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ORIGINAL PAPER

Quinoline conjugated imidazopyridine and pyridopyrimidine synthesis in water as highly selective fluoride sensors via a catalyst-free four-component reaction

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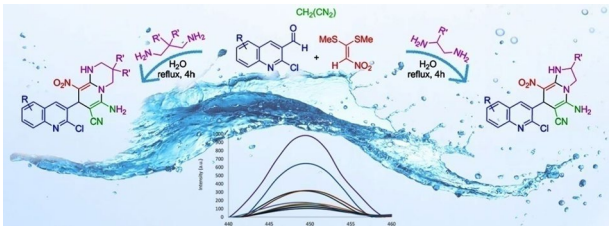
Abstract

A green and convenient procedure for the synthesis of quinoline-conjugated imidazopyridines and pyridopyrimidines has been developed by a simple one-pot reaction in the absence of any transition metal catalyst in water. This green process can be readily performed by reacting inexpensive starting materials of 2-chloroquinoline-3-carbaldehyde, malononitrile, 1,1-bis(methylthio)-2-nitroethylene, and diamine in aqueous solution. The present synthesis shows attractive characteristics, such as the use of water as reaction media, convenient one-pot operation, and reduced waste production without the use of any base or metal promoters. The products are purified by crystallization from ethanol, and the process does not involve any hazardous solvent. Also, the fluorescence study of these conjugated systems was also considered, which revealed that they have highly selective sensing of fluoride.

Graphic abstract



Keywords Indeno[1,2-*b*]furan · 2-chloroquinoline-3-carbaldehyde · Quinoline conjugated imidazopyridine and pyridopyrimidine · Nitro ketene dithioacetal · Fluoride sensors

Introduction

The quinoline nucleus comprises a class of heterocycles, which has been exploited more immensely than any other nucleus for the development of potent drugs. Since quinoline is a core structure present in various natural products and pharmaceuticals, compounds containing this scaffold have been extensively used in medicinal chemistry [1–4].

Compounds incorporating quinoline ring system exhibited various biological [5, 6], and pharmaceutical activities e.g. anti-tuberculosis [7], antiplasmodial [8], antibacterial [9, 10], antihistamine [11], antifungal [12], antimalarial [13, 14], anti-HIV [15], anticancer [16], anti-inflammatory [17, 18], anti-hypertensive [19], and antioxidant activities [20]. In addition, the use of quinolines as tyrokinase PDGF-RTK inhibitor [21], inositol 50-phosphatase (SH2) [22], DNA gyrase B inhibitors as *Mycobacterium tuberculosis* [23], and DNA topoisomerase inhibitors [24] were reported.

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Additionally, quinoline derivatives find use in the synthesis of biocides, fungicides, alkaloids, flavoring agents, rubber chemicals, and as an antifoaming agent in refineries [25–28].

Also, quinoline has a privileged scaffold in cancer drug discovery [8]. The diarylquinoline TMC207 (Fig. 1), developed at Johnson & Johnson Pharmaceutical Research and Development, was shown to possess a new mechanism of action based on the interaction with the enzyme adenosine triphosphate (ATP) synthase, the energy source for the bacterium [29, 30]. This drug, which is very promising against multidrug-resistant tuberculosis (MDR-TB), is currently in phase 2 clinical trials.

Imidazo[1,2-*a*]pyridines and pyrido[1,2-*a*]pyrimidines possess a wide-range spectrum of biological activities, including antitumor, antiviral, and mutagenicity activities. Pyrido[1,2-*a*]pyrimidines exist in the structure of several prescribed drugs such as the pirenperone [31], tranquilizer, pemirolast [32], antiasthmatic agent, antiallergic agent, antiulcerativeagent [33], barmastine [34]. They are also renowned for their antidepressant [35], gastrointestinal protective [36], stress-protecting [37], neurotropic, and anticancer properties. They also exhibit promising antiviral (anti-HIV), antinociceptive, and antibacterial activities [38]. Imidazo[1,2-*a*]pyridine scaffold exhibits a remarkably wide range of biological activities, such as antitumoral [39], anti-inflammatory [40], antiviral [41], antiulcer [42], antiprotozoal [43], antifungal [44], inhibitors of cyclin-dependent kinase [45], inhibitors of gastric acidsecretion [46], and so on.

On the other hand, the reactions in water have attracted considerable interest in recent times because of the use of large volumes of volatile, hazardous organic solvents in chemical processes also poses a serious threat to the environment, because these solvents contribute significantly to chemical waste [47]. The development of an efficient procedure using water as the reaction medium, and environmentally benign solvents for isolation and purification of products has received high priority in the design of green processes [48–50].

Because of the importance of these heterocycles and significant enhancement expectation in biological activity in the presence of two different heterocyclic motifs in a single molecule, we synthesized new prototypes of quinoline-pyridine and pyrimidine nucleus in a single molecular framework in water that successively evaluated them for sensor activity.

Results and discussion

With given our interest and experience in the area of one-pot multicomponent reactions [51–59], we became attracted how Knoevenagel adduct generated in situ from 2-chloroquinoline-3-carbaldehyde and malononitrile could be trapped by nitro ketene aminal to give a heterocycle product. Since the electrophilic nature of the conjugated Knoevenagel adduct **6** makes it subjected to nucleophilic attack, on the other hand, the versatility of nitro ketene aminal (NKA) in the synthesis of useful heterocyclic scaffolds is well documented [60–65] and relies on their ability to exhibit intriguing multinucleophilic reactivity. For this purpose, we investigated the reaction of 2-chloroquinoline-3-carbaldehydes, malononitrile, diamines, and 1,1-bis(methylthio)-2-nitroethylene (BMTNE) in water at room temperature that afforded quinoline-imidazo[1,2-*a*]pyridines and quinoline-pyrido[1,2-*a*]-pyrimidines in excellent yields.

To test this new process, initially, we investigated the reaction of 2-chloroquinoline-3-carbaldehydes (that was prepared based on the previously reported procedure, Scheme 1) [66, 67], with malononitrile at room temperature in the absence of any catalysis that afforded the expected Knoevenagel adduct intermediate.

After the formation of Knoevenagel adduct, ethylenediamine and 1,1-bis(methylthio)-2-nitroethylene (BMTNE) were introduced at room temperature. When the reaction was carried out at room temperature, any product was not obtained after 48 h (Table 1, entry 1). However, when the reaction was heated at 70 °C, we found that the reaction

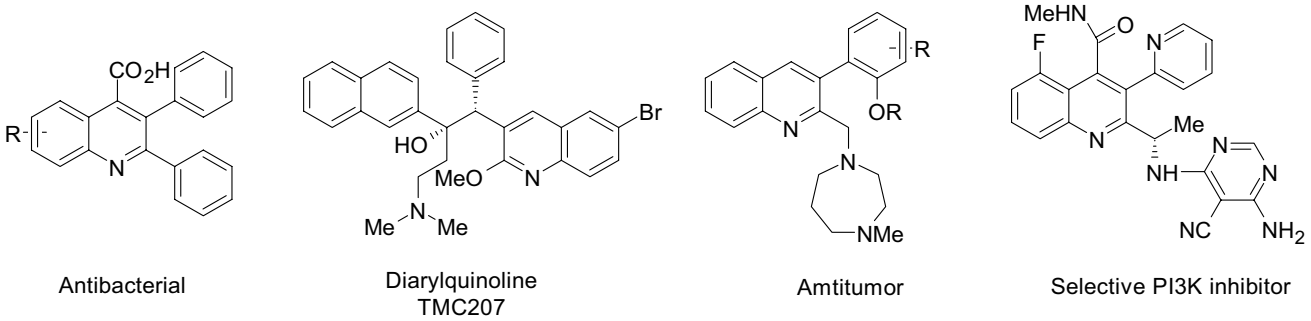


Fig. 1 Some biologically important quinoline nucleus

was complete, and the desirable product was obtained in an isolated yield of 81% within 4 h (Table 1, entry 2).

A series of conditions were screened to set up a standard reaction condition for high yields of the desired product in short reaction time. For this purpose, several solvents such as H_2O, CH_3CN, and THF (Table 1, entries 3–6) were examined, and experimental results showed that the reaction proceeded with excellent yields when water was utilized as the solvent at 70 °C. With optimal conditions established, we then examined the scope of the reaction for the construction of various conjugated quinolines, and the results are summarized in Table 2. Different types of diamines and 2-chloroquinoline-3-carbaldehydes were examined under the standard conditions (Scheme 2). As depicted in Table 2, they could react and smoothly generate the desired products **4** and **5** in excellent yields. The reaction was completely finished within 4 h in all cases at 70 °C.

The structures of compounds **4** and **5** were deduced from their elemental analysis, IR, and high-field ^{1}H, ^{13}C NMR spectra (see the Supporting Information). The mass spectrum of **4a** displayed the molecular ion peak at $m/z = 369$, which is in agreement with the proposed structure. The IR spectrum of this compound showed absorption bands due to the NH_2 and NH stretching frequency at 3433, 3377, and 3298 cm^{-1}. Absorption bands at 2172, 1659, and 1586 cm^{-1} are due to the CN, C = N, and NC = C groups that clearly indicated the most significant functional groups of the product. The ^{1}H NMR spectrum of **4a** showed four singlets at $\delta = 5.25$, 6.62, 8.36, and 9.64 ppm and was assigned as CH, NH_2, CH of aromatic and NH protons. Four aromatic hydrogens gave rise to characteristic signals in the aromatic region of the spectrum. The ^{1}H decoupled ^{13}C NMR spectrum of **4a** showed 17 distinct resonances in agreement with the suggested structure. The most important region of the spectrum

Scheme 1

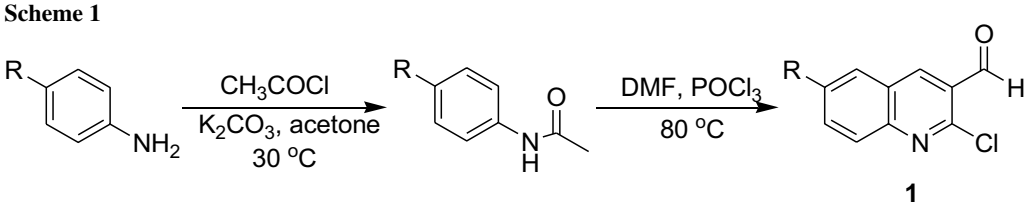
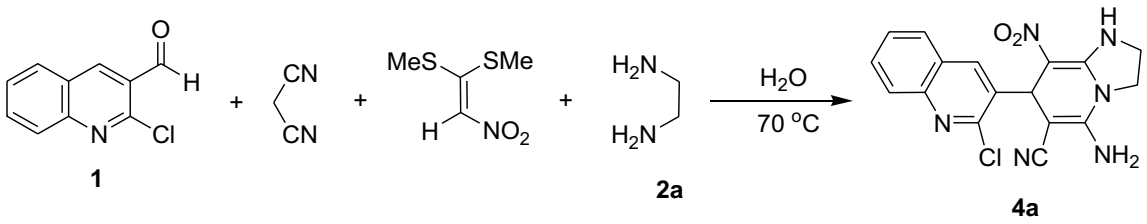


Table 1 Optimization conditions for the formation of quinoline-imidazo[1,2-*a*]pyridine **4a**



Entry	Solvent	Temp /°C	Time /h	Yield[a] /%
1	EtOH	r.t	48	–
2	EtOH	70	4	81
3	H_2O	r.t	48	–
4	H_2O	70	4	90
5	MeCN	70	10	52
6	THF	70	10	38

Scheme 2

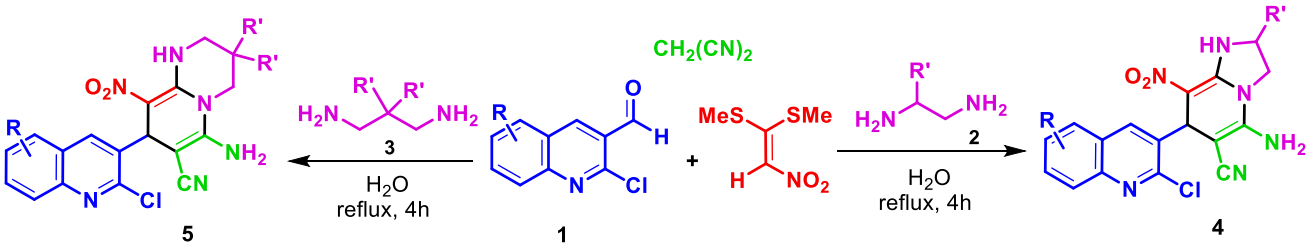
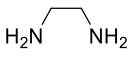
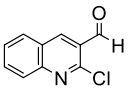
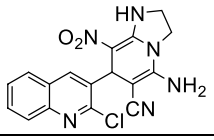
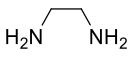
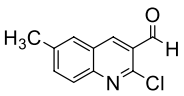
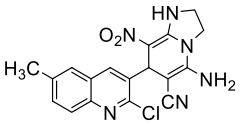
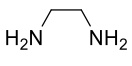
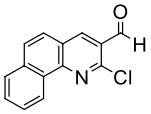
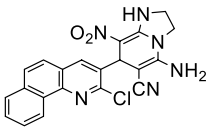
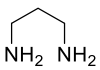
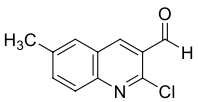
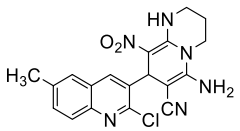
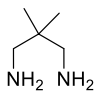
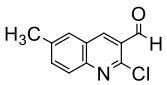
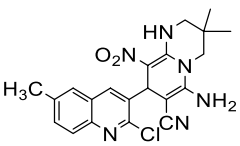
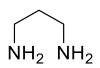
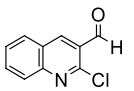
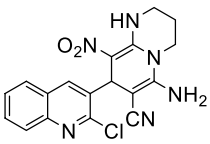
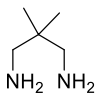
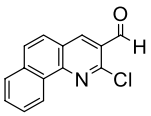
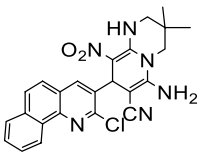
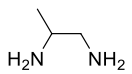
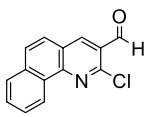
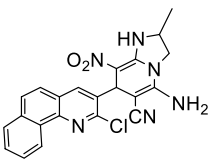


Table 2 Quinoline conjugated imidazopyridine and pyridopyrimidines **4** and **5** synthesized by the procedures shown in Scheme 2

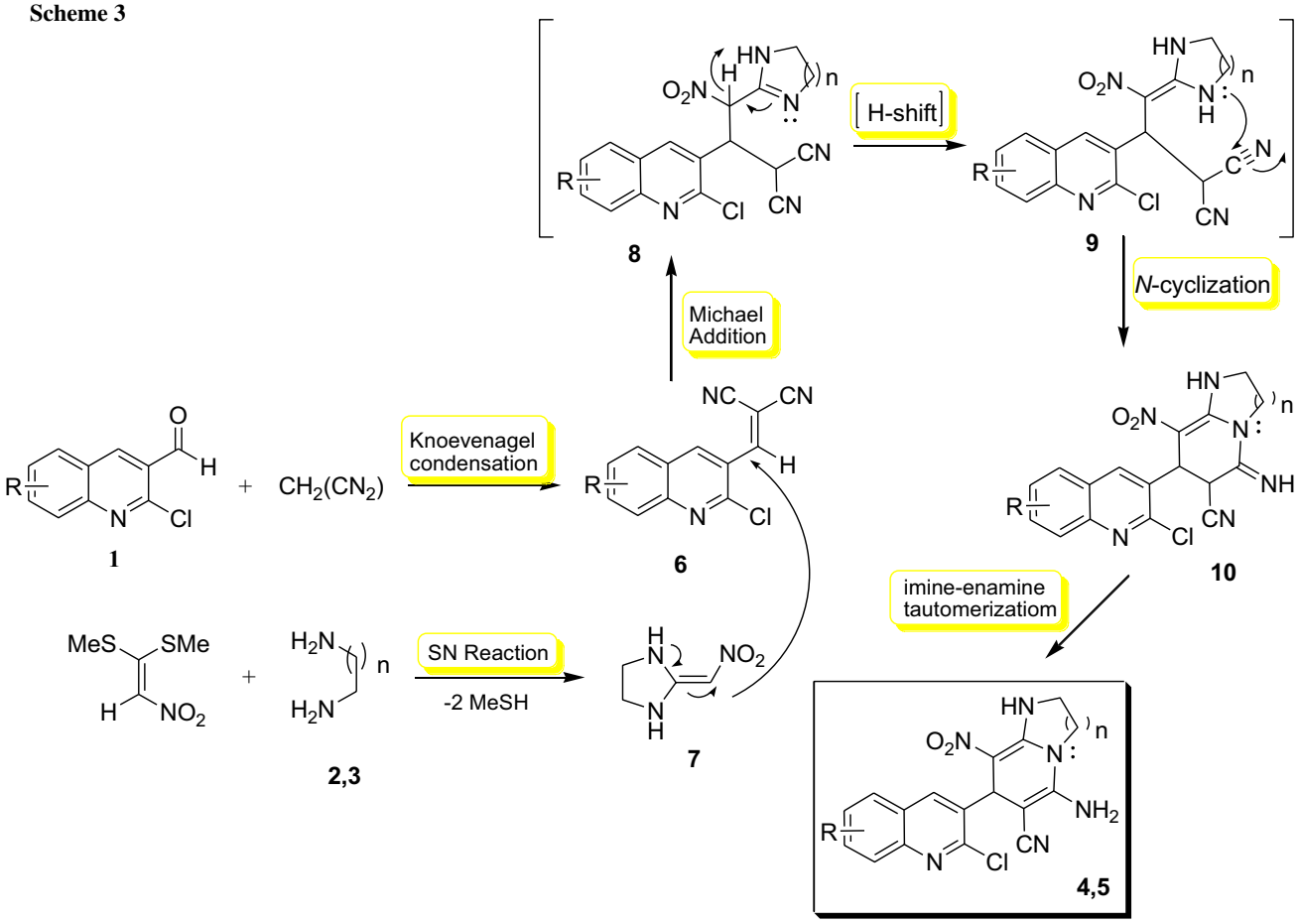
Entry	Product	Diamine	2-Chloroquinoline-3-carbaldehyde	Product **4**, **5**	Yield /%
1	**4a**				90
2	**4b**				83
3	**4c**				80
4	**5a**				78
5	**5b**				72
6	**5c**				81
7	**5d**				74
8	**4d**				70

is related to resonances due to CH, *C*CN, CN, CNO_2, CNH_2, which appear at $\delta = 43.8$, 57.4, 105.3, 120.8, 152.2 ppm.

Although the precise mechanism is not known, a mechanistic postulate, as shown in Scheme 2 may be invoked to rationalize the formation of **4** and **5**. It is conceivable that the ketene aminal **7**, formed by the interaction between the nitro ketene dithioacetal and diamine attacks the Knoevenagel adduct **6** obtained from the condensation of 2-chloroquinoline-3-carbaldehyde (**1**) with malononitrile, leading to Michael adduct **8**. The subsequently generated **8** is transformed into **9** and finally **4** and **5** presumably upon ring closure and tautomerization processes, respectively (Scheme 3).

Fluoride ions (F^-) are important due to application in dentistry and treatment of osteoporosis as a result, a high concentration of F^- ions could be dangerous as producing

Scheme 3



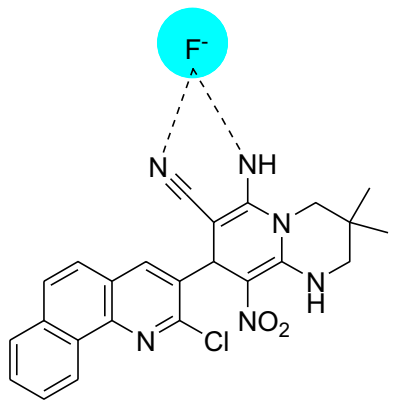


Fig. 2 The structure of (2-chlorobenzo[*h*]quinolin-3-yl)pyrido[2,1-*b*] pyrimidine-7-carbonitrile (**5d**) with F^-

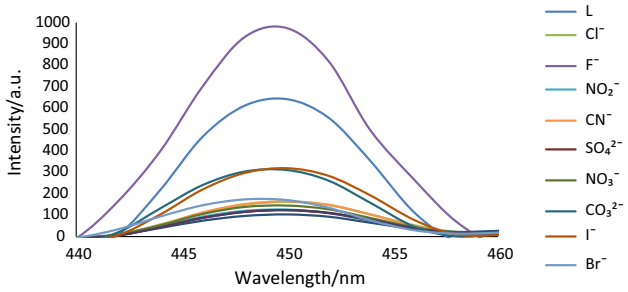


Fig. 3 Fluorescence emission (2-chlorobenzo[*h*]quinolin-3-yl) pyrido[2,1-*b*]pyrimidine-7-carbonitrile (**5d**) (3 cm^3 DMSO suspension, 0.2 g dm^{-3}) in the presence of different metal ions

H-bond action with NH or OH fragment to artificial sensors. These features observed in some amide-, phenol-, and urea groups due to having electron-withdrawing structures [68–71].

The synthesized compound was assessed as sensor F^- in DMSO. To evaluate products **4** and **5** as a selective fluorescence probe for a particular anions, the influence of different anions (F^-, Cl^-, Br^-, I^-, CN^-, SCN^-, NO_2^-, NO_3^-) on the fluorescence response of the **5d** was studied. The solution was prepared in DMSO with 0.2 g dm^{-3} and its fluorescence response upon addition of 100 mm^3 of A^{n-} was recorded. All spectra were immediately recorded after

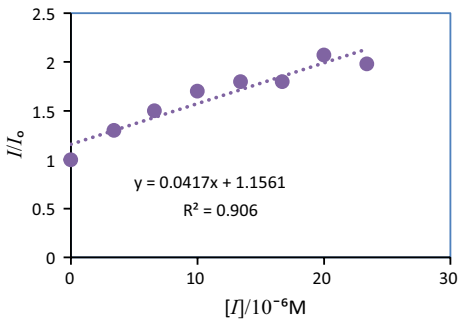


Fig. 4 Stern–Volmer plot for titration of (2-chlorobenzo[*h*]quinolin-3-yl)pyrido[2,1-*b*]pyrimidine-7-carbonitrile with different concentrations of F^- ions

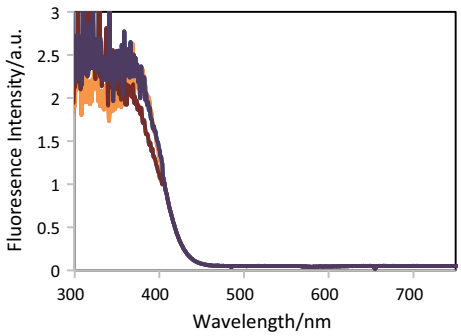


Fig. 5 Absorption spectra of ligand and ions (3 cm^3 DMSO solution 0.2 g dm^{-3}) upon addition of various metal-ions (100 $mm^3 \times 10^{-2}$ M)

the addition of the anions to the suspension. The results (Figs. 2, 3) revealed that the fluorescence intensity of **5d** enhanced in the presence of F^- ions, whereas the addition of other relevant anion quenched under the experimental conditions. Hence F^- among other anions was selected by **5d,** which is most likely to bind with F^- ions via the electron-donor nitrogen atoms as the theory of hard and soft acids and bases (HSAB theory).

The selectivity of (2-chlorobenzo[*h*]quinolin-3-yl)-pyrido[2,1-*b*]pyrimidine-7-carbonitrile toward F^- ions in DMSO was studied in the presence of other anions Cl^-, Br^-, I^-, CN^-, SCN^-, NO_2^-, NO_3^-, and SO_4^{2-} which demonstrated good selectivity toward F^- ions. Furthermore, excellent linearity was achieved through the fluorescence intensity of (2-chlorobenzo[*h*]quinolin-3-yl)pyrido[2,1-*b*]-pyrimidine-7-carbonitrile and different concentrations of F^- ions with a detection limit of 3.51×10^{-7}.

The sensitivity examination of the (2-chlorobenzo[*h*]-quinolin-3-yl)pyrido[2,1-*b*]pyrimidine-7-carbonitrile for F^- ions in DMSO was recorded by various concentrations of F^- in 10^{-3} M. The titration results in Fig. 4 demonstrated that, the fluorescence intensity of (2-chlorobenzo[*h*]-quinolin-3-yl)pyrido[2,1-*b*]pyrimidine-7-carbonitrile was regularly increased by F^- concentrations. The linear relationship was attained through the increase of fluorescence intensity and various concentrations of F^- ions by a linearly dependent coefficient $R^2 = 0.906$. Moreover, the detection limit based on DL = $3S_d/m$ where S_d is the standard deviation of the blank solution measured by five times, and m is the slope of fluorescence intensity of (2-chlorobenzo[*h*]quinolin-3-yl)pyrido[2,1-*b*]pyrimidine-7-carbonitrile with F^- ions which the calculated DL was 3.51×10^{-7}.

The addition of different metal ions (100 mm^3) to the ligand solution was examined, as shown in Fig. 5. The absorption spectrum of the ligand in DMSO was recorded from visible to UV region, and there is no pick. It is essential to mention that the observed color does not change when adding ions in the ligand solution.

Conclusion

In conclusion, the reaction of 2-chloroquinoline-3-carbaldehyde, malononitrile, with diamines and nitro ketene dithioacetal underwent one-pot multicomponent reaction in water, affording a variety of biologically interesting quinolone-pyridopyrimidines and pyrolopyrimidine conjugates. The reaction proceeds at room temperature with excellent yields of the desired products. This metal-free approach offers an easy access to diverse quinolines for applications in pharmaceuticals and materials. Further investigations in this area are currently underway and will be reported in due course.

Experimental

The malononitrile, diamines, and 1,1-bis(methylthio)-2-nitroethylene (nitro ketene dithioacetal)obtained from Merck (Germany) and Fluka (Switzerland) were used without further purification. 2-Chloroquinoline-3-carbaldehyde synthesized by Ref. [45]. Elemental analyses for C, H, and N were performed using a Heraeus CHN–O–Rapid analyzer. Mass spectra were recorded on a FINNIGAN-MATT 8430 mass spectrometer operating at an ionization potential of 70 eV. ^{1}H NMR (500 and 300 MHz), and ^{13}C NMR (125 and 75 MHz) spectra were obtained using Bruker DRX-500 AVANCE and Bruker DRX-300 AVANCE spectrometers. IR spectra were recorded as KBr pellets on a NICOLET FT-IR 100 spectrometer. Melting points were measured on an Electrothermal 9100 apparatus.

Typical synthesis procedure (for example 4a)

A mixture of 0.19 g 2-chloroquinoline-3-carbaldehyde (1 mmol) and 0.068 g malononitrile (1 mmol) and 2 cm^3 H_2O was mixed in a 50 cm^3 round bottom flask at room temperature. After 30 min, 0.06 g ethylenediame (1 mmol) and 0.165 g nitro ketene dithioacetal (1 mmol) were added to the reaction mixture, and stirring was allowed to continue at reflux for 3 h. The completion of the reaction was monitored using thin layer chromatography. After completion of the reaction the precipitated product was filtered and washed with cold ethanol to afford the pure product **4a**.

5-Amino-7-(2-chloroquinolin-3-yl)-8-nitro-1,2,3,7-tetrahydroimidazo[1,2-*a*]pyridine-6-carbonitrile (4a, $C_{17}H_{15}ClN_6O_2$) Yellow powder; m.p.: 285 °C (decomp); yield: 0.331 g (90%); IR (KBr): $\overline{\nu}$ = 3433 (NH), 3377, 3298 (NH_2), 2172 (CN), 1659 (C = N), 1586 (C = C), 1472, 1377 (NO_2) cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 369 (M^+-1, 3), 313 (6), 239 (9), 177 (5), 57 (58), 43 (100); ^{1}H NMR (500 MHz, DMSO-d_6): δ = 3.86 (m, 2H, CH_2NH), 4.06 (m, 2H, CH_2N), 5.25 (s, 1H, CH), 6.62 (s, 2H, NH_2), 7.62 (t, $^3J_{HH}$ = 7.5 Hz, 1H, CH of Ar), 7.77 (t, $^3J_{HH}$ = 8 Hz, 1H, CH of Ar), 7.92 (d, $^3J_{HH}$ = 8.35 Hz, 1H, CH of Ar), 8.01 (d, $^3J_{HH}$ = 8.5 Hz, 1H, CH of Ar), 8.36 (s, 1H, H of Ar), 9.64 (s, 1H, NH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ = 39.9 (CH), 43.8 (CH_2), 45.1 (CH_2), 57.4 (C–CN), 105.3 (CN), 120.8 (C–NO_2), 127.6 (CH of Ar), 127.8 (CH of Ar), 127.9 (CH of Ar), 128.0 (CH of Ar), 130.8 (CH of Ar), 138.6 (C_{ipso} of Ar), 146.3 (C_{ipso}-N and C_{ipso} of Ar), 149.9 (C_{ipso} of Ar), 150.2 (C_{ipso} of Ar), 152.2 (C–NH_2) ppm.

5-Amino-7-(2-chloro-6-methylquinolin-3-yl)-8-nitro-1,2,3,7-tetrahydroimidazo[1,2-*a*]pyridine-6-carbonitrile (4b, $C_{18}H_{17}ClN_6O_2$) Yellow powder; m.p.: 297 °C (decomp); yield: 0.317 g (83%); IR (KBr): $\overline{\nu}$ = 3434 (NH), 3371, 3300 (NH_2), 2173 (CN), 1658 (C = N, C = C), 1475, 1346 (NO_2) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.46 (s, 3H, CH_3), 3.85 (t, $^3J_{HH}$ = 8.3 Hz, 2H, CH_2NH), 4.05 (t, $^3J_{HH}$ = 10 Hz, 2H, CH_2N), 5.20 (s, 1H, CH), 6.59 (s, 2H, NH_2), 7.58 (d, $^3J_{HH}$ = 8.8 Hz, 1H, CH of Ar), 7.75 (s, 1H, CH of Ar), 7. 79 (d, $^3J_{HH}$ = 8.65 Hz, 1H, CH of Ar), 8.22 (s, 1H, CH of Ar), 9.61 (s, 1H, NH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ = 21.5 (CH_3), 39.9 (CH), 43.8 (CH_2), 45.1 (CH_2), 57.6 (C–CN), 95.3 (CN), 104.7 (C–NO_2), 120.8 (CH of Ar), 126.7 (CH of Ar), 127.5 (CH of Ar), 127.8 (CH of Ar), 132.9 (C_{ipso} of Ar), 137.2 (C_{ipso} of Ar), 138.0 (C_{ipso} of Ar), 144.9 (C_{ipso}-N), 148.9 (C_{ipso} of Ar), 150.2 (C_{ipso} of Ar), 152.2 (C–NH_2) ppm.

5-Amino-7-(2-chlorobenzo[*h*]quinolin-3-yl)-8-nitro-1,2,3,7- tetrahydroimidazo[1,2-*a*]pyridine-6-carbonitrile (4c, $C_{21}H_{17}ClN_6O_2$) Orange powder; m.p.: 268 °C (decomp); yield: 0.335 g (80%); IR (KBr): $\overline{\nu}$ = 3453 (NH), 3351, 3409 (NH_2), 2168 (CN), 1654 (C = N), 1590 (C = C), 1355, 1565 (NO_2) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 3.90 (m, 2H, CH_2NH), 4.09 (t, $^3J_{HH}$ = 8.75 Hz, 2H, CH_2N), 5.33 (s, 1H, CH), 6.65 (s, 2H, NH_2), 7.77 (t, $^3J_{HH}$ = 3.75 Hz, 2H, CH of Ar), 7.90 (d, $^3J_{HH}$ = 8.8 Hz, 1H, CH of Ar), 7.97 (d, $^3J_{HH}$ = 8.8 Hz, 1H, CH of Ar),8.04 (t, $^3J_{HH}$ = 4 Hz, 1H, CH of Ar), 8.43 (s, 1H, CH of Ar), 8.99 (t, $^3J_{HH}$ = 5.2 Hz, 1H, CH of Ar), 9.66 (s, 1H, NH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ = 39.4 (CH), 43.9 (CH_2NH), 45.18 (CH_2N), 66.8 (C–CN), 77.6 (CN), 105.0 (CNO_2), 120.9 (CH of Ar), 124.0 (CH of Ar), 125.1 (CH of Ar), 126.1 (CH of Ar), 127.9 (CH of Ar), 128.51 (CH of Ar), 128.59 (CH of Ar), 129.2 (CH of Ar),129.9 (C_{ipso} of Ar), 133.7 (C_{ipso} of Ar), 139.2 (C_{ipso} of Ar), 144.3 (2C_{ipso} of Ar), 148.8 (C_{ipso}-N), 150.2 (C_{ipso} of Ar), 152.3 (C–NH_2) ppm.

6-Amino-8-(3-chloro-7-methylnaphthalen-2-yl)-9-nitro-1,3,4,8-tetrahydro-2*H*-pyrido[1,2-*a*]pyrimidine-7-carbonitrile (5a, $C_{19}H_{19}ClN_6O_2$) Yellow powder; m.p.: 281 °C (decomp); yield: 0.309 g (78%); IR (KBr): $\overline{\nu}$ = 3395, 3342 (NH_2), 3231 (NH), 2179 (CN), 1659 (C = N), 1630 (C = C), 1495, 1346 (NO_2) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.03–2.07 (m, 1H, CH_2), 2.13–2.17 (m, 1H, CH_2), 2.47 (s, 3H, CH_3), 3.41–3.45 (m, 1H, CH_2NH), 3.65–3.69 (m, 1H, CH_2NH), 3.74–3.79 (m, 1H, CH_2N), 3.85–3.89 (m, 1H, CH_2N), 5.24 (s, 1H, CH), 6.54 (s, 2H, NH_2), 7.60 (d, $^3J_{HH}$ = 8.55 Hz, 1H, CH of Ar), 7.80 (d, $^3J_{HH}$ = 3.45 Hz, 2H, CH of Ar), 7.82 (s, 1H, CH of Ar), 8.12 (s, 1H, CH of Ar), 11.75 (s, 1H, NH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ = 19.9 (CH_2), 21.5 (CH_3), 38.3 (CH), 38.8 (CH_2NH), 43.6 (CH_2N), 59.2 (C–CN), 107.6 (CN), 120.7 (C–NO_2), 126.9 (CH of Ar), 127.5 (CH of Ar), 127.7 (CH of Ar), 133.0 (CH of Ar), 136.2 (C_{ipso} of Ar), 137.2 (C_{ipso} of Ar), 137.4 (C_{ipso} of Ar), 144.9 (C_{ipso}-N), 148.7 (C_{ipso} of Ar), 151.1 (C_{ipso} of Ar), 151.8 (C–NH_2) ppm.

6-Amino-8-(3-chloro-7-methylnaphthalen-2-yl)-3,3-dimethyl-9-nitro-1,3,4,8-tetrahydro-2*H*-pyrido[1,2-*a*]pyrimidine-7-carbonitrile (5b, $C_{21}H_{23}ClN_6O_2$) Yellow powder; m.p.: 283 °C (decomp); yield: 0.305 g (72%); IR (KBr): $\overline{\nu}$ = 3392, 3322 (NH_2), 3187 (NH), 2184 (CN), 1664 (C = N), 1628 (C = C), 1540, 1339 (NO_2) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.08 (s, 3H, CH_3), 1.12 (s, 3H, CH_3), 2.48 (s, 3H, CH_3), 3.25 (d, $^3J_{HH}$ = 13.4 Hz, 2H, CH_2NH), 3.54 (d, $^3J_{HH}$ = 12.25 Hz, 1H, CH_2N), 3.62 (d, $^3J_{HH}$ = 12.15 Hz, 1H, CH_2N), 5.13 (s, 1H, CH), 6.51 (s, 2H, NH_2), 7.62 (d, $^3J_{HH}$ = 8.55 Hz, 1H, CH of Ar), 7.73 (s, 1H, CH of Ar), 7.83 (d, $^3J_{HH}$ = 8.65 Hz, 1H, CH of Ar), 8.08 (s, 1H, CH of Ar), 11.72 (s, 1H, NH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ = 21.5 (CH_3), 23.6 (CH_3), 24.1 (CH_3), 27.5 (CH), 38.8 ($C(CH_3)_2$), 49.6 (CH_2), 53.2 (CH_2), 59.4 (C–CN), 107.2 (CN), 120.6 (C–NO_2), 126.7 (CH of Ar), 127.6 (CH of Ar),

133.1 (CH of Ar), 135.8 (CH of Ar), 137.4 (C_{ipso} of Ar), 137.6 (C_{ipso} of Ar), 144.9 (C_{ipso}-N), 148.4 (C_{ipso} of Ar), 150.3 (C_{ipso} of Ar), 151.7 (C_{ipso}Ar), 159.19 (C–NH_2) ppm.

Amino-8-(2-chloroquinolin-3-yl)-9-nitro-1,3,4,8-tetrahydro-2*H*-pyrido[1,2-*a*]pyrimidine-7-carbonitrile (5c, $C_{18}H_{17}ClN_6O_2$) Yellow powder; m.p.: 270 °C (decomp); yield: 0.31 g (81%); IR (KBr): $\overline{\nu}$ = 3436 (NH), 3312, 3253 (NH_2), 2174 (CN), 1658 (C = N), 1626 (C = C), 1491, 1363 (NO_2) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.99–2.08 (m, 1H, CH_2), 2.14–2.16 (m, 1H, CH_2), 2.49 (s, 1H, CH), 3.40–3.44 (m, 1H, CH_2NH), 3.65–3.68 (m, 1H, CH_2NH), 3.78–3.80 (m, 1H, CH_2N), 3.86–3.89 (m, 1H, CH_2N), 5.26 (s, 1H, CH), 6.51 (s, 2H, NH_2), 7.62 (t, $^3J_{HH}$ = 7.55 Hz, 1H, CH of Ar), 7.77 (t, $^3J_{HH}$ = 8.15 Hz, 1H, CH of Ar), 7.92 (d, $^3J_{HH}$ = 10 Hz, 1H, CH of Ar), 8.035 (d, $^3J_{HH}$ = 8.15 Hz, 1H, CH of Ar), 8.25 (s, 1H, CH of Ar), 11.72 (s, 1H, NH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ = 19.9 (CH_2), 38.5 (CH), 38.8 (CH_2NH), 43.6 (CH_2N), 59.3 (C–CN), 107.5 (CN), 120.6 (C–NO_2), 127.6 (CH of Ar), 127.7 (CH of Ar), 127.8 (CH of Ar), 128.2 (CH of Ar), 130.9 (CH of Ar), 136.2 (C_{ipso} of Ar), 138.1 (C_{ipso} of Ar), 146.3 (C_{ipso}-N), 149.7 (C_{ipso} of Ar), 151.1 (C_{ipso} of Ar), 151.8 (C–NH_2) ppm.

6-Amino-8-(2-chlorobenzo[*h*]quinolin-3-yl)-3,3-dimethyl-9-nitro-3,4-dihydro-2*H*,8*H*-pyrido[2,1-*b*]pyrimidine-7-carbonitrile (5d, $C_{24}H_{23}ClN_6O_2$) Yellow powder; m.p.: 284–288 °C (decomp); yield: 0.36 g (79%); IR (KBr): $\overline{\nu}$ = 3400, 3345 (NH_2), 3231 (NH), 2187 (CN), 1663 (C = N), 1629 (C = C), 1503, 1341 (NO_2) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.10 (s, 3H, CH_3), 1.15 (s, 3H, CH_3), 3.27 (d, $^3J_{HH}$ = 17.55 Hz, 1H, CH_2NH), 3.36 (d, $^3J_{HH}$ = 18.9 Hz, 1H, CH_2NH), 3.57 (d, $^3J_{HH}$ = 12.4 Hz, 1H, CH_2N), 3.63 (d, $^3J_{HH}$ = 12.25 Hz, 1H, CH_2N), 5.33 (s, 1H, CH), 6.55 (s, 2H, NH_2), 7.77 (d, $^3J_{HH}$ = 5.15 Hz, 2H, CH of Ar), 7.84 (d, $^3J_{HH}$ = 8.95 Hz, 1H, CH of Ar), 7.97 (d, $^3J_{HH}$ = 8.75 Hz, 1H, CH of Ar), 8.04 (t, $^3J_{HH}$ = 5.5 Hz, 1H, CH of Ar), 8.25 (s, 1H, CH of Ar), 8.97 (t, $^3J_{HH}$ = 5.6 Hz, 1H, CH of Ar), 11.73 (S, 1H, NH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ = 23.6 (CH_3), 24.2 (CH_3), 28.0 ($C(CH_3)_2$), 38.8 (CH), 49.6 (CH_2NH), 53.3 (CH_2N), 59.3 (C–CN), 93.9 (CN), 107.8 (C–NO_2), 120.6 (CH of Ar), 124.0 (CH of Ar), 125.1 (CH of Ar), 125.9 (CH of Ar), 128.0 (CH of Ar), 128.62 (CH of Ar), 128.68 (CH of Ar), 129.2 (CH of Ar), 129.8 (C_{ipso} of Ar), 133.8 (C_{ipso} of Ar), 136.8 (C_{ipso} of Ar), 138.4 (C_{ipso} of Ar), 144.9 (C_{ipso} of Ar), 148.5 (C_{ipso}-N), 150.3 (C_{ipso} of Ar), 151.8 (C–NH_2) ppm.

5-Amino-7-(2-chlorobenzo[*h*]quinolin-3-yl)-3-methyl-8-nitro-1,2,3,7-tetrahydroimidazo[1,2-*a*]pyridine-6-carbonitrile (4d, $C_{22}H_{19}ClN_6O_2$) Yellow powder; m.p.: 295 °C(decomp); yield: 0.303 g (70%); IR (KBr): $\overline{\nu}$ = 3479 (NH), 3389, 3342 (NH_2), 2177 (CN), 1657 (C = N), 1616 (C = C), 1370, 1568 (NO_2) cm^{-1}; *Major isomer:* ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.37 (d, $^3J_{HH}$ = 6.25 Hz, 3H, CH_3), 3.68–3.71 (m, 2H, CH_2), 4.19–4.24 (m, 1H, CH), 5.33 (s, 1H, CH), 6.61 (s, 2H, NH_2), 7.76–7.78 (m, 1H, CH of Ar), 7.90–8.0 (m, 3H, CH of Ar), 8.04–8.05 (m, 1H, CH of Ar), 8.42 (s, 1H, CH of Ar), 8.93–9 (m, 1H, CH of Ar), 9.77 (s, 1H, NH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ = 18.7 (CH–N), 20.9 (CH_3), 22.9 (CH), 51.6 (CH_2), 53.5 (C–CN), 78 (CN), 120.8 (CNO_2), 124 (CH of Ar), 125.1 (CH of Ar), 126.18 (CH of Ar), 127.99 (CH of Ar), 128.6 (CH of Ar), 129.2 (CH of Ar), 129.9 (CH of Ar), 133.7 (CH of Ar), 144.3 (CH of Ar), 148.8 (CH of Ar), 150.2 (CH of Ar), 151.5 (N-C_{ipso}-N),), 166 (C_{ipso}H-Ar), 178.7 (C_{ipso}H-Ar), 197.2 (C–NH_2) ppm; *Minor isomer:* ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.31 (d, $^3J_{HH}$ = 5.95 Hz, 3H, CH_3), 3.94–4.01 (m, 2H, CH_2), 4.31–4.36 (m, 1H, CH), 5.31 (s, 1H, CH), 6.68 (s, 2H, NH_2), 7.76–7.78 (m, 1H, CH of Ar), 7.90–8.0 (m, 3H, CH of Ar), 8.04–8.05 (m, 1H, CH of Ar), 8.39 (s, 1H, CH of Ar), 8.93–9 (m, 1H, CH of Ar), 9.67 (s, 1H, NH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ = 19.7 (CH–N), 21.2 (CH_3), 26.5 (CH), 52 (CH_2), 52.8 (C–CN), 75.7 (CN), 120.9 (CNO_2), 123.9 (CH of Ar), 125.2 (CH of Ar), 126.14 (CH of Ar), 128 (CH of Ar), 128.5 (CH of Ar), 129.1 (CH of Ar), 129.8 (CH of Ar), 133.6 (CH of Ar), 144.2 (CH of Ar), 148.7 (CH of Ar), 150.3 (N-C_{ipso}-N), 151.2 (CH of Ar), 151.34 (CH of Ar), 151.57 (C–NH_2) ppm.

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