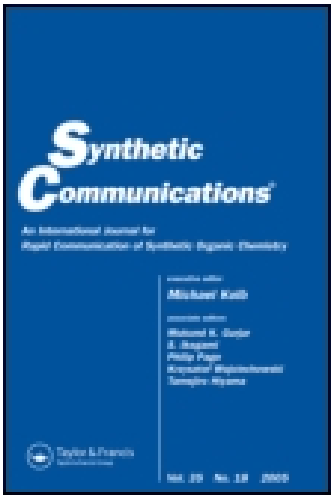

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New N-Substituted (E)-4-Arylidene Isoquinoline-1,3-dione Derivatives: NMR Spectroscopic Investigation and Antibacterial Activity

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NEW *N*-SUBSTITUTED (*E*)-4-ARYLIDENE ISOQUINOLINE-1,3-DIONE DERIVATIVES: NMR SPECTROSCOPIC INVESTIGATION AND ANTIBACTERIAL ACTIVITY

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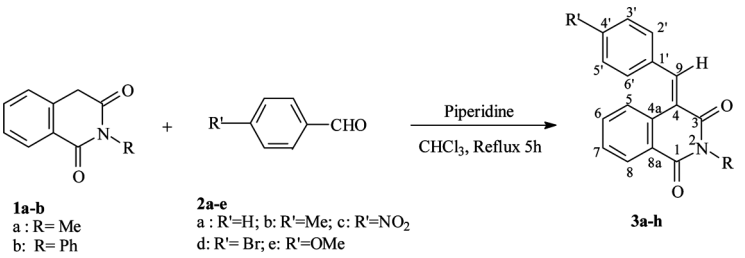
GRAPHICAL ABSTRACT



1a-b
a : R= Me
b: R= Ph

2a-e
a : R'=H; b: R'=Me; c: R'=NO_2
d: R'= Br; e: R'=OMe

3a-h

Abstract *New* N-*substituted 4-arylidene-isoquinoline-1,3-dione derivatives were obtained as one geometrical isomer by aldol condensation of the appropriate aldehyde and the corresponding* N-*substituted homophthalimides. The structural elucidation of compounds* ***3a–h*** *was established by infrared and NMR spectroscopy including* ^{1}H, ^{13}C, *CH CORR, and distortionless enhancement by polarization transfer measurements. Compounds* ***3d–h*** *were evaluated for their antibacterial activity against some strains of bacteria using the disc diffusion method and microdilution tests.*

Keywords Antibacterial activity; ASIS effect; (*E*)-4-arylidene-*N*-methyl-(2H)-isoquinoline-1,3-diones; (*E*)-4-arylidene-*N*-phenyl-(2H)-isoquinoline-1,3-diones; IR and NMR spectra

INTRODUCTION

Synthetic and natural α,β-unsaturated carbonyl compounds are of great interest from both biological and chemical points of view.[1–4] In particular, exocyclic α,β-unsaturated ketones have been used as starting materials for the synthesis of new nitrogen-containing spiroheterocyclic ring systems[5–10] by 1,3-dipolar cycloaddition

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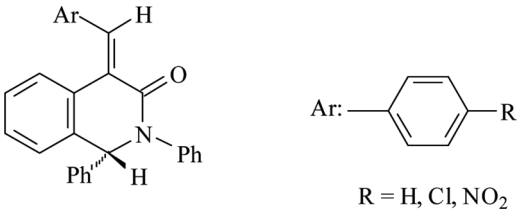


Figure 1. Isoquinoline 4-ylidene derivatives exhibiting antiproliferative activity.

reaction with different dipoles. Moreover, they have a good reactivity with dinucleophiles leading to polycyclic fused ring systems such as tricyclic pyrazolines,[11,12] tetracyclic benzothiazepines, tetracyclic benzodiazepines, thiazines,[13,14] pyrimidines,[15] and quinazolines.[16]

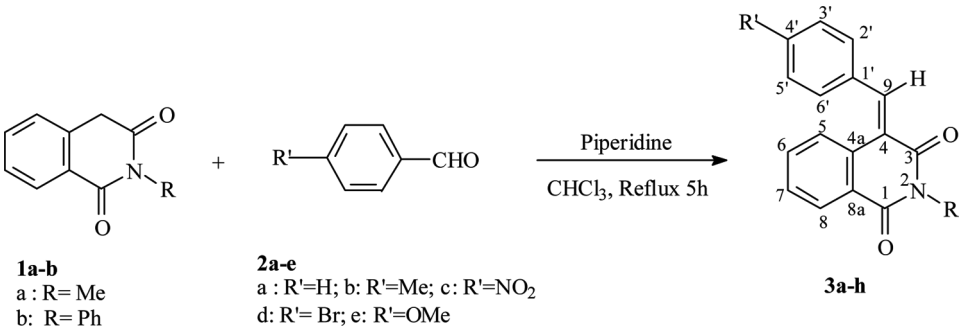
Among exocyclic α,β-enones, isoquinolinone 4-ylidene derivatives have been reported to possess important biological activity[17] (Fig. 1). However, few studies reporting the stereochemistry of these compounds have been mentioned in the literature. As far as we know, no pure isoquinoline-1,3-dione-4-ylidene stereoisomer has been isolated and no attempt has been made to determine their isomeric configuration.[18] Herein, we report the synthesis and stereochemistry study of new isoquinoline-1,3-dione-4-ylidene derivatives. Because the aim of our work is drug discovery,[19,20] we have conducted some biological tests on the prepared (*E*)-4-arylidene isoquinoline-1,3-diones to evaluate their antibacterial activity.

RESULTS AND DISCUSSION

Synthesis and Spectroscopic Investigation

The (*E*)-4-arylideneisoquinoline-1,3-diones derivatives **3a–h** were obtained by condensation of aromatic aldehydes **2a–e** with *N*-methylhomophthalimide **1a** or *N*-phenylhomophthalimide **1b** in dry chloroform using piperidine as catalyst (Scheme 1).The chemical yields and the melting points of the novel compounds **3a–h** are summarized in Table 1.

Based on the infrared (IR) and NMR studies, we have proved that the 4-arylidene isoquinoline-1,3-dione derivatives **3a–h** were formed in a *trans* configuration



1a-b
a : R= Me
b: R= Ph

2a-e
a : R'=H; b: R'=Me; c: R'=NO_2
d: R'= Br; e: R'=OMe

3a-h

Scheme 1. Synthesis of *N*-substituted 4-arylidene-isoquinoline-1,3-diones derivatives **3a–h**.

Table 1. Chemical yields and melting points of compounds **3a–h**

Compound	R	R′	Yield[a] (%)	Mp (°C)
3a	Me	H	70	89
3b	Me	Me	75	119
3c	Me	NO_2	68	194
3d	Ph	H	72	183
3e	Ph	Me	80	173
3f	Ph	NO_2	70	168
3g	Ph	Br	65	179
3h	Ph	OMe	75	189

[a]Yields of isolated products after crystallization.

in all cases. The (*E*)-configuration was proved by aromatic solvent-induced shift (ASIS) effect.[21,22] We have found that the ^{1}H NMR spectra of compounds **3a–h**, recorded in $CDCl_3$ and C_6D_6, present a negative solvent effect for proton H-9 ($\Delta\delta < 0$; $\Delta\delta$ (H-9) = δ (H-9) $CDCl_3$-δ (H-9) C_6D_6 and positive ($\Delta\delta > 0$; $\Delta\delta = \delta CDCl_3$-$\delta C_6D_6$) for aromatic protons H-2′,6′ and H-3′,5′ (Table 2), which places the proton H-9 *cis* to the carbonyl group. The signal of the proton H-9 of compound **3h** appears as singlet at 8.15 ppm in $CDCl_3$ and at 8.31 ppm in C_6D_6 (Fig. 2).

Table 2. Aromatic solvent-induced shift effect ($\Delta\delta = \delta CDCl_3$-$\delta C_6D_6$)

Compounds	$\Delta\delta$ (H-9)	$\Delta\delta$ (H-2′,6)	$\Delta\delta$ (H-3′,5′)
3a	−0.08	0.25	0.28
3b	−0.12	0.23	0.35
3c	−0.09	0.20	0.27
3d	−0.15	0.29	0.30
3e	−0.13	0.21	0.43
3f	−0.17	0.22	0.33
3g	−0.14	0.26	0.20
3h	−0.16	0.36	0.17

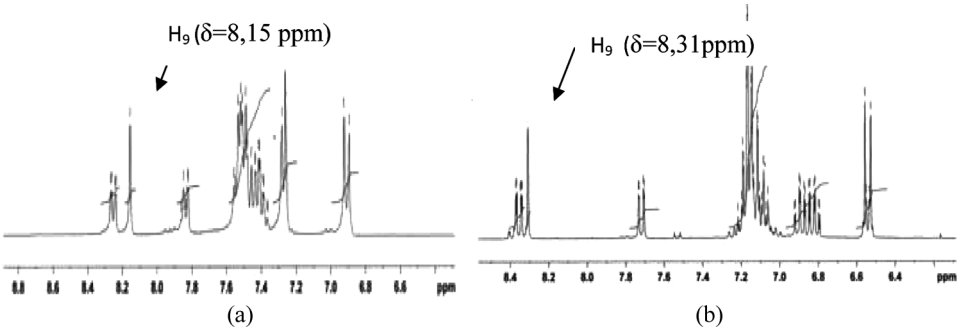


Figure 2. Signals of proton H_9 of compound **3h** recorded in (a) $CDCl_3$ and (b) C_6D_6.

Table 3. ^{1}H NMR data,[a] characteristic IR frequencies,[b] and elemental analyses of the compounds **3a–h**

Product	**3a**	**3b**	**3c**	**3d**	**3e**	**3f**	**3 g**	**3 h**
R	Me	Me	Me	Ph	Ph	Ph	Ph	Ph
R′	H	Me	NO_2	H	Me	NO_2	Br	OMe
δR	2.39	3.45	3.45	7.41–7.47	7.40–7.52	7.46–7.53	7.30–7.52	7.40–7.55
δR′	—	2.39	—	—	2.41	—	—	3.89
δH$_5$	7.54	7.64	7.31	7.64	7.74	7.36	7.61	7.84
δH$_6$	7.39	7.29	7.44	7.57	7.56	7.52	7.57	7.42
δH$_7$	7.31	7.40	7.28	7.38	7.35	7.34	7.40	7.36
δH$_8$	8.25	8.22	8.24	8.29	8.26	8.16	8.28	8.26
δH$_9$[c]	8.24	8.18	8.15	8.27	8.28	8.27	8.12	8.15
δH$_{2',6'}$	—	7.18 (d, J = 8.1 Hz)	7.58 (d, J = 8.7 Hz)	—	7.22 (d, J = 8.1 Hz)	7.61 (d, J = 8.7 Hz)	7.50 (d, J = 8.1 Hz)	6.91 (d, J = 8.7 Hz)
δH$_{3',5'}$	—	7.35 (d, J = 8.4 Hz)	8.25 (d, J = 8.7 Hz)	—	7.28 (d, J = 8.1 Hz)	8.26 (d, J = 8.7 Hz)	7.38 (d, J = 8.1 Hz)	7.27 (d, J = 8.7 Hz)
ν(c = o)	1703	1702	1700	1711	1711	1710	1709	1707
ν(c = o)	1661	1653	1655	1672	1669	1668	1671	1669
ν(c = c)	1599	1589	1587	1603	1597	1578	1603	1603
Found **C** (%)	77.51	77.91	66.27	81.25	81.37	71.31	65.31	77.69
Calculated	77.55	77.96	66.23	81.21	81.40	71.35	65.36	77.73
Found **H** (%)	4.95	5.41	3.89	4.60	5.01	3.76	3.45	4.86
Calculated	4.98	5.45	3.92	4.65	5.05	3.81	3.49	4.82
Found **N** (%)	5.28	5.01	9.04	4.27	4.10	7.52	3.41	3.91
Calculated	5.32	5.05	9.09	4.30	4.13	7.56	3.46	3.94

[a]Chemical shifts (in ppm, δ_{TMS} at 0 ppm) and coupling constants (in Hz) at 300 MHz in $CDCl_3$ solution. The assignments were supported by 2D-XH CORR measurements.

[b]In KBr discs (cm^{-1}).

[c]Side chain.

Table 4. ^{13}C NMR chemical shifts[a] (in ppm) of compounds **3a–h**

Product	3a	3b	3c	3d	3e	3f	3g	3h
R	Me	Me	Me	Ph	Ph	Ph	Ph	Ph
R′	H	Me	NO_2	H	Me	NO_2	Br	OMe
δR	27.84	27.82	27.67	—	—	—	—	—
δR′	—	21.87	—	—	21.64	—	—	55.47
δC=O	166.52	166.62	166.58	166.09	166.22	165.81	166.24	166.34
δC=O	164.83	164.86	164.11	164.42	164.48	164.36	164.61	164.53
δC_4	125.96	125.16	126.18	126.18	125.04	126.68	124.29	123.86
δC_{4a}	135.99	132.84	130.85	135.86	135.57	135.44	135.70	135.62
δC_5	127.45	127.33	127.14	127.66	127.21	127.68	127.53	127.30
δC_6	129.96	129.04	129.80	129.44	129.40	129.85	129.70	129.06
δC_7	132.52	132.44	132.60	132.97	132.55	133.32	133.10	132.88
δC_8	129.19	129.24	129.54	129.75	129.76	130.13	129.70	129.06
δC_{8a}	126.24	126.16	128.24	126.36	125.95	128.93	126.46	125.93
δC_9[b]	144.61	144.87	140.46	144.81	145.07	141.27	143.34	144.77
$\delta C_{1'}$	132.32	132.55	142.54	131.26	131.53	142.70	132.28	126.94
$\delta C_{2',6'}$	—	129.28	129.64	—	128.92	129.97	129.76	128.93
$\delta C_{3',5'}$	—	130.02	124.41	—	130.08	124.80	130.78	114.39
$\delta C_{4'}$	128.28	140.32	147.93	128.01	140.27	148.37	126.75	161.08

[a]The assignments were supported by DEPT and 2D-XH CORR measurement.
[b]Side chain.

The IR and ^1H and ^{13}C NMR data (Tables 3 and 4) proved the expected structures of 4-arylidene isoquinoline-1,3-dione derivatives. As shown in Table 3, the chemical shift values of the H-8 proton of the condensed benzene ring, in *peri* position to the carbonyl groups, were measured in series **a** and **b**, ranging from 8.16 to 8.29 ppm. The anisotropic effect of the carbonyl causes an even larger downfield shift on the H-8 signal.[23]

From this data and the IR frequency characteristics, it may be remarked that the wave numbers (mean values) of the C=O band reveal higher frequencies (Table 3) due to the ring strain[24] in compounds **3a-h**. The deshielding effect resulting from the diamagnetic anisotropy of the carbonyl group leads to the vinyl proton in the *trans* isomer (with the proton *cis* to the carbonyl group), giving a signal at a greater chemical shift than in the *cis* isomer. As result, the (*Z*) configuration may be highly unfavorable because of strong steric interaction between the aryl and carbonyl groups.

Biological Activity

Compounds **3d–h** were tested at concentrations ranging from 1 to 0.25 mg mL^{-1} for antibacterial activity against bacterial strains. The strains of microorganisms employed were *Pseudomonas aeruginosa* ATCC 27853, *Staphylococcus aureus* ATCC 25923, *Echerichia coli* ATCC 35218, *Salamonelia typhimurium* ATCC 1408, and *Enterococcus faecalis* ATCC 29212. Antibacterial activity was studied along with an antibacterial drug named penicillin. Table 5 summarizes the results obtained by the disc diffusion method showing that the tested products have a moderate antibacterial activity compared to the controlled antibiotic (penicillin). Reported compound

Table 5. Antibacterial activity of compounds **3d–h** (DD: mm; MIC, MBC: mg mL^{-1})

Compound	Parameter	*P. aeruginosa* ATCC27853	*S. aureus* ATCC25923	*E. coli* ATCC35218	*S. typhimurim* ATCC1408	*E. feacalis* ATCC29212
3d	DD[a]	11	9	10	11	14
	MIC	0.2	0.4	0.2	0.4	0.2
	MBC	>0.2	>0.4	>0.2	>0.4	0.2
3e	DD[b]	7	11	10	9	8
	MIC	0.1	0.1	0.1	0.1	0.1
	MBC	0.2	0.2	0.1	0.1	0.1
3f	DD[b]	7	11	12	5	12
	MIC	0.8	0.2	0.2	0.18	0.2
	MBC	>0.8	>0.2	>0.2	0.3	0.2
3g	DD[b]	8	6	9	9	7
	MIC	0.2	0.3	0.05	0.1	0.1
	MBC	>0.2	>0.3	0.05	>0.1	0.1
3h	DD[b]	11	12	9	7	12
	MIC	0.04	0.1	0.1	0.1	0.1
	MBC	0.08	0.1	0.1	0.1	0.1
Penicillin	DD[c]	24	53	11	6	25

Note. DD, diameter of zone of inhibition (mm) including disc diameter of 6 mm; MIC, minimum inhibitory concentrations; MBC, minimum bactericidal concentrations values given as mg mL^{1}.

[a]Tested at a concentration of 1 mg mL^{-1}.

[b]Tested at a concentration of 0.5 mg mL^{-1}.

[c]Tested at a concentration of 6 μg/disc.

3 h was found to be more active than the other products against most of the tested bacterial strains. These results were confirmed by the determination of the minimum inhibitory concentrations (MIC) and the minimum bactericidal concentrations (MBC) values of the tested compounds (Table 5). Compound **3 h** shows good antibacterial activity against *P. aeruginosa* at a concentration (MIC) of 0.04 mg mL^{-1} and minimum bactericidal concentration (MBC) of 0.08 mg mL^{-1}. Compounds **3e** and **3 g** exhibit acceptable antibacterial activity at low concentrations (MIC and MBC), 0.05 and 0.1 mg mL^{-1} respectively, against *E. coli*.

CONCLUSION

In this article, we have described a simple method for the synthesis of new (*E*)-4-arylidene isoquinoline-1,3-dione derivatives. Spectroscopic study was affected to confirm the structure and the configuration of obtained compounds. Some of the reported compounds were screened for their antibacterial activity against a spectrum of microbial organisms and show moderate antibacterial activity.

EXPERIMENTAL

All chemicals were purchased commercially and used without further purification. Solvents were purified by standard methods, freshly distilled under nitrogen, and dried before use. *N*-Phenylhomophthalimide or *N*-methylhomophthalimide were prepared according to the reported method.[25] Melting points were determined on a

Kofler bank and were uncorrected. Elemental analyses were carried out by the service of Microanalyse of the Institut National de Recherche et d'Analyse Physico-Chimique de Tunis. IR spectra were recorded at room temperature in the region of 1800–1600 cm^{-1} on a Perkin-Elmer 197 spectrometer and were taken in KBr discs. The concentrations of the measured solutions were chosen to reach a transmittance ranging from 25% and 30% for the investigated bands. The ^{1}H and ^{13}C NMR spectra were recorded in a $CDCl_3$ solution on a Bruker-Spectrospin AC 300 spectrometer, operating at 300 MHz for ^{1}H and 75.5 MHz for ^{13}C, using tetramethylsilane (TMS) as internal standard. Distortionless enhancement by polarization transfer (DEPT) spectra[26] were run in a standard manner,[27] using only the $\theta = 135^{\circ}$ pulse. The 2D-XH CORR spectra[28] were obtained by using the standard Bruker pulse program HXCO.AU.

General Procedure for the Synthesis of (*E*)-4-Arylidene Isoquinoline-1,3-dione Derivatives 3a–h

N-Substituted homophthalimide (0.01 mol) was dissolved in dry chloroform (20 mL), then the aromatic aldehyde (0.01 mol) and the piperidine (0.2 mL) were added, and the reaction mixture was stirred and refluxed for 5 h under an argon atmosphere. After cooling to room temperature, the solution was washed with 10 mL of water. After separation, the aqueous layer was extracted with chloroform (2×10 mL). The combined organic layers were dried with sodium sulfate and filtered, and the solvent was evaporated in vacuum. The obtained product was crystallized in ethanol. The purity of the samples was checked by thin-layer chromatography (TLC) using Merck silica gel 60 F_{254} aluminum sheets and cyclohexane–ethyl acetate (9:1).

Biological Activity Testing

Disc diffusion method. The agar disc method[29] was used as preliminary assay for testing antibacterial effects of compounds **3d–h**. A suspension of the tested bacterial (2×10^{6} cfu/mL) was spread on the solid media plates. Filter paper discs (6 mm in diameter) were individually impregnated with 10 μL of the products **3d–h** and then placed on the previously inoculated agar plates. The Petri dishes were kept at 4 °C for 2 h and then incubated at 37 °C for 24 h. The diameters of the inhibition zones were measured in millimeters. Penicillin was used as positive control.

Microwell dilution assays. MIC and MBC values were determined by a micro-titre plate dilution method described by Sahin et al.[30] All tests were performed in Mueller–Hinton broth (MHB). The inoculums of the bacteria were prepared from 12 h broth cultures, and suspensions were adjusted to 0.5 McFarland standard turbidity. The synthesized compounds were first dissolved in 10% dimethylsulfoxide (DMSO) and then diluted to be tested. In brief, the 96-well plates were prepared by dispensing into each well 100 μL of nutrient broth and 5 μL of the inoculums. A 200-μL stock solution of the compound initially prepared at the concentration of 1 mg mL^{-1} was added into the first well. Then, 100 μL from their serial dilutions was transferred into nine consecutive wells. The last well containing 100μL of nutrient broth without compound and 5μL of the inoculums on each strip was used as negative

control. The plate was covered with a sterile plate sealer and then incubated for 18 h at 37 °C. The MIC was defined as the lowest concentration of the compounds **3d–h** to inhibit the growth of microorganisms, after incubation. To determine MBC, broth was taken from each well and inoculated in Mueller–Hinton agar for 24 h at 37 °C. The MBC was defined as the lowest concentration of the compounds **3d–h** at which inoculated bacteria were totally killed. The results were expressed in milligram per milliliter.

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