Novel quinazolinone-isoazoxoline hybrids: synthesis, structural elucidation and theoretical DFT mechanistic study

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Abstract

Quinazolinone and isoxazoline systems have attracted more attention due to their interesting pharmacological properties. The association of these two pharmacophores in a single hybrid structure can boost the biological activity or bring a new one. Inspired by this new paradigm, we report in the present work, the synthesis and spectroscopic characterization of a new quinazolinone-isoxazoline hybrids. The target compounds were obtained via 1,3-dipolar cycloaddition reaction of arylnitriloxides and N-allylquinazolinone. The synthesized compounds were characterized using spectroscopic techniques such as: IR, 1D NMR (\(^1\)H and \(^{13}\)C), 2D NMR (COSY and HSQC), and high-resolution mass spectrometry (HRMS). The spectral data show that this reaction leads only to the 3,5-disubstituted isoxazoline regioisomer and the observed regiochemistry is not affected by the nature of the substituents in the phenyl ring of the dipole. In addition, a theoretical study was performed using the density functional theory (DFT) to support the experimental results regarding the regiochemistry of the studied reactions. The computational mechanistic study is in perfect agreement with experimental data.

Introduction

Heterocycle compounds continue to attract much attention due to their astonishing bioactivity [1–4]. Over the last century, heterocyclic compounds have been widely invested as preferred structures in the investigation of new drug candidates capable of remedying various diseases [5–7]. Oxygen and nitrogen containing heterocyclic compounds have gained considerable importance due to their applications in various fields [1, 8–10]. Quinazolin-4(3H)-one derivatives, in particular, have occupied a primordial place in medicinal chemistry thanks to their wide range of biological activity, namely antifungal [11, 12], antibacterial [11, 13], antioxidant [14], antitubercular [11], anticonvulsant [15], antimalarial [16], and as potential inhibitors of MERS-CoV and SARS-CoV-2 [2], etc. Furthermore, they possess also insecticidal [17] and fungicidal activities [18]. Due to the excellent biological properties of quinazolin-4(3H)-ones [19, 20], as well as their presence in the molecular skeleton of several natural alkaloids with pharmacological properties [5, 19, 21] (Fig. 1), many methods devoted to their synthesis have been reported [12, 22, 23].

On the other hand, isoxazoline nucleus has received great attention of researchers on account of its significant pharmacological properties [24]. Indeed, isoxazoline motif is found in the molecular skeleton of several synthetic and natural compounds used in various fields including agriculture and medicine [24–27] (Fig. 2). Thus isoxazoline ring constitute a source of motivation in the investigation and the design of new therapeutic agents [28, 29]. In addition to their interesting properties, they has been used as a key intermediate to synthesis a large array of polyfunctional molecules with pharmaceutical interest [28, 29]. The synthesis of these heterocyclic compound is often achieved by cyclocondensation or 1,3-dipolar cycloaddition reactions [30].

Recently, molecular hybridization has emerged as a promising approach to design and develop novel heterocyclic compounds with interesting biological properties [1, 8]. The synthesis of new heterocycle molecules based on the hybridization of quinazolinone and isoxazoline pharmacophores is a promising
avenue in modern medicinal chemistry [31]. In this regard and in continuation of our ongoing research focused on the design of new bioactive compounds [32–35], we reported in this work, the synthesis and characterization of new quinazolinone-isoxazoline hybrids. The synthesis of the target compounds 4a-h was performed using 1,3-dipolar cycloaddition reaction between arylnitriloxides 3a-h and N-allylquinazolinone 2. We describe also mechanistic and regiochemistry studies of this reaction using density functional theory (DFT) at the B3LYP functional with the cc-pVDZ basis set as computational methods.

Materials And Methods

Chemical reagents and instruments

All chemicals used were of analytical grade and were purchased from commercial suppliers. The progress of the reactions was monitored by TLC (Merck, silica gel 60 F254), and spots were visualized under UV light (VILBER LOURMAT, VL-215.LC). Column chromatography was performed using Merck silica gel (70–230 mesh) and n-hexane/ethyl acetate mixture as eluent. The melting points were determined with an uncertainty of ± 2°C using a KOFLER BENCH. The IR spectra were recorded in the range of 450–4000 cm⁻¹ on a BRUKER VERTEX 70 FT-IR Spectrometer, and wavenumbers are given in cm⁻¹. The NMR spectra (¹H and ¹³C) were recorded at room temperature on a BRUKER AVANCE II 300 Ultra-Shield (300 MHz for ¹H and 75 MHz for ¹³C) spectrometer using CDCl₃ as solvent. The chemical shifts are expressed in ppm and the coupling constants J are expressed in Hertz (Hz). The spin multiplicities are reported as singlet (s), doublet (d), triplet (t), multiplet (m), doublet of doublets (dd), doublet of triplets (dt) and broad (br). High-resolution mass spectra were recorded on a Waters/Vion IMS-QTOF: Spectrometer–, equipped with an electrospray ionization (ESI), source operating in either positive and negative ion mode.

The quinazolin-4(3H)-one 1 was prepared according to the literature (white solid, yield 92%, m.p. 214 ~ 216°C (lit., m.p. 214 ~ 215°C)) [36]. The 3-allylquinazolin-4(3H)-one 2 was obtained from the condensation reaction of quinazolin-4(3H)-one 1 with allyl bromide in DMF and in the presence of sodium hydride, according to previous studies (White crystals, yield 75%; m.p. 64 ~ 66°C; (lit., m.p. 63–65°C)) [36]. The NMR spectra of quinazolin-4(3H)-one 1 and 3-allylquinazolin-4(3H)-one 2 are given in the Supplementary Information. The arylhydroxamoyl chlorides 3a–h as arylnitriloxide precursors were prepared in accordance with the method described in the literature [37].

Procedure for the synthesis of compounds (4a-h)

In a 100 ml flask, 1 mmol of dipolarophile 2 and 1.2 mmol of arylhydroxamoyl chlorides 3a-h were dissolved in 40 ml of chloroform. Then 1.2 mmol of anhydrous triethylamine was added dropwise. Once the addition is finished, the reaction mixture is kept under magnetic stirring at room temperature for the appropriate period of time. Once the reaction is completed as indicated by TLC, the reaction mixture was transferred into a separatory funnel and extracted with dichloromethane, washed three times with water.
The organic layer was dried over anhydrous sodium sulfate (Na₂SO₄), filtered and the solvent was removed by rotary evaporator. The residue obtained was purified on silica gel column using a mixture of hexane and ethyl acetate (4/1) as eluent.

3-((3-(4-bromophenyl)-4,5-dihydroisoxazol-5-yl)methyl)quinazoline-4(3H)-one (4a): Yield (96%); m.p.: 194°C; FT-IR (υmax, cm⁻¹): 3057 (Ar-H), 2923 (–CH₂), 1670 (C = O), 1610 (C = N), 1562, 1490, 1471 (C = C), 1159 (C = O); ¹H NMR (300 MHz, CDCl₃) (δ/ppm): 8.29 (d, 1H, J = 7.8 Hz, Ar–H), 8.17 (s, 1H, N = CH–N), 7.80–7.72 (m, 2H, Ar–H), 7.54–7.48 (m, 5H, Ar–H), 5.20–5.11 (m, 1H, CH₂isoxazoline), 4.44 (dd, 1H, J = 14.1, 3 Hz, N–CH₂), 4.05 (dd, 1H, J = 14.1, 7.5 Hz, N–CH₂), 3.52 (dd, 1H, J = 17.1, 10.8 Hz, CH₂isoxazoline), 3.20 (dd, 1H, J = 17.1, 6.9 Hz, CH₂isoxazoline). ¹³C NMR (75 MHz, CDCl₃) (δ/ppm): 161.48 (C = Oamide), 156.19 (C = Nisoxazoline), 148.14, 146.90 (N = CH–N), 134.56, 132.04, 128.20, 127.73, 127.70, 127.38, 126.63, 124.84, 121.78, 78.63 (CHisoxazoline), 49.16 (N–CH₂), 37.88(CH₂isoxazoline); ESI-QTOF-MS (m/z): mass calculated for [C₁₈H₁₄N₃O₂Br + H]⁺ 384.03331, found 384.03367.

3-((3-(4-chlorophenyl)-4,5-dihydroisoxazol-5-yl)methyl)quinazoline-4(3H)-one (4b): Yield (82.5%); m.p.: 176°C; FT-IR (υmax, cm⁻¹): 3058 (Ar-H), 2925 (–CH₂), 1672 (C = O), 1598 (C = N), 1566, 1494, 1471 (C = C), 1159 (C = O); ¹H NMR (300 MHz, CDCl₃) (δ/ppm): 8.31 (d, 1H, J = 8 Hz, Ar–H), 8.18 (s, 1H, N = CH–N), 7.80–7.74 (m, 2H, Ar–H), 7.65–7.50 (m, 3H, Ar–H), 7.40–7.37 (d, 2H, J = 7 Hz, Ar–H), 5.22–5.12 (m, 1H, CH₂isoxazoline), 4.46 (dd, 1H, J = 14.1, 3 Hz, N–CH₂), 4.07 (dd, 1H, J = 14.1, 7.5 Hz, N–CH₂), 3.54 (dd, 1H, J = 17.1, 10.5 Hz, CH₂isoxazoline), 3.22 (dd, 1H, J = 17.1, 7.2 Hz, CH₂isoxazoline). ¹³C NMR (75 MHz, CDCl₃) (δ/ppm): 161.47 (C = Oamide), 156.11 (C = Nisoxazoline), 148.03, 146.92 (N = CH–N), 136.55, 134.61, 129.11, 128.02, 127.65, 127.44, 127.28, 126.66, 121.76, 78.59 (CHisoxazoline), 49.19 (N–CH₂), 37.96(CH₂isoxazoline); ESI-QTOF-MS (m/z): mass calculated for [C₁₈H₁₄N₃O₂Cl + H]⁺ 340.08404, found 340.08417.

3-((3-(4-methoxyphenyl)-4,5-dihydroisoxazol-5-yl)methyl)quinazoline-4(3H)-one (4c): Yield (74.5%); m.p.: 210°C; FT-IR (υmax, cm⁻¹): 3080 (Ar-H), 2954 (–CH₂), 1666 (C = O), 1600 (C = N), 1562, 1504, 1469 (C = C), 1159 (C = O); ¹H NMR (300 MHz, CDCl₃) (δ/ppm): 8.32 (d, 1H, J = 8.1 Hz, Ar–H), 8.19 (s, 1H, N = CH–N), 7.82–7.74 (m, 2H, Ar–H), 7.67 (d, 2H, J = 2.1 Hz, Ar–H), 7.56–7.50 (m, 2H, Ar–H), 6.94 (d, 1H, J = 8.7 Hz, Ar–H), 5.19–5.10 (m, 1H, CH₂isoxazoline), 4.45 (dd, 1H, J = 14.1, 3 Hz, N–CH₂), 4.05 (dd, 1H, J = 14.1, 7.5 Hz, N–CH₂), 3.95 (s, 3H, –OCH₃), 3.52 (dd, 1H, J = 16.8, 10.5 Hz, CH₂isoxazoline), 3.19 (dd, 1H, J = 16.8, 6.9 Hz, CH₂isoxazoline). ¹³C NMR (75 MHz, CDCl₃) (δ/ppm): 161.49 (C = Oamide), 156.63 (C = Nisoxazoline), 155.67 (> C–OCH₃), 148.12, 146.94 (N = CH–N), 134.56, 128.67, 127.69, 127.39, 126.66, 123.05, 122.17, 111.90, 78.35 (CHisoxazoline), 56.28 (–OCH₃), 49.18 (N–CH₂), 38.09 (CH₂isoxazoline); ESI-QTOF-MS (m/z): mass calculated for [C₁₉H₁₇N₃O₃ + H]⁺ 336.12871, found 336.13332.

3-((3-(4-nitrophenyl)-4,5-dihydroisoxazol-5-yl)methyl)quinazoline-4(3H)-one (4d): Yield (84.4%); m.p.: 236°C; FT-IR (υmax, cm⁻¹): 3047 (Ar-H), 2941 (–CH₂), 1662 (C = O), 1610 (C = N), 1579, 1514, 1473 (C = C), 1159 (C = O); ¹H NMR (300 MHz, CDCl₃) (δ/ppm): 8.30–8.24 (m, 3H, Ar–H), 8.18 (s, 1H, N = CH–N), 7.84–
7.74 (m, 4H, Ar–H), 7.56–7.51 (m, 1H, Ar–H), 5.32–5.21 (m, 1H, CH$_{2}$isoaxazine), 4.47 (dd, 1H, J = 14.1, 3.3 Hz, N–CH$_{2}$), 4.17 (dd, 1H, J = 14.1, 10.5 Hz, N–CH$_{2}$), 3.59 (dd, 1H, J = 17.1, 7.2 Hz, CH$_{2}$isoaxazine), 3.31 (dd, 1H, J = 17.1, 7.2 Hz, CH$_{2}$isoaxazine); $^{13}$C NMR (75 MHz, CDCl$_{3}$) (δ/ppm): 167.51 (C = Oamide), 155.54 (C = Nisoaxazoline), 148.71 (C = NO$_{2}$), 147.89, 146.77 (N = CH–N), 134.79, 134.72, 127.68, 127.55, 126.67, 124.06, 121.71, 79.50 (CH$_{isoaxazine}$), 49.05 (N–CH$_{2}$), 37.53 (CH$_{2}$isoaxazine); ESI-QTOF-MS (m/z): mass calculated for [C$_{18}$H$_{14}$N$_{4}$O$_{4}$ + H]$^{+}$ 351.10846, found 351.10835

3-((3-(p-tolyl)-4,5-dihydroisoaxazol-5-yl)methyl)quinazoline-4(3H)-one (4e): Yield (92.6%); m.p.: 174°C; FT-IR (υ$_{max}$, cm$^{-1}$): 3033 (Ar–H), 2949 (–CH$_{2}$), 1674 (C = O), 1612 (C = N), 1564, 1515, 1473 (C = C), 1159 (C-O); $^{1}$H NMR (300 MHz, CDCl$_{3}$) (δ/ppm): 8.34–8.30 (m, 1H, Ar–H), 7.82–7.73 (m, 2H, Ar–H), 7.58–7.50 (m, 3H, Ar–H), 7.52–7.44 (m, 3H, Ar–H), 5.20–5.11 (m, 1H, CH$_{isoaxazine}$), 4.48 (dd, 1H, J = 14.1, 3.0 Hz, N–CH$_{2}$), 4.04 (dd, 1H, J = 14.1, 7.5 Hz, N–CH$_{2}$), 3.58 (dd, 1H, J = 16.8, 10.5 Hz, CH$_{2}$isoaxazine), 3.23 (dd, 1H, J = 16.8, 6.9 Hz, CH$_{2}$isoaxazine); $^{13}$C NMR (75 MHz, CDCl$_{3}$) (δ/ppm): 161.51 (C = Oamide), 156.99 (C = Nisoaxazoline), 148.14, 146.98 (N = CH–N), 134.54, 130.54, 128.82, 127.68, 127.36, 126.81, 126.66, 121.81, 78.28 (CH$_{isoaxazine}$), 49.26 (N–CH$_{2}$), 38.13 (CH$_{2}$isoaxazine); ESI-QTOF-MS (m/z): mass calculated for [C$_{19}$H$_{13}$N$_{3}$O$_{2}$ + H]$^{+}$ 320.13908, found 320.13944.

3-((3-phenyl)-4,5-dihydroisoaxazol-5-yl)methyl)quinazoline-4(3H)-one (4f): Yield (59.6%); m.p.: 166°C; FT-IR (υ$_{max}$, cm$^{-1}$): 3055 (Ar–H), 2956 (–CH$_{2}$), 1662 (C = O), 1608 (C = N), 1564, 1498, 1469 (C = C), 1190 (C-O); $^{1}$H NMR (300 MHz, CDCl$_{3}$) (δ/ppm): 8.33–8.30 (d, 1H, Ar–H), 8.19 (s, 1H, N = CH–N), 7.82–7.73 (m, 2H, Ar–H), 7.56–7.50 (m, 1H, Ar–H), 7.46–7.44 (m, 3H, Ar–H), 5.20–5.11 (m, 1H, CH$_{isoaxazine}$), 4.48 (dd, 1H, J = 14.1, 3.0 Hz, N–CH$_{2}$), 4.04 (dd, 1H, J = 14.1, 7.5 Hz, N–CH$_{2}$), 3.58 (dd, 1H, J = 16.8, 10.5 Hz, CH$_{2}$isoaxazine), 3.23 (dd, 1H, J = 16.8, 6.9 Hz, CH$_{2}$isoaxazine); $^{13}$C NMR (75 MHz, CDCl$_{3}$) (δ/ppm): 161.51 (C = Oamide), 156.99 (C = Nisoaxazoline), 148.14, 146.98 (N = CH–N), 134.54, 130.54, 128.82, 127.68, 127.36, 126.81, 126.66, 121.81, 78.28 (CH$_{isoaxazine}$), 49.26 (N–CH$_{2}$), 38.13 (CH$_{2}$isoaxazine); ESI-QTOF-MS (m/z): mass calculated for [C$_{18}$H$_{15}$N$_{3}$O$_{2}$ + H]$^{+}$ 306.12337, found 306.12318.

3-((3-(2-chlorophenyl)-4,5-dihydroisoaxazol-5-yl)methyl)quinazoline-4(3H)-one (4g): Yield (91.3%); m.p.: 168°C; FT-IR (υ$_{max}$, cm$^{-1}$): 3072 (Ar–H), 2962 (–CH$_{2}$), 1670 (C = O), 1608 (C = N), 1562, 1471, 1433 (C = C), 1157 (C-O); $^{1}$H NMR (300 MHz, CDCl$_{3}$) (δ/ppm): 8.33 (dd, 1H, J = 8.1, 1.2 Hz, Ar–H), 8.21 (s, 1H, N = CH–N), 7.83–7.75 (m, 2H, Ar–H), 7.56–7.51 (m, 2H, Ar–H), 7.42–7.28 (m, 3H, Ar–H), 5.24–5.15 (m, 1H, CH$_{isoaxazine}$), 4.43 (dd, 1H, J = 14.1, 3 Hz, N–CH$_{2}$), 4.12 (dd, 1H, J = 14.1, 7.5 Hz, N–CH$_{2}$), 3.68 (dd, 1H, J = 17.1, 10.5 Hz, CH$_{2}$isoaxazine), 3.44 (dd, 1H, J = 17.1, 6.3 Hz, CH$_{2}$isoaxazine); $^{13}$C NMR (75 MHz, CDCl$_{3}$) (δ/ppm): 161.46 (C = Oamide), 157.01 (C = Nisoaxazoline), 148.11, 146.98 (N = CH–N), 134.54, 132.87, 130.54, 128.35, 127.66, 127.38, 127.07, 126.66, 121.87, 78.83 (CH$_{isoaxazine}$), 49.09 (N–CH$_{2}$), 40.51 (CH$_{2}$isoaxazine); ESI-QTOF-MS (m/z): mass calculated for [C$_{18}$H$_{14}$N$_{3}$O$_{2}$Cl + H]$^{+}$ 340.08430, found 340.08428.

**Computational details**
Recently, the density function theory (DFT) is considered the most widely used method, as it gives realistic and reliable results, in the reproducing experimental region and stereoselectivity cycloaddition reactions [38–42]. Therefore, the geometry optimizations of the stationary points were carried out using DFT methods at the B3LYP/ cc-pVDZ level theory [43]. The use of the cc-pVDZ base gives good results in many works [42, 44]. We confirmed the active sites by the electrophilic function indices of Parr (Pr+) [45, 46]. The transition state theory (TST) developed in 1935 by Eyring is the most widely used theory for calculating reaction rates [47, 48], and to locate the structure of the transition state we used qstn [49]. IRC was made to give the reaction path according to the coordinates of the reaction [50]. The QTAIM method has been used to highlight the topology of the molecular structures [51]. All calculations were carried out with Gaussian 09 suite of software [52].

**Results And Discussion**

**Synthesis and characterization**

The presence of heterocyclic compounds as the main structural motif in a variety of biologically active, natural and synthetic molecules has led to the development of new methodologies of their synthesis. In this context, we have been interested in the synthesis of various aza-heterocyclic derivatives with potential biological activities, using easy and reproducible synthesis strategies [32–35]. In the present work, we describe the synthesis of quinazolin-4(3H)-one-isoxazoline hybrids according to the pathway shown in Scheme 1. Quinazolin-4(3H)-one \( 1 \) was obtained by the condensation of anthranilic acid onto formamide according to literature procedure [36], then was reacted with allyl bromide in N,N-dimethylformamide (DMF) in the presence of sodium hydride (NaH) to result in the formation of N-allylated quinazolin-4(3H)-one \( 2 \) [36]. The intermediate 2 was subjected to a series of arylnitriloxides to synthesis the targeted compounds \( 4a-h \). The arylnitriloxides are generated *in situ* from hydroxamoyl chlorides \( 3a-h \) in chloroform at room temperature in the presence of triethylamine.

The structure and regiochemistry of the synthesized compounds were established on the basis of spectroscopic data. The physical properties and spectroscopic data of all synthesized products have been summarized in Table 1. The analysis of NMR data reveals that the reaction led to the formation of one regio-isomer only, regardless donor or attractor nature of the substituent carried by the phenyl ring of the dipole in all studied cases.

The mass spectra of the newly synthesized hybrid molecules showed the existence of a molecular ion peak [M + H]\(^+\) corresponding to the exact mass of a single molecule, and are consistent with the chemical formula of the proposed structures. For example, the mass spectrum of compound \( 4a \) shows a peak for the protonated molecular ion [M + H]\(^+\) at \( m/z \): 384.03331 which affirms the molecular formula \( [C_{18}H_{14}N_{3}O_{2}Br] \) of the proposed structure (Fig. S10). In addition, the FT-IR spectrum of compound \( 4a \) reveals the presence of two absorption bands that appear around 1159 cm\(^{-1}\) and 1610 cm\(^{-1}\) characteristic of the vibrations of the C-O and C = N bonds of the isoxazoline nucleus. It also shows the
existence of another absorption band at 1670 cm\(^{-1}\) attributed to the vibration of the C = O bond of the carbonyl of the quinazolin-4(3H)-one ring.

In the \(^1\)H-NMR spectrum of compound 4a (Fig. S5), we note the presence of four signals as a doublet of doublets (dd) attributable to the four diastereotopic hydrogens attached to the two methylene groups neighboring the stereogenic center. The doublet-of-doublets centered at 4.05 ppm and 4.44 ppm correspond to the two protons of the methylene group near the nitrogen atom (N-CH\(_2\)), whereas the two other doublet of doublets at 3.20 ppm and 3.52 ppm are attributed to the two hydrogen atoms of the methylene group belonging to isoxazoline ring. The presence of a multiplet signal in the spectrum of compound 4a between 5.11 and 5.20 ppm is consistent with the chemical shift of the H\(_5\) proton of the 3,5-disubstituted isoxazoline regioisomer (Fig. 3). The chemical shift value of the H\(_5\) proton of the isoxazoline ring is in good agreement with that found in the literature [28, 53, 54]. The singlet signal at 8.17 ppm attributed to the proton of methine group (= CH\(^\) attached to the two nitrogen atoms of quinazolin-4(3H)-one.

The \(^{13}\)C-NMR spectrum of compound 4a (Fig. S7) shows the presence of three signals located at 37.88 ppm, 78.63 ppm, and 156.19 ppm attributed the carbons of the methylene (CH\(_2\)), methine (CH), and imine (C = N) groups of the isoxazoline nucleus, respectively. These obtained chemical shift values are in good agreement with the literature, and confirm the formation of a single regioisomer namely 3,5-disubstituted isoxazoline [28, 53, 54]. Other signals located at 146.90 ppm and 161.48 ppm are assigned to the methine (N = CH–N) and ketone (C = O) carbons of quinazolin-4(3H)-one, respectively. The signal at 49.16 ppm correspond to the methylene spacer carbon (CH\(_2\)) that links isoxazoline ring with quinazolin-4(3H)-one. The obtained 13C NMR data for compound 4a are in perfect agreement with the 3,5-disubstituted isoxazoline regioisomer [28, 53, 54]. Moreover, the homonuclear (\(^1\)H-\(^1\)H) and heteronuclear (\(^1\)H-\(^{13}\)C) 2D NMR spectra of compound 4a confirm unambiguously the assignment of the different signals made on the 1D NMR spectra (\(^1\)H and \(^{13}\)C). The 2D NMR correlations are presented in Figs. S8 and S9.

On the basis of the spectroscopic data, it can be concluded that the 1,3-dipolar cycloaddition reaction between allylated quinazolin-4(3H)-one 2 and aryl nitrooxides led only to the formation of the 3,5-disubstituted isoxazoline regioisomer. The formation of the 3,4-disubstituted isoxazoline regioisomer is not observed in any case as evidenced by TLC and NMR of the reaction mixture. To further explain the mechanism and the regiochemistry observed in this work, a theoretical study using DFT, and B3LYP methods was carried out.
Table 1
Physical properties and spectroscopic data of compounds 4a-g

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<th>N°</th>
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<th>Formula (M. g/mol)</th>
<th>M.p (°C)</th>
<th>Yield (%)</th>
<th>NMR-1H (ppm)</th>
<th>13C-NMR (ppm)</th>
<th>IR (cm⁻¹)</th>
<th>HRMS (m/z) [M + H]⁺</th>
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<td>1672</td>
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<td>5.12–5.22 (m, 1H)</td>
<td>78.63</td>
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<td>49.19</td>
<td>1666</td>
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<td></td>
<td>(335.13)</td>
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<td></td>
<td>3.19 (dd, 1H); 3.53 (dd, 1H)</td>
<td>37.96</td>
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<td>5.10–5.19 (m, 1H)</td>
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<td>4-NO₂</td>
<td>C₁₈H₁₄N₄O₄</td>
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<td>4.17 (dd, 1H); 4.47 (dd, 1H)</td>
<td>49.16</td>
<td>1662</td>
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<td>(350.1)</td>
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<td>3.31 (dd, 1H); 3.59 (dd, 1H)</td>
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<td>1610</td>
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<td>5.21–5.32 (m, 1H)</td>
<td>78.63</td>
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* Yield of products after purification.
<table>
<thead>
<tr>
<th>N°</th>
<th>R</th>
<th>Formula (M. g/mol)</th>
<th>M.p (°C)</th>
<th>Yielda (%)</th>
<th>NMR-1H (ppm)</th>
<th>13C-NMR (ppm)</th>
<th>IR (cm⁻¹)</th>
<th>HRMS (m/z)</th>
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<td>4e</td>
<td>4-CH₃</td>
<td>C₁₉H₁₇N₃O₂</td>
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<td>92.6</td>
<td>4.01 (dd, 1H); 4.47 (dd, 1H); 3.21 (dd, 1H); 3.56 (dd, 1H); 5.09-5.18 (m, 1H)</td>
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<td>38.25</td>
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<tr>
<td>4f</td>
<td>H</td>
<td>C₁₈H₁₅N₃O₂</td>
<td>166</td>
<td>59.6</td>
<td>4.45 (dd, 1H); 4.04 (dd, 1H); 3.34 (dd, 1H); 3.58 (dd, 1H); 5.11 – 5.20 (m, 1H)</td>
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<td>306.12318</td>
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<td></td>
<td></td>
<td>(305.12)</td>
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<td>38.13</td>
<td>1608</td>
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<tr>
<td>4g</td>
<td>2-Cl</td>
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<td>91.3</td>
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<td>(339.08)</td>
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<td></td>
<td></td>
<td>78.83</td>
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</tr>
</tbody>
</table>

a Yield of products after purification.

**DFT studies**

Mulliken atomic spin density analysis at the cation and anion level by removing or adding an electron. The most nucleophilic and electrophilic sites will correspond to the highest values of p- and p+ respectively [55, 56].

The Fig. 4 show a high value of p- (0.455) for the reagent 1 on the O1 atom compared to C3 means a nucleophilic character for this site (O1), so a low value of p+ on the same atom confirms this character. The sites C13 and C14 have almost the same values of p- and p+ means that they have almost the same nucleophile and electrophile character. The C3 site has two low values of p- and p+, while N2 has a remarkable electrophilic character (p+ 0.172) and a very low value of (p- 0.06). This clearly explains a concerted mechanism for the 1,3-dipolar reaction.
The transition state structure (Fig. 5) has been localized following the Berny algorithm. In this structure, we have shown the bond lengths of C16-C17 (2.231) and C13-O14 (2.379). These obtained values show a starting of formation of two covalent bonds between C16-C17 and C13-O14. The negative value of the imaginary frequency confirms the localization of the transition state structure for this reaction.

The kinetics and variables of the 1,3-dipolar cycloaddition reaction between dipole 1 and dipolarophile 2 were investigated in order to disclose the more favorable product. It involves two electrons from the dipolarophile and four electrons from the 1,3-dipole. Figure 6 shows the energy profile corresponding to the cyclization mode. At the appropriate level of theory (B3LYP/ cc-pVDZ), all reactants, transition states and products were optimized.

The IRC (Fig. 7) method confirms the reaction path of the reaction and shows that the product has a low energy compared to the products and the energy of the transition state is high.

We have also shown the TS-1 structure just before the transition structure and the structure just after TS (TS + 1). This further justifies the location of the transition state.

The quantum theory of the atom in the molecule (QTAIM) is considered as a technique giving a direct relation between the distribution of the electron density \( \rho(r) \) and the structure, which allows highlighting the topology of the molecule. The presence of a critical point (3, -1) of an interatomic contour line indicates that the electron density is gathered among the nuclei. In Fig. 8, BCP 67 and 82 show a chemical bond between C16-C17 and C13-O14 as the beginning of the formation of a new covalent bond.

<table>
<thead>
<tr>
<th>BCP</th>
<th>bonding</th>
<th>( \rho )</th>
<th>( \nabla^2 \rho )</th>
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<tbody>
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<td>TS</td>
<td>C16-C17</td>
<td>0.53</td>
<td>0.55</td>
</tr>
<tr>
<td>82</td>
<td>C13-O14</td>
<td>0.33</td>
<td>0.83</td>
</tr>
</tbody>
</table>

The values shown in Table 2 for the electron density between C16-C17 (0.53) and a positive value of Laplacian (0.55) indicate a chemical gap in this interatomic region, the same for the C13-O14 bond.

The localized orbital localizer LOL was introduced by Schmider and Becke to describe the properties of the bond in terms of kinetic energy [57]. According to Fig. 9, the green color between the two carbon atoms confirms the existence of a chemical bond in this region. In addition, a remarkable weak interaction between the carbon atom and the oxygen atom. The theoretical results with experimental data are in agreement regarding the regiochemistry.

**Conclusion**
This study showed an elegant and efficient synthesis of a new series of hybrid molecules incorporating the quinazolinone and isoxazoline cores through 1,3-dipolar cycloaddition reaction of N-allylquinazolinone with arylnitriloxides in a highly regioselective manner. The structures of the synthesized compounds are well established using spectroscopic techniques (IR, $^1$H and $^{13}$C NMR, 2D NMR) and high-resolution mass spectrometry. The regiochemistry of the synthesized cycloadducts was proposed on the basis of $^1$H and $^{13}$C NMR data. The regioselectivity was farther investigated using DFT method, and the obtained results are in good agreement with the experimental data.

Declarations

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Conflict of interest

The authors have no conflicts of interest to declare that are relevant to the content of this article

Author contributions

R. Y. and C. M.: designed the experiments, analyzed the data, methodology, wrote–original draft, Wrote–review & editing. H. I. and C. S.: computational DFT and interpretation of results. A. M.: Spectroscopic analyses and interpretation of results. B. M.: English correction, validation of article and improve the manuscript, edited the final version. N. A. and E. Y. M.: conceptualization, methodology, manuscript preparation and review, validation of results, and supervision. All authors reviewed and approved the final manuscript to be published.

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References


**Scheme**

Scheme 1 is available in the Supplementary Files section.

**Figures**

![Scheme](image)

**Figure 1**

Natural alkaloids containing quinazolinone scaffold.
Figure 2

Selected examples of therapeutic agents encompassing an isoxazoline ring.

Figure 3

Characteristic signals in the $^1$H and $^{13}$C NMR spectra of compound 4a
Figure 4

Nucleophilic p- and Electrophilic p+ functions of reagents 1 and 2.
Figure 5

Transition state, length of the chemical bond and in parenthesis imaginary frequency.

Figure 6

Energy profiles for the 1,3-dipolar cycloaddition reaction between dipole 1 and dipolarophile 2 at the B3LYP/ cc-pVDZ in gas phase.
Figure 7

Intrinsic Reaction Coordinate and TS-1, TS and TS+1.

Figure 8
BCP Bond Critical Point (3, -1) for to bonds C16-C17 and C13-O14 for compound TS.

Figure 9

Map of functions LOL for the transition state.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.