Taylor & Francis
Taylor & Francis Group

Synthetic Communications

An International Journal for Rapid Communication of Synthetic Organic Chemistry

ISSN: 0039-7911 (Print) 1532-2432 (Online) Journal homepage: https://www.tandfonline.com/loi/lsyc20

Synthesis and antitumor activity evaluation of some thienopyrimidine derivatives

Amira T. A. Mohamed, Mohsen K. Abou-Elregal, Ahmed S. A. Youssef, Magdy M. Hemdan, Sandy S. Samir & Wael S. I. Abou-Elmagd

To cite this article: Amira T. A. Mohamed, Mohsen K. Abou-Elregal, Ahmed S. A. Youssef, Magdy M. Hemdan, Sandy S. Samir & Wael S. I. Abou-Elmagd (2019): Synthesis and antitumor activity evaluation of some thienopyrimidine derivatives, Synthetic Communications, DOI: 10.1080/00397911.2019.1697822

To link to this article: https://doi.org/10.1080/00397911.2019.1697822

SYNTHETIC COMMUNICATIONS®
https://doi.org/10.1080/00397911.2019.1697822

Taylor & Francis
Taylor & Francis Group

Synthesis and antitumor activity evaluation of some thienopyrimidine derivatives

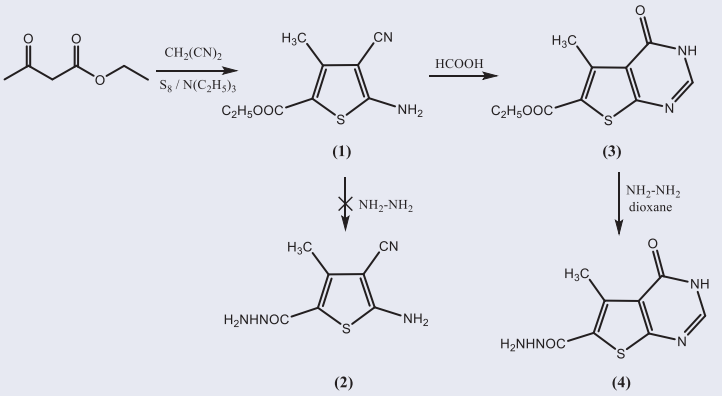
Amira T. A. Mohamed, Mohsen K. Abou-Elregal, Ahmed S. A. Youssef, Magdy M. Hemdan, Sandy S. Samir, and Wael S. I. Abou-Elmagd

Chemistry Department, Faculty of Science, Ain Shams University, Abassia, Cairo, Egypt

ABSTRACT

Some novel thienopyrimidine derivatives were synthesized via the reaction of 5- methyl-4-oxo-3,4-dihydrothieno[2,3-d]pyrimidine-5-carbohydrazide with different carbonyl compounds such as anhydrides, acid chlorides, carbon disulfide, phenyl isothiocyanate, triethyl orthoformate, diethyl acetylene dicarboxylate, acetylacetone, pyrazole-4-carboxaldehyde, and isatin. Also, the reaction of this carbohydrazide derivative with sodium nitrite in the presence of hydrochloric acid to give the corresponding azide derivative was discussed. The latter azide derivative was reacted with different amines to give the corresponding diheteryl urea derivatives. The antitumor activity evaluation of some representative examples of the synthesized compounds was examined against HePG2 and MCF-7 cell lines. Some of the newly synthesized compounds showed significant activity.

GRAPHICAL ABSTRACT



ARTICLE HISTORY
Received 28 September 2019

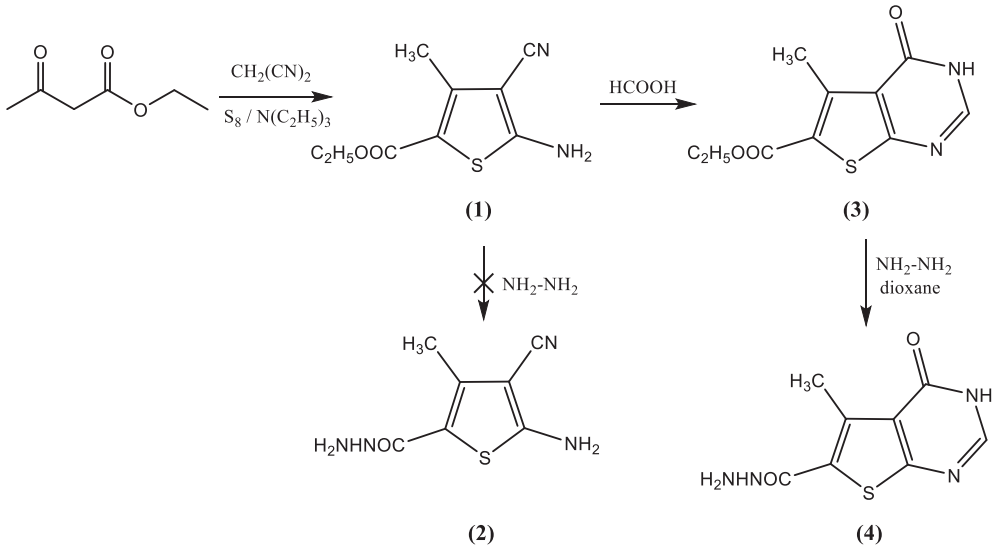
KEYWORDS
1,3,4-Oxadiazol-2-yl-thienopyrimidines; thieno[2,3-d]pyrimidines; 1,2,4-triazol-3-yl-thienopyrimidines

Introduction

Heterocyclic compounds containing thienopyrimidine moiety have attracted a great deal of interest because of their pharmacological and biological activities as antimicrobial,[1,2] analgesic,[3,4] anti-inflammatory,[5,6] antiviral,[7] antioxidant,[8] antidepressant,[9] and

CONTACT Amira T. A. Mohamed amirataher_82@yahoo.com Chemistry Department, Faculty of Science, Ain Shams University, Abassia, Cairo, Egypt.

Supplemental data for this article can be accessed on the publisher's website.



Scheme 1. Reaction steps for formation of the acid hydrazide derivative **4.**

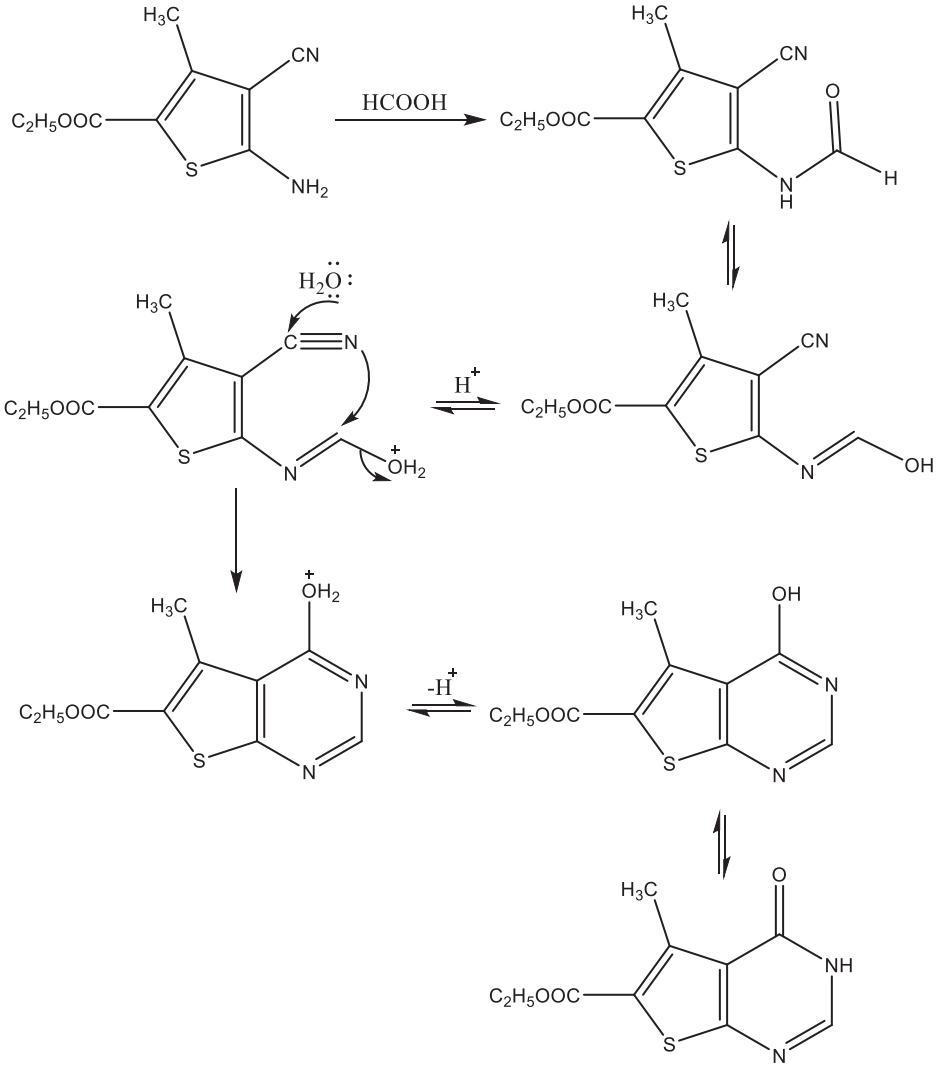
antitumor.[10–15] Thienopyrimidines are structural analogs of biogenic purines and can be considered as potential nucleic acid antimetabolites so that large number of thieno [2,3-d]pyrimidine derivatives were found to be against different cancer types exerting their anticancer activities via various mechanisms.[16–18] In continuation of our efforts to develop synthetic methods as well as our interest establishing biologically active heterocyclic compounds,[19–31] prompted us to design some novel thienopyrimdine derivatives with anticipated antitumor activity.

Results and discussion

Our interest in the synthesis and use of acid hydrazide derivatives,[30] prompted us to study the synthesis and the reactivity of 5-methyl-4-oxo-3, 4-dihydrothieno[2,3-d]pyrimidine-6-carbohydrazide **4** toward different carbon electrophiles.

At the first point of view, ethyl 2-amino-3-cyano-4-methyl thiophene-5-carboxylate **1** was prepared by *Gewald* reaction of ethyl acetoacetate with malononitrile and sulfur in the presence of triethylamine as a base catalyst under reflux conditions.[32]

Attempts to convert the thiophene ester **1** to the hydrazide derivative **2** by heating with hydrazine hydrate in dioxane was unsuccessful probably due to weak electrophilicity of the C=O ester by the free amino group. In order to increase the electrophilicity of the C=O of the ester group, the thiophene derivative **1** was treated with boiling formic acid to afford the corresponding theinopyrimidone derivative **3**, via condensation followed by molecular cyclization reaction (Scheme 1). The structure of theinopyrimidone derivative **3** was proved by the disappearance of cyano group band in its IR spectrum, but it showed two absorption bands at 1704 and 1687 cm^{-1} corresponding to (C=O) of ester and cyclic amide, respectively, in addition to N–H at 3172 cm^{-1}. The ^{1}HNMR displayed signals at δ 12.60, 8.20 ppm for protons of NH and CH=N groups as well as the triplet and quartet signals for protons of ethyl ester group. Heating of ethyl



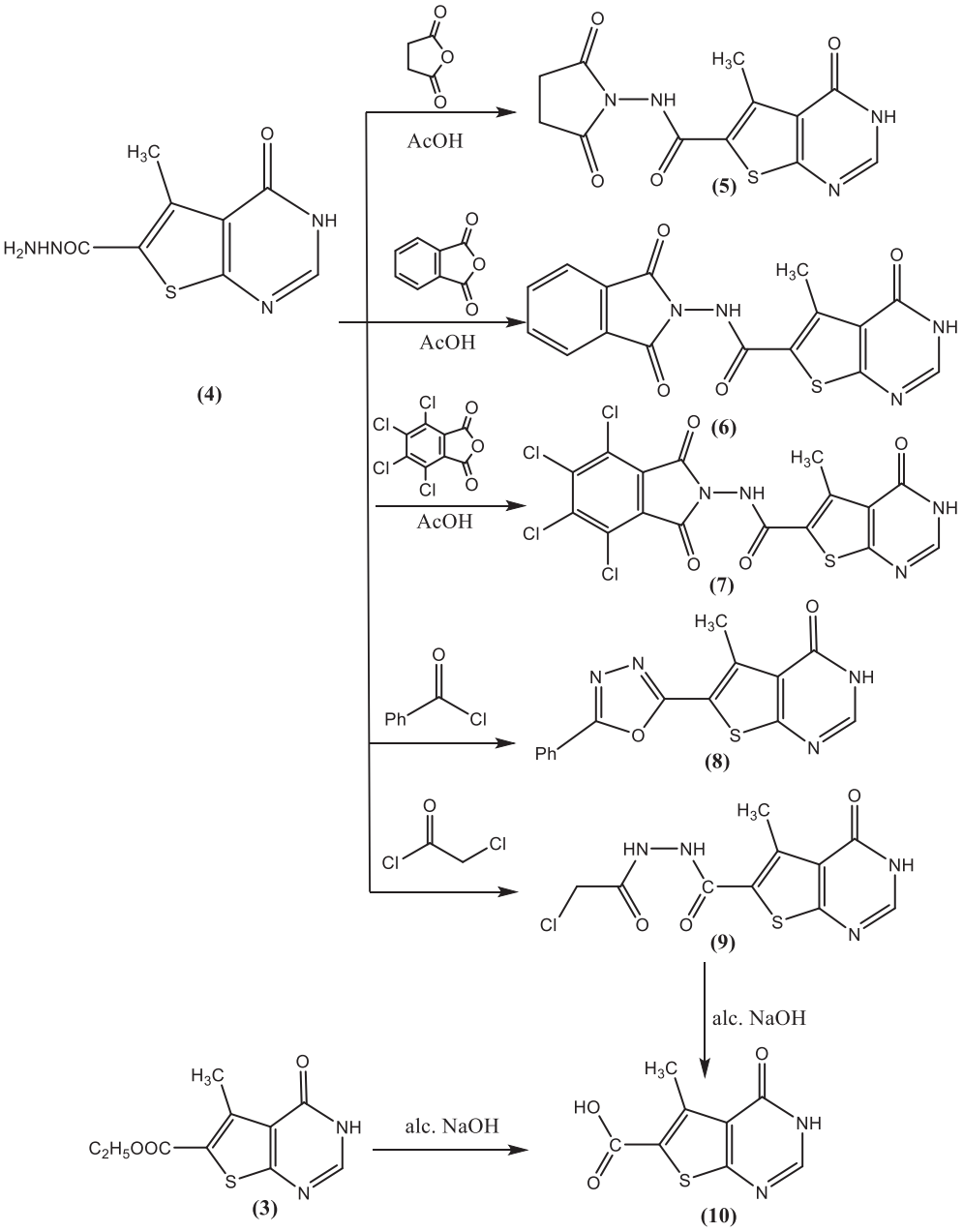
Scheme 2. Mechanistic pathway for the formation of compound **3.**

thienoprimidine-6-carboxylate **3** with hydrazine hydrate in dioxane afforded the corresponding acid hydrazide **4**. The structure of compound **4** is evidenced from its IR, ^{1}HNMR and mass spectral data (Cf. Experimental part).

The suggested mechanism for intramolecular cyclization of compound **1** with formic acid has been shown in (Scheme 2).

The free amino group of the acid hydrazide **4** underwent condensation reaction with different acid anhydrides such as succinic, phthalic and 3,4,5,6-tetrachlorophthalic anhydrides in boiling acetic acid to gives the corresponding pyrrolidine, isoindoline, and tetrachloro isoindoline derivatives **5–7,** respectively (Scheme 3).

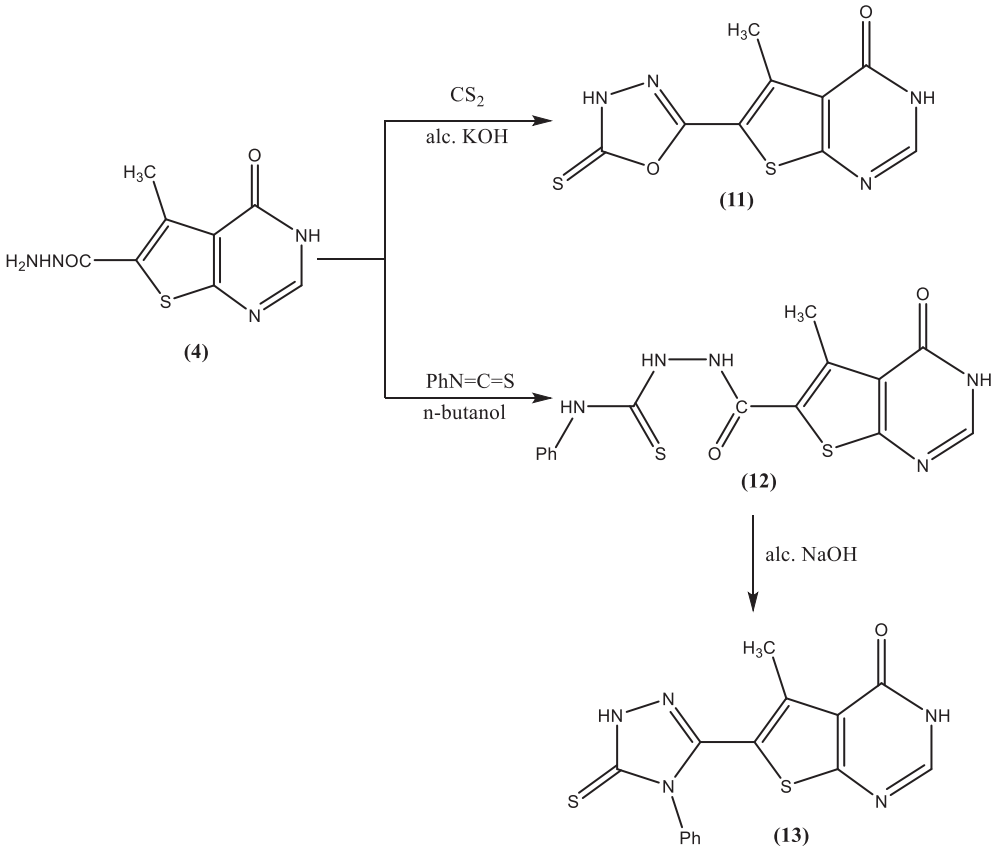
The structures of the products **5–7** were proved by IR spectra, which showed two absorption bands of symmetrical and asymmetrical stretching viberation of C=O in the



Scheme 3. Reaction of acid hydrazide **4** with different acid anhydrides and acid chlorides.

dioxopyrrolidine ring in addition to absorption of C=O of pyrimidone nucleus. Further evidence for the proposed structures that were gained from their ^{1}HNMR spectra that were in accordance with the suggested structures and EIMS spectra that revealed their correct molecular ion peak, as well as some of abundant peaks (Cf. Experimental part).

Benzoylation of the acid hydrazide **4** with benzoyl chloride afforded the 1, 3, 4-oxadiazole derivative **8.** However, its reaction with chloroacetyl chloride gave the acetylation product



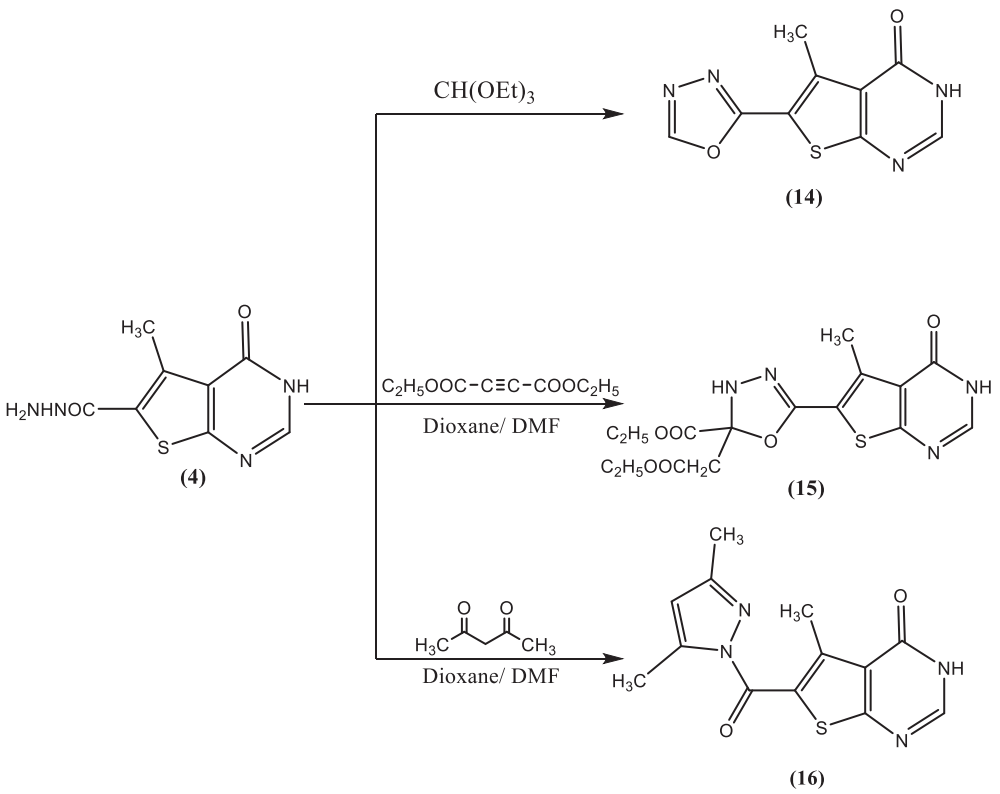
Scheme 4. The reaction of acid hydrazide **4** with CS_2 and phenyl isothiocyanate.

9. Attempt to cyclize **9** by boiling with alcoholic NaOH (10%) led to the acid derivative **10**, which was proved authentically by alkaline hydrolysis of the ester derivative **3** with alcoholic NaOH (10%) **(cf.** Scheme 3**)**.

The structures of compounds **8–10** were evidenced by studying their spectral as well as analytical data. Their IR spectra exhibited absorption bands correlated with C=O and NH groups as well as a band for OH group in case of compound **10.** Their ^{1}HNMR spectra were in accordance with their proposed structures. Further support is gained from their EIMS spectra that revealed their correct molecular ion peaks beside some of important peaks (Cf. Experimental part).

Moreover, the reaction of acid hydrazide **4** with carbon disulfide in the presence of alcoholic KOH (10%) afforded the cyclization product 1,3,4-oxadiazol-2-thione derivative **11**, via nucleophilic addition of the free amino group followed by intramolecular cyclization. Similar reaction was carried out by treatment of acid hydrazide **4** with phenyl isothiocyanate in boiling n-butanol, it gave the addition product **12**, which underwent cyclization by heating with alcoholic NaOH (10%) to give the triazolyl thienopyrimidine derivative **13** (Scheme 4).

The structures of compounds **11–13** were evidenced from their analytical as well as spectral data. Their IR spectra revealed absorption bands for NH, C=O and C=S groups. Further support for their proposed structures was gained from their ^{1}HNMR as



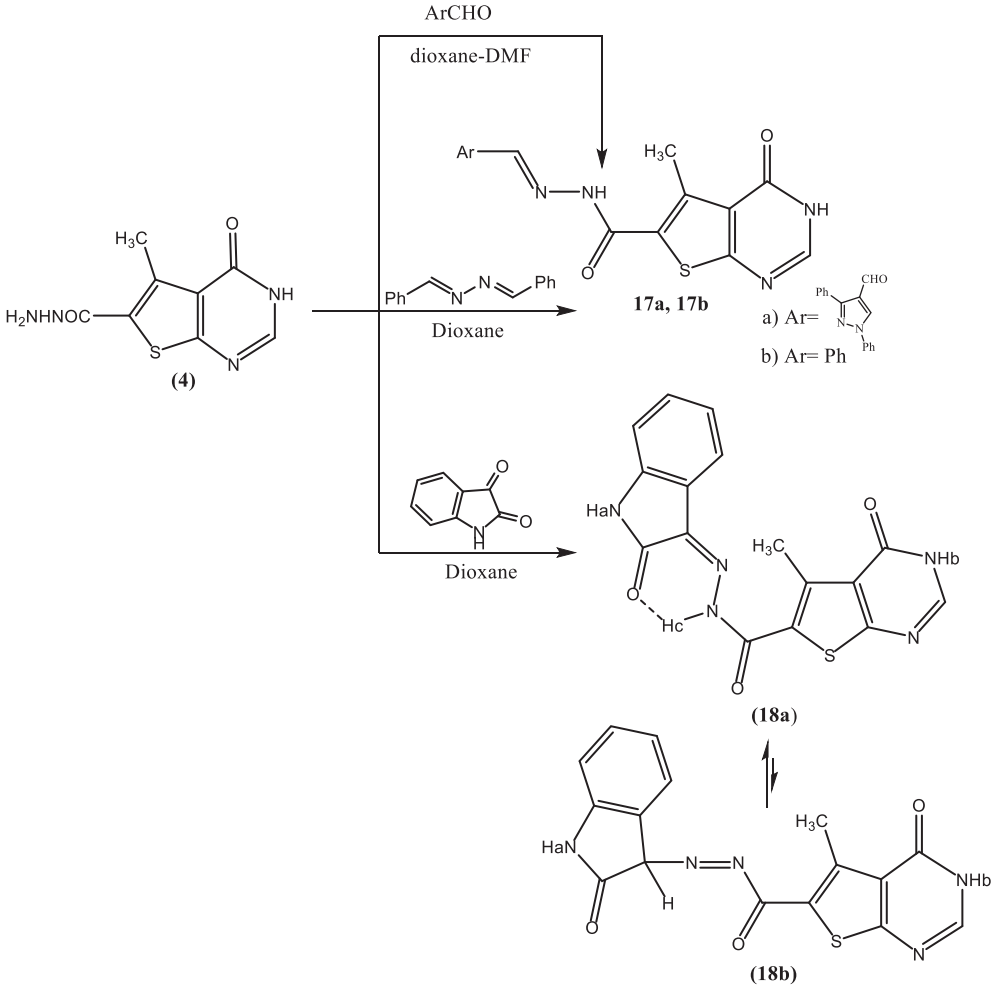
Scheme 5. Reaction of acid hydrazide **4** with different carbon electrophiles.

well as mass spectral data. The EIMS spectra exhibited the correct molecular ion peaks of compounds **11** and **13**; however, it was missed in case of compound **12** probably due to its ease decomposition in the ionization chamber (cf. Experimental part).

The pronounced biological activity of pyrazoles and oxadizoles,[33,34] promoted us to utilize the amino function of the hydrazide derivative **4** in the design synthesis of new heterocyclic systems incorporating pyrazole or oxadiazole nucleus. Thus, hydrazide **4** has been allowed to react with triethyl orthoformate, diethyl acetylene dicarboxylate and/or acetyl acetone to afford the oxadiazole and pyrazole derivatives **14–16** (Scheme 5).

The structures of compounds **14–16** were evidenced from their IR spectra that exhibited bands corresponding to NH and C=O groups. Their structures were supported by their ^{1}HNMR spectra that revealed signals for protons of NH, CH, and CH_3 groups as well as multiplet signals for protons of two ethyl groups in the case of compound **15.** Evidence was gained from their mass spectra that showed their correct molecular ion peaks (cf. Experimental part).

On the other hand, reactions of acid hydrazide **4** with a series of carbon electrophiles such as 1,3-diphenyl pyrazole 4-carboxaldehyde, dibenzylidine hydrazine and/or isatin, yielded the *Schiff* bases **17a, 17b, and18** as shown in (Scheme 6). The IR spectra of compounds **17a, 17 b, 18** showed band characteristic for NH and C=O groups. Their ^{1}HNMR spectra were in accordance with the suggested structures (cf. Experimental part). Inspection of the ^{1}HNMR spectrum of compound **18** revealed the existence of a

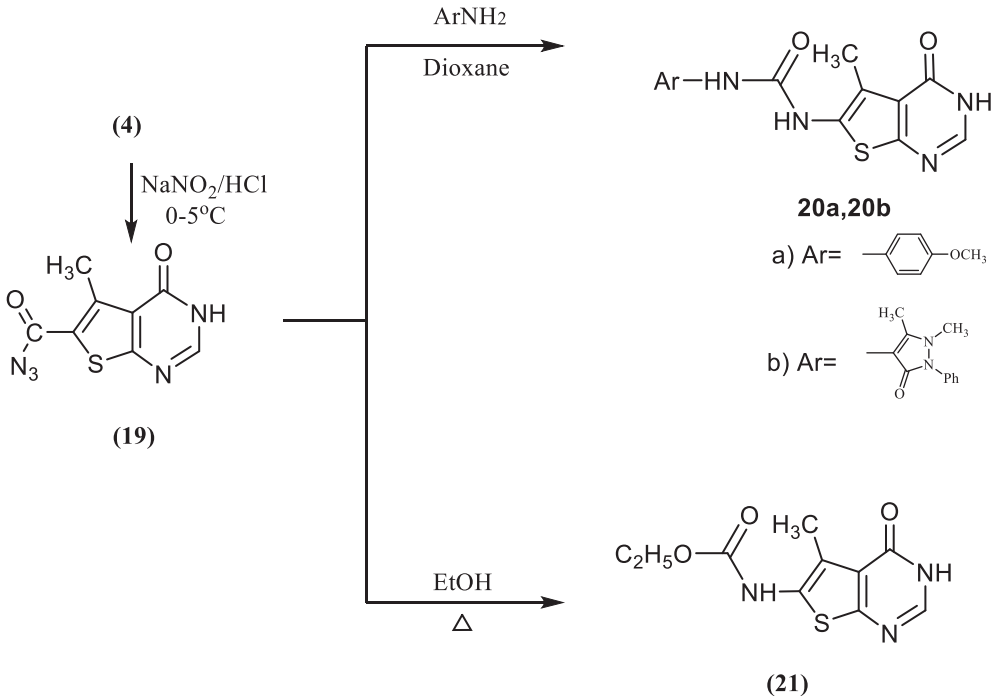


Scheme 6. Reaction of acid hydrazide **4** with different carbonyl compounds.

singlet signal in the upfield region at δ 2.73 ppm for methine proton CH, as well as a broad singlet for NH_c proton. This suggests the existence of compound **18** as an equilibrium mixture of tautomers **18a and b** in the ratio of **3:7,** respectively. The higher δ value for the broad singlet of NH_c proton suggests its existence as its chelated form shown (Scheme 6). Also, the higher percentage of the tautomer **18a** may be due to the extended conjugation. Further support for the assigned structures of compounds **17a, 17b, 18** is found in their mass spectra that revealed their molecular ion peaks and other abundant peaks.

A chemical proof for the structure of compound **17b** was gained by heating the hydrazide derivative **4** with benzaldehyde in dioxane that gave a substance which was identical in all respects m.p., m.m.p., and TLC with compound **17b**.

A further aspect of the behavior of acid hydrazide compound **4** was exemplified by reaction with nitrous acid at a temperature between 0 and 5 °C, which afforded the corresponding 5-methyl-4-oxo-3,4-dihydrothieno[2,3-d]pyrimidine-6-carbonylazide **19.** The aroyl azide **19** reacted with different nucleophilic reagents such as *p*-anisidine, 4-amino-



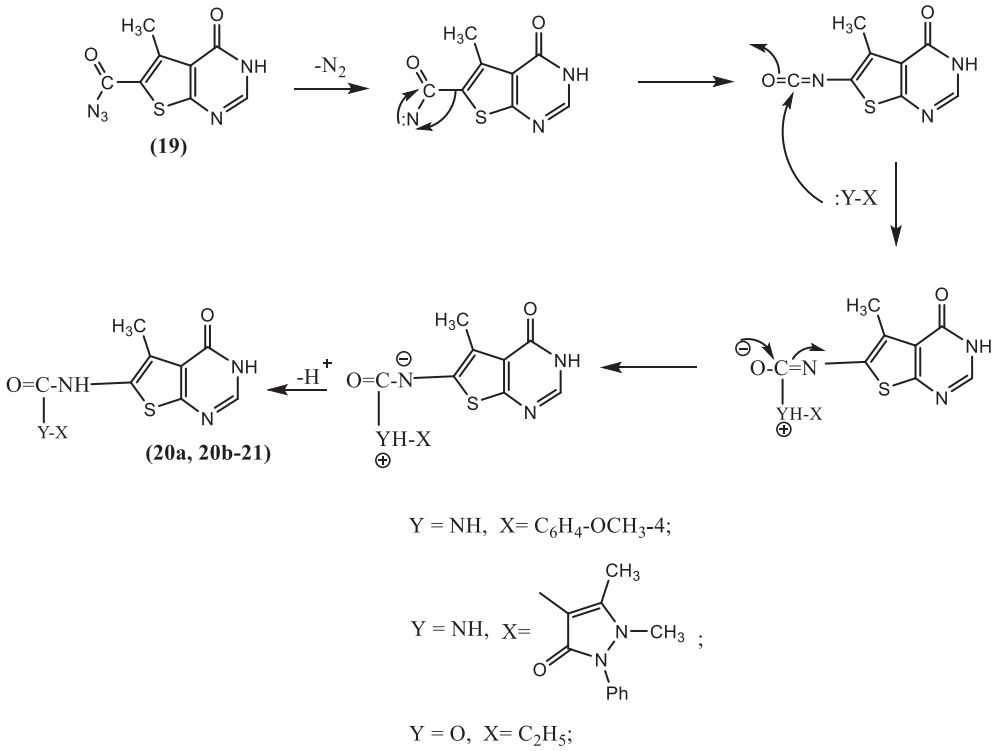
Scheme 7. Formation of acid azide **19** and reactions with different nucleophiles.

1,5-dimethyl-2-phenyl-1,2- dihydro-3*H*-pyrazol-3-one and ethanol to afford the urea derivatives **20a**, **20b,** and the ethyl carbamate derivative **21**. It is rationalized that the reaction proceeded through the conversion of the aroyl azide **19** to the isocyanate intermediate (not isolated) through Curtius rearrangement, followed by the concurrent attack of the nucleophilic reagents to afford the adduct **20a, 20b, 21** (Scheme 7). The IR spectra of compounds **20a, 20b, 21** exhibited bands correlated with NH and C=O groups as well as a band for azido group for compound **19**. The ^{1}HNMR spectra supported the structures of compounds **20a, 20b, 21** as they showed signals for protons of NH, alkyl, and multiplet signals for aromatic protons of compounds **20a** and **20b**. Further proof for the structures of compounds **20a, 20b** is gained from their EIMS spectra that showed their molecular ion peaks as well as some important peaks (cf. Experimental part).

The proposed mechanism for the formation of compounds **20a, 20b, 21** can be explained as depicted in (Schemes 8).

Antitumor activity evaluation

The anti-tumor efficacy of the compounds against HePG2 and MCF-7 cell lines was established compared with doxorubicin by using the MTT assay.[35,36] The results revealed that compounds **4, 14, 19, and 21** were the most active derivatives among the series of tested compounds whereas other compounds exhibited little or no activity. The effective dose calculated as IC_{50}, which corresponds to the compound concentration resulted in 50% mortality in the total cells count and presented in (Table 1).



Scheme 8. Mechanistic pathway for the formation of compounds **20a, 20b, 21**.

Table 1. Cytotoxic activity of some compounds against human tumor cells.

	In vitro cytotoxicity IC50 (μM)	
Compounds	HePG2	MCF-7
DOX	4.50 ± 0.3	4.17 ± 0.2
3	62.75 ± 3.0	70.61 ± 3.9
4	6.65 ± 0.5	7.08 ± 0.8
5	29.51 ± 2.1	25.81 ± 1.9
6	23.67 ± 1.7	14.50 ± 1.3
7	74.13 ± 3.3	61.17 ± 3.4
8	86.40 ± 3.9	81.23 ± 4.5
11	36.01 ± 2.5	42.35 ± 2.9
12	41.68 ± 2.8	32.56 ± 2.3
14	13.81 ± 1.2	17.23 ± 1.5
15	65.28 ± 3.1	38.42 ± 2.6
16	47.22 ± 2.9	53.48 ± 3.1
17a	33.84 ± 2.3	45.05 ± 3.0
17b	18.93 ± 1.4	21.39 ± 1.8
18	88.49 ± 4.2	92.48 ± 5.1
20a	9.49 ± 0.8	10.67 ± 1.1
21	12.05 ± 1.0	8.79 ± 0.9

IC50 (μM): 1–10 (very strong); 11–20 (strong); 21–50 (moderate); 51–100 (weak and above 100 non-cytotoxic). DOX: doxorubicin.

Experimental

Melting points were determined using an electrothermal Gallenkamp Scientific melting point apparatus and are uncorrected. The infrared (IR) spectra were recorded on Nicolet 7600 (USA)FT-IR infrared spectrophotometer using the KBr pellet technique at

the Central Laboratory of Faculty of Science, Ain Shams University. ^{1}HNMR spectra were recorded on a GEMINI 300 BB-400 MHz spectrometer using tetramethylsilane (TMS) as internal standard in dimethyl sulfoxide (DMSO-d6) as a solvent with chemical shift δ expressed in ppm at the main defense chemical laboratory and ^{13}C-NMR spectra were recorded on a Mercury 300 BB-75 MHZ spectrometer and referenced to solvent signal $\delta = 39.50$ ppm for DMSO-d6 at Cairo University. Mass spectra were measured on a GC-MSQP 1000-Ex spectrometer at the Regional Center for Mycology and Biotechnology of Al-Azhar university and on Agilent technologies 5977 AMSD 7890B CTC system at the Central Laboratory of Faculty of Science, Ain Shams University. Elemental analyses were carried out at the Microanalytical Center of Faculty of Science, Cairo University. Followup of the reactions and checking the homogeneity of the compounds were made by TLC on silica gel-protected aluminum sheets (F254, Merck) and the spots were detected by exposure to UV-lamp. The anticancer activity was done at the Micro Analytical Center at Mansoura University.

Reaction of the cyano amino derivative 1 with formic acid

A solution of compound **1** (1 g, 0.005 mol) in formic acid (20 mL), was refluxed on a hot plate for 15 h, then left to cool at room temperature. The precipitated solid obtained was filtered off, washed with water several times and recrystallized from benzene-ethanol to give compound **3**.

Ethyl-5-methyl-4-oxo-3,4-dihydrothieno[2,3-d]pyrimidine-6-carboxylate (3)

Off white crystals (60%), m.p. 288–290^{o}C, (benzene/ethanol); FTIR (KBr) cm^{-1}: 3172 (NH), 3063 (Aryl-H), 2924, 2874 (Alkyl-H), 1704 (C=O) of conjugated ester, 1687(C=O) of amide. ^{1}HNMR (DMSO-d6): δ 1.31 (t, 3H, CH_2CH_3, $J = 7.2$, 6.9 Hz), 2.82 (s, 3H, CH_3 of thiophene), 4.29 (q, 2H, CH_2CH_3 $J = 7.2$, 6.9 Hz), 8.20 (s,1H, CH=N), 12.60 (br.s, 1H, NH of pyrimidinone, exchangeable). *M/Z* (70 ev) *m/z* (%): 238 (M^{+}, 74), 228(23), 203(48), 202(89), 193(40), 188(26), 150(36), 139(40), 105(38), 95(75), 90(100). Anal.calcd for $C_{10}H_{10}N_2O_3S$ (238.26): C, 50.41; H, 4.23; N, 11.76; S, 13.46. Found: C, 50.19; H, 4.52; N, 11.31; S, 13.63%.

Reaction of the thieno pyrimidine derivative 3 with hydrazine hydrate

To a solution of compound **3** (1 g, 0.002 mol) in dioxane (20 mL), hydrazine hydrate (1 mL, 0.02 mol) was added. The reaction mixture was heated under reflux for 7 h. A solid product was precipitated while hot, filtered off, washed with water for several times and recrystallized from dioxane.

5-Methyl-4-oxo-3,4-dihydrothieno[2,3-d]pyrimidine-6-carbohydrazide (4)

Off white crystals (64%), m.p. >300^{o}C, (dioxane); FTIR (KBr) cm^{-1}: 3429, 3263, 3122 (NH), 3058 (Aryl-H), 2925, 2855 (Alkyl-H), 1690 (C=O). ^{1}HNMR (DMSO-d6): δ 2.67 (s, 3H, CH_3), 4.57 (br.s, 2H, NH_2, exchangeable), 8.13 (s,1H, CH=N), 9.49 (br.s,

1H,NH, exchangeable), 12.50 (br.s, 1H,NH of pyrimidinone, exchangeable). *M/Z* (70 ev) *m/z* (%): 225(M^+ +1, 48), 224(M^+, missed), 193(100), 165(51), 91(38), 89(59), 83(47), 81(60), 63(31), 52(28), 45(26). Anal.calcd for $C_8H_8N_4O_2S$ (224.24): C, 42.85; H, 3.60; N, 24.99; S, 14.30. Found: C, 42.53; H, 3.76; N, 24.68; S, 14.01%.

Reaction of the carbohydrazide derivative 4 with sodium nitrite. Formation of azide derivative 20

To a stirred solution of compound **4** (1 g, 0.004 mol) in cold diluted hydrochloric acid (20 mL), solution of sodium nitrite (1.1 g, 10 mL, 0.03 mol) was added dropwise. The reaction mixture was stirred for 1 h. A solid product was precipitated while stirring, filtered off, and washed with water several times to give compound **20.**

5-Methyl-4-oxo-3,4-dihydrothieno[2,3-d]pyrimidine-6-carbonyl azide (20)

Beige powder (94%), m.p. 130°C (dec); FTIR (KBr) cm^{-1}: 3173 (NH), 3068 (Aryl-H), 2941, (Alkyl-H), 2161(N_3), 1692, 1667(C = O). ^{1}HNMR (DMSO-d6): δ 2.83 (s, 3H, CH_3), 8.26 (s,1H, CH = N), 12.74 (br.s, 1H,NH of pyrimidinone, exchangeable).

ORCID

Sandy S. Samir http://orcid.org/0000-0002-5637-8200
Wael S. I. Abou-Elmagd http://orcid.org/0000-0002-8317-3972

References

[1] Mohmoud, M. R. A.; EL-Azm, F. S.; Ali, A. T.; Ali, Y. M. Design, Synthesis and Antimicrobial Evaluation of Novel Thienopyrimidines. *Synth. Commun.* **2015**, *45*, 982. DOI: 10.1080/00397911.2014.999340.
[2] Khan, A. Y.; Kalashetti, M. B.; Belaragi, N. S.; Deshapa, N.; Khazi, I. A. M. Synthesis, Characterization and Biological Evaluation of Novel Thienopyrimidine and Triazolothienopyrimidine Derivatives. *Am. J. Pharm. Tech. Res.* **2014**, *4*, 283.
[3] Dave, C. G.; Shah, P. R.; Dave, V. J. Synthesis and Biological Activity of Pyrido[3′, 2′, 4,5] Thieno[3,2-d]Pyrimidines. *J. Indian. Chem. Soc.* **1989**, *66*, 48.
[4] Bousquet, E.; Romeo, G.; Guerrera, F.; Caruso, A.; Amico-Roxas, M. Synthesis and Analgesic Activity of 3-Substituted Derivatives of Pyrido[3′, 2′, 4,5]Thieno[3,2-d]Pyrimidin-4(3*H*)-One. *Farmaco.* **1985**, *40*, 869.
[5] Alagarsamy, V.; Meena, S.; Ramseshu, K. V.; Solomon, V. R.; Thirumurugan, K.; Dhanabal, K.; Murugan, M. Synthesis Analgesic, anti-Inflammatory, Ulcerogenic Index and Antibacterial Activities of Novel 2-Methylthio-3-Substituted-5,6,7,8-Tetrahydrobenzo[b]Thieno[2,3-d] Pyrimidin-4-(3*H*)-Ones. *Eur. J. Med. Chem.* **2006**, *41*, 1293. DOI: 10.1016/j.ejmech.2006.06.005.
[6] El-Gazzar, A.-R.; Hussein, H.; Hafez, H. Synthesis and Biological Evaluation of Thieno[2,3-d]Pyimidine Derivatives for Anti-Inflammatory, Analgesic and Ucerogenic Activity. *Acta Pharm.* **2007**, *57*, 395. DOI: 10.2478/v10007-007-0032-6.
[7] Rashad, A. E.; Shamroukh, A. H.; Abdel-Megeid, R. E.; Mostafa, A.; EL-Shesheny, R.; Kandeil, A.; Ali, M. A.; Banert, K. Synthesis and Screening of Some Novel Fused Thiophene and Thienopyrimidine Derivatives for anti-Avian Influenza Virus (H5N1)Activity. *Eur. J. Med. Chem.* **2010**, *45*, 5251. DOI: 10.1016/j.ejmech.2010.08.044.

[8] Nagaraju, K.; Harikrishna, N.; Vasu, K.; Rao, C. V. Synthesis and Biological Activity of Novel Bis and Monocycles of Thienopyrimidine Derivatives. *Indo Am. J. Pharm. Res.* **2015**, *5*, 1604.

[9] Geoge, T.; Kaul, C. L.; Grewal, R. S.; Tahilramani, R. Antihypertensive and Monoamine Oxidase Inhibitory Activity of Some Derivatives of 3-Formyl-4-Oxo-4*H*-Pyrido[1,2-a]Pyrimidine. *J. Med. Chem.* **1971**, *14*, 913. DOI: 10.1021/jm00292a005.

[10] Kassab, A. A.; Gedawy, E. M. Synthesis and Anticancer Activity of Novel 2-Pyridyl Hexahyrocyclooctathieno[2,3-d]pyrimidine Derivatives. *Eur. J. Med. Chem.* **2013**, *63*, 224. DOI: 10.1016/j.ejmech.2013.02.011.

[11] Guo, Y.; Li, J.; Ma, J. L.; Yu, Z.; Wang, H.; Zhu, W.; Liao, X.; Zhao, Y. Synthesis and Antitumor Activity of α-Aminophosphonate Derivatives Containing Thieno[2,3-d]Pyrimidines. *Chin. Chem. Lett.* **2015**, *26*, 755. DOI: 10.1016/j.cclet.2015.03.026.

[12] Kaizhen, S.; Junjie, M.; Xiao, W.; Ping, G.; Yanfang, Z. Synthesis and Antitumor Activities of Novel 4-Morpholinothieno[2,3-d]Pyrimidine Derivatives. *Chem. Res. Chin. Univ.* **2014**, *30*, 750.

[13] Zhu, W.; Chen, C.; Sun, C.; Xu, S.; Wu, C.; Lei, F.; Xia, H.; Tu, Q.; Zheng, P. Design, Synthesis and Docking Studies of Novel Thienopyrimidine Derivatives Bearing Chromone Moiety as mTOR/PI3Ka Inhibitors. *Eur. J. Med.* **2015**, *93*, 64. DOI: 10.1016/j.ejmech.2015.01.061.

[14] Mghwary, A. E. S.; Gedawy, E. M.; Kamal, A. M.; Abuel-Maaty, S. M. Novel Thienopyrimidine Derivatives as Dual EGFR and VEGFR-2-Inhibitors: Design, Synthesis, Anticancer Activity and Effect on Cell Cycle Profile. *J. Enzyme Inhib. Med. Chem.* **2019**, *3*, 838. DOI: 10.1080/14756366.2019.1593160.

[15] Adly, M. E.; Gedawy, E. M.; EL-Malah, A. A.; EL-Telbany, F. A. Synthesis of Novel Thieno[2,3-d]Pyimidine Derivatives and Evaluation of Their Cytotoxicity and EGFR Inhibitor Activity. *ACAMC.* **2018**, *18*, 747. DOI: 10.2174/1871520618666180124121441.

[16] Ganjee, A.; Qiu, Y.; Kisliuk, R. L. Synthesis of Classical and Nonclassical 2-Amino-4-Oxo-6-Benzylthieno[2,3-d]Pyrimidines as Potential Thymidylate Synthase Inhibitoprs. *J. Heterocycl. Chem.* **2004**, *41*, 941. DOI: 10.1002/jhet.5570410613.

[17] Dai, Y.; Guo, Y.; Frey, R. R.; Ji, Z.; Curtin, M. L.; Ahmed, A. A.; Albert, D. H.; Arnold, L.; Arries, S. S.; Barlozzari, T.; et al. Thienopyrimidine Ureas as Novel and Potent Multitargeted Receptor Tyrosine Kinase Inhibitors. *J. Med. Chem.* **2005**, *48*, 6066. DOI: 10.1021/jm050458h.

[18] Wang, Y. D.; Johnson, S.; Powell, D.; McGinnis, J. P.; Miranda, M.; Rabindran, S. K. Inhibition of Tumor Cell Proliferation by Thieno[2,3-d]pyrimidin-4(1H)-One-Based Analogs. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3763. DOI: 10.1016/j.bmcl.2005.05.127.

[19] Hashem, A. I.; Youssef, A. S. A.; Kandeel, K. A.; Abou-Elmagd, W. S. I. Conversion of Some 2(3*H*)-Furanones Bearing a Pyrazolyl Group into Other Heterocyclic Systems with a Study of Their Antiviral Activity. *Eur. J. Med.* **2007**, *42*, 934. DOI: 10.1016/j.ejmech.2006.12.032.

[20] Abou-Elmagd, W. S. I.; Hashem, A. I. Synthesis of 1-Amidoalkyl-2-Naphthols and Oxazine Derivatives with Study of Their Antibacterial and Antiviral Activities. *Med. Chem. Res.* **2013**, *22*, 2005. DOI: 10.1007/s00044-012-0205-9.

[21] Abou-Elmagd, W. S. I.; Hashem, A. I. Novel Synthesis of Some Isatin Hydrazones and Pyridazinophthalazines. *Synth. Commun.* **2013**, *44*, 1083. DOI: 10.1002/chin.201329119.

[22] Abou-Elmagd, W. S. I.; Hashem, A. I. Conversion of Some 2(3*H*)-Furanones into Pyrrolinotriazine and Oxazolopyrimidine Derivatives. *J. Heterocyclic Chem.* **2012**, *49*, 947. DOI: 10.1002/jhet.889.

[23] Abou-Elmagd, W. S. I.; El-Ziaty, A. K.; Abdalha, A. A. Ring Transformation and Antimicrobial Activity of Indolyl-Substituted 2(3*H*)-Furanones. *Heterocycl. Commun.* **2015**, *21*, 179.

[24] Hashem, A. I.; Kandeel, K. A.; Youssef, A. S. A.; Abou-Elmagd, W. S. I. Behaviour of Some 2(3*H*)- Furanones Bearing a Pyrazolyl Group as Alkylating Agents. *J. Chem. Res.* **2006**, *2006*, 315. DOI: 10.3184/030823406777411115.

[25] El-Ziaty, A. K.; Abou-Elmagd, W. S. I.; Ramadan, S. K.; Hashem, A. I. Synthesis and Biological Screening of Some Chromonyl Substituted Heterocycles Derived from 2(3*H*)-Furanone Derivative. *Synth. Commun.* **2017**, *47*, 471. DOI: 10.1080/00397911.2016.1271896.

[26] Abou-Elmagd, W. S. I.; Hashem, A. I. Synthesis and Antitumor Activity Evaluation of Some Novel Fused and Spiro Heterocycles Derived from a 2(3*H*)-Furanone Derivative. *J. Heterocyclic Chem.* **2016**, *53*, 202. DOI: 10.1002/jhet.2401.

[27] Abou-Elmagd, W. S. I.; El-Ziaty, A. K.; El-Zahar, M. I.; Ramadan, S. K.; Hashem, A. I. Synthesis and Antitumor Activity Evaluation of Some N-Heterocycles Derived from Pyrazolyl-Substituted 2(3*H*)-Furanone. *Synth. Commun.* **2016**, *46*, 1197. DOI: 10.1080/00397911.2016.1193755.

[28] Abou-EL Regal, M. K.; Ali, A. T.; Youssef, A. S. A.; Hemdan, M. M.; Samir, S. S.; Abou-El Magd, W. S. I. Synthesis and Antitumor Activity Evaluation of Some 1,2,4-Triazine and Fused Triazine Derivatives. *Synth.Commun.* **2018**, *48*, 2347. DOI: 10.1080/00397911.2018.1482350.

[29] EL-Hashash, M. A.; Ali, A. T.; Hussein, R. A.; EL-Sayed, W. M. Synthesis and Reactivity of 6,8-Dibromo-2-Ethyl-4*H*-Benzo[d][1,3]Oxazin-4-One towards Nucleophiles and Electrophiles and Their Anticancer Activity. *ACAMC.* **2019**, *19*, 538. DOI: 10.2174/1871520619666190201145221.

[30] Youssef, A. S. A.; Kandeel, K. A.; Abou-Elmagd, W. S. I.; Haneen, D. S. A. Synthesis of Novel Heterocycles Derived from 4-Arylmethylene-2-Phenyl-1,3-Oxazole-5(4*H*)-Ones. *J. Heterocyclic Chem.* **2016**, *53*, 809. DOI: 10.1002/jhet.2329.

[31] Hashem, A. I.; Abou-Elmagd, W. S. I.; Salem, A. E.; El-Kasaby, M.; El-Nahas, A. M. Conversion of Some Vegetable Oils into Synthetic Lubricants. *Energy Sour A.* **2013**, *35*, 397. DOI: 10.1080/15567036.2010.514587.

[32] Mohareb, R. M.; Abdallah, A. E. M.; Helal, M. H. E.; Shaloof, S. M. H. Synthesis and Structure Elucidation of Some Novel Thiophene and Benzothiophene Derivatives as Cyctotoxic Agents. *Acta Pharm.* **2016**, *66*, 53. DOI: 10.1515/acph-2016-0005.

[33] Karrouchi, K.; Radi, S.; Ramli, Y.; Taoufik, J.; Mabkhot, Y.; Al-Aizari, F.; Ansar, M. Synthesis and Pharmacological Activities of Pyrazole Derivatives. *Molecules.* **2018**, *23*, 134. DOI: 10.3390/molecules23010134.

[34] Bhat, K. I.; Sufeera, K.; Chaitanya Sunil Kumar, P. Synthesis, Characterization and Biological Activity Studies of 1,3,4-Oxadiazol Analogs. *J. Young Pharm.* **2011**, *3*, 310. DOI: 10.4103/0975-1483.90243.

[35] Mosmann, T. Rapid Colorimetric Assay for Cellular Growth and Survival Application to Proliferation and Cytotoxicity Assays. *J. Immunol.Methods.* **1983**, *65*, 55. DOI: 10.1016/0022-1759(83)90303-4.

[36] Denizot, F.; Lang, R. Rapid Colorimetric Assay for Cell Growth and Survival. Modifications to the Tetrazolium Dye Procedure Giving Improved Sensitivity and Reliability. *J. Immunol. Methods.* **1986**, *89*, 271. DOI: 10.1016/0022-1759(86)90368-6.