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Design and Synthesis of Novel 4-Amino-2,3-dihydro-2-imino-3-(1-iminododecyl) thiazole-5-Carbonitrile Derivatives as Antimicrobial Agents

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ABSTRACT

We report the synthesis and antimicrobial evaluation of some 4-amino-2,3-dihydro-2-imino-3-(1-iminododecyl) thiazole-5-carbonitrile derivatives 8a-e. The target compounds were synthesized via a multi-step methods involving the conversion of dodecanoyl chloride to the corresponding dodecanimidoyl chlorides 4a-e (via dodecanamide derivatives) and then to the imidoylisothiocyanate derivatives 5a-e followed by their conversion to thiourea derivatives and finally to the desired thiazole derivatives. All the synthesized compounds were characterized by IR and ^{1}HNMR spectral data and elemental analysis. Most of these compounds showed moderate antibacterial and antifungal activity when tested in vitro.

Keywords: Synthesis, Design, Dodecanoyl chloride, Thiazole-5-carbonitrile and thionyl chloride

INTRODUCTION

1,3-Thiazoles are considered as important heterocyclic compounds and have low toxicity to mammals and have high a broad field in biological activities such as insecticidal [1], antifungal [2-4], herbicidal [5-6], regulating plant growth [7,8], and antiviral activities [9]. A series of thiazole derivatives like thiamethoxam (A) [10], thiabendazole (B), imidaclothiz (C) [11], and benthiavalicarbisopropyl [12] used as agrochemicals. Furthermore, the compounds with an amide or ester group were a versatile class of agrochemicals with a wide range of biological activities (Figure 1) [13,14].

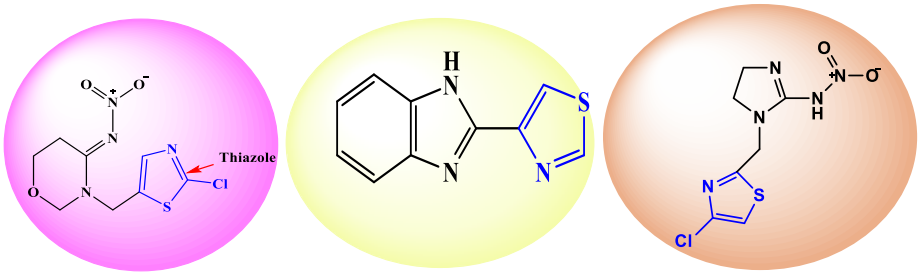


Figure 1: Thiazole derivatives

2-Aminothiazole considered as a skeleton heterocyclic amine, and used as the starting point for synthesis of numerous compounds, containing sulfur drugs, biocides, fungicides, dyes and chemical reaction accelerators and used as intermediates in the preparation of antibiotics, where many of 2-aminothiazoles derivatives have been substituted with different groups for pharmaceutical activities, [15,16] and are also used in the synthesis of many types of dyes for preparation of fibers,[17-19] besides it is used as corrosion activity inhibitors for mild steel protection. Therefore, we synthesized a series of 4-amino-thiazole-5-carbonitrile derivatives.

EXPERIMENTAL SECTION

General information

The melting points were detected on a Gallenkamp electro thermal melting point apparatus (Weiss-Gallenkamp, Lough borough, UK) and are uncorrected. The ^{1}HNMR spectra were determined with a Varian Mercury VXR-400 NMR spectrometer (Palo Alto, CA) at plus 400 MHz and used DMSO-$d_6$as the solvent. Mass spectra were recorded on a Hewlett Packard MS-5988 spectrometer (Palo Alto, CA) at 70 eV.Microanalyses were confirmed by used Mario El Mentar apparatus. The antimicrobial activity of the synthesized compounds was studies at department of Botany and Microbiology, college of Science, Jouf University,Saudi Arabia.

The general method for preparation of *N*-phenyldodecanimidoyl chloride derivatives 4a-e

Thionyl chloride (4 ml) was added dropwise to a cold solution of *N*-phenyldodecanamide derivatives 3a-e (5 mmol) in benzene (10 ml). The reaction mixture stirring at room temperature for 5 h. The solvent was then evaporated and the solid was recrystallized from aqueous ethanol to afford the pure products 4a-e.

The general method for preparation (Z)-*N'*-phenyl-*N*-(phenylcarbamothioyl)dodecanimidamide derivatives 6a-e

A solution of dodecanimidoyl chloride derivatives 4a-e (2ml, 0.01 mol) and sodium isothiocyanate (0.01) dissolved in dry acetone (25ml); aniline derivatives (0.01mol) dissolved in dry acetone and added to the solution after stirred at room temperature for 1hr. The solution was refluxed for 4hrs. The solution after cooling was poured into ice-water. The residue was precipitated filtrated and crystallized from petroleum ether (60-80^{o}C) with ethyl acetate to give 6a-e

(*Z*)-*N'*-(4-Methoxyphenyl)-*N*-((4-methoxyphenyl) carbamothioyl) dodecanimidamide (6a).

M.P. 96-98^{o}C.. Yield: 65%. IR (KBr, νmax cm^{-1}): 3320 (NH), 3052 (CH-arom), 2927 (aliph-CH), 1359 (C=S), 1605 (C=N). ^{1}H NMR (DMSO-d_6, ppm):δ 11.98 (s,1H, NH), 7.29 (d, 4H, Ar-H), 6.89 (d, 4H, Ar-H), 5.76 (s, 1H, NH), 3.82 (s, 6H, $(OCH_3)_2$), 2.32 (t,2H, CH2), 1.59 (m, 2H, CH_2), 1.29 (s, 16H, $(CH_2)8$), 0.93 (s, 3H, CH_3). Anal. Calcd. For ($C_{27}H_{39}N_3O_2S$; 469.69): C, 69.05; H, 8.37; N, 8.95; S, 6.83. Found: C, 69.15; H, 8.35; N, 8.99; S, 6.86

***(Z)*-*N*-((4-Methoxyphenyl) carbamothioyl)-*N'*-(4-nitrophenyl) dodecanimidamide (6b).**

M.P. 115-117 ^{o}C.Yield: 73%. IR (KBr, νmax cm^{-1}):3315(NH), 3043 (CH-arom), 2937-2836 (aliph-CH), 1356 (C=S), 1654 (C=N), 1514-1313 (NO_2). ^{1}H NMR (DMSO-d_6, ppm):δ 12.29 (s,1H, NH), 7.30 (d, 4H, Ar-H), 6.93 (d, 4H, Ar-H), 5.86 (s, 1H, NH), 3.82 (s, 3H, OCH_3), 2.32 (t,2H, CH2), 1.59 (m, 2H, CH_2), 1.29 (s, 16H, $(CH_2)8$), 0.93 (s, 3H, CH_3). Anal. Calcd. For ($C_{26}H_{36}N_4O_3S$; 484.66): C, 64.43; H, 7.49; N, 11.56; S, 6.61. Found: C, 64.48; H, 7.45; N, 11.59; S, 6.64.

(*Z*)-*N'*-(4-Methoxyphenyl)-*N*-((4-nitrophenyl) carbamothioyl) dodecanimidamide (6c).

M.P. 127-129^{o}C. Yield: 63% IR (KBr, νmax cm^{-1}):3332 (NH), 2935- 2838 (aliph-CH), 1337 (C=S), 1632 (C=N) 1515-1388 (NO_2).

(*Z*)-*N'*-(4-Methoxyphenyl)-*N*-(phenylcarbamothioyl) dodecanimidamide (6d).

M.P. 162-164 ^{oC}. Yield: 83%. IR (KBr, νmax cm^{-1}):3332 (NH), 2928(aliph-CH), 1347 (C=S), 1639 (C=N).

(*Z*)-*N*-((4-Methoxyphenyl) carbamothioyl)-*N'*-phenyldodecanimidamide (6e)

M.P.196-198^{o}C. Yield: 59%. IR (KBr, νmax cm^{-1}):3325 (NH), 2927 (aliph-CH), 1313 (C=S), 1636 (C=N). ^{1}H NMR (DMSO-d_6, ppm):δ12.23 (s,1H, NH), 7.34 (d, 4H, Ar-H), 7.02 (m,1H, Ar-H), 6.98 (d, 4H, Ar-H),5.96 (s, 1H, NH), 3.89 (s, 3H, OCH_3), 2.36 (t,2H, CH2), 1.56 (m, 2H, CH_2), 1.28 (s, 16H, $(CH_2)8$), 0.98 (s, 3H, CH_3).MS, *m/z* (%) (439, 2.49 %, M+). Anal Calcd. For ($C_{26}H_{37}N_3OS$; 439.66):C, 71.03; H, 8.48; N, 9.56; S, 7.29. Found: C, 71.07; H, 8.51; N, 9.52; S, 7.32

The general procedure of 4-amino-2,3-dihydro-2-(phenylimino)-3-((*Z*)-1-(phenylimino) dodecyl) thiazole-5-carbonitrile derivatives (8a-e)

A mixture of 6a-e (2.5 mmol) and 7 (1.7 mmol) was dissolved in ethyl acetate and refluxed for 10 hrs, and, then precipitated by adding a mixture of ethyl acetate and diethyl ether to yield compounds 8a-e, crystallization from toluene.

2-(4-Methoxyphenylimino)-3-((*Z*)-1-(4-methoxyphenylimino) dodecyl)-4-amino-2,3-dihydrothiazole-5-carbonitrile (8a)

^{1}HNMR (DMSO-d_6, ppm): δ 9.73 (brs, 2H, NH_2 exchangable with D_2O), 7.36-7.34 (dd, 2H, methoxy-ph, *J*=9.0), 7.13-7.12 (dd, 2H, methoxy-Ph, *J*=6.0), 7.03 (dd, 2H, methoxy-Ph, *J*=6.0), 7.00 (dd, 2H, methoxy-Ph, *J*=6.0 3), 3.75 (s, 3H, OCH_3), 3.30 (s, 3H,OCH_3), 2.53 (t, 2H,CH_2), 2.03 (s, 18H, $(CH_2)_9$), 1.42 (s, 3H, CH_3). MS,*m/z* (%) (533.73, 1.49%, M+). Anal. Calcd. For ($C_{30}H_{39}N_5O_2S$; 533.74): C, 67.51; H, 7.37; N, 13.12; S, 6.01. Found: C, 67.54; H, 7.40; N, 13.16; S, 6.05

3-((*Z*)-1-(4-Methoxyphenylimino) dodecyl)-2-(4-nitrophenylimino)-4-amino-2,3-dihydrothiazole-5-carbonitrile 8b.

^{1}H NMR (DMSO-d_6, ppm): δ9.98 (s, 2H,NH_2 exchangable with D_2O), 7.79-7.94 (dd, 2 H, nitro-ph, *J*=6.0), 7.77 (dd, 2 H, methoxy-Ph, *J*=6.0), 7.56 (dd, 4H,Ar-H), 3.76 (t, 2H,CH_2), 3.32(s, 3H, OCH_3), 2.45(s, 18H, $(CH_2)_9$), 1.42 (s, 3H, CH_3). Anal. Calcd. For ($C_{29}H_{36}N_6O_3S$; 548.71): C, 63.48; H, 6.61; N, 15.32; S, 5.84. Found: C, 63.51 H, 6.58 N, 15.34; S, 5.80.

2-(4-Methoxyphenylimino)-3-((*Z*)-1-(4-nitrophenylimino) dodecyl)-4-amino-2,3-dihydrothiazole-5-carbonitrile (8c)

^{1}H NMR (DMSO-d_6, ppm):δ9.38(brs, 2H, NH_2 exchangable with D_2O), 7.95-7.92 (dd, 2H, nitro-ph, *J*=9.0), 7.36 (dd, 2H, methoxy-Ph, *J*=6.0), 7.14(dd, 4H,Ar-H), 3.32(s, 3H, OCH_3), 1.42 (s, 3H, CH_3), 2.45(s, 18H, $(CH_2)_9$), 3.07 (t, 2H,CH_2).MS, *m/z* (%) (548, 1.17 %, M+). Anal. Calcd. For ($C_{29}H_{36}N_6O_3S$; 548.71): C, 63.48; H, 6.61; N, 15.32; S, 5.84. Found: C, 63.45; H, 6.64; N, 15.36; S, 5.87.

2-(4-Methoxyphenylimino)-4-amino-2,3-dihydro-3-((*Z*)-1-(phenylimino) dodecyl) thiazole-5-carbonitrile (8d)

1H NMR (DMSO-d_6, ppm): δ 10.18 (brs, 2H, NH_2 exchangable with D_2O), 7.67 (dd, 2H, methoxy-ph, *J*=9.0), 7.12 (dd, 2 H, methoxy-Ph, *J*=6.0), 6.98-6.95(m, 5H, Ar-H), 3.77 (t, 2H,CH_2), 2.51 (s, 3H, OCH_3), 2.48 (s, 18H, $(CH_2)_9$), 1.82 (s, 3H, CH_3). MS, *m/z* (%) (503, 3.19%, M+). Anal. Calcd. For ($C_{29}H_{37}N_5OS$; 503.7): C, 69.15; H, 7.40; N, 13.90; S, 6.37. Found: 69.18; H, 7.45; N, 13.94; S, 6.40.

3-((*Z*)-1-(4-Methoxyphenylimino) dodecyl)-4-amino-2,3-dihydro-2-(phenylimino) thiazole-5-carbonitrile 8e

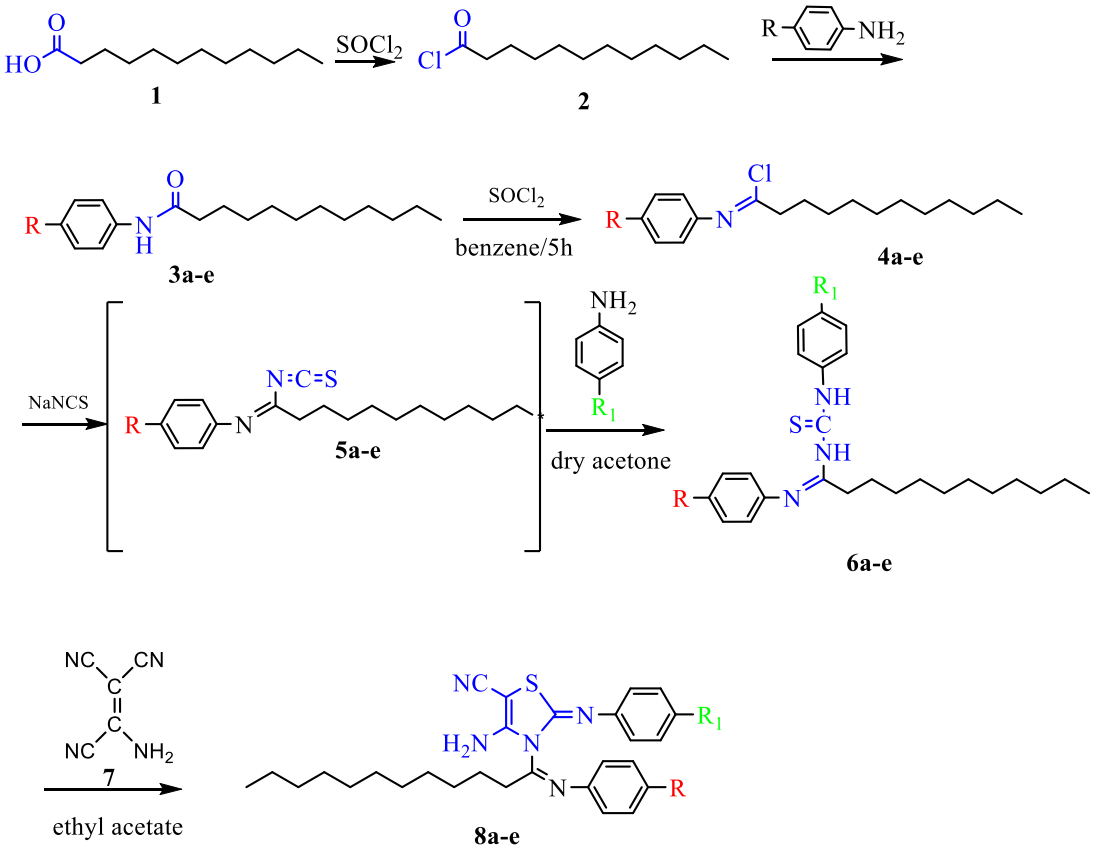
^{1}H NMR (DMSO-d_6, ppm): δ10.18 (brs, 2H, NH_2 exchangable with D_2O), 7.69 (dd, 2H, methoxy-ph, *J*=9.0), 7.50-7.42(m, 5H, thiadiazole Ar-H),

7.26 (dd, 2H, methoxy-Ph, *J*=6.0), 3.31 (t, 2H,CH_2), 2.80 (s, 3H, OCH_3), 2.41(s, 18H, $(CH2)_9$), 1.45 (s,3H,CH3). Anal. Calcd. For $C_{29}H_{37}N_5OS$; 503.7): C, 69.15; H, 7.40; N, 13.90; S, 6.37. Found: C, 69.11; H, 7.43; N, 13.93; S, 6.32.

RESULTS AND DISCUSSION

Treatment of dodecanoic acid 1with thionyl chloride in benzene with stirring at room temperature produced dodecanoyl chloride 2. Aniline derivatives was added to dodecanoyl chloride 2 dropwise in ether at room temperature to give dodecanamide derivatives 3a-e. The dodecanimidoyl chloride 4a-e was prepared according to methods in literature [20]. Treatment of 4a-e with sodium isothiocyanate afforded the intermediate imidoylisothiocyanates derivatives 5a-e (Scheme 1). A reaction of 5 with aniline derivatives in the presence of dry acetone as a solvent at room temperature with stirring for 7 h., as methods in literature [21,22] afforded the thiourea derivatives 6a-e. IR spectrum of 6a-e showed the appearance of a band for υ NH at the range 3183 cm^{-1}. Furthermore, ^{1}H NMR spectrum showed the appearance of two signals at range δ 12.62, 11.19 ppm exchangeable with D_2O due to two NH protons.

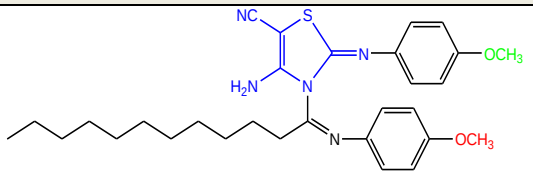
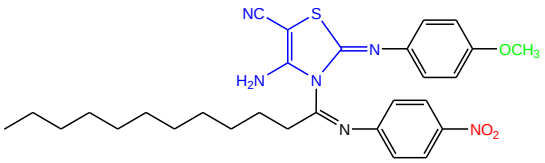
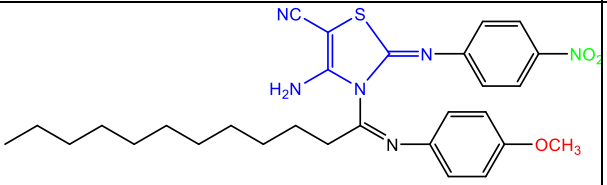
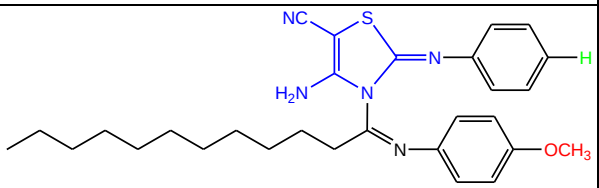
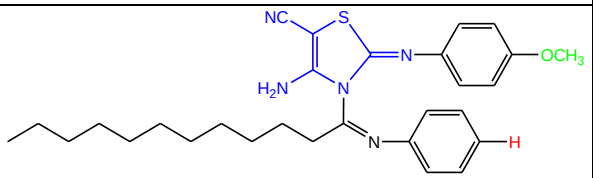
Compound 6a-e was reacted with tricyanovinylamine7 (prepared from tetracyanoethylene with ammonium acetate) [23], which produced thiazole derivatives 8a-e. Compounds 8a-e were characterized by elemental analysis and spectral data. IR spectrum of 8a-e showed the appearance of two bands for υNH_2 in a range 3432-3456 cm^{-1} and other absorption band at 2135 for υ C≡N cm^{-1}showed in Table 1. ^{1}HNMR spectrum showed a signal as singlet peak at range δ 10.82 ppm exchangeable with D_2O due to the presence of NH_2.



	R	R1
a	OCH_3	OCH_3
b	NO_2	OCH_3
c	OCH_3	NO_2
d	OCH_3	H
e	H	OCH_3

Scheme 1: Synthesis of 4-amino-2,3-dihydro-2-(phenylimino)-3-((Z)-1-(phenylimino)dodecyl)thiazole-5-carbonitrile.

Table 1: Physical properties and IR spectrum of compounds 8a-e

Comp.	Structure	Yield	M.P.°C	IR KBr, ν_{max} cm^{-1})
8a		67%	105-107	3430 (NH_2), 2927 (aliph-CH), 2207 (CN), 1609(C=N).
8b		65%:	143-145 .	3433-3343 (NH_2), 2938-2838 (aliph-CH), 2256 (CN), 1654 (C=N), 1516-1315 (NO_2).
8c		45%	146-148	3432-3343 (NH_2), 2936-2838 (a CH), 2207 (CN), 1630 (C=N) 1511-1389 (NO_2).
8d		44%;	176-178	3432 (NH_2), 2927 (aliph-CH), 2207 (CN), 1609(C=N).
8e		56%	225-227	3425-3432 (NH_2), 2929 (aliph-CH), 2213 (CN), 1634 (C=N)

ANTIMICROBIAL ACTIVITY

The antibacterial activities of 8a-e were tested by the agar well diffusion method [24]. The experiment was repeated 3 times, and the average inhibition zones were measurement. As reported in Table 2, it is obviously observed that the newly synthesized thiazole derivatives have low to moderate effect versus Gram (+ve) (and Bacillus cereus and *Staphylococcus aureus*) and (*Pseudomonas aeruginosa* and *Escherichia coli*) used as Gram (-ve), which compared with Cefotaxime as standard control, while in Table 3, indicate moderate antifungal activity versus (*Aspergillus flavus* and *Aspergillus niger*) compared with Clotrimazole drug as control.

Table 2: Antibacterial activities of some synthesized thiazole derivatives (inhibition zones mm)

Synthesized compounds	**Gm (+ve) bacteria**		**Gm (-ve) bacteria**	
	Staphylococcus aureus	**Bacillus cereus**	**Pseudomonas aeruginosa**	**Escherichia coli**
8a	16	14	19	17
8b	22	24	22	23
8c	23	22	22	23
8d	18	15	20	21
8e	18	15	20	21
Cefotaxime	31	27	33	32

Table 3: Antifungal activities of some new synthesized thiazole derivatives (inhibition zones mm).

Fungi		
Synthesized compounds	***Aspergillus flavus***	***Aspergillus niger***
8a	33	20
8b	20	22
8c	21	22
8d	31	18
8e	31	18
Clotrimazole	32	22

CONCLULSION

In summary, we report the synthesis and antimicrobial evaluation of some 4-amino-2,3-dihydro-2-imino-3-(1-iminododecyl)thiazole-5-carbonitrile derivatives 8a-e. The prepared compounds showed antimicrobial activity revealing moderate to good activities.

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