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Intermolecular cyclization of cinnamoyl isothiocyanate: A new synthetic entry for pyrimidine, triazine, and triazole candidates

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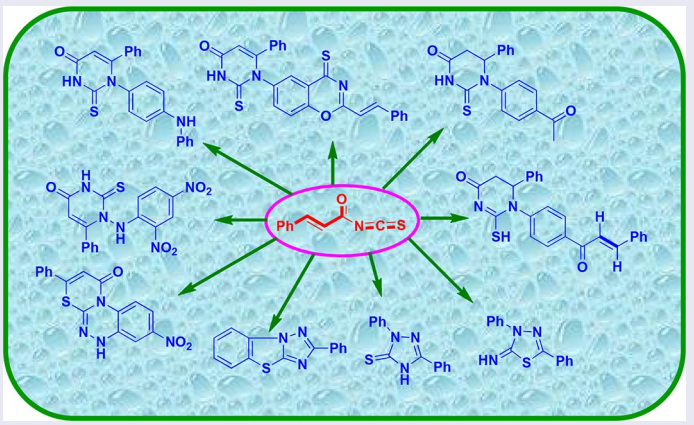
ABSTRACT

An efficient and facile protocol for the synthesis of azine and azole ring systems was reported. Whereas, reaction of cinnamoyl isothiocyanate with *N*-nucleophile containing compounds (namely, *p*-aminophenol (**2**), N^1-phenylbenzene-1,4-diamine (**5**) and *p*-aminoacetophenone (**8**)) tolerated thiourea derivatives **3, 6**, and **9**, respectively. The later compounds underwent intramolecular cyclization upon treatment with EtONa to give pyrimidinethiones **4, 7**, and **10**, respectively, in moderate yield (74–79%). Compound **9** underwent intramolecular cyclization and condensation upon reaction with NaOH and benzaldehyde to give pyrimidinethione **12**. Thiosemicarbazides **14** and **19** were obtained through reaction of heteroallen **1** with 2,4-dinitrophenylhydrazine **13** and hydrazone **18**, respectively. Compound **14** was cyclized to pyrimidinethione **15** and triazine derivatives **17** through its reaction with EtONa at room temperature and refluxing temperature, respectively. Finally, base mediated and oxidative cyclization of thiourea derivative **19** with EtONa, Br_2/AcOH, and $Pb(OAc)_2$ afforded thiadiazole **20**, benzothiazolotriazole **21**, and triazolethione **22** derivatives, respectively.

GRAPHICAL ABSTRACT



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Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/lsyc.
Supplemental data (Full experimental detail on syntheses of compounds **4**, **7**, **9**, **10**, **12**, **14**, **15**, **17**, **19-22**, IR, mass, ^{1}H-NMR, and ^{13}C-NMR spectra) can be accessed on the publisher's website.

Introduction

Nitrogen containing heterocyclic compounds have promising pharmaceutical interests which have drawn the attention of scientists in recent years. One of such compounds is

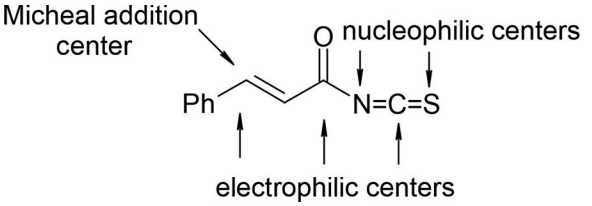
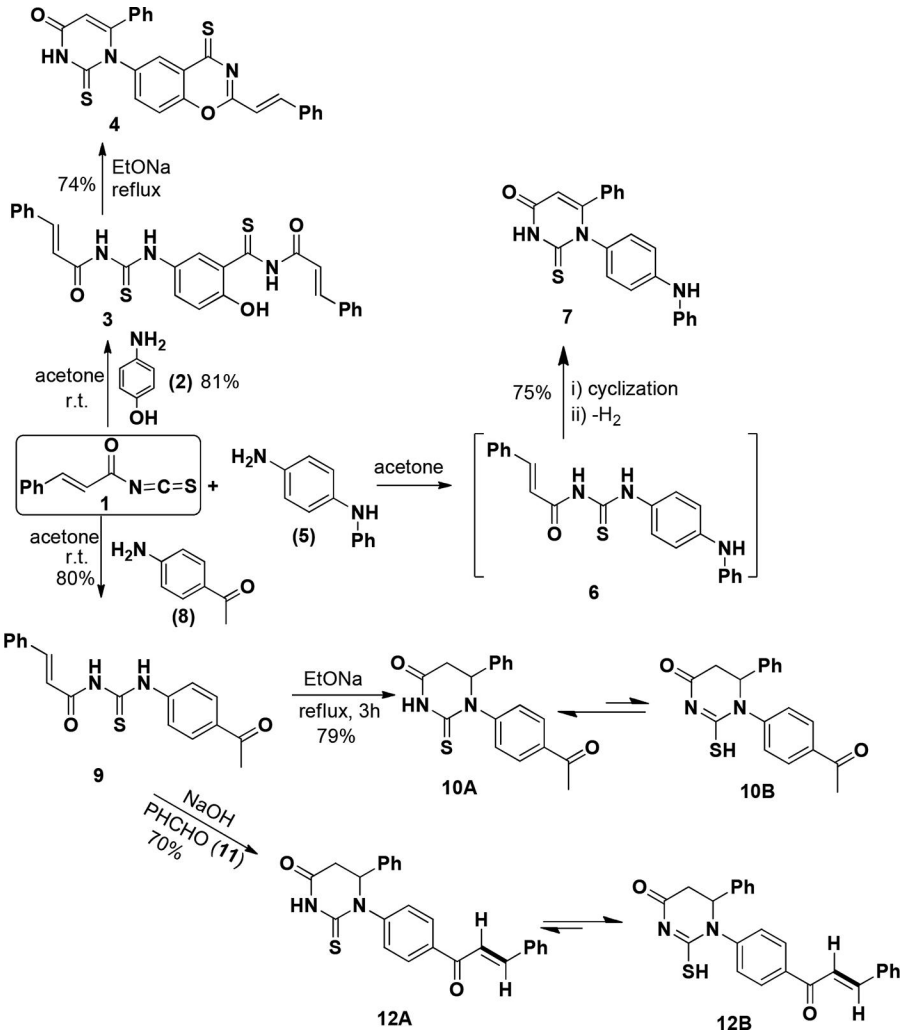
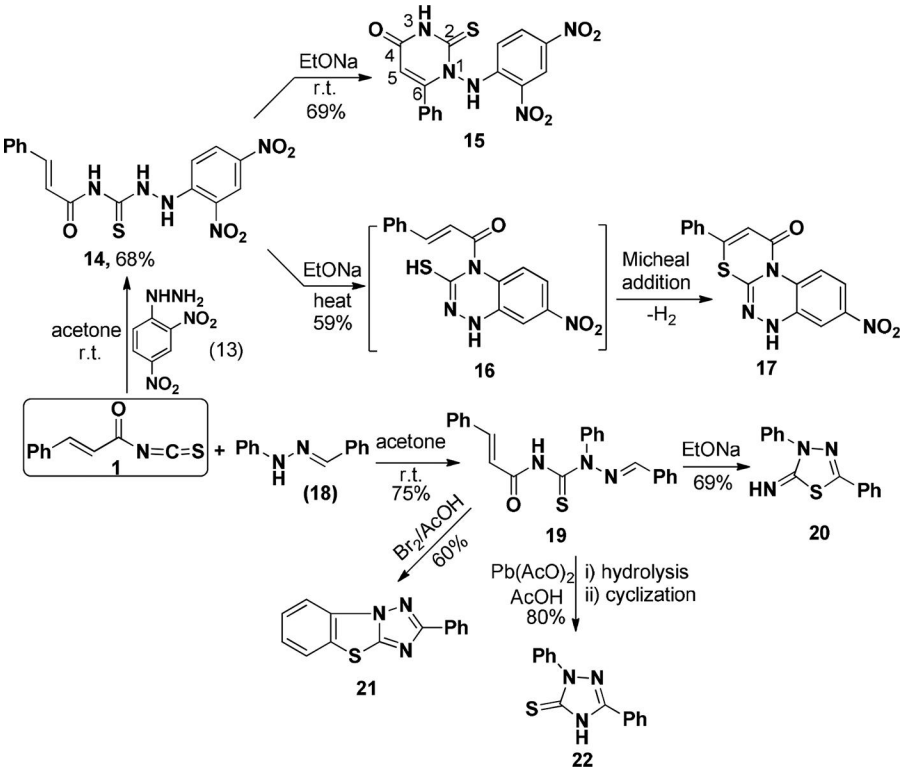


Figure 1. Reactivity profile of cinnamoyl isothiocyanate.



Scheme 1. Synthetic approaches of pyrimidines **4**, **7**, **10**, and **12**.

pyrimidine which acts as the main unit in a wide range of industrially and biologically important compounds. For example, many pyrimidine derivatives act as anti-inflammatory,[1] antihypertensive,[2] antifungal,[3] antiviral,[4] antioxidant,[5] antitumor,[6] and anti-HIV agents.[7] Similarly, triazine ring is an interest six-membered heterocycle component for designing new biologically active compounds. Therefore, triazine containing compounds have anticancer,[8] antitumor,[9] antimicrobial,[10] antibacterial,[11] antimalarial,[12] herbicidal,[13] and anti-HIV activities.[14] In addition, some new triazoles are also an important group of heterocyclic derivatives of important biological activities. They have been investigated as anticonvulsant,[15] antibacterial, anticancer,[16] anti-inflammatory,[17] antitubercular[18] agents. In addition, the core moiety of 1,2,4-triazole is present in a variety of medically used drugs such as tricyclazole (5-methyl-1,2,4-triazolo[3,4-*b*]benzothiazole), fluconazole,[19] and ribavirin[20] as antifungal and antiviral drugs, respectively. Acyl isothiocyanates, well-known as very important synthons in synthetic organic chemistry, particularly in the construction of heterocyclic ring systems such as functionalized pyrimidines, triazines, triazoles, pyridines, pyrazoles, isothiazoles, pyrans, and pyridazines.[21,22] In particularly, cinnamoyl isothiocyanate is an example for the reactive intermediates in organic chemistry, thus it contains several active centers (three electrophilic and two nucleophilic centers, in addition to Michael addition center) (Fig. 1), this reactivity was the reason for synthesize some biologically active heterocyclic systems through its reaction with simply available reagents. Completing to our



Scheme 2. Synthetic routes for compounds **14–17** and **19–22**.

experience[23–26] in design and synthesis of heterocyclic compounds of interesting biological activity from simply available reagents, we wish herein to use an efficient and a facile approach to synthesize novel heterocyclic compounds utilizing cinnamoyl isothiocyanate as a synthon (Schemes 1 and 2).

Results and discussion

A good example of the reactivity of cinnamoyl isothiocyanate **1** (prepared through reaction of cinnamoyl chloride with amm.thiocyanate in acetone)[27] can be found in the synthesis of benzoxazine with pyrimidine moiety **4**. The reaction sequence started with treating of heteroallen **1** with *p*-aminophenol (**2**) to yield the isolable thiourea derivative **3** (Scheme 1), then undergo double pyrimidine oxazine cyclization affording pyrimidine derivative **4** (Scheme 1). ^{1}H NMR spectrum of compound **3** displayed four singlets at δ 9.60, 11.50, and 12.36 ppm indicating the presence of phenolic OH and 3NH protons, respectively, in addition multiplet at δ 6.67–7.87 ppm corresponding to olefinic and aromatic protons. Its IR bands confirm the presence of OH, NH, C=O, and C=S functional groups at 3423, 1672, and 1258 cm^{-1}, respectively. ^{1}H NMR spectrum of compound **4** provided two doublets at δ 6.54 and 7.57 ppm with coupling constant $^{3}J = 16.0$ Hz for the trans olefinic protons, two singlets at δ 6.90 and 12.36 ppm for pyrimidine ring and NH protons, respectively, in addition two multiplet signals at δ 7.41 and 7.68 ppm for aromatic protons. Its ^{13}C NMR spectral parameter confirm the presence of carbonyl and two thiocarbonyl signals at δ 167.5, 177.4, and 178.0 ppm, respectively, which were approved from the IR analysis. Compound **7** was obtained when cinnamoylisothiocyanate derivative **1** was treated with aniline derivative **5** presumably through the nonisolable thiourea derivative **6** [followed by intramolecular cycloaddition and dehydrogenation] (Scheme 2). The key signal of this compound in its ^{1}H NMR spectrum is the singlet at 12.58 ppm due to the NH proton of the pyrimidine ring, the spectrum also showed the other NH at 11.48 ppm and aromatic protons. The ^{13}C NMR of pyrimidine derivative **7** illustrated signals at 166.2, 178.2 ppm for C=O and C=S, respectively, while C=N and aromatic carbon appeared at the expected chemical shift. IR bands of 7 showed a sharp medium peak at 3392, 3235, and 1668 cm^{-1} for 2NH and C=O function also strong absorption for C=C was observed at 1599 cm^{-1} in addition to C=S absorption frequency that was detected at 1266 cm^{-1}. Upon using electron deficient amine derivative **8** (namely, *p*-aminoacetophenone) to react with isothiocyanate **1**, the thiourea **9** was obtained in good yield (80%) (Scheme 2), its structure was confirmed by the spectral analysis, which were agreement with the structure (see the "Experimental" section). When compound **9** was left to cyclize intramoleculary at room temperature the reactant **9** was recovered completely unchanged. While refluxing of thiourea derivative **9** in the presence of base led to pyrimidine **10** (Scheme 1). ^{1}H NMR spectrum of pyrimidine derivative **10** showed the equilibrium mixture of thion-form **10A** and thiol form **10B**, the thiol form can be detected by singlet at δ 11.64 ppm due to SH group, while the singlet at δ 10.07 ppm result from the NH proton of the thione-tautomer (Scheme 1). In addition the multiplet in the region δ 7.22–7.94 ppm is due to the absorption of aromatic protons, while H-5 and H-6 of pyrimidine ring appeared as doublet and triplets at δ 5.34 and 3.70 ppm with coupling constant $^{3}J = 4.0$ Hz, respectively, finally $COCH_3$ protons signal was observed as a singlet at δ 2.5 ppm. Its ^{13}C-NMR data showed signals at 165.9 and 181.1 ppm for the C=O and

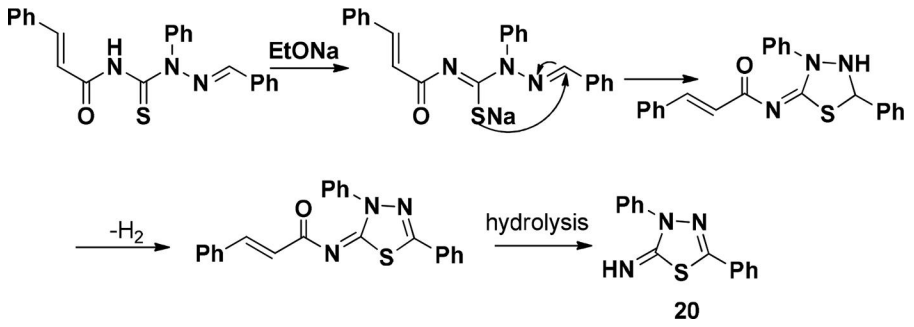
C=S SP^2 carbon, in addition aliphatic SP^3 carbon of C-6, C-5, and CH_3 were observed at δ 26.56, 26.84, and 62.39 ppm.

Thiourea derivative **9** underwent condensation beside the intramolecular cyclization when treated with benzaldehyde in basic medium to furnish cinnamoyl pyrimidine derivative **12** (Scheme 1). The presence of the thiol-thione tautomerizatin of **12** was indicated by two signals at δ 11.67 ppm and δ 11.71 ppm for NH and SH. Its ^{13}C NMR data illustrate signals at δ 182.0, 187.5, and 193.2 ppm for electronic different 2 C=O and C=S, also the signal for aromatic and styryl moiety appeared at the expected chemical shift.

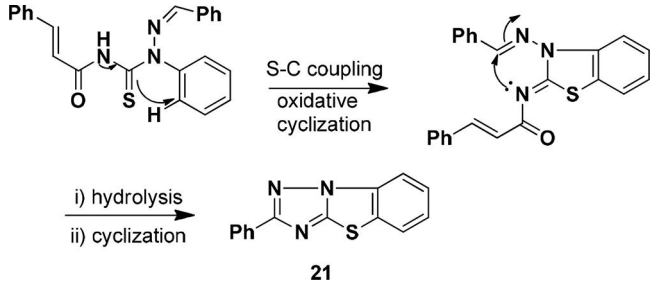
In the same manner, the thiosemicarbazide derivative **14** was obtained as a result of addition of NH_2 of **13** to isothiocyanate electrophilic carbon of **1** (Scheme 2). The structure of thiosemicarbazide derivative **14** was established from the spectral data and the elemental analysis and was agreed with its structure (see the "Experimental" section). Introduction of a second nucleophilic group besides the amino functionality, offers the possibility to form several products depending on the reaction condition, thus 6-phenylpyrimidine derivative **15** was produced by base-induced intramolecular conjugate addition reaction at room temperature (Scheme 2). Refluxing of base mediated solution of **14** resulted in triazine cyclization leading to formation of triazine intermediate **16** followed by intramolecular conjugate addition reaction to produce 8-nitro-3-phenylbenzo[*e*][1,3]thiazino[2,3-*c*][1,2,4]triazin-1(6*H*)-one (**17**) in moderate yield (59%) (Scheme 2). The ^1H NMR spectrum of compound **15** exhibited down field two singlets arising from 2NH (δ 10.78 and 12.38 ppm) and multiplet at δ 7.40–8.35 ppm representing the aromatic protons, in addition singlet at δ 6.53 ppm characterizes pyrimidine-H-5. Its ^{13}C NMR potentiated the pyrimidine structure **15**. The IR spectrum **15** showed absorption bands at 1681 and 1617 cm^{-1} which are attributed to C=O and C=C stretching. ^1H NMR spectrum of the benzotriazine **17** showed two singlets, at δ 11.62 ppm corresponding to NH proton, the multiplet of aromatic protons was observed at δ 7.40–7.58 ppm. The ring olefinic proton (thiazine-H-2) appeared as singlet at δ 5.13 ppm. The ^{13}C NMR of compound **17** revealed SP^2 carbons at δ 115.8, 119.1, 120.6, 120.8, 122.9, 127.5, 128.5, 128.7, 129.8, 130.0, 136.5, 144.5, 157.4, 168.3 ppm.

Finally, when Schiff base **18** was allowed to react with heteroallene **1** yielded thiosemicarbzide derivative **19**, which gave different heterocyclic systems through its reaction with strong base or different oxidizing agents, thus refluxing of **19** in sod.ethoxide solution afforded 2-imino-1,3,4-thiadiazole derivative **20**[28] in good yield (≈70%). While, treating of compound **19** with bromine or lead acetate in acetic acid tolerated triazole derivatives **21**[29] and **22**[30] in 60 and 80% yields, respectively (Scheme 2). The structure of thiadiazole and triazole derivatives **20–22** were proved from their spectral parameter and elemental analysis. Thus, ^1H NMR of **20** showed a deshielded NH signal at δ 10.33 ppm and aromatic protons at δ 6.73–7.87 ppm. The ^{13}C NMR of compound **20** clarified two C=N carbons at 145.2 ppm and 159.3 ppm beside aromatic SP^2 carbon. Its IR data showed two absorption bands at 3321 and 1601 cm^{-1} for NH and C=N, respectively. The ^1H NMR parameter of 2-phenylbenzo[4,5]thiazolo[3,2-*b*][1,2,4]triazole (**21**) showed aromatic multiplet in the region δ 7.48–7.92 ppm. The ^{13}C NMR of compound **21** gives 12 signals for SP^2 carbons at δ 108.2, 112.5, 116.9, 122.9, 127.6, 128.8, 129.0, 130.2, 131.9, 134.1, 139.3, 147.6 ppm. The structure of triazole thione derivative **22** was established from the spectral data and the elemental analysis and was agreement with its structure (see the "Experimental" section).

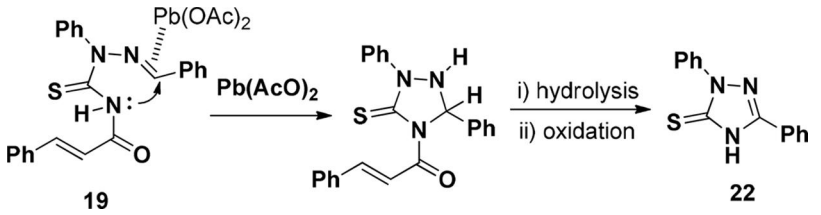
Scheme 3 illustrates the mechanistic route for formation of thiadiazole **20**, where the reaction started with nucleophilic attack of thiolate anion to the electrophilic C=N carbon,



Scheme 3. Mechanistic route of thiadiazole **20**.



Scheme 4. Mechanistic route of thiadiazole **21**.



Scheme 5. Mechanistic route of triazole **22**.

followed by dehydrogenation and subsequent hydrolysis with the extrusion of cinnamic acid (Scheme 3).

While the formation of compound **21** proceeds through oxidation thiazole cyclization, hydrolysis, imino attack to C=N electrophilic carbon and finally aromatization producing polyheterocyclic derivative **21** (Scheme 4).

In Scheme 5, lead acetate reacted with thiosemicarbazone **19** to achieve oxidation triazole cyclization with losing of cinnamic acid molecule and aromatization forming 22.

Experimental

General

The elemental analyses were obtained on a PerkinElmer 240. The mass spectra (Ms) were measured with Shimadzu GCMS-QP 1000 EX mass spectrometer. The IR spectra were

acquired in KBr on a Pye Unicam Sp-3–300 infrared spectrophotometer. The ^{1}H NMR spectra were measured on a Bruker Avance 400 spectrometer at 400.0 MHz. The chemical shifts were measured relative to DMSO-d_6 proton signal. The melting points were determined on an Electro thermal IA 9100 apparatus and are uncorrected.

N-((3-(Cinnamoylcarbamothioyl)-4-hydroxyphenyl)carbamothioyl)cinnamamide (3)

A mixture of cinnamoyl isothiocyanate (0.02 mol, 3.78 g) and 4-aminophenol **2** (0.02 mol, 2.18 g) in acetone (30 mL) was stirred at room temperature for 2 h, then poured onto cold water, the solid formed was heated with sodium bicarbonate, filtered and recrystallized from ethanol to give **3**. Yield: 7.89 g (81%); brown crystals; m.p. > 340 °C. IR (KBr): 3423 (NH, OH) 1672, 1623 (C=O), 1258 (C=S) cm^{-1}. ^{1}H NMR (DMSO-d_6, ppm) δ 6.67–7.78 (m, 17H, olefinic-H and Ar-H), 9.60 (s, 1H, OH), 11.50 (s, 1H, 2NH), 12.49 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6, ppm): 89.7, 97.3, 114.1, 115.9, 120.5, 120.8, 120.9, 124.8, 126.6, 127.4, 128.2, 128.9, 129.1, 129.96, 131.6, 134.0, 143.8, 144.8, 155.6, 166.1, 175.5, 178.7. Anal: $C_{26}H_{21}N_3O_3S_2$ (487.59); Calcd: C, 64.04; H, 4.34; N, 8.62. Found: C, 64.11; H, 4.38; N, 8.57.

Conclusion

In summary, we report an efficient and facile synthetic approaches for some pyrimidine thiones, triazines, triazoles, and thiadiazole. Cinnamoyl isothiocyanate was treated with a variety of *N*-nucleophilic reagents affording thiourea or thiosemicarbazide derivatives, the later intermediates were underwent intramolecular cyclization to give the target compounds.

References

[1] Tozkoparan, B.; Ertan, M.; Kelicen, P.; Demirdamar, R. Synthesis and Anti-Inflammatory Activities of Some Thiazolo[3,2-a]Pyrimidine Derivatives. *Farmaco* **1999**, *54*, 588–593. DOI: 10.1016/s0014-827x(99)00068-3.

[2] Jeanneau-Nicolle, E.; Benoit-Guyod, M.; Namil, A.; Leclerc, G. New Thiazolo[3,2-a]Pyrimidine Derivatives, Synthesis and Structure-Activity Relationships. *Eur. J. Med. Chem.* **1992**, *27*, 115–120.

[3] Pan, B.; Huang, R.; Zheng, L.; Chen, C.; Han, S.; Qu, D.; Zhu, M.; Wei, P. Thiazolidione Derivatives as Novel Antibiofilm Agents: Design, Synthesis, Biological Evaluation, and Structure - Activity Relationships. *Eur. J. Med. Chem.* **2011**, *46*, 819–824.

[4] Mohamed, S. F.; Flefel, E. M.; Amr, A. E. G. E.; El-Shafy, D. N. Anti-HSV-1 Activity and Mechanism of Action of Some New Synthesized Substituted Pyrimidine, Thiopyrimidine and Thiazolopyrimidine Derivatives. *Eur. J. Med. Chem.* **2010**, *45*, 1494–1501.

[5] Maddila, S.; Damu, G.; Oseghe, E.; Abafe, O.; Rao, C. V.; Lavanya, P. Synthesis and Biological Studies of Novel Biphenyl-3,5-dihydro-*2H*-Thiazolopyrimidines Derivatives. *J. Korean Chem. Soc.* **2012**, *56*, 334–340.

[6] Flefel, E.; Salama, M.; El-Shahat, M.; El-Hashash, M.; El-Farargy, A. A Novel Synthesis of Some New Pyrimidine and Thiazolopyrimidine Derivatives for Anticancer Evaluation. *Phosphorus Sulfur Silicon Relat. Elem.* **2007**, *182*, 1739–1756.

[7] Danel, K.; Pedersen, E. B.; Nielsen, C. Synthesis and Anti-HIV-1 Activity of Novel 2,3-Dihydro-7H-thiazolo[3,2-a]pyrimidin-7-ones. *J. Med. Chem.* **1998**, *41*, 191–198. DOI: 10.1002/chin.199820192.

[8] Alterman, M.; Samulsson, B. J.; Danielson, H. Design and Synthesis of New Potent C2-Symmetric HIV-1 Protease Inhibitors. Use of l-Mannaric Acid as a Peptidomimetic Scaffold. *J. Med. Chem.* **1998**, *41*, 3782–3792.

[9] Dhainaunt, A.; Regnier, G.; Tizot, A.; Berthier, L. K. New Purines and Purine Analogs as Modulators of Multidrug Resistance. *J. Med. Chem.* **1996**, *39*, 4099–4108. DOI: 10.1021/jm960361i.
[10] Brzozowski, Z.; Saczewski, F.; Gdaniec, M. Synthesis, Structural Characterization and Antitumor Activity of Novel 2,4-Diamino-1,3,5-Triazine Derivatives. *Eur. J. Med. Chem.* **2000**, *35*, 1053–1064. DOI: 10.1002/chin.200116161.
[11] Gahtori, P.; Ghosh, S. K.; Singh, B.; Singh, U. B.; Bhat, H. R.; Uppal, A. Synthesis, SAR and Antibacterial Activity of Hybrid Chloro, Dichloro-Phenylthiazolyl-s-triazines. *Saudi Pharmaceutical J.* **2012**, *20*, 35–43. DOI: 10.1016/j.jsps.2011.05.003.
[12] Dutta, M. M.; Goswami, B. N.; Kataky, J. C. S. Studies on biologically active heterocycles. Part I. Synthesis and antifungal activity of some new aroyl hydrazones and 2,5-disubstituted-1,3,4-oxadiazoles. *J. Heterocyclic Chem.* **1986**, *23*, 793–795. DOI: 10.1002/jhet.5570230328.
[13] Srinivas, K.; Bhanuprakash, K.; Murtly, U. S. N. Synthesis and Antibacterial Activity of 2,4,6-Trisubstituted s-Triazines. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1121–1129. DOI: 10.1002/chin.200710176.
[14] Klenke, B.; Stewart, M.; Barrett, M. P. Synthesis and Biological Evaluation of s-Triazine Substituted Polyamines as Potential New Anti-Trypanosomal Drugs. *J. Med. Chem.* **2001**, *44*, 3440–3452. DOI: 10.1021/jm010854+.
[15] Botros, S.; Khalil, N. A.; Naguib, B. H.; El-Dash. Y. Synthesis and Anticonvulsant Activity of New Phenytoin Derivatives. *Eur. J. Med. Chem.* **2013**, *60*, 57–63 DOI: 10.1016/j.ejmech.2012.11.025.
[16] Al-Soud, Y. A.; Al-Masoudi, N. A.; Ferwanah, A. E. S. Synthesis and Properties of New Substituted 1,2,4-triazoles: Potential Antitumor Agents. *Bioorg. Med. Chem.* **2003**, *11*, 1701–1708. DOI: 10.1016/s0968-0896(03)00043-9.
[17] Tozkoparan, B.; Gokhan, N.; Aktay, G.; Yesilada, E.; Ertan, M. 6-Bnzyllidenethiazolo[3,2-b]-1,2,4-triazole-5(6H)-one substituted with Ibuprofen: Synthesis, Characterization and Evaluation of Anti-Inflammatory Activity. *Eur. J. Med. Chem.* **2000**, *35*, 743–750. DOI: 10.1016/s0223-5234(00)00157-4.
[18] Varvaressou, A.; Siatra-Papastaikoudi, T.; Tsotinis, A.; Tsantili-Kakoulidou, A.; Vamvakides, A. Synthesis, Lipophilicity and Biological Evaluation of Indole-Containing Derivatives of 1,3,4-thiadiazole and 1,2,4-triazole. *Farmaco* **1998**, *53*, 320–326. DOI: 10.1016/s0014-827x(98)00024-x.
[19] Tsukuda, T.; Shiratori, Y.; Watanabe, M.; Ohtsuka, H.; Hattori, K.; Shirai, M.; Shimma, N. Modeling, Synthesis and Biological Activity of Novel Antifungal Agents (1). *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1819–1827. DOI: 10.1016/s0960-894x(98)00316-3.
[20] Witoaski, J. T.; Robins, R. K.; Sidwel, R. W.; Simon, L. N. Design, Synthesis, and Broad Spectrum Antiviral Activity of 1-.beta.-D-ribofuranosyl-1,2,4-triazole-3-carboxamide and Related Nucleosides. *J. Med. Chem.* **1972**, *15*, 1150–1154. DOI: 10.1021/jm00281a014.
[21] Sherif, M.; Assy, M.; Yousif, N.; Galahom, M. Studies on Heterocyclization of Acetoacetanilide. *J. Iran. Chem. Soc.* **2013**, *10*, 85–91. DOI: 10.1007/s13738-012-0128-x.
[22] Sayed, H. A.; Moustafa, A. H.; Yousif, N. M.; Assy, M. G.; Abd El-Halim, M. A. Synthesis and Reactions of Some Novel Mercaptopyrimidine Derivatives for Biological Evaluation. *Phosphorus Sulfur Silicon Relat. Elem.* **2008**, *183*, 2318–2329.
[23] El-Sayed, H. A. Design and Synthesis of Some Tricyclic Pyrimidines and Triazines via Cycloaddition and Intermolecular Cyclization of Cyclic Amidine. *J. Iran. Chem. Soc.* **2017**, *14*, 2239–2246. DOI: 10.1007/s13738-017-1160-7.
[24] El-Sayed, H. A.; Said, S. A.; Amr, A. E. Synthesis of Some Fused Heterocyclic Systems and Their Nucleoside Candidates. *Res. Chem. Intermed.* **2014**, *40*, 833–845. DOI: 10.1007/s11164-012-1006-y.
[25] Abdelghani, E.; Said, A. S.; Assy, M. G.; Abdel Hamid, A. M. Heterocyclization of Thiouracil Derivative: Synthesis of Thiazolopyrimidines, Tetrazolopyrimidines and Triazolopyrimidines of Potential Biological Activity. *J. Iran. Chem. Soc.* **2015**, *12*, 1809–1817. DOI: 10.1007/s13738-015-0656-2.

[26] Abdelghani, E.; Said, A. S.; Assy, M. G.; Abdel Hamid, A. M. Synthesis and Antimicrobial Evaluation of Some New Pyrimidines and Condensed Pyrimidines. *Arab. J. Chem.* **2017**, *10*, S2926–S2933. DOI: 10.1016/j.arabjc.2013.11.025.
[27] Assy, M. G. Some Reactions with ethyl 2-aryl-4-mercapto-6-methylpyrimidine-5-carboxylates. *Sulfur Lett.* **1990**, *11*, 75–82.
[28] Wolkoff, P.; Nemeth, S. T.; Gibson, M. S. Reaction of Hydrazonyl Halides with Derivatives of Thiourea and Thiosemicarbazide; A New Source of C- amino- and C-hydrazino- l,2,4-triazoles. *Can. J. Chem.* **1975**, *53*, 3211–3215.
[29] Deshmukh, M. B.; Patil, S. S.; Jadhav, S. D.; Shejwal, R. V. Synthesis of New Triazolo and Pyrazolo Benzothiazoles. *Indian J. Heterocycl. Chem.* **2010**, *20*, 163–166.
[30] y Barnikow, G.; Ebeling, H. Isothiocyanates. XXXVII. Reactions of Imidoyl Isothiocyanates with Substituted Hydrazines. *Zeitschrift fuer Chemie* **1980**, *20*, 55–56.