

## Original Research Article

# Synthesis, Characterisation and Antimicrobial evaluations of Acetyloxyphenyl-1,2,3-triazole linked Hexahydroacridinediones

### Abstract

10-(2-hydroxyphenyl)-hexahydro acridinediones were treated with chloroacetyl chloride to give 10-(2-chloroacetyloxyphenyl) hexahydro acridinediones, which were treated with  $\text{NaN}_3$  in acetone followed by reaction with DMAD yielded 10-[2-(1-triazolo-4,5-dicarboxymethyl)acetyloxyphenyl]-3,4,6,7,9,10-hexahydro-1,8-(2H,5H)-acridinediones.

**Key words:** Antimicrobial, Acetyloxyphenyl, Acridinediones, Triazoles, Triazolo-acridinedione.

### INTRODUCTION

Acridine derivatives form an important class of heterocycles containing nitrogen due to their broad range of pharmaceutical properties. Acridine derivatives are characterised by unique physical and chemical properties, biological activities and industrial applications. Notably the anticancer activity of acridine/acridone derivatives has attracted increasing interest. To date, many derivatives of acridine have been synthesized and tested for antitumor activity. Acridine derivatives have exhibited bioactivities such as anti-inflammatory [1], anticancer [2], antimicrobial [3], antitubercular [4], antiparasitic [5], antimalarial [6], antiviral [7], antifungicidal [8] and antibacterial [9] activities. Among nitrogen containing heterocyclic compounds 1,2,3-triazoles are privileged structure motif and received a great deal of attention in academics and industry. Even though absent in nature, 1,2,3-triazoles have found broad applications in drug discovery, organic synthesis, polymer industry, fluorescent imaging and material science. Triazoles are a class of heterocyclic compounds with broad spectrum of biological activities [10-11]. A variety of acridine/acridone derivatives have been synthesized; analogues such as triazoloacridone has entered clinical studies [12]. The synthesis, laser activity [13-15] and photophysical properties [16] of hexahydroacridinedione derivatives were reported earlier by us and therefore, the development of a facile and straightforward methodology for the synthesis of 1,2,3-triazole linked hexahydro acridinedione derivatives and antimicrobial activity is of noteworthy.

### 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.  $^1\text{H-NMR}$  was taken in Jeol GSX 400 (400 MHz) instrument using TMS as internal standard and  $\text{CDCl}_3$ ,  $\text{DMSO-d}_6$  as solvents. Mass spectrum was taken using Hewlett-Packard 5985 (70 eV) and Shimadzu QP 1000A instrument. The elemental analysis was carried out on Perkin-Elmer 2400 CHN analyser. Thin layer chromatography (TLC) was performed using glass plates coated with silica gel (ACME) of 2.5 mm thickness. Spots were visualised using iodine vapour. Anhydrous magnesium sulphate was used as the drying agent.

Synthesis of 10-(2-hydroxyphenyl) and 9-substituted-10-(2-hydroxyphenyl) acridinedione derivatives were carried out according to our earlier procedure [13-15] by reacting cyclohexane-1,3-dione with different aldehydes to give tetraketones which on reaction with o-aminophenol gives the 10-(2-hydroxyphenyl) and 9-substituted-10-(2-hydroxyphenyl) acridinedione derivatives. The synthesis of the title compounds 4 a-i is shown in Scheme-I.

**Synthesis of 10-(2-chloroacetyloxyphenyl)-3,4,6,7,9,10-hexahydro-1,8-(2H,5H) acridinediones and 9-substituted 10-(2-chloroacetyloxyphenyl)-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 NaHCO<sub>3</sub> solution and water, dried over anhydrous magnesium sulphate and concentrated to obtain additional amount of the product. The solid product obtained was recrystallised from methanol.

10-(2-chloroacetyloxyphenyl)-3,4,6,7,9,10-hexahydro-1,8-(2H,5H) acridinedione 2a: yield 79%, M.P. 210-12°C, IR (KBr, cm<sup>-1</sup>): 1710, 1640, 1600, 1590, 1250; <sup>1</sup>H-NMR (CDCl<sub>3</sub>-DMSO-d<sub>6</sub>): δ 1.80 – 2.10 (m, 8H, =C-CH<sub>2</sub>-CH<sub>2</sub>-), 2.20 (m 4H, -CO-CH<sub>2</sub>-), 3.10 (dd, gem coupling, J<sub>gem</sub> = 21 Hz, 2H, =C-CH<sub>2</sub>-C=), 4.10 (s, 2H, -CO-CH<sub>2</sub>-Cl), 6.9 – 7.15 (m, 4H, Aro.); MS: m/z. 385 m<sup>+</sup>, m+2 387; Anal.calcd.(found) % C<sub>21</sub>H<sub>20</sub>NO<sub>4</sub>Cl: C, 65.37 (65.28); H, 5.23 (5.19); N, 3.63 (3.54).

9-methyl-10-(2-chloroacetyloxyphenyl)-3,4,6,7,9,10-hexahydro-1,8-(2H,5H)-acridinedione 2b: yield 78%, M.P. 212-14°C, IR (KBr cm<sup>-1</sup>): 1710, 1650, 1595, 1590; <sup>1</sup>H-NMR (CDCl<sub>3</sub>-DMSO-d<sub>6</sub>): δ 1.05 (d, 3H, -CH<sub>3</sub>), 1.80 -2.05 (m, 8H, =C-CH<sub>2</sub>-CH<sub>2</sub>-), 2.20-2.40 (m, 4H, -CO-CH<sub>2</sub>-), 4.10 (s, 2H, -CO-CH<sub>2</sub>-Cl), 4.20 (q, 1H, =C-CH-C=), 6.80 -7.15 (m, 4H, Aro.); MS: m/z. 399 m<sup>+</sup>, m+2 401; Anal.calcd.(found) % C<sub>22</sub>H<sub>22</sub>NO<sub>4</sub>Cl: C, 66.08 (65.92); H, 5.54 (5.66); N, 3.50 (3.40).

9-phenyl-10-(2-chloroacetyloxyphenyl)-3,4,6,7,9,10-hexahydro-1,8-(2H,5H) acridinedione 2c: yield 82%, M.P. 228-29°C, IR (KBr, cm<sup>-1</sup>): 1710, 1640, 1595, 1590; <sup>1</sup>H-NMR (CDCl<sub>3</sub>-DMSO-d<sub>6</sub>): δ 1.80-2.05 (m, 8H, =C-CH<sub>2</sub>-CH<sub>2</sub>-), 2.20-2.40 (m, 4H, -CO-CH<sub>2</sub>-), 4.10 (s, 2H, -CO-CH<sub>2</sub>-Cl), 4.30 (s, 1H, =C-CH-C=), 6.80-7.20 (m, 9H, Aro.); MS: 461 m<sup>+</sup>, m+2 463; Anal.calcd.(found) % C<sub>27</sub>H<sub>24</sub>NO<sub>4</sub>Cl: C, 70.20 (70.02); H, 5.23 (5.38); N, 3.03 (2.91).

9-(4-chlorophenyl)-10-(2-chloroacetyloxyphenyl)-3,4,6,7,9,10-hexahydro-1,8-(2H,5H) acridinedione 2d: yield 82%, M.P. 232-34°C, IR (KBr cm<sup>-1</sup>): 1700, 1640, 1595, 1585; <sup>1</sup>H-NMR (CDCl<sub>3</sub>-DMSO-d<sub>6</sub>): δ 1.80-2.05 (m, 8H, =C-CH<sub>2</sub>-CH<sub>2</sub>-), 2.20 – 2.40 (m, 4H, -CO-CH<sub>2</sub>-), 4.20 (s, 2H, -CO-CH<sub>2</sub>-Cl), 4.40 (s, 1H, =C-CH-C=), 6.80 – 7.20 (m, 8H, Aro.); MS: m/z. 495 m<sup>+</sup>, m+2 497, m+4 499; Anal.calcd.(found) % C<sub>27</sub>H<sub>23</sub>NO<sub>4</sub>Cl<sub>2</sub>: C, 65.33 (65.18); H, 4.67 (4.74); N, 2.82 (2.64).

9-(2-chlorophenyl) -10-(2-chloroacetyloxyphenyl)-3,4,6,7,9,10-hexahydro-1,8-(2H, 5H) acridinedione 2e: yield 78%, M.P. 212-14°C, IR (KBr cm<sup>-1</sup>): 1710, 1645, 1595, 1585; <sup>1</sup>H-NMR (CDCl<sub>3</sub>-DMSO-d<sub>6</sub>): δ 1.80 -2.05 (m, 8H, =C-CH<sub>2</sub>-CH<sub>2</sub>-), 2.20-2.40 (m, 4H, -CO-CH<sub>2</sub>-), 4.10 (s, 2H, -CO-CH<sub>2</sub>-Cl), 4.40 (s, 1H, =C-CH-C=), 6.80 -7.15 (m, 8H, Aro.); MS: m/z. 495, m<sup>+</sup>, m+2 497, m+4 499; Anal.calcd.(found) % C<sub>27</sub>H<sub>23</sub>NO<sub>4</sub>Cl<sub>2</sub>: C, 65.33 (65.12); H, 4.67 (4.80); N, 2.82 (2.70).

9-(4-fluorophenyl)-10-(2-chloroacetyloxyphenyl)-3,4,6,7,9,10-hexahydro-1,8-(2H,5H) acridinedione 2f: yield 78%, M.P. 222-44°C, IR (KBr  $\text{cm}^{-1}$ ): 1705, 1645, 1600, 1595;  $^1\text{H}$ -NMR ( $\text{CDCl}_3$ -DMSO- $d_6$ ):  $\delta$  1.80-2.05 (m, 8H,  $=\text{C}-\text{CH}_2-\text{CH}_2-$ ), 2.20 – 2.40 (m, 4H,  $-\text{CO}-\text{CH}_2-$ ), 4.20 (s, 2H,  $-\text{CO}-\text{CH}_2-\text{Cl}$ ), 4.40 (s, 1H,  $=\text{C}-\text{CH}-\text{C}=\text{C}$ ), 6.90 – 7.30 (m, 8H, Aro.); MS:  $m/z$ . 479 $m^+$ ,  $m+2$  481; Anal.calcd.(found) %  $\text{C}_{27}\text{H}_{23}\text{NO}_4\text{ClF}$ : C, 67.57 (67.38); H, 4.83 (4.70); N, 2.91 (2.80).

9-(2-fluorophenyl)-10-(2-chloroacetyloxyphenyl)-3,4,6,7,9,10-hexahydro-1,8-(2H, 5H) acridinedione 2g: yield 74%, M.P. 208-10°C, IR (KBr  $\text{cm}^{-1}$ ): 1715, 1645, 1600, 1595;  $^1\text{H}$ -NMR ( $\text{CDCl}_3$ -DMSO- $d_6$ ):  $\delta$  1.80 -2.05 (m, 8H,  $=\text{C}-\text{CH}_2-\text{CH}_2-$ ), 2.20-2.40 (m, 4H,  $-\text{CO}-\text{CH}_2-$ ), 4.10 (s, 2H,  $-\text{CO}-\text{CH}_2-\text{Cl}$ ), 4.40 (s, 1H,  $=\text{C}-\text{CH}-\text{C}=\text{C}$ ), 6.90 -7.20 (m, 8H, Aro.); MS:  $m/z$ . 479 $m^+$ ,  $m+2$  481; Anal.calcd.(found) %  $\text{C}_{27}\text{H}_{23}\text{NO}_4\text{ClF}$ : C, 67.57 (67.36); H, 4.83 (4.70); N, 2.91 (2.82).

9-(4-methoxyphenyl)-10-(2-chloroacetyloxyphenyl)-3,4,6,7,9,10-hexahydro-1,8-(2H, 5H) acridinedione 2h: yield 82%, M.P. 234-36°C, IR (KBr  $\text{cm}^{-1}$ ): 1690, 1640, 1595, 1585;  $^1\text{H}$ -NMR ( $\text{CDCl}_3$ -DMSO- $d_6$ ):  $\delta$  1.80 -2.05 (m, 8H,  $=\text{C}-\text{CH}_2-\text{CH}_2-$ ), 2.20-2.40 (m, 4H,  $-\text{CO}-\text{CH}_2-$ ), 3.70 (s, 3H,  $\text{OCH}_3$ ), 4.20 (s, 2H,  $-\text{CO}-\text{CH}_2-\text{Cl}$ ), 4.40 (s, 1H,  $=\text{C}-\text{CH}-\text{C}=\text{C}$ ), 6.80 -7.20 (m, 8H, Aro.); MS:  $m/z$ . 491 $m^+$ ,  $m+2$  493; Anal.calcd.(found) %  $\text{C}_{28}\text{H}_{26}\text{NO}_5\text{Cl}$ : C, 68.36 (68.15); H, 5.32 (5.14); N, 2.84 (2.78).

9-(2-methoxyphenyl)-10-(2-chloroacetyloxyphenyl)-3,4,6,7,9,10-hexahydro-1,8-(2H, 5H) acridinedione 2i: yield 84%, M.P. 236-38°C, IR (KBr  $\text{cm}^{-1}$ ): 1690, 1635, 1595, 1585;  $^1\text{H}$ -NMR ( $\text{CDCl}_3$ -DMSO- $d_6$ ):  $\delta$  1.80 -2.05 (m, 8H), 2.20-2.40 (m, 4H,  $-\text{CO}-\text{CH}_2-$ ), 3.70 (s, 3H,  $\text{OCH}_3$ ), 4.20 (s, 2H,  $-\text{CO}-\text{CH}_2-\text{Cl}$ ), 4.40 (s, 1H,  $=\text{C}-\text{CH}-\text{C}=\text{C}$ ), 6.80 -7.20 (m, 8H, Aro.); MS:  $m/z$ . 491 $m^+$ ,  $m+2$  493; Anal.calcd.(found) %  $\text{C}_{28}\text{H}_{26}\text{NO}_5\text{Cl}$ : C, 68.36 (68.16); H, 5.32 (5.44); N, 2.84 (2.73).

### **Preparation of 10-(2-azidoacetyloxyphenyl)-3,4,6,7,9,10-hexahydro-1,8-(2H,5H)-acridinediones 3 (a-i):**

To a mixture of 10-(2-chloroacetyloxyphenyl)-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-azidoacetyloxyphenyl)-3,4,6,7,9,10-hexahydro-1,8-(2H,5H) acridinedione 3a: yield 76%, M.P. 196-198°C (decomp.), IR (KBr  $\text{cm}^{-1}$ ): 2105, 1710, 1645, 1660, 1595, 1255;  $^1\text{H}$ -NMR ( $\text{CDCl}_3$ -DMSO- $d_6$ ):  $\delta$  1.80 – 2.10 (m, 8H,  $=\text{C}-\text{CH}_2-\text{CH}_2-$ ), 2.20 (m, 4H,  $-\text{CO}-\text{CH}_2-$ ), 3.10 (dd, gem coupling,  $J_{\text{gem}} = 21$  Hz, 2H,  $=\text{C}-\text{CH}_2-\text{C}=\text{C}$ ), 4.06 (s, 2H,  $-\text{CO}-\text{CH}_2-\text{N}_3$ ), 6.90 – 7.15 (m, 4H, Aro.); MS:  $m/z$ . 392  $m^+$ . Anal.calcd.(found) %  $\text{C}_{21}\text{H}_{20}\text{N}_4\text{O}_4$ : C, 64.27 (64.14); H, 5.13 (5.02); N, 14.27 (14.08).

9-methyl-10-(2-azidoacetyloxyphenyl)-3,4,6,7,9,10-hexahydro-1,8-(2H,5H)-acridinedione 3b: yield 74%, M.P. 194-196°C (decomp.), IR (KBr  $\text{cm}^{-1}$ ): 2105, 1700, 1645, 1600, 1590;  $^1\text{H}$ -NMR ( $\text{CDCl}_3$ -DMSO- $d_6$ ):  $\delta$  1.05 (d, 3H,  $-\text{CH}_3$ ), 1.80 -2.05 (m, 8H,  $=\text{C}-\text{CH}_2-\text{CH}_2-$ ), 2.20-2.40 (m, 4H,  $-\text{CO}-\text{CH}_2-$ ), 4.06 (s, 2H,  $-\text{CO}-\text{CH}_2-\text{N}_3$ ), 4.20 (q, 1H,  $=\text{C}-\text{CH}-\text{C}=\text{C}$ ), 6.80 -7.15 (m, 4H, Aro.); MS:  $m/z$ . 405  $m^+$ . Anal.calcd.(found) %  $\text{C}_{22}\text{H}_{22}\text{N}_4\text{O}_4$ : C, 65.01 (64.85); H, 5.45 (5.61); N, 13.78 (13.64).

9-phenyl-10-(2-azidoacetyloxyphenyl)-3,4,6,7,9,10-hexahydro-1,8-(2H,5H) acridinedione 3c: yield 79%, M.P. 206-208°C (decomp.), IR (KBr,  $\text{cm}^{-1}$ ): 2105, 1695, 1630, 1595, 1585;  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ -DMSO- $d_6$ ):  $\delta$  1.80-2.05 (m, 8H,  $=\text{C-CH}_2\text{-CH}_2-$ ), 2.20-2.40 (m, 4H,  $-\text{CO-CH}_2-$ ), 4.06 (s, 2H,  $-\text{CO-CH}_2-\text{N}_3$ ), 4.30 (s, 1H,  $=\text{C-CH-C=}$ ), 6.80-7.20 (m, 9H, Aro.); MS: 468  $m^+$ . Anal.calcd.(found) %  $\text{C}_{27}\text{H}_{24}\text{N}_4\text{O}_4$ : C, 69.22 (69.03); H, 5.16 (5.08); N, 11.96 (11.82).

9-(4-chlorophenyl)-10-(2-azidoacetyloxyphenyl)-3,4,6,7,9,10-hexahydro-1,8-(2H,5H) acridinedione 3d: yield 82%, M.P. 204 -206°C (decomp.), IR (KBr  $\text{cm}^{-1}$ ): 2105, 1695, 1635, 1595, 1585;  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ -DMSO- $d_6$ ):  $\delta$  1.80-2.05 (m, 8H,  $=\text{C-CH}_2\text{-CH}_2-$ ), 2.20 - 2.40 (m, 4H,  $-\text{CO-CH}_2-$ ), 4.08 (s, 2H,  $-\text{CO-CH}_2-\text{N}_3$ ), 4.40 (s, 1H,  $=\text{C-CH-C=}$ ), 6.80- 7.20 (m, 8H, Aro.); MS:  $m/z$ . 502 $m^+$ ,  $m+2$  504; Anal.calcd.(found) %  $\text{C}_{27}\text{H}_{23}\text{N}_4\text{O}_4\text{Cl}$ : C, 64.47 (64.31); H, 4.60 (4.72); N, 11.13 (10.96).

9-(2-chlorophenyl) -10-(2-azidoacetyloxyphenyl)-3,4,6,7,9,10-hexahydro-1,8-(2H, 5H) acridinedione 3e: yield 76%, M.P. 210-212°C (decomp.), IR (KBr  $\text{cm}^{-1}$ ): 2105, 1705, 1640, 1595, 1585;  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ -DMSO- $d_6$ ):  $\delta$  1.80 -2.05 (m, 8H,  $=\text{C-CH}_2\text{-CH}_2-$ ), 2.20-2.40 (m, 4H,  $-\text{CO-CH}_2-$ ), 4.07 (s, 2H,  $-\text{CO-CH}_2-\text{N}_3$ ), 4.40 (s, 1H,  $=\text{C-CH-C=}$ ), 6.80 -7.15 (m, 8H, Aro.); MS:  $m/z$ . 502 $m^+$ ,  $m+2$  504; Anal.calcd.(found) %  $\text{C}_{27}\text{H}_{23}\text{N}_4\text{O}_4\text{Cl}$ : C, 64.47 (64.34); H, 4.60 (4.42); N, 11.13 (10.98).

9-(4-fluorophenyl)-10-(2-azidoacetyloxyphenyl)-3,4,6,7,9,10-hexahydro-1,8-(2H,5H) acridinedione 3f: yield 78%, M.P. 204 -206°C (decomp.), IR (KBr,  $\text{cm}^{-1}$ ): 2105, 1695, 1635, 1595, 1585;  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ -DMSO- $d_6$ ):  $\delta$  1.85-2.05 (m, 8H,  $=\text{C-CH}_2\text{-CH}_2-$ ), 2.20 - 2.40 (m, 4H,  $-\text{CO-CH}_2-$ ), 4.05 (s, 2H,  $-\text{CO-CH}_2-\text{N}_3$ ), 4.45 (s, 1H,  $=\text{C-CH-C=}$ ), 6.90 - 7.20 (m, 8H, Aro.); MS:  $m/z$ . 486 $m^+$ . Anal.calcd.(found) %  $\text{C}_{27}\text{H}_{23}\text{N}_4\text{O}_4\text{F}$ : C, 66.65 (66.48); H, 4.76 (4.69); N, 11.51 (11.45).

9-(2-fluorophenyl) -10-(2-azidoacetyloxyphenyl)-3,4,6,7,9,10-hexahydro-1,8-(2H, 5H) acridinedione 3g: yield 72%, M.P. 208-210°C (decomp.), IR (KBr  $\text{cm}^{-1}$ ): 2105, 1705, 1640, 1595, 1585;  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ -DMSO- $d_6$ ):  $\delta$  1.85 -2.05 (m, 8H,  $=\text{C-CH}_2\text{-CH}_2-$ ), 2.20-2.40 (m, 4H,  $-\text{CO-CH}_2-$ ), 4.06 (s, 2H,  $-\text{CO-CH}_2-\text{N}_3$ ), 4.40 (s, 1H,  $=\text{C-CH-C=}$ ), 6.85 -7.15 (m, 8H, Aro.); MS:  $m/z$ . 486 $m^+$ . Anal.calcd.(found) %  $\text{C}_{27}\text{H}_{23}\text{N}_4\text{O}_4\text{F}$ : C, 66.65 (66.50); H, 4.76 (4.64); N, 11.51 (11.42).

9-(4-methoxyphenyl)-10-(2-azidoacetyloxyphenyl)-3,4,6,7,9,10-hexahydro-1,8-(2H, 5H) acridinedione 3h: yield 84%, M.P. 202-204°C (decomp.), IR (KBr,  $\text{cm}^{-1}$ ): 2105, 1700, 1635, 1600, 1595;  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ -DMSO- $d_6$ ):  $\delta$  1.80 -2.05 (m, 8H,  $=\text{C-CH}_2\text{-CH}_2-$ ), 2.2-2.4 (m, 4H,  $-\text{CO-CH}_2-$ ), 3.70 (s, 3H,  $\text{OCH}_3$ ), 4.06 (s, 2H,  $-\text{CO-CH}_2-\text{N}_3$ ), 4.40 (s, 1H,  $=\text{C-CH-C=}$ ), 6.80 -7.20 (m, 8H, Aro.); MS:  $m/z$ . 498 $m^+$ . Anal.calcd.(found) %  $\text{C}_{28}\text{H}_{26}\text{N}_4\text{O}_5$ : C, 67.45 (67.39); H, 5.25 (5.35); N, 11.23 (11.12).

9-(2-methoxyphenyl)-10-(2-azidoacetyloxyphenyl)-3,4,6,7,9,10-hexahydro-1,8-(2H, 5H) acridinedione 3i: yield 84%, M.P. 210-212°C (decomp.), IR (KBr  $\text{cm}^{-1}$ ): 2105, 1695, 1630, 1590, 1585;  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ -DMSO- $d_6$ ):  $\delta$  1.80 -2.05 (m, 8H,  $=\text{C-CH}_2\text{-CH}_2-$ ), 2.20-2.40 (m, 4H,  $-\text{CO-CH}_2-$ ), 3.70 (s, 3H,  $\text{OCH}_3$ ), 4.06 (s, 2H,  $-\text{CO-CH}_2-\text{N}_3$ ), 4.40 (s, 1H,  $=\text{C-CH-C=}$ ), 6.80 -7.20 (m, 8H, Aro.); MS:  $m/z$ . 498 $m^+$ . Anal.calcd.(found) %  $\text{C}_{28}\text{H}_{26}\text{N}_4\text{O}_5$ : C, 67.45 (67.37); H, 5.25 (5.34); N, 11.23 (11.11).

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

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 obtained was recrystallised from methanol to obtain 4 (a-g).

10-[2-(1-triazolo-4,5-dicarboxymethyl)acetyloxyphenyl]-3,4,6,7,9,10-hexahydro-1,8-(2H,5H)-acridinedione 4a: yield 64%; M.P. 202-204°C, IR (KBr,  $\text{cm}^{-1}$ ): 1715, 1645, 1600, 1595, 1685;  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ -DMSO- $d_6$ ):  $\delta$  1.8-2.10 (m, 8H,  $=\text{C-CH}_2\text{-CH}_2-$ ), 2.20 (s, 4H,  $-\text{CO-CH}_2-$ ), 3.10 (dd, gem coupling,  $J_{\text{gem}} = 21$  Hz, 2H,  $=\text{C-CH}_2\text{-C=}$ ), 3.95 (s, 6H,  $-\text{COOCH}_3$ ), 5.60 (s, 2H,  $-\text{CO-CH}_2\text{-triazole}$ ), 7.20-7.40 (m, 4H, Aro.); MS:  $m/z$ . 534  $m^+$ ; Anal. calcd. (found) %  $\text{C}_{27}\text{H}_{26}\text{N}_4\text{O}_8$ : C, 60.67 (60.51); H, 4.90 (4.79); N, 10.48 (10.34).

9-methyl-10-[2-(1-triazolo-4,5-dicarboxymethyl)acetyloxyphenyl]-3,4,6,7,9,10-hexahydro-1,8-(2H,5H)-acridinedione 4b: yield 76%, M.P. 210-212°C, IR (KBr,  $\text{cm}^{-1}$ ): 1725, 1650, 1610, 1595, 1590;  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ -DMSO- $d_6$ ):  $\delta$  1.05 (d, 3H), 1.80-2.05 (m, 8H,  $=\text{C-CH}_2\text{-CH}_2-$ ), 2.20-2.40 (m, 4H,  $-\text{CO-CH}_2-$ ), 3.95 (s, 6H,  $-\text{COOCH}_3$ ), 4.02 (q, 1H,  $=\text{C-CH-C=}$ ), 5.65 (s, 2H,  $-\text{CO-CH}_2\text{-triazole}$ ), 6.80-7.20 (m, 4H, Aro.); MS:  $m/z$ . 548  $m^+$ ; Anal. calcd. (found) %  $\text{C}_{28}\text{H}_{28}\text{N}_4\text{O}_8$ : C, 61.30 (61.18); H, 5.14 (5.04); N, 10.21 (10.08).

9-phenyl-10-[2-(1-triazolo-4,5-dicarboxymethyl)acetyloxyphenyl]-3,4,6,7,9,10-hexahydro-1,8-(2H,5H)-acridinedione 4c: yield 78%, M.P. 206-08°C, IR (KBr,  $\text{cm}^{-1}$ ): 1720, 1635, 1600, 1595, 1590;  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ -DMSO- $d_6$ ):  $\delta$  1.80-2.05 (m, 8H,  $=\text{C-CH}_2\text{-CH}_2-$ ), 2.20-2.40 (m, 4H,  $-\text{CO-CH}_2-$ ), 3.95 (s, 6H,  $-\text{COOCH}_3$ ), 4.06 (s, 1H,  $=\text{C-CH-C=}$ ), 5.60 (s, 2H,  $-\text{CO-CH}_2\text{-triazole}$ ), 6.75-7.2 (m, 9H, Aro.); MS:  $m/z$ . 610  $m^+$ ; Anal. calcd. (found) %  $\text{C}_{33}\text{H}_{30}\text{N}_4\text{O}_8$ : C, 64.91 (64.79); H, 4.95 (4.86); N, 9.17 (9.04).

9-(4-chlorophenyl)-10-[2-(1-triazolo-4,5-dicarboxymethyl)acetyloxyphenyl]-3,4,6,7,9,10-hexahydro-1,8-(2H,5H)-acridinedione 4d: yield 76%, M.P. 210-12°C, IR (KBr,  $\text{cm}^{-1}$ ): 1725, 1635, 1600, 1585, 1590;  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ -DMSO- $d_6$ ):  $\delta$  1.80-2.05 (m, 8H,  $=\text{C-CH}_2\text{-CH}_2-$ ), 2.20-2.40 (m, 4H,  $-\text{CO-CH}_2-$ ), 3.95 (s, 6H,  $-\text{COOCH}_3$ ), 4.06 (s, 1H,  $=\text{C-CH-C=}$ ), 5.65 (2H,  $-\text{CO-CH}_2\text{-triazole}$ ), 6.8-7.1 (m, 8H, Aro.); MS:  $m/z$ . 644  $m^+$ ,  $m+2$  646; Anal. calcd. (found) %  $\text{C}_{33}\text{H}_{29}\text{N}_4\text{O}_8\text{Cl}$ : C, 61.44 (61.21); H, 4.53 (4.42); N, 8.68 (8.54).

9-(2-chlorophenyl)-10-[2-(1-triazolo-4,5-dicarboxymethyl)acetyloxyphenyl]-3,4,6,7,9,10-hexahydro-1,8-(2H,5H)-acridinedione 4e: yield 76%, M.P. 206-8°C, IR (KBr,  $\text{cm}^{-1}$ ): 1725, 1645, 1610, 1595;  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ -DMSO- $d_6$ ):  $\delta$  1.80-2.05 (m, 8H,  $=\text{C-CH}_2\text{-CH}_2-$ ), 2.20-2.40 (m, 4H,  $-\text{CO-CH}_2-$ ), 3.95 (s, 6H,  $-\text{COOCH}_3$ ), 4.06 (s, 1H,  $=\text{C-CH-C=}$ ), 5.65 (2H,  $-\text{CO-CH}_2\text{-triazole}$ ), 6.8-7.10 (m, 8H, Aro.); MS:  $m/z$ . 644  $m^+$ ,  $m+4$  646; Anal. calcd. (found) %  $\text{C}_{33}\text{H}_{29}\text{N}_4\text{O}_8\text{Cl}$ : C, 61.44 (61.32); H, 4.53 (4.46); N, 8.68 (8.64).

9-(4-fluorophenyl)-10-[2-(1-triazolo-4,5-dicarboxymethyl)acetyloxyphenyl]-3,4,6,7,9,10-hexahydro-1,8-(2H,5H)-acridinedione 4f: yield 74%, M.P. 204-06°C, IR (KBr,  $\text{cm}^{-1}$ ): 1725, 1640, 1610, 1595;  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ -DMSO- $d_6$ ):  $\delta$  1.85-2.10 (m, 8H,  $=\text{C-CH}_2\text{-CH}_2-$ ), 2.20-2.40 (m, 4H,  $-\text{CO-CH}_2-$ ), 3.95 (s, 6H,  $-\text{COOCH}_3$ ), 4.06 (s, 1H,  $=\text{C-CH-C=}$ ), 5.60 (2H,  $-\text{CO-CH}_2\text{-triazole}$ ), 6.80-7.10 (m, 8H, Aro.); MS:  $m/z$ . 628  $m^+$ ; Anal. calcd. (found) %  $\text{C}_{33}\text{H}_{29}\text{N}_4\text{O}_8\text{F}$ : C, 63.05 (63.91); H, 4.64 (4.76); N, 8.91 (8.79).

9-(2-fluorophenyl)-10-[2-(1-triazolo-4,5-dicarboxymethyl)acetyloxyphenyl]-3,4,6,7,9,10-hexahydro-1,8-(2H,5H)-acridinedione 4g: yield 72%, M.P. 202-4°C, IR (KBr,  $\text{cm}^{-1}$ ): 1725, 1645, 1615, 1605, 1585;  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ -DMSO- $d_6$ ):  $\delta$  1.85-2.05 (m, 8H,  $=\text{C-CH}_2\text{-CH}_2-$ ), 2.20-2.40 (m, 4H,  $-\text{CO-CH}_2-$ ), 3.95 (s, 6H,  $-\text{COOCH}_3$ ), 4.06 (s, 1H,  $=\text{C-CH-C=}$ ), 5.60 (s, 2H,  $-\text{CO-CH}_2\text{-triazole}$ ), 6.80-7.10 (m, 8H, Aro.); MS:  $m/z$ . 628  $m^+$ ; Anal. calcd. (found) %  $\text{C}_{33}\text{H}_{29}\text{N}_4\text{O}_8\text{F}$ : C, 63.05 (62.95); H, 4.64 (4.76); N, 8.91 (8.84).

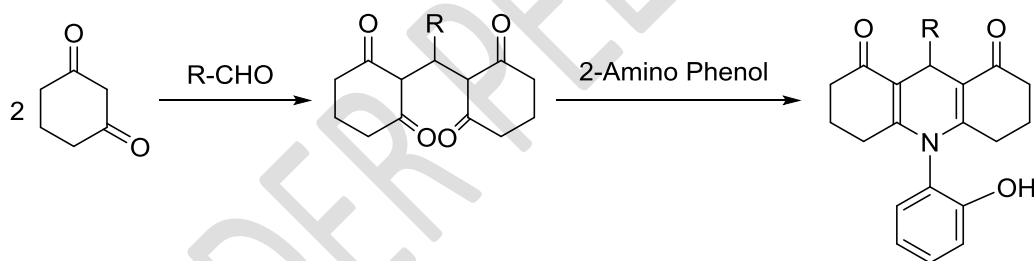
9-(4-methoxyphenyl)-10-[2-(1-triazolo-2,3-dicarboxymethyl)acetyloxyphenyl]-3,4,6,7,9,10-hexahydro-1,8-(2H, 5H) acridinedione 4h: yield 82%, M.P. 214-16°C, IR (KBr,  $\text{cm}^{-1}$ ): 1720, 1645, 1615, 1600, 1585;  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ - $\text{DMSO-d}_6$ ):  $\delta$  1.80 -2.05 (m, 8H,  $=\text{C-CH}_2\text{-CH}_2-$ ), 2.20-2.40 (m, 4H,  $-\text{CO-CH}_2-$ ), 3.70 (s, 3H,  $\text{OCH}_3$ ), 3.95 (s, 6H,  $-\text{COOCH}_3$ ), 4.05 (s, 1H,  $=\text{C-CH-C=}$ ), 5.65 (s, 2H,  $-\text{CO-CH}_2\text{-triazole}$ ), 6.80 -7.15 (m, 8H, Aro.); MS:  $m/z$ . 640 $m^+$ ; Anal.calcd.(found) %  $\text{C}_{34}\text{H}_{32}\text{N}_4\text{O}_9$ : C, 63.74 (63.61); H, 5.03 (4.94); N, 8.74 (8.64).

9-(2-methoxyphenyl)-10-[2-(1-triazolo-2,3-dicarboxymethyl)acetyloxyphenyl]-3,4,6,7,9,10-hexahydro-1,8-(2H, 5H) acridinedione 4i: yield 84%, M.P. 212-14°C, IR (KBr,  $\text{cm}^{-1}$ ): 1720, 1645, 1615, 1600, 1585;  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ - $\text{DMSO-d}_6$ ):  $\delta$  1.80 -2.05 (m, 8H,  $=\text{C-CH}_2\text{-CH}_2-$ ), 2.20-2.40 (m, 4H,  $-\text{CO-CH}_2-$ ), 3.70 (s, 3H,  $\text{OCH}_3$ ), 3.95 (s, 6H,  $-\text{COOCH}_3$ ), 4.05 (s, 1H,  $=\text{C-CH-C=}$ ), 5.60 (s, 2H,  $-\text{CO-CH}_2\text{-triazole}$ ), 6.75 -7.2 (m, 8H, Aro.); MS:  $m/z$ . 640 $m^+$ ; Anal.calcd.(found) %  $\text{C}_{34}\text{H}_{32}\text{N}_4\text{O}_9$ : C, 63.74 (63.60); H, 5.03 (4.92); N, 8.74 (8.62).

## ANTIMICROBIAL ACTIVITY

The synthesized compounds in the present study have been investigated for antimicrobial activity by well diffusion method. The microorganisms selected for antibacterial activity were *Bacillus subtilis* (MTCC-441), *Staphylococcus aureus* (ATCC-3750), *Escherichia coli* (MTCC-443) and for antifungal activity were *Aspergillus niger* (MTCC-282) and *Candida albicans* (MTCC-227). 100  $\mu\text{g/ml}$  and 150  $\mu\text{g/ml}$  concentrations were used to test the synthesized compounds. Norfloxacin and Fluconazole were used as standard drugs for antibacterial and antifungal activities respectively. The plates were prepared as per the standard procedures [17-18]. Antimicrobial activity of all the synthesised compounds were evaluated by measuring the zone of inhibition against the test microorganisms.

### Scheme I Chemical transformation



Scheme - II

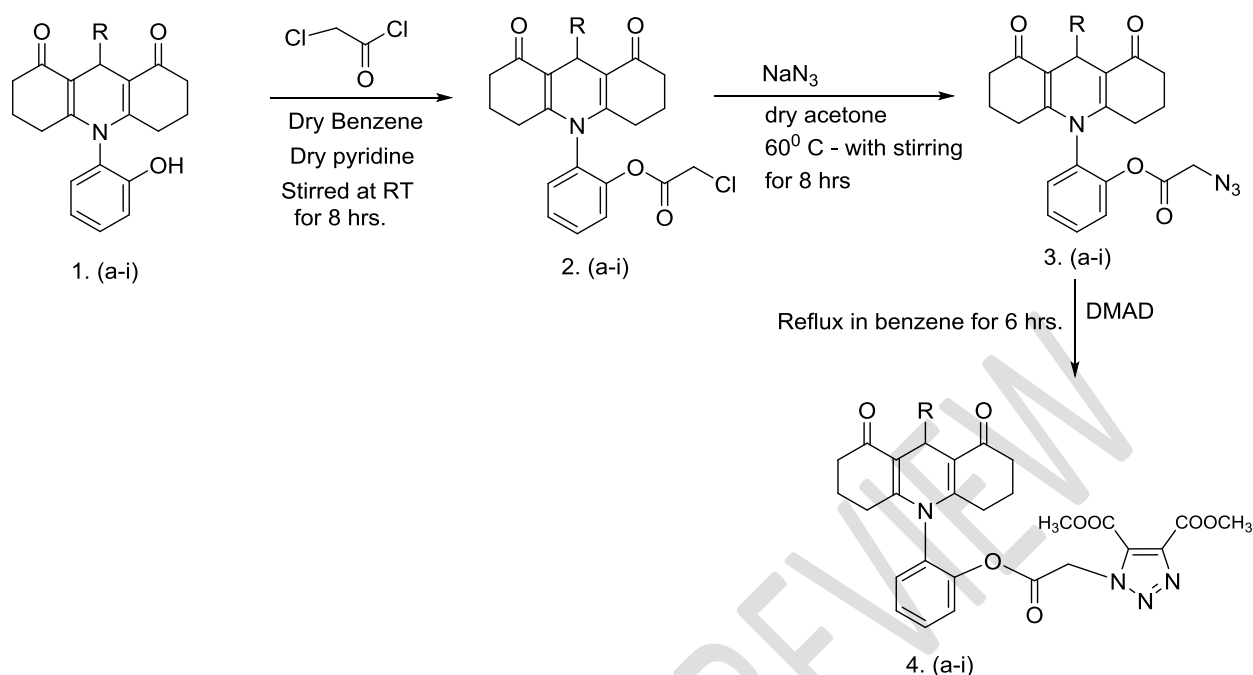


Table1: Chemical formula

Compound	a	b	c	d	e	f	g	h	i
R	H	CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	4-Cl-C <sub>6</sub> H <sub>4</sub>	2-Cl-C <sub>6</sub> H <sub>4</sub>	4-F-C <sub>6</sub> H <sub>4</sub>	2-F-C <sub>6</sub> H <sub>4</sub>	4-OCH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>	2-OCH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>

## RESULTS AND DISCUSSION

The target molecule was synthesized according to the Scheme I and II. The initial compounds were synthesized according to our earlier procedure [13-15]. Cyclohexane-1,3-dione in aqueous methanol treated with different aldehydes gives the tetraketones, which were reacted with o-aminophenol yielded the starting compounds (**1a-i**). The acridinediones **1a-i**, on treatment with chloroacetyl chloride in dry benzene at room temperature yielded the chloroacetyloxyphenyl compounds (**2a-i**). The chloroacetyloxyphenyl compounds on reaction with sodiumazide in dry acetone and dry benzene at room temperature yielded the azidoacetyloxyphenyl compounds (**3a-i**). The azidoacetyloxyphenyl compounds were refluxed with dimethylacetylenedicarboxylate in benzene yielded the target molecules triazoloacetyloxyphenyl compounds (**4a-i**). The structures of all the synthesized compounds were confirmed by IR, <sup>1</sup>H-NMR and Mass spectral data and elemental analysis. The IR spectrum of the compound **2a** showed a characteristic peak at 1710 cm<sup>-1</sup> for carbonyl group in Ph-O-CO-CH<sub>2</sub>-Cl, 1640cm<sup>-1</sup> for ring carbonyl group, at 1600 cm<sup>-1</sup> for C=C in the ring and at 1590 cm<sup>-1</sup> for aromatic double bonds. The <sup>1</sup>H-NMR spectrum showed a multiplet at δ 1.80 - 2.10 for =C-CH<sub>2</sub>-CH<sub>2</sub>-, multiplet at δ 2.20 for -CO-CH<sub>2</sub>-, doublet of doublet (J = 21 Hz) at δ 3.10. The splitting of the ninth position methylene protons is due to the diastereotopic nature because of the bulky substituent on the acridine nitrogen atom. A singlet at δ 4.10 confirms the presence -CO-CH<sub>2</sub>-Cl and a multiplet at δ 6.90-7.15 indicates the presence of aromatic protons. The presences of chlorine in the compounds were confirmed by the presence of isotopic peak m+2 in the mass spectrum. In the compound **2b** the presence of methyl group at ninth position of the acridinedione is confirmed by a doublet at δ 1.05 and

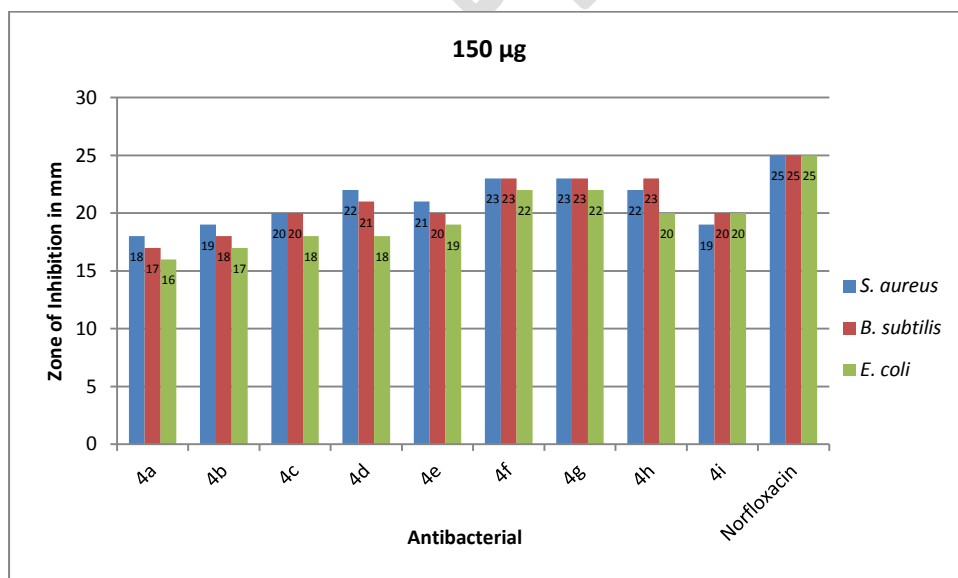
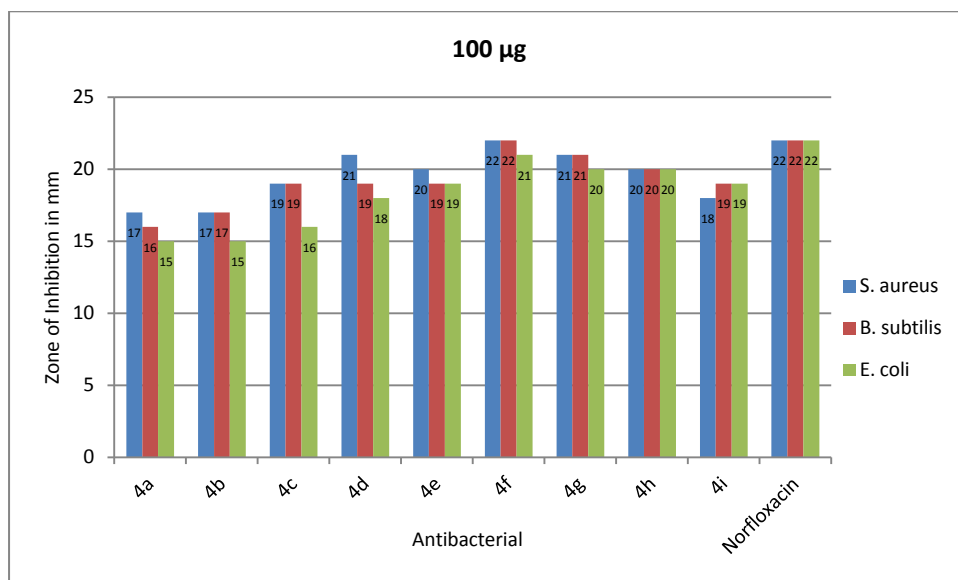
quartet at  $\delta$  4.20 for  $=C-CH-C=$  and by mass spectral data. The phenyl group in the compound **2c** was established by the presence of singlet accounted one proton at  $\delta$  4.30 for  $=C-CH-C=$  and multiplet at  $\delta$  6.80-7.20 for nine aromatic protons. Presence of isotopic peaks  $m+2$ ,  $m+4$  peaks in the mass spectrum confirms two chlorine atoms in **2c** and **2d**. The multiplet accounted for nine protons at  $\delta$  6.90-7.30 for compound **2d** indicates the presence of two aromatic rings at the nine and tenth positions. In **2f** a multiplet at  $\delta$  6.90 – 7.30 accounted for eight protons and molecular mass obtained from mass spectral data indicates the presence of fluorine. In compound **2h** the presence of singlet at  $\delta$  3.70 confirms the presence of  $-OCH_3$  group and a multiplet at  $\delta$  6.80-7.20 for eight protons indicates the presence of two substituted aromatic rings. The characteristic peak at  $2105\text{ cm}^{-1}$  in the IR spectrum of compound **3a** indicates the presence of azide group and for carbonyl group at  $1710\text{ cm}^{-1}$  in  $-O-CO-N_3$ ,  $1645\text{ cm}^{-1}$  for ring carbonyl group and  $1600\text{ cm}^{-1}$  for  $C=C$  in the ring and  $1595\text{ cm}^{-1}$  for double bonds in aromatic ring. The proton NMR shows a multiplet at  $\delta$  1.80 – 2.10 for  $=C-CH_2-CH_2-$ , multiplet at  $\delta$  2.20 for  $-CO-CH_2-$ , a doublet of doublet at  $\delta$  3.10 (gem coupling,  $J_{\text{gem}} = 21\text{ Hz}$ ) for diastereotopic protons in  $=C-CH_2-C=$ , a singlet at  $\delta$  4.06 for  $-CO-CH_2-N_3$  and a multiplet at  $\delta$  6.90 – 7.15 for aromatic protons. The presence of methyl group in the compound **3b** was confirmed by the presence of doublet at  $\delta$  1.05 and quartet at  $\delta$  4.20 for  $=C-CH=C=$ . The presence of phenyl group in the azido compound **3c** was established by the presence of singlet at  $\delta$  4.30 for  $=C-CH-C=$  and a multiplet accounted for nine protons at  $\delta$  6.80-7.20 for two aromatic rings. The presence of chlorine in compound **3d** was confirmed by the presence of  $m+2$  isotopic peak in the mass spectrum in addition to the IR and proton NMR data. In the fluorophenyl azido compound **3f**, the presence of two aromatic rings was established by the multiplet at  $\delta$  6.90 – 7.20 for eight aromatic protons. The  $-OCH_3$  group in the methoxyphenylazido compound **3h** was confirmed by the presence of singlet at  $\delta$  3.70 and a multiplet at  $\delta$  6.80 – 7.20 for eight aromatic protons.

The presence of carboxymethyl group in the triazolodicarboxymethyl acetyloxyphenyl compound **4a** was confirmed by a strong peak at  $1715\text{ cm}^{-1}$ , the ring carbonyl group absorption is at  $1645\text{ cm}^{-1}$ ,  $C=C$  absorption in the ring takes place at  $1600\text{ cm}^{-1}$  and aromatic  $C=C$  at  $1595\text{ cm}^{-1}$ . The proton NMR has a multiplet at  $\delta$  1.8-2.10 for  $=C-CH_2-CH_2-$ , singlet at  $\delta$  2.20 for  $-CO-CH_2-$ , doublet of doublet due to diastereotopic nature occur at  $\delta$  3.10 (gem coupling,  $J_{\text{gem}} = 21\text{ Hz}$ ) for  $=C-CH_2-C=$ , a singlet at  $\delta$  3.95 equivalent to six protons for two  $-COOCH_3$ , and a singlet at  $\delta$  5.60 for  $-CO-CH_2$ -triazole ring and a multiplet at  $\delta$  7.20-7.40 for aromatic protons. In compound **3b**, the methyl group in the ninth position of the acridinedione ring was established by the presence of doublet at  $\delta$  1.05 and quartet at  $\delta$  4.02 for  $=C-CH-C=$ . In the compound **3c**, a singlet at  $\delta$  4.06 for  $=C-CH-C=$  and a multiplet at  $\delta$  6.75-7.20 equivalent to nine protons confirms the presence of one aromatic ring at ninth position and other at tenth position in the acridinedione skeleton. In addition to other spectral data, the isotopic peak  $m+2$  in the mass spectrum confirms the presence of chlorine in compound **4d** and **4e**. In the compound **4f** ester carbonyl absorbs at  $1725\text{ cm}^{-1}$ , carbonyl group present in  $-OCO-CH_2$ -azide ring absorbs at  $1640\text{ cm}^{-1}$ , ring carbonyl absorbs at  $1620\text{ cm}^{-1}$  and  $C=C$  in the ring absorbs at  $1610\text{ cm}^{-1}$ . The presence of fluorine in compound **4f** and **4g** was confirmed by a multiplet at  $\delta$  6.80-7.10 accounted for eight aromatic protons and molecular mass from the mass spectrum. The  $-OCH_3$  group in **4h** and **4i** were confirmed by the presence of singlet at  $\delta$  3.70 and singlet at  $\delta$  3.95 for six protons confirms two carboxymethyl groups.

The synthesized compounds were screened for antibacterial activity against *B. subtilis*, *S. aureus*, *E. coli* and antifungal activity against *A. niger*, *C. albicans*. The compounds **4d**, **4e**, **4f** and **4g** have shown the highest antimicrobial activity when compared with standard drugs Norfloxacin and Fluconazole and the remaining compounds **4a**, **4b**, **4c**, **4h**, **4i** exhibited

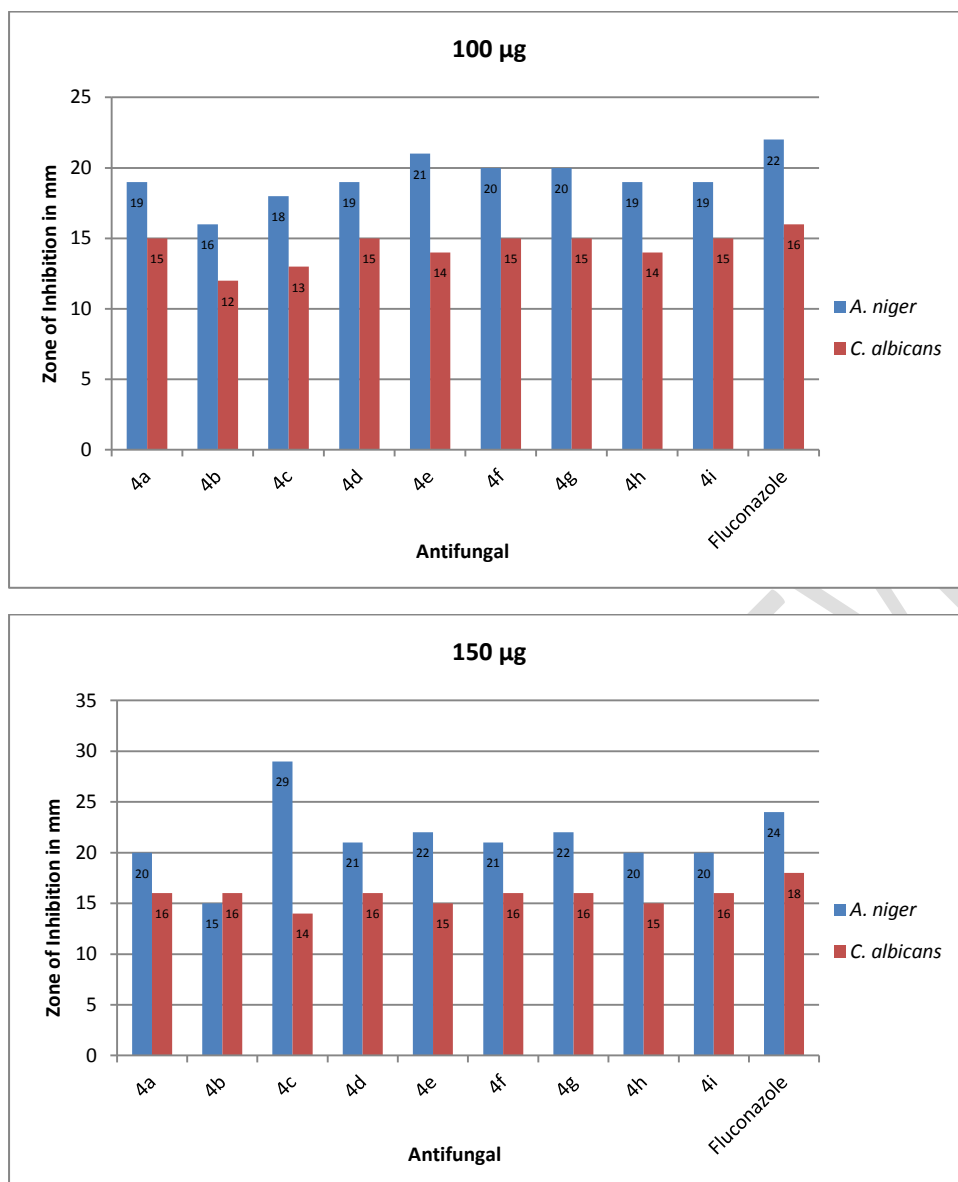
moderate activity. The molecular framework has shown broad spectrum of antimicrobial activity which is substantiated by the presence of heterocyclic rings, carbonyl groups and in addition electronegative atoms containing compounds (**4 d-g**) in the molecular framework exhibited higher antimicrobial activity among the synthesized compounds. The antimicrobial activities are presented in the following diagrams.

**Fig 1: Antibacterial Activity**



**Fig 2: Antibacterial assay**

**Fig 3: Antifungal Activity**



**Fig 4: Antifungal Assay**

## CONCLUSIONS

The purpose of this research is to report a facile route for the synthesis of triazole linked hexahydroacridinediones that is 10-acetyloxyphenyl 1, 2, 3-triazoloacridinedione derivatives, which has broad spectrum of antimicrobial activity. The compounds having electronegative atoms in the molecular framework have exhibited potent antimicrobial activity compared with other compounds.

## CONSENT

It is not applicable.

## ETHICAL APPROVAL

It is not applicable.

## REFERENCES

1. YL.Chen, CM.Lu, IL.Chen, LT. Tsao, JP.Wang, *J. Med. Chem.*, 2002;45 (21); 4689-4694. <https://DOI: 10.1021/jm020102v> PMID: 12361395
2. SA.Gamage, JA.Spicer, GJ.Atwell, GJ.Finlay, BC.Baguley, WA.Denny, *J. Med. Chem.*, 1999, 42(13), 2383-2393. <https://doi.org/10.1021/jm980687m>
3. M. Kaya , Y. Yildirim, GY.Çelik , *Med. Chem. Res.*, 2011, 20(3), 293-299. <https://doi.org/10.1007/s00044-010-9321-6>
4. EI.Aly, AH.Abadi, *Arch. Pharm. Res.*, 2004, 27(7), 713-719. <https://doi.org/10.1007/BF02980137>
5. Di Giorgio Carole, De Meo Michel, Chiron Julie, Delmas Florence, Nikoyan Anna, Jean Severine, Du menil Ferard, Timon David Pierre, Galy Jean-Pierre, *Bioorg. & Med. Chem.*, 2005, 13( 19), 5560-5568. <https://doi.org/10.1016/j.bmc.2005.06.045>
6. A. Kumar , K. Srivastava , SR. Kumar , SK. Puri , PM. Chauhan , *Bioorg. & Med. Chem. Let.*, 2009, 19(24), 6996-6999.<https://doi.org/10.1016/j.bmcl.2009.10.010>
7. HC. Gupta , V. Jaiswal, *Indian J. Heterocycl. Chem.*, 2010,19(4), 409-10.
8. A. Almasirad , SA. Tabatabai, M. Faizi , A. Kebriaeezadeh , N. Mehrabi , A. Dalvandi , A. Shafiee , *Bioorg. & Med. Chem. Let.*, 2004, 14( 24), 6057-6059. <https://doi.org/10.1016/j.bmcl.2004.09.072>
9. M. Wainwright , DA. Phoenix , J. Marland , DR. Wareing , FJ. Bolton , *J. Antimicrobial Chemotherapy*, 1997, 40( 4), 587-589. <https://doi.org/10.1093/jac/40.4.587>
10. S. Sathish Kumar , P Kavitha , *Rev. in Org. Chem.*, 2013, 10(1), 40-65. <http://dx.doi.org/10.2174/1570193X11310010004>
11. Fatih Cleik, Yasemin Unver, Burak Barut, Arzu Ozal, Kemal Sancak, *Med. Chem.*, 2018,14( 3), 230-241, .<https://doi.org/10.2174/1573406413666171120165226>
12. K. Lemke, V. Poindessous, A. Skladanowski and Annette K. Larsen , *Molecular Pharmacology* , 2004, 66 ( 4) 1035-1042. DOI: <https://doi.org/10.1124/mol.104.000703>
13. P.Shanmugasundaram , P.Murugan , VT.Ramakrishnan , N. Srividya , P. Ramamurthy, *Heteroatom Chem.*, 1996, 7( 1 ), 17-22. [https://doi.org/10.1002/\(SICI\)1098-1071\(199601\)7:1%3C17::AID-C3%3E3.0.CO;2-%23](https://doi.org/10.1002/(SICI)1098-1071(199601)7:1%3C17::AID-C3%3E3.0.CO;2-%23)
14. P. Shanmugasundaram , KJ. Prabahar , VT. Ramakrishnan , *J. Heterocycl. Chem.*, 1993, 30(4), 1003-1007. <https://doi.org/10.1002/jhet.5570300428>

15. P. Murugan , P. Shanmugasundaram , VT. Ramakrishnan , B. Venkatachalapathy , N. Srividya , P. Ramamurthy , K. Gunasekaran , D. Velmurugan , *J. Chem. Soc., P. Trans.*, 1998, 2( 4), 999-1004. <https://doi.org/10.1039/A701401E>
16. N. Srividya , P.Ramamurthy , P.Shanmugasundaram , VT.Ramakrishnan , *J. Org. Chem.*, 1996, 61(15), 5083-5089. <https://doi.org/10.1021/jo9600316>
17. V.Jatav, SK.Jain , SK. Kashaw, P. Mishra, *Indian J. Pharm. Sci.*, 2006,68( 3 ), 360-363. <https://doi.org/10.4103/0250-474X.26679>
18. A. Alagarsamy , R. Giridhar , MR. Yadav , R. Revathi , K. Ruckmani , E. De Clercq, *Indian J. Pharm. Sci.*, 2006, 68(4), 532-535. <https://doi.org/10.4103/0250-474X.27840>