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Synthesis and Antibacterial Activities of Some Substituted Quinolines

G. ANUKUMARI[1,*], M. ANAND RAO[1] and P.K. DUBEY[2]

[1]Department of Chemistry, Osmania University, Hyderabad-500 007, India
[2]Department of Chemistry, J.N.T. University, Kukatpally, Hyderabad-500 085, India

*Corresponding author: E-mail: anukumari.g@gmail.com

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p-Anisidine (**1**) on treatment with ethyl acetoacetate in refluxing ethanol for 4 h gave ethyl-3-[(4-methoxyphenyl)imino]butanoate (**2**) which on thermal cyclization in hot Dowtherm oil at 250 °C gave 4-hydroxy-6-methoxy-2-methylquinoline (**3**). The latter on heating with $POCl_3$ gave 4-chloro-6-methoxy-2-methylquinoline (**4**) which on treatment with aromatic aldehydes (**5a-e**) gave the corresponding 4-chloro-6-methoxy-2-styrylquinolines (**6a-e**). 4-Hydroxy-6-methoxy-2-methylquinoline (**3**) on treatment with ethyl acetoacetate gave the coumarin substituted quinoline, *i.e.* 9-methoxy-4,5-dimethyl-2*H*-pyrano[3,2-*C*]quinolin-2-one (**7**). The products thus obtained have been characterized based on their spectral data and have been evaluated for their antibacterial activities.

Keywords: Styrylquinolines, Aromatic aldehydes, Coumarins.

INTRODUCTION

Quinoline ring system is prevalent in a variety of pharmacologically active compounds as well as in natural products[1]. A number of biological activities have been associated with quinoline-containing compounds such as anti-inflammatory, antiallergic[2], antimalarial[3], antibacterial[4], antiproliferative[5], anticancer[6,7] *etc*. Beside these, quinoline ring also occupies a unique position in the design and synthesis of novel biologically active compounds[8]. Halogen-containing quinolines are of particular interest, because the halogen atom can play a crucial role in the compound's bioactivity and provides an avenue for further structure elaboration[9,10]. In view of these considerations it was considered worthwhile to synthesize new quinoline derivatives and evaluate them for their antibacterial activities.

EXPERIMENTAL

Melting points were determined on a Buchi melting-point apparatus and are uncorrected. The IR spectra (in KBr pellets) were recorded on a Shimadzu FTIR 157 spectrometer. All ^1H and ^{13}C NMR spectra were recorded on a Bruker instrument, using TMS as an internal standard at 400 and 100 MHz, respectively. The mass spectra were recorded either on Single Quadrupole Mass or XCT Ion trap Spectrometers. Completion of the reaction was monitored by TLC, plates being visualized by UV light and/or iodine vapours. *p*-anisidine and ethylacetoacetate were obtained from commercials supplier and used as such.

Preparation of ethyl-3-[(4-methoxyphenyl)imino]-butanoate (2): A mixture of *p*-anisidine (**1**) (12.3 g, 100 mmol), ethyl acetoacetate (13 g, 100 mmol) and ethanol (150 mL) was refluxed on a hot water bath for 4 h. At the end of this period, the mixture was distilled to half its volume. The residual mixture was cooled in ice-water at 0-5 °C when a crystalline solid separated out from the reaction mixture. The mixture was filtered and the insoluble solid was washed with cold ethanol (2 × 20 mL) and dried. The crude product was recrysrallized from methanol[11]. Yield 25 g (75 %), m.p.: 35 °C (Lit[11] m.p.: 38 °C).

Preparation of 4-hydroxy-6-methoxy-2-methylquinoline (3): Compound **2** (17 g, 80 mmol) was added slowly to preheated Dowtherm oil at 250 °C in small lots. After completion of addition, the reaction mixture was cooled to room temperature and diluted with hexane (10 mL). The separated solid was filtered, washed with hexane (2 × 5 mL) and dried. The solid obtained was dissolved in 10 % NaOH (100 mL), filtered and neutralized with dil. HCl (20 %, 20 mL). The separated, off white, solid was filtered, washed with water (2 × 10 mL) and dried[11]. Yield 10 g (72 %) m.p.: 284 °C (Lit[11] m.p.: 267-269 °C).

Preparation of 4-chloro-6-methoxy-2-methylquinoline (4): A mixture of compound **3** (14.15 g, 75 mmol) and $POCl_3$ (8 mL, 80 mmol) in 1:3 ratio (w/v) was heated on a water bath at 100 °C for 1 h. The reaction mixture was cooled to room temperature, diluted with ice-cold water (30 mL) and neutralized with saturated $NaHCO_3$ (20 mL) solution. The separated

solid was filtered, washed with water (2 × 20 mL) and dried[12]. Yield 10 g (64.5 %), m.p.: 91-93 °C (Lit[12]. m.p.: 92-95 °C).

Synthesis of 4-chloro-6-methoxy-2-styrylquinolines (6): A mixture of compound **4** (0.52 g, 2.5 mmol) and the respective benzaldehyde (7.5 mmol), in 1:3 ratio (w/v), was heated in an oil-bath is at 175-180 °C when water elimination was observed by water drops appearing on the flask neck. After 0.5 h of heating, the mixture was cooled to room temperature and washed with hexane (3 × 15 mL) to remove excess benzaldehyde. The residue was recrystallized from methanol to obtain compound **6**.

Compound 6a: Yield 0.42 g (56.7 %); m.p. 123-125 °C.

Compound 6b: Yield 0.52 g (66.1 %); m.p. 133-135 °C; IR (KBr, ν_{max}, cm^{-1}): 2878 (C-H), 1498 (C-H), ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 3.81 (s, 3H, OCH_3), 7.01-7.95 (m, 10H, eight aromatic + two styryl protons); LC/MS; *m/z* 314 (M^+ + 1) and 316 (M^+ + 3).

Compound 6c: Yield 0.57 g; (68.7 %); m.p. 142-145 °C; IR (KBr, ν_{max}, cm^{-1}): 2878 (C-H), 1498 (C-H), ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ ppm 3.81 (s, 3H, OCH_3), 6.94-7.95 (m, 10H, eight aromatic + two styryl protons); LC/MS; *m/z* 331 (M^+ + 1) and 333 (M^+ + 3).

Compound 6d: Yield 0.44 g (51.5%); m.p. 148-150 °C; IR (KBr, ν_{max}, cm^{-1}): 2878 (C-H), 1498 (C-H), ^{1}H NMR (400 MHz,$CDCl_3$/TMS): δ ppm 3.81 (s, 3H, OCH_3), 7.01-8.32 (m, 10H, eight aromatic + two styryl protons); LC/MS; *m/z* 341 (M^+ + 1) and 343 (M^+ + 3).

Compound 6e: Yield 0.42 g (51.33 %); m.p. 153-155 °C; IR (KBr, ν_{max}, cm^{-1}): 2878 (C-H), 1498 (C-H), ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ ppm 3.81 (s, 3H, OCH_3), 4.1 (s, 3H, OCH_3), 6.96-7.95 (m, 11H, nine aromatic + two styryl protons); LC/MS; *m/z* 326 (M^+ + 1) and 328 (M^+ + 3).

Preparation of 9-methoxy-4,5-dimethyl-2H-pyrano-[3,2-*C*]quinolin-2-one (7): A mixture of compound **6** (2.5 mmol) and ammonium acetate (12.5 mmol) in 1:6 ratio (w/w) was heated at 130-140 °C. The reaction was cooled to room temperature and diluted with water (20 mL). The separated solid was filtered, washed with water (2 × 10 mL) and dried. The solid thus obtained was dissolved in acetic acid (15 mL) and neutralized with ammonia solution (25 mL). The separated brown coloured solid was filtered, washed with water (2 × 15 mL) and dried to obtain compound **7**.

Compound 7a: Yield 0.22 g (33.8 %); m.p. 163-165 °C.

Compound 7b: Yield 0.42 g (60 %); m.p. 173-175 °C; IR (KBr, ν_{max}, cm^{-1}): 2878 (C-H), 3000 (-NH); ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 3.21 (s, 4H, NH_2), 7.01-7.95 (m, 10H, eight aromatic + two styryl protons); LC/MS *m/z* 280 (M^+ + 1).

Compound 7c: Yield 0.35 g (50.7 %); m.p. 183-184 °C; IR (KBr, ν_{max}, cm^{-1}): 2878 (C-H), 1498 (C-H); ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 3.21 (s, 4H, NH_2), 6.94-7.95 (m, 10H, eight aromatic + two styryl protons); LC/MS *m/z* 262 (M^+ + 1).

Compound 7d: Yield 0.45 g (58.8 %); m.p. 153-155 °C; IR (KBr, ν_{max}, cm^{-1}): 2878 (C-H), 1498 (C-H); ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 3.21 (s, 4H, NH_2), 7.01-8.32 (m, 10H, eight aromatic + two styryl protons); LC/MS; *m/z* 282 (M^+ + 1).

Compound 7e: Yield 0.42 g (54.9 %); m.p. 172-175 °C; IR (KBr, ν_{max}, cm^{-1}): 2878 (C-H), 1498 (C-H); ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 3.21 (s, 4H, NH_2), 6.96-7.95 (m, 11H, nine aromatic + two styryl protons); LC/MS; *m/z* 274 (M^+ + 1).

Preparation of 9-methoxy-4,5-dimethyl-2*H*-pyrano-[3,2-*c*]quinoline-2-one (8): A mixture ofcompound **3** (0.45 g, 2.38 mmol), ethyl acetoacetate (0.5 mL, 3 mmol) and conc. H_2SO_4 (5 mL) was stirred at room temperature for 2 h. After completion of the reaction, the mixture was cooled in ice-water at 0-5 °C and neutralized with aqueous NaOH (25 %, 40 mL). The separated solid was filtered, washed with water (2 × 20 mL) and dried. Yield 0.4 g (66 %); m.p.: 180 °C; IR (KBr, ν_{max}, cm^{-1}): 2878 (C-H), 1498 (C-H); ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 2.56 (s,3H, CH_3), 2.67 (s, 3H, CH_3), 3.81 (s, 3H, OCH_3), 5.96-7.44 (m, 4H, aromatic protons); LC/MS; *m/z* 256 (M^+ + 1).

Preparation of 4,6-dimethoxy-2-methylquinoline (9): A mixture of compound **3** (14.15 g, 75 mmol), dimethyl sulphate (8 mL, 80 mmol) and toluene (60 mL) was refluxed on an oil bath at 115 °C for 1 h. Then, the reaction mixture was cooled to room temperature, dissolved in conc. HCl (30 mL) and filtered. The filtrate was neutralized with 10 % NaOH (50 mL) solution. The separated solid was filtered, washed with water (2 × 10 mL) and dried to afford compound **3** as a pale pink solid[13]. Yield 10 g (65.7 %), 91-93 °C, (Lit[13] m.p.: 92-95 °C).

Preparation of 4,6-diamino-2-methylquinoline (10): A mixture of compound **9** (1.015 g, 5 mmol) and ammonium acetate (2.31 g, 30 mmol) in 1:6 ratio (w/w) was heated at 130-140 °C. The reaction was cooled to room temperature and diluted with water (20 mL). The separated solid was filtered, washed with water (2 × 10 mL) and dried. The solid thus obtained was dissolved in acetic acid (15 mL) and neutralized with ammonia solution (25 mL). The separated brown solid was filtered, washed with water (2 × 15 mL) and dried to obtain compound **10**. Yield 0.62 g (70 %), m.p.: 135 °C (Lit[14]. m.p.: 138 °C).

Synthesis of compound 11: A mixture of compound **10** (0.44 g, 2.5 mmol) and the respective benzaldehyde (0.75 mmol), in 1:3 ratio (w/v), was heated in an oil bath is at 175-180 °C when water elimination was observed by water drops appearing on the flask neck. After 0.5 h of heating, the mixture was cooled to room temperature and washed with hexane (3 × 15 mL) to remove excess benzaldehyde. The residue was recrystallized from methanol.

Compound 11a: Yield 0.22 g (38 %); m.p. 163-165 °C.

Antibacterial studies: The newly synthesized final compounds were evaluated for their antibacterial activity against *Escherichia coli* (ATTC-25922) *Staphylococcus aureus* (ATTC-25923), strains by serial plate dilution method[15]. Serial dilutions of the drug in Muller-Hinton broth were taken in tubes. Their pH was adjusted to 5 using phosphate buffer. A standardized suspension of the test bacterium was inoculated and incubated for 16-18 h at 37 °C. The minimum inhibitory concentration (MIC) was noted by observing the lowest concentration of the drug at which there was no visible growth. A number of antimicrobial discs are placed on the agar for the sole purpose of producing zones of inhibition in the bacterial lawn. Twenty milliliters of agar media was poured into each

Petri dish. Excess of suspension was decanted and plates were dried by placing in an incubator at 37 °C for 1 h. Using an agar punch, wells were made on these seeded agar plates and minimum inhibitory concentrations of the test compounds in dimethyl sulfoxide (DMSO) were added into each labeled well. A control was also prepared for the plates in the same way using solvent DMSO. The Petri dishes were prepared in triplicate and maintained at 37 °C for 3 to 4 days. Antibacterial activity was determined by measuring the diameter of inhibition zone. Activity of each compound was compared with ampicillin as standard. MIC (mg/mL) and zone of inhibition (mm) were determined for **6a** to **6e** and the corresponding results are summarized in Table-1.

TABLE-1
SCREENING OF 2-STYRYLQUINOLINE DERIVATIVES FOR ANTIBACTERIAL ACTIVITY

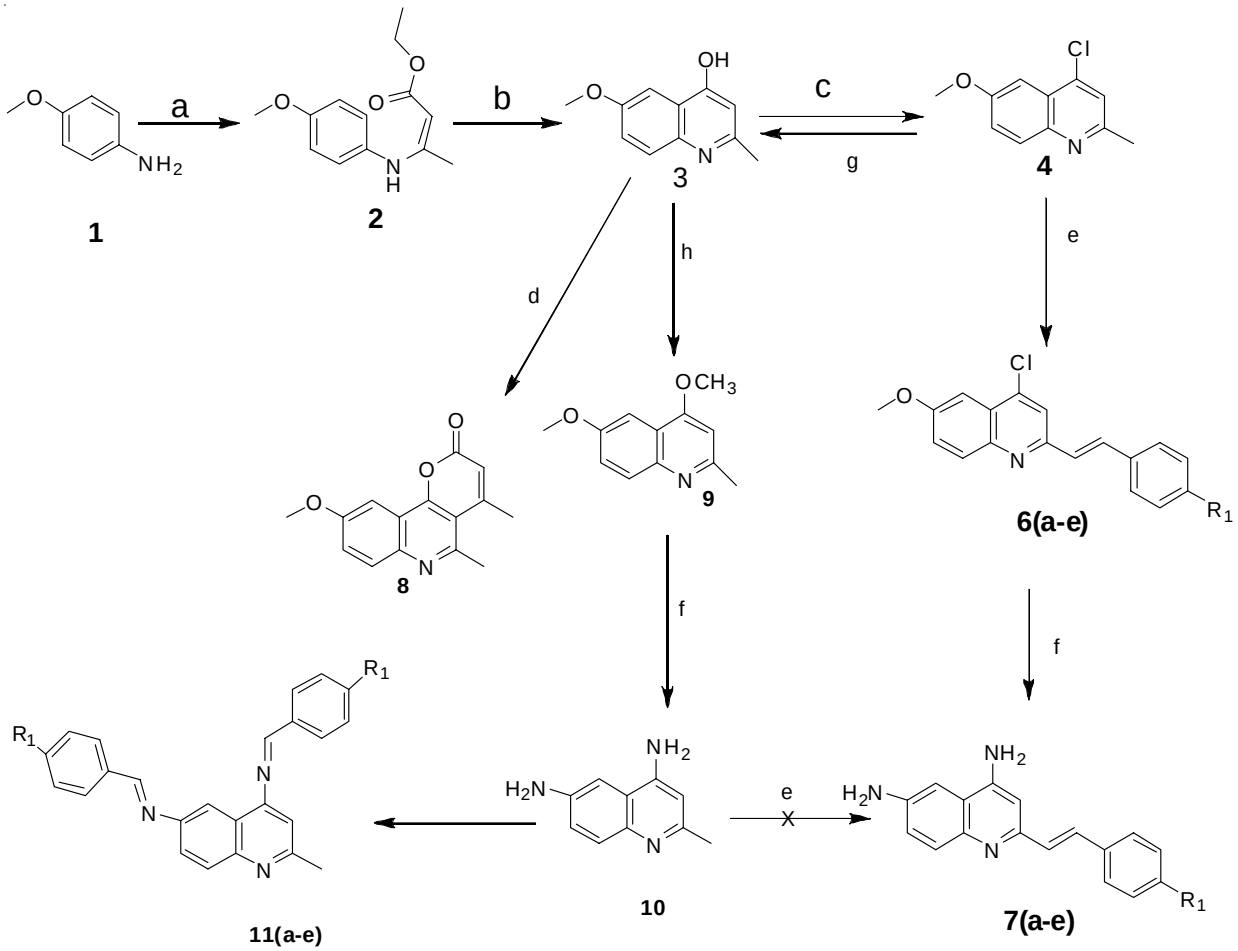
Entry	Compound and standard	Zone of inhibition	
		Bacterial strains	
		S. aureus	*E. coli*
1	Ampicillin	9	10
2	**6a**	3.5	5
3	**6b**	5	5.5
4	**6c**	6	5
5	**6d**	6	5.5
6	**6e**	8	6.5

Compounds concentration-1 mg/mL; Ac-active

RESULTS AND DISCUSSION

p-Anisidine (**1**) was condensed with ethyl acetoacetate in refluxing ethanol to obtain the previously reported[11] ethyl-3-[(4-methoxyphenyl)imino]butanoate (**2**). The latter was thermally cyclized by heating at 250 °C in hot dowtherm oil for 0.5 h to obtain 4-hydroxy-6-methoxy-2-methylquinoline (**3**), which is also known in literature[11]. Compound **3** on treatment with $POCl_3$ followed by aq. $NaHCO_3$ treatment gave 4-chloro-6-methoxy-2-methylquinoline (**4**), which is also reported[12] in literature. Also, **4** could be reconverted to **3** by treatment with hot aqueous NaOH. When **4** was treated with benzaldehyde (**5a**) in 1:3 ratio (w/v) at 180 °C followed by simple processing, 4-chloro-6-methoxy-2-styrylquinoline (**6a**) was obtained as product whose structure was assigned based on its spectral characteristics. Thus, its IR in KBr phase showed no diagnostic absorption assignable to a functional group in the regions 3500-3000 and 1800-1600 cm^{-1}. Its ^1H NMR (400 MHz, $CDCl_3$) spectrum showed signals at δ 3.81 (s, 3H, OCH_3), 6.69-8.05 (m, 11H, nine aromatic + two styryl protons); LC/MS (ESI-MS) showed *m/z* 295 ($M^+ + 1$) and 297 ($M^+ + 3$) as twin peaks corresponding to molecular masses of 294 and 296 when recorded in the Q + 1 mode.

The above reaction of **4** with **5a** has been extended to other aldehydes (**5b-5e**) and the products obtained have all been assigned structures **6b-6e**, respectively.



Scheme-I: (a) Ethylacetoacetate, ethanol, reflux, 90 °C, 4 h, (b). Dowtherm oil, 250 °C, 0.5 h, (c). $POCl_3$/reflux/1 h, (d). EAA, H_2SO_4, RT, 3 h e). Aromatic aldehydes (**5a-e**), 175-180 °C, 2 h, f). CH_3COONH_4, g). 5 % NaOH, 100 °C, 0.5 h. h). Dimethylsulphate/toluene, 115 °C, 1 h. i). Aromatic aldehydes (**5a-e**)/DMF/reflux, 4 h

Compound **6a** on heating with ammonium acetate in 1:6 ratio (w/w) at 130 °C gave 4,6-diamino-2-styrylquinoline (**7a**), whose structure was assigned based on its spectral data. Thus, its IR in KBr phase showed a broad absorption at 3000 cm^{-1} which may be due to a combination of -NH- stretching vibrations. No other diagnostic absorption assignable to a functional group could be seen in IR. Its ^1H NMR (400 MHz, DMSO-d_6) spectrum showed signals at δ 3.21 (s, 4H, NH_2), 6.69-8.85 (m, 11H, nine aromatic + two styryl protons); Its LC/MS (ESI-MS) showed *m/z* at 262 ($M^+ + 1$) corresponding to a molecular mass of 261 when recorded in Q + 1 mode. The above reaction of ammonium acetate with **7a** has been extended to other styrylquinolines (**6b-6e**) and the products obtained have all been assigned structures **7b-7e**, respectively.

Compound **3** on treatment with ethyl acetoacetate in conc. H_2SO_4 gave the coumarin substituted quinoline *i.e*. 9-methoxy-4,5-dimethyl-2*H*-pyrano[3,2-*c*]quinoline-2-one (**8**) whose structure has been assigned based on its spectral data, its IR in KBr phase showed no diagnostic absorption in the region 3500-3000 and showed diagnostic absorption ≈ 1700 cm^{-1} assignable to a functional group. Its ^1H NMR (400 MHz, DMSO-d_6) spectrum showed signals at δ 2.26 (s, 6H, CH_3), δ 3.81 (s, 3H, OCH_3), 5.67 (s, 1H, =CH), 5.69-8.05 (m, 3H, aromatic); Its LC/MS (ESI-MS) showed *m/z* 256 ($M^+ + 1$) corresponding to a molecular mass of 255 when recorded in the Q + 1 mode.

Compound **3** on treatment with dimethyl sulphate in refluxing toluene followed by hydrolysis with aq. NaOH gave 4,6-dimethoxy-2-methylquinoline (**9**), which is reported in literature[13]. Compound **9** on heating with ammonium acetate in 1:6 ratio (w/w) at 130 °C gave 4,6-diamino-2-methylquinoline (**10**) which is also reported in literature[14]. Compound **10** on heating with benzaldehyde (**5a**) in 1:2 ratio (w/v) in DMF gave a Schiff's base *i.e*. ($N^{4'}$,$N^{6'}$)-N^4,N^6-dibenzylidene-2-methylquinoline-4,6-diamine (**11a**) whose structure was assigned based on its spectral characteristics. Thus, its IR in KBr phase showed no diagnostic absorption assignable to a functional group. Its ^1H NMR (400 MHz, DMSO-d_6) spectrum showed signals at δ 2.61 (s, 3H, CH_3), 6.69-8.85 (m, 14H, twelve aromatic + two imine protons); Its LC/MS (ESI-MS) showed *m/z* 350 ($M^+ + 1$) corresponding to a molecular mass of 349 when recorded in the Q + 1 mode. The above reaction of **10** with **5a** has been extended to other aldehydes (**5b-5e**) and the products obtained have all been assigned structures **11b-11e**, respectively.

Biological results: *in vitro* preliminary antimicrobial screening of newly synthesized compounds against antibacterial strains exhibited moderate to very good activity at MIC of 6.25 to 12.5 mg/mL in DMSO. The styryl derivatives **6a** to **6e** showed comparatively good activity against all the bacterial strains. The enhanced antibacterial activity can be attributed to the presence of active styryl moiety in their structures. It was also observed that chloro, nitro, methoxy, fluoro-substituted styryl compounds displayed a significant increase in antibacterial activity.

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