

Synthesis, Characterisation and Antimicrobial Studies of Triazolo – Acridinedione Derivatives

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Abstract

10-(2-aminophenyl)-hexahydro acridinediones were treated with chloroacetyl chloride to give 10-(2-chloroacetamidophenyl) hexahydro acridinediones, which were treated with NaN_3 in acetone followed by reaction with DMAD yielded 10-[2-(1-triazolo-4,5-dicarboxymethyl)acetamidophenyl]-3,4,6,7,9,10-hexahydro-1,8-(2H,5H)-acridinediones.

Key words: Acridinediones, Synthesis, Triazole-acridinedione, Antimicrobial activity, *E. coli*.

Introduction:

Acridines and their fused derivatives possess wide spectrum of pharmacological activities like anti-inflammatory¹, antibacterial², fungicidal³, antimicrobial⁴, anticancer⁵, antimalarial⁶ and antiviral⁷ properties. Triazoles are a class of heterocyclic compounds with broad spectrum of biological activities⁸. In continuation of our studies on the synthesis of

acridinedione derivatives⁹⁻¹², we herein report a facile synthesis of triazolo-acridinedione derivatives (Scheme-1).

Experimental:

The melting points were determined in open capillary tube and were uncorrected. IR spectra were recorded using KBr pellets method in Perkin-Elmer 258 instrument. ¹H-NMR was taken in Jeol GSX 400 (400 MHz) instrument using TMS as internal standard. Mass spectrum was taken using Hewlett-Packard 5985 (70 ev) and Shimadzu QP 1000A instrument.

Synthesis of 10-(2-aminophenyl) and 9-substituted-10-(2-aminophenyl) acridinedione derivatives were carried out according to our earlier procedure¹⁰ by reacting cyclohexane-1,3-dione with different aldehydes to give tetraketones which on reaction with o-phenylenediamine gives the 10-(2-aminophenyl) and 9-substituted-10-(2-aminophenyl) acridinedione derivatives.

Synthesis of 10-(2-chloroacetamidophenyl)-3,4,6,7,9,10-hexahydro-1,8-(2H,5H) acridinediones and 9-substituted 10-(2-chloroacetamidophenyl)-3,4,6,7,9,10-hexahydro-1,8-(2H,5H) acridinediones:

To an ice cold solution of acridinediones (1) (10 mmol) in dry benzene (25 ml) and dry pyridine (1 ml) was added chloroacetylchloride (12 mmol) in benzene (10 ml) and stirred for 12 hours at room temperature. Water was added and the solid obtained was filtered. The benzene layer was washed with dilute HCl and NaHCO₃ solution and water, dried and concentrated to obtain additional amount of the product.

10-(2-chloroacetamidophenyl)-3,4,6,7,9,10-hexahydro-1,8-(2H,5H) acridinedione 2a: yield 78%, M.P. 208-10°C, IR (KBr): 3320, 1700, 1640, 1250, 1570, ¹H-NMR (CDCl₃): δ 1.8 – 2.1 (m, 8H), 2.2 (m 4H), 3.10 (dd,2H), 4.10 (s, 2H), 6.9 – 7.15 (m, 4H), 8.50 (bs, 1 H), MS: m/z. 384 m⁺.

9-methyl-10-(2-chloroacetamidophenyl)-3,4,6,7,9,10-hexahydro-1,8-(2H,5H)-acridinedione 2b: yield 79%, M.P. 210-12°C, IR (KBr): 3320, 1700, 1640, 1590, 1570, ¹H-NMR (CDCl₃): δ 1.05 (d,3H), 1.80 -2.05 (m,8H), 2.2-2.4 (m,4H), 4.1 (s, 2H), 4.20 (q,1H),6.8 -7.15(m,4H), 8.5 (bs,1H); MS: m/z. 398 m⁺.

9-phenyl-10-(2-chloroacetamidophenyl)-3,4,6,7,9,10-hexahydro-1,8-(2H,5H) acridinedione 2c. yield 80%, M.P.225-27°C, IR (KBr): 3310, 1690, 1630, 1580, 1570; ¹H-NMR (CDCl₃): δ 1.8-2.05 (m,8H), 2.2-2.4 (m,4H), 4.1 (s, 2H), 4.3 (s,1H), 6.8-7.2 (m,9H), 8.5(bs, 1H); MS: 460 m⁺.

9-(4-chlorophenyl)-10-(2-chloroacetamidophenyl)-3,4,6,7,9,10-hexahydro-1,8-(2H,5H) acridinedione 2d. yield 81%, M.P. 230°C, IR (KBr): 3310, 1690, 1635, 1585, 1570; ¹H-NMR (CDCl₃): δ 1.8-2.05 (m,8H), 2.2 – 2.4 (m, 4H), 4.2 (s, 2H), 4.4 (s, 1H), 6.8 – 7.2 (m, 8H), 8.5 (bs, 1H), MS: m/z. 494 m⁺.

9-(2-chlorophenyl) -10-(2-chloroacetamidophenyl)-3,4,6,7,9,10-hexahydro-1,8-(2H, 5H) acridinedione 2e: yield 79%, M.P. 210-12°C, IR (KBr): 3320, 1700, 1640, 1590, 1570, ¹H-NMR (CDCl₃): δ 1.80 -2.05 (m,8H), 2.2-2.4 (m,4H), 4.1 (s,2H), 4.4 (s, 1H), 6.8 - 7.15(m,.8H), 8.5 (bs, 1H); MS: m/z. 494m⁺.

9-(4-methoxyphenyl)-10-(2-chloroacetamidophenyl)-3,4,6,7,9,10-hexahydro-1,8-(2H, 5H) acridinedione 2f: yield 80%, M.P. 236-38°C, IR (KBr): 3310, 1685, 1630, 1570, 1565, ¹H-NMR (CDCl₃): δ 1.80 -2.05 (m,8H), 2.2-2.4 (m,4H), 3.7 (s, 3H), 4.2 (s, 2H), 4.4 (s, 1H), 6.8 - 7.2 (m, 8H), 8.5 (bs, 1H); MS: m/z. 490m⁺.

9-(2-methoxyphenyl)-10-(2-chloroacetamidophenyl)-3,4,6,7,9,10-hexahydro-1,8-(2H, 5H) acridinedione 2g: yield 82%, M.P. 232-34°C, IR (KBr): 3310, 1690, 1630, 1580, 1565, ¹H-NMR (CDCl₃): δ 1.80 -2.05 (m,8H), 2.2-2.4 (m,4H), 3.7 (s, 3H), 4.2 (s, 2H), 4.4 (s, 1H), 6.8 -7.2(m, 8H), 8.5 (bs, 1H);) MS: m/z. 490m⁺.

Preparation of 10- (2-azidoacetamidophenyl)-3,4,6,7,9,10-hexahydro-1,8-(2H,5H)-acridinediones 3 (a-g):

To a mixture of 10-(2-chloroacetamidophenyl)-3,4,6,7,9,10-hexahydro-1,8(2H,5H) acridinediones (10 mmol) in dry acetone (20 ml) and DMF (1 ml), sodium azide (12 mmol) was added and heated to 60°C with stirring for 8 hours. Acetone was distilled off and water (100 ml) added. The separated azido compound was filtered, dried and recrystallised from methanol.

10-(2-azidoacetamidophenyl)-3,4,6,7,9,10-hexahydro-1,8-(2H,5H) acridinedione 3a: yield 76%, M.P.198-200°C (decomp.), IR (KBr): 3320, 2100, 1700, 1640, 1250, 1570, ¹H-NMR

(CDCl₃) : δ 1.8 – 2.1 (m, 8H), 2.2 (m 4H), 3.10 (dd,2H), 4.06 (s, 2H), 6.9 – 7.15 (m, 4H), 8.50 (bs, 1 H), MS: m/z. 391 m⁺.

9-methyl-10-(2-azidoacetamidophenyl)-3,4,6,7,9,10-hexahydro-1,8-(2H,5H)-acridinedione
3b: yield 75%, M.P. 196-198°C (decomp.), IR (KBr): 3320, 2100, 1700, 1640, 1590, 1570,
¹H-NMR (CDCl₃): δ 1.05 (d,3H), 1.80 -2.05 (m,8H), 2.2-2.4 (m,4H), 4.06 (s, 2H), 4.20
(q,1H), 6.8 -7.15(m,8H), 8.5 (bs,1H); MS: m/z. 405 m⁺.

9-phenyl-10-(2-azidoacetamidophenyl)3,4,6,7,9,10-hexahydro-1,8-(2H,5H) acridinedione 3c.
yield 79%, M.P. 200-202°C (decomp.), IR (KBr): 3310, 2100,1690, 1630, 1580, 1570; ¹H-
NMR (CDCl₃): δ 1.8-2.05 (m,8H), 2.2-2.4 (m,4H), 4.06 (s, 2H), 4.3 (s,1H), 6.8-7.2 (m,9H),
8.5(bs, 1H); MS: 467 m⁺.

9-(4-chlorophenyl)-10-(2-azidoacetamidophenyl)-3,4,6,7,9,10-hexahydro-1,8,-(2H,5H)
acridinedione 3d. yield 80%, M.P. 200 -202°C (decomp.), IR (KBr): 3310, 2100,1690, 1635,
1585, 1570; ¹H-NMR (CDCl₃): δ 1.8-2.05 (m,8H), 2.2 – 2.4 (m, 4H), 4.06 (s, 2H), 4.4 (s,
1H), 6.8 – 7.2 (m, 8H), 8.5 (bs, 1H), MS: m/z. 501m⁺.

9-(2-chlorophenyl) -10-(2-azidoacetamidophenyl)-3,4,6,7,9,10-hexahydro-1,8-(2H, 5H)
acridinedione 3e: yield 78%, M.P. 204-206°C (decomp.), IR (KBr): 3320, 2100,1700, 1640,
1590, 1570, ¹H-NMR (CDCl₃): δ 1.80 -2.05 (m,8H), 2.2-2.4 (m,4H), 4.1 (s,2H), 4.06 (s, 1H),
6.8 -7.15(m,8H), 8.5 (bs, 1H); MS: m/z. 501m⁺.

9-(4-methoxyphenyl)-10-(2-azidoacetamidophenyl)-3,4,6,7,9,10-hexahydro-1,8-(2H, 5H)
acridinedione 3f: yield 81%, M.P. 206-208°C (decomp.), IR (KBr): 3310, 2100,1685, 1630,
1570, 1565, ¹H-NMR (CDCl₃): δ 1.80 -2.05 (m,8H), 2.2-2.4 (m,4H), 3.7 (s, 3H), 4.06 (s, 2H),
4.4 (s, 1H), 6.8 -7.2 (m, 8H), 8.5 (bs, 1H); MS: m/z. 497m⁺.

9-(2-methoxyphenyl)-10-(2-azidoacetamidophenyl)-3,4,6,7,9,10-hexahydro-1,8-(2H, 5H)
acridinedione 3g: yield 80%, M.P.206-208° C (decomp.), IR (KBr): 3310, 2100,1690, 1630,
1580, 1565, ¹H-NMR (CDCl₃): δ 1.80 -2.05 (m,8H), 2.2-2.4 (m,4H), 3.7 (s, 3H), 4.2 (s, 2H),
4.06 (s, 1H), 6.8 -7.2(m, 8H), 8.5 (bs, 1H);) MS: m/z. 497m⁺.

Preparation of 10-[2-(1-triazolo-4,5-methyldicarboxyl) acetamidophenyl]-3,4,6,7,9,10-hexahydro-1,8,-(2H,5H)-acridinediones 4 (a-g):

A mixture of azidoacridinediones (10 mmol) and dimethylacetylenedicarboxylate (DMAD) (10 mol) was refluxed in benzene (30 ml) for 6 hours. Benzene was distilled off and the residue crystallised from methanol to obtain 4 (a-g).

10-[2-(1-triazolo-4,5-dicarboxymethyl)acetamidophenyl]-3,4,6,7,9,10-hexahydro-1,8-(2H,5H)-acridinedione 4a: yield 65%; M.P. 204-206°C, IR (KBr): 3320, 1720, 1635, 1615, 1580; ¹H-NMR (CDCl₃): δ 1.8-2.10 (m,8H), 2.20 (s, 4H), 3.1 (s, 2H), 3.95 (s,6H), 4.06 (s, 2H), 7.2-7.4 (m,4H), 8.55 (s, 1H); MS: m/z. 533 m⁺.

9-methyl-10-[2-(1-triazolo-4,5-dicarboxymethyl) acetamidophenyl]-3,4,6,7,9,10-hexahydro-1,8-(2H,5H)-acridinedione 4b: yield 74%, M.P. 206-208°C, IR (KBr): 3320, 1720, 1645, 1595, 1570, ¹H-NMR (CDCl₃): δ 1.05 (d,3H), 1.80 -2.05 (m,8H), 2.2-2.4 (m,4H), 3.95 (s,6H), 4.06 (s, 2H), 4.20 (q,1H), 6.8 -7.20(m,4H), 8.5 (bs,1H); MS: m/z. 547m⁺.

9-phenyl-10-[(2-(1-triazolo-4,5-dicarboxymethyl)acetamidophenyl)-3,4,6,7,9,10-hexahydro-1,8-(2H,5H) acridinedione 4c. yield 76%, M.P. 208-10°C, IR (KBr): 3310, 1695, 1630, 1585 1570; ¹H-NMR (CDCl₃): δ 1.8-2.05 (m,8H), 2.2-2.4 (m,4H), 3.95 (s,6H), 4.06 (s, 2H), 4.3 (s,1H), 6.75-7.2 (m,9H), 8.5(bs, 1H); MS: 609m⁺.

9-(4-chlorophenyl)-10-[2-(1-triazolo-4,5-dicarboxymethyl)acetamidophenyl]-3,4,6,7,9,10-hexahydro-1,8,-(2H,5H) acridinedione 4d. yield 78%,M.P. 212-14°C, IR (KBr): 3310, 1695, 1635, 1580, 1570; ¹H-NMR (CDCl₃): δ 1.8-2.05 (m,8H), 2.2 - 2.4 (m, 4H), 3.95 (s,6H), 4.06 (s, 2H), 4.4 (s, 1H), 6.8 - 7.1 (m, 8H), 8.5 (bs, 1H), MS: m/z. 643m⁺.

9-(2-chlorophenyl)-10-[2-(1-triazolo-4,5-dicarboxymethyl)acetamidophenyl]-3,4,6,7,9,10-hexahydro-1,8-(2H, 5H) acridinedione 4e: yield 75%, M.P. 208-10°C, IR (KBr): 3320, 1700, 1645, 1595 1570, ¹H-NMR (CDCl₃): δ 1.80 -2.05 (m,8H), 2.2-2.4 (m,4H), 3.95 (s,6H), 4.1 (s,2H), 4.06 (s, 1H), 6.8 -7.10(m,8H), 8.5 (bs, 1H); MS: m/z. 643m⁺.

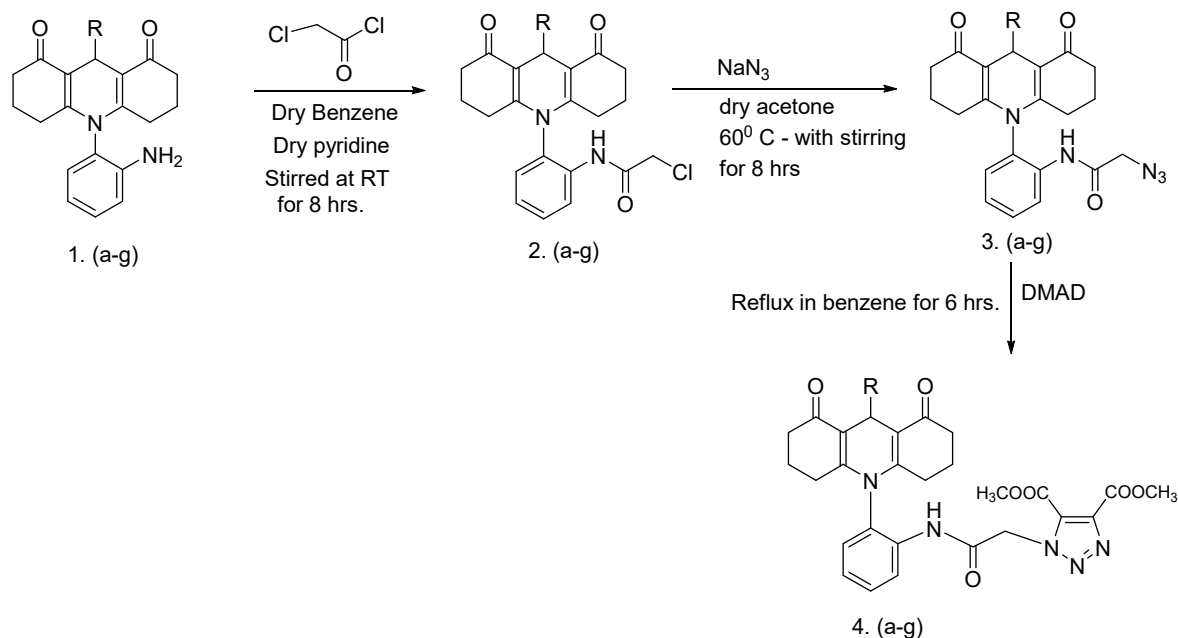
9-(4-methoxyphenyl)-10-[2-(1-triazolo-2,3-dicarboxymethyl)acetamidophenyl]-3,4,6,7,9,10-hexahydro-1,8-(2H, 5H) acridinedione 4f: yield 80%, M.P. 212-14°C, IR (KBr): 3310,1685, 1635, 1575, 1565, ¹H-NMR (CDCl₃): δ 1.80 -2.05 (m,8H), 2.2-2.4 (m,4H), 3.7 (s, 3H), 3.95 (s,6H), 4.06 (s, 1H), 4.4 (s, 1H), 6.8 -7.15 (m, 8H), 8.5 (bs, 1H); MS: m/z. 639m⁺.

9-(2-methoxyphenyl)-10-[2-(1-triazolo-2,3-dicarboxymethyl)acetamidophenyl]-3,4,6,7,9,10-hexahydro-1,8-(2H, 5H) acridinedione 4g: yield 81%, M.P.214-16°C , IR (KBr): 3310, 1690, 1635, 1585, 1560, ¹H-NMR (CDCl₃): δ 1.80 -2.05 (m,8H), 2.2-2.4 (m,4H), 3.7 (s, 3H), 3.95 (s,6H), 4.2 (s, 2H), 4.06 (s, 1H), 6.75 -7.2(m, 8H), 8.5 (bs, 1H);) MS: m/z. 639m⁺.

Antimicrobial activity:

The synthesized compounds in the present study have been tested for antibacterial activity by well diffusion method. The microorganisms selected for antibacterial were *Bacillus subtilis* (MTCC-441), *Staphylococcus aureus* (ATCC-3750) and *Escherichia coli* (MTCC-443). 100 µg/ml and 150 µg/ml concentrations were used to test the synthesized compounds. Norfloxacin was used as standard for antibacterial activity. The plates were prepared as per the standard procedures^{13,14,15}. The results are presented in Table-1.

Scheme - I



Compound	A	B	C	D	E	f	g
R	H	CH ₃	C ₆ H ₅	4-Cl-C ₆ H ₄	2-Cl-C ₆ H ₄	4-OCH ₃ -C ₆ H ₄	2-OCH ₃ -C ₆ H ₄

Results and Discussion:

The structures of all the synthesized compounds were confirmed by IR, H-NMR and Mass spectral data and then screened for antibacterial activity against *B. subtilis*, *S. aureus* and *E. coli*. The synthesized compounds 4d, 4e, 4f and 4g have shown the highest antibacterial activity when compared with standard drug Norfloxacin and the remaining compounds exhibited whether moderate or weak activity. The antibacterial activities are presented in Table-1.

Table-1

Compound	Zone of Inhibition in mm					
	<i>S. aureus</i>		<i>B. subtilis</i>		<i>E. coli</i>	
	100 µg	150 µg	100 µg	150 µg	100 µg	150 µg
4a	16	17	15	16	14	15
4b	16	18	16	17	14	16
4c	18	19	18	19	16	17
4d	20	21	19	20	18	18
4e	20	21	19	20	18	19
4f	21	22	21	22	20	21
4g	21	23	21	22	20	21
Norfloxacin	22	25	22	25	22	25

Conclusion:

The present study concludes that few compounds containing triazole-acridinedione skeleton has good antibacterial activity and in this aspect more number of derivatives of acridinedione may be synthesized to study antimicrobial activities.

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