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A review on lawsone-based benzo[*a*]phenazin-5-ol: synthetic approaches and reactions

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Phenazine systems are an important class of aza-polycyclic compounds that are easily found in nature and isolated as secondary metabolites primarily from *Pseudomonas*, *Streptomyces*, and a few other genera from soil or marine habitats. Moreover, various synthetic phenazine analogs are known for their pharmaceutical activities. Among various phenazines, benzo[*a*]phenazines are structural subunits in a variety of important natural products and have been given special attention due to their unique biological properties in various fields. In this review article, we highlight the synthesis of benzo[*a*]phenazin-5-ol derivatives from lawsone and benzene-1,2-diamines and their applications for the construction of a variety of five and six membered fused heterocycles such as pyranophenazines, spiropyranophenazines, pyridophenazines, furophenazines, benzochromenophenazines and oxazinophenazines during the period of 1995 to 2021.

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1 Introduction

Phenazine systems are an important class of aza-polycyclic compounds that are easily found in nature. More than 6000 phenazine-containing compounds have been recognized and reported during the past century, including natural phenazines and compounds synthesized based on the phenazine skeleton. Phenazine natural products are isolated as secondary metabolites primarily from *Pseudomonas*, *Streptomyces*, and a few other genera from soil or marine habitats. The biological properties of

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this class of natural products have been reviewed. In 1986, Turner and Messenger described the natural occurrence and some properties of phenazines, biosynthesis, secondary metabolism and the physiological significance of phenazine production in a review article.[1] After that, the role of phenazine pigments as antibiotics and virulence factors was reviewed by Kerr in 2000.[2] Next, Laursen and Nielsen described exclusively with a representative selection of biologically significant phenazines, their natural occurrence, their biosynthesis, the design and synthesis of analogues, and their biological function and possible mode of action in 2004.[3] The progress in the isolation of new phenazine natural products, new insights in their biological function, and particularly the now almost completely understood biosynthesis has been briefly reviewed recently.[4]

Moreover, various synthetic phenazine analogs are known for their pharmaceutical activities such as antifungal, antimalarial, antileishmanial, antihepatitis C viral replication, trypanocidal, inhibition of the cyclooxygenase, interactions of serum albumins, antimicrobial, anti-inflammatory, antitumor, as well as insecticidal activity.[5–16] Fluorescent phenazine derivatives both natural and synthetic, are also of interest because of their rapidly expanding applications as emitters for electroluminescence devices,[17] organic semiconductors,[18] photo-sensitizers in photodynamic therapy,[19] promoter for proliferation,[20] dye-sensitized solar cells (DSSCs),[21] electrochemical, and biosensors sensitive to H_2O_2, glucose, and lactose.[22–24] The synthetic routes for the synthesis of this scaffold have been reviewed. The general approaches for synthesis of phenazines include the Wohl–Aue method, Beirut method, condensation of 1,2-diaminobenzenes with 2C-units, reductive cyclization of diphenylamines, oxidative cyclization of 1,2-diaminobenzene/diphenylamines, Pd-catalyzed N-arylation, multicomponent approaches and benzyne intermediate has been reviewed by Chaudhary and Khurana in 2018.[25] Recently, Elhady and co-workers reviewed the synthesis of phenazines, either chemically or biologically and, also the different reactions of them and some of their biological importance, and their applications in the development of electrochemical sensors, biosensors and dye-sensitized solar cells (DSSCs).[26] Among various phenazine derivatives, benzo[*a*]phenazines that have a napthoquinone and phenazin backbone in their structures are structural subunits in a variety of important natural products and has been given special attention due to their unique biological properties in various fields such as dual inhibitors of topoisomerase I and II and are useful as antitumor agents.[27]

2-Hydroxy-1,4-naphthoquinone, or lawsone, or hennotannic acid, is one of the simplest naturally occurring naphthoquinones which can be obtained from the extract of dried powdered leaves of henna. Lawsone as a red-orange pigment is traditionally used for coloring hair and dying nails and skin, silk, wool and leather. It is reveals a long list of applications, including skin protection from ultraviolet radiation, corrosion inhibition for steel, antiaging additive to vulcanized natural rubber, oxidation of chlorinated compounds and sensitive colorimetric and electrochemical sensor for anions. Moreover, it has been used as the starting material for the synthesis of a variety of biologically active compounds and materials with interesting properties.[28–31] This review highlights the synthesis of benzo[*a*]phenazin-5-ol derivatives from lawsone and benzene-1,2-diamines and their applications for the construction of a variety of five and six membered fused heterocycles.

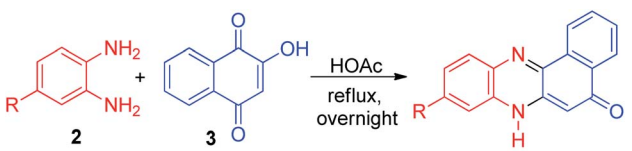
2 Synthesis of benzo[*a*]phenazin-5-ols

The first synthesis of 5,7-dihydrobenzo[*a*]phenazin-5-one derivatives **1** in good yields (62–94%) was reported by Rehberg and Rutherford in 1995. The general synthesis involved condensation of aromatic 1,2-diamines **2** with 2-hydroxy-1,4-naphthoquinone (lawsone) (**3**) in the presence of acetic acid under reflux conditions for overnight (Scheme 1).[32]

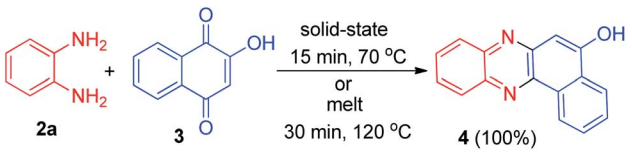
In 2002, Kaupp and Naimi-Jamal reported synthesis of benzo[*a*]phenazin-5-ol (**4**) in 100% yield by the one-pot condensation reaction of **3** and *o*-phenylenediamine (**2a**) in solid-state 1 : 1 runs in 15 min at 70 °C. If the same reaction was performed as a melt at 120 °C for 30 min, a 100% yield was also obtained (Scheme 2).[33]

In 2013, Jain and co-workers described synthesis of tetracyclic phenazine derivatives **4** and **5** in 38–97% yields. The reaction of **3** with **2a** in refluxing EtOH in the presence of AcOH as catalyst for 4 h afforded **4** while refluxing with 2,3-diaminotoluene (**2e**) gave the mixture of the regioisomers **5a–b**. These reactions were also carried out under mortar-pestle grinding technique, where the reaction was complete in lesser time and in enhanced yield (Scheme 3).[34]

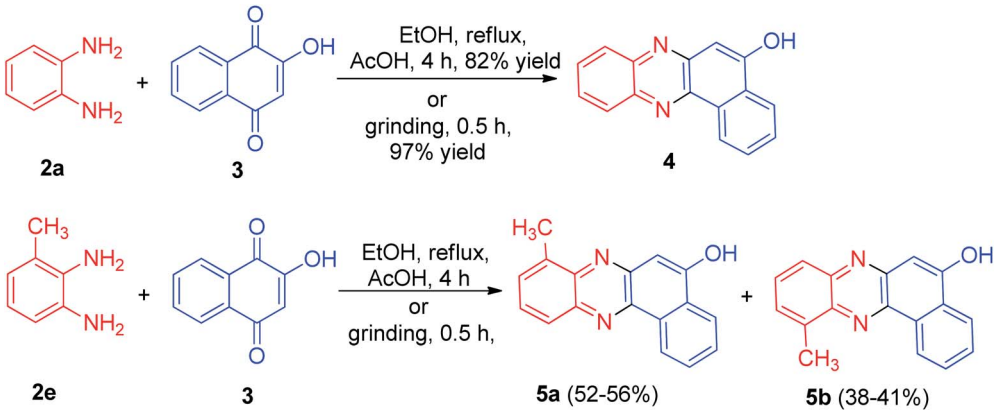
In 2014, Sekar and co-workers developed synthesis of benzophenazines **4** and **6a–c** in 96–98% yields from lawsone (**3**) and 1,2-benzenediamines **2** under ultrasound irradiation in an aqueous media at 27 °C for 20–24 min. Also, the reaction of **3** and **2a** was carried out by conventional method by refluxing in glacial acetic-acid for 2 h afforded the desired product **4** in 89% yield (Scheme 4).[35]



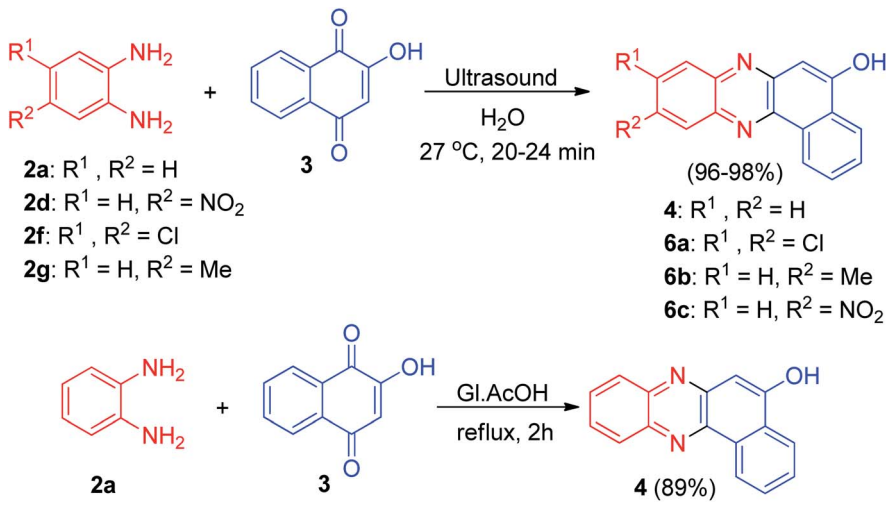
Scheme 1 Synthesis of 5,7-dihydrobenzo[*a*]phenazin-5-one derivatives **1**.



Scheme 2 Quantitative synthesis of benzo[*a*]phenazin-5-ol (**4**).



Scheme 3 Synthesis of tetracyclic phenazine derivatives **4** and **5**.



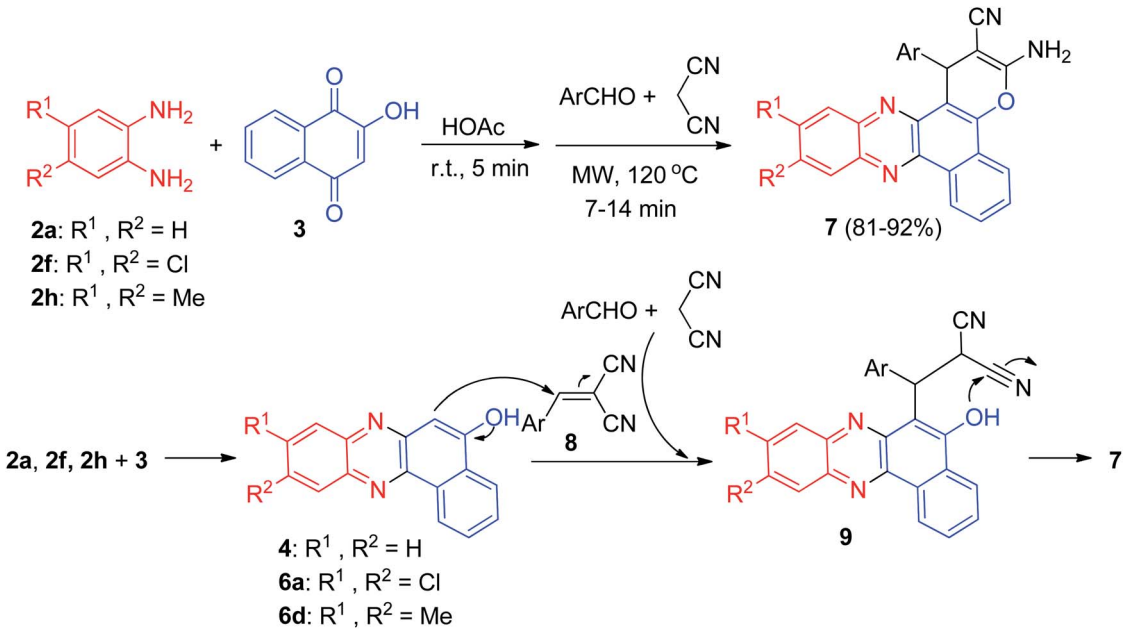
Scheme 4 One-pot synthesis of benzophenazines **4** and **6a–c**.

2.1 Synthesis of benzopyranophenazines

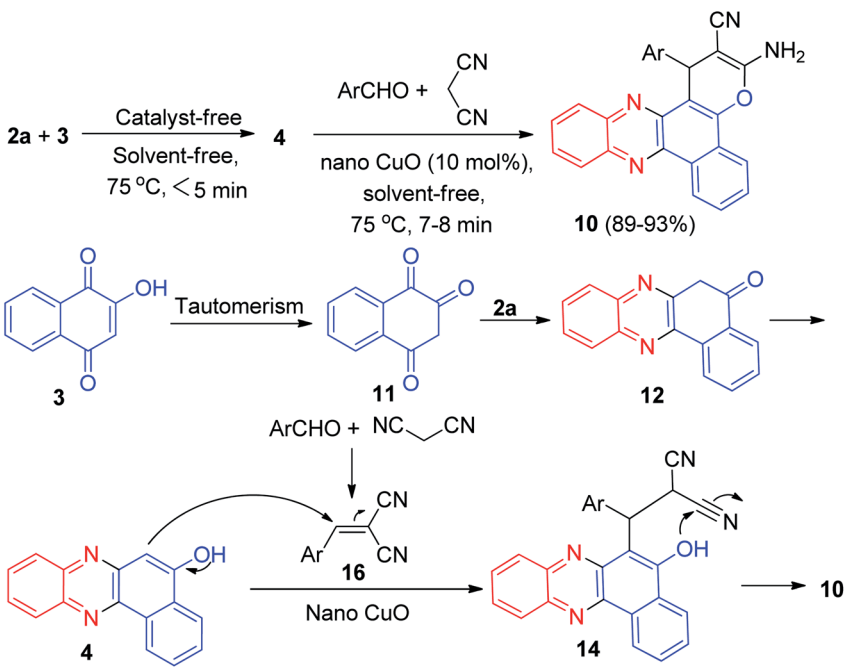
In 2011, Jiang and co-workers synthesized highly functionalized benzo[*a*]pyrano[2,3-*c*]phenazine derivatives **7** in 81–92% yields *via* one-pot two-step reactions of **3**, diamines, aldehydes and malononitrile in AcOH under microwave irradiation at 120 °C for 7–14 min. The formation of **7** is expected to proceed *via* initial condensation of **3** and diamine to afford benzo[*a*] phenazin-5-ol derivatives **4**, **6a** and **6d**, which undergoes *in situ* Michael addition with 2-benzylidenemalononitrile **8**, formed from condensation of aldehydes with malononitrile, to yield intermediate **9**, which is then cyclized to afford the product **7** (Scheme 5).[36]

Next, an efficient one-pot two step quantitative procedure for the preparation of functionalized benzo[*a*]pyrano[2,3-*c*]phenazine derivatives **10** was reported from four-component reaction of **3**, **2a**, aromatic aldehydes, and malononitrile in the presence of nano CuO (10 mol%) as the catalyst at 75 °C under solvent-free conditions. The mechanism for the formation of the products has been suggested in Scheme 6. First, **3** tautomerizes to intermediate **11**. The initial condensation of **11** with **2a** affords 6*H*-benzo[*a*]phenazin-5-one (**12**), which in tautomerism equilibrium causes to prepare **4**. In addition, standard Knoevenagel condensation of malononitrile and aryl aldehydes in the presence of nano CuO as the catalyst afforded benzylidenemalononitrile (**13**). The Michael addition of **4** with **13** formed intermediate **14**, which in subsequent cyclization and tautomerism gave the corresponding product **10**. The wide ranges of substituted and structurally diverse aldehydes afforded the corresponding products in high to excellent yields (89–93%).[37]

After that, an efficient one-pot two-step quantitative procedure for the preparation of functionalized benzo[*a*]pyrano[2,3-*c*] phenazine derivatives **15** in 87–94% yields reported from four-component reaction of **3**, **2a**, aromatic aldehydes, and malononitrile in the presence of basic ionic liquids such as 1-butyl-3-methylimidazolium hydroxide, 3-hydroxypropanaminium acetate, pyrrolidinium formate, pyrrolidinium acetate, 1,8-diazabicyclo[5.4.0]-undec-7-en-8-ium acetate, and piperidinium formate as the catalysts under solvent-free conditions in 75 °C for 6–10 min (Scheme 7). The mechanism of the reaction is similar to the proposed mechanism in Scheme 6.[38]



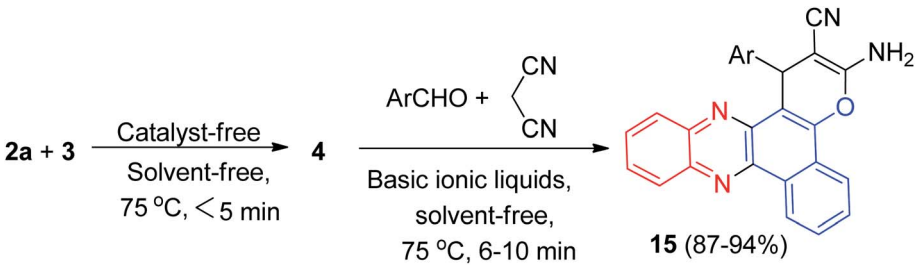
Scheme 5 One-pot two-step synthesis of benzo[*a*]pyrano[2,3-*c*]phenazine derivatives **7**.



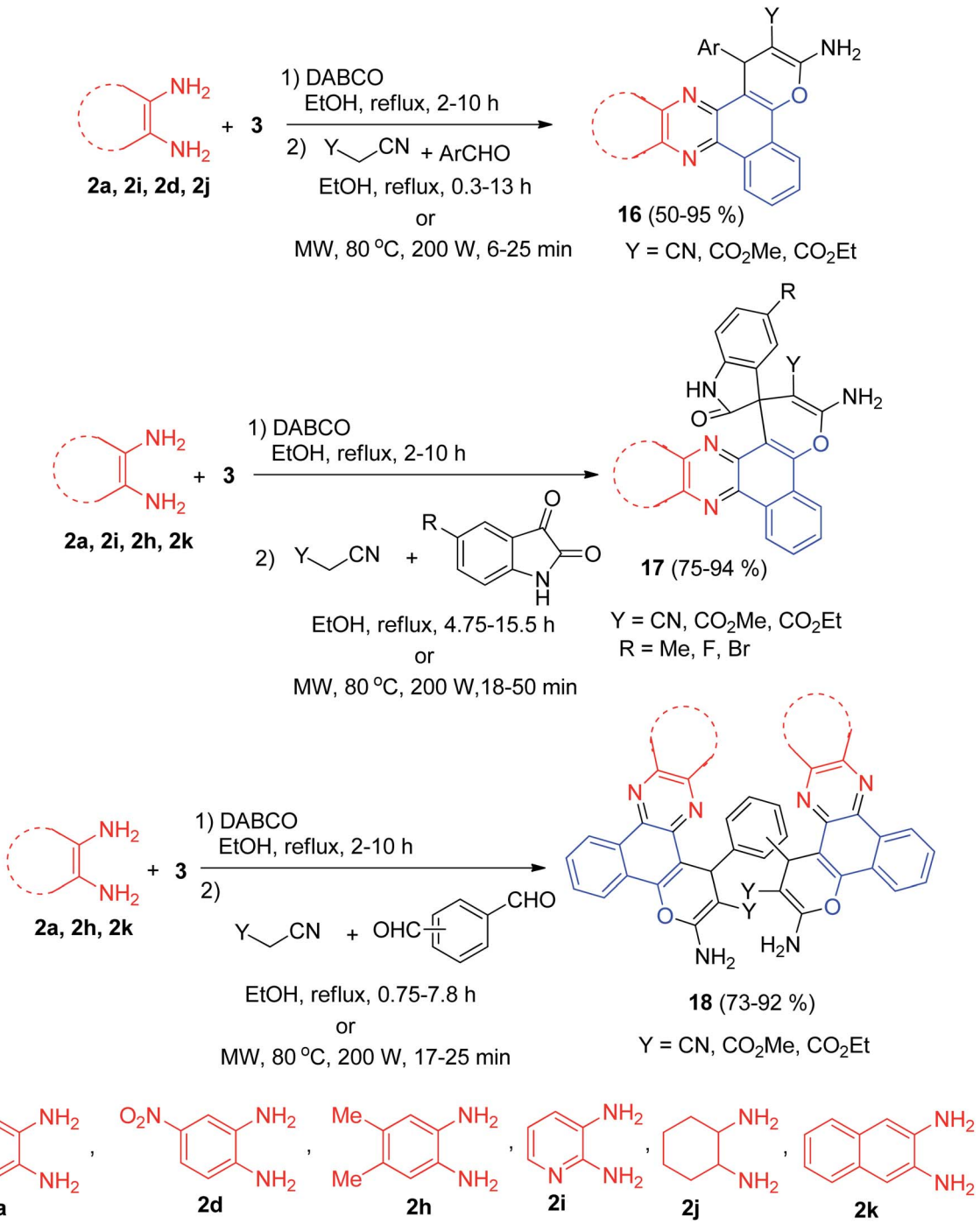
Scheme 6 Nano CuO catalyzed synthesis of 3-amino-2-cyano-1-aryl-1*H*-benzo[*a*]pyrano[2,3-*c*]phenazines **10**.

Later, DABCO as an efficient and reusable solid base catalyst was used for the one-pot, two-step, four-component synthesis of benzo[*c*]pyrano[3,2-*a*]phenazines **16** in 50–95% yields, oxospirobenzo[*c*]pyrano[3,2-]phenazines **17** in 75–94% yields and bisbenzo[*c*]pyrano[3,2-*a*]phenazines **18** in 73–92% yields by the condensation reaction of **3**, 1,2-diamines, carbonyl compounds and alkylmalonates under conventional heating (EtOH, under reflux conditions) as well as microwave irradiation (80 °C, 200 W) (Scheme 8).[39]

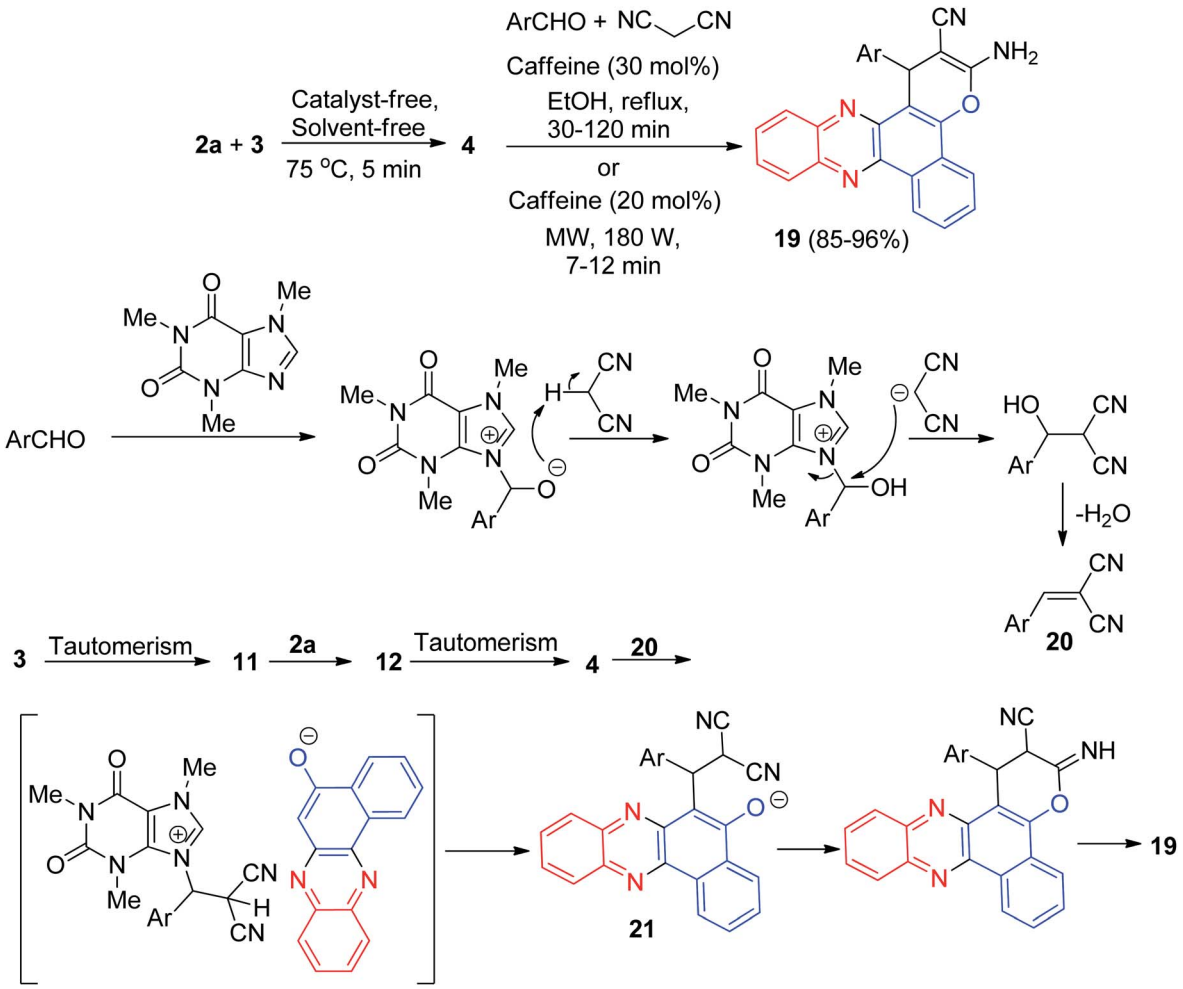
In 2016, a one-pot, two-step procedure was used to synthesize functionalized benzo[*a*]pyrano[2,3-*c*]phenazine derivatives **19** in 85–96% yields from a four-component condensation reaction of **3**, **2a**, aromatic aldehydes, and malononitrile in the presence of 1,3,7-trimethylpurine-2,6-dione (caffeine) as an expedient and reusable solid base catalyst under conventional heating and microwave irradiation. The mechanism for the formation of the products has been proposed in Scheme 9. On the basis of this mechanism, at first, **3** tautomerizes to



Scheme 7 Basic ionic liquid catalyzed synthesis of 3-amino-2-cyano-1-aryl-1*H*-benzo[*a*]pyrano[2,3-*c*]phenazines **15**.



Scheme 8 Synthesis of pyrano[3,2-*a*]phenazine derivatives **16–18**.



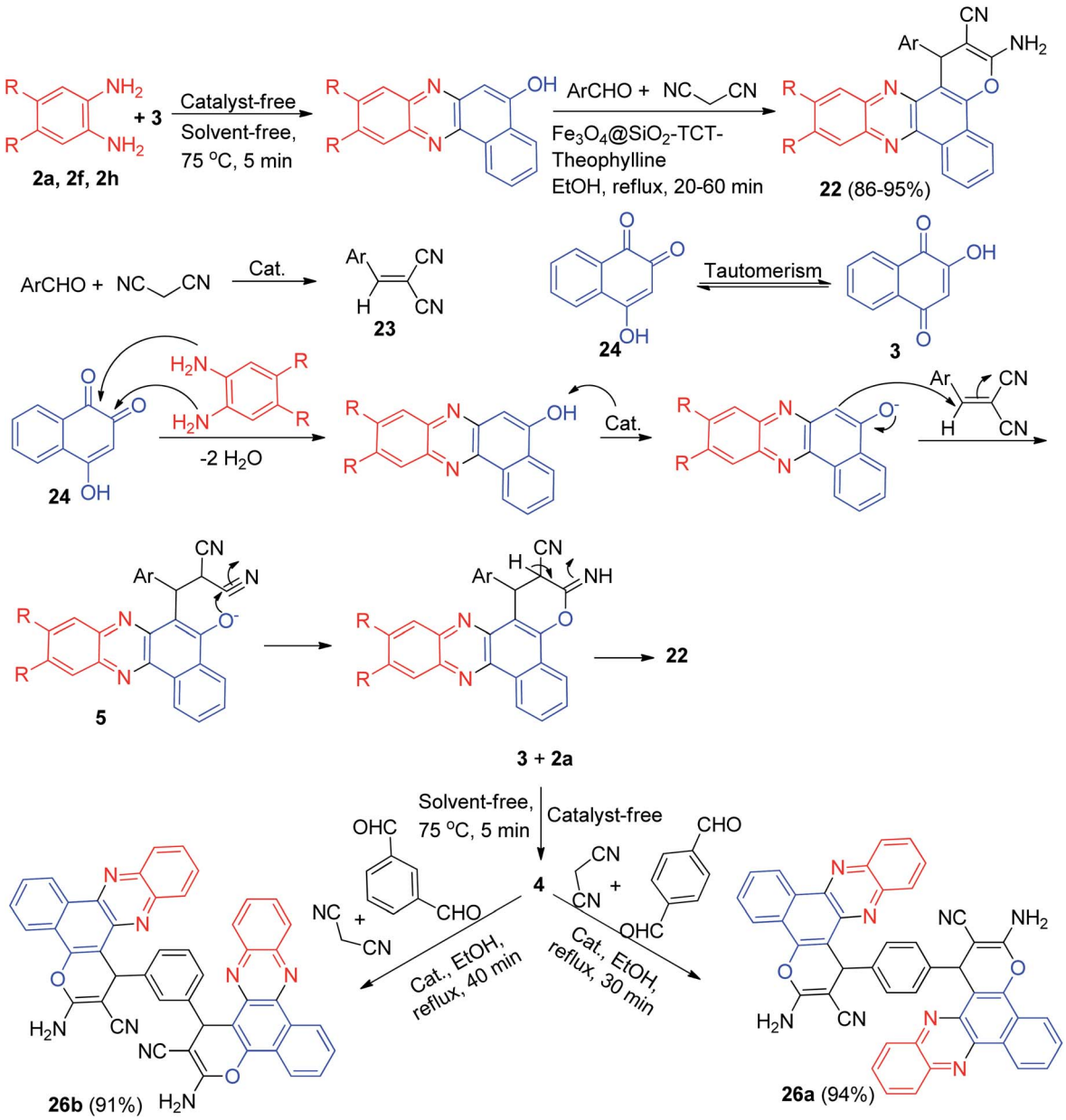
Scheme 9 Synthesis of 3-amino-2-cyano-1-aryl-1*H*-benzo[*a*]pyrano[2,3-*c*]phenazines derivatives **19**.

intermediate **11**. The primary condensation of **11** with **2a** obtains **12**, which in tautomerism equilibrium reasons to prepare **4**. On this mechanism, caffeine is an impressive catalyst to form the olefin **20**, which easily prepares *in situ* from Knoevenagel condensation of aldehyde with malononitrile. The Michael addition of **4** with **20** in the presence of caffeine finally give intermediate **21**, which then causes the intermolecular ring to be formed after a tautomeric proton shift to produce **19**.[40]

Next, Firouzabadi and his group described theophylline immobilized on superparamagnetic Fe_3O_4@SiO_2 nanoparticles catalyzed synthesis of poly-substituted benzo[*a*]pyrano-[2,3-*c*] phenazine derivatives **22** in 86–95% yields from four-component reaction of **3**, diamines, aldehydes, and malononitrile in refluxing EtOH within 20–60 min. The proposed mechanism has been shown in Scheme 10. The intermediate **23** was constructed upon initial condensation of malononitrile with aldehyde in the presence of the catalyst. The condensation reaction of **3**'s tautomer **24** with phenylenediamine derivatives presents the corresponding benzo[*a*]phenazin-5-ol which reacts with intermediate **23** to form **25**. Intramolecular cyclization of **25** affords the desired compound **22**. Moreover, the synthesis of bis 3-amino-1*H*-benzo[*c*]pyrano[3,2-*a*]phenazine derivatives **26a–b** in 91–94% yields has been reported *via* the reaction between **3** (2 mmol), **2a** (2 mmol), malononitrile (2 mmol) and terephtalaldehyde or isophtalaldehyde (1 mmol) in the presence of Fe_3O_4@SiO_2-TCT-theophylline in EtOH under reflux conditions for 30–40 min (Scheme 10).[41]

After that, the nanostructured α-chitin/ZnO was used as reusable nanocatalyst in the green synthesis of benzo[*a*]pyrano(2,3-*c*)phenazine derivatives **27** in 80–95% yields through a four-component domino reaction of **3**, *o*-phenylenediamines, aromatic aldehydes and malononitrile under microwave irradiation in EtOH at 78 °C within 4–7 min. The mechanism is shown in Scheme 11. 6*H*-Benzo[*a*]phenazin-5-one (**12**) in tautomeric equilibrium with **4** was obtained after the nucleophilic attack of **2a** to **3** followed by dehydration. Subsequent Michael addition of **4** to benzylidenemalononitrile, produced *via* Knoevenagel condensation of arylaldehydes with malononitrile catalyzed by Ch/ZnO, provided the desired product **27** after cyclization of intermediate **28**.[42]

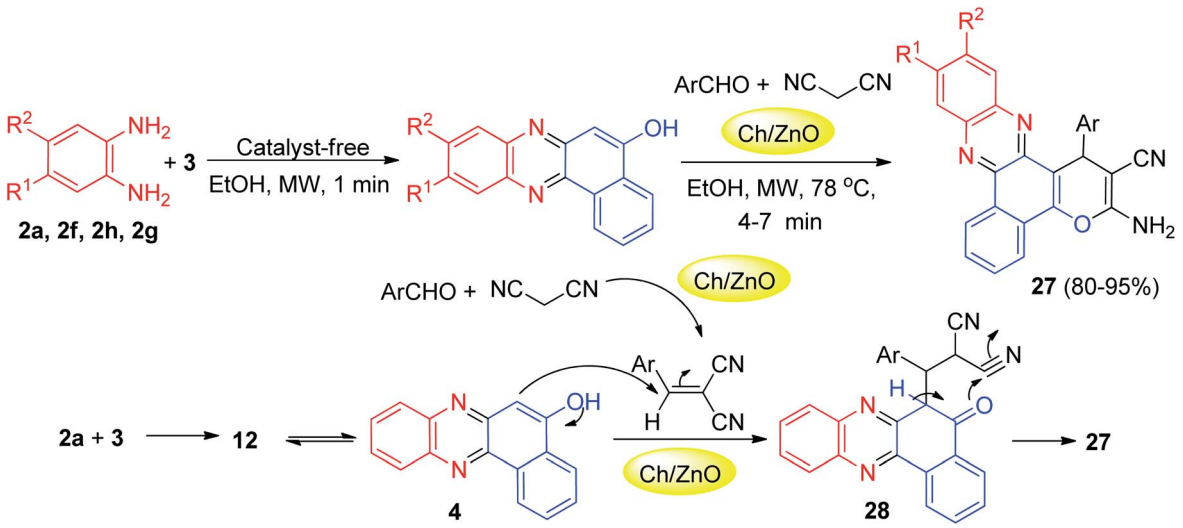
In addition, hyperbranched polyglycerol functionalized graphene oxide (GO-HPG-SO_3H) as an efficient reusable catalyst was employed in the synthesis of benzo[*a*]pyrano-[2,3-*c*]phenazine dyes **29** in 85–95% yields *via* one-pot reaction between **3**,



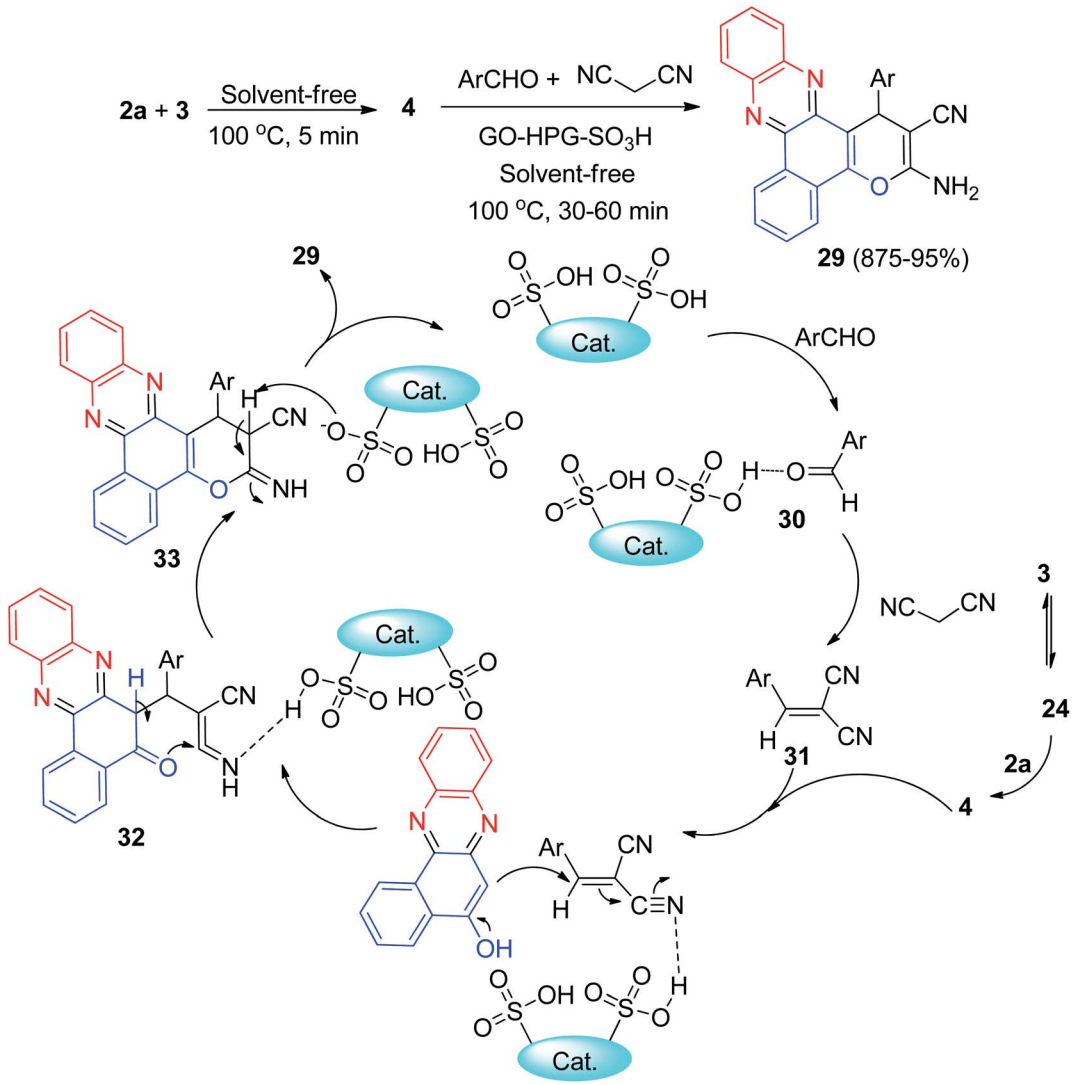
Scheme 10 Synthesis of 3-amino-2-cyano-1-aryl-1*H*-benzo[*a*]pyrano[2,3-*c*]phenazine derivatives **22** and **26a–b**.

2a, aromatic aldehydes and malononitrile under solvent-free conditions at 100 °C for 30–60 min. A plausible mechanism for the synthesis of **29** is depicted in Scheme 12. Firstly, **3** tautomerizes to intermediate **24**. The primary condensation of **24** with **2a** gives **4**. On this mechanism, the GO-HPG-SO_3H catalyst activates the carbonyl group of the aromatic aldehyde to afford intermediate **30**. The Knoevenagel condensation of **30** and malononitrile forms the arylidene malononitrile **31**. Subsequently, the Michael addition of **4** with **31** in the presence of the catalyst gives intermediate **32**. The intermediate **32** undergo tautomerization and intramolecular cyclization using the catalyst to form intermediate **33**. Ultimately, after tautomerization of intermediate **33**, the desired products **29** are formed.[43]

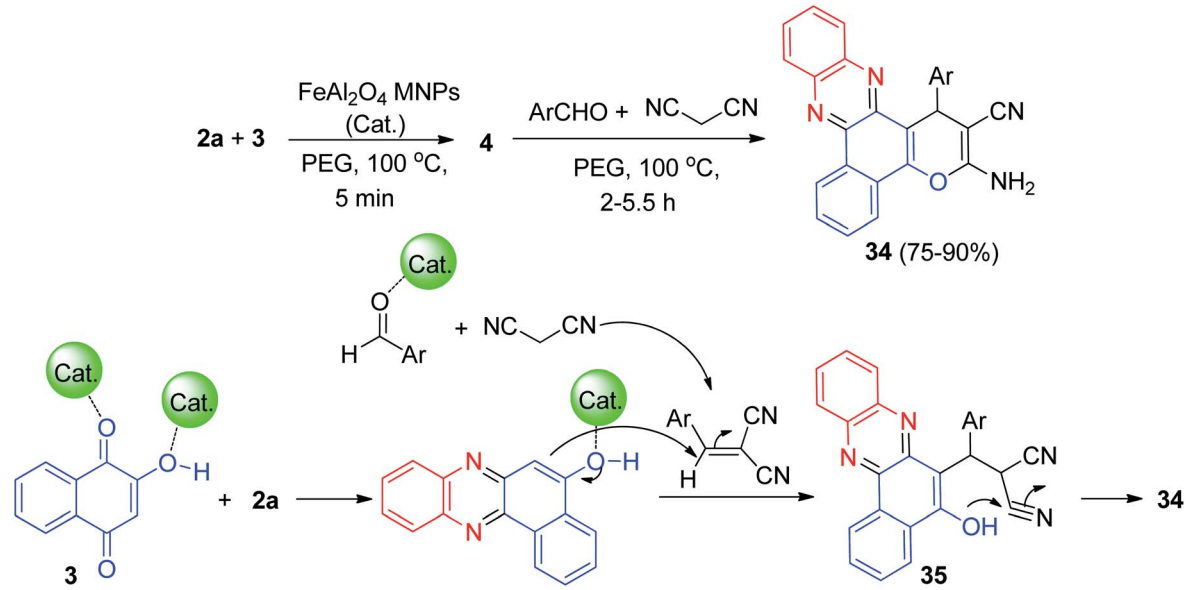
Further, Ghorbani-Choghamarani and his group synthesized benzo[*a*]pyrano[2,3-*c*]phenazine derivatives **34** in 75–90% yields by the reaction of **3**, **2a**, aromatic aldehydes/isatine and malononitrile in the presence of spinel $FeAl_2O_4$ (hercynite) magnetic nanoparticles as recyclable catalyst in PEG-400 at 100 °C for 2–5.5 h. The suggested reaction mechanism is depicted in Scheme 13. Initially, intermediate **4** was formed from the Schiff-base condensation of **2a** and **3** in the presence of $FeAl_2O_4$ MNPs. Sequentially; a possible intermediate **35** was formed *via* Michael addition of 2-benzylidenemalononitrile. 2-Benzylidenemalononitrile was formed *via* the Knoevenagel condensation of aldehyde with malononitrile. Finally, intermolecular cyclization of intermediate **35** produced a final product **34**.[44]



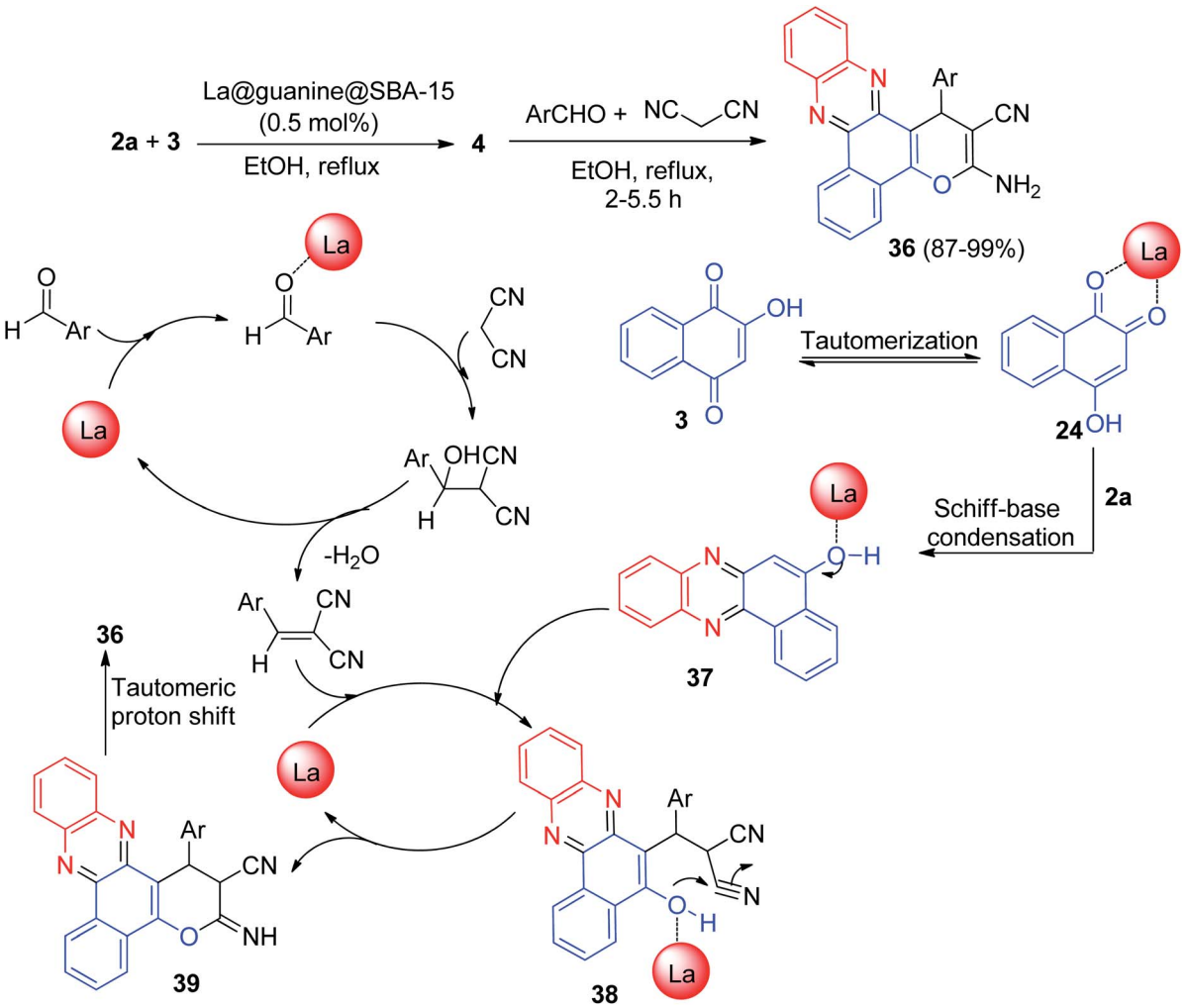
Scheme 11 Ch/ZnO catalyzed synthesis of benzo[*a*]pyrano[2,3-*c*]phenazine derivatives **27**.



Scheme 12 GO-HPG-SO_3H catalyzed synthesis of benzo[*a*]pyrano-[2,3-*c*]phenazine dyes **29**.



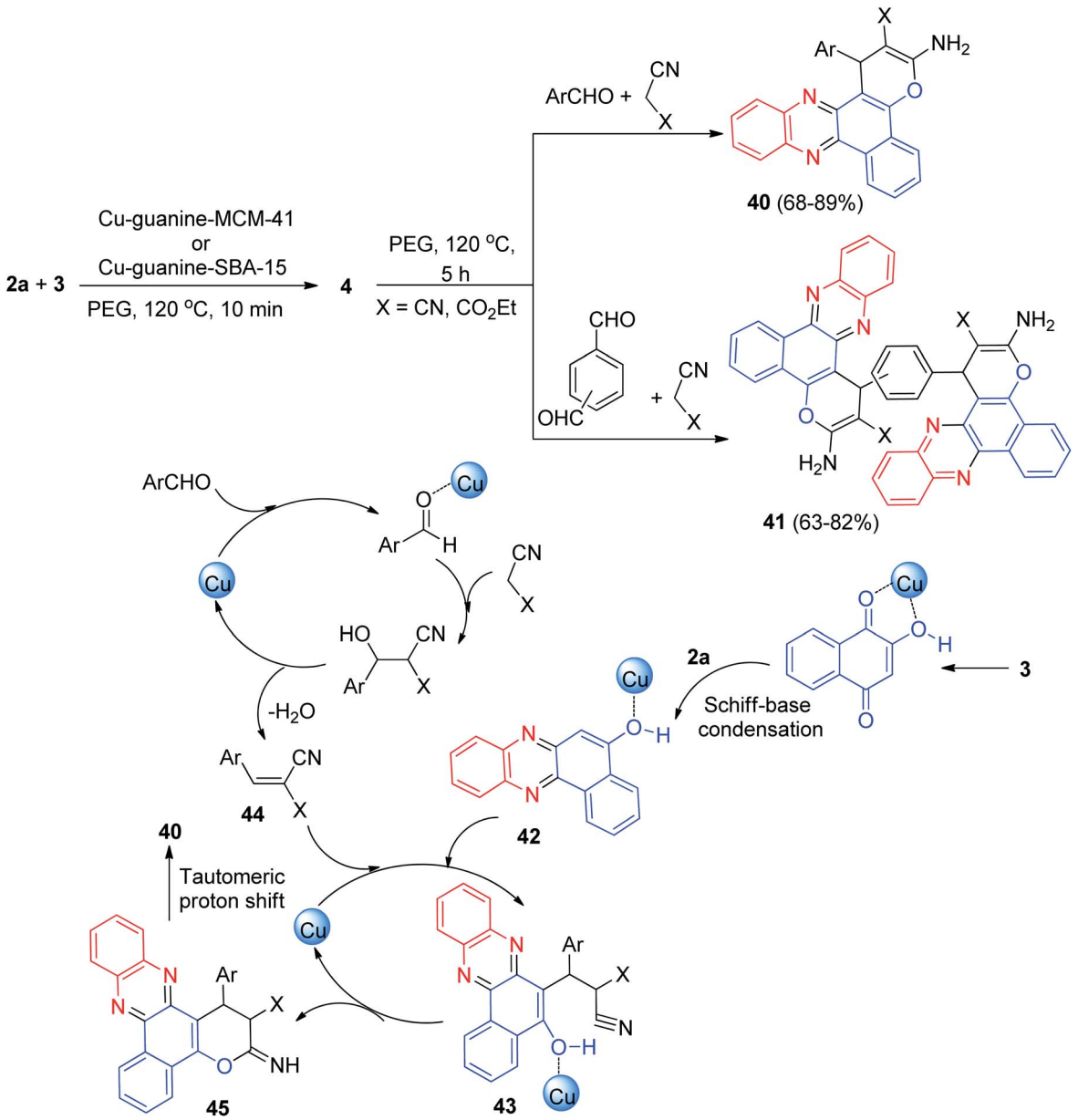
Scheme 13 $FeAl_2O_4$ MNPs catalyzed synthesis of benzo[*a*]pyrano[2,3-*c*]phenazines **34**.



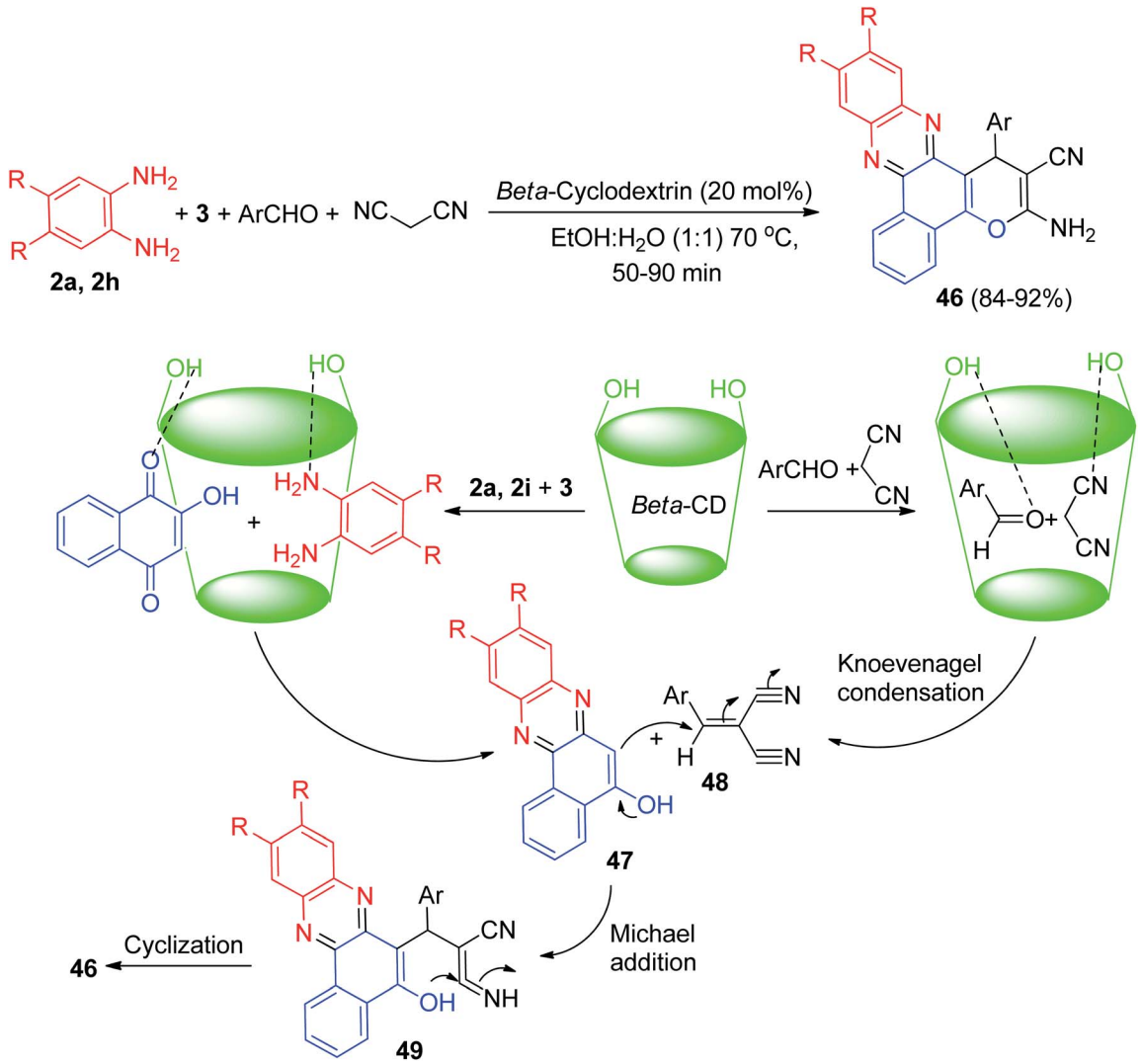
Scheme 14 La@guanine@SBA-15 catalyzed synthesis of benzo[*a*]pyrano[2,3-*c*]phenazine derivatives **36**.

In 2020, Nikoorazm *et al.* synthesized benzo[*a*]pyrano[2,3-*c*] phenazine derivatives **36** in 87–99% yields by the reaction of **3**, **2a**, aromatic aldehydes/isatine and malononitrile in the presence of La@guanine@SBA-15 (0.5 mol%), in EtOH at reflux conditions for 2–5.5 h. The suggested reaction mechanism has been depicted in Scheme 14. Initially, the intermediate **37** was formed from the Schiff-base condensation of **2a** and **3** in the presence of the catalyst. Sequentially, a possible intermediate **38** was formed *via* Michael addition of 2-benzylidenemalononitrile with **37**. In the next step, intermolecular cyclization of intermediate **38** produced intermediate **39**. Finally, a tautomeric proton shift produced the final product **36**.[45]

Next, Nikoorazm and Khanmoradi described the preparation of benzo[*c*]pyrano[3,2-*a*]phenazines **40** in 68–89% yields and bis-benzo[*c*]pyrano[3,2-*a*]phenazine derivatives **41** in 63–82% yields by the one-pot, two-step, four-component reaction of **3**, **2a**, carbonyl compounds and alkylmalonates using copper(II) ions complexes of guanine (2-amino-1*H*-purin-6(9*H*)-one) supported into MCM-41(Cu-guanine-MCM-41) and SBA-15 (Cu-guanine-SBA-15) channels as efficient and heterogeneous catalysts in PEG at 120 °C for 5 h. Scheme 15 depicts the possible reaction mechanism for the synthesis of **40**. Initially, the intermediate **42** was formed from the Schiff-base condensation of **2a** and **3** in the presence of the catalyst. Sequentially, a possible intermediate **43** was formed *via* Michael addition of **44** with **42** (intermediate **44** is formed *via* the Knoevenagel condensation of aldehyde with malononitrile in the presence of Cu-guanine-MCM-41 and Cu-guanine-SBA-15 catalysts). In the



Scheme 15 Preparation of benzo[*c*]pyrano[3,2-*a*]phenazines **40**–**41**.



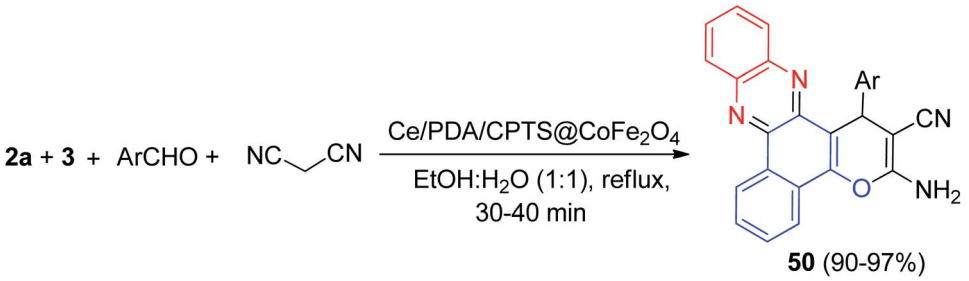
Scheme 16 β-CD catalyzed synthesis of benzo[*a*]pyrano[2,3-*c*]phenazine derivatives **46**.

next step, intermolecular cyclization of intermediate **43** produced intermediate **45**. Ultimately, a tautomeric proton shift produced the final product **40**.[46]

Further, Singh *et al.* described a pragmatic and swift method for the synthesis of benzo[*a*]pyrano[2,3-*c*]phenazine derivatives **46** in 84–92% yields *via* one-pot, multi-component reaction of **3**, benzene-1,2-diamines, aromatic aldehydes and malononitrile in the presence of supramolecular β-cyclodextrin as a biodegradable and reusable catalyst in EtOH : H_2O (1 : 1) solvent at 70 °C for 50–90 min. A plausible reaction mechanism is depicted in Scheme 16. The desired product is expected to form by the Knoevenagel condensation followed by Michael addition and at last cyclization within the cavity of β-CD where it is anticipated that seven free primary –OH groups of β-CD execute synergistically as a proficient host and supramolecular catalyst. Initially, the condensation of **3** and diamine takes place to afford the intermediate **47**. Similar condensation of aldehyde and malanonitrile occurs to form the intermediate **48**. After that, intermediate **47** reacts with intermediate **48** *via* Michael addition to yield an intermediate **49**. Finally, intermediate **49** undergo cyclization to afford the desired product **46**.[47]

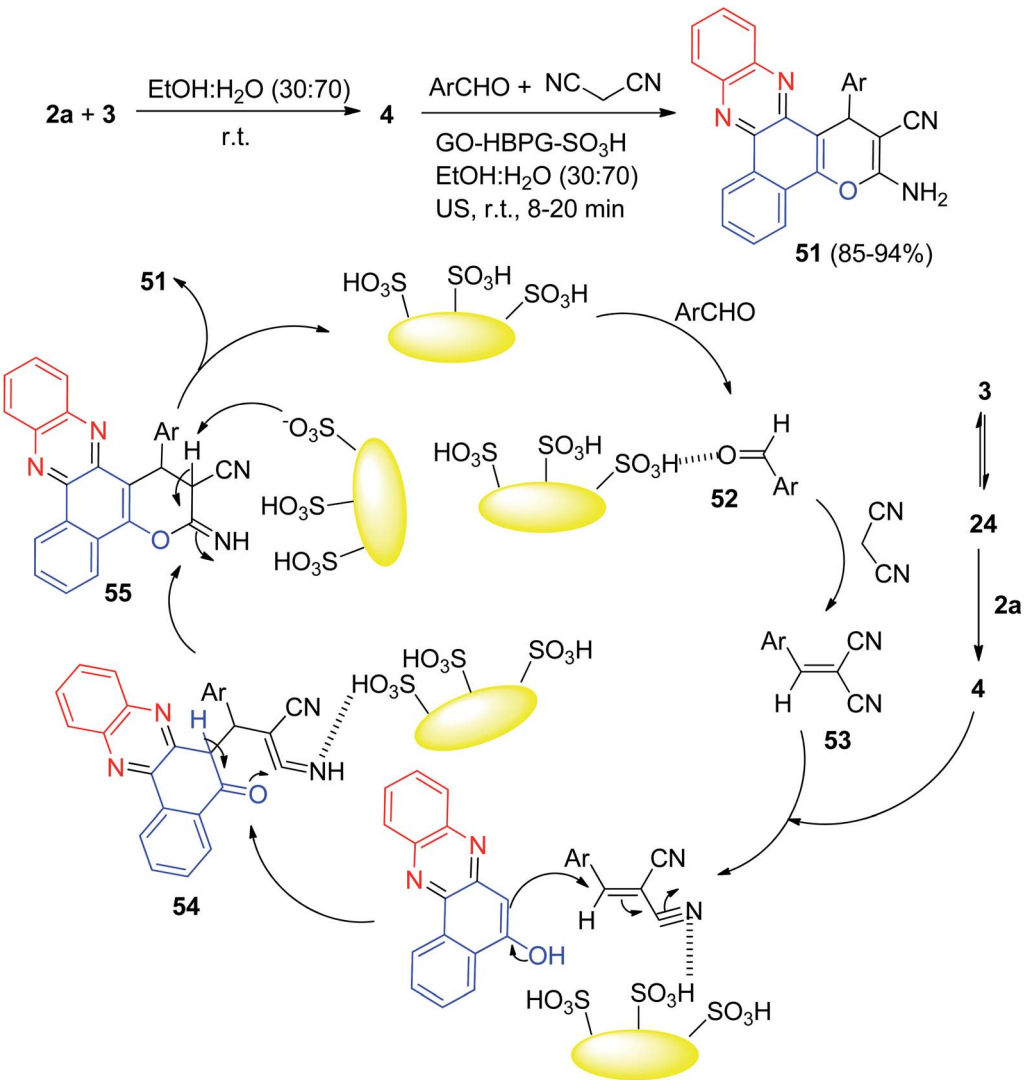
In 2021, Heravi and his co-workers reported synthesis of benzo[*a*]pyrano[2,3-*c*]phenazine derivatives **50** in 90–97% yields by condensing **3**, **2a**, malononitrile and different aryl aldehydes in the presence of Ce/PDA/CPTS@$CoFe_2O_4$ as a nanocomposite catalyst in EtOH : H_2O (1 : 1) under reflux conditions for 30–40 min (Scheme 17). In the proposed mechanism, initially, **3**, an enolated 1,2-diketo compound, being activated by the Lewis acidity of Ce^{4+} ions attached on the catalyst surface, undergoes condensation with **2a** to generate the orange colored benzo[*a*]phenazin-5-ol. In the mean time, Ce ions also trigger the aromatic aldehyde to condense with malononitrile, an active methylene compound, to form the Knoevenagel adduct. Now, benzo[*a*]phenazin-5-ol, adds up to the Knoevenagel adduct, being an excellent activated Michael acceptor, following 1,4-addition, intramolecular cycloacondensation affords the final desired product **50**.[48]

After that, a green and rapid sonochemical research to preparation of the benzo[*a*]-pyrano[2,3-*c*]phenazines **51** in 85–



Scheme 17 Synthesis of benzo[*a*]pyrano[2,3-*c*]phenazine derivatives **50**.

94% yields was carried out through a four-component reaction of **3**, **2a**, aldehydes, and malononitrile by using multisulfonic acid hyperbranched polyglycerol modified graphene oxide (GO-HBPG-SO_3H) as an effective and recyclable nanocatalyst in EtOH : H_2O (30 : 70) under ultrasonic irradiation at 45 kHz at room temperature for 8–20 min. A possible mechanism for the synthesis of **262** is outlined in Scheme 18. Firstly, **3** tautomerizes to intermediate **24**. The primary condensation of intermediate **24** with **2a** obtains **4**. On this mechanism, the GO-HBPG-SO_3H catalyst activates the carbonyl group of the aromatic aldehyde to afford intermediate **52**. The Knoevenagel condensation of intermediate **52** and malononitrile forms the



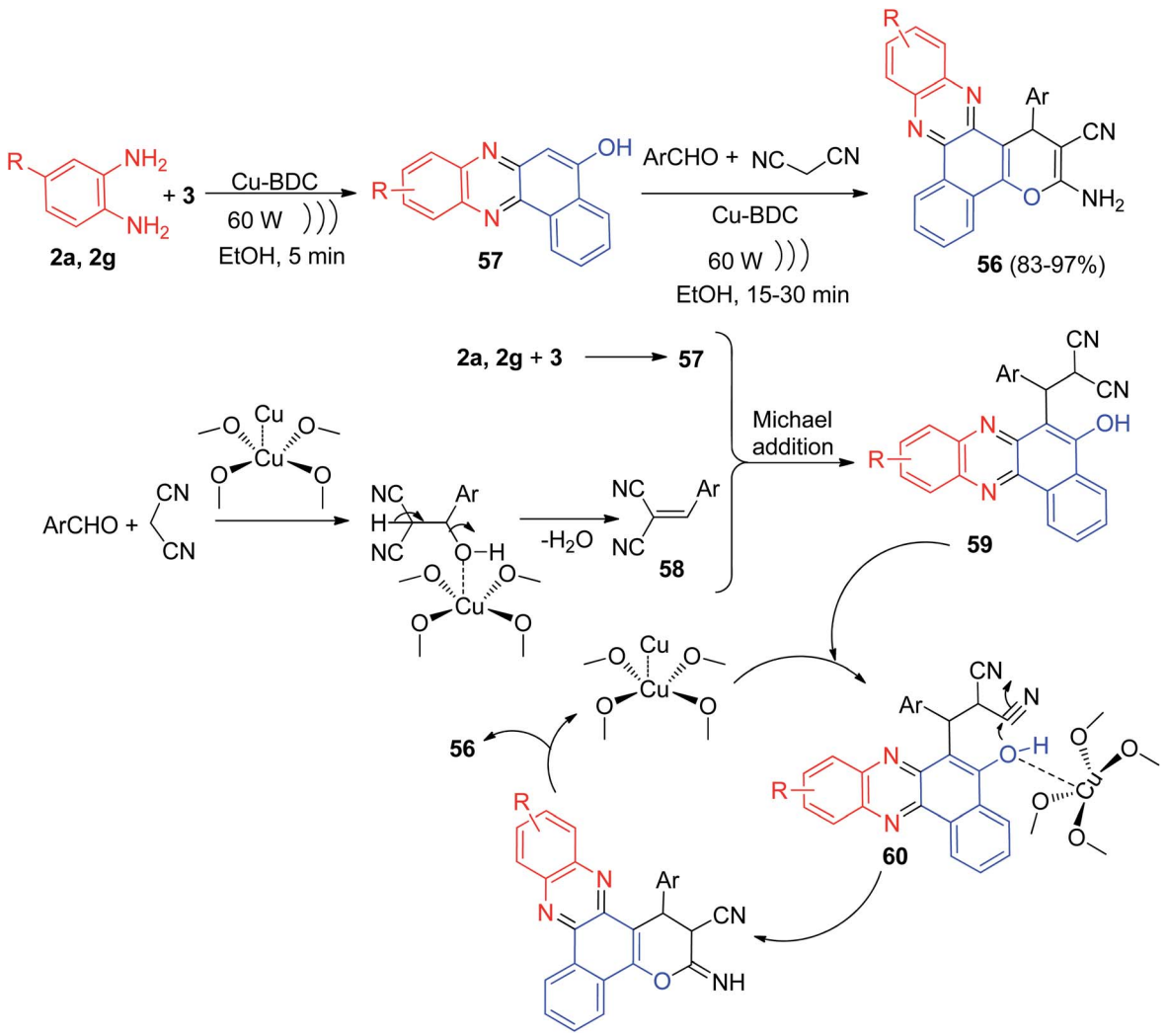
Scheme 18 Preparation of the benzo[*a*]-pyrano[2,3-*c*]phenazines **51**.

arylidene malononitrile **53**. Subsequently, the Michael addition of **4** with intermediate **53** in the presence of GO-HBPG-SO_3H catalyst gives intermediate **54**. The intermediate **54** undergo tautomerization and intramolecular cyclization using the catalyst to form intermediate **55**. Ultimately, after tautomerization of intermediate **55**, the desired products **51** are formed.[49]

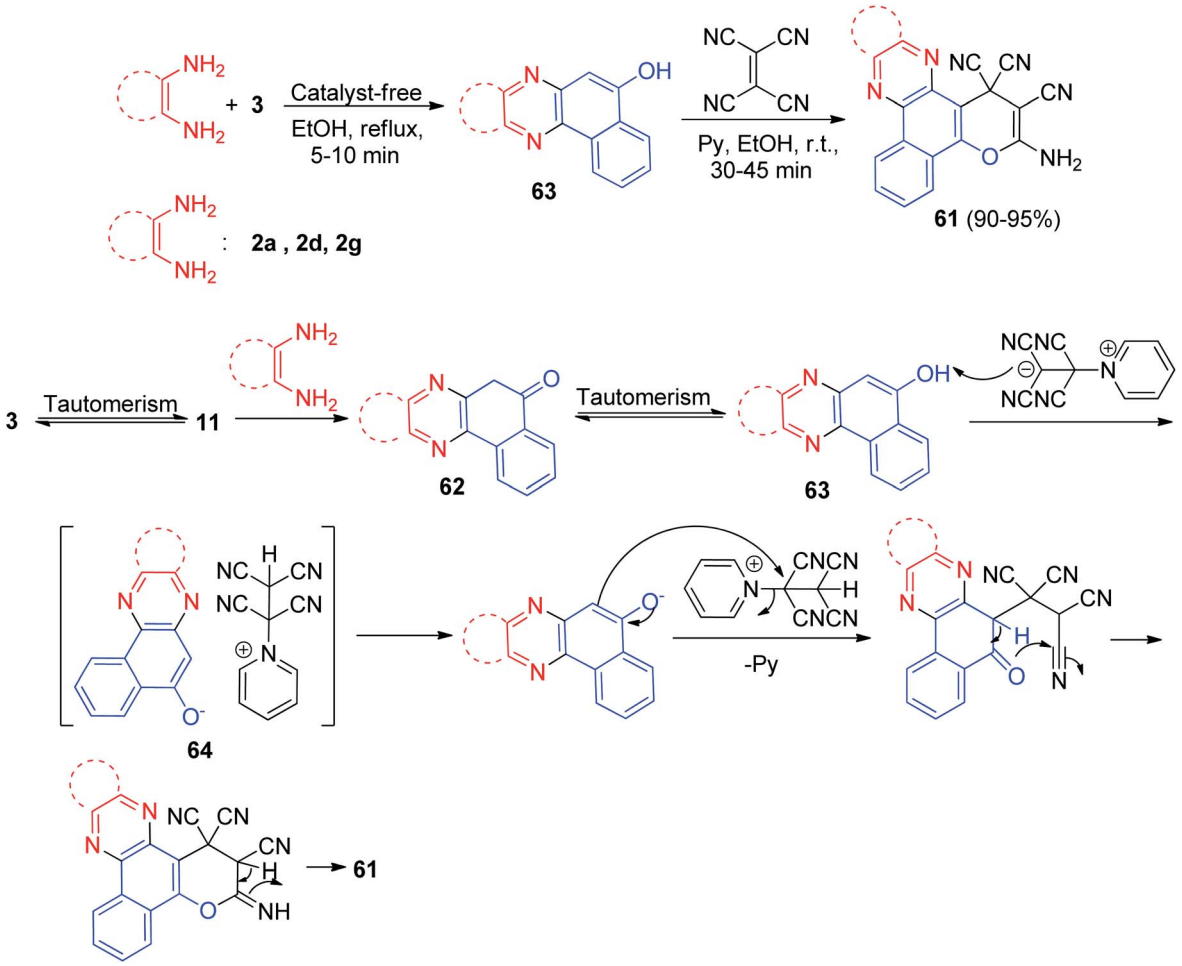
Further, Taheri and his group described the reaction of **3** with benzene-1,2-diamines, aldehydes and malononitrile in the presence of Cu-benzene dicarboxylic acid (Cu-BDC) under ultrasonic irradiation at 60 W power for 15–30 min afforded benzophenazine derivatives **56** in 83–97% yields. The proposed mechanism for the production of **56** is presented in Scheme 19. In the first stage, the condensation of **3** and *o*-phenylenediamines leads to the production of benzo[*a*]phenazin-5-ol **57**. Additionally, the Knoevenagel condensation aldehyde and malononitrile in the presence of Cu-BDC as acid catalyst produce intermediate **58**. The Michael addition of **57** with **58** from Knoevenagel condensation leads to the production of **59** that occurs in the presence of acidic Cu-BDC and an intermediate **60** is produced. Finally, in the course of a cyclization followed by tautomerism, the final product **56** produced and the catalyst returns to the reaction cycle.[50]

In 2016, benzo[*a*]pyrano[2,3-*c*]phenazine derivatives **61** were synthesized in 90–95% yields *via* a one-pot, two-step procedure from a three-component condensation reaction of **3**, 1,2-diamines, and tetracyanoethylene in the presence of pyridine (20 mol%) as an efficient catalyst in EtOH at room temperature for 30–45 min. The mechanism for the formation of the products is proposed in Scheme 20. On the basis of this mechanism, at first, **3** tautomerizes to intermediate **11**. The primary condensation of **11** with 1,2-diamine gives compound **62**, which in tautomerism equilibrium helps to prepare compound **63**. Then, based on the nucleophilicity of pyridine, the nucleophilic addition of pyridine to the electron-deficient tetracyanoethylene and subsequent protonation in the presence of compound **63** gives intermediate **64**, followed by the attack of the anion on the cation part of intermediate **64** to form the product **61** *via* intramolecular cyclization and a tautomeric proton shift.[51]

In 2012, one-pot two-step domino protocol for the efficient synthesis of fluorescent benzo[*a*]-phenazine fused derivatives



Scheme 19 Cu-BDC catalyzed synthesis of benzophenazine derivatives **56**.



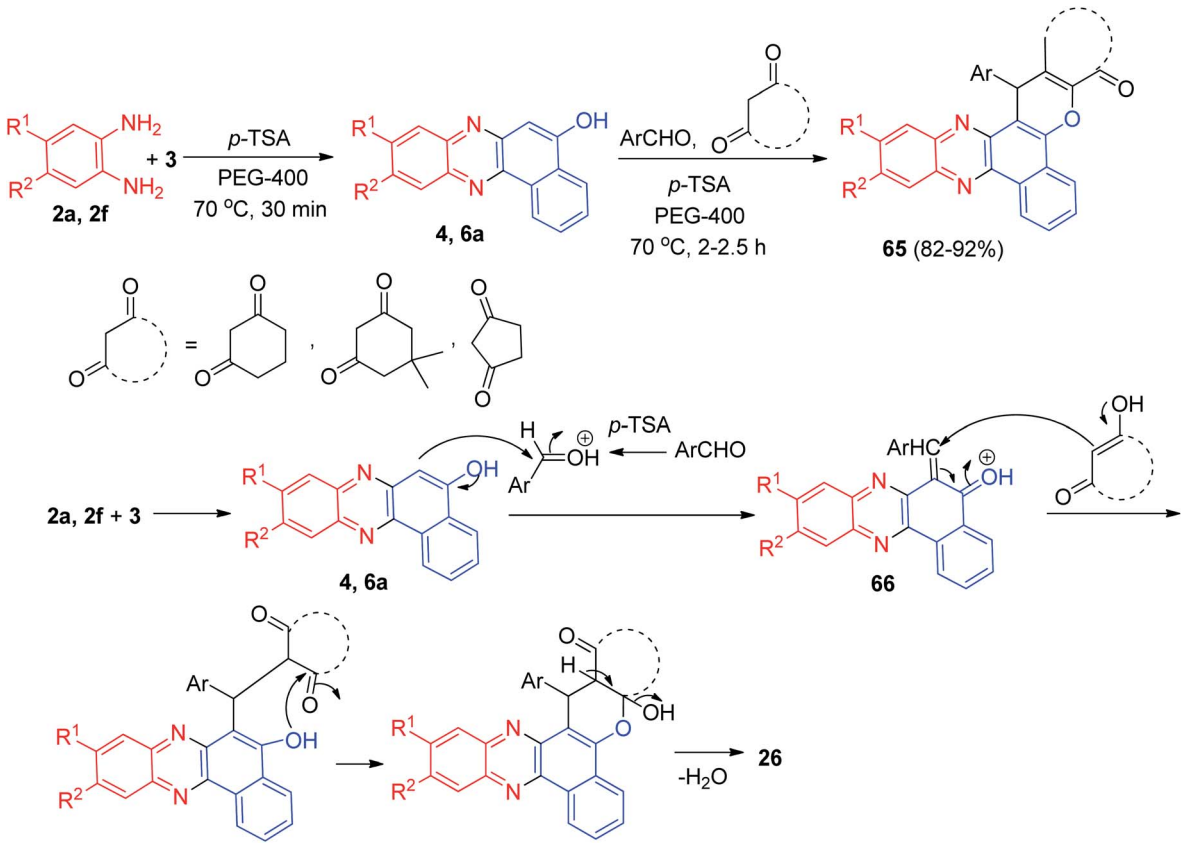
Scheme 20 Synthesis of benzo[*a*]pyrano[2,3-*c*]phenazines **61**.

65 in 82–92% yields was developed. The synthesis was achieved by reacting **3**, *ortho*-phenylenediamines, aromatic aldehydes and cyclic 1,3-dicarbonyl compounds in the presence of a catalytic amount of *p*-TSA in PEG-400 at 70 °C for 2–2.5 h. A speculative mechanistic explanation for this reaction is provided in Scheme 21. The formation of **65** proceeds *via* initial condensation of **3** and diamine to afford benzo[*a*]phenazin-5-ol derivatives **4** and **6a** as reported which *in situ* generates an *ortho*-quinone methide (*o*-QM) intermediate **66** upon nucleophilic addition to aldehyde. Subsequent Michael addition of the *o*-QM with a cyclic 1,3-dicarbonyl compound, followed by cyclization and dehydration leads to the formation of **65**.[52]

In 2015, Jeong and co-workers reported a synthetic route to produce tetrahydro-1*H*-benzo[*a*]-chromeno[2,3-*c*]phenazin-1-ones **67** in 88–95% yields by the straightforward, efficient and convenient approach of a three-component reaction between aromatic aldehydes, **4** and active methylene compounds under neat conditions in the presence of an ionic liquid, tetramethyl guanidiniumchlorosulfonate (TMG IL), at 60 °C for 45–65 min. The TMG IL was used as a solvent and as a catalyst under reusable conditions. The title compounds were screened for their *in vitro* antioxidant activity and it was found that most of the compounds are effective against reactive oxygen species. The majority of them also have excellent *in vitro* anti-cancer activity on two human cancer cell lines, HeLa and SK-BR-3, compared with standard drugs. The TMG IL-catalyzed synthetic sequence of the title compounds is presented in Scheme 22, and may proceed *via* an *ortho*-quinone methide (*o*-QM) intermediate. At the beginning, nucleophilic addition of **4** to an aldehyde takes place and subsequently Michael addition of the *o*-QM to an enolic form of a cyclic 1,3-dicarbonyl, followed by the addition of the benzyl hydroxy moiety to the carbonyl of the ketone **68**, provides a cyclic hemiketal **69**, which on dehydration affords **67**.[53]

Next, an efficient and quantitative procedure for the synthesis of functionalized benzo[*c*]chromeno[2,3-*a*]phenazine derivatives **70** in 77–99% yields by one-pot, two-step four-component condensation of **3**, **2a**, aromatic aldehydes, and cyclic 1,3-dicarbonyl compounds were developed using catalytic amounts of H_2SO_4 and phosphotungstic acid in EtOH/H_2O (1 : 1) under reflux and also with Brønsted acidic ionic liquid [NMP]H_2PO_4, which acts as catalyst and medium at 80 °C (Scheme 23).[54]

In 2018, silica sulfuric acid (SiO_2–SO_3H) has been used as an effective and reusable solid catalyst for the one-pot, two-step, four-component synthesis of benzo[*a*]chromeno[2,3-*c*]



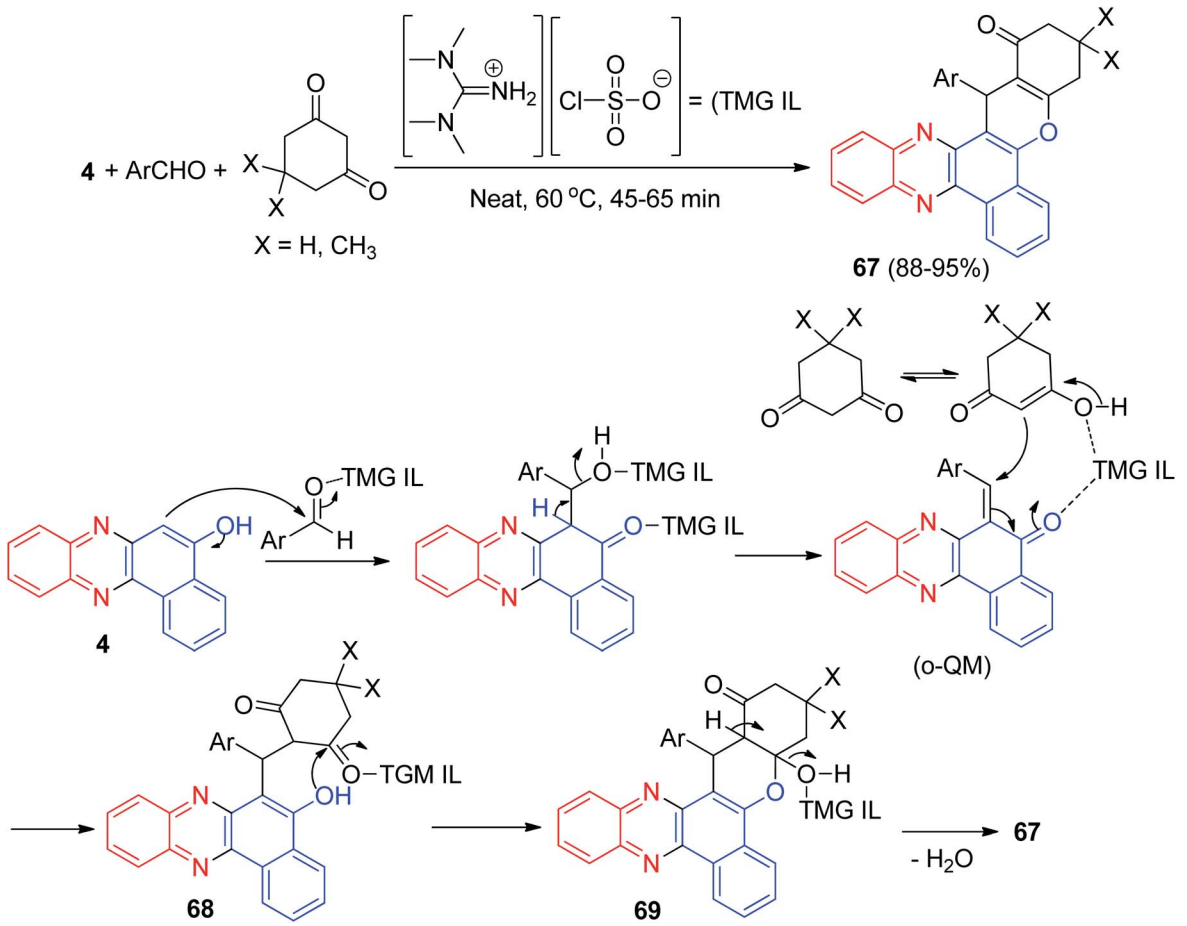
Scheme 21 Synthesis of fluorescent benzo[*a*]phenazine fused derivatives **65**.

phenazine derivatives **71** by the condensation reaction of **3**, **2a**, aldehydes, and cyclic 1,3-dicarbonyl compounds. The reaction was carried out under conventional heating at 70 °C or microwave irradiation at 70 °C afforded the desired products **71** in 60–75 min with 80–87% and 7–10 min with 88–96% yields, respectively. The probable mechanism is given in Scheme 24. On the basis of this mechanism, at first, **3** tautomerizes to intermediate **11**. The primary condensation of **11** with **2a** gives 6*H*-benzo[*a*]phenazin- 5-one **12**, which in tautomerism equilibrium reasons to prepare **4**. On this mechanism, SiO_2–SO_3H is an efficient catalyst to form (6-benzylidenebenzo[*a*]phenazin-5(6*H*)-ylidene)oxonium **72**, which easily prepares *in situ* from condensation of aldehyde with **4**. Subsequent Michael addition of cyclic 1,3-dicarbonyl compounds with **72**, followed by cyclization and dehydration leads to the formation of product **71**.[55]

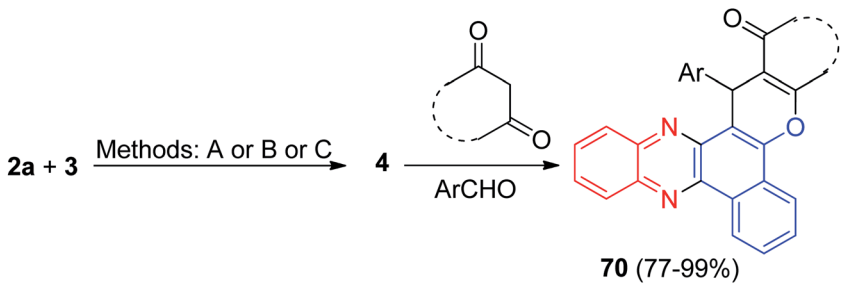
After that, Harichandran and co-workers developed an efficient protocol for the synthesis of fluorescent 4*H*-chromenes and benzo[*a*]chromenophenazines **73–74** in 35–92% yields starting from the reaction of **2a**, **3**, 2-hydroxy benzaldehydes, and 1,3-diketones in EtOH/H_2O (1/1, v/v) as solvent in the presence of Amberlite resin at 80 °C for 3–4 h. These compounds have been found to be good photophysical properties such as solvatochromism, absorption, emission, Stocks shift and quantum yield, fluorescent chemosensors and metal ion sensors for the detection of Fe^{3+} and Cu^{2+} ions. A plausible mechanism for the formation of compounds **73–74** with Amberlite IR-120 H^+ resin has been proposed in Scheme 25. Initially, condensation of **2a** and **3** gives **4**. Next two possible pathways of mechanism (pathway-A and pathway-B) are possible. Pathway-A explains the formation of compounds **73**. In pathway B, the *in situ* generated *o*-quinonemethide (*o*-QM) intermediate **75** is believed to form from **4** upon nucleophilic addition of salicylaldehyde. Subsequent Michael addition of intermediate **75** to diketone followed by dehydration affords benzo[*a*]chromenophenazines **74**.[56]

In 2020, Siddiqui *et al.* described the preparation of benzo[*a*]chromeno[2,3-*c*]phenazine derivatives **76** in 89–95% yields through an efficient one-pot, multi-component ecofriendly reaction of **3**, *o*-phenylenediamines, cyclic 1,3-dicarbonyl compounds and aromatic aldehydes, promoted by glycerol at 90 °C for 2–3 h. A plausible mechanism for the disclosed synthetic transformation has been proposed in Scheme 26. The reaction is presumed to initiate *via* Knoevenagel condensation of **3** and *o*-phenylenediamines resulting in benzo[*a*]phenazin-5-ol derivative **4** and **6a** as the first intermediate. A second Knoevenagel condensation of **4** or **6a** with aromatic aldehydes leads to benzo[*a*]phenazin-5(6*H*)-ones. Finally, cyclization resulting from Michael attack of benzo[*a*]phenazin-5(6*H*)-ones on cyclic 1,3-dicarbonyl compounds followed by dehydration results in the desired product **76**.[57]

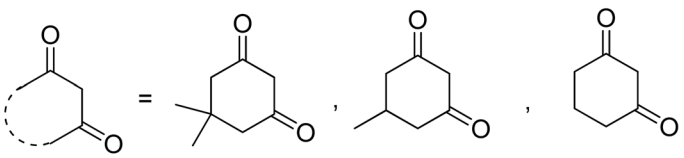
In 2016, a sequential one-pot two-step four-component reaction for the efficient synthesis of 16-(aryl)benzo[a]indeno



Scheme 22 Synthesis of tetrahydro-1*H*-benzo[*a*]chromeno[2,3-*c*]phenazin-1-ones **67**.

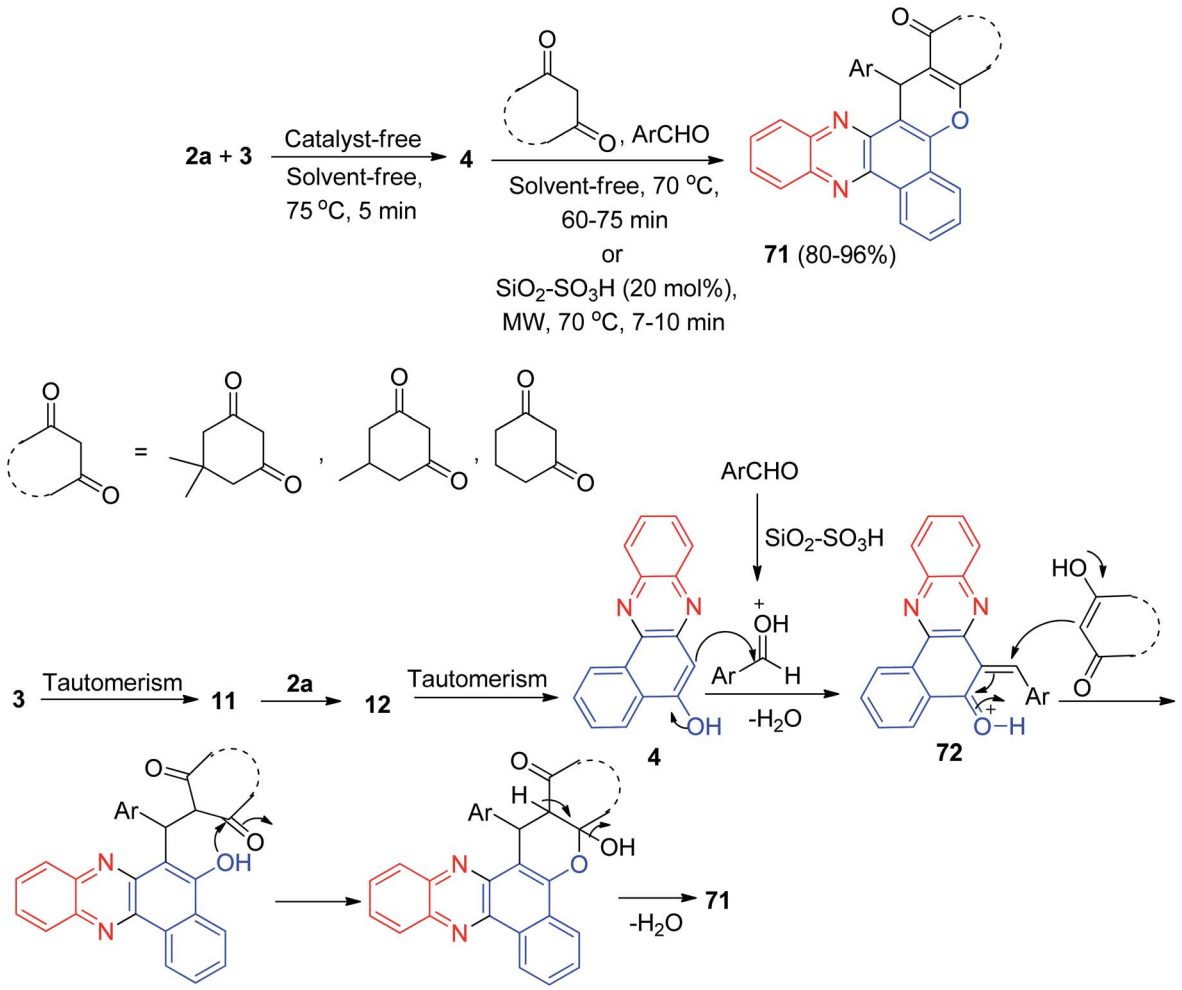


Method A = H_2SO_4, EtOH:H_2O (1:1, v/v), 80 °C, 4.5-5.0 h
Method B = Phosphotungstic acid, EtOH:H_2O (1:1, v/v), 80 °C, 4.5-5 h
Method C = [NMP]H_2PO_4, 80 °C, 2.5-3.0 h



Scheme 23 Synthesis of functionalized benzo[*c*]chromeno[2,3-*a*]phenazine derivatives **70**.

[2′,1′:5,6]pyrano[2,3-c]phenazin-15(16*H*)-one derivatives **77** in 85–92% yields was developed. The synthesis was achieved by reacting **3**, **2a**, aromatic aldehydes, and 1,3-indandione in the presence of oxalic acid (20 mol%) as a reusable and homogeneous organocatalyst in EtOH/H_2O (1 : 1) under reflux for 2–2.5 h. A reaction mechanism is shown in Scheme 27. Oxalic acid



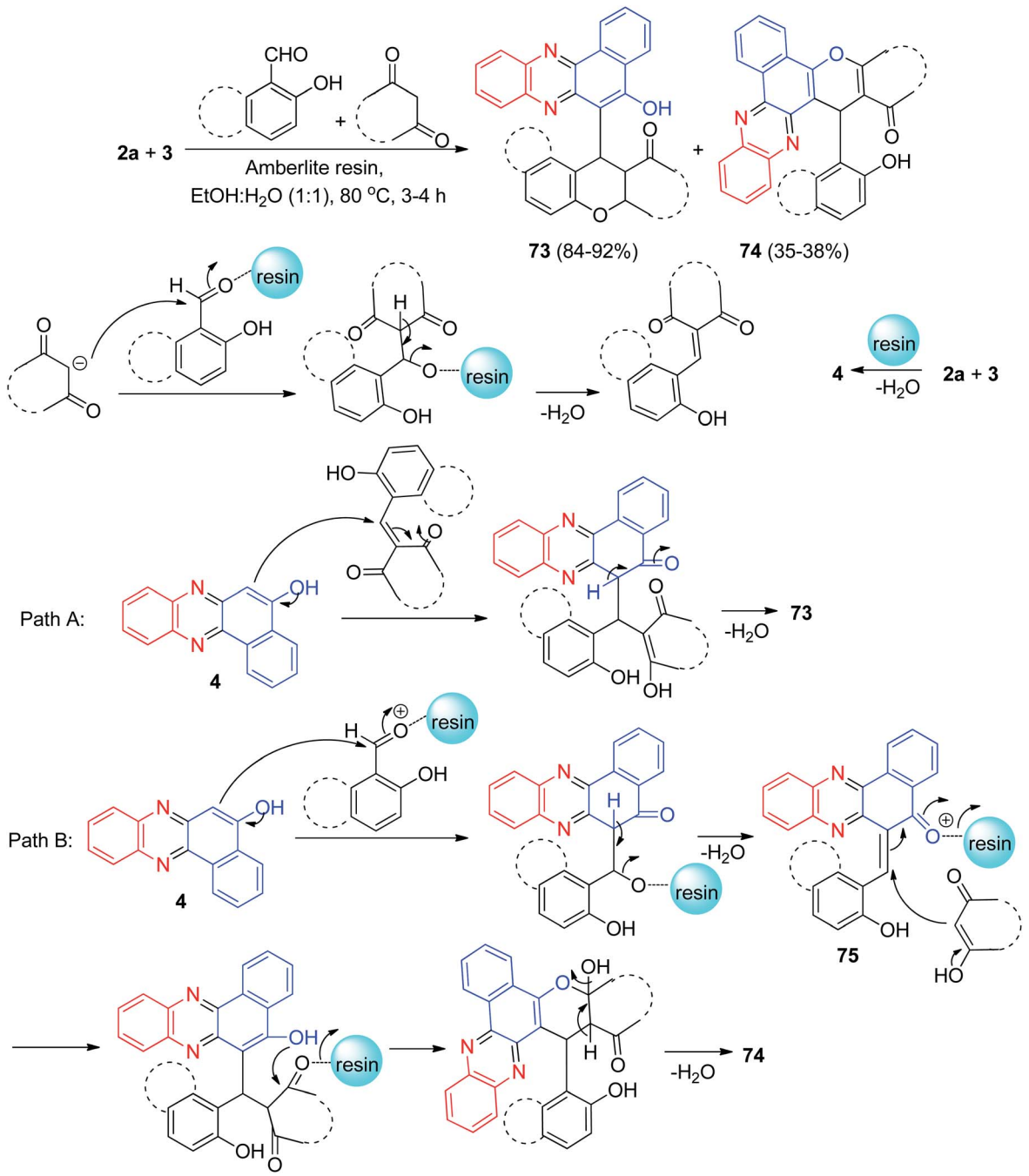
Scheme 24 Synthesis of benzo[*a*]chromeno[2,3-*c*]phenazines **71**.

plays a key role as a Brønsted-Lowry acid catalyst in this reaction. The formation of **77** proceeds *via* initial condensation of **3** and **2a** to afford **4** as reported, which *in situ* generates an *ortho*-quinone methide (*o*-QM) intermediate **78** upon nucleophilic addition to aldehyde. Subsequent Michael addition of the *o*-QM with 1,3-indandione, followed by cyclization and dehydration, leads to the formation of product **77**.[58]

After that, a highly efficient one-pot, two-step microwave-assisted procedure was applied for the rapid and green synthesis of benzo[*a*]phenazine annulated heterocyclic ring systems **79** in 83–94% and **80** in 85–95% yields from the three- or four-component condensation reactions of **3**, **2a**, aromatic aldehydes and 1,3-indandione or **3** using L-proline as a bifunctional organocatalyst in water at 70 °C for 10–20 min (Scheme 28). Moreover, the catalyst can be recovered and reused several times without much loss of its performance. Also, the reactions were examined with aliphatic aldehydes such as *n*-heptanal and *n*-octanal but the related products were not obtained in these reaction conditions even after 20 min. The probable mechanism for the domino synthesis of **79** and **80** using L-proline is similar to the proposed mechanism in Scheme 28.[59]

In 2018, Mohebat and co-workers developed single-pot synthesis of heteroaryl-substituted benzo[*a*]pyrimido[5′,4′:5,6]pyrano[2,3-*c*]phenazines **81** in 76–91% yields *via* initial Knoevenagel, subsequent Michael, and final heterocyclization reactions of **3**, **2a**, aromatic aldehydes, and barbituric acid in the presence of $H_3PW_{12}O_{40}$@nano-ZnO as a recyclable heterogeneous catalyst in EtOH under microwave irradiation (180 W, max. 70 °C) for 15–20 min. The proposed mechanism for this four-component sequential reaction is shown in Scheme 29. $H_3PW_{12}O_{40}$@nano-ZnO plays a key role as a Brønsted acid catalyst in this reaction. The formation of **81** proceeds *via* initial condensation of **3** and **2a** to afford **4** as reported, which *in situ* gives the *ortho*-quinone methide (*o*-QM) intermediate **82** upon nucleophilic addition to benzaldehyde. Subsequent Michael addition of the *o*-QM with barbituric acid, followed by cyclization and dehydration leads to the formation of the desired product **81**.[60]

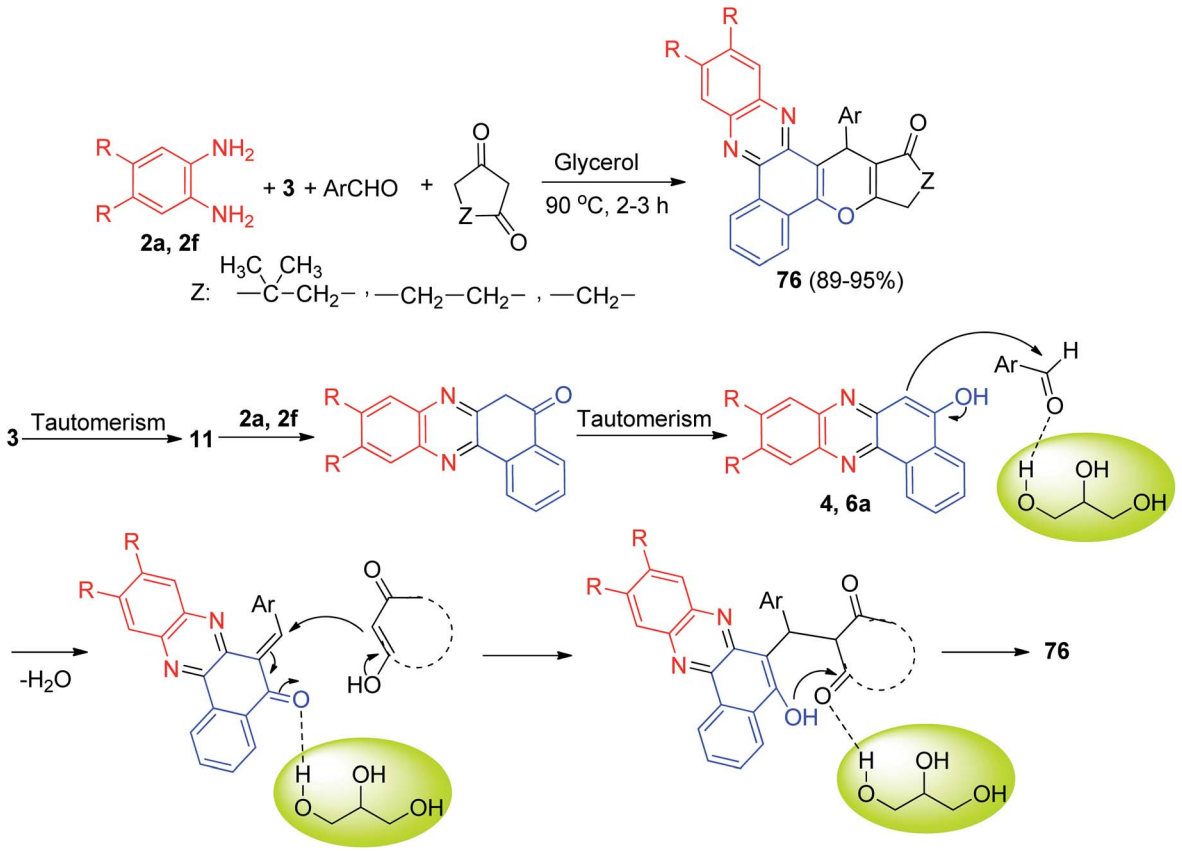
In 2020, DABCO-catalyzed five-component domino protocol for the synthesis of benzo[*a*]pyrazolo[4′,3′:5,6]pyrano[2,3-*c*]phenazines **83** in 72–84% yields has been reported by Mohebat and co-workers. The condensation reaction of **3**, benzene-1,2-diamines, hydrazines, aromatic aldehydes and ethyl



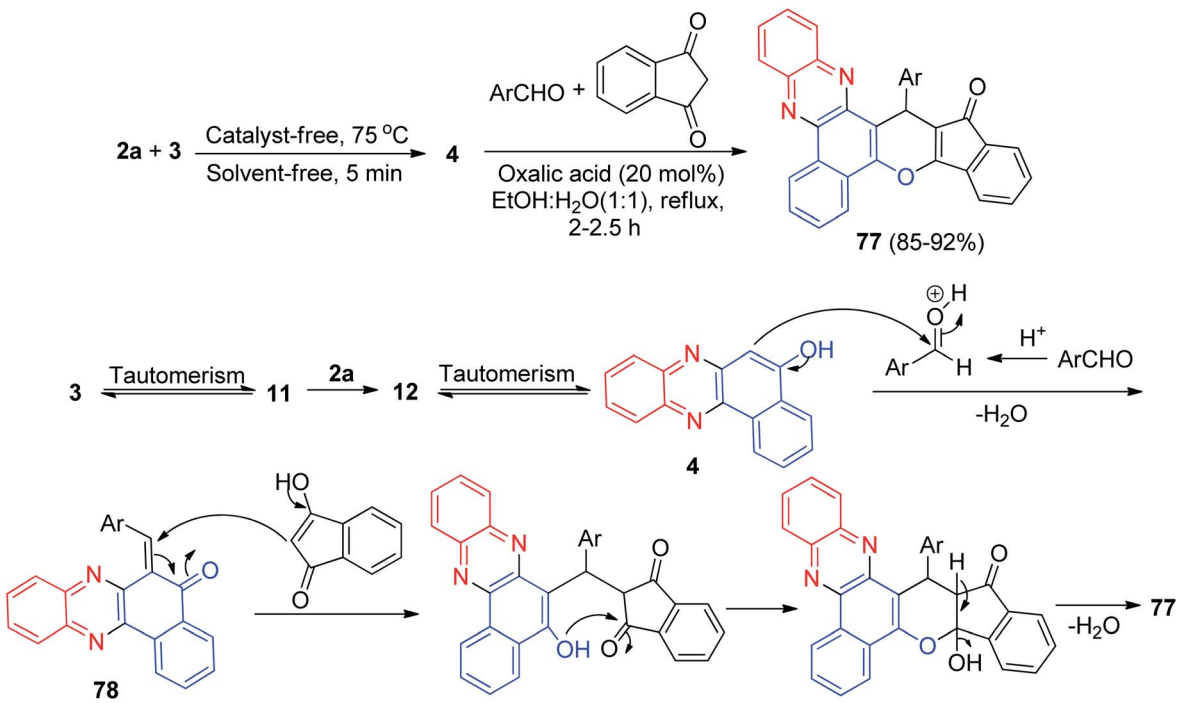
Scheme 25 Synthesis of 4*H*-chromenes and benzo[*a*]chromenophenazines **73–74**.

acetoacetate was carried out in PEG-400 as a green catalyst in the presence of BABCO (10 mol%) at 70 °C for 90–120 min. A detailed reaction mechanism is outlined in Scheme 30. The primary condensation of **3** with benzene-1,2-diamine in the presence of DABCO gives benzo[*a*]phenazin-5-ol **84**. Then, hydrazine condenses with ethyl acetoacetate to generate the pyrazolone ring **85**, which is then isomerized to intermediate **86**. In this mechanism, DABCO is a catalyst to form the olefin **87**, which is readily formed *in situ* from the Knoevenagel condensation of aromatic aldehyde with pyrazole **86**. In the presence of DABCO, **84** converts to its corresponding enolate form **88**, to react easily with olefin **87** (Michael addition) and give intermediate **89**, which then produces **83**.[61]

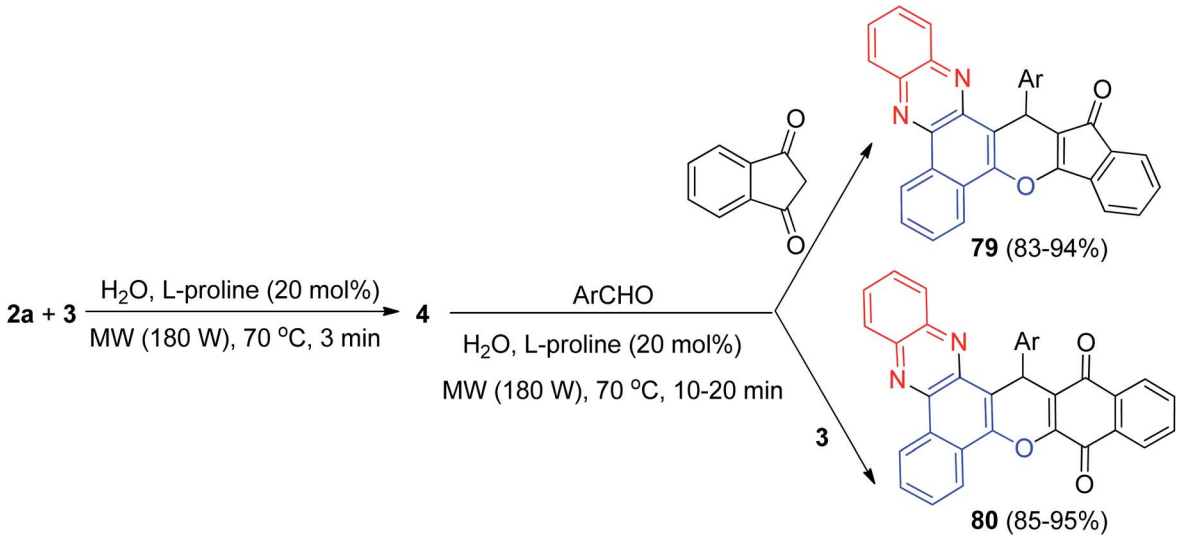
Next, one-pot method for the synthesis four-component of (pyrazolo[4′,3′:5,6]pyrano[2,3-*c*]phenazin-15-yl)methanone derivatives **90** in 83–95% yields has been developed by the reaction of **24**, benzene-1,2-diamines, 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one and arylglyoxal derivatives in the presence of nano Fe_3O_4@TiO_2–SO_3H as a recoverable magnetic catalyst under microwave irradiation (180 W) and in a solvent-



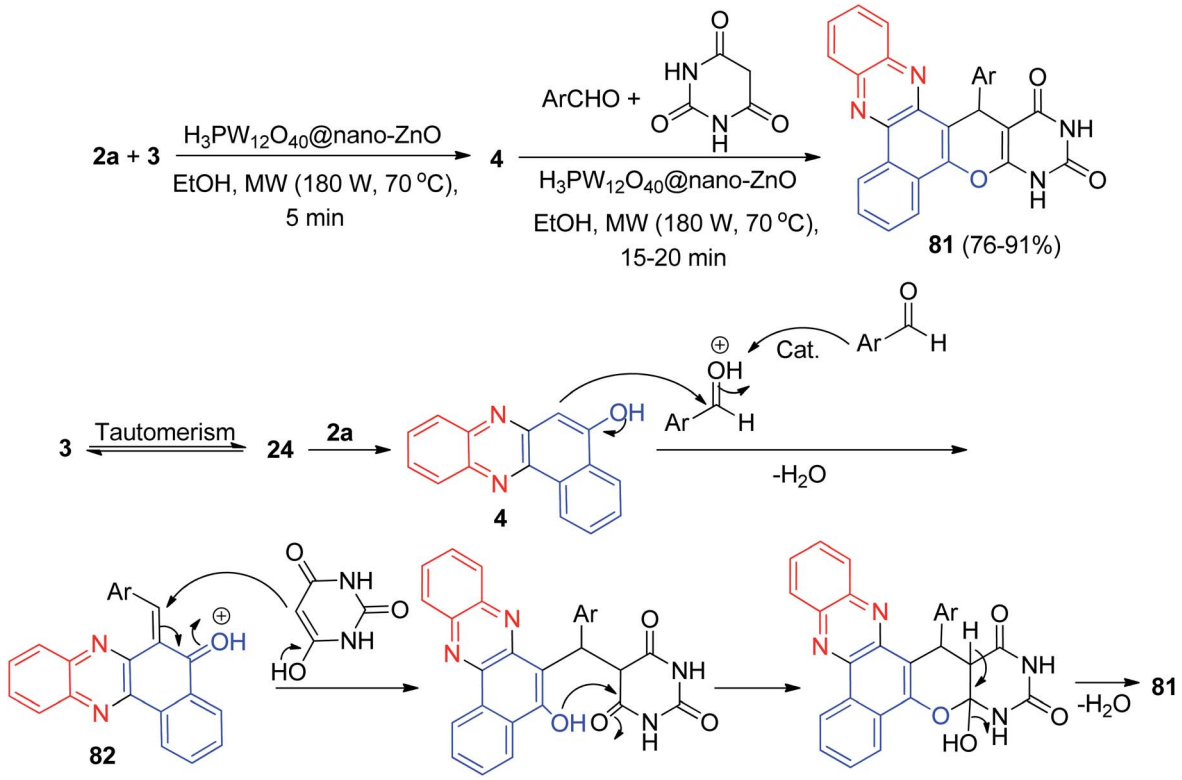
Scheme 26 Preparation of benzo[*a*]chromeno[2,3-*c*]phenazine derivatives **76**.



Scheme 27 Oxalic acid catalyzed synthesis of 16-(aryl)benzo[*a*]indeno[2′,1′:5,6]pyrano[2,3-*c*]phenazin-15(16*H*)-ones **77**.



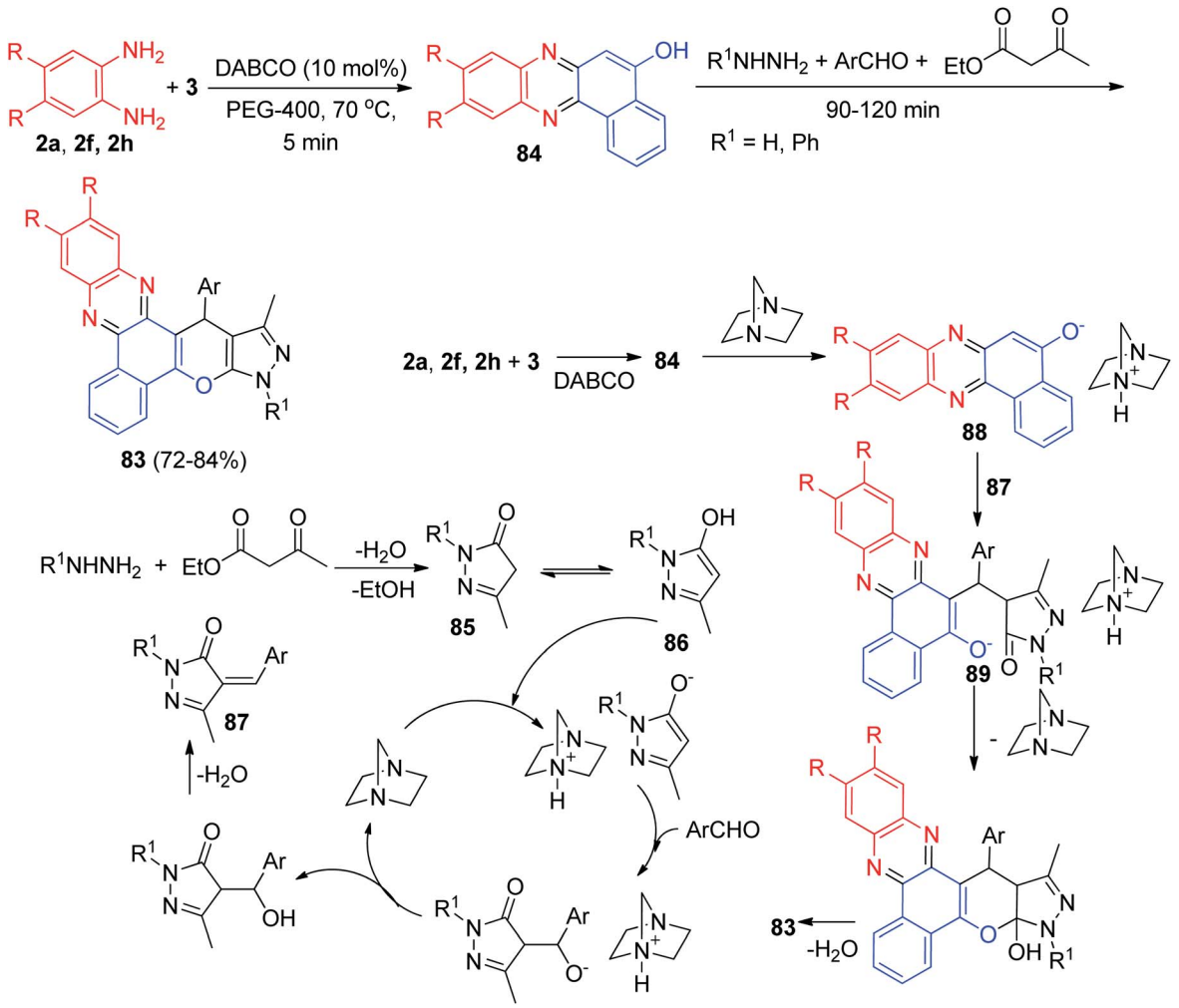
Scheme 28 Microwave-assisted synthesis of benzo[*a*]phenazine annulated heterocycles **79–80**.



Scheme 29 Domino synthesis of benzo[*a*]pyrimido[5′,4′:5,6]pyrano[2,3-*c*]phenazines **81**.

free environment at 75 °C for 4–7 min. A plausible rational mechanism is illustrated under the results in Scheme 31. Based on this mechanism, at first, **3** tautomerizes to intermediate **24**. The primary condensation of **24** with benzene-1,2-diamine obtain benzo[*a*]phenazin-5-ol **91**. Then, **91** condenses with arylglyoxal derivatives to generate intermediate **92** after dehydration. Subsequent Michael addition of 3-methyl-1-phenyl-1H-pyrazol-5-ol with intermediate **92**, followed by cyclization and dehydration leads to the formation of product **90**.[62]

After that, (pyrano[2,3-*c*]phenazin-15-yl)methanone derivatives **93** were prepared in 76–93% yields by the reaction of **3**, benzene-1,2-diamines, 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one and arylglyoxal in the presence of Fe_3O_4@ZnO–SO_3H as a recyclable heterogeneous catalyst under solvent-free



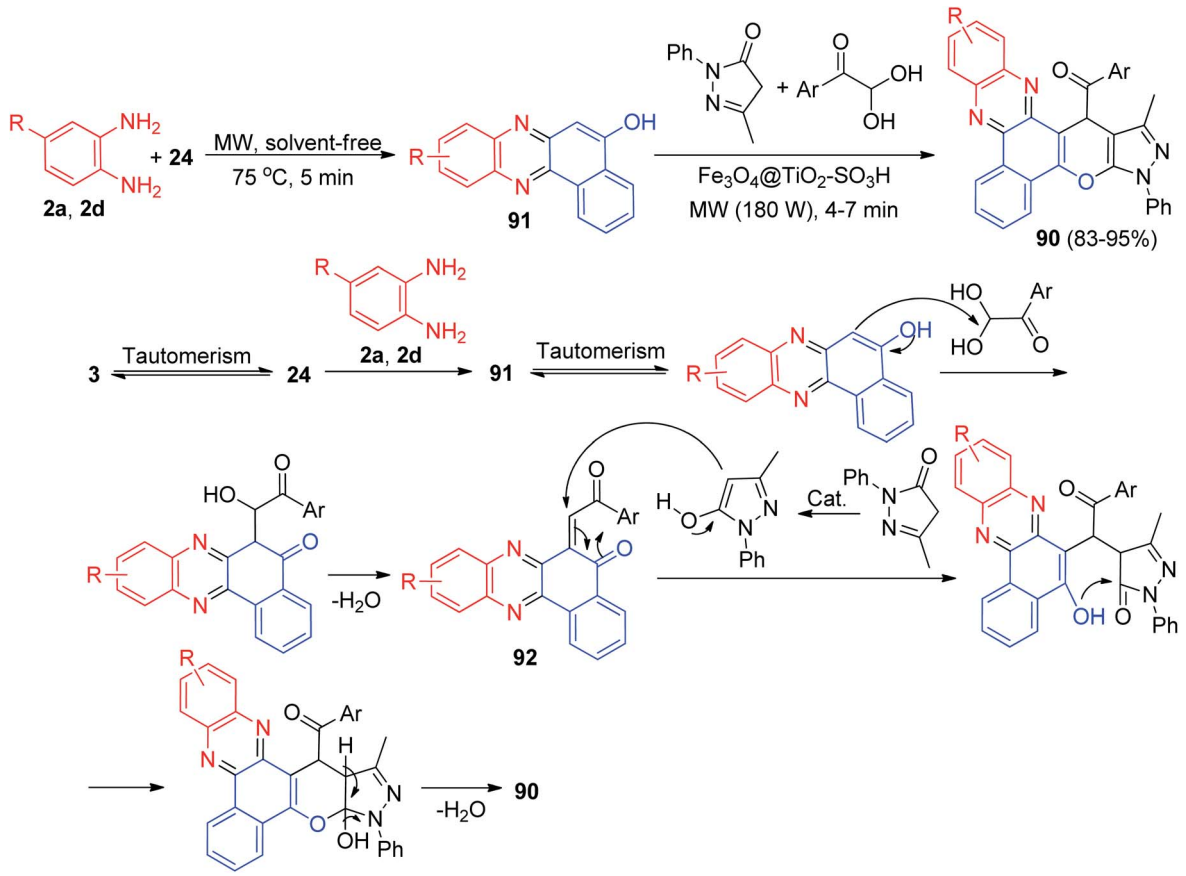
Scheme 30 Synthesis of benzo[*a*]pyrazolo[4′,3′:5,6]pyrano[2,3-*c*]phenazine derivatives **83**.

conditions, using microwave irradiation (180 W, 75 °C) for 7–10 min. A plausible mechanism is illustrated in Scheme 32. Based on this mechanism, at first, **3** tautomerizes to intermediate **24**. The primary condensation of **24** with diamine gives 6*H*-benzo[*a*]-phenazin-5-one **94**, which in tautomerizes to benzo[*a*]phenazin-5-ol **95**. On the other hand, intermediate **96** was generated by nucleophilic addition of pyrazol to the arylglyoxal after elimination of water. Subsequent Michael addition of **95** to the intermediate **96**, followed by cyclization and dehydration leads to the formation of product **93**.[63]

Mohebat *et al.* constructed benzo[*a*]pyrano[3′,4′:5,6]pyrano[2,3-*c*]phenazines **97** in 79–88% yields by the reaction of **3**, **2a**, benzaldehydes and 4-hydroxy-6-methyl-2*H*-pyran-2-one **98** in the presence of phosphotungstic acid ($H_3PW_{12}O_{40}$) under microwave irradiation (180 W, max. 70 °C) in EtOH/H_2O (1 : 1) for 20–30 min (Scheme 33).[64]

Bazgir *et al.* described simple method for the synthesis of biologically interesting benzo[*a*]pyrano[2,3-*c*]phenazines **99** in 80–95% yields by a one-pot two step four-component reaction of **3**, diamines, isocyanides, and dialkyl acetylenedicarboxylates in *N*,*N*-dimethylformamide at 100 °C for 22 h. A plausible mechanism for the synthesis of **99** has been shown in Scheme 34. First, the condensation of diamine and **3** gave intermediate **100**. Then, the 1 : 1 zwitterionic ionic intermediate **101**, formed from the isocyanide and the acetylenic ester, is protonated by **100** to furnish intermediate **102**, which is attacked by the anion of the CH-acidic **102** in a Michael fashion to produce ketenimine **103**. The latter then can undergo cyclization under the reaction conditions to afford the desired product **99**.[65]

After that, Khurana *et al.* have published synthesis of fluorescent benzo[*a*]pyrano[2,3-*c*]phenazines **104** in 78–91% yields *via* one-pot, two-step condensation of **3**, 1,2-phenylenediamines, aromatic aldehydes, and Meldrum's acid in glacial acetic acid as catalyst at 70 °C for 2–3.5 h. Photophysical studies of these compounds have been reported. Moreover, reactions involving cyclohexane-1,3-dione/5-methylcyclohexane-1,3-dione/dimedone in the place of Meldrum's acid yielded corresponding benzo[*a*]chromeno[2,3-*c*]phenazine derivatives **105** in 81–90% yields after 2–3 h. The synthesis of **104** is believed to be proceeding *via* sequential condensation, Michael addition, cyclization, and elimination (Scheme 35). Initially, **3** and 1,2-phenylenediamine undergo condensation to afford benzo[*a*]



Scheme 31 Synthesis of (pyrazolo[4′,3′:5,6]pyrano[2,3-*c*]phenazin-15-yl)methanone derivatives **90**.

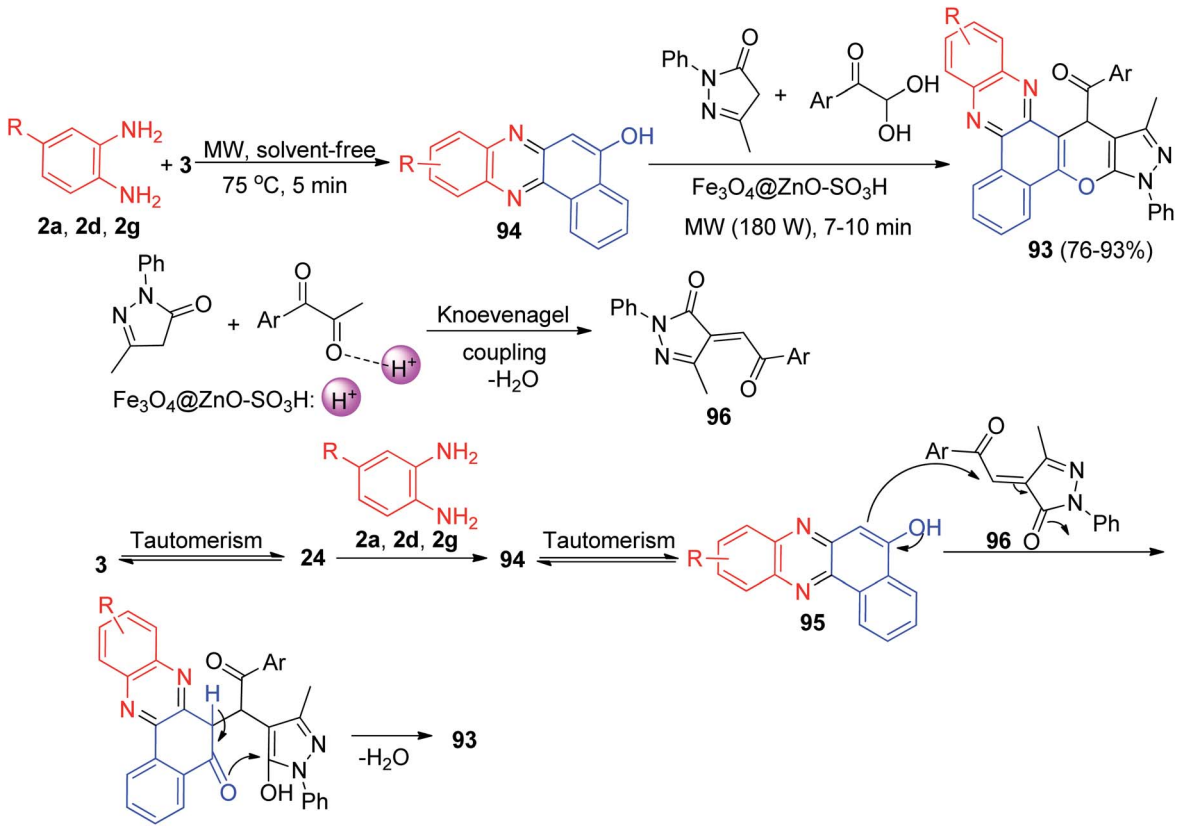
phenazin-5-ol **106**. Simultaneously the Knoevenagel condensation between an aldehyde and Meldrum's acid yields the arylidene Meldrum's acid **107**. Subsequently **106** undergoes Michael type addition to arylidene Meldrum's acid **107** to give intermediate **108** which undergoes cyclization with loss of acetone and carbon dioxide simultaneously to afford the desired compound **104**.[66]

Next, the pyrano-phenazine derivatives **109** were synthesized by an efficient procedure using the reaction between benzo[*a*]phenacin-5-ols with the condensation product of an aldehyde with Meldrum's acid in the presence of a catalytic amount of Et_3N at ambient temperature. The first step consists in the condensation reaction between diamines and **3** in AcOH as solvent for 24 h to afford benzo[*a*]phenazin-5-ols **110** in 76–91% yields. The latter were used as C-nucleophiles to react with the condensation product of aromatic aldehyde with electron-donating and electron-withdrawing functional groups with Meldrum's acid in MeCN/EtOH (3 : 1) in the presence of Et_3N (10 mol%) for 24 h to furnish the desired product **109** in 68–92% yields (Scheme 36).[67]

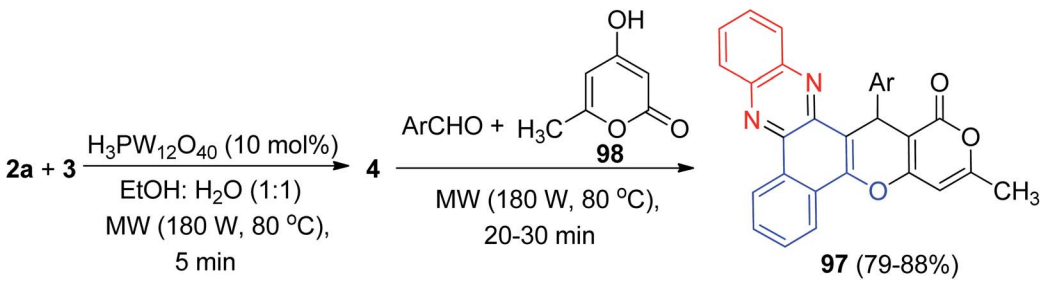
Further, Yazdani-Elah-Abadi and his co-workers reported an efficient and environmentally benign procedure for the synthesis of 3-oxo-3*H*-benzo[*a*]pyrano[2,3-*c*]phenazine-1-carboxylates **111** in 85–94% yields and 3-(5-hydroxybenzo[*a*]phenazin-6-yl)acrylate derivatives **112** in 81–92% yields has been developed by domino three-component condensation reaction between **3**, benzene-1,2-diamines and acetylenic esters in the presence of a catalytic amount of DABCO as an expedient, eco-friendly and reusable base catalyst in water at 50 °C for 2–3 h. The suggested mechanism for the formation of the products is shown in Scheme 37. At first, **3** tautomerizes to intermediate **24**. The primary condensation of **24** with benzene-1,2-diamine obtain benzo[*a*]phenazin-5-ol **113**. Then, based on nucleophilicity of DABCO, the nucleophilic addition of DABCO to the acetylenic ester **114** or **115** and subsequent protonation in the presence of compound **113** gives intermediates **116** or **117**, followed by attack of the anion on the cation part of intermediates **116** or **117** to form the intermediates **118** or **119**. Intramolecular lactonization of the intermediate **118** leads to produce compound **111** and also, intermediate **119** followed by a tautomeric proton shift leads to the formation of desired product **112**.[68]

In 2019, Kucherenko and co-workers reported synthesis of enantioselectively tetrahydropyran-fused benzo[*a*]phenazins **120** in 85–95% yields from β,γ-unsaturated α-keto esters and benzo[*a*]phenazin-5-ol (**4**) in the presence of bifunctional tertiary amine-squaramide catalyst in THF at room temperature for 4–6 h (Scheme 38).[69]

A one pot three-component reaction for the synthesis of benzo[*a*]pyrano-[2,3-*c*]phenazine derivatives **121** in 76–93%



Scheme 32 Preparation of (pyrano[2,3-*c*]phenazin-15-yl)methanone derivatives **93**.

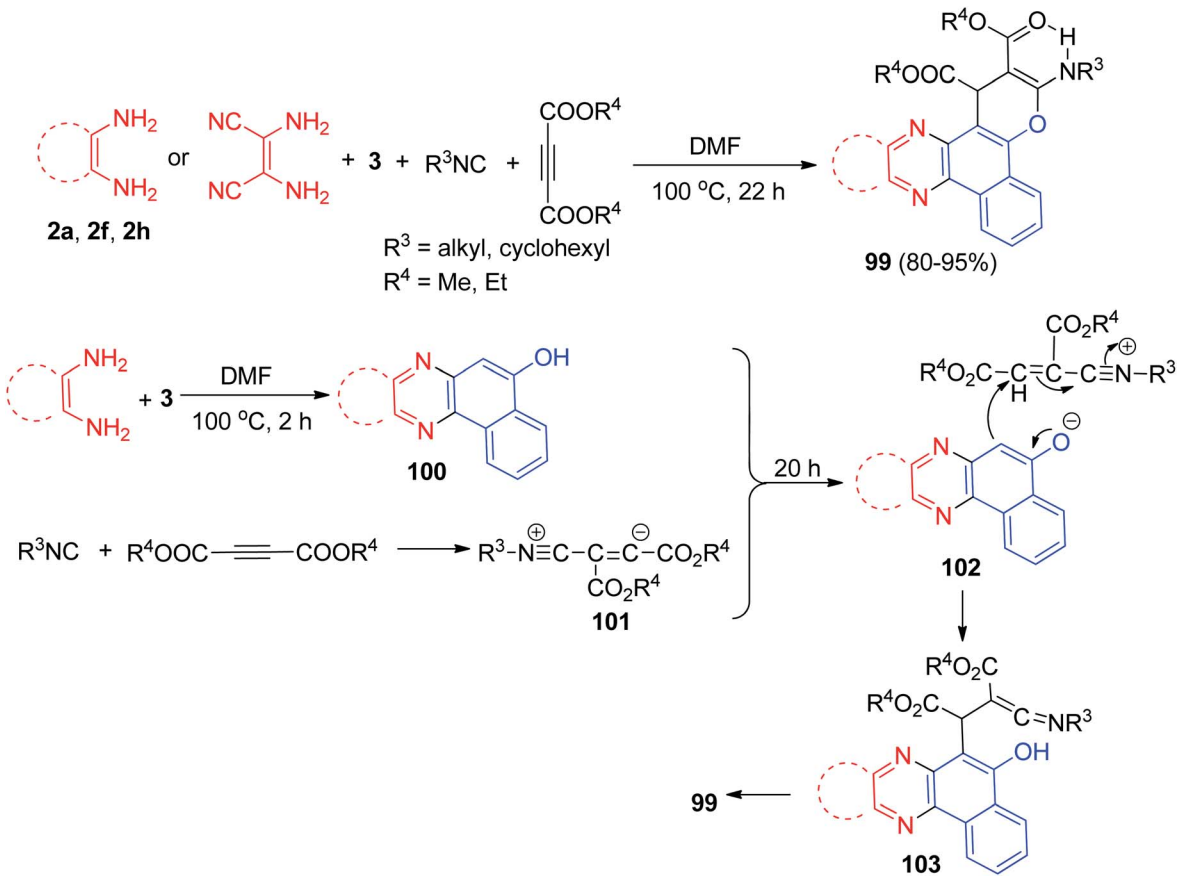


Scheme 33 Microwave-assisted synthesis of benzo[*a*]pyrano[3′,4′:5,6]pyrano[2,3-*c*]phenazines **97**.

yields has been reported by Padmaja and co-workers. The synthesis was achieved by reacting benzo[*a*]phenazin-5-ol (**4**), aromatic aldehydes and (*E*)-*N*-methyl-1-(methylthio)-2-nitroethenamine at 120 °C under neat reaction conditions within 10 min. In addition, the synthesized products were screened for their *in vitro* anticancer properties.

Some of these compounds displayed good antiproliferative activity against B16–F10 cells compared to the standard drug doxorubicin. A proposed mechanism for the formation of **121** is shown Scheme 39. At first, the condensation reaction of **4** and aromatic aldehyde affords adduct **122**. Then the adduct **122** upon Michael-type addition with (*E*)-*N*-methyl-1-(methylthio)-2-nitroethenamine affords the open-chain intermediate **123**. The intermediate **123** obviously tautomerized to another intermediate **124** *via* an imine–enamine tautomerism. Finally, the intermediate **124** undergoes intramolecular O-cyclization to form **121** through the elimination of MeSH.[70]

The authors proposed synthesis of phenazine fused benzo coumarins **125a–d** with negative solvatochromism and positive solvatochromic emission. The coumarin derivatives **125a–d** were synthesized by following the sequence of reactions illustrated in Scheme 40. 2-Hydroxy-1,4-napthaquinone (**3**) was condensed with the substituted 1,2-diaminobenzenes in AcOH : EtOH (50 : 50) at 80 °C for 1–1.5 h to afford **126** in excellent yield. The electron rich **126** were subjected to formylation reaction under Vilsmeier–Haack conditions to obtain 5-hydroxybenzo[*a*]phenazine-6-carbaldehyde **127** in 55–59% yields. The condensation of **127** with the active methylene compounds **128a–b** in refluxing EtOH in the presence of piperidine for 2 h under Knoevenagel conditions followed by an



Scheme 34 Synthesis of benzo[*a*]pyrano[2,3-*c*]phenazines **99**.

intramolecular cyclization gave **125** in 71–84% yields. Solutions of benzimidazole containing dyes (**125c–d**) in various solvents exhibited yellow to orange fluorescence while benzothiazole containing dyes (**125a–b**) showed brilliant bluish green fluorescence.[71]

A facile ruthenium(II)-catalyzed regiospecific C–H/O–H oxidative annulation methodology was developed to construct isochromeno[8,1-*ab*]phenazines **129** in 39–80% yields by the reaction of benzo[*a*]phenazin-5-ols with alkynes in 1,2-DCE at reflux conditions for 12 h. The synthesized compounds showed prominent.

FR fluorescence, with high quantum yield, and exhibited better cancer cell-imaging properties, with excellent biocompatibility. The plausible mechanism for the formation of **129** is shown in Scheme 41. The additive $AgSbF_6$ likely initiates the catalytic reaction by dissociation of the dimeric form of the ruthenium complex $[RuCl_2(p\text{-cymene})]_2$ and gives a reactive cationic ruthenium species. Then, the ruthenium complex gets attached with the directing group OH and forms the intermediate **130**. Then, *peri*-C–H metalation of the intermediate **130** provides a five-membered ruthenacycle intermediate **131**. Now, alkyne attaches with the intermediate **131** giving rise to intermediate **132**. At this point, coordinative regioselective insertion of alkyne into the Ru–C bond of intermediate **132** gives intermediate **133**. Finally, the ruthenium complex that is regenerated by $Cu(OAc)_2$ forms the desired product **129**.[72]

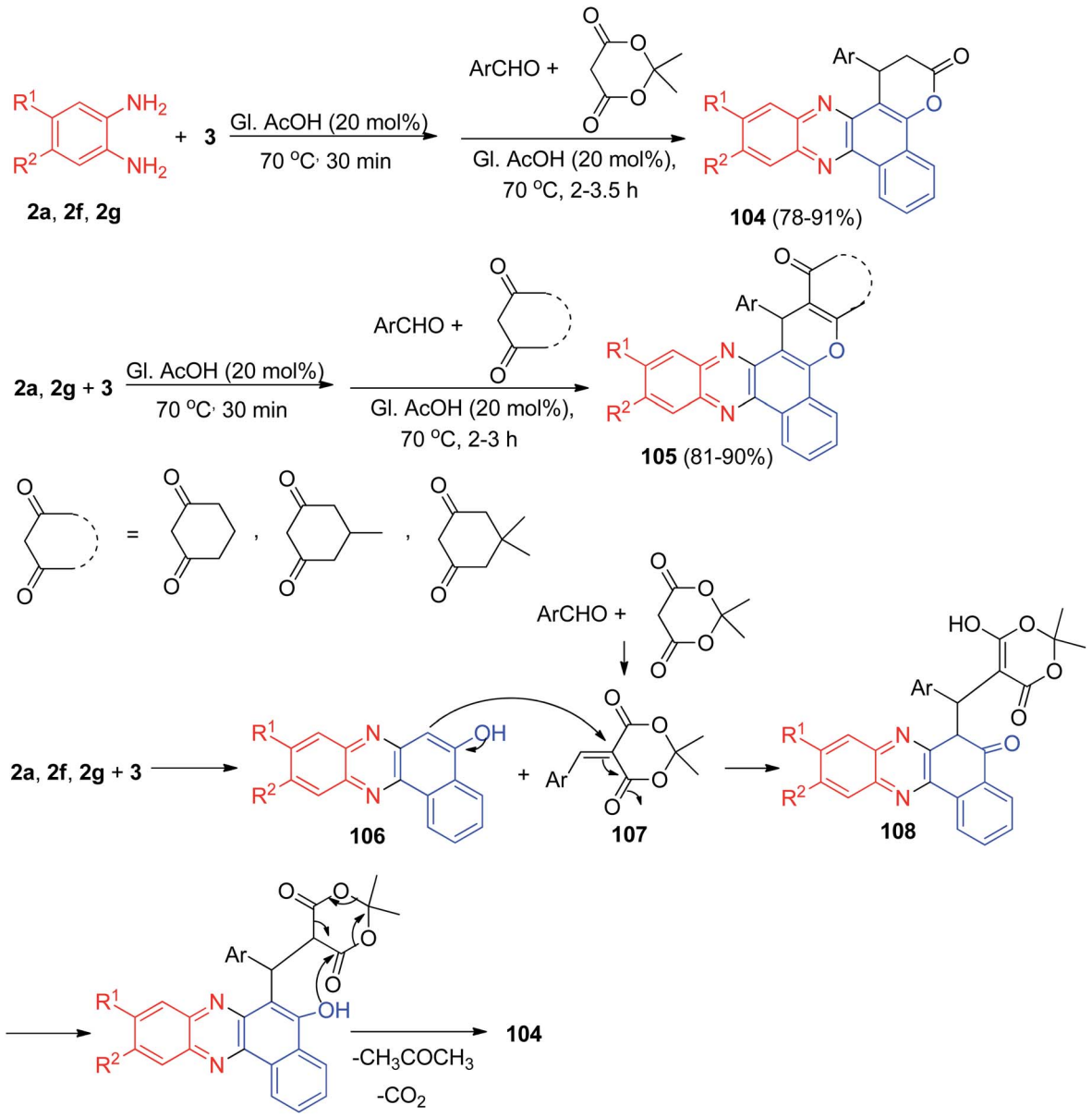
Recently, Kucherenko *et al.* reported highly stereo and enantioselective synthesis of 2-nitro-1-phenyl-2,3-dihydro-1*H*-benzo[*a*]pyrano[2,3-*c*]phenazine **134** (84% yield, 90% ee) by the reaction of 2-nitroallylic carbonate **135** with **4** in the presence of bifunctional Rawal-type tertiary amine **136** (5 mol%) in DCM at room temperature (Scheme 42).[73]

2.2 Synthesis of spirobenzopyranophenazines

In 2013, Mahdavinia and his co-workers described an efficient regio- and chemoselective method for the synthesis of 3-amino-2′-oxospiro[benzo[*c*]pyrano[3,2-*a*]phenazine-1,3′-indoline]-2-carbonitrile/carboxylate derivatives **137** in 95–100% yields *via* the one-pot, two-step four-component domino coupling of **3**, benzene-1,2-diamines, isatins, and malononitrile/cyanoacetic ester in the presence of DABCO in EtOH under reflux conditions for 10–15 min.

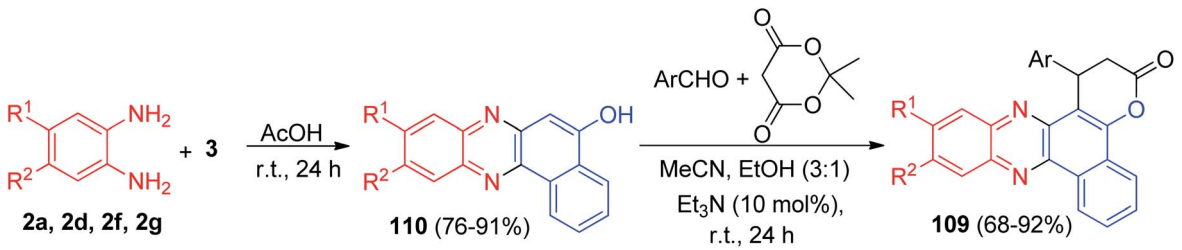
A plausible mechanism for the formation of **137** is shown in Scheme 43. 2-Hydroxynaphthalene-1,4-dione (**3**) is converted into the corresponding benzo[*a*]phenazin-5-ol **138** on reaction with benzene-1,2-diamines; isatin can be easily attacked by the carbon nucleophilic center of malononitrile leading to Knoevenagel condensation products (intermediate **139**) finally; the Knoevenagel products attacked by **138** leading to the desired product **137**.[74]

In 2017, a series of benzo[*a*]-phenazine derivatives **140** as hybrid molecules of phenazine, pyran, indole and 1,2,3-triazole pharmacophores were constructed in 55–82% yields. Firstly, the

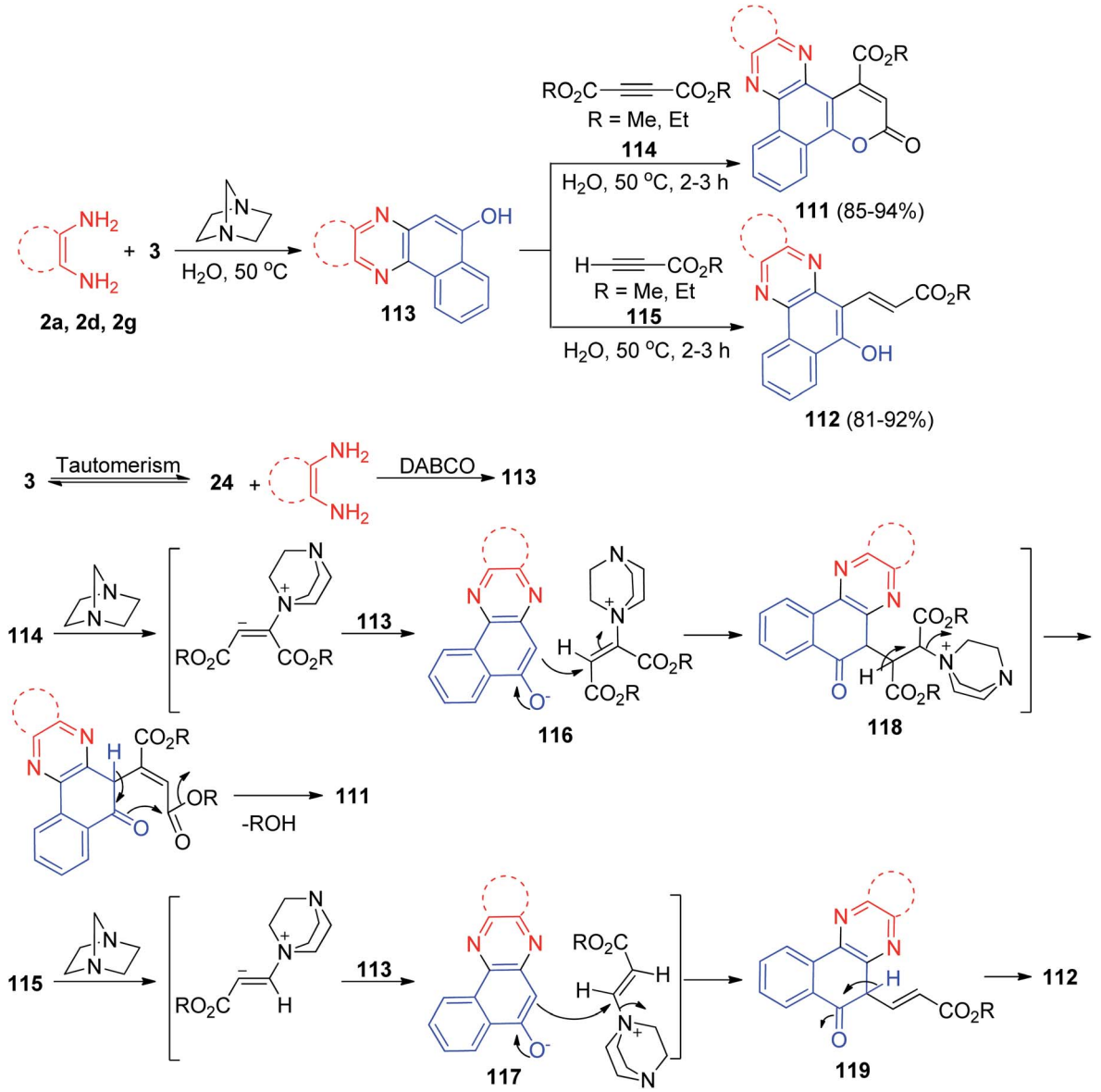


Scheme 35 Synthesis of benzo[*a*]pyrano[2,3-*c*]phenazines **104** and benzo[*a*]chromeno[2,3-*c*]phenazines **105**.

reaction of **3**, **2a**, malononitrile and 1-(prop-2-yn-1-yl)indoline-2,3-dione in the presence of DABCO in refluxing EtOH for 30 min afforded the desired compound **141** in 72% yield. Finally, target compounds were synthesized using compound **141**, and aromatic azide in the presence of sodium ascorbate and $CuSO_4$ in THF/H_2O (Scheme 44). Cytotoxic evaluation indicated that some compounds exhibited moderate cytotoxicity against HCT116, MCF7, HepG2 and A549 cancer cell lines *in vitro*. Moreover, all compounds had low or no effect against L02 and HUVEC non-cancer cell lines.[75]

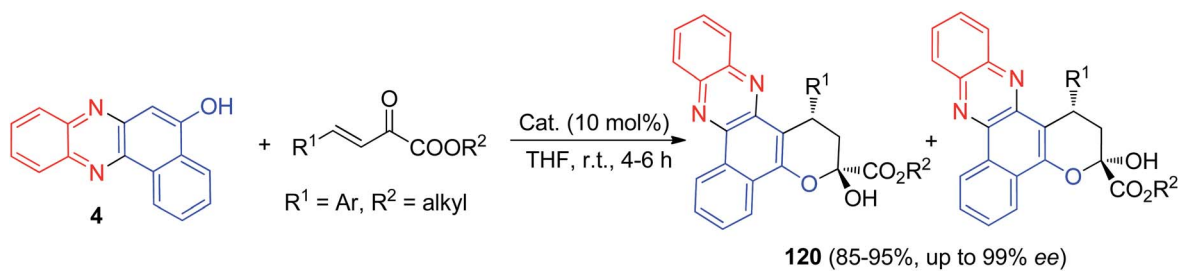


Scheme 36 Synthesis of pyrano-phenazine derivatives **109**.

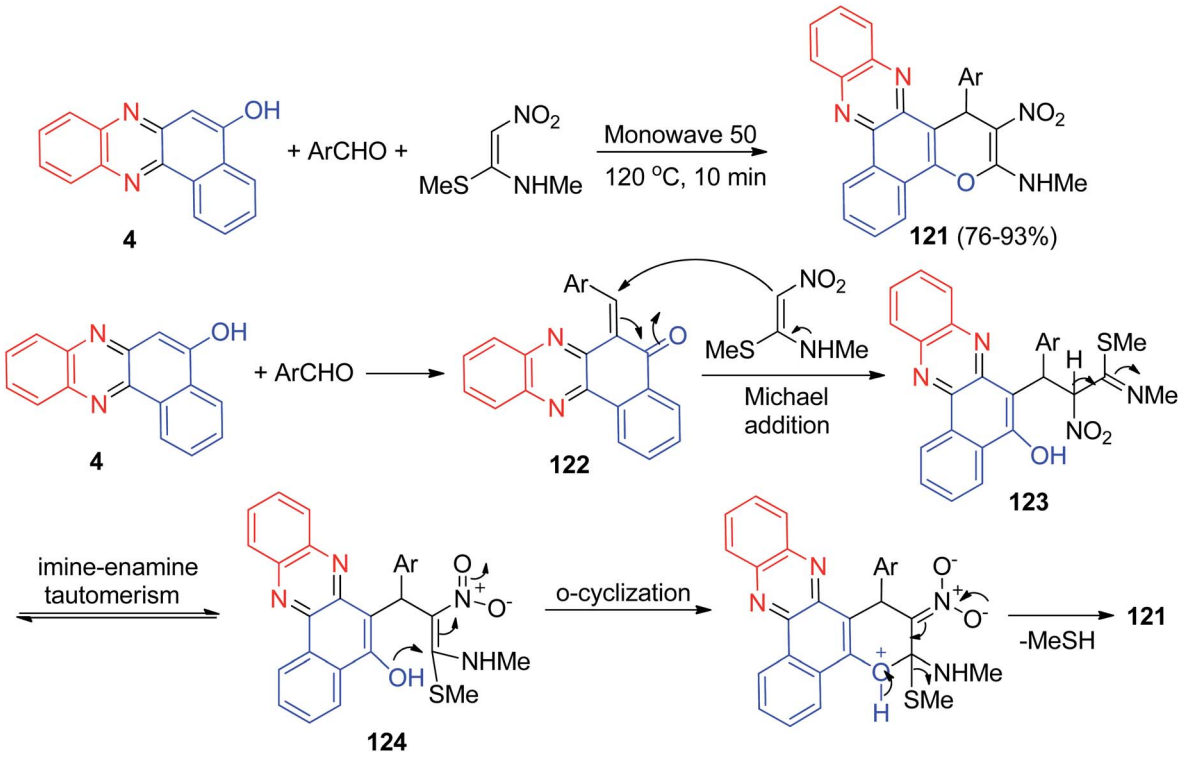


Scheme 37 DABCO-catalyzed synthesis of 3-oxo-3*H*-benzo[*a*]pyrano[2,3-*c*]phenazine-1-carboxylate and 3-(5-hydroxybenzo[*a*]phenazin-6-yl)acrylate derivatives **111–112**.

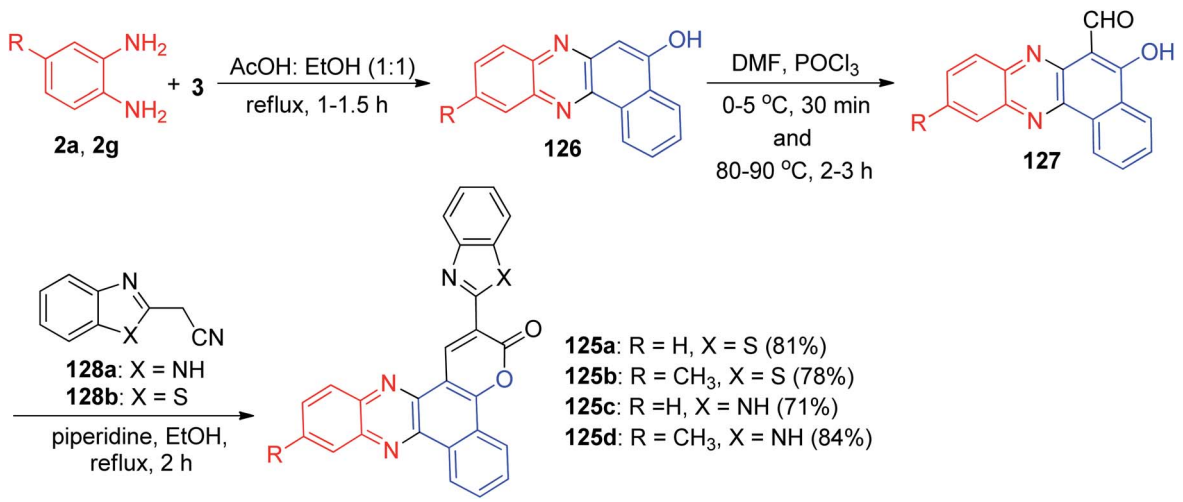
In addition, Hasaninejad *et al.* reported synthesis of poly-functionalized spiro[benzo[*c*]pyrano[3,2-*a*]phenazine] derivatives **142** in 68–94% yields by the one-pot two-step condensation of **3** with aromatic 1,2-diamines to form the corresponding quinoxalines and then cyclo-condensation with an alkylmalonate and a cyclic carbonyl compound in EtOH under reflux conditions in the presence of L-proline as a bifunctional catalyst leads to the corresponding products **142** in high yields (68–94%) and short



Scheme 38 Synthesis of enantioselectively tetrahydropyran-fused benzo[*a*]phenazins **120**.



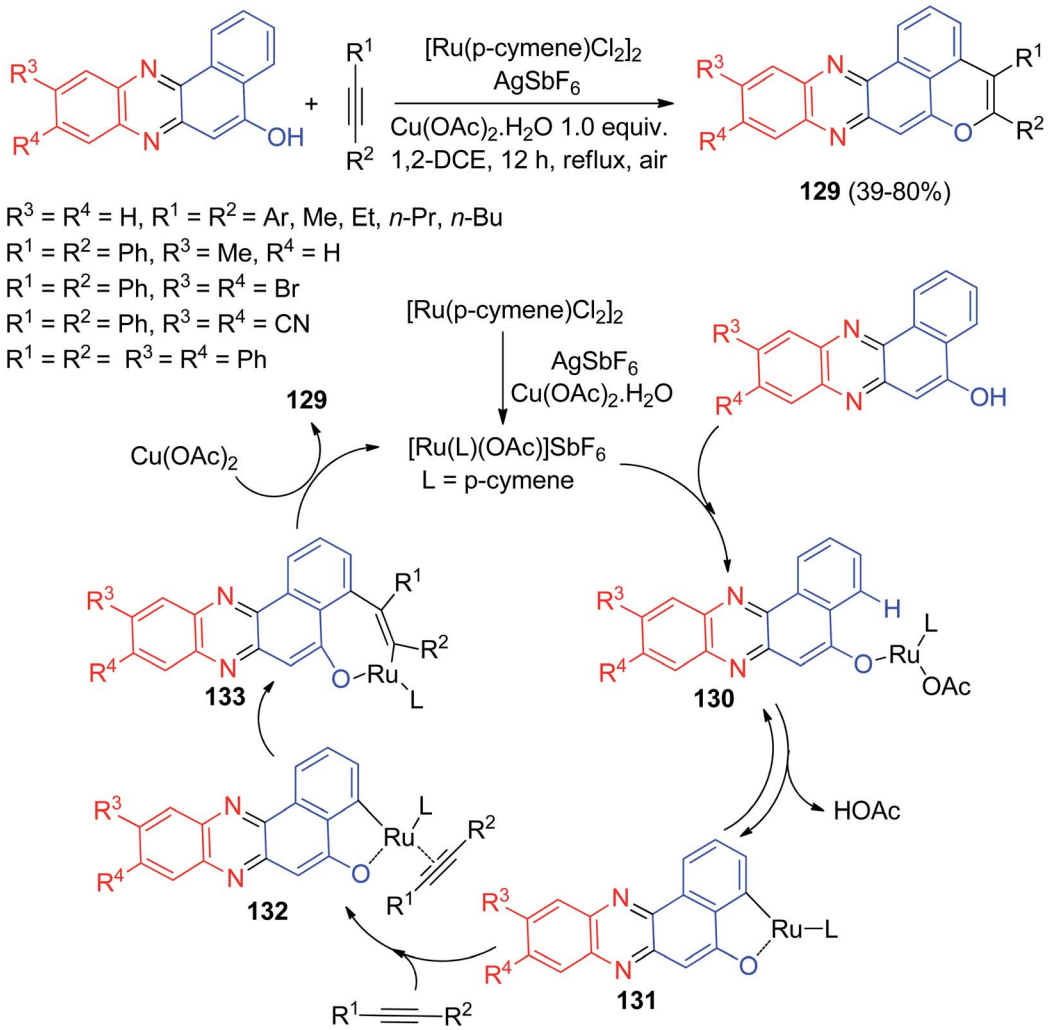
Scheme 39 Synthesis of benzo[*a*]pyrano-[2,3-*c*]phenazine derivatives **121**.



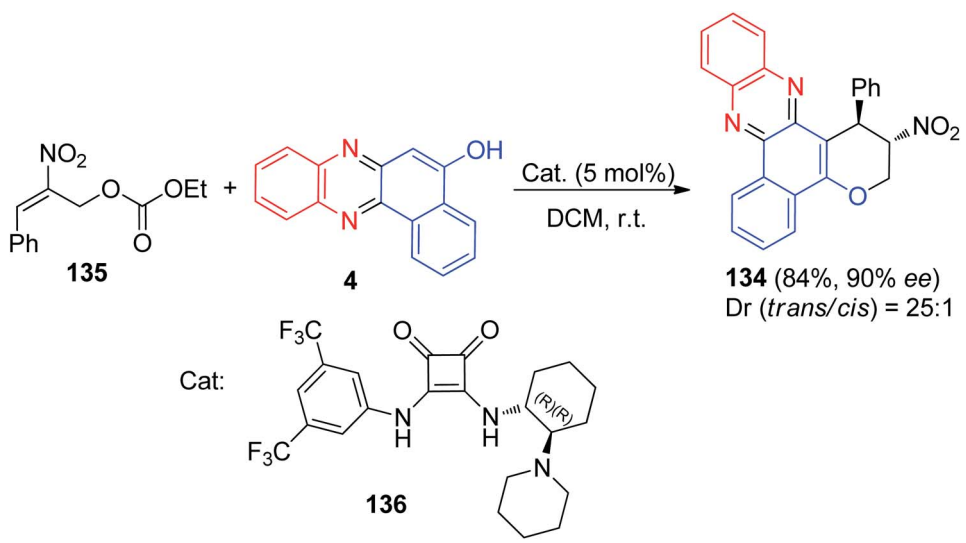
Scheme 40 Synthesis of phenazine fused benzo coumarins **125**.

reaction times (2–10.5 h). The proposed mechanism for the synthesis of **142** is shown in Scheme 45. Initially, **3** and the benzene-1,2-diamine react to form the corresponding quinoxalinone **143**. Knoevenagel condensation of cyclic ketones with malono derivative affords an intermediate **144**, which undergoes Michael addition with **143** to form intermediate **145**. The enolate O-atom of the formed intermediate **145** attacks the CN group, and a subsequent H-atom shift leads to compound **142**.[76]

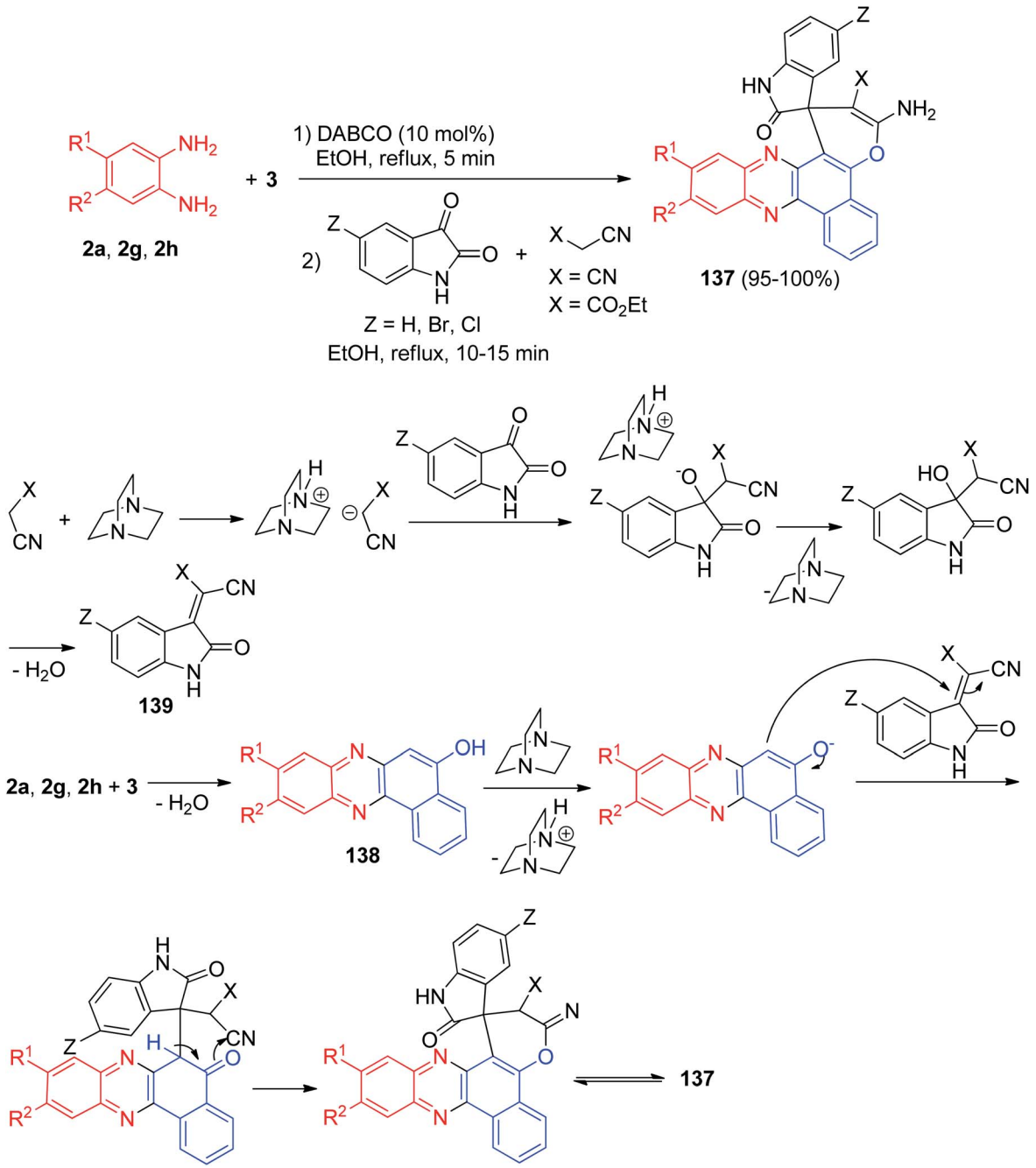
Further, a series of pyrano-fused benzophenazines **146–147** in 75–92% yields were synthesized using a bifunctional thiourea-based organocatalyst from the one-pot, two-step four-component reaction of **3**, benzene-1,2-diamines, malononitrile or its derivatives and isatins or aromatic aldehydes in water under reflux conditions for 2–7 h. The proposed mechanism is outlined in Scheme 46. They believe that the condensation reaction between **3** and the benzene-1,2-diamine leading to the corresponding benzo[*a*]phenazin-5-ol **148** does not need any catalyst. However, organocatalyst plays significant role in other steps, and it activates both the electrophile and nucleophile through its thiourea moiety and basic amine moiety,



Scheme 41 Synthesis of isochromeno[8,1-*ab*]phenazines **129**.



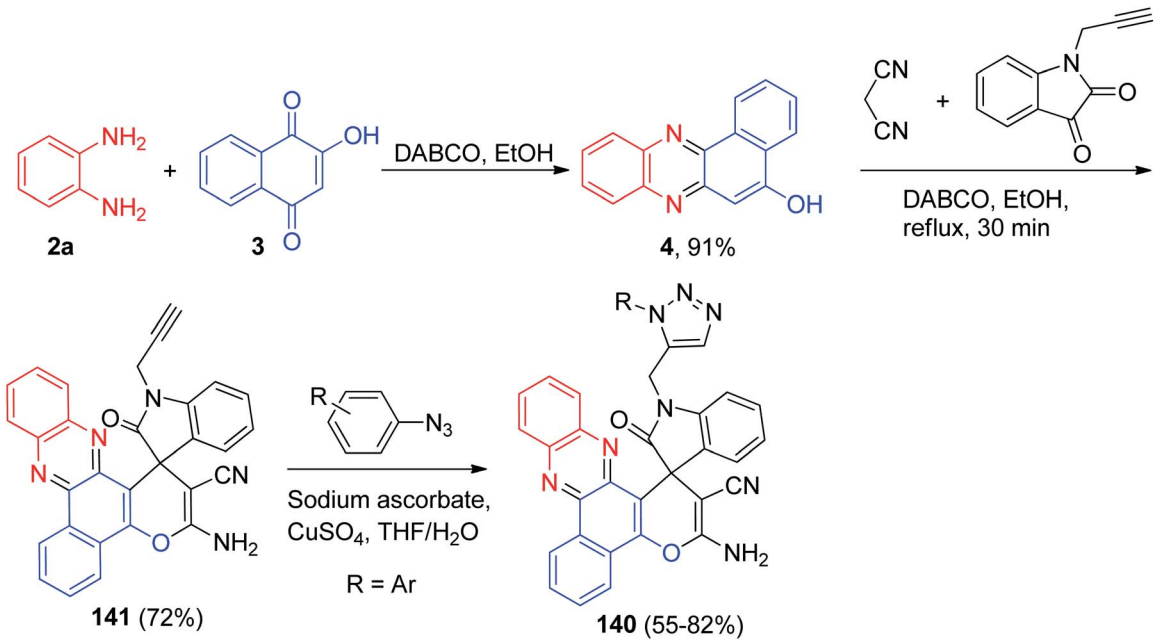
Scheme 42 Enantioselective synthesis of 2-nitro-1-phenyl-2,3-dihydro-1*H*-benzo[*a*]pyrano[2,3-*c*]phenazine **134**.



Scheme 43 Synthesis of 3-amino-2′-oxospiro[benzo[*c*]pyrano[3,2-*a*]phenazine-1,3′-indoline]-2-carbonitrile/carboxylate derivatives **137**.

respectively. The Knoevenagel condensation of isatin or aldehyde with malononitrile affords **149**, which undergoes a Michael addition with **148** to form intermediate **150** in the presence of organocatalyst. A subsequent cyclization leads to the formation of **151** which undergoes tautomerization to form the corresponding final products **146–147**.[77]

In addition, Maghsoodlou *et al.* have demonstrated a green one-pot procedure for the synthesis of benzo[*a*]pyrano[2,3-*c*] phenazine derivatives **152–153** in 83–95% yields by domino multi-component condensation reaction between **3**, **2a**, malononitrile and cyclic ketones or aromatic aldehydes in the presence of a catalytic amount of 1,3-dimethyl-7*H*-purine-2,6-dione (theophylline) as are usable solid base catalyst under thermal (70 °C), microwave irradiation (180 W, max. 70 °C) and solvent-free conditions. The suggested mechanism for the formation of the products is shown in Scheme 47. On the basis of this mechanism, at first, **3** tautomerizes to intermediate **24**. The primary condensation of **24** with **2a** obtains **4**. On this mechanism, theophylline is an efficient catalyst to form the olefin **154**, which readily prepares *in situ* from Knoevenagel condensation of carbonyl groups of aldehyde or cyclic ketones with malononitrile. The Michael addition of **4** with olefin **154** in



Scheme 44 Preparation of benzo[*a*]-phenazine derivatives **140**.

the presence of theophylline finally give intermediate **155**, which then makes the inner molecular ring to be formed after a tautomeric proton shift to produce benzo[*a*]pyrano[2,3-*c*] phenazines **152** and spiro[benzo[*a*]pyrano[2,3-c] phenazine] derivatives **153**.[78]

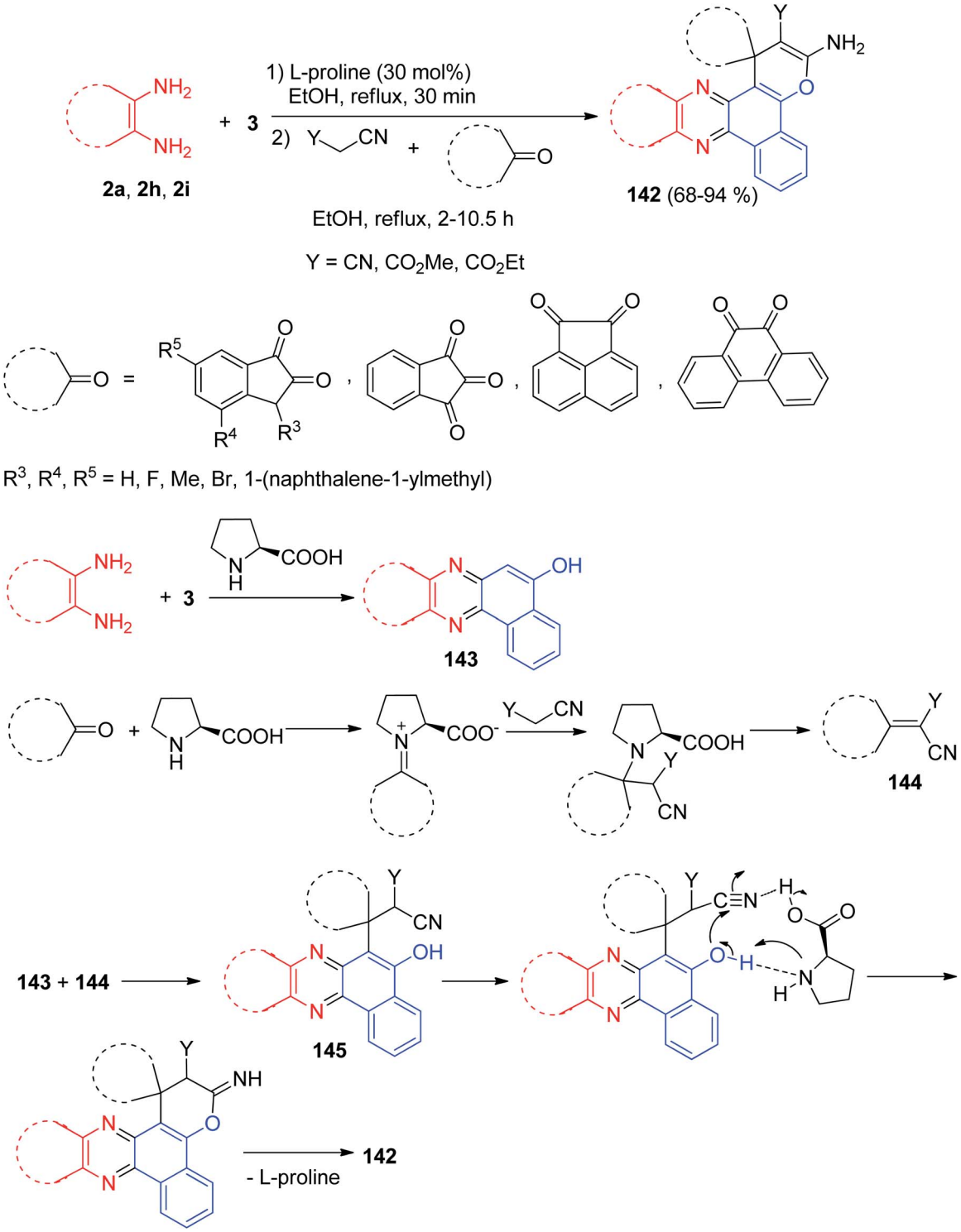
Later, a green strategy for the synthesis of a biologically and pharmaceutically interesting multi-functionalized diverse spiro-benzo[*a*]phenazine annulated heterocycles **156** in 76–91% yields by one-pot, two-step domino reaction starting from **3**, benzene-1,2-diamines, a cyclic carbonyl compound, and 1,3-indandione in the presence of a basic ionic liquid (1-butyl-3-methylimidazolium hydroxide: [BMIM]OH) as a reusable catalyst with the assistance of microwave irradiation (300 W) under solvent-free conditions at 100 °C for 8–12 min. The probable mechanism is given in Scheme 48. On the basis of this suggested mechanism, the primary condensation of **3** with benzene-1,2-diamines in the presence of [BMIM]OH gives benzo [*a*]phenazin-5-ols **157**. Then, the Knoevenagel condensation between **157** and cyclic ketones produce adduct **158**, which act as a Michael acceptor. The 1,3-indandione attacks the Knoevenagel adduct **158** in a Michael-type addition to produce the intermediate **159**, which then makes the inner molecular ring to be formed after a tautomeric proton shift to generate **156**.[79]

After that, for synthesis of 3-amino-2′-oxospiro[benzo[*c*]pyrano[3,2-a]phenazine-1,3′-indoline]-2-carbonitrile/carboxylate derivatives **160** in 90–98% yields, Safaei-Ghomi and Bakhtiari developed a domino coupling reaction involving **3**, benzene-1,2-diamines, malone derivatives and isatin derivatives catalyzed by $H_3PMo_{12}O_{40}$/Hyd-SBA-15 in EtOH at 50 °C for 10–12 min. A mechanism for a plausible catalytic cycle for this domino MCR is outlined in Scheme 49. Coordination of the carbonyl groups of **3** to a molybdenum sites at the surface of $H_3PMo_{12}O_{40}$/Hyd-SBA-15 would increase the activity. On the other side, the electrophilicity of malono derivatives increased by coordination with the $H_3PMo_{12}O_{40}$/Hyd-SBA-15. Molybdenum sites at the surface of $H_3PMo_{12}O_{40}$/Hyd-SBA-15 increased the electrophilicity of reactants, which simplifies the reaction. Moreover, in the presence of monosubstituted benzene-1,2-diamine, major and minor isomers of the corresponding products are generated.[80]

Next, Kumar *et al.* described a domino protocol for the synthesis of structurally diverse spiroannulated pyrimidophenazines **161** in 89–96% yields involving a four-component reaction of **3**, **2a**, cyclic ketones and amino derivatives in the presence of erbium doped.

TiO_2 nanoparticles as a recyclable and reusable heterogeneous acid catalyst in EtOH under reflux conditions for 19–32 min. The mechanism of the reaction proceeds with the following steps involving the Michael addition, cyclization and dehydration as presented in Scheme 50. The doping of erbium with TiO_2 NPs increased the efficiency of the resulting catalyst and thus facilitated the reaction in better way as compared with TiO_2 NPs.[81]

In 2019, *p*-toluenesulfonic acid was applied as an efficient and solid acid catalyst for the one-pot, four-component condensation between **3**, benzene-1,2-diamines, cyclic 1,3-dicarbonyl compounds and isatin or ninhydrin to afford the corresponding spiro[benzo[*a*]chromeno[2,3-*c*]phenazine] derivatives **162** in 75–94% yields *via* a new two-step domino protocol under conventional heating (100 °C, 30 min) and microwave irradiation (300 W, 100 °C, 7–10 min) under solvent-free conditions. The probable mechanism for the domino synthesis of **162** using *p*-TSA is given in Scheme 51. Initially, **3** tautomerizes to intermediate **24**. The early condensation of **24**

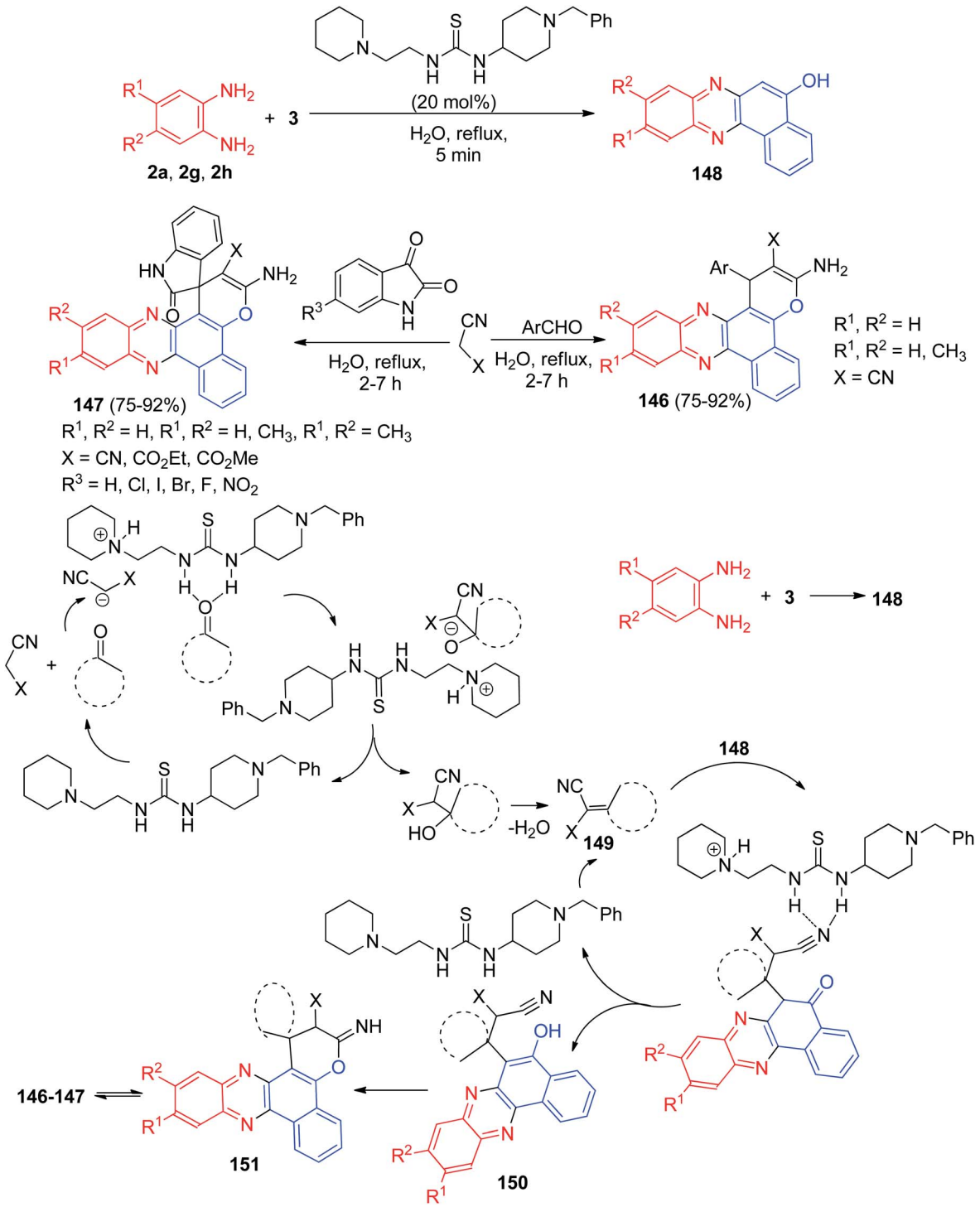


Scheme 45 Synthesis of spiro[benzo[*c*]pyrano[3,2-*a*]phenazines] **142**.

with benzene-1,2-diamines obtain benzo[*a*]phenazin-5-ol **163**. Then, the Knoevenagel condensation between the dimedone and cyclic ketone to produce adduct **164**, which acts as a Michael acceptor. The enol **163** attacks Knoevenagel adduct **164** in a Michael-type addition to produce intermediate **165** which then makes the inner molecular ring to be formed after a tautomeric proton shift to generate **162**.[82]

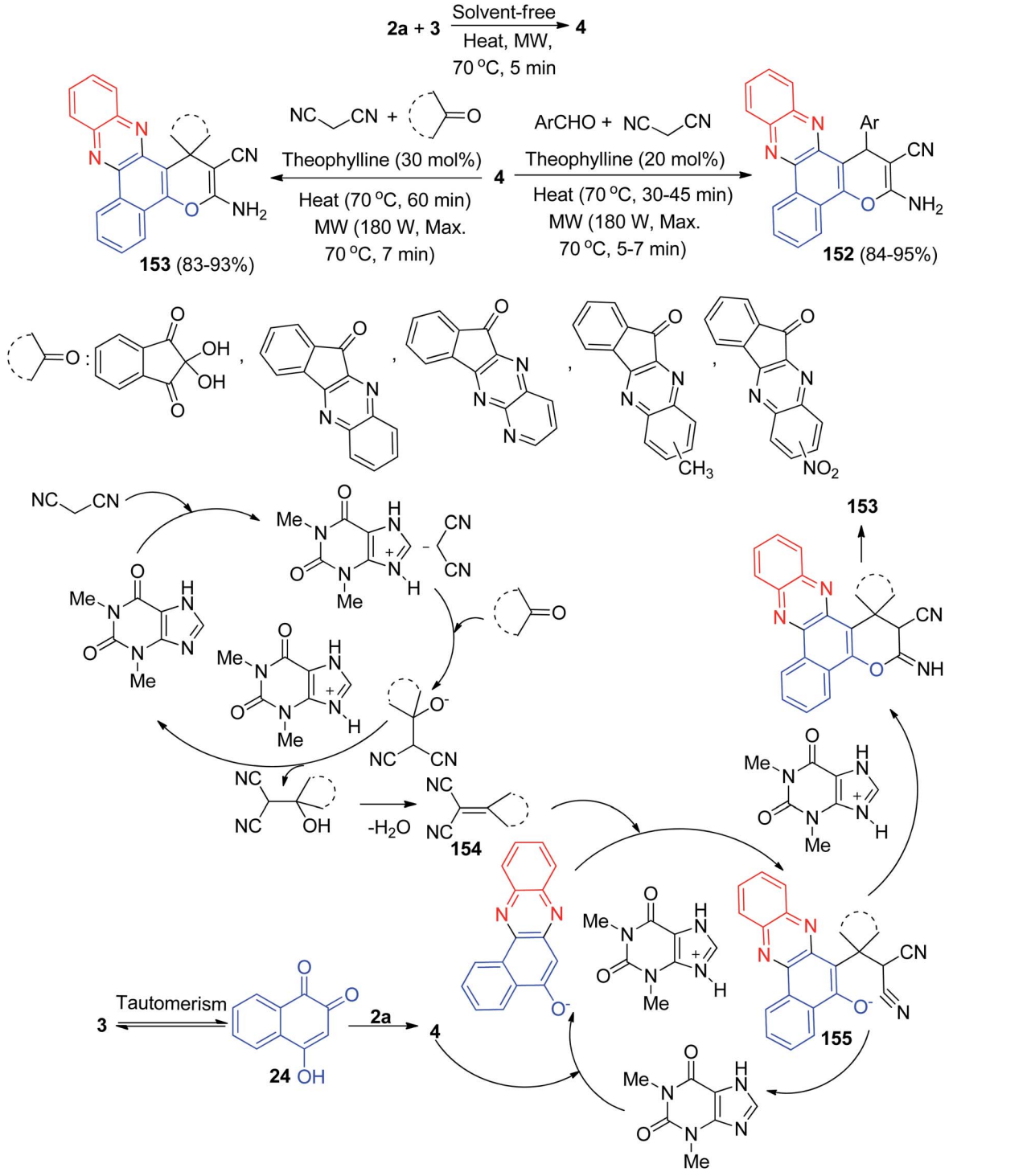
2.3 Synthesis of benzo[*a*]benzochromeno phenazine

In 2016, an efficient *p*-toluenesulfonic acid catalyzed synthesis of 11*H*-benzo[*a*]benzo[6,7]chromeno[2,3-*c*]phenazine-11,16(17*H*)-



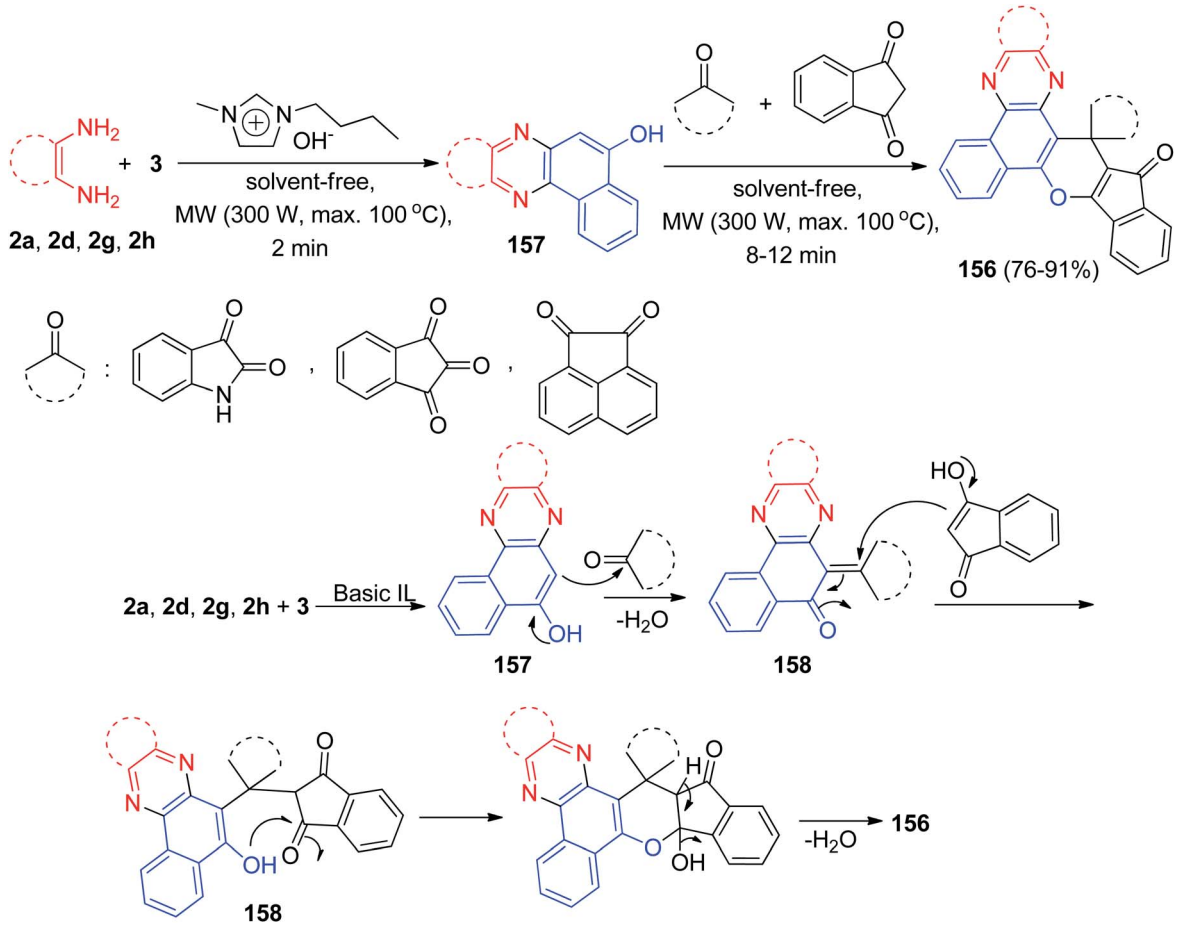
Scheme 46 Synthesis of pyrano-fused benzophenazines **146–147**.

dione derivatives **166** in 85–93% yields has been described by one-pot, two-step four-component condensation of **3**, **2a**, aromatic aldehydes using polyethylene glycol as solvent at 80 °C for 2–3 h. The plausible mechanism of this domino reaction is depicted in Scheme 52. Initially, **3** tautomerizes to intermediate **11**. The primary condensation of **11** with **2a** obtains 6*H*-benzo[*a*] phenazin-5-one (**12**), which in tautomerism equilibrium prepares **4**. The catalyst *p*-TSA appears to play a key role as acid in the reaction to form (6-benzylidenebenzo[*a*]phenazin-5(6*H*)-ylidene) oxonium **167**, which prepares *in situ* from condensation of aldehyde with **4**. Subsequent Michael addition of **3** with **167**, followed by cyclization and dehydration, leads to the formation of the desired product **166**.[83]



Scheme 47 Theophylline catalyzed synthesis of benzo[*a*]pyrano[2,3-*c*]phenazines **152** and spiro[benzo[*a*]pyrano[2,3-*c*]phenazine] derivatives **153**.

Next, Yazdani-Elah-Abadi *et al.* reported superparamagnetic nanoparticles of modified thioglycolic acid (γ-Fe_2O_3@SiO_2–SCH_2CO_2H) as a green catalyst for the one-pot synthesis of spiro [benzo[*a*]benzo[6,7]chromeno[2,3-*c*]phenazine] derivatives **168** in 79–92% yields and benzo[*a*]benzo[6,7]chromeno[2,3-*c*]phenazine **169** in 83–94% yields *via* domino Knoevenagel–Michael–cyclization reaction of **3**, **2a** and ninhydrin or isatin or cyclic ketones **170** or aromatic aldehydes in EtOH : H_2O (1 : 1) at 70 °C for 2–3 h. This magnetic organocatalyst was easily isolated from the reaction mixture by magnetic decantation using an external magnet. The suggested mechanism for the formation of the products is shown in Scheme 53. On the basis of this



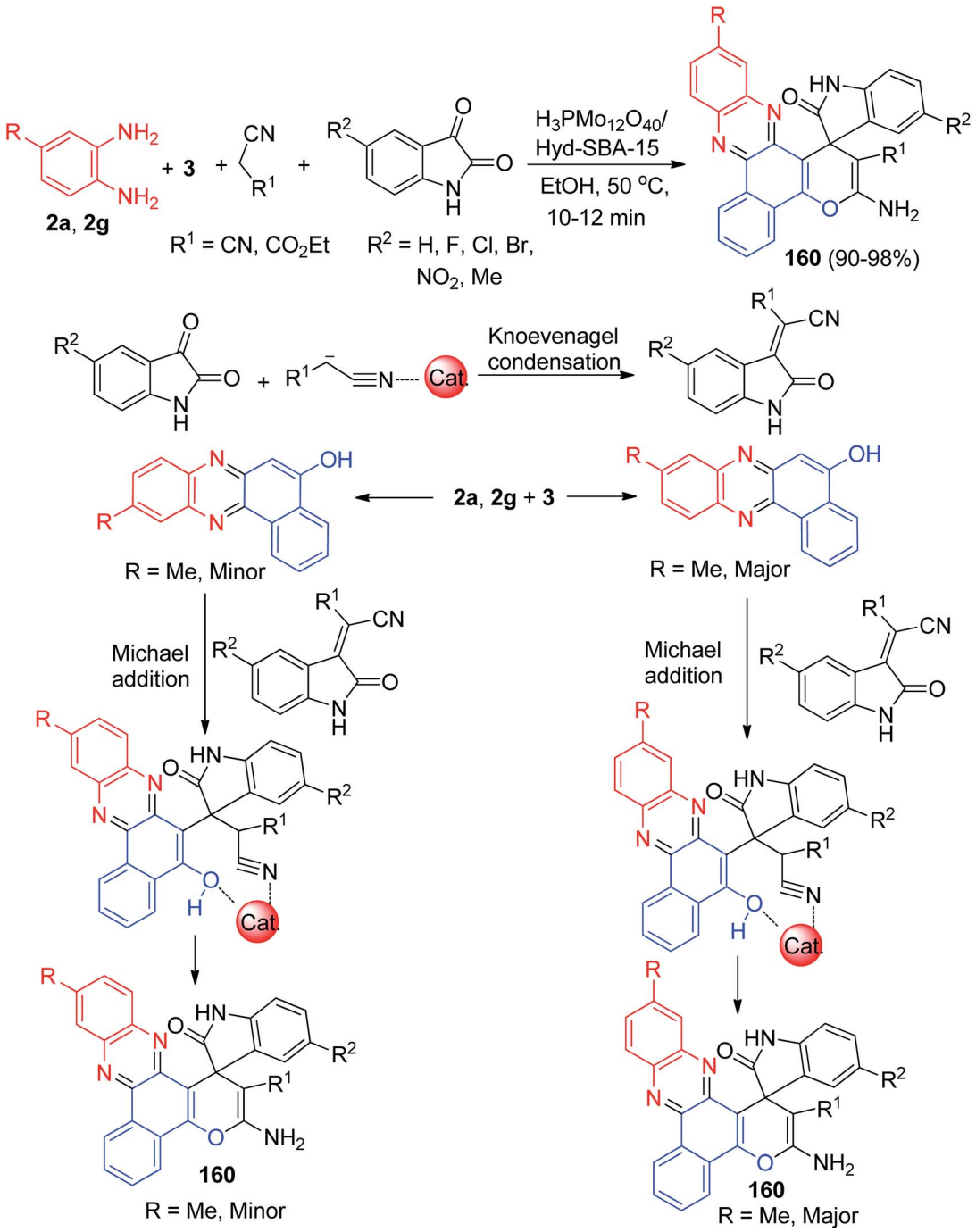
Scheme 48 MW-assisted synthesis of spiro-benzo[*a*]phenazines **156** in the presence of [BMIM]OH.

mechanism, at first, **3** tautomerizes to intermediate **24**. The primary condensation of **24** with **2a** produces **4**. With this mechanism, MNPs-thioglycolic acid is an efficient catalyst for forming the olefin **171**, which is readily prepared *in situ* from Knoevenagel condensation of carbonyl groups of aldehyde or cyclic ketones **170** with **3**. The Michael addition of **4** with olefin **171** in the presence of MNPs-thioglycolic acid finally gives intermediate **172**, which then makes the inner molecular ring to be formed after a tautomeric proton shift to produce the target products **168–169**.[84]

After that, Yazdani-Elah-Abadi and his co-workers described the preparation of benzo[*a*]chromeno[2,3-*c*]phenazine derivatives **173–175** in 54–89% yields by domino four-component condensation reaction between **3**, **2a**, aromatic aldehydes, and naphthols or phenol in the presence of a catalytic amount of DABCO (20 mol%) as a reusable base catalyst under microwave irradiation (at 300 W and max. 100 °C) in EtOH/H_2O (1 : 1) within 20–40 min. The probable mechanism is outlined in Scheme 54. On the basis of this mechanism, the primary condensation of **3** with **2a** in the presence of DABCO gives **4**. Based on this mechanism, DABCO is an efficient catalyst to form the olefin **176**, which is readily prepared *in situ* from the Knoevenagel condensation of aromatic aldehyde with naphthols. In the presence of DABCO, **4** converts to its corresponding enolate form **177**, to be able to react (Michael addition) easily with **176** and to eventually give rise to the formation of intermediate **178**, which then makes the inner molecular ring be formed after a tautomeric proton shift to produce the desired products **173–175**.[85]

2.4 Synthesis of benzopyridophenazines

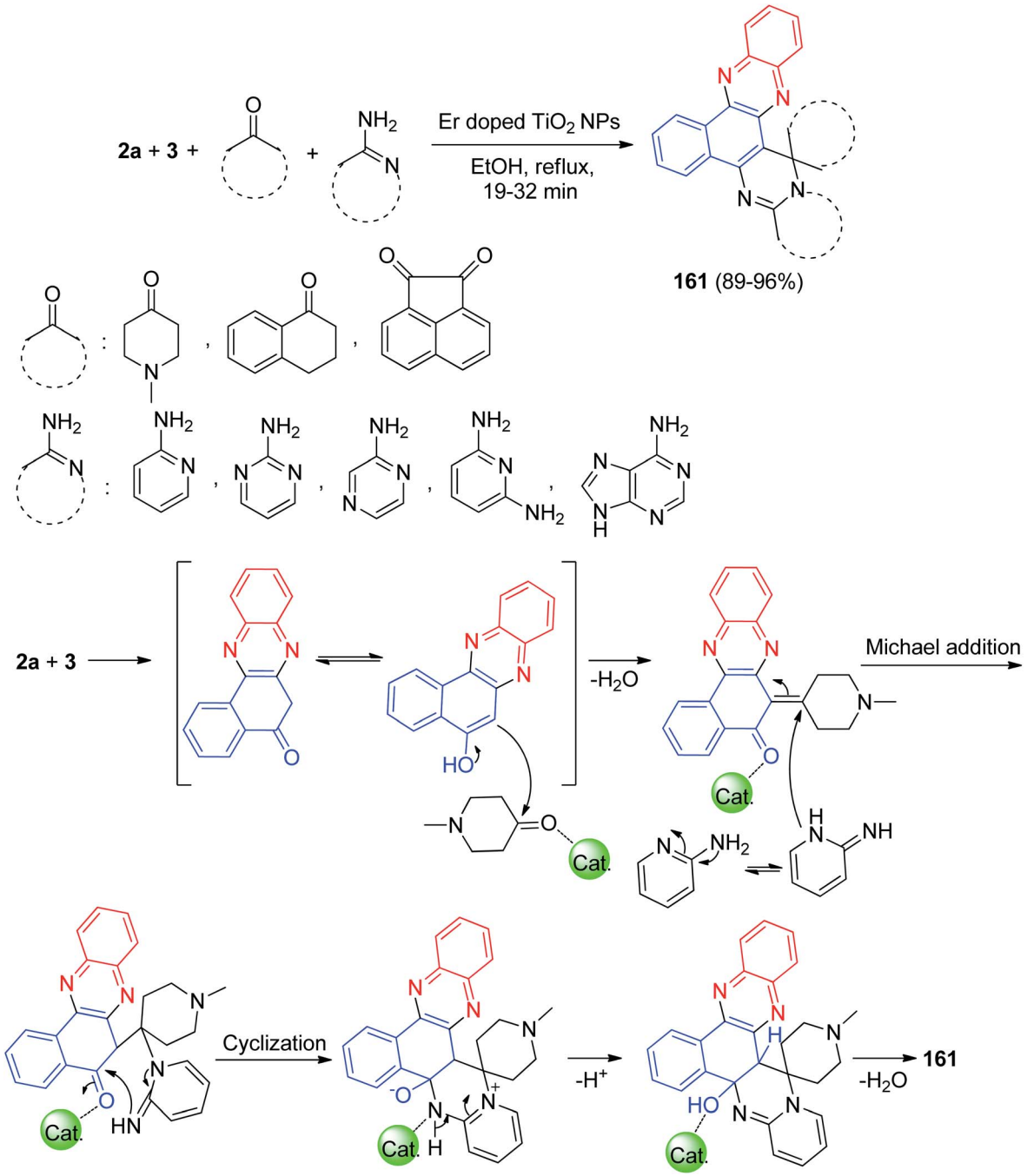
In 2017, L-proline has been used as a reusable and bifunctional organocatalyst for the one-pot, two-step, five-component synthesis of 1,4-dihydrobenzo[*a*]pyrido[2,3-*c*]phenazines **179** in 76–87% yields by the condensation reaction of **3**, aromatic 1,2-diamines, aldehydes, ammonium acetate and ethyl acetoacetate under conventional heating in solvent-free conditions at 80 °C for 20–30 min. The probable mechanism is outlined in Scheme 55. On the basis of this mechanism, the primary condensation of **3** with benzene-1,2-diamines in the presence of L-proline gives benzo[*a*]phenazin-5-ol **180**. On this mechanism, L-proline is an efficient catalyst to form the olefin **181**, which readily prepares *in situ* from Knoevenagel condensation of aromatic aldehyde with **180**. On the other hand, NH_3 resulting from ammonium acetate and ethyl acetoacetate by L-proline yields enamine **182**. Subsequently, the reaction between olefin **181** and enamine **182** gives the corresponding intermediate **183**. Tautomerization of intermediate **183** affords intermediate **184**



Scheme 49 Synthesis of 3-amino-2′-oxospiro[benzo[*c*]pyrano[3,2-*a*]phenazine-1,3′-indoline]-2-carbonitrile/carboxylate derivatives **160** catalyzed by $H_3PMo_{12}O_{40}$/Hyd-SBA-15.

which suffer an intramolecular nucleophilic attack of the NH_2 group to the activated carbonyl group providing intermediate **185**. At the end, dehydration of this intermediate yields the desired target molecule **179**.[86]

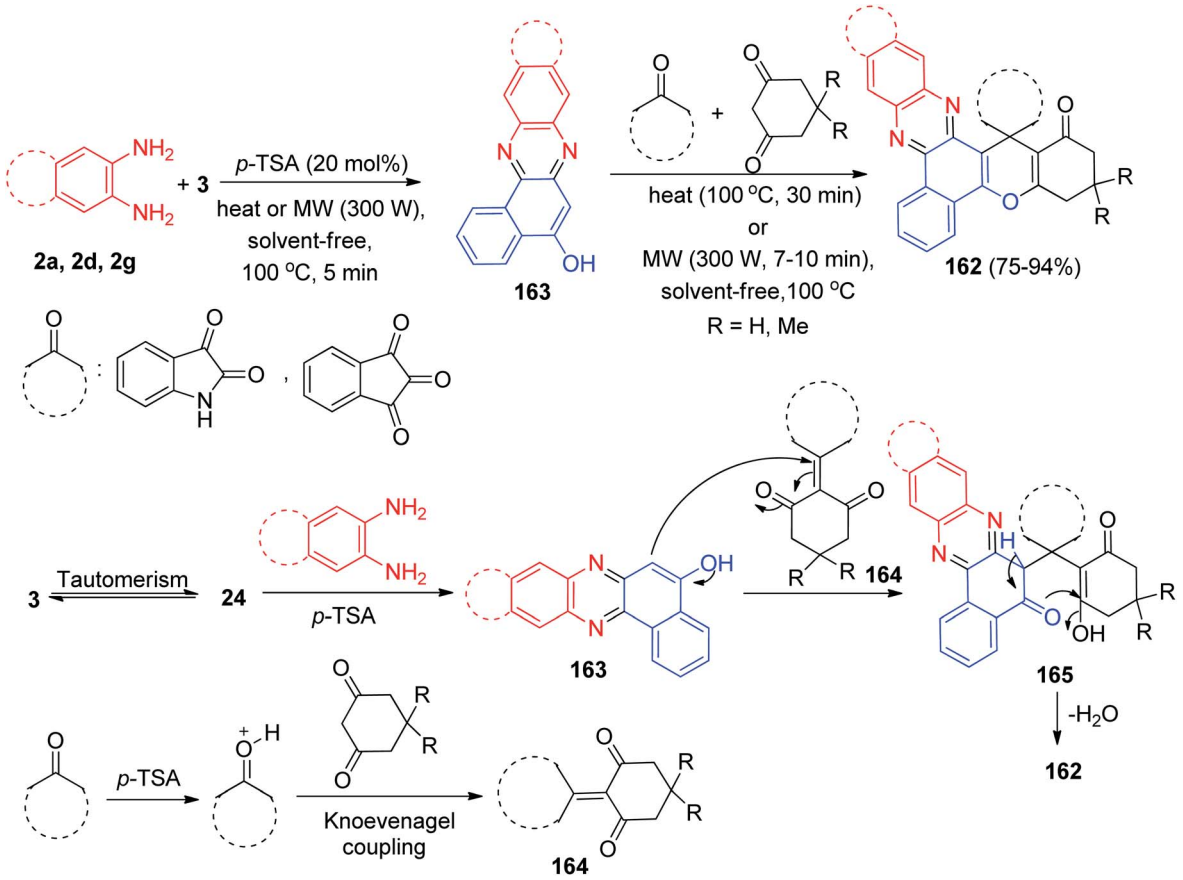
After that, Mohebat *et al.* synthesized polyfunctionalized benzo[*a*]pyrimido[5′,4′:5,6]pyrido[2,3-*c*]phenazine derivatives **186** in 72–94% yields by a one-pot, four-component sequential reaction between **3**, benzene-1,2-diamines, benzaldehydes, and 6-amino-1,3-dimethyluracil in the presence of *p*-TSA as solid acid catalyst under solvent-free microwave irradiation (300 W for 100 °C, 10–15 min) or conventional heating conditions at 100 °C for 30–50 min. A suggested mechanism is proposed in Scheme 56. First, the organization of benzo[*a*]phenazin-5-ol (**187**) can be explained *via* a condensation of **3** and benzene-1,2-diamines. Then the efficient Knoevenagel condensation of **187** and aryladehyde created product **188**. Lastly, compound **186** was offered by a sequence of facile Michael addition/cyclization/



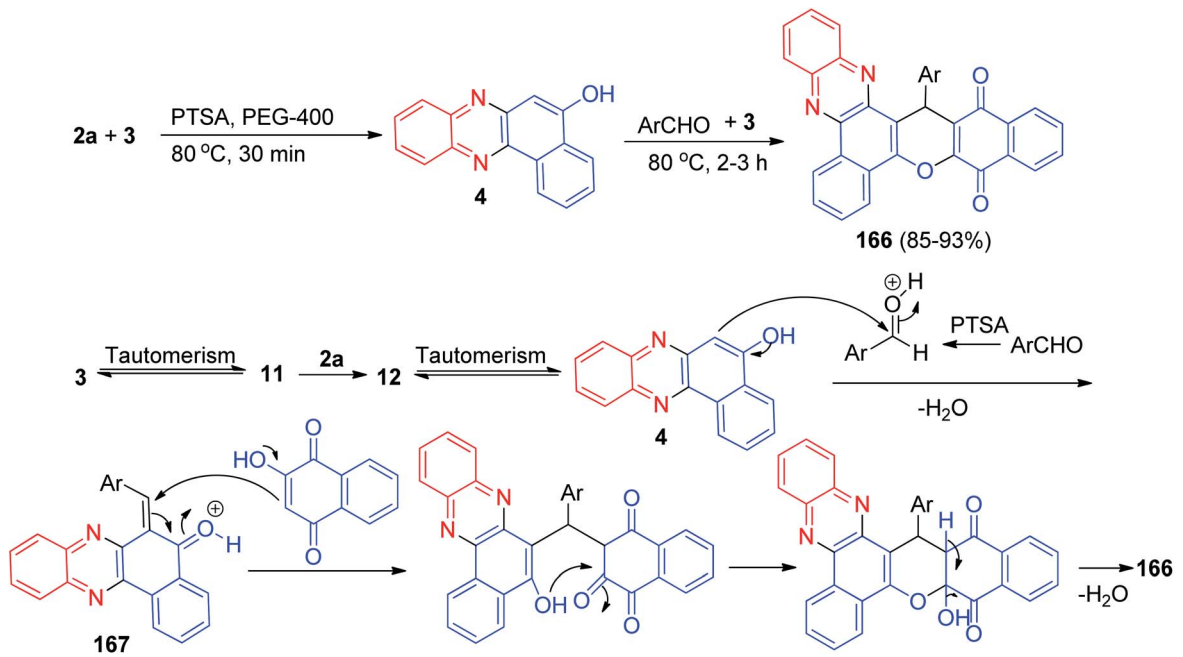
Scheme 50 Synthesis of spiroannulated pyrimidophenazines **161**.

dehydration reactions between **188** and 6-amino-1,3-dimethyluracil.[87]

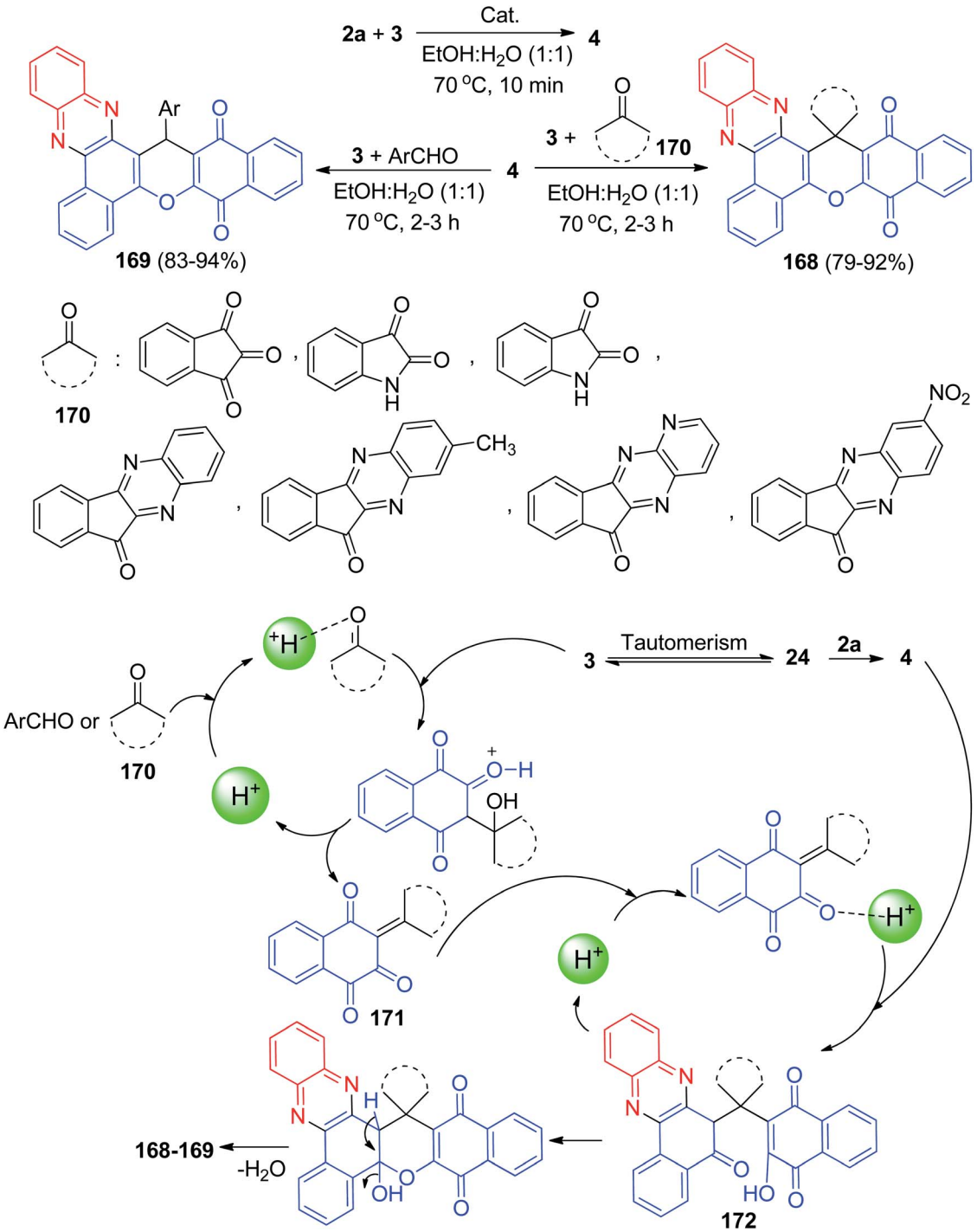
Next, an environmentally benign procedure for the synthesis of heteroaryl-substituted dihydrobenzo[*a*]pyrimido[5′,4′:5,6]pyrido[2,3-*c*]phenazines **189** in 85–94% yields has been developed *via* condensation/Knoevenagel/Michael/heterocyclization reactions of **3**, **2a**, aromatic aldehydes, and 6-amino-1,3-dimethyluracil in the presence of $H_3PW_{12}O_{40}$@nano-ZnO as a recyclable heterogeneous catalyst in aqueous medium under microwave irradiation (300 W, max. 100 °C) for 10–15 min. A detailed reaction mechanism is outlined in Scheme 57. On the basis of this mechanism, the primary condensation of **3** with **2a** in the presence of $H_3PW_{12}O_{40}$@nano-ZnO gives **4**. On the other hand, the catalyst to form the olefin **190**, which readily prepares *in situ* from Knoevenagel condensation of aromatic aldehyde with **4**. The Michael addition of 6-amino-1,3-dimethyluracil with olefin **190** in the presence of the catalyst finally give intermediate **191**, which then makes the inner molecular ring to be formed after a tautomeric proton shift to produce the corresponding product **189**.[88]



Scheme 51 Synthesis of novel spiro[benzo[*a*]chromeno[2,3-*c*]phenazine] derivatives **162** in the presence of *p*-TSA.

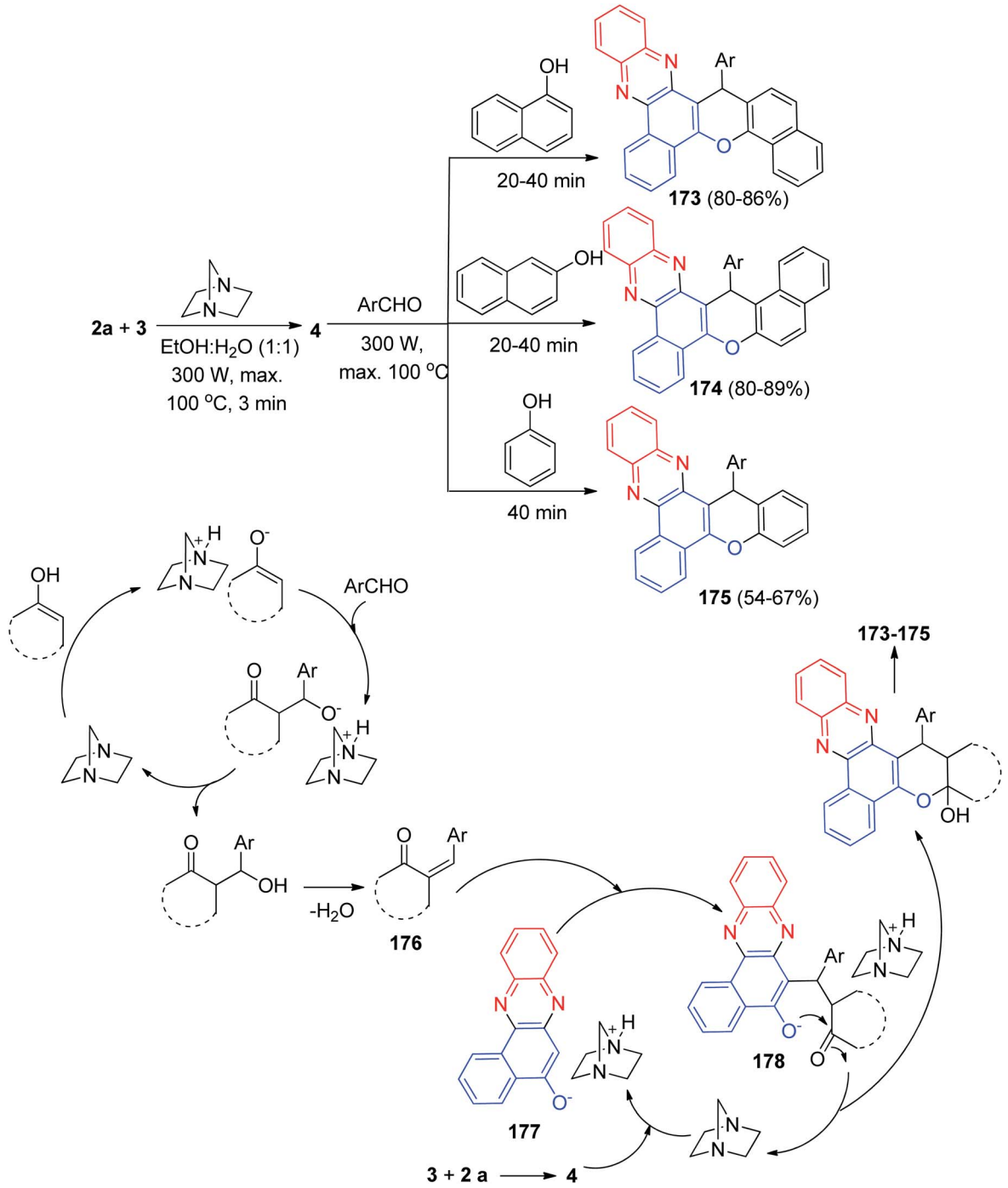


Scheme 52 *p*-TSA catalyzed synthesis of 11*H*-benzo[*a*]benzo[6,7]chromeno[2,3-*c*]phenazine-11,16(17*H*)-diones **166**.



Scheme 53 Thioglycolic acid catalyzed synthesis of benzo[*a*]benzo[6,7]chromeno[2,3-*c*]phenazine derivatives **168–169**.

In 2020, an environmentally benign procedure for the synthesis of heteroaryl-substituted dihydrobenzo[*a*]pyrimido[5′,4′:5,6]pyrido[2,3-*c*]phenazines **192** in 85–94% yields has been developed *via* condensation/Knoevenagel/Michael/heterocyclization reactions of **3**, **2a**, aromatic aldehydes, and 6-amino-1,3-dimethyluracil in the presence of $H_3PW_{12}O_{40}$@-nano-ZnO as a recyclable heterogeneous catalyst in aqueous medium under microwave irradiation (300 W, max. 100 °C) for 10–15 min. A detailed reaction mechanism is outlined in Scheme 58. On the basis of this mechanism, the primary condensation of **3** with **2a** in the presence of the catalyst gives **4**. On the other hand, $H_3PW_{12}O_{40}$@nano-ZnO is an efficient catalyst to form the olefin **193**, which readily prepares *in situ* from Knoevenagel condensation of aromatic aldehyde with **4**. The Michael addition of 6-amino-1,3-dimethyluracil with olefin **193** in the presence of the catalyst finally give intermediate **194**,



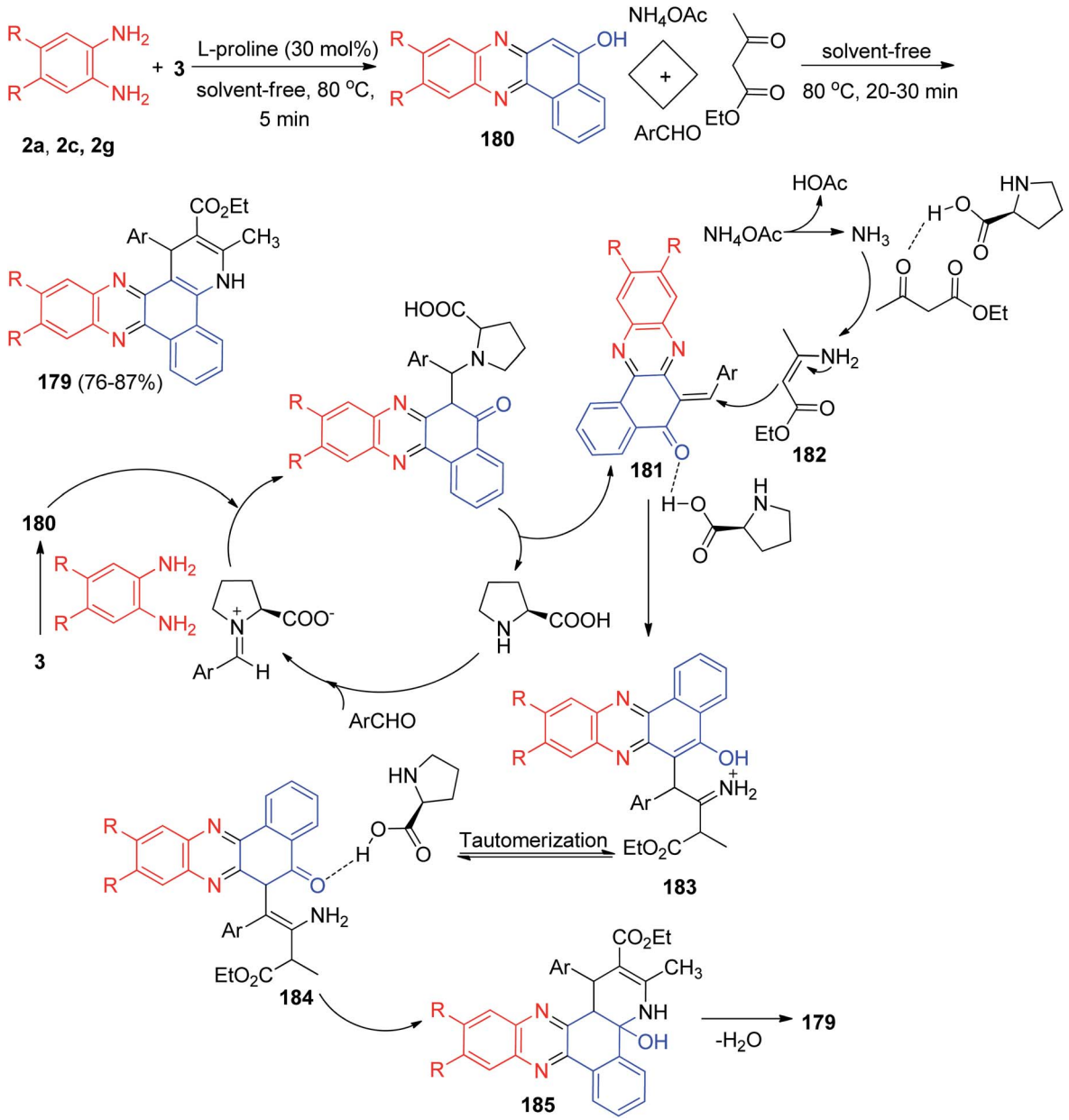
Scheme 54 DABCO catalyzed synthesis of benzo[*a*]chromeno[2,3-*c*]phenazine derivatives **173–175**.

which then makes the inner molecular ring to be formed after a tautomeric proton shift to produce the corresponding product **192**.[89]

2.5 Synthesis of benzofurophenazines

In 2015, pH on–off fluorescent chemosensors based on indenofuran derivative **195** has been synthesized. The synthesis of the compound was achieved firstly synthesize benzo[*a*]phenazine-5-ol (**4**) *via* condensation of **3** and **2a** in glacial acetic acid at 70 °C for 30 min. Then, the reaction of ninhydrin with **4** catalyzed by glacial acetic acid at 100 °C led to the formation of desired compound **195** in 94% yield (Scheme 59). The change in fluorescence of **195** is reversible within the wide pH range of 2 to 11. The color change of this sensor could also be detected by naked eyes thus making them promising candidate as colorimetric pH indicator also.[90]

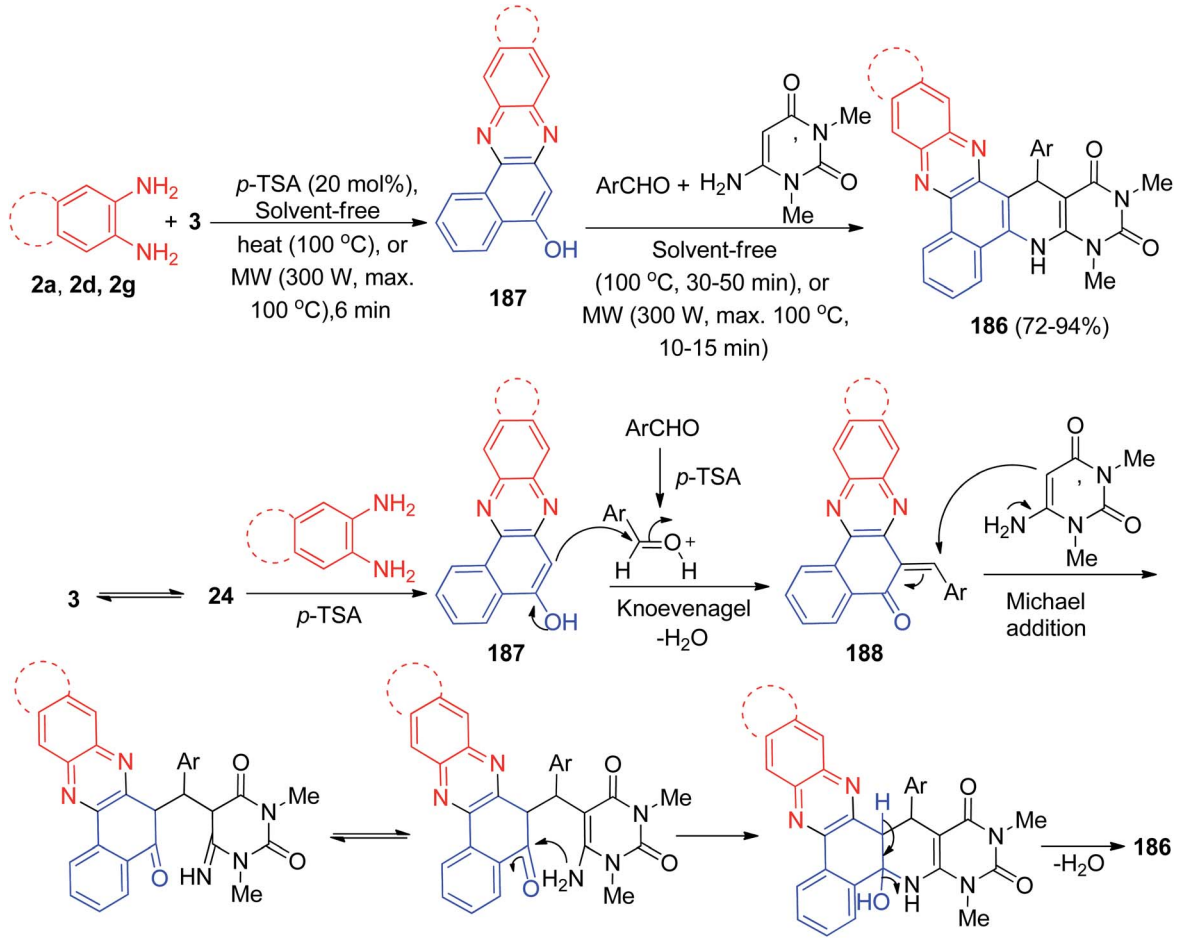
Next, Khurana *et al.* have prepared 10a,15a-dihydroxy-10a-*H*-benzo[*a*]indeno[2′,1′:4,5]furo[2,3-*c*]phenazin-15(15a*H*)-one **196**



Scheme 55 L-Proline catalyzed synthesis of 1,4-dihydrobenzo[*a*]pyrido[2,3-*c*]phenazines **179**.

in 94% yield as a fluorescent sensor *via* a one-pot, two-step procedure from a three-component condensation reaction of **3**, **2a** and ninhydrin in glacial acetic acid (Scheme 60). Compound **196** exhibits high sensitivity and selectivity towards Cu^{2+} and Pb^{2+} ions over other metal ions by fluorescence quenching. Moreover, this sensor exhibited a visible color change from light orange to pink, and yellow in the presence of Cu^{2+} and Pb^{2+}, respectively.[91]

After that, Mohebat *et al.* reported a one-pot, two-step procedure for the synthesis of 1,2-dihydrobenzo[*a*]furo[2,3-*c*] phenazine derivatives **197** in 78–90% yields with high diastereoselectivity by condensation reaction between **3**, benzene-1,2-diamines, aromatic aldehyde and pyridinium ylide **198** in the presence of a catalytic amount of theophylline (20 mol%) as an expedient, eco-friendly and reusable solid base catalyst in water at 70 °C for 3–4 h. The suggested mechanism is depicted in Scheme 61. At first, **3** tautomerizes to intermediate **24**. The primary condensation of **24** with benzene-1,2-diamine obtain **199**. On this mechanism, theophylline is an efficient catalyst to form the 6-benzylidenebenzo[*a*]phenazin-5(6*H*)-one **200**, which easily prepares *in situ* from Knoevenagel condensation of **199** with carbonyl group of aldehyde. On the other hand, the pyridinium ylide **198**, which forms from the reaction of 1-(2-(4-bromophenyl)-2-oxoethyl)pyridinium with theophylline undergoes Michael addition to intermediate **200** to afford the enolate intermediate **201**. Eventually, the enolate **201** eliminates pyridine (intramolecular S_N2) and cyclizes instantly to produce **197**.[92]

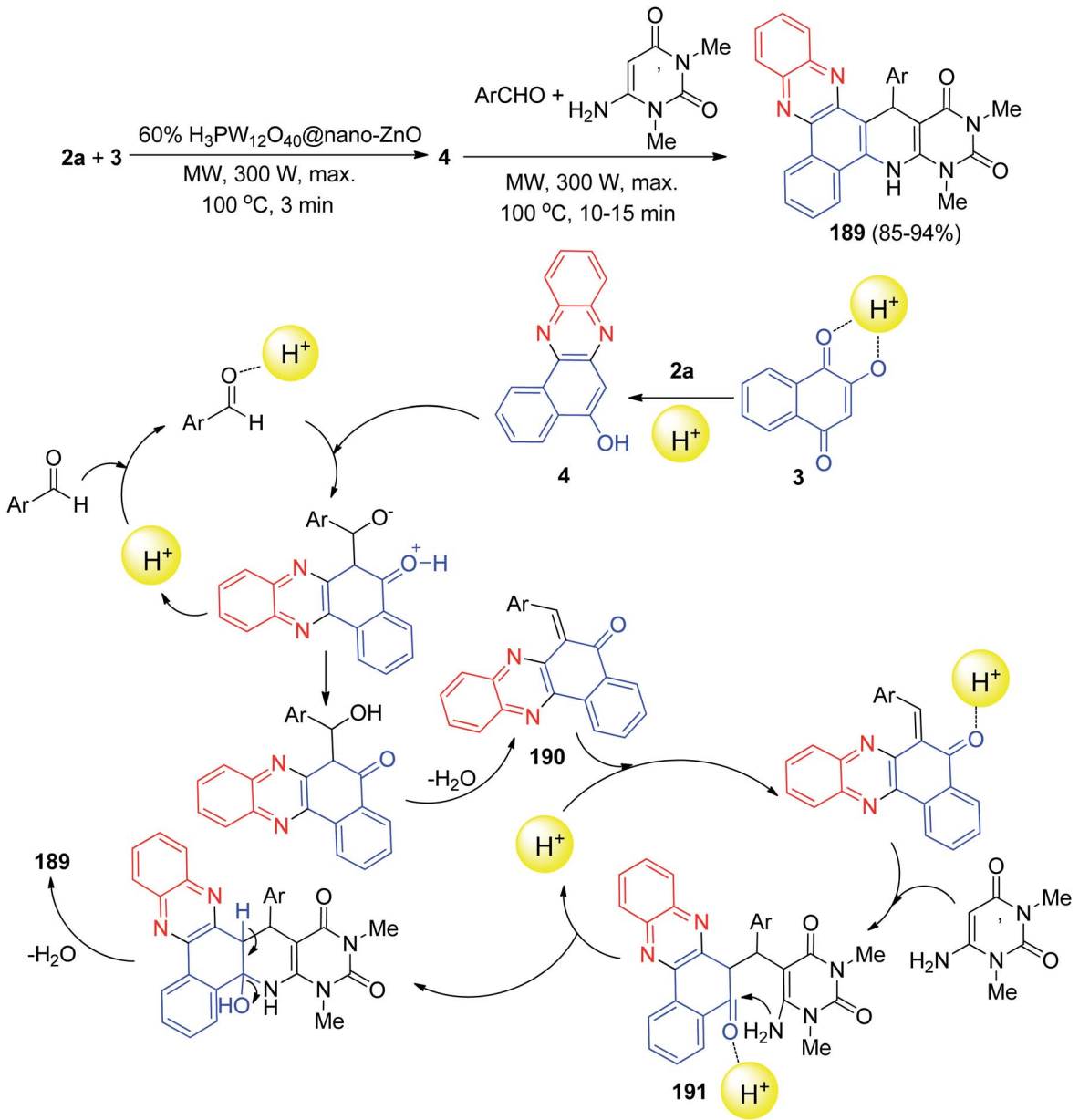


Scheme 56 *p*-TSA catalyzed synthesis of pyrimido-fused benzophenazines **186**.

In addition, Mohebat *et al.* developed an efficient protocol for the one-pot four-component synthesis of benzo[*a*]furo[2,3-*c*]phenazines **202** in 56–95% yields starting from the reaction of **3**, **2a**, isocyanide and aromatic aldehydes under catalyst- and solvent-free microwave conditions (180 W) at 70 °C for 7–10 min. The mechanism of these reactions is plausibly based on the key intermediate **4** of **3** and **2a**, as analyzed from the experimental results. On the other side, condensation of alkyl isocyanides with aryl aldehydes afforded intermediate **203**. In the following, intermediate **4** attacks intermediate **203** to give the formed intermediate **204**, which in subsequent cyclization formed intermediate **205** and tautomerism affords the corresponding product **202** (Scheme 62).[93]

In 2021, one-pot synthesis of benzo[*a*]furo[2,3-*c*]phenazine derivatives **206** reported in 85–97% yields *via* a multi-component of **3**, benzene-1,2-diamines, arylglyoxal and indoles in the presence of $H_3PW_{12}O_{40}$@Fe_3O_4–ZnO magnetic core–shell nanoparticles (MCNPs) under solvent-free conditions using microwave irradiation (300 W, max. 100 °C) for 6–12 min. A plausible mechanism is depicted in Scheme 63. Based on this mechanism, at first, **3** tautomerizes to intermediate **24**. The primary condensation of **24** with benzene-1,2-diamine obtains benzo[*a*]phenazin-5-ol **207**. On the other hand, the reaction of indole with arylglyoxal afforded intermediate **208**. After that, intermediate **207** reacts with intermediate **208** to give an intermediate **209**. This then forms intermediate **210** through the intramolecular ring closure, followed dehydration leads to the formation of the desired product **206**.[94]

Next, Mohebat and co-workers developed an environmentally benign procedure for the synthesis of furo[2,3-*c*]phenazine derivatives **211** in 75–96% yields *via* reactions of **3**, 1,2-phenylenediamines, arylglyoxals, and indole in the presence of TiO_2–SO_3H-catalyst (TSAC) as a recyclable heterogeneous catalyst under solvent-free conditions using microwave irradiation (180 W, 75 °C) for 6–8 min. A plausible reaction mechanism is shown in Scheme 64. Based on this mechanism, at first, **3** tautomerizes to intermediate **24**. The primary condensation of **24** with benzene-1,2-diamine yielded benzo[*a*]phenazin-5-ol **212**. A reaction pathway involves the formation of an intermediate **213** medium when reacted with the indole group after being added to the carbonyl group or upon the replacement of the side-chain hydroxy group. Based on the second route, arylglyoxal and indole developed the open shaft **213** or the OH group electron pair. This, then forms intermediate **214** informing the C–C and C–N bonds through the intermolecular [3 + 2] ring reaction, which is made after reacting with the intermediate middle



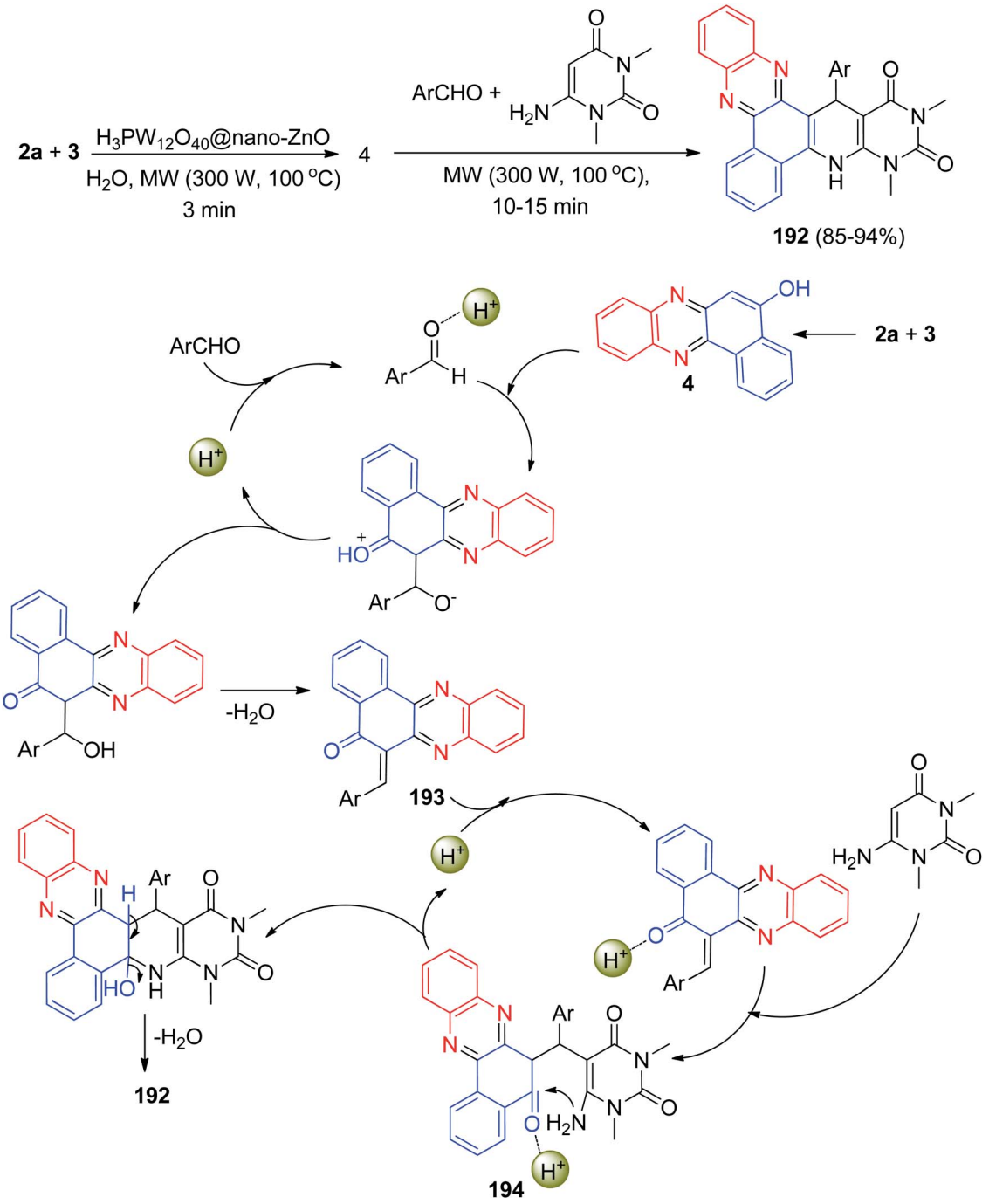
Scheme 57 $H_3PW_{12}O_{40}$@nano-ZnO-catalyzed synthesis of pyrimido-fused benzophenazines **189**.

benzo[*a*] phenazine-5-ol, caused by the loss of water during the ring formation process before the desired product is obtained.[95]

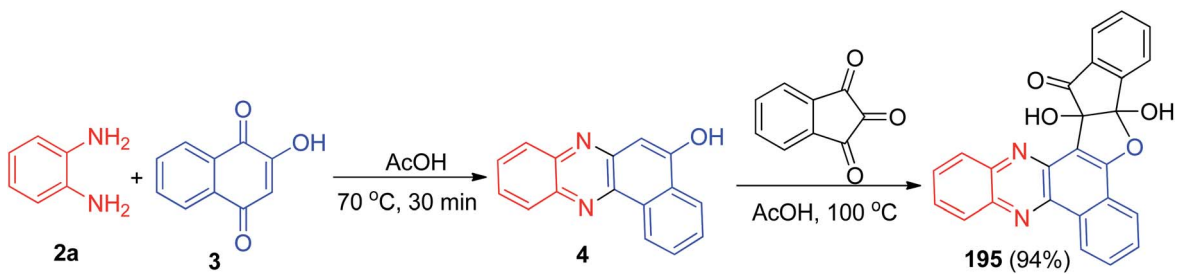
2.6 Synthesis of benzooxazinophenazines

In 2014, a catalyst-free multi-component reaction capable of affording a wide range of benzo[*a*][1,3]oxazino[6,5-*c*]phenazine derivatives **215** in 80–93% yields has been reported *via* the reaction of **3**, 1,2-diaminobenzene, aromatic/aliphatic amines and formaldehyde at 50 °C in water within 60–90 min. It should be noted that he same reaction did not proceed with heterocyclic amines *viz.* 2-aminobenzothiazole, 5-amino-3-methylpyrazole, 1,3-dimethyl-5-aminouracil *etc.* A proposed mechanistic route for the formation of the products is exhibited in Scheme 65. At first, amination reaction occurs between the formaldehyde and amine followed by H_2O elimination providing imine intermediate **216**. **216** is then attacked by **4** to form **217** which further reacts with formaldehyde and eliminates H_2O, further cyclization occurs to form the final product **215**.[96]

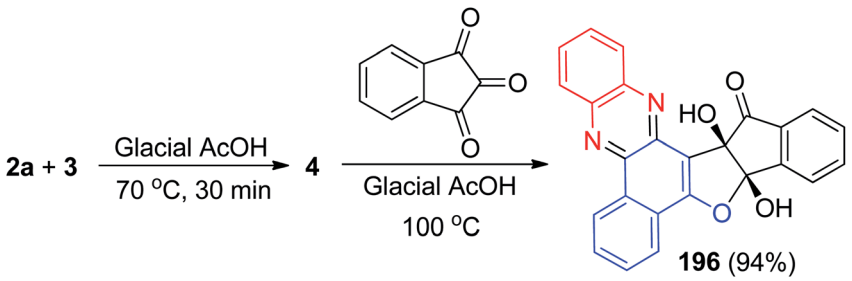
Next, Mohebat and Yazdani-Elah-Abadi synthesized benzo[*a*][1,3]oxazino[6,5-*c*]phenazine derivatives **218** in 86–92% yields by the one-pot, four-component sequential condensation between **3**, aromatic 1,2-diamines, ammonium thiocyanate and acid chlorides in the presence of caffeine as a green and natural catalyst in a basic ionic liquid (1-butyl-3-methylimidazolium hydroxide) at room temperature for 2–4 h. The proposed mechanism is outlined in Scheme 66. Initially, **3** tautomerizes to intermediate **24**. The condensation of **24** with benzene-1,2-



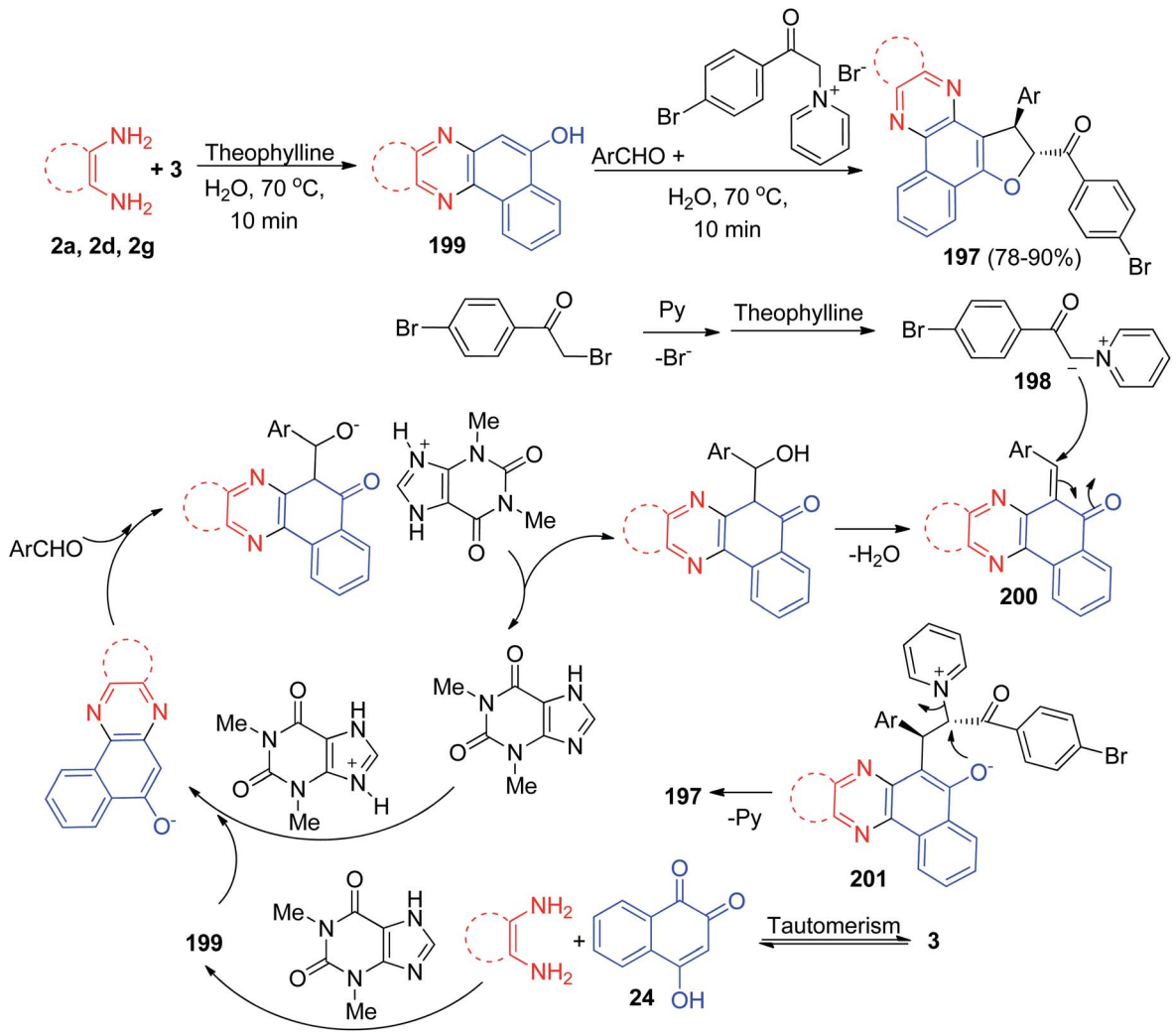
Scheme 58 Synthesis of heteroaryl-substituted dihydrobenzo[*a*]pyrimido[5′,4′:5,6]pyrido[2,3-*c*]phenazines **192**.



Scheme 59 Synthesis of indeno-furan derivative **195**.



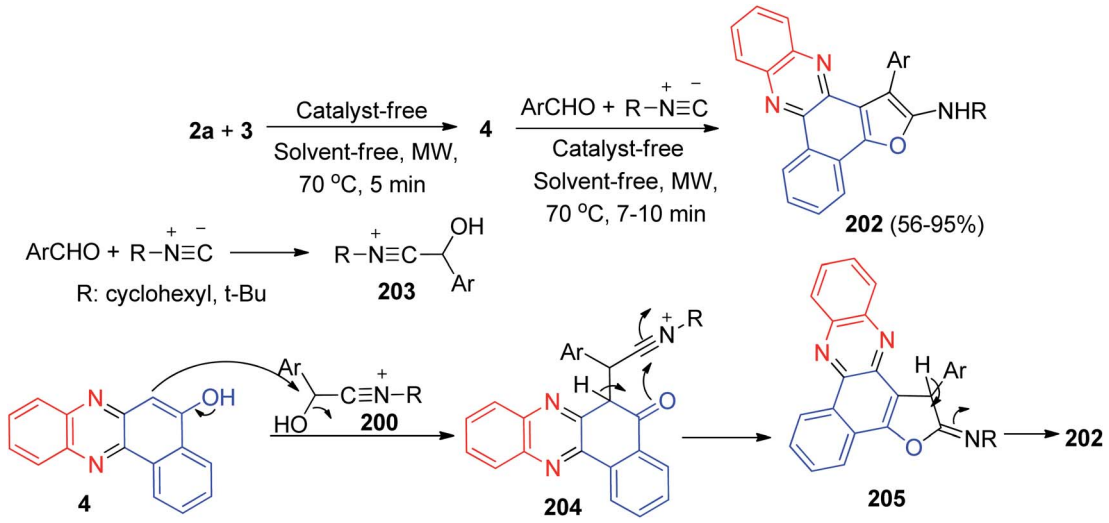
Scheme 60 Synthesis of 10a,15a-dihydroxy-10a-*H*-benzo[*a*]indeno[2′,1′:4,5]furo[2,3-*c*]phenazin-15(15a*H*)-one **196**.



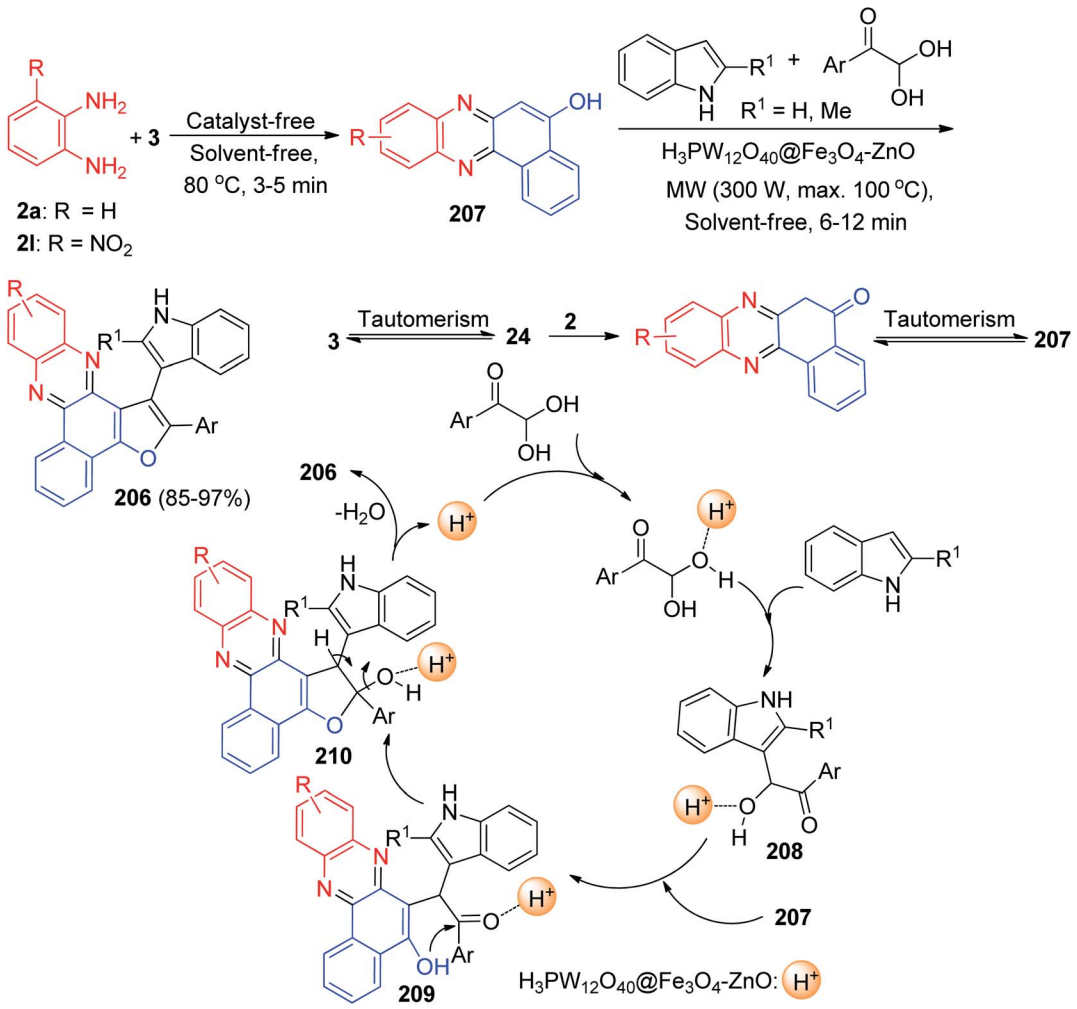
Scheme 61 Synthesis of 1,2-dihydrobenzo[*a*]furo[2,3-*c*]phenazines **197** by using theophylline.

diamine produces benzo[*a*]phenazin-5-ol **219**. Then, the formation of aroyl isothiocyanate **220**, followed by formation of the 1 : 1 adduct **221** and its subsequent protonation by benzo[*a*]phenazin-5-ol **219** produces **222**. The positively charged ion **222** is attacked by the anion of benzo[*a*]phenazin-5-ol **223**. Finally, intermediate **224** undergoes a cyclization reaction and elimination of water to produce **218**.[97]

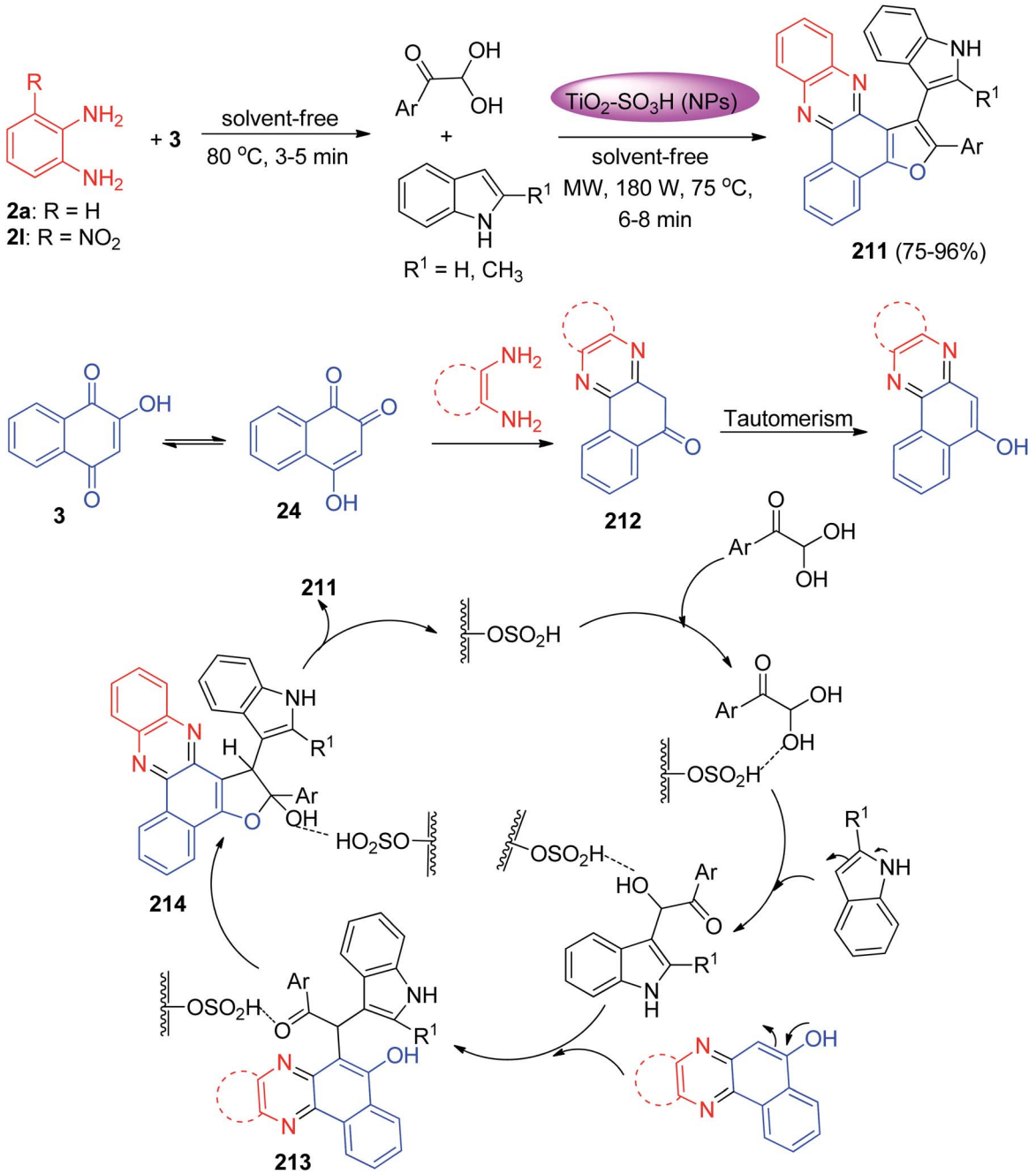
In 2020, Mohebat and co-workers reported a one-pot procedure for the synthesis of 3-phenyl-3,4-dihydro-2*H*-benzo[*a*][1,3]oxazino[5,6-*c*]phenazine derivatives **225** in 68–96% yields by four-component coupling reaction between benzo[*a*]phenazine-5-ol, formaldehyde and amine in the presence of a catalytic amount ZnOPTA@Fe_3O_4/EN-MIL-101(Cr) nanopowder in EtOH–CH_2Cl_2 at room temperature under stirring condition



Scheme 62 Synthesis of benzo[*a*]furo[2,3-*c*]phenazines **202**.



Scheme 63 Synthesis of benzo[*a*]furo[2,3-*c*]phenazine derivatives **206**.



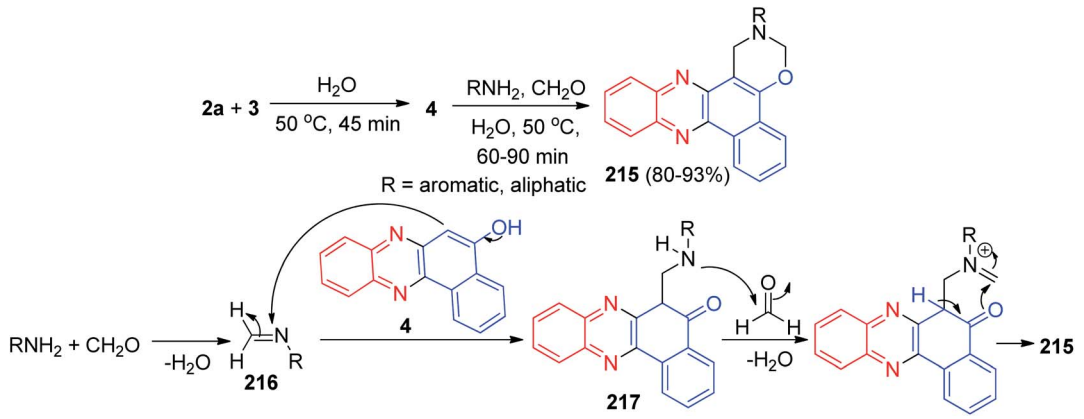
Scheme 64 Microwave-assisted synthesis of benzo[*a*]furo[2,3-*c*]phenazine derivatives **211**.

within 1.5–5 h. A plausible rational mechanism for the four-part reaction is illustrated in Scheme 67. Based on this mechanism, at first, **3** tautomerizes to intermediate **24**. The condensation of **24** with 1,2-diamines produces benzo[*a*]phenazin-5-ol **226**. At first, amination reaction occurs between the activated formaldehyde (by coordination with catalyst nanoparticle) and amine followed by H_2O elimination provides imine intermediate **227** that is further activated by nanocatalyst. Intermediate **227** is then attacked by **226** to form **228** which further reacts with formaldehyde and eliminate H_2O. Next cyclization occurs to form the final product.[98]

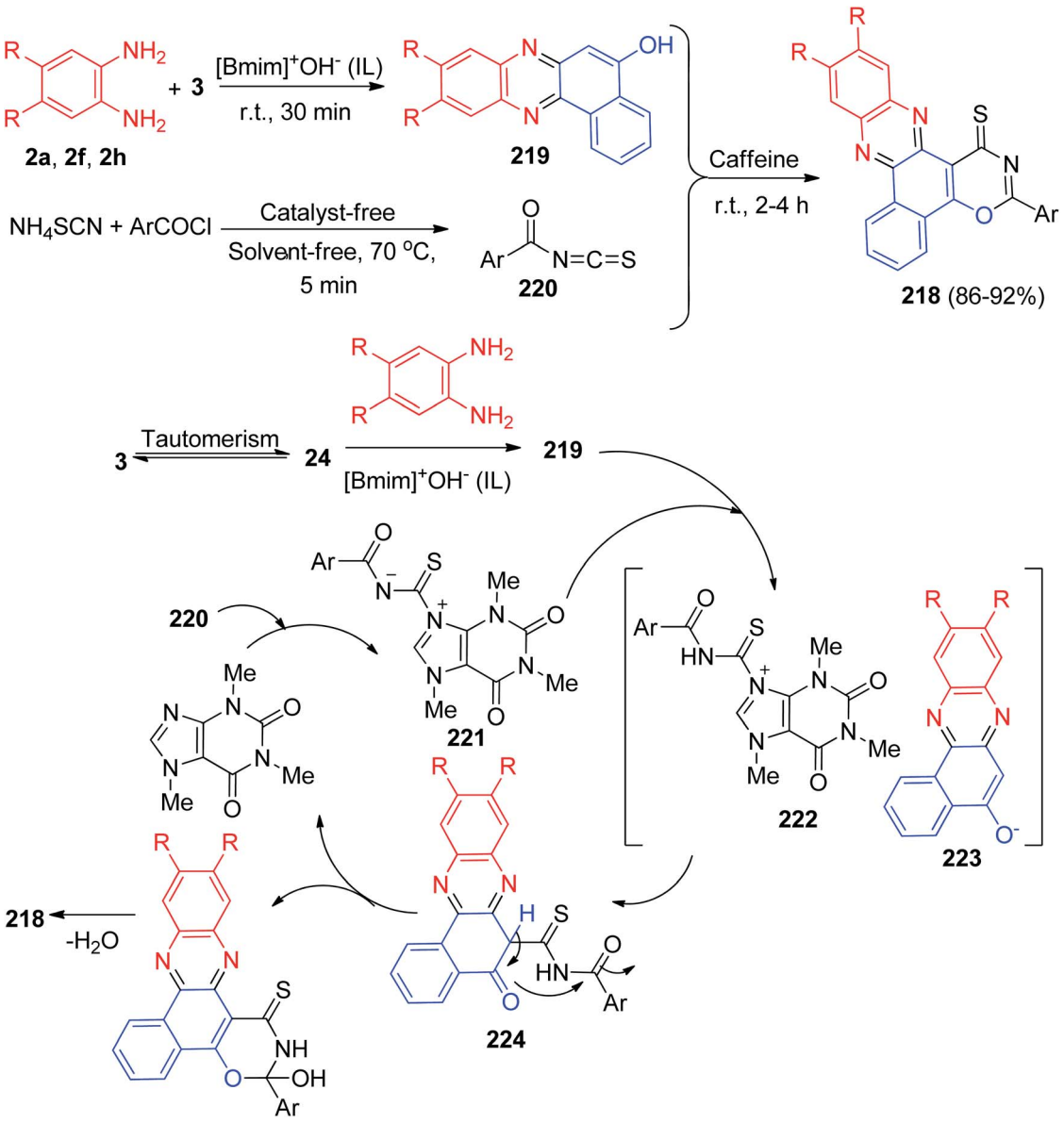
2.7 Synthesis of the other benzo[*a*]phenazine-5-ol derivatives

In 2002, a series of 2-hydroxy-3-arylazo-1,4-naphthoquinones **229** in 69–93% yields were prepared by coupling of **3** with aryldiazonium chlorides **230** in water or aqueous alcohol (1 : 1) in the presence of sodium carbonate or hydrocarbonate for 1–1.5 h. Then, condensation of **229** with **2a** in refluxing EtOH for 2 h led to the formation of 2-hydroxy-6-arylazobenzo[*a*]phenazines **231** in 63–80% yields (Scheme 68).[99]

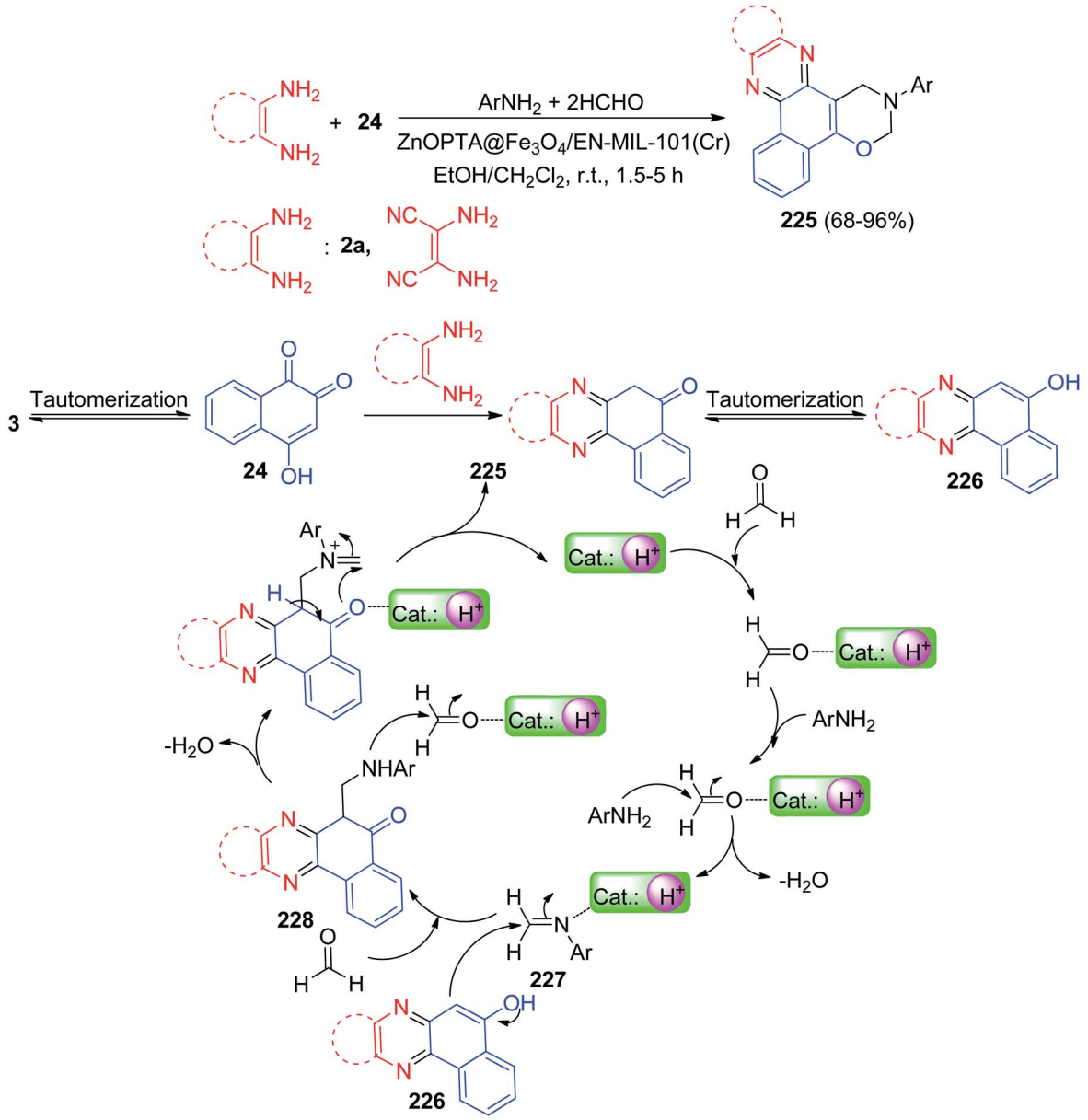
In 2013, Huang and co-workers described synthesis of benzo[*a*]phenazine derivatives **232a–i** in 50–68% yields *via* one-pot



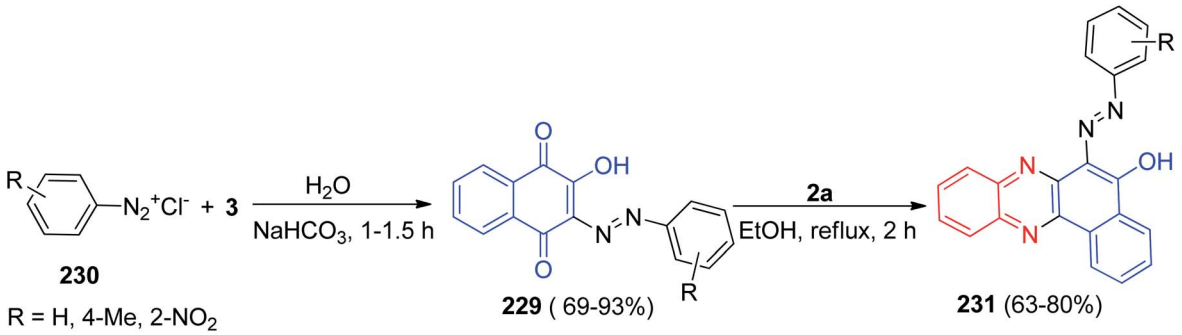
Scheme 65 Synthesis of benzo[*a*][1,3]oxazino[6,5-*c*]phenazine derivatives **215**.



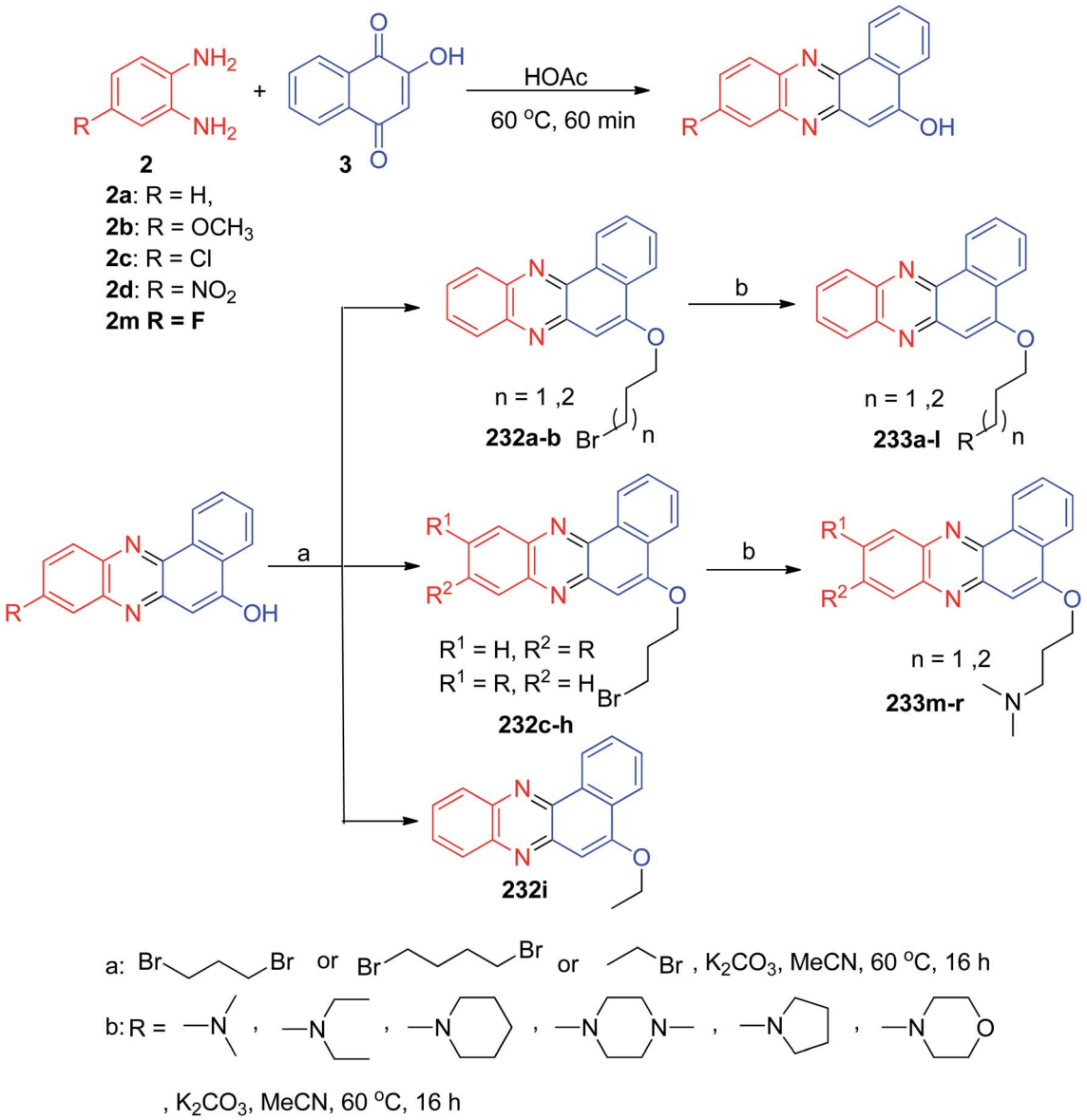
Scheme 66 Caffeine catalyzed synthesis of benzo[*a*][1,3]oxazino[6,5-*c*]phenazine derivatives **218**.



Scheme 67 Synthesis 3-phenyl-3,4-dihydro-2*H*-benzo[*a*][1,3] oxazino[5,6-*c*]phenazine derivatives **225**.

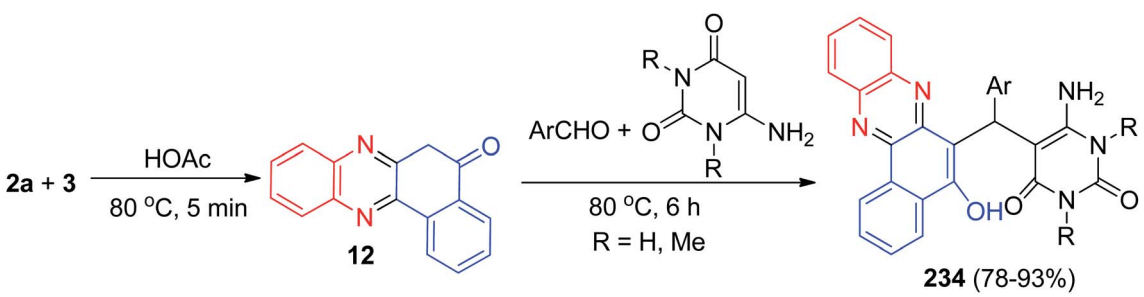


Scheme 68 Synthesis of 2-hydroxy-6-arylazobenzo[*a*]phenazines **231**.

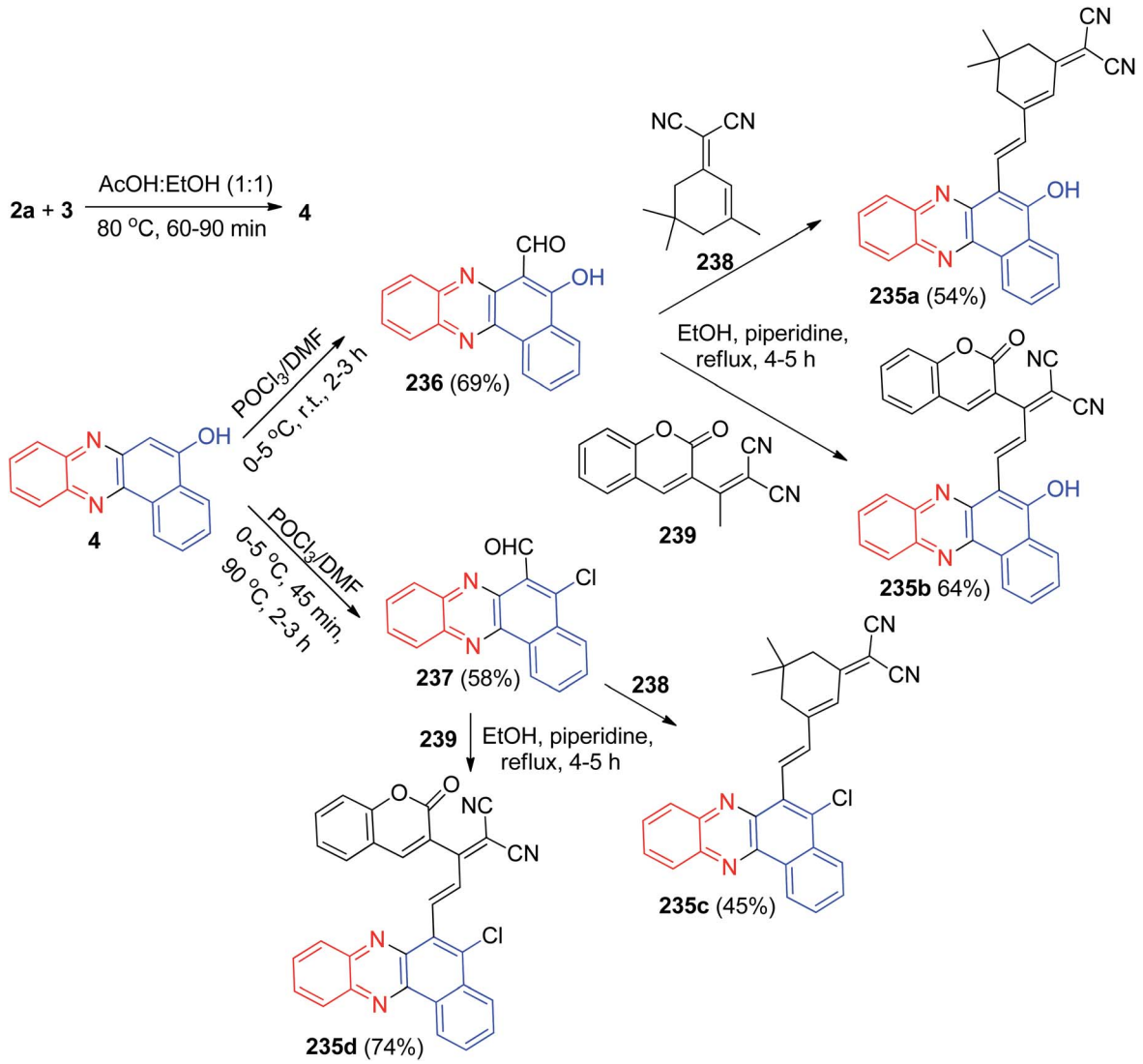


Scheme 69 Synthesis of benzo[*a*]-phenazine derivatives **232–233**.

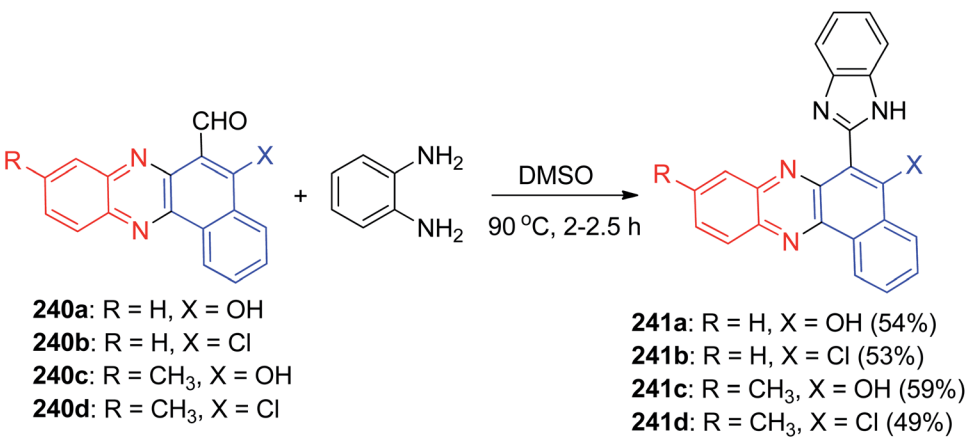
two-step procedure by the reaction of **3**, 1,2-phenylene diamines and 1,3-dibromopropane or 1,4-dibromobutane or 2-bromoethane in CH_3CN with K_2CO_3 at 60 °C for 16 h. Subsequent amination of **232** with secondary amines in CH_3CN at 60 °C with K_2CO_3 afforded the desired compounds **233a–r** in 55–78% yields after 16 h (Scheme 69). Most of derivatives showed good antiproliferative activity with a range of IC_{50} values of 1–10 μM on the four cancer cell lines HeLa, A549, MCF-7, and HL-60.



Scheme 70 Synthesis of aminouracil-tethered tri-substituted methane derivatives **234**.



Scheme 71 Synthesis and fluorescence of benzofused phenazine π-conjugated skeleton 235.



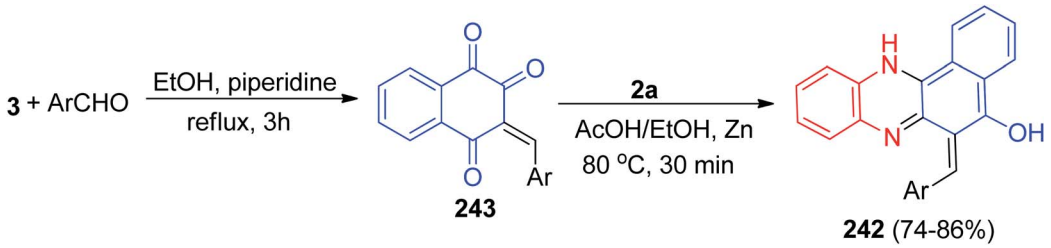
Scheme 72 Synthesis of 6-(1*H*-benzo[*d*]imidazol-2-yl) benzo[*a*] phenazin-5-ols 241a–d.

Topoisomerase-mediated DNA relaxation assay results showed that derivatives could effectively inhibit the activity of both Topo I and Topo II, and the structure–activity relationship studies indicated the importance of introducing an alkylamino side chain.[100]

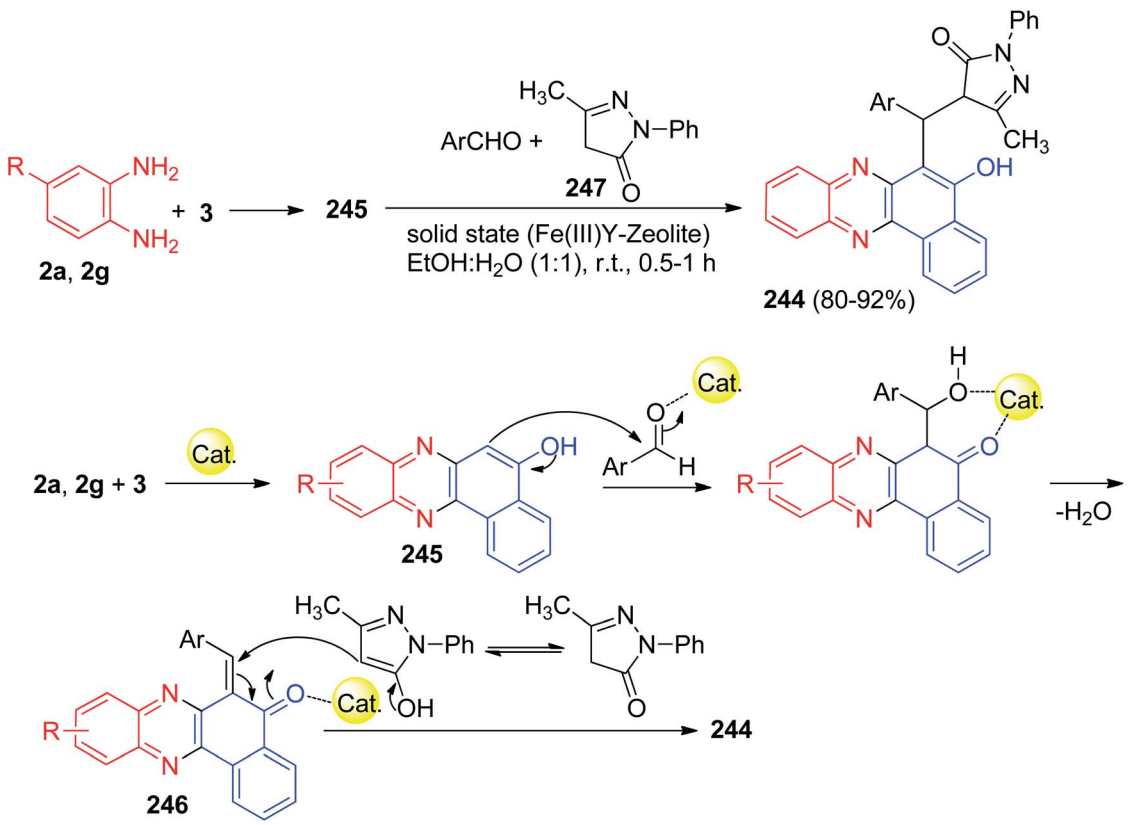
In 2014, Cai and Lu reported synthesis of aminouracil-tethered tri-substituted methane derivatives **234** in 78–93% yields by the reaction of **3**, **2a**, aromatic aldehydes and amino-uracil derivatives in AcOH at 80 °C for 6 h (Scheme 70).[101]

After that, benzofused phenazine π-conjugated skeleton **235a–d** with a coumarin and isophoron core was synthesized by Sekar and co-workers. Benzo[*a*]phenazin-5-ol (**4**) was prepared by condensation of **3** with **2a** in AcOH : EtOH (50 : 50) at 80 °C for 60–90 min. 5-Hydroxybenzo[*a*]phenazine-6-carbaldehyde **236** and 5-chloro[*a*]phenazine-6-carbaldehyde **237** were prepared by the Vilsmeier–Haack reaction. The compounds **236** or **237** on treatment with **238** or **239** active methylene compounds, respectively, in the DMSO/ethanol in the presence of catalytic amount of piperidine atreflux temperature (70–80 °C) for 4–5 h gave (*E*)-2-(3-(5-hydroxybenzo[*a*]phenazin-6-yl)-1-(2-oxo-2*H*-chromen-3-yl)allylidene)malononitrile **235a–b** and (*E*)-2-(3-(5-chlorobenzo[*a*]phenazin-6-yl)-1-(2-oxo-2*H*-chromen-3-yl) allylidene) malononitrile **235c–d** (Scheme 71).[102]

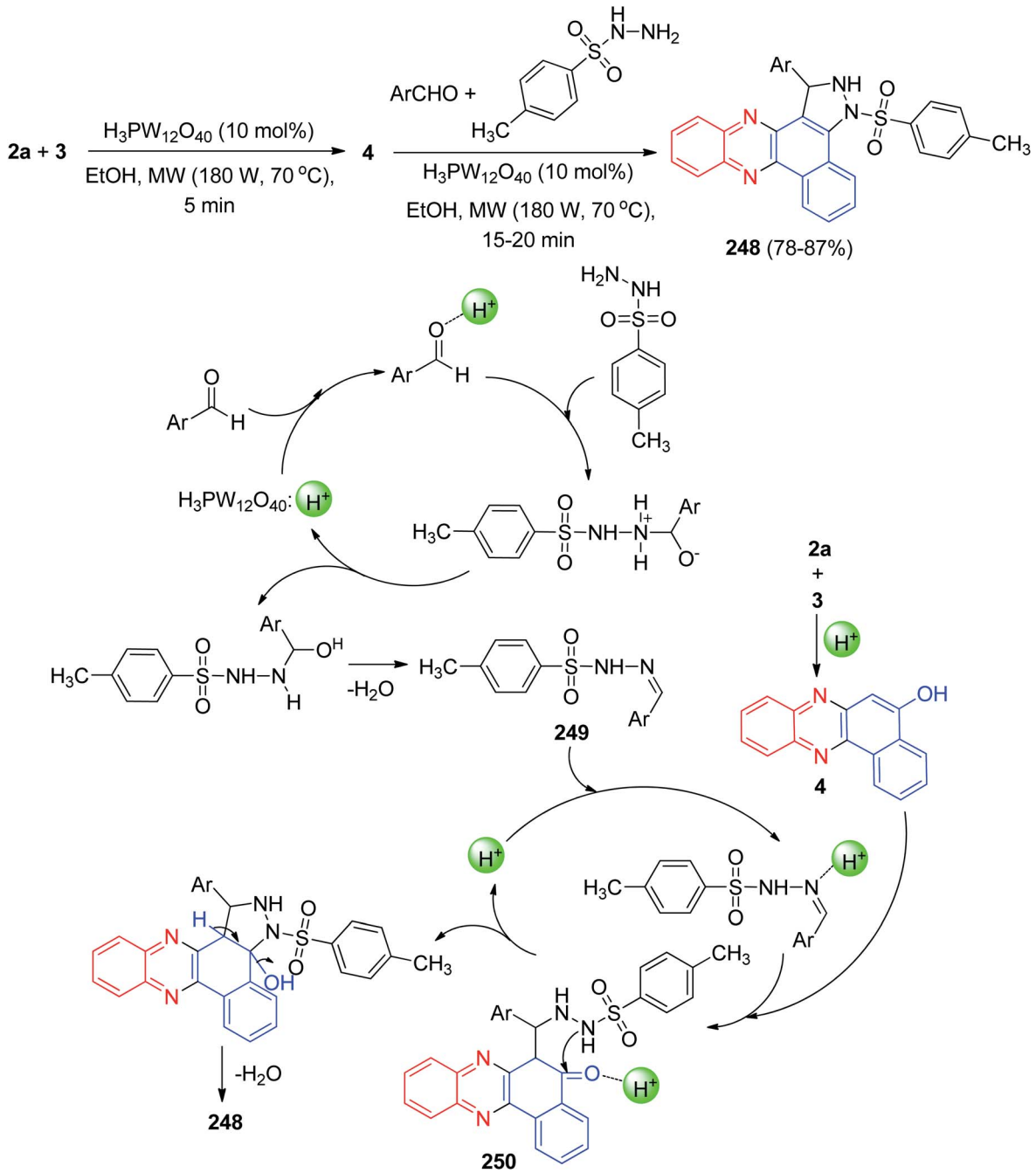
In addition, Sekar and Choudhary prepared 5-hydroxybenzo [*a*]phenazine-6-carbaldehyde **240a–d** by the Vilsmeyer Haack reaction. Then, these compounds on treatment with **2a** in the presence of DMSO at 90 °C for 2–2.5 h gave 6-(1*H*-benzo[*d*] imidazol-2-yl) benzo[*a*]phenazin-5-ol derivatives **241a–d** in 49–59% yields (Scheme 72). Also, the UV-vis absorption and fluorescence emission spectra of these compounds were studied in solvents of differing polarity; the dyes exhibited excited state intramolecular proton transfer.[103]



Scheme 73 Synthesis of styryl-dihydrobenzo[*a*]phenazine chromophores **242**.



Scheme 74 Fe(III)Y-zeolite catalyzed synthesis of hydroxybenzo[*a*]phenazine pyrazol-5(4*H*)-one derivatives **244**.



Scheme 75 $H_3PW_{12}O_{40}$ catalyzed synthesis of 11*H*-benzo[*a*]pyrazolo[3,4-*c*]phenazine derivatives **248**.

Next, Sekar and co-workers have synthesized styryl-dihydrobenzo[*a*]phenazine chromophores **242** in 74–86% yields by a two-step process as outlined in Scheme 73. In the first step, **3** was treated with the corresponding aromatic aldehydes in the presence of a catalytic amount of piperidine and ethanol at reflux temperature for 3 h to yield 3-substituted 1,2,4-triketo naphthoquinone styryl derivatives **243**. The substituted naphthoquinones **243** were conveniently converted to dihydrobenzo[*a*]phenazines **242** by refluxing with **2a** in AcOH/EtOH at 80 °C and subsequently reduced by Zn. They respond to acids and bases through changes in absorption resulting in strong bathochromic shift (>437 nm). The emission quantum yields of the dyes were in the range 0.11–0.14.[104]

Later, Perumal *et al.* described the series of fabrication of nanofibrous scaffold loaded with potential biologically active hydroxybenzo[*a*]phenazine pyrazol-5(4*H*)-one derivatives **244** were designed, synthesized by a simple one-pot, two step four component condensation based on Michael type addition reaction of **3**, benzene-1,2-diamines, aromatic aldehydes and 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one as the substrates. The heterogeneous solid state catalyst (Fe(III)Y-zeolite) could effectively catalyze the reaction in EtOH : H_2O (1 : 1) at room

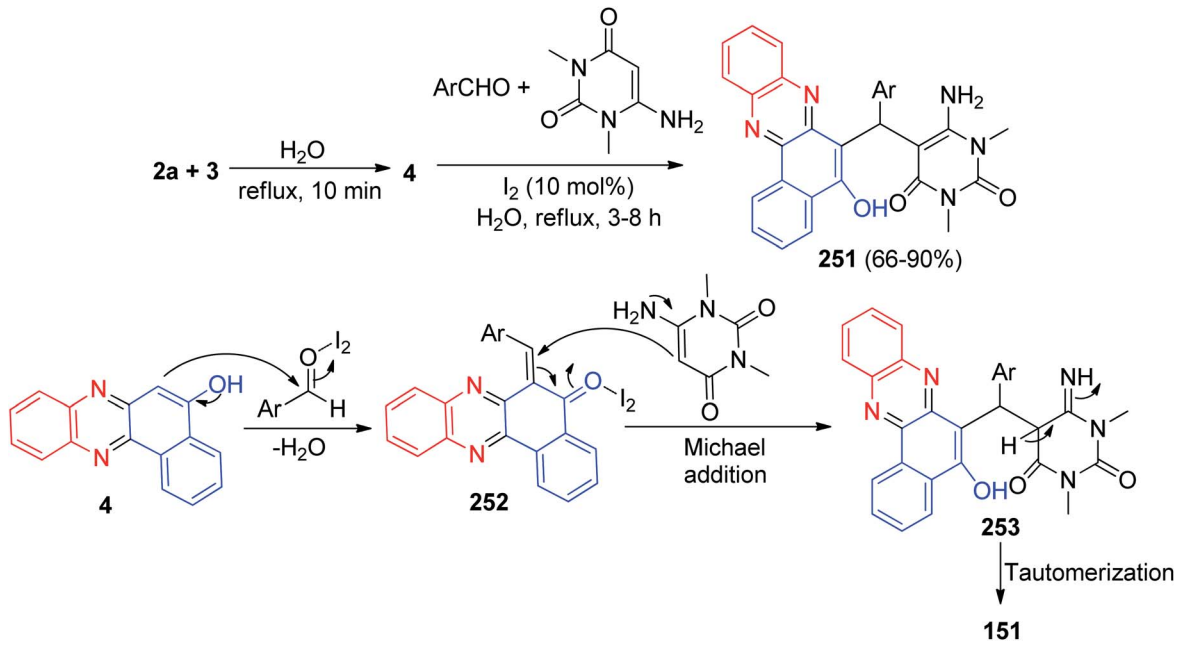
temperature for 0.5–1 h to obtain the products with high yields (80–92%). Furthermore, the synthesized derivatives showed anticancer and antimicrobial activities. The formation of the products is expected to proceed through two steps. Initially there occurs condensation between **3** with **2** to give the intermediate benzo[*a*]phenazin-5-ol **245**, the second step is an aldol-type condensation that takes place between aromatic aldehyde with **245**, resulting *in situ* C=C bond formation of intermediate **246**, which on further reaction undergoes Michael-type addition with another molecule of 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one **247** keto–enol tautomerism under the influence of the Fe(III) Y-zeolite solid state catalyst to furnish the desired product **244**(Scheme 74).[105]

In 2018, for the synthesis of pyrazolo-fused benzophenazines **248** in 78–87% yields, Mohebat and co-workers developed a multi-component condensation reaction involving **3**, **2a**, aromatic aldehydes, and 4-methylbenzenesulfonohydrazide in the presence of phosphotungstic acid ($H_3PW_{12}O_{40}$) under microwave irradiation (180 W, max. 70 °C) in EtOH within 15–20 min. A detailed reaction mechanism is shown in Scheme 75. In this mechanism, the primary condensation of **3** with **2a** gives **4**. On the other hand, $H_3PW_{12}O_{40}$ is an efficient catalyst to form the hydrazone **249**, which readily forms *in situ* from the condensation of the aromatic aldehyde with 4-methylbenzenesulfonohydrazide. The Michael addition of **4** with **249** in the presence of the catalyst finally gives the intermediate **250**, which then forms the inner molecular ring after a tautomeric proton shift to produce the corresponding product **248**.[106]

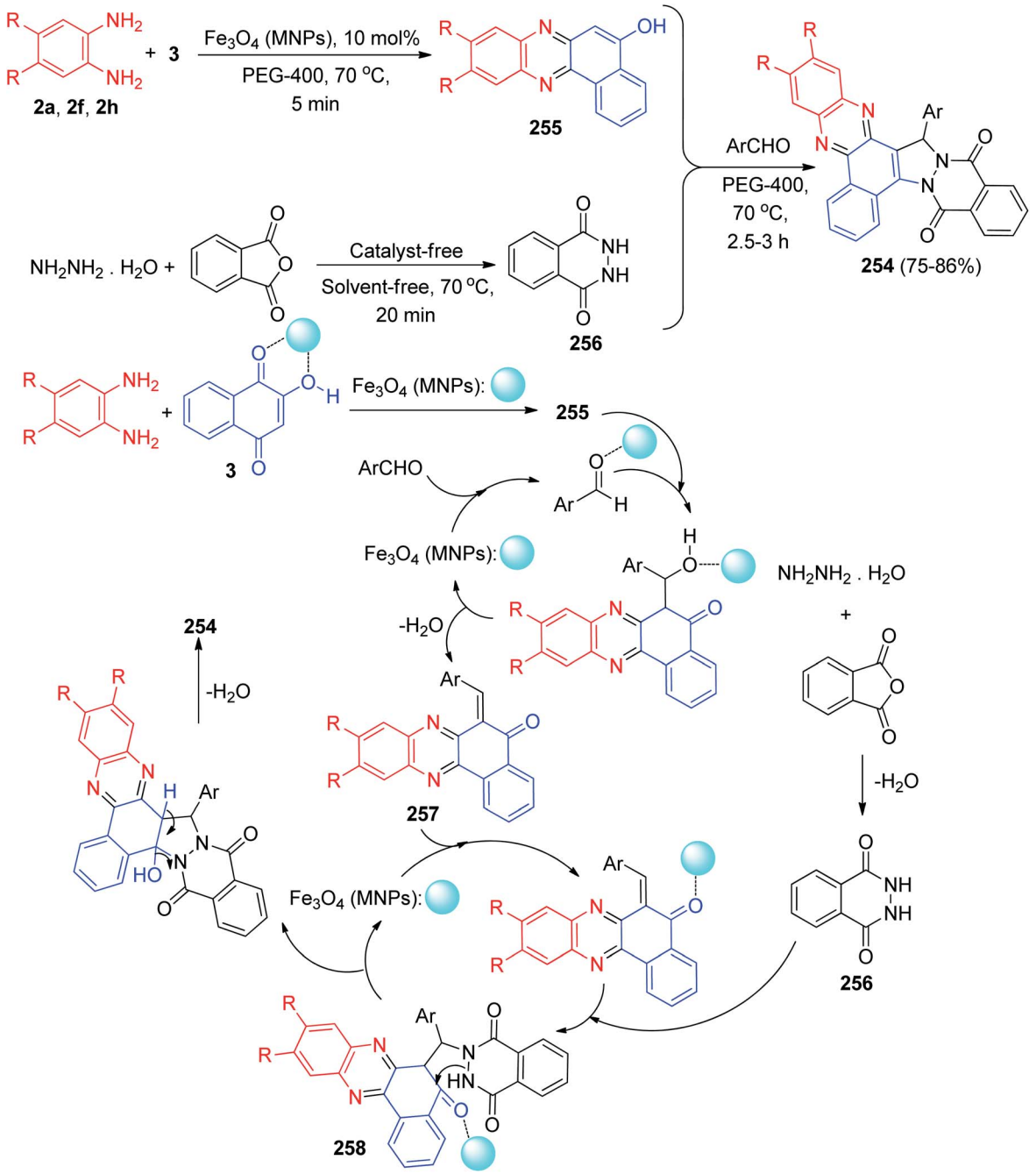
In 2019, Further, Parvin *et al.* developed a one-pot four-component reaction involving **3**, **2a**, aromatic aldehydes and aminouracil derivatives. The reaction was catalyzed by molecular iodine in water under reflux conditions for 3–8 h affording in aminouracil-tethered tri-substituted methane derivatives **251** in 66–90% yields. The proposed mechanism for the synthesis of **251** has been presented in Scheme 76. Firstly, iodine activates the carbonyl group of aldehyde as it acts as a mild Lewis acid by forming aldehyde–iodine complex and increases the electrophilicity of carbonyl carbon. The aldol condensation of aldehyde and 5-hydroxybenzophenazine (formed from the reaction of **3** and **2a**) followed by dehydration resulted in **252**. Then, molecular iodine also activates carbonyl group of **252** and facilitates the Michael addition with 1,3-dimethyl-6-aminouracil and provided **253**. Next, tautomerization of **253** resulted in the final product **251**.[107]

In 2020, benzo[*a*]phthalazino[2,3:1,2]pyrazolo[3,4-*c*]phenazines **254** are synthesized in 75–86% yields by using a single-pot, five-component reaction involving **3**, aromatic 1,2-diamines, hydrazine hydrate, phthalic anhydride, and benzaldehydes catalyzed by magnetic iron(III) oxide nanoparticles (Fe_3O_4 MNPs) in polyethylene glycol (PEG-400) as an inexpensive, non-toxic, and effective medium at 70 °C for 2.5–3 h. A detailed reaction mechanism is outlined in Scheme 77. The primary condensation of **3** with benzene-1,2-diamine in the presence of Fe_3O_4-MNPs gives benzo[*a*]phenazin-5-ol **255**. Then, hydrazine hydrate condenses with phthalic anhydride to generate the phthalhydrazide **256** with the loss of water. On this mechanism, Fe_3O_4-MNPs is an efficient catalyst to form the olefin **257**, which readily prepares *in situ* from Knoevenagel condensation of aromatic aldehyde with **255**. The Michael addition of phthalhydrazide **256** with olefin **257** in the presence of the catalyst finally gives intermediate **258**, which then makes the inner molecular ring to be formed after a tautomeric proton shift to produce the corresponding product **254**.[108]

In 2021, Olyaei and his group synthesized 6,6′-(arylmethylene)bis(benzo[*a*]phenazin-5-ol) derivatives **259** in 79–89% yields *via* a sequential one-pot, two-step, pseudo-five-



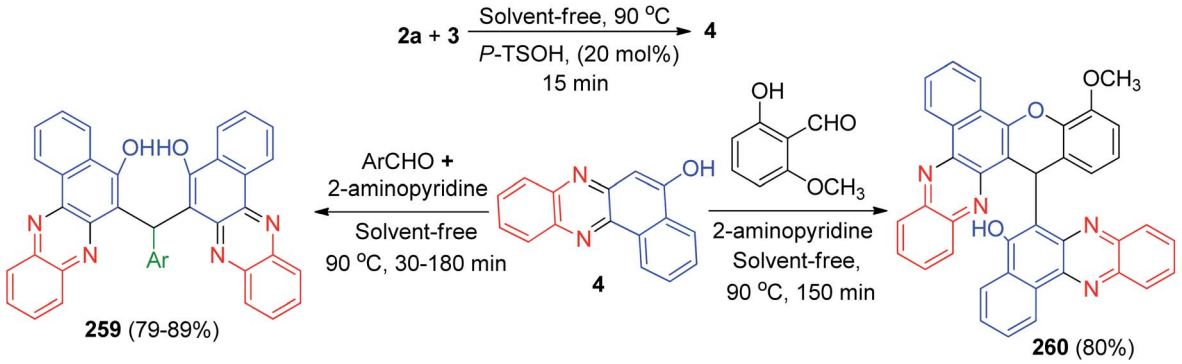
Scheme 76 I_2 catalyzed synthesis of aminouracil-tethered tri-substituted methane derivatives **251**.



Scheme 77 Fe_3O_4 MNPs catalyzed synthesis of benzo[*a*]phthalazino[2,3:1,2]pyrazolo[3,4-*c*]phenazines **254**.

component tandem reaction starting from **3**, **2a** and aromatic aldehydes in the presence of 2-aminopyridine as co-catalyst and *p*-TsOH (20 mol%) as catalyst at 90 °C under solvent-free conditions within 30–180 min. Moreover, 6-(4-methoxy-16*H*-benzo[*a*]chromeno[2,3-*c*]phenazin-16-yl)benzo[*a*]phenazin-5-ol (**260**) prepared by the reaction of **3**, **2a** and 2-hydroxy-3-methoxybenzaldehyde in the same reaction condition after 150 min (Scheme 78). A reaction mechanism consistent with the above results is shown in Scheme 79. Initially, **3** tautomerizes to intermediate **11**. The primary condensation of intermediate **11** with **2a** affords **4**. On the other hand, condensation of aromatic aldehyde with 2-aminopyridine in the presence of *p*-TsOH afforded Schiff base **261** as intermediate. Subsequently, nucleophilic addition of **4** to intermediate **261** led to the formation of intermediate **262**. Intermediate **262** tautomerizes to intermediate **263**. By leaving of 2-aminopyridine from intermediate **263**, *ortho*-quinonemethide **264** was produced. It should be noted that, 2-aminopyridine might act as a good leaving group in the acidic environment. Finally, Michael addition of **4** to *o*-QM **264** afforded the corresponding product **259**.

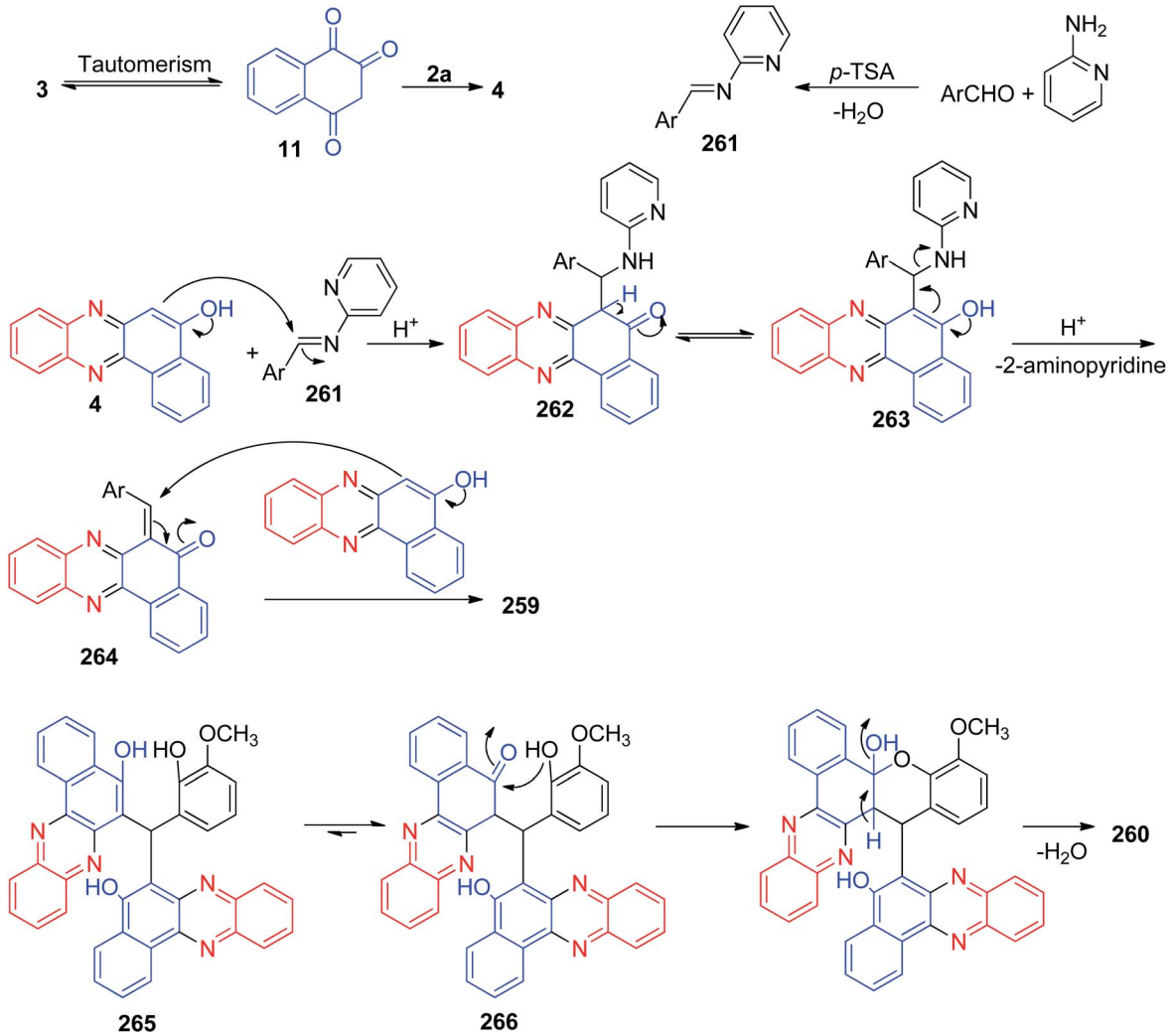
For the formation of compound **260**, initially, intermediate **265** was formed according to the same proposed mechanism for



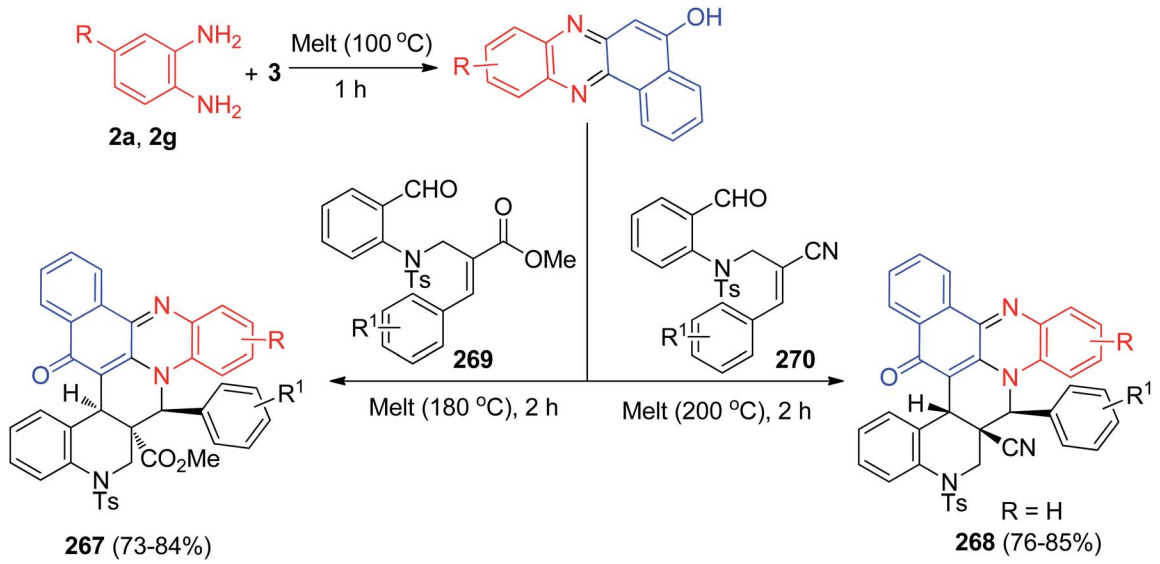
Scheme 78 Synthesis of 6,6′-(arylmethylene)bis(benzo[*a*]phenazin-5-ol) derivatives **259**.

the preparation of **259.** Then, intermediate **265** tautomerizes to the keto form **266**, which undergoes intramolecular cyclization *via* an oxygen atom attacking to the carbonyl group and elimination of water to afford the desired product **260.**[109]

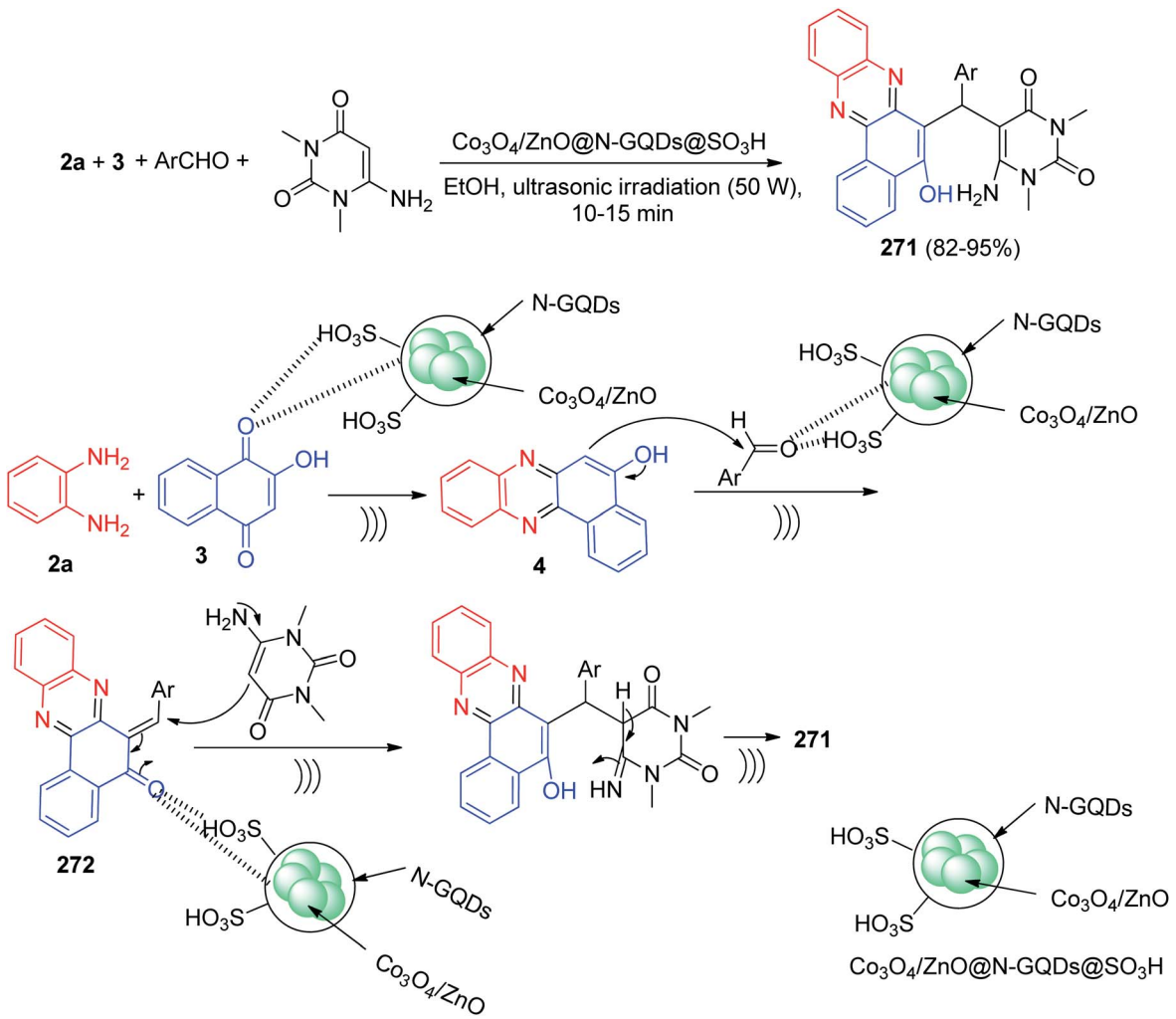
Next, an efficient and versatile protocol for the synthesis of hybrid polycyclic quinolinobenzo[*a*]phenazinones **267** (73–84% yields) and **268** (76–85% yields) has been developed by the reaction of **3**, benzene-1,2-diamines and *N*-allylated 2-aminoarylaldehyde derivatives **269** and **270** under solid-state melt reaction (SSMR) condition at 180–200 °C for 2 h (Scheme 80). The reaction was carried out *via* intramolecular domino Knoevenagel-hetero-Diels–Alder reaction involving the generation of



Scheme 79 Proposed mechanism for the synthesis of 6,6′-(arylmethylene)bis(benzo[*a*]phenazin-5-ol) derivatives **252** and compound **260**.



Scheme 80 Synthesis of hybrid polycyclic quinolinobenzo[*a*]phenazinones **267**–**268**.



Scheme 81 Synthesis of phenazinpyrimidines **271**.

six membered fused rings and three contiguous stereogenic centers.[110]

Recently, Safaei-Ghomi and his group synthesized phenazinpyrimidines **271** in 82–95% yields *via* one-pot four-component reaction of **3**, **2a**, aldehydes and 6-amino-1-3-dimethyluracil using Co_3O_4/ZnO@N-GQDs@SO_3H nanocomposite as a robust heterogeneous catalyst under ultrasonic irradiations in EtOH for 10–15 min. Scheme 81 shows a plausible mechanism for this reaction in the presence of nanocatalyst. First, the formation of **4** can be explained *via* a condensation of **3** and **2a**. Then the efficient Knoevenagel condensation of **4** and arylaldehyde created intermediate **272**. Finally, the product **271** was formed by Michael addition/dehydration reactions between 6-amino-1,3-dimethyluracil and intermediate **272**.[111]

3 Conclusions

Phenazine and its derivatives such as benzophenazins are a large group of natural and synthesized N-containing heterocycles. Benzophenazins have attracted interest because they exhibit a wide range of biological activities. In this article review, we focused on the important methods for synthesis of lawsone-based benzo[*a*]phenazin-5-ol derivatives and reported the different important reactions of them in synthesis of five and six membered fused heterocycles and the other derivatives. Moreover, the present work contributes the different classical methods with green approach, homogeneous and heterogeneous-catalyzed reactions, microwave irradiation and ultrasound-mediated reactions for the synthesis of benzophenazine derivatives. Thus, this review article will help not only to the synthetic chemists but also to the medicinal and pharmaceutical chemists to update information on recent developments in this field.

Conflicts of interest

There are no conflicts to declare.

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