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Synthesis, antibacterial evaluation and computational studies of new acridone-1,2,3-triazole hybrids

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ABSTRACT

In continuation of our efforts to develop new drugs with antibacterial properties we have synthesized and evaluated new 1,2,3-triazole derivatives from acridone. The synthetic approach was started by the preparation of acridone skeleton through the Ullman condensation of 2-bromobenzoic acid and aniline derivatives. Subsequently, acridone nucleus was functionalized with propargyl bromide. Then, a click reaction of the latter compound and aromatic azides led to the formation of the title compounds in good yields. The synthesized compounds were screened for their *in vitro* antibacterial activity against one gram-positive bacteria *S. aureus* and three gram-negative bacteria *P. putida, K. pneumoniae* and *E. coli*. Among the synthesized compounds, 2-methyl-10-((1-(o-tolyl)-1H-1,2,3-triazol-4-yl)methyl)acridone (**4e**) had the most potent inhibitory activity against *S. aureus* with MIC = 10.1 µg/mL. Then, *in silico* docking studies were used in order to understand the binding interactions and mode of action of these compounds.

Introduction

The nitrogen-containing heterocyclic compounds continue to attract considerable attention in different scientific fields because of their practical usefulness, principally, due to a very wide spectrum of their pharmacological activities [1–5]. Acridones occupy an interesting position among these compounds and they represent significant building blocks in synthetic bioactive compounds, which display antimalarial [6], anticancer [7,8], antimicrobial [9,10], antiviral [11,12] and antitumor activities [13]. On the other hand, 1,2,3-triazoles derivatives are attractive candidates in medicinal chemistry as they constitute the building blocks of wide range of many 1,2,3-triazole compounds possessing an important pharmacological properties such as antitumoral [14,15], antibacterial [16–19], antityrosinase [20], anti-inflammatory [21] and anticancer [22–24]. In addition, many 1,2,3-triazole well-known drugs have been developed, among them Tazobactam (antifungal), Cefatrizine (antibacterial) and Rufinamide (anticonvulsants) can be mentioned (Fig. 1).

Microbial infections are a growing problem worldwide, producing mortality mainly in developing countries [25]. Considering the many adverse effects and development of bacteria resistance to a wide variety of antibacterial agents [26], there is a big demand for novel and efficient antimicrobial agents. Herein, in continuation of our studies on the development of new antibacterial agents [27,28], and focusing on the versatile biological activity of acridone-1,2,3-triazole system, we synthesized, and evaluated new 1,2,3-triazole derivatives from acridone against four pathogenic bacteria. *In silico* molecular docking and ADMET predication studies have been performed to rationalize the results of *in vitro* studies on antibacterial activity.

Results and discussions

Synthesis

By the strategy briefly depicted in Scheme 1, we have synthesized 1,2,3-triazole derivatives from acridone *via* cycloaddition reaction between aromatic azides and N-propargyl acridones. Initially, acridone (**2**) was prepared by condensation reaction between 2-bromobenzoic acid with aniline or p-toluidine in the presence of copper and potassium carbonate in isoamyl alcohol at reflux to produce 2-arylamino benzoic acids [29,30]. Then compound (**1**) was cyclized with sulfuric acid at 80 °C for three hours to give compounds (**2**). The N- propargyl acridone was obtained in high yield by N-alkylation of acridone moiety (**2**) with the propargyl bromide in the presence of catalytic amounts of TBAB in DMF at 70 °C. The last step was 1,3-dipolar cycloaddition reaction between

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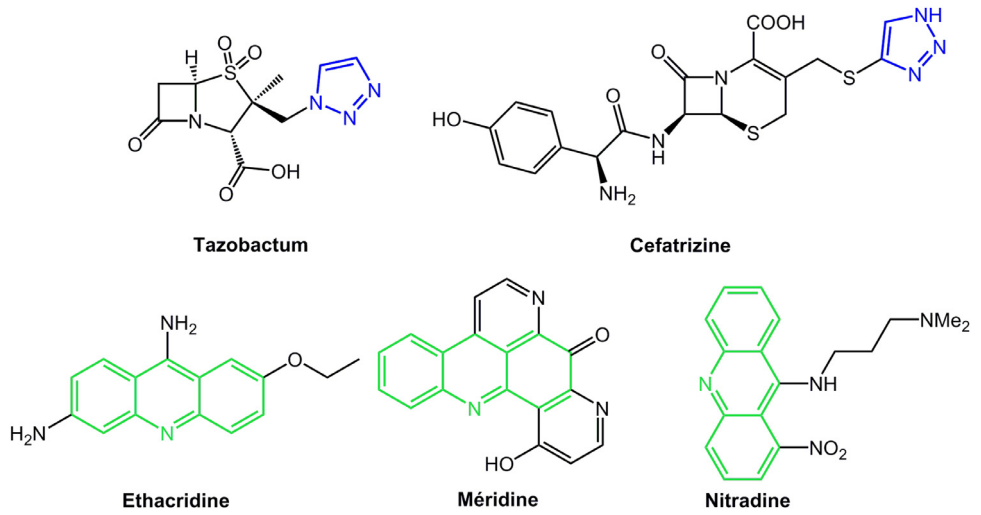
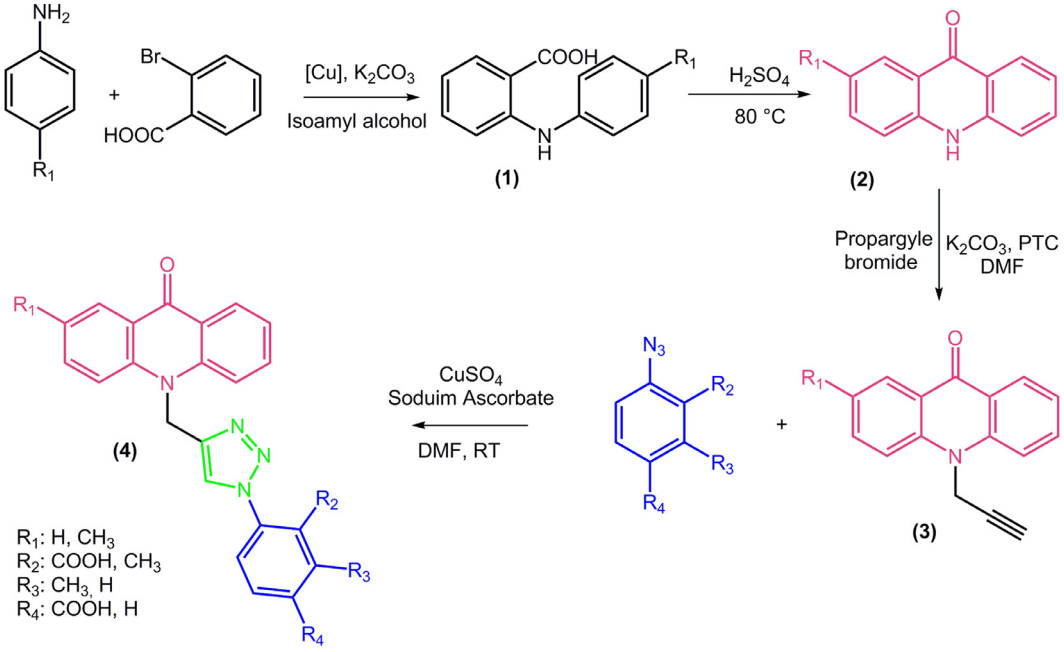


Fig. 1. Previously reported antimicrobial compounds.



Scheme 1. Synthesis route of new 1,2,3-triazole derivatives from acridone (**4a-h**).

aromatic azides and N-propargyl acridones (**3**) in the presence of copper sulfate and sodium ascorbate in DMF, the 1,2,3-triazoles (**4**) was obtained with good yield.

The structures of the synthesized compounds (**4a-h**) were fully characterized by IR, ^{1}H & ^{13}C NMR and HRMS analysis. The FTIR spectra of compounds (**4a**–**h**) showed characteristic bands of 1,2,3-triazole nucleus in the range of 1500–1300 cm^{-1} corresponding to C=C & N=N bonds. The characteristic bands of acridone ring was detected in the range 1640–1635 cm^{-1} corresponding to C=O bond. The ^{1}H NMR spectra of compounds (**4a-h**) showed characteristic signals of the protons corresponding to 1,2,3-triazole nucleus between 8.95 ppm and 8.59 ppm, in addition to aromatic protons in the region of 8.95–7.25 ppm. We also noticed the presence of signal at 5.89 ppm corresponded to methylene groups attached to acridone and 1,2,3-triazole groups. In ^{13}C NMR spectra all expected carbon signals corresponding to acridone-1,2,3-triazole derivatives were observed, principally the signals of methylene carbons between 50 ppm and 41 ppm and signals of aromatic carbons at 125 ppm and 143 ppm corresponding to 1,2,3-triazole nucleus.

Antibacterial activity

The antibacterial activity of the synthesized compounds **(4a-h)** were investigated against one gram-positive bacteria *Staphylococcus aureus* and three gram-negative bacteria *Pseudomonas putida, Klebsiella pneumonia,Escherichia coli.* The antibacterial activity has been primarily tested as the observed growth inhibition zones by disk-diffusion method using Mueller Hinton Broth (MBH) medium. Then, Minimum inhibitory concentrations (MIC) were determined for the synthesized compounds. Chloramphenicol and DMSO were used as positive and negative controls for antibacterial activity, respectively.

The observed minimum inhibitory concentration (MIC) antibacterial data of the synthesized compounds **4a-h** and the reference drugs are given in Table 1. The antibacterial activity re-

Table 1
MIC values (µg/mL) of the synthesized compounds (**4a-h**) against *S. aureus, E. coli, K. pneumonia* and *P. putida.*

	Staphylococcus aureus	Escherichia coli	Klebsiella pneumoniae	Pseudomonas putida
2a	*122.83*	*133.41*	*137.93*	*156.31*
2b	*118.43*	*124.22*	*130.43*	*145.52*
3a	*97.10*	*80.66*	*97.25*	*100.95*
3c	*83.20*	*70.14*	*102.20*	*115.20*
4a	*12,31*	*36,61*	*70,45*	*60,13*
4b	*31,32*	*66,36*	*81,32*	*119,36*
4c	*19,61*	*56,60*	*90,91*	*122,81*
4d	*38,46*	*56,64*	*74,07*	*77,16*
4e	*10,11*	*36,61*	*70,45*	*60,13*
4f	*31,52*	*60,15*	*80,00*	*119,36*
4 g	*19,61*	*56,60*	*85,90*	*120,81*
4h	*38,46*	*56,64*	*74,07*	*77,16*
Chloramphenicol	*11,65*	*22,41*	*15,38*	*37,03*
DMSO	–	–	–	–

sults revealed that the tested compounds exhibited various degrees of inhibition against Gram-positive and Gram-negative bacteria. *Staphyloccocus aureus* was observed to be the most sensitive bacteria, Compounds **4e** and **4a** with *o*-methylphenyl group on the acridone-1,2,3-triazole skeleton showed the best antibacterial activity against *Staphyloccocus aureus* with MIC values 10.11 and 12.31 μg/mL, respectively, compared to the standard drug Chloramphenicol (11.65 µg/mL). Beside this, compound **4c** and 4 g with *m*-methylphenyl group on the 1,2,3 triazole-acridone skeleton showed moderate antibacterial activity against *Staphyloccocus aureus* with MIC value 19.61 μg/mL. Also, the compound **4e** and **4a** showed moderate antibacterial potential against *E. coli* (36.61 µg/mL), compared to the standard drug Chloramphenicol (22.41 µg/mL). Moreover, all 1,2,3-triazole derivatives (**4a-h**) demonstrated a poor antibacterial activity against the germs *Pseudomonas putida* and *Klebsiella pneumonia.*

Structure-activity relationship studies revealed that the presence of 1,2,3-tiazole ring increased the antibacterial activity against all bacteria. The results of the antibacterial activity showed that *Staphyloccocus aureus* is the most sensitive bacteria to the synthesized compounds **(4a–h)**. Regarding, the effect of the substituent on the phenyl moiety of the acridone-1,2,3-triazole skeleton, the results revealed that the best MIC against *Staphyloccocus aureus* has been attained by the *o*-methylphenyl **(4e, 4a)**. However, the presence of carboxylic acid group on the phenyl moiety of the acridone-1,2,3-triazole skeleton decreased the antibacterial activity against *Staphyloccocus aureus*.

Molecular docking

The molecular-docking study was used to determine the binding modes of the synthesized compounds against Dihydrofolate Reductase from *S. aureus* (DHFR). Dihydrofolate reductase is a critical enzyme that catalyzes the chemical reaction for the reduction of tetrahydrofolate (THF) from dihydrofolate (DHF) through NADPH [31]. DHFR is essential in the biosynthesis pathways of the thymidylate and purines, as well as several other amino acids. Inhibition of DHFR leads to the depletion of tetrahydrofolate and eventual cell death [32]. We chose this target because the Dihydrofolate reductase (DHFR) is the target of many antibiotics and other natural compounds. Several classes of compounds have been explored for their potential antifolate activity; among the most outstanding are 1,2,3-triazoles [33,34], diaminotriazines [35], diaminopyrimidine [36] and diaminoquinazolines [37].

In this study, molecular docking of the most active compounds have been applied to study the different type of interactions and elucidate the probable binding modes between acridone derivatives and Dihydrofolate Reductase of *S. aureus* [38]. In order to validate the applied molecular docking approach, the co-crystallized ligand Trimethoprim (TOP) was docked into the active site of Dihydrofolate Reductase of *S. aureus* to determine RMS (Root Mean Square) distance that was satisfactory (RMSD=1.12 Å less than 2 Å), Figure S1 shows that the docked structure (green color) and the X-ray crystal structure (yellow color) are quite similar. Also, the synthesized acridones were docked into the binding pocket of Dihydrofolate Reductase enzyme successfully. The molecular docking representation for each synthetic compound and the superposition of all best docking pose in the enzyme binding pocket are shown in Figures S2-S10 (supplementary data).

The docking results showed that the synthesized compounds (**4a-h)** fit snugly making various close contacts with the residues lining the active site of Dihydrofolate Reductase enzyme, the interacting amino acids of all compounds with Dihydrofolate Reductase enzyme are shown at Table 2. The docking pose of the most active compound (**4e**) showed high docking score against Dihydrofolate Reductase enzyme, as the free energy of binding was (−7.97 Kcal/mol) (Table 2), the analysis of best scoring pose of compound (**4e**) in the Dihydrofolate Reductase pocket of 2W9S revealed important hydrophobic as well as hydrogen bonding interactions between them (Fig. 2). The phenyl group exhibit hydrophobic interactions with the residues Ile50, Leu20, Leu28, Leu54 and Ile31. Moreover phenyl group of acridone nucleus present hydrophobic interactions with Ile5, Phe92, Ile14, and Ile31, while carbonyl of the acridone ring exhibit hydrogen bonding interaction with Ala7. Also the active compounds **4a, 4c** and 4 g showed one favorable hydrogen bond between the carbonyl of acridone nucles and the hydrogen of the side chain of Ala7, and hydrophobic interactions with the residues Ile5, Ile31, Ile50, Leu20 and Ile14. From the different interactions of the compounds (**4a-h)** in Table 2, it can be concluded from the docking results that the most active compounds **4e, 4a, 4c** and 4 g had H-bond interaction with the hydrogen of the side chain of Ala7 in the active site of Dihydrofolate Reductase enzyme.

Furthermore, the synthesized compounds (**4a-h**) bind to active site of Dihydrofolate Reductase and share largely homogeneous in binding mode specially with Ala7, Ile50, Leu20, Leu28, Leu54, Ile31, Phe92 and Ile14 to several Dihydrofolate Reductase inhibitors reported in the literature [39,40]. Therefore, docking studies revealed the strong binding affinity of **4e** at the active site of Dihydrofolate Reductase enzyme, which may be responsible for its significant *in vitro* antibacterial activity especially against *S. aureus*.

In silico *ADMET prediction*

In silico metabolic, toxicity and pharmacokinetic parameters of synthesized compounds (**4a-h**) were predicted using pkCSM online tool [41] and DruLito software [42]. Hence, Blood-brain barrier penetration (BBB), human intestinal absorption, total clearance,

Table 2
The interactions and binding affinities of the synthesized compounds.

Compound	Interaction with nucleic acid	Hydrogen bonding	Binding affinity
4a	*Ala7, Val6, Ile5, Ile31, Phe92, Ile50, Leu20, Ile14*	*Ala7*	*−7.62*
4b	*Ile50, Leu20, Ile14, Lys45, Asn18, Aser49*	–	*−7.40*
4c	*Ala7, Leu28, Ile5, Phe92, Ile50, Leu20, Ile14, Leu54, Val6, Ile31*	*Ala7-*	*−7.51*
4d	*Tyr98, Gln19, Thr46, Ile50, Leu20, Ala7, Val6, Ile5, Phe92, Ile31, Ile14*	–	*−7.74*
4e	*Ala7, Val6, Ile5, Phe92, Ile50, Leu20, Ile14, Leu28, Leu54, Ile31*	*Ala7*	*−7.97*
4f	*Ile5, Phe92, Ile50, Leu20, Ile31*	–	*−7.29*
4 g	*Ala7, Val6, Ile5, Phe92, Leu28, Ile31, Ile14, Ile50, Leu20, Leu54*	*Ala7*	*−7.66*
4h	*Ser49, Ile50, Leu20, Ile5, Ile31, Phe92, Leu28*	*Ser49*	*−7.32*

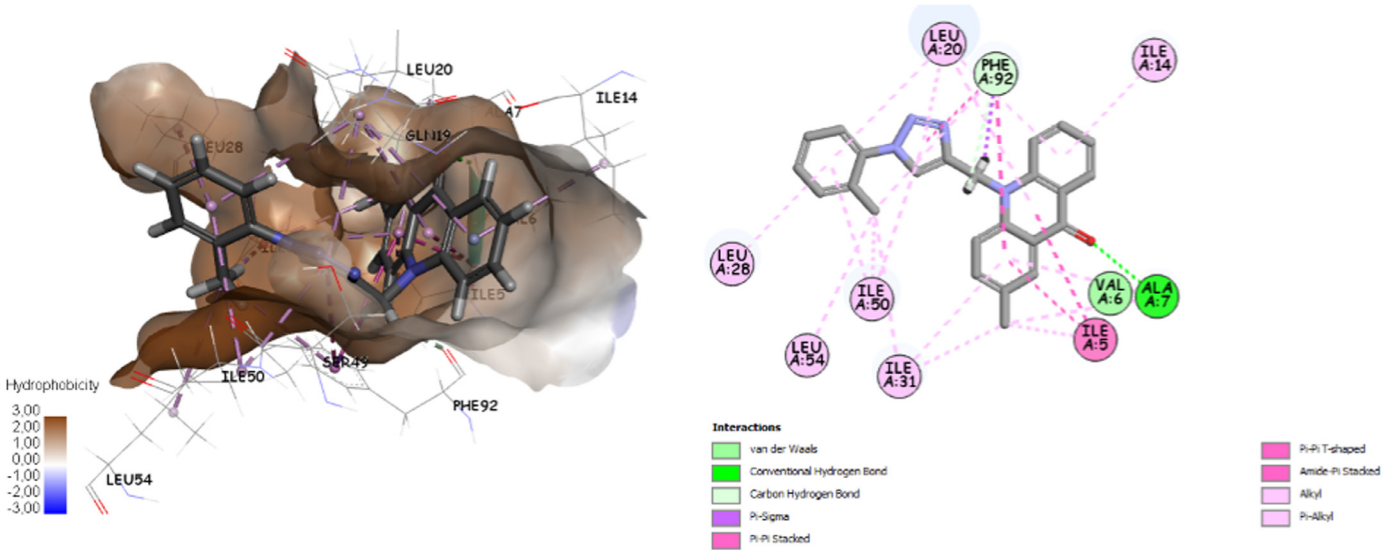


Fig. 2. Binding mode of compound **4e** with Dihydrofolate Reductase (DHFR) complex, the hydrogen bonds are presented in green dashed lines.

acute oral toxicity, AMES toxicity, HEGR inhibitor, skin sensitization and some drug-likeness properties were calculated.

The results of *in silico* AMDET predication are reported in Table S1, showed acceptable range of Blood-brain barrier penetration (BBB) for an ideal drug candidate, corresponding to its entry to the central nervous system, is less than 0.3, which indicates that compounds (**4a-h**) present small chance to cross the blood-brain barrier. Also compounds (**4a-h**) present good human intestinal absorption (HIA) with a high percentage (>90%), which indicates that the synthesized compounds would be easily absorbed from intestine and circulated through blood. The toxicity profile of the synthesized compounds (**4a-h**) counting the Hepatoxicity, human ether-a-go-go related gene (hERG), Max. Tolerated dose (human), Minnow toxicity and Skin sensitization indicate that the 1,2,3-triazoles apparently do not have potential toxicity. Moreover, Metabolism plays an important role in the bioavailability of drugs. Cytochrome CYP450 enzymes are the most interesting class to study this effect. Synthesized compounds (**4a-h**) were studied either to act as inhibitors or substrate of Cytochrome CYP450 enzymes. Most of the compounds were found to be the inhibitors of CYP2C9, CYP2C19 and CYP1A2 and substrate of CYP3A4.

The DruliTo software was used to calculate the molecular properties such as topological polar surface area (TPSA), hydrogen bond donors and acceptors, partition coefficient (Log P), molecular weight and rotatable bonds (Table 3). Hence, Lipinski's rule of five were calculated to evaluate the drug likeness of the synthesized compounds. Thus all the synthesized compounds (**4a-h**) have the potential to be developed as an orally active drug like candidates and may be potentially active antibiotic drug candidates against *S. aureus.*

Conclusion

In summary new 1,2,3-triazole derivatives from acridone were prepared, characterized and biologically evaluated. The synthesized compounds (**4a-h)** were screened for their *in vitro* antibacterial activity against four bacteria pathogenic strains, compound **4e** was found to be the most potent against *S. aureus* compared with the standard drug Chloramphenicol. Molecular docking studies revealed that, occupation of compounds (**4a-h**) at the active site of Dihydrofolate Reductase *via* hydrogen bonding and hydrophobic interactions may be the reason for its significant *in vitro* antibacterial activity against *S. aureus.* Finally, *in silico* ADMET predictions suggested that synthesized compounds have good drug-likeness and ADMET profiles.

Experimental

Materials

All materials were purchased from commercial suppliers. Spectrometer.IR spectra were recorded using JASCO FT-IR 4100 spectrophotometer. The ^{1}H, ^{13}C NMR spectra was recorded with Bruker Avance 300. Mass spectrometric measurements were recorded using Exactive^{TM} Plus Orbitrap.

Synthesis

2-(Phenylamino)benzoic acid (1)

A mixture of aniline (0.35 g, 3.6 mmol), o-bromobenzoic acid (0.5 g, 2.5 mmol), anhydrous potassium carbonate (0.42 g,

Table 3
Lipinski's properties of the newly synthesized compounds.

Compound	Property						Lipinski violation
	Log*P*	H-bond acceptor	H-bond donor	Polar surface area (A^2)	Rotatable Bonds	Molecular weight	
4a	2.62	5	0	48.27	3	366.15	*0*
4b	1.76	7	1	85.57	4	396.12	*0*
4c	2.83	5	0	48.27	3	366.15	*0*
4d	1.97	7	1	85.57	4	396.12	*0*
4e	3.01	5	0	48.27	3	380.16	*0*
4f	2.16	7	1	85.57	4	410.14	*0*
4 g	3.23	5	0	48.27	3	380.16	*0*
4h	2.37	7	1	85.57	4	410.14	*0*

3.1 mmol), 0.05 g of metallic copper powder and 0.02 g of copper oxide was refluxed for 4 h in 10 mL of amyl alcohol. The amyl alcohol was evaporated then poured into (50 mL) hot water, cooled to room temperature. The medium pH was then adjusted to 4 by adding HCl (0.5 M). Compound **1** was obtained as a white precipitate which was then recrystallized from ethanol.

White yellow solid; yield: 70%, mp = 183 °C. IR (KBr): 3330, 3040, 2984, 1661, 1513, 1415 cm^{-1}. ^1H NMR (300 MHz, DMSO–d_6, 25 °C, TMS): 13.06 (s, 1H, OH), 9.68 (s, 1H, NH), 7.93 (m, 1H, Ar-H), 7.39–7.36 (m, 3H, Ar-H), 7.26–7.25 (m, 1H, Ar-H), 7.26 (m, 3H, Ar-H), 7.08(m, 2H, Ar-H). ^{13}C NMR (75 MHz, DMSO–d_6, 25 °C, TMS): 169.0 (*C = O*), 147.0, 140.8, 134.6, 130.5, 129.3, 123.2, 121.9 (2C), 116.3 (2C), 113.1, 112.2.

Acridone (2)

The N-phenylantranilic acid (1 g, 4.8 mmol) was taken in 3.5 mL of concentrated sulfuric acid and heated on water bath for 3 h. Reaction mixture was added to hot water and the resulting precipitates were filtered to get acridone (**2**). The sample of acridone was recrystallized from acetic acid.

Yellow solide, yield 78%, m.p. > 330 C. IR (KBr) 3275, 3084, 1640, 1570 cm^{-1}. ^1H NMR (300 MHz, DMSO–d_6, 25 °C, TMS): 11.74 (s, 1H, NH), 8.23 (dd, *J* = 8.1, 1.2 Hz, 2H, Ar-H), 7.70 (td, *J* = 8.4, 1.5 Hz, 2H, Ar-H), 7.53 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.23 (td, *J* = 8.4, 1.5 Hz, 2H, Ar-H). ^{13}C NMR (75 MHz, DMSO–d_6, 25 °C, TMS): 177.2 (*C = O*), 141.3, 133.9, 126.4, 121.4, 120.9, 117.8.

10-(Prop-2-yn-1-yl)acridone. ***(3)***

To a mixture of acridone (5 g, 25 mmol), potassium carbonate (5.5 g, 30 mmol) and TBAB (5 g, 25 mmol) in DMF (50 ml), propargyl bromide (4 g, 36 mmol) was added and the mixture was stirred at room temperature for 6 h. After that, it was poured into water and the white yellow formed precipitate was recrystallized from methanol-DMF.

White yellow solid; yield: 75%, mp = 206 °C. IR (KBr): 3208, 3010, 2210, 1638, 1598 cm^{-1}. 1H NMR (300 MHz, DMSO–d_6, 25 °C, TMS): δ= 8.34 (d, *J* = 7.8 Hz,1H, Ar–H), 8.12 (s,1H, Ar–H), 7.87- 7.86 (m, 4H, Ar–H), 7.37–7.38 (m, 2H, Ar–H), 5.32 (s, 2H, CH_2), 2.41 (s, 1H, CH), 2,38 (s, 3H, CH_3). 13C NMR (75 MHz, DMSO–d_6, 25 °C, TMS) δ 177.1 (*C = O*), 141.7, 134.7, 134.4, 127.7, 127.0, 123.3 (2C), 122.2, 118.4, 116.3 (2C), 79.1, 76. 1 (CH), 36.1 (CH_2).

General procedure for the synthesis of acridone-1,2,3-triazole derivatives (4a-h)

To a solution of 10-(prop-2-yn-1-yl)acridone (0.48 g, 2 mmol) in DMF (5 mL), aromatic azide (3 mmol), copper sulfate (0.08 g, 0.4 mmol) and sodium ascorbate (0.11 g, 0.6 mmol) were added and the reaction mixture was stirred at room temperature for 8 h. After completion of the reaction, water (50 ml) was added, and the precipitate was filtered off, washed with cold water, and purified by recrystallization in DMF

10-((1-(o-Tolyl)−1H-1,2,3-triazol-4-yl)methyl)acridin-9(10H)-one (4a)

Yellow solid; yield: 90%, mp = 224–226 °C. IR (KBr): 3112, 3063, 1638, 1600, 1502 cm^{-1}. ^1H NMR (300 MHz, DMSO–d_6, 25 °C, TMS) δ 8.62 (s, 1H, CH-triazole), 8.40 (dd, *J* = 8.0, 1.7 Hz, 2H, Ar–H), 8.05 (d, *J* = 8.8 Hz, 2H, Ar–H), 7.86 (ddd, *J* = 8.7, 6.9, 1.8 Hz, 2H, Ar–H), 7.57 – 7.34 (m, 6H, Ar–H), 5.91 (s, 2H, CH2), 2.11 (s, 3H, CH3). ^{13}C NMR (75 MHz, DMSO–d_6, 25 °C, TMS) δ 176.6 (C=O), 142.5, 141.9 (2C), 136.0, 134.1 (2C), 132.9, 131.2, 129.7, 126.9, 126.5 (2C), 125.9, 125.1 (2C), 121.7, 121.4 (2C), 116.3 (2C), 41.5 (CH_2), 17.3 (CH_3). MS (ESI) for $C_{23}H_{18}N_4O$ $[M + H]^+$, calcd: 367.1511, found: 367.1511.

4-(4-((9-Oxoacridin-10(9H)-yl)methyl)−1H-1,2,3-triazol-1-yl)benzoic acid (4b)

Yellow solid; yield: 79%, mp >300 °C. IR (KBr): 3397, 3112, 3063, 1702, 1638, 1600, 1502 cm^{-1}. ^1H NMR (300 MHz, DMSO–d_6, 25 °C, TMS) δ 8.95 (s, 1H, CH-triazole), 8.41 (dd, *J* = 8.0, 1.7 Hz, 2H, Ar–H), 8.08–7.95 (m, 6H, Ar–H), 7.87–7.81 (m, 2H, Ar–H), 7.41–7.36 (m, 2H, Ar–H), 5.92 (s, 2H, CH2). ^{13}C NMR (75 MHz, DMSO–d_6, 25 °C, TMS) δ 176.7 (C=O), 164.5 (C=O), 144.1, 141.8 (2C), 139.2, 137.2, 134.2 (2C), 132.2, 131.0, 128.0, 126.6 (2C), 121.8, 121.6 (2C), 121.5, 119.8, 117.1, 116.2 (2C), 41.8 (CH_2). HRMS (ESI) for $C_{23}H_{16}N_4O_3$ $[M + H]^+$, calcd: 397.1255, found: 397.1255.

10-((1-(m-Tolyl)−1H-1,2,3-triazol-4-yl)methyl)acridin-9(10H)-one (4c)

Yellow solid; yield: 85%, mp >300 °C. IR (KBr): 3120, 3063, 1637, 1606, 1597, 1507 cm^{-1}. ^1H NMR (300 MHz, DMSO–d_6, 25 °C, TMS) δ 8.73 (s, 1H, CH-triazole), 8.40 (dd, *J* = 8.0, 1.7 Hz, 2H, Ar–H), 7,99 (d, *J* = 8,1 Hz, 2H, Ar–H), 7.83 (t, 2H, Ar–H), 7.70 (d, *J* = 7.2 Hz, 2H, Ar–H), 7.36 (d, *J* = 7.2 Hz, 4H, Ar–H), 5.86 (s, 2H, CH_2), 2.36 (s, 3H, CH_3). ^{13}C NMR (75 MHz, DMSO–d_6, 25 °C, TMS) δ 177.1 (C=O), 144.1, 142.5 (2C), 138.8, 134.6 (2C), 132.7, 131.1, 129.5 (2C), 126.2 (2C), 125.3 (2C), 122.4, 121.9 (2C), 120.5, 116.6 (2C), 42.3 (CH_2), 20.9 (CH_3). MS (ESI) for $C_{23}H_{16}N_4O_3$ $[M + H]^+$, calcd: 367.1401, found: 367.1404.

2-(4-((9-Oxoacridin-10(9H)-yl)methyl)−1H-1,2,3-triazol-1-yl)benzoic acid (4d)

Yellow solid; yield: 75%, mp >300 °C. IR (KBr): 3405, 3109, 3053, 1700, 1639, 1602, 1500 cm^{-1}. ^1H NMR (300 MHz, DMSO–d_6, 25 °C, TMS) δ 8.93 (s, 1H, CH-triazole), 8.37 (dd, *J* = 8.0, 1.7 Hz, 2H, Ar–H), 8.04–7.98 (m, 3H, Ar–H), 7.69–7.62 (M, 5H, Ar–H), 7.34–7.26 (m, 2H, Ar–H), 5.84 (s, 2H, CH2). ^{13}C NMR (75 MHz, DMSO–d_6, 25 °C, TMS) δ 177.0 (*C = O*), 163.9 (*C = O*), 144.0, 141.9 (C2), 139.3, 137.5, 134.1 (C2), 131.2, 128.1 (C2), 126.5 (C2), 121.8, 121.6, 121.4 (C2), 119.7, 117.3, 116.1 (C2), 41.7(CH_2). MS (ESI) for $C_{23}H_{16}N_4O_3$ $[M + H]^+$, calcd: 397.1507, found: 397.1507.

2-Methyl-10-((1-(o-tolyl)−1H-1,2,3-triazol-4-yl)methyl)acridin-9(10H)-one
(4e)

Yellow solid; yield: 89%, mp >300 °C. IR (KBr): 3110, 3065, 1637, 1610, 1601, 1502 cm^{-1}. ^1H NMR (300 MHz, DMSO–d_6, 25 °C, TMS)

δ 8.59 (s, 1H, CH-triazole), 8.38 (d, J = 7.9 Hz, 1H, Ar–H), 8.25 – 8.12 (m, 1H, Ar–H), 8.01 (dd, J = 19.3, 8.7 Hz, 2H, Ar–H), 7.83 (t, J = 7.9 Hz, 1H, Ar–H), 7.68 (d, J = 8.7 Hz, 1H, Ar–H), 7.58 – 7.25 (m, 5H, Ar–H), 5.89 (s, 2H, CH2), 2.46 (s, 3H, CH3), 2.10 (s, 3H, CH3). ^{13}C NMR (75 MHz, DMSO–d_6, 25 °C, TMS) δ 176.5 (C = O), 144.2, 141.7, 140.0, 136.0, 135.4, 133.9, 132.9, 131.2, 130.6, 129.7, 126.8, 126.6 (C2), 125.9, 125.8, 125.1, 121.6, 121.2, 116.4, 116.2, 41.4 (CH_2), 20.1 (CH_3), 17.3 (CH_3). MS (ESI) for $C_{24}H_{20}N_4O$ $[M + H]^+$, calcd: 381.1669, found: 381.1669.

2-Methyl-4-(4-((9-oxoacridin-10(9H)-yl)methyl)−1H-1,2,3-triazol-1-yl)benzoic acid
(4f)

Yellow solid; yield: 82%, mp >300 °C**.** IR (KBr): 3398, 3110, 3063,1700, 1638, 1609, 1502 cm^{-1}. ^{1}H NMR (300 MHz, DMSO–d_6, 25 °C, TMS) δ 8.93 (s, 1H, CH-triazole), 8.40 (s, 1H, Ar–H), 8.14 (s, 1H, Ar–H), 8.04–7.95 (m, 5H, Ar–H), 7.87–7.82 (m, 2H, Ar–H), 7.37 (t, J = 7.4 Hz, 2H, Ar–H), 5.90 (s, 2H, CH2), 2.29 (s, 3H, CH3). ^{13}C NMR (75 MHz, DMSO–d_6, 25 °C, TMS) δ 176.5 (C = O), 164.9 (C = O), 144.2, 141.7, 139.9, 139.2, 136.4, 135.5, 134.0 (C2), 130.7, 129.3, 126.6 (C2), 125.9, 125.8, 121.6 (C2), 121.2, 116.2, 116.0, 41.6 (CH_2), 20.1 (CH_3). MS (ESI) for $C_{24}H_{18}N_4O_3$ $[M + H]^+$, calcd: 411.1403, found: 411.1408.

2-Methyl-10-((1-(m-tolyl)−1H-1,2,3-triazol-4-yl)methyl)acridin-9(10H)-one
(4 g)

Yellow solid; yield: 81%, mp >300 °C**.** IR (KBr): 3112, 3063, 1638, 1600, 1502 cm^{-1}. ^{1}H NMR (300 MHz, DMSO–d_6, 25 °C, TMS) δ 8,70(s, 1H, triazole), 8.33 (d, J = 7.2 Hz, 1H, Ar–H), 8.14 (s, 1H, Ar–H), 7,94–7.53 (m, 6H, Ar–H'), 7.33 (d, J = 7.2 Hz, 3H, Ar–H), 5.78 (s, 2H, CH_2), 2,42 (s, 3H, CH_3), 2.32 (s, 3H, CH_3). ^{13}C NMR (75 MHz, DMSO–d_6, 25 °C, TMS) δ 177.0 (C = O), 144.2, 142.2, 140.4 (C2), 138.8, 135.9, 134.5 (C2), 131.1, 130.6, 127.1, 126.3 (C2), 122.1, 121.8, 121.7, 120.3, 116.8, 116.6 (C2), 42.6 (CH_2), 21.0 (CH_3), 20.6 (CH_3). MS (ESI) for $C_{24}H_{20}N_4O$ $[M + H]^+$, calcd: 381.1669, found: 381.1660.

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

Yellow solid; yield: 78%, mp >300 °C**.** IR (KBr): 3400, 3121, 3052, 1704, 1640, 1605, 1501 cm^{-1}. ^{1}H NMR (300 MHz, DMSO–d_6, 25 °C, TMS) δ 8.92 (s, 1H, CH-triazole), 8.39 (d, J = 7.9 Hz, 1H, Ar–H), 8.15 (s, 1H, Ar–H), 7.96–7.87 (m, 2H, Ar–H), 7.69–7.61 (m, 5H, Ar–H), 7.31–7.26 (m, 2H, Ar–H), 5.81 (s, 2H, CH2), 2.44 (s, 3H, CH3). ^{13}C NMR (75 MHz, DMSO–d_6, 25 °C, TMS) δ 176.0 (C = O), 166.9 (C = O), 142.4, 141.7 (C2), 140.5, 138.3, 136.6, 134.8 (C2), 133.0, 129.8, 126.7 (C2), 125.8, 121.7 (C2), 121.1, 120.8, 116.3 (C2), 115.0, 41.9 (CH_2), 20.3 (CH_3). MS (ESI) for $C_{24}H_{18}N_4O_3$ $[M + H]^+$, calcd: 411.0883, found: 411.0884.

Antibacterial activity

The 1,2,3-triazoles (**4a-h**) were evaluated for their *in vitro* antibacterial activity by the disk diffusion method, the active compounds were subjected to the determination of the MIC, using the broth Microdilution method. The microorganisms utilized for the test were *E. coli, Staphylococcus aureus, Pseudomonas putida* and *Klebsiella pneumonia*. They were collected from clinical isolates. Bacterial inoculums were prepared by subculturing microorganisms into MHB at 37 °C for 18 h and were diluted to approximately 10^6 CFU mL^{-1}. Initial solution with concentration 0.5 mg/mL of the compounds (**4a-h**) were prepared in DMF, further serial dilutions were made in the microplates and 100 μl of MHB containing each test microorganism were added to the microplate [43], then incubated at 36 °C for 24 h. After incubation, 20 μL of TTC (0.04 mg/mL) were added to each microplate. The Color changes of TTC from colorless to red were accepted as microbial growth [44].

Molecular docking studies

Molecular docking of the synthesized compounds (**4a-h**) with the Dihydrofolate Reductase complex (PDB ID: 2W9S) of *S. aureus* [38] was carried out using the AutoDock software [45]. For preparation of protein and ligands see supporting information. The Discovery Studio (version 4.5) was used for graphical visualization. Different types of interactions between protein and the docked compounds (**4a-h**) were analyzed using Discovery Studio.

ADMET and drug-likeness profiles

The physicochemical and pharmacokinetic properties of the 1,2,3-triazole derivatives from acridone were predicted using the pkCSM [41]and DurLiTo [42] online tools.

Declaration of Competing Interest

There are no conflicts to declare.

CRediT authorship contribution statement

Mohammed Aarjane: Conceptualization, Methodology, Writing - original draft. **Siham Slassi:** Data curation, Software, Investigation. **Amina Amine:** Supervision.

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