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## REVIEW

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## Recent advances in the chemistry of 2chloroquinoline-3-carbaldehyde and related analogs

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This review highlights the recently cited research data in the literature on the chemistry of 2chloroguinoline-3-carbaldehyde and related analogs and their applications over the period from 2013 to 2017. It covers: synthesis of quinoline ring systems and reactions adopted to construct fused or binary quinoline-cord heterocyclic systems. The biological evaluation and the synthetic applications of the target compounds were illustrated.

#### Introduction and scope 1.

Quinolines are aromatic compounds that consist of a benzene ring fused with a pyridine heterocyclic system. Quinolines are known also as benzo[b]pyridine and 1-azanaphthalene with one nitrogen atom in one benzene ring and none in the other ring or at the ring junction. Heterocycles containing a nitrogen atom possess high and interesting medicinal and pharmaceutical properties.<sup>1-4</sup> Montelukast (1) is a drug used as an antiasthma agent (Fig. 1).5

In addition, quinolines are the main core of many types of natural products,<sup>6,7</sup> drugs,<sup>8-10</sup> and were found in many synthetic

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heterocyclic compounds in order to enhance the biological and medicinal properties. Compounds incorporating quinoline ring system exhibited various biological,11,12 and pharmaceutical activities e.g. anti-tuberculosis,13 antiplasmodial,14 antibacterial,15,16 antihistamine,17 antifungal,18 antimalarial,19,20 anti-HIV,<sup>21</sup> anticancer,<sup>22</sup> anti-inflammatory,<sup>23,24</sup> anti-hypertensive,<sup>25</sup> and antioxidant activities.26 In addition, the use of quinolines as tyrokinase PDGF-RTK inhibitor,27 inositol 5'-phosphatase (SH<sub>2</sub>),<sup>28</sup> DNA gyrase B inhibitors as Mycobacterium tuberculosis,<sup>29</sup> and DNA topoisomerase inhibitors,30 were reported. Nadifloxacin (2) is a racemic fluoroquinolone launched as a topical antibiotic in Japan in 1993 to treat acne and methicillinresistant staphylococcal infections. The S-enantiomer was found to be more active than the racemic mixture and had pharmacokinetic properties amenable to systemic use.31



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Mona Elsayed Ibrahim: was born in Matria, Egypt. She Mansoura graduated from University where she carried out her M.Sc. and PhD. studies under the supervision of Professor H. H. Zoorob and Professor W. S. Hamama and was awarded the M.Sc. and PhD. in chemistry from faculty of science, Mansoura University in 2003 and 2010, respectively. Her research focused on the

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Fig. 1 Structure of antiasthma agent incorporating guinoline nucleus.

Ozenoxacin (3) is a non-fluorinated quinolone with broadspectrum activity against a variety of susceptible and resistant Gram-positive bacteria.<sup>32</sup> Ciprofloxacin (4) and Grepafloxacin (5) were considered as the most effective drugs with the IC<sub>50</sub>s of <10 mg mL<sup>-1</sup>.<sup>33</sup> Sparfloxacin (6) is reported as the antibiotic standard for antimicrobial tests.<sup>34</sup> Hexahydro-[3,4'-biquinoline]- 3'-carboxylate 7 showed a compelling antimicrobial activity at 6.25  $\mu g~mL^{-1}$  with a 96% inhibition (Fig. 2).<sup>35</sup>

Camptothecin (8) was extracted from Chinese plant; bark and stem of *Camptotheca acuminate* as a natural alkaloid prevent the growth of tumor cells.<sup>36</sup> Topotecan (10),<sup>37</sup> belotecan (11),<sup>38</sup> and irinotecan (12),<sup>39</sup> were reported as anticancer drugs. 22-Hydroxyacuminatine (13) is a synthetic structure related to natural products (Fig. 3).<sup>40</sup>

Recently, Abdel-Wahab and R. E. Khidre,<sup>41</sup> have reviewed the chemistry of 2-chloroquinoline-3-carbaldehyde during the period from 1979 to 1999. The reactions are classified according to the reactivity of chlorine atom and aldehydic group. In 2012, Abdel-Wahab *et al.*,<sup>42</sup> have reviewed the chemical reactions, synthetic methods and biological applications of 2-chloroquinoline-3-carbaldehydes which were reported from 1999 to 2011. The reactions are classified as addition, reduction, condensation and substitution reactions.



Fig. 2 Structures of the most potent antibiotics and antimicrobial agents.



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In continuation of the previous researches on the synthesis and reactions of quinolines,<sup>43–47</sup> we described herein the literature survey of different strategies developed so far for the synthesis of 2-chloroquinoline-3-carbaldehyde and their analogs as well as to highlight their reactivity and their use as building blocks in the synthesis of variable heterocyclic systems of potent biological properties.

### 2. Synthesis of quinoline ring systems

### 2.1. Synthesis of 2-chloro-3-formylquinolines

Meth-Cohn synthesis of quinolines,<sup>48</sup> was reported using Vilsmeier formylating agent resulting from the reaction of DMF with phosphorus oxychloride.49 Treatment of acetanilides 15 with phosphorus pentachloride (4.5 equiv.) in N,N-alkylformamide (3 mol equiv.) at 120 °C for 4 h gave 2-chloro-3formylquinolines 16a-i. Phosphorus pentachloride reacted in situ with N,N-alkylformamide 17 to form the formylating agent 18.50 Acetylation of aromatic amines 14a-m (dissolved in HCl) with acetic anhydride gave the corresponding substituted Nphenylacetamides 15a-m, which after treatment with Vilsmeafforded the substituted ier's reagent 2-chloro-3formylquinolines 16a-m following the methods reported by Meth-Cohn (Scheme 1).<sup>5,49,51-56</sup> The better method for the synthesis of quinolines depending on the nature of the substituents in order to obtain the best yields.



d: R= 8-CH<sub>3</sub> (60%, 67%); e: R= 6-OCH<sub>3</sub> (49%, 54%); f: R= 7-OCH<sub>3</sub> (74%, 65%); g: R= 6-Br (28%, 30%); h: R= 7-Cl (30%, 35%); i: R= 6-NO<sub>2</sub> (0%, 0%)

Pathway B: 16 a: R= H (62.82%); b: R= 6-CH<sub>3</sub>; c: R= 7-CH<sub>3</sub>; d: R= 8-CH<sub>3</sub> (63%); e: R= 6-OCH<sub>3</sub>, f: R= 7-OCH<sub>3</sub>; g: R= 6-Br; h: R= 7-Cl; i: R= 6-NO<sub>2</sub>; j: R= 6-Cl (69%); k: R= 8-NO<sub>2</sub> (65%); l: R= 8-Cl; m: R= 8-OCH<sub>3</sub>

Scheme 1 Synthesis of 2-chloro-3-formylquinolines 16a-m.







Aneesa *et al.*,<sup>57</sup> have reported the effect of transition metal ions such as  $Cu(\pi)$ ,  $Ni(\pi)$ ,  $Co(\pi)$ , and  $Cd(\pi)$  on the synthesis of quinolines through the Vilsmeier reagent with acetanilides 15. Vilsmeier reagent was prepared by reaction of thionyl chloride (SOCl<sub>2</sub>) or phosphorus oxychloride (POCl<sub>3</sub>) with N,N-dimethylformamide (DMF). The reactions of each of acetanilide, 2methyl-4-nitro-acetanilide, 2,4-dimethyl-acetanilide or 4-nitroacetanilide with the prepared Vilsmeier reagent afforded the respective quinolines 16 through the mechanistic pathway reported in Scheme 2. Kinetically, the followed reaction is a second order in which it depends on the Vilsmeier reagent and anilide substrate and the rate determining step is the reaction between them.

Vilsmeier-Haack formylation of N-(4-(methylsulfonamido)-3-phenoxy-phenyl)acetamide (19),<sup>58</sup> with phosphorus oxychloride in DMF gave a mixture of two substituted quinolone derivatives 20 and 21 in (1:1) molar ratio (Scheme 3).59,60

#### 2.2. Synthesis of 2-oxo-3-formyl-1,2-dihydroquinolines

Microwave irradiation reactions of 2-chloro-3formylquinolines 16a-j with acetic acid containing sodium acetate at 320 W under the optimized reaction conditions afforded 6,7,8-trisubstituted-2-oxo-1,2-dihydro-quinoline-3carbaldehydes 22a-j (Scheme 4).61



(i) acetic acid (87.5 mmol), sodium acetate (25 mmol), mw, 320W; a:  $R_1 = R_2 = R_3 = H$  (98%); b:  $R_1 = CH_3$ ,  $R_2 = R_3 = H$  (94%); c:  $R_1 = R_3 = H$ ,  $R_2 = CH_3$  (93%); d:  $R_1 = R_2 = H$ ,  $R_3 = CH_3$  (96%); e:  $R_1 = 0CH_3$ ,  $R_2 = R_3 = H$  (98%); f:  $R_1 = R_2 = H$ ,  $R_2 = 0CH_3$  (97%); g:  $R_1 = R_2 = H$ ,  $R_3 = 0CH_3$  (97%); h:  $R_1 = Br$ ,  $R_2 = R_3 = H$  (72%); i:  $R_1 = CI$ ,  $R_2 = R_3 = H$  (87%); j:  $R_2 = CI$ ,  $R_1 = R_3 = H$  (75%)

Scheme 4 Synthesis of 3-formyl-1,2-dihydroguinolin-2-ones 22a-j.



Scheme 5 Synthesis of (2-chloroquinolin-3-yl)methanamine (25).



## 3. Reactions

### 3.1. Reductive amination of formyl group

Reduction of C=N was achieved using lithium aluminum hydride (LiAlH<sub>4</sub>) and sodium boron hydride (NaBH<sub>4</sub>) reagents. Condensation of quinoline **16** with hydroxylamine hydrochloride followed by treatment with thionyl chloride in DMF afforded the respective 2-chloro-3-cyanoquinoline (24). Reduction of nitrile group of **24** with LiAlH<sub>4</sub> in THF yielded the desired (2chloroquinolin-3-yl)methanamine (25) in a good yield. The mechanism of reduction process of the nitrile function with LiAlH<sub>4</sub> proceeded as shown in Scheme 5.<sup>62</sup>

Treatment of quinolines **16** with morpholine in the presence of catalytic amount of dimethylaminopyridine gave 2morpholinoquinoline-3-carbaldehydes **26a–d**. Further refluxing of **26a–d** with 2-amino-5-methyl-thiophene-3-carbonitrile (**27**) in isopropyl alcohol followed by reduction of the formed imine (C==NH) bond with sodium boron hydride in methanol afforded substituted 3-cyano-5-methyl-2-(((2-morpholinoquinolin-3yl)methyl)amino)thiophenes **28a–d** (Scheme 6). The corresponding bromo derivative **28d** exhibited the highest antibacterial activity against *Escherichia coli*, *Staphylococcus aureus* and *Bacillus spizizenii* and antifungal activity against *Aspergillus Niger*, *Aspergillus Brasiliensis* and *Curvularia Lunata* microorganisms.<sup>5</sup>

### 3.2. Alkylation at C<sub>2</sub> carbon atom

Sonogashira coupling reaction of alkyne derivatives with quinolones **16** in anhydrous DMF or THF containing trimethylamine in the presence of  $[PdCl_2(PPh_3)_2]$  and CuI as catalysts yielded the desired 2-alkynyl-3-formyl-quinolines **29a-r** (Scheme 7).<sup>63</sup>

### 3.3. Synthesis of Schiff bases

Condensation of 2-chloro-8-methylquinoline-3-carbaldehyde (**16d**) with substituted anilines **14** in acetone afforded the respective 1-(2-chloro-8-methylquinolin-3-yl)-*N*-(substituted-phenyl)methanimine **30a-c**.<sup>51</sup> Schiff base **32** was synthesized by condensation of quinoline **16** with phenyl hydrazine (**31**) in the presence of natural surfactant (Acacia pods) in a short reaction time.<sup>64</sup> Condensation of quinoline **16** with hydrazine

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hydrate gave 2-chloro-3-(hydrazonomethyl)quinoline (33) which reacted with each of 2-naphthaldehyde (34) and 1*H*-indole-3carbaldehyde (36) by condensation in refluxing ethanol to produce the desired hydrazono-quinolines 35 and 37, respectively (Scheme 8).<sup>62</sup> The addition of a catalyst increases the reaction yield and lower the reaction time.



Scheme 8 Condensation of 16 with aromatic amines and hydrazine derivatives.



i. NH<sub>2</sub>NH<sub>2</sub>·H<sub>2</sub>O, EtOH, rt, 18 h. ii. EDC, DMF, TEA, rt, 18 h

Scheme 9 Condensation of quinolines 16 with hydrazine followed by reaction with substituted-carboxylic acids.



Scheme 10 Condensation of 16 with carbohydrazide.

Condensation of each of quinolines **16a**, **16f** and **16n** in ethanol with hydrazine hydrate gave the respective hydrazonoquinolines **33**, **38** and **39**, respectively. Further condensation reaction of hydrazono-quinolines **33**, **38** and **39** with substituted-carboxylic acids **40–43** in DMF containing 1-ethyl-3-(3-dimethyl-aminopropyl)carbodiimide hydrochloride (EDC) and TEA afforded the corresponding amides **44–49**, respectively (Scheme 9).<sup>65</sup> Condensation of quinolones **16** with 2-oxo-2*H*-chromene-3carbohydrazide (**50**) in DMF containing catalytic drops of glacial acetic acid gave the respective Schiff bases **51a–j** (Scheme 10). Compounds **51a–j** has no antifungal activity against *A. Niger* and *A. Clavatus* microorganisms.<sup>66</sup>

Refluxing of the desired 2-chloro-3-formylquinoline (**16a**) in acetic acid gave quinolin-2-one derivative **22**. Condensation of **22** with isonicotino-hydrazide (**52**) in refluxing ethanol yielded



Scheme 11 Condensation of 3-formyl-quinolin-2-one 16a with hydrazide derivatives.



Scheme 12 Synthesis of quinoline-curcumin analogues.



Conventional method (I); MW (II): a: Ar=  $C_6H_5$  (I: 70%, II: 81%); b: Ar=  $4-CH_3C_6H_4$  (I: 75%, II: 83%); c: Ar=  $4-CH_3OC_6H_5$  (I: 75%, II: 84%); d: Ar=  $4-NO_2C_6H_5$  (I: 64%, II: 72%); e: Ar=  $4-CIC_6H_5$  (I: 72%, II: 71%); f: Ar=  $4-BrC_6H_5$  (I: 78%, II: 78%); g: Ar=  $4-OIC_6H_5$  (I: 74%, II: 76%); h: Ar=  $2,4-di-CIC_6H_5$  (I: 70%, II: 80%); i: Ar= thienyl (I: 74%, II: 86%)

Scheme 13 Synthesis of 1-aryl-3-(2-thiomorpholinoquinolin-3-yl) prop-2-en-1-ones.

the desired benzohydrazide **53**. *N'*-((2-Oxo-1,2-dihydroquinolin-3-yl)methylene)benzohydrazide (**53**) was used as a ligand for the preparation of complexes.<sup>67</sup> Condensation of **16a** with cyanoacetic acid hydrazide **54** in refluxing ethanol gave the corresponding acetohydrazide **55** (Scheme 11). 2-Cyano-*N'*-((2-Oxo-1,2-dihydroquinolin-3-yl)methylene)aceto-hydrazide (**55**) was considered as a reactive synthetic precursor for the synthesis of several heterocycles *i.e.* pyrazoles, pyridines, coumarines and pyrazines.<sup>68</sup>

### 3.4. Synthesis of $\alpha$ , $\beta$ -unsaturated ketones

Heating of quinolines **16** with hydrochloric acid afforded the respective quinolinones **22**, which was alkylated with propargylor benzyl- or allyl-bromides in DMF containing potassium carbonate at room temperature to give *N*-alkylquinolines **56**. Condensation of *N*-alkylquinolines **56** with complex of feruloyl acetone difluoroboronite in the presence of *n*-butylamine followed by heating in a mixture of methanol/water afforded the respective 3-(5-hydroxy-7-(4-hydroxy-3-methoxyphenyl)-3-oxohepta-1,4,6-trien-1-yl)-1,6-disubstituted-quinolin-2(1*H*)-ones **58** (Scheme 12).<sup>69</sup>

On the other hand, 2-chloroquinoline-3-carbaldehyde (16a) reacted with thiomorpholine (59) by heating in ethanol containing anhydrous potassium carbonate to furnish 2thiomorpholino-quinoline-3-carbaldehyde (60). Compound 60 reacted with acetophenones 61a–j in ethanol containing anhydrous  $K_2CO_3$  under microwave (MW) irradiation conditions to afford the respective unsaturated ketones 62a–j, respectively (Scheme 13).<sup>70</sup> The best method to obtain the highest yield is reported using MW technique.

Heating of 2-chloro-3-formylquinolines **16** in methanol containing potassium carbonate and iodine gave the respective esters **63a–q**, respectively. The role of iodine is to oxidize the aldehydic group to the corresponding acid followed by condensation with methanol to form the esters **63a–q** (70–98%). Refluxing of **63a–q** in sodium alkoxides or aryloxides followed by hydrolysis of the ester group in acid medium afforded carboxylic acids **64a–t**. Esterification followed by





Scheme 14 Synthesis of disubstituted-3-oxocyclohexenyl-2-chloroquinoline-3-carboxylates.

chloroformylation of 64a-t afforded the respective quinolines 65a-l, 67 and 68 (Scheme 14).<sup>71</sup>

### 3.5. Amination at C<sub>2</sub> of quinoline nucleus

Treatment of quinolines **16a** and **16e** with ethylene glycol in refluxing toluene containing *p*-toluenesulfonic acid led to the formation of the desired intermediate 2-chloro-3-(1,3-dioxolan-2-yl)-quinoline **69**. Heating of the formed intermediate (separated in a dried organic layer from the previous step) with each of 4*H*-1,2,4-triazol-4-amine (**71**) or 1*H*-tetrazol-5-amine (**72**) in

DMF containing potassium carbonate afforded the corresponding amino-triazolyl and tetrazolyl derivatives **73a,b** and **74a,b**, respectively. The products **73a,b** and **74a,b** were obtained through nucleophilic displacement of chlorine atom with the hydrogen of amino group (Scheme 15).<sup>72</sup>

Multicomponent reactions of 1,2,4-triazolylaminoquinolines 73**a**,**b** with each of malononitrile (75**a**) or methyl 2cyanoacetate (75**b**) and 4-hydroxy-2*H*-chromen-2-one (76) in water under heating conditions or microwave or ultrasonic irradiation in the presence of L-proline as a catalyst afforded the respective triazolylamino-quinolinyl-pyrano[3,2-*c*]chromenones



i. ethylene glycol, p-TSA, toluene, reflux, 5-6 h ii. (1) DMF,  $K_2CO_3$ , 2-3 h; (2) X/ Y; (3) H<sup>+</sup>/ H<sub>2</sub>O

Scheme 15 Synthesis of quinoline attached 2-aminotriazole and aminotetrazole skeletons.

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a: R= H, R<sub>1</sub>= CN (i, 75%), (ii, 85%), (iii, 94%) b: R= H, R<sub>1</sub>= CO<sub>2</sub>CH<sub>3</sub> (i, 75%), (ii, 87%), (iii, 94%) c: R= OCH<sub>3</sub>, R<sub>1</sub>= CN (i, 75%), (ii, 86%), (iii, 95%) d: R= OCH<sub>3</sub>, R<sub>1</sub>= CO<sub>2</sub>CH<sub>3</sub> (i, 73%), (ii, 84%), (iii, 95%)  $\begin{array}{l} \mathbf{c}: \mathsf{R} = \mathsf{H}, \mathsf{R}_1 = \mathsf{CN} (i, 74\%), (ii, 85\%), (iii, 95\%) \\ \mathbf{f}: \mathsf{R} = \mathsf{H}, \mathsf{R}_1 = \mathsf{CO}_2\mathsf{CH}_3 (i, 76\%), (ii, 83\%), (iii, 91\%) \\ \mathbf{g}: \mathsf{R} = \mathsf{OCH}_3, \mathsf{R}_1 = \mathsf{CN} (i, 73\%), (ii, 85\%), (iii, 94\%) \\ \end{array}$ h: R= OCH<sub>3</sub>, R<sub>1</sub>= CO<sub>2</sub>CH<sub>3</sub> (i, 75%), (ii, 84%), (iii, 93%)

Scheme 16 Synthesis of pyranochromenones and pyranopyranones systems.

78a-d in good to excellent yields. Similarly, compounds 73a,b reacted via one-pot reactions with nitriles 75a,b and 4-hydroxy-6-methyl-2H-pyran-2-one (77) to give the corresponding 1,2,4triazolyl-amino-quinolinyl-pyrano[4,3-b]pyranones 78e-h (Scheme 16). The reactions were carried out using different catalysts such as piperidine, pyridine, triethylamine, sodium

hydroxide and 1-proline. The best products yield (80-85%) and lowest reactions time were achieved in case of using L-proline as a catalyst.72

Similarly, multicomponent one-pot reactions of 1Htetrazolyl-amino-quinolines 74a,b with each of malononitrile (75a) or methyl 2-cyanoacetate (75b) and 4-hydroxy-2H-



i. Conventional, H<sub>2</sub>O, 100 °C, 60 min or ii. MW, H<sub>2</sub>O, 420 W, 20 min or iii. Ultrasonic, H<sub>2</sub>O, 50 °C, 15 min, L-proline, 2 drops of water

- a: R= H, R<sub>1</sub>= CN (i, 77%), (ii, 88%), (iii, 94%)
- **b** $: R=H, R_1=CO_2CH_3 (i, 72\%), (ii, 85\%), (iii, 95\%)$ **c** $: R=OCH_3, R_1=CN (i, 75\%), (ii, 84\%), (iii, 93\%)$ **d** $: R=OCH_3, R_1=CO_2CH_3 (i, 76\%), (ii, 86\%), (iii, 94\%)$
- e: R= H, R<sub>1</sub>= CN (i, 72%), (ii, 86%), (iii, 95%)

Scheme 17 Synthesis of guinolinyl-pyrano(chromenones) and (pyranones).



Scheme 18 Suggested mechanism for the formation of pyrano[3,2-c]chromenones and pyrano[4,3-b]pyranones derivatives.



chromen-2-one (**76**) or 4-hydroxy-6-methyl-2*H*-pyran-2-one (**77**) under the optimized conditions in the presence of L-proline as a catalyst afforded the respective 1*H*-tetrazolylamino-quinolinyl-pyrano[3,2-*c*](chromenones) and (pyranones) **79a–d** and **79e–h**, respectively (Scheme 17).<sup>72</sup>

The reaction mechanism for the formation of 1*H*-(triazolyl)/ (tetrazolyl) amino-quinolinyl-pyrano[3,2-*c*](chromenones) and (pyranones) **78a–h** and **79a–h** is reported through initial condensation of L-proline with *N*-heteryl-quinolines **73a,b** or

74a,b followed by nucleophilic addition of the active methylenes, Knoevenagel condensation and intramolecular cyclization with the loss of the L-proline catalyst molecule (Scheme 18).<sup>72</sup>

The reaction of quinoline **16a** with *N*-methylpiperazine (**80**) in the presence of basic medium of potassium carbonate afforded 2-(4-methyl piperazin-1-yl)quinoline-3-carbaldehyde (**81**) through elimination of HCl molecule (Scheme 19).<sup>73</sup>



Scheme 20 Mechanistic pathway to prepare pyrrolo[3,4-b]quinolin-3-one 82.



Scheme 22 Synthesis of 3-amino-1H-pyrazolo[3,4-b]quinoline

# 4. Synthesis of fused heterocyclic systems

### 4.1. Synthesis of pyrrolo[3,4-b]quinolinone

Heating of quinoline **16a** with formamide and formic acid in ethanol for 8 h afforded the fused cyclic 1,2-dihydro-3*H*-pyrrolo [3,4-*b*]quinolin-3-one (**82**). The mechanism of the reaction was illustrated through the initial addition of an amino group of formamide to the aldehydic carbonyl of quinoline **16a**, followed by condensation to form *N*-((2-chloroquinolin-3-yl)methylene) formamide intermediate. Elimination of HCl molecule from the formed intermediate gave the target product **82** (Scheme 20).<sup>62</sup>

### 4.2. Synthesis of pyrazoloquinolines

Cycloaddition reaction of quinoline **24** with hydrazine hydrate gave 1*H*-pyrazolo[3,4-*b*]quinolin-3-amine (**83**). Treatment of **83** with benzoyl isocyanate (**84**) in dichloromethane containing triethylamine afforded the corresponding carbamoylbenzamide **85**. The reaction was preceded by the addition of the amino group to the imino carbonyl. Heating of **83** with each of 2-naphthaldehyde (**86**) and 1*H*-indole-3-carbaldehyde (**88**) in ethanol containing catalytic amount of acetic acid (3 drops) yielded the respective Schiff bases **87** and **89**, respectively, through condensation in acidic medium (Scheme 21).<sup>62</sup>

Treatment of quinoline **16a** with aqueous ammonia in the presence of ceric ammonium nitrate gave 2-chloroquinoline-3-



Scheme 23 Synthesis of 1H-pyrazolo[3,4-b]quinoline.



[a: R= H; b: R= 6-CH<sub>3</sub>; c: R= 7-CH<sub>3</sub>; d: R= 8-CH<sub>3</sub>; e: R= 6-OCH<sub>3</sub>; f: R= 7-OCH<sub>3</sub>]

Scheme 24 Synthesis of tetrazolo[1,5-a]quinoline-4-carbaldehydes.



carbonitrile (24). Cycloaddition of 24 with hydrazine hydrate gave 1H-pyrazolo[3,4-*b*]quinolin-3-amine (90) (Scheme 22).<sup>74</sup>

Further condensation of 2-chloro-6-methoxyquinoline-3carbaldehyde (**16e**) with phenyl hydrazine (**31**) gave the desired Schiff base **91**, which followed intramolecular cyclization through heating in nitrobenzene containing a catalytic amount of pyridine to afford 6-methoxy-1-phenyl-1*H*-pyrazolo [3,4-*b*]quinoline (**92**) (Scheme 23).<sup>74</sup>

### 4.3. Synthesis of tetrazoloquinolines

Tetrazolo[1,5-*a*]quinoline-4-carbaldehydes **93a–f** were prepared through reactions of 2-chloroquinoline-3-carbaldehydes **16** with sodium azide in acetic acid (Scheme 24).<sup>55,75,76</sup>

Reduction of tetrazolo[1,5-*a*]quinoline-4-carbaldehyde (**93a**) with sodium borohydride in methanol yielded the corresponding alcohol **94** which after methylation with methanesulfonyl chloride in dichloromethane containing catalytic triethylamine



Scheme 26 Synthesis of 1*H*-tetrazolyl-tetrazolo[1,5-*a*]quinolinyl-methanamines through Ugi-azide/S<sub>N</sub>Ar/ring chain azido-tautomerization method.



Scheme 27 Synthesis of tetrazolo[1,5-a]quinoline 101 according to S<sub>N</sub>Ar/ring chain azido-tautomerization/nucleophilic addition conditions.



(i) CH\_3OH (1 M), MW, 85  $^{\rm o}$ C, 100 W, 1 h; (ii) CH\_3OH (1 M), US, 60  $^{\rm o}$ C, 42 kHz, 2 h

Compound	R <sub>1</sub>	$R_3$	R₄	Yield % (i)	Yield % (ii)
а	c-Hex	Н	Н	94	47
b	<i>t</i> -Bu	н	н	86	55
С	4-OCH <sub>3</sub> Ph	н	н	79	44
d	Bn	н	н	91	54
е	c-Hex	Br	н	89	69
f	<i>t</i> -Bu	Br	н	0	0
g	4-OCH <sub>3</sub> Ph	Br	н	67	31
h	Bn	Br	н	77	34
i	c-Hex	н	OBn	75	59
j	<i>t</i> -Bu	н	OBn	65	28
k	4-OCH <sub>3</sub> Ph	н	OBn	0	0
I	Bn	н	OBn	69	32

Scheme 28 Synthesis of imidazopyridin-tetrazoloquinolines using GBB/S<sub>N</sub>Ar/ring chain azido-tautomerization method.

gave 4-(methoxymethyl)tetrazolo[1,5-*a*]quinoline (**95**). Stirring of **95** with 4-hydroxybenzaldehyde in hot DMF containing potassium carbonate afforded the respective ether **96** in 76% yield (Scheme 25).<sup>77</sup>

A four-component reaction of quinoline **16** with alkyl isocyanides **97**, azido-trimethylsilane (**98**) and amines **99** in methanol under microwave or ultrasound (US) irradiation conditions gave the respective 1*H*-tetrazolyl-tetrazolo[1,5-*a*] quinolinyl-methanamines **100a-r** in moderate yields (Scheme 26). The products **100a-r** were obtained through a one-pot Ugiazide method, nucleophilic substitution and ring chain azidotautomerization.<sup>78</sup>

Treatment of quinoline **16** with azidotrimethylsilane in methanol gave tetrazolo[1,5-*a*]quinoline-4-carbaldehyde (**93**), which reacted with another mole of azidotrimethylsilane to produce the respective 4-(dimethoxy-methyl) tetrazolo[1,5-*a*] quinoline (**101**). The product **101** was also obtained through one-pot reaction of quinoline **16** with two moles of azidotrimethylsilane (Scheme 27). The reaction proceeded *via* nucleophilic substitution reaction followed by ring chain azidotautomerization and nucleophilic addition.<sup>78</sup>

Groebke–Blackburn–Bienaymé (GBB) reaction was used for the synthesis of imidazopyridines.<sup>79</sup> One-pot multicomponent reactions of quinolone **16** with alkyl isocyanides **97**, azidotrimethylsilane (98) and aminopyridines 102 under optimized conditions (microwave or ultrasound (US) irradiation) afforded a series of imidazopyridin-tetrazoloquinolines 103a–l (Scheme 28). The products 103a–l prepared in better yields using MW irradiation conditions. Compound 103f was not formed due to the steric hindrance between a *tert*-butyl group and bromine atom of the pyridine ring. Also, compound 103k was not obtained due to the steric hindrance between tetrazoloquinoline ring and NH of the isocyanide group.<sup>78</sup> Kishore *et al.* have reported similar synthetic routes to prepare imidazo[1,2-*a*] pyridine-chromones and the bulky substituents such as bromine and *tert*-butyl substituents did not give the products due to the high steric hinderance.<sup>80</sup>

Multicomponent reaction of phthalic anhydride (104), hydrazine hydrate, 5,5-dimethylcyclohexane-1,3-dione (105) and each of quinolines 16 or tetrazolo[1,5-*a*]quinoline-4carbaldehyde 93a-f in refluxing ethanol in the presence of  $Pr_{x}$ -CoFe<sub>2</sub>-*x*O<sub>4</sub> (5 mol%) nanoparticles as a catalyst yielded quinolinyl-indazolo[1,2-*b*]phthalazine-triones 106a-f and tetrazolo [1,5-*a*] quinolinyl-indazolo[1,2-*b*]phthalazine-triones 107a-f, respectively (Scheme 29). The synthesized compounds 106 and 107a-f are considered as amalgamation biofilm inhibitors. Quinolines 106a (IC<sub>50</sub> = 30 µM), 106b (IC<sub>50</sub> = 46.5 µM) and 107e



Scheme 30 Synthesis of 2H-pyrano[2,3-b]quinolin-2-ones

 $(IC_{50}=46.5~\mu M)$  are potent antimicrobial agents more than the antibiotic standard ciprofloxacin.  $^{55}$ 

### 4.4. Synthesis of pyranoquinolinones

Microwave irradiation (MW) reactions of 2-chloro-3formylquinolines **16** with concentrated buffer solution of acetic acid containing sodium acetate afforded the respective 7,8,9trisubstituted-2*H*-pyrano[2,3-*b*]quinolin-2-ones **108a–j** (Scheme 30).<sup>61</sup>

### 4.5. Synthesis of thiopyranoquinolines

The reaction of 2-mercaptoquinoline-3-carbaldehyde **16** with malononitrile (75a) and thiophenol (**110a**) to yield 2-amino-4-(phenylthio)-4*H*-thio-pyrano[2,3-*b*]quinoline-3-carbonitrile (**111a**) was carried out following different reaction conditions in various solvents such as (ethanol, acrylonitrile, toluene, DMF, 1,4-dioxane, methylene chloride, water and methanol) at room

temperature  $\rightarrow$  120 °C in the presence of a catalyst *e.g.* (L-proline, K<sub>2</sub>CO<sub>3</sub>, CS<sub>2</sub>CO<sub>3</sub>, piperidine, NaOH, TEA or a mixture of pyrrolidine: AcOH (1 : 1)). The highest reaction yield% (94%) was obtained using L-proline as a catalyst in ethanol at 80 °C (Scheme 31).<sup>81</sup>

The mechanism of the formation of thiopyrano[2,3-*b*] quinoline-3-carbonitrile **111a** as shown in Scheme  $32.^{81}$  L-Proline catalyze the Knoevenagel condensation and the addition of thiol. The next step is the interaction of L-proline with the formed arylidene to facilitate the Michael addition step.

### 4.6. Synthesis of dihydrodibenzo[1,8]naphthyridinones

Condensation of equimolar amounts of phenyl hydrazine (31) with 5,5-dimethylcyclohexane-1,3-dione (105) followed by reaction with substituted-2-chloro-3-formyl-quinolines 16 in the presence of potassium carbonate through one-pot



i. L-proline (0.5 mmol), EtOH,80 °C, 10-20 min (75-97%)

a: R<sub>1</sub>= H, R<sub>2</sub>= C<sub>6</sub>H<sub>5</sub> (94%); b: R<sub>1</sub>= H, R<sub>2</sub>= 4-CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub> (97%); c: R<sub>1</sub>= H, R<sub>2</sub>= 4-FC<sub>6</sub>H<sub>4</sub> (91%); d: R<sub>1</sub>= H, R<sub>2</sub>= Bn (83%); e: R<sub>1</sub>= H, R<sub>2</sub>= cyclopentane (75%); f: R<sub>1</sub>= H, R<sub>2</sub>= cyclohexane (80%); g: R<sub>1</sub>= CH<sub>3</sub>, R<sub>2</sub>= C<sub>6</sub>H<sub>5</sub> (93%); h: R<sub>1</sub>= CH<sub>3</sub>, R<sub>2</sub>= 4-CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub> (89%); i: R<sub>1</sub>= CH<sub>3</sub>, R<sub>2</sub>= 4-FC<sub>6</sub>H<sub>4</sub> (86%); j: R<sub>1</sub>= CH<sub>3</sub>, R<sub>2</sub>= Bn (81%); k: R<sub>1</sub>= CH<sub>3</sub>, R<sub>2</sub>= cyclopentane (85%); l: R<sub>1</sub>= CH<sub>3</sub>, R<sub>2</sub>= cyclohexane (88%); m: R<sub>1</sub>= OCH<sub>3</sub>, R<sub>2</sub>= 4-CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub> (90%); n: R<sub>1</sub>= CI, R<sub>2</sub>= Bn (92%); o: R<sub>1</sub>= CI, R<sub>2</sub>= 4-FC<sub>6</sub>H<sub>4</sub> (87%)

Scheme 31 Synthesis of 4H-thio-pyrano[2,3-b]quinolines.



Scheme 32 Mechanistic pathway to synthesize 4H-thiopyrano[2,3-b]quinolines.

multicomponent reaction afforded dihydrodibenzo[b,g][1,8] naphthyridin-1(2H)-ones **112a-f** (Scheme 33).<sup>82</sup>

Multicomponent reaction of substituted 2-chloro-3formylquinolines **16** with 4-hydroxy-2*H*-chromen-2-one (**76**) and substituted 5,5-dimethyl-3-(phenylamino)-cyclohex-2-en-1ones **113** in refluxing ethanol containing L-proline yielded the respective tetrahydrodibenzo[b,g][1,8]naphthyridin-1(2H)-ones **114a–n** (Scheme 34). It was noticed that the best yields were obtained using L-proline as a catalyst in refluxing ethanol rather than using catalysts such as cesium carbonate or sodium



Scheme 33 Synthesis of fused dihydrodibenzo[*b*,*g*][1,8]naphthyridin-1(2*H*)-ones.



a: R= H, R<sub>1</sub>= 4-OCH<sub>3</sub> (80%); b: R= H, R<sub>1</sub>= 3-CH<sub>3</sub> (79%); c: R= 6-CH<sub>3</sub>, R<sub>1</sub>= H (83%); d: R= 6-CH<sub>3</sub>, R<sub>1</sub>= 4-Br (84%); e: R= 6-OCH<sub>3</sub>, R<sub>1</sub>= 4-Br (85%); f: R= 6-CH<sub>3</sub>, R<sub>1</sub>= 4-Br (83%); g: R= 5,7-(CH<sub>3</sub>)<sub>2</sub>, R<sub>1</sub>= 4-Cl (83%); h: R= 6-CH<sub>3</sub>, R<sub>1</sub>= H (86%); i: R= 7,8-(CH<sub>3</sub>)<sub>2</sub>, R<sub>1</sub>= 4-OCH<sub>3</sub> (87%); j: R= 7,8-(CH<sub>3</sub>)<sub>2</sub>, R<sub>1</sub>= 4-Cl (82%); k: R= 7,8-(CH<sub>3</sub>)<sub>2</sub>, R<sub>1</sub>= H (85%); l: R= 7,8-(CH<sub>3</sub>)<sub>2</sub>, R<sub>1</sub>= 3-Cl-4-CH<sub>3</sub> (84%); m: R= 7,8-(CH<sub>3</sub>)<sub>2</sub>, R<sub>1</sub>= 2-Cl (76%); n: R= 6-C(CH<sub>3</sub>)<sub>3</sub>, R<sub>1</sub>= H (84%)

Scheme 34 Synthesis of tetrahydrodibenzo[*b*,*g*][1,8]naphthyridin-1(2*H*)-ones.

hydroxide or piperidine, *etc...* and solvents such as water or DMF or chloroform or toluene or acetonitrile.<sup>83</sup>

The mechanism of formation of compounds **114a–n** is explained as shown in Scheme 35. The formation of iminium

ion (intermediate A) was catalyzed by L-proline by a reversible reaction with aldehydes 16. Knoevenagel condensation of 76 with the reactive iminium ion (intermediate A) produces intermediate (B). Elimination of L-proline led to the formation of



Scheme 35 Mechanistic pathway for the synthesis of compounds 114a-n.

8



a:  $R_1$ = H,  $R_2$ = 4-OCH<sub>3</sub> (95%); b:  $R_1$ = H,  $R_2$ = 4-CH<sub>3</sub> (85%); c:  $R_1$ = H,  $R_2$ = 4-Cl (83%); d:  $R_1$ = 6-CH<sub>3</sub>,  $R_2$ = 4-Cl (89%); e:  $R_1$ = 6-Br,  $R_2$ = 4-OCH<sub>3</sub> (56%); f:  $R_1$ = 8-CH<sub>3</sub>,  $R_2$ = 4-CH<sub>3</sub> (89%); g:  $R_1$ = 8-CH<sub>3</sub>,  $R_2$ = 4-OCH<sub>3</sub> (94%); h:  $R_1$ = 8-CH<sub>3</sub>,  $R_2$ = 4-Cl (87%)

Scheme 36 Synthesis of tetrahydrodibenzo[b,g][1,8]naphthyridin-1(2H)-ones.



**118**a: R<sub>1</sub>= 6-CH<sub>3</sub>, R<sub>2</sub>= H (87%); b: R<sub>1</sub>= 6-CH<sub>3</sub>, R<sub>2</sub>= CH<sub>3</sub> (85%); c: R<sub>1</sub>= 6-OCH<sub>3</sub>, R<sub>2</sub>= CH<sub>3</sub> (79%) **119**a: R<sub>1</sub>= H, R<sub>2</sub>= H (87%); b: R<sub>1</sub>= 8-CH<sub>3</sub>, R<sub>2</sub>= H (91%); c: R<sub>1</sub>= 6-CI, R<sub>2</sub>= CH<sub>3</sub> (88%); d: R<sub>1</sub>= 6-Br, R<sub>2</sub>= H (93%)

Scheme 37 Synthesis of dihydrobenzo[b]pyrimido[1,8]naphthyridine-diones and 1H-chromenoquinolinyl-pyrimidine-diones.



Scheme 38 Mechanistic pathway for the synthesis of compounds 118 and 119.

Review



**120a**: R<sub>1</sub>= H, R<sub>2</sub>= H (87%); b: R<sub>1</sub>= 6-CH<sub>3</sub>, R<sub>2</sub>= H (92%); c: R<sub>1</sub>= 8-CH<sub>3</sub>, R<sub>2</sub>= H (90%); d: R<sub>1</sub>= 6-Cl, R<sub>2</sub>= CH<sub>3</sub> (86%); e: R<sub>1</sub>= 6-Br, R<sub>2</sub>= CH<sub>3</sub> (80%)

Scheme 39 Synthesis of dihydropyrazolo[4',3':5,6]pyrano[2,3-b]quinolinyl-pyrimidine-diones.



Scheme 40 Synthesis of benzo[2,3][1,4]oxazepino[7,6-b]quinolines.

intermediate (C) which reacted with enaminone **113** to produce the intermediate **D**. Finally, intramolecular cyclization of intermediate **D** gave tetrahydrodibenzo[b,g][1,8]naphthyridin-1(2*H*)-ones **114a–n**.<sup>83</sup>

A series of tetrahydrodibenzo[b,g][1,8]naphthyridin-1(2H)ones **116a-h** were prepared through multicomponent reactions of substituted 2-chloro-3-formylquinolines **16** with 5-methyl-2,4-dihydro-3H-pyrazol-3-one (**115**) and 5,5-dimethyl-3-(phenylamino)cyclohex-2-en-1-one **113** by heating in ethanol in the presence of catalytic L-proline (Scheme 36).<sup>84</sup>

## 4.7. Synthesis of pyrimido[1,8]naphthyridines and chromenoquinolinyl-pyrimidines

Multicomponent reactions of substituted 2-chloro-3formylquinolines **16** with 5,5-dimethylcyclohexane-1,3-dione (**105**) and 6-amino-pyrimidine-2,4(1*H*,3*H*)-diones **117** in refluxing ethanol containing L-proline yielded the desired dihydrobenzo[*b*]pyrimido[1,8]naphthyridine-2,4(1*H*,3*H*)-diones **118a–c** and 1*H*-chromeno[2,3-*b*]quinolinyl-pyrimidine-2,4(1*H*,3*H*)-diones **119a–d** (Scheme 37).<sup>85</sup>

The mechanistic pathways for the formation of compounds **118a–c** and **119a–d** were explained as shown in Scheme 38. The iminium ion (intermediate **A**) was formed through a reversible reaction of L-proline with aldehyde **16**. The higher reactivity of intermediate **A** facilitate the Knoevenagel condensation with **105**, through intermediate **B**, and after L-proline elimination, the intermediate **C** might be formed. The addition of aminouracil derivatives **117** furnish the intermediate **D**, which followed intramolecular cyclization initiated from N or O atoms to give compounds **118a–c** and **119a–d**, respectively.<sup>85</sup>

### 4.8. Synthesis of pyrazolopyrano-quinolinyl-pyrimidines

Multicomponent one-pot reactions of substituted 2-chloro-3formylquinolines **16** with 6-amino-pyrimidine-2,4(1*H*,3*H*)-diones **117** and 5-methyl-2,4-dihydro-3*H*-pyrazol-3-one (**115**) in refluxing ethanol catalyzed by L-proline gave the corresponding dihydropyrazolo[4',3':5,6]pyrano[2,3-*b*]quinolinyl-pyrimidine-2,4(1*H*,3*H*)-diones **120a–e** (Scheme 39).<sup>85</sup>

### 4.9. Synthesis of oxazepinoquinolines

One-pot multicomponent reaction of quinolines **16** with 2aminophenol (**121**), acids **122** and isocyanides **97** in refluxing methanol to give the corresponding benzo[2,3][1,4]oxazepino [7,6-*b*]quinolines **124a-n** (Scheme 40). Ugi-4CR reaction conditions were used to prepare the investigated compounds **124a-n** in (58–85%) yields in the absence of bases.<sup>86</sup>

## 5. Synthesis of binary heterocyclic systems

### 5.1. Synthesis of quinolinyl-azetidinones

Condensation of quinolines **16** with phenylhydrazine in refluxing DMF gave the respective Schiff bases **32**. Cycloaddition

reactions of **32** with chloroacetyl chloride in DMF containing triethylamine (TEA) yielded 3-chloro-4-(2-chloroquinolin-3-yl)-1-(phenylamino)azetidin-2-ones **125a-i** in moderate to good yields (Scheme 41). The investigated compounds **125a-i** exhibited good diuretic activity.<sup>54</sup>

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### 5.2. Synthesis of quinolinyl-furan derivatives

One-pot multicomponent reactions of **16** with dialkyl but-2ynedioates **126a,b**, and isocyano alkanes **97a–c** in acetonitrile gave quinolinyl-furan-3,4-dicarboxylates **127a–q** in good yields (Scheme 42). The reaction was proceeded by the nucleophilic attack of carbonium ion of isocyanides to C=C followed by nucleophilic attack of the formed anion to formyl group of **16** to afford the target compounds **127a–q**.<sup>87</sup>

### 5.3. Synthesis of quinolinyl-pyrazoles

Claisen–Schmidt condensation of quinoline **16a** with acetophenones **128a–o** in ethanol containing sodium hydroxide as a base at room temperature gave the respective chalcone derivatives phenylpropenones **129a–o**. Condensation of chalcones **129a–o** with isonicotinohydrazide in refluxing glacial acetic acid afforded the corresponding chloroquinolinyl-



Scheme 41 Synthesis of quinolin-3-yl-azetidin-2-ones.



a:  $R_1$ = H,  $R_2$ = CH<sub>3</sub>,  $R_3$ = C(CH<sub>3</sub>)<sub>3</sub> (90%); b:  $R_1$ = H,  $R_2$ = CH<sub>3</sub>,  $R_3$ = cyclohexyl (90%); c:  $R_1$ = H,  $R_2$ = CH<sub>3</sub>,  $R_3$ = C(CH<sub>3</sub>)<sub>2</sub>-CH<sub>2</sub>-C(CH<sub>3</sub>)<sub>3</sub> (95%); d:  $R_1$ = H,  $R_2$ = CH<sub>2</sub>CH<sub>3</sub>,  $R_3$ = C(CH<sub>3</sub>)<sub>3</sub> (92%); e:  $R_1$ = H,  $R_2$ = CH<sub>2</sub>CH<sub>3</sub>,  $R_3$ = C(CH<sub>3</sub>)<sub>3</sub>, CCH<sub>2</sub>-C(CH<sub>3</sub>)<sub>3</sub> (95%); d:  $R_1$ = H,  $R_2$ = CH<sub>2</sub>CH<sub>3</sub>,  $R_3$ = C(CH<sub>3</sub>)<sub>3</sub> (92%); g:  $R_1$ = 6-CH<sub>3</sub>,  $R_2$ = CH<sub>2</sub>CH<sub>3</sub>,  $R_3$ = C(CH<sub>3</sub>)<sub>3</sub> (86%); h:  $R_1$ = 6-CH<sub>3</sub>,  $R_2$ = CH<sub>2</sub>CH<sub>3</sub>,  $R_3$ = cyclohexyl (90%); i:  $R_1$ = 6-CH<sub>3</sub>,  $R_2$ = CH<sub>2</sub>CH<sub>3</sub>,  $R_3$ = C(CH<sub>3</sub>)<sub>3</sub> (92%); g:  $R_1$ = 6-CH<sub>3</sub>,  $R_2$ = CH<sub>2</sub>CH<sub>3</sub>,  $R_3$ = C(CH<sub>3</sub>)<sub>3</sub> (86%); h:  $R_1$ = 6-CH<sub>3</sub>,  $R_2$ = CH<sub>2</sub>CH<sub>3</sub>,  $R_3$ = cyclohexyl (90%); i:  $R_1$ = 6-CH<sub>3</sub>,  $R_2$ = CH<sub>2</sub>CH<sub>3</sub>,  $R_3$ = C(CH<sub>3</sub>)<sub>2</sub>-CH<sub>2</sub>-C(CH<sub>3</sub>)<sub>3</sub> (86%); j:  $R_1$ = 6-CH<sub>3</sub>,  $R_2$ = cyclohexyl,  $R_3$ = CH<sub>2</sub>CH<sub>3</sub> (87%); k:  $R_1$ = 6-CH<sub>3</sub>,  $R_2$ = CH<sub>3</sub>,  $R_3$ = C(CH<sub>3</sub>)<sub>2</sub>-CH<sub>2</sub>-C(CH<sub>3</sub>)<sub>3</sub> (86%); j:  $R_1$ = 6-CH<sub>3</sub>,  $R_2$ = cyclohexyl,  $R_2$ = CH<sub>3</sub>,  $R_3$ = C(CH<sub>3</sub>)<sub>3</sub> (76%); m:  $R_1$ = 6-OCH<sub>3</sub>,  $R_2$ = CH<sub>2</sub>CH<sub>3</sub>,  $R_3$ = C(CH<sub>3</sub>)<sub>3</sub> (76%); m:  $R_1$ = 6-OCH<sub>3</sub>,  $R_2$ = CH<sub>3</sub>,  $R_3$ = cyclohexyl (80%); p:  $R_1$ = 6-OCH<sub>3</sub>,  $R_2$ = CH<sub>3</sub>,  $R_3$ = cyclohexyl (80%); p:  $R_1$ = 6-OCH<sub>3</sub>,  $R_2$ = CH<sub>3</sub>,  $R_3$ = C(CH<sub>3</sub>)<sub>2</sub>-CH<sub>2</sub>-C(CH<sub>3</sub>)<sub>3</sub> (76%); m:  $R_1$ = 6-OCH<sub>3</sub>,  $R_2$ = CH<sub>3</sub>,  $R_3$ = cyclohexyl (80%); p:  $R_1$ = 6-OCH<sub>3</sub>,  $R_2$ = CH<sub>3</sub>,  $R_3$ = C(CH<sub>3</sub>)<sub>3</sub> (76%); m:  $R_1$ = 6-OCH<sub>3</sub>,  $R_2$ = CH<sub>3</sub>,  $R_3$ = cyclohexyl (80%); p:  $R_1$ = 6-OCH<sub>3</sub>,  $R_2$ = CH<sub>3</sub>,  $R_3$ = C(CH<sub>3</sub>)<sub>3</sub> (75%)

Scheme 42 Synthesis of guinolinyl-furan-3,4-dicarboxylates.







(i) Ethanol, NaOH, stirring, 24 h; (ii) NH<sub>2</sub>CSNHNH<sub>2</sub>, Ethanol, Reflux 8 h; (iii) BrCH<sub>2</sub>COOC<sub>2</sub>H<sub>5</sub>, Ethanol, Reflux 1 h

[a: R= H; b: R= 2-OH; c: R= 4-OH; d: R= 4-OCH<sub>3</sub>; e: R= 2-Cl; f: R= 4-Cl; g: R= 2-F; h: R= 3-F; i: R= 4-F; j: R= 2-NO<sub>2</sub>; k: R= 3-NO<sub>2</sub>; l: R= 4-NO<sub>2</sub>]

Scheme 44 Synthesis of quinolin-3-yl-pyrazol-1-yl-thiazol-4(5H)-ones.



Scheme 45 Synthesis of 2-chloroquinolinyl-oxazolidines.





Scheme 46 Synthesis of 2-(2-chloroquinolin-3-yl)-3-(phenylamino)thiazolidin-4-ones.



Scheme 47 Synthesis of quinolinyl-thiazolidin-4-ones.

pyrazolyl-pyridines **130a–o** (Scheme 43). Compounds **130f**, **130n**, and **130o** exhibited good antibacterial activity against *E. coli* at 50 µg mL<sup>-1</sup> MIC, while at lower concentration (MIC = 12.5 µg ml<sup>-1</sup>), compound **130e** have the highest inhibition against *E. coli*. Most of compounds **130a–o** exhibited no to moderate toxicity against HeLa cells cultured at 100 µg mL<sup>-1.88</sup>

Furthermore, condensation of 2-chloro-3-formyl-6methylquinoline (16b) with acetophenones 128 in ethanol containing sodium hydroxide gave the respective unsaturated ketones 131a–l. Cyclocondensation of 131a–l with hydrazinecarbothioamide by heating in ethanol afforded quinolinylpyrazole-1-carbothioamides **132a–l**, respectively. Refluxing of **132a–l** with ethyl bromoacetate gave the respective thiazol-4(5*H*)-ones **133a–l** (Scheme 44).<sup>89</sup>

### 5.4. Synthesis of quinolinyl-oxazolidines

Multicomponent reactions of quinolines **16** with methylglycine and formaldehyde in boiling toluene afforded the desired chloroquinolinyl-oxazolidine derivatives **134a–h** in excellent yields (Scheme 45). The products were obtained through cycloaddition **1**,3-dipolar reactions of the formed *N*-methyl-*N*methylenemethanideaminium intermediate to quinolines **16**.<sup>52</sup>



Scheme 48 Synthesis of guinolin-3-yl-1,3,4-oxadiazole-2-thiol.



Scheme 49 Synthesis of quinolinyl-1,2-dihydropyridine-3-carboxylate derivative.

### 5.5. Synthesis of quinolinyl-thiazolidinones

Condensation of quinolines **16** with phenyl hydrazine (**31**) in refluxing methanol gave the respective Schiff bases **135a–e**. Treatment of 2-chloro-3-((2-phenylhydrazono) methyl) quinolines **135a–e** with thioglycolic acid in boiling methanol containing a catalytic amount of zinc chloride afforded substituted 2-(2-chloroquinolin-3-yl)-3-(phenylamino)thiazolidin-4-ones **136a–e** (Scheme 46). Compounds **136a–e** have no antibacterial activity against *Salmonella typhi, E. coli, Bacillus subtilis* and *Staphylococcus aureus* microorganisms and no antifungal activity against *Aspergillus niger*. Compounds **136a–e** exhibited good activity against *Penicillium chrysogenum*, while compounds **136a**, **136c** and **136e** have activity towards *Fusarium moniliforme* and **136d** against *Aspergillus flavus* microorganisms.<sup>90</sup>

Solvent free multicomponent reactions of substituted 2chloro-3-formylquinolines **16** with substituted anilines **14** and 2-mercaptoacetic acid (**137**) in the presence of catalytic  $\beta$ cyclodextrin-SO<sub>3</sub>H furnished the respective quinolinylthiazolidinones **138a–i** (Scheme 47). The best yields were obtained under the optimized conditions rather than using solvents such as methanol, ethanol, toluene, DMF or acetic acid and the yield% depends on the type of the catalyst.<sup>91</sup>

### 5.6. Synthesis of quinolinyl-1,3,4-oxadiazole

Oxidation of quinoline **16a** with silver nitrite in the presence of sodium hydroxide gave the corresponding acid **139**, which was esterified in ethanol containing sulfuric acid to yield the corresponding ester **140**. Treatment of this ester **140** with hydrazine hydrate followed by reaction with carbon disulfide and hydrochloric acid gave 5-(2-chloroquinolin-3-yl)-1,3,4-oxadiazole-2-thiol (**142**) (Scheme **48**).<sup>92</sup>

### 5.7. Synthesis of quinolinyl-pyranones and 1,2dihydropyridone

Condensation of *N*-pyridylquinoline **143** with each of acetophenone and 1-(thiophen-2-yl)ethan-1-one in ethanol



Scheme 50 Synthesis of guinolinyl-guinazoline systems.



**150a**: R= H, quinolin-3-yl-quinazolinone (95%)**150b**: R= 8-CH3, quinolin-3-yl-quinazolinone (93%)**150c**: R= 6-OCH3, quinolin-3-yl-quinazolinone (89%)**150d**: R= 7-Cl, quinolin-3-yl-quinazolinone (85%)**150e**: R= H, quinolin-4-yl-quinazolinone (76%)

### Scheme 51 Synthesis of substituted-quinolinyl-quinazolines.



Scheme 52 Synthesis of 4-chloro-2-(2-chloro-quinolin-3-yl)quinazolines.

containing sodium hydroxide gave unsaturated ketones **144a**,**b**, respectively. Cyclocondensation of **144a**,**b** with ethyl cyanoacetate (**75b**) in ethanol containing piperidine gave the corresponding quinolinyl-pyranones **145a**,**b**. Aminolysis of **145a** with hydrazine hydrate gave quinolinyl-1,2-dihydropyridine-3carboxylate **146**. The reaction was preceded by nucleophilic addition at carbonyl group of lactone followed by condensation (Scheme 49).<sup>92</sup>



Scheme 53 Synthesis of quinolinyl-pyrimidine systems.



Scheme 54 Synthesis of pyrimidinyl-quinoline systems

### 5.8. Synthesis of quinolinyl-quinazolines

Treatment of each of quinolines **16a** and **16d** with 2-aminobenzamide (**147**) in hot DMF containing potassium carbonate gave 2-(2-chloro-quinolin-3-yl)-2,3-dihydroquinazolin-4(1*H*)-one **149a** and its 8-methyl analog **149b** was obtained in very low yield (3%). Unfortunately, the same reaction was carried out under the same conditions with the addition of iodine, but 2-(2-chloroquinolin-3-yl)quinazolin-4(3*H*)-ones **148a** and **148b** were not obtained (Scheme 50).<sup>93</sup>

Similarly, a series of quinolinyl-quinazolinones **150a–e** were prepared in good to excellent yields by heating the reactants **147** and **16** in DMF containing potassium carbonate without the addition of iodine (Scheme 51).<sup>93</sup>

Treatment of 2-(2-chloro-quinolin-3-yl)-2,3-dihydroquinazolin-4(1H)-ones **150a** and **150b** with iodine in hot DMF furnished 2-(2-chloro-quinolin-3-yl)quinazolin-4(3H)-ones **148a** and **148b**, respectively, through oxidation process using iodine or KMnO<sub>4</sub>. Refluxing of each of **148a** and **148b** with phosphorus oxychloride gave 4-chloro-2-(2-chloro-quinolin-3-yl) quinazolines **151a** and **151b**, respectively, in good yields (76 and 73%). It is noteworthy to mention that the product **151a** was separated from resinous crude reaction products by recrystallization from ethanol (Scheme 52).<sup>93</sup>

### 5.9. Synthesis of quinolinyl-pyrimidines

Quinolinyl-tetrahydropyrimidine derivatives **153a,b**, and **157a,b** were synthesized from one-pot multicomponent reactions of quinoline **16** with urea (**152a**) or thiourea (**152b**) and ethyl ace-toacetate or acetylacetone in refluxing ethanol containing acetic acid (1 mL). Treatment of **153b** with hydrazine hydrate gave 4-(2-chloroquinolin-3-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydro-

pyrimidine-5-carbohydrazide (154) through the elimination of ethanol molecule. The reaction of 153a with *o*-aminophenol in acetic acid gave 155, while the same reaction produced 156 by refluxing the reactants in ethanol instead of acetic acid for 6 h (Scheme 53).<sup>62</sup>

Multicomponent reactions of substituted-2-chloro-3-formylquinolines **16** with urea (**152a**), and each of ethyl acetoacetate (**158**) and 5,5-dimethylcyclohexane-1,3-dione (**105**) in the presence of catalytic NaNO<sub>3</sub> yielded tetrahydropyrimidine-5carboxylates **159a–c** and tetrahydro-quinazoline-2,5(1*H*,3*H*)diones **160a–c**, respectively. The presence of NaNO<sub>3</sub> facilitate the condensation process of aldehydic carbonyl with amino group of urea followed by nucleophilic attack of the condensed nitrogen to active the hydrogen of ethyl acetoacetate (**158**) and condensation of another terminal amino group of urea with



i. NH<sub>2</sub>NH<sub>2</sub>. H<sub>2</sub>O (1.5 mmol), sulfonylmethanediamine (15 mol %), H<sub>2</sub>O (5 mL), 80  $^{\circ}$ C, 32 min

Scheme 55 Multicomponent synthesis of guinolinyl-pyranopyrazole.



a: R= H (95%); b: R= 2-NO<sub>2</sub> (90%); c: R=  $3NO_2$  (85%); d: R=  $4-NO_2$  (87%); e: R= 2F (90%); f: R= 3-F (88%); g: R= 4-F (95%); h: R= 4-CI (90%); i: R=  $3,4-CI_2$  (85%); j: R= 3-CI-4-F (90%); k: R= 4-Br (85%); I: R=  $2-CH_3$  (80%); m: R=  $3-CH_3$  (85%); n: R=  $4-CH_3$  (83%); o: R=  $2,4-(CH_3)_2$  (90%); p: R=  $2-OCH_3$  (80%); q: R= 4-NO (75%); r: R= fused 2,3-pyridyl ( $C_3H_3N$ ) (90%); s: R=  $4-CH_3$ - fused 2,3-pyridyl ( $C_4H_6N$ ) (90%); t: R= fused 1,2-naphthyl (85%)





carbonyl group to produce the respective products **159a-c** (Scheme 54).<sup>94</sup>

### 5.10. Synthesis of quinolinyl-pyranopyrazole

A multicomponent reaction of 2-chloro-3-formyl-quinoline (**16a**) with ethyl 3-oxobutanoate and malononitrile (**75a**) in water containing sulfonyl methane-diamine as a catalyst gave the respective quinolinyl-pyranopyrazole **161** (Scheme 55). The reaction was initiated by abstraction of active hydrogen from methylene group of malononitrile in the presence of a catalytic sulfonyl methanediamine followed by nucleophilic attack of the formed anion to formyl group of quinoline. Knoevenagel condensation of the produced alcohol produced the corresponding arylidene. Next, hydrazine hydrate reacted with ethyl acetoacetate to form pyrazole derivative which reacted with the formed arylidene in the previous step through Michael-type addition followed by intramolecular nucleophilic cyclization to give quinolinyl-pyranopyrazole **161**.<sup>95</sup>

### 5.11. Synthesis of piperazinyl-quinolinyl-acridinones

A multicomponent type reactions have been preferred than multistep synthetic reaction due to the high obtained yields%, low reaction time, high purified product, selectivity and formation of several bonds through a one-pot reactions.96-98 A multicomponent and solvent-free reaction of piperazinylquinoline **81** with 5,5-dimethylcyclohexane-1,3-dione (105) and substituted amines 14 under microwave conditions in the presence of catalytic amount of BN-Pr-SO<sub>3</sub>H afforded the respective piperazinyl-quinolinyl-acridinones 162a-t (Scheme 56). The reaction to prepare 3,3-dimethyl-9-(2-(4-methyl-piperazin-1-yl)quinolin-3-yl)-3,4,9,10-tetra-hydroacridin-1(2H)-ones 162a was carried out in different solvents such as ethanol, methanol, acrylonitrile and solvent-free conditions at room temperature or at 140 °C. It was found that the best yield was obtained (95%) following the conditions of solvent-free reaction at 140 °C after 10 minutes.73



(iii) 70% acetic acid, reflux; (iv) Allyl bromide, K<sub>2</sub>CO<sub>3</sub>, DMF, rt, 12 h.

(v) pyridine-2,3-diamine and 3-hydroxy-5,5-dimethylcyclohex-2-en-1-one or

3-hydroxycyclohex-2-en-1-one/ 120 °C, 2.5-3.5 h.

Scheme 58 Synthesis of dihydroquinolinyl-benzopyrido[1,4]diazepinones and tetrazoloquinolinyl-benzopyrido[1,4]diazepinones.

The reaction mechanism for the preparation of substituted 3,3-dimethyl-9-(2-(4-methylpiperazin-1-yl)quinolin-3-yl)-3,4,9,10tetrahydro-acridin-1(2*H*)-ones **162a–t** as shown in Scheme 57. The reaction was initiated through activating the aldehyde **81** using BN-Pr-SO<sub>3</sub>H followed by Knoevenagel condensation to form intermediate **I**. Next, Michael addition of the aromatic amines to the previously formed intermediate activated by BN-Pr-SO<sub>3</sub>H produced intermediate **II** which possess intramolecular condensation to yield 3,4,9,10-tetrahydroacridin-1(2*H*)-ones **162a–t** after condensation of the formed intermediate **III**.<sup>73</sup>

### 5.12. Synthesis of quinolinyl-benzopyrido[1,4]diazepinones

Refluxing of each of **16a** and **16b** with phenol in  $DMF/K_2CO_3$  afforded 2-phenoxyquinolines **163a** and **163b**, while the treatment with sodium azide in DMSO/TBA-HS gave tetrazolo[1,5-*a*] quinolines **93**. Refluxing of **16** in acetic acid followed by

treatment with allyl bromide in DMF/K<sub>2</sub>CO<sub>3</sub> gave **164a,b**. Multicomponent reactions of **93, 163** and **164a,b** with pyridine-2,3-diamine and 3-hydroxy-5,5-dimethylcyclohex-2-en-1-one or 3-hydroxy-cyclohex-2-en-1-one gave quinolinyl-benzopyrido[1,4] diazepinones and tetrazoloquinolinyl-benzo-pyrido[1,4] diazepinones **165a-j** in excellent yields (Scheme 58).<sup>99</sup>

### 5.13. Synthesis of piperazinyl-quinolinyl-benzothiazepines

Treatment of quinoline **16a** with *N*-phenylpiperazine in hot DMF containing potassium carbonate yielded the desired 2-(4-phenyl-piperazin-1-yl)quinoline-3-carbaldehyde. Condensation of 2-(4-phenyl-piperazin-1-yl)quinoline-3-carbaldehyde with 4-substituted acetophenone in ethanol catalyzed by sodium hydroxide gave the respective unsaturated ketones **166a–c**. Michael addition reaction of **166a–c** with *o*-aminothiophenol in acetic acid yielded piperazinyl-quinolinyl-benzo-thiazepines





Scheme 59 Synthesis of piperazinyl-quinolinyl-benzothiazepines.

**167a–c.** Cycloaddition 1,3-dipolar reaction of quinolinylbenzothiazepines **167a–c** with *N*-hydroxy-4-substitutedbenzimidoyl chloride in the presence of catalytic amount of triethylamine gave quinolinyl-benzo[b][1,2,4]oxadiazolo[4,5-d] [1,4]thiazepines **168a–l** (Scheme 59).<sup>100</sup>

### 6. Synthesis of heteryl-arylidenes

### 6.1. Synthesis of quinolidene-rhodanine system

Solvent-free Knoevenagel condensation of quinolines 16 with *N*-substituted-2-thioxothiazolidin-4-ones (169) in the presence of

ionic liquids of  $[Et_3NH][HSO_4]$  and [DBUH][OAc] afforded the respective trisubstituted-quinolinyl-thioxo-thiazolidin-4-ones **170-172a-i** (Scheme 60). Quinolinyl-thioxo-thiazolidin-4-one **170g** was more potent antifungal agent against *A. niger* (MIC = 25 µg mL<sup>-1</sup>) compared to miconazole, while, **170i** is a good antifungal agent against *F. oxysporum*, *A. niger*, *C. neoformans* microorganisms (MIC = 25 µg mL<sup>-1</sup>) and *A. flavus* (MIC = 12.5 µg mL<sup>-1</sup>).<sup>101</sup>

### 6.2. Synthesis of quinoline-oxadiazoles

Refluxing of quinoline **16a** in methanol containing potassium hydroxide afforded 2-methoxyquinoline-3-carbaldehyde (**173**).



172a (86%); b (86%); c (84%); d (82%); e (87%); f (89%); g (88%); h (90%); i (80%)





Knoevenagel condensation of methoxy derivative **173** with cyanoacetic acid gave the corresponding arylidene derivative **174**. Heating of **174** with *N*-acylbenzotriazole hydroxylamine hydrochloride in a mixture of methanol/water (9 : 1) containing sodium bicarbonate gave *N'*-hydroxy-3-(2-methoxyquinolin-3-yl) acryl imidamide (**175**). Treatment of **175** with *N*-acylbenzotriazole in ethanol catalyzed by triethylamine afforded the desired ester derivatives **178a–s**. Intramolecular cyclization of **178a–s** in boiling ethanol/*n*-butanol afforded quinolinyl-1,2,4oxadiazoles **179a–s**, respectively (Scheme 61).<sup>102</sup>

## 7. Concluding remarks

2-Chloroquinoline-3-carbaldehydes represent an extremely interesting class of organic compounds that can be exploited as precursors and building blocks for the synthesis of a wide range of heterocyclic systems and potent antibiotics for microbial and cancer treatment. In addition, quinoline moiety is the basic skeleton of many naturally occurring alkaloids and anticancer drugs. The recent publications describe the synthetic routes of 2-chloroquinoline-3-carbaldehydes following the Meth-Cohn synthesis using Vilsmeier reagent (DMF +  $POCl_3$  or  $PCl_5$ ) upon 2-Oxo-1,2-dihydroquinoline-3-carbaldehydes heating. are considered as reactive synthons in organic synthesis and obtained from the respective 2-chloro derivative by heating in acetic acid containing sodium acetate. 3-Formylquinolines are reactive towards condensation reactions with amines and hydrazines to produce Schiff bases. Nevertheless, in the last five

years, the synthesis of fused quinoline heterocyclic systems was reported through a condensation reaction of formyl quinolines either with intramolecular cyclization or reaction with sodium azide or from multicomponent reaction with azidotrimethylsilane, isocyanides, and arylamines. Eventually, reactions with active methylene-containing compounds tend to yield the respective fused systems. The synthesis of binary heterocyclic systems has been attracted the researcher's interest in the last years due to the valuable biological and medicinal importance through the incorporation of other heterocycles into quinoline ring system. The present survey highlighted the recently cited research data in the literature on the chemistry of 2-chloroquinoline-3-carbaldehyde besides related analogs and their applications. It is certain that 2-chloroquinoline-3carbaldehydes will continue to attract the attention of many researchers and that improvements in their synthesis, as well as novel transformations of these compounds, will be reported in the literature in the near future.

## Conflicts of interest

The author(s) confirm that this article content has no conflict of interest.

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