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Synthesis of 2-alkynylquinolines from 2-chloro and 2,4-dichloroquinoline via Pd/C-catalyzed coupling reaction in water

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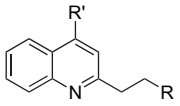
ABSTRACT

The Pd/C–CuI–PPh_3 catalyst system facilitated Sonogashira coupling of 2-chloroquinoline and 2,4-dichloroquinoline with terminal alkynes in water without generating any significant side products. A variety of 2-alkynylquinolines were prepared from 2-chloroquinoline in good to excellent yields and the 2,4-dichloroquinoline afforded monosubstituted product i.e., 2-alkynyl-4-chloro quinoline with high regioselectivity. The methodology was found to be effective for the alkynylation of 1-chloroisoquinoline and 3-methyl-2-chloroquinoline.

1. Introduction

Since the discovery of Cinchona alkaloids as anti-malarial agents the quinoline (π-electron deficient heterocycle) core has become one of the privileged structures for the design and development of potential new drugs. Substituted quinolines display a wide range of pharmacological activities.[1,2] For example, a number of naturally occurring 2-substituted quinoline derivatives have been reported to be highly effective against leishmaniasis, a widespread parasitic disease caused by protozoan parasites of the genus *Leishmania* in tropical and subtropical areas in both the old and the new worlds.[3] These include mainly 2-alkyl substituted quinolines **A**–**F** (Fig. 1), e.g., chimanine (**D**), cusparine (**E**), etc., and can be extracted from a plant of the genus *Galipea* or may be synthesized chemically by using dialkylquinolylboranes.[4] Recently, 2-alkenyl/alkynylquinolines were reported to have anti-retroviral properties[5] and the presence of unsaturation at the C-2 position of the quinoline ring seemed to play an important role in their pharmacological activities.

In view of their remarkable biological importance, many efforts have been devoted to the development of new synthetic methodologies for the preparation of 2-substituted quinolines.[6] In particular, synthetic strategies based on C–C bond formation via transition metal-catalyzed alkynylation of 2-haloquinolines as a key synthetic step (Fig. 2) have attracted considerable attention, owing to the excellent levels of selectivity and high functional group compatibility. Thus Sonogashira coupling[7] (alkynylation of aryl/heteroaryl halides) or its modified form has been used successfully for the preparation of a variety of 2-alkynylquinolines.[1c,8,9] However, the main disadvantage of all these methods is that the Pd-catalysts used are destroyed in the work-up procedure and cannot be recovered or reused. Therefore, development of improved and flexible synthetic methods for accessing existing and novel quinoline derivatives is in great demand mainly because of the increasing resistance of malarial parasites in the use of chloroquine (a widely used anti-malarial drug)[1b] requires a convenient access to its appropriate analogs. Recently, we have reported Pd/C–



A; R = 3,4-methylenedioxyphenylethyl, R' = H
B; R = methyl,R' = H
C; R = *n*-propyl, R' = OMe
D; R = methyl,R' = OMe (chimanine)
E; R = 3,4-methylenedioxyphenyl, R' = OMe (cusparine)
F; R = 3,4-dimethoxyphenyl, R' = H

Figure 1. Structures of some 2-substituted quinoline alkaloids isolated from *Galipea* species.

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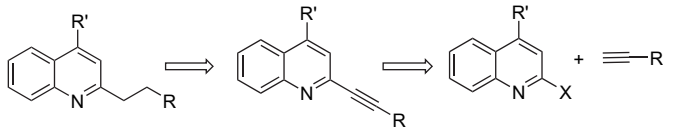
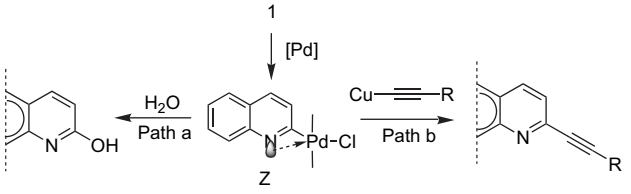


Figure 2. Synthetic strategy for the preparation of 2-alkyl quinolines.

Cu mediated alkynylation of several chloro derivatives where the chloro group was part of –Z=C(Cl)– moiety [Z=N or C] in DMF.[10] On the other hand, we have observed that Pd/C–Cu mediated alkynylation of bromo and iodo arenes/heteroarenes proceed smoothly in water.[11] Inspired by these results and due to our longstanding interest in the synthesis of quinoline derivatives[12] of potential pharmacological significance, we chose to investigate the coupling of a wide array of terminal alkynes with 2-chloroquinoline in water using air and moisture stable 10% Pd/C as a key catalyst. Herein, we report first one step efficient synthesis of 2-alkynylquinolines starting from readily available starting materials under mild conditions using 10% Pd/C–CuI–PPh_3 as a catalyst system in water.

2. Results and discussion

To assess the feasibility of this strategy, the 2-chloroquinoline (**1**) we have chosen as a key precursor due to the high reactivity of its C-2 chlorine toward nucleophiles[14] in the absence or presence of transition metal catalysts[15,16] (path a or path b, Scheme 1). Accordingly, 2-chloroquinoline (**1**) was treated with terminal alkynes (**2**, R=alkyl, hydroxyalkyl, aryl, etc.) in water in the presence of 10% Pd/C (0.026 equiv), PPh_3 (0.20 equiv), CuI (0.05 equiv), and triethylamine (3 equiv) under nitrogen. The reaction proceeded well to give 2-alkynylquinolines (**3**) in good to excellent yields via C–C bond formation (Scheme 2) and no 2-hydroxyquinoline as a result of C–O bond formation was detected in the reaction mixture.



Scheme 1. Reactivity of 2-chloroquinoline (**1**) toward nucleophiles under Pd–Cu catalysis.

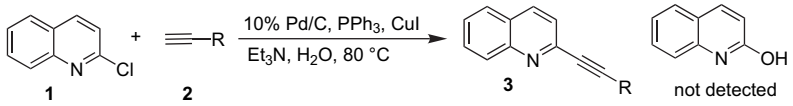
For a comparative study, the coupling reaction of **1** with 2-methyl but-3-yn-2-ol (**2a**) was investigated in a number of solvents including water using Pd/C–CuI–PPh_3 as a catalyst system at 80 °C (Table 1). Initially, the reaction was carried out in DMF for 5 h when the product **3a** was isolated in 67% yield (entry 1, Table 1). However, the yield increased to 83% with the increase of reaction time to 10 h (entry 2, Table 1). Further increase in time did not improve the product yield. The use of other solvents such as THF, MeCN, and dioxane was also examined (entries 3–5, Table 1). While the coupling reaction proceeded well in all these solvents affording good yields of product (**3a**) the best result, however, was achieved by using water as a solvent (entry 6, Table 1). The use of 2-aminoethanol as a base in place of triethylamine resulted in a mixture of products perhaps due to its direct reaction with **1** thereby lowering the yield of **3a** (entry 7, Table 1). To determine the reusability of the recovered Pd/C-catalyst the reaction mixture of **1** and **2a** (entry 6, Table 1) was allowed to cool to room temperature. After filtration, washing with water, acetone, and DCM, and drying, the catalyst was used to conduct the reaction of **1** with **2a** in the presence of same reagents, base, ligand, and cocatalyst. The process was repeated for two times when 95 and 80% conversions were observed. Since cheaply available Pd/C and water were found to be highly effective, reusable catalyst and solvent, respectively, for the Sonogashira coupling of 2-chloroquinoline with terminal alkyne hence we decided to test the generality and scope of this protocol for the preparation of 2-alkynylquinolines. Thus, a variety of commercially available terminal alkynes were employed under the reaction condition studied and results are summarized in Table 2.

Table 1
Effect of solvents on the coupling reaction of 2-chloroquinoline (**1**) with 2-methyl but-3-yn-2-ol[a] (**2a**)

Entry	Solvent	Time (h)	Yield[b] (%)
1	DMF	5	67
2	DMF	10	83
3	THF	10	76
4	MeCN	10	72
5	Dioxane	10	70
6	H_2O	10	87
7	H_2O	10	51[c]

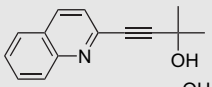
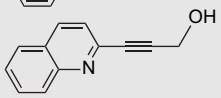
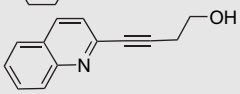
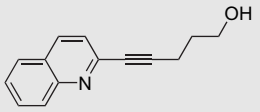
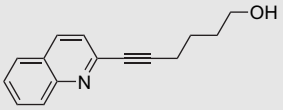
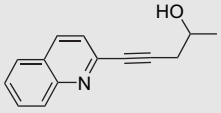
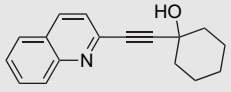
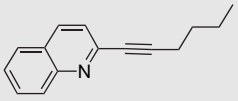
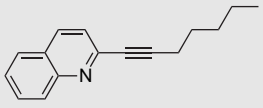
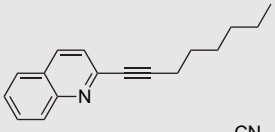
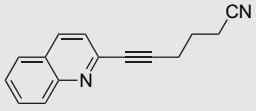
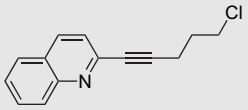
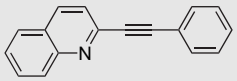
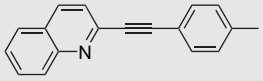
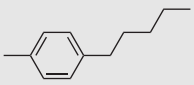
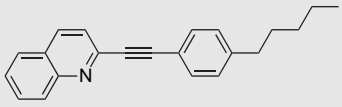
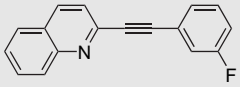
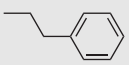
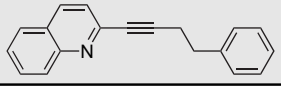
[a] All the reactions were carried out by using **1** (1.0 equiv), **2a** (1.5 equiv), 10% Pd/C (0.026 equiv), PPh_3 (0.20 equiv), CuI (0.05 equiv), and Et_3N (3 equiv) at 80 °C.
[b] Isolated yields.
[c] 2-Aminoethanol was used in place of Et_3N.

As outlined in Table 2, 2-chloroquinoline (**1**) showed good reactivity toward the present coupling reaction in water (entries 1–18, Table 1). Various functional groups including hydrophilic and hydrophobic substitutents, for example, hydroxy, alkyl, cyano, chloro, aryl, etc., present in the terminal alkynes were well tolerated. This allowed the preparation of a wide variety of 2-alkynylquinolines (**3a**–**q**) under mild condition in good to excellent yields. It is worthy to mention that like our earlier observation[11] the present coupling reaction in water was also found to be selective and no significant dimerization of terminal alkynes was observed except when arylalkynes (**3m**–**p**) were used. To test the applicability of this protocol for the preparation of quinoline derivatives of biological interest we then used 2,4-dichloroquinoline[17] for the coupling reaction with terminal alkyne. When treated with 1-octyne (**2j**) under the condition studied, 2,4-dichloroquinoline (**4**) afforded monosubstituted product i.e., 2-alkynylquinoline derivative (**5**) with high regioselectivity (Scheme 3). While regioselective Sonogashira coupling of 2,4-dihaloquinolines was mainly performed by using different halides such as iodide and bromide,[18a] 2,4-dibromoquinolines, however, showed a similar regioselectivity by providing the C-2 alkynylated product when reacted with terminal alkynes.[8a] Depending on the target compound to be synthesized, the C-4 chloro group of compound **5** can be functionalized[18b–d] further after reduction of the acetylenic moiety[8a] to provide the compound of biological interest. Compound **2b** showed nematocidal and trichomonacidal activities when tested in vitro against the nematodes *Caenorhabditis elegans*,

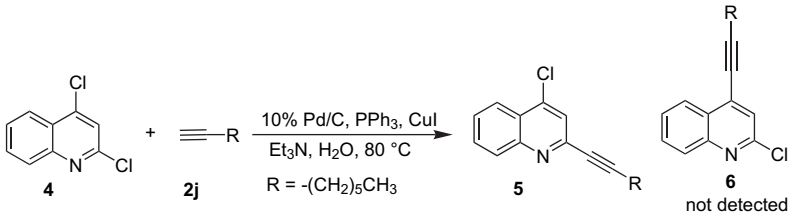


Scheme 2. Pd/C-mediated coupling reaction of 2-chloroquinoline in water.

Table 2
Pd/C-mediated synthesis of 2-alkynylquinolines in water[a]

Entry	Alkynes (**2**) R=		Products[b] (**3**)		Yield[c] (%)
1	$-C(CH_3)_2OH$	**2a**		**3a**	87
2	$-CH_2OH$	**2b**		**3b**	89
3	$-CH_2CH_2OH$	**2c**		**3c**	86
4	$-(CH_2)_2CH_2OH$	**2d**		**3d**	82
5	$-(CH_2)_3CH_2OH$	**2e**		**3e**	85
6	$-CH_2CH(OH)CH_3$	**2f**		**3f**	93
7		**2g**		**3g**	96
8	$-(CH_2)_3CH_3$	**2h**		**3h**	92
9	$-(CH_2)_4CH_3$	**2i**		**3i**	85
10	$-(CH_2)_5CH_3$	**2j**		**3j**	88
11	$-(CH_2)_3CN$	**2k**		**3k**	90
12	$-(CH_2)_2CH_2Cl$	**2l**		**3l**	94
13	$-C_6H_5$	**2m**		**3m**	87
14	$-C_6H_4CH_3$-*p*	**2n**		**3n**	84
15		**2o**		**3o**	91
16	$-C_6H_4F$-*m*	**2p**		**3p**	90
17		**2q**		**3q**	89

[a] All the reactions were carried out by using **1** (1.0 equiv), **2** (1.5 equiv), 10% Pd/C (0.026 equiv), PPh_3 (0.20 equiv), CuI (0.05 equiv), and Et_3N (3 equiv) at 80 °C for 10 h.
[b] Identified by ^1H NMR, IR, and MS.
[c] Isolated yields.



Scheme 3.

Heligmosomoides polygyrus and the protozoa *Trichomonas vaginalis*.[2] Compound **3p** is of interest for the treatment of disorder mediated by metabotropic glutamate receptor subtype 5 (mGluR5).[19]

Mechanistically, the Pd/C-mediated alkynylation of 2-chloroquinoline (**1**) proceeds via generation of an active Pd(0) species in situ that undergoes oxidative addition with **1** to give the organo-Pd(II) species **Z** (Scheme 1). However, generation of active Pd(0) species involves[20] a Pd leaching process, in which Pd leaches into the solution and becomes an active species by interacting with phosphine ligands. The active species is therefore a dissolved Pd(0)–PPh_3 complex that actually catalyzes the C–C bond forming reaction. Thus, the minor portion of the bound palladium (Pd/C) leached into the solution is the actual catalytic species, indicating that the catalytic cycle works in solution rather than on the surface. At the end of the reaction Pd re-precipitates on the surface of the charcoal.[20b] Once generated, the organo-Pd(II) species **Z** then undergoes trans organometallation with copper acetylide (path b, Scheme 1) generated in situ from CuI and terminal alkyne followed by reductive elimination of Pd(0) to afford 2-alkynylquinoline **3**. The higher reactivity of copper acetylide perhaps did not allow water molecules, although present in excess, to interact with **Z** thereby preventing the hydrolysis of 2-chloroquinoline **1** (path b, Scheme 1). It is known that due to the presence of electronegative nitrogen atom the chloro group at the azomethine carbon is more susceptible to undergo oxidative addition with Pd(0)[9a,21] than chlorobenzene. This clearly explains the participation of 2-chloroquinoline in the alkynylation reaction in water when chlorobenzene was found to be inactive[11b] under the conditions. Moreover, the higher reactivity of chloro group at C-2 over C-4 position on the quinoline ring in addition to the coordination of quinoline nitrogen to the palladium[13] explains the observed regioselectivity in alkynylation of 2,4-dichloroquinoline at C-2 position.

Having demonstrated the high reactivity of 2-chloroquinolines toward Pd/C-mediated alkynylation in pure water we then decided to examine the reactivity of other chloroquinolines under the same reaction conditions. Accordingly, commercially available 1-chloroisoquinoline (**7**) was reacted with phenylacetylene (**2m**) in the presence of Pd/C–CuI–PPh_3 as a catalyst system at 80 °C for 10 h in water. The desired product 1-phenylethynyl isoquinoline[22] (**8**) was isolated in 85% yield. Similarly, reaction of 3-methyl-2-chloroquinoline[23] (**9**) with 1-hexyne (**2h**) afforded 2-hex-1-ynyl-3-methyl quinoline[9a] (**10**) in 60% yield.

3. Conclusions

In summary, Pd/C–CuI–PPh_3 proved to be an efficient catalyst system for the cross-coupling of 2-chloroquinoline with a variety of terminal alkynes in water providing a general and practical method for the preparation of functionalized 2-alkynylquinolines in good to high yields. The air and moisture stable catalyst Pd/C can be recovered and reused. The reaction proceeds well with both hydrophobic and hydrophilic terminal alkynes and no significant side reactions such as dimerization of terminal alkynes or hydrolysis of 2-chloroquinoline was observed. The use of 2,4-dichloroquinoline afforded monosubstituted product i.e., 2-alkynyl-4-chloro quinoline with high regioselectivity. The methodology was also found to be effective for the alkynylation of 1-chloroisoquinoline and 3-methyl-2-chloroquinoline. While the process is not free from the use of phosphine ligands, however, it does not involve the use of hazardous as well as expensive organic co-solvents and thus minimize waste production and environmental pollution. The process, therefore, is safe in handling and permits to access quinoline derivatives not only for laboratory use but also for large-scale production. Since novel quinoline derivatives are in great demands due to the rise of the resistance level of malarial parasite in the use of anti-malarial drug chloroquine, we believe that the present methodology would certainly help to generate diversity based quinoline library for the identification of better anti-malarial agents.

4. Experimental section

4.1. General information

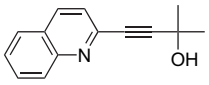
Unless stated otherwise, reactions were monitored by thin layer chromatography (TLC) on silica gel plates (60 F_{254}), visualizing with ultraviolet light or iodine spray. Flash chromatography was performed on silica gel (60–120 mesh) using distilled petroleum ether and ethyl acetate. ^1H and ^{13}C NMR spectra were determined in DMSO-d_6 solution using 400 and 50 MHz spectrometers, respectively. Proton chemical shifts (δ) are relative to tetramethylsilane (TMS, δ=0.0) as internal standard and expressed in parts per million. Spin multiplicities are given as s (singlet), d (doublet), t (triplet), and m (multiplet) as well as br (broad). Coupling constants (J) are given in hertz. Infrared spectra were recorded on a FTIR spectrometer. Melting points were determined by using thermal analysis [differential scanning calorimetry (DSC)] was generated with the help of DSC-60A detector. MS spectra were obtained on a mass spectrometer. Chromatographic purity by HPLC was determined by using area normalization method and the condition specified in each case: column, mobile phase (range used), flow rate, detection wavelength, and retention times. All the terminal alkynes and 2-chloroquinoline used are commercially available. 2,4-Dichloroquinoline was prepared according to the known procedure.[17]

4.2. General procedure for the synthesis of 2-alkynylquinolines (3)

A mixture of 2-chloroquinoline (**1**) (1.42 mmol), 10% Pd/C (0.037 mmol), PPh_3 (0.28 mmol), CuI (0.07 mmol), and triethylamine (4.26 mmol) in water (10 mL) was stirred at 25–30 °C for 30 min under nitrogen. The acetylinic compound (**2**) (2.14 mmol) was added, and the mixture was initially stirred at room temperature for 1 h and then at 80 °C for 10 h. After completion of the reaction, the mixture was cooled to room temperature, diluted with EtOAc (50 mL), and filtered through Celite. The organic layers were collected, washed with water (3×30 mL), dried over anhydrous

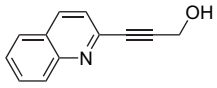
Na_2SO_4, and concentrated. The crude residue was purified by column chromatography on silica gel using light petroleum (60–80 °C)/ethyl acetate to afford the desired product.

*4.2.1. 2-Methyl-4-quinolin-2-yl-but-3-yn-2-ol (**3a**)*



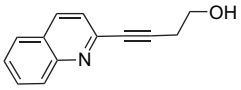
Low melting solid, mp<25 °C; R_f (20% ethyl acetate/*n*-hexane) 0.18; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.11 (d, J=8.5 Hz, 2H), 7.79–7.69 (m, 2H), 7.55–7.26 (m, 2H), 1.68 (s, 6H); IR (cm^{-1}, KBr) 3240, 3068, 2964, 2223, 1593; *m*/*z* (ES mass) 212 (M+1, 100%); ^{13}C NMR ($CDCl_3$, 50 MHz) 147.3, 143.3, 135.9, 131.7, 129.7, 129.1, 128.3, 128.1, 127.1, 90.6, 80.7, 60.4, 30.6, 15.6; HPLC: 98.0%, column: Symmetry Shield RP18 (150×4.6 mm), mobile phase A: 0.01 M KH_2PO_4, mobile phase B: CH_3CN, gradient (T/%B): 0/30, 4/30, 14/80, 20/80, 21/30, 22/30; flow rate: 1.5 mL/min; UV 210 nm, retention time 7.1 min; HRMS (ESI): calcd for $C_{14}H_{13}NO$ $(M+H)^+$ 212.1075, found 212.1069.

*4.2.2. 3-Quinolin-2-yl-prop-2-yn-1-ol (**3b**)*



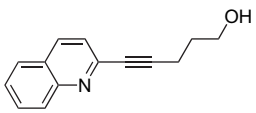
Low melting brown solid, mp<25 °C; R_f (20% ethyl acetate/*n*-hexane) 0.2; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.12–8.07 (m, 2H), 7.80–7.70 (m, 2H), 7.56–7.26 (m, 2H), 4.61 (s, 2H); IR (cm^{-1}, KBr) 3224, 3061, 2918, 2218; *m*/*z* (ES mass) 184 (M+1, 100%); ^{13}C NMR ($CDCl_3$, 50 MHz) 147.3, 142.7, 136.3, 130.0, 128.3, 127.3, 127.0 (2C), 126.9, 89.8, 84.2, 50.6; HPLC: 98.37%, column: Inertsil ODS3V (150×4.6 mm), mobile phase A: 0.01 M H_2PO_4, mobile phase B: CH_3CN, gradient (T/%B): 0/20, 2/20, 14/80, 22/80, 24/20, 25/20; flow rate: 1.5 mL/min; UV 210 nm, retention time 6.9 min; HRMS (ESI): calcd for $C_{12}H_9NO$ $(M+H)^+$ 184.0762, found 184.0754.

*4.2.3. 4-Quinolin-2-yl-but-3-yn-1-ol (**3c**)*



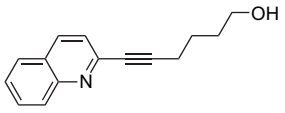
Brown gum; R_f (20% ethyl acetate/*n*-hexane) 0.16; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.35 (d, J=8.7 Hz, 1H), 7.97 (t, J=8.3 Hz, 1H), 7.80–7.78 (m, 1H), 7.64–7.59 (m, 2H), 7.55 (d, J=8.3 Hz, 1H), 3.65 (t, J=6.5 Hz, 2H), 2.65 (t, J=6.5 Hz, 2H); IR (cm^{-1}, neat) 3344, 3000, 2935, 2227, 1595; *m*/*z* (ES mass) 198 (M+1, 100%); ^{13}C NMR ($CDCl_3$, 50 MHz) 150.4, 147.7, 136.9, 136.6, 133.6, 132.1, 132.0, 131.6, 128.6, 88.0 (2C), 60.5, 29.5; HPLC: 93.26%, column: Inertsil ODS3V (150×4.6 mm), mobile phase A: 0.01 M KH_2PO_4, mobile phase B: CH_3CN, gradient (T/%B): 0/25, 3/25, 14/80, 22/80, 24/25, 25/25; flow rate: 1.5 mL/min; UV 250 nm, retention time 7.2 min; Elemental analysis found C, 79.21; H, 5.60; N, 7.01; $C_{13}H_{11}NO$ requires C, 79.16; H, 5.62; N, 7.10.

*4.2.4. 5-Quinolin-2-yl-pent-4-yn-1-ol (**3d**)*



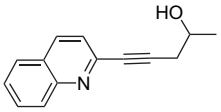
Brown gum; R_f (20% ethyl acetate/*n*-hexane) 0.15; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.09–8.06 (m, 2H), 7.78–7.60 (m, 2H), 7.54–7.44 (m, 2H), 3.88–3.73 (m, 2H), 2.86–2.63 (m, 2H), 1.96–1.26 (m, 2H); IR (cm^{-1}, neat) 3331 (br), 3059, 2947, 2225, 1595, 1425; *m*/*z* (ES mass) 212 (M+1, 100%); ^{13}C NMR ($CDCl_3$, 50 MHz) 147.2, 143.3, 135.9, 131.7, 131.5, 129.7, 129.1, 128.3, 128.1, 91.6, 80.7, 60.4, 30.6, 15.6; HPLC 97.97%, column: Inertsil ODS3V (150×4.6 mm), mobile phase A: 0.01 M KH_2PO_4, mobile phase B: CH_3CN, gradient (T/%B): 0/30, 4/30, 15/80, 22/80, 24/30, 25/30; flow rate: 1.5 mL/min; UV 250 nm, retention time 7.0 min; HRMS (ESI): calcd for $C_{14}H_{13}NO$ $(M+H)^+$ 212.1075, found 212.1083.

*4.2.5. 6-Quinolin-2-yl-hex-5-yn-1-ol (**3e**)*



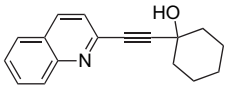
Low melting brown solid, mp<25 °C; R_f (20% ethyl acetate/*n*-hexane) 0.21; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.09 (dd, J=8.3 and 2.9 Hz, 2H), 7.78–7.70 (m, 1H), 7.69–7.66 (m, 1H), 7.56–7.44 (m, 2H), 3.68 (t, J=6.7 Hz, 2H), 2.57–2.55 (m, 2H), 2.30 (t, J=6.8 Hz, 2H), 1.79–1.78 (m, 2H); IR (cm^{-1}, KBr) 3304, 3053, 2947, 2223, 1593; *m*/*z* (ES mass) 226 (M+1, 100%); ^{13}C NMR ($CDCl_3$, 50 MHz) 147.4, 143.5, 135.9, 131.8, 131.7, 129.7, 128.2, 126.6, 126.5, 91.8, 80.9, 61.4, 31.5 (2C), 24.3; HPLC: 92.36%, column: Inertsil ODS3V (150×4.6 mm), mobile phase A: 0.01 M KH_2PO_4, mobile phase B: CH_3CN, gradient (T/%B): 0/20, 2/20, 14/80, 22/80, 24/20, 25/20; flow rate: 1.5 mL/min; UV 210 nm, retention time 8.9 min; HRMS (ESI): calcd for $C_{15}H_{15}NO$ $(M+H)^+$ 226.1232, found 226.1213.

*4.2.6. 5-Quinolin-2-yl-pent-4-yn-2-ol (**3f**)*



Low melting solid, mp<25 °C; R_f (20% ethyl acetate/*n*-hexane) 0.18; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.07 (dd, J=7.8 Hz, 2H), 7.77–7.68 (m, 2H), 7.51–7.44 (m, 2H), 4.20–4.15 (m, 1H), 2.70–2.67 (m, 2H), 1.38–1.36 (d, J=5.8 Hz, 3H); IR (cm^{-1}, neat) 3344 (br), 3061, 2981, 2229, 1595; *m*/*z* (ES mass) 212 (M+1, 100%); ^{13}C NMR ($CDCl_3$, 50 MHz) 147.2, 143.2, 136.1, 129.8 (2C), 128.2, 127.2 (2C), 126.6 (2C), 123.8, 89.1, 82.3, 29.8; HPLC: 99.02%, column: Symmetry Shield RP18 (150×4.6 mm), mobile phase A: 0.01 M KH_2PO_4, mobile phase B: CH_3CN, gradient (T/%B): 0/30, 4/30, 14/80, 20/80, 21/30, 22/30; flow rate: 1.5 mL/min; UV 210 nm, retention time 6.6 min; HRMS (ESI): calcd for $C_{14}H_{13}NO$ $(M+H)^+$ 212.1075, found 212.1068.

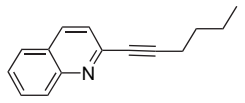
*4.2.7. 1-Quinolin-2-ylethynyl-cyclohexanol (**3g**)*



Brown gum; R_f (20% ethyl acetate/*n*-hexane) 0.25; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.10 (d, J=8.3 Hz, 2H), 7.79–7.77 (m, 1H), 7.73–7.69 (m, 1H), 7.55–7.48 (m, 2H), 2.12–2.07 (m, 2H), 1.80–1.63 (m, 4H), 1.60–1.56 (m, 4H); IR (cm^{-1}, neat) 3332 (br), 3059, 2933, 2225, 1593; *m*/*z* (ES mass) 252 (M+1, 100%); ^{13}C NMR ($CDCl_3$, 50 MHz) 147.3, 143.0, 135.8, 135.8, 129.7 (2C), 129.6, 128.5 (2C), 127.1 (2C), 94.9, 83.5, 29.3, 24.9, 22.9 (2C); HPLC: 99.79%, column: Acquity UPLCBEHC18 (2.1×100 mm), mobile phase A: 0.1% TEA,

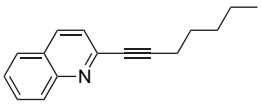
mobile phase B: CH_3CN, gradient (T/%B): 0/50, 1/50, 5/80, 9/80, 10/50, 12/50; flow rate: 1.5 mL/min; UV 249 nm, retention time 2.5 min; HRMS (ESI): calcd for $C_{17}H_{17}NO$ $(M+H)^+$ 252.1388, found 252.1376.

4.2.8. 2-Hex-1-ynyl-quinoline (**3h**)



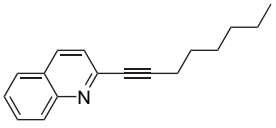
Brown oil; R_f (20% ethyl acetate/*n*-hexane) 0.24; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.06 (dd, J=8.3 and 3.4 Hz, 2H), 7.76 (d, J=7.8 Hz, 1H), 7.69–7.66 (m, 1H), 7.52–7.50 (m, 1H), 7.45 (d, J=8.3 Hz, 1H), 2.50 (t, J=7.3 Hz, 2H), 1.68–1.64 (m, 2H), 1.56–1.47 (m, 2H), 0.96 (t, J=7.3 Hz, 3H); IR (cm^{-1}, neat) 3059, 2956, 2225, 1596; *m*/*z* (ES mass) 210 (M+1, 100%); ^{13}C NMR ($CDCl_3$, 50 MHz) 147.7, 143.8, 135.6, 129.5, 128.8, 127.1, 126.6, 126.4, 126.3, 91.4, 80.3, 30.1, 21.8, 18.9, 13.3; HPLC 99.75%, column: Inertsil ODS3V, mobile phase A: 0.01 M KH_2PO_4, mobile phase B: CH_3CN, gradient (T/%B): 0/50, 2/50, 20/80, 27/80, 29/50, 30/50; flow rate: 1.5 mL/min; UV 210 nm, retention time 11.6 min; HRMS (ESI): calcd for $C_{15}H_{15}N$ $(M+H)^+$ 210.1283, found 210.1259.

4.2.9. 2-Hept-1-ynyl-quinoline (**3i**)



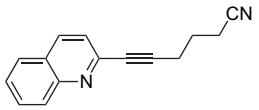
Brown gum; R_f (20% ethyl acetate/*n*-hexane) 0.2; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.08 (dd, J_1=8.3 Hz, J_2=3.9 Hz, 2H), 7.77–7.66 (m, 2H), 7.52–7.43 (m, 2H), 2.49 (t, J=7.3 Hz, 2H), 1.71–1.63 (m, 2H), 1.51–1.41 (m, 4H), 0.93 (t, J=7.3 Hz, 3H); IR (cm^{-1}, neat) 3061, 2958, 2224, 1595; *m*/*z* (ES mass) 224 (M+1, 100%); ^{13}C NMR ($CDCl_3$, 50 MHz) 147.4, 143.5, 135.3, 129.2, 128.7, 128.4, 126.8, 126.3, 126.1, 91.5, 80.6, 30.6, 29.1, 28.8, 21.6, 13.4; HPLC: 99.45%, column: Inertsil ODS3V (150×4.6 mm), mobile phase A: 0.01% TFA, mobile phase B: CH_3CN, gradient (T/%B): 0/60, 2/60, 12/80, 18/80, 19/60, 20/60; flow rate: 1.5 mL/min; UV 210 nm, retention time 8.4 min; HRMS (ESI): calcd for $C_{16}H_{17}N$ $(M+H)^+$ 224.1439, found 224.1433.

4.2.10. 2-Oct-1-ynyl-quinoline (**3j**)



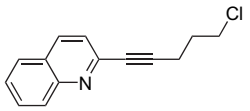
Low melting solid, mp<25 °C; R_f (20% ethyl acetate/*n*-hexane) 0.25; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.08–8.05 (m, 2H), 7.77–7.70 (m, 2H), 7.69–7.50 (m, 2H), 2.61–2.47 (m, 2H), 1.74–1.63 (m, 4H), 1.51–1.30 (m, 4H), 0.93–0.89 (m, 3H); IR (cm^{-1}, neat) 3059, 2927, 2225, 1595; *m*/*z* (ES mass) 238 (M+1, 100%); ^{13}C NMR ($CDCl_3$, 50 MHz) 147.4, 143.5, 135.4, 129.2, 128.7, 128.4, 126.8, 126.5, 126.1, 91.6, 80.6, 30.8, 29.2, 28.1, 27.8, 23.6, 13.5; HPLC: 99.51%, column: Acquity UPLCBEHC18 (2.1×100 mm), mobile phase A: 0.01% TFA, mobile phase B: CH_3CN, gradient (T/%B): 0/50, 2/50, 6/80, 12/80, 13/50, 14/50; flow rate: 1.5 mL/min; UV 249 nm, retention time 6.5 min; Elemental analysis found C, 86.17; H, 8.01; N, 5.95; $C_{17}H_{19}N$ requires C, 86.03; H, 8.07; N, 5.90.

4.2.11. 6-Quinolin-2-yl-hex-5-ynenitrile (**3k**)



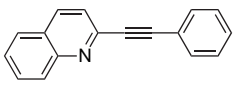
Brown gum; R_f (20% ethyl acetate/*n*-hexane) 0.35; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.11–8.06 (m, 2H), 7.79–7.71 (m, 2H), 7.55–7.51 (m, 2H), 2.70 (t, J=6.8 Hz, 2H), 2.60 (t, J=6.8 Hz, 2H), 2.07–2.00 (m, 2H); IR (cm^{-1}, neat) 3059, 2941, 2227, 1593, 1493; *m*/*z* (ES mass) 221 (M+1, 100%); ^{13}C NMR ($CDCl_3$, 50 MHz) 147.6, 143.0, 135.9, 129.7, 128.7, 127.2, 127.0, 126.7, 123.8, 118.8, 88.1, 82.3, 23.9, 18.2, 16.0; HPLC: 99.72%, column: Symmetry Shield RP18 (150×4.6 mm), mobile phase A: 0.01 M KH_2PO_4, mobile phase B: CH_3CN, gradient (T/%B): 0/30, 2/30, 12/80, 18/80, 19/30, 20/30; flow rate: 1.5 mL/min; UV 248 nm, retention time 7.5 min; HRMS (ESI): calcd for $C_{15}H_{12}N_2$ $(M+H)^+$ 221.1079, found 221.1073.

4.2.12. 2-(5-Chloro-pent-1-unyl)-quinoline (**3l**)



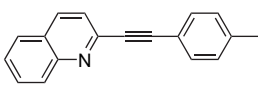
Brown gum; R_f (20% ethyl acetate/*n*-hexane) 0.34; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.08 (t, J=8.5 Hz, 2H), 7.79–7.69 (m, 2H), 7.51–7.26 (m, 2H), 3.74 (t, J=6.4 Hz, 2H), 2.71 (t, J=6.8 Hz, 2H), 2.15–1.70 (m, 2H); IR (cm^{-1}, neat) 3059, 2926, 2227, 1593; *m*/*z* (ES mass) 230 (M+1, 100%); ^{13}C NMR ($CDCl_3$, 50 MHz) 147.8, 143.4, 135.8, 129.8, 129.2, 128.9, 127.2 (2C), 126.7, 89.5, 81.7, 43.5, 30.8, 16.7; HPLC: 98.90%, column: Inertsil ODS3V (150×4.6 mm), mobile phase A: 0.01 M KH_2PO_4, mobile phase B: CH_3CN, gradient (T/%B): 0/55, 2/55, 7/80, 18/80, 19/55, 20/55; flow rate: 1.5 mL/min; UV 210 nm, retention time 5.9 min; HRMS (ESI): calcd for $C_{14}H_{12}ClN$ $(M+H)^+$ 230.0737, found 230.0731.

4.2.13. 2-Phenylethynyl-quinoline (**3m**)



White solid, mp 64–65 °C; R_f (20% ethyl acetate/*n*-hexane) 0.3; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.13 (dd, J=8.3 and 2.9 Hz, 2H), 7.80 (d, J=7.8 Hz, 1H), 7.75–7.71 (m, 2H), 7.68–7.61 (m, 2H), 7.58 (d, J=7.8 Hz, 1H), 7.56–7.52 (m, 1H), 7.39–7.37 (m, 2H); IR (cm^{-1}, KBr) 3059, 2922, 2208, 1591, 1498; *m*/*z* (ES mass) 230 (M+1, 100%); ^{13}C NMR ($CDCl_3$, 50 MHz) 147.61, 142.9, 135.7, 131.7, 129.5, 129.0, 128.7, 128.6, 127.9 (2C), 127.0 (2C), 123.8 (2C), 121.6, 89.6, 89.0; HPLC: 99.48%, column: Inertsil ODS3V (150×4.6 mm), mobile phase A: 0.01 M KH_2PO_4, mobile phase B: CH_3CN, gradient (T/%B): 0/60, 2/60, 8/80, 18/80, 19/60, 20/60; flow rate: 1.5 mL/min; UV 210 nm, retention time 6.76 min; HRMS (ESI): calcd for $C_{17}H_{11}N$ $(M+H)^+$ 230.0970, found 230.0960.

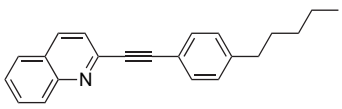
4.2.14. 2-p-Tolylethyl-quinoline (**3n**)



White solid, mp 98–100 °C; R_f (20% ethyl acetate/*n*-hexane) 0.3; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.12 (dd, J_1=8.5 Hz, J_2=3.7 Hz, 2H), 7.79 (d, J=8.3 Hz, 1H), 7.78–7.70 (m, 2H), 7.60–7.25 (m, 3H), 7.19 (d,

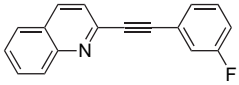
J=8.3 Hz, 2H), 2.38 (s, 3H); IR (cm^{-1}, KBr) 3043, 2914, 2220, 1591; m/z (ES mass) 244 (M+1, 100%); ^{13}C NMR ($CDCl_3$, 50 MHz) 148.0, 143.6, 139.9, 135.9 (2C), 131.9 (2C), 129.8 (2C), 129.0 (2C), 127.3 (2C), 126.8, 124.1, 90.1, 88.7, 21.4; HPLC: 97.9%, column: Inertsil ODS3V (150×4.6 mm), mobile phase A: 0.01 M KH_2PO_4, mobile phase B: CH_3CN, gradient (T/%B): 0/60, 2/60, 8/80, 18/80, 19/60, 20/60; flow rate: 1.5 mL/min; UV 250 nm, retention time 8.13 min; HRMS (ESI): calcd for $C_{18}H_{13}N$ $(M+H)^+$ 244.1126, found 244.1135.

*4.2.15. 2-(4-Pentyl-phenylethynyl)-quinoline (**3o**)*



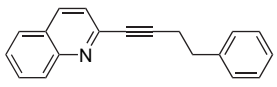
Brown oil; R_f (20% ethyl acetate/*n*-hexane) 0.3; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.09–8.06 (m, 2H), 7.77–7.71 (m, 2H), 7.52–7.47 (m, 5H), 6.42–6.39 (m, 1H), 2.31–2.27 (m, 4H), 1.72–1.60 (m, 7H); IR (cm^{-1}, neat) 3050, 2929, 2200, 1593, 1498; m/z (ES mass) 300 (M+1, 100%); ^{13}C NMR ($CDCl_3$, 50 MHz) 147.6, 143.5, 137.3, 135.4 (2C), 129.3 (2C), 128.6 (2C), 126.9, 126.3, 126.2, 123.2 (2C), 119.7, 91.7, 86.7, 28.2, 25.4, 21.7 (2C), 20.9; HPLC: 97.49%, column: Acquity UPLCBEHC18 (2.1×100 mm), mobile phase A: 0.1% TEA, mobile phase B: CH_3CN, gradient (T/%B): 0/50, 1/50, 5/80, 9/80, 10/50, 12/50; flow rate: 1.5 mL/min; UV 213 nm, retention time 5.19 min; HRMS (ESI): calcd for $C_{18}H_{13}N$ $(M+H)^+$ 244.1126, found 244.1135.

*4.2.16. 2-(3-Fluoro-phenylethynyl)-quinoline (**3p**)*



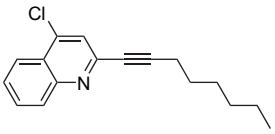
White solid, mp 75–77 °C; R_f (20% ethyl acetate/*n*-hexane) 0.27; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.14 (t, J=8.5 Hz, 2H), 7.81 (d, J=7.8 Hz, 1H), 7.76–7.74 (m, 2H), 7.72–7.54 (m, 2H), 7.10–7.08 (m, 3H); IR (cm^{-1}, neat) 3057, 2924, 2208, 1606, 1500; m/z (ES mass) 248 (M+1, 100%); ^{13}C NMR ($CDCl_3$, 50 MHz) 164.6, 148.0, 142.9, 136.1, 130.0, 129.8, 128.0 (2C), 127.9, 127.4, 127.1, 124.1, 123.9, 123.7, 116.6, 89.9, 88.2; HPLC: 98.42%, column: Acquity UPLCBEHC18 (2.1×100 mm), mobile phase A: 0.1% TEA, mobile phase B: CH_3CN, gradient (T/%B): 0/40, 1/40, 5/80, 8/80, 9/40, 10/40; flow rate: 1.5 mL/min; UV 210 nm, retention time 5.1 min; HRMS (ESI): calcd for $C_{17}H_{10}FN$ $(M+H)^+$ 248.0876, found 248.0887.

*4.2.17. 2-(4-Phenyl-but-1-ynyl)-quinoline (**3q**)*



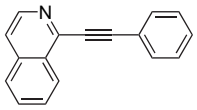
Low melting brown solid, mp<25 °C; R_f (20% ethyl acetate/*n*-hexane) 0.28; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.08–8.05 (m, 2H), 7.75 (d, J=8.3 Hz, 1H), 7.71–7.67 (m, 1H), 7.52–7.48 (m, 1H), 7.40 (d, J=8.3 Hz, 1H), 7.33–7.28 (m, 5H), 3.00 (t, J=7.8 Hz, 2H), 2.78 (t, J=7.8 Hz, 2H); IR (cm^{-1}, neat) 3061, 2930, 2226, 1594; m/z (ES mass) 258 (M+1, 100%); ^{13}C NMR ($CDCl_3$, 50 MHz) 147.2, 143.1, 139.6, 135.3, 129.2, 128.7, 128.3, 127.7, 127.3, 127.1, 126.7, 126.4, 126.2, 126.0, 125.7, 90.43, 81.18, 33.99, 20.9; HPLC: 99.01%, column: Inertsil ODS3V (150×4.6 mm), mobile phase A: 0.01% TFA, mobile phase B: CH_3CN, gradient (T/%B): 0/60, 2/60, 12/80, 18/80, 19/60, 20/60; flow rate: 1.5 mL/min; UV 210 nm, retention time 7.2 min; HRMS (ESI): calcd for $C_{19}H_{15}N$ $(M+H)^+$ 258.1283, found 258.1275.

4.3. Synthesis of 4-chloro-2-oct-1-ynyl-quinoline (5)



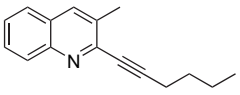
A mixture of 2,4-dichloroquinoline (**4**) (2.84 mmol), 10% Pd/C (0.074 mmol), PPh_3 (0.56 mmol), CuI (0.14 mmol), and triethylamine (8.52 mmol) in water (20 mL) was stirred at 25–30 °C for 30 min under nitrogen. To this mixture was added 1-octyne (**2j**) (4.28 mmol) and the mixture was initially stirred at room temperature for 1 h and then at 80 °C for 8 h. After completion of the reaction, the mixture was cooled to room temperature, diluted with EtOAc (110 mL), and filtered through Celite. The organic layers were collected, washed with water (3×50 mL), dried over anhydrous Na_2SO_4, and concentrated. The crude residue was purified by column chromatography on silica gel, using light petroleum (60–80 °C)/ethyl acetate to afford 4-chloro-2-oct-1-ynyl-quinoline (82% yield). Low melting brown solid, mp<25 °C; R_f (20% ethyl acetate/*n*-hexane) 0.18; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.18–8.07 (m, 2H), 7.77–7.60 (m, 2H), 7.55 (s, 1H), 2.48 (t, J=7.0 Hz, 2H), 1.70–1.63 (m, 2H), 1.58–1.44 (m, 2H), 1.36–1.28 (m, 4H), 0.92–0.89 (m, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) 148.4, 143.4, 141.9, 130.3, 129.2, 127.3, 124.9, 123.7, 123.4, 92.8, 80.0, 31.0, 28.4, 27.9, 22.2, 19.2, 13.7; IR (cm^{-1}, neat) 3057, 2927, 2216, 1593; m/z (ES mass) 272 (M+1, 100%); HPLC: 99.58%, column: ACE 5 C8 (250×4.6 mm), mobile phase A: 0.01 M H_2PO_4, mobile phase B: CH_3CN, gradient (T/%B): 0/40, 2/40, 4/45, 25/45, 28/40, 32/40; flow rate: 1.0 mL/min; UV 252 nm, retention time 9.74 min; HRMS (ESI): calcd for $C_{17}H_{18}ClN$ $(M+H)^+$ 272.1205, found 272.1206.

4.4. 1-Phenylethynyl isoquinoline[22] (8)



Light yellow oil; R_f (20% ethyl acetate/*n*-hexane) 0.28; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.47 (d, J=5.6 Hz, 1H), 8.42 (d, J=8.3 Hz, 1H), 7.76 (d, J=7.5 Hz, 1H), 7.60 (m, 4H), 7.56 (d, J=5.9 Hz, 1H), 7.33 (m, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) 144.2, 142.8, 135.7, 132.1, 130.5, 129.2, 129.1, 128.4, 127.9, 126.8, 126.8, 122.1, 120.5, 93.9, 86.7; IR (cm^{-1}, KBr) 3045, 2925, 2212, 1590; m/z (ES mass) 230 (M+1, 100%).

4.5. 2-Hex-1-ynyl-3-methyl quinoline[9a] (10)



Brown gum; R_f (20% ethyl acetate/*n*-hexane) 0.22; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.01 (d, J=8.3 Hz, 1H), 7.83 (d, J=0.7 Hz, 1H), 7.64–7.54 (m, 2H), 7.44 (dd, J=7.2 and 0.5 Hz, 1H), 2.51 (t, J=7.3 Hz, 2H), 2.50 (s, 3H), 1.68–1.64 (m, 2H), 1.56–1.46 (m, 2H), 0.96 (t,

J=7.3 Hz, 3H); IR (cm^{-1}, neat) 3060, 2955, 2226; m/z (ES mass) 224 (M+1, 100%).

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