JJC

Volume 14, Number 1, March 2019
Pages 39-47

Jordan Journal of Chemistry

ARTICLE

Utilization of 2-Ylidene-4-Thiazolidinones in the Synthesis of Heterocyclic Compounds Part III: Synthesis and In-Vitro Antibacterial Activity Evaluation of Thienopyrimidinone Derivatives

Mahmoud F. Farhat[a*], Ahmed M. El-Saghier[b], Suhilla Kh. Elnami[a], Nisrin A. Dwaya[a], Asma O. Jebril[c], Asma O. Errayes[a], Moftah O. Darwish[a] and Mohammed S. Ibrahim.[d]

a Chemistry Department, Faculty of Science, University of Tripoli, Tripoli, Libya
b Chemistry Department, Faculty of Science, Sohag University, Sohag, Egypt
c Chemistry Department, Faculty of Education, University of Tripoli, Tripoli, Libya
d General Department, Faculty of Nursing, Sebha University, Sebha, Libya

Received on: 11th Mar. 2019 *Accepted on: 19th May 2019*

Abstract: 3-Amino-2-thiophenecarboxamides (3a, d-g) were synthesized from 2-(4-oxo-3-phenyl- thiazolidin-2-ylidene)malononitrile (2) and employed in the synthesis of a variety of thiophene and thienopyrimidinone derivatives. 3-Amino-2-thiophenecarboxamides (3a, d, e) on refluxing in acetic acid gave the tetrahydrothienopyrimidinones (6a-m). On the other hand, the reaction of the 3-amino-2-thiophenecarboxamides (3a, d, e) with triethylorthoformate or with formic acid produced the dihydrothienopyrimidinones (7a-c). The synthesized heterocyclic compounds were screened for antibacterial activities using narrow spectrum against gram-positive and gram-negative bacteria.

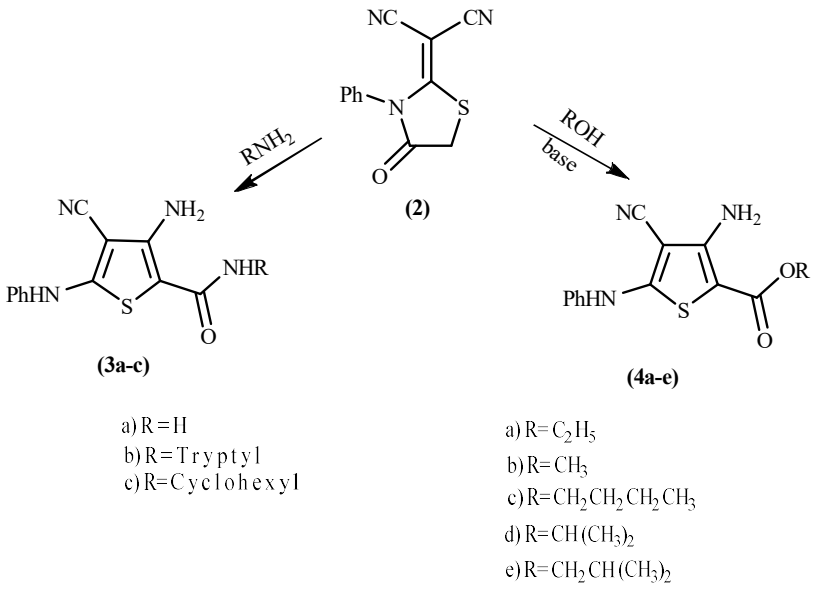
Keywords: 3-amino-2-thiophenecarboxamides, dihydrothienopyrimidinones, tetrahydrothienopyrimidinones, antibacterial activity.

Introduction

Thienopyrimidine derivatives play an essential role in several biological processes and have considerable chemical and pharmacological activities[1-3]. They were also found to possess a variety of pronounced activities, such as ulcerogenic[4] as well as antipsychotic[5] and antioxidant activities[6]. Moreover, some of 2-alkylthio or 2-alkyl substituted thieno-pyrimidines show significant antifungal and antibacterial activities[2], whereas others exhibit good anticonvulsant properties[7]. In our last publication, we have reported that 2-(4-oxo-3-phenylthiazolidin-2-ylidene)malononitrile (2) on treatment with a variety of amines and alcohols was successfully converted in a one-pot reaction into 3-aminothiophene-2-carboxamides (3a-c) and 3-aminothiophene-2-carboxylates (4a-e), respectively, (Scheme 1) [11].

In continuation of our investigations on the transformations of 2-ylidene-4-thiazolidinones into other heterocyclic compounds[8-11], we report here the utility of 3-amino-2-thiophenecarbox-amides derived from 2-(4-oxo-3-phenyl-thiazolidin-2-ylidene)malononitrile (2) in the synthesis of a variety of thiophene and thieno-pyrimidinone derivatives with anticipated biological activities.

[*]**Corresponding Author:** Mahmoud F. Farhat **Email**: mf_farhat@yahoo.com



Scheme 1: One-pot conversion of 2-(4-oxo-3-phenylthiazolidin-2-ylidene)malononitrile (2) into 3-aminothiophene-2-carboxamides (3a-c) and 3-aminothiophene-2-carboxylates (4a-e).

Experimental

General Remarks

Melting points were recorded by Koffler melting points apparatus and are uncorrected. Infrared spectra were recorded on a Bruker FTIR spectrometer in the frequency range of 3900-450 cm^{-1} using KBr discs. Nuclear Magnetic Resonance (NMR) spectra were recorded on a Bruker avance of 400 MHz for ^{1}H-NMR and 100 MHz for ^{13}C-NMR using DMSO-d_6 as a solvent and tetramethylsilane (TMS) as an internal standard. The chemical shift (δ) values are expressed in parts per million (ppm). Legend: s = singlet, d = doublet, t = triplet and m = multiplet. Mass spectra were recorded on Shimadzu QP-2010 plus mass spectrometer at 70 eV. The structures and names of all the compounds were generated using ChemDraw ultra 12.0.

Synthesis

4-Cyano-5-(phenylamino)thiophene-2-carboxamide (3a) was synthesized according to a reported method by treatment of 2-(4-oxo-3-phenylthiazolidin-2-ylidene)malononitrile (2) with ammonia[11,12].

4-Cyano-5-(phenylamino)thiophene-2-carboxamides (3d-g)

General Procedure: A mixture of 2-(4-oxo-3-phenylthiazolidin-2-ylidene)malononitrile (2) 2.88g (0.012 mol) in aqueous aliphatic amines; namely methylamine, ethylamine, dimethylamine or morpholine (30 mL) in the presence of a few drops of TEA was stirred at certain temperatures and lengths of time. The precipitated product was filtered off, dried and recrystallized from benzene.

*3-Amino-4-cyano-N-methyl-5-(phenylamino)-thiophene-2-carboxamide (3d***)**

Yield: 66%, (RT, 48h), white crystals, mp. 202-204 °C; ν_{max} (cm^{-1}) 3458-3266 br. (NH_2, NH), 2200 (CN), 1586 (C=O); δ_H 9.98 (br. 1H, NH), 7.37-7.10 (m,5H, arom and br,1H,NH), 6.58 (br,2H,NH_2), 3.20 (s,3H,CH_3); δ_C (ppm) 164.77 (C=O), 159.95, 151.69, 141.28, 129.86, 124.76, 121.08, 87.03, 83.21 (C arom.), 114.41 (CN), 26.13 (CH_3); *m/z* (ESI) = 272.00.

3-Amino-4-cyano-N-ethyl-5-(phenylamino)thiophene-2-carboxamide (3e)

Yield: 54%, (RT, 48h), yellow crystals, mp. 164-166 °C; ν_{max} (cm^{-1}) 3386-3253 (NH_2 and NH), 2207 (CN), 1596 (C=O); δ_H (ppm) 9.87 (br, 1H, NH), 7.40-7.15 (m, 5H, arom, and br 1H, NH), 6.59 (br. 2H, NH_2), 3.20 (q, 2H, CH_2), 1.04 (t, 3H, CH_3); δ_C (ppm) 164.16 (C=O), 160.00, 151.84, 141.32, 129.87, 124.75, 121.13, 87.04, 83.19 (C arom), 114.42 (CN), 33.89 (CH_2), 15.53 (CH_3); *m/z* (ESI) = 286.10.

3-Amino-4-cyano-N,N-dimethyl-5-(phenylamino)-thiophene-2-carbox-amide (3f)

Yield: 84%, (Reflux, 3h), pale yellow crystals, mp. 178-180 °C; ν_{max} (cm^{-1}) 3374-3273 (NH_2, 3191 (NH), 2203 (CN), 1598 (C=O), δ_H (ppm)

9.97 (br, 1H, NH), 7.40-6.85 (m, 5H, arom), 6.56 (br. 2H, NH_2), 2.95 (s, 6H, $2CH_3$); δ_C (ppm) 166.13 (C=O), 160.21, 152.37, 141.12, 129.86, 124.61, 120.76, 86.39, 83.19 (C arom), 114.44 (CN), 37.79 (CH_3); *m/z* (ESI) = 286.85.

4-Amino-5-(morpholine-4-carbonyl)-2-(phenyl-amino)thiophene-3-carbonitrile (3g)

Yield: 84%, (Reflux,3h), white powder, mp. 238-240 °C; ν_{max} (cm^{-1}), 3440-3340 (NH_2), 3247 (NH), 2207 (CN), 1609 (C=O); δ_H 10.01 (s,1H, NH), 7.41-6.85 (m, 5H, arom), 6.40 (br,2H, NH_2), 3.57-3.26 (4 $CH_{2\ morpholine}$); δ_C 165.92 (C=O), 160.65, 151.81, 141.05, 129.87, 124.81, 120.00, 86.8, 83.03 (C arom.), 114.33 (CN); *m/z* (ESI) = 328.00.

2-(2-Morpholino-2-oxoethylthio)(phenyl-amino)methylene)malononitrile (5g)

A mixture of 2-(4-oxo-3-phenylthiazolidin-2-ylidene)malononitrile (2) (1g, 0.004mol) and morpholine (0.016 mol,1.3 mL) in dioxane (15 mL) in the presence of a few drops of TEA was stirred at room temperature for 48 h. The precipitated product was filtered off and recrystallized from dioxane.

Yield: 58%, white crystals, mp. 138-140°C; ν_{max} (cm^{-1}) 3184 (NH), 2202 (CN), 1629 (C=O); δ_H 10.74 (br, 1H, NH), 7.44-7.26 (m, 5H, arom), 3.95 (s,2H,CH_2-S), 4.37-4.2 (t,3H, H_5); δ_C (ppm) 169.28 (C=O), 166.19 (=C-NPh), 139.09 (=$C(CN)_2$, 129.98, 129.57, 126.97, 124.25 (C arom.), 115.77 (CN), 66.86 (C morpholine), 46.51 (C morpholine), 35.29 (CH_2-S); *m/z* (ESI) = 328.85.

2-Aryl-4-oxo-6-(phenylamino)-1,2,3,4-tetra-hydrothieno[3,2-*d*]pyrimidine-7-carbonitriles (6a-m)

General procedure: A solution of 3-amino-4-cyano-5-(phenylamino)thiophene-2-carboxamide (3a,d,e) (0.0019 mol) and the aromatic aldehyde (0.0019 mol) in 15 mL glacial acetic acid was refluxed for 7 h. The reaction mixture was then left overnight at room temperature and the precipitated solid that formed was filtered off and recrystallized from ethanol.

2-(4-Methoxyphenyl)-3-methyl-4-oxo-6-phenyl-amino-1,2.3,4-tetrahydro-thieno [3,2-d]pyrimi-dine-7-carbonitrile (6a)

Yield: 64%, white powder, mp. 258-260 °C; ν_{max} (cm^{-1}) 3321 (br. 2NH), 2205 (CN), 1596 (C=O); δ_H (ppm) 10.22 (br,1H, NH), 8.09 (br,1H, NH), 7.42-7.93 (m, 9H, arom.), 5.77 (d, 1H, CH), 3.87 (s, 3H, OCH_3), 2.81 (s, 3H, NCH_3); δ_C (ppm) 164.60 (C=O), 159.68, 159.20, 149.00, 140.20, 131.88, 129.43, 127.83, 127.34, 124.77, 113.77, 89.80, 79.05 (C arom), 113.46 (CN), 71.76 (CH), 55.09 (OCH_3), 31.47 (CH_3); *m/z* (ESI) = 390.70

2-(4-Chlorophenyl)-3-methyl-4-oxo-6-phenyl-amino-1,2,3,4-tetrahydro-thieno[3,2-d]pyrimi-dine-7-carbonitrile (6b)

Yield: 66%, pale yellow powder, mp. 254-256 °C; ν_{max} (cm^{-1}) 3302 br (2NH), 2211 (CN), 1630 (C=O); δ_H (ppm) 10.26 (br, 1H, NH), 8.21 (br, 1H, NH), 7.16-7.13 (m, 9H, arom) 5.87 (d, 1H, CH), 2.81(s, 3H, CH_3),; δ_C (ppm) 164.23 (C=O), 159.43, 149.40, 140.17, 136.79, 132.64, 129.46, 128.41, 126.16, 124.85, 120.87, 89.94, 78.89 (C arom.), 113.39 (CN), 71.23 (CH), 31.71 (NCH_3); *m/z* (ESI) = 394.75.

3-Methyl-2-(4-nitrophenyl)-4-oxo-6-phenyl-amino-1,2,3,4-tetrahydrothieno- [3,2-d]pyrimi-dine-7-carbonitrile (6c)

Yield: 80%, pale brown powder, mp. 234-238 °C; ν_{max} (cm^{-1}) 3320 br. (2NH), 2197 (CN), 1608 (C=O); δ_H (ppm) 10.20 (br, 1H, NH), 8.43-7.16 (m, 9H, arom + br 1H, NH), 6.04 (d, 1H, CH), 2.94 (s, 3H, CH_3); δ_C (ppm) 164.96 (C=O), 160.73, 159.74, 149.94, 148.00, 140.24, 137.55, 136.74, 129.44, 128.83, 126.64, 121.55, 91.11, 79.62 (C arom), 113.77 (CN), 71.65 (CH), 32.36 (CH_3); *m/z* (ESI) =405.80

3-Methyl-4-oxo-6-phenylamino-2-p-tolyl-1,2,3,4-tetrahydro-thieno[3,2-d]pyrimidine-7-carbo-nitrile (6d)

Yield: 75%, yellow powder, mp. 268-270 °C; ν_{max} (cm^{-1}) 3310 (NH), 3230 (NH), 2207 (CN), 1597 (C=O); δ_H (ppm) 10.22 (br, 1H, NH), 8.12 (d, 1H, NH), 7.42-7.14 (m, 9H arom), 5.79 (s, 1H, CH) 2.83 (s, 3H, CH_3Ph), 2.29 (s, 3H, CH_3),; δ_C (ppm) 164.02 (C=O), 159.64, 149.42, 140.24, 137.55, 136.74, 129.44, 128.83, 126.64, 121.55, 120.84, 89.88 C arom), 113.44 (CN), 72.63 (NCH_3), 71.76 (CH), 20.00 (CH_3Ph); *m/z* (ESI)= 437.70.

2-(4-Chlorophenyl)-3-ethyl-4-oxo-6-phenyl-amino-1,2,3,4-tetrahydro-thieno [3,2-d]pyrimi-dine-7-carbonitrile (6e)

Yield: 66%, pale yellow powder, mp. 256-258 °C; ν_{max} (cm^{-1}) 3297 (br 2NH), 2208 (CN) 1620 (C=O); δ_H (ppm) 10.25 (s, 1H, NH),8.23 (d, 1H, NH), 7.46-7.13 (m, 5H, arom), 5.91-5.90 (d,1H, CH), 3.86-3.80, (q, 1H, CH_2), 2.95-2.88,

(q,1H, CH_2),1.05-1.01 (t, 3H, CH_3); δ_C (ppm) 164.75 (C=O), 159.50, 149.85, 140.68 140.09, 133.22, 129.96, 128.76, 128.66, 125.30, 121.36, 91.21, 79.47 (C arom), 113.90 (CN), 69.58 (CH), 39.30 (NCH_2), 14.51 (CH_3).

3-Ethyl-2-(4-nitrophenyl)-4-oxo-6-phenylamino-1,2,3,4-tetrahydro-thieno[3,2-d]pyrimidine-7-carbonitrile (6f)

Yield: 79 %, brown powder, mp. 228-230 °C; ν_{max} (cm^{-1}) 3284 br (2NH), 2208 (CN), 1625 (C=O); δ_H (ppm) 10.27 (br, 1H, NH), 8.42-7.14 (m, 9H, arom and br 1H, NH), 6.07 (d, 1H, CH), 3.92-3.83 (q,1 H,CH_2), 3.02-2.96 (q, 1H, CH_2), 1.15 (t,3H, CH_3); δ_C (ppm) 164.94 (C=O), 159.23, 149.91, 148.75, 147.80, 140.61, 130.21, 130.08, 129.97, 128.06, 125.47, 124.25, 124.00, 122.12, 121.42, 91.11,79.60 (C arom.), 113.97 (CN), 69.38 (CH),39.30 (NCH_2), 14.61 (CH_3).

3-Ethyl-2-(4-methoxyphenyl)-4-oxo-6-phenyl-amino-1,2,3,4-tetrahydro-thieno[3,2-d]pyrimi-dine-7-carbonitrile (6g)

Yield:74 %, white powder, mp. 262-264 °C; ν_{max} (cm^{-1}) 3302 (NH), 3175 (NH), 2209 (CN), 1620 (C=O); δ_H (ppm) 10.20 (br, 1H, NH), 8.08-6.88 (m, 9H, arom. and br,1H, NH), 5.80(d, 1H, CH) 3.86 (s, 3H, OCH_3), 3.92-3.84 (q, 1H, CH_2), 3.02-2.9 (q, 1H, CH_2),1.04 (t, 3H, CH_3); δ_C (ppm) 165.40 (C=O), 159.78, 149.86, 140.87, 132.91, 131.75, 129.90, 128.38, 121.25, 115.34, 114.22, 91.57, 80.01(C arom), 113.97 (CN), 70.47 (CH), 55.63 (OCH_3Ph), 39.18 (NCH_2), 14.28 (CH_3).

3-Ethyl-4-oxo-6-phenylamino-2-p-tolyl-1,2,3,4-tetrahydro-thieno[3,2-d]-pyrimidine-7-carbo-nitrile (6h)

Yield: 71 %, yellow powder, mp. 260-262 °C; ν_{max} (cm^{-1})3301 (br. 2NH), 2210 (CN) 1620 (C=O); δ_H (ppm) 10.21 (s, 1H, NH), 8.13 (d, 1H, NH), 7.41-7.13 (m, 5H, arom), 3.84-3.01 (q, 1H, CH_2), 2.90-2.86 (q, 1H, CH_2), 2.27 (s, 3H, CH_3Ph), 1.04-0.99 (t, 3H, CH_3); δ_C (ppm) 164.53 (C=O), 159.60, 149.85, 140.75, 137.95, 137.93, 129.94, 129.28, 126.75, 125.38, 121.25, 91.11, 79.60, (C arom), 113.97 (CN), 39.20 (CH), 70.17 (CH_2), 21.09 (CH_3Ph), 14.43 (CH_3).

2-(4-Nitrophenyl)-4-oxo-6-phenylamino-1,2,3,4-tetrahydrothieno[3,2-d]-pyrimidine-7-carbo-nitrile (6i)

Yield: 88 %, orange powder, mp. 284-287 °C; ν_{max} (cm^{-1}) 3356 (NH), 3238 (NH), 2214 (CN) 1647 (C=O); δ_H (ppm) 10.20 (br, 1H, NHPh), 8.43-7.38 (m, 9H, arom and br,1H, NH), 7.19 (br. 1H, NH), 5.87 (br 1H, CH); δ_C (ppm) 164.98 (C=O), 160.73, 151.22, 149.41, 147.93, 140.75, 129.75, 128.79, 125.47, 123.83, 121.55, 91.50, 79.62 (C arom), 113.83 (CN), 66.04 (CH).

2-(4-Methoxyphenyl)-4-oxo-6-phenylamino-1,2,3,4-tetrahydrothieno[3,2-d]pyrimidine-7-carbonitrile (6j)

Yield: 81 %, white powder, mp: 295-297 °C; ν_{max} (cm^{-1}) 3480 (NH), 3411 (NH), 2217 (CN), 1635 (C=O); δ_H 10.30 (s, 1H, NH), 7.81 (s, 1H, NH), 7.71 (s, 1H, NH), 7.45-6.95 (m, 9H, arom.), 5.70 (s, 1H, CH), 3.76 (s, 3H, OCH_3); δ_C 164.67 (C=O), 161.48, 159.52, 151.66, 140.83, 133.21, 129.93, 128.49, 124.29, 121.34, 91.33, 80.05 (C arom), 113.99 (CN), 67.05 (CH), 55.62 (OCH_3).

(4-Chlorophenyl)-4-oxo-6-phenylamino-1,2,3,4-tetrahydrothieno[3,2-d]-pyrimidine-7-carbo-nitrile (6k)

Yield: 90 %, pale yellow, mp: 310-312 °C; ν_{max} (cm^{-1}) 3409 (NH), 3242 (NH), 2214 (CN), 1678 (C=O); δ_H 10.25 (br, 1H, NH), 7.95 (s, 1H, NH), 7.80 (s, 1H, NH), 7.50-7.37 (m, 9H, arom.), 5.70 (s, 1H, CH); δ_C 164.82 (C=O), 161.13, 151.44, 140.76, 140.56, 133.31, 129.94, 128.99, 128.60, 125.38, 121.44, 121.10, 91.00, 79.85 (C arom), 113.00 (CN), 66.40 (CH).

2-(Benzo[d][1,3]dioxol-5-yl)-4-oxo-6-(phenyl-amino)-1,2,3,4-tetrahydro-thieno[3,2-d]pyrimi-dine-7-carbonitrile (6l)

Yield: 74 %, pale yellow, mp: 230-232 °C; ν_{max} (cm^{-1}) 3417 (NH), 3233 (NH), 2214 (CN), 1641 (C=O); δ_H 10.30 (br, 1H, NH), 7.90 (br, 1H, NH), 7.80 (br, 1H, NH), 7.40-6.70 (m, 9H, arom.), 5.70 (s,1H, CH), 6.02 (s, 2H, OCH_2); δ_C 164.71 (C=O), 161.13, 151.53, 147.69, 140.77, 135.20, 129.95, 125.33, 121.33, 120.67, 107.59, 101.58, 91.0, 79.83 (C arom), 113.00 (CN), 66.98 (CH).

4-Oxo-6-phenylamino-2-p-tolyl-1,2,3,4-tetra-hydrothieno[3,2-d]-pyrimidine-7-carbonitrile (6m)

Yield: 68%, white powder, mp: 299-300 °C; ν_{max} (cm^{-1}) 3347 br (2NH), 2214 (CN) 1681 (C=O); δ_H 10.30 (br, 1H, NH), 7.90 (br, 1H, NH), 7.80 (br, 1H, NH), 7.19-7.40 (m, 9H, arom), 5.70 (s,1H, CH), 2.31 (s, 3H, CH_3Ph); δ_C 164.68 (C=O), 161.36, 159.95, 151.55, 140.84, 138.48, 137.97, 129.92, 129.11, 127.05, 125.29, 121.37, 91.38, 80.07 (C arom), 113.97 (CN), 67.04 (CH), 21.43 (CH_3).

Synthesis of 4-oxo-6-(phenylamino)-3,4-dihydrothieno-[3,2-d]pyrimidine-7-carbonitriles (7a-c)

Method I: General Procedure

A solution of 3-amino-4-cyano-N-alkyl-5-(phenylamino)thiophene-2-carboxamide (3a,d,e) (0.0018 mol) and triethylorthoformate (0.5 mL) in glacial acetic acid (20 mL) was refluxed for 3 h. The reaction mixture was cooled and the precipitated solid was filtered off and recrystallized from glacial acetic acid.

Method II: General Procedure:

A solution of 3-amino-4-cyano-N-alkyl-5-(phenylamino)thiophene-2-carboxamide (3a,d,e) (0.002 mol) in formic acid (15 mL) was refluxed for 5 h. The reaction mixture was then cooled and the precipitated solid was filtered off and recrystallized from glacial acetic acid.

4-Oxo-6-(phenylamino)-3,4-dihydrothieno[3,2-d]pyrimidine-7-carbonitrile (7a)

Yield: method I; 55%, method II; 34%, light brown powder, mp. 295-298 °C; ν_{max} (cm^{-1}) 3219 (NH), 3129 (NH), 2214 (CN), 1641 (C=O), 1586 (C=N); δ_H (ppm) 12.54 (br. 1H, NH), 10.67 (br. 1H, NH), 8.16 (s, 1H, CH), 7.48-7.23 (m, 5H, arom); δ_C (ppm) 165.26 (C=O), 157.97, 155.96, 149.11, 140.43, 130.28, 126.10, 122.08, 108.09, 84.43, [(C arom.) and (C=N)], 114.04 (CN); *m/z* (ESI) = 268.85.

3-Methyl-4-oxo-6-(phenylamino)-3,4-dihydrothieno[3,2-d]pyrimidine-7-carbonitrile (7b)

Yield: method I; 61%, method II; 40%, yellow powder, mp. 228-230 °C; ν_{max} (cm^{-1}) 3259 (NH), 3129 (NH), 2212 (CN), 1668 (C=O), 1578 (C=N); δ_H (ppm) 10.67 (br. 1H, NH), 8.16 (s, 1H, CH), 7.48-7.23 (m, 5H, arom.); δ_C (ppm) 164.89 (C=O), 156.84, 155.96, 151.42, 140.43, 131.81, 129.64, 125.78, 121.60, 106.84, 83.52, [(C arom) and (C=N)], 113.47 (CN),33.54 (CH_3); *m/z* (ESI) = 285.75.

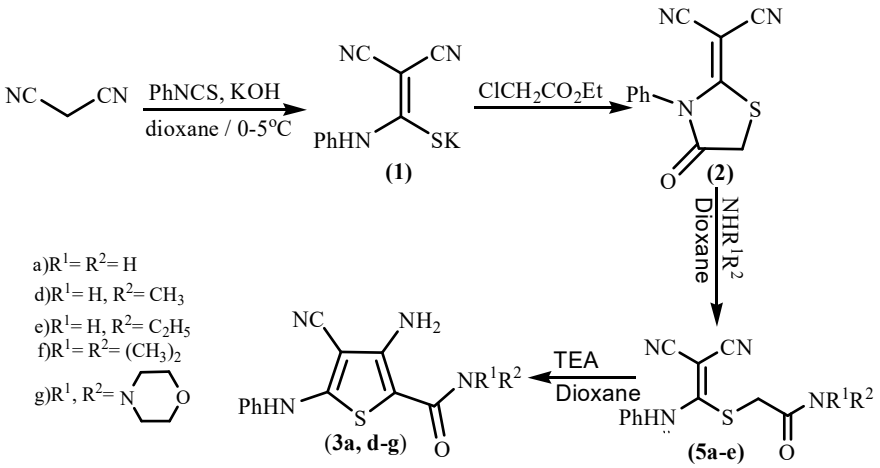
3-Ethyl-4-oxo-6-phenylamino-3,4-dihydrothieno[3,2-d]pyrimidine-7-carbonitrile (7c)

Yield: method I; 70%, method II; 44%, white crystals, mp. 264-266 °C; ν_{max} (cm^{-1}) 3239 (NH), 2214 (CN), 1660 (C=O), 1592 (C=N); δ_H (ppm) 10.59 (br 1H, NH), 8.47 (s, 1H, CH), 7.48-7.26 (m, 5H, arom), 3.98 (q, 2H, CH), 1.30 (t, 3H, CH_3); δ_C (ppm) 165.24 (C=O), 157.29, 155.28, 151.32, 140.43, 122.20, 107.89, 84.40 [(C arom) and (C=N)], 113.83 (CN) 41.79 (CH_2), 15.19 (CH_3); *m/z* (ESI) = 296.85.

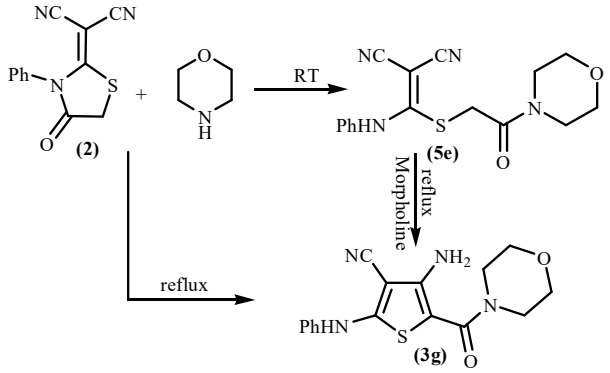
Results and Discussion

2-(4-Oxo-3-phenylthiazolidin-2-ylidene)malononitrile (2) was synthesized according to our reported method[8] by the reaction of ethyl chloroacetate with ketene-N,S-acetal (1) which was prepared from malononitrile, phenylisothiocyanate and potassium hydroxide. The reaction of 2-(4-oxo-3-phenylthiazolidin-2-ylidene)malononitrile (2) with ammonia[12] and a number of amines; namely, methyl amine, ethyl amine, diethylamine and morpholine gave the corresponding 3-amino-4-cyano-5-(phenylamino)thiophene-2-carboxamides (3a, d-g) in a similar fashion to our reported method[10]. The assignment of these carboxamides (3a, d-g) was based on their spectral analysis. IR spectra showed bands at *v* 3458-3353, 3340-3253 and 3266-3185 cm^{-1} representing NH_2, NHPh and amidic NH groups, respectively. The ^{1}H-NMR spectrum for each carboxamide lacked the CH_2 signal which is characteristic of 4-thiazolidinone ring. It also revealed new D_2O-exchangable signals at δ 10.01-9.80 and δ 6.58-6.40 ppm representing NHPh and NH_2 protons, respectively. The NH amidic protons and aromatic protons appeared as multiplets at δ 7.40-7.15 ppm. Their ^{13}C-NMR spectra did not also show any signals for the methylene carbons which are characteristic of the starting thiazolidinone rings when DEPT135 technique was performed but revealed new signals at δ 165.92-164.16 ppm which were assigned to the amidic carbonyl carbons. The molecular ion peaks in the mass spectra of these compounds (3d-g) gave (m/z) = 272.00, 286.10, 286.85 and 328.00, respectively. This amination reaction is similar to our previously proposed mechanism and involves ring opening of the thiazolidinone ring to give the intermediates (5a-e) followed by intramolecular cyclization producing the thiophene-2-carboxamides (3a, d-g) (Scheme 2).

The mechanism shown in Scheme 3 was supported by the isolation of the intermediate 4e. This intermediate (4e) was refluxed in dioxane in the presence of morpholine, which acts as a Lewis base accelerating the formation of the carbanion that attacks the cyano group causing cyclization into the expected thiophene-2-carboxamide (3g).



Scheme 2. Synthesis of thiophene-2-carboxamides (3a,d-g).



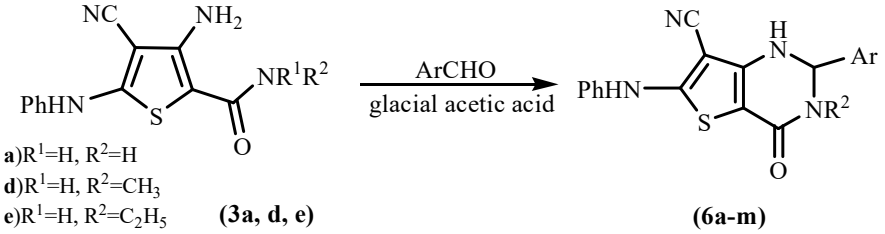
Scheme 3. Proposed mechanism of the formation of 4-amino-5-(morpholine-4-carbonyl)-2-phenylaminothiophene-3-carbonitrile (3g).

The IR spectrum of compound (5e) showed bands at ν 3184, 2202 and 1629 cm^{-1} representing NHPh, cyano and amidic carbonyl groups, respectively. The ^{1}H-NMR spectrum of compound (5e) exhibited a new D_2O-exchangable signal at δ 10.74 ppm for NHPh group and a singlet at δ 4.20 ppm representing CH_2-S-, in addition to a set of signals at δ 3.58-3.20 ppm for the morpholine CH_2 protons. The ^{13}-CNMR spectrum also confirmed the proposed structure of this intermediate. It showed a signal at 169.28 ppm which was assigned to amidic (C=O) carbon with the presence of two bands at 66.86 and 42.79 ppm for the methylene carbons ($4CH_2$) of the morpholine ring and the methylene group (CH_2-S) at 35.29 ppm. These signals were clearly confirmed when DEPT technique was used.

A number of tetrahydrothieno[3,2-*d*]pyrimidine-7-carbonitriles, specifically 6a-m, were synthesized by reacting thiophene-2-carboxamides (3a,d,e) with various aromatic aldehydes in refluxing glacial acetic acid. The ^{1}HNMR of 6a-m spectra lacked any NH_2 signals and showed D_2O-exchangable signals of NHPh and pyrimidinone NH groups at 10.27-10.20 and 8.43-8.07 ppm, respectively. The singlets at 6.08-5.91 ppm were attributed to the pyrimidinone CH protons and the NCH_3 protons appeared at 2.96-2.80 ppm. It is worthy to mention that the CH_2 protons of each ethyl group of each of tetrahydrothienopyrimidinones (6e-h) in which R_2 = C_2H_5 appeared as two quartet signals at δ 3.89-3.77 ppm and at δ 3.03- 2.85 ppm. Each quartet signal represents one of these two (CH_2) protons due to possible hydrogen bonding with the (C=O) groups as shown in Figure 1 below. The signals of the methyl protons of these ethyl groups appeared as triplets at 1.14-0.99 ppm.

The ^{13}CNMR spectra of compounds 6a-m showed signals at δ 164.96-164.01 ppm representing the C=O groups and also new signals at δ 72.09-66.04 ppm representing the methine ring carbons. Their mass spectra gave also the correct molecular weights. Primary and

secondary 3-aminothiophene-2-carboxamides **(**3a,d,e**)** when treated with triethylorthoformate in refluxing glacial acetic acid gave 4-oxo-6-(phenylamino)-3,4-dihydrothieno[3,2-*d*]pyrimidine-7-carbonitriles (7a-c) in high yields instead of the expected condensation intermediates (8a-c). The same dihydrothienopyrimidinones (7a-c), although in lesser yields, were successfully synthesized when formic acid was used instead of triethylorthoformate probably *via* the intermediates (9a-c) (Scheme 5). This last method gave less yields and purity of the target compounds 8a-c.



a)R^1=H, R^2=H
d)R^1=H, R^2=CH_3
e)R^1=H, R^2=C_2H_5 **(3a, d, e)** **(6a-m)**

Compound	R^2	Ar.	Comp.	R^2	Ar.
6a	CH_3	*p*-$OCH_3C_6H_4$	6h	C_2H_5	*p*-$CH_3C_6H_4$
6b	CH_3	*p*-ClC_6H_4	6i	H	*p*-NO_2 C_6H_4
6c	CH_3	*p*-NO_2 C_6H_4	6j	H	*p*-$OCH_3C_6H_4$
6d	CH_3	*p*-$CH_3C_6H_4$	6k	H	*p*-ClC_6H_4
6e	C_2H_5	*p*-ClC_6H_4	6l	H	5-Piperonyl
6f	C_2H_5	*p*-NO_2 C_6H_4	6m	H	*p*-$CH_3C_6H_4$
6g	C_2H_5	*p*-$OCH_3C_6H_4$	-	-	-

Scheme 4. Synthesis of tetrahydrothienopyrimidinones (6a-m).

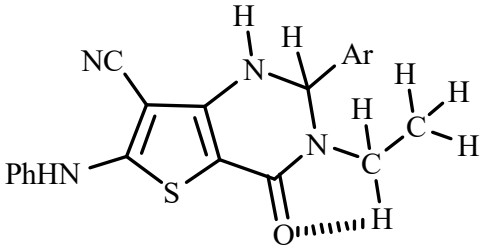
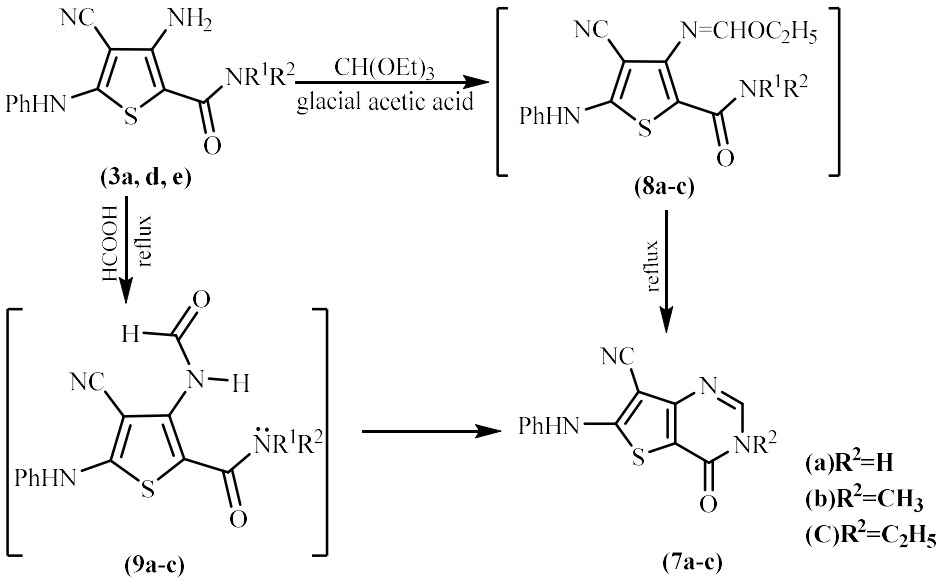


Figure 1. Hydrogen bonding between CH_2 protons and C=O groups in 6e-h.



Scheme 5. Synthesis of dihydrothienopyrimidinones (7a-c).

The IR spectra of compounds (7a-c) indicated the disappearance of NH_2 absorptions and showed amidic carbonyl bands at *v* 1668-1641 cm^{-1}. The ^{1}H-NMR spectra showed new signals at 8.47-8.16 ppm indicating N=CH protons and broad D_2O-exchangable signals at 10.70-10.59 ppm representing NH protons. The ^{13}C-NMR and mass spectra of compounds (7a-c) confirmed their proposed structures.

In-vitro Antibacterial Activity Evaluation

The objective of this part of the present study was to investigate the antimicrobial activities of newly synthesized thienopyrimidinones. This was carried out with the hope of discovering structures serving as antimicrobial agents. The synthesized dihydro and tetrahydrothienopyrimidinones were screened using the agar-diffusion two-fold serial dilution method[13] to evaluate their *in*-vitro antibacterial activity**.** Table 1 summarizes the inhibitory activity of the twelve most active compounds. Nitrofurantoin, a heterocyclic antibiotic, was used as reference drug. The bactericidal/bacteriostatic effect was assessed for all compounds using three concentrations 500, 300 and 150 µg/mL and the diameters of inhibition zones (DIZ) were recorded.

Table 1. The *invitro* antibacterial activity of thienoprymidinone derivatives.

ENTRY	µg/mL	Diameter of Inhibition Zone (mm)					
		Gram–positive			Gram–negative		
		S.aur	***MRSA***	***B. sub***	***E. coli***	***K. pne***	***P. aer***
6a	500	10	-ve	15	15	17	11
	300	-ve	-ve	12	10	16	10
	150	-ve	-ve	9	11	12	9
6b	500	10	-ve	10	12	18	15
	300	9	-ve	-ve	12	17	14
	150	8	-ve	-ve	-ve	15	10
6c	500	-ve	-ve	10	-ve	-ve	11
	300	-ve	-ve	-ve	-ve	-ve	10
	150	-ve	-ve	-ve	-ve	-ve	-ve
6d	500	10	-ve	10	13	16	13
	300	-ve	-ve	-ve	10	11	12
	150	-ve	-ve	-ve	-ve	-ve	-ve
6e	500	-ve	-ve	11	15	-ve	11
	300	-ve	-ve	-ve	14	-ve	10
	150	-ve	-ve	-ve	-ve	-ve	-ve
6f	500	10	10	12	12	11	11
	300	10	9	9	-ve	-ve	10
	150	-ve	-ve	-ve	-ve	-ve	9
6g	500	-ve	-ve	12	13	-ve	-ve
	300	-ve	-ve	-ve	-ve	-ve	-ve
	150	-ve	-ve	-ve	-ve	-ve	-ve
6h	500	-ve	-ve	-ve	16	-ve	12
	300	-ve	-ve	-ve	14	-ve	-ve
	150	-ve	-ve	-ve	11	-ve	-ve
6i	500	-ve	-ve	11	12	-ve	13
	300	-ve	-ve	9	11	-ve	10
	150	-ve	-ve	11	-ve	-ve	-ve
7a	500	-ve	-ve	-ve	12	11	13
	300	-ve	-ve	-ve	-ve	-ve	-ve
	150	-ve	-ve	-ve	-ve	-ve	-ve
7b	500	-ve	-ve	15	17	11	15
	300	-ve	-ve	12	11	11	14
	150	-ve	-ve	-ve	-ve	-ve	-ve
7c	500	-ve	-ve	12	15	17	18
	300	-ve	-ve	-ve	12	14	16
	150	-ve	-ve	-ve	-ve	-ve	-ve
Nitrofurantoin	300	20	21	12	18	19	11

S. aur: Staphylococcus aureus; MRSA: Methicillin-Resistant Staphylococcus; B. sub: Bacillus subtilis, E.coli: Escherichia coli, K. pne: Klebsiella pneumonia; P. aer: Pseudomonas aeruginosa.

The experiments were performed using test bacterial organisms belonging to Gram-positive and Gram-negative bacteria, three of each. *S. aureus*, *MRSA and B. subtilis* (Gram-positive) and *E. coli, K. pneumonia* and *P. aeruginosa* (Gram-negative) were the test organisms utilized. With a very few exceptions, compounds 6c, 6e, 6g, 6h, 6i and 7b) are inactive against Gram-positive bacteria. These exceptions, after all, are of very weak bacterio-static effect (9-11mm/hole)**.** On the other hand, most tested compounds are found to be active against most Gram-negative bacteria. The dihydrothieno-pyrimidinones 7a, 7b and 7c displayed a better activity against Gram-negative organisms. The ring in compounds 7a-c and tetrahydrothieno-pyrimidinones 6a, 6b, 6d, 6f and 6i seemed to be responsible for their distinguished activity against most tested organisms. This might be due to the presence of pyrimidinone rings which are carrying different chemically active substituents like N-methyl, N-ethyl groups and substituted phenyls, such as *p*-nitrophenyl-, *p*-chlorophenyl- *and p*-tolyl- and fused with thiophene rings.

Conclusions

1. 3-Aminothiophene-2-carboxamides (3a,d-g) were successfully synthesized by reacting 2-(4-oxo-3-phenylthiazolidin-2-ylidene)malononitrile (2) with a variety of amines (ammonia, methylamine, ethylamine, dimethylamine and morpholine).

2. 3-Aminothiophene-2-carboxamides were successfully employed as useful synthons in synthesizing dihydrothienopyrimidinones (7a-c) and tetrahydrothienopyrimidinones (6a-i).

3. In general, the screened thienopyrimidinone derivatives 6a-i and 7a-c displayed variable antibacterial activities.

Acknowledgement

We would like to express our sincere thanks to Prof. Nabil A. Saleh of Ain-Shams University, Cairo, Egypt for his help in performing the *in-vitro* antibacterial activity evaluation.

References

[1] Brown, I. D. J. *Comprehensive Heterocyclic Chem*istry, Vol. 3, Pergamon Press, Oxford, **1984**, P.443.

[2] Ashalatha, B. V.; Narayana, B.; Vijaya Raj, K. K.; Kumari, N. S. *Eur. J.Med. Chem*. **2007**, *42*:719–728.

[3] Jain, S. K.; Bariwal, J.; Kathiravan, M.; Phoujdar, M.; Shane, R.; Chauha B.; Shah, A.; Yadav, M. *Bioorg. Med.* Chem. **2008**, 4759.

[4] El-Gazzar, A. B.; Hussein, H. A.; Hafez, H. N. *Acta. Pharm*. **2007**,395.

[5] Sharma, C.; Yerande, S.; Chavan, R.; Bhosale, A. V. *E-Journal of Chem*. **2010**, 655.

[6] Salem, M. S.; Farhat, M.; Errayes, A. O.; Madkour, H. M. *Chem. Pharm Bull*. **2015**, *63*(11): 866.

[7] Chambhare, R. V.; Khadse B. G.; Bobde, A. S.; Bahekar, R. H. *Eur. J. Med. Chem.* **2003**,*38*(1): 89.

[8] Farhat, M. F.; El-Saghier, A. M.; Makhlouf, M. A.; Kreddan, K. M.; Elmezoughi, A. B. *J. Sulfur Chem*. **2007**, *28* (6) :563.

[9] El-Saghier, A. M.; Matough, F. S.; Farhat, M. F.; Saleh, N. A.; Kreddan, K. M.; El-Tier, S. O.; Bin Hussien, H. *Jordan Journal of Chemistry* **2008**, *3*(3):223.

[10] Farhat, M. F.; Makhlouf, M. A.; El-Saghier, A. M.; Elmezoughi, A. B.; Awhida, S. M.; El-Mehdi, A. A. *Arabian Journal of Chemistry* **2011**, *4*:307.

[11] Farhat, M. F.; Makhlouf, M. A.; Elmezoughi, A. B.; El-Mehdi, A. A.; El-Saghier, A. M. *Asian J. Chem*. **2016**, *28*(8): 1823.

[12] Ahmed, G. A. *Phosphorus, Sulfur and Silicon and Related Elements*, **2008**, *183*: 74.

[13] Mukerjee, A. K.; Ashare, R. *Chem. Rev.* **1991**, *91*:1**.**