



Scholars Research Library

Der Pharma Chemica, 2014, 6(2):217-220
(<http://derpharmachemica.com/archive.html>)



ISSN 0975-413X
CODEN (USA): PCHHAX

Synthesis and antibacterial activities of some substituted 2-styrylquinolines

G. Anukumari*¹, M. Anand Rao¹ and P. K. Dubey²

¹Department of Chemistry, Osmania University, Hyderabad, India

²Department of Chemistry, J. N. T. University, Kukatpally, Hyderabad, India

ABSTRACT

p-Anisidine (**1**) on treatment with ethyl acetoacetate in refluxing ethanol for 4 hrs gave ethyl 3-[(4-methoxyphenyl)imino]butanoate (**2**) which on thermal cyclisation in hot Dowtherm oil at 250 °C gave 4-hydroxy-6-methoxy-2-methylquinoline (**3**). The latter on heating with dimethyl sulphate in refluxing toluene followed by alkali treatment of the methosulphate salt gave 4,6-dimethoxy-2-methylquinoline (**4**) which on condensation with aromatic aldehydes (**5a-e**) gave the corresponding styryl compounds, 4,6-dimethoxy-2-styrylquinolines (**6a-e**). **3** on further treatment with dialkyl sulphates and aryl methyl halides in refluxing acetone containing K₂CO₃ gave *N*-alkyl and *N*-arylmethyl-6-methoxy-2-methylquinoline (**7a-c**). The products thus obtained have been characterised from their spectral data and have been evaluated for their antibacterial activities. Furthermore, **4** & **7** represent products obtained by chemoselective alkylation of **3** under different conditions.

Key words: Styrylquinolines, Aromatic aldehyde, Dialkyl sulphates.

INTRODUCTION

Quinoline derivatives represent a major class of heterocyclic compounds and a number of methods for their preparations have been known since the 1800 [1]. The quinoline ring system occurs in various natural products, especially in alkaloids [2]. The quinoline skeleton is often used for the design of many synthetic compounds with diverse pharmacological properties [3]. They have been shown to possess antimalarial [4,5], antibiotic [6], anti-inflammatory [7-8], tyrosinase PDGF-RTK inhibition [7], anticancer [9], antitumor activity [10] and anti-HIV [11] properties. In addition, styrylquinolines are important derivatives of quinolines due to their wide range of applications in pharmaceutical studies [12]. They have attracted continued interest of organic and medicinal scientists over the years because of their varied biological activities such as anti-allergic [13], antibacterial [13] and antifungal [13] etc. In view of these considerations, it was considered worthwhile to synthesise substituted styrylquinolines and study their antibacterial properties.

MATERIALS AND METHODS

General information:

Melting points were determined on a Buchi melting-point apparatus and are uncorrected. The IR spectra (in KBr pellets) were recorded on a Shimadzu FT-IR 157 spectrometer. Final compounds were purified by recrystallisation. All ¹H NMR spectra were recorded on a Bruker instrument, using TMS as an internal standard. The mass spectra were recorded either on single quadrupole mass or XCT Ion trap spectrometer. Completion of the reaction was monitored by TLC plates, visualized by UV light and/ or iodine vapours.

Synthesis of ethyl-3-[(4-methoxyphenyl) imino] butanoate (2): A mixture of *p*-anisidine (**1**) (12.3g, 100 mmol), ethyl acetoacetate (13 g, 100 mmol) and ethanol (150 mL) was refluxed on a hot water bath (100 °C) for 4 hrs. 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; the insoluble solid was washed with cold ethanol (2x10mL) and dried [14]. Yield = 21g (75%), M.P.: 35 °C (Lit [14].M.P.38 °C).

¹H NMR (400 MHz, CDCl₃) : δ 1.28 (t, 3H), 1.88 (s, 3H, CH₃), 3.79 (s, 3H, OCH₃), 4.14 (q, 2H, OCH₂), 4.65 (s, 1H), 6.84 to 6.86 (d, 2H, ArH), 7.01 to 7.04 (d, 2H, ArH); LC/MS (ESI-MS) : m/z = 236 (M⁺ + 1).

Preparation of 4-hydroxy-6-methoxy-2-methylquinoline (3): Ethyl 3-[(4-methoxyphenyl) imino] butanoate (2) (17 g, 80 mmol) was added slowly to preheated Dowtherm oil (50 mL) at 250 °C in small lots. After the completion of addition, the reaction mixture was cooled to room temperature and diluted with hexane. The separated solid was filtered, washed with hexane (30 mL) & dried. The obtained solid was dissolved in 10% NaOH (100 mL), filtered & neutralised with dil.HCl (20%, 20mL). The separated off-white solid was filtered, washed with water and dried. Yield = 10g (68%), M.P. 270 °C (Lit [14] M.P.: 267-269 °C).

IR (KBr, cm⁻¹) v_{max}: 3528 (O-H), 2878 (C-H); ¹H NMR (400 MHz, DMSO-d₆): δ 2.62 (s, 3H, CH₃), 3.81 (s, 3H, OCH₃), 5.86 (s, 1H, ArH), 6.96 to 6.99 (m, 1H, ArH), 7.43 to 7.46 (m, 2H, ArH), 11.45 (s, 1H, OH); LC/MS(ESI-MS) m/z = 190 (M⁺ + 1).

Preparation of 4,6-dimethoxy-2-methylquinoline 4 :- A mixture of 3 (14.15 g, 7.5 mmol), dimethyl sulphate (8 mL, 8 mmol) and toluene (60 mL) was refluxed on an oil bath at 115 °C for 1h. Then, the reaction mixture was cooled to room temperature and dissolved in dil. HCl (30 mL) and filtered. The filtrate was neutralised with 10% NaOH (50 mL) solution. The separated solid was filtered, washed with distilled water (2x10 mL) and dried to afford 3 as a pale pink solid. Yield = 10g (70%), 91-93 °C, (Lit [15] M.P.: 92-95 °C). IR (KBr) showed no diagnostic absorption assignable to a functional group. ¹H NMR (400 MHz, CDCl₃): δ 2.62 (s, 3H, CH₃), 3.92 (s, 3H, OCH₃), 4.01 (s, 3H, OCH₃), 6.99 (s, 1H, ArH), 7.21 (d, 1H, ArH), 7.36 (d, 1H, ArH), 7.89 (d, 1H, ArH); LC/MS(ESI-MS) m/z = 204 (M⁺ + 1).

Synthesis of 6: A mixture of 4 (0.51g, 0.25 mmol) and the respective benzaldehyde (5) (0.75 m mol) in 1:3 ratio w/v was heated in an oil-bath at 175-180 °C when water elimination was observed by water drops appearing on the flask neck. After 30 min of heating, the mixture was cooled to room temperature and washed with hexane (2x30 mL) to remove excess benzaldehyde. The residue was recrystallised from methanol to obtain 6.

6a: Yield = 0.41g (56%), M.P.: 123-125 °C; for spectral data please see under Results & Discussion.

6b: Yield = 0.45 g (57%), M.P.: 132-134 °C; IR (KBr, cm⁻¹) v_{max}: 2878 (C-H), 1498 (C-H); ¹H NMR (400 MHz, CDCl₃/TMS): δ 3.81 (s, 3H, OCH₃), 4.1 (s, 3H, OCH₃), 7.01-7.95 (m, 10H, 8H aromatic + 2H styryl protons); LC/MS; m/z = 325 (M⁺ + 1), 327 (M⁺ + 3).

6c: Yield = 0.59g (66%), M.P.: 138-140 °C; IR (KBr, cm⁻¹) v_{max}: 2878 (C-H), 1498 (C-H); ¹H NMR (400 MHz, CDCl₃/TMS) δ 3.81 (s, 3H, OCH₃), 4.1 (s, 3H, OCH₃), 6.94-7.95 (m, 10H, 8H aromatic + 2H styryl protons); LC/MS; m/z = 320 (M⁺ + 1).

6d: Yield = 0.51g (53%), M.P.: 143-145 °C; IR (KBr, cm⁻¹) v_{max}: 2878 (C-H), 1498 (C-H); ¹H NMR (400 MHz, CDCl₃/TMS) : δ 3.81 (s, 3H, OCH₃), 4.1 (s, 3H, OCH₃), 7.01-8.32 (m, 10H, 8H aromatic + 2H styryl protons); LC/MS; m/z = 322 (M⁺ + 1).

6e: Yield = 0.56g (57%), M.P.: 138-141 °C; IR (KBr, cm⁻¹) v_{max}: 2878 (C-H), 1498 (C-H), ¹H NMR (400 MHz, CDCl₃/TMS): δ 3.81 (s, 3H, OCH₃), 4.10 (s, 3H, OCH₃), 6.96-7.95 (m, 11H, 9H aromatic + 2H styryl protons); LC/MS; m/z = 308 (M⁺ + 1).

Synthesis of 1, 2-dimethyl-6-methoxy-4-quinolone (7a): A mixture of 2 (0.45g, 0.25 mmol), dimethyl sulphate (0.35mL, 0.3 mmol), K₂CO₃ (0.7 g, 0.5 mmol) and dry acetone (20 mL) was stirred at 50-60 °C for about 1hr. The completion of the reaction was monitored by TLC. On cooling to room temperature, the separated solid was filtered, washed with water (2x10 mL) and dried. The crude solid was recrystallised from methanol to obtain 7 as pure solid.

7a: Yield = 0.4g (73%), M.P.: 92 °C; IR (KBr, cm⁻¹) v_{max}: 2878 (C-H), 1498 (C-H); ¹H NMR (400 MHz, CDCl₃/TMS): δ 2.56 (s, 3H, CH₃), 3.23 (s, 3H, NCH₃), 3.81 (s, 3H, OCH₃), 5.96-7.44 (m, 4H aromatic protons); LC/MS m/z = 204 (M⁺ + 1).

7b: Yield = 0.51g (66%), M.P.: 94-96 °C; IR (KBr, cm^{-1}) ν_{max} : 2878 (C-H), 1498 (C-H), ^1H NMR (400 MHz, CDCl_3/TMS): δ 1.31 (t, 3H, CH_3), 2.56(s, 3H, CH_3), 3.81(s, 3H, OCH_3), 4.35 (q, 2H, CH_2) 5.96–7.44 (m, 4H, aromatic protons); LC/MS $m/z = 216$ ($\text{M}^+ + 1$). **7c:** yield = 0.61g (66%), M.P. 123-125 °C; IR (KBr, cm^{-1}) ν_{max} : 2878 (C-H), 1498 (C-H), ^1H NMR (400 MHz, CDCl_3/TMS): δ 2.56 (s, 3H, CH_3), δ ppm = 3.81 (s, 3H, OCH_3), 4.86 (s, 2H, CH_2), 5.96–7.45 (m, 9H aromatic); LC/MS $m/z = 278$ ($\text{M}^+ + 1$).

Antibacterial studies: The newly synthesized final compounds were evaluated for their antibacterial activity against Escherichia coli (ATTC-25922) and Staphylococcus aureus (ATTC-25923), strains by serial plate dilution method [16]. Serial dilutions of the drug in Muller-Hinton broth were taken in tubes. Their pH was adjusted to 5.0 using phosphate buffer. A standardized suspension of the test bacterium was inoculated and incubated for 16 to 18 h at 37 °C. The minimum inhibitory concentration (MIC) was noted by seeing 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 - 6e** and the corresponding results are summarized in Table.

RESULTS AND DISCUSSION

Chemistry

p-Anisidine (**1**) was condensed with ethyl acetoacetate in refluxing ethanol to obtain the previously reported [14] ethyl-3-[(4-methoxyphenyl)imino] butanoate (**2**). The latter was thermally cyclised by heating at 250 °C in hot Dowtherm oil for 30 min to obtain 4-hydroxy-6-methoxy-2-methylquinoline (**3**) which is also known in literature [14]. **3** on treatment with dimethyl sulphate in refluxing toluene followed by hydrolysis with aq. NaOH gave 4,6-dimethoxy-2-methylquinoline **4**, which is also reported in literature [15]. **4** on heating with benzaldehyde (**5a**) in 1:3 ratio (w/v) at 180 °C followed by simple processing gave 4,6-dimethoxy-2-styrylquinoline (**6a**) whose structure was assigned based on its spectral characteristics. Thus, its IR(KBr) spectrum did not show any diagnostic absorption due to a functional group. Its ^1H NMR (400 MHz, $\text{CDCl}_3\text{-TMS}$) spectrum showed signals at δ 2.62 (s, 3H, CH_3), 3.81 (s, 3H, OCH_3), 4.1 (s, 3H, OCH_3), 6.69–7.95 (m, 11H, 9H aromatic + 2H styryl protons); its LC/MS showed the molecular ion peak ($\text{M}^+ + 1$) at (ESI-MS) $m/z = 291$ corresponding to a molecular mass of 290.

The above reaction of **4** with **5a** was found to be a general one and has been extended to other aldehydes (**5b** to **5e**). The products obtained have all been assigned structures **6b** to **6e** respectively on the basis of analogy and on the basis of their spectral characteristics (IR, ^1H NMR & LCMS). For details please see the Experimental Section.

It is very interesting to note that the reaction of **3** with dimethyl sulphate, diethyl sulphate and benzyl chloride in refluxing acetone containing K_2CO_3 gave chemoselectively the N-alkylated derivatives **7a-7c** whose structures have been assigned based on their spectral data (For details please see the Experimental Section). It may be mentioned here that all the compounds **7** showed in their IR Spectra absorption at 1628 cm^{-1} due to α,β -unsaturated carbonyl group which was characteristically absent in the IR spectra of **4**. Furthermore, the peri proton at 5-position in the ^1H NMR of **7** showed selective deshielding (δ 7.49) when compared to that of proton at 5-position in the spectra of **4** (δ 7.42) and also, the proton at 3-position in **7** showed selective shielding (δ 6.16) when compared to that of proton at 3-position in the spectra of **4** (δ 6.65).

Biological results:

The *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 derivative **6a** showed less activity but other styryl derivatives, **6b-6e**, have shown comparatively good activity against all the bacterial strains. The enhanced antibacterial activity can be attributed to the presence of a substituent in the styryl moiety in their structures. It was also observed that chloro, nitro, methoxy and fluorosubstituted styryl compounds showed significantly increasing antibacterial activity in them.

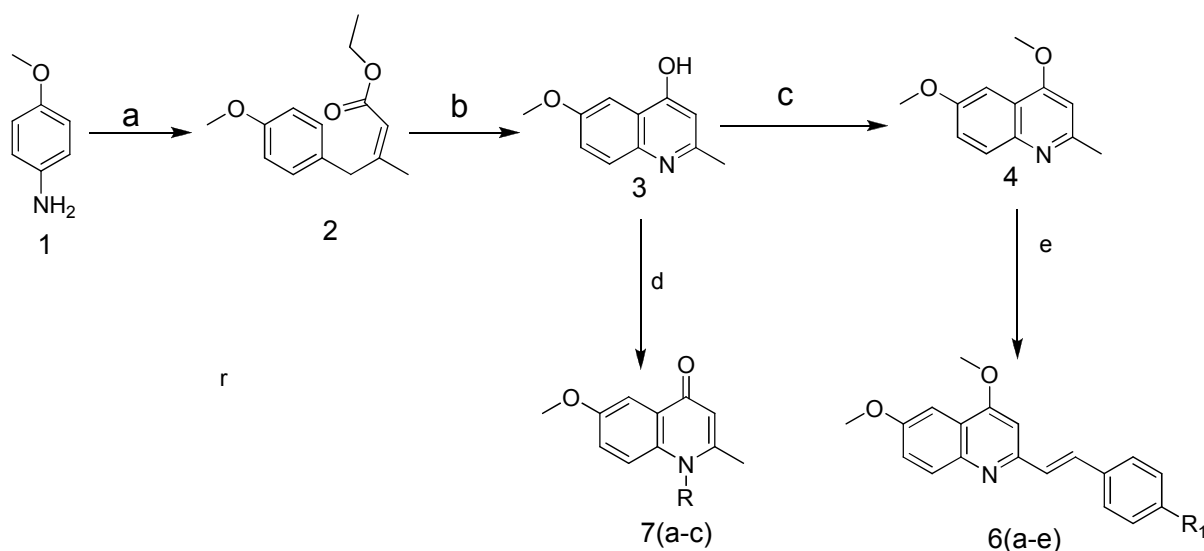
Table 1. Screening of 2-styrylquinoline derivatives for antibacterial activity

Entry	Compound and Standard	Zone of Inhibition	
		Bacterial Strains	
		S.Aures	E.Coli
1	Ampicillin	9	10
2	6a	3.5	5
3	6b	5	5.5
4	6c	6	5
5	6d	5.5	5
6	6e	7	7.5

Compounds concentration - 1mg/mL; Ac-active;

Scheme 1

a). Ethyl acetoacetate, ethanol, heat, 90 °C, 4 h, b). Dowtherm oil, 250 °C, 30 min, c). Dimethylsulphate/toluene, 1 hr. d). Me₂SO₂/Et₂SO₂/PhCH₂Cl, K₂CO₃, acetone, 55-60°C, 30-60 min, e). Aromatic Aldehydes (5a-e), 175-180°C, 2 h).



Acknowledgements

The authors are thankful to the authorities of Osmania University, Hyderabad for providing laboratory facilities and to the authorities of J.N.T. University, Hyderabad for encouragement.

REFERENCES

- [1] V. V. Kouznetsov, L.Y. Vargas Mendez, C.M. Melendez Gomez, *Current Organic Chemistry*, **2005**, 9, 141.
- [2] M.P. LaMontagne, A.M.S. Markovac, M. Sami Khan, *J. Med. Chem.* **1982**, 25, 964.
- [3] M.P. LaMontagne, P. Blumbergs, R.E. Strube, *J. Med. Chem.* **1982**, 25, 1094.
- [4] S. Eswaran, A.V. Adhikari, N.S. Shetty, *Eur. J. Med. Chem.* **2009**, 44, 4637.
- [5] P.A. Leatham, H.A. Bird, V. Wright, D. Seymour, A. Gordon, *Eur. J. Rheumatol.Inflamm.* **1983**, 6, 209.
- [6] M.P. Maguire, K.R. Sheets, K. McVety, A.P. Spada, A. Zilberstein, *J. Med. Chem.* **1994**, 37, 2129.
- [7] D.R. Buckle, C.J.M. Rockell, H. Smith, B.A. Spicer, *J. Med. Chem.* **1986**, 29, 2262.
- [8] K.S. Parikh, S.P. Vyas, *Arch.Appl.Sci.Res.* **2012**, 4, 1359.
- [9] A.S.Praveen, H.S. Yathirajan, B. Narayana, B.K. Sarojini, *Der Pharmacia Lettre*, **2014**, 6, 1.
- [10] B. Mistry, S. Jauhari, *Arch.Appl.Sci.Res.* **2010**, 2, 332.
- [11] M.P. LaMontagne, A.M.S. Markovac, M. Sami Khan, *J. Med. Chem.* **1984**, 27, 2064.
- [12] J.Finnerty, J.Wentrup, *J. Org. Chem.*, **2005**, 70, 9735.
- [13] H. Briehl, A. Lukosh, C. Wentrup, *J. Org. Chem.*, **1984**, 49, 2772.
- [14] K.D.Thomas, A.V.Adhikari, N.Suchetha Shetty, *Eur.J. Med. Chem* **2010**, 45, 3803.
- [15] B.Avrarova, A.Dimova, A.Pavlova, *Farmasiya* **1980**, 30, 52.
- [16] A.L. Barry, Procedure for testing antimicrobial agents in agar media L. Corian (Ed.), *Antibiotics in Laboratory Medicine. Williams and Wilkins, Baltimore, MD*, 1980, pp. 1 to 23.