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REGULAR ARTICLE

Novel series of acridone-1,2,3-triazole derivatives: microwave-assisted synthesis, DFT study and antibacterial activities

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Abstract. A series of novel acridones bearing a 1,2,3-triazole unit have been synthesized and characterized. The copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC) was performed using both a conventional method and a microwave-assisted synthetic method. The *in vitro* antibacterial potencies of all the synthesized compounds were determined against five clinically isolated strains: *Escherichia coli*, *Klebsiella pneumonia*, *Pseudomonas putida*, *Serratia marcescens* and *Staphyloccocus aureus*. Furthermore, DFT quantum chemical calculations were carried out to investigate geometry structures, frontier molecular orbital and gap energies, and molecular electrostatic potential maps (MEP). Lipophilicities of the studied compounds were also determined.

Keywords. Acridone; 1, 2, 3-triazole; microwave; DFT study; antibacterial activitiy.

1. Introduction

Acridones are heterocyclic compounds with important biological activities.[1] Acronycine was the first acridone alkaloid that has been isolated from an Acronychia baueri Schott plant,[2] and which displayed a broad-spectrum activity against a variety of experimental tumor models.[3,4] Due to their planar ring, these molecules could intercalate between nucleotide base pairs in the helix of the cancer cell DNA.[5–7] Many Acridone derivatives such as nitracrine, amsacrine, DACA and asulacrine[8–10] are used clinically or are under clinical observations. Moreover, exhaustive research has been conducted on acridine and acridone derivatives showing anti-cancer,[11] antitumor,[12] antiviral,[13] antimalarial,[14] antimicrobial[15] and anti-inflammatory[16] bioactivities.

On the other hand, 1,2,3-triazole and its derivatives are an important class of heterocycles, that attract the attention of organic chemists[17] due to their significant pharmacological potential[18] and a broad spectrum of applications in biochemical and medicinal chemistry such as anti-HIV,[19] antimicrobial,[20] antioxidant,[21] anti-cancer,[22] and acetylcholinesterase and butyrylcholinesterase inhibitory[23] activities. Click reaction is the most popular method for the construction of 1,2,3-triazoles. This synthetic method, introduced by Sharpless,[24] is an important topic in organic synthesis since it constitutes a powerful bond forming reaction with many applications including different fields from materials science to drug discovery.[25] The copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC) makes the reaction quantitative and selective for the synthesis of 1,4-disubstituted 1,2,3-triazole and decreases the completion reaction time.[26,27]

Considering the many adverse effects and development of antimicrobial resistance,[28] there is a big demand for novel and efficient antimicrobial agents.[29] Inspired with the biological profile of acridone and 1,2,3-triazoles and their increasing importance in pharmaceutical fields, we have synthesized novel acridon-1,2,3-triazole compounds using the copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC) to obtain novel

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drugs with antibacterial potential. The new molecules were prepared under microwave irradiations conditions then tested against five clinically isolated bacterial strains.

Additionally, a theoretical study using DFT quantum chemical calculations was carried out in order to explore the electronic properties of the synthesized compounds. Hence, optimized geometry structures, frontier molecular orbital and gap energies, molecular electrostatic potential maps (MEP) were investigated. Lipophilicities were determined to help understand the relationship between structure and biological activities of our compounds.

2. Experimental

2.1 *Materials*

All materials were purchased from commercial suppliers. Infrared spectra were recorded using a JASCO FT-IR 4100 spectrophotometer. The ^{1}H and ^{13}C NMR spectra were recorded with a Bruker Avance 300 at 25 °C. Mass spectrometric measurements were recorded using SHIMADZU 8040 LC/MS/MS. Microwave irradiation was carried out with CEM Discover^{TM}.

2.2 *Synthesis*

General procedure for the synthesis of acridon-1,2,3-triazole derivatives (4a-h) Conventional procedure: A mixture of 10-(prop-2-yn-1-yl)acridone (0.1g, 0.42 mmol), 2-azido-N-phenylacetamide (0.11g, 0.63 mmol), copper sulfate (20 mg, 0.08 mmol) and sodium ascorbate (33 mg, 0.16 mmol) in DMF (5 mL) was stirred at room temperature for 10 h. After completion of the reaction (monitored by TLC), the mixture was diluted with water, poured onto ice, and the precipitate was filtered off, washed with cold water, and purified by flash chromatography on silica gel using hexane/diethyl ether to afford desire product.

Microwave-assisted procedure: A mixture of 10-(prop-2-yn-1-yl)acridone (0.1g, 0.42 mmol), copper sulfate (20 mg, 0.08 mmol) and sodium ascorbate (33 mg, 0.16 mmol) were suspended in 5 mL of solvent in a glass vial equipped with a small magnetic stirring bar. To this, 2-azido-N-phenylacetamide (0.11g, 0.63 mmol) was added and the vial was tightly sealed. The mixture was then irradiated for 10 min at a fixed temperature (40−100 °C). Microwave irradiation power was set at 200 W maximum. After completion of the reaction, the vial was cooled and the reaction mixture poured into ice cold water, and purified by flash chromatography on silica gel using hexane/diethyl ether to afford desire product.

2-(4-((9-oxoacridin-10(9H)-yl)methyl)-1H-1,2,3-triazol-1-yl)-N-phenylacetamide (4a).

Yellow solid; yield: 81%, M.p.> 300 °C. IR (KBr): 3266, 3088, 2985, 1703, 1630, 1614, 1598, 1563, 1499 cm^{-1}. ^{1}HNMR (300 MHz, [D$_6$]DMSO, 25 °C, TMS): δ 10.40 (s, 1H, NH), 8.36 (dd, J = 8.0, 1.7 Hz, 2H, H1-H8), 8.16 (s, 1H, triazole), 7.98 (d, J = 8.8 Hz, 2H, H4, H5), 7.82 (td, J = 8.8, 6.9, 1.8 Hz, 2H, H3, H6), 7.51 (d, J = 7.8 Hz, 2H, H1′, H5′), 7.32 (m, 4H), 7.04 (t, 1H, H3′), 5.84 (s, 2H, CH2), 5.27 (s, 2H, CH2); ^{13}C NMR (75 MHz, [D$_6$]DMSO, 25 °C, TMS): 177.06, 164.52, 142.72, 142.25, 138.81, 134.66, 129.34, 127.12, 125.49, 124.21, 122.18, 121.99, 119.65, 116.82, 52.69, 41.97. MS (ESI) for $C_{24}H_{19}N_5O_2$ $[M + 1]^+$, calcd: 410.45, found: 410.44.

2-(4-((9-oxoacridin-10(9H)-yl)methyl)-1H-1,2,3-triazol-1-yl)-N-(p-tolyl)acetamide (4b).

Yellow solid; yield: 84%, M.p. > 300 °C. IR (KBr): 3267, 3078, 2935, 1704, 1629, 1616, 1594, 1555 Cm^{-1}. ^{1}HNMR (300 MHz, [D$_6$]DMSO, 25 °C, TMS): δ 10.31 (s, 1H, NH), 8.35 (dd, J = 8.0, 1.7 Hz, 2H), 8.15 (s, 1H), 7.98 (d, J = 8.8 Hz, 2H), 7.82 (td, J = 8.8, 6.9, 1.8 Hz, 2H), 7.45–7.28 (m, 4H), 7.1 (d, J = 8.0 Hz, 2H), 5.83 (s, 2H, CH2), 5.24 (s, 2H, CH2), 2.22 (s, 3H, CH3); ^{13}C NMR (75 MHz, [D$_6$]DMSO, 25 °C, TMS) δ 177.06, 164.25, 142.69, 142.25, 136.30, 134.66, 133.19, 129.70, 127.12, 125.47, 122.18, 121.99, 119.64, 116.82, 52.66, 41.96, 20.89. MS (ESI) for $C_{25}H_{21}N_5O_2$ $[M + 1]^+$, calcd: 424.47, found: 424.29.

2-(4-((9-oxoacridin-10(9H)-yl)methyl)-1H-1,2,3-triazol-1-yl)-N-(o-tolyl)acetamide (4c).

Yellow solid; yield: 88%, M.p. > 300 °C. IR (KBr): 3260, 3121, 3064, 2936, 1670, 1630, 1600, 1542, 1495 cm^{-1}. ^{1}HNMR (300 MHz, [D$_6$]DMSO, 25 °C, TMS): δ 9.76 (s, 1H, NH), 8.36 (d, J = 7.8 Hz, 2H, H1-H8), 8.19 (s, 1H, triazole), 7.99 (d, J = 8.7 Hz, 2H, H4, H5), 7.83 (t, J = 7.8 Hz, 2H, H3, H6), 7.36 (m, 3H), 7.15 (m, 3H), 5.85 (s, 2H, CH2), 5.34 (s, 2H, CH2), 2.16 (s, 3H, CH3); ^{13}C NMR (75 MHz, [D$_6$]DMSO, 25 °C, TMS) δ 177.08, 164.76, 142.77, 142.24, 135.91, 134.68, 133.94, 132.00, 130.88, 127.13, 126.15, 126.01, 125.5, 122.17, 121.48, 117.81, 52.44, 41.95, 18.22. MS (ESI) for $C_{25}H_{21}N_5O_2$ $[M + 1]^+$, calcd: 424.47, found: 424.32.

2-(2-(4-((9-oxoacridin-10(9H)-yl)methyl)-1H-1,2,3-triazol-1-yl)acetamido)benzoic acid (4d).

Yellow solid; yield: 73%, M.p. > 300 °C. IR (KBr): 3401, 3240, 2933, 2842, 1700, 1630, 1612, 1597, 1475 cm^{-1}. ^{1}HNMR (300 MHz, [D$_6$]DMSO, 25 °C, TMS): δ 11.57 (br s,1H, OH), 10.19 (s, 1H, NH), 8.60 (d, J = 8.5 Hz, 1H, H2'), 8.36 (dd, J = 8.0, 1.7 Hz, 2H, H1-H8), 8.15 (s, 1H, triazole), 8.01 (d, J = 8.8 Hz, 2H, H4, H5), 7.69–7.61 (m, 5H, Ar-H), 7.34–7.26 (m, 2H, Ar-H), 5.83 (s, 2H, CH2), 5.28 (s, 2H, CH2); ^{13}C NMR (75 MHz, [D$_6$]DMSO, 25 °C, TMS): 177.82,171.59,164.31,140.88,140.62,139.29, 133.29, 129.98, 129.71, 128.88, 125.97, 125.17, 123.11, 122.85, 121.61, 120.86, 120.49, 117.27, 115.77, 115.43, 115.39, 52.68, 41.96. MS (ESI) for $C_{25}H_{19}N_5O_4$ $[M + 1]^+$, calcd: 454.45, found: 454.40.

2-(4-((2-methyl-9-oxoacridin-10(9H)-yl)methyl)-1H-1,2,3-triazol-1-yl)-N-phenylacetamide (4e).

Yellow solid; yield: 80%, M.p. > 300 °C. IR (KBr): 3263, 3137, 3085, 2926, 1703, 1632, 1618, 1592, 1498 cm^{-1}. ^{1}HNMR (300 MHz, [D_6]DMSO, 25 °C, TMS): δ 10.59 (s, 1H, NH), 8.38 (d, J = 8.1 Hz, 1H, H1), 8.16 (s, 1H, H8), 8.15 (s, 1H, triazole), 7.96 (d, J = 8.7 Hz, 1H, H4), 7.90 (d, J = 9 Hz, 1H, H5), 7.81 (td, J = 8.8, 6.9, 1.8 Hz, 1H, H3), 7.68 (dd, J = 9, 2 Hz, 1H, H6) 7.56 (d, J = 7.5 Hz, 2H, H1', H5'), 7.34 (m, 3H), 7.07 (t, 1H, H3'), 5.83 (s, 2H, CH2), 5.28 (s, 2H, CH2), 2.43 (s, 3H, CH3); ^{13}C NMR (75 MHz, [D_6]DMSO, 25 °C, TMS) δ 176.90, 164.56, 142.08, 140.35, 138.83, 135.98, 134.49, 131.22, 129.36, 127.15, 126.34, 124.22, 122.09, 121.72, 119.63, 119.53, 116.85, 116.67, 52.66, 41.83, 20.67. MS (ESI) for $C_{25}H_{21}N_5O_2$ $[M + 1]^+$, calcd: 424.16, found: 424.04.

2-(4-((2-methyl-9-oxoacridin-10(9H)-yl)methyl)-1H-1,2,3-triazol-1-yl)-N-(p-tolyl)acetamide (4f).

Yellow solid; yield: 75%, M.p. > 300 °C. IR (KBr): 3277, 3124, 3079, 2910, 1705, 1632, 1616, 1594, 1499 cm^{-1}. ^{1}HNMR (300 MHz, [D_6]DMSO, 25 °C, TMS): δ 10.30 (s, 1H, NH), 8.34 (dd, J = 8.0, 1.7 Hz, 1H, H1), 8.14 (s, 1H, H8), 8.10 (s,1H, triazole), 7.92 (dd, J = 19.2, 8.8 Hz, 2H, H4-H5), 7.79 (td, J = 8.7, 6.9, 1.8 Hz, 1H, H3), 7.64 (dd, J = 8.9, 2.3 Hz, 1H, H6), 7.48–7.35 (m, 2H), 7.31 (td, J = 7.8, 6.9, 0.8 Hz, 1H, H2), 7.09 (d, J = 8.2 Hz, 2H, H2'-H4'), 5.81 (s, 2H,CH2), 5.23 (s, 2H,CH2), 2.42 (s, 3H, CH3), 2.22 (s, 3H, CH3); ^{13}C NMR (75 MHz, [D_6]DMSO, 25 °C, TMS): 176.88, 164.25, 142.78, 142.08, 140.36, 136.30, 135.96, 134.46, 133.19, 131.20, 129.70, 127.13, 126.33, 125.41, 122.07, 121.70, 119.64, 116.84, 116.65, 52.64, 41.84, 20.88, 20.66. MS (ESI) for $C_{26}H_{23}N_5O_2$ $[M + 1]^+$, calcd: 438.50, found: 438;36.

2-(4-((2-methyl-9-oxoacridin-10(9H)-yl)methyl)-1H-1,2,3-triazol-1-yl)-N-(o-tolyl)acetamide (4g).

Yellow solid; yield: 88%, M.p. > 300 °C. IR (KBr): 3275, 3127, 3072, 2917, 1701, 1630, 1615, 1590, 1509 cm^{-1}. ^{1}HNMR (300 MHz, [D_6]DMSO, 25 °C, TMS): δ 0.36 (s, 1H, NH), 8.38 (dd, J = 8.0, 1.7 Hz, 1H,1H), 8.18 (s, 1H, H8), 8.10 (s,1H, triazole), 7.96 (dd, J = 19.1, 8.9 Hz, 2H, H4-H5), 7.83 (td, J = 8.7, 6.9, 1.8 Hz, 1H,H3), 7.68 (dd, J = 8.9, 2.3 Hz, 1H, H6), 7.56–7.29 (m, 3H), 7.12 (d, J = 8.2 Hz, 2H,H2-H4'), 5.85 (s, 2H, CH2), 5.26 (s, 2H, CH2), 2.45 (s, 3H, CH3), 2.25 (s, 3H, CH3); ^{13}C NMR (75 MHz, [D_6]DMSO, 25 °C, TMS) δ 176.41, 163.75, 141.59, 139.87, 135.78, 135.50, 133.99, 132.72, 130.73, 129.21, 126.64, 125.83, 121.57, 121.23, 119.17, 116.34, 116.16, 52.15, 41.36, 20.39, 20.18. MS (ESI) for $C_{26}H_{23}N_5O_2$ $[M + 1]^+$, calcd: 438.50, found: 438.41.

2-(2-(4-((2-methyl-9-oxoacridin-10(9H)-yl)methyl)-1H-1,2,3-triazol-1-yl)acetamido)benzoic acid (4h).

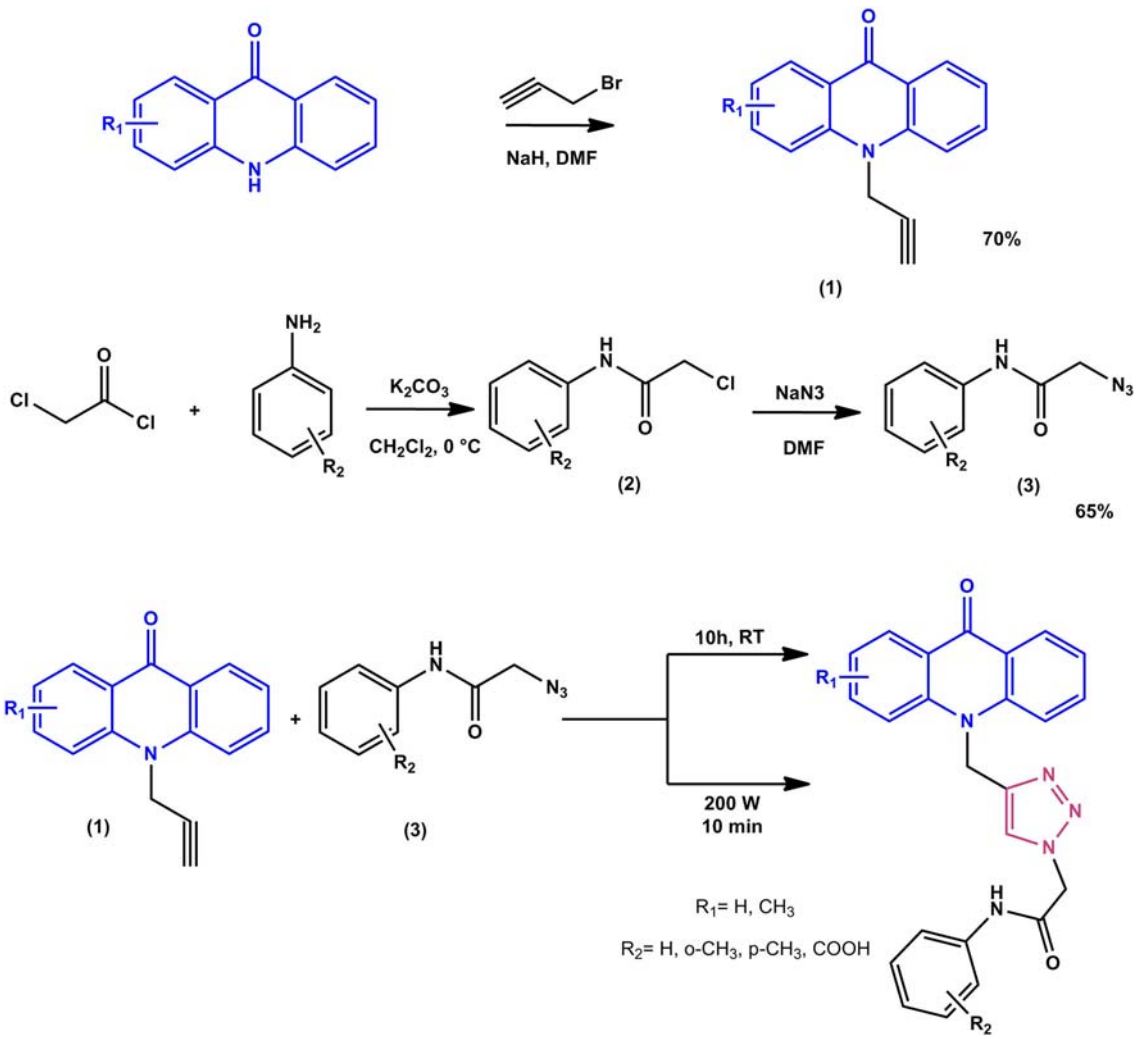
Yellow solid; yield: 76%, M.p. > 300 °C. IR (KBr): 3401, 3240, 2933, 2842, 1700, 1630, 1612, 1597, 1475 cm^{-1}. ^{1}H NMR (300 MHz, [D_6]DMSO, 25 °C, TMS): δ 11.57 (br s,1H, OH), 10.58 (s, 1H, NH), 8.60 (d, J = 8.5 Hz, 1H, H2'), 8.39 (d, J = 8.1 Hz, 1H, H1), 8.27 (d, J = 8.5 Hz, 1H, H5'), 8.18 (s, 1H, H8), 8.15 (s, 1H, triazole), 7.96 (d, J = 8.7 Hz, 1H, H4), 7.90 (d, J = 9 Hz, 1H, H5), 7.69–7.61 (m, 3H, Ar-H), 7.31–7.26 (m, 2H, Ar-H), 5.80 (s, 2H, CH2), 5.27 (s, 2H, CH2), 2.44 (s, 3H, CH3); ^{13}C NMR (75 MHz, [D_6]DMSO, 25 °C, TMS):176.80,171.60,164.38,140.98,140.32,139.00, 133.66, 129.33, 129.11, 128.69, 125.12, 124.97, 122.99, 121.85, 121.69, 120.77, 120.19, 117.55, 115.37, 115.39, 52.65, 41.86, 20.60. MS (ESI) for $C_{26}H_{21}N_5O_4$ $[M + 1]^+$, calcd: 468.48, found: 468.26.

3. Results and Discussion

3.1 *Chemistry*

In this work, the synthesis of acridone 1,2,3-triazole hybrid derivatives entails a three steps pathway (Scheme 1). The synthetic strategy started from the preparation of 10-(prop-2-yn-1-yl)acridone (1) as the terminal alkyne component by the substitution reaction of acridone with propargyl bromide, using NaH in dimethylformamide (DMF) at 80 °C. In the second setup, 2-azido-N-phenylacetamide derivatives are prepared by reacting aniline derivatives (1.0 equiv.) and chloroacetyl chloride (1.5 equiv.) in K_2CO_3/CH_2Cl_2 at 0 °C to give 2-chloroN-phenylacetamide (2). The crude amide (2) was then reacted with sodium azide in DMF as solvent under moderate heat to give 2-azido-N-phenylacetamide (3). The last step was the click reaction, where the 10-(prop-2-yn-1-yl)acridone undergoes a 1,3-dipolar cycloaddition with 2-azido-N-phenylacetamide (3) in the presence of copper sulfate and sodium ascorbate leading to the 1,4-disubstituted regioisomer (4).

Along with the conventional method, the assisted microwave irradiation was also employed for the 1,3-dipolar cycloaddition reaction. A number of variables including solvent, copper catalyst, reducing agent and time were examined in the reaction of 10-(prop-2-yn-1-yl)acridone (1a) and 2-azido-N-phenylacetamide (3a) for the optimization of the click reaction. The obtained results are summarized in (Table 1). Based on previous studies, the model click reaction was performed in water:tBuOH (1:1) as a solvent and $CuSO_4.5H_2O$/NaAsc as a catalytic system at room temperature,[30] the expected product (4a) was obtained in 55% yield with conventional method and 60% yield with microwave irradiation. In an attempt to increase the yield of the cycloaddition reaction, we have tested other solvents (DMF, DMF/H_2O, and CH_2Cl_2). An interesting increase in the yield of (4a) was observed in DMF, affording 73% yield after 10 h stirring at



Scheme 1. The synthetic route of title compounds (4a–h).

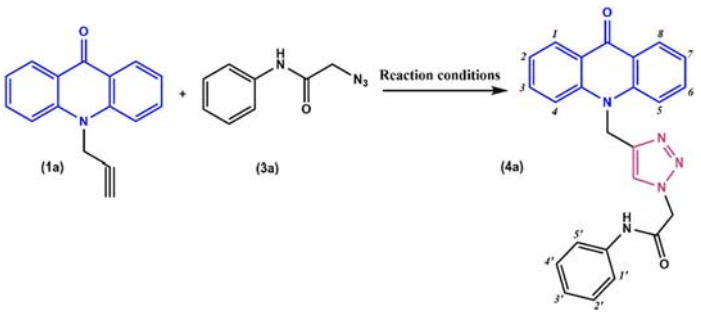
room temperature whereas a decrease in the yield was observed when water was added as a co-solvent. This is probably due to the low solubility of 10-(prop-2-yn-1-yl)acridone (1a) in aqueous media. Any change in the amount of copper catalyst and sodium ascorbate, even at reflux, was not efficient compared to optimized conditions. In order to increase the efficiency of the reaction, we used copper iodide as a source of copper and triethylamine as a protective agent. As shown in Table 1, the use of CuI in DMF as solvent gives moderate yield (60%).

By the protocol of entry 3 in Table 1, novel acridone 1,2,3-triazole derivatives were synthesized with both microwave-assisted procedure and conventional method. By using MWI, the target compounds were synthesized in 10 min with excellent overall yields of 86–69% (Table 2). Whereas with the conventional procedure, the overall yields were in the range of 60–75% and it took more than 10 h to complete the reaction.

Structures of novel acridon-1,2,3-triazole derivatives were characterized by IR, ^{1}H NMR, ^{13}C NMR. The IR spectra of the novel acridon-1,2,3-triazole compounds (4a–h) showed characteristic absorption band at 1630 cm^{-1} corresponding to a conjugated ketone (C=O) of the acridone ring and absorption bands in the region of 1704−1670 cm^{-1} corresponding to (C=O) of the amide group.

^{1}H NMR spectra of compounds 4a–h showed a singlet for NH proton at around 10.59–9.76 ppm and another singlet for triazole proton in the range of 8.19–8.10 ppm. Aromatic protons of acridone ring and N-phenylacetamide group are visible between 8.38–7.10 ppm, while the methyl proton of substituted acridone appear at 2.45 ppm. The N–CH2 attached to the acridone ring and N–CH2 attached to the amide group protons resonate at around 5.84–5.27 ppm. The substituted N-phenylacetamide group yielded an intense singlet at around 2.25–2.16 ppm corresponding to the methyl

Table 1. Optimization of reaction condition 4a.[a]



Entry	Copper salt	Reducing agent	Solvent (1:1)	Time		Yield (%)[d]	
				NO-MW	MW[f]	NO-MW	MW[f]
1	$CuSO_4.5H_2O$	NaAsc	t-BuOH/H_2O	24 h	15 min	55	60
2	$CuSO_4.5H_2O$	NaAsc	t-BuOH	24 h	15 min	55	60
3	$CuSO_4.5H_2O$	NaAsc	DMF	10 h	10 min	73	81
4	$CuSO_4.5H_2O$	NaAsc	DMF/H_2O	24 h	15 min	61	72
5	$CuSO_4.5H_2O$	NaAsc	CH_2Cl_2	24 h	15 min	68	71
6[c]	$CuSO_4.5H_2O$	NaAsc	DMF	4 h	–	69	–
7[b]	CuI	–	DMF	24 h	10 min	60	63

[a]Reaction conditions: 3a (1.2 mmol), 1a (1 mmol), Copper salt (20 mol%), sodium ascorbate (50 mol%.), solvent (5 mL) at room temperature. [b]0.5 eq Et_3N. [c]Reflux. [d]Isolated yield. [f]Microwave conditions, 200 W maximum.

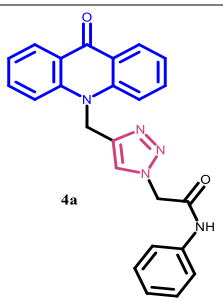
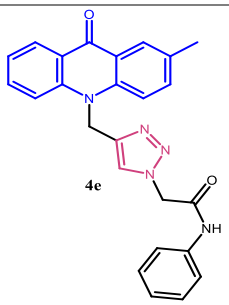
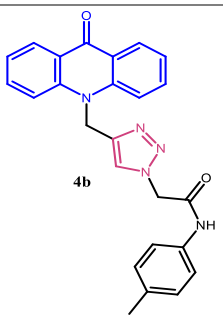
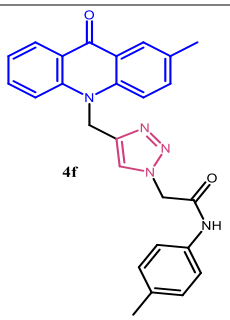
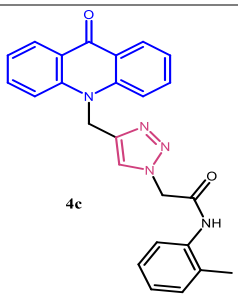
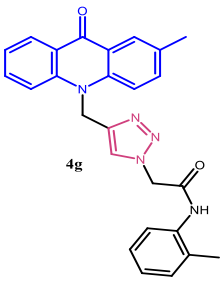
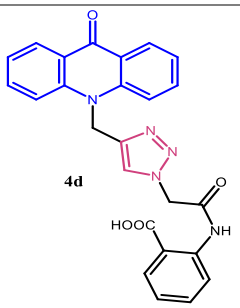
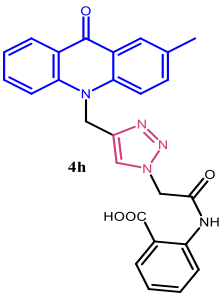
group, while the acid proton appear at 11.57 ppm. In the ^{13}C NMR spectrum, the chemical shifts of the carbonyls of the acridone ring and CONH groups of the N-phenylacetamide resonate at around 177.8–176.4 and 164.7–163.7 ppm, respectively and another signal corresponding to the carbon of acid group are resonate at 171.5. Tow signals at a range of 63.0–54.0 ppm corresponding to N–CH2 attached to the acridone ring and N–CH2 attached to the amide group protons confirmed by DEPT 135. The signal at around 125.4–142.7 ppm corresponding to the aromatic carbons of triazole ring.

3.2 *Computational studies*

Molecular geometries obtained through theoretical methods are useful to explain the structures of compounds. Optimization of all compounds was carried out at the B3LYP/6-31G (d) level of DFT. Optimized geometries of compounds (Figure 1) showed that the acridone ring is not completely planar; it is a little bend of approximately 2.6° relative to the axis that passes through the nitrogen of the amino group and the keto, and the interplanar angle between the acridone ring and the triazole ring is 47°. On the other hand in both compounds 4d and 4h bearing an acid group, intramolecular hydrogen bonds are formed between amide hydrogen and the acidic oxygen. For the other compounds, intramolecular hydrogen bonds are formed between the nitrogen of the triazole ring and the amide hydrogen.

3.2a *Frontier molecular orbitals (FMOs)*: The most important orbitals in molecules are the frontier molecular orbitals, which refer to HOMO and LUMO orbitals are the most important factors that affect the bioactivity.[31] The energy gap ($\Delta E_{gab} = E_{LUMO} - E_{HOMO}$) between HOMO and LUMO reflect the chemical activity and kinetic stability.[32–36] The gap energies, HOMO and LUMO for the novel acridone 1,2,3-triazole derivatives were calculated and their FMOs are displayed in (Table 3) sketched in (Figure 2). The calculated energy gap is almost constant for all the synthesized compounds and the results showed that the substitution has an insignificant effect on the energy gap except for molecules 4d and 4h that are substituted by an acid group. For these compounds, small decreases in the LUMO levels are observed and lead to stabilization of 4d and 4h. The distributions charges in HOMO orbitals are mainly situated over the acridone ring. In effect, they are not influenced by the nature of the substituent on the triazole rings. Concerning the LUMO orbitals, they are also located over the acridone ring for all studied compounds except 4d and 4h that are substituted by a carboxylic acid group. LUMO orbitals for compounds 4d and 4h are located on the benzoic acid unit due to the attractive effect of the acid group.

Table 2. Scope of target compounds through the reaction of terminal alkynes (1a–b) and 2-azido-N-phenylacetamide (3a–d).

Compounds	Yield (%)		Compounds	Yield (%)	
	NO-MW	MW		NO-MW	MW
 4a	73	81	 4e	70	84
 4b	69	80	 4f	75	79
 4c	77	86	 4g	70	81
 4d	64	69	 4h	60	72

Furthermore, the HOMO and LUMO energy values are used to compute global chemical reactivity descriptors such as chemical hardness (η), electrophilicity (ω) and electronegativity (χ) are reported in Table 3. Chemical hardness is related to the stability and reactivity of a chemical system represented by $\eta = (E_{LUMO} - E_{HOMO})/2$. This parameter is used as a measure of resistance to change in the electron distribution or charge in a molecule.[37] Electrophilicity index measures the propensity or capacity of a species to accept electrons.[38] It is a measure of the stabilization in energy after a system accepts an additional amount of electronic charge from the environment. Electronegativity is given by expression $\omega = \mu^2/2\,\eta$ and (μ =chemical potential). Electronegativity is given by expression $\chi = -(E_{HOMO} + E_{LUMO})/2$, which is defined as the power of an atom in a molecule to attract electrons towards it.[39]

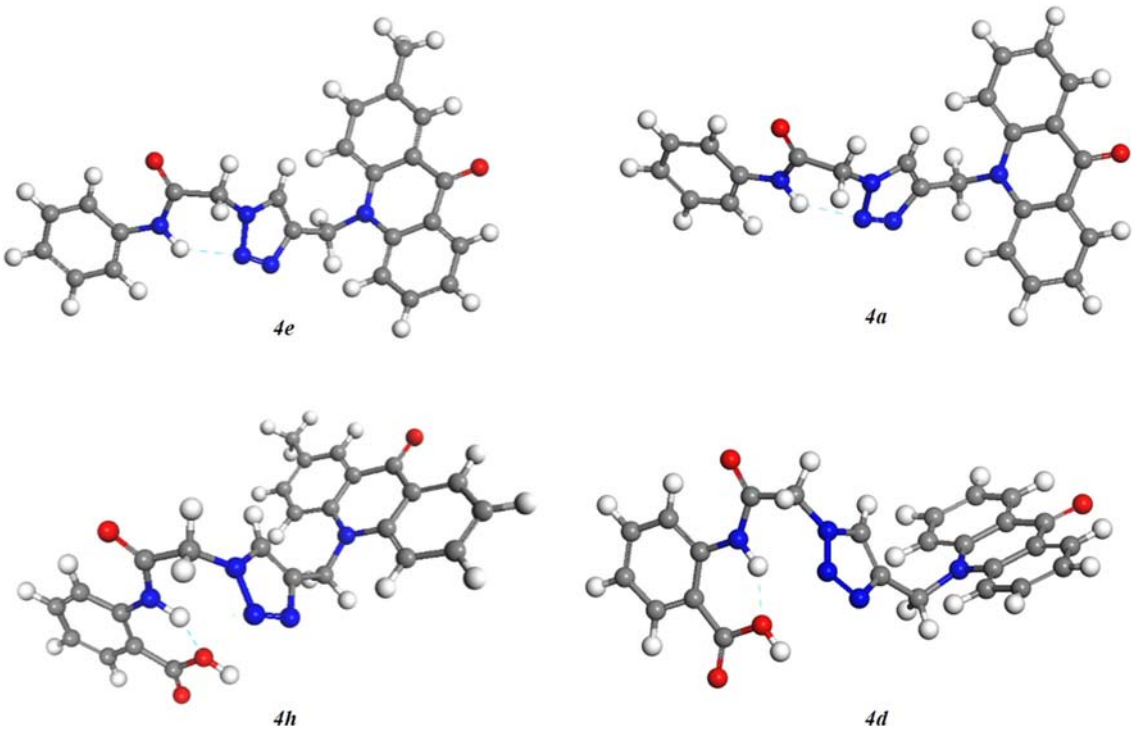


Figure 1. The optimized geometries of 4a, 4d, 4e and 4h at the B3LYP/6-31G (d) level of DFT.

Table 3. Quantum chemical parameters of acridone 1,2,3-triazole compounds calculated by B3LYP/6-31G(d) level of theory.

Compounds	E_{HOMO} (eV)	E_{LUMO} (eV)	Egap (eV)	Chemical hardness (η)	Chemical softness (S)	Electro-negativity (χ)	Electro-philicity (ω)	Lipo-phylicity Log(P)
4a	− 0.214	− 0.065	0.149	0.074	13.42	0.139	0.129	3.89
4b	− 0.213	− 0.065	0.148	0.074	13.51	0.139	0.130	4.40
4c	− 0.214	− 0.065	0.149	0.074	13.42	0.139	0.129	4.40
4d	− 0.214	− 0.074	0.140	0.070	14.28	0.144	0.148	4.20
4e	− 0.209	− 0.063	0.146	0.073	13.69	0.136	0.126	4.40
4f	− 0.209	− 0.063	0.146	0.073	13.69	0.136	0.126	4.92
4g	− 0.209	− 0.063	0.146	0.073	13.69	0.136	0.126	4.92
4h	− 0.209	− 0.073	0.136	0.068	14.70	0.141	0.146	4.71

Lipophilicity is defined by the partitioning of a compound between an aqueous and a nonaqueous phase. Log P is an important physicochemical parameter in the development of lipophilicity index.[40,41] It is generally accepted that more lipophilic molecule will interact more easily with the fatty acid tails of the lipid bilayer, thus allowing the molecule to cross cell membranes.[41] As shown in Table 3 the lipophilicity of the synthesized compounds increases with substitution of acridone ring and N-phenylacetamid unit by a methyl group.

3.2b *Molecular electrostatic potential surface*: The molecular electrostatic potential is related to the electron density and is important to identify the reactive sites of the molecule in electrophilic and nucleophilic.[42–44] Thus, it allows envisaging centers and their relative reactivity towards electrophilic and nucleophilic attacks.[45] The molecular electrostatic potential surface was calculated at the B3LYP/6-31G(d) optimized geometry for structures 4a–4h. As showing in (Figure 3), electrophilic sites are red in color which designates the negative regions of the molecule, while the nucleophilic sites are colored in blue and designate the positive regions of the molecule. The molecular electrostatic potential (MEPs) of compounds 4a–4h shows that the region with the most electronegative potential was located on nitrogen atoms in heteroaromatic 1,2,3 triazole ring and the two oxygen atoms of the carbonyl group of amide and acridone ring.

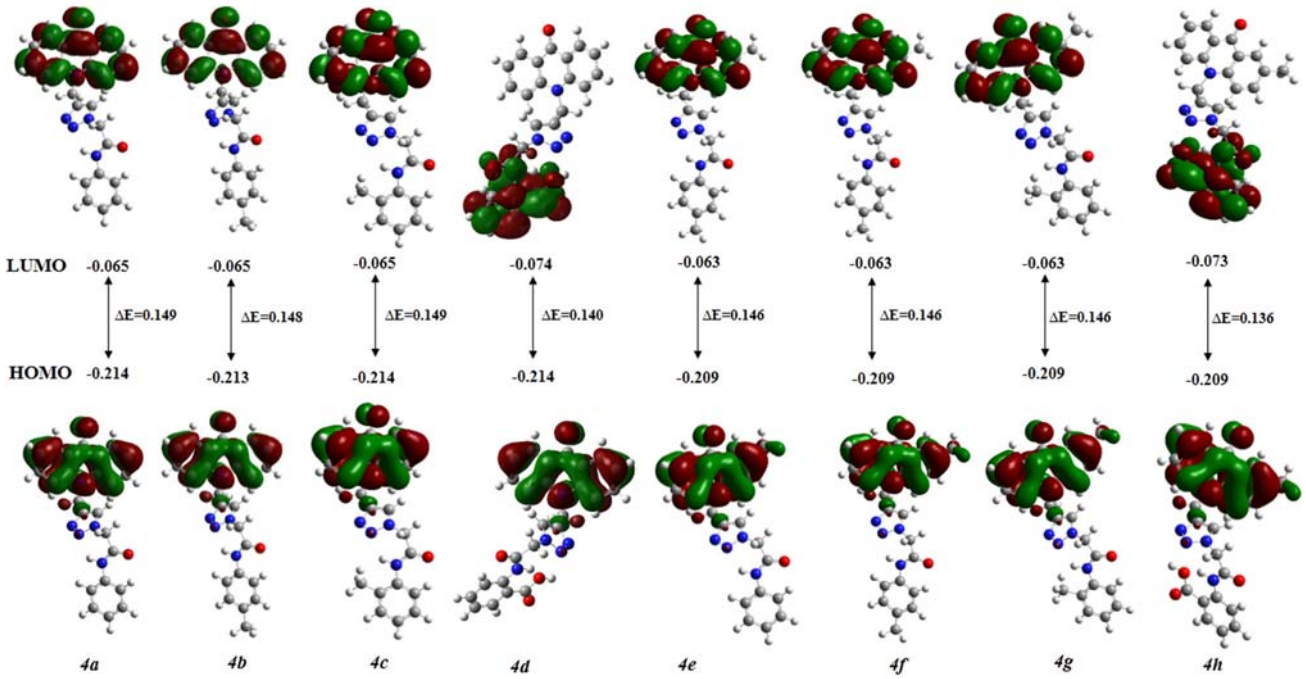


Figure 2. HOMO and LUMO plots of compounds 4a-h.

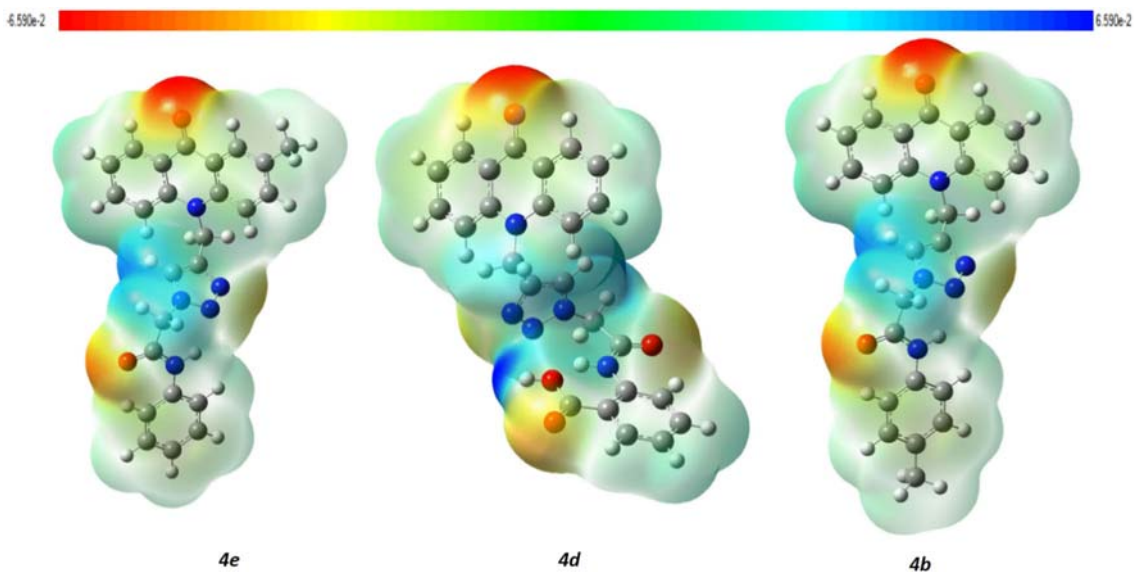


Figure 3. The molecular electrostatic potential surface of molecules 4b, 4d and 4e.

3.3 *Antibacterial activity*

The synthesized compounds were screened *in vitro* for their antibacterial activities against four gram-negative bacteria *Escherichia coli*, *Klebsiella pneumonia*, *pseudomonas putida*, *Serratia marcescens* and one gram-positive bacteria *Staphyloccocus aureus*. Initially, antibacterial activities of synthesized compounds were tested on the basis of the growth inhibition zone utilizing the disc diffusion method under standard conditions using Mueller-Hinton agar medium, according to the Clinical and Laboratory Standards Institute guidelines.[46] Then the minimum inhibitory concentration (MIC) measurement were conducted to examine the antibacterial activities of the synthesized compounds (**4a–h**). MIC data showed in Table 4 indicate that compounds 4c, 4e, 4f and 4g exhibited good inhibitory activities against *S. aureus* (MIC = 12.3−19.6 μg/mL) and *S. marcescens* (MIC = 43.6−75.2 μg/mL). Moreover, the compounds 4e and 4f showed modest inhibitory

Table 4. Antibacterial data for the synthesized compounds.

Compounds	Antibacterial activity data in MIC (μg/ml)				
	S. aureus	*E. coli*	*K. pneumonie*	*P. putida*	*S. marcescens*
1a	122.8	133.4	137.9	156.3	129.3
1b	118.4	124.2	130.4	145.5	127.3
4a	38.5	107.1	137.9	109.9	89.1
4b	28.5	74.1	86.9	90.1	66.1
4c	19.6	90.6	70.4	88.8	43.6
4d	72.9	90.9	122.8	120.3	109.0
4e	19.6	65.4	74.1	77.1	75.2
4f	12.3	38.5	56.6	74.9	48.3
4g	19.6	36.6	56.6	115.0	46.2
4h	38.5	56.6	107.1	121.8	51.3
Chloramphenicol	11.6	22.4	15.3	37.1	20.3
DMF (control)	–	–	–	–	–

activity against *P. putida* (MIC = 74.9 μg/mL) and the compounds 4f and 4g present MIC = 56.6 μg/mL against *K. pneumonia*. Noticeably, compound 4g was the most potent inhibitor against *E. coli* with a MIC value at 36.6 μg/mL. It was found that 4f was the most potent compound against Gram-positive and Gram-negative organisms, the activity of 4f was slightly weaker than that of Chloramphenicol against S. aureus (MIC = 12.3 μg/ml).

The MIC values listed in Table 4 showed an improvement in antibacterial activity after the substitution of the acridone ring by a triazole ring for all the germs, against the *Staphyloccocus aureus* the MIC was decreased from 122.8 to 19.6 μg/mL. Thus the substitution of acridone at position 2 by a methyl increases the antibacterial efficiency against all the germs. It can be observed that methyl substitution on the benzene ring was favorable to increase the antibacterial activity of the compounds. We can see that the antibacterial activity of the synthesized compounds may be due to the evolvement of the lipophilic character of the molecules, which help the crossing through the biological membrane of the bacteria and thereby inhibit their growth.

4. Conclusions

In this work, novel acridone-1,2,3-triazole hybrid derivatives were synthesized by microwave irradiation and conventional methods. The use of the MW method in the copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC) leads us to good yields and short reaction time. Structures of the novel acridon-1,2,3-triazole hybrid derivatives were determined by NMR, FTIR spectroscopy and mass spectrometry. All the synthesized compounds were screened for their *in vitro* antibacterial activities against *Escherichia coli*, *Klebsiella pneumonia*, *Pseudomonas putida*, *Serratia marcescens* and *Staphyloccocus aureus*, indicating that the substitution of the acridone ring by a 1,2,3-triazole nucleus increases the antibacterial potential of our compounds. The best antibacterial effect was exhibited by compound 4f against *S. aureus*. Theoretical calculations based on DFT were performed to determine the HOMO, LUMO, gap energies and MEPs. Results showed that gap energies are almost similar for all the synthesized compounds and that the substitution has a negligible effect on the gap energies. The molecular electrostatic potential (MEPs) maps show that the negative potential sites are on nitrogen atoms in heteroaromatic 1,2,3 triazole ring and the two oxygen atoms of the carbonyl group of amide and acridone ring.

Supplementary Information (SI)

The method of determination of minimum inhibitory concentration, quantum chemical calculation, synthesis method, ^{1}HNMR, ^{13}CNMR spectra are available at www.ias.ac.in/chemsci.

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