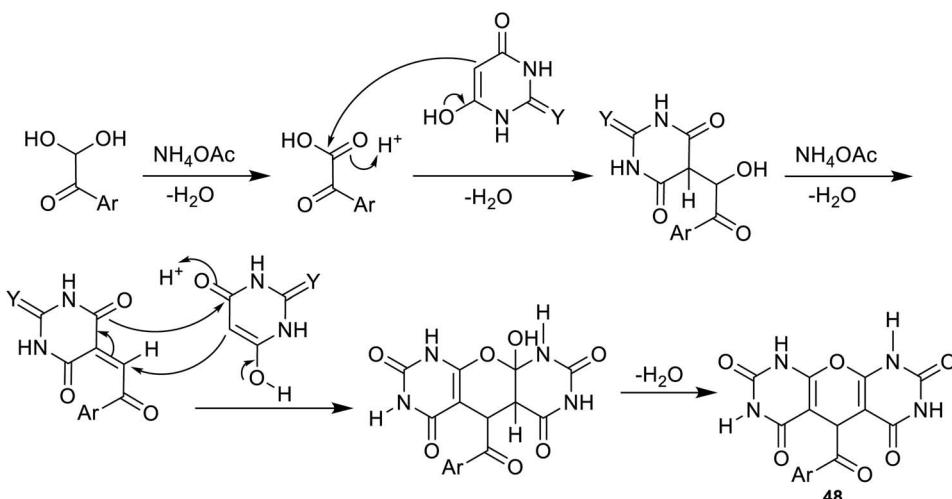
Scheme 27 Synthesis of hexahydropyranodipyrimidine-diones.

Avvadukkam *et al.*[121] have identified the synthesis of dihydro-2*H*-pyranodipyrimidine-tetraones **49a–k** under catalytic conditions of β-cyclodextrin (β-CD) as a supramolecular macrocyclic host. Thus, one-pot multicomponent reactions of aryl aldehydes with Meldrum's acid, and 6-amino-1,3-dimethyluracil catalyzed by β-cyclodextrin under microwave irradiation conditions yielded the corresponding pyranodipyrimidines **49a–k** (Scheme 28). The catalyst activation of aryl aldehydes in the Knoevenagel condensation step with Meldrum's acid generated the arylidene intermediate, which interacted with amino dimethyluracil in Michael addition-type, 1,3-dioxane ring cleavage, addition, and deamination to yield the tricyclic products. The catalyst in this procedure can generate new carbon–carbon and carbon–heteroatom bonds. The catalyst is recyclable and the method is a green technique that provides improved yields from these reactions under microwave irradiation conditions without extra purification by column chromatography.

Poola *et al.*[122] have developed the multicomponent reactions aryl aldehydes with malononitrile, and resorcinol under catalytic conditions of DBU in ethanol at reflux temperature to give the desired chromenes **50**. Multicomponent one-pot reactions of **50** with ammonium acetate and triethyl orthoformate under

catalytic "CuO–Ag nanocatalyst" and heating conditions gave the desired chromenopyrimidin-ols **51** (Scheme 29). The chromenopyrimidinol derivatives of **51** were assessed as antioxidant agents by DPPH and H$_2$O$_2$ radical scavenging assays. The results specified that compounds **51b** (Ar = 3,4-(OMe)$_2$-C$_6$H$_3$), **51d** (Ar = 4-Cl-C$_6$H$_4$), **51g** (Ar = 4-NO$_2$-C$_6$H$_4$), **51h** (Ar = 3-Cl, 6-OH-C$_6$H$_3$), and **51i** (Ar = 2-OH-C$_6$H$_4$), which are rich with a source of free radicals to trap DPPH free radicals, exhibited the most potent antioxidant activities higher than that of the standard BHT. The antibacterial activity of these compounds was also investigated against Gram-positive species *i.e. B. subtilis* and *S. aureus*, and Gram-negative species *i.e. S. aeruginosa* and *E. coli*. The antifungal activity was investigated against *Candida globrata* and *C. albicans* fungal species. The results verified that compounds **51b**, **51d**, and **51h** displayed a broad-spectrum activity against Gram-positive bacterial species and compounds **51b**, **51d**, **51h**, and **51i** displayed potent activities against Gram-negative bacterial species in comparison to the results of tetracycline. The potent antifungal activities were recorded for compounds **51b**, **51j**, and **51l** against both fungal species with higher potency than the standard, griseofulvin.
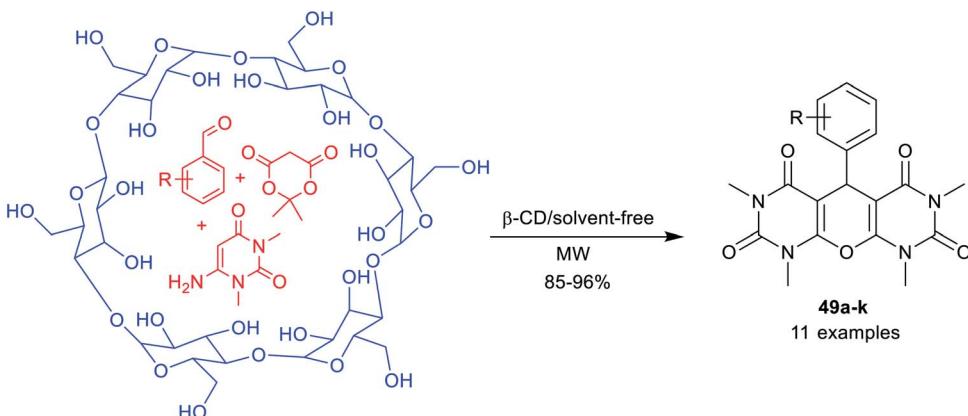
a: R= 4-Cl (87%); b: R= 4-Br (89%); c: R= 4-OH (94%); d: R= 4-CN (85%); e: R= 4-O-CH$_2$-Ph (89%);
f: R= 2,5-(OMe)$_2$ (94%); g: R= 2-OH,5-Br (90%); h: R= 3-OMe,4-OH (95%); i: R= 3,4,5-(OMe)$_3$ (95%);
j: R= 3,5-(OMe)$_2$,4-OH (96%); k: R= 3-OMe,4-OH,4-Br (94%).
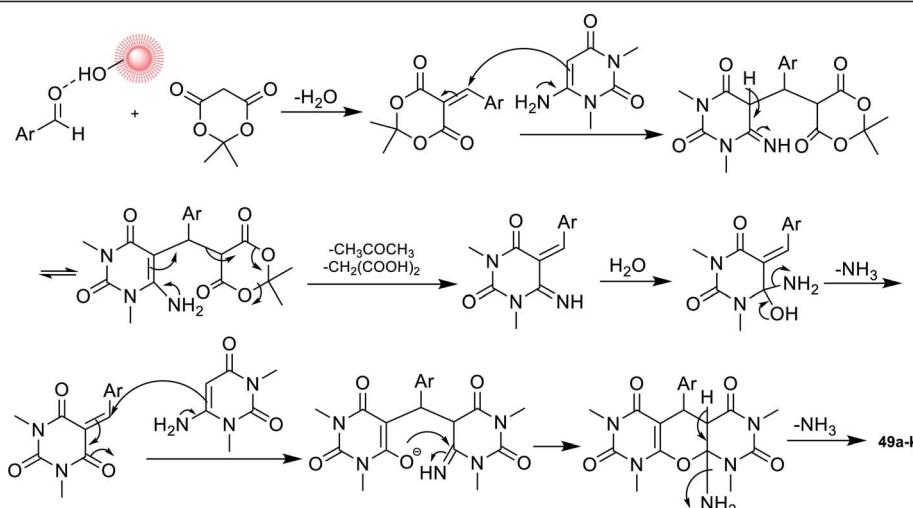
Scheme 28 Synthesis of dihydro-2H-pyranodipyrimidine-tetraones.

Scheme 29 Synthesis of 5H-chromenopyrimidinol derivatives.
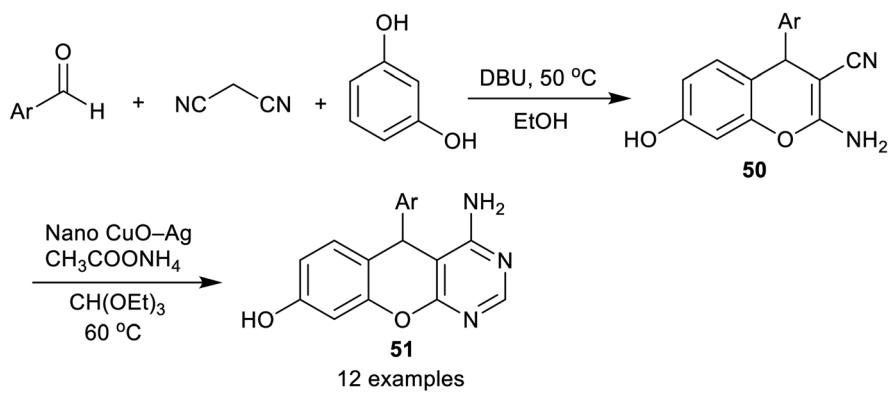
a: Ar= C$_6$H$_5$ (92%); b: Ar = 3,4-(OMe)$_2$-C$_6$H$_3$ (90%); c: Ar = 4-Br-C$_6$H$_4$ (92%); d: Ar = 4-Cl-C$_6$H$_4$ (92%);
e: Ar = 4-MeO-C$_6$H$_4$ (90%); f: Ar = 4-OEt-C$_6$H$_4$ (90%); g: Ar = 4-NO$_2$-C$_6$H$_4$ (92%);
h: Ar = 3-Cl,6-OH-C$_6$H$_3$ (90%); i: Ar = 2-OH-C$_6$H$_4$ (88%), j: Ar = benzo[d][1,3]dioxol-5-yl (90%),
k: Ar = 3-MeO,4-OH-C$_6$H$_3$ (88%), l: Ar = 2-furyl (90%).
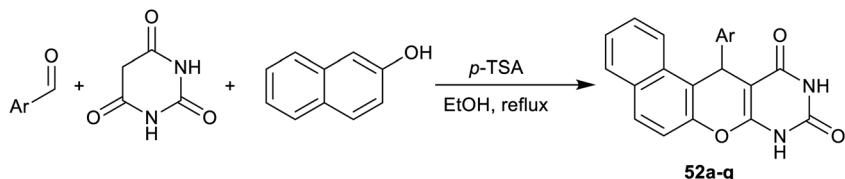
a: Ar= C$_6$H$_5$ (80%); b: Ar= 4-OH-C$_6$H$_4$ (90%); c: Ar= 4-NO$_2$-C$_6$H$_4$ (78%); d: Ar= 3,4-OMe$_2$-C$_6$H$_3$ (90%);
e: Ar= 4-F-C$_6$H$_4$ (82%); f: Ar= 3-Br-C$_6$H$_4$ (77%); g: Ar= 4-Cl-C$_6$H$_4$ (82%); h: Ar= 4-OMe-C$_6$H$_4$ (86%);
i: Ar= 3-OMe,4-OH-C$_6$H$_3$ (84%); j: Ar= 2-furyl (72%); k: Ar= 4-Me-C$_6$H$_4$ (86%); l: Ar= 2,4-Cl$_2$-C$_6$H$_3$ (74%);
m: Ar= 2-OH-C$_6$H$_4$ (80%); n: Ar= 2-thienyl (70%); o: Ar= 4-NMe$_2$-C$_6$H$_4$ (87%); p: Ar= 2-OH,3,5-Cl$_2$-C$_6$H$_2$ (80%);
q: Ar= indol-3-yl (70%).

Scheme 30 Synthesis of dihydro-9*H*-benzochromenopyrimidine-diones.

4. Synthesis of polycyclic systems

Karad *et al.*[123] have developed the synthesis of polycyclic dihydro-9*H*-benzochromeno-[2,3-*d*]pyrimidine-diones **51** in an acid medium in a one-pot multicomponent procedure. Thus, aryl aldehydes reacted with barbituric acid, and naphthalen-2-ol in ethanol/*p*-toluene sulfonic acid at their reflux temperature to furnish the desired compounds **52** in 70–90% yields (Scheme 30). The acid medium enabled the Knoevenagel condensation and Michael-type addition interactions throughout the projected mechanism of these reactions.

Rahmatinejad, and Naeimi,[124] have employed the utility of molybdenum-doped LaFeO$_3$ nano-sheets (8 mol%) as an effective catalyst for the synthesis of naphthopyranopyrimidine **53a–**

q. Thus, following the same previous reaction sequence of the reactants, β-naphthol reacted with aryl aldehydes, and (thio) barbituric acids in a one-pot multicomponent procedure under catalytic, free-solvent, and heating conditions giving the appraised naphthopyranopyrimidine derivatives **53a–q** in 82–92% yields. Most of the compounds prepared in this example using the molybdenum-doped LaFeO$_3$ nanocatalyst were previously prepared under other catalytic conditions, for example, iodine, lactic acid, and Fe$_3$O$_4$@MCM-48–SO$_3$H.[125–127] The LaMo$_{0.1}$Fe$_{0.9}$O$_3$ nano-catalyst was prepared from La(NO$_3$)$_3$·6H$_2$O in deionized water, Fe(NO$_3$)$_3$·9H$_2$O, and (NH$_4$)$_6$Mo$_7$O$_{24}$·4H$_2$O under stirring for 10 min followed by the addition of citric acid with continuous stirring at 80 °C. The product was calcified at 750 °C for 3 h. The use of this catalyst
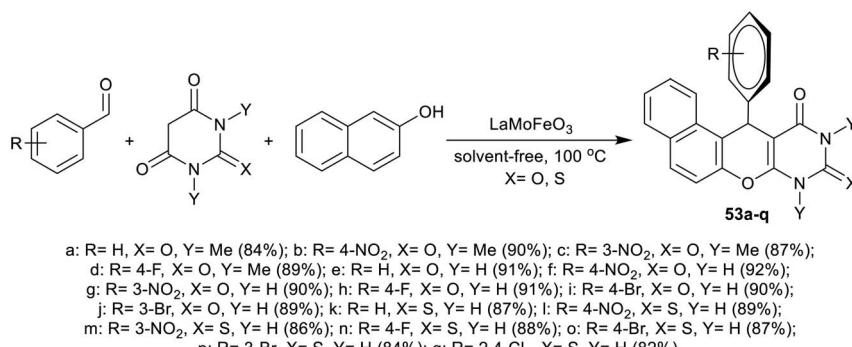
a: R= H, X= O, Y= Me (84%); b: R= 4-NO$_2$, X= O, Y= Me (90%); c: R= 3-NO$_2$, X= O, Y= Me (87%);
d: R= 4-F, X= O, Y= Me (89%); e: R= H, X= O, Y= H (91%); f: R= 4-NO$_2$, X= O, Y= H (92%);
g: R= 3-NO$_2$, X= O, Y= H (90%); h: R= 4-F, X= O, Y= H (91%); i: R= 4-Br, X= O, Y= H (90%);
j: R= 3-Br, X= O, Y= H (89%); k: R= H, X= S, Y= H (87%); l: R= 4-NO$_2$, X= S, Y= H (89%);
m: R= 3-NO$_2$, X= S, Y= H (86%); n: R= 4-F, X= S, Y= H (88%); o: R= 4-Br, X= S, Y= H (87%);
p: R= 3-Br, X= S, Y= H (84%); q: R= 2,4-Cl$_2$, X= S, Y= H (82%).
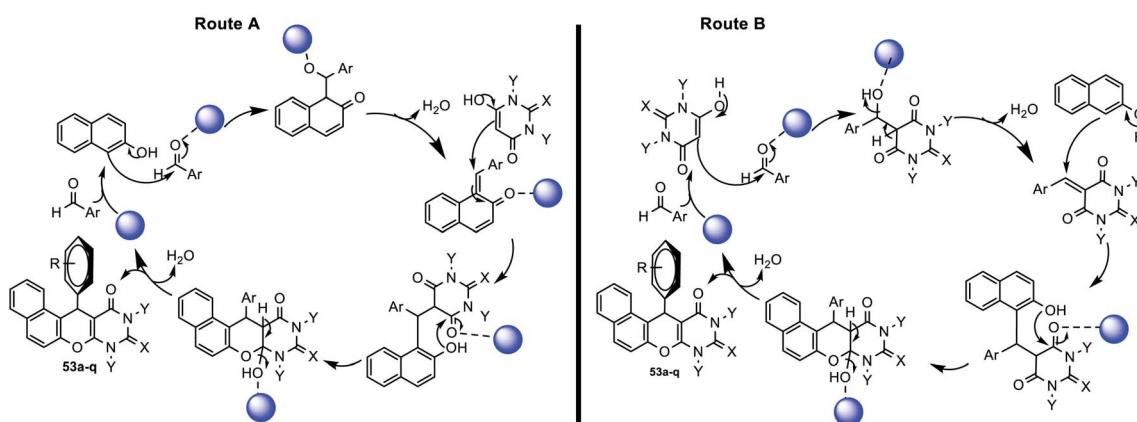
Scheme 31 Synthesis of benzochromenopyrimidinones.
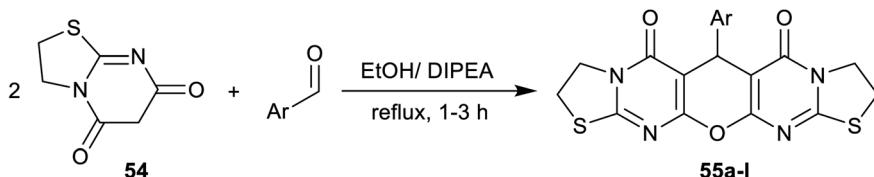
a: Ar= C$_6$H$_5$ (91%); b: Ar= 2-Cl-C$_6$H$_4$ (93%); c: Ar= 4-Cl-C$_6$H$_4$ (90%); d: Ar= 4-Br-C$_6$H$_4$ (90%);
e: Ar= 2-NO$_2$-C$_6$H$_4$ (93%); f: Ar= 4-NO$_2$-C$_6$H$_4$ (90%); g: Ar= 4-Me-C$_6$H$_4$ (92%); h: Ar= 3-Me-C$_6$H$_4$ (91%);
i: Ar= 4-MeO-C$_6$H$_4$ (93%); j: Ar= 2-thienyl (91%); k: Ar= 1-naphthyl (90%); l: Ar= 2-naphthyl (91%).

Scheme 32   Synthesis of polycyclic pyrano-bis-thiazolopyrimidinones.

enabled its reusability, ease of product separation, and relatively worthy yields. The procedure has a drawback in the difficulty of nanocatalyst preparation although this method provided improved product yields by the green protocol than the preceding method. The proposed mechanism for the naphthopyranopyrimidines 53a–q formation, as designed in Scheme 31 may follow two possible routes A and B. The Knoevenagel condensation could take place between the aryl aldehydes with either β-naphthol reacted or (thio)barbituric acids in the first step. The mechanism in both cases followed Michael's addition in the second step and succeeding cyclocondensation of the produced intermediates.

Esmaeili et al.[128] have progressed the usage of DIPEA as a basic catalyst for the synthesis of pyrano-bis-thiazolopyrimidinones 55 under mild conditions. In this approach, two moles of thiazolopyrimidine-dione 54 were reacted with one mole of the aryl aldehydes in a one-pot procedure under catalytic, and heating conditions. The reactions were accomplished in ethanol under heating conditions,

in which this green technique supported the synthesis of the target compounds 55 with magnificent yields (90–93%) (Scheme 32). Besides, this type of reaction has proceeded through three steps of the plausible mechanism involving initial Knoevenagel condensation, Michael addition with the other mole of compound 54, and pyran ring closure by intramolecular cyclocondensation of the generated intermediates.

In another route, Algethami et al.[129] have progressed to the synthesis of naphthopyranopyrimidinones 58 through a three-step approach. In this route, heating of naphthopyrans 56 with acetic anhydride containing phosphoric acid, subsequently treatment with sodium hydride, and 3-bromoprop-1-yne gave the corresponding N-propargylated naphthapyranopyrimidines 57. Subsequent 1,3-dipolar cycloaddition reactions of N-hydroxybenzimidoyl chlorides with naphthapyranopyrimidines 57 under either thermal (method A) or microwave irradiation (method B) conditions gave hybrid compounds 58 (Scheme 33). Compounds 57 revealed remarkable binding scores relative to the N3 inhibitor, in which
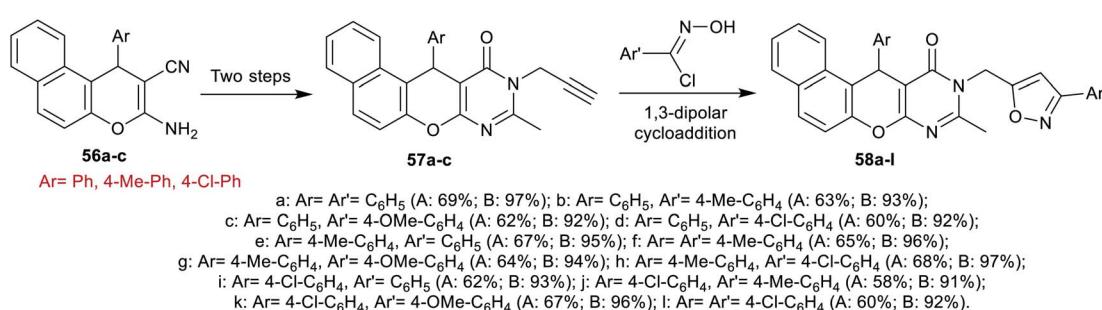
a: Ar= Ar'= C$_6$H$_5$ (A: 69%; B: 97%); b: Ar= C$_6$H$_5$, Ar'= 4-Me-C$_6$H$_4$ (A: 63%; B: 93%);
c: Ar= C$_6$H$_5$, Ar'= 4-OMe-C$_6$H$_4$ (A: 62%; B: 92%); d: Ar= C$_6$H$_5$, Ar'= 4-Cl-C$_6$H$_4$ (A: 60%; B: 92%);
e: Ar= 4-Me-C$_6$H$_4$, Ar'= C$_6$H$_5$ (A: 67%; B: 95%); f: Ar= Ar'= 4-Me-C$_6$H$_4$ (A: 65%; B: 96%);
g: Ar= 4-Me-C$_6$H$_4$, Ar'= 4-OMe-C$_6$H$_4$ (A: 64%; B: 94%); h: Ar= 4-Me-C$_6$H$_4$, Ar'= 4-Cl-C$_6$H$_4$ (A: 68%; B: 97%);
i: Ar= 4-Cl-C$_6$H$_4$, Ar'= C$_6$H$_5$ (A: 62%; B: 93%); j: Ar= 4-Cl-C$_6$H$_4$, Ar'= 4-Me-C$_6$H$_4$ (A: 58%; B: 91%);
k: Ar= 4-Cl-C$_6$H$_4$, Ar'= 4-OMe-C$_6$H$_4$ (A: 67%; B: 96%); l: Ar= Ar'= 4-Cl-C$_6$H$_4$ (A: 60%; B: 92%).
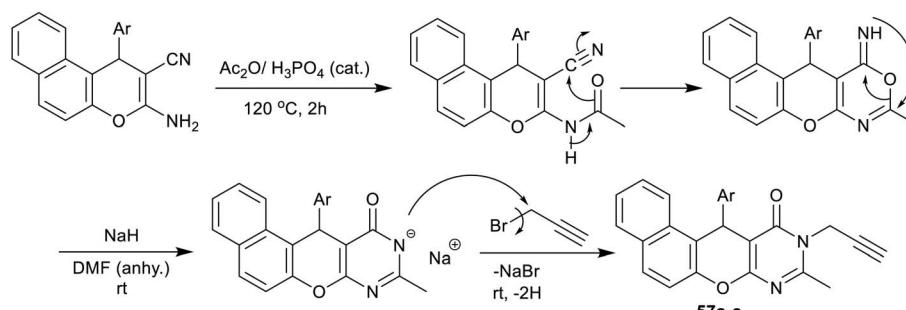
Scheme 33   Synthesis of naphtha-pyranopyrimidinones.
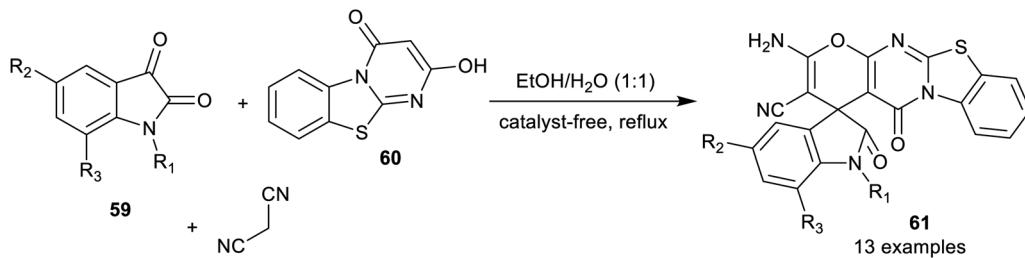
Scheme 34 Synthesis of spiro[benzothiazolopyranopyrimidine-indolines].

compounds **58a**, **58e**, **58h**, **58i**, **58j**, and **58k** achieved significantly analogous binding marks and modes of interaction than N3, demonstrating a hopeful tendency concerning SARS-CoV-2 M^{pro} with the expectation to cover the approach for the detection of anti-SARs-CoV-2 drugs.

5. Synthesis of spirocyclic systems

Zangouei, and Esmaeili,[130] have developed the synthesis of spiro [benzothiazolopyranopyrimidine-indoline] derivatives **61a–m** through an efficient green technique. The procedure involved
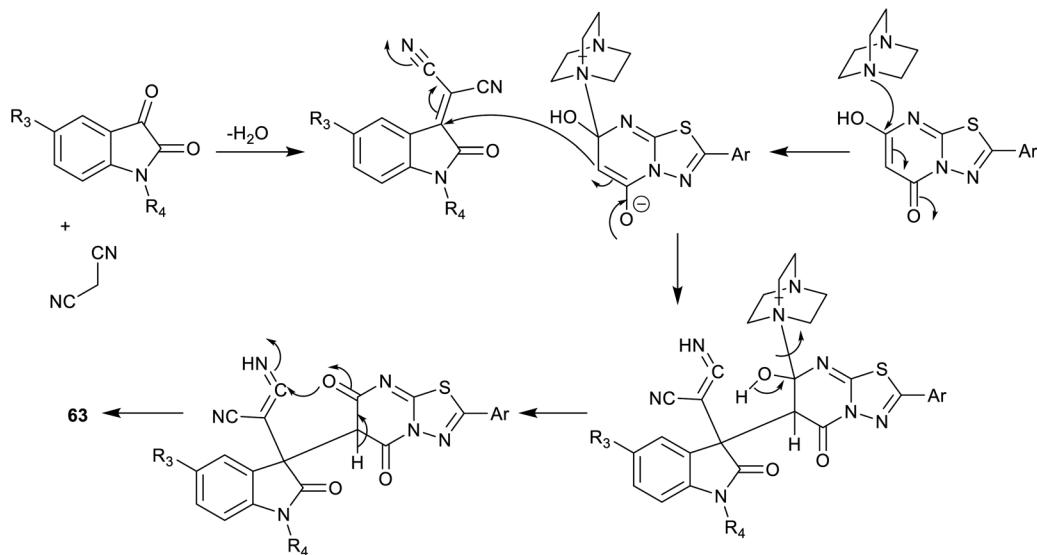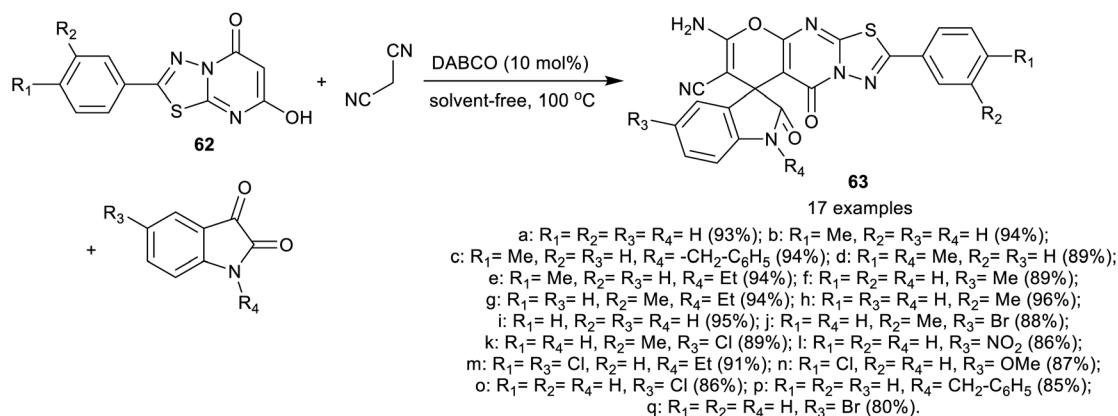
Scheme 35 Synthesis of spiro[indoline-pyranothiadiazolopyrimidines].

Scheme 36 Synthesis of spiro[benzothiazolo-pyranopyrimidine-indolines].
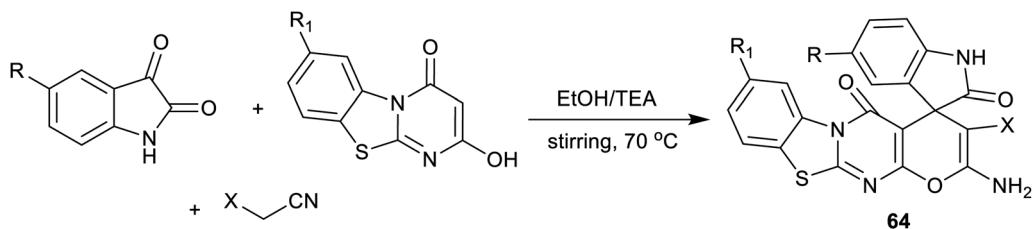
a: R= H, R$_1$= H, X= CN (94%); b: R= H, R$_1$= Me, X= CN (94%); c: R= OMe, R$_1$= H, X= CN (92%);
d: R= OMe, R$_1$= H, X= CO$_2$Et (86%); e: R= OMe, R$_1$= Me, X= CN (92%);
f: R= OMe, R$_1$= Me, X= CO$_2$Et (88%); g: R= R$_1$= H, X= CO$_2$Me (90%);
h: R= OMe, R$_1$= Me, X= CO$_2$Me (89%).

free-catalyzed one-pot multicomponent reactions of isatins **59** with malononitrile, and 2-hydroxy-4*H*-benzothiazolo-pyrimidinone **60** in a water/ethanol mixture under heating conditions giving the desired spiro[benzothiazolo-pyranopyrimidine-indoline] derivatives **61a–m** (Scheme 34). In this method, excellent yields were achieved (85–95%) along with reduced reaction time, and simplicity of purification without column chromatography.

The procedure reported by Hosseini *et al.*[131] delivered reduced the reaction time (10–60 min), green technique, and

exceptional yields (80–96%). Thus, solvent-free one-pot multi-component reactions of [1,3,4]thiadiazolo-pyrimidinones **62** with malononitrile, and isatin derivatives by heating under catalytic conditions of DABCO gave the anticipated 9'*H*-spiro [indoline-3,8'-pyrano[1,3,4]-thiadiazolopyrimidine] derivatives **63**. The conceivable mechanism, in this case, was introduced by the condensation of malononitrile with isatins in the first step to form arylidene intermediates. Next, activation of the active methylene of [1,3,4]thiadiazolo-pyrimidinones by the action of basic catalyst "DABCO" supported the nucleophilic attack at the


X= H, NO$_2$, F, Cl, Br
Y= H, Me
Z= O, S
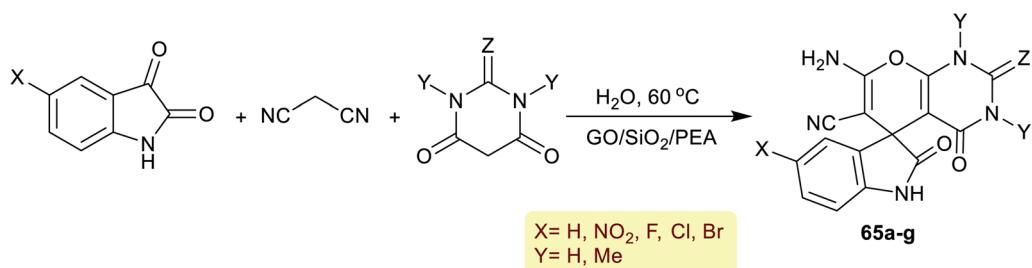
a: X= H, Y= H, Z= S (90%); b: X= F, Y= H, Z= S (93%); c: X= Cl, Y= H, Z= S (92%);
d: X= Br, Y= H, Z= S (91%); e: X= Cl, Y= Me, Z= O (89%); f: X= F, Y= Me, Z= O (90%);
g: X= H, Y= Me, Z= O (90%).
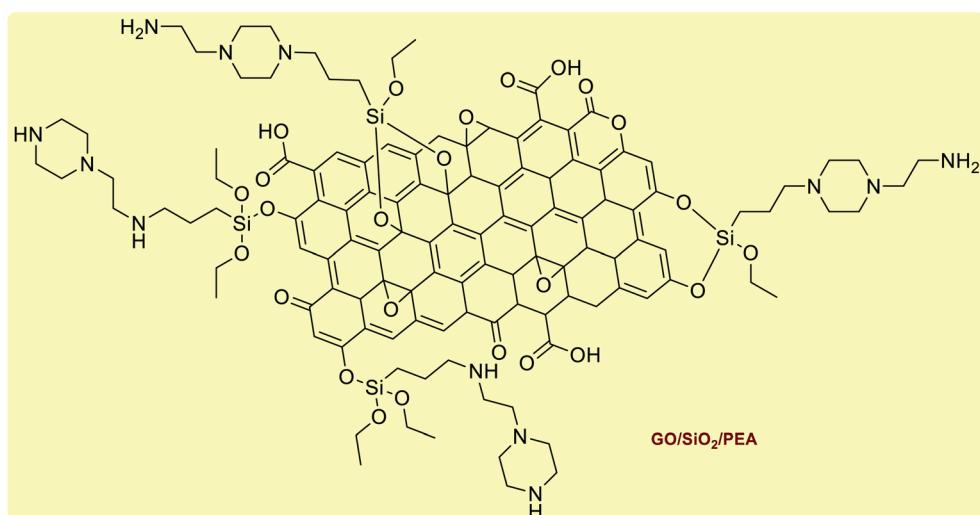
Scheme 37 Synthesis of spiro[indoline-pyranopyrimidines].

generated arylidene carbon. The removal of the base reinforced the cyclization of the pyran ring by the nucleophilic attack of the oxygen atom of the carbonyl group at the enamine carbon (Scheme 35).

Gholami *et al.*[132] have specified the synthesis of spiro [benzothiazolo-pyranopyrimidine-indolines] **64** by multicomponent one-pot reactions of isatins with active methylene compounds, *i.e.*, malononitrile or alkyl 2-cyanoacetates, and 4*H*-benzothiazolo-pyrimidinone in ethanol/trimethylamine at reflux temperature (Scheme 36). The function of the catalytic base is to ease the condensation of isatin with active methylene to generate the individual arylidene intermediates. Products **64** were formed as the suggested mechanisms that involved

Knoevenagel condensation, Michael addition, intramolecular cyclization, and rearrangement through [1,3]-H shift.

Toorbaf and Moradi,[133] have utilized GO/SiO$_2$/PEA as a heterogeneous base catalyst for the synthesis of tetrahydrospiro[indoline-pyranopyrimidines] **65a–g** in considerably tremendous yields (89–93%) (Scheme 37). The reactions proceeded in a one-pot multicomponent sequence for isatins, malononitrile, and (thio)barbituric acids in water under heating conditions to give the corresponding spirooxoindole derivatives **65**. The catalyst "GO/SiO$_2$/PEA" was efficiently prepared by heating graphene oxide with (3-chloropropyl)-triethoxysilane followed by heating with 2-(1-piperazinyl)ethylamine in dry toluene. This procedure is a green technique and the catalyst,
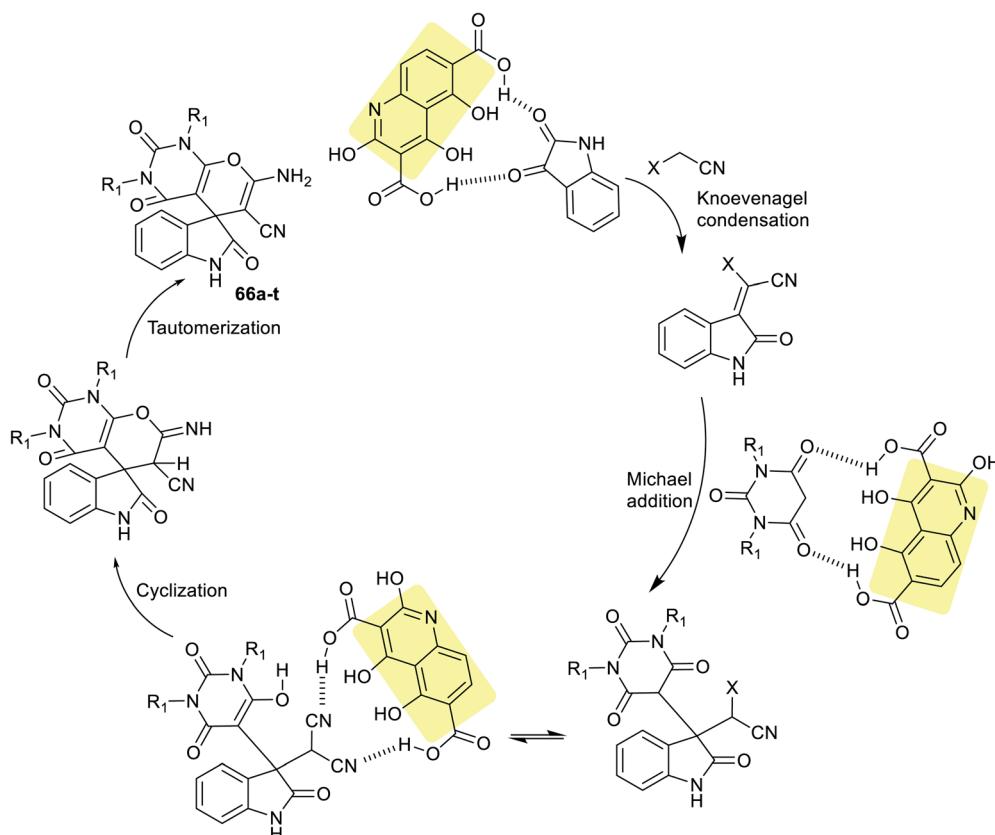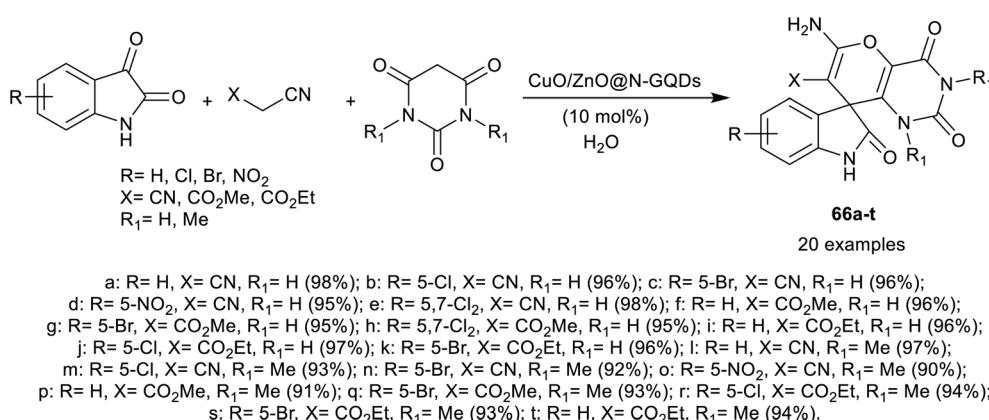
Scheme 38 Synthesis of spiro[indoline-3,8′-pyranopyrimidines].

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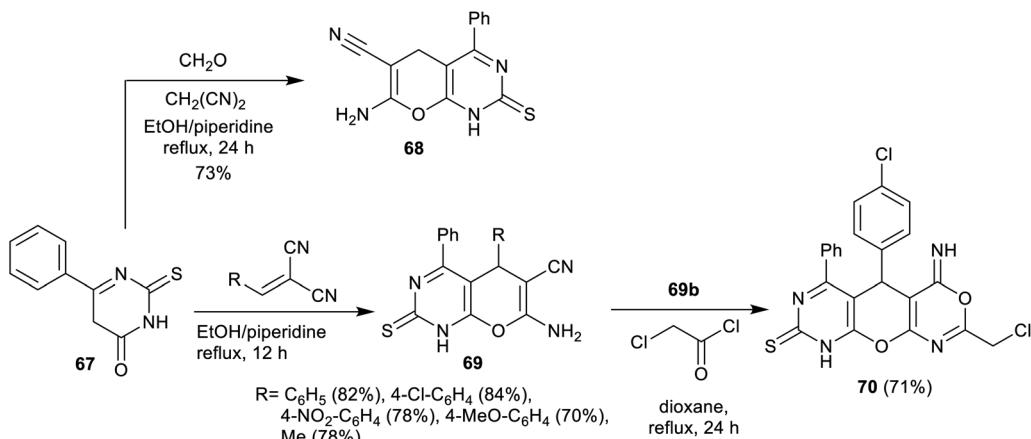
Scheme 39 Reactivity of dihydropyrimidinone in the multi-step synthesis of pyranopyrimidines.

"graphene oxide functionalized with 2-(1-piperazinyl)-ethyl-amine" GO/SiO$_2$/PEA is recyclable, providing the products in reduced reaction time. The mechanism of the formation of this class "spirooxoindoles" is complemented with the same sequence of the aforementioned spiro[benzothiazolopyr-anopyrimidine-indolines].[132]

Safaei-Ghomi et al.[134] have developed the use of the CuO/ZnO@N-GQD nanocomposite for the synthesis of tetrahy-drospiro[indoline-3,8'-pyranopyrimidines] via one-pot three-component reactions. Therefore, isatins reacted with active methylene compounds such as malononitrile, or methyl/ethyl 2-cyanoacetate and barbituric acids with 10 mol% of the nano-catalyst in water to give the desired products **66a–t**. The method is a green route applied to improve the product yields than the earlier reported approaches for the preparation of these series of compounds.[135–137] The synthesis of the nanocatalyst involved the stirring of a solution of ethane-1,2-diamine with citric acid in deionized water at 30 °C, followed by the addition of the CuO/

ZnO heterojunction prepared from "copper acetate with zinc acetate (1 : 4) in the sodium hydroxide medium under thermal conditions" and the mixture was placed in a Teflon-lined stainless-steel autoclave. This technique is a modification of N-GQDs with CuO-nanoparticle/ZnO-nanorod hetero-structures. The reaction mechanism followed the nanocatalyst activation of the carbonyl groups of isatin in Knoevenagel condensation with active methylene to produce the arylidene intermediate and subsequently activated the carbonyl groups of barbituric acid for the Michael addition step (Scheme 38).

6. Synthetic applications

Abdel-Reheim et al.[138] have reported the synthesis of dihy-dropyrimidinone **67** from the reaction of thiourea with ethyl benzoyl acetate and applied this compound in the multi-step synthesis of bicyclic pyranopyrimidines by reactions with arylidenes, or by the multicomponent reaction with
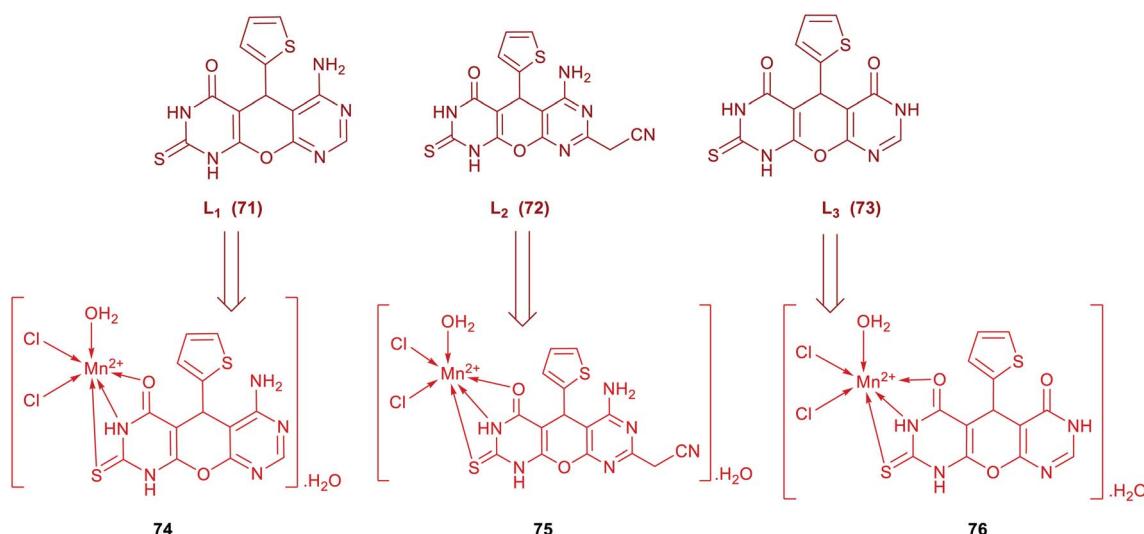

Fig. 3 The tetrahydro-pyranodipyrimidine ligands for the synthesis of Mn(ɪɪ) metal complexes.

formaldehyde, and malononitrile. Also, the reactivity of pyranopyrimidine **69b** towards diverse reagents *e.g.* chloroacetyl chloride, DMF-DMA, arylidenes, and formamide were investigated (Scheme 39). The relatively moderate yields of the reactions involved in the enaminonitrile moiety relied upon the nature of the enaminonitrile precursor, and the reactivity of the reacting reagents in addition to the applied method for each reaction; this performance is realized with our previous work and cited literature on the synthesis of heterocycles from enaminonitriles.[139–141]

Alternatively, El-Shwiniy *et al.*[142] have reported the employment of tetrahydro-pyranodipyrimidines as ligands "**L1–L3**" (compounds **71–73**) for the synthesis of Mn(II) metal complexes **74–76** (Fig. 3). The anticancer activity of the metal complexes and the ligands was assessed against the breast cancer cell line (MCF-7) and colon cancer cell line (HCT-116), in which the complex of $[Mn(L_2)Cl_2(H_2O)] \cdot H_2O$ introduced the most potent activity than the free-ligands. Also, the antimicrobial activity of these ligands and complexes was investigated with broad-spectrum activities for the metal complexes than the free ligands.

7. Concluding remarks

The current review highlights the recent methods adopted for the multicomponent synthesis of pyrano[2,3-*d*]pyrimidines. Therefore, many efficient approaches for the synthesis of the target compounds were discussed, whether applying the green protocol to improve the product yield or enable the catalyst preparation, using readily available materials, or the ease of product separation, and reduced reaction time. The topic of this review included the synthesis of bicyclic systems with the pyrano[2,3-*d*]pyrimidine core through multicomponent reactions of malononitrile or curcumin or Meldrum's acid with aryl aldehydes, and (thio)barbituric acids or their derivatives. Also, the bicyclic systems were prepared by four-component one-pot reactions of 4-hydroxycoumarin with aryl aldehydes, thiobarbituric acid, and piperidine. The second section comprises the synthesis of tricyclic systems through multicomponent reactions of (phenyl)hydrazine with aryl aldehydes, ethyl acetoacetate, or dimethyl but-2-ynedioate, and (thio)barbituric acids or through multi-step synthesis starting from enaminonitriles of pyranopyrazole. Also, varied tricyclic systems were prepared using different reactants, such as the reactions of aryl glyoxal monohydrates (1 equiv.) with (thio)barbituric acids (2 equiv.) in water to synthesize the desired pyrano-dipyrimidines. The synthesis of polycyclic systems was achieved by multicomponent reactions of aryl aldehydes with barbituric acid, and naphthalen-2-ol in ethanol/*p*-toluene sulfonic acid. The spirocyclic systems were synthesized by multicomponent reactions of isatins with malononitrile, and 2-hydroxy-4*H*-benzothiazolopyrimidinone or [1,3,4]thiadiazolopyrimidinones or (thio)barbituric acids. The synthesis of spirocyclic systems by multicomponent reactions of 8-methylindolo[2,1-*b*]quinazoline-6,12-dione with (thio)barbituric acids, and malononitrile in basic medium was recently identified.[143] The literature overview indicated that the multicomponent synthesis of pyrano[2,3-*d*]

pyrimidines excreted various analogs with significant biological profiles, which is also featured by high reactivity, particularly the enaminonitrile derivatives attached to bicyclic systems with different reagents.

8. Future prospective

In view of the numerous advantages and methodologies of the catalysts mentioned in this review, it was found that most of these catalysts suffer from many drawbacks, such as the difficulty of the preparation, the catalyst stability, the high cost of the reagents used in their preparation, long reaction times, and the use of large quantities of them during the reaction procedure with moderate yields. Consequently, there is an increasing need for many efforts of researchers to find more efficient and green methods using low-cost reagents and easy-to-prepare catalysts for the synthesis of the above-specified heterocyclic compounds. Through the multicomponent synthesis discussed in this review, we found that there is very little attention from researchers on the reactivity of these compounds towards many reagents, especially those bicyclic compounds that contain an enaminonitrile or an enaminoester nucleus, which can undergo many reactions with diverse reagents in the future to prepare new heterocyclic compounds of predicted biological characteristics.

Abbreviations

MIC	Minimum inhibitory concentration
IC_{50}	Half-maximal inhibitory concentration
MTT	3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyl-2*H*-tetrazolium bromide
MDW	Magnetized deionized water
TMDP	4,4′-Trimethylenedipiperidine
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
MW	Microwave irradiation
US	Ultrasonic-assisted
DES	Deep eutectic solvent
DFT	Density functional theory of computational
POM	Petra/osiris/molinspiration
DABCO	1,4-Diazabicyclo[2.2.2]octane
IZD	Inhibition zone diameter in mm
PEG-400	Polyethylene glycol 400
β-CD	β-Cyclodextrin
PBCMO-amine	Poly-3,3-bis(chloromethyl)oxetane
EAA	Ethyl acetoacetate
SCMNPs	Silica-coated magnetite nanoparticles
DBU	1,8-Diazabicyclo(5.4.0)undec-7-ene
TMG	1,1,3,3-Tetramethyl-guanidine
DIPEA	*N*,*N*-Diisopropylethylamine
DMF-DMA	*N*,*N*-Dimethylformamide dimethyl acetal
THF	Tetrahydrofuran
Ph-PCl₂	Dichloro(phenyl)-phosphine
p-TSA	*p*-Toluene sulfonic acid
DIPEA	Diisopropylethylamine

Conflicts of interest

The authors state no conflict of interest.

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