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Novel conversion of 4-aminoquinolines to new tricyclic (*R,S*)-3-methylazeto[3,2-*c*] quinolin-2(2a*H*)-ones and versatile one step synthesis of *N*-(quinolin-4-yl) carbamates from 4-aminoquinolines

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ABSTRACT

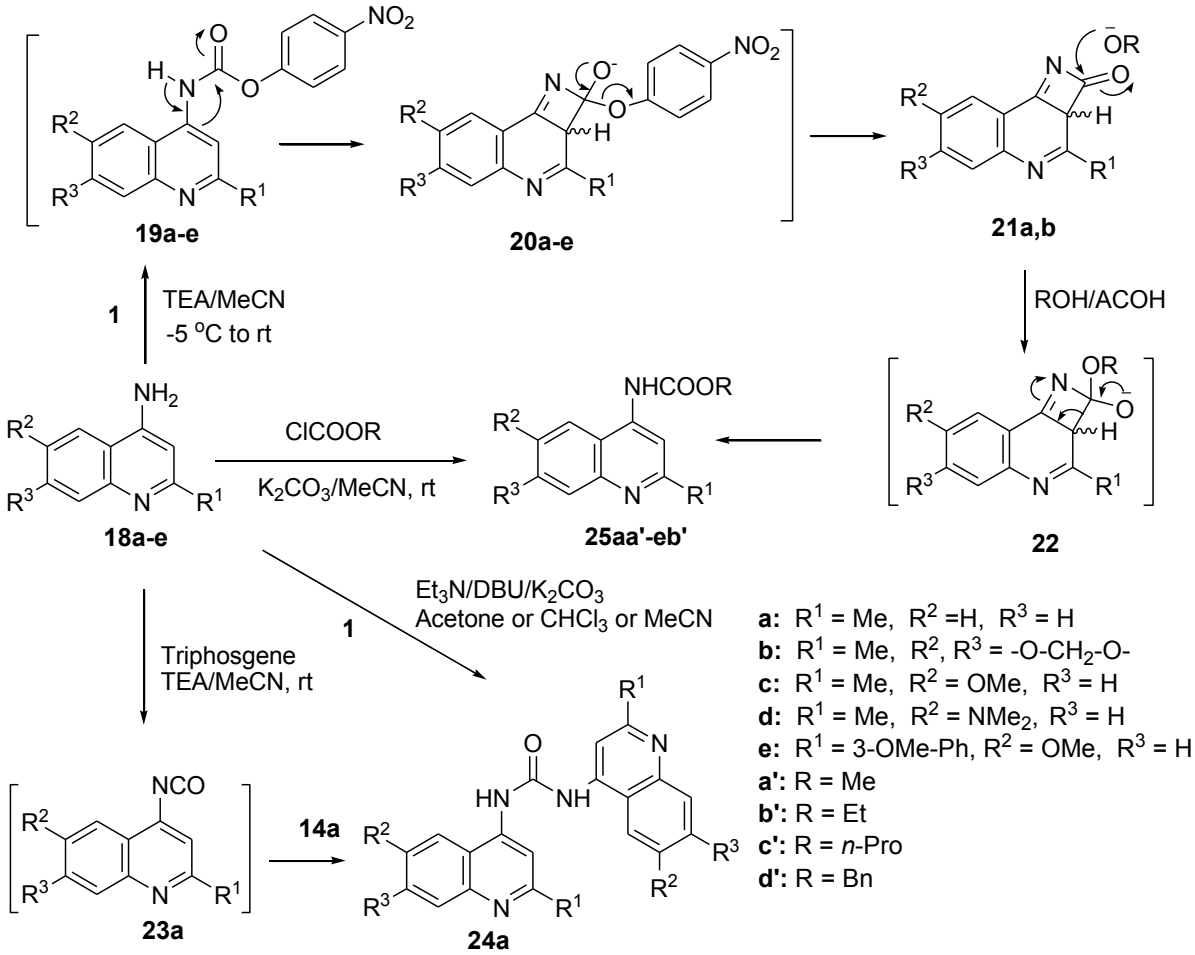
Reaction of 4-aminoquinolines with 4-nitrophenyl chloroformate have resulted in finding a novel transformation of 4-aminoquinolines to tricyclic (*R,S*)-3-methylazeto[3,2-*c*]quinolin-2(2a*H*)-ones. The structure of azeto-quinolinone was determined via spectroscopic and chemical methods. Various alcohols were used as nucleophiles to open the 1-azetinone ring to give the corresponding *N*-(quinolin-4-yl)carbamates in good yields. We also found a new and versatile one step synthesis of *N*-(quinolin-4-yl)carbamates by reacting 4-aminoquinolines with alkyl chloroformates in the presence of anhyd K_2CO_3 in acetonitrile.

***Keywords*:** quinolin; carbamates; azeto-quinolinone; aminoquinolines

1. INTRODUCTION

4-Nitrophenyl chloroformate (**1**) has been applied for many synthetic purposes. For example, previous studies have demonstrated the ability of 4-nitrophenyl chloroformate to react with isolated hydroxyl groups to form 4-nitrophenyl carbonate esters and with vicinal *cis*-diols (**2**) to yield cyclic carbonates (**3**)[1,2] (Scheme 1). The latter reaction most likely involves the formation of a nitrophenyl 2′- or 3′-carbonate intermediate, which then interacts with the unprotected neighboring hydroxy group in the presence of base to produce cyclic carbonate. Since the 4-nitrophenyl esters are relatively stable in acidic and neutral medium and labile in solution containing imidazole, this reagent is used for blocking hydroxyl group in nucleoside or carbohydrate chemistry. Similarly, interacting the intermediate 4-nitrophenyl carbonate ester with the adjacent amino function (**4**) leads to the formation of oxazolidin-2-one derivatives (**5**).[2-5] Using the same approach, Izdebski et al.[6] reported a convenient method for the preparation of symmetrical and unsymmetrical 1,3-disubstituted ureas (**9**) by treating

amines (**6**) with **1** to give 4-nitrophenyl *N*-alkylcarbamates (**7**), followed by reacting the mixture with the second amines (**8**).



Scheme 2. Synthetic route for compounds **21a,b, 20a** and **25.**

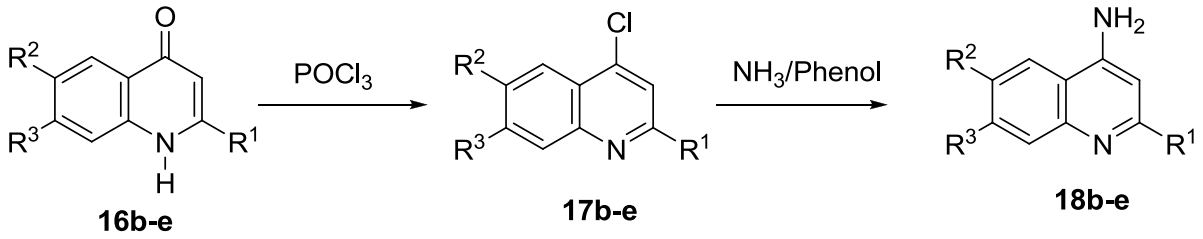
This strategy was later utilized to prepare biologically active compounds including: 1) pyridyl urea analogues as cardioselective anti-ischemic ATP-sensitive potassium channel openers; 2) *N*-(ureidoalkyl)-benzyl-piperidines as potent CC chemokine receptor-3 (CCR-3) antagonists;[7,8] and 3) anticancer nitrogen mustard prodrugs linked glutamic acid residue via a urea or carbamate spacer for antibody-directed enzyme prodrug therapy (ADEPT).[9-12] Previous studies also revealed that reaction of **1** with 2-, 3-, or 4-aminopyridine (**10**) afforded corresponding pyridin-2-, 3-, or 4-yl carbamic acid 4-nitrophenyl ester (**11**).[7,8] While reaction of 1 or 3,4,5-trichlorophenyl chloroformate with di-2-pyridylmethanol (**12**) resulted in the formation of 5-(2′-pyridyl)pyrido[1,2-*c*]oxazol-2-one (**13**) via *N*-acylation followed by intramolecular cyclization.[13] On the other hand, Devraj et al.[14] reported that reaction of naturally occurring anticancer ellipticine (**14**) with 1 followed by *in situ* reduction of the *N*-acylated intermediate gave 2-acyl-1,2-dihydroellipticine (**15**). Thus, the facileness of compound **1** was demonstrated by the formation of quaternary pyridinium cation with the heterocyclic nitrogen atom.

During the course of developing new chemical entities, the synthesis of quinoline carbamates (**19**) was needed. We reasoned that **19a** can be easily prepared by a reaction of 4-

aminoquinaldine with p-nitrophenyl chloroformate. Instead, we surprisingly isolated a novel tricyclic (*R,S*)-azeto[3,2-*c*]quinolin-2(2a*H*)-one (**21a**) as a racemic mixture (Scheme 2). We also found that azetoquinolinones (**21a,b**) are susceptible to nucleophilic attack by various alcohols leading to the formation of new *N*-(quinolin-4-yl)carbamates (**25**). Herein, we report a novel conversion of 4-aminoquinolines to azetoquinolinones and its subsequent transformation into *N*-(quinolin-4-yl)carbamates by treatment with different alcohols. In addition, we also described a novel and convenient way to prepare *N*-(quinolin-4-yl)carbamates from 4-aminoquinolines.

2. RESULTS AND DISCUSSION

2-Methylquinolin-4-amine (**18a**) is commercially available. 4-Aminoquinolines (**18b-e**) were synthesized from the corresponding known 4-quinolones (**16b-e**)[15-18] via chlorination ($POCl_3$)[19] and amination (NH_3/phenol)[20] by following the literature methods (Scheme 3). Compound **18a** was treated with **1** in dry acetonitrile in the presence of triethylamine at -5 °C, instead of **19a**, we surprisingly isolated a novel tricyclic (*R,S*)-3-methylazeto[3,2-*c*]quinolin-2(2a*H*)-one (**21a**) in 41 % yield (Table 1). To further explore this novel transformation, compound **18b-e** were selected to study the effect of the substituent(s) on the 4-aminoquinoline ring with respect to the formation of the tricyclic azetoquinoline[21]. By following the same reaction conditions, 4-amino-6,7-methylenedioxyquinaldine (**18b**) was reacted with **1**. We found that compound **21b** was isolated in low yield (20 %). Additionally, this compound was converted into methylcarbamate of quinoline (**25ba′**) during purification by silica gel column chromatography (solvent: chloroform containing a trace amount of methanol).



16b-e **17b-e** **18b-e**

b: R^1 = Me, R^2, R^3 = -O-CH_2-O-
c: R^1 = Me, R^2 = OMe, R^3 = H
d: R^1 = Me, R^2 = NMe_2, R^3 = H
e: R^1 = 3-OMe-Ph, R^2 = OMe, R^3 = H

Scheme 3. Synthetic route for 4-aminoquinolines (**18b-e**).

However, we were able to isolate **21b** when chloroform/acetone (100:3 v/v) was used as an eluent. Attempts to convert compounds **18c-e** into the corresponding tricyclic (*R,S*)-3-methylazeto[3,2-*c*]quinolin-2(2a*H*)-ones (**21c-e**) under the same reaction conditions were unsuccessful, demonstrating that the formation of azetoquinoline is greatly affected by the substituent at C6 and/or the electron-withdrawing phenyl moiety at C2.

As a further examination, we continued to investigate the effect of solvent used in the intramolecular cyclization. The reaction was carried out in THF, acetone or chloroform solution. The results showed that **21a** (5 %) together with 1,3-bis(quinolin-4-yl)urea (**24a**) (23 %) were isolated after column chromatography when the reaction was proceeded in THF

(Table 1). No desired product was obtained when acetone or chloroform was used as the reaction medium. However, we obtained compound **24a** in 30 and 23 % yield, respectively. The formation of urea derivative **24a** may be caused by the interaction of the C4-NH_2 function of the unreacted **18a** with **19a**. This demonstrated that the intramolecular cyclization of intermediate **19a** to **21a** was preferable in acetonitrile over THF. To optimize the yield of **21a** by using various bases, we found that the reaction did not occur or caused a complex decomposition. However, when DBU or anhyd K_2CO_3 was used as the base, urea **24a** was isolated in 11 and 54 %, respectively with decomposed tar. To prove the formation of urea **24a**, an alternative synthetic way was developed. We found that compound **24a** can be synthesized in low yield (29 %) from the treatment of **18a** with triphosgene in acetonitrile in the presence of triethylamine at room temperature (Scheme 2). This suggests that compound **18a** may be converted into *N*-(quinolin-4-yl)isocyanate (**23a**), which simultaneously reacts with the unreacted **18a** to form **24a**.

Table 1. Synthesis of (*R,S*)-3-methylazeto[3,2-c]quinoline-2-(2a*H*)-one (**21a,b**) and 1,3-bis(2-methylquinolin-4-yl)urea (**20a**).

Reactant 1	Reactant 2[a]	Solvent[†]	Base	Temperature (°C)	Time (h)	Product 21	(%)[b] 24
14a	A	I	Et_3N	-5 to RT	12	**21a** (41)	-
14a	A	II	Et_3N	-5 to RT	12	**21a** (5)	**24a** (23)
14a	A	III	Et_3N	-5 to RT	12	-	**24a** (30)
14a	A	IV	Et_3N	-5 to RT	2	-	**24a** (23)
14a	A	I	DBU	-5 to RT	2	-	**24a** (11)
14a	B	I	Et_3N	-5 to RT	12	-	**24a** (29)
14b	A	I	Et_3N	-5 to RT	12	**21b** (20)	-

[a]Reactant 2: A: 4-nitrophenyl chloroformate (**1**); B: triphosgene.
[b]Solvent: I: acetonitrile, II: THF, III: acetone, IV: chloroform. [‡]Products: Isolated yields.

The structures of **21a** and **21b** were elucidated by Mass, IR, ^{1}H NMR, and ^{13}C NMR spectroscopies. The IR (MeOH/$CHCl_3$) spectrum showed an absorption at 1720 cm^{-1} for the C=O function. One can anticipate that compound **21a** (Fig. 1) might exist as an azetoquinolinone and/or its β-lactam form (**21a′**). However, the ^{1}H NMR (DMSO-d_6) spectrum showed two singlet (δ 7.78 and 7.94 for **21a**) assigned for H-3 in a ratio of 2:1 suggested that compound **21a** might be a racemic mixture. The H-3 proton appeared at the aromatic proton region likely due to the highly deshielding effect of the neighboring carbonyl and imine functions. In addition, the long range ^{1}H-^{13}C correlations (HMBC, Fig. 2) of H-3/H-4, H-3/H-4a, H-3/C-9, H-3/C-2, H-11/C-3, and H-11/C-9 supported that 1-azetinone ring is incorporated with the quinoline ring in **21a**. The NOESY (Fig. 1) analysis also provided evidence that H-3 was vicinal to the methyl protons (H-11). The ^{13}C NMR spectrum of this compound revealed that only the chemical shifts for C-3 (122.6 and 122.7) and C-5 (123.1

and 123.2) have noticeable difference between the two isomers. Furthermore, the ^{1}H NMR spectra of **21a** lacked an exchangeable NH proton. From these analytical data, it is clear that compound **21a** exists as an azetoquinolinone form (**21a**) rather than its β-lactam tautomeric form (**21a′**, Fig. 1). A plausible mechanism for the formation of (*R,S*)-3-methylazeto[3,2-c]quinolin-2(2a*H*)-ones (**21a,b**) is shown in Scheme 2. The 4-aminoquinolines (**18a,b**) reacts with **1** to give the intermediate **19a,b** which was then transformed into the tricyclic **21a,b** via an intramolecular ring closure reaction, which was followed by elimination of 4-nitrophenol.

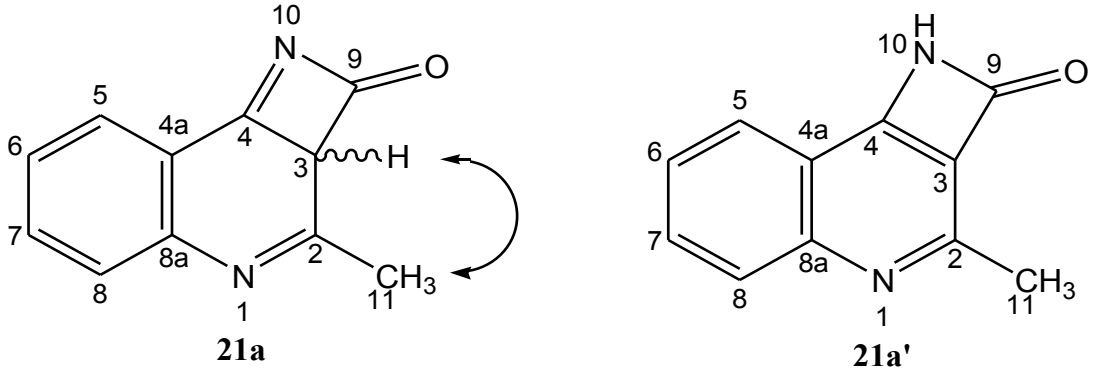


Figure 1. The NOE correlation between H-3 and H-11 of **21a.**

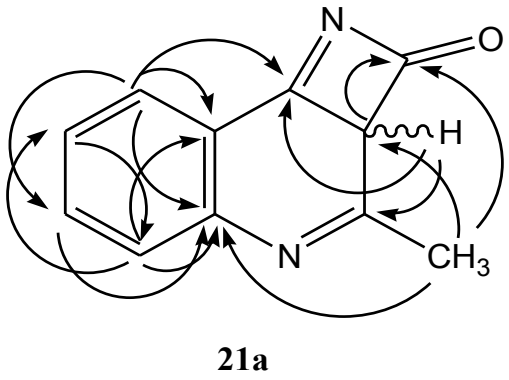
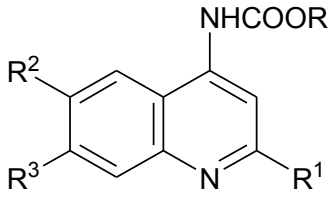


Figure 2. The HMBC correlations of compound **21a.**

In the meantime we found an interesting paper by Rao and co-workers, which described that 1-azetinone ring is susceptible to nucleophilic attack.[21] As noted above, the compound **21b** was converted into methyl carbamate **25ba′** in the presence of methanol. This transformation prompted us to investigate the reaction of **21a** with various alcohols. We treated **21a** with methanol, ethanol, *n*-propanol or benzyl alcohol at reflux temperature and isolated *N*-(quinolin-4-yl)carbamates (**25aa′**, **25ab′**, **25ac′**, and **25ad′**) in good yields (Table 2). The proposed mechanism for the formation of *N*-(quinolin-4-yl)carbamates from **21a** is illustrated in Scheme 2. The nucleophilic attack on **21a** lead to ring opening at C3 position to give *N*-(quinolin-4-yl)carbamates (**25aa′**, **25ab′**, **25ac′**, and **25ad′**). The opening of the 1-azetinone ring was fast in the presence of catalytic amount of acid (i.e., acetic acid or silica gel). For example, the reaction was completed within 24 h when **21a** was reacted with methyl alcohol in the presence of acetic acid at reflux temperature to yield **25aa′** (62 %). While in the absence of acid, the reaction could not be completed even after 48 h under reflux.

Furthermore, we found that **21a** did not react with amino nucleophile, such as anilines or alkylamines, to form urea derivatives under various reaction conditions.

Table 2. Synthesis of *N*-(quinolin-4-yl)carbamates (**25**).



Compd.	R^1	R^2	R^3	R	Yield (%)		mp (°C)
					Method 1	Method 2	
25aa′	Me	H	H	Me	62	84	175-176
25ab′	Me	H	H	Et	80	81	178-179
25ac′	Me	H	H	*n*-Pro	75	n.d.[a]	165-166
25ad′	Me	H	H	Bn	76	n.d.	94-95
25ba′	Me	-O-CH_2-O-		Me	n.d.	42	193-195
25ca′	Me	OMe	H	Me	n.d.	79	215-216
25cb′	Me	OMe	H	Et	n.d.	71	216-217
25da′	Me	$N(Me)_2$	H	Me	n.d.	45	214-215
25db′	Me	$N(Me)_2$	H	Et	n.d.	46	235-237
25ea′	3-OMe-Ph	OMe	H	Me	n.d.	66	160-161
25eb′	3-OMe-Ph	OMe	H	Et	n.d.	64	156-157

[a]n.d = not determined

Alternatively, compounds **25aa′** and **25ab′** were successfully synthesized in good yield from the reaction of either methyl chloroformate or ethyl chloroformate with 2-methylquinolin-4-amine (**18a**) in acetonitrile in the presence of anhyd K_2CO_3 (Scheme 2). Comparing spectrophotometric analysis and mixed melting point measurements, **25aa′** and **25ab′** synthesized under these conditions, were identical with the compounds previously synthesized from azetoquinolinone **21a**. These results further prove that the structures of **21a,b** exist as an azetoquinolinone ring system and the ring opening takes place at C3 position upon nucleophilic attack. To extend the scope of this new procedure for the synthesis of the *N*-(quinolin-4-yl)carbamates, 4-aminoquinolines (**18b-e**) were then examined for their reactions with methyl chloroformate of ethyl chloroformate in the presence of anhyd K_2CO_3.

Under the optimized reaction conditions, compounds **18b-e** gave *N*-(quinolin-4-yl)carbamates (**25ba′**, **ca′**, **cb′**, **da′, db′**, **ea′**, and **eb′**) in fair to good yields (Table 2). It is of great interest to note that the carbamate formation was affected by the substituent at C6 of the

quinoline ring. Experiments revealed that the product was formed in low yields when *N,N*-dimethylamino or methylenedioxy groups (i.e. **25ba′**, **25da′** and **25db′**) were attached to the quinoline ring at C6 or C6,7 positions, respectively. The higher yields of compound **25ca′** and **25cb′** were obtained when methoxy function substituted at C6 position of the quinoline ring. *N*-(quinolin-4-yl)carbamate analogues were previously synthesized in low yield starting from quinolin-4-carboxylic acid ester in one-pot reaction via formation of the corresponding hydrazide, azide, curtius rearrangement to isocyanate, followed by reaction with alcohols.[22,23] Our current studies provide an alternative versatile synthetic method to prepare *N*-(quinolin-4-yl)carbamates.

3. EXPERIMENTAL SECTION

3. 1. Chemistry: General Methods

All commercial chemicals and solvents were reagent grade and were used without further purification unless otherwise specified. Melting points were determined on a Fargo melting point apparatus and are uncorrected. Column chromatography was carried out on silica gel G60 (70-230 mesh, ASTM; Merck and 230-400 mesh, Silicycle Inc.). Thin-layer chromatography was performed on silica gel G60 F_{254} (Merck) with short-wavelength UV light for visualization. All reported yields are isolated yields after chromatography or crystallization. Elemental analyses were done on a Heraeus CHN-O Rapid instrument. ^{1}H NMR and ^{13}C NMR spectra were recorded on a 600 MHz, Brucker AVANCE 600 DRX and 400 MHz, Brucker Top-Spin spectrometers in the indicated solvent. The chemical shifts were reported in ppm (δ) relative to TMS.

Synthesis of 4-aminoquinolines (18b-e). Detailed procedures for the synthesis of compound **18b-e**, intermediate **17b-e** along with their spectroscopic data are provided in the supplementary information.

Synthesis of (*R,S*)-3-methylazeto[3,2-*c*]quinoline-2(2a*H*)-one (21a). A solution of 4-nitrophenyl chloroformate (**1**, 59.31 g, 0.286 mol) in dry acetonitrile (200 mL) was added dropwise to a solution of 2-methylquinolin-4-amine (18a, 33.5 g, 0.21 mol) and triethylamine (126 mL, 0.9 mol) in dry acetonitrile (700 mL) at -5 ^{o}C. The reaction mixture was then allowed to stir at room temperature for 12 h. The precipitates appeared were collected by filtration. The solid product was dissolved in acetone (1.2 L) and filtered to remove the insoluble salt. The filtrate was concentrated in vacuo to dryness, the solid residue was suspended in water (500 mL) and extracted with ethyl acetate (2 × 250 mL). The organic layer was washed with water (2 × 50 mL), dried over anhyd Na_2SO_4 and evaporated to dryness. The product was purified by silica gel column using chloroform/ethyl acetate (100:30 v/v) as the eluent. The fractions containing product were combined and concentrated to 200 mL. The solid product was collected by filtration to give **21a**, 16.0 g (41 %); mp > 280 °C; ^{1}H NMR (DMSO-d_6): isomer A: δ 2.76 (3H, s, Me), 7.73 (1H, t, J = 7.4 Hz, ArH_6), 7.78 (1H, s, ArH_3), 7.83 (1H, t, J = 7.7 Hz, ArH_7), 8.05 (1H, d, J = 8.4 Hz, ArH_8), 8.55 (1H, d, J = 8.3 Hz, ArH_5). ^{13}C NMR isomer A: 25.02 (C_{11}), 122.6 (C_3), 123.1 (C_5), 123.8 (C_{4a}), 127.0 (C_6), 128.8 (C_8), 130.4 (C_7), 139.7 (C_4), 148.0 (C_2), 148.7 (C_{8a}), 159.6 (C_9). ^{1}H NMR isomer B: δ 2.76 (3H, s, Me), 7.72 (1H, t, J = 6.6 Hz, $ArH_{6'}$), 7.83 (1H, t, J = 7.7 Hz, $ArH_{7'}$), 7.94 (1H, s, $ArH_{3'}$), 8.05 (1H, d, J = 8.4 Hz, $ArH_{8'}$), 8.54 (1H, d, J = 8.3 Hz, $ArH_{5'}$). ^{13}C NMR isomer B: 25.05 ($C_{11'}$), 122.7 ($C_{3'}$), 123.2 ($C_{5'}$), 123.8 ($C_{4a'}$), 127.0 ($C_{6'}$), 128.8 ($C_{8'}$), 130.4

($C_{7'}$), 139.7 ($C_{4'}$), 148.0 ($C_{2'}$), 148.7 ($C_{8a'}$), 159.6 ($C_{9'}$). HRMS (ESI) calcd. for $C_{11}H_8N_2OH$ 185.0709, found 185.0707. Anal. Calcd. for ($C_{11}H_8N_2O \cdot 0.2H_2O$): C, 69.95; H, 4.55; N, 14.83. Found. C, 70.16; H, 4.77; N, 14.45.

Synthesis of (*R,S*)-3-methylazeto[3,2-*c*][1,3]dioxolo[4,5-*g*]quinoline-2(2a*H*)-one (21b). By following the same procedure as that for **21a**, compound **21b** was prepared from 6-methyl-[1,3]dioxolo[4,5-*g*]-8-aminoquinoline (**18b**, 0.10 g, 0.5 mmol), 4-nitrophenyl chloroformate (**1**, 0.13 g, 0.71 mmol), triethylamine (0.4 mL, 2.87 mmol) and DMAP (0.06 g, 0.5 mmol) in dry acetonitrile. The solvent used for column chromatography was chloroform/acetone (100:3 v/v). Yield: 0.023 g, (20 %); mp 262-263 °C; isomer A: ^{1}H NMR (DMSO-d_6) δ 2.66 (3H, s, Me), 6.26 (2H, s, CH_2), 7.38 (1H, s, ArH), 7.53 (1H, s, ArH), 7.95 (1H, s, ArH); ^{13}C NMR isomer A: 24.5, 98.6, 102.6, 105.1, 120.4, 121.0, 139.0, 147.3, 147.9, 148.5, 151.2, 156.9. isomer B: ^{1}H NMR (DMSO-d_6) δ 2.67 (3H, s, Me), 6.26 (2H, s, CH_2), 7.38 (1H, s, ArH), 7.64 (1H, s, ArH), 7.97 (1H, s, ArH); ^{13}C NMR: 24.5, 98.8, 102.6, 105.1, 120.4, 121.0, 139.0, 147.3, 147.9, 148.5, 151.2, 156.9. MS (EI) *m/z:* 228 (M^+). The product is unstable, thus, C, H, N analytical data could not provided. Detailed procedures for the reaction of **18a** with **1** in various solvents (THF, acetone and $CHCl_3$), bases (DBU, triethylamine and K_2CO_3) and the reaction of **18a** with triphosgene are provided in the supporting information.

General Procedure for Synthesis of *N*-(quinolin-4-yl) carbamates (25aa′, ab′, ac′, ad′).

Method 1.

A suspension of **21a** in appropriate alcohols containing catalytic amount of acetic acid (2–3 drops) was refluxed for 24 h, while the reaction of **21a** with benzyl alcohol was heated at 100 °C for 2 h. After all starting material was consumed; the clear reaction mixture was concentrated under reduced pressure to dryness. The residue was diluted with water, extracted with dichloromethane, washed with water and dried over anhyd Na_2SO_4. The dichloromethane extract was concentrated in vacuo to dryness. The desired product was purified either by recrystallization (ethyl acetate, for **25aa′**, **ab′**, **ac′**) or by silica gel column chromatography (solvent: ethyl acetate/hexane, 6:4 v/v, for **25ad′**).

Methyl 2-methylquinolin-4-yl-carbamate (25aa′). Compound **25aa′** was prepared from **21a** (0.30 g, 1.6 mmol) in methanol (5 mL). Yield: 0.22 g, (62 %); mp 175-176 °C; ^{1}H NMR (DMSO-d_6) δ 2.61 (3H, s, Me), 3.79 (3H, s, OMe), 7.47–7.51 (1H, m, ArH), 7.67–7.71 (1H, m, ArH), 7.84 (1H, s, ArH), 7.87–7.89 (1H, m, ArH), 8.29–8.31 (1H, m, ArH), 10.03 (1H, s, exchangeable, NH). ^{13}C NMR (DMSO-d_6) δ 25.4, 52.4, 110.9, 119.2, 122.3, 125.0, 128.8, 129.5, 142.3, 148.4, 154.5, 159.0. HRMS (ESI) calcd. for $C_{12}H_{12}N_2O_2H$ 217.0972, found 217.0917.

Ethyl 2-methylquinolin-4-yl-carbamate (25ab′). Compound **25ab′** was prepared from **21a** (1.0 g, 5.43 mmol) in ethanol (20 mL). Yield: 1.0 g, (80 %); mp 178–179 °C; ^{1}H NMR (DMSO-d_6) δ 1.32 (3H, t, J = 7.08 Hz, Me), 2.61 (3H, s, Me), 4.24 (2H, q, J = 7.08 Hz, CH_2), 7.47–7.51 (1H, m, ArH), 7.67–7.71 (1H, m, ArH), 7.85 (1H, s, ArH), 7.87–7.89 (1H, m, ArH), 8.30–8.32 (1H, m, ArH), 10.02 (1H, s, exchangeable, NH). ^{13}C NMR (DMSO-d_6) δ 14.6, 25.4, 61.1, 110.9, 119.2, 122.3, 125.0, 128.7, 129.4, 142.3, 148.4, 154.1, 159.0. HRMS (ESI) calcd. for $C_{13}H_{14}N_2O_2H$ 231.1128, found 231.1125.

Propyl 2-methylquinolin-4-yl-carbamate (25ac′). Compound **25ac′** was prepared from **21a** (1.5 g, 8.0 mmol) in 1-propanol (5 mL). Yield: 1.5 g (75 %); mp 165-166 °C; ^{1}H NMR (DMSO-d_6) δ 0.98 (3H, t, J = 7.40 Hz, Me), 1.71 (2H, m, CH_2), 2.60 (3H, s, Me), 4.15 (2H, t, J = 6.8 Hz, CH_2), 7.47–7.51 (1H, m, ArH), 7.67–7.71 (1H, m, ArH), 7.84 (1H, s, ArH), 7.87–7.89 (1H, m, ArH), 8.30–8.32 (1H, m, ArH), 9.98 (1H, s, exchangeable, NH). ^{13}C NMR (DMSO-d_6) δ 10.4, 22.0, 25.4, 66.6, 110.9, 119.3, 122.4, 125.0, 128.8, 129.4, 142.3, 148.4, 154.2, 159.0. HRMS (ESI) calcd. for $C_{14}H_{16}N_2O_2H$ 245.1285, found 245.1287.

Benzyl 2-methylquinolin-4-yl-carbamate (25ad′). Compound **25ad′** was prepared from **21a** (1.0 g, 5.4 mmol) in benzyl alcohol (5 mL). Yield: 1.2 g (76%); mp 94-95 °C; ^{1}H NMR (DMSO-d_6) δ 2.61 (3H, s, Me), 5.27 (2H, s, CH_2), 7.35–7.38 (1H, m, ArH), 7.41–7.44 (2H, m, 2×ArH), 7.47–7.51 (3H, m, 3×ArH), 7.67–7.71 (1H, m, ArH), 7.86–7.89 (2H, m, 2×ArH), 8.30–8.32 (1H, d, J = 8.30 Hz, ArH), 10.13 (1H, s, exchangeable, NH). ^{13}C NMR (DMSO-d_6) δ 25.4, 66.6, 111.0, 119.2, 122.3, 125.0, 128.4 (2×C), 128.6 (2×C), 128.8 (2×C), 129.5, 136.4, 14.2, 148.4, 153.9, 159.0. HRMS (ESI) calcd. for $C_{18}H_{16}N_2O_2H$ 293.1285, found 293.1265.

Method 2.

General procedure for the synthesis of 25aa′-eb′ by reacting 18a-e with alkyl chloroformates. Compound **25aa′**: A mixture of 2-methylquinolin-4-amine (0.79 g, 5 mmol) and anhyd K_2CO_3 (1.38 g, 10 mmol) in dry acetonitrile (50 mL) was sonicated for 30 min. Methyl chloroformate (1.2 mL, 15 mmol) was added dropwise to this mixture at room temperature within a period of 30 min. The reaction mixture was stirred at room temperature for additional 10 h and then concentrated under reduced pressure. The solid product was purified by column chromatography on a silica gel column using EA/Hexane (3:7 v/v) as the eluent. The fractions containing the main product were combined and evaporated under reduced pressure to give **25aa′**, 0.91 g (84 %); mp 177–178 °C; which was identical with the product synthesized from compound **21a**. By following the same procedure the following compounds were synthesized. **Compound 25ab′**. Compound **25ab′** was synthesized from 2-methylquinolin-4-amine (1.58 g, 10 mmol) and ethyl chloroformate (2.9 mL, 30 mmol). Yield: 1.85 g (81 %); mp 180-181 °C. The product is identical with the one previously synthesized from **21a**.

Methyl 6-methyl-[1,3]dioxolo[4,5-g]quinolin-8-yl-carbamate (25ba′). Compound **25ba′** was synthesized from 6-methyl-[1,3]dioxolo[4,5-g]quinolin-8-ylamine (**18b**, 0.51 g, 2.5 mmol) and methyl chloroformate (2.0 mL, 26 mmol). Yield: 0.27 g (42 %); mp 193-195 ^{o}C; ^{1}H NMR (DMSO-d_6) δ 2.52 (3H, s, Me), 3.73 (3H, s, OMe), 6.17 (2H, s, -CH_2), 7.21 (1H, s, ArH), 7.65–766 (2H, m, 2×ArH), 9.76 (1H, s, exchangeable, NH). ^{13}C NMR (DMSO-d_6) δ 24.6, 52.0, 97.8, 101.7, 104.8, 109.8, 114.8, 141.4, 146.4, 146.4, 149.8, 154.2, 156.1. HRMS (ESI) calcd. for $C_{13}H_{12}N_2O_4H$ 261.0870, found 261.0870.

Methyl 6-methoxy-2-methyl-quinolin-4-yl-carbamate (25ca′). Compound **25ca′** was synthesized from 6-methoxy-2-methyl-quinolin-4-ylamine (**18c**, 0.47 g, 2.5 mmol) and methyl chloroformate (2.0 mL, 26 mmol). Yield: 0.49 g (79 %); mp 215-216 °C; ^{1}H NMR (DMSO-d_6) δ 2.56 (3H, s, Me), 3.79 (3H, s, OMe), 3.91 (3H, s, OMe), 7.30–7.33 (1H, m, ArH), 7.66–7.67 (1H, m, ArH), 7.77–7.79 (1H, m, ArH), 7.84 (1H, s, ArH), 9.98 (1H, s, exchangeable, NH). ^{13}C NMR (DMSO-d_6) δ 25.2, 52.5, 56.0, 101.1, 110.9, 119.8, 121.8, 130.4, 141.5, 144.4, 154.7, 156.2, 156.8. HRMS (ESI) calcd. for $C_{13}H_{14}N_2O_3H$ 247.1077, found 247.1066.

Ethyl 6-methoxy-2-methyl-quinolin-4-yl-carbamate (25cb′). Compound **25cb′** was synthesized from 6-methoxy-2-methyl-quinolin-4-ylamine (**18c**, 0.47 g, 2.5 mmol) and ethyl chloroformate (2.9 mL, 30 mmol). Yield: 0.46 g (71%); mp 216-217 °C; ^{1}H NMR (DMSO-d_6) δ 1.33 (3H, t, J = 7.1 Hz, Me), 2.56 (3H, s, Me), 3.91 (3H, s, OMe), 4.25 (2H, q, J = 7.1 and 14.2 Hz, CH_2), 7.29–7.32 (1H, m, ArH), 7.66–7.67 (1H, m, ArH), 7.76–7.78 (1H, m, ArH), 7.86 (1H, s, ArH), 9.96 (1H, s, exchangeable, NH). ^{13}C NMR (DMSO-d_6) 25.1, 55.9, 61.1, 100.9, 110.7, 119.6, 121.6, 130.3, 141.4, 144.3, 154.1, 156.0, 156.6. HRMS (ESI) calcd. for $C_{14}H_{16}N_2O_3H$ 261.1234, found 261.1216.

Methyl 6-dimethylamino-2-methyl-quinolin-4-yl-carbamate (25da′). Compound **25da′** was synthesized from 6-dimethylamino-2-methyl-quinolin-4-ylamine (**18d**, 0.50 g, 2.5 mmol) and methyl chloroformate (2.0 mL, 26 mmol). Yield: 0.29 g (45 %); mp 214-215 °C; ^{1}H NMR (DMSO-d_6) δ 2.52 (3H, s, Me), 3.02 (6H, s, $N(Me)_2$), 3.77 (3H, s, OMe), 7.16–7.19 (1H, m, ArH), 7.34–7.37 (1H, m, ArH), 7.69–7.71 (1H, m, ArH), 7.72 (1H, s, ArH), 9.87 (1H, s, exchangeable, NH). ^{13}C NMR (DMSO-d_6) δ 24.8, 40.7, 52.2, 100.2, 110.9, 119.1, 120.3, 129.2, 140.5, 141.9, 153.7, 154.6. HRMS (ESI) calcd. for $C_{14}H_{17}N_3O_2H$ 260.1394, found 260.1411.

Ethyl 6-dimethylamino-2-methyl-quinolin-4-yl-carbamate (25db′). Compound **25db′** was synthesized from 6-dimethylamino-2-methyl-quinolin-4-ylamine (**18d**, 0.50 g, 2.5 mmol) and ethyl chloroformate (2.9 mL, 30 mmol). Yield: 0.31 g (46 %); mp 235-237 °C; ^{1}H NMR (DMSO-d_6) δ 1.32 (3H, t, J = 7.1 Hz, Me), 2.51 (3H, s, Me), 3.03 (6H, s, $N(Me)_2$), 4.23 (2H, q, J = 7.1 and 14.2 Hz, CH_2), 7.16–7.17 (1H, m, ArH), 7.33–7.36 (1H, m, ArH), 7.68–7.70 (1H, m, ArH), 7.73 (1H, s, ArH), 9.82 (1H, s, exchangeable, NH). ^{13}C NMR (DMSO-d_6) 24.9, 40.7, 60.9, 100.3, 110.9, 119.0, 120.3, 129.4, 140.3, 142.2, 147.8, 153.8, 154.2. HRMS (ESI) calcd for $C_{15}H_{19}N_3O_2H$ 274.1550, found 274.1517.

Methyl 6-methoxy-2-(3-methoxyphenyl)-quinolin-4-yl-carbamate (25ea′). Compound **25ea′** was synthesized from 6-methoxy-2-(3-methoxyphenyl)quinolin-4-ylamine (**18e**, 0.56 g, 2.5 mmol) and methyl chloroformate (2.0 mL, 26 mmol). Yield: 0.44 g (66 %); mp 160-161 °C; ^{1}H NMR (DMSO-d_6) δ 3.84 (3H, s, OMe), 3.87 (3H, s, OMe), 3.95 (3H, s, OMe), 7.04–7.07 (1H, m, ArH), 7.39–7.42 (1H, m, ArH), 7.44–7.48 (1H, m, ArH), 7.66–7.70 (2H, m, ArH), 7.74–7.75 (1H, m, ArH), 7.94–7.96 (1H, m, ArH), 8.54 (1H, s, ArH), 10.15 (1H, s, exchangeable, NH). ^{13}C NMR (DMSO-d_6) 52.4, 55.4, 56.0, 100.9, 107.8, 112.2, 114.8, 119.2, 120.5, 122.3, 130.0, 131.3, 140.4, 142.2, 144.5, 153.8, 154.7, 157.3, 159.9. HRMS (ESI) calcd. for $C_{19}H_{18}N_2O_4H$ 339.1339, found 339.1311.

Ethyl 6-methoxy-2-(3-methoxyphenyl)-quinolin-4-yl-carbamate (25eb′). Compound **25eb′** was synthesized from 6-methoxy-2-(3-methoxyphenyl)quinolin-4-ylamine (**18e**, 0.56 g, 2.5 mmol) and ethyl chloroformate (2.9 mL, 30 mmol). Yield: 0.43 g (64 %); mp 156–157 °C; ^{1}H NMR (DMSO-d_6) δ 1.36 (3H, t, J = 7.1 Hz, Me), 3.87 (3H, s, OMe), 3.96 (3H, s, OMe), 4.30 (2H, q, J = 7.1 and 14.2 Hz, CH_2), 7.04–7.07 (1H, m, ArH), 7.38–7.41 (1H, m, ArH), 7.44–7.48 (1H, m, ArH), 7.66–7.70 (2H, m, ArH), 7.75–7.76 (1H, m, ArH), 7.94–7.96 (1H, m, ArH), 8.55 (1H, s, ArH), 10.14 (1H, s, exchangeable, NH). ^{13}C NMR (DMSO-d_6) 55.3, 56.0, 61.2, 100.9, 107.8, 112.3, 114.8, 119.2, 120.5, 122.3, 130.0, 131.3, 140.9, 142.3, 144.5, 153.8, 154.3, 157.3, 159.9. HRMS (ESI) calcd. for $C_{20}H_{20}N_2O_4H$ 353.1496, found 353.1473.

4. CONCLUSIONS

We found a novel conversion of 4-aminoquinolines to tricyclic (*R,S*)-3-methylazeto[3,2-*c*]quinolin-2(2a*H*)-ones, which are acceptable to nucleophilic attack and can be further converted into *N*-(quinolin-4-yl)carbamates upon treatment with various alcohols. Our current studies also generated a new versatile one-step synthetic method for *N*-(quinolin-4-yl)carbamates from 4-aminoquinolines. These new findings demonstrate that the chemistry of 4-aminoquinoline is of particular interest and may be useful for other synthetic applications.

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References

[1] C. Hammer, R. Loranger, P. Schein, *J. Org. Chem*. 46 (1981) 1521.

[2] H. Kuzuhara, S. Emoto, *Tetrahedron Lett.* 1975, 1853.

[3] S. Umezawa, T. Tsuchiya, Y. Takagi, *Bull. Chem. Soc. Jap.* 43 (1970) 1602.

[4] S. Umezawa, Y. Takagi, Tsuchiya, T. *Bull. Chem. Soc. Jap.* 44 (1971) 1411.

[5] J. Izdebski, D. Pawlak, *Synthesis*, 6 (1989) 423.

[6] K. Atwal, G. Grover, S. Ahmed, P. Sleph, S. Dzwonczyk, A. Baird, D. Normandin, *J. Med. Chem*. *38* (1995) 3236.

[7] G. De Lucca, U. Kim, C. Johnson, B. Vargo, P. Welch, M Covington,. P. Davies, K. Solomon, R. Newton, G. Trainor, C. Decicco, S. Ko, *J. Med. Chem*. 45 (2002) 3794.

[8] A. Mauger, P.Burke, H.Somani, F. Friedlos, R. Knox, *J. Med. Chem.* 37 (1994) 3452.

[9] R. Dowell, C. Springer, D. Davies, E. Hadley, P. Burke, F. Boyle, R. Melton, T. Connors, D. Blakey, A. Mauger, *J. Med. Chem.* 39 (1996) 1100.

[10] A. Jordan, T. Khan, H. Malkin, H. Osborn, A. Photiou, P. Riley *Bioorg. Med. Chem.* 9 (2001) 1549.

[11] A. Jordan, T. Khan, H.Malkin, H. Osborn, *Bioorg. Med. Chem.* 10 (2002) 2625.

[12] S. Coyle, O. Keller, G .Young, *J. Chem. Soc. Perkins Trans I*. (1979), 1459.

[13] R. Devraj, J. Barrett, J. Fernandez, J. Katzenellenbogen, M. Cushman, *J. Med. Chem*. 39 (1996) 3367.

[14] C. Pellerano, L. Savini*Farmaco Ed. Sci.* 39(7) (1984) 640.

[15] H. Rebert, *J. Chem. Soc*., 1931, 107.

[16] H. Bader, *J. Chem. Soc.*, 1956, 3293.

[17] Li Wang, H. Kuo, S. Wu, T. Mauger, A. Lin, C. Hamel, E. Lee, *J. Med. Chem*. 37 (1994) 3400.

[18] S. Coffey, J. Thomason, F. Wilson, *J. Chem. Soc*., 1936, 856.

[19] K.Andersen, B. Lundt, A. Jorgensen, C. Braestrup *Eur. J. Med. Chem.* 31 (1996) 417.

[20] S. Rao, R. More O′Ferrall, *J. Am. Chem. Soc*. 112 (1990) 2729.

[21] V. J. Faldu, P. K. Talpara, N. H. Bhuva, P. R. Vachharajani, V. H. Shah, *International Letters of Chemistry, Physics and Astronomy* 6 (2014) 26-32.