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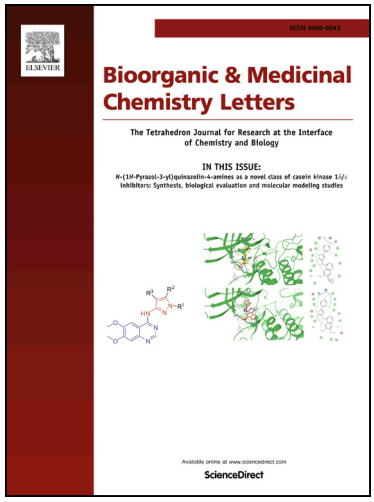

Synthesis and Biological Evaluation of 5-Fatty-acylamido-1, 3, 4-Thiadiazole-2-Thioglycosides

Srikanth Vudhgiri, Dhevendar Koude, Dileep Kumar Veeragoni, Sunil Misra, RBN. Prasad, Ram Chandra Reddy Jala

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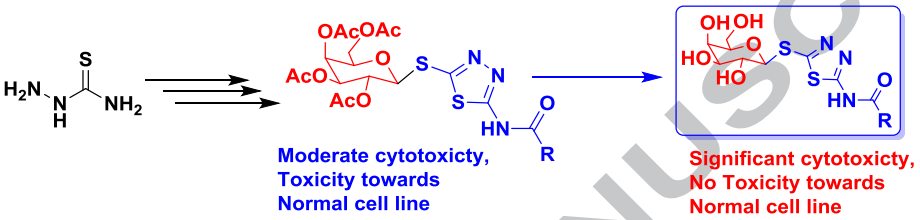
Srikanth Vudhgiri[a, c], Dhevendar Koude[b, c], Dileep Kumar Veeragoni[b, c], Sunil Misra[b, c], R. B. N. Prasad[a, c], Ram Chandra Reddy Jala* [a, c]



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ABSTRACT

In the present study, the synthesis of 1, 3, 4-thiadiazole-based thioglycosides were accomplished in good yields with employing a convergent synthetic route. The starting material 5-amino-1, 3, 4-thiadiazole-2-thiol and followed by a series of 5-fatty-acylamido-1, 3, 4-thiadiazole-2-thiols (**4a-4j**) were synthesized with different fatty acid chlorides. The glycosylation of compounds **4a-4j** were achieved with trichloroacetimidate methodology. Antimicrobial and cytotoxicity activities of title compounds were evaluated. Among the entire compounds lauric acid and myristic acid derivatives showed good and moderate antimicrobial activity. In case of cytotoxicity results of compounds **8a-8j** and **9a-9j**, the acetate protected short chain (C6:0, C8:0, C10:0) compounds and the free hydroxyl long chain saturated (C16:0, C18:0) and unsaturated (C18:1, C22:1) compounds exhibited good activity against different cancer cell lines. Further, the free hydroxyl compounds **9a, 9c-9j** did not show any toxicity towards normal CHO-K1 cell line whereas acylated compounds **8a-8j** exhibited toxicity.

Various types of glycosides are found in nature in the form of glycoconjugates such as glycopeptides, glycolipids and glucosinolates (thioglycosides) in which glycosidic linkage plays a crucial role for the biological activity[1]. Recently, thioglycosides have gained much attention due to their broad spectrum of properties[2-5] such as anti tumour, anti diabetic, biological inhibitors, inducers, *in vitro* inhibitory effects on the replication of a number of DNA viruses. Thioglycosides occur rarely in nature[2] although sulphur is an essential element found in all living systems. Many of the thioglycoside derivatives[2, 4, 6-8] are having common glucosylthio moiety attached to carbon linked to nitrogen either in an open chain or cyclic form (heterocyclic ring). These glycosylthio moiety attached to the heterocyclic ring is known as glycosylthio heterocycles. In these glycosylthio heterocycles, glycone and aglycone (different heterocyclic rings) were modified for extensive biological activities. Earlier reports[2-8] on heterocyclic thioglycosides such as pyridine, benzylisoquinoline, oxadiazole and triazole thioglycosides reveal their potential antitumor activities.

Thiadiazole is a five-membered ring heterocyclic compound having sulphur and two nitrogen atoms. This moiety acts as a good pharmacophore[9], hydrogen binding domain and two electron donor system. Many drugs such as sulfamethazole, methazolamide, acetazolamide are available in the market[10] with thiadiazole nucleus. 1, 3, 4-Thiadiazoles and its' derivatives are having a wide range of biological applications[9-12] in different fields such as agriculture (pesticides, herbicides), petroleum (lubricants, dyes) and medicine (antibacterial, antitumor, anti inflammatory, anti diabetic). Moreover, a few reports[13-15] are available on synthesis of thiadiazole-based thioglycosides and these are evaluated as SGLT2 inhibitors and anti diabetic agents with aromatic substituted analogues. However, these studies were limited to anti diabetic activity evaluation.

On the other hand, fatty acids are important molecules for exhibiting different biological activities. Fatty acid substrates exhibit different biological activities[16, 17] such as antimicrobial, antidepressant, anti tumor activities. Moreover, Garcia-Alvarez *et al*., reported[18] that oleyl-α-thioglycoside effectively reduced the

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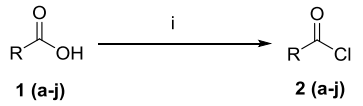
tumour volume compared to oleyl-α-*O*-glycoside. These findings suggest that combination of sugar moiety with fatty acids or oleic acid chain gives the good antitumor activity.

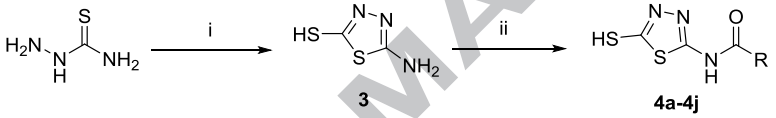
Based on the above facts, we felt that in glycosylthio heterocycles, substitution of the aglycone with new heterocyclic ring fatty acid derivatives yields novel, potential biological entities. Therefore, in the present study we report the synthesis and evaluation of 1, 3, 4-thiadiazole-based thioglycoside fatty acid (short, medium, long and unsaturated) derivatives for antimicrobial and anti cancer activities.



R = - $(CH_2)_4$-CH_3 **(a)**, - $(CH_2)_6$-CH_3 **(b)**, - $(CH_2)_8$-CH_3 **(c)**, - $(CH_2)_8$-$CH{=}CH_2$ **(d)**, - $(CH_2)_{10}$-CH_3 **(e)**, - $(CH_2)_{12}$-CH_3 **(f)**, - $(CH_2)_{14}$-CH_3 **(g)**, - $(CH_2)_{16}$-CH_3 **(h)**, - $(CH_2)_7$-$CH{=}CH$-$(CH_2)_7$-CH_3 **(i)**, - $(CH_2)_{11}$-$CH{=}CH$-$(CH_2)_7$-CH_3 **(j)**.

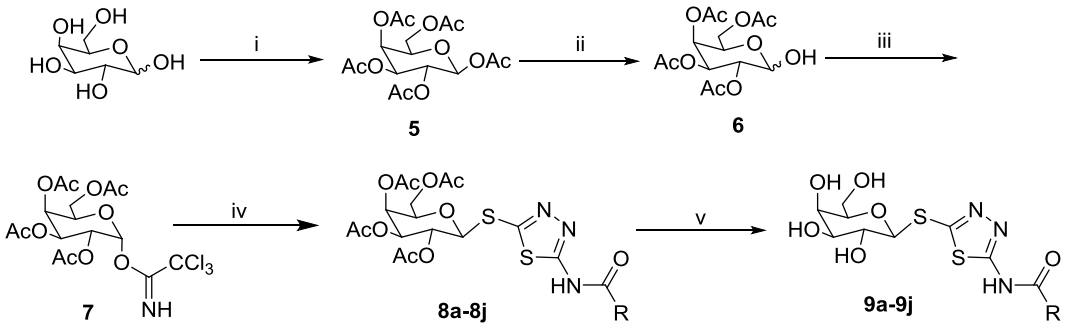
Scheme 1. Reagents and conditions: (i) $(COCl)_2$, cat. DMF, DCM, 3 h.

The synthesis of title compounds, 5-fatty-acylamido-1, 3, 4-thiadiazole-2-thioglycosides, was accomplished in a convergent synthesis. In Scheme 2, the starting material 5-amino-1, 3, 4-thiadiazole-2-thiol (**3**) was synthesized[12] from carbon disulfide addition to thiosemicarbazide under reflux conditions. The compound **3** was confirmed by ESI-Mass, ^{1}H-NMR, ^{13}C-NMR and IR. A series of compounds **4a-4j** were synthesized in a single step using fatty acid chlorides (**2a-2j**) (As per Scheme 1, these fatty acid chlorides were prepared from fatty acids using oxalyl chloride at 0 ^{o}C.) under catalytic amount of triethyl amine at room temperature. These compounds were confirmed by ^{1}H-NMR, the characteristic amide proton appears at δ = 11.5 to 12.5 ppm as a broad singlet, where as in case of compound **3** the amine proton appears at δ = 13.12 ppm as a broad singlet.



Scheme 2. Reagents and conditions: i) EtOH, CS_2, reflux, 4 h, 84%; ii) Acid chloride, Et_3N, DCM, rt, 6 h, 80-88%.

The glycosylation of compounds **4a-4j** was achieved as outlined in the Scheme 3, the 1, 2, 3, 4, 6-penta-*O*-acetyl-β-D-galactopyranose (**5**) was synthesiszed from galactose with Ac_2O and NaOAc under reflux conditions for 4 h, the compound **5** was purified by simple recrystalization with 92% yield. The anomeric acetyl group was chemo selectively removed by hydrazine acetate[19] in DMF to give **6** with 92% yield. Subsequently, hemiacetal **6** was reacted with trichloroacetonitrile in the presence of DBU at room temperature to give exclusively α-trichloroacetimidate (**7**) due to anomeric effect[20]. The coupling of imidate (**7**) was carried out with compounds **4a-4j** in presence of TMSOTf under overnight stirring at room temperature[21] to yield acylated compounds **8a-8j** in β–configuration. This β-orientation was achieved by NGP of C-2′ acetate group of sugar with C-1′ carbon of sugar as it allowed only equatorial attack of acceptor. ^{1}H-NMR analysis revealed that the signals of H-1′ proton was observed as a doublet at δ = 4.97 ppm, J = 10.07 Hz. Finally, 5-fatty-acylamido-1, 3, 4-thiadiazole-2-thioglycosides (**9a-9j**) were prepared by employing Zemplen deacetylation[22] on the acylated compounds **8a-8j**.



Scheme 3. Reagents and conditions: i) Ac_2O, NaOAc, reflux, 4 h, 92%; ii) Hydrazine Acetate, DMF, 50 ^{o}C, 2 h, 92%; iii) CCl_3CN, DBU, DCM, rt, 3h, 77%; iv) **4a-4j**, TMSOTf, DCM, 4 A^o MS., 0 ^{o}C to rt, overnight, 72-80%; v) NaOMe, MeOH, Amberlite IR-120, rt, 3 h, 95-97%.

Antimicrobial activities[23] of compounds **9a-9j** and acylated compounds **8a-8j** were evaluated against three Gram-positive and three Gram-negative bacterial strains such as *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Bacillus subtilis*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumonia* and the results to this regard are shown in Table 1. Lauric and myristic acid derivatives showed good antimicrobial activity against Gram-negative bacterial strain *Klebsiella pneumonia* with MIC values 12.5, 25 µg/mL and moderate activity exhibited against Gram-positive bacterial strain *Bacillus subtilis* with MIC values 25 and 50 µg/mL, respectively. Moreover, acylated compounds **8a-8j** did not show any significant activity against the tested strains.

Table 1. Antimicrobial Activity Minimum Inhibitory Concentration of *N*-(5-(β-D-Galactopyranosylthio)-1, 3, 4-Thiadiazol-2-yl) Fatty-acylamides (9a-9j)

	Minimum inhibitory concentration (µg/mL)					
Test compound	***Staphylococcus aureus***	***Staphylococcus epidermidis***	***Bacillus subtilis***	***Escherichia coli***	***Pseudomonas aeruginosa***	***Klebsiella pneumoniae***
9a	>150	>150	>150	>150	>150	>150
9b	>150	>150	>150	>150	>150	>150
9c	>150	>150	>150	>150	>150	>150
9d	>150	>150	>150	>150	>150	>150
9e	>150	>150	25	>150	>150	12.5
9f	>150	>150	50	>150	>150	25
9g	>150	>150	>150	>150	>150	>150
9h	>150	>150	>150	>150	>150	>150
9i	>150	>150	>150	>150	>150	>150
9j	>150	>150	>150	>150	>150	>150
Penicillin	1.562	3.125	1.562	12.5	12.5	6.25
Streptomycin	6.25	3.125	6.25	6.25	1.562	3.125

Compounds **9a-9j** and acylated compounds **8a-8j** were examined for cytotoxicity (MTT assay[24]) against four cancer cell lines and one normal cell line such as human ovarian cancer (SKOV3), cervical cancer (HeLa), breast cancer (MDAMB-231), human prostate cancer (DU145) cell lines and normal Chinese hamster ovary cancer (CHO-K1) cell line. The results are presented in Table 2 and 3. Compounds **9a-9j** exhibited moderate to promising activity against HeLa, MDA-MB-231, SKOV3 cancer cell lines with IC_{50} values ranging between 8.7-80.6 µM (Table 2). Among all the compounds, medium chain lauric acid derivative (**9e**) and unsaturated oleic acid derivative (**9i**) exhibited promising activity against cervical cancer cell line with IC_{50} values 8.7, 8.8 µM, respectively. In addition, the saturated long chain stearic, palmitic acid derivatives (**9h**, **9g**) and long chain unsaturated erucic acid derivative (**9j**) showed good activity with IC_{50} values 11.2, 14.2 and 13.5 µM, respectively against HeLa cancer cell line. All the tested compounds exhibited moderate activity against MDA-MB-231 cancer cell line. Moreover, all these compounds (**9a, 9c-9j**) did not show any toxicity against normal CHO-K1 cell line except for octanoic acid derivative (**9b**).

Table 2. Cytotoxicity Evaluation of *N*-(5-(β-D-Galactopyranosylthio)-1, 3, 4-Thiadiazol-2-yl) Fatty-acylamides (9a-9j)

Test compound	IC_{50} values (µM)				
	SKOV3	**HeLa**	**MDA-MB-231**	**DU145**	**CHO-K1**
9a	[a]-	45.6 ± 0.51	28.7 ± 0.47	-	-
9b	56.0 ± 0.79	50.8 ± 0.76	30.8 ± 0.62	-	60.1 ± 0.83
9c	-	25.9 ± 0.49	53.1 ± 0.83	-	-
9d	-	58.3 ± 0.78	80.6 ± 0.94	-	-
9e	-	8.7 ± 0.59	32.0 ± 0.58	-	-
9f	-	31.0 ± 0.71	33.3 ± 0.67	-	-
9g	-	14.2 ± 0.35	62.3 ± 0.70	-	-
9h	-	11.2 ± 0.43	67.1 ± 0.88	-	-
9i	-	8.8 ± 0.61	43.6 ± 0.61	-	-
9j	-	13.5 ± 0.39	70.4 ± 0.88	-	-
Doxorubicin	0.7 ± 0.23	0.7 ± 0.22	0.7 ± 0.20	0.8 ± 0.19	-
Mitomycin c	-	-	-	-	13.4 ± 0.21

[a] -: No activity, SKOV3-Ovarian cancer (ATCC® HTB 77™), HeLa-Cervical cancer (ATCC® CCL2™), MDAMB-231-Breast cancer (ATCC® HTB26™), DU145-Prostate cancer (ATCC® HTB81™), CHO-K1-Normal Chinese hamster ovary (ATCC® CCL-61™) cell lines

Acylated compounds **8a-8j** exhibited moderate to good activity against HeLa, MDA-MB-231, DU145 cancer cell lines with IC_{50} values ranging between 16.9 to 97.5 µM (Table 3). Among the tested compounds lauric acid derivative (**8e**) exhibited good activity against prostate cancer cell line with IC_{50} value 16.9 µM. In a similar way, octanoic, decanoic acid derivatives (**8b, 8c**) and

hexanoic acid derivative (**8a**) showed good activity with IC_{50} values 18.9, 19.2 and 19.8 µM against MDA-MB-231 and HeLa cancer cell lines respectively. All the other compounds showed moderate and poor activity against MDA-MB-231, DU145 and HeLa cancer cell lines respectively. Moreover, all the tested acylated compounds **8a-8j** exhibited toxicity against normal CHO-K1 cell line unlike compounds **9a, 9c-9j**.

Table 3. Cytotoxicity Evaluation of *N*-(5-(2′, 3′, 4′, 6′-Tetra-*O*-Acetyl-β-D-Galactopyranosylthio)-1, 3, 4-Thiadiazol-2-yl) Fatty-acylamides (8a-8j)

Test compound	IC_{50} values (µM)				
	SKOV3	HeLa	MDA-MB-231	DU145	CHO-K1
8a	[a]-	19.8 ± 0.49	25.4 ± 0.73	-	24.4 ± 0.54
8b	-	43.6 ± 0.53	18.9 ±0.65	-	19.2 ± 0.49
8c	-	44.9 ± 0.64	19.2 ± 0.59	34.4 ± 0.63	19.4 ± 0.38
8d	-	77.7 ± 0.83	60.9 ± 0.86	22.9 ± 0.55	16.3 ± 0.75
8e	-	51.9 ± 0.84	26.7 ± 0.66	16.9 ± 0.48	27.7 ± 0.81
8f	-	61.3 ± 0.92	26.2 ± 0.58	34.7 ± 0.61	16.3 ± 0.77
8g	-	58.3 ± 0.70	25.4 ± 0.75	30.1 ± 0.72	90.4 ± 0.96
8h	-	97.5 ± 0.91	23.6 ± 0.49	31.2 ± 0.69	44.7 ± 0.67
8i	-	54.4 ± 0.65	23.6 ± 0.71	42.0 ± 0.75	26.3 ± 0.59
8j	-	58.5 ± 0.70	25.3 ± 0.57	28.4 ± 0.47	25.2 ± 0.60
Doxorubicin	0.8 ± 0.13	0.7 ± 0.11	0.8 ± 0.12	0.7 ± 0.13	-
Mitomycin c	-	-	-	-	13.2 ± 0.71

[a] -: No activity, SKOV3-Ovarian cancer (ATCC® HTB 77™), HeLa-Cervical cancer (ATCC® CCL2™), MDAMB-231-Breast cancer (ATCC® HTB26™), DU145-Prostate cancer (ATCC® HTB81™), CHO-K1-Normal Chinese hamster ovary (ATCC® CCL-61™) cell lines

Based on the cytotoxicity results of compounds **8a-8j** and **9a-9j**, the free hydroxyl compounds (**9a, 9c-9j**) did not show any toxicity against normal Chinese hamster ovary cell line as compared to the acylated compounds (**8a-8j**). Moreover, in case of lauric acid (C12:0) derivatives both free hydroxyl (**9e**) and acylated (**8e**) compounds exhibited good cytotoxicity against different cancer cell lines. Further, acylated short chain (C6:0, C8:0, C10:0) and free hydroxyl long chain saturated (C16:0, C18:0) and unsaturated (C18:1, C22:1) compounds exhibited good activity against different cancer cell lines.

From a mechanistic perspective, the 1, 3, 4-thiadiazole ring exhibit cancer activity due to the presence of two nitrogen atoms having the high electron donating ability. These nitrogens atoms involve in building favorable H bonds or to chelate certain metal ions. Further, various substituents present at C2/C5 positions of 1, 3, 4-thiadiazole scaffold also responsible in enhancing the activities[9]. Earlier it was reported that, 1, 3, 4-thiadiazole and its derivatives showed broad spectrum of anticancer activities against various human cancer cells[25-28]. However, their mode of anti cancer activity is different which depends on the type of modification of 1, 3, 4-thiadiazole ring. Such types of molecules mostly show apoptosis and angiogenesis properties considered to be the most potent anticancer agents[25-28].

As per the earlier reports of amphiphilic thiadiazole derivatives[26-28], the present molecule 5-fatty-acylamido-1, 3, 4-thiadiazole-2-thioglycosides are expected to inhibit the cancer cells through cell cycle arrest due to its amphiphilic nature (presence of hydrophilic sugar and hydrophobic fatty acid).

Further, based on the thioglycoside aspect, the target molecule might be responsible for the inhibition of cancer cells either by arresting the cells at G_2/M-phase similar to that of antimetabolites[29] or may be inducing apoptosis by altering the phospholipid metabolism[18, 30].

Overall, as earlier it was proven that, these two fragments (Thiadiazole ring and Thioglycoside) show considerable anticancer activities and therefore, it is assumed that the hybrid molecules of these fragments exhibit the similar kind of mechanisms in inhibiting the cancer cells.

In conclusion, synthesis, antimicrobial and cytotoxic activity evaluation of 5-fatty-acylamido-1, 3, 4-thiadiazole-2-thioglycosides with short, medium, long and unsaturated fatty acids was carried out in the present study. 1, 3, 4-Thiadiazole-based thioglycosides were synthesized by employing a convergent synthetic route. Initially, 5-amino-1, 3, 4-thiadiazole-2-thiol (**3**) and a series of compounds **4a-4j** were synthesized and latter, the glycosylation of compounds **4a-4j** were achieved with trichloroacetimidate methodology. Anti microbial and cytotoxicity activities of 1, 3, 4-thiadiazole-based thioglycosides were evaluated against three Gram-positive, three Gram-negative bacterial strains and four cancer cell lines and one normal cell line. Lauric and myristic acid derivatives showed good, moderate antimicrobial activity against *Klebsiella pneumonia* and *Bacillus subtilis* respectively. On the other hand, the free hydroxyl lauric (**9e**) and oleic acid derivative (**9i**) exhibited promising activity against cervical cancer cell line. Further, the free hydroxyl compounds **9a, 9c-9j** did not show any toxicity towards normal CHO-K1 cell line and acylated compounds **8a-8j** exhibited toxicity against CHO-K1 cell line.

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Supplementary Information (SI)

All the synthesized compounds ^{1}H-NMR, ^{13}C-NMR and HRMS spectral data and biological assays were present in the supplementary information.

REFERENCES

1. Kren, V.; Martinkova, L. *Curr. Med. Chem.* **2001**, *8*, 1303.

2. Lian, G.; Zhang, X.; Yu, B. *Carbohydr. Res.* **2015**, *403*, 13.
3. Elgemeie, G. H.; Farag, A. B.; Amin, K. M.; El-Badry, O. M.; Hassan, G. S. *Med. Chem.* **2014**, *4*, 814.
4. El Ashry, E. S. H.; Awada, L. F.; Attab, A. I. *Tetrahedron* **2006**, *62*, 2943.
5. Abu-Zaied, M. A.; El-Telbani, E. M.; Elgemeie, G. H.; Nawwar, G. A. M. *Eur. J. Med. Chem.* **2011**, *46*, 229.
6. Elgemeie, G.; Abu-Zaied, M. *Nucleosides, Nucleotides and Nucleic Acids* **2015**, *34*, 834.
7. El-Sayed, W. A.; Nassar, I. F.; Abdel-Rahman, A. A. H. *J. Heterocyclic Chem.* **2011**, *48*, 135.
8. Petrova, K. T.; Potewar, T. M.; Correia-da-Silva, P.; Barros, M. T.; Calhelha, R. C.; Ciric, A.; Sokovic, M.; Ferreira. I. C. *Carbohydr. Res.* **2015**, *417*, 66.
9. Hu, Y.; Li, C. Y.; Wang, X. M.; Yang, Y. H.; Zhu, H. L. *Chem. Rev.* **2014**, *114*, 5572.
10. Li, Y.; Geng, J.; Liu, Y.; Yu, S.; Zhao, G. *Chem. Med. Chem.* **2013,** *8*, 27.
11. Yusuf, M.; Khan, R. A.; Ahmed, B. *Bioorg. Med. Chem.* **2008,** *16*, 8029.
12. Dubey, V.; Pathak, M.; Bhat, H. R.; Singh, U. P. *Chem. Biol. Drug Des.* **2012**, *80*, 598.
13. El-Sayed, W. A.; Ali, O. M. *Phosphorus, Sulfur and Silicon and the Related Elements* **2014**, *189*, 88.
14. Gao, Y.; Zhao, G.; Liu, W.; Wang, Y.; Xu, W.; Wang, J. *Chin. J. Chem.* **2010**, *28*, 605.
15. Wang, Z.; Zhao, G.; Liu, W.; Wang, Y.; Shao, H.; Xu, W.; Tian, L. *Chin. J. Org. Chem.* **2010,** *30*, 849.
16. Ahmad, A.; Ahmad, A.; Sudhakar, R.; Varshney, H.; Subbarao, N.; Anasari, S.; Rauf, A.; Khan, A. U. *J. Biomol. Struct. Dyn.* **2016**, *1*, 1.
17. Moriyama, R.; Sugimoto, K.; Miyata, S.; Katsuragi, T.; Makino, S. *J. Antibact. Antifung. Agents, Jpn.* **1996**, *24*, 3.
18. Garcia-Alvarez, I.; Groult, H.; Casas, J.; Barreda-Manso, M. A.; Yanguas-Casas, N.; Nieto-Sampedro, M.; Romero-Ramírez, L.; Fernandez-Mayoralas, A. *J. Med. Chem*. **2011**, *54*, 6949.
19. Cheng, H.; Cao, X.; Xian, M.; Fang, L.; Cai, T. B.; Ji, J. J.; Tunac, J. B.; Sun, D.; Wang, P. G. *J. Med. Chem.* **2005**, *48*, 645.
20. Stubs, G.; Rupp, B.; Schumann, R. R.; Schroder, N. W.; Rademann, J. *Chem. Eur. J.* **2010**, *16*, 3536.
21. Schmidt, R. R. *Angew. Chem. Int. Ed.* **1986**, *25*, 212.
22. Zemplen, G.; Kunz, A. *Chem. Ber.* **1923**, *56*, 1705.
23. Braude, A. I.; W. B. Sauders Company, London, *Microbiology* **1982**.
24. Vishnu Sravan, B.; Susheel Kumar, N.; Rama Krishna, D.; Nageshwara Rao, S. S.; Misra, S.; Ranjan Patra, C. *Nanotoxicology* **2016**, *10*, 413.
25. Matysiak, J. *Chem. Pharm. Bull*. **2006,** *54*, 988.
26. Matysiak, J.; Opolski, A. *Bioorg. Med. Chem.* **2006**, *14*, 4483.
27. Matysiak, J.; Niewiadomy, A.; Paw, B.; Dybala, I. *Arch. Pharm. (Weinheim)* **2011**, *344*, 340.
28. Matysiak, J. *Eur. J. Med. Chem.* **2007**, *42*, 940.
29. Elgemeie, G. H.; Mahdy, E. M.; Elgawish, M. A.; Ahmed, M. M.; Shousha, W. G.; Eldin, M. E. *Z Naturforsch C.* **2010**, *65*, 577.
30. Garcia-Alvarez, I.; Garrido, L.; Romero-Ramirez, L.; Nieto-Sampedro, M.; Fernandez-Mayoralas, A.; Campos-Olivas, R. *PLoS One*. **2013**, *8*, e78391.

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Synthesis and Biological Evaluation of 5-Fatty-acylamido-1, 3, 4-Thiadiazole-2-Thioglycosides

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