RASĀYAN *J. Chem.*
Vol. 15 | No. 2 |946-953| April - June | 2022
ISSN: 0974-1496 | e-ISSN: 0976-0083 | CODEN: RJCABP
http://www.rasayanjournal.com
http://www.rasayanjournal.co.in

SYNTHESIS, CHARACTERISATION AND ANTIMICROBIAL EVALUATIONS OF ACETYLOXYPHENYL-1,2,3-TRIAZOLOTETRAMETHYL HEXAHYDROACRIDINEDIONES

P. Shanmugasundaram[1,✉], R. Sujatha[2], M. Vijey Aanandhi[3], K. Saravanan[1] and P. Subbramaniyan[1]

[1]Deprtment of Chemistry, Thiruvalluvar Government Arts College, Rasipuram, Namakkal-637 401, Tamilnadu, India.

[2]Department of Nutrition and Dietetics, N.K.R Government Arts College for Women, Namakkal-637 001, Tamilnadu, India.

[3]Department of Pharmaceutical Chemistry and Analysis, School of Pharmaceutical Sciences, Vel's Institute Science, Technology and Advanced Studies (VISTAS), Pallavaram, Chennai-600 117, Tamilnadu, India.

✉Corresponding Author: pshansunder@gmail.com

ABSTRACT

Tetramethyl-10-(2-hydroxyphenyl)-hexahydro acridinediones were treated with chloroacetyl chloride to give 10-(2-chloroacetyloxyphenyl)hexahydro acridinediones, which were treated with NaN_3 in acetone followed by reaction with DMAD yielded tetramethyl-10-[2-(1-triazolo-4,5-dicarboxymethyl)acetyloxyphenyl]-3,4,6,7,9,10-hexahydro-1,8-(2H,5H)-acridinediones. All the derivatives were screened for antimicrobial activity.

Keywords: Antimicrobial, Acridinediones, Acetyloxyphenyl, Triazoles, Triazolo-tetramethyl acridine dione.

RASĀYAN *J. Chem.*, Vol. 15, No.2, 2022

INTRODUCTION

Acridine-based compounds form an important class of heterocycles containing nitrogen due to their broad range of pharmaceutical properties. Acridine derivatives are characterized by unique physical and chemical properties, biological activities and industrial applications. Notably, the anticancer activity of acridine/acridone compounds has attracted increasing interest. To date, many compounds of acridine have been synthesized and tested for antitumor activity. Acridine derivatives have exhibited biological activities such as anti-inflammatory[1], anticancer[2], antimicrobial[3], antitubercular[4], antiparasitic[5], antimalarial[6], antiviral[7] and antifungicidal[8] and antibacterial activities.[9] Among nitrogen-containing heterocyclic compounds 1,2,3-triazoles are privileged structure motifs 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 a broad spectrum of biological activities.[10-14] A verity of acridine/acridone compounds have been synthesized; analogues such as triazoloacridone have entered clinical studies.[15] The synthesis, laser activity[16-18] and photophysical properties[19]of hexahydroacridinedione compounds were reported earlier by us and therefore, the development of a facile and straightforward methodology for the synthesis of 1,2,3-triazole linked hexahydroacridinedione derivatives and antimicrobial activity is of noteworthy.

EXPERIMENTAL

The melting points were determined in an open capillary tube and were uncorrected. IR spectra were recorded using the KBr pellets method in Perkin-Elmer 258 instruments. ^{1}H-NMR was taken in Jeol GSX 400 (400 MHz) instrument using TMS as internal standard and $CDCl_3$, DMSO-d_6 as solvents.The mass spectrum was taken using Hewlett-Packard 5985 (70 ev) and Shidmadzu QP 1000A instrument. The elemental analysis was carried out on Perkin-Elmer 2400 CHN analyzer. Thin-layer chromatography

http://dx.doi.org/10.31788/RJC.2022.1526718

(TLC) was performed using glass plates coated with silica gel (ACME) of 2.5 mm thickness. Spots were visualized using iodine vapor. Anhydrous magnesium sulphate was used as the drying agent. The compounds tetramethyl-10-(2-hydroxyphenyl) and 9-substituted-tetramethyl-10-(2-hydroxyphenyl) acridinediones were synthesized according to our earlier procedure[16-18] by treating dimedone with different aldehydes to get tetraketones which reacted with o-aminophenol gave the tetramethyl-10-(2-hydroxyphenyl) and 9-substituted-10-(2-hydroxyphenyl) acridinedione derivatives.The synthesis of the title compounds 4 a-i is shown in Scheme-1.

Synthesis of tetramethyl-10-(2-chloroacetyloxyphenyl)-3,4,6,7,9,10-hexahydro-1,8-(2H,5H) acridinediones and 9-substituted tetramethyl-10-(2-chloroacetyloxyphenyl)-3,4,6,7,9,10-hexahydro-1,8-(2H,5H) acridinediones, (2a–i)

An ice-cold solution of tetramethylacridinediones (1) (10 mmol) in dry benzene (25 ml) and dry pyridine (1 ml) was added to chloroacetylcholoride (12 mmol) in benzene (10 ml) and stirred for 12 hours at room temperature. Poured in to water and the solid obtained was filtered. The benzene layer was washed with dilute HCl and $NaHCO_3$ solution and water, dried over anhydrous magnesium sulphate and concentrated to obtain the additional amount of the product. The solid obtained was recrystallized from methanol.

Tetramethyl-10-(2-chloroacetyloxyphenyl)-3,4,6,7,9,10-hexahydro-1,8-(2H,5H)acridinedione, 2a Yield 76%, M.P. 214-16ºC, IR (KBr): υ 1705, 1645, 1600, 1590 cm^{-1}; ^{1}H-NMR ($CDCl_3$-DMSO-d_6, ppm): δ0.85 (12H, gem dimethyl), 1.75 (s,4H, =C-CH_2-), 2.4 (s,4H, -CO-CH_2-), 3.10 (dd , gem coupling , Jgem= 21 Hz, 2H, =C-CH_2-C=), 4.90 (s, 2H, -CO-CH_2-Cl), 6.90–7.15 (m, 4H, Aro.); MS: m/z. 441 m^+, 443 m^{+2}; Anal.calcd.(found) % $C_{25}H_{28}NO_4Cl$: C, 67.94 (67.82); H, 6.38 (6.24); N, 3.16 (3.02).

Pentamethyl-10-(2-chloroacetyloxyphenyl)-3,4,6,7,9,10-hexahydro-1,8-(2H,5H)acridinedione,2b
Yield 76%, M.P. 224-26ºC, IR (KBr): 1710, 1635, 1595, 1590 cm^{-1}; ^{1}H-NMR($CDCl_3$-DMSO-d_6, ppm): δ 0.86 (12H, gem dimethyl), 1.50 (d,3H, -CH_3), 1.75 (s,4H, =C-CH_2-), 2.4 (s,4H, -CO-CH_2-), 4.0(q, 1H, =C-CH-C=), 4.80 (s, 2H, -CO-CH_2-Cl), 6.90–7.15 (m, 4H, Aro.); MS: m/z. 455 m^+, m^{+2} 457; Anal.calcd.(found) % $C_{26}H_{30}NO_4Cl$: C, 68.48 (68.31); H, 6.63 (6.52); N, 3.07 (2.94).

9-phenyl-tetramethyl-10-(2-chloroacetyloxyphenyl)-3,4,6,7,9,10-hexahydro-1,8-(2H,5H)acridinedione, 2c
Yield 82%, M.P.232-34ºC, IR (KBr): υ 1695, 1635, 1590, 1585 cm^{-1}; ^{1}H-NMR ($CDCl_3$-DMSO-d_6, ppm): δ 0.85 (12H, gem dimethyl), 1.80 (s,4H, =C-CH_2-), 2.5 (s,4H, -CO-CH_2-),4.10 (s, 1H, =C-CH-C=), 4.90 (s,2H, -CO-CH_2-Cl), 6.80-7.20 (m,9H, Aro.); MS: 517 m^+, m^{+2} 517; Anal.calcd.(found) % $C_{31}H_{32}NO_4Cl$: C, 71.87 (71.70); H, 6.22 (6.34); N, 2.70 (2.55).

9-(4-chlorophenyl)-tetramethyl-10-(2-chloroacetyloxyphenyl)-3,4,6,7,9,10-hexahydro-1,8-(2H,5H) acridinedione, 2d
Yield 84%, M.P. 234-36ºC, IR (KBr): υ 1695, 1640, 1595, 1590 cm^{-1}; ^{1}H-NMR ($CDCl_3$-DMSO-d_6, ppm): δ 0.90 (12H, gem dimethyl), 1.80 (s,4H, =C-CH_2 -), 2.50 (s,4H, -CO-CH_2-), 4.40 (s, 1H, =C-CH-C=), 4.80 (s, 2H, -CO-CH_2-Cl), 6.80–7.20 (m, 8H, Aro.); MS: m/z. 551 m^+, m^{+2} 553, m^{+4} 555; Anal.calcd.(found) % $C_{31}H_{31}NO_4Cl_2$: C, 67.37 (67.22); H, 5.65 (5.50); N, 2.53 (2.44).

9-(2-chlorophenyl)–tetramethyl-10-(2-chloroacetyloxyphenyl)-3,4,6,7,9,10-hexahydro-1,8-(2H,5H) acridinedione, 2e
Yield 76%, M.P. 232-34ºC, IR (KBr): υ 1705, 1645, 1595, 1590, 1585 cm^{-1}; ^{1}H-NMR ($CDCl_3$-DMSO-d_6, ppm): δ0.95 (12H, gem dimethyl), 1.78 (s,4H, =C-CH_2 -), 2.50 (s,4H, -CO-CH_2-), 4.10 (s,1H, =C-CH-C=), 4.90 (s, 2H, -CO-CH_2-Cl), 6.80-7.15(m,8H, Aro.); MS: m/z. 551m^+, m^{+2}553, m^{+4}555; Anal.calcd.(found) % $C_{31}H_{31}NO_4Cl_2$: C, 67.37 (67.23); H, 5.65 (5.72); N, 2.53 (2.41).

9-(4-fluorophenyl)-tetramethyl-10-(2-chloroacetyloxyphenyl)-3,4,6,7,9,10-hexahydro-1,8-(2H,5H) acridinedione, 2f
Yield 80%, M.P. 224-26ºC, IR (KBr): υ 1700, 1645, 1595, 1585 cm^{-1}; ^{1}H-NMR ($CDCl_3$-DMSO-d_6, ppm): δ 0.95 (12H, gem dimethyl), 1.80 (s,4H, =C-CH_2 -), 2.45 (s,4H, -CO-CH_2-), 4.10 (s, 1H, =C-CH-C=),

4.95 (s, 2H, -CO-CH_2-Cl), 6.89–7.40 (m, 8H, Aro.); MS: m/z. 535 m^+, m^{+2} 537;Anal.calcd.(found) % $C_{31}H_{31}NO_4ClF$: C, 69.46 (69.31); H, 5.82 (5.74); N, 2.61 (2.52).

9-(2-fluorophenyl)–tetramethyl-10-(2-chloroacetyloxyphenyl)-3,4,6,7,9,10-hexahydro-1,8-(2H,5H) acridinedione, 2g

Yield 72%, M.P. 218-20ºC, IR (KBr): υ 1705, 1645, 1595, 1585cm^{-1};^{1}H-NMR ($CDCl_3$-DMSO-d_6, ppm): δ 0.95 (12H, gem dimethyl), 1.85 (s,4H, =C-CH_2-), 2.45 (s,4H, -CO-CH_2-), 4.15 (s,1H, =C-CH-C=), 4.90 (s, 2H, -CO-CH_2-Cl), 6.90 -7.20(m,8H, Aro.); MS: m/z. 535m^+, m^{+2} 537; Anal.calcd.(found) % $C_{31}H_{31}NO_4ClF$: C, 69.46 (69.32); H, 5.82 (5.94); N, 2.61 (2.56).

9-(4-methoxyphenyl)-tetramethyl-10-(2-chloroacetyloxyphenyl)-3,4,6,7,9,10-hexahydro-1,8-(2H,5H) acridinedione, 2h

Yield 82%, M.P. 242-44ºC, IR (KBr): υ 1695, 1635, 1595, 1585 cm^{-1}; ^{1}H-NMR ($CDCl_3$-DMSO-d_6, ppm): δ 0.95(12H, gem dimethyl), 1.75 (s,4H, =C-CH_2-), 2.40 (s,4H, -CO-CH_2-), 3.70 (s, 3H, -OCH_3), 4.10 (s, 1H, =C-CH-C=), 4.95 (s, 2H, -CO-CH_2-Cl), 6.80 -7.20 (m, 8H, Aro.); MS: m/z. 547m^+, 549 m^{+2} ; Anal.calcd.(found) % $C_{32}H_{34}NO_5Cl$: C, 70.12 (70.02); H, 6.25 (6.12); N, 2.55 (2.42).

9-(2-methoxyphenyl)-tetramethyl-10-(2-chloroacetyloxyphenyl)-3,4,6,7,9,10-hexahydro-1,8-(2H,5H) acridinedione, 2i

yield 84%, M.P. 246-48ºC, IR (KBr): υ 1690, 1635, 1600, 1595cm^{-1}; ^{1}H-NMR ($CDCl_3$-DMSO-d_6, ppm): δ 0.95(12H, gem dimethyl), 1.75 (s,4H, =C-CH_2-), 2.40 (s,4H, -CO-CH_2-), 3.70 (s, 3H, -OCH_3), 4.10 (s, 1H, =C-CH-C=), 4.90 (s, 2H, -CO-CH_2-Cl),6.80-7.20 (m, 8H, Aro.); MS: m/z. 547m^+, 549 m^{+2} ;Anal.calcd.(found) % $C_{32}H_{34}NO_5Cl$: C, 70.12 (69.92); H, 6.25 (6.32); N, 2.55 (2.42).

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

To a mixture of tetramethyl-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 60ºC with stirring for 8 hours. Acetone was distilled off and 100 ml of water was added. The separated azido compound was filtered, dried, and recrystallized from methanol.

Tetramethyl-10-(2-azidoacetyloxyphenyl)-3,4,6,7,9,10-hexahydro-1,8-(2H,5H) acridinedione, 3a

Yield 76%, M.P.216-218ºC (decomp.), IR (KBr): υ 2105, 1705, 1645, 1600,1595, 1585 cm^{-1}; ^{1}H-NMR ($CDCl_3$-DMSO-d_6, ppm): δ 0.95 (12H, gem dimethyl, =C-CH_2-C=), 1.80 (s,4H, =C-CH_2-), 2.45 (s,4H, -CO-CH_2-), 3.10 (dd, gem coupling , Jgem= 21 Hz, 2H), 4.95 (s, 2H, -CO-CH_2-N_3), 6.90 – 7.15 (m, 4H, Aro.); MS: m/z. 448 m^+. Anal.calcd.(found) % $C_{25}H_{28}N_4O_4$: C, 66.94 (66.78); H, 6.29 (6.40); N, 12.49 (12.31).

Pentamethyl-10-(2-azidoacetyloxyphenyl)-3,4,6,7,9,10-hexahydro-1,8-(2H,5H)-acridinedione, 3b

Yield 78%, M.P.216-18ºC (decomp.),IR (KBr): υ 2105, 1705, 1645, 1590, 1585 cm^{-1};^{1}H-NMR ($CDCl_3$-DMSO-d_6, ppm): δ1.00(12H, gem dimethyl), 1.50 (d,3H), 1.75 (s,4H, =C-CH_2-), 2.50 (s,4H, -CO-CH_2-), 4.20 (q, 1H, =C-CH-C=), 4.90(s ,2H, -CO-CH_2-N_3), 6.80-7.15(m,4H, Aro.); MS: m/z. 462 m^+. Anal.calcd.(found) % $C_{26}H_{30}N_4O_4$: C, 67.51 (67.38); H, 6.53 (6.39); N, 12.11 (11.92).

9-phenyl-tetramethyl-10-(2-azidoacetyloxyphenyl)3,4,6,7,9,10-hexahydro-1,8-(2H,5H) acridinedione, 3c

Yield 76%, M.P. 214-16ºC (decomp.), IR (KBr): υ 2105,1695, 1630, 1595, 1590 cm^{-1}; ^{1}H-NMR ($CDCl_3$-DMSO-d_6, ppm): δ 1.00 (12H, gem dimethyl), 1.75 (s,4H, =C-CH_2-), 2.45 (s,4H, -CO-CH_2-), 4.30 (s, 1H, =C-CH-C=), 4.95 (s,2H, -CO-CH_2-N_3), 6.80-7.20 (m,9H, Aro.); MS: 524 m^+. Anal.calcd.(found) % $C_{31}H_{32}N_4O_4$: C, 70.97 (70.81); H, 6.14 (6.02); N, 10.67 (10.49).

9-(4-chlorophenyl)-tetramethyl-10-(2-azidoacetyloxyphenyl)-3,4,6,7,9,10-hexahydro-1,8,-(2H,5H) acridinedione, 3d

Yield 84%, M.P.214 -16ºC (decomp.), IR (KBr): υ 2105,1695, 1635, 1595, 1585 cm^{-1}; ^{1}H-NMR ($CDCl_3$-DMSO-d_6, ppm): δ 0.90 (12H, gem dimethyl), 1.75 (s,4H, =C-CH_2-), 2.45 (s,4H, -CO-CH_2-), 4.20 (s, 1H,

=C-CH-C=), 4.95 (s, 2H, -CO-CH_2-N_3), 6.80–7.20 (m, 8H, Aro.); MS: m/z. 558m^+,m^{+2} 560; Anal.calcd.(found) % $C_{31}H_{31}N_4O_4Cl$: C, 66.60 (66.42); H, 5.58 (5.69); N, 10.02 (9.92).

9-(2-chlorophenyl)–tetramethyl-10-(2-azidoacetyloxyphenyl)-3,4,6,7,9,10-hexahydro-1,8-(2H,5H) acridinedione, 3e

Yield 76%, M.P.216-18ºC (decomp.), IR (KBr): υ 2105,1705, 1645, 1595, 1590 cm^{-1} ;^{1}H-NMR ($CDCl_3$-DMSO-d_6, ppm): δ0.95 (12H, gem dimethyl), 1.80 (s,4H, =C-CH_2-), 2.45 (s,4H, -CO-CH_2-), 4.10 (s,1H, =C-CH-C=), 4.85 (s, 2H, -CO-CH_2-N_3), 6.80-7.15(m,8H, Aro.); MS: m/z. 558m^+, m^{+2}560. Anal.calcd.(found) % $C_{31}H_{31}N_4O_4Cl$: C, 66.60 (66.42); H, 5.58 (5.69); N, 10.02 (9.85).

9-(4-flurophenyl)-tetramethyl-10-(2-azidoacetyloxyphenyl)-3,4,6,7,9,10-hexahydro-1,8,-(2H,5H) acridinedione, 3f

Yield 80%, M.P. 210 -12ºC (decomp.), IR (KBr): υ 2105,1690, 1630, 1595, 1590 cm^{-1}; ^{1}H-NMR ($CDCl_3$-DMSO-d_6, ppm): δ 1.0 (12H, gem dimethyl), 1.80 (s,4H, =C-CH_2-), 2.45 (s,4H, -CO-CH_2-), 4.10 (s, 1H), 4.90 (s, 2H, -CO-CH_2-N_3), 6.80–7.20 (m, 8H, Aro.); MS: m/z. 542m^+. Anal.calcd.(found) % $C_{31}H_{31}N_4O_4F$: C, 68.62 (68.44); H, 5.75 (5.90); N, 10.32 (10.18).

9-(2-flurophenyl)–tetramethyl-10-(2-azidoacetyloxyphenyl)-3,4,6,7,9,10-hexahydro-1,8-(2H,5H) acridinedione, 3g

Yield 72%, M.P. 212-14ºC (decomp.), IR (KBr): υ 2105,1700, 1645, 1595, 1585 cm^{-1} ;^{1}H-NMR ($CDCl_3$-DMSO-d_6, ppm): δ0.95 (12H, gem dimethyl), 1.80 (s,4H, =C-CH_2-), 2.50 (s,4H, -CO-CH_2-), 4.10 (s,1H, =C-CH-C=), 4.85 (s, 2H, -CO-CH_2-N_3), 6.80-7.15(m,8H, Aro.); MS: m/z. 542m^+. Anal.calcd.(found) % $C_{31}H_{31}N_4O_4F$: C, 68.62 (68.43); H, 5.75 (5.91); N, 10.32 (10.17).

9-(4-methoxyphenyl)-tetramethyl-10-(2-azidoacetyloxyphenyl)-3,4,6,7,9,10-hexahydro-1,8-(2H,5H) acridinedione, 3h

Yield 84%, M.P.216-18ºC (decomp.), IR (KBr): υ 2105,1685, 1630, 1590, 1585 cm^{-1};^{1}H-NMR ($CDCl_3$-DMSO-d_6, ppm): δ 0.95 (12H, gem dimethyl), 1.80 (s,4H, =C-CH_2-), 2.45 (s,4H, -CO-CH_2-), 3.7 (s, 3H, -OCH_3), 4.10 (s, 1H, =C-CH-C=), 4.85 (s, 2H, -CO-CH_2-N_3), 6.8-7.2 (m, 8H, Aro.); MS: m/z. 554m^+.Anal.calcd.(found) % $C_{32}H_{34}N_4O_5$: C, 69.29 (69.11); H, 6.17 (6.05); N, 10.10 (9.92).

9-(2-methoxyphenyl)-tetramethyl-10-(2-azidoacetyloxyphenyl)-3,4,6,7,9,10-hexahydro-1,8-(2H, 5H) acridinedione, 3i

Yield 84%, M.P.212-14º C (decomp.), IR (KBr): υ 2105,1695, 1635, 1595, 1585 cm^{-1};^{1}H-NMR ($CDCl_3$-DMSO-d_6, ppm): δ0.95 (12H, gem dimethyl), 1.80 (s,4H, =C-CH_2-), 2.50 (s,4H, -CO-CH_2-), 3.70 (s, 3H, -OCH_3), 4.05 (s, 1H, =C-CH-C=), 4.85 (s, 2H, -CO-CH_2-N_3), 6.80 -7.20 (m, 8H, Aro.); MS: m/z. 554m^+. Anal.calcd.(found) % $C_{32}H_{34}N_4O_5$: C, 69.29 (69.10); H, 6.17 (6.02); N, 10.10 (9.94).

Preparation of tetramethyl-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 mmol) was refluxed in benzene (30 ml) for 6 hours. Benzene was distilled off and the residue crystallized from methanol to obtain 4(a-i).

Tetramethyl-10-[2-(1-triazolo-4,5-dicaroxymethyl)acetyloxyphenyl]-3,4,6,7,9,10-hexahydro-1,8-(2H,5H)-acridinedione, 4a

Yield 68%; M.P. 214-16ºC, IR (KBr): υ 1710, 1640, 1615, 1595, 1580 cm^{-1}; ^{1}H-NMR ($CDCl_3$-DMSO-d_6, ppm): δ 0.95 (12H, gem dimethyl), 1.75 (s,4H, =C-CH_2-), 2.45 (s,4H, -CO-CH_2-), 3.25(s, gem coupling , Jgem= 21 Hz, 2H, =C-CH_2-C=), 3.95 (s,6H, -$COOCH_3$), 5.60 (s, 2H, -CO-CH_2-triazole), 7.20 -7.40 (m,4H, Aro.); MS: m/z. 590 m^+; Anal.calcd.(found) % $C_{31}H_{34}N_4O_8$: C, 63.04 (62.91); H, 5.80 (5.65); N, 9.48 (9.29).

Pentamethyl-10-[2-(1-triazolo-4,5-dicaroxymethyl)acetyloxyphenyl]-3,4,6,7,9,10-hexahydro-1,8-(2H,5H)-acridinedione, 4b

Yield 70%, M.P. 212-14°C ; IR (KBr): υ 1710, 1650,1620, 1595, 1590 cm^{-1};^{1}H-NMR ($CDCl_3$-DMSO-d_6, ppm): δ 0.95 (12H, gem dimethyl), 1.60 (d, 3H), 1.80 (s,4H, =C-CH_2-), 2.45 (s,4H, -CO-CH_2-), 3.95 (s,6H, -$COOCH_3$),4.20 (q,1H, =C-CH-C=), 5.65 (s,2H, -CO-CH_2-triazole), 6.80 -7.20(m,4H, Aro.); MS: m/z. 604m^+; Anal.calcd.(found) % $C_{32}H_{36}N_4O_8$: C, 63.56 (63.36); H, 6.00 (6.14); N, 9.26 (9.10).

9-phenyl-tetramethyl-10-[(2-(1-triazolo-4,5-dicarboxymethyl)acetyloxyphenyl]-3,4,6,7,9,10-hexahydro-1,8-(2H,5H) acridinedione, 4c

Yield 72%, M.P. 212-14°C , IR (KBr): υ1720, 1640, 1615, 1595, 1585 cm^{-1}; ^{1}H-NMR ($CDCl_3$-DMSO-d_6, ppm): δ0.95 (12H, gem dimethyl), 1.80 (s,4H, =C-CH_2-), 2.45 (s,4H, -CO-CH_2-), 3.95 (s,6H, -$COOCH_3$),4.30 (s,1H, =C-CH-C=), 5.60 (s, 2H,-CO-CH_2-triazole), 6.75-7.20(m,9H, Aro.); MS: m/z 666m^+; Anal.calcd.(found) % $C_{37}H_{38}N_4O_8$: C, 66.65 (66.48); H, 5.74 (5.46); N, 8.40 (8.23).

9-(4-chlorophenyl)-tetramethyl-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. 214-16°C, IR (KBr): υ1710, 1640, 1610, 1595, 1580 cm^{-1}; ^{1}H-NMR ($CDCl_3$-DMSO-d_6, ppm): δ 0.95 (12H, gem dimethyl), 1.80 (s,4H, =C-CH_2-), 2.45 (s,4H, -CO-CH_2-),3.95 (s,6H, -$COOCH_3$), 4.35 (s, 1H, =C-CH-C=), 5.65 (s, 2H, -CO-CH_2-triazole), 6.80–7.10 (m, 8H, Aro.); MS: m/z. 700m^+,m^{+2} 702; Anal.calcd.(found) % $C_{37}H_{37}N_4O_8Cl$: C, 63.38 (63.20); H, 5.31 (5.43); N, 7.99 (7.79).

9-(2-chlorophenyl)-tetramethyl-10-[2-(1-triazolo-4,5-dicarboxymethyl)acetyloxyphenyl]-3,4,6,7,9,10-hexahydro-1,8-(2H,5H) acridinedione,4e

Yield 72%, M.P. 224-26°C,IR (KBr): υ 1715, 1650, 1620,1595, 1585 cm^{-1};^{1}H-NMR ($CDCl_3$-DMSO-d_6, ppm): δ0.95 (12H, gem dimethyl), 1.80 (s,4H, =C-CH_2-), 2.50 (s,4H-CO-CH_2-), 3.95 (s,6H, -$COOCH_3$), 4.30 (s,1H, =C-CH-C=), 5.60 (s, 2H, -CO-CH_2-triazole), 6.80-7.10(m,.8H, Aro.); MS: m/z. 700m^+, m^{+2} 702; Anal.calcd.(found)% $C_{37}H_{37}N_4O_8Cl$: C, 63.38 (63.18); H, 5.31 (5.27); N, 7.99 (7.86).

9-(4-fluorophenyl)-tetramethyl-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. 208-10°C, IR (KBr): υ1715, 1645, 1615, 1595, 1585 cm^{-1}; ^{1}H-NMR ($CDCl_3$-DMSO-d_6, ppm): δ 0.95 (12H, gem dimethyl), 1.80 (s,4H, =C-CH_2-), 2.45 (s,4H, -CO-CH_2-), 3.95 (s,6H, -$COOCH_3$), 4.30 (s, 1H, =C-CH-C=), 5.60 (s, 2H, -CO-CH_2-triazole), 6.80–7.10 (m, 8H, Aro.); MS: m/z. 684m^+; Anal.calcd.(found) % $C_{37}H_{37}N_4O_8F$: C, 64.90 (64.74); H, 5.44 (5.53); N, 8.18 (8.01).

9-(2-fluorophenyl)-tetramethyl-10-[2-(1-triazolo-4,5-dicarboxymethyl)acetyloxyphenyl]-3,4,6,7,9,10-hexahydro-1,8-(2H,5H) acridinedione, 4g

yield 70%, M.P. 214-16°C ,IR (KBr): υ 1715, 1655, 1610, 1595 1585 cm^{-1};^{1}H-NMR (CDCl-DMSO-d_6, ppm): δ 0.95 (12H, gem dimethyl), 1.80 (s,4H, =C-CH_2-), 2.45 (s,4H,-CO-CH_2-), 3.95 (s,6H, -$COOCH_3$), 4.20 (s,1H, =C-CH-C=), 5.60 (s, 2H, -CO-CH_2-triazole), 6.80 -7.10(m,.8H, Aro.); MS: m/z. 684m^+; Anal.calcd.(found) % $C_{37}H_{37}N_4O_8F$: C, 64.90 (64.72); H, 5.44 (5.34); N, 8.18 (8.04).

9-(4-methoxyphenyl)-tetramethyl-10-[2-(1-triazolo-4,5-dicarboxymethyl)acetyloxyphenyl]-3,4,6,7,9,10-hexahydro-1,8-(2H,5H) acridinedione,4h

Yield 76%, M.P. 218-20°C, IR (KBr): υ1715, 1640, 1615, 1590,1685 cm^{-1};^{1}H-NMR ($CDCl_3$-DMSO-d_6, ppm): δ 0.95 (12H, gem dimethyl), 1.80 (s,4H, =C-CH_2-), 2.45 (s,4H, -CO-CH_2-), 3.70 (s, 3H, -OCH_3), 3.95 (s,6H, -$COOCH_3$), 4.10 (s, 1H, =C-CH-C=), 5.65 (s, 2H, -CO-CH_2-triazole), 6.8-7.15 (m, 8H, Aro.); MS: m/z. 696m^+;Anal.calcd.(found) % $C_{38}H_{40}N_4O_9$: C, 65.50 (65.32); H, 5.78 (5.61); N, 8.04 (7.92).

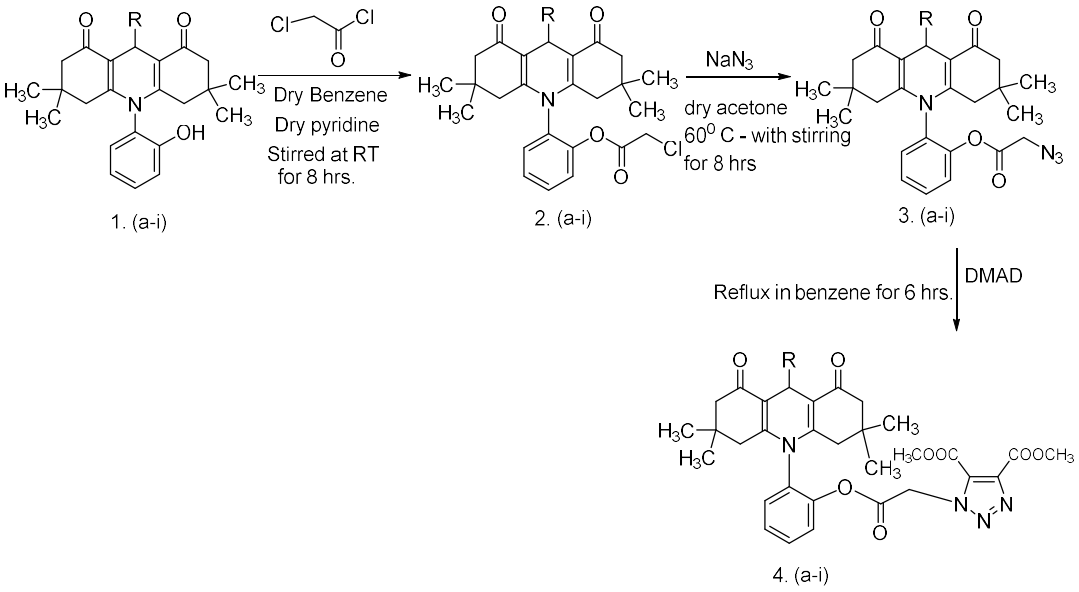
9-(2-methoxyphenyl)-tetramethyl-10-[2-(1-triazolo-4,5-icarboxymethyl)acetyloxyphenyl]-3,4,6,7,9,10-hexahydro-1,8-(2H,5H) acridinedione,4i

Yield 84%, M.P.224-26°C , IR (KBr): υ 1720, 1640, 1615, 1595, 1585 cm^{-1}; ^{1}H-NMR ($CDCl_3$-DMSO-d_6, ppm): δ 0.95 (12H, gem dimethyl), 1.80 (s,4H, =C-CH_2-), 2.45 (s,4H, -CO-CH_2-), 3.70 (s, 3H, -OCH_3), 3.95 (s,6H, -$COOCH_3$), 4.20 (s, 1H, =C-CH-C=), 5.55(s, 2H, -CO-CH_2-triazole), 6.75 -7.2(m, 8H, Aro.); MS: m/z. 696m^+;Anal.calcd.(found) % $C_{38}H_{40}N_4O_9$: C, 65.50 (65.34); H, 5.78 (5.92); N, 8.04 (7.92).

Antibacterial Activity

The synthesized compounds in the present study were investigated for antimicrobial activity by the 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 µg/ml and 150 µg/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 producers[20-21].The antimicrobial activity of all the synthesized compounds was evaluated by measuring the zone of inhibition against the test microorganisms and the results are presented in Figs.-1 to 4.

Scheme - I



Scheme-1

Compounds	a	b	c	d	e	f	g	h	I
R	H	CH_3	C_6H_5	4-Cl-C_6H_4	2-Cl-C_6H_4	4-F-C_6H_4	2-F-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, ^{1}H-NMR, and mass spectral data. The IR spectrum clearly indicates the presence of azides near 2100 cm^{-1}, ester carbonyl groups in the range of 1720 cm^{-1}, side-chain keto group near 1700 cm^{-1}, triazole linked keto group near 1640cm^{-1}, ring keto group conjugated to double bond near 1615 cm^{-1}, aromatic -C=C- and double bond conjugated to ring carbonyl group near 1600 cm^{-1}, 1585 cm^{-1} respectively. The ^{1}H-NMR showed peaks around δ 0.90 (s, 12H, gem dimethyl),1.75 (s, 4H, = C–CH_2-) , near 2.50 (s, 4H, - CO-CH_2-), 3.15-4.05 (2H, = C-CH_2-C=, 1H =C-CH-C=), 4.06 (2H, -CH_2-Cl ; -CH_2-N_3-), 5.60 (-CH_2-triazole ring) and for aromatic protons multiplet near δ 7.20 – 7.80 in the aromatic region for all the compounds. In the mass spectrum in addition to the fragmentation peaks, molecular ion peak is obtained clearly for all the compounds. The presence of m^{+2}, m^{+4} isotopic peaks clearly indicates the presence of one chlorine atom in 2a-c, 2f-i, 3e, 3f, 4d, 4e, and two chlorine atoms in 2d, 2e. The spectral data mentioned above, confirms the structure of the compounds. 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, 4f, 4g exhibited moderate activity. The molecular framework has shown a broad spectrum of antimicrobial activity which is substantiated by the presence of heterocyclic rings, carbonyl groups, in addition, electronegative atoms containing compounds (4 d-g) in

the molecular framework exhibited higher antimicrobial activity among the compounds. The antimicrobial activities are presented in Figs.-1 to 4.

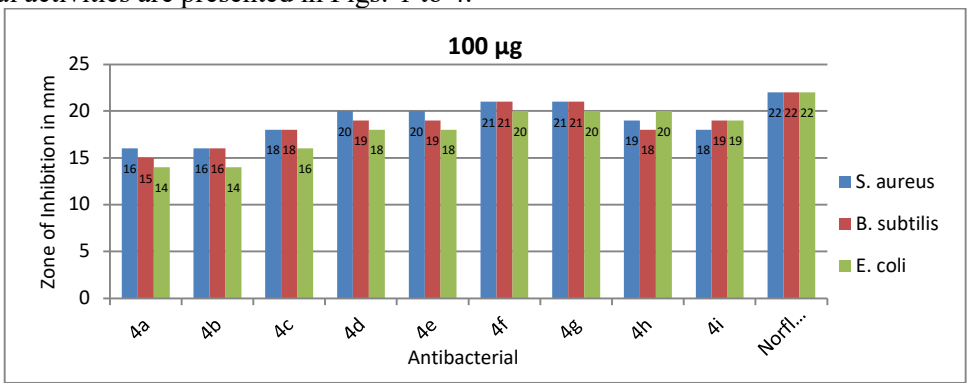


Fig.-1: Antibacterial Activity

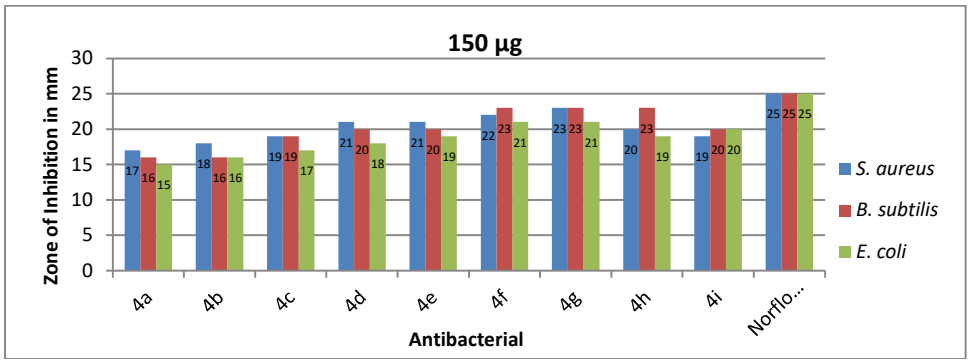


Fig.-2: Antibacterial Activity

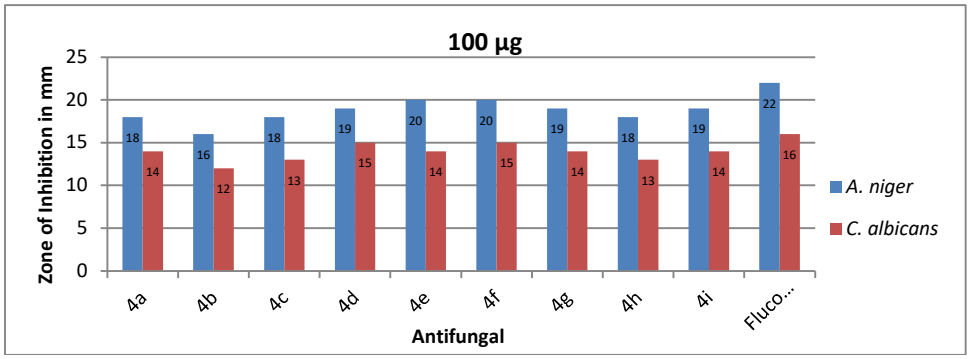


Fig.-3: Antifungal Activity

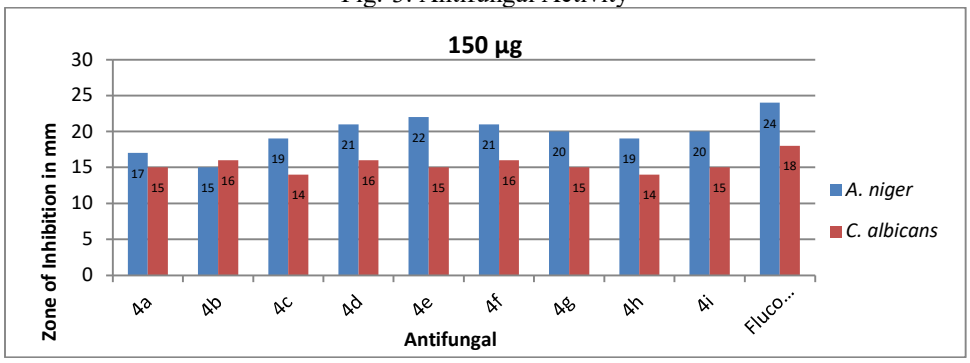


Fig.-4: Antifungal Activity

CONCLUSION

The scope of this study is to report a facile route for the synthesis of triazoles linked hexahydroacridinedione derivatives, that is 10-acetyloxyphenyl-1,2,3-triazolo hexahydroacridinediones ,

which has a broad spectrum of antimicrobial activity. The compounds having electronegative atoms in the molecular framework have exhibited potent antimicrobial activity compared with other compounds.

REFERENCES

1. Y. L. Chen, C. M. Lu, I. L. Chen, L.T. Tsao, J. P. Wang, *Journal of Medicinal Chemistry*, **45(21)**, 4689, (2002), https://DOI: 10.1021/jm020102v PMID: 12361395
2. S. A. Gamage, J. A. Spicer, G. J. Atwell, G. J. Finlay, B. C. Baguley, W. A. Denny, *Journal of Medicinal Chemistry*, **42(13)**, 2383(1999), https://doi.org/10.1021/jm980687m
3. M. Kaya, Y. Yildirir, G. Y. Çelik, *Medicinal Chemistry Research*, **20(3)**, 293(2011), https://doi.org/10.1007/s00044-010-9321-6
4. E. I. Aly, A. H. Abadi, *Archives of Pharmaceutical Research*, **27(7)**, 713,(2004), https://doi.org/10.1007/BF02980137
5. Di Giorgio Carole, De Meo Michel, Chiron Julieu, Delmas Florence, Nikoyan Anna, Jean Severine, Du menil Ferard, Timon David Pierre, Galy Jean-Pierre, *Bioorganic & Medicinal Chemistry*, **13(19)**, 5560(2005), https://doi.org/10.1016/j.bmc.2005.06.045
6. A. Kumar, K. Srivastava, S.R. Kumar, S.K. Puri, P.M. Chauhan, *Bioorganic & Medicinal Chemistry Letters*, **19(24)**, 6996(2009), https://doi.org/10.1016/j.bmcl.2009.10.010
7. H. C. Gupta, V. Jaiswal, *Indian Journal of Heterocyclic Chemistry*, **19(4)**,409(2010).
8. A. Almasirad, S.A. Tabatabai, M. Faizi, A. Kebriaeezadeh, N. Mehrabi, A. Dalvandi, A. Shafiee, *Bioorganic & Medicinal Chemistry Letters*, **14(24)**, 6057, (2004), https://doi.org/10.1016/j.bmcl.2004.09.072
9. M. Wainwright, D.A. Phoenix, J. Marland, D.R. Wareing, F.J. Bolton, *The Journal of Antimicrobial Chemotherapy*, **40(4)**,587(1997), https://doi.org/10.1093/jac/40.4.587
10. S. Sathish Kumar, P. Kavitha, *Reviews in Organic Chemistry*, **10(1)**, 40(2013), http://dx.doi.org/10.2174/1570193X11310010004
11. Fatih Cleik, Yasemin Unver, Burak Barut, Arzu Ozal, Kemal Sancak, *Medicinal Chemistry*, **14(3)**, 230(2018), https://doi.org/10.2174/1573406413666171120165226
12. Thummala Rajamani and K. Bhasker, *Rasayan Journal of Chemistry*, **14(3)**,1534 (2021), http://doi.org/10.31788/RJC.2021.1436259
13. B. Ashok Gugulothu, Sreenivas Enaganti and J.V. Shanmuk Kumar, *Rasayan Journal of Chemistry*, **14(3)**,1551(2021), http://doi.org/10.31788/RJC.2021.1436249
14. Kiran Sing, Bavita Kumari and Amit Sharma, *Rasayan Journal of Chemistry*, **14(1)**, 29(2021), http://dx.doi.org/10.31788/RJC.2021.1416108
15. K. Lemke, V. Poindessous, A. Skladanowski and Annette K. Larsen, *Molecular Pharmacology*, **66(4)**,1035(2004), https://doi.org/10.1124/mol.104.000703
16. P. Shanmugasundaram, K. J. Prabahar, V.T. Ramakrishnan, *Journal of Heterocyclic Chemistry*, **30(4)**,1003(1993), https://doi.org/10.1021/jo9600316
17. P. Shanmugasundaram, P. Murugan, V. T. Ramakrishnan, N. Srividya, P. Ramamurthy, *Heteroatom Chemistry*, **7(1)**, 17(1996), https://doi.org/10.1002/(SICI)1098-1071(199601)7:1%3C17::AID-C3%3E3.0.CO;2-%23
18. P. Murugan, P. Shanmugasundaram, V.T. Ramakrishnan, B. Venkatachalapathy, N. Srividya, P. Ramamurthy, K. Gunasekaran, D. Velmurugan, *Journal of the Chemical Society, Perkin Transactions* **2(4)**, 999(1998), https://doi.org/10.1039/A701401E
19. N. Srividya, P. Ramamurthy, P. Shanmugasundaram, V. T. Ramakrishnan, The Journal of Organic Chemistry, **61(15)**, 5083(1996), https://doi.org/10.1002/jhet.5570300428
20. V. Jatav, S. K. Jain , S. K. Kashaw, P. Mishra, *Indian Journal of Pharmaceutical Sciences*, **68(3)**, 360, (2006), https://doi.org/10.4103/0250-474X.26679
21. A. Alagarsamy, R. Giridhar, M.R. Yadav, R. Revathi, K. Ruckmani, E. De Clercq, *Indian Journal of Pharmaceutical Sciences*, **68(4)**, 532(2006), https://doi.org/10.4103/0250-474X.27840

[RJC-6718/2021]