Asian Journal of Chemistry; Vol. 35, No. 5 (2023), 1269-1275

ASIAN JOURNAL OF CHEMISTRY

https://doi.org/10.14233/ajchem.2023.27873

Design, Synthesis and Characterization of Novel 1*H*-1,2,3-Triazole Quinoline-Isatin Tethered Conjugates

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Received: 13 March 2023; *Accepted*: 20 April 2023; *Published online*: 28 April 2023; AJC-21239

Quinoline is an important heterocyclic scaffold which is found in a variety of natural compounds (cinchona alkaloids) and therapeutically active drugs with various biological functions. Because of its varied chemical and pharmacological characteristics, quinoline and its derivatives have long drawn the attention of both synthetic and biological chemists. A newer class of quinoline-isatin tethered 1,2,3-triazole conjugates was synthesized in this context, using copper-promoted click chemistry with various organic systems. Ten derivatives of 1,2,3-triazole-tethered 8-hydroxyquinoline and 5-chloro-8-hydroxyquinoline derivatives of isatin were synthesized and well characterized by using analytical techniques such as mass spectrometry, IR, ^{1}H NMR and ^{13}C NMR spectroscopy.

Keywords: Quinolines, 1,2,3-Triazoles, Isatin, Design, Synthesis, Click reaction.

INTRODUCTION

Over 50% of all known chemical compounds are heterocycles, a group of molecules having striking biological and pharmacological characteristics [1]. Heterocycles are the main structural unit in many drugs, natural products, biomolecules, vitamins and biologically active compounds [2,3], which include antiproliferative, anti-HIV, antibiotic, antidepressant, antimalarial, anti-inflammatory, antimicrobial, antifungal, antiviral, antibacterial, antidiabetic, fungicidal, insecticidal and herbicidal agents, *etc.* They've also been identified as an important structural unit in synthetic pharmaceuticals and agrochemicals [4]. As a result, organic chemists have been working hard to discover innovative and efficient synthetic transformations to synthesize heterocyclic molecules. Quinoline scaffolds also have an important place in heterocyclic chemistry. The presence of the quinoline moiety in a diverse spectrum of naturally occurring compounds and chemically useful molecules with a variety of biological functions [5] is of great importance to both chemists and biologists. Many quinoline derivatives have been used as antimicrobials [6], antibiotics [7], malaria preventatives [8], cancer treatments [9], anti-inflammatory, anti-HIV, antioxidants and antihypertensive medicines such as mefoquine, chloroquine [10], amodiaquine [11], piperaquine, primaquine, pitavastatin, carbozatinib [12], bosutinib, saquinavir and bedaquiline [13].

Another heterocyclic molecule isatin is also significant because of its function in the synthesis of other heterocyclic compounds including quinolinic, indolic, *etc.* Isatin (1*H*-indole-2,3-dione) is a physiologically active heterocyclic moiety also known as indenedione [13]. Therefore, isatin scaffolds are the important building blocks, since all positions in isatin may be modified [14,15]. Isatin and its derivatives exhibit varied pharmacological characteristics like antibacterial, anticancer, antifungal and antioxidant, anticonvulsant, anti-inflammatory, anti-HIV, antimalarial, antidiabetic and antiglycation activities [16-18].

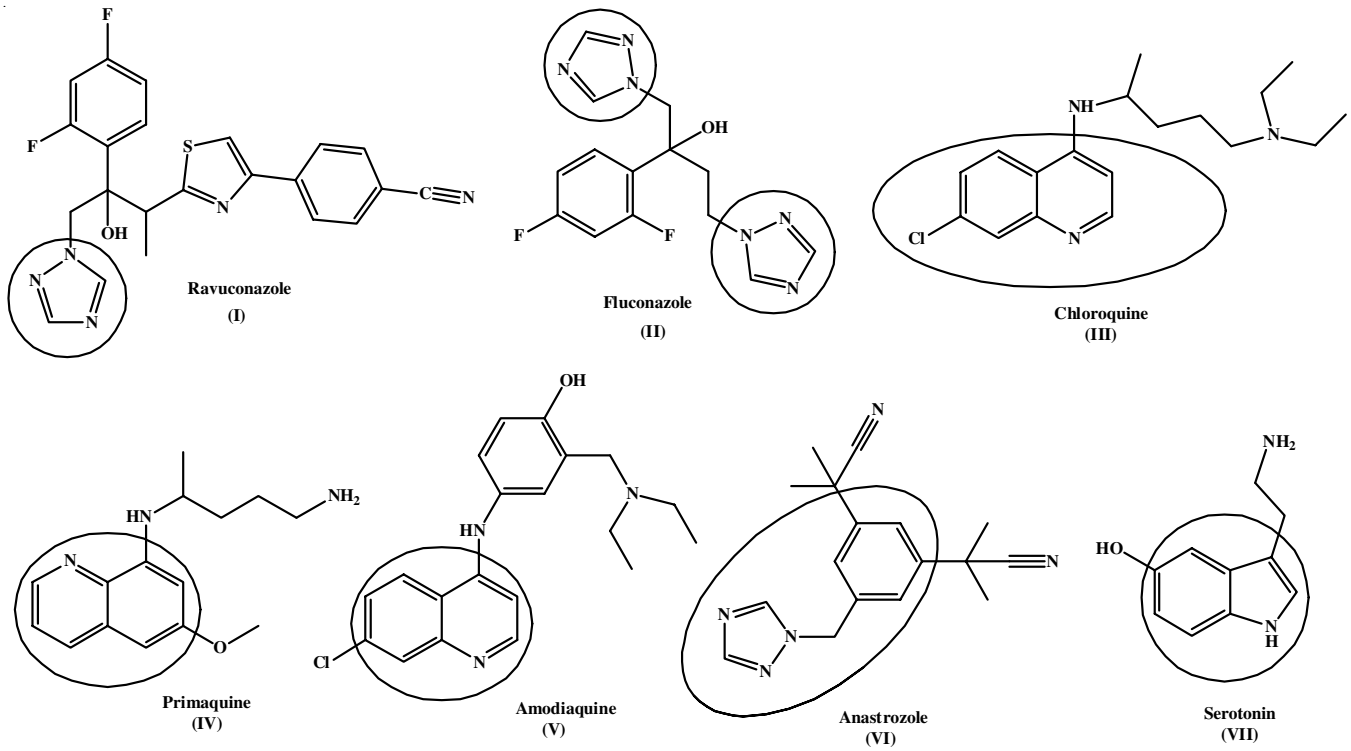


Fig. 1. Structures of some commercially available drug containing quinoline, chloroquinoline triazole and isatin scaffolds (I-VII)

Similarly, azoles belong to an important class of heterocyclic compounds that contain nitrogen atoms. 1,2,3-Triazoles, 1,2,4-triazoles and their derivatives have attracted the attention of biological and medicinal chemists. The advantageous features of the triazole ring [19], such as its mild dipole nature, hydrogen bonding ability, stiffness and stability under *in vivo* conditions, are accountable for their elevated biological activities [20,21]. 1,2,3-triazole derivatives have been shown to have a wide range of chemotherapeutic activities [22], including antimicrobial [23], anti-inflammatory, antidepressant, anticancer [24], anti-convulsant, antifungal [25] and antibacterial properties [26], *etc*. In fact, some of their derivatives are active ingredients in commonly used pharmaceuticals. Some of the commercially available drugs containing quinolone [27], indoline moiety [28] and 1,2,3-triazole are shown in Fig. 1.

Recently, tethered compounds in organic chemistry are gaining popularity on basis of the far better pharmacological properties. Kumar *et al.* [29] reported synthesis of 1*H*-1,2,3-triazol-4-yl-methyl tethered 3-pyrrolylisatins as potent anti-breast cancer agents by using click chemistry. Thus, in view of importance of various moieties mentioned above quinoline-isatin tethered 1,2,3-triazole conjugates have been synthesized in order to evaluate their antimicrobial properties the design protocol for target compound is shown in Fig. 2.

In general, the copper-promoted click reaction is known as a mild reaction that does not require many specific precautions. It proceeds to completion in 10 min to 16 h at ambient temperature in water and organic solvents, such as DMF, *tert*-butanol, ethanol and CH_3CN. However, more efficient methods can be developed for cycloaddition reactions [30]. Generally, the reactions of azides and alkynes have low reactivity, require a long time and give a low yield. It is reported [31] that the addition of the catalyst, copper(I), improved reaction yields and reduced reaction times. In view of the significance of various scaffolds as stated above, 1,2,3-triazole tethered quinoline-isatin conjugates have been synthesized and characterized.

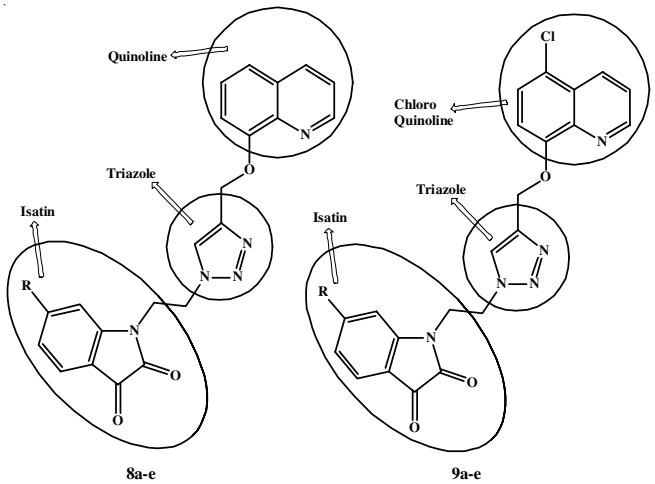


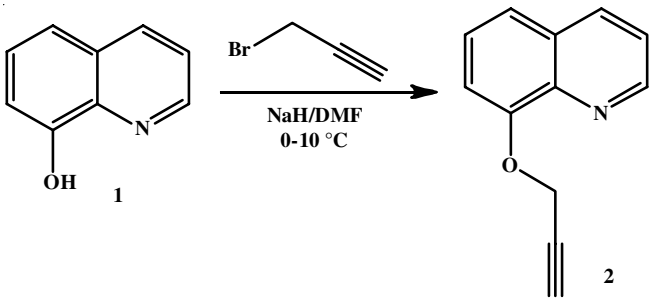
Fig. 2. Design protocol for target compounds

EXPERIMENTAL

All the chemicals and solvents used for the synthesis were of analytical grade and purchased from Sigma-Aldrich, India and Tokyo Chemical Industry (TCI) Chemicals. A silica gel-precoated thin layer chromatographic (TLC) plate was used to monitor reaction optimization. The M-560 Buchi equipment was used to measure the uncorrected melting points. Infrared

spectra were recorded using KBr disks on a Shimadzu IR Affinity 1S spectrophotometer. The JEOL ECX-400P Spectrometer USA was used to record ^{1}H NMR and ^{13}C NMR spectra in deuterated DMSO-d_6 at 400 MHz and 100 MHz, respectively. Measurements of mass spectrometry were made using a 6530 Accurate-Mass Q-TOF LC/MS spectrometer.

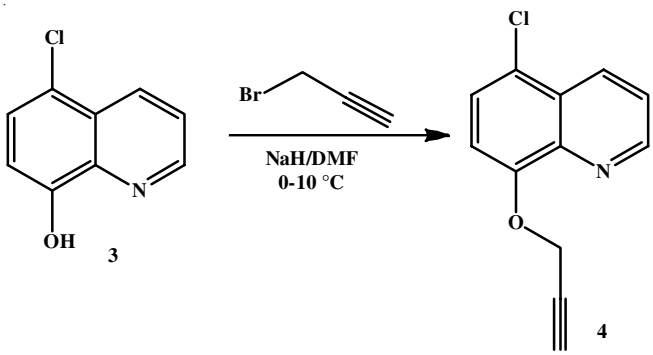
Synthesis of 8-(prop-2-yn-1-yloxy)quinoline (2): To a stirred solution of 8-hydroxyquinoline (**1**) (2.5 g, 17.22 mmol) in dry DMF (25 mL) and added sodium hydride (620 mg, 25.83 mmol) at 0-5 ºC for 10-15 min, followed by propargyl bromide solution (80% in toluene, 2.6 mL, 34.44 mmol) dropwise and stirred again for 25-30 min. The completion of the reaction was monitored by TLC. The product formed was poured onto crushed ice (500 g); the obtained precipitated was filtered, washed with distilled water (50 mL) and dried at vacuum to yield compound **2** as white solid (**Scheme-I**). The product was purified by column chromatography using silica gel (100-200 mesh) and ethyl acetate-hexane (0-30%) as eluent system.



Scheme-I: Synthetic route of propargylated quinoline

Synthesis of 5-chloro-8-(prop-2-yn-1-yloxy)quinoline (4): To a stirred solution of 5-chloro-8-hydroxyquinoline (**3**) (3.0 g, 16.70 mmol) in dry DMF (30 mL), added sodium hydride (701 mg, 29.23 mmol) at 0-5 ºC for 10-15 min followed by propargyl bromide solution (80% in toluene, 2.53 mL, 33.40 mmol) dropwise and stirred again for 25-30 min. The completion of the reaction was monitored by TLC. The product formed was poured onto crushed ice (500 g), then the obtained precipitate was filtered, washed with distilled water (50 mL) and dried at vacuum to yield compound **4** as off-white solid (**Scheme-II**). The product was purified by column chromatography using silica gel (100-200 mesh) and ethyl acetate-hexane (0-30%) as eluent system.

Synthesis of 1-(2-azidoethyl)indoline-2,3-dione (7a-e): A solution of sodium hydride (1.5 mmol) in dry DMF (20 mL) was cooled in an ice bath under the nitrogen atmosphere and



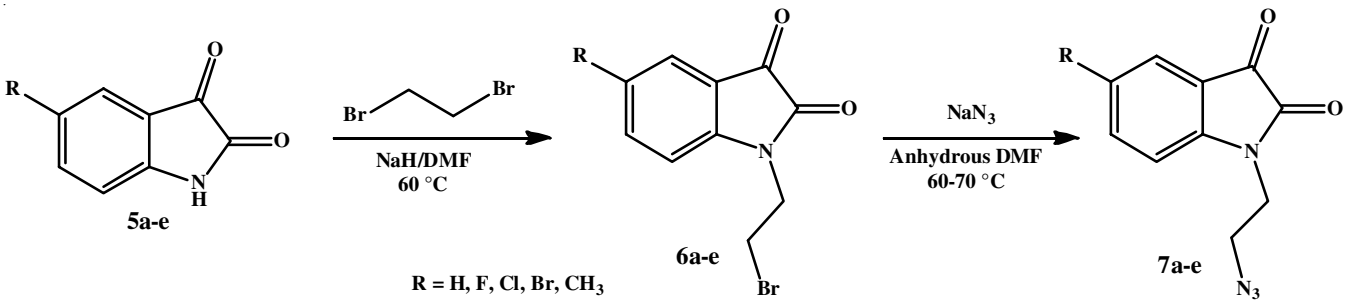
Scheme-II: Synthetic route of propargylated 5-chloroquinoline

5-substituted isatin (**5a-e**, 1 mmol) was added according to batch size. Remove the ice bath and added 1,2-dibromoethane (2 mmol) dropwise to the reaction mixture to obtain compound **7a-e** followed by the reaction with NaN_3 (2 mmol) in the presence of DMF and nitrogen atmosphere to form the desired precursor (**Scheme-III**). The product was purified by column chromatography using silica gel (100-200 mesh) and ethyl acetate-hexane (0-15%) eluent system.

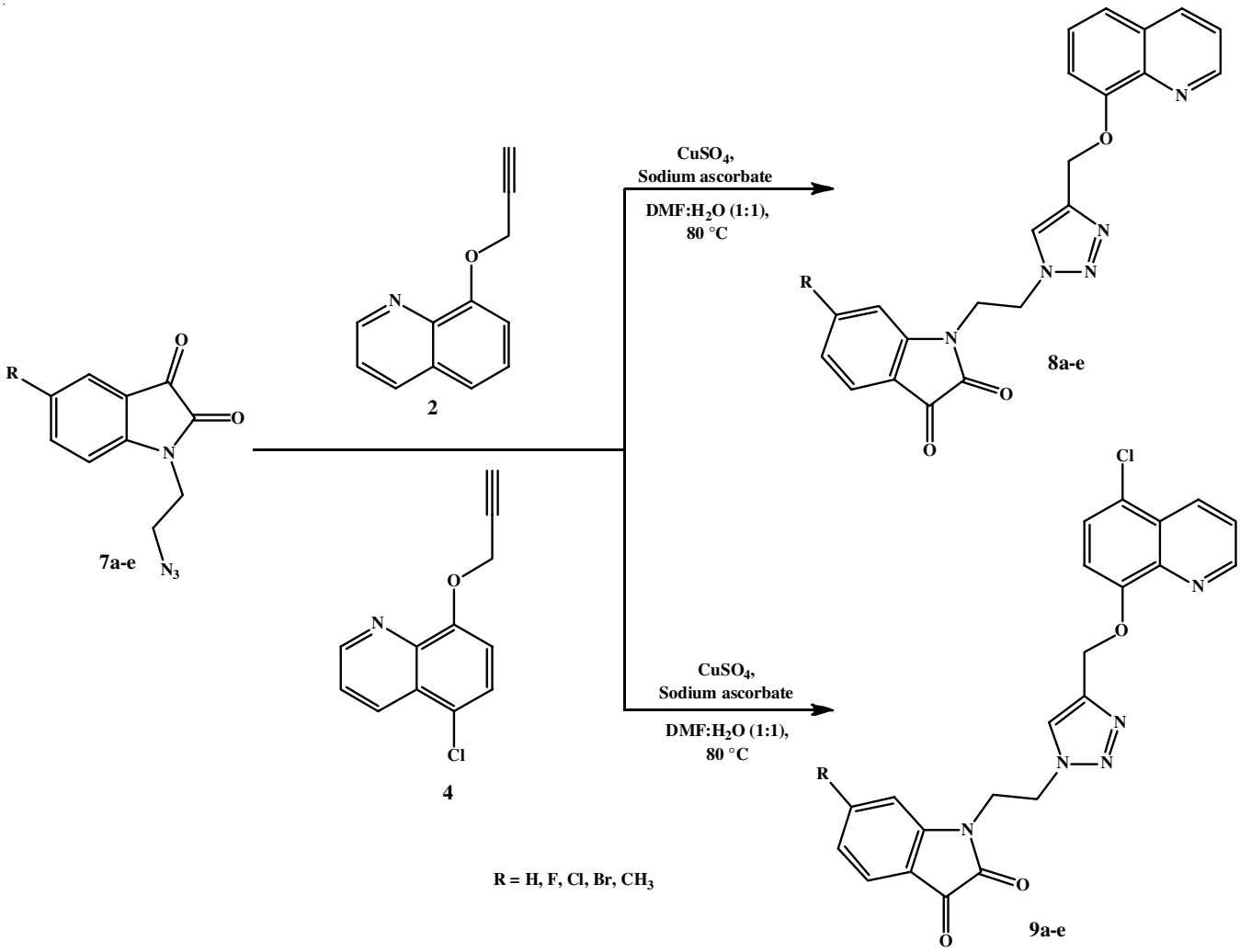
Synthesis of 1-(2-(4-((quinolin-8-yloxy)methyl)-1*H*-1,2,3-triazol-1-yl)ethyl)indoline-2,3-dione (8a-e): The target compounds, 1,2,3-triazole derivatives (**8a-e**) were synthesized *via* a Cu-promoted click reaction, by heating compound **2** (1 mmol), **6a-e** (2.1 mmol) in DMF:H_2O (1:1), copper sulphate (0.45 mmol) and sodium ascorbate (0.9 mmol) for 10 min at 80 ºC. It was obtained as yellow-orange solid with a 90-95% yield (**Scheme-IV**). The derivatives were purified by column chromatography using silica gel (100-200 mesh) and a methanol-chloroform (0-15%) eluent system.

1-(2-(4-((Quinolin-8-yloxy)methyl)-1*H*-1,2,3-triazol-1-yl)ethyl)indoline-2,3-dione (8a): Yellow solid; yield: 90%; m.p.: 154-156 ºC; IR (KBr, ν_{max}, cm^{-1}): 1738, 1614, 1515, 766, 474; ^{1}H NMR (400 MHz, DMSO) δ ppm: 8.83 (s, 1H), 8.40 (s, 1H), 8.31 (d, *J* = 8.2 Hz, 1H), 7.52 (dd, *J* = 11.6, 7.1 Hz, 5H), 7.35 (d, *J* = 7.3 Hz, 1H), 7.02 (t, *J* = 7.5 Hz, 1H), 6.90 (d, *J* = 8.2 Hz, 1H), 5.30 (s, 2H), 4.70 (t, *J* = 5.6 Hz, 2H), 4.16 (t, *J* = 5.6 Hz, 2H). ^{13}C NMR (101 MHz, DMSO) δ ppm: 183.40 (s), 162.77 (s), 158.63 (s), 154.25 (s), 150.66 (s), 149.42 (s), 143.26 (s), 140.21 (s), 138.65 (s), 136.26 (s), 129.54 (s), 127.22 (s), 126.03 (s), 124.95 (s), 123.70 (s), 122.33 (s), 120.48 (s), 117.81 (s), 110.63 (d, *J* = 19.7 Hz), 62.23 (s), 47.42 (s), 36.18 (s). HRMS data: calcd. mass $(M+H)^+$, 399.1336; found, 400.1409.

5-Chloro-1-(2-(4-((quinolin-8-yloxy)methyl)-1*H*-1,2,3-triazol-1-yl)ethyl)indoline-2,3-dione (8b): Dark yellow solid;



Scheme-III: Synthetic route of azide derivatives of 5-substituted isatin



Scheme-IV: Synthetic route of triazole derivatives **8a-e** and **9a-e**

yield: 90%; m.p.: 159-161 ºC; IR (KBr, ν_{max}, cm^{-1}): 1741, 1614, 1521, 783, 467. ^{1}H NMR (400 MHz, DMSO) δ ppm: 8.84 (s, 1H), 8.40 (s, 1H), 8.31 (d, *J* = 9.7 Hz, 1H), 7.61-7.47 (m, 5H), 7.35 (d, *J* = 8.8 Hz, 1H), 6.84 (d, *J* = 8.4 Hz, 1H), 5.30 (s, 2H), 4.69 (t, *J* = 5.7 Hz, 2H), 4.16 (t, *J* = 5.7 Hz, 2H). ^{13}C NMR (101 MHz, DMSO) δ ppm: 182.32 (s), 158.42 (s), 154.29 (s), 149.33 (d, *J* = 20.5 Hz), 149.22-149.13 (m), 143.32 (s), 140.19 (s), 137.56 (s), 136.29 (s), 129.56 (s), 127.98 (s), 127.20 (s), 126.09 (s), 124.45 (s), 122.33 (s), 120.51 (s), 119.13 (s), 112.42 (s), 110.52 (s), 62.24 (s), 47.53 (s). HRMS data: calcd. mass $(M+H)^+$, 433.0943; found, 434.1015.

5-Bromo-1-(2-(4-((quinolin-8-yloxy)methyl)-1*H*-1,2,3-triazol-1-yl)ethyl)indoline-2,3-dione (8c): Red solid; yield: 90%; m.p.: 163-165 ºC; IR (KBr, ν_{max}, cm^{-1}): 1736, 1615, 1515, 783, 467; ^{1}H NMR (400 MHz, DMSO) δ ppm: 8.84 (s, 1H), 8.40 (s, 1H), 8.31 (d, *J* = 8.3 Hz, 1H), 7.73 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.67 (d, *J* = 2.0 Hz, 1H), 7.56-7.48 (m, 3H), 7.35 (d, *J* = 8.9 Hz, 1H), 6.80 (d, *J* = 8.5 Hz, 1H), 5.30 (s, 2H), 4.68 (t, *J* = 5.7 Hz, 2H), 4.16 (t, *J* = 5.7 Hz, 2H). ^{13}C NMR (101 MHz, DMSO) δ ppm: 182.18 (s), 158.25 (s), 154.28 (s), 149.53 (d, *J* = 15.0 Hz), 143.33 (s), 140.28 (d, *J* = 17.8 Hz), 136.30 (s), 129.57 (s), 127.20 (s), 126.07 (s), 124.95 (s), 123.72 (s), 122.34 (s), 120.52 (s), 119.51 (s), 115.52 (s), 112.86 (s), 110.53 (s), 62.25 (s), 47.50 (s). HRMS data: calcd. mass $(M+H)^+$, 477.043; found, 478.045.

5-Fluoro-1-(2-(4-((quinolin-8-yloxy)methyl)-1*H*-1,2,3-triazol-1-yl)ethyl)indoline-2,3-dione (8d): Dark red solid; yield: 90%; m.p.: 159-161 ºC; IR (KBr, ν_{max}, cm^{-1}): 1748, 1614, 1518, 773, 475. ^{1}H NMR (400 MHz, DMSO) δ ppm: 8.83 (dd, *J* = 4.1, 1.7 Hz, 1H), 8.40 (s, 1H), 8.31 (d, *J* = 8.3 Hz, 1H), 7.55-7.49 (m, 3H), 7.45-7.39 (m, 2H), 7.35 (d, *J* = 7.2 Hz, 1H), 6.86 (dd, *J* = 9.4, 3.8 Hz, 1H), 5.29 (s, 2H), 4.69 (t, *J* = 5.8 Hz, 2H), 4.16 (t, *J* = 5.8 Hz, 2H). ^{13}C NMR (101 MHz, DMSO) δ ppm: 182.83 (s), 160.07 (s), 158.68 (s), 157.67 (s), 154.26 (s), 149.41 (s), 146.94 (s), 143.27 (s), 140.17 (s), 136.28 (s), 129.54 (s), 127.20 (s), 126.11 (s), 124.76 (s), 124.52 (s), 122.33 (s), 120.47 (s), 118.65 (d, *J* = 7.3 Hz), 112.28-111.91 (m), 111.78 (s), 110.47 (s), 62.20 (s), 47.50 (s). HRMS data: calcd. mass $(M+H)^+$, 417.1242; found, 418.1314.

5-Methyl-1-(2-(4-((quinolin-8-yloxy)methyl)-1*H*-1,2,3-triazol-1-yl)ethyl)indoline-2,3-dione (8e): Orange solid; yield: 88%; m.p.: 160-162 ºC; IR (KBr, ν_{max}, cm^{-1}): 1734, 1616, 1511, 780, 474. ^{1}H NMR (400 MHz, DMSO) δ ppm: 8.83 (dd, *J* = 4.1, 1.7 Hz, 1H), 8.39 (s, 1H), 8.31 (dd, *J* = 8.3, 1.7 Hz, 1H),

7.56-7.47 (m, 3H), 7.37-7.27 (m, 3H), 6.75 (d, *J* = 8.1 Hz, 1H), 5.30 (s, 2H), 4.68 (t, *J* = 5.7 Hz, 2H), 4.13 (t, *J* = 5.7 Hz, 2H), 2.16 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ ppm: 183.61 (s), 158.68 (s), 154.27 (s), 149.43 (s), 148.55 (s), 143.26 (s), 140.20 (s), 138.93 (s), 136.28 (s), 133.08 (s), 129.54 (s), 127.22 (s), 126.00 (s), 125.16 (s), 122.33 (s), 120.47 (s), 117.74 (s), 110.56 (s), 62.24 (s), 47.48 (s), 20.40 (s). HRMS data: calcd. mass $(M+H)^+$, 413.1488; found, 414.1559.

Synthesis 1-(2-(4-(((5-chloroquinolin-8-yl)oxy)methyl)-1*H*-1,2,3-triazol-1-yl)ethyl)indoline-2,3-dione (9a-e): 1,2,3-Triazole derivatives **9a-e** were also synthesized *via* Cu-promoted click reaction, by heating compound **4** (1 mmol), **7a-e** (2.1 mmol) in DMF:H_2O (1:1), copper sulphate (0.45 mmol) and sodium ascorbate (0.9 mmol) for 10 min at 80 ºC. It was obtained as yellow-orange solid with a 90-95% yield (**Scheme-IV**). The derivatives were purified by column chromatography using silica gel (100-200 mesh) and a methanol-chloroform (0-15%) eluent system.

1-(2-(4-(((5-Chloroquinolin-8-yl)oxy)methyl)-1*H*-1,2,3-triazol-1-yl)ethyl)indoline-2,3-dione (9a): Orange solid; yield: 90%; m.p.: 160-162 ºC; IR (KBr, ν_{max}, cm^{-1}): 1748, 1616, 1521, 766, 474. ^{1}H NMR (400 MHz, DMSO) δ ppm: 8.93 (s, 1H), 8.49 (d, *J* = 10.0 Hz, 1H), 8.39 (s, 1H), 7.71 (dd, *J* = 8.5, 4.1 Hz, 1H), 7.65 (d, *J* = 8.4 Hz, 1H), 7.49 (t, *J* = 7.3 Hz, 2H), 7.34 (d, *J* = 8.5 Hz, 1H), 7.00 (t, *J* = 7.3 Hz, 1H), 6.88 (d, *J* = 8.2 Hz, 1H), 5.31 (s, 2H), 4.69 (t, *J* = 5.8 Hz, 2H), 4.15 (t, *J* = 5.8 Hz, 2H). ^{13}C NMR (101 MHz, DMSO) δ ppm: 183.37 (s), 158.61 (s), 153.66 (s), 150.64 (s), 150.21 (s), 142.93 (s), 140.73 (s), 138.62 (s), 132.65 (s), 127.19 (s), 126.67 (s), 126.13 (s), 124.93 (s), 123.61 (d, *J* = 17.1 Hz), 121.55 (s), 117.77 (s), 110.72 (d, *J* = 5.7 Hz), 62.40 (s), 47.44 (s). HRMS data: calcd. mass $(M+H)^+$, 433.0943; found, 434.1014.

5-Chloro-1-(2-(4-(((5-chloroquinolin-8-yl)oxy)methyl)-1*H*-1,2,3-triazol-1-yl)ethyl)indoline-2,3-dione (9b): Orange solid; yield: 90%; m.p.: 167-169 ºC; IR (KBr, ν_{max}, cm^{-1}): 1744, 1616, 1511, 762, 474. ^{1}H NMR (400 MHz, DMSO) δ ppm: 8.94 (d, *J* = 2.7 Hz, 1H), 8.50 (d, *J* = 8.5 Hz, 1H), 8.40 (s, 1H), 7.74-7.64 (m, 2H), 7.60-7.52 (m, 2H), 7.36 (d, *J* = 8.5 Hz, 1H), 6.83 (d, *J* = 8.3 Hz, 1H), 5.32 (s, 2H), 4.68 (t, *J* = 5.6 Hz, 2H), 4.16 (t, *J* = 5.6 Hz, 2H). ^{13}C NMR (101 MHz, DMSO) δ ppm: 182.30 (s), 158.40 (s), 153.73 (s), 150.23 (s), 149.21 (s), 142.96 (s), 140.70 (s), 137.49 (s), 132.68 (s), 127.96 (s), 127.17 (s), 126.68 (s), 126.23 (s), 124.41 (s), 123.50 (s), 121.56 (s), 119.12 (s), 112.38 (s), 110.67 (s), 62.41 (s), 47.55 (s). HRMS data: calcd. mass $(M+H)^+$, 467.0562; found, 468.0631.

5-Bromo-1-(2-(4-(((5-chloroquinolin-8-yl)oxy)methyl)-1*H*-1,2,3-triazol-1-yl)ethyl)indoline-2,3-dione (9c): Reddish-orange solid; yield: 90%; m.p.: 170-172 ºC; IR (KBr, ν_{max}, cm^{-1}): 1744, 1626, 1531, 782, 474. ^{1}H NMR (400 MHz, DMSO) δ ppm: 8.94 (dd, *J* = 4.1, 1.6 Hz, 1H), 8.50 (dd, *J* = 8.5, 1.6 Hz, 1H), 8.40 (s, 1H), 7.73-7.65 (m, 4H), 7.36 (d, *J* = 8.5 Hz, 1H), 6.79 (d, *J* = 8.5 Hz, 1H), 5.31 (s, 2H), 4.68 (t, *J* = 5.7 Hz, 2H), 4.15 (t, *J* = 5.7 Hz, 2H). ^{13}C NMR (101 MHz, DMSO) δ ppm: 182.15 (s), 158.24 (s), 153.73 (s), 150.26 (s), 149.58 (s), 142.93 (d, *J* = 4.8 Hz), 140.69 (s), 140.30 (s), 138.60 (s), 132.70 (s), 127.18 (s), 126.68 (s), 126.23 (s), 123.52 (s), 121.55 (s), 119.51 (s), 115.48 (s), 112.83 (s), 110.66 (s), 62.41 (s), 47.52 (s). HRMS data: calcd. mass $(M+H)^+$, 511.0047; found, 512.0049.

1-(2-(4-(((5-Chloroquinolin-8-yl)oxy)methyl)-1*H*-1,2,3-triazol-1-yl)ethyl)-5-fluoroindoline-2,3-dione (9d): Dark red solid; yield: 90%; m.p.: 161-163 ºC; IR (KBr, ν_{max}, cm^{-1}): 1744, 1626, 1532, 762, 474. ^{1}H NMR (400 MHz, DMSO) δ ppm: 8.93 (dd, *J* = 4.1, 1.6 Hz, 1H), 8.49 (dd, *J* = 8.6, 1.6 Hz, 1H), 8.40 (s, 1H), 7.74-7.64 (m, 2H), 7.38 (dd, *J* = 17.5, 8.3 Hz, 3H), 6.84 (dd, *J* = 8.7, 3.6 Hz, 1H), 5.31 (s, 2H), 4.68 (t, *J* = 5.7 Hz, 2H), 4.15 (t, *J* = 5.7 Hz, 2H). ^{13}C NMR (101 MHz, DMSO) δ ppm: 182.80 (s), 160.04 (s), 158.67 (s), 157.64 (s), 153.69 (s), 150.20 (s), 146.91 (s), 142.92 (s), 140.67 (s), 132.67 (s), 127.18 (s), 126.66 (s), 126.26 (s), 124.69 (s), 124.45 (s), 123.51 (s), 121.52 (s), 118.63 (d, *J* = 7.3 Hz), 112.40-111.84 (m), 111.73 (s), 110.63 (s), 62.35 (s), 47.52 (s). HRMS data: calcd. mass $(M+H)^+$, 451.0853; found, 452.0926.

1-(2-(4-(((5-Chloroquinolin-8-yl)oxy)methyl)-1*H*-1,2,3-triazol-1-yl)ethyl)-5-methylindoline-2,3-dione (9e): Red solid; yield: 87%; m.p.: 168-170 ºC; IR (KBr, ν_{max}, cm^{-1}): 1744, 1616, 1535, 762, 467. ^{1}H NMR (400 MHz, DMSO) δ ppm: 8.93 (dd, *J* = 4.1, 1.6 Hz, 1H), 8.49 (dd, *J* = 8.5, 1.6 Hz, 1H), 8.39 (s, 1H), 7.71 (dd, *J* = 8.5, 4.1 Hz, 1H), 7.67 (d, *J* = 8.5 Hz, 1H), 7.36 (d, *J* = 8.5 Hz, 1H), 7.31 (s, 1H), 7.27 (d, *J* = 8.1 Hz, 1H), 6.75 (d, *J* = 8.1 Hz, 1H), 5.32 (s, 2H), 4.68 (t, *J* = 5.7 Hz, 2H), 4.12 (t, *J* = 5.7 Hz, 2H), 2.15 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ ppm: 183.58 (s), 158.66 (s), 153.71 (s), 150.22 (s), 148.54 (s), 142.91 (s), 140.72 (s), 138.86 (s), 133.05 (s), 132.65 (s), 127.20 (s), 126.66 (s), 126.13 (s), 125.13 (s), 123.51 (s), 121.50 (s), 117.74 (s), 110.63 (d, *J* = 18.7 Hz), 62.42 (s), 47.50 (s), 20.39 (s). HRMS data: calcd. mass $(M+H)^+$, 447.1104, found, 448.1177.

RESULTS AND DISCUSSION

In order to achieve the synthesis of novel 1,2,3-triazole tethered quinoline-isatin conjugates, a linear and convergent approach has been followed. It is accomplished in three steps by using copper-promoted click chemistry. In the first step, 8-hyhroxyquinoline (**1**) and 5-chloro-8-hydroxyquinoline (**3**), treated with propargyl bromide in the presence of sodium hydride in DMF at 0-10 ºC to yield the propargylated quinoline (**2**) and propargylated 5-chloroquinoline (**4**) with 90% yield. The reactions are shown in **Scheme-I**.

In the second step, azides of isatin **7a-e** were synthesized as per the procedure reported in the literature [32]. A solution of sodium hydride in DMF was cooled in an ice bath under the nitrogen atmosphere and 5-substituted isatin was added according to batch size. Remove the ice-bath and then added 1,2-dibromoethane to the reaction mixture to obtain compound **6a-e** followed by the reaction with NaN_3 in the presence of DMF to form the desired precursor (**6a-e**).

The target compounds, 1,2,3-triazole derivatives **8a-e** and **9a-e** were synthesized by *via* Cu-promoted click reaction, by heating compounds **2/4** and **7a-e** in DMF:H_2O (1:1), copper sulphate and sodium ascorbate for 10 min at 80 ºC. It was obtained as a yellow-orange solid with a range of 90-95% yield and a melting point of 154-156 and 162-164 ºC.

The structures of all the synthesized conjugates were characterized by the determination of their physico-chemical properties, spectral data and analytical evidence. The chemical structures of the synthesized derivatives **2**, **4**, **6a-e**, **7a-e**, **8a-e** and **9a-e** were established by high-resolution mass spectrometry, IR, ^{1}H NMR and ^{13}C NMR spectroscopy studies and elemental analysis. The formation of compounds **2** and **4** from **1** (quinolin-8-ol) and **3** (5-chloroquinolin-8-ol) was identified by high-resolution mass spectrometry, with a molecular ion peak at *m/z* 180.0218 and 218.0310 $[M + H]^+$, respectively. Its IR spectra showed bands at 3330, 3344 and 2136, 2140 cm^{-1}, indicating the presence of a terminal alkyne.

The structures of compounds **8a-e** and **9a-e** was confirmed by high-resolution mass spectrometry (HRMS), FTIR and NMR. Compounds **8a** (1-(2-(4-((quinolin-8-yloxy)methyl)-1*H*-1,2,3-triazol-1-yl)ethyl)indoline-2,3-dione) and **9a** (1-(2-(4-(((5-chloroquinolin-8-yl)oxy)methyl)-1*H*-1,2,3-triazol-1-yl)ethyl)indoline-2,3-dione) were identified by high-resolution mass spectrometry, with a molecular ion peak at *m/z* 400.1409 $[M + H]^+$, 433.1014 $[M + H]^+$, respectively. The peaks in the IR spectrum at 1738, 1748 and 1515, 1521 cm^{-1} were assigned to the C=O (keto) group of isatin and the N=N group of the triazole ring, respectively.

A singlet was observed in the ^{1}H NMR spectra of **8a** and **9a**; the characteristic peak appeared as a singlet at δ 8.83 ppm and 8.93 ppm for one proton in the triazole hydrogen. The two triplets at δ 4.71, 4.69 and δ 4.16, 4.15 ppm for 8 protons were observed to the methylene groups linked with the isatin ring. The ^{13}C NMR spectra of compounds **8a** and **9a** displayed significant absorptions corresponding to isatin carbonyls at δ 158.63, 158.61 and 183.40, 183.37 ppm, respectively that were compatible with isatin carbonyls.

Conclusion

In view of the pharmacological properties associated with quinoline and isatin, scaffolds, a number of quinoline-isatin tethered 1,2,3-triazole conjugates (**8a-e**) and (**9a-n**) were synthesized using reliable and authentic procedures. The use of DMF/H_2O (1:1) in the copper-promoted click cycloaddition of isatin azides **7a-e** and alkynes of quinoline **2** and 5-chloroquinoline **4** significantly enhances the reaction rates in contrast to other organic systems. As a result, these substances could be utilized as an alternative to the widely prescribed established drugs for the suppression of microbial growth in a variety of plants and organism.

ACKNOWLEDGEMENTS

Two of the authors, RK and LSK are thankful to the School of Sciences, Indira Gandhi National Open University, New Delhi, India for the financial support towards procurement of chemicals and providing the infrastructural facilities. The authors are also thankful to the University Science Instrumentation Centre (USIC), University of Delhi, for the necessary characterization facilities.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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