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RESEARCH ARTICLE

Microwave-assisted Synthesis of 2-Styrylquinoline-4-carboxylic Acids as Antitubercular Agents

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ARTICLEHISTORY

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Abstract: ***Background*:** Many 2-substituted quinolines and especially 2-arylvinyl derivatives isolated from plants or prepared by synthesis have been designed from ethnopharmacological studies.

***Objective*:** In order to explore new aspects of the structure-antituberculosis activity relationship, a series of styrylquinoline derivatives was prepared.

***Method*:** A series of styrylquinoline derivatives was prepared from quinaldic acid and a variety of arylbenzaldehydes under eco-friendly conditions via Knoevenagel reaction and trifluoroacetic acid (TFA) as catalyst.

***Results*:** The products were obtained in short reaction times and good yields and were evaluated for growth inhibitory activity towards Mycobacterium tuberculosis H37Rv (Mtb) through the National Institute of Allergy and Infectious Diseases (NIAID, USA).

***Conclusion*:** Three compounds had activity under aerobic conditions.


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Keywords: Synthesis, microwave, styrylquinolines, catalysis, *Mycobacterium tuberculosis*, tuberculosis.

1. INTRODUCTION

Several parasitic illnesses caused by protozoa, as well as tuberculosis (TB) produced by *Mycobacterium tuberculosis*, are diseases that the developing world suffers from, yet the range of drugs available for the treatment of many of them is limited. Moreover, some drugs in use are difficult to access or administer, meanwhile, there is increasing resistance to some drugs so new leads are needed [1].

Heterocyclic compounds with a quinoline core represent privileged moieties in medicinal chemistry and many of these structures have been designed from ethnopharmacological studies. Thus, 2-substituted quinolines and especially 2-arylvinyl derivatives isolated from plants or prepared by synthesis, exhibited a wide spectrum of biological activities such as leishmanicidal [2, 3], trypanocidal [4] and were found to be potent inhibitors of the human immunodeficiency virus of type-1 (HIV-1) integrase [5], as well as active against HUT-102 cell lines [6, 7].

In contrast to the derivatives of 4-aminoquinoline, the corresponding derivatives of 4-aminoquinaldine (4-amino-2-methylquinoline) have no antimalarial properties. However, conversion of 4-aminoquinaldines to the corresponding 2-styrylquinolines re-established and even increased antimalarial properties [8]. Furthermore, it was observed that such 2-styrylquinoline derivatives have pronounced activity not only against protozoa but also against bacteria, actinomycetes and fungi so the same authors extend the investigation of 2-styrylquinolines against *M. tuberculosis*. These compounds have been prepared by condensation of the corresponding substituted quinaldines with aldehydes in the presence of piperidine in xylene at 170-175 ºC for 5 hours or in acetic anhydride at 155-160 ºC for 1.5 hours.

Among other 2-substituted quinolines which exhibited nematocidal and trichomonacidal activities, 2-styryl derivatives from quinaldine and cinnamaldehyde (or 4-quinaldehyde) were synthesized also in acetic anhydride under reflux for 2 hours [9]. A one-pot combination of a modified Friedländer annulation and a Knoevenagel condensation provided 4-aryl-2-styrylquinolines in good to excellent yields in the presence of 1-methylimidazolium trifluoroacetate ([Hmim]TFA) under conventional heating [10]. More recently the synthesis, properties and biological activities of similar compounds [11] prepared by same method described by Rubtsov were reported.

We have reported the microwave-assisted Döbner synthesis of 2-phenylquinoline-4-carboxylic acids and their antiparasitic activities [12]. Furthermore, they were evaluated

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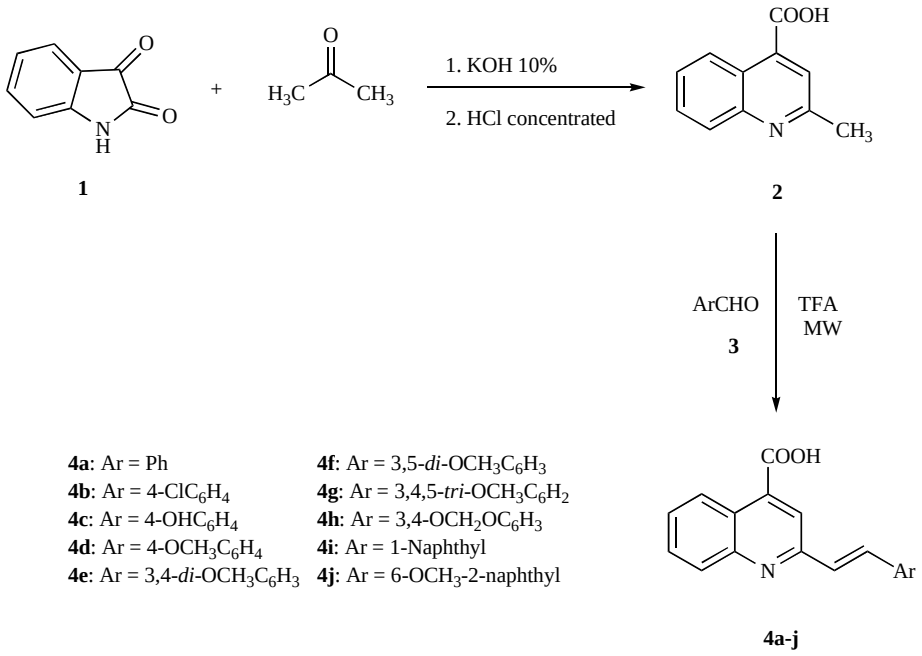


Scheme 1. Pfitzinger synthesis of quinaldic acid **2** and synthesis of compounds **4a-j**.

against *M. tuberculosis* $H_{37}Rv$ and showed weak inhibitory activity. Since 2-styrylquinoline-4-carboxylic acids have not been sufficiently explored as anti-TB agents and thus the effect of a vinyl group, we designed a series of analogues in order to determine this activity.

Herein we describe the synthesis of 2-methylquinoline-4-carboxylic acid (**2**) from isatine (**1**) *via* the Pfitzinger reaction followed by the microwave-assisted condensation with a variety of arylaldehydes (**3**) under acid catalysis to give **4a-j** (Scheme **1**) and their evaluation as anti-TB agents.

2. MATERIALS AND METHOD

Melting points were determined in a capillary Electrothermal 9100 SERIES-Digital apparatus and are uncorrected. ^{1}H and ^{13}C-NMR spectra were recorded at room temperature using a Bruker 300 MHz spectrometer and DMSO-d_6 as solvent. The operating frequencies for protons and carbons were 300.13 and 75.46 MHz, respectively. The chemical shifts (δ) were given in ppm. IR spectra were recorded on an FT Perkin Elmer Spectrum One from KBr discs. Mass spectra were measured on MS/DSQ II. Elemental analysis (C, H and N) were performed on an Exeter CE 440 and the results were within ± 0.4 % of the calculated values. Analytical TLCs were performed on DC-Alufolien Kieselgel 60 F_{254} Merck. Microwave-assisted reactions were carried out in a CEM Discover oven.

2.1 Synthesis

2. The starting material was prepared *via* the Pfitzinger reaction: a mixture of 6.8 mmoles (1.0 g) of isatine and 16 mmoles (1.50 mL) of acetone in 20 mL 10 % KOH was stirred at reflux temperature for 7 h. The reaction mixture was cooled to room temperature and concentrated HCl was added to pH 6.5 and the crystalline solid was filtered and crystallized from EtOH. Pale yellow solid, mp 242-244 °C, lit. 244 °C [13], yield 0.61 g (48 %). ^{1}H-NMR: δ 2.71 (3H, s, CH_3), 7.60-7.66 (1H, m, Het-H), 7.75-7.80 (1H, m, Het-H), 7.82 (1H, s, Het-H), 7.99 (1H, d, *J*= 8.5 Hz, Het-H), 8.61 (1H, d, *J*= 8.5 Hz, Het-H), 13.6 (1H, s, COOH). ^{13}C-NMR: δ 24.7, 122.7, 125.4, 126.9, 128.9, 129.6, 136.3, 148.1, 158.7, 167.6. IR: υ_{max} 3417, 1673, 1600, 1367, 1085, 847, 718 cm^{-1}. Anal. Calcd. for $C_{11}H_9NO_2$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.53; H, 4.87; N, 7.51.

General Procedure for the Synthesis of (*E*)-2-styrylquinoline-4-carboxylic Acids 4a-j

A neat mixture of 2.1 mmol (0.4 g) of **2** and 4.8 mmol of the corresponding **3** with 0.15 mL TFA was subjected to MW irradiation, at 300 W and 250 ºC. After reaction completion (TLC), the mixture was cooled to room temperature to give a solid product which was triturated with EtOH, at room temperature, unless other solvent was stated.

4a. Time 11 min, CH_2Cl_2. Yellow solid, mp >290 ºC (lit. 289-290 ºC [14]), yield 0.32 g (54 %). ^{1}H-NMR: δ 6.91 (1H, d, *J*= 7.0 Hz, Ph-H), 7.04 (1H, t, *J*= 7.0 Hz, Ph-H), 7.28 (1H, d, *J*= 7.0 Hz, Ph-H), 7.37 (1H, d, *J*= 7.0 Hz, Ph-H), 7.44 (1H, t, *J*= 8.0 Hz, Het-H), 7.56 (1H, d, *J*= 16.0 Hz, CH=C*H*Ar), 7.63- 7.82 (1H, m, Ph-H), 7.93 (1H, d, *J*= 16.0 Hz, HetC*H*=CH), 8.07 (1H, t, *J*= 8.0 Hz, Het-H), 8.26 (1H, s, Het-H), 8.53 (1H, d, *J*= 9.0 Hz, Het-H), 8.61 (1H, d, *J*= 9.0 Hz, Het-H). ^{13}C-NMR: δ 120.7, 123.5, 125.5, 127.1, 127.5, 127.7, 128.9, 130.3, 135.2, 135.7, 137.2, 141.5, 141.7, 148.2, 155.3, 167.6. IR: υ_{max} 3320, 1710, 1630, 1198, 981, 763, 691 cm^{-1}. Anal. Calcd. for $C_{18}H_{13}NO_2$: C, 78.53; H, 4.76; N, 5.09. Found: C, 78.49; H, 4.79; N, 5.11.

4b. Time 6 min, acetone. Orange solid, mp > 260 °C, yield 0.41 g (62 %). ^{1}H-NMR: δ 7.08 (1H, d, *J*= 8.2 Hz, Ph-H), 7.29 (1H, d, *J*= 8.2 Hz, Ph-H), 7.48 (1H, d, *J*= 8.2 Hz, Ph-H), 7.57 (1H, d, *J*= 16.1 Hz, CH=C*H*Ar), 7.62- 7.70 (2H, m, Het-H), 7.79 (1H, d, *J*= 8.2 Hz, Ph-H), 7.89 (1H, d, *J*= 16.5 Hz, HetC*H*=CH), 8.05 (1H, d, *J*=8.5 Hz, Het-H), 8.23 (1H, s, Het-H), 8.58 (1H, d, *J*= 8.5 Hz, Het-H), 13.7 (1H, s,

COOH). ^{13}C-NMR: δ 121.2, 123.4, 124.0, 128.2, 129.4, 129.6, 130.3, 131.0, 133.8, 133.9, 135.5, 137.4, 148.4, 148.9, 155.6, 168.1. IR: υ_{max} 3430, 1633, 1589, 1380, 1085, 977, 765, 688 cm^{-1}. Anal. Calcd. for $C_{18}H_{12}ClNO_2$: C, 69.80; H, 3.90; N, 4.52. Found: C, 69.84; H, 3.87; N, 4.55.

4c. Time 7 min, refluxing CH_2Cl_2. White solid, mp 314-316 °C, yield 0.58 g (94 %). ^{1}H-NMR: δ 6.53 (1H, d, *J*= 8.3 Hz, Het-H), 6.84 (2H, d, *J*= 8.5 Hz, H-Ph), 7.03 (1H, d, *J*= 8.3 Hz, Het-H), 7.33 (1H, d, *J*= 16.3 Hz, CH=C*H*Ar), 7.61 (2H, d, *J*= 8.5 Hz, Ph-H), 7.87 (1H, d, *J*= 16.4 Hz, HetC*H*=CH), 8.01-8.06 (1H, m, Het-H), 8.24 (1H, s, Het-H), 8.54- 8.61 (1H, m, Het-H), 9.86 (1H, s, OH). ^{13}C-NMR: δ 115.8, 116.1, 120.9, 123.8, 124.0, 124.9, 128.0, 128.7, 128.9, 129.8, 130.9, 131.4, 136.6, 137.9, 148.5, 167.5. IR: υ_{max} 3320, 1732, 1605, 1310, 1060, 964, 748, 699 cm^{-1}. Anal. Calcd. for $C_{18}H_{13}NO_3$: C, 74.22; H, 4.50; N, 4.81. Found: C, 74.19; H, 4.52; N, 4.84.

4d. Time 15 min. Yellow solid, mp 295-297 °C (lit. 285 ºC [15]), yield 0.47 g (72 %). ^{1}H-NMR: δ 3.79 (3H, s, OCH_3), 7.01 (2H, d, *J*= 8.8 Hz, Ph-H), 7.40 (1H, d, *J*= 16.8 Hz, CH=C*H*Ar), 7.62 (1H, t, *J*= 8.0 Hz, Het-H), 7.71 (2H, d, *J*= 8.1 Hz, Ph-H), 7.79 (1H, t, *J*= 8.1 Hz, Het-H), 7.83 (1H, d, *J*= 16.8 Hz, HetC*H*=CH), 8.04 (1H, d, *J*= 8.1 Hz, Het-H), 8.21 (1H, s, Het-H), 8.60 (1H, d, *J*= 8.8 Hz, Het-H), 14.0 (1H, s, COOH). ^{13}C-NMR: δ 55.2, 114.3, 120.5, 123.3, 125.5, 125.6, 127.2, 128.7, 128.9, 129.2, 130.0, 134.6, 136.7, 141.7, 148.5, 155.7, 167.6. IR: υ_{max} 3180, 1724, 1625, 1245, 1136, 850, 771, 701 cm^{-1}. Anal. Calcd. for $C_{19}H_{15}NO_3$: C, 74.74; H, 4.95; N, 4.59. Found: C, 74.71; H, 4.93; N, 4.62.

4e. Time 17 min. Yellow solid, mp 258-260 °C (lit. 253-254 ºC, [15]), yield 0.41 g (57 %). ^{1}H-NMR: δ 3.60 (3H, s, OCH_3), 3.70 (3H, s, OCH_3), 6.99 (1H, d, *J*= 8.5 Hz, Ph-H), 7.28 (1H, d, *J*= 8.0 Hz, Ph-H), 7.41 (1H, d, *J*= 2.2 Hz, Ph-H), 7.50 (1H, d, *J*= 16.0 Hz, CH=C*H*Ar), 7.62 (1H, t, *J*= 7.0 Hz, Het-H), 7.76 (1H, t, *J*= 7.0 Hz, Het-H), 7.83 (1H, d, *J*= 16.0 Hz, HetC*H*=CH), 8.03 (1H, d, *J*= 8.0 Hz, Het-H), 8.58 (1H, s, Het-H), 8.60 (1H, d, *J*= 8.0 Hz, Het-H). ^{13}C-NMR: δ 56.0, 56.3, 110.3, 112.2, 121.0, 121.9, 123.8, 125.9, 126.2, 127.7, 129.4, 129.6, 130.6, 135.6, 137.2, 148.9, 149.5, 150.3, 156.2, 168.1. IR: υ_{max} 3435, 1633, 1593, 1345, 1024, 965, 766, 680. EM (m/z): 335 (M^+, 100), 336 ([M^++1], 20.33), 334 ([M^+-1], 98), 318 ([M^+-OH], 17), 304 ([M^+-OCH_3], 30), 290 ([M^+-COOH], 58). Anal. Calcd. for $C_{20}H_{17}NO_4$: C, 71.63; H, 5.11; N, 4.19. Found: C, 71.68; H, 5.08; N, 4.22.

4f. Time 9 min. Yellow solid, mp 272-274 °C, yield 0.38 g (53 %). ^{1}H-NMR: δ 3.55 (6H, s, OCH_3), 6.49 (1H, s, Ph-H), 6.95 (2H, s, Ph-H), 7.58 (1H, d, *J*= 16.0 Hz, CH=C*H*Ar), 7.64 (1H, t, *J*= 8.0 Hz, Het-H), 7.78- 7.80 (2H, m, Het-H and HetC*H*=CH), 8.06 (1H, d, *J*= 8.0 Hz, Het-H), 8.23 (1H, s, Het-H), 8.61 (1H, d, *J*= 8.0 Hz, Het-H). ^{13}C-NMR: δ 56.0, 110.6, 112.7, 121.4, 121.9, 123.4, 125.8, 126.7, 127.8, 129.1, 130.3, 135.9, 137.6, 148.2, 149.8, 151.3, 156.4, 169.1. IR: υ_{max} 3401, 1710, 1599, 1302, 1158, 962, 765, 687 cm^{-1}. Anal. Calcd. for $C_{20}H_{17}NO_4$: C, 71.63; H, 5.11; N, 4.18. Found: C, 71.67; H, 5.07; N, 4.20.

4g. Time 13 min. Yellow solid, mp > 300 °C, yield 0.37 g (48 %). ^{1}H-NMR: δ 3.69 (3H, s, OCH_3), 3.85 (6H, s, OCH_3), 7.11 (2H, s, Ph-H), 7.54 (1H, d, *J*= 16.0 Hz, CH=C*H*Ar), 7.64 (1H, t, *J*= 7.0 Hz, Het-H), 7.79 (1H, d, *J*= 7.1 Hz, Het-H), 7.85 (1H, d, *J*= 16.0 Hz, HetC*H*=CH), 8.04 (1H, d, *J*= 8.0 Hz, Het-H), 8.24 (1H, s, Het-H), 8.62 (1H, d, *J*= 8.0 Hz, Het-H). ^{13}C-NMR: δ 56.4, 60.6, 105.4, 121.1, 123.9, 125.9, 127.5, 127.8, 129.5, 130.3, 130.7, 132.2, 138.8, 147.4, 148.8, 153.6, 155.9, 168.0. IR: υ_{max} 3436, 1723, 1628, 1327, 1067, 997, 765, 681 cm^{-1}. Anal. Calcd. for $C_{21}H_{19}NO_5$: C, 69.03; H, 5.24; N, 3.83. Found: C, 69.07; H, 5.29; N, 3.87.

4h. Time 6 min. Orange solid, mp > 300 °C (lit. >305 ºC, [15]), yield 0.35 g (51 %). ^{1}H-NMR: δ 6.07 (2H, s, OCH_2O), 6.96 (1H, d, *J*= 8.0 Hz, Ph-H), 7.22 (1H, d, *J*= 8.0 Hz, Ph-H), 7.42 (1H, d, *J*= 16.0 Hz, CH=C*H*Ar), 7.44 (1H, s, Ph-H), 7.64 (1H, t, *J*= 7.0 Hz, Het-H), 7.80 (1H, t, *J*= 8.0 Hz, Het-H), 7.87 (1H, d, *J*= 16.0 Hz, HetC*H*=CH), 8.03 (1H, d, *J*= 8.0 Hz, Het-H), 8.19 (1H, s, Het-H), 8.60 (1H, d, *J*= 8.0 Hz, Het-H), 13.93 (1H, s, COOH). ^{13}C-NMR: δ 32.5, 101.3, 106.0, 108.6, 120.5, 123.3, 125.4, 126.0, 127.2, 129.1, 130.1, 130.6, 134.8, 136.8, 148.0, 148.4, 155.6, 167.6. IR: υ_{max} 3401, 1716, 1633, 1320, 1038, 965, 760, 719 cm^{-1}. EM (m/z): 320 ([M^++1], 13), 319 (M^+, 63), 318 ([M^+-1], 75), 274 ([M^+-COOH], 45). Anal. Calcd. for $C_{19}H_{13}NO_4$: C, 71.47; H, 4.10; N, 4.39. Found: C, 71.43; H, 4.11; N, 4.37.

4i. Time 5 min. Orange solid, mp > 300 °C, yield 0.36 g (52 %). ^{1}H-NMR: δ 7.60 (1H, d, *J*= 16.2 Hz, CH=C*H*Ar), 7.64- 7.69 (4H, m, Ph-H), 7.79- 7.85 (1H, m, Ph-H), 7.95-7.85 (2H, m, Ph-H), 8.04 (1H, d, *J*= 7.3 Hz, Het-H), 8.12 (1H, d, *J*= 7.6 Hz, Het-H), 8.43 (1H, s, Het-H), 8.46 (1H, d, *J*= 8.5 Hz, Het-H), 8.58 (1H, d, *J*= 8.5 Hz, Het-H), 8.70 (1H, d, *J*= 16.1 Hz, HetC*H*=CH), 13.8 (1H, s, COOH). ^{13}C-NMR: δ 113.2, 121.1, 122.3, 123.9, 124.2, 124.6, 125.9, 126.4, 126.6, 127.2, 128.0, 129.0, 129.6, 129.9, 130.6, 131.3, 131.7, 133.7, 134.5, 137.7, 155.9, 168.2. IR: υ_{max} 3435, 1713, 1601, 1369, 1091, 970, 762, 703 cm^{-1}. EM (m/z): 324 ([M^+-1], 19), 325 (M^+, 100), 280 ([M^+-COOH], 10). Anal. Calcd. for $C_{22}H_{15}NO_2$: C, 81.21; H, 4.65; N, 4.30. Found: C, 81.19; H, 4.67; N, 4.33.

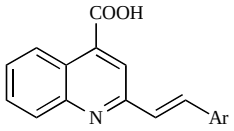
4j. Time 9 min, acetone. Orange solid, mp 309-311 °C, yield 0.46 g (61 %). ^{1}H-NMR: δ 3.89 (3H, s, OCH_3), 7.19 (1H, dd, *J*= 2.2 y 8.8 Hz, Ph-H), 7.35 (1H, d, *J*= 2.2 Hz, Ph-H), 7.63 (1H, d, *J*= 16.1 Hz, CH=C*H*Ar), 7.67 (1H, t, *J*= 6.2 Hz, Het-H), 7.80 (1H, d, *J*= 8.8 Hz, Het-H), 7.86 (2H, d, *J*= 8.8 Hz, Ph-H), 7.94-7.98 (1H, m, Ph-H), 8.04 (1H, d, *J*= 16.1 Hz, HetC*H*=CH), 8.07 (1H, d, *J*= 8.8 Hz, Het-H), 8.14 (1H, s, Ph-H), 8.27 (1H, s, Het-H), 8.62 (1H, d, *J*= 8.1 Hz, Het-H), 13.9 (1H, s, COOH). ^{13}C-NMR: δ 55.3, 106.2, 119.0, 120.7, 123.4, 124.3, 125.4, 127.3, 128.1, 128.5, 129.3, 129.8, 130.1, 131.4, 134.6, 135.0, 136.7, 148.5, 155.5, 157.9, 167.6. IR: υ_{max} 3429, 1745, 1618, 1318, 1090, 964, 762, 683 cm^{-1}. Anal. Calcd. for $C_{23}H_{17}NO_3$: C, 77.73; H, 4.82; N, 3.94. Found: C, 77.70; H, 4.84; N, 3.91.

2.2. Antituberculosis Tests

In vitro Activity Against M. tuberculosis (Mtb)

The antimicrobial activity of compounds against ~~*Mycobacterium*~~ *tuberculosis* H_{37}Rv grown under aerobic conditions is assessed by determining the minimum inhibitory concentration (MIC) of compound i.e. the concentration required to prevent growth. The assay is based on measurement of growth in liquid medium of a fluorescent reporter

Table 1. *In vitro* activity against *M. tuberculosis* $H_{37}Rv$.



Compd.	Ar	MIC (μM)	IC_{50} (μM)	IC_{90} (μM)
4a	C_6H_5	> 200	> 200	> 200
4b	4-ClC_6H_4	> 200	> 200	> 200
4c	4-OHC_6H_4	> 200	> 200	> 200
4d	4-$OCH_3C_6H_4$	> 200	> 200	> 200
4e	3,4-*di*-$OCH_3C_6H_3$	> 200	> 200	> 200
4f	3,5-*di*-$OCH_3C_6H_3$	> 200	**120**	> 200
4g	3,4,5-*tri*-$OCH_3C_6H_2$	> 200	> 200	> 200
4h	3,4-$OCH_2OC_6H_3$	> 200	**200**	> 200
4i	1-Naphthyl	> 200	**120**	> 200
4j	6-OCH_3-2-naphthyl	> 200	> 200	> 200
	Rifampicin	0.007	0.004	0.008

strain of $H_{37}Rv$ where the readout is either optical density (OD) or fluorescence. The use of two readouts minimizes problems caused by compound precipitation or autofluorescence. A linear relationship between OD and fluorescence readout has been established justifying the use of fluorescence as a measure of bacterial growth. The strain has been fully characterized and is equivalent to the parental strain in microbiological phenotypes and virulence. The MIC of compound was determined by measuring bacterial growth after 5 d in the presence of test compounds. Compounds were prepared as 10-point two-fold serial dilutions in DMSO and diluted into 7H9-Tw-OADC medium in 96-well plates with a final DMSO concentration of 2%. The highest concentration of compound was 200 μM where compounds were soluble in DMSO at 10 mM. For compounds with limited solubility, the highest concentration was 50X less than the stock concentration e.g. 100 μM for 5 mM DMSO stock, 20 μM for 1 mM DMSO stock. Each plate included assay controls for background (medium/DMSO only, no bacterial cells), zero growth (100 μM rifampicin) and maximum growth (DMSO only), as well as a rifampicin dose response curve. Plates were inoculated with *M. tuberculosis* and incubated for 5 days: growth was measured by OD_{590} and fluorescence (Ex 560/Em 590) using a BioTek™ Synergy 4 plate reader. Growth was calculated separately for OD_{590} and RFU. To calculate the MIC, the 10-point dose response curve was plotted as % growth and fitted to the Gompertz model using GraphPad Prism 5. The MIC was defined as the minimum concentration at which growth was completely inhibited and was calculated from the inflection point of the fitted curve to the lower asymptote (zero growth). In addition dose response curves were generated using the Levenberg-Marquardt algorithm and the concentrations that resulted in 50% and 90% inhibition of growth were determined (IC_{50} and IC_{90} respectively), Table **1**.

3. RESULTS AND DISCUSSIONS

In this synthesis, trifluoroacetic acid was used as catalyst, exhibiting a more suitable and efficient performance compared with concentrated hydrochloric acid as we have previously described [16, 17]. ^1H NMR spectra let us know that the compounds **4a-j** are *E* stereoisomers owing to the value of 16.0-16.8 Hz for the double bond hydrogen atoms coupling constant *J* and the proton signals were assigned to their bonded carbons from the HSQC spectrum (supplementary material).

Hanns reported the synthesis of compounds **4d**, **4e** and **4h** and other derivatives from the reaction of isatine and the corresponding benzylideneacetone (benzalacetone) in alkali media. Only compound **4a** (R = H) was subsequently described in 1970 and recently a group of six analogues were prepared on heating quinaldine neat with the corresponding arylaldehyde at 180 ºC. They exhibited moderate to very good antibacterial activity and the regioselectivity of the reaction was not discussed [14-15,18].

Furthermore, 2-styrylquinolines have been synthesized from 2-methyl-3-acetyl-4-phenyl quinoline by using sodium acetate in binary system (water:acetic acid) as a green solvent. These compounds were further evaluated for their antimicrobial, bactericidal and biofilm inhibition activities [19].

For the exposed studies, this synthetic procedure represents an *eco*-friendly method [20] to afford **4a-j** in short reaction times and good to excellent yields.

The synthesized products were evaluated for growth inhibitory activity towards *M. tuberculosis* $H_{37}Rv$ (Mtb) through the National Institute of Allergy and Infectious Diseases (NIAID, USA). The structure of the named compounds and their MIC, IC_{50} and IC_{90} values are shown in Table **1** and rifampin was used as reference drug.

Only three compounds **4f**, **4h** and **4i** had activity against *M. tuberculosis* under aerobic conditions (Table **1**). Their IC_{50} values were 120.0, 200.0 and 120.0 μM, respectively and their MIC and IC_{90} values were > 200.0 μM as well as for all compounds of the series. Rifampin has exhibited MIC = 0.007 μM, IC_{50} = 0.004 μM and IC_{90} = 0.008 μM. Although these compounds possess weak activity, they have been considered as lead structures of similar shape, volume and electronic properties for designing the new derivatives, possessing the same aryl moieties directly attached to position 2 of the quinoline (which are actually under evaluation against Mtb) and the introduction of other heterocyclic rings as was recently suggested by Mangalagiu. [21, 22]

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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