Synthesis, Characterisation and Antimicrobial Studies of Triazolo-Tetramethylacridinedione Derivatives

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Abstract

Tetramethyl-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 tetramethyl-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-tetramethylacridine, Antimicrobial activity, *S. aureus*.

Introduction:

Acridine derivatives have exhibited bioactivities such as anti-inflammatory[1], anticancer[2], antimicrobial[3], antitubercular[4], antiparasitic[5], antimalarial[6], antiviral[7] and fungicidal[8], antibacterial[9] activities. Triazoles are a class of heterocyclic compounds with broad spectrum of biological activities[10]. In continuation of our studies on the synthesis of acridinedione derivatives[11-14], we herein report a facile synthesis of tetramethyltriazolo-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. ^{1}H-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 Shidmadzu QP 1000A instrument.

Synthesis of tetramethyl-10-(2-aminophenyl) and 9-substituted-tetramethyl-10-(2-aminophenyl) acridinedione derivatives were carried out according to our earlier procedure[11] by reacting dimedone with different aldehydes to give tetraketones which on reaction with o-phenylenediamine gives the tetramethyl-10-(2-aminophenyl) and 9-substituted-10-(2-aminophenyl) acridinedione derivatives.

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

To an ice cold solution of tetramethyl acridinediones (1) (10 mmol) in dry benzene (25 ml) and dry pyridine (1 ml) was added chloroacetylcholoride (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 $NaHCO_3$ solution and water, dried and concentrated to obtain additional amount of the product.

Tetramethyl-10-(2-chloroacetamidophenyl)-3,4,6,7,9,10-hexahydro-1,8-(2H,5H) acridinedione 2a: yield 78%, M.P. 218-20^{o}C, IR (KBr): 3320, 1700, 1640, 1250, 1570, ^{1}H-NMR ($CDCl_3$): δ 1.11(12H, gem dimethyl), 2.25 (s,4H), 2.4 (s,4H), 3.10 (dd,2H), 4.10 (s, 2H), 6.9 – 7.15 (m, 4H), 8.50 (bs, 1 H), MS: m/z. 440 m^+.

Pentamethyl-10-(2-chloroacetamidophenyl)-3,4,6,7,9,10-hexahydro-1,8-(2H,5H)-acridinedione 2b: yield 79%, M.P. 220-22^{o}C, IR (KBr): 3315, 1705, 1640, 1590, 1570, ^{1}H-NMR ($CDCl_3$): δ 1.0 (d,3H),1.11(12H, gem dimethyl), 2.25 (s,4H), 2.4 (s,4H), 4.1(q, 1H), 4.15 (s, 2H), 4.25 (q,1H),6.8 -7.15(m,4H), 8.5 (bs,1H); MS: m/z. 454 m^{+}.

9-phenyl-tetramethyl-10-(2-chlorocetamidophenyl)-3,4,6,7,9,10-hexahydro-1,8-(2H,5H) acridinedione 2c. yield 80%, M.P.235-37^{o}C, IR (KBr): 3315, 1690, 1630, 1580, 1570; ^{1}H-NMR ($CDCl_3$): δ 1.11(12H, gem dimethyl), 2.25 (s,4H), 2.4 (s,4H), 4.1 (s, 2H), 4.3 (s,1H), 6.8-7.2 (m,9H), 8.5(bs, 1H); MS: 516 m^{+}.

9-(4-chlorophenyl)-tetramethyl-10-(2-chloroacetamidophenyl)-3,4,6,7,9,10-hexahydro-1,8-(2H,5H) acridinedione 2d. yield 81%, M.P. 232-34^{o}C, IR (KBr): 3315, 1695, 1635, 1585, 1570; ^{1}H-NMR ($CDCl_3$): δ 1.11(12H, gem dimethyl), 2.25 (s,4H), 2.4 (s,4H), 4.2 (s, 2H), 4.4 (s, 1H), 6.8 – 7.2 (m, 8H), 8.5 (bs, 1H), MS: m/z. 550 m^{+}.

9-(2-chlorophenyl)–tetramethyl-10-(2-chloroacetamidophenyl)-3,4,6,7,9,10-hexahydro-1,8-(2H, 5H) acridinedione 2e: yield 79%, M.P. 234-36^{o}C, IR (KBr): 3315, 1705, 1645, 1590, 1570, ^{1}H-NMR ($CDCl_3$): δ 1.11(12H, gem dimethyl), 2.25 (s,4H), 2.4 (s,4H), 4.1 (s,2H), 4.4 (s, 1H), 6.8 -7.15(m,8H), 8.5 (bs, 1H); MS: m/z. 550m^{+}.

9-(4-methoxyphenyl)-tetramethyl-10-(2-chloroacetamidophenyl)-3,4,6,7,9,10-hexahydro-1,8-(2H, 5H) acridinedione 2f: yield 80%, M.P. 246-48^{o}C, IR (KBr): 3315, 1680, 1630, 1570, 1565, ^{1}H-NMR ($CDCl_3$): δ 1.11(12H, gem dimethyl), 2.25 (s,4H), 2.4 (s,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. 546m^{+}.

9-(2-methoxyphenyl)-tetramethyl-10-(2-chloroacetamidophenyl)-3,4,6,7,9,10-hexahydro-1,8-(2H, 5H) acridinedione 2g: yield 82%, M.P. 242-44^{o}C, IR (KBr): 3315, 1695, 1630, 1580, 1565, ^{1}H-NMR ($CDCl_3$): δ 1.11(12H, gem dimethyl), 2.25 (s,4H), 2.4 (s,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. 546m^{+}.

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

To a mixture of tetramethyl-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^{o}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.

Tetramethyl-10-(2-azidoacetamidophenyl)-3,4,6,7,9,10-hexahydro-1,8-(2H,5H) acridinedione 3a: yield 76%, M.P.210-212^{o}C (decomp.), IR (KBr): 3315, 2105, 1700, 1640, 1250, 1570, ^{1}H-NMR ($CDCl_3$) : δ 1.11(12H, gem dimethyl), 2.25 (s,4H), 2.4 (s,4H), 3.10 (dd,2H), 4.06 (s, 2H), 6.9 – 7.15 (m, 4H), 8.50 (bs, 1 H), MS: m/z. 447 m^+.

Pentamethyl-10-(2-azidoacetamidophenyl)-3,4,6,7,9,10-hexahydro-1,8-(2H,5H)-acridinedione 3b: yield 75%, M.P. 212-14^{o}C (decomp.), IR (KBr): 3315, 2105, 1700, 1640, 1590, 1570, ^{1}H-NMR ($CDCl_3$): δ 1.0 (d,3H),1.11(12H, gem dimethyl), 2.25 (s,4H), 2.4 (s,4H), 4.06 (s, 2H), 4.20 (q,1H), 6.8 -7.15(m,4H), 8.5 (bs,1H); MS: m/z. 461 m^+.

9-phenyl-tetramethyl-10-(2-azidoacetamidophenyl)3,4,6,7,9,10-hexahydro-1,8-(2H,5H) acridinedione 3c. yield 79%, M.P. 210-12^{o}C (decomp.), IR (KBr): 3315, 2105,1690, 1630, 1580, 1570; ^{1}H-NMR ($CDCl_3$): δ 1.11(12H, gem dimethyl), 2.25 (s,4H), 2.4 (s,4H), 4.06 (s, 2H), 4.3 (s,1H), 6.8-7.2 (m,9H), 8.5(bs, 1H); MS: 523 m^+.

9-(4-chlorophenyl)-tetramethyl-10-(2-azidoacetamidophenyl)-3,4,6,7,9,10-hexahydro-1,8,-(2H,5H) acridinedione 3d. yield 80%, M.P. 212 -14^{o}C (decomp.), IR (KBr): 3315, 2105,1690, 1635, 1585, 1570; ^{1}H-NMR ($CDCl_3$): δ 1.11(12H, gem dimethyl), 2.25 (s,4H), 2.4 (s,4H), 4.06 (s, 2H), 4.4 (s, 1H), 6.8 – 7.2 (m, 8H), 8.5 (bs, 1H), MS: m/z. 557m^+.

9-(2-chlorophenyl) –tetramethyl-10-(2-azidoacetamidophenyl)-3,4,6,7,9,10-hexahydro-1,8-(2H, 5H) acridinedione 3e: yield 78%, M.P. 214-16^{o}C (decomp.),, IR (KBr): 3325, 2105,1705, 1640, 1590, 1570, ^{1}H-NMR ($CDCl_3$): δ1.11(12H, gem dimethyl), 2.25 (s,4H), 2.4 (s,4H), 4.1 (s,2H), 4.4 (s, 1H), 6.8 -7.15(m,8H), 8.5 (bs, 1H); MS: m/z. 557m^+.

9-(4-methoxyphenyl)-tetramethyl-10-(2-azidoacetamidophenyl)-3,4,6,7,9,10-hexahydro-1,8-(2H, 5H) acridinedione 3f: yield 81%, M.P. 212-14^{o}C (decomp.), IR (KBr): 3315, 2105,1680, 1630, 1570, 1565, ^{1}H-NMR ($CDCl_3$): δ1.11(12H, gem dimethyl), 2.25 (s,4H), 2.4 (s,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. 553m^+.

9-(2-methoxyphenyl)-tetramethyl-10-(2-azidoacetamidophenyl)-3,4,6,7,9,10-hexahydro-1,8-(2H, 5H) acridinedione 3g: yield 80%, M.P.214-16^{o} C (decomp.), IR (KBr): 3315, 2105,1695, 1630, 1580, 1565, ^{1}H-NMR ($CDCl_3$): δ 1.11(12H, gem dimethyl), 2.25 (s,4H),

2.4 (s,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. 553m^+.

Preparation of tetramethyl-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 dimethylacetylenedicorboxylate (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).

Tetramethyl-10-[2-(1-triazolo-4,5-dicaroxymethyl)acetamidophenyl]-3,4,6,7,9,10-hexahydro-1,8-(2H,5H)-acridinedione 4a: yield 65%; M.P. 212-14^{o}C, IR (KBr): 3325, 1715, 1635, 1615, 1580; ^{1}H-NMR ($CDCl_3$): δ 1.11(12H, gem dimethyl), 2.25 (s,4H), 2.4 (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. 589 m^+.

Pentamethyl-10-[2-(1-triazolo-4,5-dicaroxymethyl)acetamidophenyl]-3,4,6,7,9,10-hexahydro-1,8-(2H,5H)-acridinedione 4b: yield 74%, M.P. 216-18^{o}C ,IR (KBr): 3325, ,1715, 1645, 1595, 1570, ^{1}H-NMR ($CDCl_3$): δ 1.05 (d,3H), 1.11(12H, gem dimethyl), 2.25 (s,4H), 2.4 (s,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. 603m^+.

9-phenyl-tetramethyl-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. 214-16^{o}C , IR (KBr): 3315, 1695, 1630, 1585 1570; ^{1}H-NMR ($CDCl_3$): δ 1.11(12H, gem dimethyl), 2.25 (s,4H), 2.4 (s,4H), 3.95 (s,6H), 4.06 (s, 2H), 4.3 (s,1H), 6.75-7.2 (m,9H), 8.5(bs, 1H); MS: 665m+.

9-(4-chlorophenyl)-tetramethyl-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. 218-20^{o}C, IR (KBr): 3315, 1695, 1635, 1580, 1570; ^{1}H-NMR ($CDCl_3$): δ 1.11(12H, gem dimethyl), 2.25 (s,4H), 2.4 (s,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. 699m^+.

9-(2-chlorophenyl)-tetramethyl-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. 220-22^{o}C ,IR (KBr): 3315, 1705, 1645, 1595 1570, ^{1}H-NMR ($CDCl_3$): δ 1.11(12H, gem dimethyl), 2.25 (s,4H), 2.4 (s,4H), 3.95 (s,6H), 4.1 (s,2H), 4.4 (s, 1H), 6.8 -7.10(m,.8H), 8.5 (bs, 1H); MS: m/z. 699m^+.

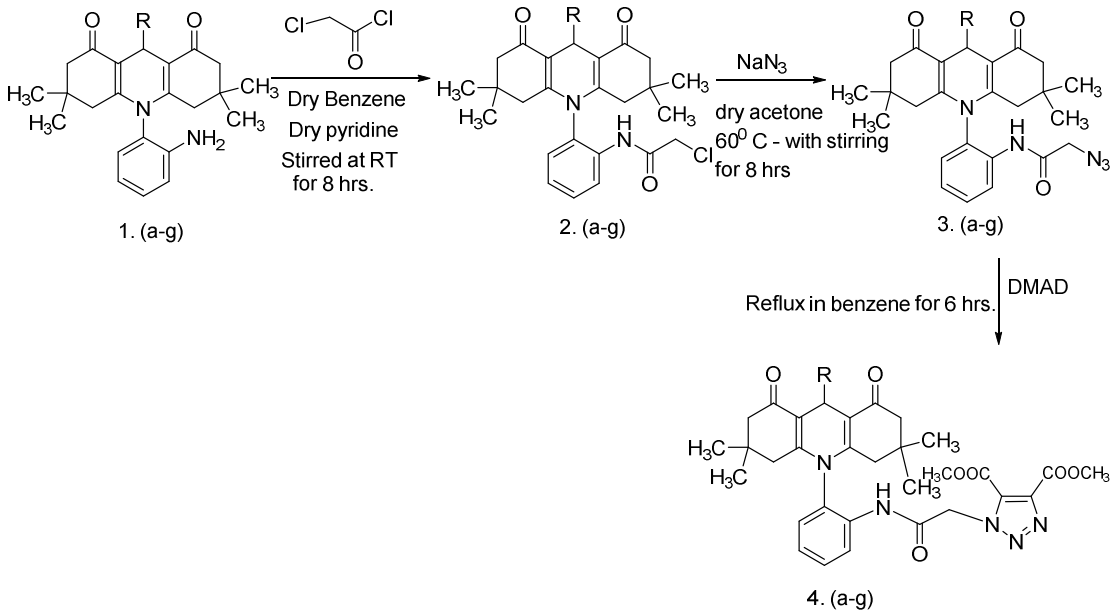
9-(4-methoxyphenyl)-tetramethyl-10-[2-(1-triazolo-4,5-dicarboxymethyl)acetamidophenyl]-3,4,6,7,9,10-hexahydro-1,8-(2H,5H) acridinedione 4f: yield 80%, M.P. 224-26^{o}C, IR (KBr): 3315,1695, 1635, 1575, 1565, ^{1}H-NMR ($CDCl_3$): δ 1.11(12H, gem dimethyl), 2.25 (s,4H), 2.4 (s,4H), 3.7 (s, 3H), 3.95 (s,6H), 4.06 (s, 1H), 4.4 (s, 1H), 6.8 -7.15 (m, 8H), 8.5 (bs, 1H); MS: m/z. 695m^{+}.

9-(2-methoxyphenyl)-tetramethyl-10-[2-(1-triazolo-4,5-dicarboxymethyl)acetamidophenyl]-3,4,6,7,9,10-hexahydro-1,8-(2H,5H) acridinedione 4g: yield 81%, M.P.220-22^{o}C , IR (KBr): 3315, 1695, 1635, 1585, 1560, ^{1}H-NMR ($CDCl_3$): δ 1.11(12H, gem dimethyl), 2.25 (s,4H), 2.4 (s,4H), 3.7 (s, 3H), 3.95 (s,6H), 4.2 (s, 2H), 4.4 (s, 1H), 6.75 -7.2(m, 8H), 8.5 (bs, 1H);) MS: m/z. 695m^{+}.

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 producures[15,16,17]. The results are presented in Table-1.

Scheme - I



Compound	A	b	C	D	E	f	g
R	H	CH_3	C_6H_5	4-Cl-C_6H_4	2-Cl-C_6H_4	4-OCH_3-C_6H_4	2-OCH_3-C_6H_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					
	S. aureus		*B. subtilis*		*E. coli*	
	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 triazolo-tetramethylacridine 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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