İstanbul Üniversitesi Sağlık Bilimleri Enstitüsü Sağlık Bilimlerinde İleri Araştırmalar Dergisi
Istanbul University Institute of Health Sciences Journal of Advanced Research in Health Sciences

Sağlık Bilimlerinde İleri Araştırmalar Dergisi 2019, Cilt 2, Sayı 2
DOI: 10.26650/JARHS2019-616357 Derleme / Review

Discovery, Synthesis and Activity Evaluation of Novel Compounds Bearing 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazine Moiety: A Review

1,2,4-triazolo[3,4-b][1,3,4]tiyadiazin Artığı İçeren Yeni Bileşiklerin Keşfi, Sentezi ve Biyolojik Aktiviteleri: Bir Derleme

Efe Doğukan Dincel[1], **Nuray Ulusoy Güzeldemirci**[2]

[1] Res. Asst., Istanbul University, Faculty of Pharmacy, Department of Pharmaceutical Chemistry, 34116 Beyazıt, Istanbul, Turkey

[2] Prof. Dr., Istanbul University, Faculty of Pharmacy, Department of Pharmaceutical Chemistry, 34116 Beyazıt, Istanbul, Turkey

ORCID: E.D.D. 0000-0002-5445-0600;
N.U.G. 0000-0002-4495-4282

Sorumlu yazar/Corresponding author:
Efe Doğukan Dincel,
Istanbul University, Faculty of Pharmacy, Department of Pharmaceutical Chemistry, 34116 Beyazıt, Istanbul, Turkey
E-posta: efe.dincel@istanbul.edu.tr

Başvuru/Submitted: 23.01.2019
Revizyon Talebi/Revision Requested: 02.04.2019
Son Revizyon/Last Revision Received: 07.06.2019
Kabul/Accepted: 10.06.2019

Atıf/Citation: Dincel E.D., Ulusoy-Guzeldemirci N. (2019): Discovery, synthesis and activity evaluation of novel compounds bearing 1,2,4-triazolo[3,4-b][1,3,4]thiadiazine moiety: a review, *Sağlık Bilimlerinde İleri Araştırmalar Dergisi*, 2(2): 60-70.
https://doi.org/10.26650/JARHS2019-616357

ABSTRACT

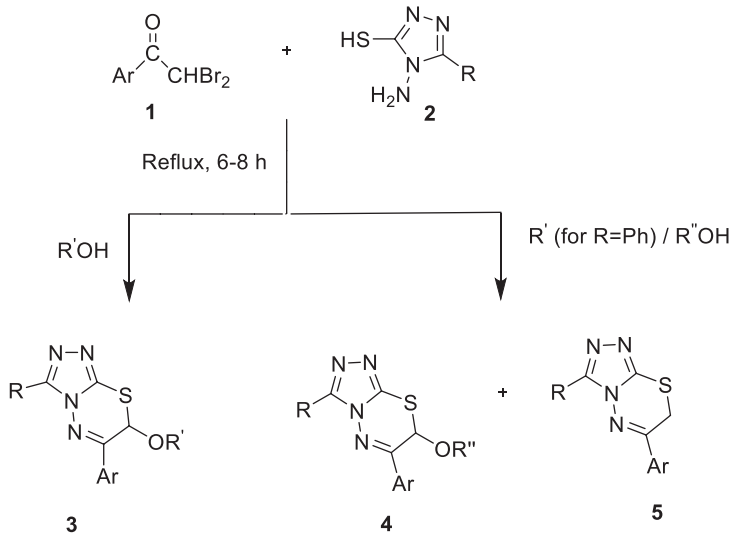
Lately, much interest has been focused on the chemistry and the biological activity of fused heterocyclic compounds carrying nitrogen atoms because of their utility in various applications, and over the years N-bridged heterocyclic systems derived from 1,2,4-triazoles attracted the interest of researchers owing to the hopeful promise of their pharmacological activities such as antimicrobial, antifungal, molluscicidal, nematicidal, analgesic, anti-inflammatory, anticancer, phosphodiesterase 4 inhibitor, acetylcholinesterase, butyrylcholinesterases and alkaline phosphatase inhibitor. The fused ring of triazole and thiadiazines, named as triazolothiadiazines, represents a specific and important class of N-bridged heterocycles with their remarkable and wide range of biological activity and there are not enough studies that include the current developments associated with the new synthesis techniques and novel biological evaluation results of 1,2,4-triazolo[3,4-*b*][1,3,4] thiadiazine derivatives. In an attempt to overcome this deficiency in the literature, we deeply researched the literature and formed a review study about the discovery, synthesis and activity evaluation of new compounds bearing 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazine moiety within the years of 1996-2019. We aimed to provide scientists with a wide data resource about 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazine derivatives, thus helping them perform a more organized and fertile drug discovery operation during their experimental studies.
Keywords: 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazine, synthesis, biological activity

ÖZ

Son zamanlarda, geniş ölçekte çeşitlilik gösteren uygulamalardaki kullanımları nedeniyle azot atomu taşıyan kaynaşmış heterosiklik bileşiklerin kimyası ve biyolojik aktivitesi üzerine olan ilgi artmış ve yoğunlaşmıştır. Yıllar boyunca 1,2,4-triazollerden türetilen azot köprülü heterosiklik sistemler antimikrobiyal, antifungal, mollusisidal, nematisidal, analjezik, anti-inflamatuvar, antikanser, fosfodiesteraz-4 inhibitörü, asetilkolinesteraz, butirilkolinesteraz ve alkalen fosfataz inhibitörü gibi farklı biyolojik yönlerde, umut vadeden farmakolojik aktiviteler göstermiş ve buna bağlı olarak araştırmacıların ilgisini çekmiştir. Triazol ve tiyadiazin halkalarının kaynaşmasıyla oluşan triazolotiyadiazinler azot köprülü heterosiklik bileşikler arasında önemli ve dikkat çekici bir alt sınıfı oluşturmaktadır, buna karşın 1,2,4-triazolo[3,4-*b*][1,3,4]tiyadiazin türevlerinie ait güncel sentez teknikleri ve yeni biyolojik aktivite bulgularını içeren çalışmalar literatürde yeterli oranda bulunmamaktadır. Bu noktadan hareketle 1996-2019 tarih aralığını referans alarak 1,2,4-triazolo[3,4-*b*][1,3,4] tiyadiazin yapısı taşıyan yeni bileşiklerin keşfi, sentezi ve aktivite değerlendirmeleri ile ilişkili bir derleme çalışması yürütülmüştür. Araştırmacıların daha organize ve verimli bir ilaç keşif prosesi gerçekleştirmelerine yardımcı olmak amaçlanmıştır.
Anahtar Kelimeler: 1,2,4-triazolo[3,4-*b*][1,3,4]tiyadiazin, sentez, biyolojik aktivite

INTRODUCTION

1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazines are 9 membered heterocyclic compounds containing 4 carbon atoms, 4 nitrogen atoms and 1 sulfur atom, and the main structure of the compound is formed by fused triazole and thiadiazine rings. The structure is capable of acting as both a hydrogen bond acceptor and a hydrogen bond donor. This qualification gives the group the characteristic of being a specific pharmacophore group capable of making significant interactions with the active site of various target receptors. In addition, due to the polar nature of the structure, the triazole moiety can increase the solubility of the ligand and thereby the pharmacokinetic profile of the drug is positively affected. 1,2,4-triazolo[3,4-*b*][1,3,4] thiadiazine derivatives have been reported in the literature by their antimicrobial[1,4,7,8,9,10,11,14,15,17,18], antifungal[8,13], molluscicidal[6] and nematicidal[13,14], analgesic[3,16], anti-inflammatory[3,6,11,16], anticancer[2,8,16], phosphodiesterase-4 inhibitor[5], acetylcholinesterase[12], butyrylcholinesterase[12] and alkaline phosphatase[12] inhibitor activity. Due to the wide pharmacological effect of 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazine derivatives researchers are interested in the synthesis of novel compounds bearing the 1,2,4-triazolo[3,4-*b*][1,3,4] thiadiazine moiety.



Compound	Ar	R	R'	Compound	Ar	R	R"
3a	C_6H_5	C_2H_5	Et	**4a**	C_6H_5	C_2H_5	Me
3b	4-MeC_6H_4	C_2H_5	Et	**4b**	4-ClC_6H_4	C_2H_5	Me
3c	4-ClC_6H_4	C_2H_5	Et	**4c**	C_6H_5	H	Me
3d	4-BrC_6H_4	C_2H_5	Et	**4d**	C_6H_5	n-C_3H_7	Me
3e	4-FC_6H_4	C_2H_5	Et	**4e**	C_6H_5	C_2H_5	n-Pr
3f	4-$NO_2C_6H_4$	C_2H_5	Et	**4f**	4-ClC_6H_4	C_2H_5	n-Pr
3g	C_6H_5	H	Et	**4g**	C_6H_5	H	n-Pr
3h	C_6H_5	n-C_3H_7	Et	**4h**	C_6H_5	n-C_3H_7	n-Pr
3i	C_6H_5	C_2H_5	i-Pr	**4i**	C_6H_5	C_6H_5	Me
3j	4-ClC_6H_4	C_2H_5	i-Pr	**4j**	C_6H_5	C_6H_5	n-Pr
3k	C_6H_5	H	i-Pr	**5a**	C_6H_5	C_2H_5	Me/n-Pr
3l	C_6H_5	n-C_3H_7	i-Pr	**5b**	4-ClC_6H_4	C_2H_5	Me/n-Pr
3m	C_6H_5	C_6H_5	Et	**5c**	C_6H_5	H	Me/n-Pr
3n	C_6H_5	C_6H_5	i-Pr	**5d**	C_6H_5	n-C_3H_7	Me/n-Pr
				5e	C_6H_5	C_6H_5	Et/Me/n-Pr/i-Pr

Scheme 1. The synthesis pathway of the novel 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazine derivatives[15]

Biological Activity of 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazine Derivatives

Compounds bearing the 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazine ring structure are disclosed in the literature as antimicrobial, antifungal, molluscicidal and nematicidal, analgesic, anti-inflammatory, anticancer, phosphodiesterase-4 inhibitor, acetylcholinesterase, butyrylcholinesterase and alkaline phosphatase inhibitor agents.

Antimicrobial and antifungal activity

A series of novel 7*H*-7-alkoxy-3-alkyl/phenyl-6-aryl-s-triazolo[3,4-*b*][1,3,4]thiadiazines were synthesized by Pundeer et al. and the antimicrobial and antifungal activity of the compounds were evaluated[15]. The biological activites of the compounds were compared with the antibacterial ciprofloxacin and antifungal amphotericin-B. The activity results showed that the novel compounds possess significant activity against the gram-positive bacteria, *Staphylococcus aureus,* and *Bacillus subtilis* and the yeasts, *Saccharomyces cerevisiae* and *Candida albicans*.

In another study, a series of novel 4-(alkylidene/arylidene)-amino-5-(2-furanyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thiones and 6-aryl-3-(2-furanyl)-7*H*-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazines were synthesized by Ergenç et al. and the antimicrobial and antifungal activity of the compounds were evaluated[7]. Of the novel compounds tested, **2b**, **2g** and **4f** were found as active against *Staphylococcus aureus* and/or *Staphylococcus epidermidis*, whereas all exhibited different degrees of antifungal activity.

Table 1. *In vitro* antimicrobial activity of the tested compounds through agar well diffusion method[15]

Compounds	**Diameter of growth of inhibition zone (mm)**[a]			
	S. aureus	*B. subtilis*	*S. cerevisiae*	*C. albicans*
3a	13.6	18.3	-	-
3b	12.3	17	10.6	-
3c	-	-	18.3	15.6
3d	12.3	13.6	-	-
3e	-	-	13.6	13
3f	-	-	15.6	13.3
3g	16.3	20.3	13.6	13.6
3h	13.6	17.6	-	-
3i	13.6	12.3	-	-
3j	11.3	12.3	11.3	-
3k	14.6	13.6	13.3	-
3l	12.3	14.6	-	-
3m	24.3	17.6	17.6	15.6
3n	18.3	15.6	13.3	-
4a	22.3	21.6	15.3	16.3
4b	19.3	16.3	12.6	13.0
4c	19.6	18.6	13.6	13.3
4d	16.0	18.3	12.6	-
4e	14.0	13.6	-	-
4f	12.6	16.3	10.3	-
4g	15.6	18.3	-	-
4h	13.6	16.3	15.3	-
4i	25.6	18.0	18.6	-
4j	20.6	17.3	17.3	-
Ciprofloxacin	26.6	24.0	Nt	Nt
Amphotericin-B	Nt	Nt	13.6	14.3
(-) no activity, *Nt* not tested				
[a] Values, including diameter of the well (8mm), are means of three replicates				

Table 2. MIC (in µg/ml) of the tested compounds by using macrodilution method[15]

Compounds	*S. aureus*	*B. subtilis*	*S. cerevisiae*	*C. albicans*
3a	256	64	-	-
3b	>256	128	>256	-
3c	-	-	32	64
3d	>256	256	-	-
3e	-	-	128	128
3f	-	-	64	128
3g	128	64	128	-
3h	256	128	-	-
3i	256	>256	-	-
3j	>256	>256	>256	-
3k	256	256	128	-
3l	>256	256	-	-
3m	16	128	32	64
3n	128	256	128	-
4a	32	32	64	64
4b	64	128	128	128
4c	64	64	128	128
4d	128	64	256	-
4e	256	256	-	-
4f	>256	128	>256	-
4g	128	64	-	-
4h	256	128	64	-
4i	16	64	32	-
4j	64	128	64	-
Ciprofloxacin	5	5	Nt	Nt
Amphotericin-B	Nt	Nt	100	100
(-) no activity, *Nt* not tested				
[a] Values, including diameter of the well (8mm), are means of three replicates				

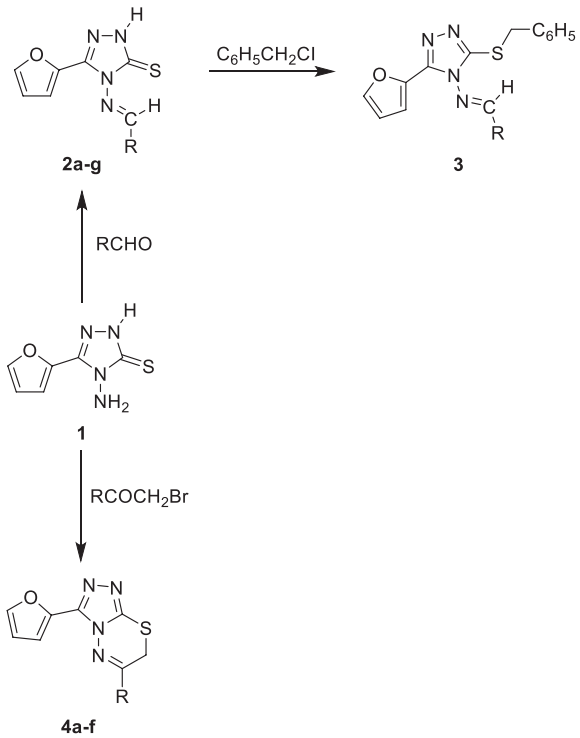
Molluscicidal and Nematicidal activity

A series of pyrazolyl-[1,2,4]triazolo[3,4-*b*][1,3,4] thiadiazin-6-yl)-2*H*-pyran-2-one derivatives were synthesized by Penta et al. and the novel compounds were evaluated for their *in vitro* antimicrobial activity against gram-positive bacteria (*Staphylococcus aureus* and *Bacillus subtilis*), gram-negative bacteria (*Escherichia coli* and *Klebsiella pneumoniae*), antifungal activity against *Candida albicans*, and nematicidal activity against *Meloidogyne incognit*[14]. It was found that, among the newly synthesized compounds, there were compounds having excellent antimicrobial and nematicidal activity against tested bacteria, fungi and nematodes.

In another study, a series of 3-(2,4-dichlorophenoxy)methyl)-1,2,4-triazolo(thiadiazoles and thiadiazines) were synthesized by El Shehry et al. and the novel compounds were evaluated for their molluscicidal activity[6]. The compounds **3**, **4b**, **8** and **10** exhibited significant molluscicidal activities.

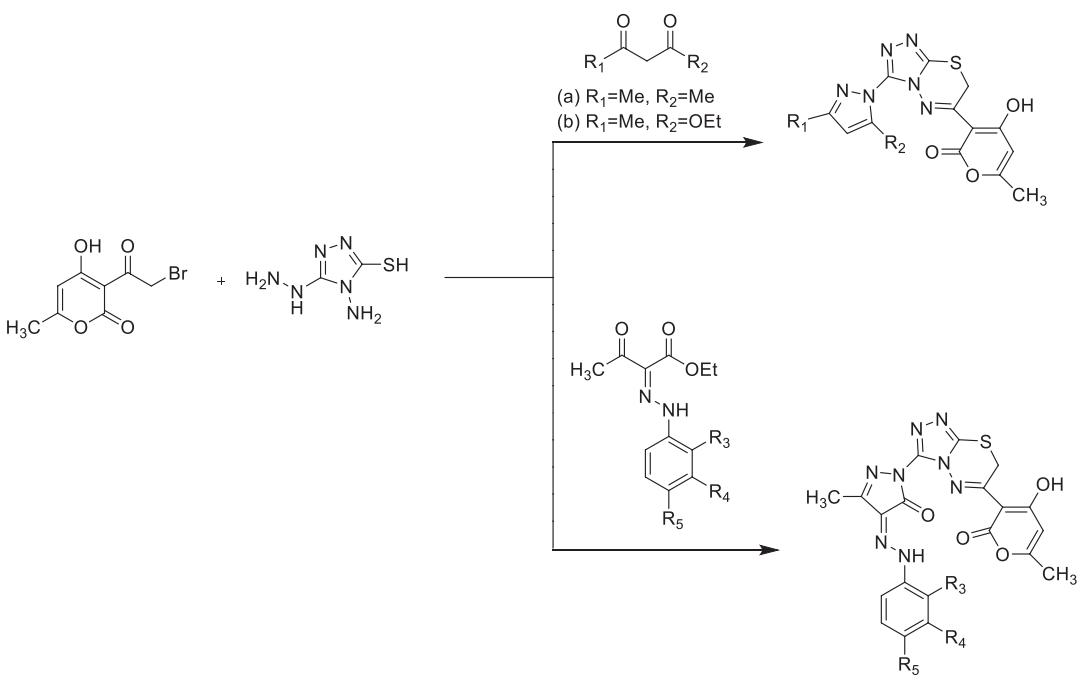
Analgesic and anti-inflammatory activity

A series of 3,6-disubstituted 7*H*-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazines were synthesized by Aytaç et al. and the novel compounds were evaluated for their analgesic/anti-inflammatory activity[3]. Among the newly synthesized compounds, the compounds **4**, **1c**, **2b** and **4c** showed the highest anti-inflammatory activity. Also compounds **2**, **3**, **4**, **2b**, **3a** and **4b** showed higher or similar analgesic activity to that of aspirin at the 100 mg/kg dose level. The activity results showed that some of the novel



Compound	R	Mp [ºC]	Yield [%]	Formula (molecular mass)
2b	4-BrC_6H_4	219-220	67	$C_{13}H_9BrN_4OS$ (349.21)
2g	2-(5-nitro-2-furyl)-ethenyl	219-220	87	$C_{13}H_9N_5O_4S$ (333.31)
4f	4-$NO_2C_6H_4$	>300	91	$C_{14}H_9N_5O_3S$ (327.32)

Scheme 2. The synthesis of the novel compounds[7]



Scheme 3. The reagents and the synthesis pathway[14]

Table 3. Nematicidal activity of the tested compounds[14]

Compounds	24h			48h		
	250 (µg/ml)	150 (µg/ml)	50 (µg/ml)	250 (µg/ml)	150 (µg/ml)	50 (µg/ml)
5a	5	3	2	8	5	4
5b	5	3	2	9	6	4
6a	42	28	15	55	33	26
6b	8	5	2	11	6	3
6c	35	20	10	51	28	19
6d	18	10	6	28	16	10
6e	40	23	19	44	28	20
6f	67	43	32	85	63	45
6g	52	35	20	73	55	28
6h	5	3	1	8	5	3
6i	5	3	2	9	5	3
6j	5	3	2	8	6	3
6k	5	3	2	12	5	3
6l	3	0	0	5	2	0
6m	2	0	0	3	2	0
DMSO	0	0	0	0	0	0

compounds possess significant activity and have potential for being a new analgesic/anti-inflammatory agent.

Anticancer activity

A series of 1,2,4-triazolo[3,4-b][1,3,4]thiadiazine derivatives were synthesized by Ahmad et al. and the novel compounds were evaluated for their anticancer activity[2]. In this study, compounds having a triazolothiadiazine nucleus were found as potentially active anticancer molecules.

Phosphodiesterase-4 Inhibitor Activity

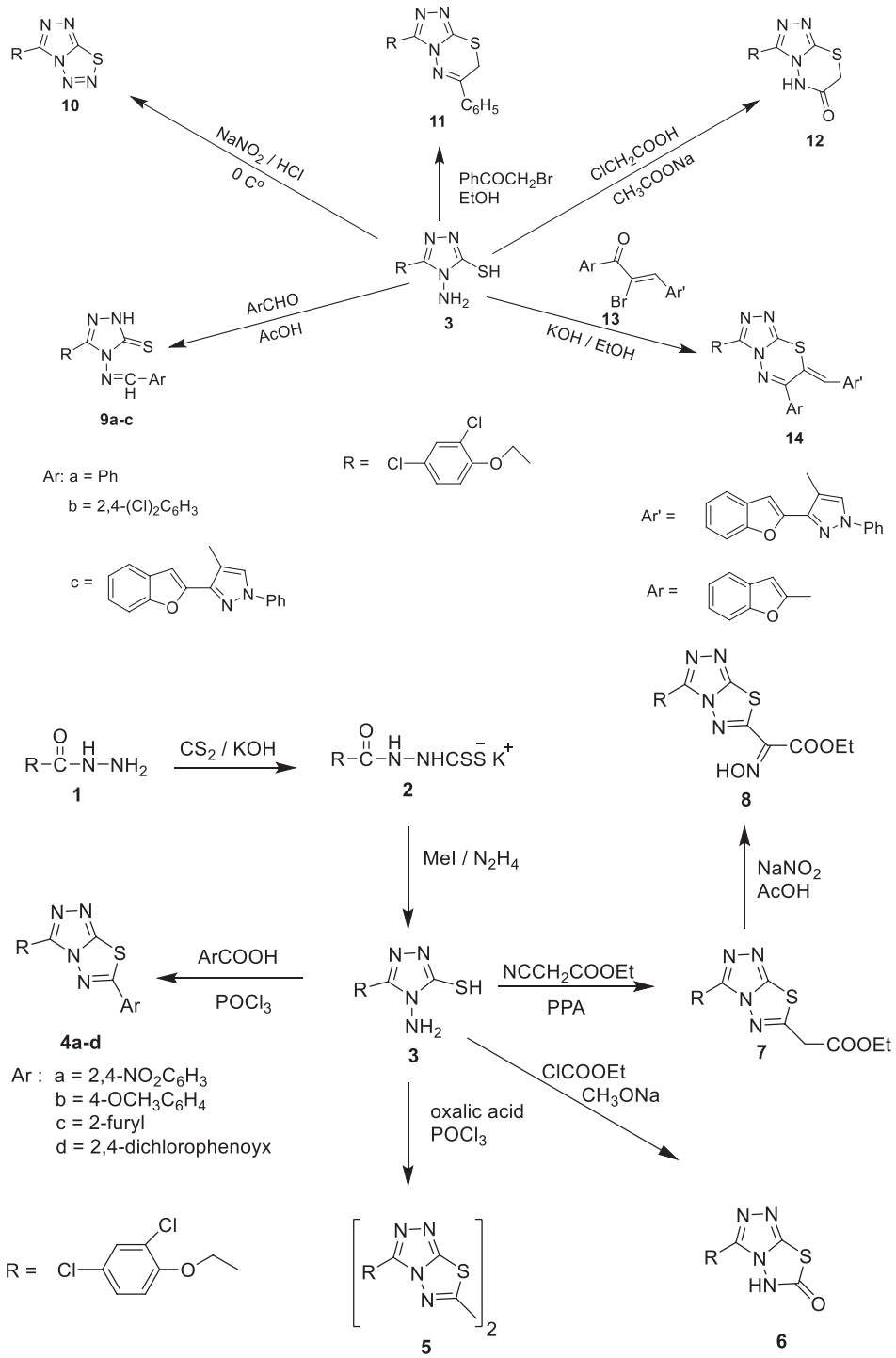
A series of 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazine derivatives were synthesized by Baeeri et al. and the new compounds were evaluated for their phosphodiesterase-4 (PDE-4) inhibitor activity[5]. The novel compounds were tested on cultured NIH-3T3 cells to analyze their safety and activity in NIH-3T3 mouse fibroblastic cells in comparison with rolipram, which is a selective PDE-4 inhibitor. Extracellular cyclic guanosine monophosphate (cGMP) and cyclic adenosine monophosphate (cAMP) concentrations were evaluated to understand the PDE inhibition rate. The results showed that all tested compounds caused a marked increase in the concentration of cAMP, whereas the concentration of cGMP stayed approximately unchanged.

Acetylcholinesterase, butyrylcholinesterases and alkaline phosphatase inhibitor activity

In another study, a series of 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole and 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazine derivatives were synthesized by Khan et al. and the new compounds were evaluated for their acetylcholinesterase, butyrylcholinesterases and alkaline phosphatase inhibitor activity[12]. According to activity results, the novel compounds showed significant biological activity.

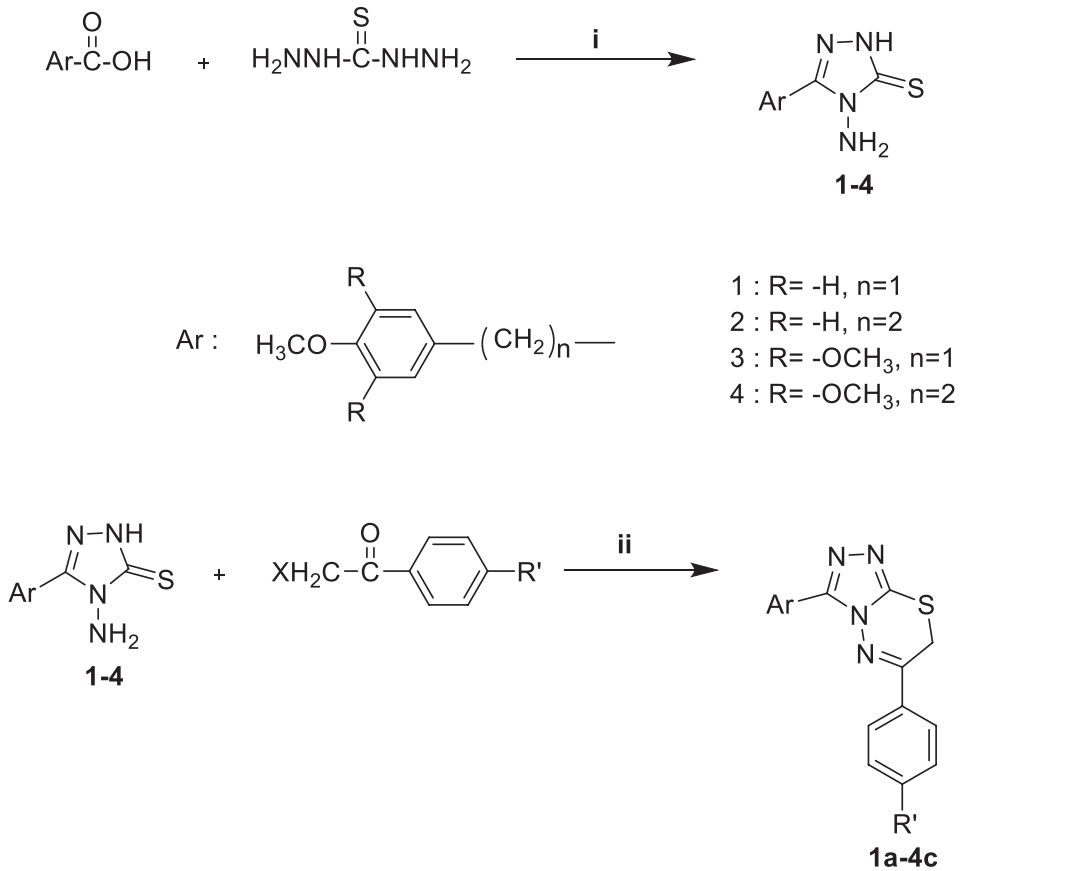
RESULTS

As a result of our study, it has been detected that there are many different 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazine derivatives that exhibit serious pharmacological activity and possess the potential to be a leading compound. However, in the literature, there are not enough studies supported by computer-aided drug design techniques associated with 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazine derivatives. Computer-aided drug design tools potentially minimize time and cost in drug discovery processes. By



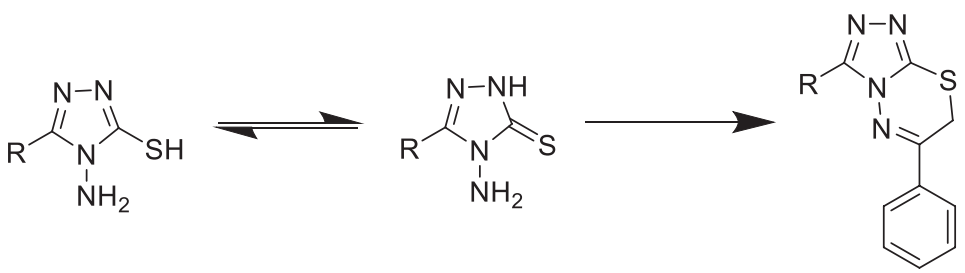
Scheme 4. The synthesis pathway of the novel compounds[6]

taking advantage of computer-aided drug design technology, researchers may be able to design potentially active and original molecules. Researchers may also carry out in silico simulations using the software to determine binding modes of the compounds with the related target and calculate potential drug-likeness and other properties that are related to absorption, distribution, metabolism,



1a: R= -H, n=1, R'= -H; **1b:** R= -H, n=1, R'= 4-Cl; **1c:** R= -H, n=1, R'= 4-F
2a: R= -H, n=2, R'= -H; **2b:** R= -H, n=2, R'= 4-Cl; **2c:** R= -H, n= 2, R'= 4-F
3a: R= $-OCH_3$, n=1, R'= -H; **3b:** R= $-OCH_3$, n=1, R'= 4-Cl; **3c:** R= $-OCH_3$, n=1, R'= 4-F
4a: R= $-OCH_3$, n=2, R'= -H; **4b:** R= $-OCH_3$, n=2, R'= 4-Cl, **4c:** R= -OCH3, n=2, R'= 4-F

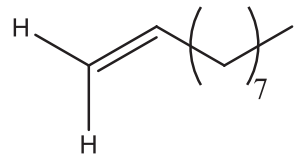
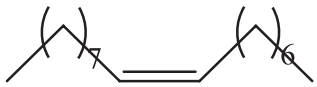
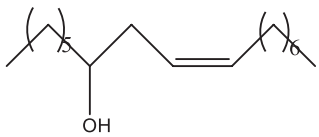
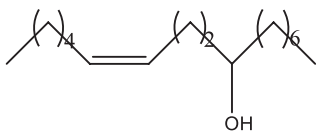
Scheme 5. The synthesis pathway of the novel 3,6-disubstituted 7*H*-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazines[3]

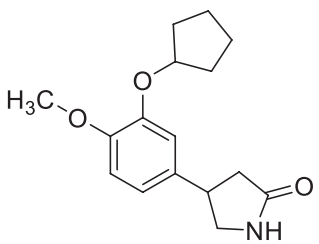


Scheme 6. The synthesis pathway of the novel 3,6-disubstituted 7*H*-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazines[2]. Reaction conditions: $PhCOCH_2Br$, EtOH, reflux (90°C), 12h, neutralization with NH_4OH

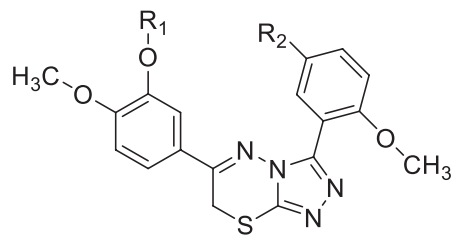
excretion, and the toxicity of the compounds. The overall results obtained from molecular modeling studies and the pharmacological responses of the synthesized molecules can provide insight into the synthesis of more efficient target-specific agents, which might also have higher selectivity and activity. Hence, researchers definitely should continue their drug discovery investigations and researches should be supported by computer-aided drug design techniques.

Table 4. Physico-chemical properties of the novel 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazine derivatives[2]

Compounds	R	Molecular formula	Physical state	Melting Point (°C)	% Yield	Molecular Weight
4a		$C_{20}H_{26}N_4S$	Brown sticky liquid	-	65	354.470
4b		$C_{27}H_{40}N_4S$	Brown sticky liquid	-	62	452.631
4c		$C_{27}H_{40}N_4OS$	Brown sticky liquid	-	60	468.630
4d		$C_{27}H_{40}N_4OS$	Brown sticky liquid	-	60	468.630

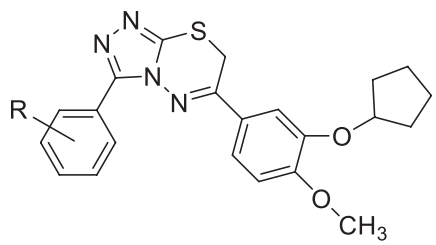


1



2

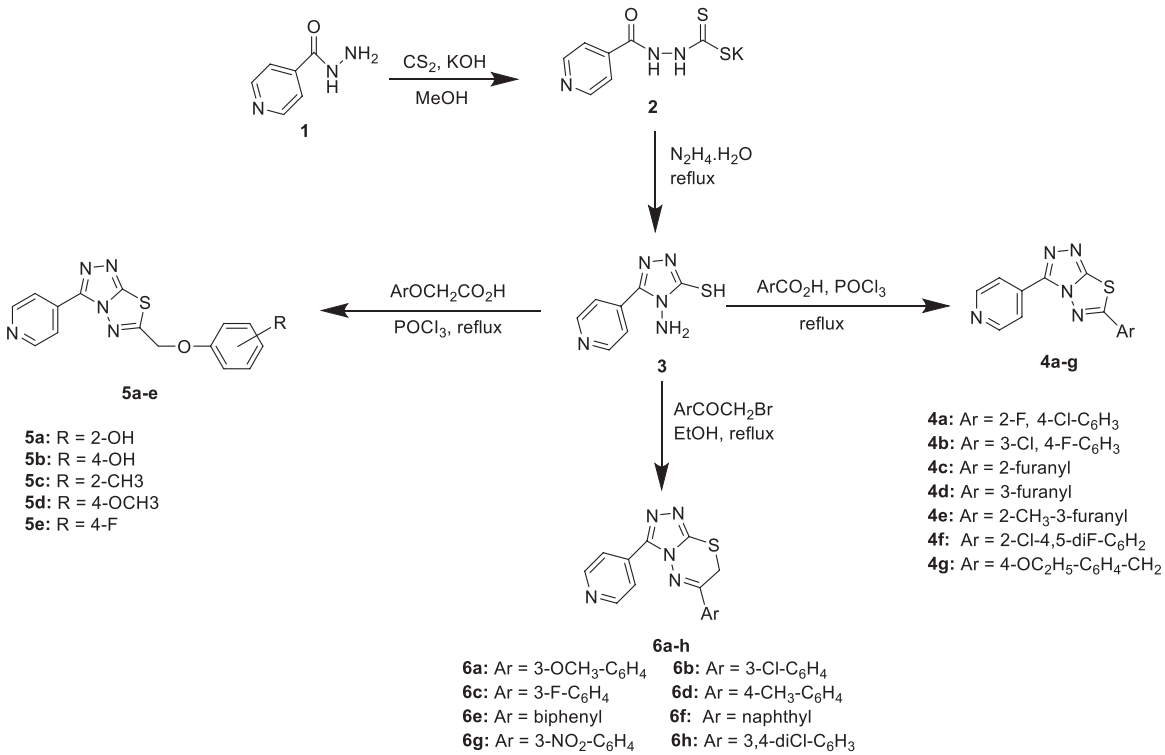
R_1 = OMe, Cyclopentyl
R_2 = H, OMe



3

3a: R = 2-OMe
3b: R = 3-OMe
3c: R = 4-Me
3d: R = H

Scheme 7. Rolipram (**1**), alkoxy-substituted 3,6,-diphenyl-7*H*-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazines (**2**), and some new 6-(3-(cyclopentyloxy)-4-methoxyphenyl)-3-aryl-7*H*-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazines (**3**)[5]



Scheme 8. The synthesis of the novel 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole and 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazine derivatives[12]

Peer Review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study- E.D.D., N.U.G.; Data Acquisition- E.D.D., N.U.G.; Data Analysis/Interpretation- E.D.D., N.U.G.; Drafting Manuscript- E.D.D., N.U.G.; Critical Revision of Manuscript- E.D.D., N.U.G.; Final Approval and Accountability- E.D.D., N.U.G.; Technical or Material Support- E.D.D., N.U.G.; Supervision- E.D.D., N.U.G.

Conflict of Interest: Authors declared no conflict of interest.

Financial Disclosure: Authors declared no financial support.

Hakem Değerlendirmesi: Dış bağımsız.

Yazar Katkıları: Çalışma Konsepti/Tasarım- E.D.D., N.U.G.; Veri Toplama- E.D.D., N.U.G.; Veri Analizi/Yorumlama- E.D.D., N.U.G.; Yazı Taslağı- E.D.D., N.U.G.; İçeriğin Eleştirel İncelemesi- E.D.D., N.U.G.; Son Onay ve Sorumluluk- E.D.D., N.U.G.; Malzeme ve Teknik Destek- E.D.D., N.U.G.; Süpervizyon- E.D.D., N.U.G.

Çıkar Çatışması: Yazarlar çıkar çatışması beyan etmemişlerdir.

Finansal Destek: Yazarlar finansal destek beyan etmemişlerdir.

REFERENCES

1. Abdel-Wahab, B.F., Abdel-Aziz, H.A., Ahmed, E.M. (2009): Synthesis and antimicrobial evaluation of some 1,3-thiazole, 1,3,4-thiadiazole, 1,2,4-triazole, and 1,2,4-triazolo[3,4-b][1,3,4]-thiadiazine derivatives including a 5-(benzofuran-2-yl)-1-phenylpyrazole moiety, *Monatshefte für Chemie-Chemical Monthly*, 140(6): 601-605.
2. Ahmad, A., Varshney, H., Rauf, A., Sherwani, A., Owais, M. (2017): Synthesis and anticancer activity of long chain substituted 1,3,4-oxadiazol-2-thione, 1,2,4-triazol-3-thione and 1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazine derivatives, *Arabian Journal of Chemistry*, 10: 3347-3357.
3. Aytac, S.P., Tozkoparan, B., Kaynak, F.B., Aktay, G., Göktaş, Ö., Ünüvar, S. (2009): Synthesis of 3,6-disubstituted 7*H*-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazines as novel analgesic/anti-inflammatory compounds, *European Journal of Medicinal Chemistry*, 44(11): 4528-4538.

4. Badr, S.M., Barwa, R.M. (2011): Synthesis of some new [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazines and [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles starting from 5-nitro-2-furoic acid and evaluation of their antimicrobial activity, *Bioorganic & Medicinal Chemistry*, 19(15): 4506-4512.

5. Baeeri, M., Foroumadi, A., Motamedi, M., Yahya-Meymandi, A., Firoozpour, L., Ostad, S.N., Shafiee, A., Souzangarzadeh, S., Abdollahi, M. (2011): Safety and Efficacy of New 3,6-diaryl-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine Analogs as Potential Phosphodiesterase-4 Inhibitors in NIH-3T3 Mouse Fibroblastic Cells, *Chemical Biology & Drug Design*, 78(3): 438-444.

6. El Shehry, M.F., Abu-Hashem, A.A., El-Telbani, E.M. (2010): Synthesis of 3-((2,4-dichlorophenoxy)methyl)-1,2,4-triazolo(thiadiazoles and thiadiazines) as anti-inflammatory and molluscicidal agents, *European Journal of Medicinal Chemistry*, 45(5): 1906-1911.

7. Ergenc, N., Ulusoy, N., Çapan, G., Sanis, G.Ö., Kiraz, M. (1996): Synthesis and Antimicrobial Properties of New 4-(Alkylidene/arylidene)-amino-5-(2-furanyl)-2, 4-dihydro-3*H*-1,2,4-triazole-3-thiones and 6-Aryl-3-(2-furanyl)-7*H*-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazines, *Archiv der Pharmazie*, 329(8-9): 427-430.

8. Holla, B.S., Rao, B.S., Sarojini, B.K., Akberali, P.M., Kumari, N.S. (2006): Synthesis and studies on some new fluorine containing triazolothiadiazines as possible antibacterial, antifungal and anticancer agents, *European Journal of Medicinal Chemistry*, 41(5): 657-663.

9. İlhan, E., Ergenç, N., Ulusoy, N., Ötük Sanış, G. (1996): Synthese und antimikrobielle Untersuchung einiger 4-Arylidenamino-3-(α,α-diphenyl-α-hydroxymethyl)-1,4-dihydro-5*H*-1,2,4-Triazol-5-thione und 6-Aryl-3-(α,α-diphenyl-α-hydroxymethyl)-7*H*-s-Triazolo[3,4-*b*][1,3,4]thiadiazine, Die *Pharmazie*, 51(2): 123-124.

10. Karabasanagouda, T., Adhikari, A.V., Shetty, N.S. (2007): Synthesis and antimicrobial activities of some novel 1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazoles and 1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazines carrying thioalkyl and sulphonyl phenoxy moieties, *European Journal of Medicinal Chemistry*, 42(4): 521-529.

11. Karegoudar, P., Prasad, D.J., Ashok, M., Mahalinga, M., Poojary, B., Holla, B.S. (2008): Synthesis, antimicrobial and anti-inflammatory activities of some 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazoles and 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazines bearing trichlorophenyl moiety, *European Journal of Medicinal Chemistry*, 43(4): 808-815.

12. Khan, I., Zaib, S., Ibrar, A., Rama, N.H., Simpson, J., Iqbal, J. (2014): Synthesis, crystal structure and biological evaluation of some novel 1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazoles and 1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazines, *European Journal of Medicinal Chemistry*, 78: 167-177.

13. Mekala, R.V.R., Yata, M.R., Talagadadivi, R.P. (2014): Synthesis, characterizatıon and bilogical screening of some novel indole based 1,2,4-trıazolo 1,3,4 thiadiazines, *Journal of Drug Delivery and Therapeutics*, 4(2): 43-46.

14. Penta, S., Gadidasu, K.K., Basavoju, S., Rao, V.R. (2013): An efficient one-pot synthesis of pyrazolyl-[1,2,4]triazolo[3,4-*b*][1,3,4] thiadiazin-6-yl)-2*H*-pyran-2-one derivatives via multicomponent approach and their potential antimicrobial and nematicidal activities, *Tetrahedron Letters*, 54(42): 5663-5666.

15. Pundeer, R., Kiran, V., Prakash, R., Bhatia, S.C., Sharma, C., Aneja, K.R. (2012): α,α-Dibromoacetophenones mediated synthesis of some new 7*H*-7-alkoxy-3-alkyl/phenyl-6-aryl-s-triazolo[3,4-*b*][1,3,4]thiadiazines and their antimicrobial evaluation, *Medicinal Chemistry Research*, 21(12): 4043-4052.

16. Puthiyapurayil, P., Poojary, B., Buridipad, S.K. (2014): Synthesis, Characterization and Biological Evaluation of a Novel Series of 1,2,4-triazolo-[3,4-*b*]-1,3,4-thiadiazines Containing an Amide Linkage, *Journal of Heterocyclic Chemistry*, 51(S1): E55-E67.

17. Sahu, J.K., Ganguly, S., & Kaushik, A. (2014): Synthesis and antimicrobial activity of some novel fused heterocyclic 1,2,4-triazolo [3,4-*b*][1,3,4] thiadiazine derivatives, *Journal of advanced pharmaceutical technology & research*, 5(2): 90.

18. Sumangala, V., Poojary, B., Chidananda, N., Arulmoli, T., Shenoy, S. (2012): Facile synthesis, cytotoxic and antimicrobial activity studies of a new group of 6-aryl-3-[4-(methylsulfonyl)benzyl]-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazines, *European Journal of Medicinal Chemistry*, 54: 59-64.