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REVIEW

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1. Introduction

Quinoline, a well known heterocyclic compound, itself has few applications in chemical domains, but many of its derivatives are useful in diverse applications including pharmaceuticals, agrochemicals, materials and dyestuffs. Today they are available as drugs. The prominent ones are the fluoroquinolone antibiotics (Ciprofloxacin and its analogs), antimalarials (Quinine, Chloroquine, Quinidine, Mefloquine, Primaguine, Amodiaquinine), antibacterials (Sparfloxacin, Gatifloxacin), a cholesterol lowering agent (Pitavastatin), an antiviral agent (Saquinavir), an anthelmintic agent (Oxamniquine), an antifungal-antiprotozoal agent (Clioquinol), a local anesthetic (Dibucaine), an antiretroviral agent (Saquinavir), an antiasthmatic (Montelukast), antipsychotics (Aripiprazole, Brexpiprazole), an anti-TB agent (Bedaquiline), anticancer agents (Camptothecin, Irinotecan, Topotecan), antiglaucoma (Cartiolol) and cardiotonic (Vesnarinone) agents, protein kinase inhibitors (Lenvatinib, Bosutinib and Cabozantinib), and a farnesyl transferase inhibitor for leukemia (Tipifarnib). Moreover, several quinolines have been reported to display various useful biological and pharmacological activities as

Advancements in the synthesis of fused tetracyclic quinoline derivatives

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Fused tetracyclic systems containing a quinoline nucleus represent an important class of heterocyclic bioactive natural products and pharmaceuticals because of their significant and wide-spectrum biological properties. Several of these compounds have been obtained with diverse pharmacological and biological activities, such as antiplasmodial, antifungal, antibacterial, potent antiparasitic, antiproliferative, anti-tumor and anti-inflammatory activities. This information will be beneficial for medicinal chemists in the field of drug discovery to design and synthesize new fused tetracyclic quinolines as potent therapeutical agents. This review article provides a comprehensive report regarding the methods developed for the synthesis of fused tetracyclic quinolines reported so far (till October 2019). The article includes synthesis by one-pot domino reaction, microwave synthesis using a catalyst, using ionic liquids, photocatalytic synthesis (UV radiation), Pfitzinger reaction, I₂-catalyzed cyclization reaction, Wittig reaction, cascade reaction, imino Diels–Alder reaction, Friedel–Crafts reaction, CDC reaction, solvent-free reactions and using small chiral organic molecules as catalysts. To the best of our knowledge, this is the first review focused on the synthesis of fused tetracyclic quinolines along with mechanistic aspects.

antiinflammatory agents,^{1,2} antipsychotics,³ antiprotozoals,⁴⁻⁹ antituberculosis agents,¹⁰⁻¹² anti-Alzheimers agents,¹³ anti-HIV agents,¹⁴⁻¹⁶ antiasthmatics,¹⁷ potent melaninconcentrating hormone 1 receptor (MCH1R) antagonists,¹⁸⁻²² antioxidants,²³ antivirals,²⁴ antifungals,^{25,26} Src kinase inhibitors,²⁷ antihypertensive agents,²⁸ anti-microbials,²⁹⁻³¹ antibiotics,³² tyrokinase PDGF-RTK inhibiting agents,³³ agents for treatment of lupus^{34,35} and neurodegenerative diseases³⁶ and efflux pump inhibitors.³⁷

Fused tetracyclic systems containing a quinoline moiety are an important class of organic molecules since many of them exhibit excellent biological activities. They have been well established to be useful as potent topoisomerase I and II inhibitor, antifungal, antiplasmodial, antibacterial, potent antiparasitic, antiproliferative, anti-inflammatory and antitumor agents.³⁸⁻⁴³ In addition, mappicine ketone, as fused quinoline natural product, is an antiviral lead compound with selective activities against herpes viruses HSV-1 and HSV-2 and human cytomegalovirus (HCMV).⁴⁴ A fused quinoline alkaloids cryptolepine, neocryptolepine, and isocryptolepine are antimalarial natural products having cytotoxic activities.^{45,46} The chemical structures of these natural products are shown in Fig. 1.

Due to their tremendous pharmacological and biological importance, chemists have developed a large number of protocols for the synthesis of fused tetracyclic systems comprising quinoline nucleus, to the best of our knowledge,

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this has never been reviewed. The present review article provides, for the first time, a comprehensive compilation of synthetic methods on the synthesis of these tetracyclic ring systems, as a significant family in the field of organic chemistry.



Ramadan Ahmed Mekheimer was born in El-Minia, Egypt, on March 9, 1960 and graduated in chemistry with distinction degree at the university of Minia. He received his B.Sc. (1982) degree from Minia University. In 1987– 1989, the University of Minia awarded him a channel system program to complete his PhD thesis under the supervision of Prof. Dr Thomas Kappe in Institute of organic chemistry, Karl-

Franzens University, Graz, Austria, and he received his PhD (1990) degrees from Chemistry Department, Faculty of Science, Minia University. After his PhD degree he take time in establishing his organic synthesis lab. In, 1994 the University of Minia awarded him the University Prize designated for the outstanding organic researcher scientist. In 1995, he became assistant Professor. During a postdoctoral stay in 1997–1998 at the University of Connecticut, Storrs, USA, he joined the group of Professor M. Smith. In 2000, the Academy of Science and Technology, Cairo, Egypt awarded him "The State's Encouragement National Prize in Organic Chemistry". Since 2001, he has been Full Professor of Organic Chemistry at the University of Minia. At the beginning of his career, he was interested in the development of new methodologies for the synthesis of new nitrones, heterocyclic azides and studying their chemical behavior, synthesis of amino-quinolines as anti-malaria and the synthesis of novel fused-heterocyclic ring systems, especially those containing pyridine or quinoline nucleus, of biological and pharmacological interest. His current research interests include the design of efficient environmental benign synthetic approaches for the synthesis of potentially bioactive heterocyclic compounds utilizing microwave and ultrasound irradiations and solar energy as energy sources besides the use of eco-friendly catalysts and solvents (particularly water) in organic synthesis. To date, he has synthesized with his research group more than 500 new organic substances, mainly heterocyclic structure.

2. Synthesis of tetracyclic quinolines

2.1. Tetracyclic quinolines with one heteroatom

2.1.1. Isoindolo[2,1-*a*]quinolines. A novel series of tetracyclic isoindolo[2,1-*a*]quinoline-5,11-dione derivatives 3 have been synthesized and evaluated as potent inhibitors of human topoisomerase-II and DNA-gyrase by Sui *et al.*⁴⁷ On heating 2-aminoacetophenones 1 with phthalic anhydrides 2 at reflux in xylene in the presence of TEA, as a base catalyst, the tetracyclic products 3 were obtained in 35–74% yields (Scheme 1). Only in one case the imide intermediate 5 was isolated. The isolation of

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Hanadi Yousef Medrasi was born in 1976 in Makkah-Kingdom of Saudi Arabia. She obtained her MSc degree in Organic Chemistry from the University of King AbdulAziz-Jeddah-Saudi Arabia, involving a dissertation entitled "Novel approaches to functionally substituted condensed azoles and azines" in 2003. She received her PhD degree from the University of King AbdulAziz-Jeddah-Saudi Arabia, completing her doctoral thesis on alkylation reactions of arenes in 2010. In, 2013 the University of King AbdulAziz awarded her the University Prize designated for the outstanding organic researcher scientist. She is currently working as Assistant Professor of Organic Chemistry at the University of Jeddah, Saudi Arabia. Her research interests include the study of synthesis and reactivity of biologically important heterocycles and organic chemistry education.



Scheme 1 Synthesis of isoindolo[2,1-a]quinoline-5,11-diones 3.

5 confirmed that imide formation occurs prior to intramolecular cyclization of the amide in 4 to form the quinoline nucleous (Scheme 1).

The synthetic method to tetracyclic 3-substituted-6,6*a*-dihydroisoindolo[2,1-*a*]quinoline-5,11-diones **10** is outlined in Scheme 2.⁴⁸ Reduction of 2-arylisoindolo-1,3(2*H*)-diones **6** with



Kamal Usef Sadek was born in El-Minia (1947) and has received B.Sc. degree (honour) in Applied Chemistry from Assiut University (1969) followed by MSc and PhD from Cairo University (1980) under the supervision of Prof. M. H. Elnagdi. He was appointed as a demonstrator of Chemistry in Assiut University then he shifted to the Department of Chemistry, El-Minia University (1975). Since then he was appointed as lecturer

(1980), associate Prof. (1985) and Full Professor (1990). In 1987 he was awarded the Alexander von Hmboldt fellowship with Prof. W. Weigrebe in Pegensburg University and have several studies leaves with Prof. M. Regitz of Kuierslautern University and Prof. H. H. Otto in Freiburg University. Currently, he is working in developing green technologies for the synthesis of biologically active heterocycles. sodium borohydride (NaBH₄) in THF/MeOH at 0–5 °C produced 2-aryl-3-hydroxy-isoindolin-1-ones 7, which converted into 2-aryl-3-oxo-isoindole-1-acetic acids **8** by a Wittig reaction and subsequent hydrolysis. Treatment **8** with thionyl chloride at 70 °C gave the corresponding 2-aryl-3-oxo-isoindole-1-acetyl chlorides **9**, which underwent an intramolecular Friedel-Crafts reaction in 1,2-dichloroethane with AlCl₃ as a catalyst to give the desired isoindolo[2,1-*a*]quinolines **10**. These synthesized products exhibited a protective effect against N₂-induced hypoxia.

In 1994, Kumar and coworkers⁴⁹ have reported an efficient synthesis of isoindolo[2,1-*a*]quinoline-5,11-dione (**16**) *via* the reaction of 2-(1,3-dioxoisoindolin-2-yl)benzoic acid (**11**) with *N*-phenyl(triphenylphosphoranylidine)ethenimine (**12**) (Scheme 3). When a mixture of **11** and **12** was refluxed in toluene or dioxane, the desired isoindolo[2,1-*a*]quinoline-5,11-dione (**16**) was obtained in 97% yields. The time of reaction was not reported. The plausible mechanism of this reaction includes the initial protonation of *N*-phenyl(triphenylphosphoranylidine)ethenimine (**12**) by **11** to give the *O*-acyl-imidate **13**. Then, a migration of the intermediate **14**, which eliminates a molecule of phenyl isocyanate to afford the acylphosphorane **15**. Subsequent cyclization of **15** *via* the intramolecular Wittig reaction on the imide C==O gave the tetracyclic product **16** (Scheme 3).

In 1997, Kim and Keum⁵⁰ developed another method for the synthesis of isoindolo[2,1-a]quinolines 16 utilizing 2-(2-





acetylphenyl)isoindoline-1,3-dione (17) as starting material. When 17 was heated in DMF in the presence of a catalytic amount of K_2CO_3 at 80–90 °C, it underwent intramolecular cyclization to produce the 2-(4-oxo-1,4-dihydro-quinolin-2-yl) benzoic acid (18), in 74% yield. Refluxing 18 with trimethyl orthoformate in MeOH in the presence of H_2SO_4 as an acidic catalyst gave a mixture of methyl 2-(4-oxo-1,4-dihydroquinolin-2-yl)benzoate (19) (17% yield) and tetracyclic isoindolo[2,1-*a*] quinoline-5,11-dione (16) (79% yield). On the other hand, when **19** was treated with K_2CO_3 in DMF at room temperature, it was converted quantitatively into the desired product **16** (Scheme 4).

A novel route for the synthesis of 6*a*-methyl-5-substitutedisoindolo[2,1-*a*]quinoline-11(6*aH*)-ones 22 has been developed utilizing *N*-aryl-phthalimides 20 as the key precursors.⁵¹ The reaction of 20 with sodium borohydride in dry MeOH at 10 °C or the Grignard reagent (MeMgI) in dry ether afforded the corresponding alcohols 21. When compounds 21 ($R_1 = CH_3$) were



Scheme 4 Synthesis of isoindolo[2,1-a]quinolines 16 from 17.

refluxed in toluene in the presence of *p*-toluene-sulfonic acid (TsOH), as catalyst, they underwent intramolecular ring closure to the isoindolo[2,1-*a*]quinolines **22** (Scheme 5). In case of **21** ($R_1 = H$), the isoindoloquinolines **22** were obtained which were rapidly isomerized, under these reaction conditions, to give the stable enamides **22A**, namely, 5-substituted-isoindolo[2,1-*a*] quinolin-11(5*H*)-ones.

Heating a neat mixture of phthalimide (23) with ethyl bromobenzoylacetate (24) in the presence of Cu(I) oxide at 100 °C produced the 2-acetylphenylphthalimide (17) as the major product (27% yield), *via* the coupling reaction followed by the deethoxycarbonylation process, along with isoindolo[2,1-*a*] quinoline-5,11-dione (25) (7% yield) which formed *via* the coupling reaction followed by the deethoxycarbonylation and intramolecular cyclo-dehydration process, and ethyl 5,11-dioxo-5,11-dihydroisoindolo[2,1-*a*]quinoline-6-carboxylate (26) (20% yield) (Scheme 6). The product 26 was assumed to be formed through the coupling reaction followed by a thermal cyclodehydration reaction.⁵⁰







Scheme 6 Synthesis of 5,11-dihydroisoindolo[2,1-a]quinoline-5,11-diones 25 and 26.



A simple route for the synthesis of 11-benzoyl-8,10-dinitroisoindolo[2,1-*a*]quinoline (**30**) has been reported by Reuschling and Kröhnke.⁵² Reacting *N*-phenacylquinolinium bromide (**27**) with picryl chloride (**28**) at room temperature, under basic conditions, afforded the respective tetracyclic product **30** in low yield (27%), *via* intermediacy **29** (Scheme 7).

Alkhathlan and his group⁵³ have described the synthesis of 6azido-isoindolo[2,1-*a*]quinoline,11-diones **34**. On reacting 2aminoacetophenone (**31**) with phthalic anhydride derivatives **2** in xylene in the presence of a catalytic amount of Et₃N under reflux for 5 h, 2-(2-acetylphenyl)-isoindolo-1,3-diones **32** were obtained. Bromination of **32** with CuBr₂ in a EtOAc/CHCl₃ mixture under reflux for 5 h gave the corresponding bromo derivatives 33. When the bromo compounds 33 were heated with sodium azide in a mixture of acetone/H₂O at 65 °C for 2 h, they underwent intramolecular cyclocondensation to furnish directly the new tetracyclic ring system 34 in 42–76% yields (Scheme 8). Attempts to isolate the azido analogs of 34 by conducting the reaction at different reaction conditions were failed.

In 2009, Zhang *et al.*⁵⁴ have described as the first one-pot synthesis of isoindolo[2,1-*a*]quinolin-11-ones **36** by reacting 2aryl-3-hydroxy-isoindol-1-ones **7** with 1,3-dicarbonyls **35** *via* coupling of *N*-acyliminium ion intermediates **37** with **35** followed by intramolecular Friedel–Crafts reaction catalyzed by $H_3PO_4-P_2O_5$ or $H_3PO_4-H_2SO_4$. Reactions were carried out by



Scheme 8 Synthesis of 6-azido-isoindolo[2,1-a]quinoline-5,11-diones 34.



Scheme 9 One-pot synthesis of isoindolo[2,1-a]quinolin-11-ones 36 by reacting 7 with 35.



Scheme 10 A plausible mechanism for the formation of isoindolo[2,1-a]quinolin-11-ones 36.

stirring 7 with 35 under the catalysis of $H_3PO_4-P_2O_5$ or $H_3PO_4-H_2SO_4$ at room temperature for 6–24 h to give the desired isoindolo[2,1-*a*]quinoline-11-ones 36 in 45–93% yields (Scheme 9). The structures of all the newly synthesized compounds were fully characterized by ¹H NMR, ¹³C NMR, and MS. Furthermore, X-ray crystallographic analysis was performed to determine the absolute configuration of the products 36. A plausible mechanism for the formation of 36 is given in Scheme 10. The reaction was initiated by the formation of an *N*-acyliminium intermediate 37 which was reacted with 35 to give the intermediate 38. Intramolecular Friedel–Crafts reaction between the protected aniline and the ketone gave the desired tetracyclic product 36.

In 2011, Svete and his co-workers⁵⁵ reported that the treatment of 2-(2-acetylphenyl)-1*H*-isoindole-1,3(2*H*)-dione (17) with *N*,*N*-dimethylformamide dimethyl acetal (DMF-DMA) in refluxing toluene resulted in the formation of the isoindolo[2,1-*a*] quinoline-5,11-dione (16) in 93% yield (Scheme 11). The mechanism of this reaction began with the formation of enaminone 40, which next underwent intramolecular cyclization to give the intermediate 41. The formed adduct 41 was subsequently underwent β -elimination of DMF and H₂O to furnish the desired tetracyclic 16 (Scheme 11).

Sakhautdinov *et al.*⁵⁶ have described the synthesis of isoindolo[2,1-*a*]quinoline-5,11-diones **45** *via* intramolecular cyclization of *N*-[2-(triphenyl- λ^5 -phosphanylidene)acetyl]phthalimides **44** under microwave-heating. Refluxing a mixture of *o*-phthalimidobenzoic acid (**11**) and SOCl₂ in dry benzene for 3 h afforded the corresponding acid chlorides intermediate **43**, and the latter was reacted *in situ* with alkylidenephosphorane (2 equiv.) to give keto-stabilized phosphorus ylides **44**. The compounds **44** when heated in dry toluene in the presence of a catalytic amount of benzoic acid (5 mol%) at reflux



temperature under argon atmosphere for 56 h, they underwent intramolecular cyclization to afford the tetracyclic products **45** in low yields (15–27% yields). Interestingly, it was observed that use of microwave irradiation gave much faster reaction and improved the yields, thereby allowing rapid access to this class of compounds **45**. Thus, the ylides **44** when heated in dry toluene for 30 min under microwaves, they underwent intramolecular cyclization followed by elimination of a triphenylphosphine oxide (O=PPh₃) molecule to afford tetracyclic isoindolo[2,1-*a*]quinoline-5,11-diones **45**, in good yields (Scheme 12). However, one drawback of this methodology is electron-acceptor substituents on the ylide carbon atom hamper the intramolecular cyclization process.

In 2014, Fu *et al.*⁵⁷ have described a new and efficient synthesis of 2-chloro-isoindolo[2,1-*a*]quinoline-5(11*H*)-one (47) through the intramolecular Heck coupling cyclization of 1-(2-bromobenzyl)-7-chloroquinolin-4(1*H*)-one (46). The reaction



Scheme 12 Microwave-assisted synthesis of isoindolo[2,1-a]quinoline-5,11-diones 45.

was carried out by heating **46** (1 equiv.) with AcOK (2 equiv.) as the base and PdBr₂ (0.05 equiv.) as the catalyst in DMA at 90 °C under N₂ atmosphere for 12 h to provide the tetracyclic product **47** in 62% yield (Scheme 13). Noticeably, a definite mechanism for the synthesis of compound **47** has not been reported.

2.1.2. Indino[1,2-*b*]quinolines. Recently, Mishra *et al.*⁵⁸ have developed an eco-friendly, metal-free and TBHP-promoted economical method for the synthesis of 11*H*-indeno[1,2-*b*] quinolin-11-ones **49**, as antibacterial agent. The reactions were carried out by heating a solution of 2-aryl-quinoline-3-carbaldehyde derivatives **48** (1 equiv.) and *tert*-butyl hydroper-oxide (TBHP) (3 equiv.) in toluene at 100 °C for 14–24 h and furnished the desired tetracyclic indenoquinolinones **49** in 68–91% yields (Scheme 14). Depending on product formation, they suggested the free radical mechanism of this reaction in Scheme 15.

An interesting utility of Pfitzinger reaction for construction of tetracyclic quinolines has been reported by Deady *et al.*⁵⁹ This protocol implies Pfitzinger reaction of isatin-7-carboxylic acids **50** and 1-indanones **51** to prepare analogues of the topoisomerase inhibitor 11-oxo-11*H*-indeno[1,2-*b*]quinoline-6carboamides **56**. The one-pot reaction between **50** and **51** in NaOH (10%) at 90 °C under nitrogen atmosphere afforded tetracyclic 11*H*-indeno-[1,2-*b*]quinoline-6,10-dicarboxylic acids **52**, in 64–78% yields. Selective decarboxylation of **52**, followed by oxidation of CH₂ group in **53** with KMnO₄ produced 11-oxo-11*H*-



Scheme 13 Synthesis of 2-chloro-isoindolo[2,1-a]quinoline-5(11*H*)one (47) *via* intramolecular Heck coupling cyclization of 46.



Scheme 14 Synthesis of indeno[1,2-b]quinolin-11-ones 49 via intramolecular CDC reaction.



Scheme 15 Proposed mechanism for the formation of indeno[1,2-*b*] quinolin-11-ones 49 *via* intramolecular CDC reaction.

indeno-[1,2-*b*]quinoline-6-carboxylic acids **54**, in 15–79% yields. Refluxing **54** with 1,1'-carbonyl-diimidazole (CDI) in dioxan gave the corresponding imidazolide intermediate **55**, which was coupled, *in situ*, with *N*,*N*-dimethylethylenediamine in CH_2Cl_2 at room temperature to give the required tetracyclic 11-oxo-11*H*indeno[1,2-*b*]quinoline-6-carboxamides **56**, in 31–90% yields (Scheme 16).

2.1.3. Indino[1,2-*c*]quinolines. Tseng *et al.*⁶⁰ reported synthesis and antiproliferative evaluation of some 6-amino-11*H*-indeno[1,2-*c*]quinolin-11-ones **61** from reaction of isatin (57) with substituted phenylacetic acids **58**. Heating a mixture of **57** and **58** in the presence of a catalytic amount of CH_3CO_2Na at

200 °C produced 3-aryl-2-hydroxy-quinoline-4-carboxylic acid derivatives **59**, which were chlorinated with POCl₃ at 150 °C to give 6-chloro-indeno[1,2-*c*]quinoline-11-ones **60**, in 88–91% yields. On heating **60** with cyclic secondary amines in ethoxyethanol at 200 °C, the corresponding 6-amino-indeno[1,2-*c*] quinoline-11-ones **61** were obtained in 55–83% yields (Scheme 17).

Chen *et al.*⁶¹ reported synthesis of a series of novel tetracyclic 6-amino-9-chloro-11*H*-indeno[1,2-*c*]quinoline-11-ones **65**, as potential anticancer agents, through the Pfitzinger synthetic reaction of isatin (57) and 4-chlorophenyl-acetic acid (**62**). At first, a mixture of **57** and **62** was stirred at 200 °C with sodium acetate to produce 3-(4-chlorophenyl)-2-hydroxy-quinolin-4carboxylic acid (**63**) as a key intermediate. Treatment of **63** with POCl₃ at 150 °C afforded 6,9-dichloro-11*H*-indeno[1,2-*c*] quinoline-11-one (**64**), in 30% yield. Reaction of **64** with an appropriate primary and secondary amines in DMF at 150 °C gave the corresponding side chain tetracyclic compounds **65** in 18–86% yields (Scheme 18).

2.2. Tetracyclic quinolines with two heteroatoms

2.2.1. Indolo[2,3-b]quinolines. In 2004, Chen's group⁶² reported an efficient synthesis of some 11-substituted-6H-indolo [2,3-b]quinolines 70a-c, starting from 4-hydroxy-quinolin-2(1H)one (66). In this cascade reaction, the hydroxyquinoline 66 was methylated with Me_2SO_4 in acetone in the presence of K_2CO_3 to produce 4-methoxy-quinoline-2(1H)-one (67a). Refluxing 66 with aniline or p-anisidine in Ph₂O yielded 4-anilino-quinolin-2(1H)-one (67b) or its 4-methoxy derivative 67c, respectively. Heating 67a-c with POCl₃ at 90 °C afforded the 2-chloroquinolines 68a-c. Treatment of 68a-c with 1H-benzo[1,2,3]triazole in ethoxyethanol at reflux temperature gave the corresponding triazoles 69a-c, which underwent decomposition reaction in polyphosphoric acid (PPA) to afford the respective tetracyclic indolo[2,3-b]quinolines 70a-c, in 32-56% yields (Scheme 19). The products exhibited selective cytotoxicities for K-562, HL-60, RPMI-8226 and MOLT-4.



In 2018, Salman *et al.*⁶³ have developed a simple and regioselective synthesis of two series of 10*H*-indolo[3,2-*b*]quinolines 75 and 6*H*-indolo[2,3-*b*]quinolines **76** *via* palladium catalyzed Suzuki reaction of 2,3-dihaloquinolines with 2-bromophenylboronic acid, followed by double C–N coupling. The Suzuki reaction of 2-chloro-3-bromoquinoline (**71**) and 3-bromo-2iodoquinoline (**73**) with 2-bromophenylboronic acid gave 3-(2bromophenyl)-2-chloroquinoline (**72**) and 3-bromo-2-(2bromophenyl)quinoline (**74**) in 75 and 60% yield, respectively

The double carbon–nitrogen coupling reaction was performed by heating 72 and 74 with various amines in the presence of the catalyst tris(dibenzylideneacetone)-dipalladium $[Pd_2(dba)_3]$ with the base NaO^tBu in toluene at 100 °C to give the desired 10*H*-indolo[3,2-*b*]quinolines 75 and 6*H*-indolo[2,3-*b*] quinoline 76, in moderate to excellent yields (Scheme 21).⁶³

Peczyńska-Czoch and his group^{64a,b} have described the synthesis of 6H-indolo[2,3-*b*]-quinolines **79** and **84**, as novel and more efficient DNA Topoisomerase I1 inhibitors, *via* the methods showed in Schemes 22 and 23. Heating the chlor-oquinolines **77** with 1*H*-benzo[1,2,3]triazole at 110–120 °C gave

the corresponding triazoles **78** (Scheme 22). However, compounds **83** were prepared by heating chloroquinoline derivatives **80** with 4-methyl-3-nitroaniline (**81**) at 150–160 °C, followed by the reduction of the NO₂ group in intermediate **82** and diazotization of the amino obtained (Scheme 23). Subsequent decomposition of triazoles **78** and **83** in polyphosphoric acid (PPA) at 130–180 °C afforded the respective indolo[2,3-*b*] quinolines **79** and **84**, respectively, in low yields.

Wang *et al.* and Lu *et al.*^{43,65*a*-*d*} developed an efficient protocol for the synthesis of a series of 11-chloro-5-methyl-5*H*-indolo[2,3*b*]quinolines (neocryptolepines) **89** with different substituents on the quinoline ring, as useful scaffold for the synthesis of anticancer and antimalaria agents. In this cascade reaction, various *N*-methyl-anilines **85** were treated with *N*-chlorosuccinimide (NCS) in CH₂Cl₂ at room temperature, followed by the addition of methyl 1*H*-indole-3-carboxylate (**86**) producing the corresponding methyl 2-((4-substituted phenyl)(methyl) amino)indole-3-carboxylates **87**. Upon refluxing **87** in diphenyl ether at 250 °C, it underwent intramolecular cyclization to give the tetracyclic ketones **88** in 68–98% yields. Chlorination of **88** was carried out in POCl₃ under reflux conditions to yield the

(Scheme 20).

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Scheme 17 Synthesis of indeno[1,2-c]quinolines 61



Scheme 18 Synthesis of 6-amino-9-chloro-11H-indeno[1,2-c]quinoline-11-ones 65.

desired 11-chloroneocryptolepines **89** in 67–94% yields, with high purity (Scheme 24).

Ali *et al.*⁶⁶ reported synthesis of highly substituted indolo[2,3*b*]quinolines **92** *via* metal-free, one-pot annulation reaction of substituted indoles **90** with 1-(2-tosylaminophenyl)-ketones **91**. The reaction occurs *via* an activation of C-2 and C-3 of indoles **90** by molecular iodine and Cs_2CO_3 , as a base catalyst, followed by *in situ* reaction with 1-(2-tosylamino-phenyl)ketones **91** in acetonitrile at 90 °C to afford polyfunctionalized indolo[2,3-*b*] quinolines **92**, in moderate to excellent yields (Scheme 25). In this reaction, electrophilic addition of iodonium ion to the 3-position of indoles **90** afforded cation intermediate **I**. 2-Amination of **I** with **91** gives **II**, which undergoes elimination of one molecule of HI in the presence of base to furnish **III**. Subsequent alkylation, followed by detosylation of **III** in the presence of HCl (12 M) affords **92** (Scheme 25).



Scheme 19 Synthesis of indolo[2,3-b]quinoline derivatives 70a-c.



Scheme 20 Chemoselective Suzuki reaction of 2,3-dihaloquinsolines 71 and 73.

In 2015, Pal *et al.*⁶⁷ have developed a new one-pot strategy for the synthesis of novel 11-carboxymethyl substituted 6*H*-indolo [2,3-*b*]quinolines **95**, as potential inducers of apoptosis, involving Pd(π)-catalyzed intramolecular oxidative C3–H alkenylation of the indole ring of (*E*)-alkyl-3-(2-(1*H*-indol-2-ylamino) phenyl)acrylates **94** followed by desulfonylation. In the present study, the starting material **94** was prepared *via* I₂-mediated addition of sulfonamide derivative **93** to indoles **90**. Heating a mixture of **93** (1 mmol), Pd(OAc)₂ (5 mol%), Cu(OAc)₂ (1.50 mol) and trifluoroacetic acid (TFA) (1.20 mol) in CH₃CN at 60 °C under an aerobic atmosphere for 5–7 h afforded the target tetracyclic products **95** in 52–89% yields (Scheme 26). A mechanism for the Pd(π)-catalyzed formation of **95** is outlined in Scheme 27.

Ghorbani-Vaghei and Malaekehpoor⁶⁸ described a simple and one-pot synthesis of novel 6*H*-indolo[2,3-*b*]quinolines **98** from the reaction of indole-3-carbaldehyde (**96**) with various aryl amines **97**, under mild conditions, utilizing *N*-bromosuccinimide (NBS) as an efficient catalyst. NBS initially catalyzed the formation of Schiff base **I** and then a 3-bromoindolinium cation intermediate **II**. The intermediate **II** on the subsequent nucleophilic attack by an another mole of aniline, followed by intramolecular cyclization and oxidation produces **98**. Reaction is outlined in Scheme 28.

A novel and efficient method for the synthesis of 11substituted-6H-indolo[2,3-b]quinolines 103 via thermolysis of the carbodiimide 100, which represents a new way of generating biradicals from unsaturated molecules having two nitrogen atoms in the conjugated system, is reported by Wang et al.69 Thus, thermolysis of the carbodiimide 100, having a different substituents at the acetylenic terminus, in refluxing p-xylene at 138 °C produced 103 in 16-91% yields. Apparently, a two-step biradical pathway through 101 or a one-step intramolecular Diels-Alder reaction produced the intermediate 102, which on subsequent tautomerization under the reaction conditions affords the final product 103 (Scheme 29). An especially attractive feature of this synthetic method is the possibility of placing a wide variety of substituents at different positions of the 6H-indolo[2,3-b]quinoline structure by selecting suitable fragments.

On heating 1-(2-alkynyl)phenyl-3-aryl-2-methylisothioureas **104** with $[Pd(\eta^3-C_3H_5)-Cl]_2$ (5 mol%) in the presence of Cs₂CO₃ (2 equiv.), CuTC (copper thiophene-carboxylate) (1.1 equiv.) and 1,4-bis(diphenylphosphino)butane (dppb) (0.3 equiv.) in xylene at 130 °C, a wide range of the desired tetracyclic adduct 6-methyl-indolo[2,3-b]quinolines 105 were obtained in 33-76% yields (Scheme 30).70 Importantly, a variety of electronrich aryl groups on the aryl ring (Ar) promoted this process. However, substrates bearing an electron-withdrawing group decreased the chemical yields. In fact, the reaction of isothiourea bearing a 3,5-bis(trifluoromethyl)phenyl group afforded no cyclized adduct. Respecting to the substituent (R) on the alkynyl group, both phenyl and alkyl groups were tolerated under these reaction conditions. In the suggested reaction mechanism, the oxidative addition of MeS-C bond to Pd(0), followed by ligand exchange with CuTC gave the alkenylpalladium complex II. Subsequent nucleophilic attack of the aryl group to the Pd(II) complex followed by reductive elimination of



Scheme 21 Synthesis of 10H-indolo[3,2-b]quinolines 75 and 6H-indolo[2,3-b]quinolines 76.



the resulting Pd-complex provided the tetracyclic product **105** (Scheme 31).

Recently, Patel *et al.*⁷¹ have described an elegant and green approach for the synthesis of 11-aryl-6*H*-indolo[2,3-*b*]quinolines **108** from 2-(phenylethynyl)anilines **106** and aryl isothiocynates **107**. The *in situ* generated *o*-alkynylthioureas, obtained by reacting **106** and **107**, underwent efficient cascade cyclization in the presence of Ag₂CO₃, as the catalyst, in DMSO to give 11-aryl-6*H*-indolo[2,3-*b*]quinolines **108**, in 59–83% yields, under microwave conditions (30 min reaction time at 130 °C, 150 W, closed vial) (Scheme 32). The authors examined the electronic effect of substituents R₃ on the aryl isothiocynates **107**, R₂ present on the other phenyl ring of 2-(phenylethynyl)anilines **106** and R₁ substituents present on the amine bearing ring of 2(phenylethynyl)anilines **106** on the product yields and they found that when substituents R_2 and R_3 are electron-donating groups the products were obtained in better yields compared to electron-withdrawing substituents. On the other hand, R_1 substituents showed a trend on the product yields opposite to that of substituents R_2 and R_3 . A plausible reaction mechanism has been proposed as outlined in Scheme 33. Reaction of **106** and **107** gives thiourea intermediate **I**, which is desulfurized in the presence of Ag_2CO_3 to a carbodiimide intermediate **II**. Intramolecular cyclization of **II** formed a carbene-type intermediate **III**. The latter **III** undergoes further cyclization *via* carbene C–H insertion to afford a non-aromatic tetracyclic intermediate **IV**, which is aromatized to furnish the desired tetracyclic product **108**.



Scheme 23 Synthesis of 6H-indolo[2,3-b]quinolines 84.



In 2019, Kundal et al.72 reported a novel, general and efficient method for the synthesis of diversely substituted indolo[2,3-*b*] quinolines 111 through a two-step domino reaction. First, the starting 3-indolines 110 were prepared by Pd-catalyzed domino Heck-Suzuki coupling of 2-bromo-N-propargylanilides 109 with aryl boronic acids (Scheme 34). Next, when the 3-indolines 110 were subjected to the oxidative cross-dehydrogenative coupling (CDC) between allylic C sp³-H of the indoline ring and the free NH₂ group in the presence of 2,3-dichloro-5,6-dicyano-1,4benzoquinone (DDQ) (2 equiv.) in CH₂Cl₂ at room temperature, the fused tetracyclic indolo[2,3-b]quinolines 111 were produced in quantitative yields within one hour (Scheme 34). Gratifyingly, it was found that there was no significant electronic effect of the substituent on the aryl ring on the olefinic motif during the formation of C-N bond. DDQ has been proven as an efficient metal-free oxidant for CDC reactions of C-C bond formation reactions, but the formation of the C-N bond via DDQ-mediated cross-dehydrogenative coupling (CDC) has been relatively rare. Therefore, this strategy for the preparation of indolo[2,3-*b*]quinolines **111** should be very attractive in the modern context of organic chemistry research. A plausible mechanism for the DDQ-mediated oxidative C–H amination is outlined in Scheme 35.

A novel and divergent approach for the synthesis of 5-methyl-5H-indolo[2,3-b]quinoline alkaloid cryptotackieine 127 was reported.⁷³ The reaction was performed in eight steps, starting from (2-nitrobenzyl)triphenylphosphonium bromide (117). First, condensation of 117 with o-azidobenzaldehyde (118) in the presence of anhydrous K₂CO₃ and catalytic amounts of dibenzo-18-crown-6 gave the 1-azido-2-(2-nitrostyryl)benzene (119). Staudinger reaction between the azide 119 and triphenylphosphine in dry CH₂Cl₂ at room temperature for 5 h followed by hydrolysis of the resulting iminophosphorane 120 provided the 2-(2-nitrostyryl)aniline (121). One-pot conversion of 121 into the 3-(2-nitrophenyl)quinoline-2(1H)-one (123) was performed by sequential treatment with bis(trichloromethyl) carbonate (triphosgene) and further microwave-promoted cyclization of the resulting 1-isocyanate-2-(2-nitrostyryl)benzene (122). Conversion of the quinoline 123 into 1methylquinoline-2-one 126 was performed by the three-step sequence: (i) methylation with CH₃I in DMF at 60 °C for 2 h to give 1-methyl-3-(2-nitrophenyl)quinoline-2(1H)-one (124); (ii) reduction of the nitro group in 124 with H₂ in the presence of Pd/c (10%) in EtOH at room temperature for 5 h to give 3-(2amiophenyl)-1-methyl-quinoline-2(1H)-one (125) and (iii) diazotization followed by the reaction with NaN₃ furnished 3-(2azidophenyl)-1-methyl-quinoline-2(1H)-one (126). Finally, when a solution of the iminophosphorane derived from 126 and Me₃P in nitrobenzene was heated under microwave irradiation at 180 °C for 30 min, the required 5-methyl-5*H*-indolo-[2,3-*b*] quinoline (127) was obtained in 40% yield (Scheme 36). The conversion of 126 into 127 represents the first example of an intramolecular aza-Wittig reaction involving a 2-pyridone carbonyls group.

A new, efficient and four-step formal synthesis of alkaloid cryptotackiene **127**, a linear 5-*N*-methyl-5*H*-indolo[2,3-*b*]



Scheme 25 Molecular iodine catalyzed synthesis of polyfunctionalized indolo[2,3-*b*]-quinolines 92.

quinoline alkaloid, isolated from the West African shrub *Cryp*tolepis sanguinolenta, is reported.⁷⁴ It should be noted that the cryptotackiene has been reported to display strong antiplasmodial activity. First, the starting 3-bis[(methylsulfanyl)methylene]-2-oxindole (**128**) was subjected to conjugate addition with cyclohexanone (129) in DMF in the presence of NaH to afford the required 3-[(methylthio)(2-oxocyclohexyl)-methylene]indolin-2-one (130). Heterocyclization of the latter adduct 130 was performed by heating with AcONH₄ in dry DMSO in the presence of 4 Å molecular sieves at 120–130 °C for



Scheme 26 Pd-mediated synthesis of 11-carboxymethyl substituted 6H-indolo[2,3-b]-quinolines 95.



Scheme 27 Proposed reaction mechanism for the formation of 11-carboxymethyl substituted 6H-indolo[2,3-b]quinolines 95.



Scheme 28 NBS catalyzed synthesis of novel indolo[2,3-b]quinolines 98.









12 h to give the 11-(methylthio)-2,3,4,6-tetrahydro-1*H*-indolo [2,3-*b*]quinoline (131). Dethiomethylation of 131 with Raney Ni in EtOH at reflux temperature for 6 h gave 2,3,4,6-tetrahydro-1*H*-indolo[2,3-*b*]quinoline (132). Subsequent dehydrogenation of 132 with DDQ in refluxing 1,4-dioxane furnished the requested 6*H*-indolo[2,3-*b*]quinoline (133) in 88% yield (Scheme 37). Finally, indoloquinoline 133 was converted into 5-methyl-5*H*-indolo[2,3-*b*]quinoline (cryptotackiene) (127) by heating with dimethylsulfate in toluene in sealed tube at 150–160 °C. Compound 127 was found to be identical in all respects with the

one prepared by heating 133 with methyl iodide in EtOH in closed glass tube at 100 °C (Scheme 37).

Vanelle *et al.*⁷⁵ have reported an original, rapid and easy twostep synthesis of new substituted indolo[2,3-*b*]quinolines based on TDAE strategy from reaction between 1-methylisatin (134) and substituted *o*-nitrobenzyl chlorides **135** followed by a onepot reduction-intramolecular cyclization-double-dehydration reaction. First, reaction of **134** (3 equiv.) with **135** in DMF in the presence of TDAE at -20 °C for 1 h gave the corresponding α -hydroxy lactame **136** (Scheme 38). Reduction of the nitro aromatic group in **136** with iron in AcOH acid at 110 °C for 48 h



Scheme 31 A suggested mechanism for the Pd-catalyzed formation of 6-methyl-indolo[2,3-b]quinolines 105.



Scheme 32 A green method for the synthesis of 11-aryl-6H-indolo[2,3-b]quinolines 108 under microwave heating

gave the desired 6-methyl-6*H*-indolo[2,3-*b*]quinolines **139** in 33–65% yields (Scheme 38). The latter step involves the nucleophilic attack of NH₂ group on lactam C=O group in intermediate **137**, followed by the acid-promoted double dehydration of the resulting 5a,6,10*b*,11-tetrahydro-6-methyl-5*H*-indolo[2,3-*b*] quinoline-5a,10*b*-diols intermediate **138** (Scheme 38).

A convenient, short and high yielding approach for the synthesis of 6H-indolo[2,3-*b*]quinoline (145) is described utilizing Wittig reaction and one-pot reduction–cyclization–dehydration method as the key steps.⁷⁶ By condensation of isatin (57) with (2-nitrobenzyl)-triphenylphosphonium bromide (140) in CHCl₃ in the presence of Et₃N at room temperature for

3 h, the corresponding Wittig product, namely 3-(2nitrobenzylidene)indolin-2-one (141), was formed. Reduction of 141 with Fe/AcOH in the presence of a catalytic amount of HCl at 120 °C for 24 h gave 6*H*-indolo[2,3-*b*]quinoline (145) in 77% yield (Scheme 39). In the last step, reduction of NO₂ group followed by isomerization of C–C double bond, cyclization and then dehydration took place in one-pot to afford the aromatized tetracyclic product 145 through intermediates 142–144.

A facile synthesis of 6H-indolo[2,3-*b*]quinolines **145** utilizing a Perkin reaction followed by a one-pot double reduction, double cyclization and isomerization has been reported by Tilve *et al.*⁷⁷ Condensation of *o*-nitrobenzaldehyde (**146**) with *o*-



Scheme 33 Proposed mechanistic pathway





Scheme 34 Synthesis of indolo[2,3-b]quinolines 111 via Heck–Suzuki coupling and DDQ-mediated C–H amination.

nitrophenyl-acetic acid (147) in the presence of Ac_2O and Et_3N under reflux for 5 h afforded the corresponding 2,3-bis(2nitrophenyl)acrylic acid (148), which on esterification gave the ester 149. Reduction of 149 with Fe/AcOH in presence of HCl at 120 °C for 24 h furnished the required 6*H*-indolo[2,3-*b*]quinoline (145) in 74% yield (Scheme 40). In this step, four reactions had happened in a tandem manner, that is, reduction of both the NO_2 groups, cyclization, isomerization of the intermediate *E*-amide to the *Z*-amide followed by a second cyclization.

An easy and one-pot procedure for the synthesis of a series of novel 6H-indolo[2,3-*b*]quinolines **150** with different substituents on quinoline ring was reported by Parvatkar *et al.*⁷⁸ This



Scheme 35 A suggested mechanism for the DDQ-mediated oxidative C-H cycloamination.



Scheme 36 A novel approach for the synthesis of 5-methyl-5H-indolo[2,3-b]quinoline (127).



Scheme 37 A four-step formal synthesis of 5-methsyl-5*H*-indolo[2,3-*b*]quinoline (127).



Scheme 38 Synthesis of 6-methyl-6*H*-indolo[2,3-*b*]quinolines 139 via one-pot reduction-cyclization-dehydration reactions of α -hydroxy lactams 136.

synthetic method involves refluxing of indole-3carboxyaldehyde (96) (1 equiv.) with aryl amines 97 (2 equiv.) in diphenyl ether in the presence of a catalytic amount of I_2 (0.1 equiv.) for 12 h to afford 6*H*-indolo[2,3-*b*]quinolines 150 in 38– 45% yields (Scheme 41). A suggested mechanism for the formation of **150** is given in Scheme 42.

In 2010, Haddadin and his co-workers⁷⁹ have described a highly efficient, easy and three-step protocol for the synthesis of biologically active 6H-indolo[2,3-*b*]quinolines **162**. An



Scheme 39 A short and convenient method for the synthesis of 6H-indolo[2,3-b]quinoline (145).



Scheme 40 A new synthesis of 6H-indolo[2,3-b]quinolines 145



optimized route to **162** is outlined in Scheme 43. Condensation of *o*-aminobenzaldehydes **158** with *o*-nitroaryl acetonitriles **159** in refluxing methanolic KOH afforded a series of novel 2-amino-3-(2-nitroaryl)quinolines **160**. Reduction of **160** with Zn/AcOH afforded the corresponding 3-(2-aminoaryl)quinolin-2-amines **161**. Diazotization of **161** followed by intramolecular cyclization under acidic conditions gave the desired tetracyclic 6*H*indolo- [2,3-*b*]quinolines **162** in 54–79% yields (Scheme 43).

A convenient method for preparation of 6H-indolo[2,3-*b*] quinolines **150** utilizing ruthenium-exchanged FAU-Y zeolite (RuY) as a recyclable heterogeneous catalyst is reported.⁸⁰ Reaction of indole-3-carbaldehyde (**96**) (1 equiv.) with aryl amines **97** (1 equiv.) in refluxing dioxane in the presence of Ru³⁺ exchanged FAU-Y zeolite (RuY, 0.1 g, activated at 550 °C for 3 h) for 4–6 h gave 6H-indolo[2,3-*b*]quinolines **150** in 50–65% isolated yields (Scheme 44). A mechanism for the RuY catalyzed formation of the 6H-indolo[2,3-*b*]-quinolines **150** is outlined in Scheme 45.

Seidel *et al.*⁸¹ have described a new acid-catalyzed indole annulation with secondary aminobenzaldehydes **163** for the rapid and one-step synthesis of neocryptolepine and various analogues, a bioactive materials as promising lead for new antimalarial agents. Condensation of **163** with indoles **164** in the presence of one equivalent of *para*-toluene sulfonic acid (*p*-TSA) in EtOH under reflux gave neocryptolepine analogues (5-methyl-5*H*-indolo[2,3-*b*]-quinolines) **165** in 56– 77% yields (Scheme 46). Condensation of **163** with **164** is expected to form azafulvenium ion **166** which undergoes direct ring-closure to furnish **167**. Subsequent oxidation of **167** completes the synthesis of the desired products **165** (Scheme 47). Interestingly, the oxidized products **165** were obtained directly and the putative intermediate **167** was not isolated, presumably because it undergoes facile oxidation by air.

A simple and concise two-step approach for the synthesis of 6H-indolo[2,3-*b*]-quinolines **171** is reported using an alkylation of 1H-indoles **164** at its more reactive 3-position and domino reduction–intramolecular cyclization–aromatization approach.⁸² Alkylation of indoles **164** was performed using 2-nitrobenzyl bromide (**168**) in the presence of methylmagnesium bromide (MeMgBr), as the base, in a mixture of acetone– H_2O (4 : 1) at 80 °C for 40 h to yield 3-(2-nitrobenzyl)-1*H*-indoles **169**. Reductive cyclization of **169** with triphenylphosphine in refluxing diphenyl ether for 4–6 h provided the tetracyclic compound **170**, which underwent oxidation followed by aromatization under reaction conditions to give the desired products **171** in 55–63% yields (Scheme 48). A suggested mechanism for the formation of **171** is depicted in Scheme 49.

An efficient and straightforward synthesis of 6H-indolo[2,3*b*]quinolines **173** in one-pot by alkylation–dehydration–cyclization–aromatization method utilizing pivalic acid with indoles **164** and *o*-aminobenzaldehyde (**172**) is described by Kadam and Tilve.⁸³ Thus, refluxing **164** with **172** in the presence of pivalic acid in Ph₂O for 6 h gave the tetracyclic 6H-indolo[2,3-*b*]quinolines **173** (Scheme 50). In the proposed reaction mechanism, the alkylation of **164** with **172**, followed by dehydration and

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Scheme 42 Postulated mechanism for the formation of 150.

 R_4 CHO R_4 R₁ MeOK / MeOH NC + NO₂ reflux 5 h R_2 NH_2 R_2 NH₂ O_2N Ν 159 160 R_3 Ŕ3 158 Zn / AcOH R_4 R R NaNO₂ ΝH₂ HCI / MeOH R_2 R_2 NH₂ Ν 161 k₃ Ŕ₃ 162 (54-79% yields) Scheme 43 Route toward the synthesis of 162.

cyclization gives dihydroindolo-quinoline intermediate 178, which oxidizes under reaction conditions to furnish the final product indoloquinolines 173 (Scheme 51).

A facile and iron-mediated synthesis of 6H-indolo[2,3-b] quinolines 180 by reaction of 2-amino-a-phenylbenzene methanol 179 and various indoles 90 was developed by Wang et al.84







Scheme 45 Proposed mechanistic pathway for the RuY catalyzed formation of 6H-indolo- [2,3-b]quinoline 150.

This synthetic approach proceeded by heating a mixture of **179** (1.5 equiv.), **90** (1 equiv.) and FeCl₃ (2.5 equiv.) in MeOH at 80 $^{\circ}$ C for 2 h (Scheme 52). In the present study, the target products

have been prepared through a new approach in 34-83% yields. When the metal salt was replaced with FeCl₂ or absent, the desired products **180** were not obtained. This indicated that



Scheme 46 One-step synthesis of 5-methyls-5*H*-indolo[2,3-*b*]quinolines 165.



Scheme 47 Proposed synthesis of 5-methyl-5*H*-indolo[2,3-*b*]quinolines 165.

 $FeCl_3$ played the role of an oxidant in the process of reaction rather than the function of catalysis. The authors also studied the influence of electronic effects on these reactions. The indoles bearing electron-withdrawing groups (EWG) on the benzene ring (R_2) seemed to be less efficient than electrondonating groups (EDG) and resulted in low yields. A mechanism for the iron-promoted synthesis of 6*H*-indolo[2,3-*b*] quinolines **180** is proposed as shown in Scheme 53. Firstly,



Scheme 48 A concise synthesis of 6H-indolo[2,3-b]quinolines 171.





Scheme 50 A pivalic-acid assisted one-pot alkylation-dehydration-cyclization-aromatization method for the synthesis of 6*H*-indolo[2,3-*b*] quinolines 173.



Scheme 51 A plausible mechanism for the synthesis of 6H-indolo[2,3-b]quinolines 173.

FeCl₃ may activate **179** to give intermediate **I**, which undergoes the Friedel–Crafts reaction to furnish intermediate **II**. The latter intermediate **II** undergoes intramolecular cyclization to afford intermediate **III**, which subsequently undergoes deprotonation and oxidation by FeCl₃ to afford the desired product **180**.

In 2016, Shi and Wang⁸⁵ have developed an environmentally friendly and efficient Rh(\mathfrak{m})-catalyzed synthetic approach for 6H-indolo[2,3-*b*]quinolines **182** from various indoles **90** and benzo[*c*]isoxazole (**181**) using H₂O as an efficient solvent. This annulation procedure undergoes tandem C–H activation, cyclization, and condensation steps. The reaction was carried out by reacting 1-(pyridin-2-yl)-1*H*-indoles **90** (1.0 equiv.) with **181** (1.5 equiv.) in the presence of a catalytic amount of $[Cp*RhCl_2]_2$ (5 mol%), AgSbF₆ (20 mol%) and AcONa (0.4 equiv.) in H₂O at 100 °C under Ar atmosphere for 12 h. The methodology furnished the desired tetracyclic **182** in 59–94% yields (Scheme 54). A control experiment showed that both $[Cp*RhCl_2]_2$ and AgSbF₆ were essential catalyst system for this transformation as their omission led to no formation of tetracyclic product **182**. In this work, the authors investigated the effect of additives in the present reaction and they have noted



Scheme 52 Iron-promoted synthesis of 6H-indolo[2,3-b]quinolines 180 from the reaction of 179 with different indoles 90.



Scheme 53 Postulated mechanism for the construction of indolo[2,3b]quinolines 180 from 179 and 90.

that the use of AcONa gave the best result as the yields of products **182** were increased. The mechanistic pathway for the reaction of **90** with **181**, using Rh(m) as a catalyst, is outlined in Scheme 55. First, indoles **90** reacted with Cp*Rh(m) *via* directed

C-H cleavage to give intermediate **I**. The coordination of **181** to **I** yields intermediate **II**. Subsequently, the migration insertion of the coordinated **181** into the Rh–C bond gives intermediate **III**. Protonation of **III** provides the further intermediate **IV** and releases the Rh(m) species for the next catalytic cycle. Finally, the latter intermediate **IV** undergoes intramolecular cyclization *via* elimination of one molecule of H₂O to afford the final product **182**.

Yin *et al.*⁸⁶ developed a facile and efficient method for the synthesis of 6-substituted 6H-indolo[2,3-*b*]quinolines **185** from isoindigo derivatives **184**, prepared from isatins 57 and indolin-2-ones **183**, in the presence of SnCl₂, in combination with AcOH/HCl under heating at 120 °C for 12–24 h in moderate yields (60–74% yields) (Scheme 56). Pyrrole and pyridine rings are synchronously constructed in one-pot for these tetracyclic products. A possible reaction mechanism for the formation of **185** is presented as shown in Scheme 57. First, reduction of the carbon–carbon double bond in **184** by SnCl₂ in an acid medium affords the saturated 1,4-diketone intermediate **185**. Hydrolysis of the amide bond of **185**, followed by a decarboxylation yields the further intermediate **187**. Subsequent intramolecular cyclization/aromatization furnishes the target tetracyclic molecule **185** *via* intermediate **188**.

In 2017, Challa *et al.*⁸⁷ reported an efficient metal-free method for the synthesis of indolo[2,3-*b*]quinolines **190** under



Scheme 54 Rh(III)-catalyzed C-H amination/annulation of substituted indole derivatives 90 with 181.





Scheme 55 Plausible catalytic cycle.

DDQ-mediated oxidative conditions from the easily accessible 3,3'-diindolylmethanes (DIMs). Treatment of 3,3'-diindolylphenylmethanes (DIPMs) **189** with DDQ (3 equiv.) at room temperature for <5 min using DCM or DMF as the solvent afforded the desired indolo[2,3-b]quinolines **190** in 51–100% yields (Scheme 58).



Scheme 56 Synthesis of 6-substituted-6H-indolo[2,3-b]quinolines 185 from isoindigo derivatives 184 in the presence of SnCl₂ in acidic media.



Scheme 57 A possible reaction mechanism for the formation of 6-substituted-6H-indolo-[2,3-b]quinolines 185.



A clean and expeditious microwave-mediated one-pot methodology for the synthesis of a series of 6H-indolo[2,3-*b*] quinolines **98** using eco- and user-friendly bismuth-nitrate [Bi(NO₃)₃·5H₂O] as a catalyst under mild reaction conditions is reported.⁸⁸ A mixture of indole-3-carboxyaldehyde **96** (1 equiv.), aryl amines **97** (2 equiv.) and Bi(NO₃)₃·5H₂O (10 mol%, 0.1 equiv.) in tightly sealed vessel under solvent-free condition were irradiated in microwave at 60 °C (300 W) for 3–5 min to provide different linear 6H-indolo[2,3-*b*]quinolines **98** in good yields (52–61% yields) (Scheme 59). Aryl amines containing electron-withdrawing or electron-donating groups and heteroaryl moiety are compatible with these reaction conditions yielding the desired tetracyclic products in good yields within short period of time. In contrast to all available approaches, this is the fastest method reported so far for the synthesis of linear indolo[2,3-*b*]quinolines. A proposed mechanism for the Bi(m)-



Scheme 59 Microwave-mediated Bi(NO₃)₃-catalyzed synthesis of indolo[2,3-b]quinolines 98



Scheme 60 Plausible reaction mechanism for Bi(III)-catalyzed synthesis of indolo[2,3-b]-quinolines 98 through activation of the *in situ* formed imine.

catalyzed for the formation of the indolo[2,3-*b*]quinolines **98** is given in Scheme 60.

2.2.2. Indolo[3,2-*c*]quinolines. The synthesis and cytotoxic activity evaluation of 5,11-dihydro-6*H*-indolo[3,2-*c*]quinolin-6 ones **193** were reported by Chen and his co-workers⁸⁹ in 2002. The starting 4-hydrazinoquinolin-2(1*H*)-ones **191** were synthesized by refluxing 4-hydroxy-quinolin-2(1*H*)-ones **66** with hydrazine hydrate in ethoxyethanol as a solvent. Stirring **191** with cyclohexanone (**129**) in glacial AcOH at room temperature afforded the corresponding hydrazones **192**. The thermal Fischer indolization of **192** followed by the dehydrogenation

gave the fused heterocyclic compounds **193**, in good yields (Scheme 61).

Molina *et al.*⁹⁰ have developed a new, simple and general methodology for the synthesis of indolo[3,2-c]quinolines **197–199**, bearing an amino, oxygen, or a sulfur atom at the 5-position. This approach based on the aza-Wittig type reaction of iminophosphoranes with hetero-cumulenes to afford the 2-azahexatriene moiety containing a cumulated double bond at one end and the C=C bond of the pyrrole ring at the other, which subsequently underwent ring closure to give the fused tetracyclic products **197–199**. Thus, iminophosphorane **195**, which was obtained from 2-(*o*-aminophenyl)indole (**194**) and



Scheme 61 Synthesis of 5,11-dihydro-6H-indolo[3,2-c]quinolin-6-ones 193.



Scheme 62 A new methodology for the synthesis of indolo[3,2-c]quinolines 197-199

triphenylphosphine dibromide, reacted with aromatic isocyanates, (1:2) molar ratio, in dry CH₂Cl₂ at room temperature for 12 h to afford the new tetracyclic 5-[*N*-aryl-*N*(arylcarbamoyl)]amino-11*H*-indolo[3,2-*c*]quinolines **197** in 79–96% yields (Scheme 62). The compounds **197** when heated in EtOH at reflux temperature for 12 h, they underwent elimination of the isocyanate to give 5-arylamino-11H-indolo[3,2-c]quinolines **199** in 78–91% yields (Scheme 62). The authors believed that the



Scheme 63 A one-pot procedure for the synthesis of 6-aryl-11H-indolo[3,2-c]quinolines 203.



Scheme 64 A plausible reaction mechanism for the formation of 203.

mechanism of the conversion of **195** into **197** involves initial aza-Wittig reaction to afford a carbodiimide **196**, as highly reactive intermediate, which underwent electrocyclic ring closure followed by 1,3-H shift with concomitant addition of the formed exocyclic NH group to the second molecule of the

isocyanate. On the other hand, treatment of iminophosphorane **195** with an excess of CO_2 at 90 °C in a sealed vessel or CS_2 in toluene at 90 °C led to the formation of indolo-[3,2-*c*]quinolin-6-one **198a** and indolo[3,2-*c*]quinolin-6-thione **198b** in 83 and 94% yield, respectively (Scheme 62).



Scheme 65 A convenient synthesis of 6-substituted-11-methyl-11H-indolo[3,2-c]quinolines 205, 206 and 208.



Scheme 66 Synthesis of D-ring substituted 11*H*-indolo[3,2-*c*]quinolines 212 *via* auto-tandem Pd-catalyzed intermolecular C–N and intramolecular C–C bond formation.



Scheme 67 Reductive cyclization of 2-(2-nitrophenyl)indoles 213 to indolo[3,2-c]quinolines 214.

A one-pot and highly efficient procedure for the preparation of 6-aryl-11*H*-indolo[3,2-*c*]quinolines **203** *via* Pd-catalyzed carbonylative cyclization of *o*-(*o*-aminophenyl)-ethynyltrifluoro acetanilide **200** with aryl iodides **201** followed by the cyclization of the resultant 3-aroylindoles **202** was described.⁹¹ By reaction of **200** with **201** in the presence of a catalytic amount of Pd(Ph₃P)₄ and K₂CO₃ in MeCN at 50 °C for 24 h, under a balloon of carbon monoxide, the corresponding *N*-(2-(3-aroyl-1*H*-indol-2-yl)phenyl)-2,2,2-trifluoro-acetamides **202** were obtained, *in situ*, which underwent basic hydrolysis followed by intramolecular cyclization to give the desired indolo[3,2-*c*]quinolines **203** in 35–86% yields (Scheme 63). A suggested mechanism for the formation of **203** is illustrated in Scheme 64.

A convenient synthetic method for the synthesis of 11*H*indolo[3,2-*c*]quinolines carrying a different substituents at the 6-position, by electrophile-mediated cyclization reactions of 2-(2-isocyanophenyl)-1-methyl-1*H*-indole (**204**), was reported by Kobayashi and his group⁹² in 2005. Treatment of **204** with various aldehydes (or ketones) and acetals in the presence of a catalytic amount of boron trifluoride–diethyl ether (BF₃–OEt₂) in CH₂Cl₂ at 0 °C for 30 min afforded 6-(1-hydroxy)-11-methyl-11*H*-indolo[3,2-*c*]quinolines **205** and 6-(1-ethoxyalkyl)-11methyl-11*H*-indolo[3,2-*c*]quinolines **206**, respectively, in moderate to good yields (Scheme 65). However, the reaction of **204** with iminium salts **207** was carried out in the absence of catalyst in CH_2Cl_2 at 0 °C for 10 min to give 6-dimethylaminomethyl-11-methyl-11*H*-indolo[3,2-*c*]quinolines **208** in moderate to excellent yields.

Maes and his group⁹³ have developed the first synthesis of Dring substituted 11*H*-indolo[3,2-*c*]quinolines 212 *via* autotandem Pd-catalyzed intermolecular carbon–nitrogen and intramolecular carbon–carbon bond formation. The reaction was carried out by heating 4-chloroquinoline (209) (2 mmol) with a wide variety of *o*-chloroanilines 210 (2.4 mmol) in the presence of Pd₂(dba)₃ (2.5 mol%), P(*t*-Bu)₃ (10 mol%) and K₃PO₄ (20 mmol) in dioxane at 125 °C for 24 h to give 11*H*-indolo[3,2-*c*] quinolines 212 in 50–82% yields, *via* intermediacy of 211 (Scheme 66). In the present work, the authors also reported that amine 211 is certainly an intermediate since TLC and MS analyses clearly revealed its presence during the process of the reaction and this reaction requires Pd catalysis since omitting the catalyst gave no 211 and 212.

A simple and new synthesis of indolo[3,2-c]quinolines **214** *via* reductive cyclization of a series of 2-(2-nitrophenyl)indoles **213** was reported.⁹⁴ Treatment of **213** with Fe in AcOH under reflux for 5 min gave directly 11*H*-indolo[3,2-*c*]quinolines **214**, in one step, in high yields (Scheme 67). In the proposed reaction mechanism, the reduction of NO₂ group gave the corresponding



aniline intermediate **I**, which underwent intramolecular Michael addition to afford the intermediate 6-acetonyl-5,6dihydro-11*H*-indolo[3,2-*c*]quinolines **II**. The aromatization of **II**, *via* elimination of one molecule of acetone, gave the desired indolo-[3,2-*c*]quinolines **214** (Scheme 68). The authors also reported that the reaction has a general character, electron-withdrawing halide substituents as well as electron-donating alkoxy and alkyl groups have no significant effect on the yields of products **214**.

In 2014, Inokuchi *et al.*⁹⁵ reported the synthesis of a new series of 6-amino-11*H*-indolo[3,2-*c*]quinolines **218**, with different substituents on the quinoline ring, utilizing isatins **57** and 2-aminobenzylamine (**215**) as starting materials. Thus, the reaction of **57** with **215** in AcOH under reflux for 8–20 h provided the 6-dihydro-11*H*-indolo[3,2-*c*]quinoline-6(5*H*)-ones **216**. Dehydrative chlorination of **216** was accomplished in POCl₃ at 130 °C for 8 h to afford the corresponding 6-chloro-11*H*-indolo

[3,2-c]quinoline **217**. The 6-chloro compounds **217** when heated with the appropriate amines at 90–140 °C within 20 min to 4 h, they underwent the addition–elimination reaction of the anilines and alkyl amines to produce the new 6-amino-11*H*-indolo[3,2-*c*]quinolines **218** in 35–97% yields (Scheme 69).

A convenient and highly selective synthesis of 11*H*-indolo [3,2-*c*]quinolines **221** through Cu-catalyzed one-pot two-step cascade reactions of 2-(2-bromoaryl)-1*H*-indoles **219** with alde-hydes **220** and aq. NH₃ was developed by Guo *et al.*⁹⁶ in 2015. First, indoles **219** were treated with **220** and aq. NH₃ in the presence of CuI, K₂CO₃, and L-proline under nitrogen at 100 °C for 12 h. Then, the reaction mixture was acidified with HCl and stirred at 120 °C for 8 h under air to provide the required tetracyclic product **221** in modest to good yields (32–81%) (Scheme 70). A mechanism for the Cu-catalyzed formation of **221** is outlined in Scheme 71. For aldehydes **220**, it was found that alkenyl- and aryl-substituted aldehydes usually afforded the



Scheme 69 Synthesis of 11H-indolo[3,2-c]quinolines 218 with amino group substituted at the C-6 position.



Scheme 70 $\,$ One-pot two-step synthesis of 221 from 219, 220 and aq. $\rm NH_{3.}$

products **221** in yields higher than alkyl-substituted aldehydes. For indoles **219**, different substituents (R_1 and R_2 group) exhibited a slight influence on the yields of the products **221**.

In 2017, Langer *et al.*⁹⁷ have developed a new and convenient synthesis of 11-aryl-11*H*-indolo[3,2-*c*]quinolines **224** by chemoselective Suzuki reaction of *o*-dihalo-quinolines with *o*-bromophenylboronic acid, followed by double carbon–nitrogen coupling

with primary amines. The chemoselective Suzuki reaction of 3,4dihalo-2-methylquinolines **222** with *o*-bromophenylboronic acid in the presence of Pd(PPh₃)₄ (5 mol%) and Na₂CO₃ (2 equiv.) in DMF/ H₂O (10:1) at 100 °C for 24 h afforded 3-(2-bromophenyl)-4chloro-2-methylquinoline (**223**). Heating **223** with various electron-poor, -neutral and -rich arylamines **97** (1.5 equiv.) in the presence of Pd₂dba₃ (5 mol%), PtBu₃·HBF₄ (10 mol%), and



Scheme 71 Plausible mechanism for the formation of 221.









Scheme 74 A plausible mechanism for the formation of 227 from 225 and 226.

NaO^tBu (2.4 equiv.) in toluene at 100 °C for 14–24 h furnished the novel tetracyclic indolo[3,2-c]-quinolines **224** in 83–97% yields (Scheme 72). In this approach, the substituents located at the 11

position are installed directly, thereby avoiding the problem of selectivity in the alkylation of the 11-unsubstituted heterocyclic compounds.



Scheme 75 Synthesis of indolo[3,2-c] quinolines 230 via PPA-mediated cyclization reaction between 228 and 229.



In the same year, Sanz et al.98 have reported a novel domino nitro reduction, imine formation, intramolecular cyclization, oxidation for the efficient, clean and one-pot synthesis of indolo [3,2-*c*]quinolines 227 from easily available nitrobenzenes as the nitrogen source and glycols as the carbonyl source and reducing agents. The process utilizes the carbonyl byproduct of the initial dioxomolybdenum(vi)-catalyzed reduction of nitrobenzenes with glycols as a reagent for the imine generation. This method represents the first sustainable domino reaction in which the waste byproduct of a reaction has been used as a reactant for the next step and included into the final product. This synthetic method proceeded by treatment 2-(2-nitrophenyl)indole (225) (1 equiv.) with secondary glycols 226 (2.2 equiv.) in the presence of a catalytic amount of a dioxomolybdenum(vi) complex and PTSA (25 mol%) in DMA as solvent and under MW irradiation at 180 °C for 30 min to give the new indolo[3,2-c]quinolines 227 in high yields (Scheme 73). A suggested mechanism for the synthesis of 227 is outlined in Scheme 74.

Very recently, Aksenov and his coworkers99 have reported a one-pot synthesis of indolo[3,2-c]quinolines 230 via PPAmediated unexpected cyclization reaction between 2-(2-aminophenyl)indoles 228 and 2-nitrostyrene (229). The reaction was carried out by heating a mixture of 228 and 229 in PPA (80%) at 90-95 °C for 90 min (Scheme 75). The mechanistic pathway for the formation of 230 via cyclization of 228 with 229 is given in Scheme 76. The reaction of 228 with 229 gave the nitroalkane intermediate I. In the PPA medium, nitroalkane I is exist in the phosphorylated aci form II, with a highly electrophilic C=N bond, which underwent intramolecular N-Nef reaction to provide the corresponding cyclic aminal intermediate III. Subsequent elimination of H₃PO₄ afforded cyclic imidoxime intermediate IV. The latter IV was protonated in acidic medium to give intermediate V, which further underwent a sevenmembered ring cleavage (Werner rearrangement) to provide N-cyano-aniline VI. A subsequent 6-endo-trig cyclization of the resulting VI involving the iminium moiety of the indole to yield



Scheme 77 Pd-catalyzed synthesis of benzofuro[3,2-c]quinolin-6(5H)-ones 233.



Scheme 78 Synthesis of 6H-chromeno[4,3-b]quinoline-6-ones 236.

the indoloquinoline core in the form of *N*-cyano-ammonium **VII**. The elimination of HCN afforded 5H-indolo[3,2-*c*] quinolin-11-ium ion **VIII**, which underwent deprotonation, under basic conditions during the post-reaction work-up, to afford the desired tetracyclic indolo[3,2-*c*]quinolines **230**.

2.2.3. Benzofuro[3,2-*c*]quinolines. The synthesis of certain benzofuro[3,2-*c*]quinolin-6(5*H*)-ones **233** *via* Pd-catalyzed cyclodehydrogenation of 4-hydroxy-3-phenyl-quinolin-2(1*H*)-ones **232** was reported.⁸⁹ Fusion of diethyl 2-phenylmalonate (**231**) with anilines **97** at 250–350 °C leading to the formation of **232**. Refluxing **232** in diphenyl ether in the presence of a catalytic amount of Pd/C (10%) gave the respective tetracyclic products **233**, in low yields (27–36%) (Scheme 77).

2.2.4. Chromenoquinolines. Buu-Hoi *et al.*¹⁰⁰ have reported the first synthesis of 6*H*-chromeno[4,3-*b*]quinoline-6-ones 236, which are analogues of the carcinogenic dibenzacridines and benzacridines, *via* reaction of 4-hydroxycoumarin (234) with paraformaldehyde and primary arylamines 97 (Scheme 78). The novel synthesis of this ring system has developed by Tabaković



Scheme 79 Synthesis of CFQ 237 and CFDQ 238.



Scheme 80 Possible mechanism for the formation CFDQ 238.



Scheme 81 Plausible mechanism for the formation CFQ 237 from CFDQ 238

*et al.*¹⁰¹ The reaction was carried by refluxing a 1 : 1 molar ratio of 234 with 2-aminobenzaldehyde in abs. EtOH in the presence of a catalytic amount of piperidine to give 2-((2-oxo-2*H*-chromen-4-yl)amino)benzaldehyde (235), which was converted to the tetracyclic products 236 (after refluxing 6 h) by losing a molecule of H₂O *via* formation of intramolecular Schiff base (Scheme 78).

A facile one-pot, three-component reaction of 4-hydroxycoumarin (234), aromatic amines 97 and aromatic aldehydes 220 using an environmentally benign bismuthtriflate $Bi(OTf)_3$ as a catalyst under neat and conventional heating conditions at 140 °C produced the coumarin fused quinoline (CFQ), namely 7-aryl-6*H*-chromeno[4,3-*b*]quinoline-6-ones 237, in 85–90% yields (Scheme 79). On the other hand, microwave (MW) assisted multicomponent reactions of the same combination in the presence of Bi(OTf)₃ as a catalyst in H₂O at 130 °C gave coumarin fused dihydroquinolines (CFDQ) 238, in 82–94% yields (Scheme 79).¹⁰² Authors also reported an alternative and rapid route for the synthesis of CFQ 237 by stirring CFDQ 238 in the presence of *N*-bromosuccinamide (NBS) in THF at room temperature (Scheme 79). The plausible mechanism for the formation of CFDQ 238 is described in Scheme 80. Initially,



scheme 83 Inree steps synthesis of 3,9-almethoxy-6,12-almyaro-6H-chromeno[4,3-b]-quinoline-7-one (24

aldehyde **220** condensed with aromatic amine **97** to form an imine **I**. Nucleophilic addition of **234** to intermediate **I** afforded an unstable intermediate **II**, which in equilibrium with intermediate **III**. Subsequent, 1,2-addition of the aromatic amines **97** to **III**, followed by 6π -electrocyclization and isomerisation yielded products (CFDQ) **238**. The formation of **237** can be explained *via* the formation of **238**, followed by free radical mechanism involving Bi(m)/Bi(0) as outlined in Scheme 81. The fluorescence property studies of the synthesized CFDQ **238** and CFQ **237** in different solvents showed that CFDQ **238** are more fluorescent than the CFQ **237**.

Plaskon *et al.*¹⁰³ have described a versatile and facile method for the synthesis of 7*H*-chromeno[3,2-*c*]quinolin-7-ones **240** utilizing chlorotrimethylsilane (TMSCl) as a potential promoter and water scavenger. On heating a solution of 4-oxo-4*H*chromene-3-carbaldehyde (**239**) and anilines **97** in the presence of TMSCl in DMF at 100 °C, the tetracyclic products **240** were obtained in 39–67% yields (Scheme 82).

The synthesis of 3,9-dimethoxy-6,12-dihydro-6*H*-chromeno [4,3-b]quinoline-7-one (245), as a new class of estrogen receptor β -selective ligands, was achieved in three steps as shown in Scheme 83. Reactions were carried out by heating 3-methoxyphenol (241) with 3-bromo-propanoic acid under basic



Scheme 84 Synthesis of 7-halogenated-6H-chromeno[4,3-b]quinolines 247 via Cu-catalyzed cascade reaction.

conditions at 100 °C for 3 h to give the corresponding 3-(3methoxyphenoxy)propanoic acid (242), which underwent intramolecular Friedel–Crafts acylation when treated with TfOH at 0 °C for 3 h to provide 7-methoxychroman-4-one (243). By condensation of 243 with 5-methoxyanthranilic acid (244) in diphenyl ether at 200 °C for 7 h, the desired tetracyclic product 245 was formed in 68% yield (Scheme 83).¹⁰⁴

In 2016, Bao *et al.*¹⁰⁵ have developed a new, efficient and convenient halogenation method to synthesize 7-halogenated chromeno[4,3-*b*]quinolines 247 through Cu-catalyzed cascade reactions (intramolecular aza-Diels–Alder reaction of Schiff base, followed by chlorination utilizing chloranil) (Scheme 84). The reaction was carried out by treatment Schiff base 246 (1 equiv.) with a mixture of Cu₂O (10 mol%), *p*-chloranil (*p*-CHL) (2 equiv.), and NaCl (1.5 equiv.), as an additive, in

dimethoxyethane (DME). The mixture was heated at 80 °C under a nitrogen atmosphere for 8 h to give the new tetracyclic product 247 in satisfactory yields (38–65%) (Scheme 84). In the proposed reaction mechanism, the reaction of Schiff base substrate 246 with a Cu(1) species in the presence of chloranil produced Cu(II) acetylide I, which undergoes intramolecular aza-Diels–Alder reaction to give intermediate II. The Cl radical originated from *p*-CHL reacts with intermediate II to afford intermediate III, which subsequently undergoes reductive elimination reaction to give a chlorinated intermediate IV and Cu(1) species. Oxidation of intermediate IV with *p*-CHL occurs to provide the desired tetracyclic product 247 (Scheme 85).

In the same year, Novák and his group¹⁰⁶ reported the development of a novel and highly modular Cu-catalyzed oxidative transformation for the construction of chromeno-



Scheme 85 A suggested mechanism for the formation of 247 from 246.







Scheme 87 A plausible mechanism for the formation of chromeno[4,3-b]quinolines 250 via arylation-cyclization reaction.





Scheme 89 Proposed mechanism for the formation of tetracyclic 252 from 251.

[4,3-*b*]quinolines **250**, starting from arylpropynyloxybenzonitriles **248** and arylmesityl-iodonium triflates **249**. Reaction of nitriles **248** with **249** in EtOAc in the presence of a catalytic amount of CuCl (10 mol%) at 75 °C for 30 min – 5 h afforded the polyfunctionally substituted chromeno[4,3-*b*]quinolines **250** in 35–85% yields (Scheme 86). A plausible mechanism was proposed (Scheme 87).



Scheme 90 One-pot synthesis of cyclopenta[b]pyrrolo[3,2-f]quinolins 255 and pyrrolo-[3,2-a]acridines 258 under catalyst-free conditions.



Scheme 91 Synthesis of benzopyrano[4,3-c]quinoline (262) from N-methylformanilide (259) and homophthalic acid (260).



Scheme 92 Synthesis of benzopyrano[4,3-b]quinoline derivatives 266 and 267.

Morris and Jackson¹⁰⁷ reported the Pd-catalyzed intramolecular cyclization of 2-[(3-substituted-phenoxy)methyl] quinolines **251** to prepare chromeno[3,4-*b*]quinolines **252**. The cyclization was carried out, under typical Heck conditions, by refluxing a mixture of appropriate quinoline **251** (1 equiv.), Pd(OAc)₂ (2 equiv.), triphenylphosphine (4 equiv.) and K₂CO₃ (20 equiv.) in CH₃CN for 6–12 h under an atmosphere of nitrogen (Scheme 88). It was found that compound **251** containing a strong electron-withdrawing groups on the phenoxy ring retarded the cyclization and no products were obtained after heating at reflux for a long time, while electron-donating groups increased the rate of the reaction and produced the desired products **252** in reasonable yields (40–58% yields). A proposed mechanism for the formation of tetracyclic chromeno [3,4-*b*]quinolines **252** from **251** is shown in Scheme 89.

2.2.5. Cyclopenta[*b*]pyrrolo[3,2-*f*]quinolines. A combinatorial synthesis of fused heterocyclic compounds, cyclopenta[*b*]pyrrolo[3,2-*f*]quinolin-9(3*H*)-ones **255**, 10-aryl-6,7,8,10-tetrahydrocyclopenta[*b*]pyrrolo[3,2-*f*]quinolin-9(3*H*)-ones **256** and 8,9-dihydro-8,8-dimethyl-11-aryl-3*H*-pyrrolo[3,2-*a*]acridin 10(6*H*,7*H*,11*H*)-ones **258**, *via* three-component reaction of 1*H*-indol-5-amine (**253**), aromatic aldehydes **220** and 1,3-dicarbonyl compounds **254**, **257**, under catalyst-free conditions, has been

reported by Zhou et al. in 2013.108 It was interesting that the designed reactions gave un-aromatized or aromatized products depending on the reaction temperature and the type of 1,3-dicarbonyl compounds. Treatment of aromatic aldehydes 220, 1Hindol-5-amine (253), and cyclopentane-1,3-dione 254 in refluxing DMF, without catalyst, resulted in the aromatized cyclopenta[b]pyrrolo[3,2-f]quinolin-9(3H)-ones 255, in high yields (83-92%). When the same reaction was carried out in refluxing EtOH, without catalysts, the un-aromatized 10-aryl-6,7,8,10-tetrahydrocyclopenta[b]pyrrolo[3,2-f]quinolin-9(3H)-ones 256 were obtained in 84-96% yields (Scheme 90). On the other hand, when 5,5dimethylcyclohexane-1,3-dione (dimedone) (257) was subjected to react with 220 and 253, under catalyst-free conditions, the unaromatized 11-aryl-8,9-dihydro-8,8-dimethyl-3H-pyrrolo[3,2-a]acridin-10(6H,7H,11H)-ones 258 were obtained, whether they were refluxed in DMF or EtOH (Scheme 90).

2.2.6. Benzopyranoquinolines. Meth-Cohn¹⁰⁹ has developed an approach for the synthesis of 12-methyl-6-oxo-11,12dihydro-6H-[2]benzopyrano[4,3-c]quinoline (262), in high yield. The reaction was accomplished by heating a mixture of *N*-methylformanilide (259) and homophthalic acid (260) in POCl₃ at 100 °C for 10 min to give 12-methyl-6-oxo-6H-[2]benzopyrano [4,3-c]quinolinium phosphorodichloridate (261). The salt 261



showed kinetic presence for attack at the quinoline α -position. Thus, reduction of **261** with sodium borohydride in ethyl acetate at room temperature produced the desired benzopyranoquinoline **262** Scheme 91).

Ullmann Jordan condensation reaction of 4-chlorocoumarins 263 with anthranilic acid (264) afforded 4-(2'-carbox-yphenylamino)-2*H*-[1]benzopyran-2-ones 265. When compounds 265 were heated with polyphosphoric acid (PPA) at 110 °C for 2 h, they underwent intramolecular cyclocondensation to furnish directly the tetracyclic ring system namely 7,12-dihydro-6*H*-[1] benzopyrano[4,3-*b*]quinoline-6,7-diones 266 in ~90% yields (Scheme 92). On the other hand, refluxing 265 with phosphoryl chloride (POCl₃) for 3 h afforded 7-chloro-benzo-pyrano[4,3-*b*] quinoline-6-ones 267 in ~80% yields (Scheme 92).¹¹⁰

2.2.7. Benzothiopyranoquinolines. In 2003, Junjappa and his coworkers¹¹¹ have reported a simple and highly efficient regioselective synthesis of new benzothiopyrano[2,3-*b*]quinolines **270** through TBTH/AIBN-mediated radical cyclization of the corresponding 3-(2-bromobenzoyl)-2-methylthioquinoline derivatives **268a**, **b**. As shown in Scheme 93, the reaction proceeded by heating a solution of **268a**, **b** (1 equiv.), TBTH (2.5

equiv.) and AIBN (catalytic) in toluene for 8–10 h under nitrogen atmosphere. The products were found to be not the tetracyclic quinolines **269**, but were characterized as the novel benzothiopyrano[2,3-*b*]quinolines **270a**, **b** on the basis of their spectral and analytical data. The proposed mechanistic pathway for radical cyclization of **268a**, **b** is outlined in Scheme 93. The initially formed *o*-benzoyl radical **271** undergoes radical translocation by attack on the methylthio group (MeS–) to afford radical intermediate **272**, which on loss of the methyl radical gives the benzothiopyranoquinolines **270a** and **270b** in quantitative and 98% yield, respectively.

2.2.8. Benzothienoquinolines. Deady *et al.*¹¹² reported a one-pot, two-component synthesis of benzothieno[3,2-*b*] quinoline-4,11-dicarboxylic acid (275), as a new class of putative topoisomerase inhibitors, by the reaction of isatin-7-carboxylic acid (273) and benzo[*b*]thiophen-3(2*H*)-one (274). The reaction takes place at 100 °C for 8 h using NaOH (10%) as a base delivering the benzo-thieno[3,2-*b*]quinolines 275 in 55% yield (Scheme 94).

In 2000, Rádl *et al.*¹¹³ developed a new procedure for the synthesis of benzothieno-[3,2-*b*]quinoline-11(5*H*)-one (**280**) in



88% yield, as shown in Scheme 95. Treatment of 2-mercaptobenzonitrile 276 with phenacylbromides 277a, **b** in DMF in the presence of K_2CO_3 at room temperature for 1 h gave the corresponding benzothiophenes 278, 279. When these compounds were stirred with NaH in DMF at room temperature for 2 h, they underwent intramolecular nucleophilic cyclization to provide the desired tetracyclic 280 (Scheme 95). In the same year, Zanardi *et al.*¹¹⁴ have devised a novel protocol for the one-pot construction of benzothieno[2,3-*b*] quinolines **284** based on a radical cascade reaction of the 2- (phenylalkynyl)aryl radicals **282** with some aryl isothiocyanates **283**. The aryl radicals **282** were easily generated upon portion-wise addition of the diazonium tetrafluoroborate **281** (1 equiv.) to a stirred pyridine solution of **283** (3 equiv.) at -10 to -20 °C. After one hour, the reaction mixture was normally subjected to







Scheme 97 Reaction mechanism for the formation of benzothieno[2,3-b]quinolines 284.



Scheme 99 A highly efficient synthesis of new benzothieno[3,2-b]quinolines 296 via the Pd-catalyzed reaction of 293 with 97.

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chromatographic separation to give the desired benzothieno [2,3-b]quinolines **284** in 30–60% yields (Scheme 96). The reaction mechanism for the formation of **284** is outlined in Scheme 97. The aryl radicals **282** attacks the sulfur atom of the isothiocyanate **283** giving α -sulfanylimidoyl radical **285**. Subsequent tandem 5-*exo-dig* cyclization onto the adjacent ethynyl moiety gave a linear 1-phenylvinyl radical **286**. The latter intermediate **286** underwent intramolecular 6-membered cyclization onto the isothiocyanate ring to give the benzothienoquinolines **284**, through the cyclohexadienyl radical **287**.

Zhu *et al.*¹¹⁵ in 2007, synthesized benzothieno[3,2-*b*]quinolines **292** by the reaction of anthranilic acid derivatives **265** with 2-(phenylthiol)acetyl chloride (**288**). In this reaction the substituted anthranilic acids **265** were acylated with **288** under basic conditions to give the intermediates **289**. These intermediates **289** then underwent a double intramolecular cyclization reaction with polyphosphoric acid (PPA) at 130 °C for 3 h to furnish benzothieno[3,2-*b*]quinoline-11(5*H*)-ones **290**. Chlorination of **290** with POCl₃ at 110 °C for 24 h provided the corresponding chloro compounds **291**, which hydrogenated in H₂ atmosphere on Pd/C (10%) in MeOH at room temperature to give the desired tetracylic benzothieno[3,2-*b*]quinoline derivatives **292** in 16–85% yields (Scheme 98).

Langer and his group,¹¹⁶ developed a highly efficient synthesis of new benzothieno-[3,2-*b*]quinolines **296** *via* the Pd-catalyzed reaction of 2-alkynyl-3-bromobenzothiophenes **293** with anilines **97**. When a mixture of **293** (1 equiv.), **97** (1.3 equiv.), Pd(OAc)₂ (10 mol%), Pd(*t*-Bu)₃·HBF₄ (20 mol%), KO-*t*-Bu (2 equiv.) and CuI (25 mol%) was heated in toluene at 105 °C for 12 h, the desired benzothieno[3,2-*b*]quinolines **296** were indeed produced in 60–70% yields *via* intermediates **294** and **295** (Scheme 99).

A new one-pot method for the synthesis of benzothieno[3,2*b*]quinoline (300) from the reaction of 3-bromobenzo[*b*] thiophene-2-carbaldehyde (297) with 2-aminophenylpinacolborane (298) under Suzuki coupling conditions utilizing a stereochemically hindered ligand, 2-(cyclo-hexylphosphane) biphenyl and Ba(OH)₂·8H₂O, as the base, was reported by Castanheira and co-workers¹¹⁷ in 2014. This synthetic approach proceeded by heating a mixture of **297** (1 equiv.), **298** (1 equiv.), Pd(AcO)₂ (5 mol%), 2-(cyclohexylphosphane)-biphenyl (20 mol%), Ba(OH)₂·8H₂O (3 equiv.) in dioxane at 100 °C for 5 h to give the tetracyclic product **300** in 30% yield (Scheme 100). The formation of **300** is assumed to proceed *via* a Pdcatalyzed C–N coupling followed by an intramolecular cyclization that probably occur by nucleophilic attack of the activated *ortho* position of the diarylamine intermediate **299** on the aldehydic carbonyl group, after deboronation (Scheme 100).

In 2009, Wang's group¹¹⁸ have developed a simple and efficient route for construction of several tetracyclic quinolines viz. benzo[f]pyrano[3,4-c]quinolines 305, benzo[f]thiopyrano[3,4-c] quinolines 306 and benzo[f]thieno[2,3-c]quinolines 307 via three-component reaction of aromatic aldehydes 220, naphthalene-2-amine (301) and heterocyclo-ketones 302-304, including tetrahydropyran-4-one 302, tetrahydrothiopyran-4one 303 and dihydro-thiophen-3(2H)-one 304, in THF catalyzed by molecular iodine (5 mol%) at reflux temperature (Scheme 101). The mechanism involves the condensation reaction between amine 301 and aromatic aldehydes 220 to form the imine I, which reacts with iodine to produce the activated intermediate II. The enol form of cyclic ketones 302-304 attacks the latter intermediate II to give intermediate III, followed by an intramolecular cyclization to produce IV. Subsequent dehydration of IV affords dihydroquinoline V, which then undergoes air auto-oxidation to produce aromatized tetracyclic quinolines 305-307 (Scheme 102).

2.3. Tetracyclic quinolines with three heteroatoms

2.3.1. Furothiopyrano[2,3-*b*]quinolines. Recently, Singh and his co-workers¹¹⁹ have reported a facile synthesis of tetracyclic, furothiopyrano[2,3-*b*]quinoline derivatives **312** *via* basefree I₂-catalyzed cyclization reactions of 3-homoallylquinoline2-thiones **311**. The starting 3-homoallylquinoline-2-thinoes **311** were prepared, in two steps, from reaction of 2-chloroquinoline-3-carbaldehydes **308** with allyl bromides **309** in DMF (Barbies reaction), followed by treatment with Na₂S in



Scheme 101 Molecular iodine catalyzed synthesis of fused tetracyclic quinolines 305-307.



Scheme 102 A plausible mechanism for the synthesis of products 305–307.



Scheme 103 Synthesis of furothiopyrano[2,3-b]quinolines 312 via iodocyclization of 3-homoallylquinolin-2-thiones 311.



Scheme 104 Plausible mechanism for the formation of furothiopyrano[2,3-b]quinolines 312.

DMF at room temperature (Scheme 103). The cyclization reaction of **311** with I_2 in THF at room temperature afforded the required tetracyclic quinoline, furothiopyrano[2,3-*b*]quinolines **312**, in 80–90% yields (Scheme 103). All reactions were completed under aerobic conditions. The plausible mechanism for the formation of tetracyclic furothiopyranoquinolines **312** is shown in Scheme 104. The electrophilic addition of I_2 to olefinic bond of 3-homo-allaylquinoline-2-thiones **311** leads to the formation of iodonium ion **313**, which undergoes intramolecular attack by sulfide anion to give the tricyclic intermediate **314**. Neighboring group participation of sulfur atom on 2-iodomethyl carbon atom in **314** gives the sulfonium salt intermediate **315**. Finally, sulfonium salt ring open by the hydroxy group to give the tetracyclic ring system **312**.

2.3.2. Quinoxalino[2,3-*b*]quinolines. In 2014, Che *et al.*¹²⁰ described a rapid synthesis of fused tetracyclic quinolines, 6,11-dihydroquinoxalino[2,3-*b*]quinolines **319**, a family of novel heterocycles with potential antitumor activity, *via* a sequential



Ugi-variant multicomponent reaction and Pd-catalyzed bisannulation in one-pot procedure. Reaction of cinnamic aldehydes **316**, two molecules of *o*-iodoanilines **317** and isocyanides **318** was carried out in MeOH at room temperature in the presence of *p*-toluenesulfonic acid (PTSA). The reaction mixture was then treated with $Pd_2(dba)_3$, 2-dicyclohexylphosphino-2'methylbiphenyl (Me-phos) and cesium carbonate (CsCO₃) in MeCN and refluxed to produce the desired tetracyclic 6,11dihydroquinoxalino-[2,3-*b*]quinolines **319**, in 36–61% yields (Scheme 105). It was found that the electronic properties of substituents on the aromatic ring of cinnamic aldehyde had no effect on the reactivity, while the anilines with either electronwithdrawing or electron-donating group showed a slightly lower reactivity.

2.3.3. Pyridoimidazoquinolines. Tetracyclic ring system combining an imidazo[1,2-a]pyridine skeleton condensed with a quinoline nucleus are stimulating increasing interests since they are close isosteres of a series of powerful antiproliferative compounds such as datelliptium, pazellipticine as well as ellipticinem.¹²¹

2.3.3.1. Pyrido[2',1':2,3]*imidazo*[4,5-*c*]*quinolines.* In 2015, Fan *et al.*¹²¹ developed a facile and unprecedented methodology



Scheme 107 Plausible mechanism for the formation of pyrido[2',1':2,3] imidazo[4,5-c]-quinolines 322.







Scheme 109 Proposed mechanism for the formation of pyrido[2',1':2,3]imidazo[4,5-b]-quinolines 326.

for the synthesis of pyrido[2',1':2,3]imidazo[4,5-c]quinolines 322 via Cu-catalyzed one-pot four-component sequential reactions of 2-aminopyridine (320), 2-bromophenacyl bromide (321), aldehydes 220 and aq. NH₃. The reactions were performed in three steps as shown in Scheme 106. (1) treatment of 320 with 321 in the presence of $K_3PO_4 \cdot 3H_2O$, as a base, in DMF at 80 °C for 4 h; (2) the reaction mixture was added with CuI, 1,10-phenanthroline (1,10-Phen) and aq. NH₃ and then stirred at 80 °C for 8 h; (3) finally, the resulting mixture was added with HCl and aldehydes 220 and then stirred at 80 °C under air for 4 h to produce the desired tetracyclic 322 in 35-63% yields. It was shown that phenyl substituted aldehydes with either electron-withdrawing or electron-donating substituents on the phenyl ring underwent this cascade process easily to furnish 322 in good yields. A plausible mechanism to account for the formation of 322 is suggested in Scheme 107. The reaction is presumed to take place by an initial condensation of 320 with **321** to afford 2-(2-bromophenyl)imidazo[1,2-a]pyridine (I). The following Cu-catalyzed amination of I with NH₃, as the nitrogen source, through intermediates II and III gives 2-imidazo[1,2-a]

pyridine-2-yl-phenylamine (**IV**). Condensation of **IV** with aldehydes **220** affords the corresponding imine intermediate **V**. The subsequent intramolecular nucleophilic cyclization of **V** affords **VI**, which then undergoes an oxidative dehydrogenation under these reaction conditions to give **322** as the final products.

2.3.3.2. Pyrido[2',1':2,3]imidazo[4,5-b]quinolines. Rahimizadeh et al.¹²² reported a new and efficient synthetic route for the synthesis of pyrido[2',1':2,3]imidazo[4,5-b]quinolines **326**, as novel tetracyclic ring system containing a quinoline nucleus which have strong fluorescence emission, utilizing (4substituted) (3-hydroxyimino-2,3-dihydroimidazo[1,2-a]pyridin-2-yliden)methyl cyanides **325** as starting materials. The key intermediates **325** were synthesized by refluxing 3-nitro-imidazo [1,2-a]-pyridine **323** with arylacetonitriles **324** in MeOH in the presence of KOH for 4 h in excellent yields (Scheme 108). Acylation of hydroxyl group in **325** with acetyl chloride led to heterocyclization and afforded highly fluorescent **326** in 90– 96% yields, *via* the intramolecular electrophilic aromatic substitution (Scheme 108). The proposed mechanism to explain the formation of **326** is shown in Scheme 109. Other reagents







Scheme 111 DBU-catalyzed synthesis of pyrido[2',1':2,3]imidazo[4,5-b]quinolines 330.



(78-94% yields)

Scheme 112 Acetic acid catalyzed synthesis of imidazo[1',2':1,2]pyrrolo[3,4-c]quinolin-11-ones 334 via cascade of reactions.





Synthesis of benzo[h]pyrimido[4,5-b]quinoline-8,10-diones 339 in ionic liquid.

such as POCl₃ and SOCl₂ act in same way but the products 326 were obtained in low yields.

A new strategy for the synthesis of pyrido[2',1':2,3]imidazo [4,5-b]quinoline (328) via a regioselective auto-tandem Pdcatalyzed inter- and intramolecular double Buchwald-Hartwig amination of 2-chloro-3-iodoquinoline (327) with aminopyridine (320) was reported.¹²³ When a mixture of 327 (1 equiv.), 320 (1 equiv.), Pd(OAc)₂ (4 mol%), XANTPHOS (4 mol%), Cs₂CO₃ (4 equiv.) in toluene was heated at 140 °C (pressure tube) under N2 atmosphere for 17 h, the tetracyclic 328 was obtained in 96% yield (Scheme 110).

Guillaumet et al.124 have developed a rapid and efficient metal-free method for the synthesis of pyrido[2',1':2,3]imidazo [4,5-b]quinolines 330 from 2-(arylethynyl)imidazo[1,2-a]pyridin-3-amines 329 catalyzed by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Microwave irradiation of 329 in 1,4-dioxane with a catalytic amount of DBU at 220 °C produced a series of unusual fused heterocyclic quinolines 330, in 65-97% yields (Scheme 111). A proposed reaction pathway for the formation of 330 is shown in Scheme 111. The electron rich secondary amines 329 assists in the hydroarylation of the triple bond after deprotonation by DBU. Next, aromatization produces the respective pyrido[2',1':2,3]imidazo[4,5-b]quinolines 330.

2.3.4. Imidazo[1',2':1,2]pyrrolo[3,4-c]quinolines. A simple and new synthetic route for the synthesis of imidazo[1',2':1,2]pyrrolo-[3,4-c]quinolin-11-ones 334 based on the cascade reaction of isatins with heterocyclic ketene aminals (HKAs) has developed by Yu et al.¹²⁵ in 2011. Refluxing a reaction mixture of isatins 57 and five-member heterocyclic ketene aminals (HKAs) 331 in toluene catalyzed by AcOH, forming the respective products 334 with good to excellent yields (78-94%) (Scheme 112). A suggested mechanism for the formation of 334 is shown in Scheme 112. At first, the α -C of 331 was added to the more electrophilic carbonyl center of 57 to furnish the intermediate 332. This intermediate underwent imine-enamine tautomerization, intramolecular cyclization, dehydration, and ringopening reactions to produce the further intermediate 333. Finally, protonation of 333 followed by intramolecular cyclization resulted in the formation of the target tetracyclic 334.

2.3.5. Cyclopenta[*c*]pyrazolo[4,3-*f*]quinolines. Α threecomponent imino Diels-Alder reaction of 1H-indazol-5-amine (335), aromatic aldehydes 220 and cyclopentanone in boiling THF catalyzed by molecular iodine led to the formation of a series of cyclopenta[c]pyrazolo[4,3-f]quinolines 336 in high vields (Scheme 113).126

2.3.6. Benzo[h]pyrimido[4,5-b]quinolines. Guo and Yu127 reported a three component reaction between 1-naphthylamine



Scheme 115 L-Proline mediated synthesis of benzo[g]pyrazolo[3,4-b]quinoline-5,10-diones 342.



Scheme 116 Proposed mechanism for the formation of benzo[g]pyrazolo[3,4-b]quinoline-5,10-diones 342.



 $\label{eq:scheme117} Scheme 117 \ \ A \ multistep \ synthesis \ of \ thieno[3',2':4,5] thieno[2,3-c] quinolones \ 347.$

(337), aromatic aldehydes 220 and barbituric acid (338) in ionic liquid [bmim]BF₄, as a green solvent, produced a novel tetracyclic 7-aryl-11,12-dihydrobenzo[h]pyrimido[4,5-b]quinoline-8,10(7H,9H)-diones 339, in 76–92% yields (Scheme 114).

2.3.7. Benzo[g]pyrazolo[3,4-b]quinolines. In 2014, Karamthulla and coworkers¹²⁸ have described a L-proline mediated synthesis of 2*H*-benzo[g]pyrazolo[3,4-b]quinoline-5,10(4*H*,11*H*)-diones 342, in 52–88% yields, *via* a three-component one-pot reaction of 3-aminopyrazoles 340, aldehydes 220 and 2-hydroxy-1,4-naphthoquinone (341) in boiling ethanol (Scheme 115). The plausible mechanism for the formation of 342 is shown in Scheme 116. The reaction proceeds *via* domino aldol reaction/Michael addition/intramolecular condensation/ tautomerism sequence to afford the desired products 342 regioselectively.

2.3.8. Thieno[3',2':4,5]thieno[2,3-*c*]quinolines. A multistep synthesis of novel thieno[3',2':4,5]thieno[2,3-*c*]quinolones 347 has been developed by Koružnjak *et al.*¹²⁹ Refluxing a solution of 5-substituted-thiophene-3-carboxaldehyde 343 and malonic acid in pyridine gave 5-substituted 3-(3-thienyl)acrylic acids 344. When 344 was heated with SOCl₂ in the presence of a catalytic amount of pyridine in chlorobenzene at 140 °C, they underwent cyclization to give the corresponding 3-chloro-thieno[2,3-*b*] thiophene-2-carboxyl chlorides 345. Reacting 345 with aniline derivatives 97 in refluxing toluene produced the 3-cholorothieno[2,3-*b*]thiophene-2-carboxamides 346, which were photochemically dehydrohalogenated at room temperature to

afford the respective tetracyclic **347**, in 31–76% yields (Scheme 117). The products **347** showed cytostatic activities against malignant cell lines and marked antitumor activity.

2.4. Tetracyclic quinolines with more than three heteroatoms

Since twenty-six years ago, Mekheimer and his group have developed different successful routes for the synthesis of a new tetracyclic systems containing the quinoline nucleus of biological importance utilizing for the first time 2,4-dichloroquinoline-3-carbonitrile (**348**) as a good precursor. It is well known that the chlorine atom at C-4 in **348** is more reactive than that at C-2 and is more easy to displace using nucleophiles.¹³⁰⁻¹³⁴

2.4.1. 1-Thia-3,5,6-triazaaceanthrylenes and 1-thia-3,4,5,6-tetraazaaceanthrylenes. Mekheimer *et al.*¹³⁵ have reported the synthesis of novel tetracyclic ethyl 5-alkyl-5*H*-1-thia-3,5,6-triazaaceanthrylene-2-carboxylates and ethyl 5-alkyl-5*H*-1-thia-3,4,5,6-tetraaza-aceanthrylene-2-carboxylates using ethyl 3-amino-4-chloro-thieno[3,2-*c*]quinoline-2-carboxylate (**350**) as starting material, which was prepared from reaction of **348** with ethyl 2-mercaptoacetate (**349**) in DMF in the presence of TEA at room temperature in 98% yield (Scheme 118). Refluxing **350** in an excess of primary alkylamines furnished **351** in 70–75% yields, which were treated with an excess of TEO at reflux temperature to afford the angularly annulated tetracyclic ethyl 5-alkyl-5*H*-1-thia-3,5,6-triazaaceanthrylene-2-carboxylates **352**



Scheme 118 Synthesis of ethyl 5-alkyl-5H-1-thia-3,5,6-triazaaceanthrylenes 352–354, 357 and ethyl 5-alkyl-5H-1-thia-3,4,5,6-tetraazaa-ceanthrylenes 355.



in 72–88% yields (Scheme 118). In contrast to the other amines, when **350** was reacted with excess of benzylamine, thieno[3,2-*c*] quinoline derivative **356** was obtained, as a viscous oil, which was refluxed with TEO to give 1-thia-3,5,6-triazaaceanthrylenes **357** in 64% yield (Scheme 118). Refluxing **351** with ethyl chloroformate and phenyl isothiocyanate furnished the new tetracyclic **353** and **354** in 86–96% and 78–83% yields, respectively. On the other hand, diazotization of **351** with NaNO₂ in H₂SO₄ (70%) at -5 °C gave the novel ethyl 5-alkyl-5*H*-1-thia-3,4,5,6-tetraazaaceanthrylene-2-carboxylates **355** in 73–89% yields (Scheme 118).

2.4.2. 1,2,3,5,6-Pentaazaaceanthrylenes. In 2003. Mekheimer et al.¹³⁶ described the synthesis of new tetracyclic ring systems combining both a pyrimidine and a pyrazoloquinoline moieties starting from 3-amino-4-chloro-1phenyl-1H-pyrazolo[4,3-c]quinoline (358), which was obtained by reaction of 348 with phenylhydrazine.136 Reaction of 358 with phenyl isothiocyanate in absolute pyridine under reflux conditions led to the formation of 1,5-diphenyl-1,2,3,5,6-pentaazaaceanthrylene-4(3H)-thione (359) in 68% yield. When 358 was reacted with primary aliphatic amines in DMF at reflux temperature, the corresponding 3,4-diaminopyrazolo[4,3-c] quinolines 360 were obtained in 79-85% yields, which refluxed with an excess of TEO to afford the novel 1,2,3,5,6-pentaazaaceanthrylenes 361 in 80-92% yields (Scheme 119). Also, compounds 361 were prepared by an alternative route. As an example, reacting 358 with TEO under reflux conditions gave the intermediate 4-chloro-3-(ethoxymethyleneamino)-1-phenylpyrazolo-[4,3-c]quinoline (362), which then refluxed, in situ, with iso-butylamine in DMF to furnish the desired tetracyclic 361 (Scheme 119).

2.4.3. 1,2,3,4,5,6-Hexaazaaceanthrylenes and 5,7,8,10*a*,11pentaazabenzo[*a*]fluorenes ring systems. The synthesis of new 5-alkyl-1,5-dihydro-1,2,3,4,5,6-hexaazaaceanthrylenes **366** was developed by Mekheimer¹³⁷ in 2001. Reactions were carried out by heating the key 3-amino-4-chloro-1*H*-pyrazolo[4,3-*c*]quinoline (**363**) with an excess of the primary alkylamines at reflux temperature to afford the corresponding 4-alkylamino-3-amino-1*H*-pyrazolo[4,3-*c*]-quinolines **364**, in 82–86% yields, which were



Scheme 120 Synthesis of 1,2,3,4,5,6-hexaazaaceanthrylenes 366 from 363.



Scheme 121 Synthesis of 5,7,8,10a,11-pentaazabenzo[a]fluorenes 372.



 $R = c-C_6H_{11}$, Me, Et, *i*-propyl, *i*-Bu

Scheme 122 Synthesis of novel 1*H*-5-thia-1,2,3,6-tetraazaacephenanthrylenes **376**, 1*H*-5-thia-1,3,6-triazaacephenanthrylenes **377** and linear pyrimidothienoquinolines **380**.

transformed into the tetracyclic 5-alkyl-1,5-dihydro-1,2,3,4,5,6-hexaazaaceanthrylenes **366**, when treated with NaNO₂ in H₂SO₄ (70%) at -5 °C. The yields of the last step are 66–87% (Scheme 120). The author discarded the other possible structure **365** based on the spectral data.

On the other hand, reacting compound **363** with arylamines **97** in DMF under reflux conditions afforded the corresponding 4-arylamino-pyrazolo[4,3-*c*]quinolines **367** in 80–88% yields. Diazotisation of the amines **367** under ordinary conditions gave the 4-arylamino-3-diazo-1*H*-pyrazolo[4,3-*c*]quinolines **369** in 82–94% yields. Treatment the 3-diazo compounds **369** with ethyl acetoacetate (**370**) in absolute EtOH at room temperature gave the intermediate **371**, which then underwent intramolecular cyclo-condensation to afford directly the novel tetracyclic ring system **372** in 70–83% yields, for which the alternative isomeric structure **373** is theoretically possible (Scheme 121).¹³⁷

2.4.4. 5-Thia-1,2,3,6-tetraazaacephenanthrylenes and 5thia-1,3,6-triazaacephenan-thrylenes. Mekheimer *et al.*¹³⁸ have reported a new protocol for the construction of novel tetracyclic pyrimidothienoquinolines and 1,2,3-triazinothienoquinolines through 4-alkyl-amino-2-chloro-quinoline-3-carbonitriles **374**. By heating a mixture of **374** with ethyl 2-mercaptoacetate (**349**) and excess of sodium ethoxide in absolute EtOH at reflux temperature, 3-aminothieno[2,3-*b*]quinolines **375** were formed in 70–94% yields (Scheme 122). Diazotization of **375** resulted in the formation of 5-thia-1,2,3,6-tetraazaacephenanthryl-enes **376** in 67–75% yields (Scheme 122). However, when **375** were refluxed with TEO, 5-thia-1,3,6-triazaacephenanthrylenes **377** were indeed obtained in 65–81% yields (Scheme 122).¹³⁸ On the other hand, reaction of **375** with cyclohexylamine in DMF under reflux conditions afforded the corresponding amides **378**, which in treatment with an excess of TEO did not afford the perianellated tetracyclic system **379**, but furnished instead the unexpected linear isomeric pyrimidothienoquinoline derivatives **380** in good yields (Scheme 122).¹³⁸

1,3,5,6-tet-2.4.5. 1,4,5,6,6a-Pentaazabenzo[a]indacenes, raazaaceanthrylenes and 5,7,9,11 tetraazabenzo[a]fluorenes. The reaction of 348 with methyl glycinate hydrochloride (381) was investigated by Mekheimer139 to synthesize the new 1,4,5,6,6*a*-pentaazabenzo[*a*]indacenes 387. The reaction was carried out by treatment 348 with an excess of 381 in DMF in the presence of TEA at room temperature to afford one of the two isomeric structures 382 or 383 (Scheme 123). Spectral data could not unequivocally differentiate these isomers. To chemically verify the structure of 383, tetrazolo[1,5-a]quinolines 385 was prepared, in 98% yield, by heating 383 with sodium azide in DMF at 70-75 °C (Scheme 123). The azidoquinolines 384 was ruled out based on the IR spectrum which has no azido band. When 383 was heated with sodium methoxide in MeOH at reflux temperature, it underwent intramolecular cyclization to provide methyl 3-amino-4-chloro-1H-pyrrolo[3,2-c]quinoline-2carboxylate (386) in 85% yield. Refluxing 386 with sodium azide in DMF afforded the novel tetracyclic 1,4,5,6,6a-pentaazabenzo[a]indacenes 387 in 96% yield. Alternatively, compound 387 could also be obtained by refluxing 385 with sodium methoxide in MeOH (Scheme 123).

On the other hand, when a solution of **386** in dry DMF was treated with ethyl iodide in the presence of anhydrous K_2CO_3 at 55–60 °C, the methyl 3-amino-4-chloro-1-ethyl-pyrrolo-[3,2-*c*] quinoline-2-carboxylate (**388**), major product, was obtained in

Scheme 123 Synthesis of methyl 3-amino-1,4,5,6,6a-pentaazabenzo[a]indacene-2-carboxylate (387).



61% yield. In addition to **388**, minor amounts of **390** was also obtained. Reaction of **388** and **390** with sodium azide, under similar reaction conditions as described before for the synthesis of **387**, yielded the novel tetracyclic systems **389** and its analog **391**, respectively, in quantitative yields (Scheme 124). Alternatively, compound **391** could also be obtained by heating a solution of **389** in dry DMF with ethyl iodide at 55–60 °C (Scheme 124).¹³⁹

Also, Mekheimer and his co-workers¹³⁹ have reported the synthesis of novel tetracyclic systems incorporating a pyrimidine nucleus in addition to the pyrroloquinoline moiety utilizing the *N*-ethylpyrrolo[3,2-c]quinoline derivative **388** as starting material. Thus, reaction of **388** with isothiocyanates in dry pyridine under reflux conditions gave the corresponding novel methyl 1-ethyl-5-substituted-4-thioxo-3(4H)-1,3,5,6tetraazaaceanthrylene-2-carboxylates 392 in 63-80% yields. On the other hand, treatment of 388 (1 equiv.) with morpholine (10 equiv.) in boiling absolute EtOH yielded the corresponding pyrrolo[3,2-c]quinoline derivative 393a, in 79% yield, which reacted with isothiocyanates, under the same conditions described above, to yield the interesting 5,7,9,11-tetraazabenzo [a]fluorenes 394, in 55–81% yields, as new model systems for pyrrolopyrimidoquinolines (Scheme 125). Furthermore, when 388 was heated in an excess of butylamine at reflux temperature, the versatile intermediate pyrrolo[3,2-c]quinolines 393b was formed. Refluxing 393b with ethyl chloroformate yielded 5-butyl-1-ethyl-4-oxo-3(4H)-1,3,5,6the new methyl



Scheme 124 Synthesis of new 1,4,5,6,6a-pentaazabenzo[a]indacenes 389 and 391.



Scheme 125 Synthesis of methyl 1-ethyl-4-thioxo-3(4H)-1,3,5,6-tetraazaaceanthrylene-2-carboxylates **392** and 5,7,9,11-tetraazabenzo[a]fluorenes **394**.

tetraazaaceanthrylene-2-carboxylate (**395**) in 63% yield. Meanwhile, refluxing **393b** with TEO afforded the methyl 5-butyl-1ethyl-1,3,5,6-tetraazaaceanthrylene-2-carboxylate (**396**) in 70% yield (Scheme 126).

2.4.6. 1,2,3,4,5,6-Hexaazaacephenanthrylenes ring systems. Refluxing 4-amino-2-chloro-quinoline-3-carbonitriles 397 with an excess of hydrazine hydrate (80%) afforded 3-amino-4-arylamino-1*H*-pyrazolo[3,4-*b*]quinolines 398 in 58–67% yields. Diazotization of 398 yielded the new tetracyclic 1-aryl-1,5-dihydro-1,2,3,4,5,6-hexaazaacephenanthrylenes 399, in 67–76% yields (Scheme 127). The other possible structure 400

was readily ruled out for the reaction products on the basis of spectral data. $^{\rm 140}$

2.4.7. Isoxazolo[3',4':4,5]pyrrolo(or thieno)[2,3-*c*]quinolines. An efficient approach was developed by Mekheimer and co-workers¹⁴¹ to synthesis the new tetracyclic isoxazolo[3',4':4,5] pyrrolo(or thieno)[3,2-*c*]quinolines **403**. By refluxing of **350** and **386** with primary aliphatic amines in DMF, the corresponding amines **351**, **401** were obtained, which were transformed into the 3-azido-pyrrolo(or thieno)quinolines **402** in 74–93% yields, when treated with sodium nitrite in H₂SO₄ (70%) at -5 °C, followed by reaction of the non-isolated pyrrolo(or thieno) quinoline diazonium sulfate with an aqueous solution of NaN₃



Scheme 126 Synthesis of methyl 5-butyl-1-ethyl-4-oxo-3(4*H*)-1,3,5,6-tetraazaaceanthrylene-2-carboxylate (**395**) and methyl 5-butyl-1-ethyl-1,3,5,6-tetraazaaceanthrylene-2-carboxylate (**396**).



Scheme 127 Synthesis of 1-aryl-1,2,3,4,5,6-hexaazaacephenanthrylenes 399 from 348.

at -5 °C. Conversion of azides **402** into the angular tetracyclic isoxazolo[3',4':4,5]pyrrolo(or thieno)[2,3-*c*]quinolines **403** was performed by refluxing in bromo-benzene (Scheme 128).

2.4.8. [1,2,4]Triazino[4',3':1,5]pyrazolo[4,3-*c*]quinolines. In 2017, Mekheimer *et al.*¹⁴² have described the first synthesis of new four heterocyclic ring systems 10-amino-6,9-disubstituted-[1,2,4]triazino[4',3':1,5]pyrazolo[4,3-*c*]quinoline derivatives. Reacting **348** with cyanoacetic acid hydrazide (**404**) in refluxing MeOH in the presence of Et₃N gave the unexpected 3-amino-4-chloro-1*H*-pyrazolo[4,3-*c*]quinoline (**363**) (Scheme 129). The mechanism for the formation of **363** is shown in Scheme 130. Heating **363** with cyclic secondary amines (piperidine, morpholine and 1-methyl-piperazine) in DMF at reflux temperature

furnished the corresponding 4-amino-pyrazolo[4,3-*c*]quinolines **405** (Scheme 129).

Then, compounds **363** and **405** were utilized as precursors for the synthesis of the new tetracyclic systems **413**. Diazotization of **363** and **405** yielded the corresponding diazonium salts **411**, which were then subjected to couple with different active methylene nitriles **412**, in aqueous EtOH containing sodium acetate, to give the novel perianellated tetracyclic ring system 10-amino-6,9-disubstituted-[1,2,4]triazino[4',3':1,5]pyrazolo [4,3-*c*]quinolines **413** (Scheme 131).¹⁴² The structures of all the newly synthesized compounds were unambiguously confirmed by spectroscopic and analytical techniques. Furthermore, X-ray crystallographic analysis on compound **413c** was performed to determine the absolute configuration of the products **413**. The



Scheme 128 Synthesis of isoxazolo[3',4':4,5]pyrrolo(or thieno)[3,2-c]quinolines 403.



Scheme 129 Synthesis of 3-amino-1*H*-pyrazolo[4,3-*c*]quinoline derivatives 405.



Scheme 130 Reaction mechanism for the formation of 3-amino-4-chloro-1H-pyrazolo-[4,3-c]quinoline (363).



Scheme 131 Coupling reaction of 411 with active methylenes 412.



Scheme 132 Reaction mechanism for the formation of 9-substituted-[1,2,4]triazino[4',3':1,5]-pyrazolo[4,3-c]quinolines 413.



Scheme 133 Synthesis of 3-alkyl-4-amino-5-chloro-2-oxo-2,3-dihydrobenzo[c][2,7]naphthy-ridine-1-carbonitriles 418.

probable mechanism leading to the formation of 9-substituted-[1,2,4]triazino[4',3':1,5]pyrazolo[4,3-*c*]quinolines **413** is outlined in Scheme 132.

2.4.9. Benzo[*c*]pyrimido[4,5,6-*ij*][2,7]naphthyridines. In 2018, Mekheimer and his group¹⁴³ have developed unprecedented synthesis of benzo[*c*]pyrimido[4,5,6-*ij*][2,7]naphthyridines with structural analogy to pyrido[4,3,2-*mn*]-acridines present in the marine tetracyclic pyridoacridine alkaloids. Reaction of **348** with an equimolecular amount of cyanoaceta-mides **417** in absolute MeOH containing a catalytic amount of

 K_2CO_3 at room temperature gave the new benzo[*c*][2,7]naphthyridines **418**, only in one step (Scheme 133). When **418** were reacted with phenyl isothiocyanate in refluxing dry pyridine, the corresponding novel 3-alkyl-2-oxo-6-phenyl-5-thioxo-3,4,5,6-tetrahydro-2*H*-benzo[*c*]pyrimido[4,5,6-*ij*][2,7]naphthyridine-1-carbonitriles **420** were indeed formed in good yields, *via* intermediacy of **419** (Scheme 134).

When 421, obtained by reacting 418 (R = butyl) with various alkyl amines, were heated with acetic anhydride under reflux conditions, the novel 3,6-dialkyl-5-methyl-2-oxo-3,6-dihydro-2*H*-



Scheme 134 Synthesis of 3-alkyl-2-oxo-6-phenyl-5-thioxo-3,4,5,6-tetrahydro-2*H*-benzo[*c*]-pyrimido[4,5,6-*ij*][2,7]naphthyridine-1-carbon-itriles 420.



Scheme 135 Synthesis of 3,6-dialkyl-5-methyl-2-oxo-3,6-dihydro-2H-benzo[c]pyrimido-[4,5,6-ij][2,7]naphthyridine-1-carbonitriles 424.

benzo[*c*]pyrimido[4,5,6-*ij*][2,7]naphthyridine-1-carbonitriles **424** were isolated in very good yields (Scheme 135).¹⁴³

Moreover, refluxing **421** with TEO gave the new 3,6-dialkyl-2oxo-3,6-dihydro-2*H*-benzo[*c*]pyrimido[4,5,6-*ij*][2,7]naphthyridine-1carbonitriles **425** in 80–86% yields (Scheme 136). On the other hand, treatment of **421** with NaNO₂ in H₂SO₄ (70%) at -5 °C yielded the previously unreported 3,6-dialkyl-2-oxo-3,6-dihydro-2*H*- benzo[*c*][1,2,3]triazino[4,5,6-*ij*]-[2,7]naphthyridine-1-carbonitriles **427** in excellent yields (Scheme 136).¹⁴³

2.4.10. Pyrimido[1',2':1,5]pyrazolo[4,3-*c*]quinolines. The synthesis of tetracyclic pyrimidopyrazoloquinolines **428** has described by Hassan and his group.¹⁴⁴ On reacting tetracyanoethylene (TCNE) (2 equiv.) (as π -acceptor) with pyrazolo[4,3-*c*] quinolines **363**, **364**¹³⁷ (1 equiv.) (as donor) in DMF furnished



Scheme 136 Synthesis of benzo[c]pyrimido[4,5,6-*ij*][2,7]naphthyridine-1-carbonitriles 425 and benzo[c][1,2,3]triazino[4,5,6-*ij*][2,7]naphthyridine-1-carbonitriles 427.



Scheme 137 Synthesis of 8-amino-6-substituted-pyrimido[1',2':1,5]pyrazolo[4,3-c]quinoline-9,10-dicarbonitriles 428

a green colour, which rapidly disappeared to give the tetracyclic products, namely, 8-amino-6-substituted-pyrimido[1',2':1,5] pyrazolo[4,3-*c*]quinoline-9,10-dicarbonitriles **428**, in 51–55% yields. This behavior can be explained as due to initial formation of unstable charge-transfer complexes between TCNE and pyrazoloquinolines **363**, **364** followed by completion of electron transfer from **363**, **364** to TCNE leading to the formation of TCNE anion radical in contact with pyrazoloquinoline cation radical I. These radicals combine to furnish the adduct **II**. Elimination of one molecule of HCN gives **III** which undergoes intramolecular cyclization *via* attack of the amino group on the CN one to afford the pyrimidopyrazoloquinolines **428** (Scheme 137).

Conflicts of interest

There are no conflicts to declare.

Notes and references

- 1 S. Mukherjee and M. Pal, Drug Discov. Today, 2013, 18, 389.
- 2 S. Mukherjee and M. Pal, Curr. Med. Chem., 2013, 20, 4386.
- 3 P. Zajdel, A. Partyka, K. Marciniec, A. J. Bojarski, M. Pawlowski and A. Wesolowska, *Future Med. Chem.*, 2014, 6, 57.
- 4 S. Bawa, S. Kumar, S. Drabu and R. Kumar, J. Pharm. BioAllied Sci., 2010, 2, 64.
- 5 B. Gryzło and K. Kulig, Mini-Rev. Med. Chem., 2014, 14, 332.
- 6 K. Kaur, M. Jain, R. P. Reddy and R. Jain, *Eur. J. Med. Chem.*, 2010, **45**, 3245.
- 7 A. P. Gorka, A. d. Dios and P. D. Roepe, *J. Med. Chem.*, 2013, **56**, 5231.

- 8 S. Bongarzone and M. L. Bolognesi, *Expet Opin. Drug Discov.*, 2011, 6, 251.
- 9 K. A. Reynolds, W. A. Loughlin and D. J. Young, *Mini-Rev. Med. Chem.*, 2013, **13**, 730.
- 10 A. Lilienkampf, J. Mao, B. Wan, Y. Wang, S. G. Franzblau and A. P. Kozikowski, *J. Med. Chem.*, 2009, **52**, 2109.
- 11 R. S. Keri and S. A. Patil, *Biomed. Pharmacother.*, 2014, 68, 1161.
- 12 S. Singh, G. Kaur, V. Mangla and M. K. Gupta, *J. Enzyme Inhib. Med. Chem.*, 2014, 25032745.
- 13 G. R. Proctor and A. L. Harvey, *Curr. Med. Chem.*, 2000, 7, 295.
- 14 R. Musiol, Curr. Pharm. Des., 2013, 19, 1835.
- J. Polanski, H. Niedbala, R. Musiol, B. Podeszwa, D. Tabak,
 A. Palka, A. Mencel, J. Finster, J. F. Mouscadet and
 M. L. Bret, *Lett. Drug Des. Discov.*, 2006, 3, 175.
- 16 J. Polanski, H. Niedbala, R. Musiol, B. Podeszwa, D. Tabak, A. Palka, A. Mencel, J. F. Mouscadet and M. Le Bret, *Lett. Drug Des. Discov.*, 2007, 4, 99.
- 17 D. Dubé, M. Blouin, C. Brideau, C. C. Chan, S. Desmarais,
 D. Ethier, J. P. Falgueyret, R. W. Friesen, M. Girard,
 Y. Girard, J. Guay, D. Riendeau, P. Tagari and
 R. N. Young, *Bioorg. Med. Chem. Lett.*, 1998, 8, 1255.
- 18 J. Jiang, M. Hoang, J. R. Young, D. Chaung, R. Eid, C. Turner, P. Lin, X. Tong, J. Wang, C. Tan, S. Feighner, O. Palyha, D. L. Hreniuk, J. Pan, A. W. Sailer, D. J. MacNeil, A. Howard, L. Shearman, S. Stribling, R. Camacho, A. Strack, L. H. Van der Ploeg, M. T. Goulet and R. J. DeVita, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 5270.
- J. Jiang, P. Lin, M. Hoang, L. Chang, C. Tan, S. Feighner,
 O. C. Palyha, D. L. Hreniuk, J. Pan, A. W. Sailer,
 N. R. Morin, D. J. MacNeil, A. D. Howard, L. H. Y. Van der

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Ploeg, M. T. Goulet and R. J. DeVita, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 5275.

- 20 T. Ulven, P. B. Little, J.-M. Receveur, T. M. Frimurer, ø. Rist, P. K. Nørregaard and T. Högberg, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 1070.
- 21 T. Ulven, T. M. Frimurer, J.-M. Receveur, P. B. Little, ø. Rist, P. K. Nørregaard and T. Högberg, *J. Med. Chem.*, 2005, 48, 5684.
- 22 R. Arienzo, D. E. Clark, S. Cramp, S. Daly, H. J. Dyke,
 P. Lockey, D. Norman, A. G. Roach, K. Stuttle,
 M. Tomlinson, M. Wong and S. P. Wren, *Bioorg. Med. Chem. Lett.*, 2004, 14, 4099.
- 23 M. Orhan Püsküllü, B. Tekiner and S. Suzen, *Mini-Rev. Med. Chem.*, 2013, 13, 365.
- 24 G. Dzimbeg, B. Zorc, M. Kralj, K. Ester, K. Pavelić, G. Andrei, R. Snoeck, J. Balzarini, E. De Clercq and M. Mintas, *Eur. J. Med. Chem.*, 2008, 43, 1180.
- 25 R. Musiol, M. Serda, S. Hensel-Bielowka and J. Polanski, *Curr. Med. Chem.*, 2010, 17, 1960.
- 26 C. M. M. Gómez, V. V. Kouznetsov, M. A. Sortino, S. L. Alvarez and S. A. Zacchino, *Bioorg. Med. Chem.*, 2008, 16, 7908.
- 27 D. H. Boschelli, Y. D. Wang, F. Ye, B. Wu, N. Zhang, M. Dutia, D. W. Powell, A. Wissner, J. M. Weber and F. Boschelli, *J. Med. Chem.*, 2001, 44, 822.
- 28 N. Muruganantham, R. Sivakumar, N. Anbalagan, V. Gunasekaran and J. T. Leonard, *Biol. Pharm. Bull.*, 2004, 27, 1683.
- 29 S. Eswaran, A. S. Adhikari and N. S. Shetty, *Eur. J. Med. Chem.*, 2009, **44**, 4637.
- 30 M. Kidwai, R. K. Bhushan, P. Sapra, K. R. Saxena and R. Gupta, *Bioorg. Med. Chem.*, 2000, **8**, 69.
- 31 N. M. Shah, M. P. Patel and R. G. Patel, *Eur. J. Med. Chem.*, 2012, **54**, 239.
- 32 A. Mahamoud, J. Chevalier, A. Davin-Regli, J. Barbe and J.-M. Pages, *Curr. Drug Targets*, 2006, 7, 843.
- 33 M. P. Maguire, K. R. Sheets, K. McVety, A. P. Spada and A. Zilberstein, J. Med. Chem., 1994, 37, 2129.
- 34 N. Costedoat-Chalumeau, B. Dunogué, N. Morel, V. Le Guern and G. Guettrot-Imbert, *Presse Med.*, 2014, 43, 167.
- 35 I. Pendrak, S. Barney, R. Wittrock, D. M. Lambert and W. D. Kingsbury, *J. Org. Chem.*, 1994, **59**, 2623.
- 36 S. Bongarzone and M. L. Bolognesi, *Expet Opin. Drug Discov.*, 2011, 6, 251.
- 37 A. Mahamoud, J. Chevalier, A. Davin-Regli, J. Barbe and J. M. Pagès, *Curr. Drug Targets*, 2006, 7, 843.
- 38 A. Shah, V. C. Diculescu, R. Qureshi and A. M. Oliveira-Brett, *Bioelectrochem*, 2010, **79**, 173.
- 39 K. Cimanga, T. De Bruyne, L. Pieters, J. Totte, L. Tona, K. Kambu, D. Vanden Berghe and A. J. Vlietinck, *Phytomedicine*, 1998, 5, 209.
- 40 Z.-W. Mei, L. Wang, W.-J. Lu, C.-Q. Pang, T. Maeda, W. Peng, M. Kaiser, I. E. El Sayed and T. Inokuchi, *J. Med. Chem.*, 2013, 56, 1431.
- 41 P. Grellier, L. Ramiaramanana, V. Millerioux, E. Deharo,
 J. Schrével, F. Frappier, F. Trigalo, B. Bodo and
 J. L. Pousset, *Phytother Res.*, 1996, 10, 317.

- 42 E. Shaban, M. Świtalska, L. Wang, N. Wang, F. Xiu, I. Hayashi, T. A. Ngoc, S. Nagae, S. El-Ghlban, S. Shimoda, A. El Gokha, I. El Sayed, J. Wietrzyk and T. Inokuchi, *Molecules*, 2017, 22, 1954.
- 43 L. Wang, M. Świtalska, Z. W. Mei, W. J. Lu, Y. Takahara, X. W. Feng, I. E. T. El-Sayed, J. Wietrzyk and T. Inokuchi, *Bioorg. Med. Chem.*, 2012, 20, 4820.
- 44 I. Pendrak, S. Barney, R. Wittrock, D. M. Lambert and W. D. Kingsbury, *J. Org. Chem.*, 1994, **59**, 2623.
- 45 C. W. Wright, J. Addae-Kyereme, A. G. Breen, J. E. Brown, M. F. Cox, S. L. Croft, Y. Gökçek, H. Kendrick, R. M. Phillips and P. L. Pollet, *J. Med. Chem.*, 2001, 44, 3187.
- 46 P. Grellier, L. Ramiaramanana, V. Millerioux, E. Deharo,
 J. Schrével, F. Frappier, F. Trigalo, B. Bodo and
 J.-L. Pousset, *Phytother Res.*, 1996, 10, 317.
- 47 Z. Sui, J. Altom, V. N. Nguyen, J. Fernandez, J. I. Bernstein, J. J. Hiliard, J. F. Barrett, B. L. Podlogar and K. A. Ohemengy, *Bioorg. Med. Chem.*, 1998, 6, 735.
- 48 Y. Ishihara, Y. Kiyota and G. Goto, *Chem. Pharm. Bull.*, 1990, 38, 3024.
- 49 P. Kumar, C. U. Dinesh and B. Pandey, *Tetrahedron Lett.*, 1994, **35**, 9229.
- 50 G. Kim and G. Keum, Heterocycles, 1997, 45, 1979.
- 51 P. Pigeon and B. Decroix, Synth. Commun., 1998, 28, 2507.
- 52 D.-B. Reuschling and F. Kröhnke, *Chem. Ber.*, 1971, **104**, 2103.
- 53 H. Z. Alkhathlan, M. A. Al-Jaradah, K. A. Al-Farhan and A. A. Mousa, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2004, 179, 373.
- 54 Y. Zhou, L. Qian and W. Zhang, Synlett, 2009, 843.
- 55 M. Janjic, R. Prebil, U. Groselj, D. Kralj, C. Malavasic, A. Golobic, K. Stare, G. Dahmann, B. Stanovnik and J. Svete, *Helv. Chim. Acta*, 2011, 94, 1703.
- 56 I. M. Sakhautdinov, I. R. Batyrshin, N. A. Sergeeva, F. Z. Galin and M. S. Yunusov, *Russ. J. Org. Chem.*, 2012, 48, 788.
- 57 B. Xu, Z. Cheng and L. Fu, Tetrahedron Lett., 2014, 55, 7194.
- 58 K. Mishra, A. K. Pandey, J. B. Singh and R. M. Singh, Org. Biomol. Chem., 2016, 14, 6328.
- 59 L. W. Deady, J. Desneves, A. J. Kaye, M. Thompson, G. J. Finlay, B. C. Baguley and W. A. Denny, *Bioorg. Med. Chem.*, 1999, 7, 2801.
- 60 C.-H. Tseng, Y.-L. Chen, P.-J. Lu, C.-N. Yangd and C.-C. Tzenga, *Bioorg. Med. Chem.*, 2008, **16**, 3153.
- 61 T.-C. Chen, D.-S. Yu, S.-J. Chen, C.-L. Chen, C.-C. Lee, Y.-Y. Hsieh, L.-C. Chang, J.-H. Guh, J.-J. Lin and H.-S. Huang, *Arabian J. Chem.*, 2019, **12**, 4348.
- 62 Y.-L. Chen, H.-M. Hung, C.-M. Lu, K.-C. Li and C.-C. Tzeng, *Bioorg. Med. Chem.*, 2004, **12**, 6539.
- 63 G. A. Salman, S. Janke, N. N. Pham, P. Ehlers and P. Langer, *Tetrahedron*, 2018, **74**, 1024.
- 64 (a) W. Peczynska-Czoch, F. Pognan, E. Kaczmarek and J. Boratyńiski, J. Med. Chem., 1994, 37, 3503; (b) L. Kaczmarek, W. Peczynska-Czoch, J. Osiadacz, M. Mordarski, W. A. Sokalski, J. Boratynski, E. Marcinkowska, H. Glazman-Kusnierczyk and C. Radzikowski, Bioorg. Med. Chem., 1999, 7, 2457.

- 65 (a) W.-J. Lu, M. Świtalska, L. Wang, M. Yonezawa, I. E.-T. El-Sayed, J. Wietrzyk and T. Inokuchi, *Med. Chem. Res.*, 2013, 22, 4492; (b) W.-J. Lu, K. J. Wicht, L. Wang, K. Imai, Z.-W. Mei, M. Kaiser, I. E.-T. El-Sayed, T. J. Egan and T. Inokuchi, *Eur. J. Med. Chem.*, 2013, 64, 498; (c) L. Wang, W.-J. Lu, T. Odawara, R. Misumi, Z.-W. Mei, W. Peng, I. E. El-Sayed and T. Inokuchi, *J. Heterocycl. Chem.*, 2014, 51, 1106; (d) M. Okada, Z.-W. Mei, Md. I. Hossain, L. Wang, T. Tominaga, T. Takebayashi, M. Murakami, M. Yasuda, T. Shigehiro, T. Kasai, A. Mizutani, H. Murakami, I. E.-T. El Sayed, S. Dan, T. Yamori, M. Seno and T. Inokuchi, *Med. Chem. Res.*, 2016, 25, 879.
- 66 S. Ali, Y.-X. Li, S. Anwar, F. Yang, Z.-S. Chen and Y.-M. Liang, J. Org. Chem., 2012, 77, 424.
- 67 R. Sunke, V. Kumar, M. A. Ashfaq, S. Yellanki, R. Medisetti, P. Kulkarni, E. V. Venkat Shivaji Ramarao, N. Z. Ehteshamc and M. Pal, *RSC Adv.*, 2015, 5, 44722.
- 68 R. Ghorbani-Vaghei and S. M. Malaekehpoor, *Tetrahedron Lett.*, 2012, 53, 4751.
- 69 C. Shi, Q. Zhang and K. K. Wang, J. Org. Chem., 1999, 64, 925.
- 70 H. Takeda, T. Ishida and Y. Takemoto, *Chem. Lett.*, 2009, **38**, 772.
- 71 W. Ali, A. Dahiya, R. Pandey, T. Alam and B. K. Patel, *J. Org. Chem.*, 2017, **82**, 2089.
- 72 S. Kundal, B. Chakraborty, K. Paul and U. Jana, *Org. Biomol. Chem.*, 2019, **17**, 2321.
- 73 P. M. Fresneda, P. Molina and S. Delgado, *Tetrahedron*, 2001, 57, 6197.
- 74 G. S. M. Sundaram, C. Venkatesh, U. K. Syam Kumar, H. Ila and H. Junjappa, *J. Org. Chem.*, 2004, **69**, 5760.
- 75 O. Amiri-Attou, Th. Terme and P. Vanelle, *Synlett*, 2005, 3047.
- 76 P. T. Parvatkar and S. G. Tilve, *Tetrahedron Lett.*, 2011, 52, 6594.
- 77 P. T. Parvatkar, P. S. Parameswaran and S. G. Tilve, *Tetrahedron Lett.*, 2007, **48**, 7870.
- 78 P. T. Parvatkar, P. S. Parameswaran and S. G. Tilve, *J. Org. Chem.*, 2009, **74**, 8369.
- 79 M. J. Haddadin, R. M. Bou Zerdan, M. J. Kurth and J. C. Fettinger, *Org. Lett.*, 2010, **12**, 5502.
- 80 A. Khorshidi and Kh. Tabatabaeian, J. Mol. Catal. A: Chem., 2011, 344, 128.
- 81 M. K. Vecchione, A. X. Sun and D. Seidel, *Chem. Sci.*, 2011, 2, 2178.
- 82 H. K. Kadam, P. T. Parvatkar and S. G. Tilve, *Synthesis*, 2012, 44, 1339.
- 83 H. K. Kadam and S. G. Tilve, *J. Heterocycl. Chem.*, 2016, 53, 2066.
- 84 Z. Yan, C. Wan, J. Wan and Z. Wang, Org. Biomol. Chem., 2016, 14, 4405.
- 85 L. Shi and B. Wang, Org. Lett., 2016, 18, 2820.
- 86 L. Fan, M. Liu, Y. Ye and G. Yin, Org. Lett., 2017, 19, 186.
- 87 C. Challa, J. Ravindran, M. M. Konai, S. Varughese, J. Jacob, B. S. D. Kumar, J. Haldar and R. S. Lankalapalli, *ACS Omega*, 2017, 2, 5187.

- 88 P. T. Parvatkar, P. S. Parameswaran, D. Bandyopadhyay, S. Mukherjee and B. K. Banik, *Tetrahedron Lett.*, 2017, 58, 2948.
- 89 Y.-L. Chen, C.-H. Chung, I.-L. Chen, P.-H. Chen and H.-Y. Jeng, *Bioorg. Med. Chem.*, 2002, **10**, 2705.
- 90 P. Molina, M. Alajarin and A. Vidal, *Tetrahedron*, 1990, 46, 1063.
- 91 S. Cacchi, G. Fabrizi, P. Pace and F. Marinelli, *Synlett*, 1999, 620.
- 92 K. Kobayashi, Y. Izumi, K. Hayashi, O. Morikawa and H. Konishi, *Bull. Chem. Soc. Jpn.*, 2005, **78**, 2171.
- 93 C. Meyers, G. Rombouts, K. T. J. Loones, A. Coelho and B. U. W. Maes, *Adv. Synth. Catal.*, 2008, **350**, 465.
- 94 M. G. Uchuskin, A. S. Pilipenko, O. V. Serdyuk, I. V. Trushkovc and A. V. Butin, *Org. Biomol. Chem.*, 2012, 10, 7262.
- 95 N. Wang, M. Switalska, M.-Y. Wu, K. Imai, T. A. Ngoc, C.-Q. Pang, L. Wang, J. Wietrzyk and T. Inokuchi, *Eur. J. Med. Chem.*, 2014, **78**, 314.
- 96 S. Guo, L. Tao, W. Zhang, X. Zhang and X. Fan, J. Org. Chem., 2015, 80, 10955.
- 97 N. N. Pham, S. Janke, G. A. Salman, T. T. Dang, T. S. Le, A. Spannenberg, P. Ehlers and P. Langer, *Eur. J. Org. Chem.*, 2017, 5554.
- 98 R. Rubio-Presa, M. R. Pedrosa, M. A. Fernández-Rodríguez,
 F. J. Arnáiz and R. Sanz, *Org. Lett.*, 2017, 19, 5470.
- 99 A. V. Aksenov, D. A. Aksenov, G. D. Griaznov, N. A. Aksenov, L. G. Voskressensky and M. Rubin, *Org. Biomol. Chem.*, 2018, 16, 4325.
- 100 N. P. Buu-Hoi, M. Mangane and P. Jacquignon, *J. Chem. Soc. C*, 1966, 50.
- 101 K. Tabaković, I. Tabaković, M. Trkovnik, A. Jurić and N. Trinajstić, *J. Heterocycl. Chem.*, 1980, **17**, 801.
- 102 M. N. Khan, S. Pal, S. Karamthulla and L. H. Choudhury, *New J. Chem.*, 2014, **38**, 4722.
- 103 A. S. Plaskon, S. V. Ryabukhin, D. M. Volochnyuk, K. S. Gavrilenko, A. N. Shivanyuk and A. A. Tolmachev, *J.* Org. Chem., 2008, 73, 6010.
- 104 A. T. Vu, A. N. Campbell, H. A. Harris, R. J. Unwalla, E. S. Manas and R. E. Mewshaw, *Bioorg. Med. Chem. Lett.*, 2007, 17, 4053.
- 105 X. Yu, J. Wang, Z. Xu, Y. Yamamoto and M. Bao, *Org. Lett.*, 2016, **18**, 2491.
- 106 K. Aradi, P. Bombicz and Z. Novák, *J. Org. Chem.*, 2016, **81**, 920.
- 107 A. L. C. Morris and Y. A. Jackson, Synthesis, 2011, 229.
- 108 Y.-J. Zhou, D.-S. Chen, Y.-L. Li, Y. Liu and X.-S. Wang, *ACS Comb. Sci.*, 2013, **15**, 498.
- 109 O. Meth-Cohn, Synthesis, 1986, 76.
- 110 V. V. Mulwad and B. S. Mahaddalkar, Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem., 1999, 38, 29.
- 111 P. K. Mahata, C. Venkatesh, U. K. Syam Kumar, H. Ila and H. Junjappa, *J. Org. Chem.*, 2003, **68**, 3966.
- 112 L. W. Deady, A. J. Kaye, G. J. Finlay, B. C. Baguley and W. A. Denny, *J. Med. Chem.*, 1997, 40, 2040.
- 113 S. Rádl, P. Konvicka and P. Váchal, *J. Heterocycl. Chem.*, 2000, **37**, 855.

- 114 L. Benati, R. Leardini, M. Minozzi, D. Nanni, P. Spagnolo and G. Zanardi, *J. Org. Chem.*, 2000, **65**, 8669.
- 115 X. Y. Zhu, L. G. Mardenborough, S. Li, A. Khan, W. Zhang, P. Fan, M. Jacob, S. Khan, L. Walkerb and S. Y. Ablordeppey, *Bioorg. Med. Chem.*, 2007, **15**, 686.
- 116 G. A. Salman, M. Hussain, V. Iaroshenko, A. Villinger and P. Langer, *Adv. Synth. Catal.*, 2011, **353**, 331.
- 117 A. R. O. Rodrigues, M. S. D. Carvalhoa, J. A. V. Cardoso, R. C. Calhelha, M.-J. R. P. Queiroz, P. J. G. Coutinho and E. M. S. Castanheira, *J. Photochem. Photobiol.*, A, 2014, 294, 20.
- 118 X.-S. Wang, Q. Li, J.-R. Wu and S.-J. Tu, *J. Comb. Chem.*, 2009, **11**, 433.
- 119 M. Asthana, N. Sharma, R. Kumar, J. B. Singh and R. M. Singh, *Tetrahedron Lett.*, 2014, 55, 4378.
- 120 C. Che, B. Yang, X. Jiang, T. Shao, Z. Yu, C. Tao, S. Li and S. Lin, *J. Org. Chem.*, 2014, **79**, 436.
- 121 X.-S. Fan, J. Zhang, B. Li and X.-Y. Zhang, *Chem.-Asian J.*, 2015, **10**, 1281.
- 122 M. Rahimizadeh, M. Pordel, M. Bakavoli and H. Eshghi, *Dyes Pigm.*, 2010, **86**, 266.
- 123 K. T. J. Loones, B. U. W. Maes and R. A. Dommisse, *Tetrahedron*, 2007, **63**, 8954.
- 124 M. Arnould, M.-A. Hiebel, S. Massip, J. M. Leger, C. Jarry,S. Berteina-Raboin and G. Guillaumet, *Chem.-Eur. J.*, 2013, 19, 12249.
- 125 F. Yu, S. Yan, L. Hu, Y. Wang and J. Lin, *Org. Lett.*, 2011, 13, 4782.
- 126 W. Wang, H. Jiang, M.-M. Zhang and X.-S. Wang, J. Heterocycl. Chem., 2014, 51, 830.
- 127 H. Y. Guo and Y. Yu, Chin. Chem. Lett., 2010, 21, 1435.

- 128 S. Karamthulla, S. Pal, T. Parvin and L. H. Choudhury, *RSC Adv.*, 2014, **4**, 15319.
- 129 J. D. Koružnjak, N. Slade, B. Zamola, K. Pavelic and G. Karminski-Zamola, *Chem. Pharm. Bull.*, 2002, **50**, 656.
- 130 W. Steinschifter and W. Stadlhauer, *J. Prakt. Chem.*, 1994, 336, 311.
- 131 A. Albert, *Chemie der Heterocyclen*, Verlag Chernie. Weinheim, 1962.
- 132 H. Lettau, *Chemie der Heterocyclen*, S. Hirzel-Verlag, Leipzig, 1981.
- 133 G. Illuminati, Adv. Heterocycl. Chem., 1964, 3, 285.
- 134 M. L. Belli, G. Illuminati and G. Marino, *Tetrahedron*, 1963, 19, 345.
- 135 R. A. Mekheimer, K. U. Sadek, H. A. Abd El-Nabi, A. A.-H. Mohamed, E. A. Ebraheem and M. B. Smith, *J. Heterocycl. Chem.*, 2005, **42**, 567.
- 136 R. A. Mekheimer, E. K. Ahmed, H. A. El-Faham, L. H. Kamel and D. Doepp, *J. Chem. Res.*, 2003, 388.
- 137 R. A. Mekheimer, Synth. Commun., 2001, 31, 1971.
- 138 R. A. Mekheimer, E. Kh. Ahmed, H. A. El-Fahham and L. H. Kamel, *Synthesis*, 2001, 97.
- 139 R. A. Mekheimer, Synthesis, 2000, 2078.
- 140 R. A. Mekheimer, J. Chem. Soc., Perkin Trans. 1, 1999, 2183.
- 141 R. A. Mekheimer, A. M. Abdel Hameed and K. U. Sadek, *Arkivoc*, 2008, **xvi**, 144.
- 142 R. A. Mekheimer, M. A. Al-Sheikh, H. Y. Medrasi and Gh. A. Bahatheg, *Synth. Commun.*, 2017, 47, 1052.
- 143 R. A. Mekheimer, M. A. Al-Sheikh, H. Y. Medrasi and Gh. A. Bahatheg, *Mol. Divers.*, 2018, **22**, 159.
- 144 A. A. Hassan, R. Mekheimer and N. K. Mohamed, *Pharmazie*, 1997, **52**, 589.