Chemical Methodologies 7(2023) 106-111

Chemical Methodologies

Journal homepage: http://chemmethod.com

Original Research Article

Design, Synthesis, and Biological Activity of New Thiazolidine-4-One Derived from Symmetrical 4-Amino-1,2,4-Triazole

Fayyadh Abed Nashaan, Muna Sameer Al-Rawi*

Department of Chemistry, College of Education for Pure Science Ibn Al-Haitham, University of Baghdad, Iraq

ARTICLE INFO

Article history

Submitted: 2022-06-17
Revised: 2022-08-30
Accepted: 2022-10-10
Manuscript ID: CHEMM-2209-1610
Checked for Plagiarism: Yes
Language Editor:
Dr. Ermia Aghaie
Editor who approved publication:
Dr. Zeinab Arzehgar

DOI:10.22034/CHEMM.2023.362512.1610

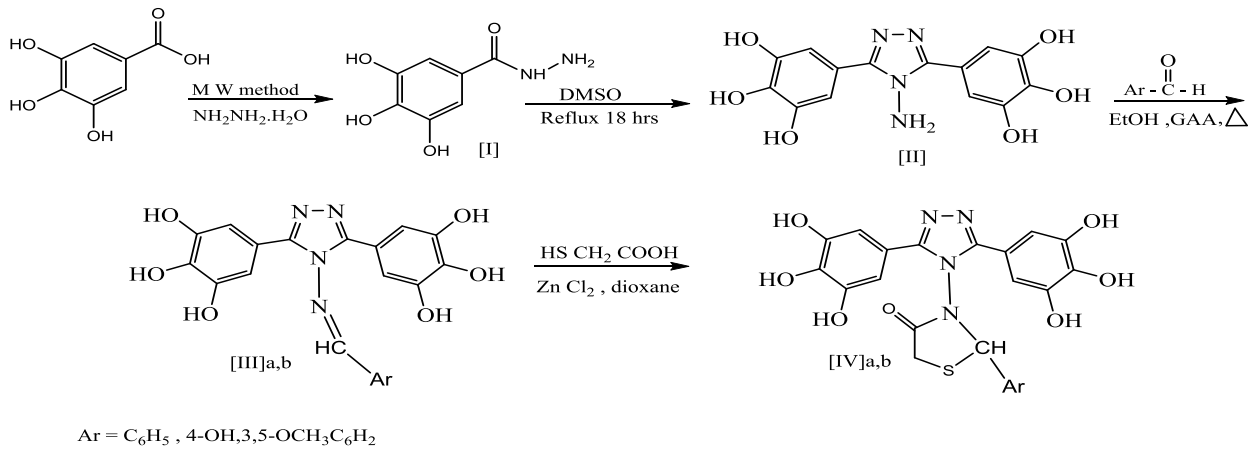
KEYWORDS

Gallic acid
Galloyl hydrazine
MW-assisted method
Thiazolidine-4-one
1,2,4-Triazole

ABSTRACT

Thiazolidine-4-one derivatives $(IV)_{a,b}$ containing 1,2,4-triazole rings linked to 3,4,5-trihydroxyphenyl moiety were designed, synthesized, and biological evaluated for the antibacterial/antifungal activities. These derivatives $(IV)_{a,b}$ were achieved from many sequence reactions. A multi-step reaction protocol was used that began with the first step involved a new and very fast one-pot solventless greener microwave-assisted method of synthesis galloyl hydrazide (I) from gallic acid and hydrazine hydrate. The galloyl hydrazide (I) was used as the starting materials for synthesizing new 5,5'-(4-amino-4*H*-1,2,4-triazole-3,5-diyl) bis (benzene-1,2,3-triol) (II) via a reflux cyclization process of galloyl hydrazide in DMSO. On the other hand, new Schiff base $(III)_{a,b}$ was prepared via condensation reaction of the symmetrical 4-amino-1,2,4-triazole compound (II) and substituted aromatic aldehyde in ethanol. Finally, the treatment of schiff bases $(III)_{a,b}$ was done with thioglycollic acid in refluxing dioxin by using zinc chloride (II) to afford the target thiazolidine-4-one derivatives $(IV)_{a,b}$. The structure identification of the newly compounds $(I\text{-}IV_{a,b})$ was elucidated by FT-IR,^{1}H-NMR, and ^{13}C-NMR. The new synthetic derivatives were subjected for antibacterial/ antifungal activity by using two type of Gram-positive and Gram-negative bacteria also test it against to *Candida albicans* as a fungi sample.

GRAPHICAL ABSTRACT



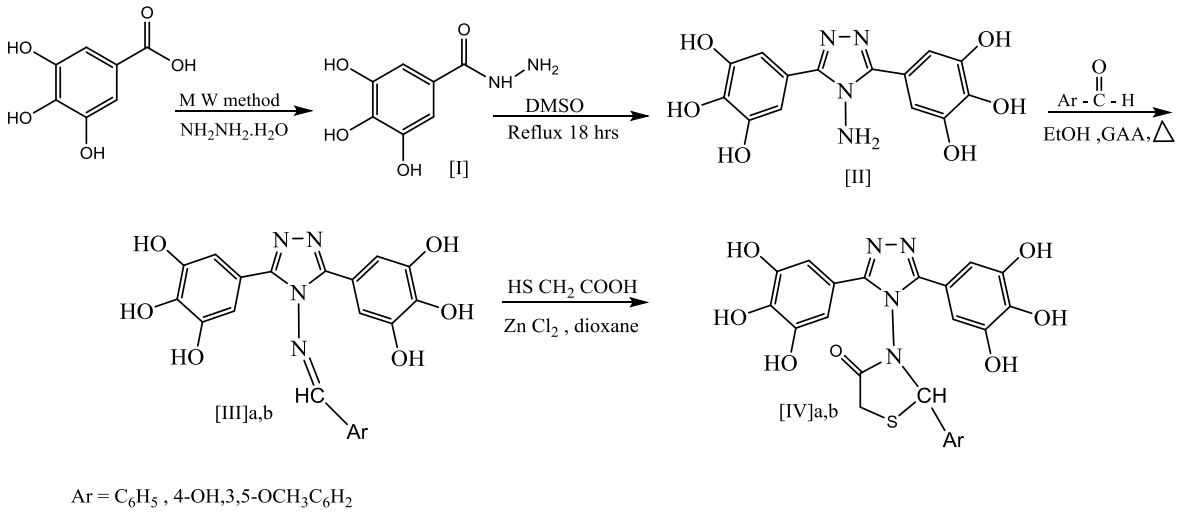
Ar = C_6H_5 , 4-OH,3,5-$OCH_3C_6H_2$

* Corresponding author: Muna Sameer Al-Rawi
✉ E-mail: Smona.s.s@ihcoedu.uobaghdad.edu.iq

Introduction

The utility of the structure formula of galloyl hydrazide (3,4,5-trihydroxybenzohydrazide) as a franchised structural system in pharmaceutical chemistry has prompted the improvement in therapeutic potentials, it acts as intermediate to synthesize the biologically active molecule synthesis and its derivatives possesses diverse biological activities like analgesic, anti-inflammatory, and antimycotic activity [1-4].

Triazole is a significant species of heterocyclic compounds display a broad range in medicinal chemistry, it is also a five-membered, unsaturated ring system including three nitrogen atoms as a heteroatoms and exists in two possible isomeric constitutes (1,2,3 and 1,2,4) triazoles. Triazoles are the core structures of various medicine drugs and pharmaceutical agents. Triazole derivatives own antibacterial, anti-diabetic, and anti-inflammatory activities [5-8]. On the other hand, the thiazolidin-4-one scaffold has also been used as a pharmacophoric moiety for several biological activities such as anti-HIV, anti-proliferative, antimicrobial, and antifungal [9-13]. Biological potential of vicinal triazole based to galloyl hydrazide has not been still fully utilized which makes a scope for medicinal chemists to improve new drug molecules for modern purpose. In the present study, an attempt was made to synthesize thiazolidin-4-one derivatives of substituted 5,5'-(4-amino-4H-1,2,4-triazole-3,5-diyl)bis(benzene-1,2,3-triol) and assess their antibacterial/antifungal efficiency. The strategy for the synthesis of the target molecules is displayed in Scheme 1.



Scheme 1: Synthesis of the target compounds (I)-(IV)$_{a,b}$

Materials and Methods

Instruments

On a Shimadzu, the FT-IR (8300s) spectra were recorded. Bruker com. (Ultra-Shield 500 MHz), Switzerland, was used to determine ^{1}H-NMR and ^{13}C-NMR spectra (in solvent DMSO-d_6) by using (TMS) as an internal standard. Mass spectra were achieved with mass agilent high resolution instrument.

General synthetic procedures

The reaction sequence leading to the formation of new compounds is outlined in Scheme 1.

Synthesis of galloyl hydrazide (I)

This compound was prepared by following the procedure described by F. A. Nashaan *via* a new green solvent-free one-pot, MW-assisted method from gallic acid: off-white fine powdered solid, and mp 294-297 °C [1].

Synthesis of 5,5'-(4-amino-4H-1,2,4-triazole-3,5-diyl)bis(benzene-1,2,3-triol) (II)

Galloyl hydrazide (0.921 g, 0.005 mol) was dissolved in dimethyl sulfoxide (15 mL), the mixture was refluxed for (18 hours), and then distilled under reduced pressure, cooled. Thereafter, (10 mL) of distilled water was added. The mixture was stirred at room temperature for (12 hours), the resulting solid was filtered, dried, and recrystallized from aqueous ethanol to give the corresponding compound (III) as a dark gray solid. Yield 59% (0.54 g), mp 318-320 °C [5].

Synthesis of 5,5'-(4-((4-hydroxy-3,5-dimethoxybenzylidene)amino)-4H-1,2,4-triazole-3,5-diyl) bis (benzene -1,2,3- triol) (III)$_{a,b}$

A mixture of compound (II) (1.66 g, 0.005 mol), (benzaldehyde or syringaldehyde 0.005 mol) in EtOH (15 mL) and 5 drops of GAA was refluxed for (6 hours), and then cooled. The solid formed was filtered, dried, and purified by recrystallization from methanol to give compounds (III)$_{a,b}$ [14].

Synthesis of thiazolidin-4-one derivatives (IV)$_{a,b}$

A mixture of Schiff base (III)$_{a,b}$ (0.01 mol), thioglycolic acid (0.01 mol) and zinc chloride (II) (0.01 mol) in dioxane (25 mL) was refluxed for (24 hours), the mixture was left for (24 hours), and then neutralized with $NaHCO_3$ solution, filtered off, and dried to give compound (IV)$_{a,b}$ [13].

5,5'-(4-(benzylideneamino)-4H-1,2,4-triazole-3,5-diyl) bis(benzene-1,2,3-triol) (III)$_a$

$C_{21}H_{16}N_4O_6$, white, yield 70%, mp 248-250, IR (KBr) (ν_{max}/ cm^{-1}): 3421, 3144, 3032, 1612, 1578, 1500. ^{1}H-NMR (500 MHz, DMSO): δ 3.74 (s, 2H, NH_2), 6.93-7.44 (d.d, 4H, Ar-H), 8.81-9.28 (s, 6H, OH). ^{13}C-NMR (100 MHz, DMSO): δ 106.84-140.83, 146.44.

5,5'-(4-((4-hydroxy-3,5-dimethoxybenzylidene) amino)-4H-1,2,4-triazole-3,5-diyl)bis(benzene-1,2,3-triol) (III)$_b$

$C_{23}H_{20}N_4O_9$, Pale white, yield 72%, mp 298-300, IR (KBr) (ν_{max}/ cm^{-1}): 3396, 3032, 1638, 1608, 1585, 1512, 1330, 1029. ^{1}H-NMR (500 MHz, DMSO): δ 3.74 (s, 2H, NH_2), 6.93-7.44 (dd, 4H, Ar-H), 8.81-9.28 (s, 9.70 (s, 1H, N=CH), 9.02-9.32 (s, 6H, OH), 6.77-7.86 (m, 9H, Ar-H). ^{13}C-NMR (100 MHz, DMSO): δ 106.58-145.51, 145.86-147.54

3-(3,5-bis(3,4,5-trihydroxy phenyl)-4H-1,2,4-triazol-4-yl)-2-phenylthiazolidin-4-one (IV)$_a$

$C_{23}H_{18}N_4O_7S$, off white, yield 74%, mp 208-210, IR (KBr) (ν_{max}/ cm^{-1}): 3421, 3101, 1717, 1612, 1573, 1475, 840. ^{1}H-NMR (500 MHz, DMSO): 8.87-8.34 (s, 6H, OH), 7.99 (s, 1H, N-CH), 7.07-7.92 (m, 9H, Ar-H), 3.55 (s, 2H, CH_2S). ^{13}C-NMR (100 MHz, DMSO): δ 60.92, 56.42, 107.50-142.51, 145.87-148.14, 167.01.

3-(3,5-bis(3,4,5-trihydroxy phenyl)-4H-1,2,4-triazol-4-yl)-2-(4-hydroxy-3,5-dimethoxy phenyl)thiazolidin-4-one (IV)$_b$

$C_{25}H_{22}N_4O_1S$, dark brown, yield 78%, mp 234-236, IR (KBr) (ν_{max}/ cm^{-1}): 3363, 3032, 1716, 1616, 1558, 1488, 899. ^{1}H-NMR (500 MHz, DMSO): δ 8.98, 8.96 (s, 6H, OH), δ 8.37 (s, 1H, CH-N), 6.81-7.74 (9H, Ar-H), 3.87 (s, 6H, OCH_3), 3.13 (s, 2H, CH_2-S). ^{13}C-NMR (100 MHz, DMSO): δ 59.20, 56.88, 106.84-142.39, 146.13, 146.44, 167.01.

Biological evaluation

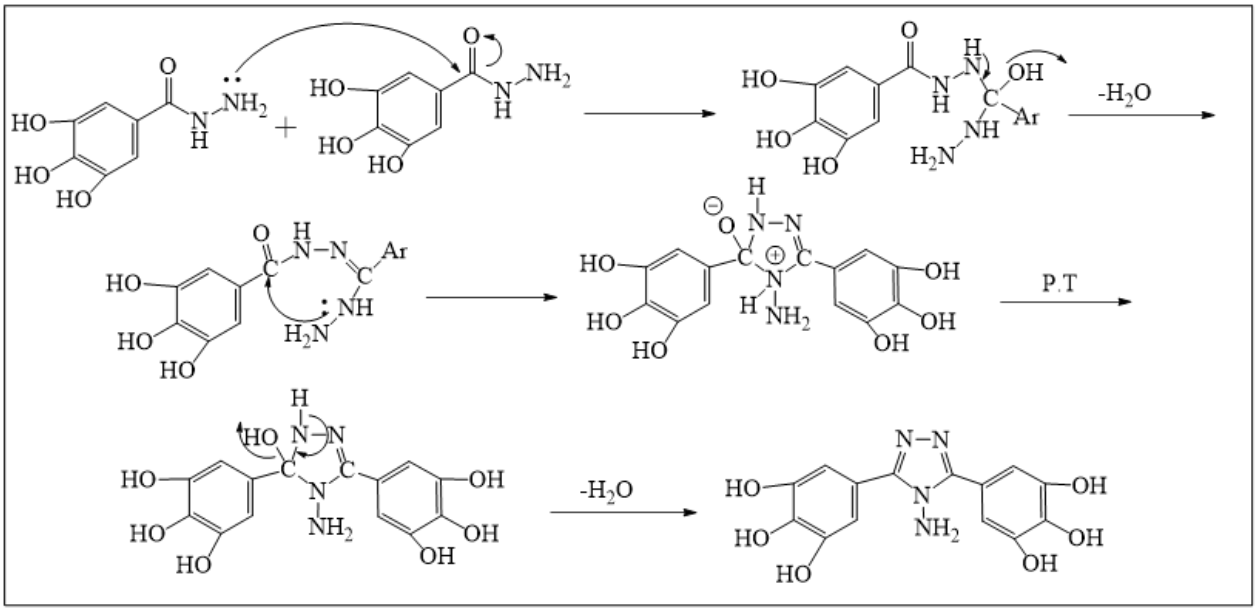
The Antibacterial/antifungal activities of the synthesized compounds were assessed by using two strains of pathogenic bacteria (*Staphylococcus aureus*) *(G+)* and (*Klebsiella pnumonia*) *(G-)* in Muller Hinton Agar medium by using agar well diffusion method and compared with the antibiotic Ampicillin. The antifungal activity of the compounds was determined against *Candida albicans*, and then was compared with the widely used antifungal fluconazole. The inhibition zones formed were measured in millimeters [15, 16].

Results and Discussion

Chemistry

Microwave-assisted method is a versatile greener technology of synthesis galloyl hydrazide (I) that can accelerate the chemical reactions and indicates the senior promise in possesses outstanding features involves solventless,

efficient, cost-effective, simple work-up procedure, excellent yield, and without catalyst. The symmetrical 4-amino- 1,2,4-triazole compound (II) was prepared by cyclization of galloyl hydrazide (I) in dimethyl sulfoxide under reflux. The reaction was obtained via amino group (NH_2) nucleophile attack in galloyl hydrazide on the carbon atom of (C=O) group in another molecule leading to form 5,5'-(4-amino-4*H*-1,2,4-triazole-3,5-diyl)bis(benzene-1,2,3-triol) (II). This compound was formed by cyclization with losing H_2O molecules, the suggested mechanism of this new compound outlined in the Scheme 2.



Scheme 2: The suggested mechanism of new symmetrical compound (II)

In this regard, a new Schiff base $(III)_{a,b}$ of 1,2,4-triazole based to 3,4,5-trihydroxyphenyl was designed, synthesized by refluxing a mixture of compound (II) and benzaldehyde or syringaldehyde in ethanol and glacial acetic acid (GAA). The workflow aimed at the new thiazolidine-4-one derived from symmetrical 4-amino-1,2,4-triazole were designed, synthesized, and identified as multi-target antibacterial/ antifungal activity, as depicted in Scheme1.The reaction was performed between Schiff bases of galloyl hydrazide $(III)_{a,b}$ and an excess of thioglycolic acid in the presence of dioxane/$ZnCl_2$, which is proceeded by cyclization with the addition of thioglycolic acid to imine C=N group under reflux. The newly synthesized derivatives were confirmed and reconditioned with their designed/proposed chemical structures by using the FT-IR, ^{1}H-NMR, and Mass spectroscopic analysis.

Antibacterial/antifungal activities

The synthesized compounds were evaluated for antibacterial/antifungal activities and revealed a good to moderate range of antibacterial activity against both types of bacteria as well as the antifungal activity of these compounds were investigated against (Candida albicans). The inhibition zones (mm) of the target compounds are as presented in Table 1. The experimental performs detected that compounds $(III)_b$ and $(IV)_b$ displayed the promising antibacterial /antifungal activity. We need more specialized future studies on these compounds in chemical medicine.

Table 1: Anti-bacterial /anti-fungal activities of synthesized compounds

Compound No.	*Staph.aurus (G+)*	*Klebsiella Pneumoniae (G-)*	*Candida albicans*
(II)	24	14	22
$(III)_a$	27	16	19
$(III)_b$	28	18	18
$(IV)_a$	25	18	16
$(IV)_b$	27	22	20
Ampicillin	22	21	Fluconazole =28

Conclusion

In this study, an efficient multistep protocol was recorded in which the design galloyl hydrazide was synthesized by using microwave-assisted method. Based on the obtained results, it can be concluded that galloyl hydrazide was used as the starting materials for the synthesized of newly symmetrical 5,5'-(4-amino-4*H*-1,2,4-triazole-3,5-diyl) bis (benzene-1,2,3-triol) (II) via cyclization process. The tagrate thiazolidine-4-one derivatives were subjected to spectral analysis by FT-IR, ^{1}H, and ^{13}C NMR for the structure elucidation. The compounds were then subjected to evaluate the antibacterial/antifungal activity against bacterial strain by using ampicillin as standard concerning a good inhibitory activity, the thiazolidine-4-one based on 1,2,4-triazole ring compounds $(IV)_b$ on both bacteria were identified to investigate the inhibitory potency antibacterial/antifungal activities of variously thiazolidine-4-one derivatives.

Acknowledgements

This is a study requirement for the Ph.D. degree for researcher Fiadh A. Neshan.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

Conflict of Interest

We have no conflicts of interest to disclose.

ORCID:

Fayyadh Abed Nashaan
https://orcid.org/0000-0002-7218-0675
Muna Sameer Al-Rawi
https://orcid.org/0000-0002-0318-8999

References

[1]. Nashaan F.A., Al-Rawi M.S., Alhammer A.H., Rabie A.M., Tomma J.H., 'Synthesis, characterization, and cytotoxic activity of some imides from galloyl hydrazide', *Eurasian Chemical Communications*, 2022, **4**:966 [Crossref], [Google Scholar], [Publisher]

[2]. Rabie A.M., Accurate conventional and microwave-assisted synthesis of galloyl hydrazide, *MethodsX*, 2020, **7**:100737 [Crossref], [Google Scholar], [Publisher]

[3]. Rabie A.M., Tantawy A.S., Badr S.M., Design, synthesis, and biological evaluation of novel 5-substituted-2-(3, 4, 5-trihydroxyphenyl)-1, 3, 4-oxadiazoles as potent antioxidants, *American Journal of Organic Chemistry*, 2016, **6**:54 [Crossref], [Google Scholar], [Publisher]

[4] El-Sabbagh S., Abdelkareem A., Synthesis and evaluation of methyl 3, 4, 5-trihydroxybenzoate and methyl 3, 4, 5-trihydroxybenzohydrazide as additives for natural rubber composites, *Egyptian Journal of Chemistry*, 2022, **65**:531 [Crossref], [Google Scholar], [Publisher]

[5]. Abdulghani S.M., Al-Rawi M.S., Tomma J.H., Synthesis of New 1, 2, 4-triazole Derivatives with Expected Biological Activities, *Chemical Methodologies*, 2022, **6**:59 [Crossref], [Google Scholar], [Publisher]

[6]. Strzelecka M., Świątek P., 1, 2, 4-Triazoles as important antibacterial agents, *Pharmaceuticals,* 2021, **14**:224 [Crossref], [Google Scholar], [Publisher]
[7]. Kazeminejad Z., Marzi M., Shiroudi A., Kouhpayeh S.A., Farjam M., Zarenezhad E., Novel 1, 2, 4-Triazoles as Antifungal Agents, *BioMed Research International*, 2022, **2022**:4584846 [Crossref], [Google Scholar], [Publisher]
[8]. Lihumis H.S., Al Talebi Z.A., Khaleel A.K., 'Synthesis and Identification of Some New Heterocyclic Compounds for Levofloxacin Drug Derivatives with Evaluating of Their Biological Efficiency and Antioxidant Activity', *Journal of Medicinal and Chemical Sciences***,** 2022, **5**:596 [Crossref], [Google Scholar], [Publisher]
[9]. Al-Rawi M.S., Hussei D.F., Al-Taie A.F., Al-Halbosiy M.M., Hameed B.A., Cytotoxic effects of new synthesis heterocyclic derivatives of Amoxicillin on some cancer cell lines. In *Journal of Physics: Conference Series*, 2018, **1003**:012012 [Crossref], [Google Scholar], [Publisher]
[10]. Neshan F.A., Al-Rawi M.S., Tomma J.H., ''Synthesis, Characterization and Study Biological Activity of Five and Seven Heterocyclic Compounds'', *International Journal of Drug Delivery Technology*, **9**:587 [Crossref], [Google Scholar]
[11]. Raza S., Srivastava S.P., Srivastava D.S., Srivastava A.K., Haq W., Katti S.B., Thiazolidin-4-one and thiazinan-4-one derivatives analogous to rosiglitazone as potential antihyperglycemic and antidyslipidemic agents. *European Journal of Medicinal Chemistry*, 2013, **63**:611 [Crossref], [Google Scholar], [Publisher]
[12]. Mech D., Kurowska A., Trotsko N., The Bioactivity of Thiazolidin-4-Ones: A Short Review of the Most Recent Studies, *International Journal of Molecular Sciences*, 2021, **22**:11533 [Crossref], [Google Scholar], [Publisher]
[13]. Trotsko N., Antitubercular properties of thiazolidin-4-ones–A review, *European Journal of Medicinal Chemistry*, 2021, **215**:113266 [Crossref], [Google Scholar], [Publisher]
[14]. Al-Rawi M.S., Tomma J.H., Mukhlus A.A., Al-Dujaili A.H., *American Journal of Organic Chemistry*, 2013, **3**:1 [Crossref], [Google Scholar], [Publisher]
[15]. Dorababu A., Recent update on antibacterial and antifungal activity of quinoline scaffolds, *Archiv der Pharmazie*, 2021, **354**:e2000232 [Crossref], [Google Scholar], [Publisher]
[16]. El-Adl K., El-Helby A.G.A., Sakr H., Eissa I.H., El-Hddad S.S., Shoman F.M., Design, synthesis, molecular docking and anticancer evaluations of 5-benzylidenethiazolidine-2, 4-dione derivatives targeting VEGFR-2 enzyme, *Bioorganic chemistry*, 2020, **102**:104059 [Crossref], [Google Scholar], [Publisher]

HOW TO CITE THIS ARTICLE
Fayyadh Abed Nashaan, Muna Sameer Al-Rawi. Design, Synthesis, and Biological Activity of New Thiazolidine-4-One Derived from Symmetrical 4-Amino-1,2,4-Triazole. *Chem. Methodol.*, 2023, 7(2) 106-111
https://doi.org/10.22034/CHEMM.2023.362512.1610
URL: http://www.chemmethod.com/article_158803.html