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Novel 1,4-benzothiazine derivatives: synthesis, crystal structure, and anti-bacterial properties

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Abstract In order to develop relatively small molecules as pharmacologically active molecules, novel 1,4-benzothiazine derivatives with triazole and oxazolidinone were synthesized. In this study, a series of 1,2,3-triazolylmethyl-1,4-benzothiazine derivatives were developed by exploiting a click chemistry reaction using a CuI-catalyzed Huisgen [3 + 2] cycloaddition. Starting from 2-(substituted)-3,4-dihydro-2H-1,4-benzothiazi-3-one, a number of 1,4-benzothiazine derivatives were also synthesized using different alkylating agents to give a 4-(substituted)-2-(substituted)-3,4-dihydro-2H-1,4-benzothiazi-3-one in good yields. The crystal and molecular structure of compound oxazolidin-2-one in basic benzothiazine was established by single-crystal X-ray diffraction. The newly synthesized products were subjected to in vitro biological evaluation. The result indicated that the compounds show convincing antibacterial activities against different microorganisms. All structures of the synthesized compounds were elucidated on the basis of spectral analyses and chemical reactions.

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Introduction

In recent years, heterocyclic compounds have received considerable attention due to their significant importance in pharmacological and agricultural fields [1]. Notably, nitrogen and sulfur-containing heterocyclic compunds are known to exhibit excellent biological and pharmaceutical activities [2]. In fact, benzothiazine derivatives have extensively been studied in different areas of chemistry, including pharmaceutical and other chemical industries. The benzothiazine core has several active sites, providing great responsiveness, making it an excellent heterocyclic precursor in the synthesis of new heterocyclic systems. With respect to biological applications, these derivatives are found to be potent anti-inflammatory, analgesic, antimicrobial, anti-viral, herbicidal, fungicidal, and anticarcinogenic compounds [3–5]. These derivatives have also been reported as synthetic intermediates for other drugs, as stabilizers in rubber vulcanization, corrosion inhibitors, and fading preventers [6–9]. Recent studies have shown that benzothiazine derivatives have a broad spectrum of action [10, 11]. Among their various biological activities, benzothiazine derivatives have been studied widely, and several synthetic approaches have been proposed [12] since their very first synthesis [13].

Alternatively, 1,3-dipolar cycloadditions form a subject of intensive research in organic synthesis in view of their enormous synthetic applications [14]. In particular, the cycloaddition between a terminal alkynes and azides. Historically, triazolic compounds have proven themselves to be very important in medicinal chemistry, as they have [15, 16] antitumor, anti-inflammation, antimicrobial, antifungal, antithrombotic, antiplatelet, and antiviral [17] properties. 1,2,3-triazoles have gained increased attention in the drug-discovery field since the introduction of the "click chemistry" concept by Sharpless [18]. These types of compounds can actively participate in hydrogen bonding and dipole–dipole interactions because of their strong dipole moments and are extremely stable to hydrolysis and oxidative/reductive conditions. Further, oxazolidinones represent a novel class of antibacterial agents with significant activity against multidrug-resistant Gram-positive pathogenic bacteria including methicillin-resistant *Staphylococcus aureus* (MRSA), *Staphylococcus epidermidis* (MRSE), and vancomycin-resistant *Enterococci* (VRE) are of major concern. Many oxazolidinone derivatives are in clinical use, such as linezolid eperezolid as antimicrobial agents [19]. Linezolid was the first oxazolidinone approved for the treatment of Gram-positive bacterial infections in humans. Since linezolid, the many attractive traits of oxazolidinone series have encouraged further research in this area, and also the literature reveals the existence of extensive chemical programs [20]. Today, a large number of oxazolidinone derivatives with diverse structural modifications have been reported in various patent reviews and scientific literature [21–23]. The main target of these efforts is to extend the spectrum of activity and reduction and/or elimination of toxic effects and potential drug–drug interactions associated with monoamine oxidase (MAO) inhibition.

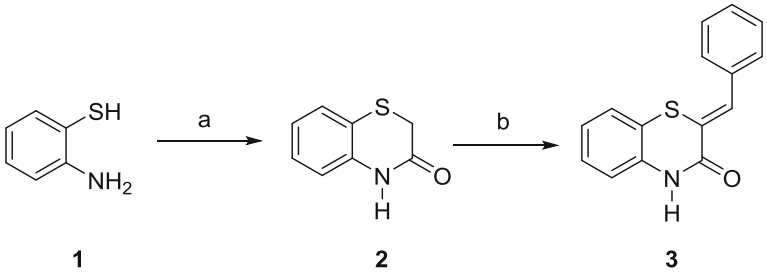
In general, the incorporation of two moieties increases biological activity of both, and thus it was of value to synthesize some new heterocyclic derivatives having two moieties in the same molecules. Considering these things, it is of our interest to integrate both 1,4-benzothiazine, triazole pharmacophore, and oxazolidinone motif, respectively, to generate a newer scaffold for biological evaluation. Herein, we will describe new synthetic alternatives to derivatives of 1,4-benzothiazine, using alkylation reactions and 1,3-dipolar cycloaddition with azide. A result evaluation of the antibacterial activity will be made on some synthesized molecules.

Results and discussion

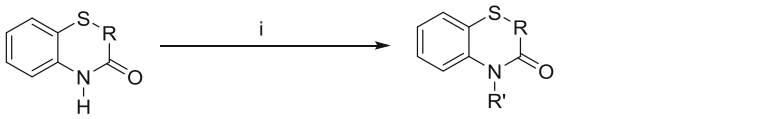
Synthesis

Initially, we prepared 1,4-benzothiazine **2** by condensation of 2-aminothiophenol **1** with methyl chloroacetate in the presence of excess potassium carbonate in DMF at reflux. Thereafter, 3,4-dihydro-2H-1,4-benzothiazin-3-one **2** was subjected to the action of benzaldehyde in the presence of an excess of sodium methylate in DMF. This reaction thus leads to the formation of compound **3**. The synthetic route to 2-(phenylmethylidene)-3,4-dihydro-2H-1,4-benzothiazin-3-one **3** is described in Scheme 1.

Given the presence of more reactive sites in the pattern of benzothiazine, this heterocycle may engage in various types of reactions such as, *N*-alkylation, electrophilic substitution, nitrating. In this respect, we were exclusively interested in the reactions of *N*-alkylation of both compounds **2** and **3** by the action of alkylating agents of choice, such as methyl chloroacetate, propargyl chloride, and 1-bromobutane. The reactions will be under the conditions of phase transfer catalysis in the presence of bromide tetra-*n*-butylammonium (TBAB) as catalyst and potassium carbonate as base in DMF. These reactions enabled us to get the products *N*-alkylated **4**–**8** with good yields (Scheme 2; Table 1). The structure of the compound **4**–**8** [24–28], has been unambiguously characterized on the basis of spectral data ^{1}H



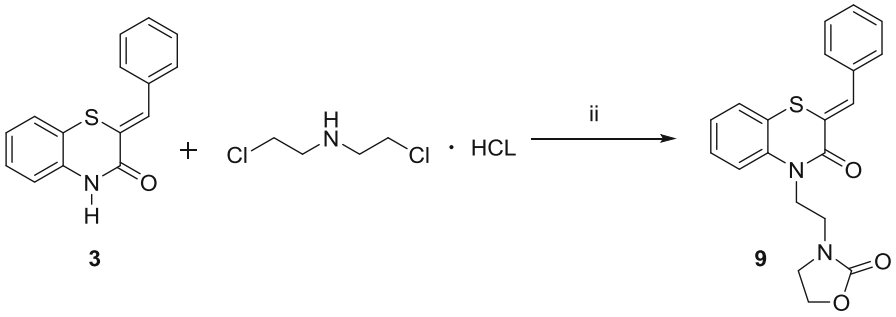
Scheme 1 Preparation of 1,4-benzothiazine **2** and 2-(phenylmethylidene)-3,4-dihydro-2H-1,4-benzothiazin-3-one **3**. Reagents and conditions: (*a*) $ClCH_3CO_2CH_3$, DMF/K_2CO_3, rt. 24 h; (*b*) benzaldehyde, CH_3ONa/DMF, reflux, 48 h



Scheme 2 Synthetic route for the preparation of *N*-alkylated **4**-**8** compounds, (*i*) substituted alkynes ($CH_2CO_2CH_3$ Cl, $CH_2C{\equiv}CH$ Cl, CH_2 $(CH_2)_2$ CH_3 Br), DMF, K_2CO_3, TBAB, rt, 24 h

Table 1 *N*-Alkyl derivatives **4**-**8** produced via alkylation reaction

Entry	R	R′	Compounds	Yield (%)
1	CH_2	$CH_2CO_2CH_3$	4	72
2	CH_2	$CH_2C{\equiv}CH$	5	75
3	C=CHPh	$CH_2C{\equiv}CH$	6	55
4	C=CHPh	$CH_2CO_2CH_3$	7	80
5	C=CHPh	CH_2 $(CH_2)_2$ CH_3	8	48



Scheme 3 Preparation of (2Z)-4-[2-(2-oxo-1,3-oxazolidin-3-yl)ethyl]-2(phenylmethylidene)-3,4-dihydro-2H-1,4-benzothiazin-3-one **9**, (*ii*) DMF, K2CO3, TBAB, 80 °C, 6 h

NMR, ^{13}C NMR. Thus, crystallographic analysis by X-ray diffraction, was performed to confirm the exact structure of the compound **4**, **7**, and **8.**

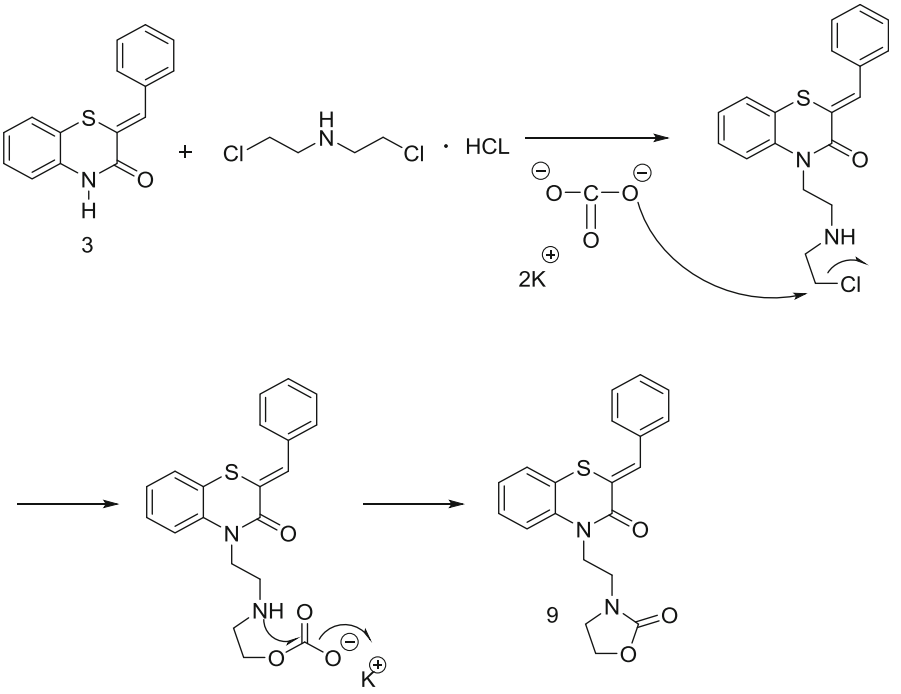
Following the method described by Alsubari et al. [29], a bond was formed between the core benzothiazine and oxazolidinone motif. Thus, the action of two equivalents of the hydrochloride of bis (2-chloroethyl) amine with the compound **3** under the conditions of transfer catalysis liquid–solid phase in DMF at 80 °C, allowed us to isolate the product **9** (Scheme 3). In this reaction, potassium carbonate simultaneously plays two roles; on the one hand, it ensured the deprotonation of the nitrogen NH, and on the other hand, it acted as a carbonating agent favoring the formation of the oxazolidinone.

NMR spectra

The structure of isolated product **9** was confirmed by ^{1}H, ^{13}C NMR spectroscopy. The ^{1}H NMR spectrum of the corresponding compound **9** exhibited four triplets, arising from the methylene groups (δ 3.30–3.65 NCH_2, 4.26 OCH_2). The aromatic protons of the benzothiazine ring system showed a multiplet in the region (7.06–7.64 ppm). The ^{13}C NMR spectrum of **9**, exhibited two signals at 158.4, 161.2 ppm for the carbonyl carbon of benzothiazine and oxazolidine ring, respectively, and four signals at 41.4, 42.2, 44.9, 62.3 ppm for the methylene groups. An X-ray crystallographic study of a single crystal of **9** confirmed the structure deduced from NMR spectroscopic studies.

According to these results, a plausible mechanism for the formation of the compound **9** was proposed. It is postulated that initial alkylation of the nitrogen atom of the lactam functionality gave intermediates that underwent a nucleophilic reaction involving potassium carbonate, and afterward, intramolecular cyclization leads to the formation of the corresponding compound **9** (Scheme 4).

In further research of synthesized new, five-membered heterocyclic systems obtained by 1,3-dipolar cycloaddition from 3-oxo-1,4-benzothiazine, we examined the action of compound **5** with 1-azidomethyl-benzene, ethyl 2-azido acetate, and 2-azidononane conditions in the click chemistry, which has led to regioselectively



Scheme 4 Plausible mechanism for formation of (2Z)-4-[2-(2-oxo-1,3-oxazolidin-3-yl)ethyl]-2-(phenylmethylidene)-3,4-dihydro-2H-1,4-benzothiazin-3-one **9**

1,4-triazoles **10–12** with high yields (Scheme 5; Table 2). The structures of 1,4-triazoles **10–12** were established on the basis of spectral data of ^{1}H NMR, ^{13}C and analysis by X-ray diffraction of a single crystal has allowed us to determine the complete structure of compounds **10–11** [30, 31].

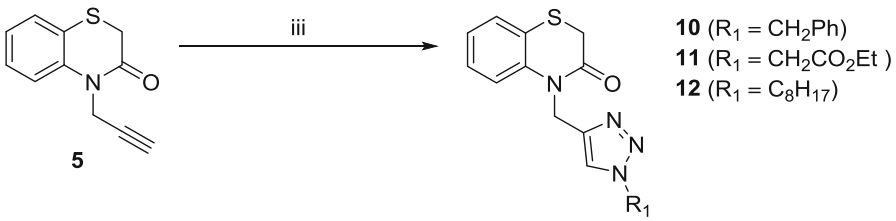
NMR spectra

In general, the 1,4-disubstituted-1H-1,2,3-triazoles can easily be distinguished from the isomeric 1,5-disubstituted-1H-1,2,3-triazoles by the large 1-bond C–H coupling constant in the gated decoupled ^{13}C NMR spectrum. Depending on the substituents within the triazole ring, The C_5 signal of 1,4 appears at $\delta \approx 120$ ppm, whereas the C_4 signal of 1,5 appears at $\delta \approx 133$ ppm. In this respect, the ^{13}C NMR signal of the 1,4 isomer was more shielded than the 1,5 isomer [32]. In our case, the 1,4-regiosmers has been obtained exclusively relative to 1,5-disubstituted triazoles. The 1,4-disubstituted-1H-1,2,3-triazoles **10** show a characteristic ^{13}C signal at $\delta \approx 124.3$ ppm for C_5, while the H triazol appears at $\delta \approx 8$ ppm (see support information). Moreover, the regioselectivity outcome can be rationalized by consideration of the substituent hindrance-demand features. It appears that the highest regioselevity is in favor of the less sterically hindered 1,4-regioisomer.

Single-crystal X-ray analysis

The molecule of the title compound **9**, $C_{20}H_{18}N_2O_3S$, is built up from two fused six-membered rings linked to one phenyl via –CH– group and to oxazolidin-2-one through $–CH_2–CH_2–$ group as shown in Fig. 1. Furthermore, the oxazolidine ring displays half chair conformation twisted on C(18)–N(2). The 1,4-benzothiazine system is almost planar with the largest deviation from the mean plan being −0.067 (3)Å at N(1) and makes dihedral angles of 17.01 (13)° and 8.88 (14)° with the phenyl ring and the oxazolidine cycle, respectively. In the crystal, the molecules halt together by C(16)–H(16B)···O(2) hydrogen bond forming inversion dimers as shown in Fig. 2. The data have been assigned to the following deposition numbers. CCDC 1433628.

The Crystal data, data collection and structure refinement details are summarized in Table 3. The H atoms were located in a difference map and treated as riding with



Scheme 5 Synthesis of triazolylmethyl benzothiazinone derivatives **10–12**. Reagents and conditions: (*iii*) substituted azides (R_1–N_3), $CuSO_4{\cdot}5H_2O$, sodium ascorbate (5 % mol), H_2O/EtOH (1:1), rt, 10 h

Table 2 1,4-Disubstituted triazole derivatives **10–12** via click chemistry

Entry	R_1–N_3	Compounds	Yield (%)
1	CH_2Ph–N_3	10	86
2	CH_2CO_2Et–N_3	11	84
3	C_8H_{17}–N_3	12	78

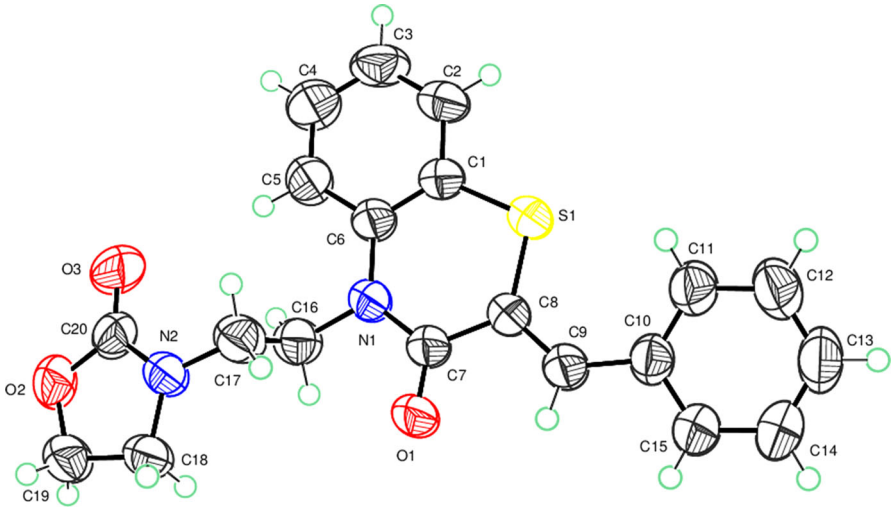


Fig. 1 Molecular structure of the title compound with the atom-labelling scheme. Displacement ellipsoids are drawn at the 50 % probability level. H atoms are represented as *small circles*

C–H = 0.93 Å (aromatic) and C–H = 0.97 Å (methylene). All hydrogen with $U_{iso}(H) = 1.2\ U_{eq}$ (aromatic and methylene) (Tables 4, 5, 6). Data collection: *APEX2*; cell refinement: *SAINT*; data reduction: *SAINT* [33]; program(s) used to solve structure and program(s) used to refine structure: *SHELXL2013* [34]; molecular graphics: *ORTEP-3* [35, 36]; software used to prepare material for publication: *PLATON* [37] and *publCIF* [38].

Antibacterial activity

Microorganisms used

The synthesized compounds were evaluated for their in vitro antibacterial activity against both Gram-positive bacteria: *S. aureus* ATCC 25923 and *Streptococcus fasciens* ATCC 29212, and two Gram-negative bacteria: *Escherichia coli* ATCC 4157 and *Pseudomonas aeruginosa* ATCC 27853. The strains used in this study are widely encountered in various pathologies in humans and were obtained from the Department of Microbiology, National Institute of Hygiene, Rabat, Morocco.

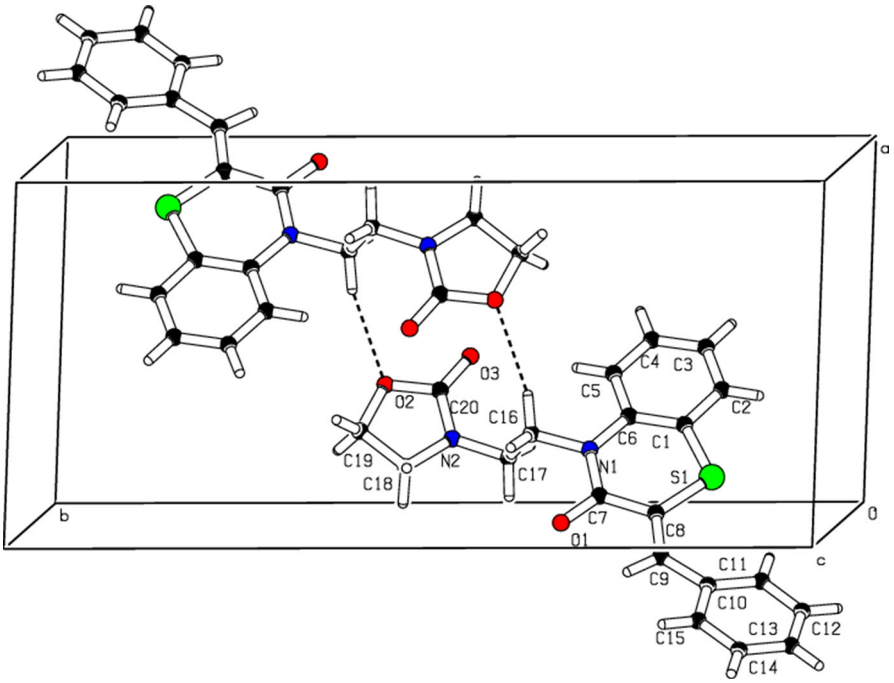


Fig. 2 Perspective view of the structure of the title compound showing two molecules linked by hydrogen bonds and forming inversion dimers

Bacterial culture

Starting with a culture of 18 h on Mueller–Hinton (MH) broth, a bactria carrying suspension is used, incubated at 37 °C for 24 h. This was transplanted into a broth (MH). This solution represents the bacterial inoculum which will be used for the entire study.

Method gel diffusion

To test antibacterial activity, we used the technique of diffusion by mid agar (MH) on a petri dish [39]. The medium was inoculated with a few milliliters of the bacterial inoculum so as to cover the entire agar surface. The tests were performed according to the method of Vincent (aromatogram). The latter was to remove the filter paper discs impregnated by our products that were dissolved in 1 % DMSO on the surface of the agar in the petri dishes previously seeded by inoculation. The dishes were then incubated in an oven at 37° C for 24 h. Biological activity manifested itself by the appearance of a halo of inhibition of microbial growth around the discs containing the test product. The reading was performed by measuring the diameter of inhibition observed.

Table 3 Crystal data, data collection, and structure refinement of crystal **9**

$C_{20}H_{18}N_2O_3S$	$F(000) = 768$
$M_r = 366.42$	$D_x = 1.377$ Mg m^{-3}
Monoclinic, $P2_1/c$	Mo Kα radiation, $\lambda = 0.71073$ Å
$a = 9.377$ (2) Å	Cell parameters from 3626 reflections
$b = 20.090$ (5) Å	$\theta = 2.4$–$26.4°$
$c = 10.133$ (2) Å	$\mu = 0.21$ mm^{-1}
$\beta = 112.146$ (13)°	$T = 296$ K
$V = 1768.1$ (7) Å^3	Block, colourless
$Z = 4$	0.36 × 0.31 × 0.26 mm
Bruker X8 APEX Diffractometer	3626 Independent reflections
Radiation source: fine-focus sealed tube	2898 Reflections with $I > 2\sigma(I)$
Graphite monochromator	$R_{int} = 0.028$
ϕ and ω scans	$\theta_{max} = 26.4°$, $\theta_{min} = 2.4°$
Absorption correction: multi-scan (SADABS; Bruker [33])	$h = -11 \rightarrow 11$
$T_{min} = 0.504$, $T_{max} = 0.748$	$k = -25 \rightarrow 25$
19,037 Measured reflections	$l = -12 \rightarrow 12$
Refinement on F2	0 Restraints
Least-squares matrix: full	Hydrogen site location: inferred from neighbouring sites
$R[F^2 > 2\sigma(F^2)] = 0.065$	H-Atom parameters constrained
$wR(F2) = 0.190$	$w = 1/\left[\sigma^2\left(F_o^2\right) + (0.0876P)^2 + 1.2706P\right]$
	where $P = \left(F_o^2 + 2F_c^2\right)/3$
$S = 1.05$	$(\Delta/\sigma)_{max} < 0.001$
3626 Reflections	$\Delta\rangle_{max} = 0.82$ e Å^{-3}
235 Parameters	$\Delta\rangle_{min} = -0.64$ e Å^{-3}

Minimum inhibitory concentration (MIC)

For MIC determination, we adopted the technique of sterile microtiter microplates using the tetrazolium (MTT) 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide as an indicator of sustainability. Into each well, we poured 100 µL of liquid culture medium MH with 100 µL of the test product. Serial dilutions were then performed. Each well was then inoculated with 10 µL of the bacterial suspension. At the end of the incubation period at the appropriate temperature, 10 µL of MTT (0.4 mg/mL) was added to each well. The plates were reincubated for 30 min at 37° C. After incubation time, wells where microbial growth occured showed a blue-violet color. The MIC was then determined and corresponded to the lowest concentration substance which produced no bacterial growth. The results of the examination are shown in Fig. 3 and Table 7.

The results are presented in the form of antibiograms below:

This study allowed us to determine the MIC of some synthesized 1,4-benzothiazine derivatives. The results of antibacterial activity of the products

Table 4 Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters ($Å^2$)

	x	*y*	*z*	U^*_{iso}/U_{eq}
C1	0.7381 (3)	0.79994 (13)	0.5945 (3)	0.0529 (6)
C2	0.6490 (3)	0.84203 (14)	0.6411 (3)	0.0637 (7)
H2	0.6653	0.8877	0.6425	0.076*
C3	0.5384 (3)	0.81775 (17)	0.6849 (4)	0.0713 (8)
H3	0.4784	0.8464	0.7145	0.086*
C4	0.5175 (4)	0.75047 (18)	0.6843 (4)	0.0826 (10)
H4	0.4437	0.7333	0.7156	0.099*
C5	0.6036 (3)	0.70750 (16)	0.6383 (4)	0.0733 (9)
H5	0.5876	0.6619	0.6398	0.088*
C6	0.7144 (3)	0.73160 (12)	0.5896 (3)	0.0515 (6)
C7	0.9205 (3)	0.70371 (13)	0.4993 (3)	0.0528 (6)
C8	0.9676 (3)	0.77442 (12)	0.4963 (3)	0.0483 (6)
C9	1.0809 (3)	0.78543 (13)	0.4474 (3)	0.0557 (6)
H9	1.1184	0.7468	0.4216	0.067*
C10	1.1567 (3)	0.84619 (13)	0.4266 (3)	0.0521 (6)
C11	1.1524 (4)	0.90819 (15)	0.4865 (3)	0.0638 (7)
H11	1.0959	0.9138	0.5440	0.077*
C12	1.2322 (4)	0.96153 (16)	0.4607 (4)	0.0759 (9)
H12	1.2294	1.0026	0.5020	0.091*
C13	1.3149 (4)	0.95455 (17)	0.3754 (4)	0.0770 (9)
H13	1.3674	0.9908	0.3584	0.092*
C14	1.3202 (4)	0.89433 (17)	0.3153 (4)	0.0778 (9)
H14	1.3763	0.8894	0.2574	0.093*
C15	1.2419 (3)	0.84073 (15)	0.3406 (4)	0.0677 (8)
H15	1.2464	0.7999	0.2991	0.081*
C16	0.7535 (3)	0.61539 (14)	0.5200 (3)	0.0587 (7)
H16A	0.7814	0.5956	0.4457	0.070*
H16B	0.6429	0.6114	0.4922	0.070*
C17	0.8340 (3)	0.57949 (14)	0.6580 (3)	0.0621 (7)
H17A	0.9444	0.5807	0.6820	0.075*
H17B	0.8123	0.6014	0.7336	0.075*
C18	0.8518 (4)	0.45677 (13)	0.5967 (4)	0.0697 (8)
H18A	0.9592	0.4511	0.6579	0.084*
H18B	0.8437	0.4641	0.4996	0.084*
C19	0.7554 (3)	0.39787 (14)	0.6068 (4)	0.0656 (8)
H19A	0.7141	0.3744	0.5166	0.079*
H19B	0.8168	0.3671	0.6799	0.079*
C20	0.6508 (3)	0.49179 (14)	0.6605 (3)	0.0571 (7)
N1	0.7982 (3)	0.68717 (10)	0.5367 (3)	0.0561 (6)
N2	0.7818 (3)	0.51007 (11)	0.6457 (3)	0.0619 (6)
O1	0.9892 (3)	0.65946 (9)	0.4651 (3)	0.0741 (7)

Table 4 continued

	x	y	z	U^*_{iso}/U_{eq}
O2	0.6331 (2)	0.42524 (10)	0.6428 (2)	0.0660 (6)
O3	0.5619 (3)	0.52645 (12)	0.6887 (3)	0.0830 (7)
S1	0.87520 (13)	0.83914 (4)	0.54441 (13)	0.0916 (4)

Table 5 Atomic displacement parameters (Å^2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
C1	0.0578 (14)	0.0478 (14)	0.0622 (15)	−0.0004 (11)	0.0329 (12)	−0.0058 (11)
C2	0.0715 (18)	0.0509 (15)	0.0783 (19)	0.0049 (13)	0.0391 (15)	−0.0116 (13)
C3	0.0626 (17)	0.074 (2)	0.088 (2)	0.0142 (15)	0.0413 (16)	−0.0116 (16)
C4	0.0672 (18)	0.076 (2)	0.130 (3)	0.0063 (16)	0.065 (2)	−0.001 (2)
C5	0.0669 (18)	0.0540 (16)	0.121 (3)	0.0014 (13)	0.0602 (19)	0.0024 (17)
C6	0.0482 (13)	0.0464 (13)	0.0671 (16)	0.0030 (10)	0.0300 (12)	−0.0005 (11)
C7	0.0539 (14)	0.0424 (13)	0.0727 (16)	0.0019 (10)	0.0358 (13)	−0.0012 (11)
C8	0.0515 (13)	0.0403 (12)	0.0582 (14)	−0.0011 (10)	0.0266 (11)	−0.0023 (10)
C9	0.0534 (14)	0.0442 (13)	0.0784 (17)	−0.0002 (11)	0.0350 (13)	−0.0011 (12)
C10	0.0479 (13)	0.0482 (14)	0.0621 (15)	−0.0026 (10)	0.0230 (12)	0.0051 (11)
C11	0.0733 (18)	0.0598 (16)	0.0636 (16)	−0.0169 (14)	0.0320 (14)	−0.0078 (13)
C12	0.094 (2)	0.0551 (17)	0.082 (2)	−0.0213 (16)	0.0366 (19)	−0.0087 (15)
C13	0.084 (2)	0.0643 (19)	0.090 (2)	−0.0214 (16)	0.0414 (19)	0.0072 (17)
C14	0.082 (2)	0.071 (2)	0.099 (2)	−0.0117 (17)	0.0560 (19)	0.0063 (18)
C15	0.0691 (18)	0.0553 (16)	0.094 (2)	−0.0041 (13)	0.0480 (17)	0.0006 (15)
C16	0.0555 (14)	0.0541 (15)	0.0710 (17)	−0.0054 (12)	0.0288 (13)	−0.0083 (13)
C17	0.0604 (16)	0.0541 (16)	0.0745 (18)	−0.0030 (12)	0.0284 (14)	−0.0091 (13)
C18	0.0706 (18)	0.0443 (14)	0.116 (3)	−0.0032 (13)	0.0596 (18)	−0.0103 (15)
C19	0.0692 (17)	0.0463 (15)	0.091 (2)	−0.0066 (13)	0.0411 (16)	−0.0075 (14)
C20	0.0539 (14)	0.0577 (16)	0.0704 (17)	0.0047 (12)	0.0357 (13)	0.0104 (13)
N1	0.0586 (12)	0.0400 (11)	0.0840 (15)	−0.0015 (9)	0.0430 (12)	−0.0032 (10)
N2	0.0626 (13)	0.0400 (11)	0.1006 (18)	−0.0005 (10)	0.0509 (13)	−0.0018 (11)
O1	0.0776 (13)	0.0415 (10)	0.1315 (19)	0.0014 (9)	0.0716 (14)	−0.0058 (11)
O2	0.0617 (11)	0.0550 (11)	0.0931 (15)	−0.0104 (9)	0.0426 (11)	0.0071 (10)
O3	0.0790 (14)	0.0821 (16)	0.1156 (19)	0.0221 (12)	0.0684 (14)	0.0167 (13)
S1	0.1255 (8)	0.0421 (4)	0.1577 (10)	−0.0133 (4)	0.1108 (8)	−0.0191 (5)

tested showed the absence of growth inhibition for compound **2** in the four bacterial strains. On the other hand, compound **3** obtained by substituting compound **2** with the benzylidene group at position 2 resulted in an MIC = 125 μg/mL for *S. aureus*, *S. fasciens*, *P. aeruginosa* and MIC = 250 μg/mL for *E. coli.*

In order to increase the inhibitory activity of compounds **2** and **3** we alkylated those compounds with alkylating agents: propargyl chloride and bis (2-chloroethyl)

Table 6 Geometric parameters and hydrogen-bond geometry (Å, °) for (shelx)

C1–C6	1.389 (4)	C12–H12	0.9300
C1–C2	1.391 (4)	C13–C14	1.363 (5)
C1–S1	1.739 (3)	C13–H13	0.9300
C2–C3	1.362 (4)	C14–C15	1.380 (4)
C2–H2	0.9300	C14–H14	0.9300
C3–C4	1.365 (5)	C15–H15	0.9300
C3–H3	0.9300	C16–N1	1.493 (3)
C4–C5	1.377 (4)	C16–C17	1.500 (4)
C4–H4	0.9300	C16–H16A	0.9700
C5–C6	1.394 (4)	C16–H16B	0.9700
C5–H5	0.9300	C17–N2	1.468 (3)
C6–N1	1.421 (3)	C17–H17A	0.9700
C7–O1	1.221 (3)	C17–H17B	0.9700
C7–N1	1.377 (3)	C18–N2	1.439 (3)
C7–C8	1.491 (3)	C18–C19	1.516 (4)
C8–C9	1.349 (3)	C18–H18A	0.9700
C8–S1	1.731 (2)	C18–H18B	0.9700
C9–C10	1.467 (4)	C19–O2	1.437 (3)
C9–H9	0.9300	C19–H19A	0.9700
C10–C15	1.391 (4)	C19–H19B	0.9700
C10–C11	1.393 (4)	C20–O3	1.200 (3)
C11–C12	1.387 (4)	C20–N2	1.343 (3)
C11–H11	0.9300	C20–O2	1.351 (3)
C12–C13	1.369 (5)		
C6–C1–C2	120.3 (3)	C13–C14–H14	120.1
C6–C1–S1	124.3 (2)	C15–C14–H14	120.1
C2–C1–S1	115.4 (2)	C14–C15–C10	121.7 (3)
C3–C2–C1	121.4 (3)	C14–C15–H15	119.1
C3–C2–H2	119.3	C10–C15–H15	119.1
C1–C2–H2	119.3	N1–C16–C17	109.7 (2)
C2–C3–C4	118.6 (3)	N1–C16–H16A	109.7
C2–C3–H3	120.7	C17–C16–H16A	109.7
C4–C3–H3	120.7	N1–C16–H16B	109.7
C3–C4–C5	121.4 (3)	C17–C16–H16B	109.7
C3–C4–H4	119.3	H16A–C16–H16B	108.2
C5–C4–H4	119.3	N2–C17–C16	110.1 (2)
C4–C5–C6	120.8 (3)	N2–C17–H17A	109.6
C4–C5–H5	119.6	C16–C17–H17A	109.6
C6–C5–H5	119.6	N2–C17–H17B	109.6
C1–C6–C5	117.5 (2)	C16–C17–H17B	109.6
C1–C6–N1	122.0 (2)	H17A–C17–H17B	108.2
C5–C6–N1	120.5 (2)	N2–C18–C19	101.3 (2)
O1–C7–N1	119.0 (2)	N2–C18–H18A	111.5
O1–C7–C8	119.7 (2)	C19–C18–H18A	111.5

Table 6 continued

N1–C7–C8	121.3 (2)	N2–C18–H18B	111.5
C9–C8–C7	116.3 (2)	C19–C18–H18B	111.5
C9–C8–S1	121.8 (2)	H18A–C18–H18B	109.3
C7–C8–S1	121.76 (18)	O2–C19–C18	105.7 (2)
C8–C9–C10	132.9 (2)	O2–C19–H19A	110.6
C8–C9–H9	113.6	C18–C19–H19A	110.6
C10–C9–H9	113.6	O2–C19–H19B	110.6
C15–C10–C11	117.5 (2)	C18–C19–H19B	110.6
C15–C10–C9	116.6 (2)	H19A–C19–H19B	108.7
C11–C10–C9	125.9 (2)	O3–C20–N2	127.9 (3)
C12–C11–C10	120.2 (3)	O3–C20–O2	123.0 (3)
C12–C11–H11	119.9	N2–C20–O2	109.1 (2)
C10–C11–H11	119.9	C7–N1–C6	126.1 (2)
C13–C12–C11	120.9 (3)	C7–N1–C16	115.4 (2)
C13–C12–H12	119.5	C6–N1–C16	118.5 (2)
C11–C12–H12	119.5	C20–N2–C18	113.0 (2)
C14–C13–C12	119.8 (3)	C20–N2–C17	122.7 (2)
C14–C13–H13	120.1	C18–N2–C17	123.7 (2)
C12–C13–H13	120.1	C20–O2–C19	110.05 (19)
C13–C14–C15	119.9 (3)	C8–S1–C1	104.22 (12)

D–H···*A*	*D*–H	H···*A*	*D*···*A*	*D*–H···*A*
C16–H16 *B*···O2[a]	0.97	2.54	3.467 (3)	160

[a] Symmetry code: $-x + 1$, $-y + 1$, $-z + 1$

amine hydrochloride. It is deducible that the presence of a prop-1-yn group in compounds **5** and **6** gives the same activity against the four bacterial strains tested with a MIC of 125 μg/mL for *E. coli* and an MIC of 250 μg/mL for *S. aureus*, *S. fasciens*, and *P. aeruginosa.* However, compound **5** shows no activity against *P. aeruginosa.* On the other hand, compound **9** also gives better activity with an MIC of about 62.5 μg/mL for *S. aureus*, *S. fasciens*, and *E. coli* and 125 μg/mL for *P. aeruginosa.* Indeed, for the three products containing 1,2,3-triazole **10–12** obtained by cycloaddition reaction 1,3-dipolar, it is worth noting that compound **11** obtained by cycloaddition with 2-ethyl azidoacetate exerted a strong inhibitory activity during the treatment of different bacteria: CMI = 31.25 μg/mL for *S. aureus*, *S. fasciens*, *E. coli*, and a CMI = 62.5 μg/mL for *Pseudomonas.*

On the other hand, it should be noted that the functionalized derivatives by ester groups and benzene rings have the highest antibacterial coefficient (92 % of pathogenic bacteria are sensitive).

This study is expected to take anti-inflammatory, antifungal, anti-parasitic, and anti-cancer activities, because the literature gives a lot of interesting results on these topics. Some other types of bacteria may possibly be tested by employing the same method so as eventually to generalize the suggested investigation method.

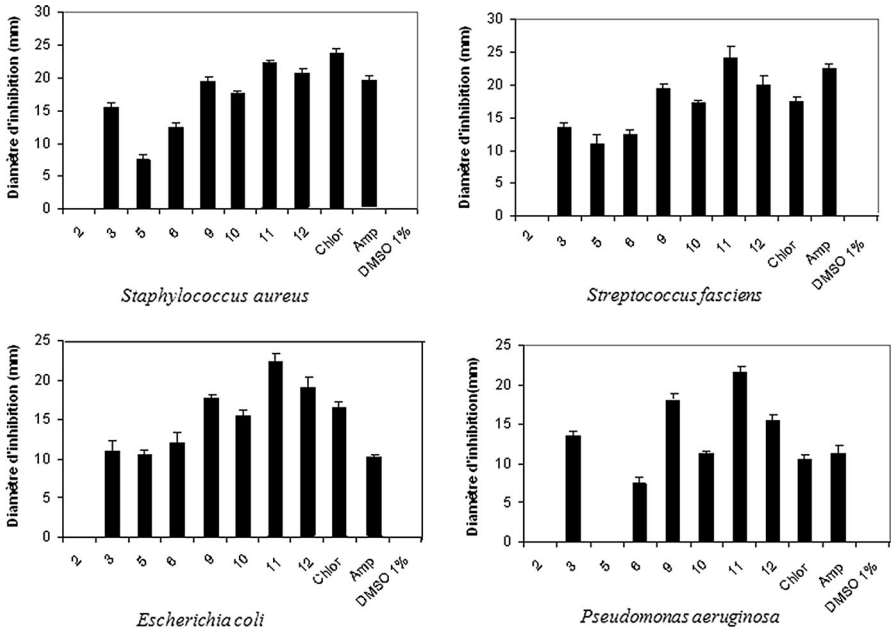


Fig. 3 The results of the antibacterial activity of the synthesized compounds **2–3, 5–6**, and **9–12** towards bacteria tested (*Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *and Streptococcus fasciens*) are summarized in the table below. Chlor, Chloramphenicol (30 μg/mL); Amp, Ampicillin (10 μg/mL); DMSO, dimethylsulfoxyde (1 %)

Table 7 Minimum Inhibitory Concentration (MIC) of the compounds **2–3, 5–6**, and **9–12**

Products	CMI in μg/mL			
	Staphylococcus aureus	*Streptococcus fasciens*	*Escherichia coli*	*Pseudomonas aeruginosa*
2	–	–	–	–
3	125	125	250	125
5	250	250	125	–
6	250	250	125	250
9	62.5	62.5	62.5	125
10	125	125	125	250
11	31.25	31.25	31.25	62.5
12	62.5	62.5	62.5	125
Chlor	1.875	3.75	15	7.5

Experimental

Column chromatography was performed on silica gel 60 (Merck 230-400 mesh). The reaction was followed by thin layer chromatography (TLC) Kiesegel 60F254 (Merck). Melting points are taken using a Kofler bench. They are not corrected.

NMR spectra were recorded on a Bruker device type AC-300. Chemical shifts are given in parts per million (ppm) and DMSO is used as solvent. key: s (singlet), d (doublet), t (triplet), m (multiplet). The analysis by X-ray diffraction was performed on a Bruker APEXII diffractometer, equipped with a Kryo-Flex Bruker cooling system.

*3,4-dihydro-2H-1,4-benzothiazin-3-**one 2*** Condensation of 2-aminothiophenol 1 (0.047 mol) with chloro ethyl acetate (0.016 mol) in 50 mL of DMF, with a large excess of K_2CO_3 (0.02 mol). Then the reaction mixture is refluxed for 24 h. After evaporating the DMF to dryness, the residue obtained is washed with distilled water and then filtered. **Yield:** 85 %; mp = 176–178 °C; **^{1}H-NMR** (300 MHz, DMSO-d_6) δ [ppm]: 3.43(s, 2H); 6.92–7.30(m, 4H, H_{ar}); 10.75(s, 1H; NH); **^{13}C-NMR** (62.5 MHz, DMSO-d_6) δ [ppm]: 30.2(CH_2); 117.7, 124.1, 127.4, 127.9 (CH_{ar}); 119.4, 137.8 (Cq); 165.8(C = O).

*2-(phenylmethylidene)-3,4-dihydro-2H-1,4-benzothiazin-3-**one 3*** A small amount (2.84 mmol) of the two compounds in 10 mL of DMF is added to an excess of sodium methoxide (0.284 mmol) and benzaldehyde (6.24 mmol). The mixutre is stirred to reflux for 48 h. After filtration of the salts, the filtrate is concentrated under reduced pressure. The residue is purified on silica gel column and recrystallized with hexane. **Yield:** 65 %; mp = 110–112 °C; **^{1}H-NMR** (300 MHz, DMSO-d_6) δ [ppm]: 7.78(s, 1H; = CH); 6.97–7.66 (m, 9H, H_{ar}); 11.02(s, 1H; NH); **^{13}C-NMR** (62.5 MHz, DMSO-d_6) δ [ppm]: 115.3 (=CH); 117.21, 120.8, 123.7, 125.6, 127.5, 2*129.3, 2*130.3 (CH_{ar}); 129.3, 131.1, 134.5, 134.7(Cq), 159.0 (C=O).

General procedure for the alkylation

To a solution of (6.05 mmol) of 2-(substituted)-3,4-dihydro-2H-1,4-benzothiazin-3-one 2 (3) in 25 mL of DMF, was added (7.26 mmol) of potassium carbonate, The mixture is stirred magnetically for 5 min then added 0.3 mmol of bromide tetra-*n*-butylammonium (BTBA) and 6.41 mmol reagent monohalo, then the mixture was stirred magnetically for 24 h. After removal of salts by filtration, DMF was evaporated under reduced pressure, and the residue obtained is dissolved in dichloromethane. The remaining salts are extracted with distilled water, and the mixture obtained is chromatographed on silica gel column (eluent ethyl acetate/hexane (1/2)).

*Methyl 2-(3-oxo-3,4-dihydro-2H-1,4-benzothiazin-4-yl) acetate **4*** **Yield:** 72 %; mp = 128–130 °C; **^{1}H-NMR** (300 MHz, DMSO-d_6) δ [ppm]: 3.54 (s, 2H; CH_2); 3.67 (s, 3H; OCH_3); 4.69 (s, 2H; NCH_2); 7.03–7.43 (m, 4H, H_{ar}); **^{13}C-NMR** (62.5 MHz, DMSO-d_6) δ [ppm]: 30.6(CH_2); 46.8(NCH_2); 52.6(OCH_3); 118.3, 124.0, 127.8, 128.5 (CH_{ar}); 123.2, 139.7 (Cq); 166.1, 169.4 (C=O).

*4-(prop-2-yn-1-yl)-3,4-dihydro-2H-1,4-benzothiazin-3-one **5*** **Yield:** 75 %; mp = 219–220 °C; **^{1}H-NMR** (300 MHz, DMSO-d_6) δ [ppm]: 2.48 (t, 1H,–C≡CH, J = 1,8 Hz); 3.38 (s, 2H; CH_2); 4.74 (d, 2H, NCH_2, J = 2.4 Hz); 7.04–7.41 (m, 4H, H_{ar}); **^{13}C-NMR** (62.5 MHz, DMSO-d_6) δ [ppm]: 30.6(NCH_2);

33.8(CH_2); 74.9 (–C≡CH); 118.4, 124.1, 127.7, 128.5 (CH_{ar}); 79.8, 123.3, 138.9 (Cq); 165.1(C=O).

*(2Z)-2-(phenylmethylidene)-4-(prop-2-yn-1-yl)-3,4-dihydro-2H-1,4-benzothiazin-3-**one 6*** **Yield:** 55 %; mp = 130–132 °C; **^{1}H-NMR** (300 MHz, DMSO-d_6) δ [ppm]: 2.48(t, 1H, –C≡CH, J = 1,8 Hz); 4.85 (d, 2H, NCH_2, J = 2,4 Hz); 7.84(s, 1H; =CH); 7.09–7.66 (m, 9H, H_{ar}); **^{13}C-NMR** (62.5 MHz, DMSO-d_6) δ [ppm]: 34.9 (NCH_2); 75.4 (–C≡CH); 126.8 (=CH); 117.8, 118.3, 124.4, 126.8, 2* 128.1, 129.1, 2*129.7, 130.6 (CH_{ar}); 79.6, 134.4, 2*135.4, 135.8 (Cq), 165.1 (C=O).

Methyl 2-[(2Z)-3-oxo-2-(phenylmethylidene)-3,4-dihydro-2H-1,4-benzothiazin-4-yl] acetate 7 **Yield:** 80 %; mp = 106–108 °C; **^{1}H-NMR** (300 MHz, DMSO-d_6) δ [ppm]: 3.75(s, 3H; OCH_3); 4.85(s, 2H; NCH_2); 7.08–7.70 (m, 9H, H_{ar}); 7.85(s, 1H; =CH); **^{13}C-NMR** (62.5 MHz, DMSO-d_6) δ [ppm]: 48.0 (NCH_2); 53.10 (OCH_3); 118.25, 124.8, 127.20, 128.46, 129.46, 130.1, 131.0, 135.76 (CH_{ar}); 118.6, 120.64, 134.81, 137.0 (Cq); 162.1, 169.7(C=O).

*(2Z)-4-butyl-2-(phenylmethylidene)-3,4-dihydro-2H-1,4-benzothiazin-3-**one 8*** **Yield:** 48 %; mp = 89–90 °C; **^{1}H-NMR** (300 MHz, DMSO-d_6) δ [ppm]: 0.93 (t, 3H; –CH_3, J = 7,2 Hz); 1.35 (m, 2H; CH_2); 1.61 (m, 2H; CH_2, J = 30 Hz); 4.07 (t, 2H; NCH_2–, J = 7.5 Hz); 7.03–7.62 (m, 9H, H_{ar}); 7.78(s, 1H; = CH–C_6H_5); **^{13}C-NMR** (62.5 MHz, DMSO-d_6) δ [ppm]: 44.4 (NCH_2); 19.9, 29.1 (CH_2); 14.1 (–CH_3); 120.9 (=CH); 117.8, 124.0, 126.8, 128.0, 2*129.03, 129.02, 2*130.4 (CH_{ar}); 2*134.2, 134.6, 136.2 (Cq), 160.7 (C=O).

Synthesis of oxazolidin-2-one in basic benzothiazine

Four eq of potassium carbonate, 0.2 eq of bromide tetra-*n*-butylammonium, and 2.2 eq of bis (2-chloroethyl) amine hydrochloride were added to a solution of 0.2 g of 2-(phenylmethylidene)-3,4-dihydro-2H-1,4-benzothiazin-3-one 3 in 20 mL of DMF. The mixture was stirred magnetically at 80 °C for 6 h. After removal of salts by filtration, DMF was evaporated under reduced pressure, and the residue obtained was dissolved in dichloromethane. The remaining salts were extracted with distilled water, and the mixture obtained was chromatographed on a silica gel column (eluent: ethyl acetate/ethanol: 4/1).

*(2Z)-4-[2-(2-oxo-1,3-oxazolidin-3-yl)ethyl]-2-(phenylmethylidene)-3,4-dihydro-2H-1,4-benzothiazin-3-**one 9*** **Yield:** 65 %; mp = 132–134 °C; **^{1}H-NMR** (300 MHz, DMSO-d_6) δ [ppm]: 3.30–3.65 (m, 6H; NCH_2); 4.26 (m, 2H, OCH_2); 7.06–7.64 (m, 9H, H_{ar}) 7.78(s, 1H, =CH–C_6H_5); **^{13}C-NMR** (62.5 MHz, DMSO-d_6) δ [ppm]: 62.3 (OCH_2); 41.4, 42.2, 44.9 (NCH_2); 117.5 (=CH–C_6H_5); 118.5, 120.7, 124.2, 126.9, 2*128.0, 129.5, 2*130.4 (CH_{ar}); 2*134.3, 134.5, 136.1 (Cq); 158.4, 161.2 (C=O).

Synthesis of triazolylmethyl benzothiazinone by Click Chemistry

In a flask, 10^{-3} mol of compound 5 and 2.5 × 10^{-3} azides prepared in 20 mL of ethanol is dissolved at room temperature. We add 0.5 × 10^{-3} mol of $CuSO_4$ and

10^{-3} mol of sodium ascorbate dissolved in 7 mL of distilled water. The mixture was stirred for 24 h, and the reaction was monitored by TLC. The crude reaction was purified by column chromatography on silica gel (ethyl acetate/hexane (3/1)) was purified.

*4-[(1-Benzyl-1H-1,2,3-triazol-4-yl)methyl]-2H-1,4-benzothiazin-3(4H)-one **10*** **Yield:** 86 %; mp = 132–134 °C; **^{1}H-NMR** (300 MHz, DMSO-d_6) δ [ppm]: 3.53(s, 2H; CH_2); 5.12, 5.53(s, 4H, NCH_2); 7.00–7.51 (m, 9H, H_{ar}); 8.00(s, 1H, $=CH_{triazole}$); **^{13}C-NMR** (62.5 MHz, DMSO-d_6) δ [ppm]: 30.7 (CH_2); 40.7, 53.2 (NCH_2); 124.3 ($=CH_{triazole}$); 118.7, 123.9, 127.7, 2*128.3, 128.4, 128.5, 2*129.2 (CH_{ar}); 136.4, 139.8, 2*143.8 (Cq); 165.4 (C=O).

*Ethyl2-{5-[(3-oxo-3,4-dihydro-2H-1,4-benzothiazin-4-yl)methyl]-1H-1,2,3-triazol-1 yl}acetate **11*** **Yield:** 84 %; mp = 139–141 °C; **^{1}H-NMR** (300 MHz, DMSO-d_6) δ [ppm]: 7.95(s, 1H, = CH $_{triazole}$); 7.00–7.52 (m, 4H, H_{ar}); 5.32, 5.15 (s, 4H, NCH_2); 3.54 (s, 2H; CH_2); 4.12 (dd, 2H; OCH_2, J = 14.4 Hz); 1.17 (t, 2H; CH_3, J = 7.2 Hz); **^{13}C-NMR** (62.5 MHz, DMSO-d_6) δ [ppm]: 118.6 ($=CH_{triazole}$); 50.8, 30.7(NCH_2); 30.7(CH_2); 61.1(OCH_2); 14.4(CH_3); (123.9, 125.6, 127.7, 128.5)CH_{ar}; 123.3, 139.8, 143.5 (Cq); 167.6, 165.4(C = O).

*4-[(1-octyl-1H-1,2,3-triazol-5-yl)methyl]-3,4-dihydro-2H-1,4-benzothiazin-3-one **12*** **Yield:** 78 %; mp = 80–82 °C; **^{1}H-NMR** (300 MHz, DMSO-d_6) δ [ppm]: 0.81(t, 2H; CH_3, J = 6.9 Hz); 1.21–1.18(m, 10H; CH_2); 1.72 (m, 2H; CH_2); 4.26 (t, 2H, NCH_2, J = 7.2 Hz); 5.11(S, 2H, NCH_2); 6.99–7.49 (m, 4H, H_{ar}); 7.92(s, 1H, =CH $_{triazole}$); **^{13}C-NMR** (62.5 MHz, DMSO-d_6) δ [ppm]: 14.4 (CH_3); 22.5, 26.2, 28.7, 28.9, 30.0, 31.5 (CH_2); (30.7) CH_2; 2*49.7(NCH_2); 118.7 ($=CH_{triazole}$); 123.8, 124.0, 127.6, 128.4 (CH_{ar}); 123.3, 139.8, 143.4 (Cq), 165.4 (C=O).

Conclusion

In summary, a practical method for synthesizing new heterocyclic series of 3-oxo-1,4 benzothiazine using a condensation reaction with hydrochloride of bis (2-chloroethyl) amine and alkylation reactions with various alkylating agents was developed. Our interest also focused on the "click chemistry," which is the uncoordinated modern version of this cycloaddition. This reaction was catalyzed by Cu (I) and form a 1,2,3-triazole heterocycles disubstituted in position 4 in a regiospecific manner. Heterocycles obtained were identified by ^{1}H NMR, ^{13}C NMR, and confirmed for certain products by X-ray. The synthesized products were subjected to the evaluation of antibacterial activity. Several of the compounds tested showed significant activity.

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