World Journal of Advanced Research and Reviews
eISSN: 2581-9615 CODEN (USA): WJARAI
Cross Ref DOI: 10.30574/wjarr
Journal homepage: https://wjarr.com/

(RESEARCH ARTICLE)

Check for updates

Synthesis and anti-bacterial activity of barbituric acid derivatives

Sangappa Teli * and Dharyappa Teli

BLDEAS SSM college of pharmacy and research centre Vijayapura.

World Journal of Advanced Research and Reviews, 2024, 21(03), 1863–1870

Publication history: Received on 08 February 2024; revised on 18 March 2024; accepted on 20 March 2024

Article DOI: https://doi.org/10.30574/wjarr.2024.21.3.0883

Abstract

When the viable solve the ents businesses launched penicillin, in the establishment of 19th century vented by Alexander Fleming, a major reduction in the number of deaths caused by bacterial infections was confirmed. Optimists have even noticed an end to the period of bacterial diseases. However, to the request, and frequently improper, applications of antibiotics have resulted in the development of drug-the resistant bacteria such as methicillin-resistant Staphylococcus aureus (MRSA), WHO generated a list of priority pathogens to focus the development of new antibacterial drugs against; MRSA ranked as a high priority. Unfortunately, the development of new antibacterial drugs has progressively declined since the 1980s. In my the research work novel derivatives of Barbituric acid obtained from Methyl propyl malonate and Thiourea give 5-methyl-5-propyl-2-sulfanyl Barbituric Acid [ST-I] it was treated with Alkyl Halides gives 5-methyl-5-propyl-2-sulfanyl Barbituric Acid Derivatives which is converted into resultant compound derivatives of (ST-IA to ST-IE). All the compounds synthesized were confirmed by spectral data and evaluated for their methicillin-resistant Staphylococcus aureus (MRSA) activity Vancomycin was used as standard. The compounds DR-IIA and DR-IID have shown good activity and the remaining show poor activity against bacteria.

Keywords: Barbituric Acid; Alkyl Halides Chloramphenicol; Antibacterial Activity; Vancomycin; Methicillin-Resistant Staphylococcus aureus (MRSA).

1. Introduction

The biological and medicinal properties of barbituric acids (BAs) are well-known. The structures, including barbiturates, have sedative-hypnotic properties.[1] Matrix metalloproteinase inhibitors [2] and cancer and AIDS therapy [3] are other vital areas in which BA derivatives have shown their efficiency. Besides, their capability for constructing polyfunctional ligands arises from having the potential metal-binding sites (O and N) in their structure.[4] Thiobarbituric acids also show a significant role in biological activities. For instance, they are used in determining lipid peroxidation.[5] 1,3-Disubstituted Thiobarbituric acids have been used as anticancer and anti-HIV agents, [6,7] and these structures, including heterocyclic moieties, have anticonvulsant properties.[8] Recently, (thio)barbituric acids have been used as herbicidal agents.[9]

The c-nucleophilic property of pyrimidine in substituted and unsubstituted (thio)barbituric acids has been thoroughly investigated. Their reaction with aldehydes, both aromatic and aliphatic, yields 5-aryl or 5-alkylmethylene barbituric acids.[10] Other electrophiles such as carbodiimides, benzophenones, 2,20 -bipyridyl, and erythrolactols react with BA to produce diamino-ethylene barbiturates,[11] triphenylmethylium salt,[12] 5,50 - (2-pyrilidine) bis barbituric acid,[13] spiro barbituric deoxyribonucleoside,[14] and spiro-linked condensed [1,2- α] quinolones.[15]

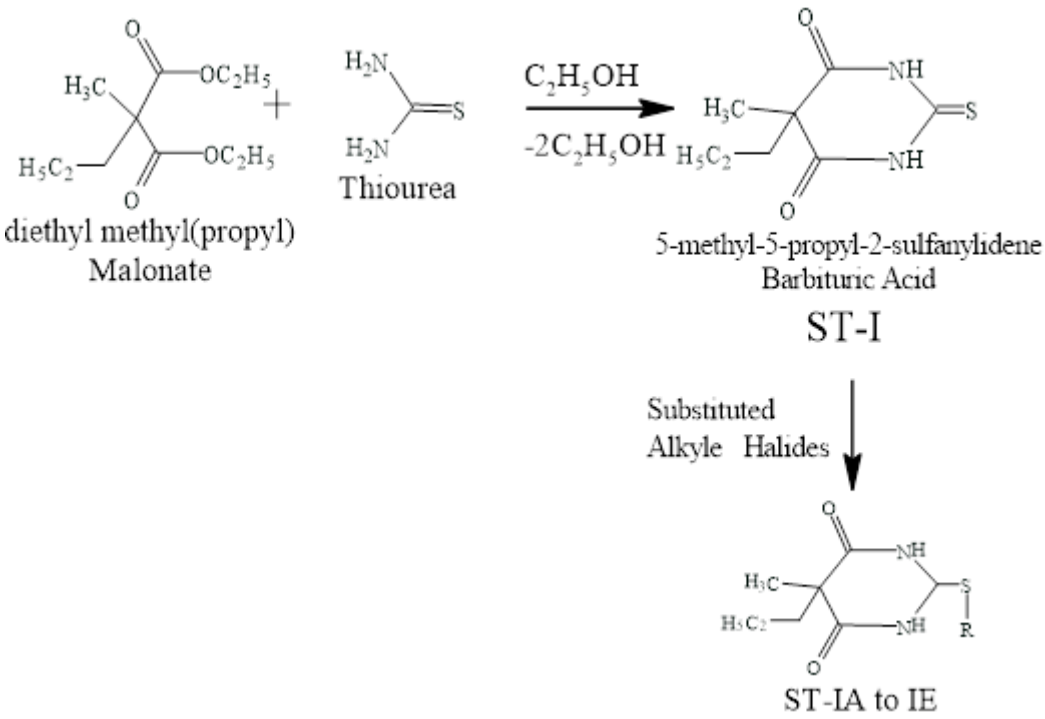
The one-pot reaction of (thio)barbituric acids with aldehydes and cyanogen bromide yield spiro furo[2,3-d] pyrimidines. [16–21] Hydrogen bonds participate in most of the biological and medicinal systems and remain a hot subject in the current research. The vast territory of H-bonding can be seen in supramolecular assemblies,[22] helical structures,[23] molecular rotors,[24] and also evaluation of H-bond acidity,[25] and so forth. The physicochemical

* Corresponding author: Sangappa Teli

behaviors of DNA and RNA show the importance of both inter- and intramolecular H-bonding.[26] There are a lot of research on a variety of organic compounds including eight-membered intramolecular H-bonds.[27–35] This type of interaction in bis-(thio)barbiturates based on triethylamine has been recently investigated in our lab.[36] In continuation of previous studies, this paper reports the intermolecular and eight-membered intramolecular H-bond in the product of the reaction of (thio)barbituric acids with aldehydes in the presence of N-methyl morpholine (4-MM). In recent years, the anticancer effect of quinolone and pyridine bis-barbiturates (Figure 1) has been studied by Neumann et al.,[37]

2. Material and methods

2.1. SCHEME



2.2. Methodology

2.2.1. Synthesis of 5-methyl-5-propyl-2-sulfanyl barbituric acid

Assemble a double surface reflux condenser with a 2-litre round-bottomed flask, and place 3.83 g of clean sodium. Mix 85 ml of absolute ethanol in a portion and if the reaction is unduly vigorous, immerse the flask in ice. When all the sodium has completed the reaction, add diethyl malonate 13.33 g (76 ml), followed by a solution of dry urea 5 g in 85 ml of hot (70 °C) absolute ethanol. Shake the mixture thoroughly, attach a calcium chloride guard tube to the top of the condenser, start reflux of the mixture for 7 h in an oil bath, and heat to 110 °C. A white solid will be separated from 5-methyl-5-propyl-2-sulfanyl Barbituric Acid.

2.2.2. Synthesis of 5-methyl-5-propyl-2-sulfanyl barbituric acid derivatives [ST-IA TO ST-IE]

A mixture of 5-methyl-5-propyl-2-sulfanyl Barbituric Acid (0.01 mol), Substituted halides (0.01 mol), and anhydrous potassium carbonate (2.0 g,0.01mol) in dimethyl Formamide (30 ml) was heated under reflux for 12 h. The solvent was evaporated *in a* vacuum and the obtained residue was washed with water, dried, and recrystallized from ethanol.

Table 1 Derivatives of 5-methyl-5-propyl-2-sulfanyl barbituric acid [ST-IA –IE]

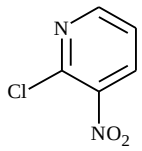
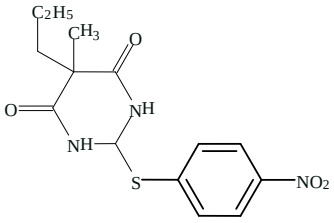
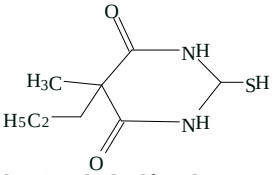
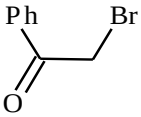
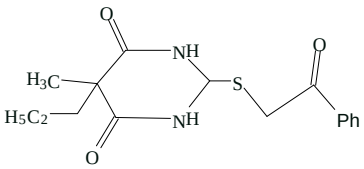
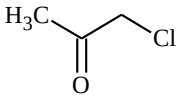
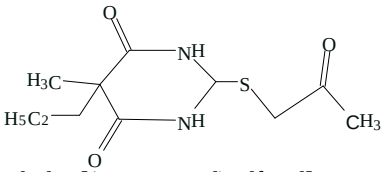
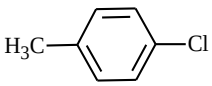
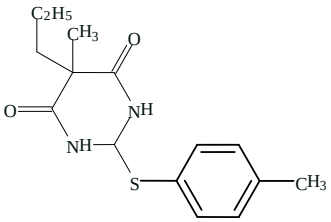
Compound Code	Substituted Halides	Derivatives of 5-Methyl-5-Propyl-2-Sulfanyl Barbituric Acid
ST-IA	 2-chloro-3-nitropyridine	 5-methyl-2-[(4-nitrophenyl)sulfanyl]-5-propyl -1,3-diazinane-4,6-dione
ST-IB	CH_3I Methyl iodide	 5-methyl-2-(methylsulfanyl)-5-propyl-1,3 -diazinane-4,6-dione
ST-IC	 2-bromo-1-phenylet han-1-one	 5-methyl-2-[(2-oxo-2-phenylethyl)sulfanyl] -5-propyl-1,3-diazinane-4,6-dione
ST-ID	 1-chloropropan-2-one	 5-methyl-2-[(2-oxopropyl)sulfanyl]-5-propyl- 1,3-diazinane-4,6-dione
ST-IE	 1-chloro-4-methylbenzene	 5-methyl-2-[(4-methylphenyl)sulfanyl]-5 -propyl-1,3-diazinane-4,6-dione

Table 2 Physicochemical properties of derivatives of compound 5-methyl-5-propyl-2-sulfanyl barbituric acid[ST-IA – IE]

Sl. No	Parameter	ST-IA	ST-IB	ST-IC
1	Molecular Formula	$C_{14}H_{17}N_3O_4S$	$C_9H_{16}N_2O_2S$	$C_{16}H_{20}N_2O_3S$
2	Molecular weight	323.36gm	216.30gm	320.40gm
3	Theoretical yield	5.16gm	2.30gm	5.06gm
4	Practical yield	3.14gm	1.8gm	4.18gm
5	% yield	60.85%	78.26%	82.60%
6	Melting point	240-245° C	286^0-289° C	305-308° C
7	Recrystallization	Ethanol	Ethanol	Ethanol
8	TLC	Benzene: Chloroform 5:1	Benzene:Chloroform5:1	Benzene:Chloroform5:1
9	R_f Value	0.85	0.96	0.90

Table 3 Physicochemical properties of derivatives of compound 5-methyl-5-propyl-2-sulfanyl barbituric acid [ST-IA – IE]

Sl. No	Parameter	ST-ID	ST-IE
1	Molecular Formula	$C_{11}H_{18}N_2O_3S$	$C_{15}H_{20}N_2O_2S$
2	Molecular weight	258.33gm	292.39gm
3	Theoretical yield	3.29gm	4.22gm
4	Practical yield	2.02gm	2.5gm
5	% yield	61.39%	59.24%
6	Melting point	310-312° C	288-290° C
7	Recrystallization	Ethanol	Ethanol
8	TLC	Benzene:Chloroform5:1	Benzene:Chloroform5:1
9	R_f Value	0.84	0.92

2.3. Spectral data

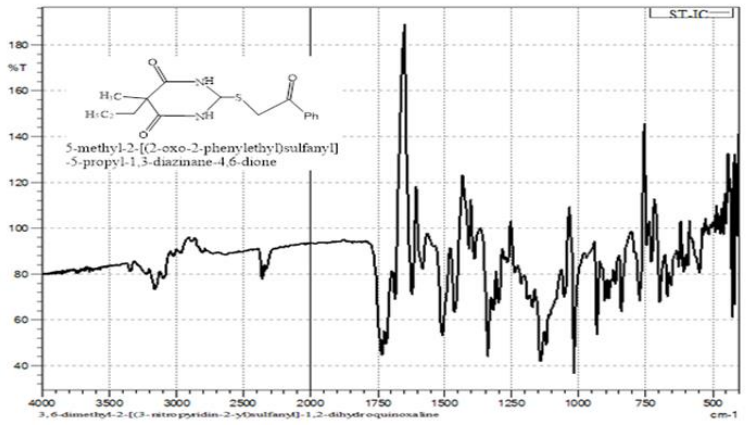


Figure 3 FT-IR Spectrum data of compound 5-methyl-2-[(2-oxo-2-phenylethyl)sulfanyl]-5-propyl-1,3-diazinane-4,6-dione [ST-IC]

Table 4 FT-IR Spectrum data of compound 5-methyl-2-[(2-oxo-2-phenylethyl) sulfanyl]-5-propyl-1,3-diazinane-4,6-dione [ST-IC]

Types of Vibrations	Group frequency in Wavenumber (cm^{-1})
-NH Stretching	3300-3390 cm^{-1}
Aromatic CH stretching	3150-3250cm^{-1}
Aliphatic CH	2910-3100cm^{-1}
-CH_3Stretching	1010 cm^{-1}
-C-S stretching	780 cm^{-1}

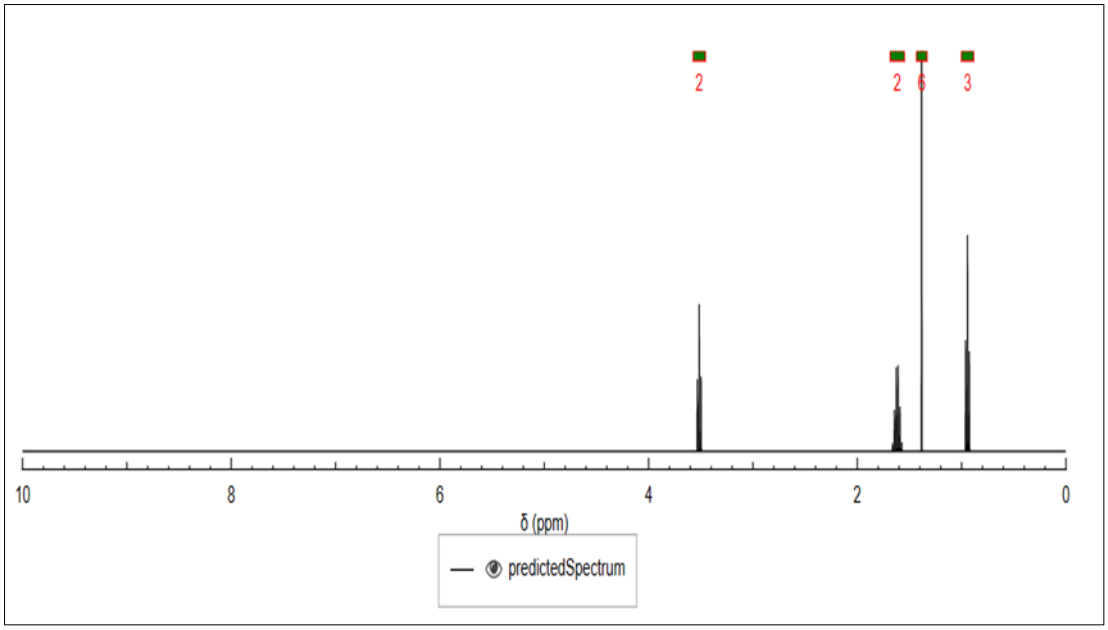


Figure 4 NMR Spectra Spectrum data of compound 5-methyl-2-[(2-oxo-2-phenylethyl) sulfanyl]-5-propyl-1,3-diazinane-4,6-dione [ST-IC]

2.3.1. NMR Spectra

^{1}H NMR: δ 0.94 (3H, t, *J* = 7.1 Hz), 1.38 (6H, s), 1.62 (2H, tq, *J* = 7.2, 7.1 Hz), 3.51 (2H, t, *J* = 7.2 Hz).

Table 6 FT-IR Spectrum data of compound 5-methyl-2-[(2-oxo-2-phenylethyl) sulfanyl] -5-propyl-1,3-diazinane-4,6-dione [ST-ID]

Types of Vibrations	Group frequency in Wavenumber (cm^{-1})
-NH Stretching	3300-3390 cm^{-1}
Aromatic CH stretching	3150-3250cm^{-1}
Aliphatic CH	2910-3100cm^{-1}
-CH_3Stretching	1010 cm^{-1}
-C-S stretching	780 cm^{-1}

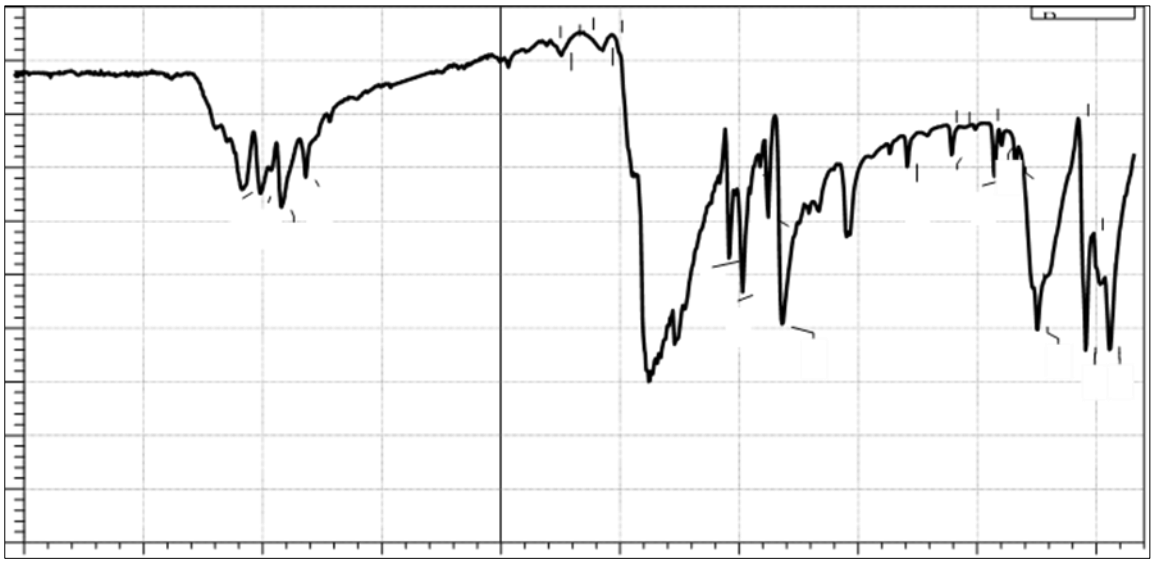


Figure 5 FT-IR Spectrum data of compound 5-methyl-2-[(2-oxo-2-phenylethyl) sulfanyl]-5-propyl-1,3-diazinane-4,6-dione [ST-ID]

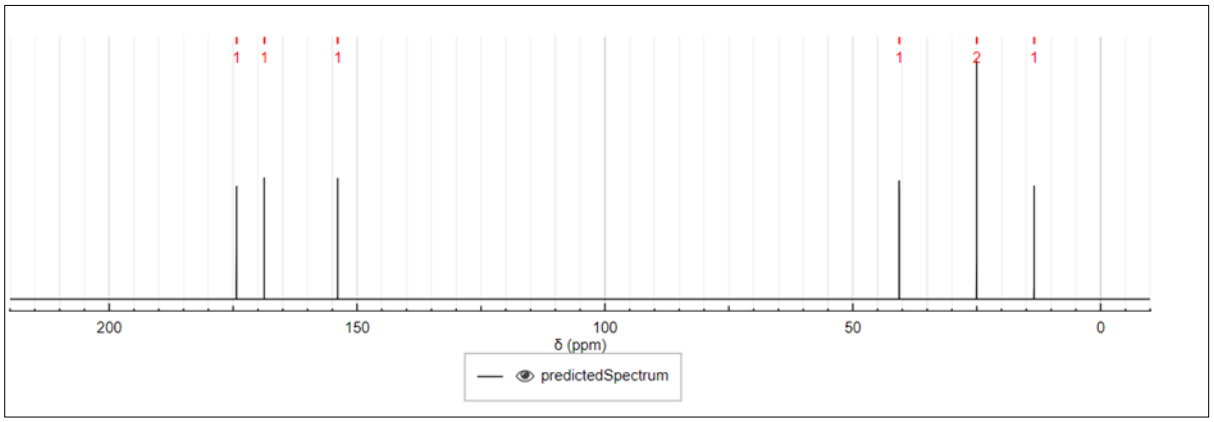


Figure 6 NMR Spectra Spectrum data of compound 5-methyl-2-[(2-oxo-2-phenylethyl) sulfanyl]-5-propyl-1,3-diazinane-4,6-dione [ST-ID]

2.3.2. ^{13}C NMR: δ 13.4 (1C, s), 25.0 (2C, s), 40.6 (1C, s),153.9 (1C, s), 168.7 (1C, s), 174.3 (1C, s).

ANTIBACTERIAL ACTIVITY

The cup plate method determined the minimum inhibitory concentration (MIC). Ciprofloxacin was employed during the test procedures as a reference. The MIC of the synthesized compounds ranges between 250-500 µg/ml. **ST-IA, ST-IB, ST-ID, and ST-IE** were found to be moderately active, while **ST-IC** was found to have an average activity compared with standard. Test compounds were found to be more sensitive toward *Staphylococcus aureus* (Gram-positive bacteria) and *Escherichia coli* (Gram-negative bacteria).

Table 7 Data of Anti-bacterial Activity of Compounds [ST-IA to ST-IE]

Sr No	Compound Code	*Escherichia coli (Gram -ve)*			*S. aureus (gram +ve)*		
		Concentration ofderivatives (µg /ml)			Concentration ofderivatives (µg /ml)		
		250	500	750	250	500	750
		Mean zone of Inhibition (mm)					
1	ST-IA	12	13	13	11	12	15

2	ST-IB	10	11	11	11	11	12
3	ST-IC	15	19	22	13	19	21
4	ST-ID	10	11	11	11	11	12
5	ST-IE	08	10	09	07	08	10
Std	Chloramphenicol	25			25		

The minimum inhibitory concentration of synthesized compounds [ST-IA to ST-IE] (Against Bacteria) Note: -Standard(S) = Chloramphenicol Control (C) = DMF (Dimethyl Formamide)

3. Results and discussion

The literature survey, reveals that pyridine has been reported for a number of pharmacological activities some molecules have shown significant activities and some compounds show moderate and good activities. Here we have synthesized some Derivatives of 5**-**methyl-2-[(2-oxo-2-phenylethyl) sulfanyl]-5-propyl-1,3-diazinane-4,6-dione and screened them for their antimicrobial activities.

The purity and homogeneity of the synthesized compounds were preliminarily checked by their physical constant and R_f value. The final compounds were found to be soluble in organic solvents. These compounds were subjected to TLC, FT-IR spectral studies, and ^1H NMR studies for structural elucidation, and studies showed satisfactory results

4. Conclusion

The novel derivatives of 5-methyl-2-[(2-oxo-2-phenylethyl) sulfanyl]-5-propyl-1,3-diazinane-4,6-dione [ST-IA-IE**]** were prepared and all the derivatives were analyzed by FT-IR spectroscopy. The synthesized derivatives confirmed the antibacterial activity by cup-plate technique. Verified derivatives exhibited significant antibacterial activity when compared to the standard drug Vancomycin. The compounds DR-IIA and DR-IID have shown good activity and the remaining show poor activity against bacteria.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

References

[1] N. Moussier, L. Bruché, F. Viani, M. Zanda, Curr. Org. Chem. 2003, 7, 1071.

[2] H. Brandstetter, F. Grams, D. Glitz, A. Lang, R. Huber, W. Bode, H.-W. Krell, R. A. Engh, J. Biol. Chem. 2001, 276, 17405.

[3] D. L. Levesque, E. –. C. Wang, D. –. C. Wei, M. H. El Kouni, F. N. M. Naguib, J. Heterocycl. Chem. 1993, 30, 1399

[4] K. T. Mahmudov, M. N. Kopylovich, A. M. Maharramov, M. M. Kurbanova, A. V. Gurbanov, A. J. L. Pombeiro, Coord. Chem. Rev. 2014, 265, 1.

[5] D. Grotto, L. S. Maria, J. Valentini, C. Paniz, G. Schmitt, S. C. Garcia, V. J. Pomblum, J. B. T. Rocha, M. Farina, Quím. Nova. 2009, 32, 169.

[6] R. Abdel-Rahman, M. Seada, M. Fawzy, I. El-Baz, Pharmazie 1994, 49, 811.

[7] A. S. Al-Harbi, R. M. Abdel-Rahman, A. M. Asiri, Eur. J. Chem. 2015, 6, 63.

[8] A. V. K. Srivastava, A. Kumar, Bioorg. Med. Chem. 2004, 12, 1257

[9] A. N. Al-Romaizan, Hindawi- J. Chem. 2019, 2019, 1. https:// doi.org/10.1155/2019/3035107.

[10] B. S. Jursic, E. D. Stevens, Tetrahedron Lett. 2003, 44, 2203.

[11] B. S. Jursic, F. Douelle, E. D. Stevens, Tetrahedron 2003, 59, 3427.

[12] S. Spange, M. Bauer, B. Walfort, H. Lang, J. Org. Chem. 2006, 71, 7850.

[13] B. S. Jursic, D. M. Neumann, K. L. Martin, E. D. Stevens, Org. Lett. 2002, 4, 811.

[14] A. Renaud, J. Lhomme, M. Kotera, J. Org. Chem. 2002, 67, 1302.

[15] I. V. Paramonov, N. A. Belyaev, T. V. Glukhareva, A. S. Volkov, E. V. Deeva, Chem. Heterocycl. Compd. 2006, 42, 127.

[16] Y. Hosseini, S. Rastgar, Z. Heren, O. Büyükgüngörc, N. Noroozi Pesyan, J. Chin. Chem. Soc. 2011, 58, 309.

[17] M. Jalilzadeh, N. Noroozi Pesyan, F. Rezaee, S. Rastgar, Y. Hosseini, E. S¸ahin, Mol. Divers. 2011, 15, 721.

[18] N. Noroozi Pesyan, H. Rashidnejad, J. Iran. Chem. Soc. 2017, 14, 1365.

[19] N. Noroozi Pesyan, A. Shokr, A. Gharib, T. Tunç, E. S¸ahin, J. Chin. Chem. Soc. 2015, 62, 234.

[20] E. Kashani, N. Noroozi Pesyan, E. S¸ahin, J. Chin. Chem. Soc. 2015, 62, 959.

[21] N. Noroozi Pesyan, Y. Hosseini, A. Shokr, E. S¸ahin, J. Chin. Chem. Soc. 2012, 59, 1561.

[22] P. Prabhakaran, V. G. Puranik, G. J. Sanjayan, J. Org. Chem. 2005, 70, 10067.

[23] I. Azumaya, D. Uchida, T. Kato, A. Yokoyama, A. Tanatani, H. Takayanagi, T. Yokozawa, Angew. Chem. Int. Ed. 2004, 43, 1360.

[24] I. Alfonso, M. I. Burguete, S. V. Luis, J. Org. Chem. 2006, 71, 2242.

[25] M. H. Abraham, R. J. Abraham, J. Byrne, L. Griffiths, J. Org. Chem. 2006, 71, 3389.

[26] G. A. Jeffrey, W. Saenger, Hydrogen Bonding in Biological Structures, Springer-Verlag, Berlin, Germany 1991.

[27] A. M. Asiri, S. A. Khan, S. W. Ng, Acta Cryst. Sect. E. 2009, 65, o1860.

[28] Y. Zhang, C. –. S. Wang, J. Comput. Chem. 2009, 30, 1251.

[29] D. D. Yang, F. –. F. Ng, Z. –. J. Li, Y. –. D. Wu, K. W. K. Chan, D. –. P. Wang, J. Am. Chem. Soc. 1996, 118, 9794.

[30] D. Yang, J. Qu, B. Li, F. –. F. Ng, X. –. C. Wang, K. –. K. Cheung, D. –. P. Wang, Y. –. D. Wu, J. Am. Chem. Soc. 1999, 121, 589.

[31] A. G. Ligtenbarg, R. Hage, A. Meetsma, B. L. Feringa, J. Chem. Soc. Trans. 1999, 2, 807.

[32] M. Jalilzadeh, N. Noroozi Pesyan, Bull. Korean Chem. Soc. 2011, 32, 3382.

[33] N. Noroozi Pesyan, M. Jalilzadeh, Turk. J. Chem. 2012, 36, 788.

[34] G. Gilli, P. Gilli, J. Mol. Struct. 2000, 552, 1.

[35] P. Gilli, V. Bertolasi, L. Pretto, V. Ferretti, G. Gilli, J. Am. Chem. Soc. 2004, 126, 3845.