Synthesis and Antimicrobial Evaluation of Thieno[2,3-d]-pyrimidine, Thieno[2’,3’:4,5]pyrimido[1,2-a][1,3,5]triazine, Thieno[2,3-d]-1,3-thiazine and 1,2,4-Triazole Systems

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Many condensed 1,3-diazines play an important role into drugs designed as analgesic, anti-inflammatory, anti-hypertensive, antipyretic, pesticides, herbicides, plant growth regulators, antitumor, antifungal, antibacterial and anticancer. Triazoles, in particular, substituted 1,2,4-triazoles are among the various heterocycles that have received the most attention during the last decades as potential antimicrobial agents. In spite of a large number of antibiotics and chemotherapeutics available for medical usage, the increasing demands make it necessary to continue the search for new antimicrobial substances. Though, various molecules were designed and synthesized for this aim, the efforts have demonstrated that 1,3-diazines and 1,2,4-triazoles could be considered as possible antimicrobial agents. For this reason some of them were synthesized in our laboratory.

Compounds that contain o-amino-ester groups are useful substrates; since they have both electrophilic (E) and nucleophilic (Nu) centers that allow them to react with a variety of compounds containing Nu and/or E centers via cyclization reactions to give various condensed 1,3-diazines. The antifungal and bactericidal properties of fatty acids have been extensively investigated. Lauric acid (C12) had the most bacteriostatic activity on Gram-positive organisms. The change of its carboxyl group to an amide group increased its bacteriostatic effects.

In the present investigation the authors synthesizes ethyl 2-(3-dodecanoylthiourea)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate from the reaction of lauroyl isothiocyanate with ethyl 2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate as starting material. Compound 3 is utilized as a novel building block in synthesis of the target heterocyclic systems like thieno[2,3-d]-pyrimidine, thieno[2’,3’:4,5]pyrimido[1,2-a][1,3,5]triazine, thieno[2,3-d]-1,3-thiazine and 1,2,4-triazole systems attached to the lauryl group. The structures of the synthesized target heterocyclic compounds were confirmed by microanalytical and spectral data. The antimicrobial activity of some of the synthesized compounds was tested.

Key words fused 1,3-diazine; fused 1,3-thiazine; 1,2,4-triazole; lauroyl isothiocyanate; 2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate

Results and Discussion

The reaction of lauroyl isothiocyanate with ethyl 2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate gave ethyl 2-(3-dodecanoylthiourea)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate 3. Compound 3 could serve as a main building block in synthesis of the target heterocyclic systems like thieno[2,3-d]-pyrimidine, thieno[2’,3’:4,5]pyrimido[1,2-a][1,3,5]triazine, thieno[2,3-d]-1,3-thiazine and 1,2,4-triazole systems attached to the lauryl group. The structures of the synthesized target heterocyclic compounds were confirmed by microanalytical and spectral data. The antimicrobial activity of some of the synthesized compounds was tested.

The reaction of a solution of lauroyl isothiocyanate 1 in a dry acetonitrile and ethyl 2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate 2 at room temperature afforded ethyl 2-(3-dodecanoylthiourea)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (3) in an excellent yield. The spectral data of the new product agree with its proposed structure. Its IR spectrum shows absorption bands correlated with NH groups at 3254 and 3199 cm⁻¹, intense broad band at 1726 cm⁻¹, indicated C=N–H vibration of combination bands due to NH-deformation and C–N stretching. It shows stretching νC=O of ester cm⁻¹ at 1702 and νC=O of amide at 1677 cm⁻¹. The 1H-NMR spectrum of compound 3 is displayed in Experimental and it is in accord with its proposed structure. The higher δ value of NH protons and the relatively low absorption value of carbonyl group of ester indicated the presence of compound 3 as its chelated form as presented in Chart 1. Mass spectrum of compound 3 revealed its correct molecular ion peak M⁺ (m/z 466) and in addition to some important abundant fragments peaks in consistency with its proposed structure.

We have recently reported the synthesis of fused 1,3-diazines from the reaction of a derivative of o-aminoanitrole with lauroyl isothiocyanate. In the present investigation we report the synthesis of a new series of target heterocycles like 1,3-diazine, 1,3-thiazine and 1,2,4-triazole. Thus, compound 3 acts as a useful building block for synthesis of annulated heterocyclic systems via synthetic strategy which depends on the fact that 3 reacts with different nucleophiles (e.g. hydrazines, thiourea, etc.) to give intermediates. The latter underwent intramolecular exo-trig. annulation to provide the target heterocyclic compounds.

Thus, refluxing a solution of compound 3 in ethanol with 3 M sodium hydroxide gave fused 1,3-diazine derivative 4. The same product was obtained upon heating ethanolic solution of 3 with sodium ethoxide or heating an acetone solution of 3 with a catalytic amount of anhydrous potassium carbonate...
as shown in Chart 2. Moreover, the reaction of compound 3 with piperidine produced fused 1,3-diazine system 5 in a good yield. Also, compound 5 is obtained upon heating of ethanol solution of pyrimidine system 4 with an equivalent amount of piperidine. On the other hand, boiling a solution of compound 3 in ethanol with thiourea in the presence of a catalytic amount of sodium hydroxide afforded fused tetracyclic compound 6. Stirring of compound 3 with concentrated sulphuric acid at room temperature furnished fused thiazine derivative 7. The infrared spectra of the synthesized compounds 4–7 showed absorption frequencies correlated with NH, as well as, C=O groups. Their 1H-NMR spectra displayed the aliphatic protons, beside the NH protons in the downfield region that exchangeable with D2O. Also, 1H-NMR of compound 5 showed its existence as an equilibrium mixture of lactam-lactim tautomers 5a and 5b. The mass spectra of the synthesized compounds revealed mass peaks in agreement with their proposed structures.

The formation of compounds 4–7 can be explained on the fact that the carbonyl group of ester is initiated intramolecular exo-trig cyclization via addtion of either SH group of the thiol tautomer of compound 3 to give compound 7, or its NH group to afford the non-isolable intermediate A. Intermediate A underwent base-catalyzed deacylation with expulsion of sodium dodecanoate molecule to give compound 4. Compound 4 reacts with piperidine to give compound 5 as depicted in Chart 3.

The formation of the target heterocyclic compound 6 can be rationalized on the basis of cyclocondensation of thiourea with compound 3 to give non-isolable intermediate B. The latter undergoes intramolecular cyclization via exo-trig annulations as shown in Chart 4.

The interaction of compound 3 with hydrazine hydrate afforded a mixture of hydrazide 8 and 1,3-diazine derivative 4. Reaction of the hydrazide 8 with lauroyl isothiocyanate 1 in boiling acetonitrile produced 3-thioxo-5-undecyl-1,2,4-triazole derivative 10. However, it has been reported that the reaction of lauroyl isothiocyanate 1 with hydrazine hydrate afforded the isomeric 5-thioxo-3-undecyl-1,2,4-triazole derivative. Moreover, a mixture of compound 8 and 1,2,4-triazole derivative 11 was obtained upon treating of compound 10 with hydrazine hydrate. On the other hand refluxing of compound 3 with phenylhydrazine furnished 1,2,4-triazole derivative 12 and the amino-ester 2 as shown in Chart 5. The expulsion

Chart 1. Reaction of Lauroyl Isothiocyanate with 2-Amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate

Chart 2. Reaction of the Title Compound 3 with NaOH, Piperidine, Thiourea and H2SO4
of the unreacted amino-ester 2 without its further reaction with phenylhydrazine was confirmed by their refluxing in a separate experiment for 4h in ethanol to give no product. The structures of the synthesized compounds 8, 10–12 were proved from their microanalytical and spectral data. IR spectra for compounds 8 and 10 showed νNH and νC=O. 1H-NMR spectra displayed signals correspond to aliphatic protons as well as NH protons exchangeable with D2O, in addition to aromatic protons for compound 12. Inspection of 1H-NMR spectrum of compound 10 showed two exchangeable singlet signal at δ: 2.62 and 2.74 ppm integrating to one proton. This suggests the existence of compound 10 in dimethylsulfoxide.
(DMSO) solution as an equilibrium mixture in thione–thiol tautomers 10a and b. Also, 1H-NMR spectrum of triazole 11, showed its existence in DMSO solution as a mixture of thione–thiol tautomers 11a and b in equal ratio.

**Biological Activity** The antimicrobial screening of some of the synthesized compounds was done using Kirby–Bauer disc diffusion method. Briefly, 100 µL of the tested bacteria/fungi were grown in 10 µL of fresh media until they reached a count of approximately 108 cells/mL for bacteria or 105 cells/mL for fungi. A hundred microliters of microbial suspension was spread onto agar plates corresponding to the broth in which they were maintained. The possible antimicrobial activities of the target heterocyclic compounds 3, 5, 6, 7, 10 and 12 were investigated to six standard organisms including the Gram-positive bacteria, *Staphylococcus aureus* and *Bacillus subtilis*, Gram-negative bacteria, *Escherichia coli* and *Pseudomonas aeruginosa* in addition to fungi, *Candida albicans* and *Aspergillus flavus*. The obtained results are presented in Table 1.

Data in Table 1 revealed that the target heterocyclic compounds 5, 6, 7 and 10 are exhibited moderate activity against the Gram-positive bacteria, *Staphylococcus aureus* and *Bacillus subtilis*, however compound 6 showed low activity against both G+ organisms. Compound 5 showed high activity against the Gram-negative bacteria *Escherichia coli* and moderate activity against *Pseudomonas aeruginosa*, while compounds 6 and 10 showed moderate

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**Table 1. Antimicrobial Activity of Selected Compounds**

| Compd. No. | *Staphylococcus aureus* G+ | *Bacillus subtilis* G+ | *Escherichia coli* G− | *Pseudomonas aeruginosa* G− | *Candida albicans* (fungus) | *Aspergillus flavus* (fungus) |
|-----------|-------------------------|----------------------|-----------------------|--------------------------|--------------------------|--------------------------|
| 3         | 00                      | 00                   | 00                    | 00                       | 00                       | 00                       |
| 5         | 16                      | 16                   | 17                    | 16                       | 00                       | 00                       |
| 6         | 14                      | 13                   | 14                    | 14                       | 9                        | 00                       |
| 7         | 14                      | 14                   | 13                    | 13                       | 10                       | 00                       |
| 10        | 14                      | 15                   | 15                    | 15                       | 00                       | 00                       |
| 12        | 13                      | 12                   | 00                    | 13                       | 00                       | 00                       |
| Am        | 18                      | 20                   | 22                    | 17                       | 19                       | 17                       |

Am = Ampicillin (antibacterial agent), AB = Amphotericin B (antifungal agent). The concentration of all synthesized compounds and the reference was (5 mg/1 mL of DMSO). Zone of inhibition: 0–13 mm (low); 14–16 mm (moderate); >16 mm (high); 00 = no inhibition.
activity against them. Compound 7 exhibited low activity against both G+ organisms. Compound 12 showed low activity against Pseudomonas aeruginosa and didn’t show activity towards Escherichia coli. Moreover, compounds 6 and 7 showed low activity against Candida albicans and the other tested compounds showed no activity against it. All the tested compounds showed no activity against Aspergillus flavus. Furthermore the title compound 3 didn’t show any activity against the six stranded organisms. Thus obtained results interpret that the lipophilic property of hydrocarbon moiety favors the permeation of the synthesized compounds through lipid barriers in the cell membrane.

Conclusion

It was noticed that the introduction of a long chain hydrocarbon moiety (lauryl group) in the synthesized heterocyclic compounds 6, 7, 10 and 12 or pipridyl moiety to compound 5 augments the antibacterial action appreciably.

Experimental

Melting points of the products were determined in open capillary tubes on an electrothermal melting point apparatus and were uncorrected. Elemental analyses were performed on a Perkin-Elmer 2400 CHN elemental analyzer. The infrared spectra were recorded on Perkin-Elmer Modle 297 Infrared Spectrometer using KBr wafer technique. The 1H-NMR spectra were measured on Varian Gemini 300 MHz spectrometer with chemical shift (δ) expressed in ppm downfield of tetramethylsilane (TMS) as internal standard, in DMSO-d6. Tetramethylsilane (TMS) was used as internal standard. Infrared spectra were recorded on Perkine-Elemer 2400 CHN elemental analyzer. The infrared absorption bands were recorded with a Perkin-Elmer PE 1600 FTIR spectrophotometer.

Uses of Compound 3 in Synthesis Different Target Heterocyclic Systems

5,6,7,8-Tetrahydrobenzothieno[2,3-d]-1,3-diazine-2-thione-4-one (4)

A solution of compound 3 (3 mmol) and (3m) sodium hydroxide (5mL) or sodium ethoxide (3mmol) in 30mL ethanol was refluxed for 2h. Vacuum-distilled to ca. half-volume and acidified with 3m hydrochloric acid. The precipitate was collected and recrystallized from ethanol to give compound 4. Also, compound 4 was obtained upon heating the acetone solution of compound 3 with a catalytic amount of anhydrous potassium carbonate for 2h. Filter the reaction mixture while hot, and evaporate acetone under vacuum leave a colorless precipitate of compound 4. Colorless crystals; yield 81%; mp 278–280°C; 1H-NMR (DMSO-d6) δ: 7.14–7.18 (4H, 2CH2, m), 2.54–2.56 (2H, CH2, m), 2.73–2.75 (2H, CH2, m), 12.24, (1H, NHCS, exchangeable, brs), 13.26, (1H, NHCO, exchangeable, brs); IR (KBr) ν: 3153, 3126 (NH), 2933, 2886, 2854 (C–Halkyl), 1694 (C=O), 179 (M+–HNCs), 65, 151 (65), 59 (28); Anal. Calcd for C24H38N2O3S2 (466.70): C, 61.56; H, 8.21; N, 11.75. Found C, 60.32; H, 7.96; N, 11.69%.

5,6,7,8-Tetrahydrobenzothieno[2,3-d]-1,3-diazine-2-piperedin-1-yl-4-one (5)

An equivalent amount of compound 3 (3mmol) and piperidine (3mmol) in ethanol (30mL) was refluxed for 6h. Cool the reaction mixture. A precipitated solid was collected by filtration and recrystallized from ethanol to give compound 5. Compound 5 is also obtained by boiling of equimolar amounts of compound 4 and piperidine in ethanol for 5h. Buff crystals; yield 93%; mp 238–236°C; 1H-NMR (DMSO-d6) δ: 1.54–1.89 (14H, 4H+10 piperidyl-H), m, 2.57 (2H, CH2, t, J=5.4, 5.2Hz), 2.72 (2H, CH2, t, J=6.3, 5.4Hz), For 5b: 9.01 (1H, OH, exchangeable, brs), For 5a: 9.18 (1H, NH exchangeable, brs); IR (KBr) ν: 3252, 3155, 3109 (NH), 2935, 2857, 2831, 2829, 2716 (C–Halkyl), 1632 (C–O), 1587 (C=N); MS (70eV) m/z (%): 291 (M+–2, 0.72), 290 (M+–1, 2), 289 (M+, 10), 274 (1), 261 (3), 210 (10), 205 (3), 189 (4), 179 (38), 151 (34), 84 (83), 59 (100); Anal. Calcd for C25H26N2O4S (458.40): C, 62.25; H, 6.62; N, 14.52. Found C, 61.91; H, 6.64; N, 14.33.

4-Undecyl-2-thioxo-6,12-dihydro-2H-7,8,9,10-tetrahydrobenzothieno[2′,3′:4,5]pyrimido[1,2-α][1,3,5]triazine-6-one (6)

A mixture of compound 3 (3mmol), thiourea (3mmol) and a catalytic amount of sodium hydroxide in ethanol (30mL) was refluxed for 3h. A solid product was obtained after cooling, filtered off, washed with water and recrystallized from ethanol to give compound 6. Colorless crystals; yield 77%; mp 247–249°C; 1H-NMR (DMSO-d6) δ: 0.85 (3H, CH3(CH2)4CH3, CH3CO, t, J=6.6Hz), 1.24 (16H, CH3(CH2)4CH3, CH3CO, m), 1.36 (2H, CH2(CH2)4CH3, CH3CO, m), 1.48 (4H, CH2, m), 2.18 (2H, CH2(CH2)4CH3, CH3CO, t, J=7.5Hz), 2.37 (2H, CH2, m), 2.62 (2H, CH2, m), 11.92 (1H, NH, exchangeable, brs); IR (KBr) ν: 3133 (NH), 2919, 2850 (C–Halkyl), 1694 (C=O), 1658 (C=N), 1576 (C=C), 1208 (C=S); MS (70eV) m/z (%): 444 (M+, 0), 442 (0.23), 441 (0.27), 362 (0.46), 276 (8), 238 (46), 222 (2), 179 (32), 155 (2), 151 (34), 81 (16), 64 (100); Anal. Calcd for C25H26N2O4S (444.66): C, 62.13; H, 7.25; N, 12.60. Found C, 62.26; H, 7.11; N, 12.43%.
5,6,7,8-Tetrahydrobenzothieno[2,3-d]-1,3-thiazine-2-yl-4-one Dodecanamide (7)

To compound 3 (1g), concentrated sulphuric acid (10mL) was added. The reaction mixture was stirred at room temperature for 3h. The solution was left overnight, then poured into ice/cold water with continuous stirring. A yellow precipitate was obtained, filtered off and recrystallized from methanol to give compound 7 as yellow crystals; yield 69%; mp 188–190°C.

1H-NMR (DMSO-d6): δ = 0.85 (3H, CH3(CH2)8CH2CH2CO, t, J = 6.9Hz), 1.24 (16H, CH2(CH2)8CH2CH2CO, m), 1.44–1.49 (2H, CH2(CH2)8CH2CH2CO, m), 1.98 (2H, CH2(CH2)8CH2CH2CO, t, J = 7.5Hz), 4.13 (2H, NH2, exchangeable, br s), IR (KBr): 3219 (NH), 2954, 2918, 2848 (C–H alkyl), 7.2, 5.4 Hz), 1183 (C=O), 123 (C=O), 3179 (NH), 2938, 2851 (C–H alkyl), 1698, 1652 (C=O), 1613 (C=N); MS (70eV) m/z (%): 420 (M+, 0), 384 (6), 365 (4), 238 (3), 215 (2), 186 (3), 179 (100), 151 (10), 133 (5), 87 (81), 64 (57); Anal. Calcd for C25H47N3OS: δ = 68.27; H, 10.73; N, 9.38%. 

Reaction of Compound 3 with the Nitrogen Nucleophiles

General Procedure

To a solution of compound 3 (3mmol) in ethanol (30mL), hydrazine hydrate (3mmol) was added. The reaction mixture was refluxed for 3h, the residue was recrystallized from ethanol to give compound 8 as colorless crystals; yield 36%; mp 148–150°C (petroleum ether 60–80°C to dissolve compound 11, the residual part was boiled with benzene to give compound 8. Colorless crystals; yield 36%; mp 148–150°C (petroleum ether 60–80°C–C); 1H-NMR (DMSO-d6): δ = 0.86 (3H, CH3(CH2)8CH2CH2CO, t, J = 6.6Hz), 1.24 (16H, CH2(CH2)8CH2CH2CO, m), 1.49 (2H, CH2(CH2)8CH2CH2CO, m), 2.30 (2H, CH2(CH2)8CH2CH2CO, t, J = 6.9Hz), 2.98 (1H, N HNHCS, exchangeable, br s), IR (KBr): 3196, 3161 (NH), 2954, 2918, 2848 (C–H alkyl), 1687 (C=O) cm−1; MS (70eV) m/z (%): 437 (M+, 4), 404 (1), 366 (6), 352 (4), 310 (16), 197 (13), 256 (16), 208 (3), 170 (23), 157 (27), 128 (31), 115 (100), 101 (45), 87 (32); Anal. Calcd for C12H12N2O4S·H2O (214.35): C, 67.24; H, 7.5; N, 9.60%.

- 5-Undecyl-1,2-dihydro-1,2,4-triazole-3-thione (11)

To a solution of compound 10 (3mmol) in ethanol (30mL), hydrazide hydrate (3mmol) was added. The reaction mixture was refluxed for 3h, then, evaporated to ca. half volume and cooled to room temperature. A solid products was obtained that was filtered off and boiled with light petroleum ether 60–80°C to dissolve compound 11, the residual part was boiled with benzene to give compound 8. Colorless crystals; yield 36%; mp 148–150°C (petroleum ether 60–80°C–C); 1H-NMR (DMSO-d6): δ = 0.86 (3H, CH3(CH2)8CH2CH2CO, t, J = 6.6Hz), 1.24 (16H, CH2(CH2)8CH2CH2CO, m), 1.49 (2H, CH2(CH2)8CH2CH2CO, m), 2.30 (2H, CH2(CH2)8CH2CH2CO, t, J = 6.9Hz), 2.98 (1H, NH), exchangeable, br s), IR (KBr): 3196, 3161 (NH), 2954, 2918, 2848 (C–H alkyl), 1687 (C=O) cm−1; MS (70eV) m/z (%): 437 (M+, 4), 404 (1), 366 (6), 352 (4), 310 (16), 197 (13), 256 (16), 208 (3), 170 (23), 157 (27), 128 (31), 115 (100), 101 (45), 87 (32); Anal. Calcd for C12H12N2O4S·H2O (214.35): C, 67.24; H, 7.25; N, 9.60%.

Measurement of Antimicrobial Activity Using Kirby–Bauer Disc Diffusion Method

Plates inoculated with filamentous fungi as Aspergillus flavus at 25°C for 48h; Gram-positive bacteria, as Staphylococcus aureus, Bacillus subtilis; Gram-negative bacteria as Escherichia coli, Pseudomonas aeruginosa they were incubated at 35–37°C for 24–48h and yeast as Candida albicans incubated at 30°C for 24–48h and then the diameters of the inhibition zones were measured in millimeters. Standard discs of Ampicillin (antibacterial agent) and Amphotericin B (antifungal agent) were served as positive controls for antimicrobial activity, but filter discs impregnated with 10μL of DMSO were used as a negative control. The agar used is Mueller–Hinton agar. Blank paper discs (Schleicher & Schull, Spain) with a diameter 8.0 mm were impregnated 10μL of tested concentration of the stock solutions. When a filter paper disc impregnated with a tested chemical is placed on agar, the chemical will diffuse from the disc into the agar. This diffusion will place the chemical in a suitable solvent to give the corresponding compound. The authors declare no conflict of interest.

Conflict of Interest

The authors declare no conflict of interest.

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